*THE JOURNAL OF* Organic Chemistry

# THE JOURNAL OF Organic Chemistry

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# THE JOURNAL OF Organic Chemistry®

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## NOTES

## COMMUNICATIONS

## AUTHOR INDEX

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## Arylsulfonoxylation of Aromatic Compounds. III.
## Kinetics of the Nitrophenylsulfonoxylation of Alkylbenzenes[1a-c]

RALPH L. DANNLEY,* JAMES E. GAGEN,[1d] AND KATHLEEN ZAK

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

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The *m*- and *p*-nitrophenylsulfonoxylation of alkylbenzenes in ethyl acetate solution is first order in peroxide and is not acid catalyzed. Although simple first-order kinetics with respect to alkylbenzenes are observed, with benzene itself the reaction first order with respect to arene competes with a reaction of the peroxide which is zero order with respect to the aromatic. In methylene chloride, arylsulfonoxylation gives simple first-order kinetics with respect to benzene as well as toluene and ethylbenzene. In ethyl acetate, the relative reactivities of the alkylbenzenes with respect to benzene are in good agreement with those previously reported from competitive reactions. The rates with benzene and hexadeuteriobenzene are identical; therefore, carbon–hydrogen bond breaking is not rate determining. Mesitylene is 1350 times as reactive as benzene for *p*-nitrophenylsulfonoxylation; therefore, π-complex formation is not rate determining. The energies of activation for *p*- and *m*-nitrophenylsulfonoxylation calculated from the pseudo-first-order rate constants are, respectively, benzene, 18, 17 (corrected for the competing solvolytic reaction); toluene, 15.9, 15.7; ethylbenzene, 16.2, 16.1; isopropylbenzene, 15.8, 15.8; *tert*-butylbenzene, 16.1, 16.0; *p*-xylene, 13.9, 14.9; and mesitylene, 12.8, 13.8.

The arylsulfonoxylation of aromatic nuclei has been tentatively classified as an electrophilic substitution for several reasons. First, the partial rate factors for the halobenzenes and alkylbenzenes are appropriate for an electrophilic but not a homolytic reaction. Second, there is a complete absence of side-chain reaction with the alkylbenzenes characteristic of free-radical processes.[1b] Third, no esr signal could be obtained using a reacting mixture of sulfonyl peroxide and benzene.[2]

In the preceding paper of this series,[1b] relative reactivities, orientations of substitution, and partial rate factors were determined for the *o*- and *m*-nitrophenylsulfonoxylation of toluene, ethylbenzene, cumene, and *tert*-butylbenzene. The relative reactivities were obtained from a competitive substitution by the peroxide of a mixture of benzene and the alkylbenzene.

$$(O_2NC_6H_4SO_3)_2 \; + \; RC_6H_5 \; \longrightarrow$$



$$+ \; O_2NC_6H_4SO_3H$$

Arylsulfonoxylation can readily be followed kinetically because the decrease in the peroxide content of the reaction mixture can be measured by iodometric titration. The present kinetic study was undertaken to determine, first, the order of the substitution with respect to the peroxide; second, whether the reaction is acid catalyzed; third, the order of the reaction with respect to arene; fourth, the relative reactivities of benzene, toluene, ethylbenzene, cumene, and *tert*-butylbenzene; fifth, whether the rate-determining step is the breaking of the carbon–hydrogen bond; sixth, whether π-complex formation is rate determining; and, seventh, the dependence of the enthalpy and entropy of activation on the nature of the alkyl group in the substrate and the orientation of the nitro group in the peroxide.

## Results and Discussion

**Selection of the Isomeric Nitrobenzenesulfonyl Peroxides.**—In the preceding paper of this series, *o*- and *m*-nitrobenzenesulfonyl peroxides were used in the substitution of alkylbenzenes. In the present work it was decided to abandon the use of *o*-nitrobenzenesulfonyl peroxide for several reasons. First, it is the least stable of the three isomeric peroxides; second, the nitro group may confer unusual steric influence when *ortho* to the reaction site; and, third, since the esters of the ortho acid needed as reference standards for glpc analyses in some of the planned future work are the lowest melting of the isomers, they are most difficult to obtain in pure state. The meta peroxide is more de-

(1) (a) Presented in part at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, Abstract No. S113. Taken in part from the Ph.D. Thesis of J. E. Gagen, Case Western Reserve University, 1967. (b) For the previous paper of this series, see R. L. Dannley, J. E. Gagen, and O. J. Stewart, *J. Org. Chem.*, **35**, 3076 (1970). (c) Supported in part by the U. S. Army Research Office (Durham) through Grant No. DA-ARO-(D)-31-124-G42. (d) NASA Trainee, 1965–1967.

(2) R. L. Dannley and G. E. Corbett, *J. Org. Chem.*, **31**, 153 (1966).

sirable in that it is the most stable of the three peroxides, and the corresponding acid chloride used in its synthesis is the lowest priced of the isomeric chlorides. Unfortunately, the esters of the meta acid are not much higher melting than those of the ortho acid. The para peroxide has as its principal advantage the fact that, as its reference esters needed for glpc analyses are the highest melting of all the isomers, they can be prepared most easily in a high state of purity. Therefore both the meta and para peroxides have some desirable attributes, and these two were used in the present work.

**Order with Respect to Sulfonyl Peroxide.**—Most of the kinetic experiments in this work were performed in ethyl acetate solution. In every case, with both peroxides, a good first-order plot was generally obtained for the disappearance of the sulfonyl peroxide through at least 2 half-lives. Occasionally there was a slight decrease in rate in the succeeding half-lives and, at the very highest temperatures used, poor first-order plots were sometimes secured. The rates were very reproducible with a particular sample of peroxide, usually within 1% and with maximum 3% differences from mean values. Deviations of 10% from average values were obtained occasionally between several investigators using different samples of peroxide, solvent, substrates, etc.

**Absence of Acid Catalysis.**—The absence of any autocatalysis is an indication that the substitution is not acid catalyzed, for the concentration of the corresponding nitrosulfonic acid rises from zero to appreciable concentrations during the course of the peroxide disappearance. However, Levi, Kovacic, and Gormish[3] have recently reported that aluminum chloride can catalyze the decomposition of *m*-nitrobenzenesulfonyl peroxide in an acetonitrile solution of toluene, and so acid catalysis might be expected.

It has been found in the present work, however, that the rate ($k = 4.77 \times 10^{-5}$ sec$^{-1}$) of reaction of *p*-nitrobenzenesulfonyl peroxide (0.01 $M$) with benzene (0.50 $M$) in ethyl acetate solution at 20° with no *p*-nitrobenzenesulfonic acid added is actually slightly greater than the rate ($k = 3.92 \times 10^{-5}$ sec$^{-1}$) with 10 mol of the acid added per mole of peroxide. The absence of catalysis by the sulfonic acid in ethyl acetate may be due to the basicity of this solvent which permits its protonation in preference to the peroxide.

**The Order of the Reaction with Respect to Arene.**—The pseudo-first-order rate constants given in Table I are based on the rate of disappearance of the peroxide and assume that the arene concentrations are large enough to remain unchanged during the reaction. In the few experiments in which the molarity of the arene was low enough to be appreciably decreased during the course of the reaction, second-order rate constants involving the arene concentration were calculated and then converted into first-order rate constants dependent only on the peroxide concentration (Table I footnote). The differences between the pseudo-first-order rate constants obtained by the two methods of calculation were too small to have any influence on the following discussion. From the pseudo-first-order rates for *p*-nitrophenylsulfonoxylation, first-order dependencies were obtained with respect to toluene (0.98) and

(3) E. M. Levi, P. Kovacic, and J. E. Gormish, private communication.

## TABLE I

DEPENDENCE OF THE PSEUDO-FIRST-ORDER RATE OF REACTION OF A NITROBENZENESULFONYL PEROXIDE (0.01 $M$) UPON AN ARENE CONCENTRATION IN ETHYL ACETATE SOLUTION

| Arene | [Arene], $M$ | $k \times 10^5$, sec$^{-1}$ | $T$, °C |
|---|---|---|---|
| *m*-Nitrophenylsulfonoxylation | | | |
| Benzene | 0.50 | 1.49 | 10 |
| Benzene | 1.00 | 2.63 | 10 |
| Benzene | 1.50 | 3.96 | 10 |
| Benzene | 0.25 | 3.34 | 20 |
| Benzene | 0.50 | 5.33 | 20 |
| Benzene | 1.00 | 8.65 | 20 |
| Benzene | 1.50 | 12.3 | 20 |
| Benzene | 0.25 | 13.74 | 30 |
| Benzene | 0.50 | 17.3 | 30 |
| Benzene | 0.75 | 22.4 | 30 |
| *p*-Nitrophenylsulfonoxylation | | | |
| Benzene | 0.50 | 1.22 | 10 |
| Benzene | 0.75 | 1.58 | 10 |
| Benzene | 1.00 | 2.06 | 10 |
| Benzene | 0.25 | 3.53 | 20 |
| Benzene | 0.50 | 4.77 | 20 |
| Benzene | 1.00 | 6.70 | 20 |
| Benzene | 2.00 | 10.45 | 20 |
| Benzene | 0.20 | 9.16 | 30 |
| Benzene | 0.50 | 13.1 | 30 |
| Benzene | 1.00 | 20.5 | 30 |
| Toluene | 0.10 | 6.99[a] | 15 |
| Toluene | 0.23 | 14.5 | 15 |
| Toluene | 0.36 | 23.4 | 15 |
| Toluene | 0.50 | 33.0 | 15 |
| *p*-Xylene | 0.10 | 5.15[a] | −15 |
| *p*-Xylene | 0.23 | 10.9 | −15 |
| *p*-Xylene | 0.36 | 19.9 | −15 |
| *p*-Xylene | 0.50 | 26.8 | −15 |

[a] Second-order ($k$[P][Ar]) calculations were also performed because the initial arene molarities were so small that these arene concentrations decreased appreciably during the course of the reaction. The resultant second-order constants were converted into pseudo-first-order rate constants: toluene, 7.25; *p*-xylene, 5.34 × 10⁻⁵ sec⁻¹.

*p*-xylene (1.05). However, for benzene the order is 0.66 for *p*-nitrophenylsulfonoxylation and 0.70 for *m*-nitrophenylsulfonoxylation. These partial orders with respect to benzene are dependent on the solvent (ethyl acetate) because in methylene chloride, the *p*-nitrophenylsulfonoxylation (Table II) of both benzene (0.94) and toluene (1.01) is first order with respect to arene.

In ethyl acetate the apparent fractional order is obtained because there are two competing reactions. The observed pseudo-first-order rate ($k_1$[P]) with benzene is the sum of a first-order ($k_2$[P]) dissociation to a reactive species plus a bimolecular nucleophilic displacement ($k_3$[P][B]) by the arene on an oxygen of the peroxide (eq 1). Thus from a plot of the observed $k_1$, against

$$-\frac{d[P]}{dt} = k_1[P] = k_2[P] + k_3[P][B] \qquad (1)$$

the concentration of benzene, the slope provides the rate constant of the bimolecular reaction ($k_3$ for the *p*-nitrophenylsulfonoxylation at 20° is $3.9 \times 10^{-5}$; for *m*-nitrophenylsulfonoxylation at 20° is $7.1 \times 10^{-5}$ $M^{-1}$ sec$^{-1}$) and the intercept at zero concentration of benzene is the pseudo-first-order rate constant for the dissociation zero order with respect to benzene ($k_2$ at

TABLE II

DEPENDENCE OF THE PSEUDO-FIRST-ORDER RATE OF REACTION
OF p-NITROBENZENESULFONYL PEROXIDE (0.01 $M$) WITH AN
ARENE IN METHYLENE CHLORIDE SOLUTION

| Arene | [Arene], $M$ | $k \times 10^6$, sec$^{-1}$ | $T$, °C |
|---|---|---|---|
| Benzene | 0.25 | 3.07[a] | 20 |
| Benzene | 0.50 | 6.07[a] | 20 |
| Benzene | 1.00 | 11.4[a] | 20 |
| Benzene | 2.00 | 21.7[a] | 20 |
| Toluene | 0.10 | 20.4[b] | 15 |
| Toluene | 0.23 | 47.6[b] | 15 |
| Toluene | 0.36 | 72.2[b] | 15 |
| Toluene | 0.50 | 14.2 | −5 |
| Toluene | 0.50 | 39.1 | 5 |
| Toluene | 0.50 | 108.[b] | 15 |
| Toluene | 0.50 | 172.[c] | 20 |
| Ethylbenzene | 0.50 | 13.2 | −5 |
| Ethylbenzene | 0.50 | 37.4 | 5 |
| Ethylbenzene | 0.50 | 108. | 15 |
| Ethylbenzene | 0.50 | 175.[c] | 20 |

[a] These rates yield a 0.94 order with respect to benzene. [b] These rates yield a 1.01 order with respect to toluene. [c] These rates obtained by extrapolation from the rates at lower temperatures.

TABLE III

PSEUDO-FIRST-ORDER RATE CONSTANTS (SEC$^{-1}$) AND RELATIVE
REACTIVITIES AT 20° FOR THE REACTION OF $m$- AND
p-NITROBENZENESULFONYL PEROXIDES (0.01 $M$) WITH
ARENES (1.0 $M$) IN ETHYL ACETATE

| | $m$-Nitrophenylsulfonoxylation | | | $p$-Nitrophenylsulfonoxylation | |
|---|---|---|---|---|---|
| | $k \times 10^6$ | $k_{Ar}/k_B$, kinetic | $k_{Ar}/k_B$, competitive | $k \times 10^5$ | $k_{Ar}/k_B$, kinetic |
| Benzene | 8.65 | 1.0 | 1.0 | 6.70 | 1.0 |
| Toluene | 172 | 19.9 | 19.0 | 121.8 | 18.2 |
| Ethylbenzene | 174[a] | 20.0 | 16.7 | 87.3[a] | 13.0 |
| Cumene | 144[a] | 16.6 | 13.5[b] | 89.4[a] | 13.3 |
| tert-Butylbenzene | 131[a] | 15.1 | 13.2 | 82.0[a] | 12.2 |
| $p$-Xylene | 2960[c] | 340 | ... | 1400[c] | 200 |
| Mesitylene | 20,300[d] | 2400 | ... | 9000[d] | 1350 |

[a] Calculated values from 0.5 $M$ rates using a 0.98 order for the arene. [b] A neat mixture of cumene-benzene. [c] Calculated from 0.5 $M$ rate at lower temperatures using 1.05 order for the arene. [d] Calculated from 0.5 $M$ rate at lower temperatures using 1.00 order for the arene.

20° for p-nitrophenylsulfonoxylation is 2.7 × 10$^{-5}$; for m-nitrophenylsulfonoxylation is 1.7 × 10$^{-5}$ sec$^{-1}$).

**Relative Reactivities of the Arenes.** —Relative reactivities of arenes in aromatic substitutions are traditionally obtained by comparing the rates with various arenes to a similar rate with benzene. In the present work benzene is obviously a poor reference compound for its substitution is unique among the arenes here studied inasmuch as it results from two competing reactions. However, to permit correlations with the published data for other aromatic substitutions, it was decided to conform to tradition and use benzene as a reference material. This decision necessitated a choice of whether to use as the reference the overall pseudo-first-order rate constant ($k_1$) with benzene or the rate constant ($k_3$) for the second-order reaction. The selection of $k_1$ as the reference value has the advantage that it permits comparisons of kinetic relative reactivities with relative reactivities based on competitive reactions.

Using the overall pseudo-first-order rate constant ($k_1$) becomes more appropriate by comparing only those rates measured or extrapolated for a 1 $M$ arene concentration. For the m-nitrophenylsulfonoxylation of these hydrocarbons, relative reactivities were previously determined[1b] by glpc of the products of the substitutions in competitive reactions. With toluene, ethylbenzene, and tert-butylbenzene at least one competitive determination was available for the 1.0 $M$ arene solution, and these are the values listed in Table III. The only available figures with cumene were obtained in neat mixtures of the arene and benzene, and therefore the value listed is not completely valid for comparison. In all cases, however, the relative reactivities obtained by competitive means differ at most by 20% from the kinetic values based on $k_1$ for benzene. Invariably the kinetic relative reactivity listed for an alkylbenzene is larger than the competitive relative reactivity value. The use of $k_3$ for benzene instead of $k_1$ would make this difference even greater. In future work, kinetic determinations with some substrates may not be feasible and competi-

tive determinations of relative reactivities might be the only ones available. Therefore, the use of $k_1$ for benzene as a reference standard seems the most attractive for it should lead to a more homogeneous volume of data. The significance of these relative reactivities has been discussed previously.[1b]

A change in solvent may, of course, affect relative reactivity of substrates. Because arylsulfonoxylation in methylene chloride is first-order with both benzene and alkylbenzenes, relative reactivities were obtained in this solvent for the p-nitrophenylsulfonoxylation of benzene (1.0), toluene (29.7), and ethylbenzene (29.7). Surprisingly, although both toluene and ethylbenzene have larger relative reactivities (which should indicate a higher specificity of the reagent) in methylene chloride than in ethyl acetate, the two alkylbenzenes have identical relative reactivities (indicating a low specificity) in the chlorinated solvent. Further work is needed to explain these anomalous effects in methylene chloride.

**Partial Rate Factors.** —Traditionally, relative reactivities are used to calculate partial rate factors. The same inherent errors (competitive reactions, etc.) are usually encountered with both the kinetic and competitive determinations of relative reactivity. The kinetic method is most reproducible in sulfonoxylations because of the precision of the titrations. In Table IV are listed partial rate factors for the m-nitrophenylsulfonoxylation of the arenes calculated from both competitive and kinetic relative reactivities using $k_1$ for benzene as a standard. At the present level of sophistication in the analysis of the mechanism of aromatic substitution, either set of values is probably suitable. The significance of these values has already been discussed.[1b]

**Carbon–Hydrogen Bond Breaking as a Rate-Determining Step.** —The rates of reaction of p-nitrobenzenesulfonyl peroxide with benzene (4.77 × 10$^{-5}$ sec$^{-1}$) and hexadeuteriobenzene (4.78 × 10$^{-5}$ sec$^{-1}$) were identical within experimental limits. Therefore, arylsulfonoxylation is similar to most nitrations, halogenations, and Friedel–Crafts reactions in that carbon–hydrogen bond breaking is not rate determining.

TABLE IV

PARTIAL RATE FACTORS CALCULATED FROM KINETIC AND
COMPETITIVE RELATIVE REACTIVITIES FOR THE
m-NITROPHENYLSULFONOXYLATION OF ALKYLBENZENES

| | Partial Rate Factors from | |
|---|---|---|
| | Kinetic $k_{Ar}/k_B$ | Competitive $k_{Ar}/k_B$ |
| Toluene | | |
| Ortho | 19.0 | 18.1 |
| Meta | 2.1 | 2.0 |
| Para | 77.3 | 73.8 |
| Ethylbenzene | | |
| Ortho | 18.9 | 15.8 |
| Meta | 2.8 | 2.3 |
| Para | 83.1 | 69.4 |
| Cumene | | |
| Ortho | 11.7 | 9.5 |
| Meta | 3.2 | 2.6 |
| Para | 69.7 | 56.7 |
| *tert*-Butylbenzene | | |
| Ortho | 3.0 | 2.6 |
| Meta | 7.4 | 6.5 |
| Para | 61.0 | 53.3 |

**π-Complex Formation.**—For the p-nitrophenylsul-fonoxylation of polyalkylbenzenes the relative reactivities with respect to benzene (Table III) are, p-xylene, 200; mesitylene, 1350. For m-nitrophenylsulfonoxylation the values are, p-xylene, 340; mesitylene, 2400. These high values are, characteristic of substitutions in which π-complex formation is not rate determining. In the reaction of nitration using nitronium tetrafluoroborate in tetramethylenesulfone solution where π-complex formation is rate determining, the relative reactivities are, p-xylene, 1.96; mesitylene, 2.71.[4]

**Reaction Parameters.**—From the rate constants ($k_1$) for benzene in Table I, the $k_2$ and $k_3$ values in Table VII were obtained. From these rate constants and those in Tables V and VI, the activation parameters (Table VIII) were calculated. The derivation of $k_2$ and $k_3$ for benzene from the measured rate constants ($k_1$) reduces precision so that the parameters derived from these $k_2$ and $k_3$ values are of very limited accuracy.

The relationships of the parameters for m-nitrophenylsulfonoxylation and p-nitrophenylsulfonoxylation in general are very similar, and the following discussion is applicable to both substitutions. The reaction parameters for all of the monoalkylbenzene are essentially identical. As expected, the enthalpies of activation for p-xylene and mesitylene are appreciably smaller than those for the monoalkylbenzenes, and these two polyalkylbenzenes also have entropies of activation with somewhat larger negative values (indicating possibly greater ionic character of their transition states). The enthalpies of activation for benzene substitution derived from the $k_3$ values (reaction first order with respect to benzene) are similar to those for the monoalkylbenzenes, but the lack of precision prevents more definitive comparisons.

The competing reaction for benzene substitution which is zero order with respect to benzene was first considered to consist of a rate-determining solvolytic ionization of the peroxide into some type of ion pair. Despite the limited accuracy of the $k_2$ values, it is

(4) G. A. Olah, S. J. Kuhn, and S. Flood, *J. Amer. Chem. Soc.*, **83**, 4571 (1961).

TABLE V

TEMPERATURE DEPENDENCE OF THE PSEUDO-FIRST-ORDER RATE
CONSTANTS FOR THE DISAPPEARANCE OF
m-NITROBENZENESULFONYL PEROXIDE (0.01 M) IN ARENES
(0.5 M) IN ETHYL ACETATE SOLUTION

| Arene | $T$, °C | $k \times 10^5$, sec$^{-1}$ |
|---|---|---|
| Benzene | 10.00 | 1.49 |
| Benzene | 20.00 | 5.33 |
| Benzene | 30.00 | 17.3 |
| Benzene | 40.00 | 55.0 |
| Toluene | −10.0 | 4.01 |
| Toluene | −0.1 | 12.3 |
| Toluene | 10.05 | 34.3 |
| Toluene | 20.10 | 87.2 |
| Ethylbenzene | 0.00 | 10.93 |
| Ethylbenzene | 10.00 | 30.9 |
| Ethylbenzene | 20.00 | 81.6 |
| Cumene | 0.00 | 9.95 |
| Cumene | 10.00 | 27.5 |
| Cumene | 20.00 | 73 |
| *tert*-Butylbenzene | 0.00 | 8.85 |
| *tert*-Butylbenzene | 10.00 | 25.1 |
| *tert*-Butylbenzene | 20.00 | 66.4 |
| p-Xylene | −33.3 | 4.99 |
| p-Xylene | −20.05 | 25.7 |
| p-Xylene | −10.0 | 79.3 |
| Mesitylene | −39.8 | 24.0 |
| Mesitylene | −33.3 | 54.3 |
| Mesitylene | −25.0 | 141 |

TABLE VI

TEMPERATURE DEPENDENCE OF THE PSEUDO-FIRST-ORDER RATE
CONSTANTS FOR THE DISAPPEARANCE OF
p-NITROBENZENESULFONYL PEROXIDE (0.01 M) IN ARENES
(0.5 M) IN ETHYL ACETATE SOLUTION

| Arene | $T$, °C | $k \times 10^5$, sec$^{-1}$ |
|---|---|---|
| Benzene | 10.00 | 1.22 |
| Benzene | 20.00 | 4.77 |
| Hexadeuteriobenzene | 20.00 | 4.78 |
| Benzene | 30.00 | 15.6 |
| Benzene | 40.00 | 49.7 |
| Toluene | 0.00 | 8.32 |
| Toluene | 10.00 | 23.5 |
| Toluene | 20.00 | 61.7 |
| Ethylbenzene | 0.00 | 7.02 |
| Ethylbenzene | 10.00 | 20.7 |
| Ethylbenzene | 20.00 | 53.9 |
| Cumene | 0.00 | 6.16 |
| Cumene | 10.00 | 17.6 |
| Cumene | 20.00 | 45.3 |
| *tert*-Butylbenzene | 0.00 | 5.42 |
| *tert*-Butylbenzene | 10.00 | 15.9 |
| *tert*-Butylbenzene | 20.00 | 41.6 |
| p-Xylene | −33.3 | 3.34 |
| p-Xylene | −15.00 | 26.8 |
| p-Xylene | −10.00 | 44.6 |
| Mesitylene | −33.3 | 34.2 |
| Mesitylene | −25.0 | 88.3 |
| Mesitylene | −20.05 | 141 |

obvious that the enthalpies of activation for this process are much higher than those derived from the $k_3$ figures. For the two reactions to compete, the entropies of activation for the $k_2$ process must be much more positive (measured value 30 ± 4 eu) than for the $k_3$ reaction (−22 eu). Such a large positive entropy of activation is not consistent with an ionization step but is more characteristic of a radical reaction. Obviously, if the reaction is a chain radical process, a good free-radical

### Table VII

$k_2$ and $k_3$ for the Arylsulfonoxylation of Benzene

| $T$, °C | $k_2 \times 10^5$, mol l.$^{-1}$ sec$^{-1}$ | $k_3 \times 10^5$, sec$^{-1}$ |
|---|---|---|
| *m*-Nitrophenylsulfonoxylation | | |
| 10 | 0.21 | 2.47 |
| 20 | 1.65 | 7.07 |
| 30 | 9.02 | 17.3 |
| *p*-Nitrophenylsulfonoxylation | | |
| 10 | 0.35 | 1.68 |
| 20 | 2.7 | 3.86 |
| 30 | 6.1 | 14.2 |

### Table VIII

Activation Parameters for the Nitrophenylsulfonoxylation of Arenes in Ethyl Acetate

| Arene | $\Delta H^{\ddagger}$, kcal mol$^{-1}$ | $\Delta S^{\ddagger}$, cal deg$^{-1}$ mol$^{-1}$ | $E_a$, kcal mol$^{-1}$ | Log $A$ |
|---|---|---|---|---|
| *m*-Nitrophenylsulfonoxylation | | | | |
| Benzene[a] | 20.6 | −7.8 | 21.1 | 11.3 |
| Benzene[b] | 32 ± 1 | +30 ± 4 | 31 ± 1 | 19 |
| Benzene[c] | 16 ± 0.5 | −22 | 17 | 8.2 |
| Toluene | 15.2 | −20.7 | 15.7 | 8.7 |
| Ethylbenzene | 15.5 | −20.0 | 16.1 | 8.8 |
| Cumene | 15.3 | −20.7 | 15.8 | 8.7 |
| *tert*-Butylbenzene | 15.5 | −20.3 | 16.0 | 8.8 |
| *p*-Xylene | 14.4 | −22.3 | 14.9 | 9.3 |
| Mesitylene | 13.3 | −22.2 | 13.8 | 9.3 |
| *p*-Nitrophenylsulfonoxylation | | | | |
| Benzene[a] | 21.2 | −6.2 | 21.7 | 11.9 |
| Benzene[d] | . . . | . . . | . . . | . . . |
| Benzene[c] | 16 ± 2 | −18 | 16 ± 2 | 9.4 |
| Toluene | 15.4 | −20.8 | 15.9 | 8.7 |
| Ethylbenzene | 15.6 | −20.1 | 16.2 | 8.8 |
| Cumene | 15.3 | −21.6 | 15.8 | 8.5 |
| *tert*-Butylbenzene | 15.6 | −20.6 | 16.1 | 8.7 |
| *p*-Xylene | 13.4 | −22.6 | 13.9 | 8.2 |
| Mesitylene | 12.3 | −22.4 | 12.8 | 8.2 |

[a] From the pseudo-first-order rate constants ($k_1$). [b] From the reaction constants ($k_2$) calculated for the reaction whose rate is independent of the benzene concentration. [c] From the reaction constants ($k_3$) calculated for the reaction first order with respect to benzene concentration. [d] The $k_2$ values were not reproducible enough to justify additional calculations.

inhibitor should eliminate it. Unfortunately most inhibitors (thiols, hydroquinone, etc.) react directly with the peroxide or are so highly colored (galvinoxyl, etc.)

that they interfere with the kinetic measurements. The alkylbenzenes are quite good radical traps, and the clean first orders observed with these hydrocarbons may be partially due to this attribute but their greater reactivity toward nuclear substitution is probably sufficient in itself to eliminate the competitiveness of any solvolytic process.

An enthalpy (21.4 kcal mol$^{-1}$) and an entropy (−5.1 cal deg$^{-1}$ mol$^{-1}$) of activation for the *m*-nitrophenylsulfonoxylation of benzene in ethyl acetate have recently been reported[5] corresponding to the value derived from $k_1$ for the reaction.

**Summary.**—All of these data (except for the $k_2$ reactions with benzene) are consistent with an electrophilic aromatic substitution in which the reaction of the peroxide with the aromatic substrate to form a σ complex is rate determining.

## Experimental Section

**Materials.**—The nitrobenzenesulfonyl peroxides, benzene, toluene, ethylbenzene, cumene, *tert*-butylbenzene and ethyl acetate were prepared or purified as described in the previous paper.[1b] Mesitylene (Matheson Coleman and Bell practical grade) was purified by glpc using a 20 ft × ³/₈ in. SE-30 column using an Aerograph Model 1525-B chromatograph. *p*-Xylene (J. T. Baker reagent grade) was distilled through a 24-ft Vigreux column collecting a fraction with bp 136°. Hexadeuteriobenzene (Merck Sharp and Dohme) was used without purification.

**Typical Kinetic Procedure.**—*p*-Nitrobenzenesulfonyl peroxide (302.9 mg, 0.745 mol) was placed in a 100-ml reaction vessel in a constant-temperature bath (20 ± 0.05°), and ethyl acetate (50 ml) equilibrated to this temperature was added. Benzene (2.93 g, 0.0375 mol) was weighed into a 25-ml volumetric flask and diluted to the mark with ethyl acetate; the vessel was placed in the bath. After 10 min the solutions had equilibrated and were mixed. An aliquot (5 ml) was removed immediately (zero time) and titrated.

(5) J. Bolte, G. Dauphin, and A. Kergomard, *Bull. Soc. Chim. Fr.*, 2291 (1970).

# Arylsulfonoxylation of Aromatic Compounds. IV. Nitrophenylsulfonoxylation of Bromobenzene, Methyl Benzoate, Nitrobenzene, and Anisole[1a-c]

RALPH L. DANNLEY* AND WARREN R. KNIPPLE[1d]

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

The *m*-nitrophenylsulfonoxylation of methyl benzoate, nitrobenzene, bromobenzene, and anisole follows the familiar pattern of orientation and activation or deactivation influences appropriate to an electrophilic substitution. The $k_{Ar}/k_B$'s determined by competitive reactions (and by direct kinetics) are, respectively, methyl benzoate, $8.3 \times 10^{-2}$ ($10.6 \times 10^{-2}$); nitrobenzene, $2.4 \times 10^{-3}$; bromobenzene, 0.47 (0.56); anisole, $7.0 \times 10^3$ ($7.5 \times 10^3$). The ortho, meta, and para orientations (partial rate factors based on competitive $k_{Ar}/k_B$) are, methyl benzoate, 24, 67, 9% (0.059, 0.17, 0.043); nitrobenzene, 24, 65, 11% (0.0017, 0.0046, 0.0015); bromobenzene, 21, 3, 76% (0.29, 0.042, 2.1); anisole, 14, –, 86% (2,940, –, 36,100). The *p*-nitrophenylsulfonoxylation of bromobenzene gave a $k_{Br}/k_B$ of 0.49 by a competitive reaction and the following orientations (partial rate factors): ortho, 22.8% (0.366); meta, 4.7% (0.068); para, 72.5% (2.1). The orders of the reactions with respect to arene were essentially first order within experimental error: methyl benzoate, 0.97; bromobenzene, 0.99; anisole, 1.00. A good Hammett $\sigma^+$ plot of these values and those previously reported gave a $\rho$ value of $-4.4$. The enthalpies (entropies) of activation are, bromobenzene, 19.1 ($-13.1$); methyl benzoate, 19.6 ($-14.7$); anisole, 12.3 ($-22.7$). The larger negative entropies with the more active aromatic substrates correspond to more complete bond formation in the transition state with these electron-rich aromatics.

In the preceding papers[1b] of this series, the nitrophenylsulfonoxylation of aromatic nuclei (eq 1) was



$$(O_2NC_6H_4SO_3)_2 \; + \; \text{arene} \longrightarrow$$

$$\text{ArX-OSC}_6\text{H}_4\text{NO}_2 \; + \; O_2NC_6H_4SO_3H \quad (1)$$
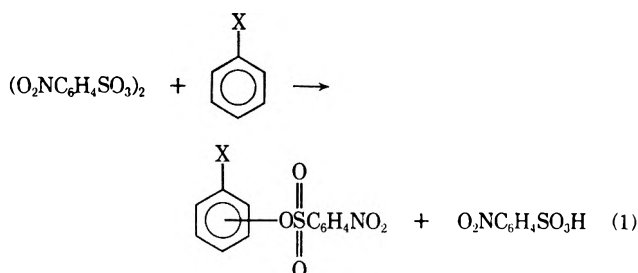
tentatively classified as an electrophilic reaction. This conclusion was based, however, on experiments involving only alkylbenzenes and two halobenzenes.

The present paper consists of several distinct units of work which were planned to establish more clearly the validity of the electrophilic classification. The thermal decomposition of *m*-nitrobenzenesulfonyl peroxide in nitrobenzene and methyl benzoate was studied to determine, first, whether arylsulfonoxylation would occur with such deactivated nuclei; second, whether any such substitution would be predominantly meta in orientation as predicted for an electrophilic process; and, third, the magnitude of the partial rate factors for reactions at the available positions. A similar reaction with anisole was planned to determine: first, whether its reactive nucleus would undergo substitution and not oxidation; second, the orientations and partial rate factors for any such substitution. A Hammett correlation of the partial rate factors would be particularly valuable in classifying the mechanism of arylsulfonoxylation. A study with bromobenzene as a substrate was proposed particularly to study the magnitude of the para partial rate factor. Finally, kinetic studies were projected to measure the activation parameters needed for a quantitative treatment of the mechanism.

## Results and Discussion

**Orientation of Substitution.**—*m*-Nitrophenylsulfonoxylation occurred in yields of 65–70% with all four of the benzene derivatives neat or in ethyl acetate solution at room temperature (Table I). Inasmuch as nitrobenzene and methyl benzoate were converted into sulfonate esters, arylsulfonoxylation must be included with nitration, halogenation, and sulfonation as one of the few electrophilic aromatic substitutions applicable to strongly deactivated nuclei. It is the mildest of these substitution reactions for it occurs at room temperature in the absence of strong Lewis acids. The substitution of anisole in high yield instead of oxidation of its reactive nucleus gives even wider scope to this new reaction of aromatic substitution.

The predominant meta substitution (Table I) with nitrobenzene (65%) and methyl benzoate (67%) is critical confirmation of the electrophilic classification of the reaction. In contrast, classical homolytic substitutions of these same aromatics such as the phenylation of methyl benzoate[2] and nitrobenzene[3] or the hydroxylation of nitrobenzene with Fenton's reagent[4] all occur with predominant ortho–para orientation.

The magnitude of the meta orientation for the arylsulfonoxylation of methyl benzoate (67%) is similar to that for the nitration of ethyl benzoate (68%).[5] The *m*-nitrophenylsulfonoxylation of nitrobenzene (65%), however, is much less selective than the chlorination (81%)[6] or nitration (93%)[5] of this substrate.

The *m*-nitrophenylsulfonoxylation of anisole (86% para, 14% ortho) is in the range of orientations for other electrophilic substitutions such as chlorination (79% para, 21% ortho),[7] bromination (96% para, 4% ortho;[8] 98.4% para, 1.6% ortho[9]), or mercuration

(1) (a) Presented in part at the International Symposium on the Chemistry of Organic Peroxides, Berlin-Aldershof, Sept 1967. Taken in part from the Ph.D. Thesis of W. R. Knipple, Case Western Reserve University, 1968. (b) For the previous paper of this series, see R. L. Dannley, J. E. Gagen, and K. Zak, *J. Org. Chem.*, **38**, 1 (1973). (c) Supported in part by the U. S. Army Research Office (Durham) through Grant No. DA-ARO-(D)-31-124-G42. (d) Standard Oil Company of Ohio Fellow, 1966–1967.

(2) R. L. Dannley and E. C. Gregg, Jr., *J. Amer. Chem. Soc.*, **76**, 2997 (1954).

(3) D. R. Augood, D. H. Hey, and G. H. Williams, *J. Chem. Soc.*, 2094 (1953).

(4) R. O. C. Norman and G. K. Radda, *Proc. Chem. Soc., London*, 138 (1962).

(5) A. F. Holleman, *Chem. Rev.*, **1**, 187 (1925).

(6) R. O. C. Norman and G. K. Radda, *J. Chem. Soc.*, 3610 (1961).

(7) P. B. D. de la Mare and C. A. Vernon, *ibid.*, 1764 (1951).

(8) B. Jones and E. N. Richardson, *ibid.*, 3939 (1956).

(9) L. M. Stock and H. C. Brown, *J. Amer. Chem. Soc.*, **82**, 1942 (1960).

TABLE I

ORIENTATIONS, COMPETITIVE RELATIVE REACTIVITIES, AND THE CORRESPONDING PARTIAL RATE FACTORS FOR THE
$m$-NITROPHENYLSULFONOXYLATION OF NITROBENZENE, METHYL BENZOATE, BROMOBENZENE, AND ANISOLE
AND THE $p$-NITROPHENYLSULFONOXYLATION OF BROMOBENZENE

| Arene | Temp, °C | Arylsulfonate yield, % | Isomer distribution, % | | | $k_{Ar}/k_B$ | Partial rate factor | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Ortho | Meta | Para | | Ortho | Meta | Para |
| $m$-Nitrophenylsulfonoxylation | | | | | | | | | |
| Nitrobenzene | 20 | 65 | 24 | 65 | 11 | 0.0024 | 0.0017 | 0.0046 | 0.0015 |
| Methyl benzoate | 20 | 70 | 24 | 67 | 9 | 0.083 | 0.059 | 0.17 | 0.043 |
| Anisole | −30 | 67 | 14 | ... | 86 | 6200$^a$ | 2600 | ... | 32,000 |
| Bromobenzene | 20 | 66 | 21 | 3 | 76 | 0.47 | 0.29 | 0.042 | 2.1 |
| $p$-Nitrophenylsulfonoxylation | | | | | | | | | |
| Bromobenzene | 20 | 72 | 22.8 | 4.7 | 72.5 | 0.49 | 0.366 | 0.068 | 2.1 |

$^a$ Competitive reaction run with mesitylene and this $k_{Au}/k_B$ calculated from the $k_{Mes}/k_B$ kinetic value reported in Table IV.

(86% para, 14% ortho).[10] Arylsulfonoxylation is therefore usually, but not invariably, as selective in orientation as other electrophilic substitutions.

**Relative Reactivities from Competitive Reactions.—** From the relative yields of phenolic esters produced by decomposition of $m$-nitrobenzenesulfonyl peroxide in a mixture of the aromatic compound with benzene, the relative reactivities ($k_{Ar}/k_B$) in Table I were calculated. Unfortunately, these competitive reactions at the selected peroxide concentration usually had to be run in the absence of ethyl acetate (the solvent in the kinetic experiments). The restriction that both aromatic substrates must be present in sufficient quantity to prevent their concentrations from changing appreciably during the course of the reaction and the practical necessity that the ratio of the least reactive substrate to the more reactive substrate must be high to give measurable competition results in such a high molarity of aromatics that little ethyl acetate can be added. The value for anisole is of particularly limited accuracy because it is so reactive that it was necessary to run the competitive reaction with mesitylene at −30° and then calculate the $k_{An}/k_B$ from the previously reported[1b] room temperature value for $k_{Mes}/k_B$. Inasmuch as the relative reactivities are dependent on temperature, the anisole value could easily be in error by a power of ten at room temperature. This value for anisole (7.0 × 10³) is much smaller than the reported $k_{An}/k_B$ for bromination (1.79 × 10⁹),[11] chlorination (9.7 × 10⁶),[11] or acetylation (2.9 × 10⁵)[12] indicating a lower selectivity for the nitrophenylsulfonoxylation reaction. This is to be expected for such a reactive reagent. Only the mercuration of anisole is reported[10] to have a $k_{An}/k_B$ (4.48 × 10²) smaller than the value reported here.

The relative reactivities of nitrobenzene (2.4 × 10⁻³) and methyl benzoate (8.3 × 10⁻²) for $m$-nitrophenylsulfonoxylation are larger than those for other electrophilic substitutions such as the $k_{Nit}/k_B$ for bromination (1.6 × 10⁻⁵)[13] or the $k_{PhCOOEt}/k_B$ (3.67 × 10⁻³)[14] for nitration, which is again consistent with a low specificity for the arylsulfonoxylation. In fact, a comparison of the relative reactivities of nitrobenzene and anisole gives a total range of reactivities for sulfonoxylation of only about 3 × 10⁶.

**Partial Rate Factors.—** From the competitive relative reactivities and the orientations already discussed, the partial rate factors for $m$-nitrophenylsulfonoxylation were calculated (Table I). These partial rate factors are consistent with an electrophilic classification of the reaction.

One set of values is reported for a $p$-nitrophenylsulfonoxylation. As in previous papers,[1b] the use of $p$- and $m$-nitrobenzenesulfonyl peroxides gave essentially the same results in all respects when used in the substitution of an aromatic substrate, in the present case bromobenzene.

The partial rate factors are those expected for an electrophilic substitution except for the high para partial rate factors for the $m$- (2.1) and $p$-nitrophenylsulfonoxylation ((2.1) of bromobenzene. Similarly, the $m$-nitrophenylsulfonoxylation of chlorobenzene has been reported[15] to give a para partial rate factor of 3.7. Although para partial rate factors over 1.0 are not unknown for the deactivated nuclei of halobenzenes, they are not normally encountered.

**π-Complex Formation.—**Arylsulfonoxylation can readily be measured kinetically by iodometric titration for the disappearance of the peroxide content of a reaction mixture. The rate of disappearance of the peroxide has been found[1b] to correspond to a pseudo-first-order rate process. In a previous paper,[1b] π-complex formation was excluded as a rate-determining step in nitrophenylsulfonoxylation by comparison of the relative rates of substitution of mesitylene, $p$-xylene, and benzene. The half-life (50 hr) for the disappearance of $m$-nitrobenzenesulfonyl peroxide in an ethyl acetate solution 1 $M$ in methyl benzoate at room temperature has now been found to be over twice as great as the corresponding half-life (20 hr) in neat ethyl acetate. A possible explanation for the longer half-life in the presence of methyl benzoate is the formation of a π complex between this substrate and the sulfonyl peroxide, although this π-complex formation need not be rate determining.

**Order of the Reaction with Respect to Arene.** From the pseudo-first-order rates of reaction (Table II) of $m$-nitrobenzenesulfonyl peroxide with varius concentrations of the arenes, the orders of reaction with respect to the aromatics were found to be, bromobenzene, 0.99; methyl benzoate, 0.97; and anisole, 1.00. The first-order relationships for these compounds are in agreement with all other benzene derivatives.[1b]

(10) H. C. Brown and M. Dubeck, *J. Amer. Chem. Soc.*, **82**, 1939 (1960).
(11) L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, **1**, 35 (1963).
(12) H. C. Brown and G. Marino, *J. Amer. Chem. Soc.*, **84**, 1658 (1962).
(13) P. B. D. de la Mare and I. C. Hilton, *J. Chem. Soc.*, 997 (1962).
(14) C. K. Ingold and M. S. Smith, *ibid.*, 905 (1938).
(15) R. L. Dannley and G. E. Corbett, *J. Org. Chem.*, **31**, 153 (1966).

TABLE II

DEPENDENCE OF THE PSEUDO-FIRST-ORDER RATE OF
DISAPPEARANCE OF m-NITROBENZENESULFONYL PEROXIDE
(0.01 M) ON THE CONCENTRATION OF AROMATIC SUBSTRATE IN
ETHYL ACETATE SOLUTIONS

| Aromatic substrate | [Aromatic], $M$ | $k \times 10^4$, $sec^{-1}$ | $T$, °C |
|---|---|---|---|
| Bromobenzene | 1.0 | 4.76 | 20 |
|  | 1.5 | 7.01 | 20 |
|  | 2.0 | 9.49 | 20 |
| Methyl benzoate | 1.0 | 0.906 | 20 |
|  | 1.5 | 1.44 | 20 |
|  | 2.0 | 1.93 | 20 |
|  | 3.0 | 2.80 | 20 |
| Anisole | 0.067 | 15.0 | −40 |
|  | 0.13 | 31.6 | −40 |
|  | 0.20 | 47.7 | −40 |
|  | 0.33 | 74.2 | −40 |

**Kinetic Relative Reactivities.**—From the pseudo-first-order rate constants (Table III), the relative reactivities given in Table IV were calculated. They differ

TABLE III

TEMPERATURE DEPENDENCE OF THE PSEUDO-FIRST-ORDER RATE
CONSTANTS FOR THE REACTION OF m-NITROBENZENESULFONYL
PEROXIDE WITH AROMATICS IN ETHYL ACETATE SOLUTION

| Aromatic | $T$, °C | [Peroxide], $M$ | [Aromatic], $M$ | $k \times 10^5$, $sec^{-1}$ |
|---|---|---|---|---|
| Benzene | 20.0 | 0.01 | 1.0 | 8.56 |
| Bromobenzene | 10.1 | 0.01 | 1.0 | 1.48 |
|  | 20.0 | 0.01 | 1.0 | 4.76 |
|  | 30.0 | 0.01 | 1.0 | 14.4 |
|  | 40.0 | 0.01 | 1.0 | 42.0 |
| Methyl benzoate | 10.1 | 0.01 | 1.0 | 0.266 |
|  | 20.0 | 0.01 | 1.0 | 0.906 |
|  | 30.0 | 0.01 | 1.0 | 2.84 |
| Anisole | −40.0 | 0.0067 | 0.067 | 15.0[a] |
|  | −35.0 | 0.0067 | 0.067 | 28.8[a] |
|  | −30.0 | 0.0067 | 0.067 | 49.4[a] |
|  | −25.1 | 0.0067 | 0.067 | 81[a] |
| Mesitylene | −30.2 | 0.0067 | 0.067 | 10.0[a] |
|  | −25.1 | 0.0067 | 0.067 | 18.0[a] |
|  | −20.0 | 0.0067 | 0.067 | 32.9[a] |
|  | −15.0 | 0.0067 | 0.067 | 56.2[a] |

[a] Second-order calculations were performed and the results then converted into pseudo-first-order rate constants at these concentrations of aromatics.

TABLE IV

PSEUDO-FIRST-ORDER RATE CONSTANTS AND RELATIVE
REACTIVITIES AT 20° FOR THE REACTION OF
m-NITROBENZENESULFONYL PEROXIDE WITH ARENES
IN ETHYL ACETATE

| Arene | [Peroxide], $M$ | [Arene], $M$ | $k \times 10^5$, $sec^{-1}$ | $k_{Ar}/k_B$, kinetic | $k_{Ar}/k_B$, competitive |
|---|---|---|---|---|---|
| Benzene | 0.01 | 1.0 | 8.56[a] | 1.00 | 1.00 |
| Anisole | 0.0067 | 0.067 | 4300[b] | 7500[c] | 7000[e] |
| Bromobenzene | 0.01 | 1.0 | 4.76 | 0.56 | 0.47 |
| Methyl benzoate | 0.01 | 1.0 | 0.906 | 0.106 | 0.083 |
| Mesitylene | 0.0067 | 0.067 | 1500[b] | 2600[c,d] | ... |

[a] Value of 8.65 × 10⁵ previously reported[1c] indicates reproducibility between different investigators using different samples of peroxides, etc.   [b] Extrapolated from the values at lower temperatures.   [c] Calculated by correcting the rate constant to 1.0 M using a first-order dependency on arene concentration.   [d] A value of 2400 was reported[1c] previously by a similar extrapolation procedure.   [e] Based on the $k_{An}/k_{Mes}$ competitive values and $k_{Mes}/k_B$ kinetic value of 2600 reported in this paper.

by from 16 to 21% from the corresponding values obtained from competitive reactions, and similar differences have been found with other benzene derivatives.[1b] This is quite a close check for the competitive values were measured in the neat (or practically neat) aromatics while the kinetics were run in ethyl acetate solution. The solvent change would be expected to have an influence on the relative reactivities. Although both methods of measurement of relative reactivity are subject to certain conceptual as well as experimental errors, the kinetic method is the most reproducible. Therefore, the authors consider the kinetic values the more reliable and partial rate factors based on them are presented in Table V.

TABLE V

PARTIAL RATE FACTORS CALCULATED FROM KINETIC AND
COMPETITIVE RELATIVE REACTIVITIES FOR THE
m-NITROPHENYLSULFONOXYLATION OF ARENES

| | Partial rate factors from Kinetic $k_{Ar}/k_B$ | Competitive $k_{Ar}/k_B$ |
|---|---|---|
| Anisole | | |
| Ortho | 3,150 | 2,940 |
| Meta | ... | ... |
| Para | 38,800 | 36,100 |
| Bromobenzene | | |
| Ortho | 0.35 | 0.29 |
| Meta | 0.050 | 0.042 |
| Para | 2.6 | 2.1 |
| Methyl benzoate | | |
| Ortho | 0.076 | 0.059 |
| Meta | 0.21 | 0.17 |
| Para | 0.057 | 0.043 |

The para partial rate factor for the m-nitrophenylsulfonoxylation of anisole ($3.4 \times 10^4$) is similar to many other partial rate factors for reactions of anisole such as bromination ($1.6 \times 10^5$),[16] acetylation ($1.8 \times 10^4$),[12] mercuration ($2.31 \times 10^3$),[10] deboronation ($2.24 \times 10^4$),[17] etc. Ortho partial rate factors are less frequently given because of the low percentage of ortho substitution, but of the above substitutions the ortho partial rate factor for the mercuration of anisole ($1.86 \times 10^2$)[10] is in the same range as the corresponding value for m-nitrophenylsulfonoxylation ($2.8 \times 10^3$).

The partial rate factors for the m-nitrophenylsulfonoxylation of methyl benzoate (Table V) are all somewhat larger than the corresponding values (ortho, $0.26 \times 10^{-2}$; meta, $0.79 \times 10^{-2}$; para, $0.9 \times 10^{-3}$) for the nitration of ethyl benzoate[18] in acetic anhydride. Similarly, the meta partial rate factor for the m-nitrophenylsulfonoxylation of nitrobenzene ($4.6 \times 10^{-3}$, Table I) is much larger than the $4.8 \times 10^{-5}$ meta partial rate factor reported[19] for its bromination. The magnitude of these partial rate factors all point to a low selectivity for nitrophenylsulfonoxylation.

**Hammett Correlation.**—A least-squares plot of the logs of the partial rate factors against the corresponding $\sigma^+$ substituent contents is shown in Figure 1. A $\rho$ value of $-4.4$ is obtained in contrast to a value of

(16) G. Illuminati, *J. Amer. Chem. Soc.*, **80**, 4945 (1958).
(17) K. V. Nahabedian and H. G. Kuivila, *ibid.*, **83**, 2167 (1961).
(18) C. K. Ingold and M. S. Smith, *J. Chem. Soc.*, 918 (1938).
(19) L. M. Stock, "Aromatic Substitution Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1968.

−3.38 reported by Kobayashi and Minato[20] based only on toluene, chlorobenzene, and nitrobenzene figures. This fairly large negative value is in the range of the $\rho$ values for mercuration (−4.0),[21] bromination (−5.78),[22] and nitration (−6.22).[23] This $\rho$ value of −4.4 is therefore excellent confirmation of the classification of arylsulfonoxylation as an electrophilic substitution.

**Activation Parameters.**—From the rate constants given in Table III, the activation parameters in Table VI were calculated. As expected, the $\Delta H^{\ddagger}$ for the

### TABLE VI

#### ACTIVATION PARAMETERS FOR THE
#### m-NITROPHENYLSULFONOXYLATION OF BROMOBENZENE, METHYL BENZOATE, AND ANISOLE

| Arene | $\Delta H^{\ddagger}$, kcal mol$^{-1}$ | $\Delta S^{\ddagger}$, cal deg$^{-1}$ mol$^{-1}$ |
|---|---|---|
| Bromobenzene | 19.1 ± 0.1 | −13.1 ± 0.1 |
| Methyl benzoate | 19.6 ± 0.1 | −14.7 ± 0.1 |
| Anisole | 12.3 ± 0.4 | −22.7 ± 0.2 |

m-nitrophenylsulfonoxylation of methyl benzoate (19.6) and bromobenzene (19.1) are appreciably larger than the corresponding values for monoalkylbenzenes (15.2–15.5 kcal/mol), while the $\Delta H^{\ddagger}$ for anisole (12.3) is even lower than the value for mesitylene (13.3).[1b] These are all consistent with an electrophilic substitution.

The entropies of activation are more interesting. The $\Delta S^{\ddagger}$ for the m-nitrophenylsulfonoxylation of anisole (−22.8) is similar to the $\Delta \Delta S^{\ddagger}$ for this substitution obtained for mesitylene (−22.2) and p-xylene (−22.3) while all the monoalkylbenzenes have values of about −20.5 cal deg$^{-1}$ mol$^{-1}$. The $\Delta S^{\ddagger}$ for methyl benzoate (−14.7) and bromobenzene (−13.1) are much less negative. Inasmuch as nitrophenylsulfonoxylation of each of these substrates occurs to only a small extent in the ortho position, steric hindrance can exert only a minor influence on the measured entropies of activation. The magnitudes of these entropies are consistent with more complete $\sigma$-bond formation (Wheland intermediate) in the transition state with electron-rich aromatics. A late transition state requires destruction of the aromatic $\pi$ system, conversion of an sp$^2$ aromatic carbon into sp$^3$ configuration together with formation of a $\sigma$ bond to a peroxidic oxygen, and probably stretching of the peroxide bond to an intimate ion pair and solvation of the ion pair. These influences cumulatively could result in a large negative $\Delta S^{\ddagger}$ for a late transition state with solvation being most significant of course.

The late transition state in electrophilic substitution of activated nuclei and an early transition state with deactivated nuclei may be a general phenomenon and not just characteristic of arylsulfonoxylation. Substitution involving other uncharged reagents, for example, sulfonation with sulfur trioxide, certainly might be expected to follow the same pattern. In addition, reactions such as bromination could behave

(20) M. Kobayashi and H. Minato, Symposium on Organic Sulfur, Venice, June 15, 1970.
(21) H. C. Brown and C. W. McGary, *J. Amer. Chem. Soc.*, **77**, 2306 (1955).
(22) Y. Okomoto and T. Inukai, *ibid.*, **80**, 4964 (1958).
(23) H. C. Brown and Y. Okomoto, *ibid.*, **79**, 1913 (1957).

### TABLE VII

#### MELTING POINTS OF ARYL NITROBENZENESULFONATES
#### $(O_2NC_6H_4SO_3R)^a$

| R | Registry no. | Mp, °C |
|---|---|---|
| *m*-Nitrobenzenesulfonates | | |
| Phenyl | | 92–93[b] |
| o-Bromophenyl | 36601-36-2 | 94.5–95.5 |
| m-Bromophenyl | | 133–134[b] |
| p-Bromophenyl | 36601-37-3 | 108–109 |
| o-Nitrophenyl | | 88–89[b] |
| m-Nitrophenyl | | 110.5–112[b] |
| p-Nitrophenyl | | 132–133[b] |
| o-Methoxyphenyl | 36601-38-4 | 72.5–73.5 |
| m-Methoxyphenyl | 36601-58-9 | 69–70 |
| p-Methoxyphenyl | 36601-39-5 | 86–88 |
| o-Carbomethoxyphenyl | 36601-40-8 | 95–97 |
| m-Carbomethoxyphenyl | 36601-41-9 | 114–116 |
| p-Carbomethoxyphenyl | 36601-42-0 | 102.5–103.5 |
| 2,4,6-Trimethylphenyl | 36601-43-1 | 106.5–108 |
| *p*-Nitrobenzenesulfonates | | |
| Phenyl | | 114–115[c] |
| o-Bromophenyl | 36601-44-2 | 111.5–112.5 |
| m-Bromophenyl | 36601-45-3 | 126–128 |
| p-Bromophenyl | 36601-46-4 | 121.5–122.5 |

[a] Analysis for the elements gave maximum deviations from the theoretical values as follows: all C values ±0.39, H values ±0.22, N values ±0.17, S values ±0.22 for new compounds. [b] Lit. mp: phenyl, 88–89°; m-bromophenyl, 135–136°; o-nitrophenyl, 88–89°; m-nitrophenyl, 110.5–111.5°; p-nitrophenyl m-nitrobenzenesulfonate, 131–132.5° [H. H. Hodgson and J. H. Crook, *J. Chem. Soc.*, 1677 (1936)]. [c] Lit. mp 114° [F. Bell, *ibid.*, 2777 (1928)].

### TABLE VIII

#### PROPERTIES[a] OF ARYL TRIMETHYLSILYL ETHERS [ROSi(CH₃)₃]

| R | Registry no. | Bp, °C (3 mm) | $n^{20}D$ |
|---|---|---|---|
| Phenyl | | 55[b] | 1.4784[b] |
| o-Bromophenyl | 36601-47-5 | 87 | 1.5136 |
| m-Bromophenyl | 76971-28-5 | 89.5 | 1.5148 |
| p-Bromophenyl | | 91.3[c] | 1.5153[c] |
| o-Nitrophenyl | | 114.5[d] | 1.5085[d] |
| m-Nitrophenyl | 34038-80-7 | 119.0 | 1.5094 |
| p-Nitrophenyl | | 130.5[d] | 1.5275[d] |
| o-Methoxyphenyl | | 86.0[e] | 1.4886[e] |
| m-Methoxyphenyl | 33285-71-1 | 91.0 | 1.4918 |
| p-Methoxyphenyl | 6689-38-9 | 92.5 | 1.4909 |
| o-Carbomethoxyphenyl | 18001-14-4 | 83.2[f] | 1.4951 |
| m-Carbomethoxyphenyl | 27798-50-1 | 92.0[f] | 1.4939 |
| p-Carbomethoxyphenyl | 27739-17-9 | 99.0[f] | 1.5014 |
| o-Carbotrimethylsiloxy-phenyl | 3789-85-3 | 111.0[f] | 1.4797 |
| m-Carbotrimethylsiloxy-phenyl | 3782-84-1 | 117.0[f] | 1.4778 |
| p-Carbotrimethylsiloxy-phenyl | 2078-13-9 | 127.6[f] | 1.4854 |

[a] Analysis for the elements gave maximum deviations from the theoretical values as follows: all C values ±0.15, H values ±0.24, N values ±0.19 for new compounds. [b] Lit. bp 181.9° (742 mm), $n^{20}D$, 1.4782 [S. Langer, S. Connell, and I. Wender, *J. Org. Chem.*, **23**, 50 (1958)]. [c] Lit. bp 126° (25 mm), $n^{25}D$, 1.5123 [L. Speier, *J. Amer. Chem. Soc.*, **74**, 1003 (1952)]. [d] Ortho: lit. bp 84° (1 mm), $n^{20}D$, 1.5090; para: lit. bp 95–96° (0.75 mm), $n^{20}D$, 1.5293 [M. Von Roshdy Ismall, *Z. Naturforsch, B*, **18**, 582 (1962)]. [e] Lit. bp 217°, $n^{20}D$ 1.4855 [J. Kramer, *Chem. Ber.*, **92**, 2585 (1959)]. [f] Pressure, 1.5 mm.

similarly provided that ion or ion-pair formation from the reagent (*e.g.*, bromine) is not sufficient to lead to extensive solvation.

### TABLE IX
### REACTION OF m-NITROBENZENESULFONYL PEROXIDE WITH AROMATICS

| Compound or quantity | Bromobenzene[a] Run 1 | Run 2 | Bromobenzene Run 1 | Run 2 | Anisole[b] Run 1 | Run 2 | Methyl benzoate[c] Run 1 | Run 2 | Nitrobenzene[d] Run 1 | Run 2 |
|---|---|---|---|---|---|---|---|---|---|---|
| Reaction in absence of benzene | | | | | | | | | | |
| Peroxide, mmol | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Aromatic substrate, mmol | 500 | 500 | 200 | 200 | 10 | 10 | 100 | 100 | 500 | 500 |
| Ethyl acetate, ml | 0 | 0 | 0 | 0 | 75 | 75 | 0 | 0 | 0 | 0 |
| Sulfonate esters, % yield | 71.1 | 72.5 | 68.4 | 62.7 | 69.5 | 64.2 | 74.1 | 66.5 | 65.3 | 65.5 |
| Original ester, mmol | | | | | | | | | | |
| Ortho | 0.184 | 0.189 | 0.184 | 0.154 | 0.0886 | 0.0899 | 0.192 | 0.177 | 0.185 | 0.210 |
| Meta | 0.036 | 0.034 | 0.023 | 0.026 | ... | ... | 0.484 | 0.435 | 0.484 | 0.472 |
| Para | 0.538 | 0.552 | 0.526 | 0.493 | 0.606 | 0.552 | 0.065 | 0.053 | 0.086 | 0.086 |
| Isomer distribution | | | | | | | | | | |
| % ortho | 22.5 | 22.6 | 24.7 | 22.4 | 12.9 | 14.0 | 25.9 | 26.6 | 23.8 | 27.0 |
| % meta | 4.8 | 4.4 | 3.0 | 3.6 | ... | ... | 65.3 | 65.4 | 64.9 | 61.7 |
| % para | 72.7 | 72.5 | 72.3 | 73.9 | 87.1 | 86.0 | 8.8 | 8.0 | 11.2 | 11.3 |
| Competitive reaction | | | | | | | | | | |
| Peroxide, mmol | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Benzene, mmol | 100 | 100 | 100 | 100 | 0[e] | 0[e] | 10. | 10. | 9. | 9. |
| Benzene derivative, mmol | 500 | 500 | 500 | 500 | 25 | 25 | 300 | 300 | 900 | 900 |
| Ethyl acetate, ml | 0 | 0 | 0 | 0 | 70 | 70 | 51 | 51 | 0 | 0 |
| Sulfonate esters, % yield | 77.3 | 70.9 | 72.6 | 70.6 | 65.4 | 67.6 | 55.6 | 58.3 | 59.6 | 69.7 |
| $k_{Ar}/k_B$ | 0.495 | 0.487 | 0.482 | 0.462 | ...[f] | ...[f] | 0.0815 | 0.0844 | 0.00232 | 0.00245 |
| Original ester, mmol | | | | | | | | | | |
| Phenyl | 0.262 | 0.238 | 0.268 | 0.252 | ...[g] | ...[g] | 0.199 | 0.204 | 0.644 | 0.721 |
| Ortho aryl | 0.144 | 0.132 | 0.116 | 0.118 | 0.0672 | 0.0736 | 0.083 | 0.097 | 0.030 | 0.050 |
| Meta aryl | 0.028 | 0.024 | 0.018 | 0.016 | ... | ... | 0.241 | 0.253 | 0.088 | 0.101 |
| Para aryl | 0.414 | 0.384 | 0.409 | 0.402 | 0.4018 | 0.4254 | 0.033 | 0.029 | 0.014 | 0.016 |
| Isomer distribution | | | | | | | | | | |
| Ortho | 22.8 | 22.8 | 21.1 | 21.6 | 14.1 | 14.8 | 23.1 | 24.7 | 22.6 | 26.1 |
| Meta | 4.7 | 4.6 | 3.1 | 2.9 | ... | ... | 67.9 | 66.8 | 66.7 | 62.9 |
| Para | 72.5 | 72.6 | 75.9 | 75.5 | 85.9 | 85.2 | 9.0 | 8.5 | 10.7 | 11.0 |

[a] Reaction with p-nitrobenzenesulfonyl peroxide. [b] Reaction run at −30° and analysis performed on a 150 ft × 0.01 in. capillary column of R-Ucon-LB 550-x at 130°. [c] Reaction run at room temperature for 48 hr and analysis performed with a 15 ft × 0.25 in. column at 180° of 5% SE-30 on Chromosorb W, DMCS, washed. [d] Reaction run at room temperature for 5 days and analysis performed on the column used for bromophenyl esters, but at 130°. [e] Mesitylene (25 mmol) used in place of benzene. [f] $k_{An}/k_{Mes}$: 2.55, 2.81. [g] Yield of 2,4,6-trimethylphenyl ester: 0.1846, 0.1774.
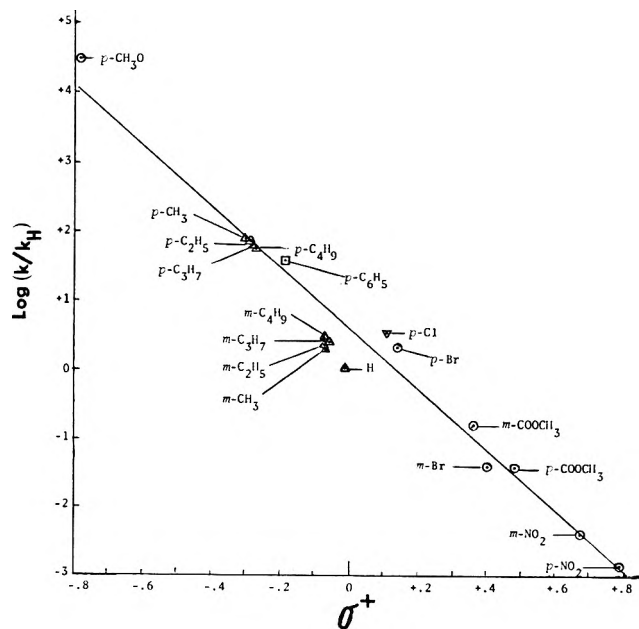


Figure 1.—Correlation of $\sigma^+$ and rate of m-nitrophenyl-sulfonoxylation: O, from the present paper; △, from ref 24; ▽, from ref 15; □, from the Ph.D. Thesis of F. Nelson Keeney, Western Reserve University.

## Experimental Section

**Aryl Nitrobenzenesulfonates.**—Sodium (1.0 g, 0.04 g-atom) was dissolved in ethanol (80 ml), and the phenol (0.04 mol) was added. This mixture was added to a hot solution of m-nitrobenzenesulfonyl chloride (8.9 g, 0.04 mol) in benzene (40 ml). The mixture was refluxed and water (200 ml) added. The ester often separated as an oil, but crystallized when cooled overnight. Recrystallization from alcohol gave the esters listed in Table VII.

**Phenyl Trimethylsilyl Ethers.**—The phenol (0.07 mol), hexamethyldisilazane (11.3 g, 0.07 mol), and a trace of sand were mixed and refluxed for several hours. Distillation at reduced pressure gave the ethers listed in Table VIII.

**m-Nitrobenzenesulfonoxylation of Benzene–Bromobenzene.**—m-Nitrobenzenesulfonyl peroxide[24] (0.404 g, 0.001 mol) was dissolved in a mixture of bromobenzene (78.5 g, 0.50 mol) and benzene (7.8 g, 0.10 mol), and the mixture was stirred (24 hr) at room temperature (20°). The excess aromatic solvents were then removed by distillation at reduced pressure leaving a residue of crude esters. This residue was dissolved in a solvent (methylene chloride and/or ethyl ether), transferred to a Fischer-Porter Aerosol tube, and the solvent evaporated in vacuo. A small magnetic stirring bar and 6 ml of a 20% potassium hydroxide solution in methanol–water (50:50) were added. The sealed tube was heated (24 hr) at 145° in an oil bath. Hydrochloric acid (3 N, 50 ml) was added and the acidic solution extracted three times with chloroform (30-ml portions) and three times with benzene (30-ml portions).

(24) R. L. Dannley, J. E. Gagen, and O. J. Stewart, *J. Org. Chem.*, **35**, 3076 (1970).

The combined extracts were concentrated by distilling the solvents at atmospheric pressure. When the volume had been reduced to 50 ml, dry benzene (10 ml) was added and the distillation continued until near dryness. The residue was treated with hexamethyldisilazane (5.0 g, 0.031 mol) and a trace of sand. The mixture was refluxed for several hours and then analyzed by glpc using a 15 ft × 0.125 in. column packed with 5% SE-30 on Chromosorb W at 110° (Table IX). Relative yields for hydrolysis of the isomeric esters and conversion into the silyl ethers were determined using authentic samples. Identification of the glpc peaks from the m-nitrophenylsulfonoxylation reaction was accomplished not only by comparison of retention times with authentic esters but also by trapping samples from the chromatographic column and comparing their infrared spectra to those of authentic samples.

Essentially the same procedure was used for the competitive reactions with other substrates with the minor differences given in Table IX.

**Kinetics.**—The procedure previously described[1b] was followed to titrate iodometrically for the disappearance of the peroxide content of the reaction mixtures.

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# The Reaction of Arylsulfonyl Azides with N-Methylindole

ROBERT E. HARMON,* GEORGE WELLMAN, AND S. K. GUPTA

*Department of Chemistry, Western Michigan University, Kalamazoo, Michigan 49001*

The reaction of several substituted arylsulfonyl azides with N-methylindole using p-dioxane as solvent yielded mixtures of the expected 2-sulfonamido and the unexpected 3-sulfonamido derivatives. In solution (DMSO-$d_6$) the 2-sulfonamides showed tautomeric equilibrium between the amino and the imino forms, whereas in crystalline form they existed mainly as the imino tautomers. The corresponding 3-sulfonamides existed only in the amino form. Using ethanol as solvent, the reaction of arylsulfonyl azides with N-methylindole afforded N-(3-diazo-1-methyl-2-indolinylidene)benzenesulfonamides. The same diazo compounds were obtained by treating the 2-sulfonamido derivatives with an excess of the appropriate arylsulfonyl azide, thereby providing the first example of a diazo transfer reaction to an amidine.

During the past several years Bailey and coworkers[1-5] have reported the results of their investigations on the reaction of arylsulfonyl azides with indole and alkylindoles. According to them the addition of p-toluenesulfonyl azide to 1,3-dimethylindole yielded an equilibrium mixture containing the 2-sulfonamido derivatives 1 and 2. Bailey, et al.,[4] observed by nmr that the equilibrium between the tautomers 1 and 2
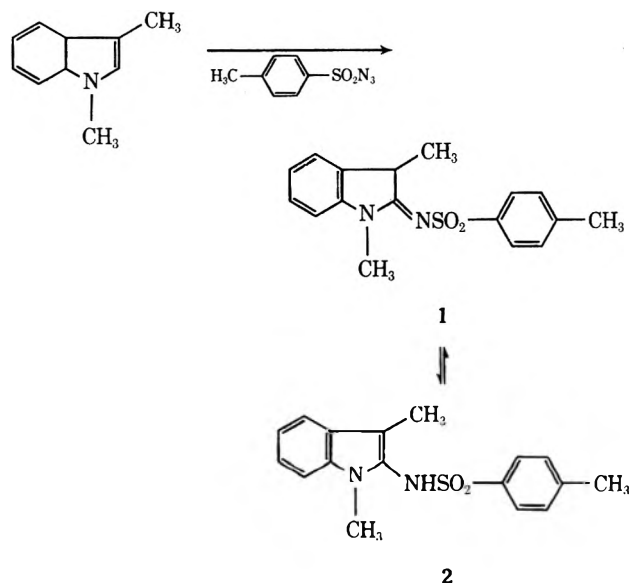
was solvent dependent, the imino form 1 predominating in chloroform while in dimethyl sulfoxide the amino form 2 predominates. In mixtures of these two solvents, both tautomers were present in appreciable amounts. We have investigated the above tautomeric equilibrium as a function of substituents on the arylsulfonyl azide. During the course of this study it was found that N-methylindole was more amenable to study the tautomeric equilibrium ratios than indole or dimethylindole used by Bailey, et al.[2,4]

**The Reactions of Arylsulfonyl Azides with Indole.**— Our preliminary investigation based on the work reported by Bailey, et al.,[2] involved the reaction between three arylsulfonyl azides (3a–c) and indole. The



1



2



3a, X = CH₃
b, X = OCH₃
c, X = NO₂

(imino) A

4a, X = CH₃
b, X = OCH₃
c, X = NO₂

(amino) B
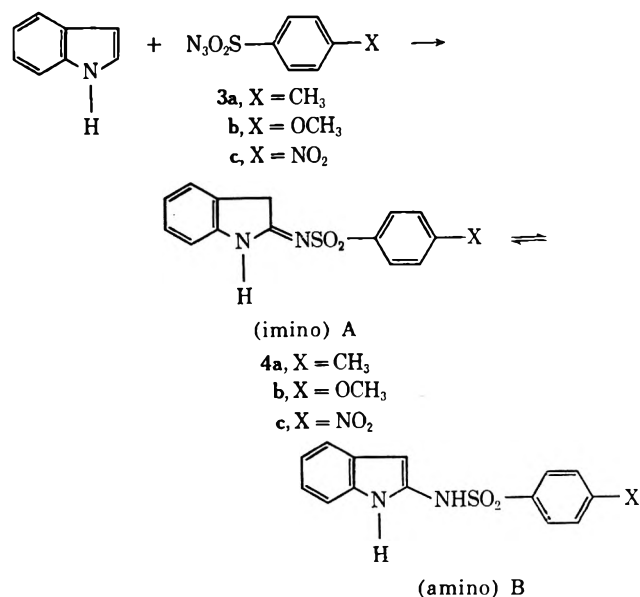
(1) A. S. Bailey and J. J. Merer, *J. Chem. Soc. C*, 1345 (1966).

(2) A. S. Bailey, N. C. Churn, and J. J. Wedgwood, *Tetrahedron Lett.*, 5953 (1968).

(3) A. S. Bailey, W. A. Warr, G. B. Allison, and C. K. Prout, *J. Chem. Soc. C*, 956 (1970).

(4) A. S. Bailey, R. Scattergood, and W. A. Warr, *Tetrahedron Lett.*, 2979 (1970).

(5) A. S. Bailey, A. J. Holton, and J. F. Seager, *J. Chem. Soc., Perkin Trans. 1*, 1503 (1972).

reactions were conducted by heating p-dioxane or ethanol solutions of indole and the appropriate sulfonyl azide at 75–80° during 6–48 hr. The resulting 2-indolinylidenebenzenesulfonamides (4a–c) gave satisfactory analyses and ir spectra. The tautomeric equilibrium between the amino and the imino forms was studied by nmr spectroscopy using DMSO-$d_6$ as solvent. The nmr spectra of the products 4a–c could not be explained by assuming the presence of only the imino A and the amino B tautomers as reported by Bailey, et al.[2] This observation made it rather difficult for us to study the desired substituent effect on the amino–imino tautomerism. Therefore we decided to use N-methylindole instead.

**The Reaction of Arylsulfonyl Azides with N-Methylindole.**—The reaction of 13 substituted arylsulfonyl azides 3a–m with N-methylindole was conducted by heating a solution of N-methylindole (0.01 mol) and the sulfonyl azide (0.015 mol) in p-dioxane at 75–80° during 18–24 hr. Cooling and diluting the reaction mixture with ethanol caused most of the 2-substituted product 5 to crystallize. After the separation of 5 by filtration, the filtrate was evaporated to dryness under reduced pressure and chromatographed over a column packed with silica gel. Elution with appropriate solvents afforded mostly 7 and small amount of 5. In crystalline form, compounds 5 appear to exist mainly in the imino form, as shown by their ir spectra which had the characteristic C=N band at 1600 cm$^{-1}$ and no absorption in the NH region. The location of the sulfonamido group at the 2 position of the indole ring was established by acid hydrolysis of 5b, which yielded 1-methyloxindole (8) and p-chlorobenzenesulfonamide (9) in high yields.



8                    9
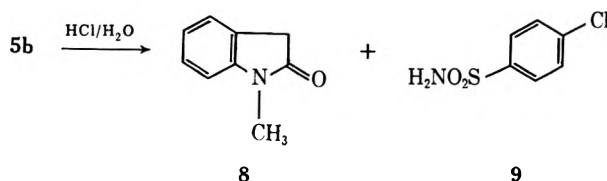
**Tautomerism of the 2-Sulfonamido Derivatives.**— The 2-sulfonamido derivatives 5a–m were found to exhibit amino–imino type of tautomerism on the basis of nmr spectroscopy using DMSO-$d_6$ and DMSO-$d_6$–CDCl$_3$ (15%) as solvents. Other nmr solvents, such as pure CDCl$_3$, could not be used owing to insufficient solubility of the products. The complete nmr data are given in Table I. The proton assignments are consistent with the proposed 2-substituted indole ring system. They are also in agreement with the assignments made by Bailey, et al.,[4] on similar compounds. In the nmr spectra the most significant differences were observed in the resonances due to the N-methyl protons as well as the proton(s) at the 3 position of the indole ring of structures 5a–m and 6a–m. For instance, in 5 the NCH$_3$ signal appeared around δ 3.4 and the two benzylic protons at the 3 position showed as a singlet near 4.2. On the other hand, the NCH$_3$ singlet of 6 appeared near δ 3.7 and the proton at the 3 position resonated as a singlet near 6.0. The relative ratios of the peaks around δ 4.2 (structure 5) and 3.7 (structure 6) were used to calculate the equilibrium ratios of these two tautomers in solution. The results are also included in Table I. It is clear from the results presented in Table I that in each case the imino



3



6



5



7
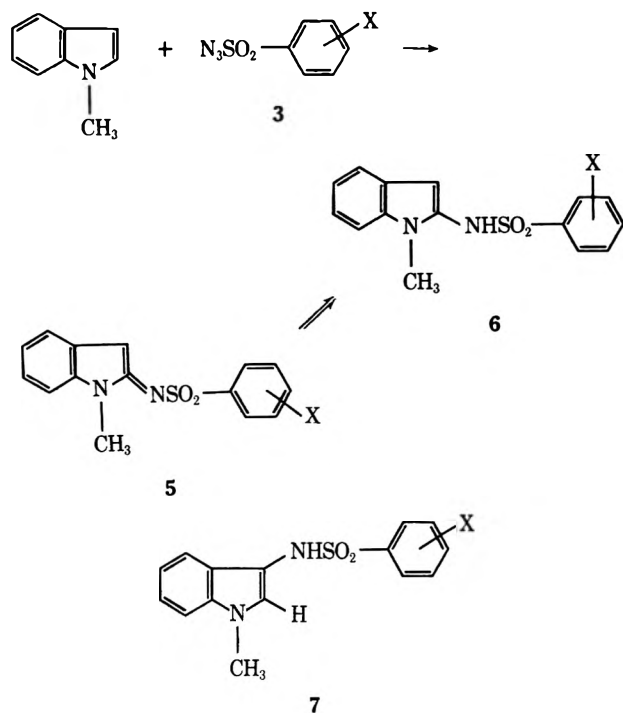
| Compd | R group(s) |
|-------|------------|
| a | 4-CH$_3$ |
| b | 4-OCH$_3$ |
| c | 4-NHCOCH$_3$ |
| d | H |
| e | 2,4,6-trimethyl |
| f | 4-Cl |
| g | 4-Br |
| h | 3,4-di-Cl |
| i | 3-NO$_2$-4-Cl |
| j | 2,4,6-triisopropyl |
| k | 4-NO$_2$ |
| l | 3-NO$_2$ |
| m | 2-NO$_2$ |

tautomer predominates in DMSO-$d_6$ solution. These results are opposite to those reported by Bailey, et al.,[4] in the case of 1,3-dimethylindole. They observed that in DMSO-$d_6$, the amino tautomer was the major species present. The addition of CDCl$_3$ (15%) shifted the tautomeric equilibrium between 5 and 6 even more in favor of the imino tautomer. This is consistent with the observations made by Bailey, et al.[4] This trend is the reverse of that reported for 2-aminoindoles.[6,7]

Further examination of Table I indicates that, in general, electron-withdrawing substituents on the benzenesulfonamido group reduce the percentage of amino tautomer in solution. Thus, the amino tautomer concentration ranges from a high of 20% with a p-methoxy group to a low of about 3% with an o-nitro group.

**The Unexpected 3-Sulfonamido Derivatives (7a–m).**—As mentioned earlier, the reaction of arylsulfonyl azides with N-methylindole yielded, in addition to the expected 2-sulfonamido derivatives 5, the unexpected 3-sulfonamido derivatives 7. In contrast to the results obtained with the 2-substituted products, compounds 7 were found by ir spectroscopy (which showed NH absorption but no C=N absorption) to exist as the amino tautomers in crystalline form. The nmr data {δ 6.8–7.0 (m, 1, C$_2$ of N-methylindole), 7.0–8.4 (m,

(6) J. Kebrle and K. Hoffmann, *Helv. Chim. Acta*, **39**, 116 (1956).

(7) W. J. Houlihan, Ed., "The Chemistry of Heterocyclic Compounds," Vol. 25, Wiley, New York, N. Y., 1972, p 50.

## TABLE I

NMR DATA FOR 2-SULFONAMIDOINDOLINES AND RELATIVE EQUILIBRIUM RATIOS OF TAUTOMERS 5 AND 6[a]



**5**     ⇌     **6**

| No. | Substituent(s) X | $H_a$ | $H_b$ | ArH | $H_c$ | $H_d$ | X | In DMSO-$d_6$ 5 | In DMSO-$d_6$ 6 | In DMSO-$d_6$-CDCl$_3$ (15%) 5 | In DMSO-$d_6$-CDCl$_3$ (15%) 6 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| a | 4-CH$_3$ | 4.24 | 3.36 | 7.17–8.35 | 3.64 | 6.00 | 3.93 (3, s, CH$_3$) | 80 | 20 | 86 | 14 |
| b | 4-OCH$_3$ | 4.24 | 3.40 | 7.19–8.17 | 3.60 | 6.00 | 2.4 (3, s, OCH$_3$) | 81 | 19 | 87 | 13 |
| c | 4-NHCOCH$_3$ | 4.17 | 3.44 | 6.70–8.15 | 3.57 | 5.89 | 10.30 (1, s, CH$_3$CONH), 2.10 (3, s, CH$_3$CONH) | 81 | 19 | 87 | 13 |
| d | H | 4.20 | 3.33 | 6.94–8.21 | 3.67 | 5.90 | | 84 | 16 | 88 | 12 |
| e | 2,4,6-Trimethyl | 4.04 | 3.30 | 6.90–7.57 | 3.50 | 5.84 | 2.63 (6, s, o-CH$_3$), 2.23 (3, s, p-CH$_3$) | 87 | 13 | 91 | 9 |
| f | 4-Cl | 4.20 | 3.44 | 6.90–8.21 | 3.60 | 5.90 | | 88 | 12 | 90 | 10 |
| g | 4-Br | 4.17 | 3.30 | 6.94–8.00 | 3.54 | 5.84 | | 89 | 11 | 90 | 10 |
| h | 3,4-di Cl | 4.24 | 3.34 | 7.00–8.35 | 3.64 | Not obsd | | 90 | 10 | 94 | 6 |
| i | 3-NO$_2$-4-Cl | 4.27 | 3.40 | 7.06–8.60 | 3.67 | Not obsd | | 90 | 10 | 93 | 7 |
| j | 2,4,6-Triiso-propyl[b] | 4.04 | 3.32 | 6.91–7.45 | 3.58 | Not obsd | 1.25 [18, m, CH(CH$_3$)$_2$, 2.93 [1, m, p-CH(CH$_3$)$_2$], 4.50 [2, m, o-CH(CH$_3$)$_2$] | 91 | 9 | 94 | 6 |
| k | 4-NO$_2$ | 4.20 | 3.46 | 7.00–8.50 | 3.57 | Not obsd | | 91 | 9 | 94 | 6 |
| l | 3-NO$_2$ | 4.24 | 3.47 | 7.00–8.73 | 3.60 | Not obsd | | 92 | 8 | 93 | 7 |
| m | 2-NO$_2$ | 4.20 | 3.47 | 7.00–8.40 | 3.57 | Not obsd | | 95 | 5 | 97 | 3 |

[a] The solvent used in all cases was DMSO-$d_6$ except as noted for j. Protons $H_a$, $H_b$, $H_c$, and $H_d$ appeared as singlets and other protons as noted. Proton $H_e$ was not observed in any spectra. Proton $H_d$ was not observed when the amino tautomer concentration was less than about 10%. Equilibrium ratios for tautomers 5 and 6 are based on the relative absorptions due to protons $H_a$ and $H_c$. The experimental error in these values is expected to be ±5%. [b] Solvent used was CD$_3$CN.

9, ArH), 9.4–10.1 (s, 1, NHSO$_2$Ar), 3.6–3.7 (s, 3, NCH$_3$), 1.0–2.3 (s, 3, CH$_3$), 2.4–2.38 (s, 3, OCH$_3$), 2.8–4.0 (m, 1, CH(CH$_3$)$_2$], etc.} using DMSO-$d_6$ as solvent (CDCl$_3$ was used as solvent for 7j) supported the proposed structures. There was one exchangeable (D$_2$O) low-field signal integrating for one proton. There was no peak near δ 6.1 which would have been expected if the products were 2-sulfonamido derivatives. The presence of one proton NH signal indicated that these compounds did not exhibit amino–imino type of tautomerism and that they existed only in the amino form, both in crystalline form as well as in solution (DMSO-$d_6$). In order to substantiate the structures 7 assigned to these compounds we attempted the following alternate synthesis of **7d**.

**Attempted Alternate Synthesis of 7d.**—The nitrosation of 1-methylindole led to the formation of the undesirable 1-methyl-2-(1-methylindol-3-yl)-3-nitrosoindole (**10**). Similar results have been reported for the nitrosation of indoles unsubstituted at the 2 position.[8] The nitroso compound **10** could be readily reduced and treated with benzenesulfonyl chloride to yield the sulfonamido derivative **11**. Therefore the alternate synthesis of **7d** could not be accomplished using this approach.

**Preparation of Model Compounds.**—Since we were unsuccessful in achieving an independent synthesis of compounds **7**, we decided to prepare certain model compounds and compare their nmr spectra with those of **7**.

(8) W. J. Houlihan, Ed., "Indoles," Part II, Wiley, New York, N. Y., 1972, p 541.



**10**



**11**

Carbobenzoxy-2- (**12**) and -3-aminoindoles (**13**) were chosen for this purpose. Compound **12** was prepared according to the procedure reported by Rinderknecht, *et al.*[9] Compound **13** was prepared analogously *via*



**13**          **12**

(9) H. Rinderknecht, H. Koechlin, and C. Niemann, *J. Org. Chem.*, **18**, 971 (1953).

Curtius rearrangement of indole-3-carbonyl azide (15) in benzyl alcohol. The carbonyl azide 15 was prepared by treatment of the known indole-3-carboxylic acid hydrazide (14) with nitrous acid.[9]
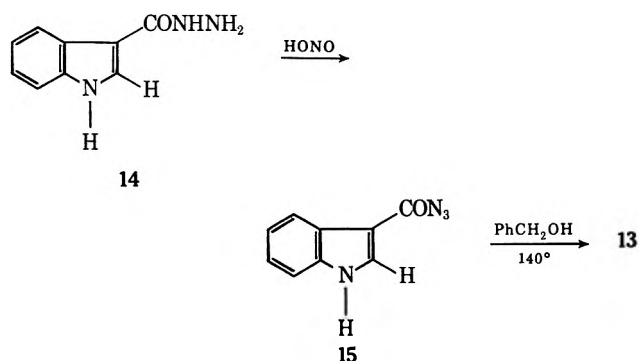


The nmr spectra of compounds 12 and 13 showed that in solution (DMSO-$d_6$) both of them exist in the amino tautomeric form as shown. Each compound had two low-field ($\delta$ 10–12) exchangeable (D$_2$O) peaks which integrated cleanly for one proton (NH) each. Hence compounds 12 and 13 were considered satisfactory models for the isomers 5 and 7, respectively.

Further examination of the nmr spectrum of 12 showed that there was a doublet at $\delta$ 6.0 attributed to the C$_3$ proton of the indole ring. This assignment is consistent with the work of Witkop, *et al.*[10,11] This observation further supports the structures assigned to compounds 5, since all of them had a peak (assigned to the amino tautomer) in this region of the nmr spectrum. The C$_2$ proton of the indole ring of 13 appeared in the aromatic region as was observed in the nmr spectra of compounds 7. These results, which are also consistent with those reported by Witkop, *et al.*,[10,11] further substantiate the position of the sulfonamido group in compounds 7.

**A New Diazo Transfer Reaction.**—The transfer of the diazo group from arylsulfonyl azides to an active methylene compound has been known for quite some time.[12] Nearly all of the reported examples have involved the transfer of a diazo group to the $\alpha$ carbon of carbonyl compounds.[12] In addition, the transfer of diazo group from sulfonyl azides generally requires the presence of a base catalyst.[12,13] The course of the reaction of arylsulfonyl azides with 1-methylindole using *p*-dioxane was different from that using ethanol as solvent.

The reaction of sulfonyl azides 3a and 3f with *N*-methylindole using ethanol as solvent gave the corresponding *N*-(3-diazo-1-methyl-2-indolinylidene)benzenesulfonamides 16a, b. The reactions were followed by thin layer chromatography, which showed the formation of small amounts of the amidines 5a and 5f as intermediates which led to the diazo compounds 16a,b as final products. This observation was further substantiated by the conversion of compound 5a to 16a in the presence of ethanol and the sulfonyl azide 3a. The diazo compounds 16a,b were light sensitive and dif-

ficult to isolate in pure form. However, treatment of these compounds with triphenylphosphine[14] afforded crystalline triphenylphosphine derivatives 17a,b which were stable and gave satisfactory analyses. To the best of our knowledge this is the first example of a diazo transfer reaction to an amidine such as 5a or 5f. In addition compounds 16a,b were formed without the aid of any added catalyst, unlike the normal diazo transfer reactions, which are base catalyzed. The isolation of 16 from the reaction of 5 with arylsulfonyl



**16a**, X = CH$_3$
**b**, X = Cl

**17a**, X = CH$_3$
**b**, X = Cl
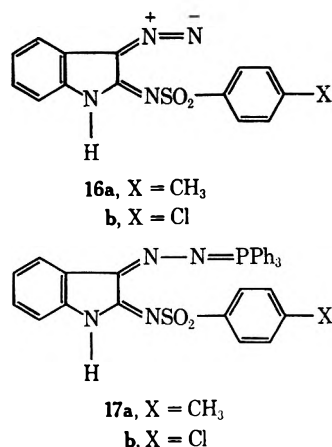
azides is of great interest regarding the mechanism of the reaction of azides with indoles.

Since the transfer of diazo group from sulfonyl azides is supposed to involve a carbanion as the reactive species, the following mechanism could be used to explain the formation of the diazo compounds 16. According to Regitz,[12] the rate of the triethylamine-catalyzed diazo transfer reaction decreases with decreasing polarity of the solvent. Perhaps the same reasoning can be used to explain the reason why the diazo compounds 16 are formed in ethanol and not in *p*-dioxane, because ethanol is more polar than *p*-



dioxane. When an ethanol solution of the 2-sulfonamido derivative 5f was heated with a differently substituted sulfonyl azide 3a or 3d, the same diazo compound 16b was obtained. These experiments substantiate our proposed mechanism for the above diazo transfer reaction.
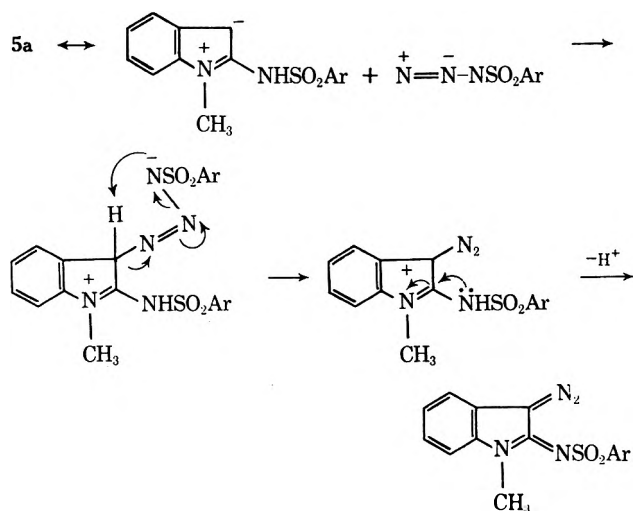
(10) L. A. Cohen, J. W. Daly, H. Kny, and B. Witkop, *J. Amer. Chem. Soc.*, **82**, 2184 (1960).

(11) R. A. Heacock, O. Hutzinger, B. D. Scott, J. W. Daly, and B. Witkop, *ibid.*, **85**, 1825 (1963).

(12) M. Regitz, "Newer Methods of Preparative Organic Chemistry," Vol. VI, Academic Press, New York, N. Y., 1971, p 81; M. Regitz, *Synthesis*, 351 (1972).

(13) R. A. Abramovitch and T. Takaya, *J. Org. Chem.*, **37**, 2022 (1972).

(14) M. Regitz and G. Himbert, *Tetrahedron Lett.*, 2823 (1970).

## Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are corrected. A Beckman IR-8 spectrophotometer was used to determine the ir spectra. The nmr spectra were run using a Varian A-60 spectrometer using tetramethylsilane as internal standard. The elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Column chromatography was done using a 3 × 60 cm² glass column packed with silica gel. For thin layer chromatography (tlc), glass microscope slides coated with silica gel G were used. The spots on these slides were detected by iodine. *N*-methylindole was prepared from indole and methyl iodide using the procedure of Alder and Stein.[15] Methyl indole-3-carboxylate was prepared from the commercially available indole-3-carboxylic acid using the procedure of Millich and Becker.[16] It was converted to indole-3-carboxylic acid hydrazide by the procedure reported by Brown, *et al.*[17] The substituted arylsulfonyl azides **3** were prepared by treating the appropriately substituted benzenesulfonyl chlorides with sodium azide according to the method of Leffler and Tsuno.[18] All except one (**3j**) of the arylsulfonyl azides used in this study have previously been reported in the literature. Analytical data on compound **3j** prepared according to the general procedure are given below.

**2,4,6-Triisopropylbenzenesulfonyl Azide (3j).**—The title compound was prepared in 80% yield: mp 41–43°; ir (Nujol) 2120 (N₃) and 1164 cm⁻¹ (SO₂); nmr (CDCl₃) δ 7.25 (s, 2, ArH), 4.10 [m, 2, *J* = 6 Hz, ortho CH[CH₃)₂], 2.97 [m, 1, *J* = 7 Hz, para CH(CH₃)₂], 1.30 [d, 12, *J* = 6 Hz, ortho CH(CH₃)₂], and 1.25 [d, 6, *J* = 7 Hz, para CH(CH₃)₂]. *Anal.* Calcd for $C_{15}H_{23}N_3$-$O_2S$: C, 58.23; H, 7.49; N, 13.58. Found: C, 58.21; H, 7.69; N, 13.42.

**Preparation of *p*-Methyl-*N*-(2-indolinylidene)benzenesulfonamide (4a).**—Indole (0.9 g, 0.0077 mol) and *p*-toluenesulfonyl azide (2 g, 0.01 mol) were heated at 75–80° for 48 hr in *p*-dioxane (5 ml). The solution was then diluted with 3 ml of ether and 3 ml of methanol, precipitating 1.0 g (46%) of **4a**: mp 234–236°; ir (Nujol) 3150 (NH), 1580, 1610 (C=N), and 1140 cm⁻¹ (SO₂); nmr (DMSO-*d₆*) δ 11.50 (s, NH), 10.08 (s, NH), 8.00–6.65 (m, 8, ArH), 5.80 (s), 4.10 (s), 3.57 (s, shoulder), and 2.37 (s, 3, CH₃). *Anal.* Calcd for $C_{15}H_{14}N_2O_2S$: C, 62.91; H, 4.92; N, 9.78; S, 11.19. Found: C, 62.85; H, 4.99; N, 9.81; S, 11.05.

**Preparation of *p*-Methoxy-*N*-(2-indolinylidene)benzenesulfonamide (4b).**—Indole (1 g, 0.0085 mol) and *p*-methoxybenzenesulfonyl azide (2 g, 0.0094 mol) were heated at 80° for 26 hr in *p*-dioxane (5 ml). The solution was diluted with 5 ml of methanol, precipitating 0.6 g (22%) of **4b**: mp 224–225° dec; ir (Nujol) 1580 (C=N), 1145, and 1135 cm⁻¹ (SO₂); nmr (DMSO-*d₆*) δ 11.40 (s, NH), 10.70 (s, NH), 10.30 (s, NH), 8.00–6.80 (m, 8, ArH), 5.73 (s), 4.04 (s), 3.80 (s, OCH₃), 3.77 (s, OCH₃), and 3.53 (s). *Anal.* Calcd for $C_{15}H_{14}N_2O_3S$: C, 59.58; H, 4.66; N, 9.26; S, 10.60. Found: C, 59.33; H, 4.94; N, 9.55; S, 10.62.

**Preparation of *p*-Nitro-*N*-(2-indolinylidene)benzenesulfonamide (4c).**—Indole (2 g, 0.017 mol) and *p*-nitrobenzenesulfonyl azide (4 g, 0.017 mol) were refluxed in 75 ml of ethanol for 6 hr. On cooling, the solution deposited 3.3 g (61%) of the product **4c**: mp 249–260° dec; ir (Nujol) 1560 (C=N), 1150, and 1145 cm⁻¹ (SO₂); nmr (DMSO-*d₆*) δ 12.20 (s, NH), 11.40 (s, NH), 8.87 (m, 4, sulfonamide ArH), 7.91–7.00 (m, 4, indole ArH), 6.07 (d, *J* = 2 Hz), and 4.37 (s). *Anal.* Calcd for $C_{14}H_{11}N_3O_4S$: C, 52.99; H, 3.49; N, 13.24; S, 10.10. Found: C, 52.80; H, 3.62; N, 13.53; S, 10.16.

**General Procedure for the Reaction of Substituted Arylsulfonyl Azides with *N*-Methylindole and Isolation of Products 5a–m and 7a–m.**—*N*-Methylindole (1.3 g, 0.01 mol) was dissolved in 5 ml of dry *p*-dioxane. A 1.5 molar excess of the appropriately substituted arylsulfonyl azide (**3a–m**) was dissolved in this solution. The solution was heated (oil bath) and stirred at 75–80° for 18–24 hr. The solution was then cooled and diluted with about 25 ml of ethanol (heptane was used for **5j** and **7j**), causing the majority of 2-substituted product (**5a–7m**) to crystallize from the solution in each case. The filtrate was evaporated to dryness and chromatographed on a column packed with silica gel using chloroform (2:8:10 ether–hexane–chloroform used for **5j** and **7j**; 9:1

ethyl acetate–heptane for **5c** and **7c**; 9:1 benzene–ethyl acetate for **5b** and **7b**; 20:1 chloroform–ethyl acetate for **5i** and **7i**; methylene chloride for **5m**) for elution of the products. The fractions containing the 2-sulfonamido products (**5a–m**) were combined and evaporated to dryness. The residue thus obtained was recrystallized from ethanol and combined with the product obtained from dilution of the reaction mixutre. The combined total yield is reported in Table II. The fractions containing the

### TABLE II[a]
ANALYTICAL DATA FOR 2-SULFONAMIDOINDOLINES
5a–m AND 3-SULFONAMIDOINDOLINES 7a–m

| Compd | Mp, °C | Yield, % | Compd | Mp, °C | Yield, % |
|---|---|---|---|---|---|
| 5a | 189–191 | 47 | 7a | 160–162 | 24 |
| 5b | 197–199 | 44 | 7b | 180–182 | 22 |
| 5c | 260–262 | 67 | 7c | 226–228 | 5 |
| 5d | 143–144 | 54 | 7d | 174–175 | 22 |
| 5e | 209–210 | 34 | 7e | 212–214 | 15 |
| 5f | 189–191 | 60 | 7f | 181–183 | 16 |
| 5g | 202–203 | 49 | 7g | 203–204 | 12 |
| 5h | 208–209 | 63 | 7h | 180–181 | 14 |
| 5i | 212–214 | 82 | 7i | 160–161 | 8 |
| 5j | 172–174 | 32 | 7j | 157–158 | 24 |
| 5k | 243–244 | 72 | 7k | 199–200 | 21 |
| 5l | 194–195 | 74 | 7l | 173–175 | 6 |
| 5m | 208–210 | 75 | 7m | 193–195 | 14 |

[a] Satisfactory analytical data (±0.4% for C, H, N, and S) were reported for all compounds listed in Table II.

3-sulfonamido derivatives (**7a–m**) were similarly treated and the yields of these products are also reported in Table II. All other chromatographic fractions and all mother liquors from recrystallizations which showed a tlc-detectable amount of either isomer were combined and evaporated to dryness. The weight of this residue was less than 0.2 g in all cases. All compounds gave satisfactory elemental analyses. Melting points are also reported in Table II.

**Hydrolysis of *p*-Chloro-(*N*-methyl-2-indolinylidene)benzenesulfonamide (5f).**—The title compound (1 g, 0.0031 mol) was refluxed for 10 hr in a solution containing 100 ml of ethanol and 3 ml of concentrated HCl. The mixture was evaporated to dryness under reduced pressure and the residue was chromatographed on silica gel, eluting the products with ether. The first fraction contained 0.55 g (92%) of *p*-chlorobenzenesulfonamide. It was recrystallized from ethanol–heptane, giving 0.5 g (84%) of pure *p*-chlorobenzenesulfonamide, mp 144–145° (lit.[19] mp 143–144°). The second fraction consisted of 1-methyloxindole in 87% crude yield. Recrystallization from heptane gave 0.3 g (66%) of pure 1-methyloxindole, mp 84–87° (lit.[6] mp 84–86°).

**Attempted Preparation of *N*-(1-Methyl-2-indolinylidene)benzenesulfonamide(5d) *via* Sulfonation of 2-Amino-1-methylindole Hydroiodide.**—In dry pyridine, 2-amino-1-methylindole hydroiodide (0.1 g) was dissolved and cooled to 0°. Benzenesulfonyl chloride (1 ml) was slowly added to it, causing the solution to turn black. The tlc of this solution showed a spot with low (0.1) $R_f$ value (developed with chloroform) and one with a higher (0.7) $R_f$ value. Neither spot corresponded to **5d** or **7d**. The use of other solvents such as ethanol, benzene, or THF in conjunction with triethylamine gave similar results.

**Attempted Hydrolysis of *p*-Chloro-*N*-(1-methylindol-3-yl)benzenesulfonamide (7f).**—A solution of the title compound (0.0 g, 0.00031 mol) in 15 ml of ethanol containing 1 ml of concentrated HCl was refluxed for 4 days. Upon work-up, 0.085 g (85%) of **7f** was recovered unchanged.

**Preparation of 1-Methyl-2-(1-methylindol-3-yl)-3-nitrosoindole (10).**—*N*-Methylindole (14.5 g, 0.123 mol) was dissolved in 500 ml of glacial acetic acid and stirred vigorously while sodium nitrite (10 g, 0.162 mol) in 14 ml of water was added to it dropwise. The temperature was maintained at below 15° throughout the addition. The solution was then diluted with 500 ml of ether and 500 ml of hexane. The mixture was cooled at 5° and, after 1 hr, the mother liquor was decanted from a black precipitated oil. The oil was triturated with ether and the brown-yellow solid was

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collected. The solid was washed with acetone to give a green solid, mp 220°, which upon crystallization from acetonitrile yielded green crystals, 3 g (20%) of compound 10: mp 243–244°; ir (Nujol) 1560 cm$^{-1}$ (N=O); nmr (DMSO-$d_6$) δ 7.10–8.30 (m, 9, ArH), 4.00 (s, 3, NCH$_3$), and 3.94 (s, 3, NCH$_3$). *Anal.* Calcd for C$_{18}$H$_{15}$N$_5$O: C, 74.72; H, 5.22; N, 14.53. Found: C, 74.59; H, 5.72; N, 14.86.

Preparation of *N*-[1-Methyl-2-(1-methylindol-3-yl)indol-3-yl]-benzenesulfonamide (11).—A solution of compound 10 (1 g, 0.00345 mol) in 50 ml of ethanol was hydrogenated at 50 psi for 10 hr in the presence of 0.2 g of Adam's catalyst. The solvent was removed under reduced pressure and the oil was dissolved in 20 ml of dry pyridine. Benzenesulfonyl chloride (2 ml) was added to it and the solution was allowed to stand for 1 hr at room temperature. It was then poured into water and extracted with chloroform. The chloroform layer was separated and dried (Na$_2$SO$_4$) and the solvent was removed under reduced pressure, leaving a yellow-green oil. The oil was crystallized from ethyl acetate–heptane, yielding 0.85 g (60%) of 11: mp 176–177°; ir (Nujol) 3270 (NH) and 1158 cm$^{-1}$ (SO$_2$); nmr (DMSO-$d_6$) δ 9.64 (s, 1, NH), 3.77 (s, 3, NCH$_3$), and 3.50 (s, 3, NCH$_3$). *Anal.* Calcd for C$_{24}$H$_{21}$N$_3$O$_2$S: C, 69.37; H, 5.09; N, 10.11; S, 7.71. Found: C, 69.17; H, 5.17; N, 10.17; S, 8.04.

Preparation of Indole-3-carbonyl Azide (15).—To a solution of indole-3-carboxylic acid hydrazide (1 g, 0.0057 mol) in 10 ml of glacial acetic acid was added a solution of sodium nitrite (1.2 g, 0.0175 mol) in 5 ml of water in small portions. After the addition of 50 ml of HCl (5%), the mixture was poured into 500 ml of water and stirred for 20 min. Filtration yielded 1.05 g (100%) of 15: mp 144° dec; ir (Nujol) 3250 (NH), 2145 (N$_3$), 2120 (N$_3$), and 1650 cm$^{-1}$ (C=O); nmr (DMSO-$d_6$) δ 12.12 (s, 1, NH) and 7.00–8.33 (m, 5, ArH). *Anal.* Calcd for C$_9$H$_6$N$_4$O: C, 58.06; H, 3.25; N, 30.03. Found: C, 57.50; H, 3.26; N, 29.79.

Preparation of Carbobenzoxy-3-aminoindole (13).—Indole-3-carbonyl azide (1 g, 0.0054 mol) was added portionwise to a refluxing solution containing 30 ml of toluene and 2 ml of benzyl alcohol. The solvent was removed by evaporation at reduced pressure and the residue was recrystallized from benzene–heptane to yield 1.1 g (79%) of 13, mp 148–155°. Repeated recrystallization from benzene–heptane yielded colorless crystals: mp 164–165°; nmr (DMSO-$d_6$) δ 10.69 (s, 1, NH), 9.41 (s, 1, NH), 7.88–6.79 (m, 10, aromatic and 2-indole H), and 5.18 (s, 2, OCH$_2$Ph). *Anal.* Calcd for C$_{16}$H$_{14}$N$_2$O$_2$: C, 72.17; H, 5.29; N, 10.52. Found: C, 72.37; H, 5.57; N, 10.76.

Preparation of Carbobenzoxy-2-aminoindole (12).—Indole-2-carbonyl azide (3 g, 0.016 mol) (prepared according to the procedure of Rinderknecht[9]) was added portionwise to a refluxing solution containing 40 ml of toluene and 6 g of benzyl alcohol. The reaction mixture was refluxed for an additional period of 2 hr and the toluene was removed by evaporation at reduced pressure. The resulting black residue was chromatographed over silica gel. Elution with methylene chloride yielded 45% of crude 12, which was crystallized from benzene–heptane to give white crystals: mp 138–139° (lit.[9] mp 139–140°); nmr (DMSO-$d_6$) δ 10.65 (s, 1, NH), 10.29 (s, 1, NH), 7.57–6.80 (m, 9, ArH), 6.00 (d, 2, *J* = 4 Hz, C-3 indole H), and 5.20 (s, 2, OCH$_2$Ph).

Addition of *p*-Toluenesulfonyl Azide to *N*-Methylindole in Ethanol. Preparation of *p*-Methyl-*N*-(3-diazo-1-methyl-2-indolinylidene)benzenesulfonamide (16a).—A solution of *N*-methylindole (1.3 g, 0.01 mol) in 100 ml of ethanol was refluxed with 3a (2.5 g, 0.0127 mol) for 20 hr. The solution deposited 1.0 g (33%) of 5a which was collected. The filtrate was refluxed for

an additional 20 hr after more of 3a (1.0 g, 0.0051 mol) had been added. Upon cooling, the solution deposited 1.0 g of 16a, mp 161–163°. The same product could be obtained in 61% yield by treating 5a with a threefold excess of 3a in refluxing ethanol for 1–2 days. This product was not obtained under the same conditions using *p*-dioxane as a solvent instead of ethanol. Compound 16a was recrystallized from butanone: mp 165–166°; ir (Nujol) 2100 cm$^{-1}$ (N$_2$). *Anal.* Calcd for C$_{16}$H$_{14}$N$_4$SO$_2$: C, 58.88; H, 4.32; N, 17.17. Found: C, 59.42; H, 4.47; N, 16.26.

Preparation of *p*-Methyl-*N*-[1-methyl-3-[(triphenylphosphoranylidene)hydrazono]-2-indolinylidene] benzenesulfonamide (17a).—Compound 16a (0.1 g, 0.000306 mol) was refluxed with a solution of triphenylphosphine (0.1 g, 0.00035 mol) in 25 ml of ethanol for 2 hr. The solution deposited 0.11 g of 17a and the concentration of the filtrate gave an additional 0.01 g of 17a (total yield 67%): mp 206–207°; ir (Nujol) 1575 and 1510 cm$^{-1}$. *Anal.* Calcd for C$_{34}$H$_{29}$N$_4$O$_2$PS: C, 69.37; H, 4.97; N, 9.52; P, 5.26. Found: C, 69.19; H, 4.85; N, 9.45; P, 5.50.

Preparation of *p*-Chloro-*N*-[1-methyl-3-[(triphenylphosphoranylidene)hydrazono]-2-indolinylidene] benzenesulfonamide (17b).—*p*-Chloro-*N*-(1-methyl-2-indolinylidene)benzenesulfonamide (5f, 1.5 g, 0.0046 mol) was refluxed with a solution of *p*-chlorobenzenesulfonyl azide (2 g, 0.0092 mol) in 125 ml of ethanol for 66 hr. After cooling, 1.1 g (68%) of the intermediate *p*-chloro-*N*-(3-diazo-1-methyl-2-indolinylidene)benzenesulfonamide (16b) was collected. This material was recrystallized from ethanol and 0.3 g (0.00029 mol) of the purified material was refluxed with a solution of triphenylphosphine (0.3 g, 0.00095 mol) in ethanol for 3 hr. The solution deposited (in two crops) a total of 0.48 g (84%) of 17b: mp 223–224° dec; ir (Nujol) 1510 and 1580 cm$^{-1}$. *Anal.* Calcd for C$_{33}$H$_{26}$ClN$_4$O$_2$PS: C, 65.07; H, 4.30; N, 9.20; Cl, 5.82; P, 5.09. Found: C, 65.01; H, 4.33; N, 9.45; Cl, 5.81; P, 5.10.

Registry No.—3j, 36982-84-0; 4aA, 36982-85-1; 4aB, 36982-86-2; 4bA, 36982-87-3; 4bB, 36982-88-4; 4cA, 36982-89-5; 4cB, 36982-90-8; 5a, 36982-91-9; 5b, 36982-92-0; 5c, 36982-93-1; 5d, 36982-94-2; 5e, 36982-95-3; 5f, 36982-96-4; 5g, 36982-97-5; 5h, 36982-98-6; 5i, 36982-99-7; 5j, 36983-00-3; 5k, 36983-01-4; 5e, 36983-01-4; 5m, 36983-03-6; 6a, 36983-04-7; 6b, 36983-05-8; 6c, 36983-06-9; 6d, 36983-07-0; 6e, 36983-08-1; 6f, 36982-13-5; 6g, 36982-14-6; 6h, 36982-15-7; 6i, 36982-16-8; 6j, 36982-17-9; 6k, 36982-18-0; 6l, 36982-19-1; 6m, 36982-20-4; 7a, 36982-21-5; 7b, 36982-22-6; 7c, 36994-49-7; 7d, 36982-23-7; 7e, 36982-24-8; 7f, 36982-25-9; 7g, 36982-26-0; 7h, 36982-27-1; 7i, 36982-28-2; 7j, 36982-29-3; 7k, 36982-30-6; 7l, 36982-31-7; 7m, 36982-32-8; 10, 36982-33-9; 11, 36982-34-0; 12, 20948-96-3; 13, 36982-36-2; 15, 36982-37-3; 16a, 36994-50-0; 17a, 36982-38-4; 17b, 36982-39-5; *N*-methylindole, 603-76-9.

# A New Synthesis of α-Chloro Sulfoxides.
# The Reaction of Diazo Compounds with Sulfinyl Chlorides[1a]

Clifford G. Venier,* Hsin-Hsiong Hsieh,[1b] and Howard J. Barager, III[1c]

*Department of Chemistry, Texas Christian University, Fort Worth, Texas 76129*

A new and facile synthesis of α-chloro sulfoxides involving the reaction of sulfinyl chlorides and diazo compounds has been developed. A comparison with previously known methods shows that this new method is superior for the preparation of many of the α-chloro sulfoxides whose reactions have generated much recent interest. In particular, methyl chloromethyl (1), bis(chloromethyl) (2), benzyl chloromethyl (4), and methyl chlorobenzyl (5) sulfoxides are produced in superior yields. A yield equal to that obtained by chlorination of phenyl methyl sulfoxide is realized for the preparation of phenyl chloromethyl sulfoxide (3). A number of new α-chloro sulfoxides have been synthesized, including n-butyl chloromethyl (6), sec-butyl chloromethyl (7), 9-fluorenyl chloromethyl (8), 9-chloro-9-fluorenyl methyl (9), and 1-chloroethyl chloromethyl (10) sulfoxides. This method is of particular merit for the preparation of α-chloro sulfoxides in cases where both the α and α' positions of the product may bear a chlorine substituent, since only one of the possible chlorine positional isomers is formed.

Recently, there has been widespread interest in the reactions of α-halo sulfoxides.[2,3] Naturally, interest has also been generated in the synthesis of various members of this series of compounds. We wish to report in this paper, a new and facile synthesis of α-chloro sulfoxides.

Most of the early workers chose to synthesize α-chloro sulfoxides by oxidation of the corresponding α-chloro sulfides with a variety of oxidizing reagents: ozone,[4] peroxy acids,[5] NaOCl,[6,7a] HNO₃,[7] and N₂O₅.[8] It is also worthwhile to note the synthesis of bis(1,2-dichloroethyl) sulfoxide by the addition of chlorine to divinyl sulfoxide.[9]

Since 1968, α-chloro sulfoxides have received much more attention. Additional oxidation methods include the use of m-chloroperbenzoic acid[10] and vanadium pentoxide[11] as oxidants. More importantly, α-chloro sulfoxides have been prepared by the α-chlorination of the corresponding unhalogenated sulfoxides by a variety of reagents. N-Chlorobenzotriazole,[12] sulfuryl chloride,[13] p-toluenesulfonyl chloride,[3] iodobenzene dichloride,[14] N-chlorosuccinimide,[15] tert-

butyl hypochlorite,[16] nitrosyl chloride,[17] and molecular chlorine[18] have all been used as sources of chlorine. A novel preparation of chloromethyl sulfoxides involving the hydrolysis of α,β-dichlorovinyl sulfoxides has been described recently.[19]

Although the reaction of diazomethane with sulfinyl chlorides is mentioned in the literature directly in one place,[20] and indirectly in another,[21] previous authors have reported this reaction simply as a slight diversion from the main topic of their work. Ayca,[20] in an attempt to modify the Arndt-Eistert reaction as a synthesis of α-diazo sulfoxides, reported that diazomethane and p-toluenesulfinyl or benzenesulfinyl chlorides react to give low yields of p-tolyl chloromethyl sulfoxide and phenyl chloromethyl sulfoxide, respectively. Saunders, et al.,[21] reported that diazomethane reacts with thionyl chloride to give a 40% yield of bis(chloromethyl) sulfoxide (2). In this last reaction, chloromethanesulfinyl chloride is undoubtedly an intermediate. In fact, we have been able to show that chloromethanesulfinyl chloride is the product of the reaction when diazomethane is added to an excess of thionyl chloride.[22] Recently, Senning and his coworkers[23] have synthesized trichloromethyl bromomethyl sulfoxide in 15% yield from trichloromethanesulfinyl bromide and diazomethane.

In this paper, we describe experiments which show that the reaction of diazo compounds with sulfinyl chlorides is a useful synthetic method for the preparation of α-chloro sulfoxides.[24]

## Results and Discussion

Although two general methods for the preparation of α-chloro sulfoxides are available, namely, the oxidation of α-chloro sulfides and the chlorination of sulfoxides,

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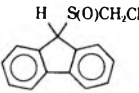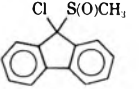
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TABLE I

DATA ON α-CHLORO SULFOXIDES PREPARED BY ADDITION OF DIAZO COMPOUNDS TO SULFINYL CHLORIDES[a]

$$RR'CN_2 + R''S(O)Cl \longrightarrow RR'CClS(O)R''$$

| Compd | Mp or bp, °C (mm) | Lit. mp or bp, °C (mm) | Yield, % | Ir, -S(O)-, cm⁻¹ | Nmr Data, δ, ppm |
|---|---|---|---|---|---|
| $CH_3S(O)CH_2Cl$ (1) | 61–62 (2) | 49–50 (0.03)[b] | 90 | 1040 | 2.68 (s, 3 H), 4.58, 4.71 (AB q, $J$ = 11 Hz, 2 H) |
| $ClCH_2S(O)CH_2Cl$ (2) | 38–39 | 39[c] | 99 | 1050 | 4.52, 4.64 (AB q, $J$ = 11 Hz) |
| $PhS(O)CH_2Cl$ (3) | Oil | 38.5–39.5[d] | 78 | 1045, 1075 | 4.35, 4.43 (AB q, $J$ = 11 Hz, 2 H), 7.50 (m, 5 H) |
| $PhCH_2S(O)CH_2Cl$ (4) | 56–58 | 54–55[e] | 99 | 1050 | 3.89, 3.98 (AB q, $J$ = 13 Hz, 2 H), 4.05, 4.16 (AB q, $J$ = 11 Hz, 2 H), 7.20 (m, 5 H) |
| $PhCHClS(O)CH_3$ (5)[f] | Oil | 50–51[e] | ≤9 | 1055 | 5a, 2.26 (s, 3 H), 5.74 (s, 1 H), 7.36 (m, 5 H), 5b, 2.43 (s, 3 H), 5.70 (s, 1 H), 7.36 (m, 5 H) |
| $n$-$BuS(O)CH_2Cl$ (6) | Dec | g | 77 | 1030 | 0.90 (m, 3 H), 1.60 (m, 4 H), 2.83 (t, 2 H), 4.47, 4.59 (AB q, $J$ = 11 Hz, 2 H) |
| $sec$-$BuS(O)CH_2Cl$ (7)[h] | Dec | g | 68 | 1040 | 0.83–1.30 (complex, 6 H), 1.30–2.15 (complex, 2 H), 2.85 (m, 1 H), 7a, 4.47, 4.55 (AB q, $J$ = 11 Hz, 0.9 H), 7b, 4.52, 4.71 (AB q, $J$ = 11 Hz, 1.1 H) |
| (8) | 101–103 | g | 47 | 1050 | 3.70 (s, 2 H), 5.26 (s, 1 H), 7.40 (m, 8 H) |
| (9) | 91–93 | g | 25 | 1060 | 1.70 (s, 3 H), 7.50 (m, 8 H) |
| $CH_3CHClS(O)CH_2Cl$ (10)[i] | 63–64 (3) | g | 90 | 1065 | 10a, 1.88 (d, 3 H), 4.69, 4.73 (AB q, $J$ = 12 Hz, 2 H), 4.89 (q, 1 H), 10b, 1.88 (d, 3 H), 4.48 (s, 2 H), 5.05 (q, 1 H) |
| $PhCHClS(O)Ph$ (11)[j] | 106–114 | 11a, 101–102[k] 11b, 122–123[k] | 36 | 1050, 1085 | 11a, 5.35 (s, 1 H), 7.25 (m, 10 H), 11b, 5.43 (s, 1 H), 7.25 (m, 1 H) |

*Structures for (8):* H S(O)CH₂Cl on a fluorene ring system.
*Structures for (9):* Cl S(O)CH₃ on a fluorene ring system.

[a] Compounds 1, 3, 4, 5, and 11 had properties consistent with those reported in the literature. Compounds 2, 6, 7, 8, 9, and 10 gave satisfactory C and H analyses (±0.4%). Compounds 2, 6, 8, and 9 gave satisfactory S analyses (±0.4%). 7 required 20.7, gave 20.0 S. 10 required 19.9, gave 18.3 S. Compounds 2, 7, 8, and 9 gave satisfactory Cl analyses (±0.4%). 6 required 23.0, gave 21.2 Cl. 10 required 44.0, gave 41.4 Cl. [b] Reference 18b. [c] Reference 21. [d] Reference 17. [e] Reference 14a. [f] Two diastereomers in the ratio 5a:5b = 4:1. [g] Previously unknown. [h] Two diastereomers in the ratio 7a:7b = 4:5. [i] Two diastereomers in the ratio 10a:10b = 2:1. [j] Two diastereomers in the ratio 11a:11b = 1:4. [k] Reference 16.

each of these methods has some drawbacks which make the elaboration of still another general method desirable. In either of the previous preparations, an important step is the oxidation of a sulfide to a sulfoxide. Even in the most skilled hands, these oxidations are treacherous. Overoxidation to the sulfone occurs with exasperating ease. In the reaction of diazo compounds with sulfinyl chlorides described herein, the oxidation of sulfur occurs in the sulfinyl chloride preparation, an easily carried out, high-yield procedure which has been thoroughly worked out by Douglass and his coworkers.[25] Additionally, a procedure avoiding the malodorous α-chloro sulfides is desirable.

An inspection of Table I reveals the high yields of α-chloro sulfoxides achievable by the diazoalkane–sulfinyl chloride reaction. In fact, for most of the compounds in Table I, the yields are equivalent to or superior to the best yields obtainable by other methods. Only in the case of phenyl chlorobenzyl sulfoxide is another method superior to this new method. In order to compare the efficacy of two routes to a single product, one must compare the yields from commonly available starting materials and not just the yields in the last step of a sequence. From the divalent sulfur compounds, mercaptans, sulfides, and disulfides, which are the commonly available starting materials for all three of the general methods of α-chloro sulfoxide prepara-

tion, the overall yields for the diazoalkane–sulfinyl chloride sequence are clearly superior in almost every case.

A further inspection of Table I will reveal that the diazoalkane–sulfinyl chloride reaction gives its highest yields when diazomethane is the diazo compound. Thus, this method is particularly well suited for the preparation of chloromethyl sulfoxides.

Since the α-chlorine of the product α-chloro sulfoxide must be on the nitrogen-bearing carbon of the reactant diazo compound, the addition of diazoalkane to sulfinyl chloride must, of necessity, give only one of the two possible chlorine positional isomers. Chlorination of sulfoxides can, and does,[14a,16] lead to mixtures of the isomers. A good example of positional specificity is illustrated in Table II. This tabulation shows the yields of the two monochloro derivatives of benzyl methyl sulfoxide (12) as prepared by a variety of means. Note that only in the case of the diazomethane–phenylmethanesulfinyl chloride reaction is 4 produced without contamination from 5. Although 5 can be prepared free of contaminating 4 by the chlorination of the sulfoxide 12, in the absence of added base, the overall yields suffer drastically, and so, for this isomer, the relatively low yield phenyldiazomethane–methanesulfinyl chloride reaction is the superior method of preparation.

Tin and Durst[13b] have shown that the chlorination of dialkyl sulfoxides can be made to give a single mono-

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Table II

Comparison of Yields for the Preparation of
Monochloro Derivatives of Benzyl Methyl Sulfoxide

| Method | 4, % | 5, % | Ref[a] |
|---|---|---|---|
| PhCH₂S(O)Cl + CH₂N₂ | 99 | 0 | This work |
| t-BuOCl, pyridine + PhCH₂S(O)CH₃ (12) | 45 | 15 | 16 |
| N-Chlorobenzotriazole, pyridine + 12 | 44 | 37 | 11 |
| PhICl₂, pyridine + 12 | 32 | 30 | 14 |
| SO₂Cl₂, no base + 12 | 0 | 25 | 12b |
| t-BuOCl, KOAc + 12 | 0 | 40 | 16 |
| PhCHN₂ + CH₃S(O)Cl | 0 | 49 | This work |

[a] Reference numbers refer to footnotes in text.

chloro isomer in good yield. For example, they were able to prepare methyl 1-chlorobutyl sulfoxide in 75% yield by the reaction of the parent methyl butyl sulfoxide with SO₂Cl₂ in the absence of added base. There is apparently no contamination from chlorine substitution on the methyl group. The diazoalkane-sulfinyl chloride reaction nicely complements this result, since it allows the production of the other isomer, butyl chloromethyl sulfoxide, in 77% yield from n-butanesulfinyl chloride and diazomethane.

It is important to note that the order of addition of the reagents is quite critical to the success of the preparation. While addition of diazoalkane to sulfinyl chloride leads to the high yields reported here, inverse addition leads to complex mixtures of products and consequently to greatly lowered yields of the desired α-chloro sulfoxides.

## Experimental Section

Infrared spectra were recorded on a Beckman IR-33 spectrophotometer. Nmr spectra were run on a Varian A-60A spectrometer using tetramethylsilane as an internal standard. Melting and boiling points are uncorrected. Combustion analyses were performed by Chemalytics, Inc., Tempe, Ariz. Diazomethane was generated from N-methyl-N-nitroso-p-toluenesulfonamide (Diazald, Aldrich Chemical Co.)[26] and dried over KOH for at least 2 hr prior to use. Phenyldiazomethane and 9-diazofluorene were prepared by the method of Smith and Howard[27] from benzalhydrazine and 9-fluorenone hydrazone, respectively. Sulfinyl chlorides were prepared by the chlorination of disulfides in the presence of acetic anhydride according to the procedure of Douglass and Norton,[25] except as noted.

**Chloromethane- and 1-Chloroethanesulfinyl Chlorides.**—A slurry of the requisite sym-trithiane and Ac₂O (1 equiv) was chlorinated at 0°. Excess Cl₂ and AcCl were removed at reduced

pressure and the sulfinyl chlorides were purified by distillation. Chloromethanesulfinyl chloride (55%) had bp 42–62° (15 mm); nmr (CDCl₃) δ 4.90 (s); ir 1150 cm⁻¹ (–S=OCl). 1-Chloroethanesulfinyl chloride (two diastereomers in the ratio of 2:1 A:B) (80%) had bp 26–27° (0.5 mm) [lit.[28] bp 36–38° (3.7 mm)]; nmr (CCl₄) δ 1.93 (d, J = 6.5 Hz, 3 H), 4.95 (isomer B), 5.11 (isomer A) (2 q, J = 6.5 Hz, 1 H); ir 1150 cm⁻¹ (–S=OCl).

**β-(9-Fluorenesulfonyl)propionitrile (13).**[29]—β-Thioacetylpropionitrile[30] (12.9 g, 0.1 mol) was added dropwise to a sodium ethoxide solution prepared by dissolving sodium (2.3 g, 0.1 g-atom) in 50 ml of absolute EtOH. 9-Bromofluorene[31] (24.6 g, 0.1 mol), dissolved in 200 ml of hot absolute EtOH, was then added in portions over a 1-hr period. After stirring overnight, the NaBr was filtered off and the solvent was removed *in vacuo*. The crude sulfide was oxidized to the sulfone 13 with H₂O₂ in HOAc.[32]

**9-Fluorenesulfinyl Chloride (14).**—13 was converted to 9-fluorenesulfinic acid, which was converted to 14 as previously described.[29] 14 was used without purification and the yield of 8 was based on 13 as the limiting reagent.

**General Procedure for the Preparation of Chloromethyl Sulfoxides.**—Excess diazomethane was added dropwise over a period of 30 min *via* a pressure-equalizing dropping funnel fitted with a CaCl₂ drying tube to a stirred, ice-cold solution of 0.07 mol of sulfinyl chloride in 50 ml of absolute ether. Stirring was continued for an additional 30 min. The ether was removed on a rotary evaporator. Liquid sulfoxides were purified by silica gel chromatography, except for chloromethyl methyl sulfoxide, which was distilled. Solid sulfoxides were recrystallized. Properties of the sulfoxides are presented in Table I.

**General Procedure for the Preparation of α-Chloro Sulfoxides.**—The procedure for the preparation of chloromethyl sulfoxides was followed, except that a stoichiometric amount of the diazo compound was used rather than an excess. The properties of these sulfoxides are presented in Table I.

(26) T. J. de Boer and H. J. Backer, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 250.

(27) L. I. Smith and K. L. Howard, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 351.

(28) J. F. King and R. P. Beatson, *J. Chem. Soc. D.*, 663 (1970). We wish to thank Dr. King for kindly supplying us with ir and nmr spectra of 1-chloroethanesulfinyl chloride.

(29) Modified from B. Zwanenburg, L. Thijs, and J. Strating, *Recl. Trav. Chim. Pays-Bas*, 86, 577 (1967).

(30) C. S. Marvel, K. G. Clark, H. K. Inskip, W. K. Taft, and B. G. Labbe, *Ind. Eng. Chem.*, 45, 2090 (1953).

(31) A. H. Wragg, T. S. Stevens, and D. M. Ostle, *J. Chem. Soc.*, 4057 (1958).

(32) Zwanenburg, Thijs, and Strating[29] report that the oxidation took 21 days. We find that it is complete in 3 days.

# Stereochemistry of Sulfur Compounds. IV. New Ring Systems of Carbon, Nitrogen, and Chiral Sulfur[1,2]

TODD R. WILLIAMS AND DONALD J. CRAM*

*Contribution No. 3002 from the Department of Chemistry of the University of California at Los Angeles, Los Angeles, California 90024*

Six new chiral heterocyclic systems have been prepared in which the sulfur, nitrogen, and carbon of the sulfoximide function are part of the ring system (compounds 1–6). From *S*-methyl-*S*-phenylsulfoximide (9a), butyllithium, and carbon dioxide was obtained 1-phenyl-3-oxo-1,2-thiazet-1-ine oxide (1). From *S*-methyl-*S*-*p*-tolylsulfoximide (9b) was formed 1-*p*-tolyl-4-oxo-2,5-dihydroisothiazole oxide (2b). The similarly prepared phenyl analog (2a) with diazomethane gave 1-phenyl-4-oxo-2,5-dihydroisothiazole oxide methyl ether (11). Treatment of *S*,*S*-dimethylsulfoximide with 1,3-diphenylpropynone and sodium hydride gave 1-methyl-3,5-diphenyl-1,2-thiazene oxide (18). Similarly optically active (−)-(*R*)-1-*p*-tolyl-3,5-diphenyl-1,2-thiazene oxide [(−)-(*R*)-3] was prepared from (−)-(*R*)-*S*-methyl-*S*-*p*-tolylsulfoximide [(−)-(*R*)-9b]. From methyl 2-methyl-thio-5-methylphenyl ketone (19) was synthesized 4*H*-1,6-dimethyl-3-oxo-1,2-thiazanaphthalene oxide (4) and 1,5-dimethyl-3-oxobenzo[*d*]-1,2-isothiazole oxide (20). From methyl 2-methylsulfinyl-5-methylphenyl ketone (24) was obtained 1,3,6-trimethylbenzo[*e*]-1,2,4-thiadiazene oxide (5), 1,6-dimethyl-3-oxobenzo[*e*]-4*H*-1,2,4-thiadiazine oxide (6), 1,6-dimethyl-3-carbomethoxybenzo[*e*]-1,2,4-thiadiazene oxide (27), 1,6-dimethyl-3-carboxylbenzo[*e*]-1,2,4-thiadiazene oxide (28), and 1,6-dimethylbenzo[*e*]-1,2,4-thiadiazene oxide (26).

The potential chirality, the stability, and the amphoteric properties of the sulfoximide group[3] make compounds containing this function of particular interest. Three of the four ligands of sulfur in sulfoximides are capable of wide structural variation, and suggest that many new heterocycles might be prepared which contain the sulfur, nitrogen, and carbons of the sulfoximide group as part of a ring system. In principle, rings of all sizes might be constructed that link one carbon to the nitrogen, one carbon to the second carbon, or each carbon to the other and to the nitrogen to give a bicyclic system.
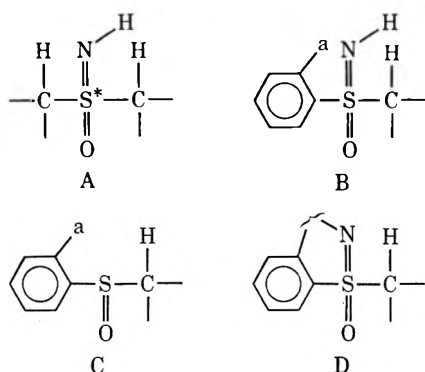


Two general strategies for synthesis are envisioned, the first of which involves reactions of a sulfoximide already in being. All three protons of A are slightly acidic, and by proton abstraction with base might be turned into nucleophilic reaction sites. In addition to the two potential nucleophilic sites of B, substituent a of the aromatic ring might be manipulated for synthetic purposes. In the second approach, the sulfoximide unit might be generated from a sulfoxide in a ring-closing nitrenation reaction (C → D).

This paper reports the syntheses of six new heterocyclic ring systems (1–6) that make use of one or the other of these strategies. The first two heterocyclic systems based on the sulfoximide function (7[4] and 8[5])
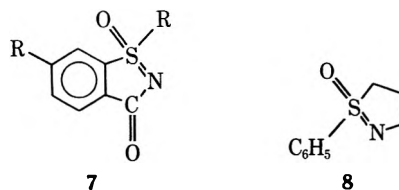


were announced when all our new systems except 3 and 20 were in hand. The syntheses of compounds 1, 2, and 3 make use of the potential nucleophilic properties of a sulfoximide unit in being, whereas those of the others involve generation of the sulfoximide during ring closure.

**Sulfoximides as Potential Nucleophiles in Syntheses.**—Preparation of the β-lactam-like compound 1 involved use of anions derived from the SCH₃ and S=NH groups of *S*-methyl-*S*-phenylsulfoximide (9a).
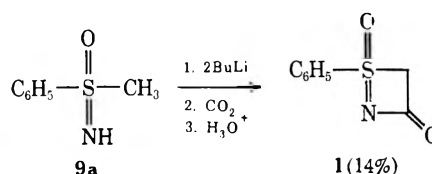


The carbonyl group of 1 absorbs at 1690 cm⁻¹ in chloroform in the infrared at somewhat lower energy than the 1745 cm⁻¹ of a normal lactam.[6] Thus, the carbonyl of 1 has more single bond character than a usual β-lactam. Possible explanations are that the N–C–C bond angle is expanded to >90° to accommodate the length of the S–C bond, or that the S=N–C=O linkage possesses considerable dipolar character (⁺S–N=C–O⁻ contributions), or both. The yield of 1 was not maximized, and the probable acidity of 1 once formed probably complicated its synthesis by consuming base.

Alkylation of nitrogen of aryl methyl sulfoximides with haloacetic esters proceeded well only with bromine

(1) This investigation was supported by the U. S. Public Health Service Research Grant No. GM12640-07 from the Department of Health, Education, and Welfare.

(2) These results appeared as a communication: T. R. Williams and D. J. Cram, *J. Amer. Chem. Soc.*, **93**, 7333 (1971).

(3) IUPAC nomenclature is employed for compounds of any complexity [see P. E. Verkade, *Pure Appl. Chem.*, **11**, 1, 155 (1965)].

(4) P. Stoss and G. Satzinger, *Angew. Chem., Int. Ed. Engl.*, **10**, 79 (1971).

(5) C. R. Johnson, G. F. Katekar, R. F. Huxol, and E. R. Janiga, *J. Amer. Chem. Soc.*, **93**, 3771 (1971).

(6) K. Nakanishi, "Infrared Absorption Spectroscopy-Practical," Holden-Day, San Francisco, Calif., 1962, p 47.

or iodine as leaving group, and went best in dimethoxy-ethane at 25° with sodium hydride as base. Use of the thallium salt led to recovered starting material. Treatment of S-methyl-S-p-tolylsulfoximide (9b) with ethyl diazoacetate and concentrated sulfuric acid also failed to produce the desired ester, 10a. Conversions of esters 10 to cycles 2 were plagued by reverse condensations of 2 to give acids 11 under aqueous basic isolation conditions. Enol ether 12 was prepared by treating unpurified 2a with diazomethane. The similarity in ultraviolet spectra of enol ether 12 and 2b coupled with the facile diazomethane reaction indicated that 2b was largely an enol. This structural assignment was supported by nmr and ir spectra of 2b. Upon melting, 2b decomposed violently to evolve a gas, possibly ketene. The substance was only slightly soluble in nonpolar spectral solvents, and nmr spectra were obtained only with difficulty.

The position of the enol double bond in 2b and 12 is inferred but not unequivocally demonstrated through nmr spectral comparisons (see Experimental Section). That 2b exists mainly in the enol form contrasts with cyclopent-3-ene-1-one, which exists to an extent of less than 3% as the enol.[7]

With either aqueous acid or base, ester 10b produced acid 11. Attempts to convert 11 to the heterocyclic



9a, R = H
b, R = CH₃

10a, R = H; R' = C₄H₉
b, R = CH₃; R' = C₂H₅

11, R = CH₃

13, R = CH₃

2a, R = H
b, R = CH₃

12, R = H

system 13 with liquid hydrogen fluoride, polyphosphoric acid (200°), thionyl chloride, or concentrated sulfuric acid (100°) failed. Interestingly, polyphosphoric acid converted 11 to the parent sulfoximide 9b in 46% yield.

That the benzene ring in S-methyl-S-phenylsulfoximide is highly deactivated toward electrophilic substitution was shown further as follows. The system when acylated with chloroacetyl chloride in pyridine gave 14, which with aluminum chloride at 110° failed to give ring-closed product, and only starting material and decomposition products were observed. Treatment of S-methyl-S-phenylsulfoximide with oxalyl

chloride in ether and then with aluminum chloride in dichloromethane also failed to produce a heterocycle. Only 15 (as a hydrate) was ultimately isolated. Ester 16a readily formed when S-methyl-S-phenylsulfoximide was heated with excess dimethyl oxalate at 150°. Ester 16b resulted from mixing S-methyl-S-p-tolylsulfoximide with the half ethyl ester of oxalyl chloride in pyridine. Attempts to ring close 16a on the S-methyl group failed to give product that survived isola-



14

15

16a, R = H; R' = CH₃
b, R = CH₃; R' = C₂H₅

17

tion. Although 17 was readily formed from S-methyl-S-phenylsulfoximide and ethyl chloroformate, its conversion to a cyclic urea *via* its carbamoyl azide failed.[8]

Syntheses of the new heterocycles 3 and 18 were modeled after that of the carbon analog of 18 (thiabenzene oxide).[9] Since optically pure (−)-(R)-S-methyl-S-p-toluenesulfoximide was used[10] and no bonds were made or broken to the chiral center, optically pure (−)-(R)-3 was produced. As expected, (−)-3 gave a much higher optical rotation than the more symmetrical starting material, whose O and NH groups are of similar polarizability. The broad melting point of 3 persisted on repeated recrystallization from many solvents. Molecular models of 3 indicate a puckered disk shape from whose convex face the oxygen protrudes. At 150° the substance starts to undergo a phase change from one solid to a second, and becomes completely liquid at 158°. The substance does not appear (polarizing microscope) to pass through a nematic phase change[11] upon melting. Analog 18 was similarly formed from dimethylsulfoxide.

Although 3 and 18 formally contain six π electrons, the nmr chemical shifts (δ in CDCl₃) of their ring protons are unlike those of aromatic model compounds. The proton in the 6 position of 18 resonated at 6.10 and the corresponding proton of 3 was found at 5.90. The analogous proton at C-6 in the carbon analogue of 18 (thiabenzene oxide) was reported[9] at 5.83. The close proximity of the three nmr signals coupled with Hortmann and Harris's full arguments[9] indicate 3 and 18 not to be aromatic. Oae, *et al.*,[12] through p$K_a$ comparisons of aryl-substituted S-methyl-S-phenylsulfox-

(7) S. Winstein, E. C. Friedlich, R. Baker, and L. Yang-i, *Tetrahedron, Suppl.*, **8**, Part II, 621 (1966).

(8) E. S. Levchenko, E. S. Koslov, and A. V. Kirsanov, *J. Gen. Chem. USSR*, **32**, 2548 (1962).

(9) A. G. Hortmann and R. L. Harris, *J. Amer. Chem. Soc.*, **93**, 2471 (1971).

(10) D. J. Cram, J. Day, D. R. Rayner, D. M. von Schriltz, D. J. Duchamp, and D. C. Garwood, *ibid.*, **92**, 7369 (1970).

(11) G. W. Gray, "Molecular Structure and the Properties of Liquid Crystals," Academic Press, New York, N. Y., 1962.

(12) S. Oae, K. Tsujihara, and N. Furukawa, *Chem. Ind. (London)*, 1569 (1968).

$p$-CH$_3$C$_6$H$_4$

(−)-(R)-9b

+   C$_6$H$_5$—C—C≡C—C$_6$H$_5$  $\xrightarrow[\text{(CH}_3)_2\text{SO}]{\text{NaH}}$

$p$-CH$_3$C$_6$H$_4$

(−)-(R)-3

**18**

imides, have shown that there is no through conjugation from the sulfoximine nitrogen to the substituted phenyl ring.

**Closures of Rings Linking the Aromatic Ring and Nitrogen of S-Aryl-S-methylsulfoximides.**—Additional new heterocycles utilized 5-methyl-2-methylthioacetophenone[13] (19) as starting material. The substance also served in an efficient two-step but multistage synthesis of 20, which contains the same ring system as the already reported substances,[4] 7. In our synthesis of the ring system, 19 underwent simultaneous bromoform and sulfide oxidation to give 21 (92%), which with hydrazoic acid–sulfuric acid gave 20 (70%) in a substitution at both carbonyl carbon and at sulfur. In a similar ring closure, the six-membered lactam 4 was prepared (60%) from 23, the homolog of 21. That heterocycle 4 exists in the "keto" rather than the potentially aromatic "enol" form is evident from its ir and nmr spectra. The carbonyl of 4 in chloroform absorbs at 1655 cm$^{-1}$, and thus has less double-bond character than the four-membered lactam, 1. Lactam 4 with base formed an open-chain salt, which upon acidification regenerated 4. In one of several attempts to form an enol ether of 4, the substance was treated with first sodium hydride and then excess methyl iodide. Dimethylation occurred (52%) at the carbon $\alpha$ to the carbonyl group.

Sulfoxide 24 (from 19 and sodium periodate) when treated with sodium azide and sulfuric acid underwent a combined imidation–Schmidt rearrangement–ring closure to give 5 (77%). Attempts to develop a good resolution of 5 gave only partially optically pure material. The open-chain hydrolysis product of 5, amino sulfoximide 25, served as starting material for preparation of interesting derivatives. Heterocycle 26 is formally 5 minus a methyl group. The chemical shift ($\delta$) of the proton at C-3 in the nmr spectrum of 26 in CDCl$_3$ occurred at 7.85. The proton at C-2 of the aromatic model compound 30 in CCl$_4$ was reported[14] at 9.29, whereas the nonaromatic formyl proton in 31 came at 7.61 (CDCl$_3$).[15] Thus heterocycle 26 resembles more the nonaromatic model.

Urea derivative, 6 (82%), gave an ir spectrum that clearly showed that the compound exists in the normal amide and not the imidol form. The substance decomposed with melting at 295–300°, and was stable enough

(13) K. Auwers and F. Arndt, *Chem. Ber.*, **42**, 537 (1909).
(14) P. J. Black and M. L. Heffernan, *Aust. J. Chem.*, **18**, 707 (1965).
(15) J. P. Marsh, Jr., and L. Goodman, *Tetrahedron Lett.*, 683 (1967).

**21**   $\xrightarrow{\text{NaN}_3,\ \text{H}_2\text{SO}_4}$   **20**

1. Br$_2$, KOH   2. H$_3$O$^+$

**19**   $\xrightarrow[\text{2. H}_3\text{O}^+]{\text{1. Willgerodt}}$   **22**

NaIO$_4$

**23**

**4**   $\xrightarrow{\text{NaN}_3,\ \text{H}_2\text{SO}_4}$

**24**   $\xrightarrow{\text{NaN}_3,\ \text{H}_2\text{SO}_4}$   **5**

10% NaOH Δ   ‖   HCl AcOH Δ

**6**   $\xleftarrow[\Delta]{\text{(N)}_2\text{CO}}$   **25**

HCO$_2$H Δ

(CH$_3$O$_2$C)$_2$   170°

**27**   **26**

H$_3$O$^+$ Cl$^-$

**28**   **29**

**30**

$p$-NO$_2$C$_6$H$_4$N═CN(CH$_3$)$_2$

**31**

to water at 100° to be recrystallized from that solvent. The new amino acid system, 28, was sensitive to even cold acid hydrolysis, and was crystallized only as a hydrate. An attempt to form triazine 32 from amino-

**25**   $\xrightarrow{\text{2HNO}_2}$

**32**   $\underset{-\text{H}^+}{\overset{\text{H}^+}{\rightleftharpoons}}$   $\xrightarrow{-\text{H}^+}$   **29**

sulfoximide **25** and nitrous acid led to azide **29**. Likely **32** was formed, at least in protonated form, but readily decomposed to azide **29**, as formulated. Attempts to cyclize **29** by both thermal and photolytic loss of nitrogen failed to yield isolable cyclic (four-membered ring) sulfoximide.

Attempts to prepare heterocycle **33** led to the unusual reaction sequence formulated (**34** → **35** → **36**). Although sulfoxide **24** gave sulfoximide **34** as expected, bromination of **34** led to complex substitution–rearrangement reactions, possibly *via* **37** and **38** as intermediates.
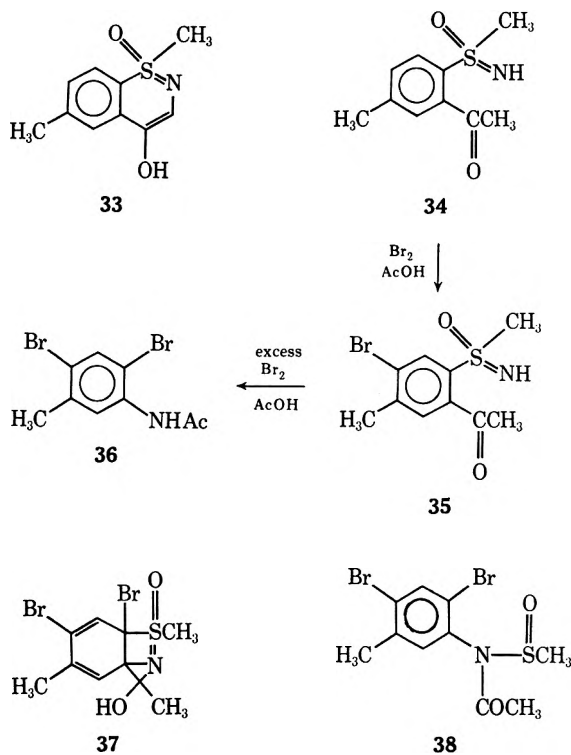


## Experimental Section

**General.**—Infrared spectra were obtained with a Beckman IR-5 spectrometer in chloroform or carbon tetrachloride solution, in a Nujol mull, or in a potassium bromide pellet. Nmr spectra were obtained with a Varian T-60, A-60, or A-60D spectrometer in deuteriochloroform, carbon tetrachloride, or deuterium oxide solution. All nmr chemical shifts are given relative to tetramethylsilane as internal standard at 10 τ unless otherwise indicated. Rotations were obtained with a Perkin-Elmer 141 polarimeter in chloroform, acetone, or methanol solution in a 1-dm, jacketed cell, thermostated at 25°. Uv spectra were obtained with a Cary 14 spectrometer in methanol solution. Mass spectra were obtained with an AEI Model MS9 mass spectrometer. Melting points were taken in capillary tubes in a Hoover capillary melting point apparatus and are uncorrected. Solvents designated as "dry" were purified by distillation from lithium aluminum hydride or calcium hybride under dry nitrogen or *in vacuo*. Unless stated otherwise, the term "extraction" describes extracting an aqueous phase with chloroform or dichloromethane, drying the combined organic layers over magnesium sulfate, filtering with vacuum, and removing solvent at aspirator pressure with a heating bath at 50–60°.

**Starting Materials.**—Methyl *p*-tolyl sulfoxide[16] (∼65%) gave bp 116–118° (0.1 mm); methyl phenyl sulfoxide[17] (50%) gave bp 76–79° (0.1 mm); *S,S*-dimethylsulfoximine was prepared as before;[18a] *S*-methyl-*S*-*p*-tolylsulfoximide[18b] (**9b**) was isolated as its

(16) N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, **27**, 282 (1962).

(17) C. C. Price and J. J. Hydock, *J. Amer. Chem. Soc.*, **74**, 1943 (1952).

(18) (a) J. K. Whitehead and H. R. Bentley, *J. Chem. Soc.*, 2081 (1950); (b) *ibid.*, 1572 (1952).

hydrochloride salt, mp 173–177° dec. *Anal.* Calcd for $C_{18}H_{12}$-ClNOS: C, 46.72; H, 5.84. Found: C, 46.69; H, 5.82. The base itself (70%) gave mp 67–71.5°.[19] Similarly, *S*-methyl-*S*-phenylsulfoximide[20] (**9a**, 85%) gave bp 110–115° (0.1 mm). The (−)-(*R*)-*S*-methyl-*S*-*p*-tolylsulfoximide [(−)-(*R*)-**9b**][10] used gave $[\alpha]^{25}_{546}$ −40.6° (*c* 1.12, acetone). Methyl 2-methylthio-5-methylphenyl ketone[13] (**19**, 59%) gave mp 49–51°.

**1-Phenyl-3-oxo-1,2-thiazet-1-ine Oxide (1).**—To a solution of 1.5 g (9.67 mmol) of **9a** in 50 ml of dry tetrahydrofuran under nitrogen was added 15 ml of a 1.6 *M* solution of butyllithium in hexane (24 mmol), and the resulting yellow solution was stirred at 25° for 1 hr. This solution was added in portions to about 100 g of solid carbon dioxide stirred under nitrogen. The resulting suspension was stirred for 5 min and quenched with 20 ml of 2 *N* hydrochloric acid. The aqueous layer was extracted to give 0.27 g (15%) solid, pure **1** as shown by its ir and nmr spectra. Recrystallization of the substance from ethyl acetate gave mp 204.5–208°. *Anal.* Calcd for $C_8H_7NO_2S$: C, 53.04; H, 3.94. Found: C, 52.92; H, 3.98. Nmr (CDCl₃) τ 2.1 (m, 5, ArH), 6.5 (s, 2, CH₂). Mass spectrum *m/e* 181 (p⁺).

**General Procedure for Alkyl (*S*-Methyl-*S*-arylsulfonimidoyl-*N*) Acetate (10).**—To a solution of sulfoximide **9** in dry dimethoxyethane under dry nitrogen was added 1.5 equiv of sodium hydride as a 50% mineral oil dispersion. The rate of hydride addition was regulated to keep the reaction mixture from foaming excessively. The resulting suspension was stirred for 3 hr to ensure reaction, and 1.5 equiv of the appropriate alkyl bromoacetate was added at a fast dropwise rate. The resulting mixture was stirred at 25° for 24 hr under nitrogen and quenched with water. After solvent evaporation (*in vacuo*), the residual oil was chromatographed on 50–70 parts of silica gel. Pentane eluted mineral oil and unreacted alkyl bromoacetate. Ether–pentane eluted product **10**, and ether eluted starting material. The product was purified by either rechromatography or vacuum distillation (Kugelrohr).

In this way 23.3 g (0.150 mol) of **9a** was converted with butyl bromoacetate to 17.5 g (50%) of **10a**, bp 150° (0.08 mm). An analytical sample was prepared by preparative vpc. *Anal.* Calcd for $C_{13}H_{19}NO_3S$: C, 57.58; H, 7.12. Found: C, 57.50; H, 7.16. Nmr (CDCl₃) τ 2.0–2.8 (m, 5, ArH), 5.8 (t, 2, CH₂-CH₂), 6.3 (q, 2, NCH₂), 6.8 (s, 3, SCH₃), 8.7 (m, 7). Similarly, 5.0 g (29.6 mmol) of **9b** was converted to 4.36 g (58%) of **10b** after rechromatography. An analytical sample was prepared by preparative vpc. *Anal.* Calcd for $C_{12}H_{17}O_3NS$: C, 56.45; H, 6.71. Found: C, 56.40; H, 6.80. Nmr (CDCl₃) τ 2.38 (q, 4, ArH), 5.85 (q, 2, *J* = 7 Hz, CH₂CH₃), 6.33 (q, 2, NCH₂), 6.82 (s, 3, SCH₃), 7.55 (s, 3, ArCH₃), 8.78 (t, 3, *J* = 7 Hz, CH₂CH₃).

**1-*p*-Tolyl-4-oxo-2,5-dihydroisothiazole Oxide (2b).**—A solution of 0.774 g (3.21 mmol) of **10b** in 40 ml of dry tetrahydrofuran was added over 2 hr to a vigorously stirred suspension of 0.46 g of sodium hydride (as a 50% mineral oil dispersion) in 100 ml of dry solvent at 25° under nitrogen. The resulting suspension was refluxed under nitrogen for 24 hr, and the reaction was quenched with 5 ml of 2 *N* hydrochloric acid. The solvent was removed *in vacuo*, the residue taken up in chloroform and filtered, the filtrate was evaporated, and the residue was chromatographed on silica gel. Starting material eluted with ether, and the product (0.14 g, 21%) eluted with 5–10% methanol–ether as a white solid, mp 160° dec. Recrystallization of the material from acetone–cyclohexane gave mp 156.5–157.5° dec, when the sample was inserted into the heating bath at 140°. *Anal.* Calcd for $C_{10}H_{11}O_2NS$: C, 57.42; H, 5.26. Found: C, 57.25; H, 5.08. Nmr (CDCl₃) τ 2.4 (q, 4, ArH), 5.55 (broad s, 1, CH), 6.0 (m, 3, CH₂ and OH), 7.55 (s, 3, ArCH₃). Uv (MeOH) 275 nm (sh) (log ε 3.53), 265 (sh) (3.72), 258 (sh) (3.83), 227 (max) (4.18).

**1-Phenyl-4-oxo-2,5-dihydroisothiazole Oxide Methyl Ether (12).**—The above procedure was applied to 1.04 g (3.84 mmol) of **10a**. However, before the product was chromatographed it was treated with a solution of diazomethane in ether until no further reaction appeared to occur. Chromatography of the resulting oil on silica gel (50 g) with 5% methanol–ether eluent gave 0.11 g (13%) of solid, mp 111–115°. Rechromatography of the material through 10 g of alumina with ether eluent, followed by recrystallization from ether, gave mp 113–115.5°. *Anal.* Calcd for $C_{10}H_{11}NO_2S$: C, 57.38; H, 5.30. Found: C, 57.21; H, 5.29. Nmr (CDCl₃) τ 2.0–2.8 (m, 5, ArH), 4.3 (s, 1, CH), 5.6

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(broad s, 2, CH$_2$), 6.22 (s, 3, OCH$_3$). Uv (MeOH) 274 nm (sh) (log ε 3.20), 266 (sh) (3.34), 259 (sh) (3.39), 225 (max) (4.05).

(*S*-Methyl-*S*-*p*-tolylsulfonimidoyl)acetic Acid (11). A. Basic Hydrolysis.—A suspension of 2.3 g (9.25 mmol) of 10b, 25 ml of water, 25 ml of methanol, and 25 ml of saturated potassium carbonate solution was stirred at 25° for 20 hr. The resulting solution was brought to pH 3 with hydrochloric acid and extracted. Trituration of the oily residue with ether gave an oil which was crystallized from ethanol–water to give 0.3 g (30%) of *p*-tolyl *p*-toluenethiosulfonate, mp 74–76° (lit.[21] mp 78–79°). The ether-insoluble residue was crystallized from chloroform or methanol to yield 0.6 g (29%) of 11, mp 99–100°.

B. Acidic Hydrolysis.—A solution of 0.5196 g (2.04 mmol) of 10b in 15 ml of 2 N hydrochloric acid was stirred at 25° for 24 hr. The pH was adjusted to about 3 by solid sodium carbonate addition, and the solution was extracted. The resulting oil was dissolved in chloroform and seeded with the above sample of 11. The crystals thus obtained weighed 0.396 g (79.4%), mp 98–100°. *Anal.* Calcd for C$_{10}$H$_{13}$O$_3$NS·H$_2$O: C, 48.97; H, 6.17. Found: C, 49.12; H, 6.10. Nmr (CDCl$_3$) τ 2.33 (q, 4, ArH), 5.89 (broad s, 3, OH), 6.42 (broad s, 2, NCH$_2$), 6.80 (s, 3, SCH$_3$), 7.55 (s, 3, ArCH$_3$).

*S*-Methyl-*S*-phenyl-*N*-chloroacetylsulfoximide (14).—To a solution of 1.55 g (10 mmol) of 9a and 7 ml of dry triethylamine in 40 ml of dry tetrahydrofuran was added *via* syringe 1.59 ml (20 mmol) of chloroacetyl chloride at a slow dropwise rate with stirring and cooling in ice. The resulting brown mixture was allowed to warm to 25° over 30 min and stirred for 1.5 hr. The reaction was quenched with 10 ml of water, the solvent was removed *in vacuo*, and the residue was dissolved in dichloromethane, washed with dilute acid, dried, and chromatographed on 150 g of silica gel. Five 400-ml fractions were taken with 50% ether–pentane eluent, and then 18 100-ml fractions with ether eluent were collected. The product in fractions 8–19 was combined to give 1.82 g (79%) of solid. Recrystallization of this material from dichloromethane–ether gave 1.43 g (62%) of 14, mp 112–115°. One recrystallization from the same solvent gave mp 113–115°. *Anal.* Calcd for C$_9$H$_{10}$ClNO$_2$S: C, 46.64; H, 4.38. Found: C, 46.87; H, 4.50. Nmr (CDCl$_3$) τ 1.8–2.5 (m, 5, ArH), 5.90 (s, 2, CH$_2$Cl), 6.60 (s, 3, SCH$_3$).

*S*-Methyl-*S*-*p*-toyl-*N*-hydrogenoxalylsulfoximide (15).—To a solution of 1.5 g (8.9 mmol) of 9b in 20 ml of dry pyridine was added a solution of 20 mmol of oxalyl chloride and 19 mmol of ethanol in 30 ml of dry dimethoxyethane. The reaction mixture became quite warm, and a white precipitate formed almost immediately. The resulting mixture was stirred at 25° for 3 hr and then quenched with water. Extraction gave a yellow solution which was washed with dilute acid, dried, and evaporated to give an oil. This oil was chromatographed on 60 g of silica gel, with 50% ether–pentane as eluent, to give 2.0 g (83%) of ester 16b, pure by tlc, ir, and nmr. Nmr (CDCl$_3$) τ 2.33 (q, 4, ArH), 5.73 (q, 2, J = 7 Hz, CH$_2$CH$_3$), 6.59 (s, 3, SCH$_3$), 7.58 (s, 3, ArCH$_3$), 8.70 (t, 3, J = 7 Hz, CH$_2$CH$_3$).

After standing in a vial for 1 year exposed to the air this oily ester hydrolyzed to solid acid 15. Recrystallization of this solid from acetone–cyclohexane gave 1.25 g (58.5% based on 9b), mp 112.5–115°. *Anal.* Calcd for C$_{10}$H$_{11}$O$_4$NS·H$_2$O: C, 46.33; H, 5.06. Found: C, 46.38; H, 5.11. Nmr (acetone-*d*$_6$) τ 2.4 (q, 4, ArH), 4.65 (broad s, 3, OH), 6.83 (s, 3, SCH$_3$), 7.68 (s, 3, ArCH$_3$).

*S*-Methyl-*S*-phenyl-*N*-carbomethoxycarbonylsulfoximide (16a). —A mixture of 1.5 g (9.7 mmol of 9a and 8 g (68 mmol) of dimethyl oxalate was heated at 150° for 5 hr under a slow stream of nitrogen. The excess dimethyl oxalate was sublimed at aspirator pressure, and the residue was chromatographed on 100 g of silica gel with ether eluent. Thirteen 400-ml fractions were taken and the product was contained in fractions 5–13, 1.43 g (60%), as an oil. A sample was purified by molecular distillation. *Anal.* Calcd for C$_{10}$H$_{11}$NO$_4$S: C, 49.78; H, 4.60. Found: C, 49.90; H, 4.69. Nmr (CDCl$_3$) τ 2.0–2.8 (m, 5, ArH), 6.1 (s, 3, OCH$_3$), 6.7 (s, 3, SCH$_3$).

*S*-Methyl-*S*-phenyl-*N*-carboethoxysulfoximide (17).—A solution of 4.0 g (25.8 mmol) of 9a in 40 ml of dry tetrahydrofuran and 10 ml of dry triethylamine was cooled under nitrogen to 0°. With good stirring, 4.12 ml (51.6 mmol) of ethyl chloroformate was added dropwise over 45 min. After the addition was complete, the reaction was allowed to warm up to 25° over 1 hr. The nitrogen was removed and 56 mmol of water was added slowly

with stirring. The resulting mixture was poured into 100 ml of water and made strongly acidic with concentrated hydrochloric acid. Extraction at this point gave 4.5 g (77%) of 17 as an oil. Addition of solid sodium carbonate to the water layer followed by extraction gave 0.8 g (20%) of unreacted 9a. Pure 17 was obtained by molecular distillation. *Anal.* Calcd for C$_{10}$H$_{13}$NO$_3$S: C, 52.84; H, 5.78. Found: C, 52.74; H, 5.84. Nmr (CCl$_4$) τ 2.0–2.4 (m, 5, ArH), 6.01 (q, 2, J = 7 Hz, CH$_2$CH$_3$), 6.73 (s, 3, SCH$_3$), 8.83 (t, 3, J = 7 Hz, CH$_2$CH$_3$).

1-Methyl-3,5-diphenyl-1,2-thiazene Oxide (18).—To a solution of 1.306 g (14 mmol) of *S*,*S*-dimethylsulfoximide[18a] in 60 ml of dry dimethyl sulfoxide [freshly distilled from calcium hydride, bp 72° (10 mm)] was added 0.74 g (15.4 mmol) of a mineral oil dispersion of sodium hydride, and the resulting mixture was stirred for 45 min under nitrogen. The mixture was cooled below 25° in ice and a solution of 1.48 g (7.18 mmol) of 1,3-diphenylpropynone in 15 ml of dry dimethyl sulfoxide was added in small portions over 8 min *via* syringe. The resulting dark brown reaction mixture was stirred at 25° for 19.5 hr and poured into 300 ml of ice and water. The mixture was allowed to warm to 25° and was filtered through Celite. The Celite was washed thoroughly with dichloromethane to give a red oil which, when triturated with pentane to remove mineral oil, crystallized to give 0.40 g (20%) of solid, mp 140–144°. Recrystallization of 18 from ethyl acetate–cyclohexane gave mp 142.5–144°. *Anal.* Calcd for C$_{17}$H$_{15}$NOS: C, 72.56; H, 5.38. Found: C, 72.63; H, 5.57. Nmr (CDCl$_3$) τ 1.9–2.7 (m, 10, ArH), 3.40 (d, 1, J = 0.7 Hz, C$_4$H), 3.9 (d, 1, J = 0.7 Hz, C$_6$H), 6.55 (s, 3, SCH$_3$).

( − )-1-*p*-Tolyl-3,5-diphenyl-1,2-thiazene Oxide [( − )-(*R*)-3].— By the above procedure, 1.24 g (6.0 mmol) of 1,3-diphenylpropynone and 1.12 g (6.6 mmol) of ( − )-(*R*)-9b,[10] were converted to 1.8 g (84%) of 3 as a yellow solid, mp 150–158°, [α]$^{25}_{546}$ −339° (c 1.15, chloroform). The same melting point and rotation were obtained for crystals from methanol, ether, or ethyl acetate solution. *Anal.* Calcd for C$_{23}$H$_{19}$NOS: C, 77.27; H, 5.37. Found: C, 77.29; H, 5.47. Nmr (CDCl$_3$) τ 1.9–2.8 (m, 14, ArH), 3.3 (broad s, 1, C$_4$H), 4.1 (broad s, 1, C$_6$H), 7.6 (s, 3, ArCH$_3$).

Methyl 2-Methylsulfinyl-5-methylphenyl Ketone (24).—The method of Leonard and Johnson[16] was applied to 16.0 g (88.9 mmol) of 19 to give 16.8 g (96.5%) of 24, mp 88–91°. A sample was recrystallized from ether, mp 89.5–91.5°. *Anal.* Calcd for C$_{10}$H$_{12}$O$_2$S: C, 61.21; H, 6.17. Found: C, 61.37; H, 6.19. Nmr (CDCl$_3$) τ 1.50–2.50 (m, 3, ArH), 7.24 (s, 3, SCH$_3$), 7.35 (s, 3, CCH$_3$), 7.46 (s, 3, ArCH$_3$).

Methyl 2-Methylsulfonimidoyl-5-methylphenyl Ketone (34).— The method of Whitehead and Bentley[18b] was applied to 3.80 g (19.4 mmol) of 24. The reaction was allowed to proceed for 3 hr and was then quenched with water. Extraction of the acidic solution gave after crystallization from dichloromethane–ether 2.0 g (49%) of ketone, mp 129–131°. *Anal.* Calcd for C$_{10}$H$_{13}$O$_2$NS: C, 56.86; H, 6.20. Found: C, 56.74; H, 6.23. Nmr (CDCl$_3$) τ −0.55 (broad, 1, NH), 1.70 (s, 1, ArH), 2.92, (m, 2, ArH), 7.13 (s, 3, SCH$_3$), 7.62 (s, 3, CCH$_3$), 7.82 (s, 3, ArCH$_3$).

Methyl 2-Methylsulfonimidoyl-4-bromo-5-methylphenyl Ketone (35).—Into a flask wrapped in aluminum foil and fitted with a nitrogen inlet was put a solution of 1.5 g (7.11 mmol) of 34 in 10 ml of glacial acetic acid, and the reaction vessel was purged with nitrogen. Bromine (0.43 ml, 7.8 mmol) dissolved in 2 ml of glacial acetic acid was added. The reaction flask was stoppered under a positive pressure of nitrogen and heated in an oil bath at 50–55° for 3 hr. The resulting solution was poured into water, excess bromine was destroyed with sodium thiosulfate solution, the pH was adjusted to 8 by addition of sodium carbonate, and the resulting suspension was extracted to give an oil. Upon trituration with ether, this oil gave 1.89 g (91.8%) of white crystals, mp 184–188°. A sample was crystallized from acetone, mp 186–188°. *Anal.* Calcd for C$_{10}$H$_{12}$BrNO$_2$S: C, 41.39; H, 4.17. Found: C, 41.31; H, 4.33. Nmr (CDCl$_3$) τ −0.32 (broad, 1, NH), 1.70 (s, 1, ArH), 2.57 (s, 1, ArH), 7.12 (s, 3, SCH$_3$), 7.59 (s, 3, CCH$_3$), 7.82 (s, 3, ArCH$_3$).

2,4-Dibromo-5-methylacetanilide (36).—A solution of 2.3 g (7.93 mmol) of 35 and 0.48 ml (8.72 mmol) of bromine in 20 ml of glacial acetic acid was heated to 50–55° under nitrogen and protected from light for 48 hr. After the reaction mixture was worked up as described above, 2.2 g of solid was obtained which was chromatographed on 115 g of silica gel with dichloromethane as eluent and 100-ml fractions. Fractions 10–12 contained 0.5 g (20%) of 36, mp 165–171°. Fractions 47–49 contained 0.95 g (41%) of unreacted starting material. Recrystallization of 36

(21) L. Field, *J. Amer. Chem. Chem. Soc.*, **74**, 394 (1952).

from ether-benzene gave a pure sample, mp 170–171° (lit.[22] mp 168–168.6°). This compound was also fully characterized by its spectral properties. *Anal.* Calcd for $C_9H_9Br_2NO$: C, 35.18; H, 2.93; Br, 52.12. Found: C, 35.18; H, 3.07; Br, 52.61.

Anilide **36** was hydrolyzed to 2,4-dibromo-5-methylaniline, mp 73.5–75° (lit.[22] mp 74.6–75.5°).

**1-(2-Methylthio-5-methyl)phenylthioacetylmorpholide.**— A mixture of 5.0 g (27.8 mmol) of **19**, 1.78 g (55.6 mmol) of sublimed sulfur, and 4.85 g (55.6 mmol) of morpholine (distilled from calcium hydride and stored over potassium hydroxide) was refluxed under nitrogen for 18–20 hr. The hot solution was poured into a total of 15 ml of 95% ethanol and cooled to 5° until crystallization was complete. The crystals were filtered, washed, and air dried to give 6.2 g (80%), mp 95–103°. This crude product was usually hydrolyzed without further purification. An analytical sample was prepared by chromatography on 100 parts of silica gel using 25–50% ether–pentane eluent, followed by crystallization from benzene, mp 107.5–109.5°. *Anal.* Calcd for $C_{14}H_{19}NOS_2$: C, 59.77; H, 6.81; S, 22.79. Found: C, 59.86; H, 6.81; S, 22.54. Nmr (CDCl₃) τ 2.78 (m, 3, ArH), 5.63 (m, 4, OCH₂), 6.4 (m, 6, ArCH₂ and NCH₂), 7.60 (s, 3, SCH₃), 7.70 (s, 3, ArCH₃).

**2-Methylthio-5-methylphenylacetic Acid (22).**—The above morpholide upon basic hydrolysis in ethanolic potassium hydroxide (3 *N*) gave **22** (60%), mp 109–111° (from carbon tetrachloride). Acid hydrolysis in 2:1 concentrated hydrochloric acid–glacial acetic acid gave 22 (55%). *Anal.* Calcd for $C_{10}H_{12}O_2S$: C, 61.21; H, 6.17. Found: C, 61.34; H, 5.95. Nmr (CDCl₃) τ −1.55 (s, 1, OH), 2.83 (m, 3, ArH), 6.20 (s, 2, ArCH₂), 7.62 (s, 3, SCH₃), 7.72 (s, 3, ArCH₃).

**2-Methylsulfinyl-5-methylphenylacetic Acid (23).**—The method of Leonard and Johnson[16] was applied to 8.0 g (40.8 mmol) of **22** to give 5.8 g (67%) of **23**, mp 151–155° (acetone). *Anal.* Calcd for $C_{10}H_{12}O_3S$: C, 56.60; H, 5.70. Found: C, 56.79; H, 5.72. Nmr (CDCl₃) τ −1.50 (s, 1, OH), 2.11 (d, 1, ArH), 2.75 (m, 2, ArH), 6.25 (q, 2, ArCH₂), 7.23 (s, 3, SCH₃), 7.66 (s, 3, ArCH₃).

**4H-1,6-Dimethyl-3-oxo-1,2-thiazanapththalene Oxide (4).**— The method of Whitehead and Bentley[18b] was applied to 3.5 g (16.5 mmol) of **23** to give 2.07 g (60%) of **4**, mp 180–185° dec, from acetone. *Anal.* Calcd for $C_{10}H_{11}NO_2S$: C, 57.42; H, 5.26. Found: C, 57.64; H, 5.32. Nmr (CDCl₃) τ 2.45 (m, 3, ArH), 6.20 (s, 2, ArCH₂), 6.63 (s, 3, SCH₃), 7.53 (s, 3, ArCH₃).

**1,4,4,6-Tetramethyl-3-oxo-1,2-thiazanaphthalene Oxide.**—To a solution of 0.519 g (2.48 mmol) of **4** in 35 ml of dry *tert*-butyl alcohol under nitrogen was added in portions 0.179 g (3.72 mmol) of a 50% dispersion of sodium hydride in mineral oil. After 0.5 hr the reaction mixture was a clear, yellow-orange solution. To this solution was added *via* syringe 0.47 ml (7.55 mmol) of methyl iodide, and the mixture was stirred at 25° for 52 hr protected from moisture. Water was added, the solvent was evaporated *in vacuo*, and the resulting yellow-brown oil was chromatographed on silica gel with ether eluent to give 0.305 g (52%) of solid, mp 181–188.5° dec. Recrystallization of the material from dichloromethane–ether gave a pure sample, mp 186–189° dec. *Anal.* Calcd for $C_{12}H_{15}NO_2S$: C, 60.76; H, 6.33. Found: C, 60.97; H, 6.49. Nmr (CDCl₃) τ 2.45 (m, 3, ArH), 6.63 (s, 3, SCH₃), 7.53 (s, 3, ArCH₃), 8.35 (d, 6, CCH₃).

**2-Methylsulfinyl-5-methylbenzoic Acid (21).**—A solution was made by adding 1.82 ml (33.3 mmol) of bromine in small portions to 6.21 g (111 mmol) of potassium hydroxide in 50 ml of water. To the resulting yellow was added at 0° a solution of 1.0 g (5.55 mmol) of **19** in 50 ml of dry tetrahydrofuran. The reaction was allowed to proceed at 0° for 1 hr and then at 25° for 15 hr, after which the solvent was removed *in vacuo* and the solution was acidified with concentrated hydrochloric acid. A few crystals of sodium sulfite were added to destroy the excess bromine, and the resulting solid was filtered and air dried to give 1.02 g (92.5%) of white powder, which when crystallized from 95% ethanol gave mp 179.5–180° dec. *Anal.* Calcd for $C_9H_{10}O_3S$: C, 54.54; H, 5.09. Found: C, 54.82; H, 5.06. Nmr (D₂O–sodium carbonate with acetone at τ 7.94) τ 2.53 (m, 3, ArH), 7.25 (s, 3, SCH₃), 7.57 (s, 3, ArCH₃).

**1,5-Dimethyl-3-oxobenzo[d]-1,2-isothiazole Oxide (20).**—The method of Whitehead and Bentley[18b] was applied to 0.50 g (2.52 mmol) of **21** to give 0.334 g (68%) of solid, mp 168–174°. Recrystallization of **20** from dichloromethane–ether gave mp 172–173.5°. *Anal.* Calcd for $C_9H_9NO_2S$: C, 55.36; H, 4.66.

Found: C, 55.45; H, 4.65. Nmr (CDCl₃) τ 1.9–2.4 (m, 3, ArH), 6.45 (s, 3, SCH₃), 7.4 (s, 3, ArCH₃).

**1,3,6-Trimethylbenzo[e]-1,2,4-thiadiazene Oxide (5).**—The method of Whitehead and Bentley[18b] was applied to 20 g (0.102 to 20 g (0.102 mol) of **24**, except that the reaction was allowed to proceed for 15 hr. Normal work-up, including extraction of the acidic reaction medium, gave 16.35 g (77%) of crystalline **5**, mp 140–145° (acetone). Recrystallization of **5** from acetone gave mp 143–145°. *Anal.* Calcd for $C_{10}H_{12}N_2OS$: C, 57.68; H, 5.81. Found, C, 57.88; H, 5.97. Nmr (CDCl₃) τ 2.32 (d, 1, ArH), 2.8 (d, 2, ArH), 6.58 (s, 3, SCH₃), 7.6 (d, 6, ArCH₃ and CCH₃).

**2-Methylsulfonimidoyl-5-methylaniline (25).**—A solution of 5.00 g (24.0 mmol) of **5** in 25 ml of 10% sodium hydroxide and 25 ml of water was refluxed for 4 hr. The resulting cloudy solution was diluted with an equal volume of water and extracted to give **25** after crystallization from ether–pentane, 4.24 g (96%) of white solid, mp 85–87.5°. *Anal.* Calcd for $C_8H_{12}N_2OS$: C, 52.17; H, 6.52. Found: C, 52.40; H, 6.65. Nmr (CDCl₃) τ 2.34 (d, 1, ArH), 3.40 (d, 2, ArH), 5.7 (broad, 3, NH), 6.93 (s, 3, SCH₃), 7.72 (s, 3, ArCH₃).

**1,6-Dimethylbenzo[e]-1,2,4-thiadiazene Oxide (26).**—A solution of 1.00 g (5.44 mmol) of **25**, 0.50 g (10.88 mmol) of formic acid, and 0.045 ml of water was heated in an oil bath at 95–100° for 2.5 hr. After cooling to 25°, the acid was neutralized by adding 10% sodium hydroxide solution to pH 7, and the mixture was extracted to give 0.99 g (94%) of solid. Recrystallization of **26** from dichloromethane–ether gave 0.819 g (78%), mp 132–134°. *Anal.* Calcd for $C_9H_{10}N_2OS$: C, 55.67; H, 5.15. Found: C, 55.54; H, 5.24. Nmr (CDCl₃) τ 2–2.9 (m, 4, ArH and CH), 6.50 (s, 3, SCH₃), 7.55 (s, 3, ArCH₃).

**Heterocycle 5 from 25.**—The method of Phillips[23] was applied to 0.208 g (1.13 mmol) of **25**, except that the reaction mixture was refluxed for 24 hr. Neutralization with concentrated ammonia and extraction gave 0.210 g (90%) of solid, mp broad to 137°. Recrystallization of **25** from dichloromethane–ether gave 0.131 g (56%) of **5**, mp 140.5–145°, identical in all spectral characteristics with **5** obtained as described earlier.

**1,6-Dimethyl-3-carbomethoxybenzo[e]-1,2,4-thiadiazene Oxide (27).**—A mixture of 0.50 g (2.72 mmol) of **25** and 2.0 g (17 mmol) of dimethyl oxalate was heated under a slow nitrogen stream at 165–170° for 4 hr. The excess dimethyl oxalate was sublimed at aspirator pressure and the residue was crystallized from methanol to give 0.458 g (67%) of white solid, mp 205–215°. Sublimation of **27** followed by crystallization from methanol gave mp 212.5–214.5°. *Anal.* Calcd for $C_{11}H_{12}N_2O_3S$: C, 52.36; H, 4.80. Found: C, 52.64; H, 4.96. Nmr (CDCl₃) τ 2.2–2.9 (m, 3, ArH), 6.05 (s, 3, OCH₃), 6.43 (s, 3, SCH₃), 7.55 (s, 3, ArCH₃).

**1,6-Dimethyl-3-carboxybenzo[e]-1,2,4-thiadiazene Oxide (28).** —A solution of 0.157 g (0.624 mmol) of **27** in 30 ml of 2 *N* hydrochloric was stirred at 25° for 3.5 hr. Solid potassium hydroxide was added until the pH reached 3–4. The solvent was removed *in vacuo*, and the white solid residue was extracted in a Soxhlet apparatus with chloroform for 24 hr. Removal of solvent and trituration of the residual oil with dichloromethane gave a white solid which was recrystallized from methanol–ether to give 8 mg (5%) crystals, mp 163.5–165° dec. *Anal.* Calcd for $C_{10}H_{10}N_2O_3S \cdot H_2O$: C, 46.88; H, 4.72. Found: C, 46.70; H, 4.90. Ir (KBr) 3300–2800 (broad, NH⁺), 1590 (CO₂⁻), 1230 cm⁻¹ (O=S=N).

**2-(Methyl-*N*-carboethoxysulfonimidoyl)-5-methylaniline.**—A solution of 0.502 g (2.73 mmol) of **25** and 0.553 g (5.46 mmol) of triethylamine in dry ether was stirred at 25° under nitrogen. Through an addition funnel a solution of ethyl chloroformate (0.296 g, 2.73 mmol) in dry ether was added dropwise. After the addition was complete, the reaction mixture was stirred for 1.5 hr, during which time a white precipitate formed. The reaction was quenched with water, the ether layer was washed with dilute acid, and the organic solution was dried. Evaporation of solvent gave 0.4 g (57%) of an oil which was pure product by tlc, ir, and nmr. The oil was passed through a short column of silica gel with ether eluent, and dried *in vacuo*. *Anal.* Calcd for $C_{11}H_{16}O_3N_2S$: C, 51.56; H, 6.25. Found: C, 51.45; H, 6.43. Nmr (CDCl₃) τ 2.4 (d, 1, ArH), 3.35 (m, 2, ArH), 5.05 (broad, 2, NH₂), 5.90 (q, 2, *J* = 7 Hz, CH₂CH₃), 6.73 (s, 3, SCH₃), 7.75 (s, 3, ArCH₃), 8.78 (t, 3, *J* = 7 Hz, CH₂CH₃).

**2-[Methyl-*N*-(1-imidazolylcarbonyl)sulfonimidoyl]-5-methylaniline.**—To a solution of 0.5058 g (2.75 mmol) of **25** in 15 ml

(22) R. H. C. Neville and A. Winther, *Chem. Ber.*, **13**, 962 (1880).

(23) M. A. Phillips, *J. Chem. Soc.*, 2393 (1928).

of dry tetrahydrofuran under nitrogen was added a solution of 0.535 g (3.3 mmol) of 1,1'-carbonyldiimidazole in 25 ml of dry tetrahydrofuran, and the resulting clear solution was stirred at 25° for 52 hr protected from moisture. Then 0.48 g (2.96 mmol) of diimidazole reagent was added and the reaction mixture was stirred for another 16 hr at 25°. The solvent was evaporated to give an oil which crystallized, recrystallization of which several times from dichloromethane–ether gave 0.5916 g (77%) of product, mp 159–163°. *Anal.* Calcd for $C_{12}H_{14}N_4O_2S$: C, 51.77; H, 5.08. Found: C, 51.92; H, 5.13. Nmr (CDCl$_3$) $\tau$ 1.6–3.4 (m, 6, ArH and ImH), 4.8 (broad s, 2, NH$_2$), 6.47 (s, 3, SCH$_3$), 7.67 (s, 3, ArCH$_3$).

**1,6-Dimethyl-3-oxobenzo[e]-4H-1,2,4-thiadiazene Oxide (6).**— A solution of 0.21 g (0.756 mmol) of the above imidazole derivative in 15 ml of p-dichlorobenzene was heated at 160–175° for 24 hr. The solvent was removed *in vacuo*, and the residue was dissolved in 100 ml of water and cooled. The resulting mixture was filtered, reduced to 30 ml, and cooled further to give 0.13 g (82%) of 6, mp 295–300° dec. *Anal.* Calcd for $C_9H_{10}N_2O_2S$: C, 51.40; H, 4.80. Found: C, 51.66; H, 4.97. Ir (Nujol) 1650 (C=O), 1220 (O=S=N).

A sample of 2-(methyl-$N$-carboethoxysulfonimidoyl)-5-methylaniline (0.20 g, 0.782 mmol) was heated neat at 170–180° for 24 hr to give a solid residue which, when recrystallized from water, gave about 10 mg (6%) of 6, mp 295–300° dec.

**2-Methylsulfinyl-5-methylphenyl Azide (29).**—To a solution of 0.30 g (1.63 mmol) of 25 in 5 ml of 2 N hydrochloric acid was added a 0.2 M solution of sodium nitrite (less than 2 equiv) until an excess of nitrous acid was present. The resulting yellow solution was stirred at 25° for 0.5 hr and then extracted to give an oil which solidified into 0.31 g (97%) of a yellow solid. Recrystallization of this solid from ether–pentane gave 0.17 g (53%) of 29, mp 59–63°. *Anal.* Calcd for $C_8H_9N_3OS$: C, 49.20; H, 4.66. Found: C, 49.40; H, 4.47. Nmr (CDCl$_3$) $\tau$ 2.1–3.1 (m, 3, ArH), 7.25 (s, 3, SCH$_3$), 7.58 (s, 3, ArCH$_3$).

# Thermal Reactions of Alkyl N-Carbomethoxysulfamate Esters

EDWARD M. BURGESS,* HAROLD R. PENTON, JR., AND E. A. TAYLOR

*School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia  30332*

(Carboxysulfamoyl)triethylammonium hydroxide, inner salt, methyl ester was synthesized and shown to react with a broad spectrum of alcohols resulting in alkyl N-carbomethoxysulfamate esters. The scope and synthetic usefulness of the sulfamate ester function as a leaving group in thermolytic dehydration reactions was demonstrated by the facile conversion of tertiary and secondary alcohols to olefins and primary alcohols to urethanes. Stereochemically the reaction was established as a cis-stereospecific elimination by the formation of only protio-*trans*-stilbene from *threo*-2-deuterio-1,2-diphenylethyl-N-carbomethoxysulfamate triethylammonium salt and only α-deuterio-*trans*-stilbene from the corresponding erythro compound. The first-order rate constants for the diphenylethanol system were determined spectrophotometrically ($k_{35}° = 2.66 \times 10^{-6}$) and a small β-deuterium isotope effect was observed ($k_H/k_D = 1.05$ for erythro and 1.08 for threo compound). Activation parameters were calculated for the thermolysis with values $E_a = 22.4$ kcal/mol, $\Delta H^{\pm} = 21.7$ kcal/mol, $\Delta G^{\pm} = 22.8$ kcal/mol, $\Delta S^{\pm} = -3.3$ eu. These kinetic and stereochemical results are consistent with an initial rate-limiting formation of an ion pair followed by a fast cis β proton transfer to the departing anion at a rate greater than the interconversion of erythro- and threo ion pairs.

The dehydration of alcohols *via* a first-order thermolytic Ei decomposition of a derived ester has been a valuable method in the portfolio of practiced synthetic organic reactions. When compared to solvolytic elimination, the cis-β hydrogen geometrical constraint and the absence of α-carbon carbonium ion character (and thus skeletal rearrangements) in the transition state of such eliminations provide a predictable and therefore strategically useful step in a directed synthetic sequence. A variant of the Ei mechanism timing exists in which ionization of the α carbon attached group results in an ion pair whose collapse involves transfer of the β hydrogen from the cation to anion. This mechanism is especially important in cases of elimination with good leaving groups in nonpolar media. Such an ion-pair mechanism may show the kinetic order and stereospecificity of an Ei scheme but in many cases carbonium ion rearrangements are observed.

In order to minimize such rearrangements but preserve the stereospecificity of a solution (for operational convenience) Ei reaction in a synthetic step, the react-ing system should be of such a design as to reduce the degree of ion-pairing character. To meet this requirement the departing anionic group should have a good incipient proton nucleophilicity in solvents of low polarity. Furthermore, if the developing anion has multiple proton acceptor sites the $\Delta G^{\pm}$ will be decreased owing to an increased positive entropy contribution. Finally, the formation of the requisite alcohol derivative should be facile even in the presence of severe steric factors.[1] With such criteria in mind we have examined the thermolytic behavior of alkyl N-carbomethoxysulfamate salts, 1, as intermediates in a potential synthetic method for the conversion of alcohols to alkenes.

The triethylammonium N-carbomethoxysulfamates (1) employed in this study were generated by the interaction of methyl(carboxysulfamoyl)triethylammonium hydroxide inner salt (2) with the candidate alcohols

(1) For example, mesylates of alcohols are more readily formed than tosylates, since the former result from an addition to a reactive sulfene generated from the dehydrohalogenation of the precursor methanesulfonyl chloride.
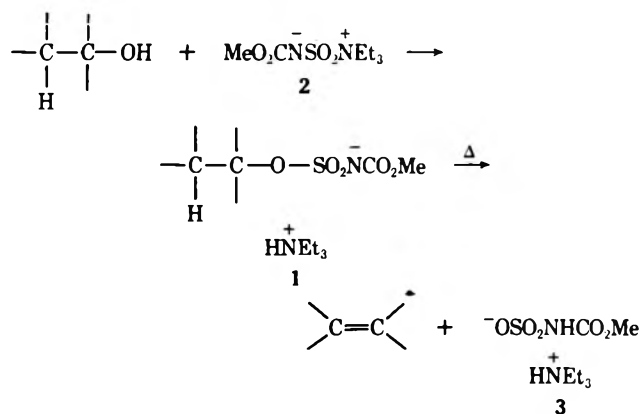
neat or in hydrocarbon solvent at 30° or below. The above inner salt was prepared as previously reported[2] from carbomethoxysulfamoyl chloride and triethylamine. The triethylammonium gegenion of these sulfamate esters was readily exchanged for either a sodium cation or a proton. If a dry tetrahydrofuran solution of an alkyl N-carbomethoxysulfamate triethylammonium salt was treated with 1 equiv of sodium hydride and the solvent and liberated triethylamine were evaporated, an infusible sulfamate ester sodium salt was obtained. The free base resulted from rapid washing of a benzene solution of the triethylammonium salt with a cold 2% aqueous hydrochloric acid solution. In the case of tert-alkyl sulfamate esters the salts were sufficiently labile at room temperature as to preclude isolation. However, all the sec- and tert-alkyl derivatives studied smoothly decomposed at temperatures between 30 and 80° in a variety of solvents to provide reasonable yields of isolated alkenes and the water-soluble salt 3.

In order to delineate the mechanistic details of the elimination reaction the observed exclusive conversion of 1,2-diphenylethyl-N-carbomethoxysulfamate triethylammonium salt to trans-stilbene was chosen as a model system for further study. When the correspond-



ing erythro- and threo-2-deuterio-1,2-diphenylethyl-N-carbomethoxysulfamates[3] were allowed to decompose in benzene solution at 50° the former provided α-deuterio-trans-stilbene (7) which contained a minimum of 0.97 deuterium atoms per molecule as demonstrated by mass spectral analysis, while the latter gave only protio-trans-stilbene (8). These stereochemical results were unchanged by substituting for benzene the more basic solvent, dimethylformamide, and indicate that a cis elimination is operative over a wide range of solvent basicities.[4]
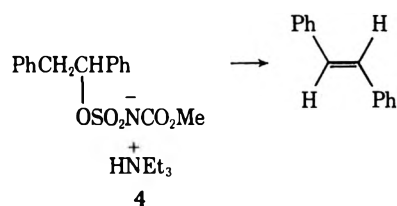
(2) G. M. Atkins, Jr., and E. M. Burgess, J. Amer. Chem. Soc., 90, 4744 (1968).

(3) The precursor deuterated alcohols were derived by reduction from the appropriate stilbene oxides: D. Y. Curtin and D. B. Kellom, ibid., 75, 6011 (1953).

(4) The competition for proton removal between basic solvents and gegenion and the result on E1 stereochemistry has been reported: P. S. Skell and W. L. Hall, ibid., 85, 2851 (1963).
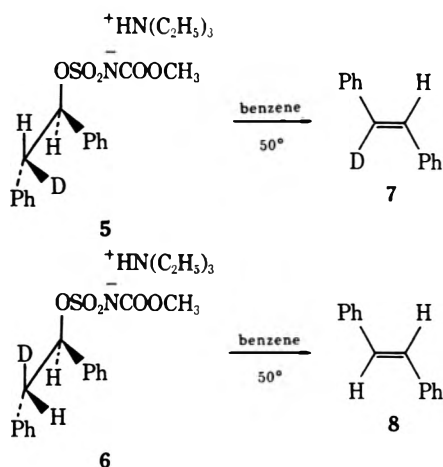
A kinetic study of the elimination reaction of 4, 5, and 6 in 95% aqueous ethanol was performed by following product development spectrophotometrically at 295 nm (see Table I).

TABLE I

THERMOLYSES OF 4, 5, AND 6 IN 95% AQUEOUS ETHANOL[a]

| Compd | Temp, °C | Concn × 10², mol/l. | $k \times 10^6$, sec$^{-1}$ |
|---|---|---|---|
| 4 | 52 | 4.00 | 16.9 |
| | | 3.00 | 15.5 |
| | | 2.00 | 16.4 |
| | 46 | 4.00 | 9.13 |
| | | 3.00 | 9.05 |
| | | 2.00 | 9.20 |
| | 35 | 4.00 | 2.65 |
| | | 3.00 | 2.63 |
| | | 2.00 | 2.71 |
| 5 | 35 | 4.00 | 2.57 |
| | | 2.00 | 2.51 |
| 6 | 35 | 4.00 | 2.43 |
| | | 2.00 | 2.49 |

[a] First-order kinetics were displayed up to 60% reaction with a rate constant at 35° of 2.66 ± 0.03 × 10⁻⁶ sec⁻¹ for 4 and activation parameters of $E_a$, +22.4 ± 0.5 kcal/mol; $\Delta H^{\ddagger}$, +21.7 ± kcal/mol; $\Delta G^{\ddagger}$, +22.8 ± 0.5 kcal/mol; and $\Delta S^{\ddagger}$, −3.3 eu. The β-deuterium isotope effect determined from this data had $k_H/k_D = 1.05 \pm 0.02$ and 1.08 ± 0.03 at 35° for the erythro and threo isomers, respectively.

The product analysis, the first-order kinetics, the activation parameters, and the isotope effect data are consistent with a mechanism with an initial rate-limiting formation of an ion pair followed by a fast cis-β-proton transfer to the departing anion at a rate greater than the interconversion of the erythro- and threo-derived ion pairs (9a, 9b). The departing anion must compete effectively with the solvent as a base in dimethylformamide to further account for the stereochemical result. Whether the proton is transferred to nitrogen or oxygen of this anion is unclear, but from a statistical and thermodynamic (based on bond energies) viewpoint, the transition state forming an O–H bond is energetically more favorable. Although the thermolysis of 4 does not represent the mechanism for all the examples investigated, it does provide a basis upon which the other results may be rationalized.

The Saytzeff rule would be expected to be operative in such an ion-pair elimination and this thesis is borne out by the observed conversion of 2-methyl-2-butanol

**9**

**a, R₁ = H; R₂ = D**
**b, R₁ = D; R₂ = H**
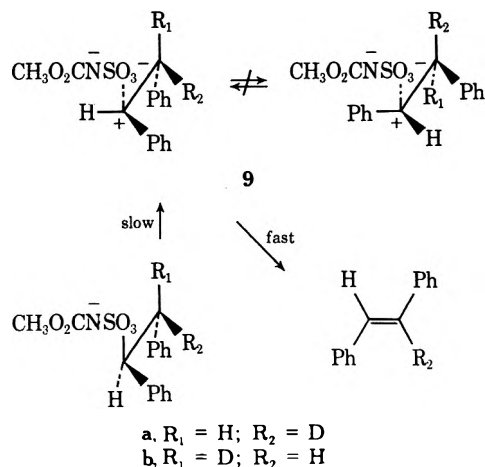
(10) to 2-methyl-2-butene (11) and 2-methyl-1-butene
(12) in a ratio of 2.4:1.[5,6]  In addition, such an ion-



**10**    **11**    **12**
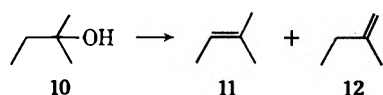
pairing mechanism would predict that, in favorable
cases, skeletal rearrangement would occur in the car-
bonium ion component.  In order to assess the scope of
this possibility we have examined the alkene product
distribution from a selected number of alcohols.

3-*tert*-Butyl-2,2,4-trimethyl-3-pentanol (13) was pre-
pared by treating ethyl isobutyrate with 2 equiv of
*tert*-butyllithium in pentane at −78° and the structure
was verified by its infrared, nmr, and mass spectral
display.  Upon treatment with 2 in acetonitrile solution
at 50°, 13 gave only 3-*tert*-butyl-2,3,4-trimethyl-1-
pentene (14) identified through the following data.



**13**    **14**
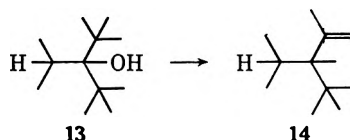
The ir spectrum had absorption at 1645 cm⁻¹ (C=CH₂)
and nmr signals (60 MHz, CDCl₃) appeared at δ 4.90–
4.82 (m, 2 H), 1.03 (d, $J$ = 7 Hz, 6 H), 1.92 (q, $J$ = 7
Hz, 1 H), 1.80 (d, $J$ = 2 Hz, 3 H), 0.97 (s, 3 H), 0.92 (s,
9 H).  Although here the mechanistic sequence re-
quires (as is often observed) conversion of one *tert*-
neopentyl cation to another by methyl rather than hy-
dried migration (to give 3-*tert*-butyl-2,4,4-trimethyl-1-
pentene) the cis-β proton conformation required for
elimination without rearrangement would not be energe-
tically accessible owing to eclipsing of the methyl and
*tert*-butyl groups.[7]  The dehydration of 3,3-dimethyl-2-
butanol (15) *via* the sulfamate ester sodium salt in
benzene solution at 70° afforded the Wagner–Meerwein
rearranged alkenes 16 and 17 as well as 18 in a ratio of



**15**    **18**    **16**    **17**
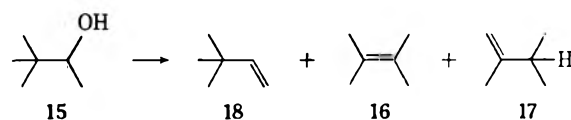
3:1.5:1.  The absence or presence of solvents with
diverse dielectric constants produced no significant
variation on this product distribution (Table II).  The

TABLE II

THERMOLYSES OF 3,3-DIMETHYL-2-BUTYL
*N*-CARBOMETHOXYSULFAMATE SODIUM SALT

| Temp, °C | Solvent | Products ratio[a] | | |
|---|---|---|---|---|
| | | **18** | **16** | **17** |
| 60 | Triglyme | 1 | 3 | 1.2 |
| 70 | Benzene | 1 | 3 | 1.5 |
| 100 | Neat | 1 | 4 | 1.2 |

[a] Determined by gas chromatography.

amount of unrearranged alkene produced is surprising,
since the competition between Wagner–Meerwein re-
arrangement and β-proton removal usually lies com-
pletely in the direction of the former.

An acetonitrile solution of 2-*endo*-methylbicyclo-
[2.2.1]heptan-2-ol (19), when treated with 2 at 50°,
afforded an 80% yield of the cycloalkenes, 2-methyl-
tricyclo[2.2.1]heptene (20) and 2-methylbicyclo[2.2.1]-
hept-2-ene (21) in a ratio of 1:1.[8]  As expected, no



**19**    **21**    **20**
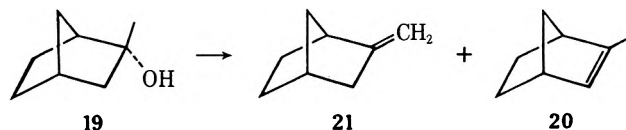
rearrangement products were found; however, in this
case from consideration of the cis stereochemical con-
straint and Saytzeff correlation observed in aliphatic
cases (see 10 → 11 + 12) the unexpected greater rate of
formation of 21 relative to 20 may be due to the rela-
tively increased strain energy content of the latter.  In
addition, the steric effect of the endo C-5 hydrogen
would interfere with formation of the ion-pair geometry
necessary for subsequent endo C-3 hydrogen removal.[9]

When neat 2-cyclopropyl-2-propanol (22) was treated
with 2 an exothermic reaction ensued from which a
moderate yield of 2-cyclopropylpropene[5,10] (23) was



**22**    **23**
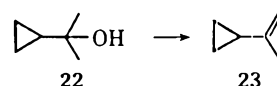
isolated.  No evidence for the formation of 2-cyclo-
propylidene propane was found and this observation is
consistent with the proposed[11] "bisected" geometry for
the cyclopropylcarbinyl cationic component of the ion
pair in which the β-cyclopropyl hydrogen would be
orthogonal to the departing group and thus sterically
unavailable for elimination.

In order to study a further example in a similar
system, 3,4-epoxy-2-methyl-2-butanol (24) was sub-
jected to the action of 2 at 55°.  Only 3,4-epoxy-2-

(5) Determined by gas chromatography and nmr spectral comparison
with authentic samples.

(6) This ratio is smaller than that obtained from a solvolytic elimination
of the corresponding halides:  H. C. Brown and M. Makagawa, *J. Amer.
Chem. Soc.*, **77**, 3610 (1955).

(7) It has been reported that upon melting di-*tert*-butylneopentylcarbinyl
*p*-nitrobenzoate gives tri-*tert*-butylethylene as well as a rearranged terminal
alkene similar to 14.  Ion pairing was invoked as a mechanistic rationaliza-
tion to account for these products:  G. J. Abruscato and T. T. Tidwell,
*J. Amer. Chem. Soc.*, **92**, 4125 (1970);  P. D. Bartlett and T. T. Tidwell,
*ibid.*, **90**, 4421 (1968).

(8) The nmr spectra observed are identical with those reported for **20** and
**21**:  R. A. Finnegan and R. S. McNeese, *J. Org. Chem.*, **29**, 3234 (1964);
H. Krieger, *Suom. Kemistilehti B*, **38**, 260 (1965).

(9) This effect is pronounced in the E2 syn *vs.* anti elimination mode ob-
served in *endo*- and *exo*-bicyclo[2.2.1]heptyl chlorides:  J. Sicker, *Angew.
Chem., Int. Ed. Engl.*, **11**, 200 (1972).

(10) V. A. Slabey, *et al., ibid.*, **71**, 1518 (1949).

(11) C. V. Pittman and G. A. Olah, *ibid.*, **87**, 2998 (1965).

methyl-1-butene (25) was isolated and identified by characteristic nmr (60 MHz, CDCl₃) signals at δ 5.17 (m, 1 H, $J = 1$ Hz), 3.35 (m, 1 H, $J = 3$ Hz), 2.75 (m, 2 H, $J = 3$ Hz), 1.63 (d, 3 H, $J = 2$ Hz), and an exact mass determination. This reaction contrasts sharply with the solvolysis of the corresponding tosylate, which provides a 3-oxetanol tosylate *via* internal return to the 1-oxabicyclobutonium cation (26).[12] If such a cation is one component of the ion-pair intermediate in the conversion of 24 to 25 it must undergo



24          25          26
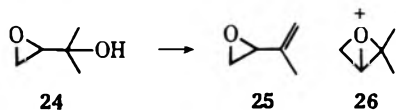
rapid proton transfer to the anion from the methyl-substituted face before any geometrical realignment of the ion-pair components occurs.

In another example, either the sodium or triethylammonium salt of the N-carbomethoxysulfamate derivative of 4-hexen-3-ol (27) underwent elimination in triglyme solution at 75° to afford only 2,4-hexadiene (28).[5] However, if the sodium salt was decomposed as a solid at 80° and the reaction mixture was treated with water, the rearranged urethane, methyl-N-(2-hex-3-enyl)carbamate (29), was isolated in high yield. The



27          28          29
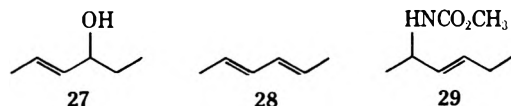
structure of 29 was established by the observed nmr (60 MHz, CDCl₃) signals at δ 5.55 (m, 2 H), 4.10 (s, 1 H), 3.60 (s, 3 H), 2.00 (m, 1 H), 1.65 (m, 2 H), 1.05 (m, 6 H), and ir (CHCl₃) absorption at 3440 (NH), 1720 (C=O), and 1675 cm⁻¹ (C=C). The latter reaction course may be a result of a solid-state configuration favorably disposed for an Sɴɪ′ rearrangement in which negligible charge separation requiring solvent stabilization develops.

With primary alkyl N-carbomethoxysulfamate salts a Sɴ2 pathway becomes energetically more favorable as compared to the Ei counterpart and urethanes result from thermolyses of these salts. For example, when 1-hexanol is treated directly with 2 and after the initial exothermic formation of 30 is complete the reaction mixture is heated to 95°, a 75% yield of methyl N-hexylcarbamate[5] (31) is obtained after treatment with water.

Benzyl alcohol (32) was likewise converted to N-benzylcarbamate[5] (33) in 80% yield.



30          31



32          33
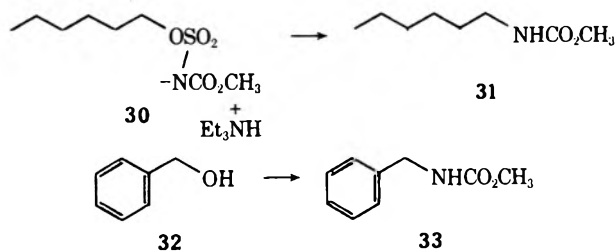
In a contrasting reaction, the neat free base derived from 30 upon thermolysis at 150° provides a 1:1 mixture of 1- and 2-hexenes[5] in what is probably an autocatalyzed elimination resulting from the presence

(12) H. G. Richey, Jr., and D. V. Kinsman, *Tetrahedron Lett.*, 2505 (1969).

of the acidic carbomethoxylsulfamoyl proton, which also promotes the observed isomerization of the initially produced terminal alkene.

When a primary sulfamate ester is examined in which severe steric restrictions to a bimolecular displacement reaction are operative, only an Ei pathway is important at the higher temperature required for decomposition. To exemplify, the sodium salt of the carbomethoxysulfamate ester of 2,2-dimethyl-1-propanol (34) when decomposed as a solid at 110° affords only 2-methyl-2-butene (35).[5] The conversion of primary alcohols to



34          35
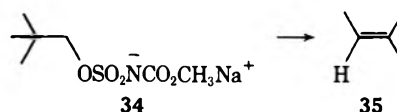
urethanes *via* the sulfamate ester salts is complementary to the reported[13] Sɴi reaction of N,N-dimethylsulfamate esters of allylic and benzylic alcohols to give dimethyl derivatives of amines, and both provide an important synthetic alternative to the more usual methods of alcohol to amine transformation. In a further synthetic application the treatment of *syn*-benzaldehyde oxime with 2 at 100° with subsequent hydrolysis provided the Beckmann rearrangement product, formanilide, in modest yield.

It was of interest to determine how other groups might compare in potential Ei reactivity to salts of N-carbomethoxysulfamate esters, and to this end a number of derivatives of cyclohexanol were prepared by addition of this alcohol to the appropriate heterocumulene followed by treatment with sodium hydride. Thermolysis of 36, 37, 38, and 39 between 100 and
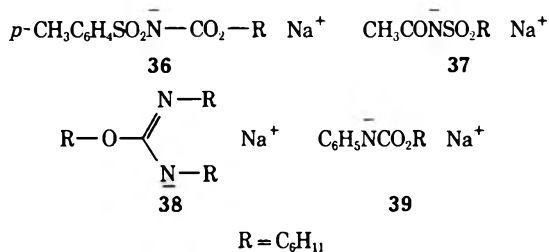


150° provided no evidence for the formation of cyclohexene, although the free base derived from 36 in *tertiary* systems has been reported[14] on pyrolysis to be a basis for a general alkene synthesis.

## Experimental Section[15]

**(Carboxysulfamoyl)triethylammonium Hydroxide Inner Salt Methyl Ester (2).**—Anhydrous methanol (18.80 g, 0.550 mol) in

(13) E. H. White and C. A. Elliger, *J. Amer. Chem. Soc.*, **87**, 5261 (1965).

(14) L. C. Roach and W. H. Daly, *J. Chem. Soc. D*, 606 (1970).

(15) Melting points are uncorrected and the microanalyses were performed by Huffman Laboratories, Wheatridge, Colo. Infrared spectra were obtained using a Perkin-Elmer Model 457 spectrometer fitted with sodium chloride optics. The nmr spectra were determined with a Varian A-60 spectrometer (TMS internal standard) and mass spectra were measured on a Varian M-66 spectrometer. Ultraviolet spectra were obtained from a Cary Model 14 recording spectrophotometer using 1-cm quartz cells and 95% aqueous ethanol solvent. Gas-liquid phase chromatography for collection of analytical samples was performed using an F & M Model 700 dual-column gas chromatograph fitted with a silicon rubber column (4 ft) with helium as the carrier gas. General analytical data were obtained using a Hewlett-Packard Model 402 dual column gas chromatograph fitted with a UCON polar column (4 ft) using nitrogen as the carrier gas. The apparatus used in the thermolyses consisted of a U-shaped glass tube with standard taper glass joints at each end. At the end to be inserted into the reaction vessel was a gas inlet tube which admitted a flow of nitrogen and the other end of the U-tube was fitted to a Dry Ice cooled trap.

25 ml of benzene was added dropwise to a solution of chlorosulfonyl isocyanate (65.72 g, 0.500 mol) in 200 ml of benzene in a 500-ml flask fitted with a 50-ml addition funnel. The mildly exothermic reaction was controlled with a cool water bath. After the addition was complete (30 min), the solvent and excess methanol were removed from the reaction mixture under reduced pressure. The resulting white, crystalline mass was crystallized once from toluene to give colorless needles (61.00 g, 91.9%) of carbomethoxysulfamoyl chloride, mp 70–71°.

*Anal.* Calcd for $C_2H_4ClNO_4S$: C, 13.88; H, 2.33; N, 8.10; S, 18.49. Found: C, 13.76; H, 2.53; N, 8.13; S, 18.72.

Carbomethoxysulfamoyl chloride (3.47 g, 0.020 mol) dissolved in 50 ml of benzene was added dropwise to a solution of triethylamine (4.60 g, 0.045 mol) in 25 ml of benzene in a 250-ml three-neck round-bottom flask fitted with a 125-ml addition funnel under a nitrogen atomsphere at ambient temperature. After the addition was complete (1 hr), the precipitate of triethylamine hydrochloride (0.56 g, 96%) was removed by filtration, and the solvent was evaporated under reduced pressure to afford a residual colorless oil which solidified on standing. Crystallization from toluene yielded colorless needles (3.87 g, 81%) of (carboxysulfamoyl)triethylammonium hydroxide inner salt methyl ester (2): mp 71–72°; nmr (CDCl₃) δ 3.66 (s, 3 H), 3.29 (q, 6 H, $J$ = 7 Hz), and 1.15 (t, 9 H, $J$ = 7 Hz).

*Anal.* Calcd for $C_8H_{18}N_2O_4S$: C, 40.32; H, 7.62; N, 11.72; S, 13.43. Found: C, 40.04; H, 7.54; N, 11.51, S, 13.36.

**Dehydration of 1,2-Diphenylethanol.**—1,2-Diphenylethanol (3.96 g, 0.020 mol) in 15 ml of benzene was added dropwise to a solution of 2 (5.00 g, 0.021 mol) in 20 ml of benzene in a 50-ml round-bottom flask fitted with a reflux condenser at ambient temperature under an atomsphere of dry nitrogen. After the addition was complete (30 min), the temperature was raised to 50° and mintained for 30 min. Water (10 ml) was added and the benzene layer was separated, dried over anhydrous sodium sulfate, and evaporated to yield a white, crystalline solid. Crystallization from ethanol gave colorless plates (3.42 g, 95%) of *trans*-stilbene, mp 124° undepressed upon admixture with an authentic sample. In another example, the reaction was repeated in exact proportions using $N,N$-dimethylformamide as the solvent. After the temperature was maintained at 50° for 30 min, water (10 ml) was added and the reaction mixture was extracted three times with 10-ml portions of ether. The ether extracts were combined, washed three times with 25-ml portions of water, dried overy anhydrous sodium sulfate, and evaporated to afford a white, crystalline solid. Crystallization from ethanol gave 3.45 g (96%) of pure *trans*-stilbene.

**Dehydration of *erythro*-2-Deuterio-1,2-diphenylethanol.**—The above procedure was carried out using *erythro*-2-deuterio-1,2-diphenylethanol[3] (3.36 g, 0.016 mol) in 10 ml of benzene and 2 (4.30 g, 0.018 mol) in 20 ml of benzene. Recrystallization from ethanol gave colorless plates (2.89 g, 94%) of α-deuterio-*trans*-stilbene (7): mp 124° (lit.[16] mp 124°); nmr (CDCl₃) δ 7.34 (m, 10 H), 6.99 (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 182 (14), 181 (97), 180 (100). For comparison *trans*-stilbene had mass spectrum (70 eV) *m/e* (rel intensity) 181 (14), 180 (100). For 7 the minimum deuterium atom/molecule is 0.97.

In another example, the reaction was repeated in exact proportions using $N,N$-dimethylformamide as the solvent. Using the same work-up as for diphenylethanol in $N,N$-dimethylformamide, 2.91 g (95%) of 7 was obtained with an identical mass spectrum.

**Dehydration of *threo*-2-Deuterio-1,2-diphenylethanol.**—The above procedure was carried out using the threo isomer[3] (3.36 g, 0.017 mol) in 10 ml of benzene and 2 (4.30 g, 0.018 mol) in 20 ml of benzene. Recrystallization from ethanol gave 2.83 g (92%) of *trans*-stilbene containing no deuterium by mass spectroscopy.

In another example, the reaction was carried out in exact proportions using $N,N$-dimethylformamide as the solvent. Again, using the same work-up as for diphenylethanol in this solvent, 2.86 g (93%) of *trans*-stilbene containing no deuterium by mass spectroscopy was isolated.

**Dehydration of 2-Methylbutan-2-ol (10).**—2-Methylbutan-2-ol (2.30 g, 0.025 mol) was added neat to 2 (7.50 g, 0.032 mol) at ambient temperature in a 50-ml round-bottom flask connected to a cold trap by a glass U-tube. Within 5 min of the addition an exothermic reaction developed, the reaction mixture became homogeneous, and a clear, colorless liquid distilled into the cold trap. The reaction mixture was flushed with a stream of dry nitrogen for 1 hr, after which the collected distillate was analyzed

by gas chromatography anc nmr spectral comparison. The alkenes (2.00 g, 95%) were shown to consist of 2-methyl-2-butene (70%) (11) and 2-methyl-1-butene (30%) (12) by comparison with an authentic mixture.

**Dehydration of 3-*tert*-Butyl-2,2,4-trimethylpentan-3-ol (13).**—A solution of 1.7 *M tert*-butyllithium (122 ml, 10.01 g, 0.16 mol) in pentane in a 500-ml three-neck round-bottom flask fitted with a 125-ml addition funnel under a nitrogen atmosphere was cooled to −78° with a Dry Ice and acetone bath. Ethyl 2-methylpropanoate (8.13 g, 0.07 mol) in 50 ml of diethyl ether was added dropwise and the reaction mixture was allowed to stir for 1 hr at −78°. After the reaction was allowed to warm to room temperature, the excess *tert*-butyllithium was destroyed by the slow addition of water. The reaction was neutralized with 30% aqueous hydrochloric acid and extracted three times with 25-ml portions of ether. The ether layer was separated, dried over anhydrous sodium sulfate, and evaporated to yield a colorless oil which crystallized on standing. Crystallization from benzene-hexane gave colorless needles (12.37 g, 95%) of 3-*tert*-butyl-2,2,4-trimethylpentan-3-ol (13): mp 24–25°; ir (CHCl₃) 3620 (OH), 2950, 2920, and 2880 cm⁻¹, no C=O band; nmr (CDCl₃) δ 3.58 (s, 1 H), 1.92 (m, 1 H, $J$ = 7 Hz), 1.02 (d, 6 H, $J$ = 7 Hz), 0.092 (s, 18 H); exact mass determination—theoretical 186.340, found 186.342.

3-*tert*-Butyl-2,2,4-trimethylpentan-3-ol (13) (3.00 g, 0.016 mol) in 10 ml of acetonitrile was added dropwise to a solution of 2 (4.75 g, 0.020 mol) in 25 ml of acetonitrile in a 50-ml round-bottom flask fitted with a reflux condenser. The temperature was raised to 50° and maintained for 1 hr, after which the reaction was cooled, treated with water, and extracted three times with 10-ml portions of ether. The ether layer was separated, dried over anhydrous sodium sulfate, and evaporated to afford a colorless liquid (1.88 g, 70%) which was shown by glc to be homogeneous and identified as 3-*tert*-butyl-2,3,4-trimethylpent-1-ene (14): nmr (CDCl₃) δ 4.90 (m, 1 H), 4.82 (m, 1 H), 1.82 (m, 1 H, $J$ = 7 Hz), 1.80 (d, 3 H, $J$ = 2 Hz), 1.03 (d, 6 H, $J$ = 7 Hz), 0.97 (s, 3 H), 0.92 (s, 9 H); mass spectrum (70 eV) *m/e* (rel intensity) 168 (1.0), 112 (100), 97 (95), 69 (90), 57 (85), 43 (65), 41 (83).

*Anal.* Calcd for $C_{12}H_{24}$: C, 85.71; H, 14.29. Found: C, 85.60; H, 14.21.

**Dehydration of 3,3-Dimethylbutan-2-ol (15).**—3,3-Dimethylbutan-2-ol (3.00 g, 0.029 mol) in 5 ml of triglyme was added dropwise to a solution of 2 (7.50 g, 0.032 mol) in 25 ml of triglyme in 50-ml round-bottom flask connected to the thermolysis apparatus at ambient temperature under a stream of dry nitrogen. The reaction mixture was treated with sodium hydride (0.77 g, 0.032 mol) (prepared from 1.35 g of sodium hydride–mineral oil dispersion by several washings with dry hexane) and maintained at ambient temperature until hydrogen evolution ceased. The temperature was raised to 6C° and a clear, colorless liquid distilled into the cold trap. Glc and nmr analysis of the distillate showed the presence of three components which were identified as 3,3-dimethylbut-1-ene (18) (18%), 2,3-dimethylbut-2-ene (16) (55%), and 2,3-dimethylbut-1-ene (17) (27%) by comparison with authentic samples. The total yield of olefinic products was 2.28 g (85%).

In another example the reaction as described above was run using benzene as a solvent. The distillate had the same components in slightly different proportion: 18 (19%), 16 (58%), and 17 (23%). The total yield of olefinic products was 2.25 g (84%).

In yet another example, tetrahydrofuran was used as the solvent. After hydrogen evolution had ceased, solvent was removed *in vacuo* to yield a white solid which when heated to 100° to yield a clear, colorless distillate with the composition 18 (16%), 16 (65%), and 17 (20%). The total yield of olefinic products was 2.30 g (86%).

**Dehydration of *endo*-2-Methylbicyclo[2.2.1]heptan-2-ol (19).**—Methyl iodide (11.36 g, 0.08 mol) dissolved in 25 ml of anhydrous diethyl ether was added dropwise to a mechanically stirred suspension of magnesium turnings (1.82 g, 0.075 mol) in 25 ml of diethyl ether. The resulting solution was treated dropwise with norcamphor (5.50 g, 0.05 mol) dissolved in 25 ml of diethyl ether. After this addition was complete (15 min), the reaction mixture was allowed to stir for 1 hr, after which it was hydrolyzed with a saturated aqueous solution of ammonium chloride and extracted with three 10-ml portions of diethyl ether. The ether layer was separated, dried over anhydrous sodium sulfate, and evaporated to yield colorless prisms (5.51 g, 89%) of *endo*-2-methylbicyclo[2.2.1]heptan-2-ol (19): mp 30–31° (lit.[8] mp 31.5–32°); ir

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(CHCl$_3$) 3620 (OH), 2950 and 2870 cm$^{-1}$, no C=O band; nmr (CDCl$_3$) δ 2.73 (s, 1 H), 1.68 (complex m, 10 H), 1.30 (s, 3 H).

*endo*-2-Methylbicyclo[2.2.1]heptan-2-ol (4.20 g, 0.032 mol) in 10 ml of acetonitrile was added dropwise to a solution of 2 (9.00 g, 0.038 mole) in 20 ml of acetonitrile in a 50-ml round-bottom flask fitted with a reflux condenser and calcium chloride drying tube. The temperature was raised to 50° and maintained for 1 hr, after which the reaction mixture was cooled, treated with 15 ml of water, and extracted with three 10-ml portions of ether. The ether layer was separated, dried over anhydrous sodium sulfate, and evaporated to give a colorless liquid (2.76 g, 80%) which was shown by glc to contain two components.

Separation was affected by collection from a gas–liquid chromatograph (20% Carbowax column, injector temperature 220°, detector temperature 220°, column temperature 65°). The peak of shorter retention time (47% of the mixture) was identified[8] as 2-methylbicyclo[2.2.1]hept-2-ene (20): nmr (CDCl$_3$) δ 5.42 (m, 1 H), 2.71 (m, 1 H), 2.54 (m, 1 H), 1.68 (d, 3 H, $J$ = 2 Hz); exact mass determination—theoretical, 108.172; found, 108.169. The other component was identified[8] as 2-methylenebicyclo[2.2.1]heptane (21): nmr (CDCl$_3$) δ 4.78 (m, 1 H), 4.52 (m, 1 H), 2.66 (m, 1 H), 2.33 (m, 1 H), 2.00 (m, 1 H); exact mass determination—theoretical, 108.172; found, 108.173.

**Dehydration of Dimethylcyclopropylcarbinol (22).**—Dimethylcyclopropylcarbinol (3.00 g, 0.034 mol) was added neat to 2 (9.50 g, 0.040 mol) in a 50-ml round-bottom flask connected to the thermolysis apparatus at ambient temperature under a stream of dry nitrogen. After 10 min an exothermic reaction ensued, the reaction mixture became homogeneous, and a clear, colorless liquid distilled into the cold trap. Glc and nmr analysis of the distillate (1.20 g, 66%) showed one component which was identified as 2-cyclopropylpropene (23): nmr (CDCl$_3$) δ 4.67 (m, 2 H), 1.64 (d, 3 H), 1.10 (complex t, 1 H), 0.56 (m, 4 H), identical with that of an authentic sample.[10]

**Dehydration of 3,4-Epoxy-2-methylbutan-2-ol (24).**—3,4-Epoxy-2-methylbutan-2-ol[17] (3.00 g, 0.029 mol) was added neat to 2 (9.50 g, 0.040 mol) in a 50-ml round-bottom flask connected to the thermolysis apparatus at ambient temperature under a stream of dry nitrogen. The reaction mixture was warmed to 55° for several minutes while a rapid distillation of a clear, colorless liquid into the cold trap occurred. Glc analysis of the distillate (1.41 g, 69%) showed one component which was subsequently identified as 3,4-epoxy-2-methylbut-1-ene (25): nmr (CDCl$_3$) δ 5.17 (m, 1 H, $J$ = 1 Hz), 3.35 (m, 1 H, $J$ = 3 Hz), 2.75 (complex m, 2 H, $J$ = 3 Hz), 1.63 (d, 3 H, $J$ = 2 Hz), identical with that previously reported;[18] exact mass determination: theoretical 84.119, found, 84.120.

**Dehydration of 4-Hexen-3-ol (27).**—4-Hexen-3-ol (4.38 g, 0.044 mol) was added to 2 (10.70 g, 0.045 mol) in 25 ml of triglyme in a 50-ml round-bottom flask connected to the thermolysis apparatus at ambient temperature under a stream of dry nitrogen. The temperature was raised to 75° and a clear, colorless liquid distilled into the cold trap. Glc and nmr analysis of the distillate (2.62 g, 73%) showed one component which was identified as 2,4-hexadiene (28) when compared to an authentic sample.

In another example, 27 (3.00 g, 0.030 mol) in 10 ml of tetrahydrofuran was added dropwise to a solution of 2 (7.50 g, 0.032 mol) and 20 ml of tetrahydrofuran in a 50-ml round-bottom flask fitted with a reflux condenser at ambient temperature under an atmosphere of dry nitrogen. After the addition was complete (20 min) the reaction mixture was treated with sodium hydride (0.72 g, 0.030 mol, prepared from 1.27 g of sodium hydride–mineral oil dispersion by several washings with dry hexane) and maintained at ambient temperature until hydrogen evolution had ceased. The solvent was removed under reduced pressure to afford a white solid which was heated to 80° for 30 min. Water (10 ml) was added and the reaction was extracted three times with 10-ml portions of ether. The ether layer was separated, dried over anhydrous sodium sulfate, and evaporated to give a pale yellow oil (2.28 g, 94%) which glc showed to be one component, and was subsequently identified as methyl *N*-2-hex-3-enyl-carbamate (29): ir (CHCl$_3$) 3440 (NH), 2960, 2900, 1720 (OCON), and 1675 cm$^{-1}$ (C=C); nmr (CDCl$_3$) δ 5.55 (complex m, 2 H), 4.10 (broad s, 1 H), 3.60 (s, 3 H), 2.00 (complex m, 1 H), 1.65 (m, 2 H), 1.05 (m, 6 H); exact mass determination—theoretical 157.215; found 157.217.

*Anal.* Calcd for C$_8$H$_{15}$NO$_2$: C, 61.15; H, 9.55; N, 8.92. Found: C, 60.92; H, 9.50; N, 8.75.

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**Methyl $N$-Hexylcarbamate (31).**—1-Hexanol (3.00 g, 0.029 mol) was added neat to 2 (7.40 g, 0.031 mol) in a 50-ml round-bottom flask fitted with a reflux condenser at ambient temperature under an atmosphere of dry nitrogen. After a mild exothermic reaction the resultant viscous yellow oil was heated to 95° for 30 min. Water (10 ml) was added and the reaction mixture was extracted three times with 10-ml portions of ether. The ether layer was separated, dried over anhydrous sodium sulfate, and evaporated to yield 4.25 g (91%) of a colorless oil which was identified as methyl $N$-hexylcarbamate (31) by nmr and ir spectral comparison with an authentic sample.

In another example, 1-hexanol (1.96 g, 0.019 mol) was added neat to 2 (5.00 g, 0.021 mol) at ambient temperature under an atmosphere of nitrogen. After the mild exothermic reaction had ceased, the reaction mixture was dissolved in 20 ml of benzene and rapidly washed with a cold aqueous solution of 2% hydrochloric acid. The benzene layer was separated, dried over anhydrous sodium sulfate, and evaporated to give a viscous oil: ir (CHCl$_3$) 3325 (NH), 3000, 1740 (C=O), 1330, and 1160 cm$^{-1}$ (SO$_2$N); nmr (CDCl$_3$) δ 8.15 (broad s, 1 H), 4.30 (t, 2 H), 3.70 (s, 3 H), 1.25 (m, 8 H), 0.90 (t, 3 H).

When placed in the thermolysis apparatus and subjected to a temperature of 150°, the oil gave a clear, colorless distillate which on glc analysis and comparison with an authentic mixture showed two components, 1-hexene (50%) and 2-hexene (50%). The total yield of olefinic products was 1.14 g (70%).

**Methyl $N$-Benzylcarbamate.**—Benzyl alcohol (2.16 g, 0.020 mol) was added neat to 2 (5.95 g, 0.025 mol) in a 50-ml round-bottom flask fitted with a reflux condenser at ambient temperature under an atmosphere of dry nitrogen. The resulting exothermic reaction produced a homogeneous reaction mixture. Reducing the pressure to 0.55 Torr and raising the temperature to 115° caused distillation of a pale yellow liquid (2.64 g, 80%) which was identified as methyl-$N$-benzylcarbamate by ir spectral comparison with an authentic sample.

**Dehydration of 2,2-Dimethylpropan-1-ol.**—2,2-Dimethylpropan-1-ol (1.76 g, 0.020 mol) in 10 ml of benzene was added dropwise to a solution of 2 (5.95 g, 0.025 mol) and 20 ml of benzene in a 50-ml round-bottom flask fitted with a reflux condenser at ambient temperature under an atmosphere of dry nitrogen. The benzene was removed under reduced pressure and the residue was dissolved in 25 ml of tetrahydrofuran. The solution was treated with sodium hydride (0.53 g, 0.022 mol, prepared from 0.93 g of sodium hydride–mineral oil dispersion by several washings with dry hexane) and maintained at ambient temperature until hydrogen evolution had ceased. The tetrahydrofuran was evaporated to yield a white solid, which was thermolyzed at 110° for 30 min. A clear, colorless liquid distilled (1.17 g, 84%) which was identified as 2-methyl-2-butene (35) by nmr spectral and glc comparison with an authentic sample.

**Beckmann Rearrangement of *syn*-Benzaldehyde Oxime.**—*syn*-Benzaldehyde oxime (2.42 g, 0.020 mol) was added to 2 (5.00 g, 0.021 mol) in a 50-ml round-bottom flask fitted with a reflux condenser at ambient temperature under an atmosphere of dry nitrogen. After an exothermic reaction, the resulting viscous oil was heated to 90° for 30 min, cooled, dissolved in 20 ml of benzene, washed once with 10 ml of a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated to yield 1.36 g (75%) of formanilide, mp 45–46°, undepressed upon admixture with an authentic sample.

# The Kinetics and Mechanism of the Reaction of 2-Thenoyl Chloride with Anilines in Benzene

A. ARCORIA,* S. FISICHELLA, G. SCARLATA, AND D. SCIOTTO

*Institute of Industrial Chemistry of the University, Viale Andrea Doria, 8—95125 Catania, Italy*

The rate of the reaction of 2-thenoyl chloride with various substituted anilines has been measured in benzene at four temperatures. The reaction is second order overall and pseudo first order with respect to each reactant. The rate constants are increased by electron-donating substituents, while they are decreased by electron-withdrawing groups. The activation parameters and the slopes of the Hammett ($-3.45$) and Bronsted (1.14) plots are similar to those of the reaction of benzoyl chloride with anilines. The results show that the reaction mechanism of 2-thenoyl chloride with anilines is the same as for reaction of benzoyl chloride; 2-thenoyl chloride, however, reacts more slowly than predicted from the $pK_a$ of 2-thenoic acid. The Tommila equation points out that the carbonyl carbon atom of 2-thenoyl chloride is less positively charged, and therefore less reactive toward aniline, than that of benzoyl chloride.

In several reactions thiophene derivatives do not behave according to the Hammett relation.[1] In fact the esters of 2-thenoic acid, in contrast to those of 3-thenoic acid, saponified at a rate considerably slower than otherwise expected from the $pK_a$ of 2-thenoic acid.[2] At first this seemed to be due to a steric effect of the adjacent sulfur atom,[2] but later, when the same effect was found in the esters of 2-furoic acid, it was ascribed to a stereospecific acid strengthening factor that causes these acids to be stronger.[3,4] Recently the heteroatom was treated as an ortho substituent and it was attempted to correlate the data of the saponification rates of 2-thenoates and 2-furoates by means of the Taft–Ingold relation.[5]

In connection with our present studies on thiophene derivatives,[6-8] in this paper we report a study of the reaction between 2-thenoyl chloride and meta- and para-substituted anilines in benzene solution in order to investigate whether 2-thenoyl chloride reacts as expected from the $pK_a$ of 2-thenoic acid. Whereas the kinetics of benzoylation of anilines have been extensively studied,[9-20] no studies of the reaction between 2-thenoyl chloride and anilines are reported.

The reaction between 2-thenoyl chloride and meta- and para-substituted anilines in benzene takes place quantitatively according to eq 1.



$$X = H, \; m\text{-}CH_3, \; p\text{-}CH_3, \; m\text{-}CH_3O, \; p\text{-}CH_3O, \; m\text{-}Cl, \; p\text{-}Cl$$
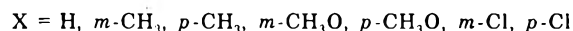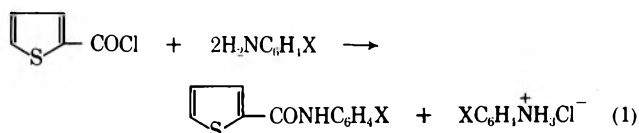
The reaction was followed kinetically by filtering the completely insoluble aniline hydrochloride, dissolving this in water, and estimating the chloride by Volhard's method (see Experimental Section).

We found that the reaction of 2-thenoyl chloride with anilines follows second-order kinetics, first order with respect to each reactant. The mechanism was the same as for benzoylation of aniline, but 2-thenoyl chloride reacts at a rate considerably slower than that expected from the $pK_a$ of 2-thenoic acid. The Tommila equation showed that the carbonyl carbon atom of 2-thenoyl chloride is less positively charged than that of benzoyl chloride.

## Results and Discussion

The observed reaction rates of 2-thenoyl chloride with large excess of aniline in benzene at 25°, listed in Table I, show that the reaction is pseudo first order.

### TABLE I

PSEUDO-FIRST-ORDER RATE CONSTANTS FOR THE REACTION OF 2-THENOYL CHLORIDE WITH ANILINE IN BENZENE AT 25°

| Run no. | Initial concn of 2-thenoyl chloride, mol/l. | $k_1 \times 10^3$, sec$^{-1}$ |
|---|---|---|
| 1 | 0.01 | 1.47 |
| 2 | 0.005 | 1.51 |
| 3 | 0.0025 | 1.48 |

The rate constants at 25° using constant molar ratios of the reactants (1:2) indicate that the reaction is second order overall (Table II). The results of Table

### TABLE II

SECOND-ORDER RATE CONSTANTS FOR THE REACTION OF 2-THENOYL CHLORIDE WITH ANILINE IN BENZENE AT 25° AT DIFFERENT DILUTIONS

| Run no. | Initial concn of 2-thenoyl chloride, mol/l. | $k_2 \times 10^2$, l. mol$^{-1}$ sec$^{-1}$ |
|---|---|---|
| 1 | 0.01 | 2.56 |
| 2 | 0.005 | 2.52 |
| 3 | 0.0025 | 2.49 |

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<div align="center">

TABLE III

SECOND-ORDER RATE CONSTANTS FOR THE REACTION OF 2-THENOYL CHLORIDE WITH META-
AND PARA-SUBSTITUTED ANILINES IN BENZENE

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| No. | Registry no. | Substituent | $pK_a{}^a$ | 10° | 15° | 17.5° | 25° | 30° | 35° | 45° |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | | | | | $k_2 \times 10^2$, l. mol$^{-1}$ sec$^{-1}$ | | | |
| 1 | 62-53-3 | H | 4.58 | | 1.63 | | 2.52 | | 4.02 | 6.04 |
| 2 | 108-44-1 | $m$-CH$_3$ | 4.69 | | | | 3.60 | 4.34 | 5.64 | 8.14 |
| 3 | 106-49-0 | $p$-CH$_3$ | 5.12 | 5.23 | | 7.56 | 10.1 | | 15.5 | |
| 4 | 536-90-3 | $m$-CH$_3$O | 4.20 | | | | 1.91 | 2.56 | 2.93 | 5.08 |
| 5 | 104-94-9 | $p$-CH$_3$O | 5.29 | 26.1 | 29.4 | 35.0 | 44.8 | | | |
| 6 | 108-42-9 | $m$-Cl | 3.34 | | | | 0.162 | 0.193 | 0.270 | 0.441 |
| 7 | 106-47-8 | $p$-Cl | 3.98 | | 0.351 | | 0.633 | | 0.964 | 1.62 |

$^a$ Reference 26.

II also show that the velocity constants do not change appreciably with the dilution. The kinetic of the reaction of 2-thenoyl chloride with anilines in benzene is thus as expected from eq 1 with the rate law (eq 2).

$$\text{rate} = k[\text{C}_4\text{H}_3\text{SCOCl}]\ [\text{H}_2\text{NC}_6\text{H}_4\text{X}] \qquad (2)$$

The reaction between 2-thenoyl chloride and anilines takes place quantitatively according to eq 1; no other products were observed. Products of the reaction were isolated as described in the Experimental Section. Numerous experiments showed that the precipitation of aniline hydrochloride was instantaneous and quantitative. In fact, when equal volumes of a 0.01 $M$ benzene solution of 2-thenoyl chloride were mixed with a 0.02 $M$ solution of aniline in benzene and maintained at the kinetic temperature until completion, the completely insoluble aniline hydrochloride was formed. The precipitate was at once filtered off, washed with benzene, and dissolved in water and the chloride was titrated with 0.01 $N$ silver nitrate by the Volhard method. The end point of the reaction was the theoretical. The amount of 2-thiophenecarboxanilide, isolated from the filtrate as described, was in all cases $\geq 95\%$ of that expected from the formation of 1 mol of anilide per 1 mol of acid chloride consumed in agreement with eq 1.

The substituent effect on the rate constants, reported in Table III, shows that the reaction rate depends on the electron density on the nitrogen atom of aniline: electron-donating substituents in aniline increase the rate, while electron-withdrawing groups decrease the rate.

A comparison of these results with those of reaction of benzoyl chloride with anilines[10,13,20] shows that 2-thenoyl chloride reacts more slowly than benzoyl chloride, although 2-thenoic acid ($pK_a$ = 3.49) is stronger than benzoic acid ($pK_a$ = 4.20).[1]

The activation energies and log $A$ values were calculated from the rate constants at different temperatures by the method of least squares, the plots of log $k$ against $1/T$ being linear in all cases (Figure 1).

The entropies of activation, $\Delta S^*$, were computed for 25° by the formula[21] of eq 3.

$$\Delta S^* = 4.576\ (\log A - \log T) - 49.21\ (\text{cal/mol °K}) \qquad (3)$$

It can be noted that the values of the activation parameters, listed in Table IV, are similar to those of the reaction of benzoylation of aniline.[10,13,20] The values of the activation energies show a regular varia-
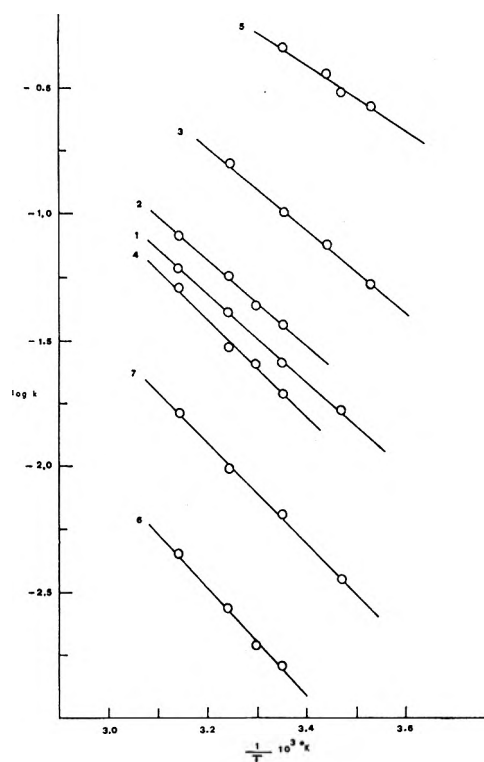


Figure 1.—The Arrhenius activation energy plots. The numbers on the curves refer to the series numbers in Table III.

<div align="center">

TABLE IV

ACTIVATION PARAMETERS FOR THE REACTION RATES IN TABLE III

</div>

| Substituent | $E_A$, kcal mol$^{-1}$ | $\Delta S^*$ at 25°, cal mol$^{-1}$ °K$^{-1}$ | log $A$ |
|-----|-----|-----|-----|
| H | 7.94 | −41.1 | 4.25 |
| $m$-CH$_3$ | 7.79 | −41.0 | 4.27 |
| $p$-CH$_3$ | 7.47 | −39.9 | 4.49 |
| $m$-CH$_3$O | 8.97 | −38.2 | 4.88 |
| $p$-CH$_3$O | 6.20 | −41.2 | 4.21 |
| $m$-Cl | 9.70 | −40.8 | 4.31 |
| $p$-Cl | 9.08 | −40.1 | 4.46 |

tion with substituents in aniline: electron-donating substituents decrease $E_A$ while electron-withdrawing groups increase $E_A$. The large negative entropies of activation are as expected by bimolecular reactions with a highly polar transition state.[22]

The plot of log $k$ at 25° against Hammett's $\sigma$ constants[23] is linear with a slope of −3.45 (Figure 2). The sensitivity of the rates to substituents in the aniline

(21) M. Simonetta, "Chimica Fisica," Manfredi, Ed., Milano, 1966, p 278.

(22) A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961, Chapter 7.

(23) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963.
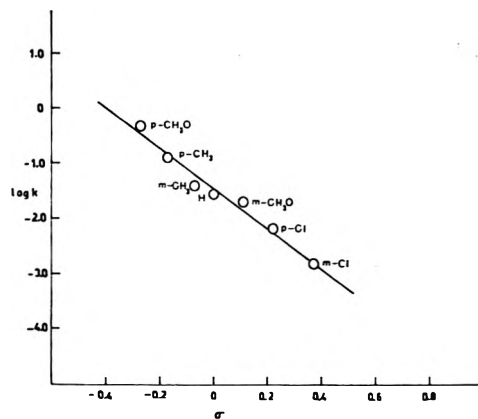
Figure 2.—Hammett plot for the reaction of 2-thenoyl chloride with substituted anilines in benzene at 25°.



Figure 3.—Plot of log $k_{25}$° for the reaction of 2-thenoyl chloride with substituted anilines in benzene against the logarithm of their dissociation constants in water at 25° (Bronsted plot).

($\rho$ −3.45) is comparable with that found for the reaction of benzoylation of aniline.[24,25]

The plot of the rate constants at 25° for the reaction of 2-thenoyl chloride with the various anilines in benzene solution against the p$K_a$ at 25° in water[26] of the corresponding protonated aniline is linear as shown by the Bronsted plot in Figure 3. The sensitivity of the reaction rates to the basicity of the nucleophile, as measured by the slope of the Bronsted plot ($\beta$ 1.14) is comparable with that found for the reaction of benzoyl chloride with anilines (0.97), calculated from the experimental data of Stubbs and Hinshelwood.[13]

The sign of the Bronsted slope is as expected for a nucleophilic substitution. We cannot discuss here the value of the Bronsted coefficient, usually related to the extent of bond formation in the transition state, since it was calculated with the reaction rates measured in benzene and the p$K_a$ values measured in water. As is well known, this is a limit to the interpretation of Bronsted coefficients.[23]

To provide some insights into the unusual rate behavior of the 2-thenoyl chloride reaction, we have made use of a simplified Tommila equation relating reaction rate ratios to local charges and bond lengths (eq 4),[20]

$$\ln \frac{k_s}{k_u} = -\frac{e_C \delta e_X}{R T r_1} - \frac{\Delta W}{RT} \qquad (4)$$

where $k_s$ = the rate constant of the substituted compound, $k_u$ = the rate constant of the unsubstituted compound, $e_C$ = the effective electric charge of the carbon atom in the reaction centre, $\delta e_X$ = the increment, positive or negative, caused to the charge by the substituent introduced in the attacking reagent X, $r_1$ = the distance X–C in the transition state, and $\Delta W/RT$ = the nonelectrostatic part of ln ($k_s/k_u$) in the reaction

$$X + C\overset{r_0}{-}Y \longrightarrow X\overset{r_1}{-}C\overset{r_2}{-}Y \longrightarrow \text{products}$$
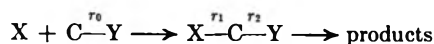
where C is the center of the reaction, usually a carbon atom, X is the attacking agent, and Y is the leaving group.

The nitrogen atom in the aniline, owing to its lone electron pair, is electrically negative, while the carbon
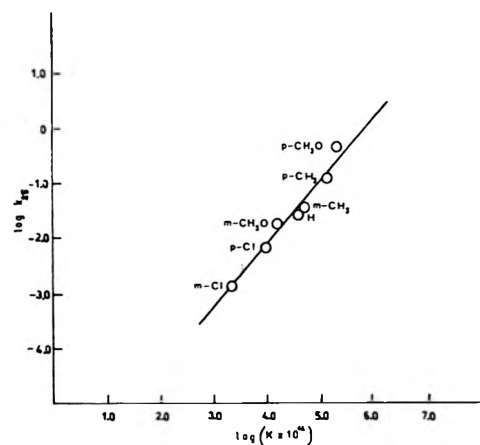
atom of the acid chloride, owing to the influences of the oxygen atom and the chlorine atom, is positively charged.

When the substituents in aniline are electron withdrawing the lone electron pair on the nitrogen atom is bound more tightly. Thus $\delta e_X$ is positive, and, as $e_C$ also is positive, the product $e_C \delta e_X$ is positive, and, if the term $-e_C \delta e_X/R T r_1$ is greater than the term $\Delta W/RT$, log ($k_s/k_u$) should be negative. The more the substituent attracts electrons, the greater is $\delta e_X$ and the more negative log ($k_s/k_u$).

On the contrary, when the substituents in aniline are electron donating, $\delta e_X$ is negative, the product $e_C \delta e_X$ is, therefore, negative, and log ($k_s/k_u$) is positive. The more the substituent repels electrons, the more negative is $\delta e_X$ and the greater log ($k_s/k_u$). This is in accordance with the experimental results listed in Table V, where

TABLE V

VALUES OF LOG ($k_s/k_u$) AT 25° FOR THE REACTION OF 2-THENOYL CHLORIDE OR BENZOYL CHLORIDE WITH META- AND PARA-SUBSTITUTED ANILINES IN BENZENE

| Substituent | 2-Thenoyl chloride[a] reaction | Benzoyl chloride reaction |
|---|---|---|
| p-Cl | −0,62580 | −0,66144[b] |
| | | −0,67800[c] |
| | | −0,69252[d] |
| m-Cl | −1,23061 | −1,23441[e] |
| p-CH₃ | 0,58506 | 0,63662[b] |
| | | 0,62578[c] |
| m-CH₃ | 0,13051 | 0,26597[e] |
| p-CH₃O | 1,23624 | |
| m-CH₃O | −0,12548 | |

[a] The rate constant values used were calculated from the Arrhenius equation. [b] Reference 10. [c] Reference 13. [d] Reference 20.

the log ($k_s/k_u$) values at 25° for the benzoyl chloride reaction are also reported.

The results show that, when the substituents in aniline are electron withdrawing, the log ($k_s/k_u$) values for the 2-thenoyl chloride reaction are less negative than those for the benzoyl chloride reaction. When the substituents in the amine are electron donating the log ($k_s/k_u$) values for reaction of 2-thenoyl chloride are less positive than those of the benzoylation reaction. Since the anilines in the reaction with 2-thenoyl chloride

(24) Jaffé[11] reports a $\rho$ value of −2.78, calculated from experimental data of other authors.[10,11] Other authors recently have found a value of −3.37.[19]

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

(26) G. M. Badger, "The Structures and Reactions of the Aromatic Compounds," Cambridge, 1954, p 196.

or benzoyl chloride are the same, the electric charge in the nitrogen atom of the $-NH_2$ group has the same value. This implies a change of the electric charge in the carbonyl carbon atom of 2-thenoyl chloride: the carbonyl carbon atom of 2-thenoyl chloride is less positively charged than that of benzoyl chloride.

The results, then, lead us to postulate that the reaction of 2-thenoyl chloride and anilines in benzene is similar to the benzoyl chloride reaction involving the attack of the lone pair of the electrons of the amino group to the carbonyl carbon atom (Scheme I).

SCHEME I
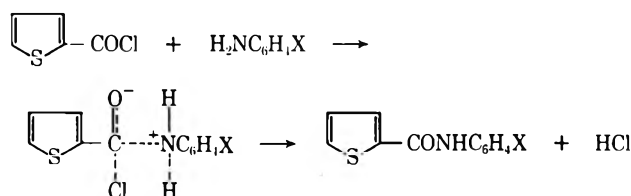


The slower reaction rate of 2-thenoyl chloride, in comparison with that of benzoyl chloride, can be ascribed to the resonance between the thiophene ring and the carbonyl group that makes it more stabilized, and therefore less reactive towards aniline, than the carbonyl group of benzoyl chloride.

## Experimental Section

**Materials.**—2-Thenoyl chloride (a Fluka commercial product) was fractionated to constant boiling point.

The various aniline derivatives were purified to constant melting point or boiling point by recrystallisation or fractionation.

The solvent used was benzene (R. P. Carlo Erba), and no special purification was undertaken, since numerous experiments showed that elaborate purification was unnecessary.

**Kinetic Procedure.**—The reaction was followed kinetically using the method described for benzoylation of aniline.[9,10] Into each of several glass-stoppered bottles were introduced, by means of volumetric pipets, equal volumes (50 ml) of standard solutions of 2-thenoyl chloride and of appropriate aniline derivative in benzene.

All the reagents were mixed at the temperature of the experiment. The bottles were immediately stoppered, shaken, and placed into a constant-temperature bath ($\pm 0.01°$). At suitable intervals, the bottles were removed from the constant-temperature bath and the aniline hydrochloride formed was filtered and washed with solvent. The precipitate was transferred to a beaker and dissolved in water, to which were added the washings from the filter and the original bottle, and the chloride was titrated with 0.01 N silver nitrate by the Volhard method.

The pseudo-first-order rate constants with a large excess of aniline over 2-thenoyl chloride and the second-order rate constants with constant molar ratios (2:1) of the reactants were calculated. The concentration ranges of 2-thenoyl chloride used for the pseudo-first order rate measurements varied from 0.01 to 0.0025 M.

The pseudo-first-order rate constants were calculated from the usual equation

$$k_1 = \frac{1}{t} 2.303 \log \frac{a}{a - x}$$

where $t$ is the time in seconds, $a$ is the initial concentration of the acid chloride in moles/liter, $x$ is the concentration of product in moles/liter at time $t$, and $k_1$ is the velocity constant in seconds$^{-1}$.

Since, according to eq 1, two molecules of aniline are removed for each molecule of 2-thenoyl chloride, the second-order rate constants are derived from the formula $dx/dt = k_2 (a - x)/(2a - 2x)$, hence

$$k_2 = \frac{1}{2 \times 60t} \left( \frac{1}{100 - X} - \frac{1}{100} \right) \frac{100}{a}$$

where $t$ is the time in minutes, $X$ is the percentage change, $k_2$ is the velocity constant (liters/mole seconds), and $a$ is the initial concentration of the acid chloride in moles/liter. For the second-order rate measurements the initial concentrations of the reactants after mixing were thus 2-thenoyl chloride 0.005 M, aniline 0.01 M. For some compounds for which the reactions were too fast to be measured accurately at this concentration (p-toluidine and p-anisidine, compounds 3 and 5 in Table III), the initial concentrations were 0.005 M aniline and 0.0025 M 2-thenoyl chloride.

Typical pseudo-first-order and second-order kinetic runs are shown in Tables VI and VII.

#### TABLE VI
#### Pseudo-First-Order Kinetic Run for the Reaction of 2-Thenoyl Chloride with Aniline in Benzene at 25°[a]

| Elapsed time, min | 0.01 N AgNO₃, ml | log (a/a − x) |
|---|---|---|
| 0 | 0 | 0 |
| 2 | 10.35 | 0.1006 |
| 4 | 15.7 | 0.1637 |
| 6 | 21.0 | 0.2369 |
| 8 | 25.9 | 0.3164 |
| 10 | 30.25 | 0.4036 |
| 12 | 33.4 | 0.4792 |
| 14 | 36.2 | 0.5593 |

[a] The data refer to the second kinetic run in Table I.

#### TABLE VII
#### Second-Order Kinetic Run for the Reaction of 2-Thenoyl Chloride with Aniline in Benzene at 25°[a]

| Time, min | Reaction % | $k_2 \times 10^3$, l. mol$^{-1}$ sec$^{-1}$ |
|---|---|---|
| 20 | 23.1 | 2.50 |
| 30 | 31.4 | 2.54 |
| 40 | 37.8 | 2.53 |
| 50 | 43.0 | 2.51 |
| 60 | 47.4 | 2.50 |
| 70 | 51.2 | 2.50 |
| 80 | 54.6 | 2.51 |
| 120 | 64.6 | 2.53 |
| 150 | 69.6 | 2.54 |
| 240 | 78.5 | 2.54 |
| | | Mean 2.52 |

[a] The data refer to the second kinetic run in Table II.

All rates were run in duplicate to the least 80% completion with less than 3% deviation between the two rate constants in all cases. At temperatures other than 15 or 25°, rate coefficients were corrected for thermal expansion or contration of the solvent. All rate constants were calculated by a least squares computer program with an Olivetti Programma 101.

**Product Analysis.**—Standard solutions of the appropriate aniline and 2-thenoyl chloride in benzene were mixed in a glass-

#### TABLE VIII
#### Physical Constants of 2-Thiophenecarboxanilides[a]

| No. | $\text{CONHC}_6\text{H}_4\text{X}$ | Mp, °C | Ref |
|---|---|---|---|
| 1 | X = H | 140 | 27 |
| 2 | m-CH₃ | 107 | 28 |
| 3 | p-CH₃ | 169 | 28 |
| 4 | m-CH₃O | 140–141 | 6 |
| 5 | p-CH₃O | 140 | 29 |
| 6 | m-Cl | 138 | 28 |
| 7 | p-Cl | 161 | 28 |

[a] All the compounds were crystallized from aqueous ethanol.

(27) G. M. Badger, R. T. Howard, and A. Simons, *J. Chem. Soc.*, 2849 (1952).

(28) Buu-Hoy and Nguyen-Hoan, *Recl. Trav. Chim. Pays-Bas*, **68**, 5 (1949).

(29) C. Tsuchiya, *Nippon Kagaku Zasshi*, **82**, 1395 (1961).

stoppered bottle and maintained at the kinetic temperature until completion. After concentration of the benzenic solution to small volume, the corresponding 2-thiophenecarboxanilide precipitated was filtered, washed free from aniline hydrochloride with water, dried, and recrystallized from suitable solvent. In all cases the amount of 2-thiophenecarboxanilide was ≥95% of that expected from the formation of 1 mol of anilide per 1 mol of acid chloride consumed. The mixture melting points with authentic samples of 2-thiophenecarboxanilides revealed no

depression. Physical constants of 2-thiophenecarboxanilides are listed in Table VIII.

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# The Synthesis of Aldehydes from Dihydro-1,3-oxazines

A. I. Meyers,* A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone,
A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy

*Department of Chemistry, Louisiana State University in New Orleans, New Orleans, Louisiana 70122
and Wayne State University, Detroit, Michigan 48202*

The use of readily available dihydro-1,3-oxazines (DHO) as precursors to substituted acetaldehydes, $\alpha,\beta$-unsaturated aldehydes, cycloalkanecarboxaldehydes, and a variety of functionalized aldehydes is reported. The method is useful for both a two-carbon homologation of electrophiles to aldehydes as well as a three-carbon homologation of nucleophiles (RMgX, malonates, enamines). The scope and limitations of this synthesis are discussed.

In 1969, a series of brief reports[2-4] appeared which outlined a technique for the preparation of aldehydes based upon the dihydro-1,3-oxazine (DHO) ring system, and this is depicted in Scheme I. It is now

SCHEME I
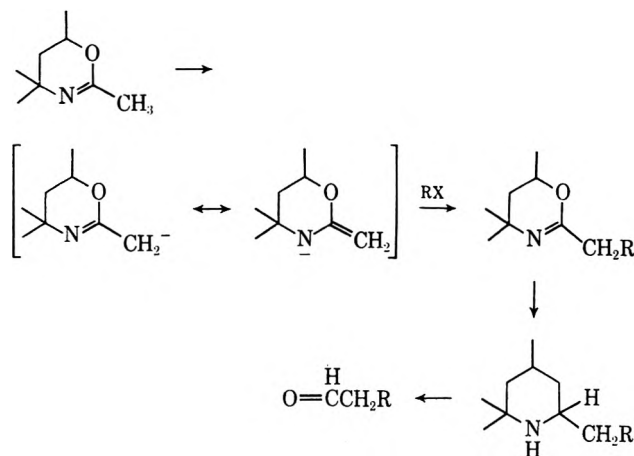


desirable to describe in detail the studies which led to the successful implementation of this process. The anticipated approach required that (a) a readily available dihydro-1,3-oxazine be utilized as starting material, (b) a stable carbanion be generated by the use of some suitable base, (c) reaction of the carbanion with carbon electrophiles lead only to C-alkylation, since N-alkylation would result in an undesirable side product, (d) a mild and efficient reduction be employed to reduce the C=N link in the sensitive oxazine ring, and (e) hydrolytic cleavage conditions be utilized to gen-

erate the aldehydic product from the tetrahydro-1,3-oxazine (THO).

The scheme would, in effect, be a two-carbon homologation of electrophiles to aldehydes and may be considered as the *aldehyde equivalent* to the malonic ester synthesis. A similar concept has been reported by Stork[5] utilizing metalated enamines which were alkylated by alkyl halides and hydrolyzed to produce the elaborated aldehyde, whereas a one-carbon homologation of electrophiles was described by Corey and Seebach[6] employing the versatile lithiodithiane system.

Oxazine systems which possessed 2 substituents other than methyl were also viewed as candidates for this sequence and are shown in Scheme II. Thus, the use of

SCHEME II
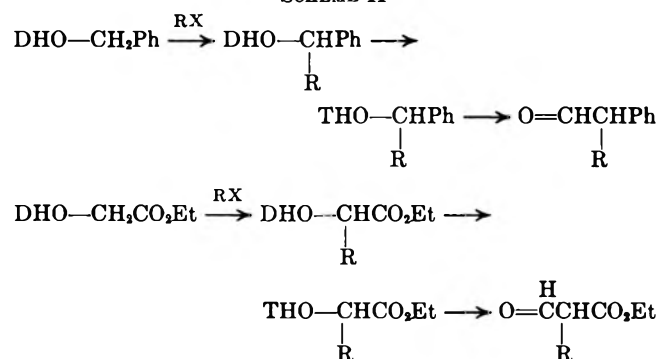


the 2-benzyl or the 2-carboethoxymethyl oxazines could serve as precursors to $\alpha$-phenyl and $\alpha$-carboethoxy aldehydes, respectively. Furthermore, the 2-vinyl-dihydro-1,3-oxazine was examined (Scheme III) to determine if it was suitable as a three-carbon homolog for organometallics. Recently, there have been reports from Walborsky[7] and this laboratory[8] which allow a

(1) Department of Chemistry, Colorado State University, Fort Collins, Colorado 80521.

(2) (a) A. I. Meyers, A. Nabeya, H. W. Adickes, and I. R. Politzer, *J. Amer. Chem. Soc.*, **91**, 763 (1969); (b) A. I. Meyers, H. W. Adickes, I. R. Politzer, and W. N. Beverung, *ibid.*, **91**, 765 (1969).

(3) A. I. Meyers, A. Nabeya, I. R. Politzer, H. W. Adickes, J. M. Fitzpatrick, and G. R. Malone, *ibid.*, **91**, 764 (1969).

(4) H. W. Adickes, I. R. Politzer, and A. I. Meyers, *ibid.*, **91**, 2155 (1969).

(5) G. Stork and S. R. Dowd, *ibid.*, **85**, 2178 (1963); T. Cuvigny and H. Normant, *Bull. Soc. Chim. Fr.*, 3976 (1970).

(6) E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **4**, 1075 (1965); for a review of this subject, *cf.* D. Seebach, *Synthesis*, **1**, 17 (1969).

(7) H. M. Walborsky and G. E. Niznik, *J. Amer. Chem. Soc.*, **91**, 7778 (1969); **92**, 6675 (1970).

(8) A. I. Meyers and E. W. Collington, *ibid.*, **92**, 6676 (1970).

SCHEME III

$$DHO—CH=CH_2 \xrightarrow{RM} DHO—CH_2CH_2R$$

$$O=CCH_2CH_2R \xleftarrow{} THO—CH_2CH_2R$$
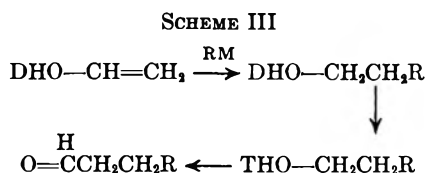
one-carbon homologation of organometallics to aldehydes.

In the following discussion, the studies to achieve the goals set forth are presented along with examples of a variety of aldehydes which demonstrate the success of this effort.

**Reduction of Dihydro-1,3-oxazines.**—In a preliminary communication,[9] the ability of 5,6-dihydro-1,3-oxazines (1) to serve as precursors to aldehydes has been described. This was accomplished by pH-controlled reduction of the C=N link in 1, affording the tetrahydro-1,3-oxazine 2 followed by hydrolysis to the aldehyde 3. Owing to the well-known ring–chain tautomerism of tetrahydro-1,3-oxazines (2, 2a) and related systems,[10] clean reduction of 1 could not be carried out by the usual means (catalytic or metal hydride[11]). The presence of the imine form 2a and
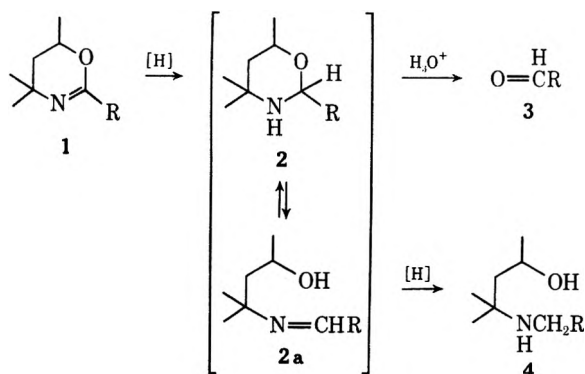
the susceptibility of 2 to further reduction constantly led to a mixture containing considerable quantities of the amino alcohol 4. A study was undertaken to determine if 1 could be reduced under conditions which would retard formation of the amino alcohol 4, and thus introduce the dihydro-1,3-oxazine system as a valuable source of aldehydes. From previous efforts in these laboratories, the use of pH control during borohydride reductions was observed to be compatible with the formation of sensitive groups (5 → 6, 7 → 8).[12-14] The 2-ethyldihydro-1,3-oxazine (9) was therefore chosen as the subject of a temperature and pH study in order to achieve the intended goal. At various temperatures and pH ranges (Table I) in ethanol–tetrahydrofuran containing aqueous acid or alkali, the borohydride reductions led to varying mixtures of tetrahydro-1,3-oxazines 10 and amino alcohols 11. As can be seen from the results in Table I, only at −40° was

(9) A. I. Meyers and A. Nabeya, *Chem. Commun.*, 1163 (1967).

(10) A. C. Cope and E. M. Hancock, *J. Amer. Chem. Soc.*, **64**, 1503 (1942); E. D. Bergman, E. Zinkin, and S. Pinchas, *Recl. Trav. Chim. Pays-Bas*, **71**, 168 (1952); A. F. McDonagh and H. E. Smith, *J. Org. Chem.*, **33**, 1 (1968); J. V. Paukstelis and R. M. Hammaker, *Tetrahedron Lett.*, **No. 32**, 3557 (1968); L. C. Dorman, *J. Org. Chem.*, **32**, 255 (1967); R. Kotani, T. Kuroda, T. Isozaki, and S. Sumoto, *Tetrahedron*, **25**, 4743 (1969).

(11) E. Schenker, *Angew. Chem.*, **73**, 81 (1961).

(12) A. I. Meyers and J. M. Greene, *J. Org. Chem.*, **31**, 556 (1966).

(13) A. I. Meyers and J. C. Sircar, *ibid.*, **32**, 4134 (1967).

(14) J. M. Greene, J. C. Getson, and A. I. Meyers, *J. Heterocycl. Chem.*, **1**, 300 (1964).

TABLE I

REDUCTION OF 9 AS A FUNCTION OF TEMPERATURE AND pH

| Reaction[a] temp, °C | pH[b] | Moles NaBH$_4$[c]/ moles 9 | % 10[d] | % 11[d] |
|---|---|---|---|---|
| 0–5 | 5 | 1 | 53 | 47 |
| 0–5 | 7 | 1 | 77 | 23 |
| 0–5 | 9 | 1 | 87 | 13 |
| −10 | 7 | 1 | 86 | 14 |
| −20 | 7 | 1 | 91 | 9 |
| −40 | 7 | 1 | 100 | 0 |

[a] Solvent used was THF–ethanol (1:1). [b] "pH" is purely apparent as measured by either pH meter or pH paper. Hydrochloric acid (6 N) was added as required. [c] Sodium borohydride was introduced as an aqueous solution. [d] Determined by vpc using Dow Silicone columns coated with 5% KOH.

it possible to effect quantitative conversion to the desired product. Furthermore, as the solution was changed during reduction from acidic (pH 5) to alkaline (pH 9) the amount of overreduction decreased. This, however, offered little in the way of a successful technique, since the degree to which the C=N link was reduced dropped off sharply. Since it was the intent of this program to maintain the mildest conditions possible for reduction, the pH was maintained at 7 and the temperature was lowered. In this fashion, the yield of reduction product was >98% and the amount of over-reduced material (11) was negligible. For all practical
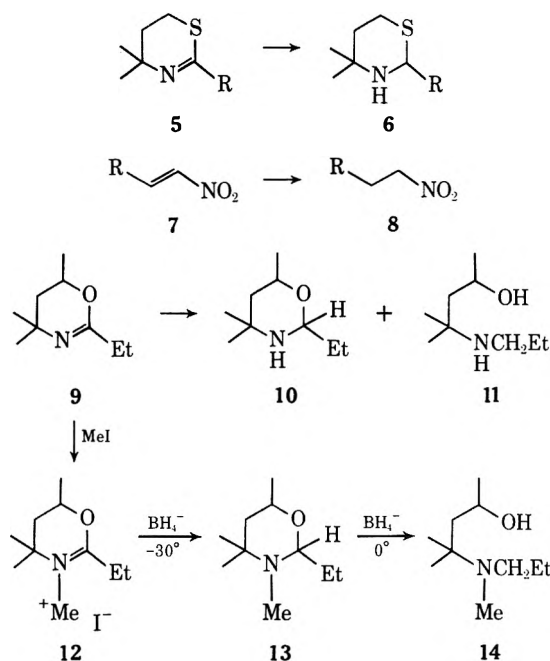
purposes, it was found that the reductions should be performed at −35 to −45°, although the pH range could vary from 5 to 8 without a significant increase in side products. In order to determine which of the two condition parameters was most critical and whether the overreduction to 11 is due to direct hydride attack on the tetrahydro-1,3-oxazine or hydride addition to the tautomeric imino form 2a, the *N*-methyl oxazinium salt 12 was prepared. This was reduced to the *N*-methyltetrahydro-1,3-oxazine (13) at −30° in methanol. When the latter, now unable to exist in tautomeric forms owing to the absence of the NH function, was treated at pH 7 (0–5°), there was indeed obtained 26% of the open-chain amino alcohol 14. When this experiment was repeated at −40°, no reaction oc-

TABLE II

2-SUBSTITUTED 4,4,6-TRIMETHYLTETRAHYDRO-1,3-OXAZINES (2)[a]

| Registry no. | R | Yield,[b] % | Bp, °C (mm) | Analysis, found[c] C | H | N | 2-H, δ[d] |
|---|---|---|---|---|---|---|---|
| 36873-27-5 | C$_2$H$_5$ | 57 | 68 (25) | 68.66 | 12.23 | 8.68 | 4.1 (t) |
| 36873-28-6 | CH$_2$CO$_2$Et | 78 | 82 (0.45) | 61.44 | 9.93 | 6.60 | 4.6 (t) |
| 36873-29-7 | CH$_2$CH$_2$NEt$_2$ | 42 | 70 (0.20) | 68.23 | 12.31 | 12.40 | 4.3 (t) |
| 36873-30-0 | CH$_2$Ph | 88 | 92 (0.25) | 76.82 | 9.80 | 6.55 | 4.4 (t) |
| 31771-33-2 | Ph | 92 | 96 (0.30)[e] | | | | 5.2 (s)[f] |
| 36873-32-2 | o-Tolyl | 89 | 94 (0.25) | 76.52 | 9.42 | 6.44 | 5.2 (s)[f] |
| 36873-33-3 | 2-Pyridyl | 72 | 108 (0.30) | 69.70 | 8.83 | 13.70 | 5.4 (s) |

[a] Reductions performed using equimolar quantities of dihydro-1,3-oxazines and sodium borohydride at −35 and −40° in THF–EtOH. [b] Crude yields were higher; some cases resulted in considerable decomposition upon distillation. [c] Agrees within ±0.3% of calculated values. [d] Nmr spectra were taken on neat samples using TMS as internal standard. [e] Lit. bp 139–140° (15 mm): T. Urbanski, *et al., Chem. Abstr.*, 51, 1186 (1957); picrate, mp 166–167° (lit. mp 166–168°). [f] Proton integration was 0.68 owing to open-chain tautomer present.

curred. On the other hand, when 13 was treated with aqueous sodium borohydride at pH 3–5 at 0–5°, a 90% yield of 14 was obtained, while this reduction at −40° produced only 13% of the amino alcohol. From this study, it may be concluded that tetrahydro-1,3-oxazines are cleaved by direct hydride attack whose facility is temperature dependent. However, if the acidity is sufficiently high (pH 3–5), hydride attack is facile even at low (−40°) temperatures, presumably owing to the protonated tetrahydro-1,3-oxazine which behaves as a more reactive electrophile. Furthermore, the omnipresent imino form of tetrahydro-1,3-oxazines (2a) appears to be inert to hydride addition under the above described conditions (pH 7, −40°). A series of 2-substituted dihydro-1,3-oxazines (1) were subjected to the reduction conditions (−40°, pH 5–8) and the products 2 were readily isolated and characterized (Table II).

**Cleavage of Tetrahydro-1,3-oxazines.**—With an efficient and mild reduction method in hand, the tetrahydro-1,3-oxazines 2 were subjected to acidic cleavage in either 90% acetic acid or aqueous oxalic acid and the aldehydes 3 derived from these were isolated and characterized (Table III). In three cases, reductions

TABLE III

HYDROLYSIS OF TETRAHYDRO-1,3-OXAZINES 2 TO ALDEHYDES 3

| 2, R = | Reaction condition[a] | Yield 3 2,4-DNP, % | Mp, °C (lit.) |
|---|---|---|---|
| Et | A, 60 min, 90° | 79 | 147–150 (148)[b] |
| | B, 90 min, 100° | 74 | |
| CH$_2$CO$_2$Et | A, 10 min, 90° | 80 | 78–80 (158)[c] |
| | B, 60 min, 100° | d | |
| CH$_2$Ph | A, 5 min, 90° | 78 | 118–120 (120)[e] |
| | | 77 (C-1D)[h] | |
| Ph | A, 5 min, 90° | 77 | 240 (237)[b] |
| | B, 75 min, 100° | 77 (C-1D)[h] | 240 |
| o-Tolyl | A, 24 hr, 25° | 56[b] | 95–100 (35 mm)[f] |
| 2-Pyridyl | A, 5 min, 90° | 57 | 227–229 (229)[g] |
| | | 62 (C-1D)[h] | |

[a] A = 90% acetic acid, B = 3 M oxalic acid. [b] I. Heilbron, "Dictionary of Organic Compounds," Oxford University Press, London, 1965. [c] This compound is reported to melt at 158°: F. Bobery, *Justus Liebigs Ann. Chem.*, 683, 132 (1965). The product obtained in this work gave correct elemental, mass, nmr, and ir analyses. [d] Free aldehyde was unstable and could not be obtained pure, except as 2,4-DNP derivative. [e] H. M. Fales, *J. Amer. Chem. Soc.*, 77, 5118 (1955). [f] Isolated as pure aldehyde. [g] P. Grammaticakis, *Bull. Soc. Chim. Fr.*, 109 (1956). [h] Yield of C-1 deuterated aldehydes obtained by using sodium borodeuteride under identical reduction conditions.

were performed using sodium borodeuteride leading to C-1 deuterated aldehydes.

The most general method found for hydrolytic cleavage of the tetrahydro-1,3-oxazines was steam distillation from oxalic acid solution. In this fashion, pure aldehydes were consistently produced directly in the steam distillate, leaving the amino alcohol segment of the tetrahydro-1,3-oxazine in the distillation flask as the nonvolatile oxalate salt. For aldehydes which were insufficiently volatile to make steam distillation practical, reflux of the oxalic acid solution for 1–2 hr usually served the purpose, with the aldehyde being removed by extraction. It was found, in certain cases, that this method would result in decomposition of acid- or heat-sensitive aldehydes, and the aqueous acetic acid method at room temperature was then employed. Other means for releasing the aldehydes involved aqueous ethanolic ammonium chloride (6 M) or refluxing an ethanolic solution with hydroxylamine hydrochloride. The latter method, of course, converts the aldehyde directly to its oxime derivative. It is desirable to sample each of these techniques on a small scale to evaluate which proceeds with the best results. There were instances which failed to produce the aldehydic product owing to its sensitivity to acid (Table III, R = CH$_2$CO$_2$Et).

**Synthesis of Dihydro-1,3-oxazines.**—The next stage in the synthesis of aldehydes required that 2-substituted dihydro-1,3-oxazines be made readily available. A search of the literature revealed that most of the preparations involved the condensation of carboxylic acids,[15] nitriles,[16] or amides[17] with amino alcohols, olefins, or glycols in a cyclodehydrative or cycloaddition process. Since various methods are available for the direct reduction of nitriles, carboxylic acids, and related derivatives, there seemed to be no real advantage in converting these functional groups into dihydro-1,3-oxazines and ultimately to aldehydes. Recently,[18] however, this avenue provided the only approach for the conversion of the cyano ester 15 to the aldehyde 16. It was decided to investigate the preparation of several 2-substituted oxazines and their potential for elaboration to a wide variety of structural features. The reaction[16] of simple nitriles with 2-

(15) Z. Eckstein and T. Urbanski, *Advan. Heterocycl. Chem.*, 2, 311 (1963).

(16) E. J. Tillmanns and J. J. Ritter, *J. Org. Chem.*, 22, 839 (1957).

(17) R. Schmidt, *Chem. Ber.*, 103, 3242 (1970).

(18) R. V. Stevens, J. M. Fitzpatrick, M. Kaplan, and R. L. Zimmerman, *Chem. Commun.*, 857 (1971).
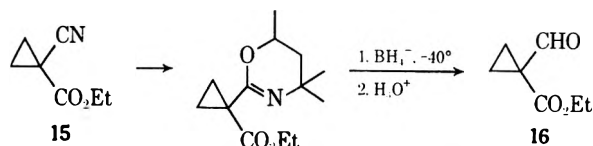
methyl-2,4-pentanediol (**17**) in concentrated sulfuric acid at 0° provided the most accessible precursors **18**–**21** for the aldehyde synthesis. All of these oxazines



18, R = CH₃
19, R = CH₂Ph
20, R = CH₂CO₂Et
21, R = CH=CH₂
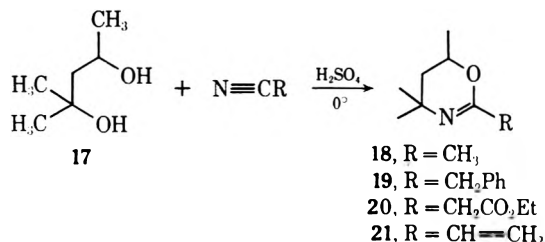
could be prepared or were available commercially in sufficient quantity to render them useful as starting materials (see Experimental Section).

If the process outlined in Scheme I could be successfully implemented with **18**, then similar reactions could be carried out on the oxazine **19** and **20** to produce α-phenyl and α-carboethoxy aldehydes, respectively. The 2-vinyl oxazine **21** contains a three-carbon unit which will be shown in later discussion to serve as a precursor to α,β-dialkylpropionaldehydes.

**Alkylation Studies.**—The 2-methyloxazine **18** was chosen as a candidate for elaboration as described in Scheme I. A search to find a suitable base that would produce a stable oxazine anion began with the usual repertoire available to the organic chemist. The results are tabulated in Table IV. Alkylation efficiency

### TABLE IV

ALKYLATION OF
2,4,4,6-TETRAMETHYL-5,6-DIHYDRO-1,3-OXAZINE WITH
METHYL IODIDE

$$DHO—CH_3 \xrightarrow[\text{2. CH}_3\text{I}]{\text{1. Base}} DHO—CH_2CH_3$$

| Base[a] | Conditions[b] | DHO— CH₃, % | DHO— CH₂CH₃, % | Material[c] balance, % |
|---|---|---|---|---|
| NaH | THF, 25°, 24 hr | 100 | 0 | 97 |
| NaCH₂SOCH₃ | DMSO, 20°, 24 hr | 100 | 0 | 93 |
| | DMSO, 70°, 24 hr | 100 | 0 | 95 |
| t-BuOK | THF, 25°, 24 hr | 100 | 0 | 90 |
| | THF, 5°, 24 hr | 100 | 0 | 90 |
| MeLi | THF, −60°, 4 hr | 94 | 6 | 85 |
| n-BuLi | THF, −20°, 2 hr | 40 | 60 | 92 |
| n-BuLi | THF, −60°, 2 hr | 4 | 96 | 96 |
| n-BuLi | Hexane, −60° | 56 | 44 | 71 |
| PhLi | THF, −60°, 2 hr | 0 | 100 | 90 |
| t-BuLi | THF, −60°, 2 hr | 0 | 100 | 95 |
| PhMgBr | Et₂O, 35°, 24 hr | 100 | 0 | 93 |
| MeMgI | Et₂O, 35°, 24 hr | 100 | 0 | 90 |
| | THF, 66°, 24 hr | 100 | 0 | 94 |

[a] The ratio of base to oxazine was 1.1:1. [b] These are conditions employed only to generate the anion, after which methyl iodide was introduced (10% excess). Reactions were stirred for 15–18 hr at room temperature. [c] Products were analyzed by gas chromatography.

was followed by gas chromatography after addition of methyl iodide to the solutions. As seen from the data, the recovery of oxazines, alkylated or not, was quite

good, indicating little decomposition during the experiments. Only n-butyl-, phenyl-, and tert-butyllithium were suitable as bases, whereas Grignard, alkoxide, hydride, and dimethylsulfinyl reagents failed. In addition, the temperature of the reaction was critical as seen by yields of alkylated oxazine at −20 and −60° using butyllithium. It should be noted that Table IV contains only a representative portion of the actual experiments performed in this study, and the results confirmed that an α-carbanion of dihydro-1,3-oxazines may indeed be efficiently prepared. For all practical purposes, the anion of the 2-methyloxazine was generated at −78° using 1.1 equiv of n-butyllithium and its formation was conveniently followed by the appearance of a bright yellow suspension. Upon addition of methyl iodide, the yellow suspension would, after several minutes, disappear, indicating that alkylation had occurred. This simple visual monitoring of the alkylation of oxazine carbanions would serve to indicate the reaction time for many different electrophiles to be described later.

An evaluation of the relative rates of anion formation (THF, −78°) with organolithium reagents followed the series

| Base | t-BuLi ＼ | n-BuLi ＼ | PhLi |
|---|---|---|---|
| Time, min | 5 ／ | 50 ／ | 85 |
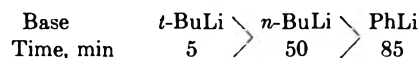
with the appearance of the yellow anion suspension at the time indicated. With regard to solvents, the use of ether or hexane failed to produce complete anion formation even after 12 hr and therefore was precluded in this process.

The nature of the alkyl halide was also investigated to determine the limitations in structure and leaving group which would be encountered. The results are given in Table V. Alkyl chlorides (entry 1) gave very

### TABLE V

EFFECT OF NATURE OF ELECTROPHILE ON ALKYLATION
OF OXAZINE CARBANION (−78°, THF)

$$DHO—CH_2Li \xrightarrow{RX} DHO—CH_2R$$

| Entry | RX | DHO— CH₂R, % | DHO—CH₃, % recovered[a] |
|---|---|---|---|
| 1 | n-BuCl | 6 | 88 |
| 2 | n-BuBr | 95 | 2 |
| 3 | n-BuI | 97 | 2 |
| 4 | n-BuOTs | 0 | 89 |
| 5 | i-PrI | 91 | 5 |
| 6 | 2-Bromopentane | 12 | 80 |
| 7 | 2-Bromobutane | 21 | 66 |
| 8 | Bromocyclopentane | 88 | 6 |
| 9 | 3-Bromocyclohexene | 93 | 2 |
| 10 | CH₃CH₂C≡CCH₂CH₂Br | 3 | 95 |
| 11 |  | 0 | 93 |
| 12 | PhCH₂Cl | 98 | 2 |
| 13 | CH₂=CHCH₂Cl | 90 | 5 |
| 14 | CH₃CH₂C≡CCH₂Cl | 94 | 2 |

[a] Estimated by vpc or nmr to be ±2% of stated value. All reactions run by generating DHO—CH₂Li at −78°, followed by addition of 1.1 equiv of alkyl halide. After the mixture was allowed to warm to room temperature overnight, it was quenched in ice–water, extracted with ether, concentrated, and examined by nmr and vpc.

TABLE VI

ALDEHYDES FROM OXAZINE CARBANIONS AND ALKYL HALIDES AND DIHALIDES
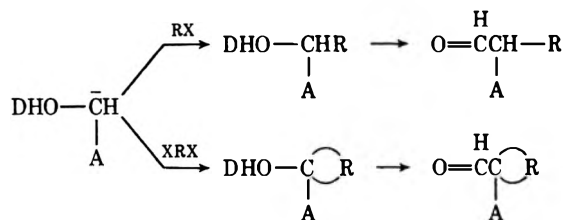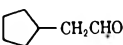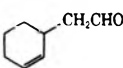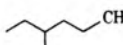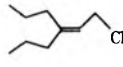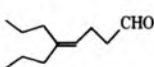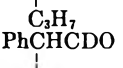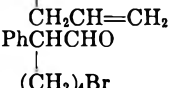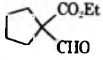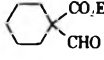


| Entry | Alkyl halide | Registry no. | Aldehyde | Yield, % | Mp of 2,4-DNP, °C | Registry no. |
|---|---|---|---|---|---|---|
| | | | **A = H** | | | |
| 1 | $CH_3I$ | 123-38-6 | $CH_3CH_2CHO$ | 60 | 149–150 | 725-00-8 |
| 2 | $n\text{-}C_3H_7I$ | 110-62-3 | $CH_3CH_2CH_2CH_2CHO$ | 65 | 102–104 | 2057-84-3 |
| 3 | $n\text{-}C_4H_9Br$ | 66-25-1 | $CH_3(CH_2)_4CHO$ | 65 | 102–103 | 1527-97-5 |
| 4 | $n\text{-}C_3H_7CD_2Br$ | | $CH_3(CH_2)_3CD_2CHO$ | a | | |
| 5 | $i\text{-}C_3H_7I$ | 590-86-3 | $(CH_3)_2CHCH_2CHO$ | 49 | 121–122 | 2256-01-1 |
| 6 | $CH_2{=}CHCH_2Br$ | 2100-17-6 | $CH_2{=}CH(CH_2)_2CHO$ | 51 | 116–118 | 1222-17-9 |
| 7 | $CH_3CH_2OCH_2CH_2Br$ | 21744-96-7 | $CH_3CH_2OCH_2CH_2CH_2CHO$ | 54 | 88–89 | 36873-54-8 |
| 8 | $ClCH_2CH_2CH_2Br$ | 20074-80-0 | $Cl(CH_2)_4CHO$ | 51 | 106–108 | 36873-55-9 |
| 9 | (cyclopentyl)–I | 5623-81-4 | (cyclopentyl)–$CH_2CHO$ | 49 | b | |
| 10 | (cyclohexenyl)–Br | 19656-95-2 | (cyclohexenyl)–$CH_2CHO$ | 50 | 93–94 | 19656-96-3 |
| 11 | $PhCH_2Br$ | 104-52-0 | $PhCH_2CH_2CHO$ | 57 | 153–154 | 1237-68-9 |
| 12 | (3-methylbutyl)–Br | 32749-94-3 | (CHO structure) | 44 | 86–87 | 14093-70-0 |
| 13 | (3-ethyl)–Cl | 34626-50-1 | (CHO structure) | 74 | b | |
| 14 | $ClCH_2CH_2Br$ | 36873-36-6 | (cyclopropyl)–CHO | 69$^d$ | 184–185 | |
| 15 | $Br(CH_2)_3Br$ | 2987-17-9 | (cyclobutyl)–CHO | 20$^c$ | 155–157 | 36873-59-3 |
| 16 | $Br(CH_2)_4Br$ | 872-53-7 | (cyclopentyl)–CHO | 38$^c$ | 153–154 | 20956-07-4 |
| | | | **A = Ph** | | | |
| 17 | $CH_3I$ | 93-53-8 | $Ph(CH_3)CHCHO$ | 65 | 133–134 | 5530-36-9 |
| 18 | $CH_3I$ (2.0 equiv) | 3805-10-5 | $Ph(CH_3)_2CCHO$ | 49 | 133–135 | 20401-28-9 |
| 19 | $n\text{-}C_3H_7Br$ | 21765-78-6 | $PhCHCHO$ <br> $\mid$ <br> $C_3H_7$ | 64 | 122–123 | 36866-52-1 |
| 20 | $CH_2{=}CHCH_2Br$ | 24036-43-9 | $PhCHCDO$ <br> $\mid$ <br> $CH_2CH{=}CH_2$ | 70$^e$ | 100–103 | 24036-44-0 |
| 21 | $Br(CH_2)_4Br$ | 29304-27-6 | $PhCHCHO$ <br> $\mid$ <br> $(CH_2)_4Br$ | 60 | 136–138 | 29304-28-7 |
| 22 | $BrCH_2CH_2Br$ | 21744-88-7 | Ph, CHO (cyclopropyl) | 57 | 186–188 | 36866-55-4 |
| 23 | $Br(CH_2)_3Br$ | 1469-83-6 | Ph, CHO (cyclobutyl) | 45$^c$ | 154–156 | 1812-69-7 |
| 24 | $Br(CH_2)_4Br$ | 21573-69-3 | Ph, CHO (cyclopentyl) | 50 | 161–163 | 1812-68-6 |
| | | | **A = CO$_2$Et** | | | |
| 25 | $C_2H_5Br$ | 36873-42-4 | $CH_3CH_2\overset{\displaystyle CO_2Et}{\underset{\mid}{C}}HCHO$ | 53 | b | |
| 26 | $C_3H_7Br$ | 36873-43-5 | $CH_3CH_2CH_2\overset{\displaystyle CO_2Et}{\underset{\mid}{C}}HCHO$ | 49 | 91–92 | 36866-58-7 |
| 27 | $n\text{-}C_4H_9Br$ | 19361-66-1 | $CH_3(CH_2)_3\overset{\displaystyle CO_2Et}{\underset{\mid}{C}}HCHO$ | 67 | 85–86 | 36866-59-8 |
| 28 | $CH_2{=}CHCH_2Cl$ | 36873-45-7 | $CH_2{=}CHCH_2\overset{\displaystyle CO_2Et}{\underset{\mid}{C}}HCHO$ | 47 | b | |

TABLE VI (*Continued*)

| Entry | Alkyl halide | Registry no. | Aldehyde | Yield, % | Mp of 2,4-DNP, % | Registry no. |
|-------|--------------|--------------|----------|----------|------------------|--------------|
| 29 | $CH_3I$ (2.0 equiv) | 14002-65-4 | $CO_2Et$ <br> $(CH_3)_2CCHO$ | 62 | 99–100 | 36866-60-1 |
| 30 | $Br(CH_2)_4Br$ | 21744-91-2 | (cyclopentane with $CO_2Et$ and CHO) | 68 | 134–135 | 21744-92-3 |
| 31 | $Br(CH_2)_5Br$ | 36873-48-0 | (cyclohexane with $CO_2Et$ and CHO) | 58 | 155–156 | 36866-62-3 |

[a] R. J. Liedtke and C. Djerassi, *J. Amer. Chem. Soc.*, 91, 6814 (1969). [b] Derivative not prepared, all spectral and elemental analyses consistent with correct structure. [c] Cycloalkyl dihydro-1,3-oxazine purified *via* bulb-to-bulb distillation prior to reduction step. [d] Isolated as 2,4-DNP derivative. [e] Reduction performed using sodium borodeuteride.

poor yields, whereas the corresponding bromides and iodides reacted efficiently (entries 2, 3). Tosylates (and mesylates), entry 4, were virtually inactive toward displacement by the oxazine carbanion, producing only the recovered oxazine and a 10% yield of the sulfone 22. The latter undoubtedly arises from nucleophilic
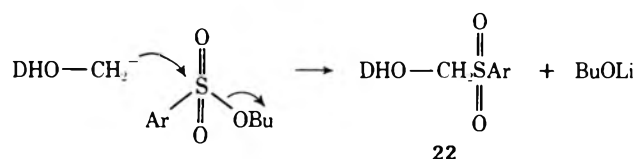


displacement on sulfur rather than carbon. Organolithium reagents have been reported[19] to displace tosylates only in ether solvent and fail to accomplish this transformation in tetrahydrofuran. Unfortunately, the oxazine carbanion cannot be prepared in good yields in ether solvent. Secondary halides of increasing steric bulk (entries 5, 6, 7) led to progressively poorer yields of alkylation and higher yields of elimination. On the other hand, secondary halides derived from alicyclic systems, where the steric bulk is reduced, afford good yields of alkylated product (entries 8, 9). A further limitation was observed when homopropargyl (or homoallylic) halides were investigated. The result was essentially complete recovery of oxazine by virtue of extensive elimination to the conjugated ene-yne (or diene) systems (entry 10). Thus, the acidity of the propargylic (or allylic) proton competes favorably with halide substitution, rendering alkylation unsatisfactory when this structural feature is present. The *endo*-bromomethylnorbornene (entry 11), owing to the limited accessibility to the electrophilic site, also failed to alkylate the oxazine carbanion. Activated chlorides (entries 12, 13, 14) behaved normally and led to good yields of alkylated oxazines. It should be noted here that *in no instance was there observed N-alkylation of the oxazine or polyalkylation of the 2-methyl group*.

The lack of polyalkylation was indeed a surprising result in light of the fact that the 2-methyloxazine 18 contains two remaining α hydrogens which should be capable of further reaction with either butyllithium or the lithio oxazine. The fact that intramolecular cyclization of 2-(ω-bromoalkyl)oxazines (23) was ef-



fected by butyllithium to the cycloalkyl derivatives 24 and ultimately to cycloalkanecarboxaldehyde (Table VI, entries 14–16) further contributed to the inconsistent behavior of 2-alkyloxazines. A systematic study of primary, secondary, and tertiary carbanions derived from 2-alkyloxazines was undertaken and led to the understanding of this behavior. The 2-methyl (18), 2-ethyl (18a), and the 2-isopropyl oxazines (18b) were examined since these are all capable of producing a primary, secondary, and tertiary carbanion, respectively.
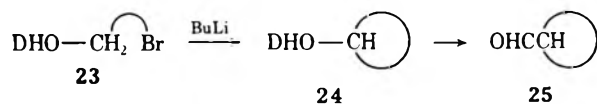
The lithio oxazine 26 was formed in the usual manner (butyllithium, −78°, THF) and allowed to warm to room temperature in the absence of an external electrophile. Upon quenching in water, the product, isolated in 84% yield, was the dimeric oxazine 30. Thus, it appears that the primary carbanion which is stable and capable of alkylation at −78° slowly rearranges, as the temperature rises, to the ketenimine 27 ($R_1 = R_2 =$ H) and is alkylated by unrearranged carbanion producing the adduct 29 ($R_1 =$ H). Hydrolysis leads to the dimer 30, which arises from cyclization of the initially formed hydroxy imine. The bicyclic dimer 30 is temperature sensitive and upon heating (∼190°) or injecting into a vpc instrument whose injection port is heated to 200°, a facile reversal occurs and the 2-methyloxazine 18 is recovered quantitatively. In the case of 18a, no secondary carbanion 26a was formed when treated with butyllithium at −78 to −50° as evidenced by the lack of methylation (methyl iodide) or deuteration ($D_2O$). When a solution containing the 2-ethyloxazine and 1.0 equiv of butyllithium was allowed to warm from −50° to room temperature with or without methyl iodide present, the yield of 2-isopropyloxazine (18b) was less than 10% while the dimer 30a was isolated in 88% yield. The latter could be obtained pure by distillation below 120°, a temperature insufficient to cause reversal to the monomeric oxazine 18a. A small volatile forerun in this distillation was also trapped in a Dry Ice collector and characterized only through its infrared spectrum, which indicated C=C=N (2060 cm$^{-1}$) and OH (3550 cm$^{-1}$) absorption. This product was presumably 27 (Li = H, $R_1 =$ H, $R_2 =$ $CH_3$) formed by hydrolysis of the O-lithio salt during aqueous work-up. This behavior is consistent with the lower acidity of the α proton in the 2-ethyloxazine, which is removed only after the temperature rises in the range −50 to 25° and rearrangement of 26a ($R_1 =$ H, $R_2 =$ $CH_3$) to the ketenimine 27 occurs. Since this secondary carbanion forms at a temperature to which it is unstable,

(19) W. D. Korte and L. Kinner, *Tetrahedron Lett.*, 603 (1970).

rearrangement ensues and alkylation by electrophiles cannot compete meaningfully. Turning to the 2-isopropyloxazine **18b** as a precursor to a tertiary carbanion, no proton abstraction takes place with butyllithium in THF from −78 to 0°. This was determined by lack of deuteration or the absence of any dimeric products. However, when **18b** in THF containing butyllithium was allowed to stand at room temperature, followed by the addition of trimethylchlorosilane, a 35% yield of the ketenimine trimethylsilyl ether **28** was isolated. The remainder of the material was addition product between the ketenimine and *n*-butyllithium acting as a nucleophile. This latter process has formed the basis for a useful ketone synthesis which will be described in detail in a future paper.[20] The ketenimine was prepared in good yield (77%) by using lithium diisopropylamide in place of butyllithium as the base to remove the tertiary proton. The reason for this improved yield is the fact that the diisopropyl amide, although serving as a good base, is too bulky to add to the ketenimine once formed. The lack of dimer from **18b** as well as the high yield of ketenimine **28** is



18, $R_1 = R_2 = H$
18a, $R_1 = H$; $R_2 = CH_3$
18b, $R_1 = R_2 = CH_3$

26, $R_1 = R_2 = H$
26a, $R_1 = H$; $R_2 = CH_3$
26b, $R_1 = R_2 = CH_3$

30, $R_1 = H$
30a, $R_1 = CH_3$
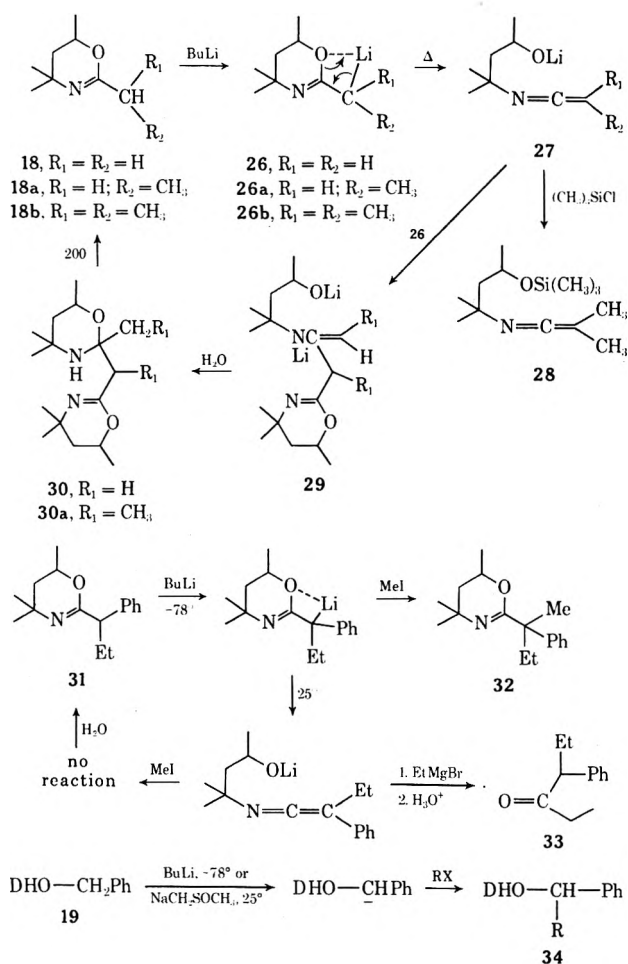
consistent with the fact that the tertiary carbanion **26b** is formed at a temperature (0–20°), which virtually forbids its existence, and rearrangement is sufficiently rapid that no opportunity for dimer formation is present.

This oxazine–ketenimine rearrangement was further studied using a system (**31**) which was deemed suitable for observing both the carbanion and the ketenimine

(20) Preliminary results have been reported: A. I. Meyers, E. M. Smith, and A. F. Jurjevich, *J. Amer. Chem. Soc.*, **93**, 2314 (1971).

intermediates. By treating **31** with butyllithium at −78° it was shown that the α proton can be removed owing to the delocalization of the anion by the adjacent phenyl group. Addition of methyl iodide at −78° led to the α-methyloxazine **32** in 95% yield. However, if the lithio oxazine was allowed to warm to room temperature and then treated with methyl iodide, the product obtained after aqueous work-up was only the starting oxazine **31**. On the other hand, if ethylmagnesium bromide was added to the lithio oxazine at room temperature and then quenched with water, the ketone **33** was isolated in good yield. The presence of the ketone confirmed that the lithio oxazine had rearranged to the ketenimine on warming to room temperature and had been alkylated by the Grignard reagent. The resulting adduct would then be a typical enamine which is expected to produce the ketone in aqueous medium.[20]

The alkylation of 2-benzyl dihydro-1,3-oxazine (**19**) was found to proceed *via* its carbanion to α-alkyl-α-phenyl oxazines (**34**) in high yield. The carbanion could be formed in this case using either butyllithium (−78°, THF) or the methylsulfinyl carbanion (DMSO, 25°) developed by Corey.[21] Furthermore, as seen from Table IV, the 2-methyloxazine was inert to prolonged contact with Grignard reagents; yet this was not the case with the 2-benzyloxazine. Owing to the increased acidity of the benzyl protons, Grignard reagents were found, after lengthy exposure (25°, 24 hr), to abstract the α proton of **19** (determined by deuteration). This behavior was not observed (Table IV) when the oxazine bears only a 2-alkyl substituent and will be shown later to provide a useful method for performing Grignard reactions in the presence of the oxazine ring.

Turning now to the 2-carboethoxy dihydro-1,3-oxazine (**20**) and its potential for elaboration, it was seen early in the study by ir and nmr that it existed in two tautomeric forms, **20a** and **20b**. The α protons in **20a** are readily exchanged with deuterium oxide and the anion **35** could be routinely prepared by the usual alkoxides in alcohol. The use of the nonnucleophilic bases, sodium hydride or potassium *tert*-butoxide, was found to be preferable, since ethoxide ion slowly caused ring rupture of the oxazine ring. When **35** was formed in THF, DMSO, or HMPA and treated with benzyl bromide, a mixture of mono- and dialkylated oxazines, **36** and **37**, was formed. The dialkylated product could be formed in high yield by utilizing 2.0 equiv of base; however, all attempts to prepare only the monoalkylated product **36** (R = benzyl) met with little success. It was further found that the mono- and dialkylated oxazine could also be formed by merely heating a solution of **20** with benzyl bromide in acetonitrile, thus confirming the enamine characteristics of the carboethoxy oxazine. However, when **20** was heated with an unactivated bromide (*n*-butyl bromide) in acetonitrile, only the monoalkylated product **38** and starting material **20** were recovered in a 1:1 mixture. It thus became obvious that the enamine **39** was incapable of being alkylated by simple alkyl bromides, even at reflux temperatures of acetonitrile. This parallels the behavior of simple enamines, which also give poor yields of alkylation products with unactivated

(21) E. J. Corey and M. Chaykovsky, *ibid.*, **84**, 867 (1962).
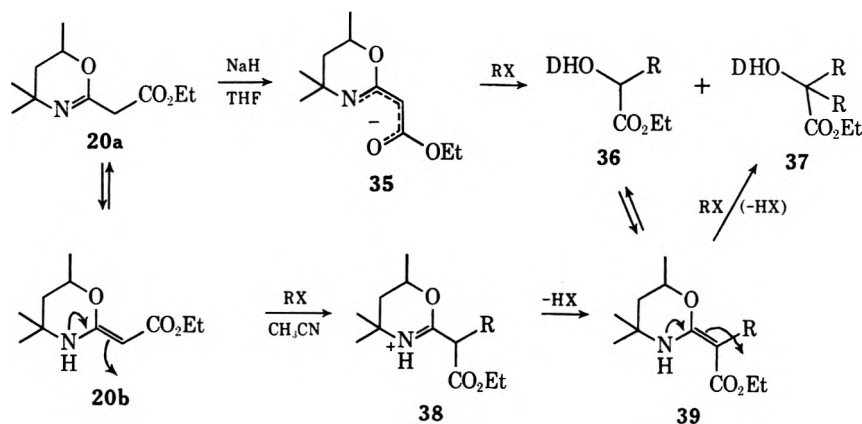
halides, whereas good yields are obtained with highly electrophilic halides.[22] The process was then reexamined using unactivated alkyl bromides on the anion **35**. The results are given in Table VII. In all cases good

### TABLE VII
#### ALKYLATION OF THE 2-CARBOETHOXYMETHYL OXAZINE 20 WITH ALKYL HALIDES

$$\text{DHO—CH}_2\text{CO}_2\text{Et} \xrightarrow[\text{2. RX, CH}_3\text{CN, 80°}]{\text{1. RX, base, 25°}}$$
**20**

$$\text{DHO—CHCO}_2\text{Et} + \text{DHO—CCO}_2\text{Et}$$

| RX | Alkylation method[a] | 20,[b] % | 36,[b] % | 37,[b] % |
|---|---|---|---|---|
| Ethyl bromide | A | 2 | 96 | 2 |
| | B | 47 | 53 | |
| n-Propyl bromide | A | 3 | 94 | 2 |
| | B | 40 | 60 | 0 |
| n-Propyl iodide | B | 29 | 67 | 4 |
| n-Butyl bromide | A | 2 | 94 | 4 |
| | B | 50 | 50 | 0 |
| Benzyl bromide | B | 10 | 50 | 40 |
| Benzyl chloride | B | 13 | 73 | 12 |
| 2-Bromohexane | A | 20 | 75 | 0 |
| BrCH₂CH(OEt)₂ | A | 20 | 80 | 0 |

[a] Method A—The anion of **20** was formed using 1.1 equiv of potassium *tert*-butoxide or sodium hydride in THF or DMSO. Reactions, after addition of the alkyl halide, were allowed to stir for 18 hr at room temperature. Method B—Equimolar quantities of **20** and alkyl halide were heated in anhydrous acetonitrile for 24–48 hr, the solvent was evaporated, and the residue was neutralized with 10% sodium bicarbonate, extracted with ether and concentrated. [b] Determined by gas chromatographic analysis.

yields of the monoalkylated oxazine **36** were produced when the anion was treated at room temperature with primary or secondary alkyl halides. A technique for synthesis of either mono- or dialkylated carboethoxy oxazines was now in hand.

With the alkylation, reduction, and cleavage of the oxazines **18–20** demonstrated to be a feasible sequence, the synthetic utility of this method was investigated to determine its scope for the preparation of a variety of aldehydes.

**Synthesis of Aldehydes. Substituted Acetaldehydes.**—The carbanions derived from dihydro-1,3-oxazines **18–20** were subjected to alkylation with

various alkyl halides and dihalides, reduced with sodium borohydride or deuteride, and hydrolyzed to the corresponding aldehydes (Table VI). Since several aldehydes were obtained directly as the 2,4-DNP derivatives (entry 14), it was of interest to determine if aldehydes could be isolated as other derivatives. When the cyclohexenyl oxazine **40** was reduced to the
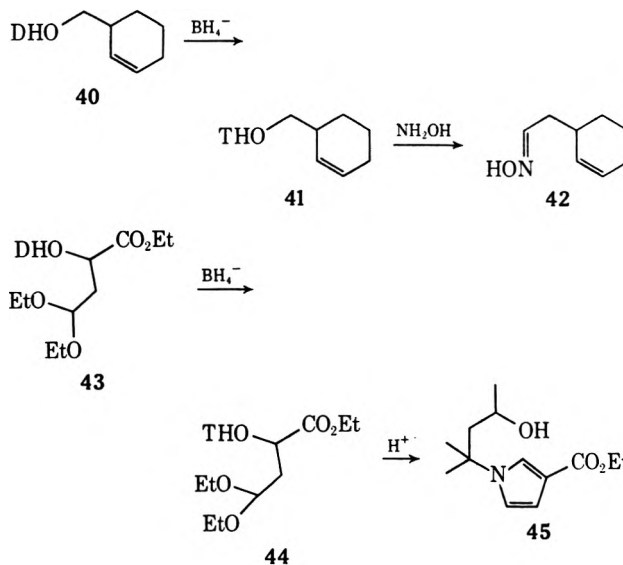


tetrahydro-1,3-oxazine **41** and treated with hydroxylamine hydrochloride in boiling ethanol, a good yield of the oxime **42** was obtained. The ester oxazine **43**, which was smoothly reduced to the tetrahydro derivative **44**, underwent pyrrole formation to **45** rather than the expected cleavage to the dialdehyde.[23] A recent report[24] described the conversion of the tetrahydro-1,3-oxazine **46** to the nitrone **47** which proceeded directly in an *in situ* intramolecular 1,3-dipolar addition to the isoxazolidine. The ability to reduce an acetylenic linkage in the presence of the oxazine ring was demonstrated by the transformation of **49** to the cis olefin without effect upon the oxazine moiety. Reduction and hydrolysis of the oxazine ring led to the cis aldehyde **50** in 54% overall yield.[25]

(22) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovic, and R. Terrell, *J. Amer. Chem Soc.*, **85**, 207 (1963).

(23) A. I. Meyers, T. A. Narwid, and E. W. Collington, *J. Heterocycl. Chem.*, **8**, 875 (1971).

(24) N. A. LeBel and E. G. Banucci, *J. Org. Chem.*, **36**, 2440 (1971).

(25) Olefin linkages present on the side chain of dihydro-1,3-oxazines may also be saturated (PtO₂, EtOH, 25°, 30 min) without any effect upon the heterocycle. We thank Dr. Harvey Taylor of these laboratories for these experiments.

SCHEME IV

$$\text{DHO—CH}_2\text{Li} \quad + \quad \text{Br(CH}_2)_5\text{Br}$$

$\downarrow$

OHCCH$_2$(CH$_2$)$_4$CH$_2$CO$_2$Et          DHO—CH$_2$(CH$_2$)$_4$CH$_2$Br $\longrightarrow$ OHCCH$_2$(CH$_2$)$_4$CH$_2$Br

**57**                                          **52**                                          **53**

$\uparrow$                                          $\downarrow$ CN$^-$/DMSO

DHO—CH$_2$(CH$_2$)$_4$CH$_2$CO$_2$Et $\xleftarrow[\text{EtOH}]{\text{HCl}}$ DHO—CH$_2$(CH$_2$)$_4$CH$_2$CN $\longrightarrow$ OHCCH$_2$(CH$_2$)$_4$CH$_2$CN

**56**                                          **54**                                          **55**

$\downarrow$ a) PhMgBr
   b) H$_3$O$^+$

OH
|
DHO—CH$_2$(CH$_2$)$_4$CH$_2$CHPh $\underset{\text{CrO}_3,\text{Py}}{\overset{\text{LiAlH}_4 \text{ or NaBH}_4}{\rightleftharpoons}}$ DHO—CH$_2$(CH$_2$)$_4$CH$_2$CPh $\longrightarrow$ OHCCH$_2$(CH$_2$)$_4$CH$_2$CPh (C=O)

**61**                                          **58**                                          **59**

$\downarrow$

OHCCH$_2$(CH$_2$)$_4$CH$_2$CHPh
|
OH

**60**



46, R = H, Me



47          48



49



50
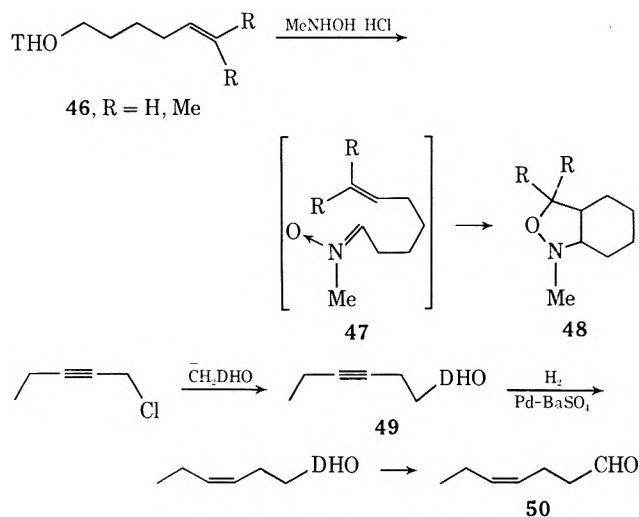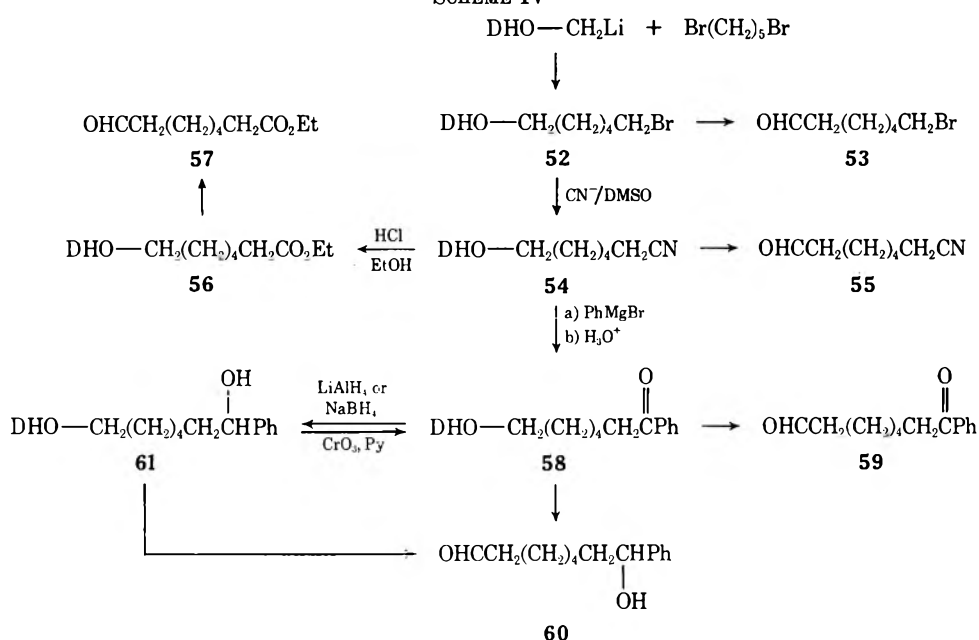
The major limitation to the aldehyde synthesis is found when the α carbon of the oxazine was completely substituted (**51**). Thus, when three alkyl



51 (R$_1$ = R$_2$ = R$_3$ > CH$_3$ or Aryl)
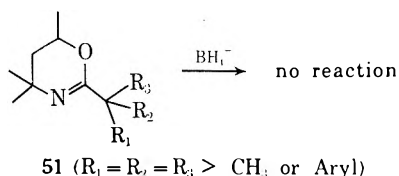
groups (except methyl) were present, the borohydride reduction failed to reduce the C=N link. This is an obvious steric effect which prohibits hydride addition when a bulky quaternary carbon is present. This limitation is not encountered when two of the substituents are part of a cyclic moiety (Table VI, entries 22–24, 30, 31) or when two of the groups are methyl (entries 18, 29). There is an advantage to this finding in that the cases where polyalkylation is possible (*i.e.*, **20**) producing mono- and dialkylated oxazines **36** and **37**, respectively (Table VII), only the former will reduce to the tetrahydro oxazine. The aldehyde thus produced is free from the dialkylated isomer, since the dihydro oxazine **20** does not form any interfering prod-

ucts (Table VI, entries 25–28) upon oxalic acid hydrolysis.

The incorporation of functionality into the aldehydes prepared by the oxazine route was further investigated using the ω-bromohexyl oxazine **52** formed from the carbanion (CH$_2$DHO) and 1,5-dibromopentane. The bromohexyl oxazine could be prepared and utilized without purification for subsequent transformations. It was found, however, preferable in some cases to isolate **52** in pure form (70–80%). This compound was chosen as a typical substrate for which a variety of reactions could be evaluated (Scheme IV). As expected, the bromohexyl oxazine was routinely converted to 7-bromoheptaldehyde **53** by the borohydride–oxalic acid sequence. Reaction of **52** with sodium cyanide in dimethyl sulfoxide[26] at 55° furnished the cyanohexyl oxazine **54** in excellent yield. The latter was also found to be a suitable precursor to 7-cyanoheptaldehyde (**55**). Treatment of the cyanohexyl oxazine with ethanolic hydrogen chloride cleanly produced the ester oxazine **56** and this was transformed into the ester aldehyde **57** in the usual fashion.

Since the metalation study mentioned earlier (Table IV) indicated no reaction of the oxazines under prolonged contact with Grignard reagents, the cyanohexyl oxazine **54** was treated with phenylmagnesium bromide and afforded the keto oxazine **58** without interference by the oxazine ring. The borohydride reduction at −45° could be controlled with the quantity of reducing agent to give either the keto aldehyde **59** or the hydroxy aldehyde **60** after oxalic acid cleavage. Of additional interest is the fact that *the keto oxazine* **58** *was reduced to the hydroxy oxazine* **61** *by sodium borohydride in ethanol–water (pH 11) at 0–25° without reducing the C=N link.*[27] The unusual stability of the dihydro-1,3-oxazine ring system was further revealed

(26) L. Friedman and H. Schechter, *J. Org. Chem.*, **25**, 877 (1960). The crude 6-bromohexyloxazine **38**, formed in 90% yield, could also be transformed into the nitrile **40**, and the latter purified by distillation. This gave somewhat higher yields of nitrile.

(27) It was also observed that lithium aluminum hydride will not attack the dihydro-1,3-oxazine ring at room temperature for 16 hr. In this fashion, **58** was reduced to **61** in ether or THF.

by its inertness to oxidizing agents and the absence of amine oxide formation during the transformation of the hydroxy oxazine **61** to the ketone **58**. The outline described by Scheme IV serves to illustrate the versatility of bromoalkyl oxazines and the ability of the heterocyclic ring to withstand a variety of reaction conditions. A similar sequence was performed using the related bromopentyl and bromobutyl oxazines. However, there was considerable production of the cyclic oxazinium salts **62** and **63**, which were isolated



$$n = 1, 2$$
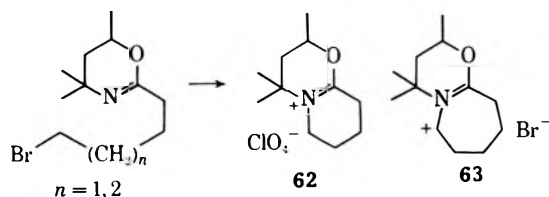
as the stable perchlorate and bromide, respectively. This facile ring closure was mainly responsible for the low yield of cyclobutanecarboxaldehyde (entry 15, Table VI). The preparation of the corresponding chlorobutyl and chloropentyl oxazines took place without undue difficulty. The former was sufficiently stable to be utilized as the precursor to 5-chlorovaleraldehyde (entry 8, Table VI). Presumably, the reactions surveyed in Scheme IV could be applied to the chlorobutyl and chloropentyl oxazines, although this was not pursued.

The inertness of the oxazines toward Grignard reagents was further demonstrated by the ready formation of the Grignard reagent **64** from the 6-bromomethyloxazine **52**. The reagent could be formed in ether or tetrahydrofuran, although it is sparingly soluble in the former solvent. A series of electrophiles, E, was examined with varying degrees of success. Addition of deuterium oxide to **64** led to the 6-deuteriohexyloxazine **65** (E = D) in over 92% yield and ultimately to the deuterated aldehyde **66** (E = D) in 52% overall yield. Surprisingly, the oxazine Grignard failed to react to any appreciable extent with benzaldehyde, benzonitrile, 3-pentanone, or ethyl chloroformate; in each instance the 2-hexyloxazine **65** (E = H) was recovered in high yield. Relying on the assumption that the lone electron pairs present on oxygen and nitrogen were complexing with the magnesium (intra- or intermolecularly) the reactions were repeated using magnesium bromide. The purpose of the salt was twofold: (a) to complex with either oxygen and nitrogen, thus releasing the Grignard complex, and (b) to enhance the electrophilic nature of the electrophiles. Indeed, when an ethereal solution of the 6-bromohexyloxazine was treated with magnesium metal containing 1 equiv of magnesium bromide (prepared from ethylene dibromide and magnesium), there was no precipitation of the Grignard reagent, but a two-phase solution. Addition of benzaldehyde led to the normal addition product **65** (E = HCOHPh) in 65% yield. The structure was proved by simple comparison to **61** prepared earlier by the route in Scheme IV. Reaction of the Grignard **64** in the presence of magnesium bromide with ethyl chloroformate or benzonitrile furnished the oxazine **65** (E = CO₂Et and COPh, respectively). These were likewise identified by comparison with the oxazines **56** and **58** prepared from the cyano-

$$DHO\!-\!CH_2(CH_2)_4CH_2MgBr \xrightarrow[MgBr_2]{E}$$
$$64$$

$$DHO\!-\!CH_2(CH_2)_4CH_2E \longrightarrow OHC(CH_2)_5CH_2E$$
$$65 \qquad\qquad\qquad\qquad 66$$

| E | 65, 66 |
| --- | --- |
| | D |
| D₂O | CO₂Et (56, 57) |
| ClCO₂Et | CH(OH)Ph (61, 60) |
| PhCHO | COPh (58, 59) |
| PhCN | |
| Et₂C=O | |
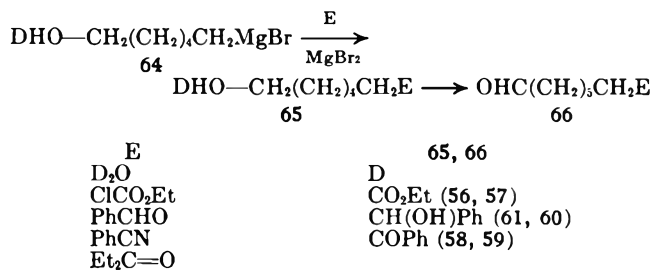
hexyl oxazine **54**. It should be noted here that these reactions were less efficient (35–50%) than those produced from the cyanohexyl oxazine, and the latter is considered to be a more advantageous route. When the Grignard **64** was treated with 3-pentanone with or without magnesium bromide present, no reaction occurred. It is therefore concluded that the oxazine Grignard reagent **64** is lacking in its nucleophilic reactivity, owing perhaps to considerable complexation, solubility (two-phase liquid system), and the length of the hydrocarbon chain. The latter feature has been noted to reduce reactivity of Grignard reagents.[28]

The successful implementation of functional group incorporation into 2-substituted dihydro-1,3-oxazine (*i.e.*, **52**) took on an added importance when it was learned that the oxazine carbanion lacked specificity in reaction with functionalized halides (Scheme V).

SCHEME V

$$DHO\!-\!CH_2Li + BrCH_2(CH_2)_nX \longrightarrow$$
$$X = CN, n = 1\text{-}4$$
$$X = CO_2Et, n = 1\text{-}4$$

$$DHO\!-\!CH_3 + DHO\!-\!CH_2\overset{\overset{\displaystyle O}{\|}}{C}(CH_2)_nCH_2Br +$$
$$DHO\!-\!CH_2CH_2(CH_2)_nX$$
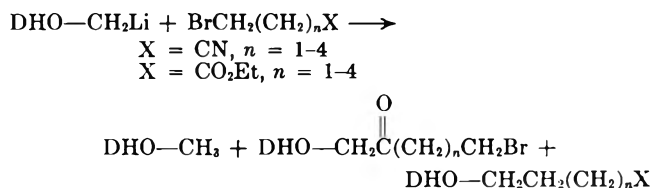
Thus, addition of bromo esters or nitriles of varying chain lengths led to products from proton abstraction, displacement of halides, and addition to the unsaturated sites.

In contrast to the results in Scheme V, the anion derived from the benzyl oxazine reacted cleanly with 5-bromovaleronitrile, displacing bromide ion only. Sequential borohydride reduction and hydrolysis produced the cyano aldehyde **67** in good overall yield.



$$67$$
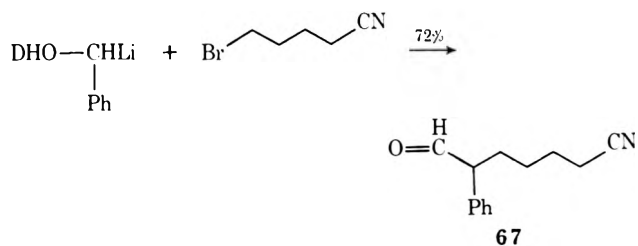
The benzyl carbanion, owing to its enhanced delocalization by the phenyl group, is significantly less reactive and therefore more selective.

Reactions of α,ω-dihalides with 2.0 equiv of the oxazine carbanions led to double halide displacements and ultimately to α,ω-dialdehydes (Scheme VI). The

(28) Long-chain Grignard reagents have been shown to react with less efficiency than their more compact counterparts (Kharash and Reinmuth, "Grignard Reaction of Non-Metallic Substances," Prentice-Hall, Englewood Cliffs, N. J., 1954).

TABLE VIII

γ-HYDROXY ALDEHYDES AND OXO DERIVATIVES FROM DIHYDRO-1,3-OXAZINES

| Oxazines | Epoxide | Additional electrophile | Aldehyde[i,j] | Registry no. | Yield, % |
|---|---|---|---|---|---|
| DHO—CH₃ | Ethylene | | OHC~~~OH | 1708-33-4 | 64[a] |
| DHO—CH₃ | Ethylene | Ethyl iodide | OHC~~~OEt | | 59[b] |
| DHO—CH₃ | Ethylene | Benzoyl chloride | OHC~~~OCOPh | 22927-31-7 (23107-26-8) | 67[c] |
| DHO—CH₃ | Styrene | | OHC~CH(Ph)OH | 36866-66-7 (22927-20-4) | 68[d] |
| DHO—CH₃ | Cyclohexene | | OHC—CH₂-cyclohexyl-OH | 36871-99-5 (23099-01-6) | 57[e] |
| DHO—CH₂Ph | Ethylene | | OHC—CH(Ph)—CH₂OH | 36866-68-9 (22927-21-5) | 69[f] |
| DHO—CH₂Ph | Styrene | | OHC—CH(Ph)—CH(Ph)OH | 36866-70-3 (22927-22-6) | 65[g] |
| DHO—CH₂Ph | Cyclohexene | | OHC—CH(Ph)-cyclohexyl-OH | 36872-01-2 (22985-63-3) | 60[h] |

[a] Owing to high aqueous solubility, product was isolated as 2,4-DNP, mp 116–118°.   [b] 2,4-DNP, mp 88–89°.   [c] 2,4-DNP, mp 103–105°.   [d] 2,4-DNP, mp 106–107°.   [e] 2,4-DNP, mp 78–79°.   [f] 2,4-DNP, mp 99–101°.   [g] 2,4-DNP, mp 146–147°.   [h] 2,4-DNP, mp 174–175°.   [i] All hydroxy aldehydes existed predominantly as their cyclic acetals.   [j] Registry numbers for 2,4-DNP derivatives are given in parentheses.

SCHEME VI
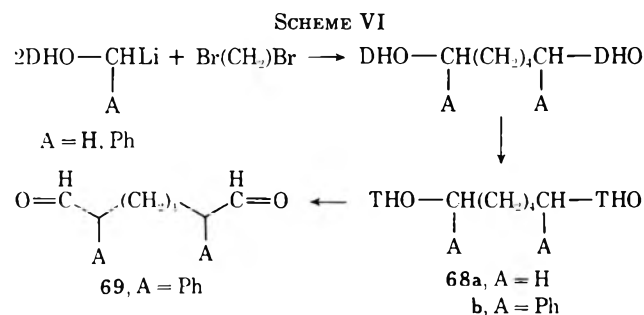


preparation of 2,7-diphenyl-1,8-octanediol (**69**) is exemplary of this approach. The unstable nature of simple α,ω-dialdehydes to oxalic acid solution and their high solubility in aqueous media precluded their efficient isolation from the cleavage of bistetrahydro-1,3-oxazines, **68a**. Nevertheless, the latter derivatives may be purified and stored in their "protected" form for subsequent use. The simplest dialdehyde prepared *via* this method was the tetrahydro-1,3-oxazine derivative of succindialdehyde. This was formed by addition of ethylene bromide to the oxazine carbanion which gave, *in situ*, the bromomethyl derivative **70** followed by rapid displacement with unreacted carbanion to the bisoxazine **71**. Reduction with sodium borohydride
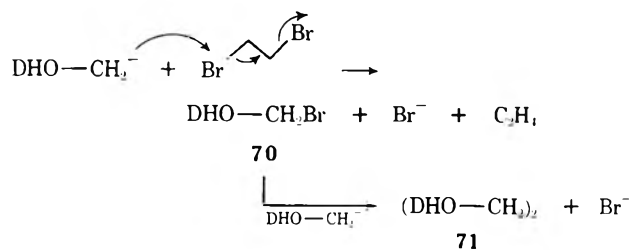


led to the masked succindialdehyde. When 1-chloro-2-bromoethane was used in place of ethylene bromide, alkylation proceeded normally to the chloropropyl derivative (Table VI, entry 14).

Epoxides also served as useful electrophiles, alkylating the oxazine carbanions in good yield (Scheme VII).

SCHEME VII
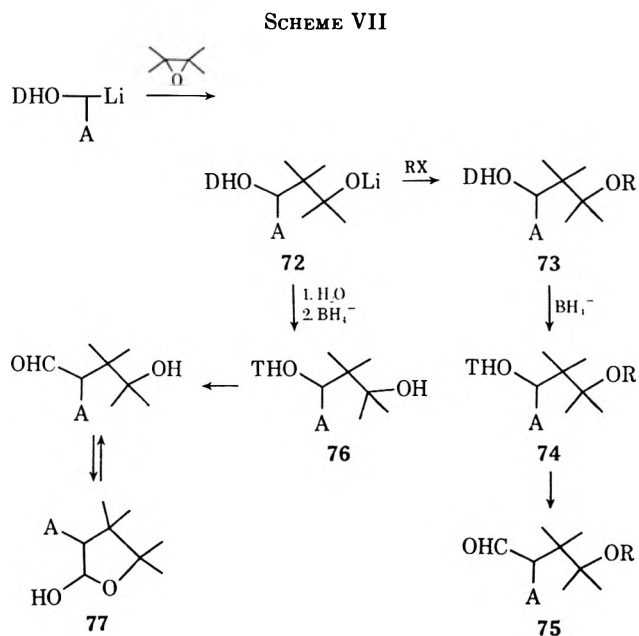


The usual borohydride hydrolysis sequence furnished γ-hydroxy aldehydes (Table VIII). The initially formed alkoxides **72** were treated as their lithio salts *in situ* with several typical electrophiles (ethyl iodide, benzoyl chloride) at room temperature in THF solution in anticipation of preparing **73**. However, no

significant amount of alkylation occurred. The highly covalent oxygen–lithium bond in **72** is undoubtedly a poor nucleophile,[29] this prohibiting any further alkylation. Nevertheless, the hydroxypropyl oxazines **73** (R = H) were conveniently alkylated by treatment with sodium hydride to form the sodium alkoxide **73** (R = Na) followed by the addition of an electrophile (Table VIII). In this fashion, after reduction to the tetrahydro oxazine **74**, the oxo derivatives **75** of the γ-hydroxy aldehydes were obtained. Similarly, borohydride reduction of crude oxazines **72** produced the tetrahydro derivatives **76** and ultimately the hydroxy aldehydes **77**, which existed predominantly in their hemiacetal forms. This approach to γ-oxygenated aldehydes represents a distinct improvement over previous methods, which require oxidative cleavage of 4-alken-1-ols and are only sparsely described in the literature.[30]

**α,β-Unsaturated Aldehydes.**—The utilization of carbonyl components as electrophiles to effect a two-carbon homologation to α,β-unsaturated aldehydes has been reported using lithio imines,[31] imino phosphoranes,[32] acetaldehyde ylides,[33] and more recently 1,3-bis(thiomethyl)allyl anions.[34]
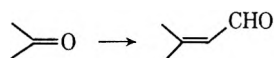
The reaction of lithio oxazines with a variety of carbonyl compounds produced at −78° the adducts **78** after quenching. Early attempts to purify these adducts by distillation resulted in facile thermal retrocondensation to starting materials. This is not unexpected owing to the built-in basic site and the well-known retro condensation of "aldol-type" products under the influence of base and heat. Fortunately, purification of **78** is not a necessary prerequisite to the success of the overall sequence and this step is readily circumvented by reduction of crude **78** to the tetrahydro-1,3-oxazine, **79**. The strong hydrogen bonding in **78** and **79** is readily seen by the infrared absorption

(3350–3200 cm⁻¹), and this property is manifested in the rapid movement of these compounds on tlc. Hydrolytic cleavage of **79** in oxalic acid solution provides the α,β-unsaturated aldehydes (Table IX). The pronounced

stability of certain hydrogen-bonded tetrahydro-1,3-oxazines (*e.g.*, **80**), derived from 2-pyridinecarboxaldehyde, precluded its use as a route to 2-pyridyl-2-acrolein.[35] The latter could not be cleaved under a variety of acidic conditions, although the 3- (and 4-) pyridine derivatives **81** behaved in the expected manner (Table IX, entry 24, 25). Attempts to disrupt the hydrogen bonding by conversion to the olefin **82** were fruitless.[36] In certain instances, the unsaturated aldehydes obtained from the acidic cleavage were mixtures containing the β,γ isomers (entries 3, 5, 6, 7) which reflected their relative thermodynamic stabilities.

**α-Alkyl Aldehydes.**—The utility of the 2-vinyl-dihydro-1,3-oxazine **21**, as a potential source of β-substituted propionaldehydes (Scheme VIII) by virtue of a
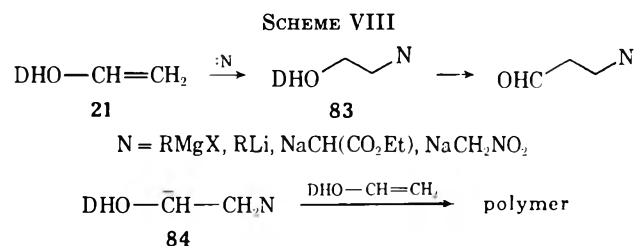
Michael-type addition of various nucleophiles, was investigated. When Grignard or organolithium reagents were added to **21** in THF, ether, or pentane in the temperature range −78 to 25°, only polymeric material was obtained. On the other hand, the use of sodiomalonic ester in ethanol produced the Michael adduct **83** [N═CH(CO₂Et)₂] in excellent yield. It therefore appears that the initially formed secondary anion **84** is highly unstable (as in **26a**) and proceeds, in the presence of vinyl functions, on to polymer. In the presence of a protic solvent, however, the anion is rapidly intercepted and the reaction produces the expected product.

In order to circumvent this problem, it was decided to introduce an electrophilic trapping agent (methyl iodide) prior to addition of the organometallic in anticipation that the carbanion **84** would be efficiently alkylated, thus intercepting the polymerization process. Indeed, this experimental modification proved to be a desirable one. The addition of phenylmagnesium bromide to a THF solution containing **21** and 1.1–1.5 equiv of methyl iodide resulted in a 85–90% yield of dialkylated oxazine **85** (R = Ph). Repeating the reaction with phenyllithium, on the other hand, still resulted in extensive polymerization. This may be

## Scheme VIII

DHO—CH═CH₂ $\xrightarrow{:N}$ DHO⁓N → OHC⁓N

**21**  **83**

N = RMgX, RLi, NaCH(CO₂Et), NaCH₂NO₂

DHO—C̄H—CH₂N $\xrightarrow{\text{DHO—CH═CH}_2}$ polymer

**84**

(29) W. E. Truce and L. W. Christensen, *J. Org. Chem.*, **36**, 2538 (1971).

(30) R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. Fr.*, 197 (1948); B. Helfrich and O. Lecher, *Chem. Ber.*, **54**, 930 (1921).

(31) G. Wittig and H. Reiff, *Angew. Chem., Int. Ed. Engl.*, **7**, 7 (1968).

(32) W. Nagata and Y. Hayase, *Tetrahedron Lett.*, 4359 (1968).

(33) For a review of this subject *cf.* A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, pp 152, 205.

(34) E. J. Corey, B. W. Erickson, and R. Noyori, *J. Amer. Chem. Soc.*, **93**, 1724 (1971).

(35) Table IX, ref *f*.

(36) A recent modification of this synthesis using the Wittig reagent of dihydro-1,3-oxazines, DHO—CH═PPh₃, has been shown to give the corresponding olefins with carbonyl compounds. This technique now allows the formation of certain α,β-unsaturated aldehydes by omitting the hydroxy adduct (G. R. Malone, Ph.D. Thesis, Wayne State University, 1972).

TABLE IX
FORMATION OF $\alpha,\beta$-UNSATURATED ALDEHYDES FROM DIHYDRO-1,3-OXAZINES

| Entry | Carbonyl component | $\alpha,\beta$-Unsaturated aldehydes | Registry no. | Overall yield, % | 2,4-DNP, mp, °C | Registry no. |
|---|---|---|---|---|---|---|
| 1 | (CH₃)₂C=O | (CH₃)₂C=CH–CHO | 107-86-8 | 50 | 221–222[g] | 6106-53-2 |
| 2 | ethyl methyl ketone | =CH–CHO | 21849-62-7 | 62 | 169–170[g] | 36866-89-4 |
| 3 | dipropyl ketone | CHO (+ 10% $\beta,\gamma$) | 34626-45-4 | 73 | | |
| 4 | cyclopentanone | =CH–CHO | 5623-82-5 | 63 | 179–180 | 7014-77-9 |
| 5 | cyclohexanone | CHO (+ 15% $\beta,\gamma$) | 1713-63-9 | 53 | 193–195[g] | 1713-65-1 |
| 6 | 3-Cholestanone | OHC= (+ 15% $\beta,\gamma$) | 36866-76-9 | 69 | 110–112 | 36866-92-9 |
| 7 | 3,3-dimethylcyclohexanone | =CH–CHO | 36872-03-4 (cis) 26532-25-3 (trans) 36866-77-0 (endo) | 61[a] | | |
| 8 | Ph₂C=O | Ph, CHO, Ph | 1210-39-5 | 60 | 197–198 | 5109-19-3 |
| 9 | PhC(O)CH₃ | CHO, Ph | 21878-52-4 (cis) 21866-70-6 (trans) | 49[b] | 200–202 | 3491-79-0 |
| 10 | p-BrPhC(O)CH₃ | CHO, p-BrPh | 21878-54-6 (cis) 21866-72-8 (trans) | 55[b] | 180–182 | 36866-95-2 |
| 11 | 2-acetylnaphthalene | CHO | 21854-58-0 | 62 | 217–219 | 21854-66-0 |
| 12 | 2-acetylthiophene | CHO | 21866-65-9 (cis) 21866-74-0 (trans) | 57[c] | 119–125 | 36866-97-4 |
| 13 | PhC(O)CH₂CH₃ | Ph, CHO | 36872-10-3 (cis) 36872-11-4 (trans) | 40[b] | | |
| 14 | cyclopentanone | CHO, Ph (via 19) | 21854-64-8 | 54 | 165–166 | 21854-67-1 |
| 15 | PhCHO | Ph–CH=CH–CHO | 104-55-2 | 64 | 200–201 | 1237-69-0 |
| 16 | p-MePhCHO | p-MePh–CH=CH–CHO | 1504-75-2 | 57 | 40–42[d] | |
| 17 | p-MeOPhCHO | p-MeOPh–CH=CH–CHO | 1963-36-6 | 61 | 58[d] | |
| 18 | 3,4-(MeO)₂PhCHO | 3,4-(MeO)₂Ph–CH=CH–CHO | 4497-40-9 | 53 | 83–84[d] | |
| 19 | CHO | CHO | 505-57-7 | 61 | 144–145 | 1560-68-5 |
| 20 | CHO | CHO | 2463-53-8 | 50 | 124–125 | 1726-79-0 |
| 21 | CHO | CHO | 26370-28-5 | 53 | 113–114 | 3013-11-4 |
| 22 | p-O₂NPhCHO | p-O₂N–Ph–CH=CH–CHO | 1734-79-8 | 60 | 117–118[d] | |
| 23 | | CHO | | 28[e] | 200–202 | 1686-81-3 |
| 24 | pyridine-3-CHO | pyridine-CH=CH–CHO | | 14[f] | 66–67[d] | |

TABLE IX (*Continued*)

| Entry | Carbonyl component | α,β-Unsaturated aldehydes | Registry no. | Overall yield, % | 2,4-DNP, mp, °C | Registry no. |
|-------|--------------------|---------------------------|--------------|------------------|-----------------|--------------|
| 25 | (CHO, pyridine structure) | (CH=CH—CHO, pyridine structure) | | 23[f] | 36–37[d] | |
| 26 | Ph—CH=CH—CHO | Ph—CH=CH—CH=CH—CHO | 13466-40-5 | 61 | 37–39[d] | |
| 27 | PhCHO | Ph—CH=C(Ph)—CHO (*via* 19) | 13702-35-7 | 63 | 240–241 | 13694-45-6 |

[a] Isolated as a three-component mixture (1:1:1) of isomers; cis, trans, endo. [b] Geometric isomers (40:60). [c] Geometric isomers (80:20). [d] Melting point of aldehyde. [e] Isolated in 54% yield as the 2,4-DNP derivative. [f] L. S. Davies and G. Jones, *J. Chem. Soc. C*, 2572 (1971). [g] Semicarbazone derivative.

attributed to the greater ionic (and nucleophilic) character of the C–MgX bond *vs.* the C–Li bond. Borohydride reduction of **85** followed by oxalic acid cleavage provided 2-methyl-3-phenylpropanol (**86**) in

$$ DHO—CH\!\!=\!\!CH_2 \xrightarrow{RMgX} $$
$$ \downarrow MeI $$

$$ DHO—\underset{\underset{Me}{|}}{CH}CH_2R \rightarrow OHC\underset{\underset{Me}{|}}{CH}CH_2Ph $$
$$ \qquad\qquad 85 \qquad\qquad 86 $$
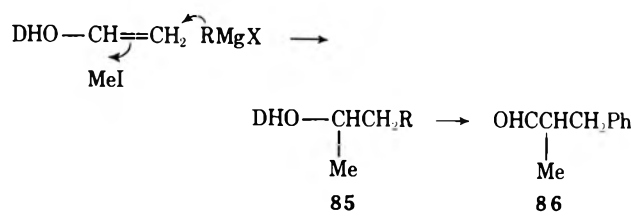
66% overall yield from **21**. The nature of the alkyl halide used as the intercepting electrophile appears to be limited to alkyl iodides only. Other highly electrophilic halides (allyl bromide, benzyl bromide) were also found to be satisfactory, whereas alkyl bromides and chlorides were unable to compete efficiently with the anionic polymerization process. The nucleophilic agent is seemingly limited, in aprotic media, to Grignard reagents, since lithium diphenylphosphide and alkyllithium reagents failed to allow clean addition. The use of cupric and magnesium salts to stabilize the carbanion **84** met with only limited success and was not pursued further. The need for *2.0 equiv* of Grignard reagent to effect complete addition was also observed. The use of 1.0 equiv gave ~50% reaction to **85**. This suggests a previously formed complex[37] between the vinyl oxazine and the Grignard reagent followed by addition of the second equivalent to form the adduct.

In view of the failure to generate the anion of 2-alkyl oxazines and limit the alkylation to the 2-methyloxazine **18**, this vinyl addition is significant since it now allows the preparation of α-alkyl aldehydes (Table X). Of additional interest is the fact that **21** may be utilized as a "protected" acrolein which undergoes 1,4 addition of Grignard reagents followed by alkylation of the intermediate α carbanion. This sequence is difficult utilizing acrolein, which is known to produce mainly 1,2-addition products with organometallics.[28] The vinyl oxazine was also found to undergo smooth reaction with enamines producing the alkylated pentanone **87**. Reduction with sodium borohydride under previously described conditions afforded the hydroxytetrahydro-1,3-oxazine **88**. However, it was possible to convert **87** to its dioxolane derivative **89** and reduce the C=N link in the dihydro-1,3-oxazine to the aldehyde

(37) E. C. Ashby, *Quart. Rev. Chem. Soc.*, **21**, 259 (1967).
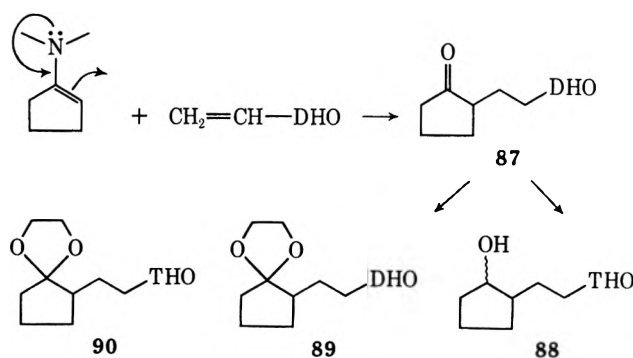
precursor **90**. These transformations demonstrate that it is now possible to carry out normal enamine additions to acrolein without the spontaneous cyclization (although a useful one) to the bicyclic ketones.[36] This aspect is under further study.

## Experimental Section[39]

**2-Substituted 4,4,6-Trimethyl-5,6-dihydro-1,3-oxazines.**—The following general procedure, which represents a modification of Ritter and Tillmanns,[16] was used in preparing all the oxazines 18–21 except where otherwise noted.

**2-Methyloxazine (18).**—To a 2-l. flask equipped with a thermometer, a stirrer, and a 250-ml addition funnel was added 400 ml of concentrated (95–97%) sulfuric acid. The acid was cooled to 0–5° with an ice bath and 90.2 g (2.2 mol) of acetonitrile was added at such a rate that the temperature was maintained at 0–5°. After the addition of the nitrile was complete, 236 g (2.0 mol) of 2-methyl-2,4-pentanediol was also added at such a rate that the same temperature (0–5°) was maintained. The mixture was stirred for an additional 1 hr and then poured onto ~1500 g of crushed ice. The aqueous solution was extracted with four 125-ml portions of chloroform (and the chloroform extracts were discarded). The aqueous solution was made alkaline with 40% sodium hydroxide solution; ice was periodically added during the addition of the sodium hydroxide solution to keep the mixture cool (below 35°). Upon becoming basic, a yellow oil appeared, which was separated. The aqueous layer was extracted with three 100-ml portions of diethyl ether, and the combined ether extracts and oil were dried over anhydrous potassium carbonate. The ether was removed by rotary evaporation, and the residue was distilled through a 25-cm fractionating column to give 183.2 g (65%) of 2,4,4,6-tetramethyldihydro-1,3-oxazine: bp 47–49° (17 mm) (the product foamed badly during distillation; this was avoided by distillation from glass wool); ir (neat) 1667, 1442 cm⁻¹; nmr (CDCl₃) δ 1.08 (s, 6), 1.22 (d, 3), 1.77 (s, 3), 4.04 (m, 1).

(38) G. Stork and H. K. Landesman, *J. Amer. Chem. Soc.*, **78**, 5129 (1956).

(39) All melting points and boiling points are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and Midwest Microlabs, Inc., Indianapolis, Ind.

TABLE X

α,β-DIALKYLPROPIONALDEHYDES FROM 2-VINYL-5,6-DIHYDRO-1,3-OXAZINE (21)

| Entry | RMgBr | RX | Registry no. | Aldehyde | Yield, % | 2,4-DNP mp, °C | Registry no. |
|---|---|---|---|---|---|---|---|
| 1 | Ph | Me | 5445-77-2 | OHC–CH(Me)–CH2Ph | 66 | 122–123[a] | |
| 2 | Ph | PhCH₂Br | 22859-80-9 | OHC–CH(CH₂Ph)–Ph | 55 | 165–166 | 24569-55-9 |
| 3 | Ph | CH₂=CHCH₂Br | 22859-81-0 | OHC–CH(Ph)–CH₂CH=CH₂ | 49 | 125–126 | 24569-56-0 |
| 4 | Ph | Ph epoxide | 36867-08-0 | OHC–CH(Ph)–CH₂–CH(Ph)OH | 40[b] | 169–172 | 36867-48-8 36867-16-0 (hemiacetal) |
| 5 | Ph | EtI | 24569-60-6 | OHC–CH(Ph)–CH₂CH₃ | 30 | 114–115[c] | |
| 6 | Me | PhCH₂Br | | | | | |
| 7 | Et | PhCH₂Br | 22859-83-2 | OHC–CH(CH₂Ph)–CH₂CH₃ | 70 | 86–87 | 24612-95-1 |
| 8 | CH₂=CHCH₂ | PhCH₂Br | 22859-84-3 | OHC–CH(CH₂Ph)–CH₂CH=CH₂ | 30 | 76–77 | 24612-96-2 |

[a] Semicarbazone [R. Lucas and L. Labaune, *Ann. Chim.* (*Paris*), 16, 293 (1931)]; mp 123–124°. [b] Exists in tautomeric equilibrium with cyclic hemiacetal. [c] I. Scriabine, *Bull. Soc. Chim. Fr.*, 1194 (1961); mp 114–115°.

**2-Benzyloxazine (19)** was prepared in exactly the same manner as the 2-methyl derivative, using the following quantities: (a) 118 g (1.0 mol) of 2-methyl-2,4-pentanediol; (b) 128.7 g (1.1 mol) of phenylacetonitrile; (c) 200 ml of 95–98% sulfuric acid. The yield was 107–115 g (49–53%) of a straw-yellow liquid: bp 78–80° (0.25 mm); ir (neat) 1660, 1600 cm⁻¹; nmr (CDCl₃) δ 1.08 (s, 6), 3.32 (s, 2), 4.04 (m, 1), 7.18 (m, 5).

**2-Carboethoxymethyloxazine (20)** was prepared in the same manner as the 2-methyl derivative, using the following quantities: (a) 118 g (1.0 mol) of 2-methyl-2,4-pentanediol; (b) 124.3 g (1.1 mol) of ethyl cyanoacetate; (c) 200 ml of 95–98% sulfuric acid. The yield was 95 g (45%) of a clear, colorless oil which solidified on standing at −20°: bp 69–71° (0.25 mm); ir (neat) 3180, 1740, 1670, 1640 cm⁻¹; nmr (neat) δ 1.1–1.9 (m, 14), 3.05 (s, 1), 3.8–4.3 (m, 4). These signals are consistent with an approximately 1:1 mixture of endo and exo tautomers. *Note.* Care was taken to add the glycol at 0 to −10° to avoid hydrolysis of the ethyl cyanoacetate. In the neutralization step (sodium hydroxide solution) the temperature was kept between 0 and 10° and extraction of the ester oxazine with ether was performed as quickly as possible.

**Alternate Procedures for Preparation of 20.**—Instead of maintaining a temperature of 0–5° with an ice bath, a Dry Ice-acetone bath was used to keep the reaction mixture at −20 to −15° during the addition of the diol. After the diol addition was complete, the reaction was stirred at 0° for 2 hr. During this period careful scrutiny was necessary to assure constancy of the temperature. Since much unreacted diol is present in the mixture during much of this stirring time, allowing the reaction to warm above 3° accelerates the reaction essentially out of control. The work-up was identical with that previously described. Using this lower temperature method the yield of 20 was improved from 45 to 57%. Furthermore, since the lower temperature and greater cooling efficiency of the Dry Ice system allowed the diol to be added faster, the reaction time was actually shorter than that for the ice bath cooled reaction. If desired, the nitrile may also be added under the lower temperature conditions, rather than at 0–5°.

**2-Vinyloxazine (21)** was prepared in exactly the same manner as the 2-methyl derivative, using the following quantities: (a) 118 g (1.0 mol) of 2-methyl 2,4-pentanediol; (b) 58.3 g (1.1 mol) of acrylonitrile; (c) 200 ml of 95–98% sulfuric acid. The yield was 100 g (66%) of a clear, colorless liquid: bp 73–74° (25 mm); ir (neat) 1652, 1600 cm⁻¹; nmr (CDCl₃) δ 1.20 (s, 6), 1.30 (d, 3), 1.58 (m, 2), 4.16 (m, 1), 5.68 (m, 3). *Note.* During and after

the basification step, the work-up should be carried out in a good fume hood, since this oxazine is a mild lachrymator. The compound has a tendency to polymerize on prolonged standing. This may be avoided by storing under nitrogen at 0 to −20°.

**Preparation of the Anion of 2-Methyloxazine (18).**—A 500-ml three-necked flask equipped with a magnetic stirring bar, a 75-ml addition funnel topped with a rubber septum, and a nitrogen inlet tube was successively evacuated and flushed with nitrogen. Anhydrous THF (100 ml) and 14.1 g (0.10 mol) of 2,4,4,6-tetramethyl-5,6-dihydro-1,3-oxazine was added from a syringe through the rubber septum. The stirred solution was cooled to −78° (Dry Ice-acetone bath) and 69.0 ml (0.11 mol, 1.6 M) of n-butyllithium in hexane was injected into the addition funnel. The n-butyllithium was added dropwise over a period of 1 hr. Approximately 1 hr[40] after the addition was complete a yellow precipitate formed. This was indicative of complete anion formation. The lithio anion may not precipitate if more than the above quantity of solvent is employed.

**General Procedure for Alkylation of Lithiooxazine.**—The electrophile (0.11 mol, halide, epoxide, ketone, etc.) in 25 ml of anhydrous THF was injected into the addition funnel and slowly added to the mixture over a period of ~30 min. The reaction mixture was allowed to slowly warm to room temperature, at which time the yellow precipitate disappeared. The mixture was then poured into ~100 ml of ice-water and acidified (pH 2–3) with 9 N hydrochloric acid. The acidic solution was extracted with three 75-ml portions of pentane (discarded) and made basic by the careful addition of 40% sodium hydroxide solution. Ice was added to keep the mixture cool during the neutralization. The resulting oil was extracted with three 75-ml portions of ether and the ether extracts were dried over anhydrous potassium carbonate. The ether was removed by rotary evaporation to give the crude alkylated dihydro-1,3-oxazine (90–98%).

**General Procedure for Reduction of the Dihydro-1,3-oxazine.**—To a 600-ml beaker was added 100 ml of THF, 100 ml of 95% ethyl alcohol, and the crude dihydrooxazine obtained in the preceding experiment. The mixture was cooled between −35 and −40° with an acetone bath to which Dry Ice was added. Hydrochloric acid (9 N) was added to the magnetically stirred solution until an approximate pH of 7 was obtained. Sodium borohydride solution was prepared by dissolving 3.78 g (0.10

(40) The use of *tert*-butyllithium in place of n-butyllithium will generate the anion in a few minutes, thus shortening the procedure.

mol) in a minimum amount of water (~4–5 ml) in which 1 drop of 40% sodium hydroxide was present. The sodium borohydride solution and the 9 N hydrochloric acid solution were introduced to the stirred solution alternately so that pH 6–8 was maintained.[41] The pH was monitored by periodic checks with pH paper. During the addition care was taken to maintain a temperature between −35 and −45°. After addition of this borohydride solution was complete, the solution was stirred with cooling for an additional 1 hr (pH 7 was maintained by the occasional addition of hydrochloric acid solution).

The contents were then poured into ~100 ml of water and made basic by the addition of 40% sodium hydroxide solution. The layers were separated and the aqueous solution was extracted with three 75-ml portions of diethyl ether. The combined organic extracts were washed with 100 ml of saturated sodium chloride solution and dried over anhydrous potassium carbonate. The ether was removed by rotary evaporation to give the crude tetrahydrooxazine (90–99%).

**Cleavage of the Tetrahydrooxazine to the Aldehyde. A. Steam Distillation.**—To a 250-ml flask equipped with a distillation head and an addition funnel with a nitrogen tube was added 50.4 g (0.40 mol) of hydrated oxalic acid and ~150 ml of water. Steam was introduced into the solution and the tetrahydrooxazine (~0.1 mol) was added dropwise over a period of 20 min. The addition funnel was then washed down with 5 ml of 1 M oxalic acid. The steam distillation was continued until the distillate was free of organic material. The distillate was extracted with three 50-ml portions of pentane or ether. The extracts were dried over anhydrous sodium sulfate and the solvent was removed to give the pure aldehyde. In some instances distillation of the product was necessary.

**B. Oxalic Acid Hydrolysis.[42]**—In cases where the aldehyde was water soluble or insufficiently volatile to make steam distillation practical, the following procedure was used. The crude tetrahydro-1,3-oxazine (0.1 mol) was added to the oxalic acid solution prepared above and heated to reflux for 2 hr. The cloudy solution was extracted with ether, pentane, or dichloromethane (depending on the nature of the aldehyde) and the extracts were washed with 5% sodium bicarbonate solution and dried (Na$_2$SO$_4$). Concentration of the solution was followed by either distillation or recrystallization.

**Direct Conversion of Tetrahydro-1,3-oxazine (40) to Oxime 42.[43]**—A solution of 4.00 g (18 mmol) of 40 in 40 ml of absolute ethanol was treated with 6.2 g (90 mmol) of hydroxylamine hydrochloride and heated under reflux for 8–15 hr. The solution was poured into 100 ml of cold 1.2 N hydrochloric acid and extracted with ether. After drying (K$_2$CO$_3$) and concentration, there was obtained 2.18 g of the crude oxime. Distillation gave a colorless oil, bp 64–65° (0.3 mm), which solidified: mp 29–32°; nmr (CDCl$_3$) δ 9.60, 7.47, 6.80, 5.67, 1.0–2.5.

*Anal.* Calcd for C$_8$H$_{13}$NO: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.30; H, 9.46; N, 9.87.

**General Procedure for the Preparation of Cycloalkane Carboxaldehydes (Table VI, Entries 14–16, 22–24).**—To a 500-ml three-necked, round-bottom flask equipped with a nitrogen inlet tube, a rubber septum, and a magnetic stirrer was added 250 ml of THF and 10.9 g (0.05 mol) of 2-benzyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (19). The mixture was cooled to −78° and 32.0 ml (0.06 mol, 1.6 M) of n-butyllithium in hexane was slowly added. After 1 hr of stirring, 11.5 g (0.05 mol) of 1,4-dibromobutane was added and allowed to react for 0.5 hr. n-Butyllithium (0.06 mol) was again added and the mixture was allowed to warm slowly to −50° and maintained at that temperature for 2 hr. The mixture was then poured into 150 ml of water and crushed ice, acidified to pH 2–3, and extracted with ether. The ether extract was discarded. The aqueous solution was basified with 40% sodium hydroxide and extracted with ether. The ether extract was dried over potassium carbonate and the solvent was removed by rotary evaporation, leaving the 2-cycloalkyloxazine (90–97%).

When the 2-methyl oxazine 18 was employed, the *cyclization* step was carried out using 2 equiv of butyllithium, since yields were found to be generally lower when only 1 equiv was employed.

The reduction and cleavage of the oxazine to the cycloalkane carboxaldehydes was performed using the procedures given above.

**General Procedure for Preparation of Ethyl α-Formyl-α-alkylacetates (Table VI, Entries 25–28).**—The following procedure for the preparation of the α-ethyl formyl ester (entry 25) is typical of compounds in this series.

A solution prepared by adding 63.9 g (0.30 mol) of 20 to 200 ml of tetrahydrofuran and purging with nitrogen was treated with 37.0 g (0.33 mol) of potassium *tert*-butoxide at room temperature. The resulting white suspension was stirred at room temperature for 1 hr and then cooled to 0°. A mixture of 32.7 g (0.30 mol) of ethyl bromide and 15 ml of tetrahydrofuran was added dropwise over a 45-min period and stirring was continued for 14 hr thereafter. The mixture was quenched in 300 ml of water and acidified (pH ~3) with dilute hydrochloric acid. After several pentane extractions, the aqueous solution was rendered alkaline (pH 7–9) with 20% sodium hydroxide and extracted with ether, dried (MgSO$_4$), and concentrated, giving 61.9 g (86%) of a yellow oil. Gas chromatography indicated 2% starting oxazine ester 20, 2% diethylated material (37, R = Et), and 96% monoethylated product (36, R = Et). The latter (52.3 g, 0.22 mol) was reduced by dissolving in 500 ml of 1:1 ethanol-tetrahydrofuran, cooling to −35 to −40°, and keeping the *pH at 5–6* by periodic adjustment with 9 N hydrochloric acid. The sodium borohydride (9.45 g, 0.25 mol) was introduced as previously described, and the pH during the addition[44] was kept between 5 and 6. After addition of borohydride, the mixture was stirred for an additional 1 hr and then poured into 250 ml of water and made alkaline (pH 7–8) by the addition of sodium hydroxide solution. Extraction with ether followed by drying (K$_2$CO$_3$) and concentration left 47.8 g (91%) of the tetrahydro-1,3-oxazine. The latter was hydrolyzed directly by gentle reflux in a solution of 87.7 g (0.70 mol) of oxalic acid in 250 ml of water for 2 hr. Extraction of the aqueous mixture with dichloromethane followed by washing the organic extract with aqueous sodium bicarbonate (5%), drying with sodium sulfate, and concentration left 19.0 g of a yellow oil. Distillation gave 14.0 g (57%) of a colorless liquid: bp 60–62° (11 mm);[45] ir (neat) 3330, 2710, 1740, 1720 cm$^{-1}$; nmr (CCl$_4$) δ 11.4, 9.7, 7.0, 4.3, 3.1, 2.3–1.6, 1.5–0.8. These data are consistent with a tautomeric mixture (1:1) of the enol-aldo forms.

**General Procedure for Preparing 1-Formyl-1-carboethoxy Cycloalkanes (Table VI, Entry 30, 31).**—The preparation of entry 30 (Table VI) is typical. To a solution of 4.25 g (20 mmol) of 20 in 25 ml of anhydrous tetrahydrofuran was added, under nitrogen, a suspension of 0.53 g (22 mmol) of sodium hydride in 25 ml of tetrahydrofuran. After hydrogen evolution had ceased, the mixture was warmed for 15 min at 60° and then cooled to −78°. The resulting suspension was treated with 4.75 g (22 mmol) of 1,4-dibromobutane and allowed to warm to room temperature (1.5 hr). The solution was again cooled to −78° and 0.53 g (22 mmol) of sodium hydride, as a suspension in 10 ml of tetrahydrofuran, was added. The mixture was stirred at room temperature overnight and then quenched with 100 ml of ice-water and acidified to pH 2–3 with 9 N hydrochloric acid. The acidic solution was extracted with pentane and the pentane extracts were discarded. The aqueous solution was made basic by slow addition of 40% sodium hydroxide and the resulting oil was removed by extraction with ether. The extracts were washed with water, dried (Na$_2$SO$_4$), and concentrated, leaving crude cycloalkyloxazine [37, R = (CH$_2$)$_4$]. Reduction of 37 was performed on 4.62 g (17.2 mmol) and using 0.6 g of sodium borohydride according to the general reduction procedure described above. After the isolation there was obtained 4.4 g of a light yellow oil (95%), ir 3200–3500, 1730 cm$^{-1}$. The C=N absorption at 1670 cm$^{-1}$ was absent. The product (4.1 g) was cleaved without any purification by the steam distillation procedure from an aqueous oxalic acid solution (7.6 g in 100 ml) affording 2.7 g of 1-formyl-1-carboethoxycyclopentane (67%), ir (neat) 1700–1750 cm$^{-1}$ (broad), 2,4-DNP mp 134–134.5°.

(41) It is convenient to introduce the acid and hydride solutions from two 50-ml burets placed above the beaker.

(42) It has been found that this procedure for isolating *all* the aldehydes prepared by this method is quite satisfactory, since steam distillation, in many instances, required prolonged heating that consumed considerable time. However, certain acid-sensitive aldehydes (*i.e.*, cyclopropane, phenylcyclopropane carboxaldehydes) are best isolated by steam distillation, since their contact time in the acid medium is minimized.

(43) We thank Dr. John F. Hansen for this experiment.

(44) Owing to the weaker base strength of this oxazine, reduction was more successful at lower pH values.

(45) Bp 71–75° (22 mm): H. Watanabe, A. Ide, N. Sugimoto, Y. Noguchi, R. Ishida, and Y. Kowa, *Yakugaku Zasshi*, **83**, 1118 (1963).

*Anal.* Calcd for $C_3H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.44; H, 8.27.

**Reaction of Lithiooxazine with *n*-Butyl Tosylate to 22.**—Using the procedure described for formation of the lithio salt of 18 (2.82 g of 18, 13.5 ml of *n*-butyllithium) was added 4.9 g of *n*-butyl tosylate at $-78°$. The solution immediately turned to a crimson color. After stirring at room temperature for 15 hr, the solution was quenched in water and worked up *via* the acid-base treatment. The crude recovered ether concentrate contained a solid which was separated by addition of pentane. Filtration gave 1.71 g (10%) of a crystalline product: mp 135–136°; ir (Nujol) 1650, 1158, 1082 cm$^{-1}$; nmr (CDCl$_3$) δ 7.88 (d, $J$ = 8 Hz), 7.40 (d, $J$ = 8 Hz, 2), 4.05 (m, 1), 4.00 (m, 2), 2.5–2.6 (m, 5), 1.1–1.2 (m, 6).

The pentane solution was evaporated and the residue was distilled to give 2.53 g (89%) of 18.

**Dimerization of Lithio Salt of 18 to 30.**—A solution of 18 (6.21 g, 44 mmol) in 50 ml of tetrahydrofuran was treated with 21.5 ml (2.23 $M$) of *n*-butyllithium in hexane at $-78°$ under nitrogen. The solution was allowed to warm to room temperature and then poured into water, extracted with ether, dried (K$_2$CO$_3$), and concentrated. The viscous oil was distilled at 88–92° (0.01 mm), keeping the pot temperature below 130°, which afforded 5.2 g (84%) of the dimer 30, ir (neat) 3220, 1660 cm$^{-1}$.

*Anal.* Calcd for $C_{16}H_{30}N_2O_2$: C, 68.04; H, 10.71; N, 9.92. Found: C, 67.89; H, 10.83; N, 9.98.

Heating 30 at 190–195° under nitrogen gave pure 18 which was identical with an authentic sample.

**Dimerization of Lithio Salt of 18a to 30a.**—The anion of 18a was prepared as above using 4.01 g (26 mmol) in 30 ml of tetrahydrofuran and 12.1 ml of butyllithium. Evaporation of the ethereal extract gave 3.52 g (88%) of dimer 30a, bp 92° (0.01 mm), ir (neat) 3210, 1660 cm$^{-1}$.

*Anal.* Calcd for $C_{18}H_{34}N_2O_2$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.90; H, 10.96; N, 8.83.

Heating at 190–200° led to pure 18a shown to be identical with an authentic sample.

**Conversion of 18b to the Ketenimine Trimethylsilyl Ether 28.**—A solution containing 22.2 g (22 mmol) of diisopropylamine in 150 ml of anhydrous tetrahydrofuran was cooled under nitrogen to $-50°$ and 22 mmol of *n*-butyllithium in hexane was added. The temperature of the solution containing lithium diisopropylamide was allowed to warm to 0° and 33.7 g (20 mmol) of 18b was added dropwise. The yellow solution was then warmed to room temperature and stirred for 2.5 hr, at which time it was cooled again to 0°. The addition of 22.0 g (20 mmol) of trimethylchlorosilane followed in a dropwise fashion as the solution turned cloudy. After 2 hr of additional stirring at 25°, the salts were removed by filtration and the solvents were removed by rotary evaporation. The residue was distilled to give 36.1 g (75%) of pure ketenimine 28, bp 65–68° (0.3 mm), ir (neat) 2050, 843 cm$^{-1}$.

*Anal.* Calcd for $C_{13}H_{27}NOSi$: C, 64.67; H, 11.27; N, 5.80. Found: C, 64.98; H, 11.17; N, 6.03.

**Reaction of Benzyloxazine 19 with Ethyl Iodide. A. Using *n*-Butyllithium.**—A solution of 10.85 g of 19 in 40 ml of tetrahydrofuran was treated with 20 ml of *n*-butyllithium at $-78°$. After 1 hr, ethyl iodide (8.6 g) was added and the solution was warmed to room temperature. The product 31 was isolated in the usual fashion: 11.8 g (96%); bp 93–96° (0.20 mm); ir (neat) 1665 cm$^{-1}$; nmr (CCl$_4$) δ 4.03 (m, 1), 3.2 (d of d, 1).

*Anal.* Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.09; H, 9.48; N, 5.63.

**B. Using Dimethylsulfinyl Carbanion.**—A solution of 6.8 g of 19 in 5 ml of DMSO was added to a solution of dimethylsulfinyl carbanion (from 2.0 g of sodium hydride in 20 ml of DMSO)[21] at room temperature and the mixture was stirred for 3 hr. The addition of 7.8 g of ethyl iodide followed dropwise with external cooling to keep the reaction temperature at 25–27°. After 30 min the mixture was poured into water, and the organic layer was removed by ethereal extraction and concentrated to give 31 (84%) which was identical with the product from *n*-butyllithium treatment.

**Reaction of 2-($\alpha$-Ethyl)benzyloxazine (31) with Methyl Iodide at $-78°$.**—Reaction of 2.47 g of 31 with 1.1 equiv (5.0 ml) of *n*-butyllithium in 30 ml of tetrahydrofuran gave the orange-colored anion after 45 min. To this mixture was added 1.1 equiv of methyl iodide and the solution was stirred for 3 hr at $-78°$, after which 20 ml of water was slowly added. The aqueous solution upon reaching ambient temperature was diluted with 50

ml of water and extracted several times with ether, dried (K$_2$CO$_3$), and concentrated to give 2.5 g (96%) of 32: bp 90–94° (0.24 mm); ir (neat) 1665 cm$^{-1}$; nmr (CCl$_4$) δ 4.03 (m, 1). The signals at δ 3.2 were absent.

*Anal.* Calcd for $C_{17}H_{25}NO$: C, 78.72; H, 9.71; N, 5.40. Found: C, 78.60; H, 9.68; N, 5.30.

**Reaction of 31 with Ethylmagnesium Bromide at 25°.**—To a solution of 2.5 g of 31 in 30 ml of tetrahydrofuran was added 1.0 equiv of *n*-butyllithium at $-78°$. The solution was allowed to warm to ambient temperature, where the color had changed from orange to dark amber. A solution of ethylmagnesium bromide (3.0 equiv) in ether was slowly added and a mild exothermic reaction ensued. Stirring was continued at room temperature for 12 hr and the mixture was poured into 50 ml of water. Extraction with ether, drying of the extracts, and concentration left 2.91 g of an oil whose infrared spectrum showed only a small C=N absorption at 1665 cm$^{-1}$. This product was heated for 1.5 hr in an oxalic acid solution (5 g per 40 ml) and then the aqueous solution was extracted with ether. Concentration of the dried ethereal extracts afforded 1.64 g (92%) of 4-phenyl-3-hexanone (33), semicarbazone mp 138–140° (lit.[46] 139–140°).

**Alkylation of Ester Oxazine 20 with Alkyl Halides in Acetonitrile. Formation of 36 (R = Allyl).**—A mixture containing 21.3 g (10 mmol) of 20, 16.8 g (10 mmol) of allyl iodide, and 10 ml of dry acetonitrile was heated under reflux for 24 hr. The solvent was removed *in vacuo* and the residue was washed with cold 5% sodium hydroxide solution and taken up in ether. The latter extracts were washed once with saturated brine solution, dried (K$_2$CO$_3$), and concentrated to give 22.4 g of an oil which was distilled bulb to bulb. The yield was 21.1 g (84%) of a colorless liquid. Tlc examination indicated spots for monoalkylated 36, starting material 20, and dialkylated oxazine 37 (ether-pentane, 70:30). Vpc analysis showed the mixture to be 71:7:22, respectively. This mixture was used to prepare the 2-alkyl formyl ester (Table VI, entry 28) without further purification.

**Ethyl 2-Formyl-2-allylacetate (Table VI, Entry 28).**—The general procedure for borohydride reduction was used except that the pH during the reaction was kept between 4 and 6. The quantities utilized were 12.15 g of the above oxazine mixture, 1.89 g of sodium borohydride, 50 ml of ethanol, and 50 ml of tetrahydrofuran. This process gave 11.1 g of reduced oxazine which exhibited only a weak band for the C=N link at 1660 cm$^{-1}$ owing to the inert dialkylated oxazine 37. The aldehyde was released by addition of the reduced oxazine (11.1 g) to a refluxing solution of 15 g of oxalic acid dihydrate in 150 ml of water and collecting the steam distillate. Extraction of the organic layer with ether and concentration gave 3.8 g (44% overall from 20) of the aldehyde: ir (neat) 3500–3400, 3080, 1670, 1720 cm$^{-1}$; nmr (CCl$_4$) δ 9.68 (d, 0.4 H), 7.0 (br s, 0.6 H) 4.8–6.2 (m, 3), 4.2 (q of d, 2), 3.3 (m, 0.4 H), 2.7 (m, 2), 1.3 (m, 3). The spectrum corresponded to a 40:60 tautomeric mixture of enol-aldo forms.

**cis-4-Heptenal (50).**—The 2-(3-hexynyl) oxazine 49 was prepared by the general procedure for alkylation of 18 using 42 g (0.41 mol) of 1-chloro-2-pentyne,[47] 52.5 g (0.37 mol) of 18, and 262 ml of *n*-butyllithium. The yield of 49 was 72.5 g (95%), bp 60–62° (1.2 mm), ir (neat) 1665 cm$^{-1}$.

*Anal.* Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.03; H, 10.28; N, 6.94.

The reduction of the triple bond in 49 was performed using 20.7 g (0.10 mol) and 1.7 g of 5% Pd on barium sulfate in 25 ml of pyridine. The solution was hydrogenated in a Paar apparatus at 39 psi for 25–45 min. The catalyst was removed by filtration through Celite and washed with pentane. Removal of the mixed solvents by rotary evaporation left 20.0 g (95%) of the olefin oxazine: bp 60–61° (1.0 mm); ir (neat) 1665 cm$^{-1}$; nmr (CDCl$_3$) δ 5.2–5.6 (t, 2).

*Anal.* Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.07; N, 6.69. Found: C, 74.29; H, 11.28; N, 6.92.

Reduction of the dihydro-1,3-oxazine was accomplished according to the general procedure using 67.4 g (0.32 mol) of the olefinic oxazine, 12.3 g (0.32 mol) of sodium borohydride, and

(46) "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1965, p 2694.

(47) Prepared according to the procedure described by A. I. Meyers and E. W. Collington, *J. Org. Chem.*, **36**, 3044 (1971), in 90% yield. The crude materials gave satisfactory alkylation results.

500 ml of 1:1 ethanol–THF. The yield of the tetrahydro-1,3-oxazine was 67.2 g (98%): bp 62–64° (0.08 mm); ir (neat) 3500–3300, 1650 cm$^{-1}$; nmr (CDCl$_3$) δ 5.3 (m, 2), 4.2 (t, 1), 3.7 (m, 1).

*Anal.* Calcd for C$_{13}$H$_{25}$NO: C, 73.88; H, 11.92; N, 6.63. Found: C, 73.79; H, 12.15; N, 6.38.

The aldehyde **50** was released by the steam distillation method using 33 g of the above tetrahydro-1,3-oxazine, 78 g of oxalic acid, and 240 ml of water. The steam distillate was saturated with salt and extracted with ether (3 × 100 ml), dried (K$_2$CO$_3$), and concentrated. Distillation of the residue showed little change in purity, bp 28–30° (2 mm). The yield of **50** was 9.45 g (54%): ir (neat) 2710, 1725, 1650, 970 cm$^{-1}$; nmr (CCl$_4$) δ 10.33 (t, 1), 5.4 (m, 2); 2,4-DNP mp 93–94° (ethanol).[48]

**2-(6-Bromohexyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (52).** —The lithio salt of **18** (40 mmol) was prepared according to the general procedure at −78°. A rapid injection of 6.9 g (60 mmol) of 1,5-dibromopentane was followed by stirring at room temperature for 4–15 hr and the mixture was poured into ice-water and acidified (pH 2–3) with 9 N hydrochloric acid. Extraction with pentane removed excess dibromopentane and the aqueous solution was then rendered alkaline to free the oxazine. The latter was removed by several ethereal extractions, dried (K$_2$CO$_3$), and concentrated *in vacuo* at room temperature, leaving 10.5 g (90%) as a pale yellow oil. Although this material was suitable for most subsequent reactions, it was distilled, bp 90° (0.05 mm), as a colorless liquid (75%): ir (neat) 1665 cm$^{-1}$; nmr (CCl$_4$) δ 4.0 (m, 1, –CHO–), 3.35 (t, 2, CH$_2$Br).

*Anal.* Calcd for C$_{13}$H$_{24}$NOBr: C, 53.84; H, 8.34; N, 4.83. Found: C, 53.61; H. 8.46; N, 4.93.

**2-(5-Bromopentyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (52, One Less Methylene Group).** —The procedure was identical with that of **52** except that 1,4-dibromobutane was used. Concentration of the ethereal extracts was done at or below room temperature in order to avoid intramolecular salt formation. Distillation through a short-path column gave pure bromopentyl oxazine (61%): bp 67° (0.075 mm), with the pot temperature not allowed to exceed 110°; ir (neat) 1664 cm$^{-1}$; nmr (CCl$_4$) δ 3.35 (t, 2, CH$_2$Br).

*Anal.* Calcd for C$_{12}$H$_{22}$NOBr: C, 52.17; H, 8.03; N, 5.08. Found: C, 52.45; H, 8.19; N, 5.09.

**Bicyclic Oxazinium Salt 63.** —If the above distillation is carried out with a pot temperature in excess of 120° or if the crude ether concentrate is warmed overnight at 120–125°, a solidified mass forms. Recrystallization from acetonitrile–ether gave colorless crystalline material: mp 184–185° (50%); ir (KBr) 1625 cm$^{-1}$ (OC=N<)$^+$; nmr (CDCl$_3$) δ 5.03 (m, 1, –CHO–).

*Anal.* Calcd for C$_{12}$H$_{22}$NOBr: C, 52.17; H, 8.03; N, 5.08. Found: C, 52.10; H, 8.10; N, 5.10.

**Bicyclic oxazinium salt 62** was prepared from the lithio salt of **18** and 1,3-dibromopropane (1.0 equiv) under the general procedure for alkylation. Upon isolation of the 2-(2-bromobutyl)oxazine a solid appeared which was collected by filtration. The bromide salt of **62** was hygroscopic and was converted to the perchlorate salt by treating an equimolar mixture of the bromide and silver perchlorate in acetonitrile, mp 201–202°, ir (Nujol) 1635 cm$^{-1}$.

*Anal.* Calcd for C$_{11}$H$_{20}$NO$_5$Cl: C, 47.00; H, 7.12; N, 4.98. Found: C, 46.94; H, 7.00; N, 5.03.

**2-(5-Chloropentyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine.** — The lithio anion of the 2-methyl oxazine (40 mmol in 40 ml of THF) was prepared as usual and 44 mmol of 1-bromo-4-chlorobutane was added *via* a syringe all at once. The standard isolation procedure yielded the chloropentyl oxazine in 95% crude yield. Distillation gave 87% pure material: bp 59° (0.12 mm); ir (neat) 1665 cm$^{-1}$; nmr (CCl$_4$) δ 3.5 (t, 2, CH$_2$Cl). There was no decomposition or quaternization during the distillaton.

*Anal.* Calcd for C$_{13}$H$_{22}$NOCl: C, 62.17; H, 9.52; N, 6.04. Found: C, 62.38; H, 9.58; N, 5.88.

**2-(6-Cyanohexyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (54).** —A solution of 14.5 g (50 mmol) of 6-bromohexyl oxazine **52** and 2.65 g of sodium cyanide in 25 ml of dimethyl sulfoxide was stirred at room temperature for 1 hr and then heated at 55° for 2 hr. Stirring was continued for an additional 15 hr (25°) and the mixture was poured into 50 ml of 5% sodium carbonate. The aqueous solution was extracted with ether and the ethereal extracts were washed with cold 1 N hydrochloric acid to remove the cyano oxazine. The acidic solution was neutralized with

aqueous alkali and then extracted with ether. Drying and concentration left an oil (95%) which was distilled, bp 95° (0.1 mm), to afford pure product (90%): ir (neat) 2245, 1660 cm$^{-1}$; nmr (CCl$_4$) δ 4.05 (m, 1, –CHO–), 2.32 (t, 2), 2.0 (t, 2); *m/e* 236. A perchlorate salt was prepared in ether, mp 75° (ethanol-ether).

*Anal.* Calcd for C$_{14}$H$_{25}$N$_2$ClO$_5$: C, 49.93; H, 7.48; N, 8.31. Found: C, 49.80; H, 7.46; N, 8.08.

**7-Cyanoheptaldehyde (55)** was prepared by the general procedure of borohydride reduction followed by oxalic acid hydrolysis and extraction with ether. The overall yield from **18** was 47%: ir (neat) 2718, 2240, 1718 cm$^{-1}$; nmr (CCl$_4$) δ 9.7 (t, 1); 2,4-DNP mp 76–77° (lit.[49]).

**2-(6-Carboethoxyhexyl)-4,4,6-trimethyloxazine (56).** —The cyanohexyl oxazine (**54**, 4.72 g) was dissolved in 95% ethanol and cooled in an ice bath as hydrogen chloride was slowly passed through for 1 hr. The solution was brought to gentle reflux for 12 hr as the ammonium chloride suspension appeared. Upon cooling and filtering off the salt, the ethanol solution was concentrated and the residue was dissolved in water and neutralized with 5% sodium carbonate. Ether extraction followed by drying (K$_2$CO$_3$) and concentration left 4.7 g (82%) of the ester **56**. Purification was accomplished either by (a) elution from Woelm alumina I with ether or (b) distillation: bp 100° (0.025 mm); ir (neat) 1737, 1666 cm$^{-1}$; nmr (CCl$_4$) δ 4.08 (m, 3, –CHO–).

*Anal.* Calcd for C$_{16}$H$_{29}$NO$_3$: C, 67.81; H, 10.31; N, 4.94. Found: C, 67.98; H, 10.33; N, 5.05.

**Ethyl 7-Formylheptanoate (57)** was prepared from **56** by the general procedures for reduction and oxalic acid hydrolysis followed by ether extraction: ir (neat) 2711, 1730 cm$^{-1}$; nmr (CCl$_4$) δ 9.74 (t, 1); 2,4-DNP mp 57–58°.

**2-(6-Benzoylhexyl)-4,4,6-trimethyldihydro-1,3-oxazine (58).** — To a stirred solution of 4.72 g (20 mmol) of the 6-cyanohexyl oxazine **54** in 35 ml of ether was added 3.0 equiv of phenylmagnesium bromide (2 M) in ether. The two-layered solution was stirred at room temperature for 15 hr and then poured onto 15 ml of 9 N hydrochloric acid containing an equal volume of cracked ice. After the aqueous mixture was stirred for 20 min, it was extracted with ether several times and the ether extracts were discarded. The acid solution was neutralized by sodium bicarbonate and then extracted with ether several times. The ethereal extracts were dried (K$_2$CO$_3$) and concentrated, leaving a waxy solid **58** (5.81 g, 92%). The product was crystallized from pentane to give 5.6 g (90%) of pure **58**: mp 34–35°; ir 1688, 1665 cm$^{-1}$; nmr (CCl$_4$) δ 2.88 (t, 2, –CH$_2$COPh).

*Anal.* Calcd for C$_{20}$H$_{29}$NO$_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 75.92; H, 9.54; N, 4.58.

**2-(7-Hydroxy-7-phenyl-*n*-heptyl)dihydro-1,3-oxazine (61).** **A. From Lithium Aluminum Hydride Reduction of 58.** —A solution of 3.15 g (10 mmol) of **58** in 10 ml of anhydrous ether was added dropwise to a stirred suspension of lithium aluminum hydride (0.76 g, 20 mmol) in 40 ml of ether. The mixture was stirred for 30 min and quenched with wet ether followed by 2 ml of 10% sodium hydroxide solution. The precipitated salts were removed by filtration and washed with ether. The combined ethereal solution was washed with saturated brine solution, dried (Na$_2$SO$_4$), and concentrated, leaving a colorless solid (recrystallized from pentane), 2.93 g (92%) of the hydroxy oxazine **61**: mp 45°; ir 3200, 1658, 1605 cm$^{-1}$; nmr (CCl$_4$) δ 7.23 (br s, 5, C$_6$H$_5$), 4.58 (t, 1, CHOH).

*Anal.* Calcd for C$_{20}$H$_{31}$NO$_2$: C, 75.67; H, 9.58; N, 4.41. Found: C, 75.55; H, 9.71; N, 4.55.

**B. From Sodium Borohydride Reduction of 58.** —The benzoyl oxazine **58** (1.57 g) was dissolved in 10 ml of 95% ethanol to which 0.5 ml of 40% sodium hydroxide had been added. To this solution was added sodium borohydride (0.19 g) dissolved in a minimum amount of water and the mixture was stirred for 1 hr at 25°. The alcohol was removed by rotary evaporation and the residue was diluted with saturated salt solution. Ether extraction followed by washing the ethereal extracts with brine, drying (Na$_2$SO$_4$), and concentration afforded **61** (1.48 g, 95%) which was identical with that obtained from the lithium aluminum hydride reduction.

**Oxidation of 61 to 58 with Chromic Anhydride.** —Hydroxy oxazine **61** (0.95 g, 3 mmol) in 5 ml of pyridine was added by drops to 15 mmol of chromic anhydride in 15 ml of pyridine which

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(48) G. Hoffman and P. Meijoom, British Patent 1,068,712 (1963).

(49) M. Ohno, N. Naruse, S. Torimitsu, and I. Teresawa, *J. Amer. Chem. Soc.*, **88**, 3168 (1966).

had been prepared by the careful addition of the powder to pyridine. On stirring at room temperature the mixture turned very dark and was allowed to stir overnight, poured into water, and filtered. Both the solid and liquid were extracted with ether (~60 ml). The ether extract was washed with brine and concentrated to an oil. The oil was dissolved in pentane and the oxazine **58** (0.63 g, 68%) crystallized on cooling, mp 34–35°. The material was identical with a sample prepared by the addition of phenylmagnesium bromide to **54**.

**7-Benzoylheptanal (59)** was prepared in 60% yield (from **52**) by subjecting **58** to the general procedure for reduction except that the reduction mixture was acidified with 3 *N* hydrochloric acid at −40° prior to quenching. In this fashion, the carbonyl was not reduced. Oxalic acid cleavage according to the general procedure followed by ether extraction gave **59**: mp 36° (pentane); ir (neat) 2715, 1724, 1684 cm$^{-1}$; nmr (CCl$_4$) δ 9.74 (t, 1); 2,4-DNP mp 105–106°.

*Anal.* Calcd for C$_{14}$H$_{18}$O$_2$: C, 77.03; H, 8.31. Found: C, 77.29; H, 8.59.

A sample of **59** was oxidized *via* the Jones reagent to 7-benzoylheptanoic acid, mp 84–85° (lit.[50] mp 83–85°).

**8-Hydroxy-8-phenyloctanal (60)** was prepared in 58% yield (from **52**) by the general procedure for reduction and hydrolysis of **61**. Alternatively, **60** was prepared by reduction of **58** using twice the usual amount of sodium borohydride and allowing the reduction solution to stir at room temperature at pH 9–10 after reduction of the C=N link at −40° had been completed. The crude product was unstable toward distillation but could be readily purified *via* the bisulfate addition compound. Thus, an aqueous solution of sodium bisulfite and the crude aldehyde was extracted several times with ether and the latter extracts were discarded. Acidification to release the aldehyde followed by ether extraction and concentration of the extract gave pure **60** as an oil: ir (neat) 3400, 2720, 1720 cm$^{-1}$; nmr (CCl$_4$) δ 9.65 (t, 1), 7.2 (s, 5), 4.65 (t, 1), 3.11 (s, 1 exchanges with D$_2$O).

*Anal.* Calcd for C$_{14}$H$_{20}$O$_2$: C, 76.33; H, 9.15. Found: C, 76.07; H, 9.28.

**Formation and Deuteration of Grignard Reagent 64 in THF.**— To a suspension of 0.6 g of magnesium shavings in 50 ml of tetrahydrofuran was added 1–2 ml of a solution of **52** (2.90 g in 10 ml of THF). The reaction was initiated by addition of an iodine crystal or a drop of methyl iodide before the remainder of the bromohexyloxazine solution was introduced. After 2–3 hr, the complete absence of the magnesium shavings was noted and the clear solution was treated with deuterium oxide (5 ml) and stirred for an additional 30 min. The mixture was poured into ice-water, extracted with ether, dried (K$_2$CO$_3$), and concentrated to give 2-(*n*-hexyl-6-*d*)oxazine (**65**, E = D), 1.94 g (92%): bp 65–67° (0.05 mm); ir (neat) 1659 cm$^{-1}$; *m/e* 212 (calcd 212).

**7-Deuterioheptaldehyde (66, E = D)** was obtained from **64** by the general procedure for reduction and hydrolysis, bp 155°; vpc was identical with that of an authentic sample of *n*-heptanal; ir (neat) 1724, 2178 (CD), 2715 cm$^{-1}$; *m/e* 115. When compared to the mass spectrum of heptanal, indications were that deuteration was complete (95%).

**Formation of Magnesium Bromide. Grignard Reagent 64.**— To an ethereal solution containing 10 mmol of magnesium bromide (from 1.88 g of 1,2-dibromoethane and 0.60 g of magnesium shavings in 50 ml of ether) was added 2.90 g (10 mmol) of 2-(6-bromohexyl)oxazine (**52**) under a nitrogen atmosphere. The mixture was stirred for 4 hr at 25°, after which a two-layered solution resulted. The latter was used in this form for all the following experiments.

**A. Ethyl Chloroformate.**—The ethereal Grignard solution was cooled to 0° and 1.3 g (12 mmol) of ethyl chloroformate was rapidly added. After stirring at room temperature for 12 hr the reaction mixture was worked up by aqueous quenching, ethereal extraction, and concentration to give 2.31 g of a mixture of 2-(*n*-hexyl)oxazine (**65**, E = H) and 2-(6-carboethoxyhexyl)-oxazine (**65**, E = CO$_2$Et). Vpc (SE-30, 175°) examination confirmed the identity with authentic samples [36% **56**, 60% **65** (E = H)].

**B. Benzaldehyde.**—The ethereal solution of **64** was treated with 1.06 g (10 mmol) of benzaldehyde in 10 ml of ether by dropwise addition. The usual isolation procedure gave 2.44 g of a mixture of **65** (E = H) and **61** or **65** [E = CH(OH)Ph] in 35 and 65% yield, respectively (estimated by nmr). Pure **61** was iso-

lated by preparative layer chromatography (1.5 mm, PF$_{254}$) after elution with ether (35% yield), mp 45°. This product was identical in all respects with that obtained by reduction of **58** with metal hydrides.

**C. Benzonitrile.**—To the refluxing Grignard solution **64** was added 1.13 g (11 mmol) of benzonitrile and heating of the mixture was continued for 24 hr. Isolation gave 2.35 g of a mixture containing **65** (E = H, 60%) and **58** (34%) as estimated by vpc (SE-30, 175°).

**Reaction of 2-Benzyloxazine with 4-Bromobutyronitrile.**— Generation of the benzyloxazine (**19**) carbanion in the usual manner was followed by addition of 6.5 g (44 mmol) of 4-bromobutyronitrile. After the standard isolation procedure there was obtained 7.4 g (65%) of 2-(4-cyano-1-phenylbutyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine, mp 44.5–45° (pentane), ir (film) 2255, 1662 cm$^{-1}$.

*Anal.* Calcd for C$_{18}$H$_{24}$N$_2$O: C, 76.02; H, 8.51; N, 9.85. Found: C, 75.74; H, 8.67; N, 9.94.

**2-Phenyl-6-cyanohexaldehyde (67).**—The benzyloxazine (**19**) carbanion was generated as usual (THF, −78°) and treated with 7.12 g (44 mmol) of 5-bromovaleronitrile. After work-up, the cyano oxazine was obtained (11 g, 92%) which was shown by nmr and tlc (ether) to be >95% pure. It was used without further purification for the borohydride reduction (general procedure) and the resulting tetrahydro oxazine was hydrolyzed in oxalic acid: yield 5.20 g (65%) of oil; ir (neat) 2710, 2243, 1720 cm$^{-1}$; nmr (CCl$_4$) δ 9.66 (d, 1); 2,4-DNP mp 116.5–117°.

*Anal.* Calcd for C$_{19}$H$_{19}$N$_3$O$_4$: C, 59.84; H, 5.02; N, 18.36. Found: C, 59.61; H, 4.89; N, 18.16.

**2,7-Diphenyl-1,8-octanedial (69).**—To 20 mmol of the lithio salt of **19** was added 2.16 g (10 mmol) of 1,4-dibromopentane at −78°. After the usual isolation treatment, the bisoxazine was obtained (4.88 g) as a viscous oil. It was reduced without further purification with sodium borohydride (general procedure) using twice the normal quantity of hydride but not increasing the amount of solvent. Isolation gave 4.96 g of the tetrahydro oxazine, which was heated in the oxalic acid solution for 1.5 hr. The crude aldehyde, recovered by extraction and recrystallized from pentane, afforded 1.2 g of the aldehyde: mp 37–39°; 2,4-DNP mp 210–213°; nmr (CDCl$_3$) δ 10.4 (d, 2), 7.3 (m, 10), 3.4 (t, 2), 1–2.2 (m, 8); ir (neat) 2700, 1715 cm$^{-1}$.

*Anal.* Calcd for C$_{20}$H$_{22}$O$_2$: C, 81.60; H, 7.53. Found: C, 81.47; H, 7.40.

**1,2-Bis(dihydro-1,3-oxazinyl)ethane (71).**—To a solution containing 30 mmol of the lithio salt of **18** at −78° was added rapidly 2.9 g (15 mmol) of 1,2-dibromoethane. After warming to room temperature, quenching, and extraction, there was formed 4.35 g of crude **71**. Distillation, bp 95° (0.1 mm), gave 3.90 g: ir (neat) 1660 cm$^{-1}$; nmr (CCl$_4$) δ 4.0 (m, 2), 2.25 (s, 4), 1.55 (t of d, 4), 1.25 (d, 6), 1.08 (s, 12). The product crystallized on standing, mp 43–44°.

*Anal.* Calcd for C$_{16}$H$_{28}$N$_2$O$_2$: C, 68.53; H, 10.06; N, 9.99. Found: C, 68.28; H, 10.22; N, 9.89.

**4-Ethoxybutanal (75, R = Et).**—The anion of **18** (40 mmol) was treated with 1.0 equiv of ethylene oxide at −78° and allowed to warm to room temperature. After quenching, extraction, and concentration, there was obtained 7.15 g (97%) of 2-(3-hydroxypropyl)oxazine (**73**, A = R = H): ir (neat) 1658, 3500 cm$^{-1}$; nmr (CDCl$_3$) δ 5.4 (s, 1, exchanges with D$_2$O), 4.1 (m, 1), 3.6 (t, 2). This product, without further purification, was treated in dry THF with 1.1 equiv of sodium hydride at 25° and after hydrogen evolution had ceased (30 min), 1.1 equiv of ethyl iodide was added and stirring was continued for 3 hr. Aqueous treatment followed by ether extraction, drying, and concentration produced the 2-(4-ethoxypropyl) oxazine **73** (A = H, R = Et) in 97% yield: ir (neat) 1658 cm$^{-1}$; nmr (CCl$_4$) δ 4.1 (m, 1), 3.4 (m, 4). Reduction with sodium borohydride and oxalic acid cleavage gave 4-ethoxybutanal, 2,4-DNP mp 88–89° (lit.[51] mp 88–89°), in 54% yield. The product was identical with that prepared using **18** and 2-bromoethyl ether (Table VI, entry 7).

**4-Benzoylbutanal (75, R = PhCO).**—The procedure was the same as above except that 1.1 equiv of benzoyl chloride was added in place of ethyl iodide. The benzoate (**73**, A = H, R = PhCO) was obtained in 94% yield (14.1 g), ir (neat) 1650, 1700 cm$^{-1}$. Reduction was performed on 5.8 g (20 mmol) of the oxazine and this resulted in 5.76 g of crude tetrahydro derivative, ir (neat) 3300–3500, 1710 cm$^{-1}$ (absorption at 1650 cm$^{-1}$

(50) T. Weil and D. Ginsberg, *J. Chem. Soc.*, 1291 (1957).

(51) H. Adkins and G. Krsek, *J. Amer. Chem. Soc.*, **71**, 3051 (1949).

was totally absent). The oxalic acid hydrolysis was performed on 2.9 g (10 mmol) and after extraction with ether, 1.31 g (62%) of 4-benzoyloxybutanal was obtained: 2,4-DNP mp 103–105°; ir (neat) 2710, 1710–1730 cm⁻¹; nmr (CCl₄) δ 9.81 (t, 1), 8.0 (m, 2), 7.4 (m, 3), 4.3 (t, 2), 1.0–2.8 (m, 6).

*Anal.* Calcd for C₁₁H₁₂O₃: C, 68.74; H, 6.29. Found: C, 68.66; H, 6.01.

**1-Deuterio-2-phenyl-4-pentenal (Table VI, Entry 20)** was prepared using 21.7 g (100 mmol) of the 2-benzyloxazine **19**, 48 ml (110 mmol) of *n*-butyllithium, and 12.1 g (100 mmol) of allyl bromide according to the general procedure for alkylation. The alkylated oxazine (21.0 g, 80 mmol) thus prepared was reduced with 3.7 g (95 mmol) of sodium borodeuteride (Merck) at −40° in THF–ethanol. The reduced oxazine was cleaved in aqueous oxalic acid after heating to reflux for 2 hr and the aldehyde was removed by ether extraction. A fractionally distilled product weighed 8.5 g: bp 64–65° (3 mm); ir (neat) 2580 (CD), 1705, 1640 cm⁻¹; nmr (CCl₄) δ 7.0–7.5 (m, 5), 4.8–6.0 (m, 3), 3.5 (t, 1), 2.0–3.1 (m, 2); 2,4-DNP mp 100–103°.

*Anal.* Calcd for C₁₁H₁₁DO: C, 81.95; H, 8.12. Found: C, 81.91; H, 8.12.

**Addition of *n*-Butylmagnesium Bromide and Methyl Iodide to the 2-Vinyldihydro-1,3-oxazine (21). Formation of 85 (R = *n*-Butyl).**—A solution of *n*-butylmagnesium bromide [from 82.2 g (0.6 mol) of *n*-butyl bromide and 15.3 g (0.63 g-atom) of magnesium] in 300 ml of tetrahydrofuran was added dropwise to a solution of 30.6 g (0.2 mol) of 2-vinyl oxazine **21** and 42.7 g (0.3 mol) of methyl iodide in 300 ml of tetrahydrofuran previously cooled in a Dry Ice–acetone bath (−60°). The resulting mixture was then allowed to warm to ambient temperature and stir overnight, after which it was treated carefully with water to decompose the excess Grignard reagent. The contents of the flask were poured into 1 l. of an ice-water mixture and acidified with dilute hydrochloric acid (6 N). The aqueous mixture was extracted with petroleum ether (bp 30–60°) and the extracts were discarded. The aqueous solution was rendered alkaline by addition of 35% sodium hydroxide solution and the resulting oil was collected and concentrated by ether extraction after drying with potassium carbonate. There remained 42 g (93%) of crude residue which after distillation, bp 59–61° (0.4 mm), gave 38.5 g (85%) of pure alkylated oxazine, **85** (R = *n*-butyl): ir (neat) 1650 cm⁻¹; nmr (CDCl₃) δ 4.0–4.3 (m, 1).

*Anal.* Calcd for C₁₄H₂₇NO: C, 74.61; H, 12.08; N, 6.21. Found: C, 74.47; H, 12.04; N, 6.27.

**2-Methyl-3-phenylpropanal (Table X, Entry 1).**—Utilizing the procedure described above for **85**, addition of phenylmagnesium bromide in ether (0.16 mol in 45 ml) to a solution of **21** (0.06 mol) and methyl iodide (0.09 mol) in 100 ml of tetrahydrofuran at −60 to −65° gave 14.8 g (93%) of crude dialkylated oxazine **85** (R = phenyl). Without further purification, the oxazine was reduced according to the general procedure using 2.5 g (0.06 mol) of sodium borohydride and this led to 13.7 g of tetrahydro-1,3-oxazine which was directly cleaved by addition to a boiling solution of oxalic acid (33 g per 150 ml of water) and collecting the aldehyde in the stream distillate. The oil was removed and concentrated from an ether solution to give 6.0 g (66% overall from **21**): ir (neat) 2710, 1730 cm⁻¹; nmr (CDCl₃) δ 9.7 (d, 1); semicarbazone mp 122–123°.

**Reaction of 2-Vinyloxazine (21) with Sodiomalonic Ester.**—A solution of 3.95 g (26 mmol) of **21** in 5 ml of absolute ethanol was added to 9.9 g (65 mmol) of diethyl malonate containing 0.05 g of sodium ethoxide in 40 ml of ethanol. The mixture was heated to reflux for 4 hr, cooled, diluted with water, acidified (6 N HCl), and extracted. The ethereal extracts were discarded and the aqueous solution was made alkaline (35% NaOH). Extraction of the oil with ether, drying (K₂CO₃), and concentration left 5.93 g (73%) of the ester oxazine **83** [N = CH-(CO₂ET)]: ir (neat) 1740–1750 (br), 1660 cm⁻¹; nmr (CDCl₃) δ 4.2 (q, m, 5), 3.4 (t, 1), 2.2 (m, 4), 1.6 (d of t, 2), 1.3 (d, 3), 1.0–1.2 (m, 17). Distillation at 0.2 mm was performed by a bulb-to-bulb apparatus.

*Anal.* Calcd for C₁₆H₂₇NO₅: C, 61.32; H, 8.68; N, 4.47. Found: C, 61.47; H, 8.49; N, 4.40.

**Reaction of Enamines with 2-Vinyldihydro-1,3-oxazine (87).**—Pyrrolidine enamines of cyclopentanone and cyclohexanone were prepared from known procedures.[52] A solution of **21** and the

pyrrolidine enamine of cyclopentanone in equivalent amounts (0.10 mol of each) in 125 ml of benzene were heated to reflux with azeotropic removal of water for 15 hr. Addition of 50 ml of water was followed by another 30 min of heating and the entire mixture was poured onto ice–water (300 ml) and acidified with 9 N hydrochloric acid. The aqueous benzene mixture was extracted twice with ether and the extracts were discarded. The aqueous phase was made basic with 40% sodium hydroxide solution and the resulting oil was removed by several ether extractions, dried over magnesium sulfate, and concentrated. The residual oil, 23 g (97%), was distilled bulb-to-bulb [bp 97–110° (0.2 mm), ir (neat) 1735, 1660 cm⁻¹)] giving pure **87**.

*Anal.* Calcd for C₁₄H₂₃NO₂: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.59; H, 9.60; N, 5.80.

In a similar manner, **21** was treated with the pyrrolidine enamine of cyclohexanone and **87** (cyclohexanone analog) was formed in 94% yield, ir (neat) 1705, 1658 cm⁻¹.

*Anal.* Calcd for C₁₃H₂₅NO: C, 71.67; H, 10.02; N, 5.57. Found: C, 71.84; H, 9.88; N, 5.46.

**Ketalization of 87 to 89.**—The procedure of Nielsen[53] was adopted in the following manner. A mixture of **87** (9.0 g, 38 mmol), 25 ml of ethylene glycol, and 100 ml of toluene was treated with 8.0 g of *p*-toluenesulfonic acid monohydrate and heated to reflux in the presence of a Dean–Stark trap. Since, in addition to water, ethylene glycol is also distilled out of the system, the reaction vessel was replenished with 25 ml of ethylene glycol after 24 hr. The azeotropic process was repeated for an additional 24 hr until no more ethylene glycol was collected in the trap. The flask was cooled, the contents were poured into cold 10% sodium carbonate solution, and the organic layer was extracted with ether, dried (MgSO₄), and concentrated using initially a water aspirator and finally a vacuum pump. The crude ketal **89** was devoid of any carbonyl stretching frequency and the yield was 10.0 g (93%). Distillation, bp 130–134° (2 mm), gave pure material, ir (neat) 1668 cm⁻¹.

*Anal.* Calcd for C₁₆H₂₇NO₃: C, 68.29; H, 9.67; N, 4.98. Found: C, 68.74; H, 9.53; N, 4.91.

**Reduction of the Dihydro-1,3-oxazinylethylcyclopentanone (87) to 88.**—The reduction using sodium borohydride was carried out according to the general procedure using 4.0 g (17 mmol) of **87** and 0.5 g (15 mmol) of sodium borohydride in 50 ml of tetrahydrofuran–ethanol (1:1). Isolation of **88** gave 3.8 g (93%) of an oil as a mixture of stereoisomers which were not separated, ir (neat), 3350 cm⁻¹ (broad). No C=N absorption at 1660 cm⁻¹ was evident.

**Reduction of Dihydro-1,3-oxazine 89 to Tetrahydro-1,3-oxazine 90.**—Reduction using sodium borohydride (0.8 g, 20 mmol) of dihydro-1,3-oxazine **89** (5.6 g, 20 mmol) in 120 ml of ethanol–tetrahydrofuran at −40° was done according to the general procedure. In this instance, the reaction mixture was stirred for only 5–10 min after completion of the borohydride addition. Isolation was performed in the usual manner leaving 5.4 g (96%) of **90** as an oil; ir (neat) showed only NH absorption at 3280 cm⁻¹ and no absorption at 1660 cm⁻¹.

**Registry No.**—**18**, 26939-18-4; **19**, 26939-22-0; *endo*-**20**, 36867-19-3; *exo*-**20**, 36867-20-6; **21**, 23878-88-8; **22**, 36867-22-8; **28**, 36867-23-9; **30**, 36867-24-0; **30a**, 36867-25-1; **31**, 36867-26-2; **32**, 36867-27-3; **42**, 36867-28-4; **49**, 36867-29-5; **50**, 6728-31-0; **52**, 36867-30-8; **54**, 36867-31-9; **54** perchlorate salt, 36900-97-7; **55**, 13050-09-4; **56**, 36867-33-1; **57**, 1540-83-6; **57** 2,4-DNP, 26385-63-7; **58**, 36867-36-4; **59**, 29304-32-3; **60**, 29822-84-2; **61**, 36867-39-7; **62**, 36867-40-0; **63**, 36867-41-1; **65** (E = D), 24314-24-7; **66** (E = D), 29304-33-4; **67**, 29304-29-8; **67** 2,4-DNP, 29304-30-1; **69**, 31859-53-7; **69** 2,4-DNP, 29304-31-2; **71**, 36871-39-3; **73** (A = H, R = Et), 36871-40-6; **73** (A = H, R = PhCO), 36871-51-9; **74** (A = H, R = PhCO), 36871-52-0; **83** [N = CH-(CO₂Et)₂], 36871-41-7; **85** (R = *n*-Bu), 36871-42-8; **87**, 36871-43-9; **87** cyclohexanone analog, 36871-44-0;

(52) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

(53) A. T. Nielsen, *J. Heterocycl. Chem.*, **7**, 232 (1970).

88, 36871-45-1;   89, 36871-46-2;   90, 36871-47-3; 2-(3-hexenyl)-DHO,  36872-13-6;  2-(3-hexenyl)-THO, 3687-14-7;    2-(5-bromopentyl)-4,4,6-trimethyl-5,6-di-hydro-1,3-oxazine,    36871-48-4;    2-(5-chloropentyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine,    36871-49-5; 2-(4-cyano-1-phenylbutyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine, 36871-50-8.

# Reactions of α,β-Dibromo Oximes and Related Compounds with Nitrosyl Chloride[1]

Edward G. Bozzi, Chyng-yann Shiue, and Leallyn B. Clapp*

*Metcalf Laboratories, Brown University, Providence, Rhode Island   02912*

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The reaction of nitrosyl chloride with α,β-dibromo oximes to give chloronitrimines consists of separate reactions even though the two reactions may occur in the same molecule.   Replacement of bromine by chlorine is an $S_N1$ reaction on the more activated secondary or on a tertiary bromine.   Oxidation of the oximino function to a nitrimine occurs later in time and under more strenuous conditions in some cases, for example, in 1,2-dibromo-1-p-methoxyphenyl-3-butanone oxime.   In other examples, the oxidation occurs without halogen displacement.   In carvone oxime derivatives the replacement and oxidation occur in separated parts of the molecule.

Nitrosyl chloride[2] is known to react with aldoximes to give chloronitroso compounds, $RCHClNO$, or hydroxamic chlorides, $ArCCl{=}NOH$, or with ketoximes to give *gem*-chloronitroso compounds.[3]   In an extension of the reaction to a series of α,β-dibromo ketoximes it was found that two reactions occurred: replacement of the α-bromine atom by chlorine and oxidation of the ketoxime to a nitrimine.[4]  The reactions are not coupled; the present work shows that the replacement reaction is of $S_N1$ character and that the oxidation is an independent reaction.

For example, 1,2-dibromo-1-p-methoxyphenyl-3-butanone oxime (**1a**) reacts with a slight excess of nitrosyl chloride in ether at 25° to replace the β-bromine with chlorine in 90% yield, without oxidizing the oxime, to give **2a** (Chart I).   Longer treatment of **2a** with excess nitrosyl chloride or a sealed tube reaction gave the oxidized product **3a** in 46% yield.   Direct treatment of **1a** with nitrosyl chloride in a sealed tube gave **3a** only.   Apparently the p-methoxy group activates the benzylic position so that an $S_N1$ type replacement occurs (see below).

The substituted dihydrocinnamaldoxime **1b** behaved similarly except that normal oxidation of the aldehydic hydrogen gave the hydroxamic chloride **2b**, which in turn was oxidized to the nitrimino chloride **3b**.   In cases **1c–f** where the benzylic bromine was not activated by substitution on the aromatic ring, the oxidation reaction occurred without accompanying substitution with one exception.   In the reaction of **1e** with nitrosyl chloride in ether, the 83% yield of α,β-dibromodihydrocinnamoyl hydroxamic chloride, a normal oxidation of the Rheinboldt type, was accompanied by a 12% yield of **2e**.   However, in the sealed tube reaction a 94% yield of **3e** was obtained.   Evidently under the more strenuous

## Chart I



1a, Y = OCH₃; R = CH₃
 b, Y = OCH₃; R = H
 c, Y = H; R = CH₃
 d, Y = Cl; R = CH₃
 e, Y = H; R = H
 f, Y = H; R = Ph

2a, R = CH₃
 b, R = Cl
 e, –CHCl–CHBr–CHCl(NO), dimer

3a, X = Cl
 b, X = Cl; R = Cl
 c, X = Br
 d, X = Br
 e, X = Br; R = Cl
 f, X = Br; R = Ph
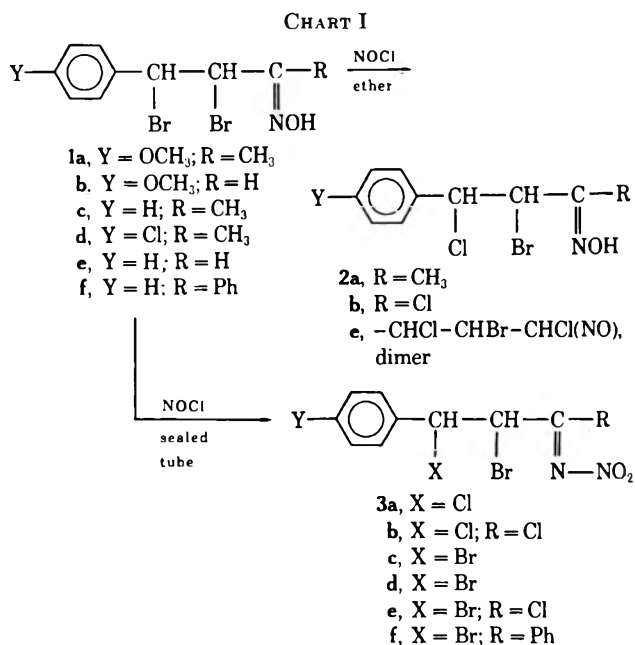
conditions of the sealed tube, oxidation of the aldoxime to nitrimino chloride was faster than substitution and the oxidation product was too unreactive for subsequent substitution.   In ether the substitution and aldehydic oxidation reactions compete without the accompanying oxime oxidation.

In the reaction of **1f**, the 70% yield of **3f** was accompanied by a 26% yield of 1-chloro-1-nitro-1,3-diphenylpropene (**5f**), suggesting that **4f** is an intermediate which is oxidized to **4g**.   It was found recently[5] that aliphatic chloronitroso compounds are oxidized to chloronitro compounds by nitrosyl chloride, whereas after isomerization to the isomeric oximes, the oxidation produces only nitrimines, the main product in this case also.   Loss of bromine to give the final product, **5f**, was not expected; none of the compounds **3c–e** behaved in that way even though these anticipated unsaturated compounds would be stabilized by more extensive conjugation than **5f**.

(1) Presented in part at the 163rd National Meeting of the American Chemical Society, Boston, Mass., April 14, 1972.

(2) P. P. Kadzyauskas and N. S. Zefirov, *Russ. Chem. Rev.*, **37**, 543 (1968); L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, pp 748–755; L. J. Beckham, W. A. Fessler, and M. A. Kise, *Chem. Rev.*, **48**, 319 (1951).

(3) H. Rheinboldt, M. Dewald, F. Jansen, and O. Schmitz-Dumont, *Justus Liebigs Ann. Chem.*, **451**, 161 (1927); H. Rheinboldt and M. Dewald, *ibid.*, **455**, 300 (1927).

(4) C.-Y. Shiue, K. P. Park, and L. B. Clapp, *J. Org. Chem.*, **35**, 2063 (1970).

(5) C.-Y. Shiue and L. B. Clapp, *ibid.*, **36**, 1169 (1971).

**4f, Z = NO**

**g, Z = NO₂**

**5f**
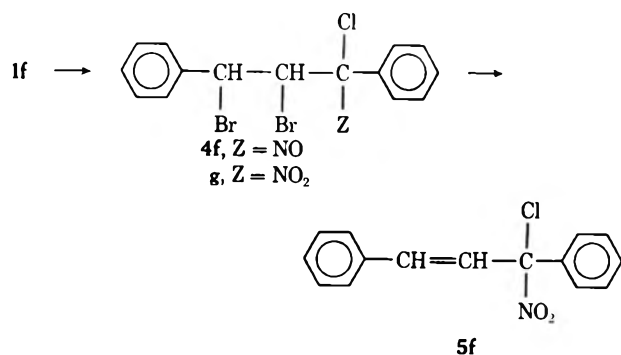
Carvone oxime (6, Chart II) contains a system in which the isolated double bond $\Delta^{8,9}$ is more reactive

**CHART II**
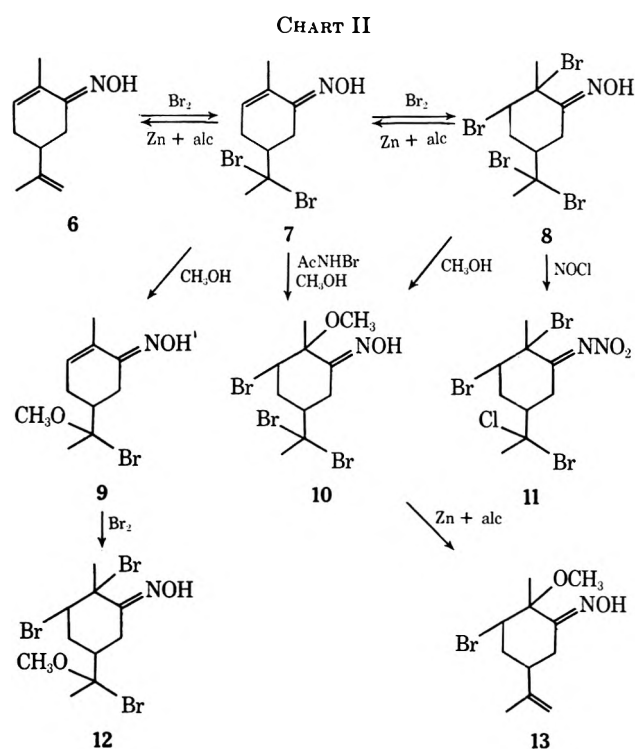


than the conjugated double bond.[6] Addition of bromine first gives the dibromo oxime 7 and then the tetrabromo oxime 8. The last bromines added are the first removed by zinc dust in alcohol or sodium iodide in acetone to regenerate 7. Methanol reacts with compound 8 to give the expected 1,4-elimination–addition[7,8] product 10, whose structure was determined by removal of 1 mol of bromine to give 13. However, nitrosyl chloride acting on the tetrabromo compound 8 replaced the bromine at C-8 rather than at C-1 to give 11. The tertiary bromine at C-8 is also reactive to methanol, since 7 was converted to 9 but bromine addition to 9 gave the tribromo compound 12, an isomer of 10. This corroborated the structure of 10.

Independence of the replacement reaction was further demonstrated by carrying out reactions of O-methyl oximes where the oxidation is impossible. In compounds 14 and 16, the tertiary bromine at C-1 was re-

placed by chlorine in 81 and 92% yields, respectively, to give 15 and 17 (Chart III).

**CHART III**



**14, X = Br**
**15, X = Cl**

**16, X = Br**
**17, X = Cl**
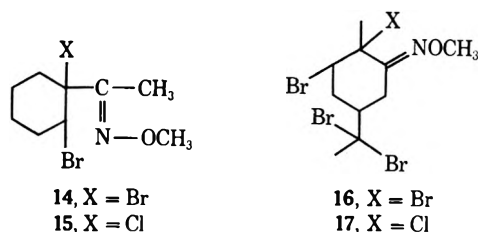
Since the displacement reaction appeared to be of the SN1 type, the reaction of nitrosyl chloride with various reactive alkyl bromides was carried out, with the results shown in Table I. The results indicate better yields in

**TABLE I**

PERCENTAGE OF ALKYL CHLORIDE BY NOCl
DISPLACEMENT IN VARIOUS SOLVENTS

| Substrate | CCl₄ | SO₂[a] | PhNO₂ | CH₃NO₂ | Liquid NOCl |
|---|---|---|---|---|---|
| t-C₄H₉Br | 15 | 100 | 100 | 100 | 100 |
| PhCH₂Br | 0 | 40 | 100 | 35 | 25 |
| PhCHBrCH₃ | 61 | 100 | 50[b] | 40[c] | 75 |

[a] In liquid sulfur dioxide at −6°. Others at 25°, including nitrosyl chloride in a sealed tube. [b] Accompanied by 50% oxidation to acetophenone. [c] Accompanied by 60% oxidation to acetophenone.

polar solvents, but the yields may be more a function of the change in polarity induced by the strongly polar nitrosyl chloride itself, which in turn is a function of the solubility of nitrosyl chloride in the particular solvent. Phenacyl bromide, a compound known to be very reactive toward SN2 reagents, did not react with nitrosyl chloride in any solvent shown in Table I, and p-nitrobenzyl bromide, containing a negatively substituted benzyl group, also did not react at all. The table shows, however, that normal SN1 substrates gave good yields of alkyl chlorides.

To pinpoint the reaction still further as an SN1 type, optically active α-bromoethylbenzene was treated with nitrosyl chloride in carbon tetrachloride and samples were removed at intervals. From this experiment it was found that the rate of replacement of bromine by chlorine was equal to the rate of racemization of the substrate. This result is considered to be diagnostic for an SN1 reaction. After 2 hr the replacement had reached 100% and the optical rotation was zero. These results are given in Table II.

**TABLE II**

ROTATION vs. CHLORIDE REPLACEMENT IN OPTICALLY
ACTIVE α-BROMOETHYLBENZENE

| Time, hr | Rotation $\alpha^{27}D$ | Optical purity, % | Per cent Cl replacement Calcd from rotation | Calcd from nmr |
|---|---|---|---|---|
| 0 | −139.3 | 82 | 0 | 0 |
| 1 | −72.2 | 42.4 | 51.5 | 50 |
| 2 | −11.3 | 6.5 | 92 | 95 |
| 9 | 0.0 | 0 | 100 | 100 |

Although we have not found an example of direct nucleophilic displacement of bromine by chlorine, hints that it should be possible do appear in the literature.

(6) J. L. Simonsen and L. N. Owen, "The Terpenes," 2nd ed, Cambridge University Press, New York, N. Y., 1947, pp 394–408.

(7) A. Dornow and H. D. Jordan, *Chem. Ber.*, **94**, 67, 76 (1961); W. Pritzkow, H. Schaefer, P. Pabst, A. Ebenroth, and J. Beger, *J. Prakt. Chem.*, [4], **29**, 123 (1965); G. Collin, W. Pritzkow, H. Huebner, W. Rolle, and M. Wahren, *Tetrahedron Lett.*, 3493 (1966).

(8) W. Pritzkow, *Z. Chem.*, **10**, 330 (1970), a review.

Winstein and others[9] suggested that the order of nucleophilicity in SN2 reactions of halides in acetone is actually Cl⁻ > Br⁻ > I⁻ when the halides are dissociated. Weaver and Hutchison[10] verified the correctness of this order in a displacement reaction run in dimethylformamide.

An SN1 mechanism has been invoked by Carlin and Larson[11] to explain a halogen interchange in a Fischer indole synthesis from acetophenone 2,6-dibromophenylhydrazone where one bromine was ciné-substituted by chlorine at C-5 of the indole when zinc chloride was the inducing agent. The authors picture one aromatic bromine changing to an allylic bromine during an intermediate stage in the reaction, which is followed by an allylic rearrangement. The corresponding 2,6-dichlorophenylhydrazone rearranged in the presence of zinc bromide to yield an indole ciné-substituted by bromine at C-5. In the present work, the reactivities of the halides might well be comparable.

Of course the replacement of bromine by chlorine is not the direction of reaction that would normally be sought, since bromine is more expensive than chlorine. Out of curiosity, in addition to the results in Table I, we found that *tert*-butyl bromide is converted to *tert*-butyl chloride at room temperature in 24 hr by other chlorinating agents: iodine monochloride to the extent of 100% in nitromethane, 60% in nitrobenzene, 0% in carbon tetrachloride; by thionyl chloride 30% in nitromethane; and by phosphorus pentachloride 60% in nitromethane. Benzyl bromide is converted to benzyl chloride in 25% yield by phosphorus pentachloride in refluxing nitromethane and by thionyl chloride to the extent of 14% in the same solvent.

The replacement reaction may well find use where it is desirable to have two halogens present (chlorine and bromine) of markedly different reactivity toward a given reagent.

## Experimental Section

Properties and identifying spectral data are given for new compounds in Table III. The ir spectra were taken with KBr pellets. The nmr spectra were taken in deuteriochloroform or deuterioacetone with TMS as an internal standard. Satisfactory analyses were obtained on all compounds except 1b, 1c, 3b, 7, and 9. Intermediates 4f and 4g were not isolated. Compounds 1f,[12] 6,[13] and 8[14] had been previously reported.

The α,β-dibromo oximes (1) were prepared by adding bromine to the unsaturated oximes.[4] Oxime synthesis from the dibromo ketones was not practical, since the dibromo oximes lost hydrogen bromide spontaneously. The β-chloro oximes (2) were prepared by treating compounds 1 with nitrosyl chloride in ether, a procedure used to make α-chloronitrimines in previous work. The nitrosyl chloride (97% minimum purity, J. T. Baker) was purified by passing the gas through a series of three tubes. The tubes were connected to each other and the cylinder of nitrosyl chloride by Tygon tubing. The tubes contained, in order, sodium nitrite, moist potassium chloride (2.4% water), and calcium chloride to remove hydrogen chloride, nitrogen dioxide, and water, respectively.[15]

**α,β-Dibromodihydrocinnamoyl Nitriminochloride (3e).**—More strenuous conditions were needed to prepare the series of compounds 3 than were needed for 2a, b, and e.

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### TABLE III

| Compd | Yield, % | Mp, °C | Ir, cm⁻¹ C=N[a] | Nmr, δ |
|---|---|---|---|---|
| 1a | 45 | 137–138 | 1610 | 7.20 (q, 4), 5.62 (s, 1), 5.45 (s, 1), 3.88 (s, 3), 2.22 (s, 3) |
| 1b | 94 | 71 | 1610 | 7.25 (q, 4), 5.25 (m, 2), 3.86 (s, 3) |
| 1c | 48 | 161–162 | 1625 | 7.43 (s, 5), 5.22 (s, 2), 2.12 (s, 3) |
| 1d | 55 | 160 | 1640 | 7.38 (s, 4), 5.18 (d, 2), 2.12 (s, 3) |
| 1e | 40 | 145 | 1625 | 7.24 (s, 5), 7.10 (s, 1), 5.10 (m, 2) |
| 1f | 37 | 165[b] | 1630 | 7.30 (m, 10), 5.30 (s, 2) |
| 2a | 90 | 158 | 1610 | 7.30 (q, 4), 5.64 (s, 1), 5.38 (s, 1), 3.90 (s, 3), 2.20 (s, 3) |
| 2b | 98 | 155–157 | 1610 | 7.30 (q, 4), 5.25 (d, 2), 3.88 (s, 3) |
| 2e | 12 | 127–129 | c | |
| 3a | 46 | 131–132 | 1620[d] | 7.40 (q, 4), 5.65 (q, 2), 3.92 (s, 3), 2.52 (s, 3) |
| 3b | 86 | Oil | 1610 | 7.35 (q, 4), 5.27 (d, 2), 3.91 (s, 3) |
| 3c | 75 | 151 | 1635 | 7.43 (s, 5), 5.28 (d, 2), 2.33 (s, 3) |
| 3d | 54 | 135–136 | 1640 | 7.40 (s, 4), 5.20 (d, 2), 2.32 (s, 3) |
| 3e | 94 | 137–138 | 1615 | 7.25 (s, 5), 5.15 (s, 2) |
| 3f | 70 | 91–92 | 1630 | 7.40 (m, 10), 5.34 (d, 2) |
| 5f | 26 | 70–72 | e | 7.25 (m, 12) |
| 6 | 63 | 66–67[f] | 1640 | 6.0 (br, 1), 4.8 (br, 2), 1.87 (s, 3), 1.77 (s, 3) |
| 7 | 71 | 104–106 dec | 1650 | 6.13 (br, 1), 3.91 (s, 2), 2.18 (s, 3), 1.91 (s, 3) |
| 8 | 30 | 127.5–129[g] | 1650 | 4.7 (br, 1), 3.9 (s, 2), 2.17 (s, 3), 1.97 (s, 3) |
| 9 | 60 | 113–114 | 1650 | 6.03 (br, 1), 3.91 (s, 2), 3.20 (s, 3), 1.93 (s, 3), 1.51 (s, 3) |
| 10 | 50 | 135 | 1645 | 4.37 (br, 1), 3.95 (br, 2), 3.18 (s, 3), 1.93 (s, 3), 1.51 (s, 3) |
| 11 | 20 | 89.0–90.5 | 1640[h] | 4.58 (br, 1), 3.85 (s, 2), 2.00 (s, 3), 1.90 (s, 3) |
| 12 | 64 | 119–120 | 1645 | 4.31 (t, 1), 3.89 (d, 2), 3.19 (s, 3), 1.75 (s, 3), 1.50 (s, 3) |
| 13 | 87 | 85–86 | 1650 | 4.80 (d, 2), 4.31 (t, 1), 3.19 (s, 3), 1.75 (s, 3), 1.50 (s, 3) |
| 14 | 35 | 36–38 | 1620 | 4.74 (br, 1), 3.87 (s, 3), 1.97 (s, 3) |
| 15 | 81 | 31–32 | 1620 | 4.60 (br, 1), 3.89 (s, 3), 1.96 (s, 3) |
| 16 | 19 | 109–111 | 1620 | 4.60 (m, 1), 3.83 (s, 3), 3.80 (br, 2), 2.08 (s, 3), 1.97 (s, 3) |
| 17 | 92 | 128–129 | 1620 | 4.42 (br, 1), 3.82 (s, 3), 3.80 (br, 2), 1.90 (s, 6) |

[a] All C=N absorptions medium. [b] K. von Auwers and M. Seyfried, *Justus Liebigs Ann. Chem.*, **484**, 178 (1930), mp 156°. [c] N–O, 1570, 1440 cm⁻¹, s: 83% of 2,3-dibromo-3-phenylpropanoyl chloride, mp 174°, obtained in the same reaction. [d] NO₂, 1570–1600 cm⁻¹ in 3a–f. [e] NO₂, 1540, 1340 cm⁻¹, s. [f] R. H. Reitsema, *J. Org. Chem.*, **23**, 2038 (1958), mp 66–69°. [g] Reference 3, mp 126–127°. [h] NO₂, 1590, 1320 cm⁻¹, s.

α,β-Dibromodihydrocinnamaldehyde oxime (1e) (0.4 g, 1.3 mmol) was sealed in glass in a Dry Ice bath with excess liquid nitrosyl chloride. The mixture was allowed to stand for 24 hr at

room temperature. Upon opening the tube and allowing nitrosyl chloride to boil away, a yellow oil was isolated which crystallized on standing to give 0.35 g (94%) of $\alpha,\beta$-dibromodihydrocinnamoyl nitriminochloride. Recrystallization from carbon tetrachloride-chloroform gave the analytical sample, mp 125–127°.

Compounds 3a–d were prepared in like manner.

**1-Chloro-1-nitro-1,3-diphenylpropene (5f).**—Excess nitrosyl chloride in 25 ml of ether acting on 0.50 g (1.4 mmol) of benzalacetophenone oxime dibromide (1f) gave a mixture of two oily products which were separated on a silica gel column. Elution with 60:40 hexane–carbon tetrachloride gave 0.29 g (70%) of nitrimine 3f (Table III). Change of eluent to 50:50 chloroform–carbon tetrachloride gave a yellow oil (0.4 g) which lost bromine on standing. After 2 days standing, the oil crystallized to give 0.10 g (26%) of 1-chloro-1-nitro-1,3-diphenylpropene, mp 70–72°.

**8,9-Dibromo-8,9-dihydrocarvone Oxime (7).**—Carvone oxime[13] (2.65 g, 0.016 mol) in 25 ml of carbon tetrachloride was treated with 2.65 g (0.016 mol) of bromine in 20 ml of carbon tetrachloride dropwise. After stirring for 1 hr the solvent was removed on a rotary evaporator and the remaining solid (3.64 g, 71%) was recrystallized from a pentane–chloroform mixture, mp 104–106° dec. The product did not give a satisfactory analysis but gave satisfactory spectral data (Table III).

Compound 7 was also obtained in 87% yield from 1,6,8,9-tetrabromotetrahydrocarvone oxime[14] (8) by warming for 10 min with an equivalent amount of sodium iodide in acetone. A comparable yield of 7 was obtained with zinc dust in refluxing ethanol (see 13 below).

**9-Bromo-8-methoxy-8,9-dihydrocarvone Oxime (9).**—A solution of 0.52 g (1.9 mmol) of 8,9-dibromo-8,9-dihydrocarvone oxime (7) in 30 ml of absolute methanol was allowed to stand at room temperature for 25 hr and then was poured onto 200 g of ice. After standing overnight in a refrigerator the crystals were collected, dried, and recrystallized from pentane–chloroform to give 0.31 g (60%) of 9-bromo-8-methoxy-8,9-dihydrocarvone oxime, mp 113–114°.

**6,8,9-Tribromo-1-methoxytetrahydrocarvone Oxime (10).**—Compound 10 was prepared by treating tetrabromotetrahydrocarvone oxime[14] (8) with methanol as just described for 9. The structure was confirmed by synthesis from 7 by the method of Winstein and Henderson[16] with N-bromoacetamide in methanol. Comparison of ir and nmr spectra showed the two samples to be identical.

**8-Chloro-1,6,9-tribromotetrahydrocarvone Nitrimine (11).**—Into a solution of 1.8 g (3.7 mmol) of 1,6,8,9-tetrabromotetrahydrocarvone oxime[14] in 40 ml of chloroform at room temperature, a slow stream of nitrosyl chloride was bubbled. After a yellow color was attained, the gas stream was stopped and the solution was stirred overnight. One gram of anhydrous sodium carbonate was added to the solution and the mixture was stirred for an additional 1 hr. The solution was decanted from the solid and the chloroform was removed on a rotating evaporator. The remaining green oil solidified in the refrigerator and was recrystallized twice from pentane–carbon tetrachloride to give 350 mg (20%) of white 8-chloro-1,6,9-tribromotetrahydrocarvone nitrimine (11), mp 89–90.5°.

The position of the chlorine at C-8 was corroborated by conversion to 8-chloro-9-bromo-8,9-dihydrocarvone in 40% yield by treatment with zinc dust in refluxing ethanol as described above: ir (CCl₄) 1660 (s, C=C-C=O), 625 (CCl), 570 cm⁻¹ (CBr); nmr (CDCl₃) δ 6.80 (br, 1), 3.85 (s, 2), 1.89 (s, 3), 1.78 (s, 3). The absorption frequency at 570 cm⁻¹ was also found in 8,9-dibromo-8,9-dihydrocarvone, synthesized by adding 1 mol of bromine to carvone, but the band at 625 cm⁻¹ was missing.

**8-Methoxyl-1,6,9-tribromotetrahydrocarvone Oxime (12).**—Addition of bromine to compound 9 in the same manner as described here for other unsaturated oximes gave 8-methoxy-1,6,9-tribromotetrahydrocarvone oxime in 64% yield, mp 119–120°.

**1-Methoxy-6-bromo-1,6-dihydrocarvone Oxime (13).**—The structure of compound 10 was also verified by treating 1 g (2.3 mmol) of 10 with 0.15 g (2.3 g-atoms) of zinc dust in 30 ml of refluxing absolute ethanol for 1 hr. The clear oil obtained after evaporating the solvent crystallized upon standing for 5 days.

Recrystallization from hexane gave 0.75 g (87%) of 1-methoxy-6-bromo-1,6-dihydrocarvone oxime, mp 85–86°.

**Methyl 1,2-Dibromo-1-cyclohexyl O-Methylketoxime (14).**—Methyl 1-cyclohexenyl ketone[4] was converted to the corresponding O-methylketoxime by the method described in the next section in 48% yield, bp 60–62° (1.5 mm). This method was more convenient than that of Müller,[17] even though the yield in the latter case using diazomethane on the oxime was 75%. Compound 14 was prepared by addition of bromine (*vide supra*) in 35% yield after recrystallization from hexane, mp 36–38°.

Compound 15, methyl 1-chloro-2-bromo-1-cyclohexyl O-methylketoxime, was obtained from 14 by treatment with nitrosyl chloride in a sealed tube at 55° for 3 days, much more strenuous conditions than were needed for any other replacement reaction reported here. By putting the brown oily product obtained by this method on a silica gel column and eluting with hexane an 81% yield of 15 was obtained, mp 31–32°.

**1,6,8,9-Tetrabromotetrahydrocarvone O-Methyloxime (16).**—Carvone (4.8 g, 32 mmol) was treated with 2.6 g (32 mmol) of O-methylhydroxylamine hydrochloride[18] in 40 ml of ethanol. To this solution 3.2 g (32 mmol) of triethylamine in 10 ml of ethanol was added dropwise and then the mixture was refluxed for 4 hr, cooled, and poured onto ice. The organic layer was extracted with ether and the solvent was evaporated to give 2.6 g (80%) of a yellow oil, identified as carvone O-methyloxime[19] by ir and nmr spectra, but not isolated: ir (neat) 3070 (s, CH), 2950 (br), 1670 cm⁻¹ (m, C=N); nmr (CCl₄) δ 5.75 (br, 1), 4.62 (s, 2), 3.72 (s, 3), 1.70 (s, 6).

To 0.4 g (2.3 mmol) of carvone O-methyloxime in 15 ml of carbon tetrachloride was added 0.74 g (4.6 mmol) of bromine in 10 ml of the same solvent. After a short time the solvent was removed on a rotary evaporator, leaving a red oil which crystallized on cooling. Recrystallization from hexane gave 0.15 g (19%) of a white solid, mp 109–111°, 1,6,8,9-tetrabromotetrahydrocarvone O-methyloxime.

**Reaction of Optically Active $\alpha$-Bromoethylbenzene with Nitrosyl Chloride.**—(−)-$\alpha$-Bromoethylbenzene[20] (0.5 g, 2.7 mmol) was dissolved in 25 ml of carbon tetrachloride and an excess of nitrosyl chloride was slowly bubbled into the solution. After the solution was stirred at 25° for 1 hr, an aliquot was taken from the reaction mixture and an nmr spectrum and the optical rotation were taken immediately. More nitrosyl chloride was bubbled through the remaining solution and aliquots were removed at the times given in Table II. The treatment finally ended in 100% conversion of the bromide to the racemic chloride. The percentages of chloride and bromide were determined by measuring the integrated areas of the chemical shifts of the respective protons in the -CHCl and -CHBr groups. The optical purity values given in Table II are based on a calculated rotation of −170° for the pure bromo compound.[20]

Since the percentage replacement from nmr measurements is accurate to ±5%, the conclusion is that the rate of replacement of bromine by chlorine from nitrosyl chloride is equal to the rate of racemization within experimental error.

The percentage yields of alkyl chlorides in Table I were also determined from the corresponding areas of peaks from chemical shifts in nmr spectra of the reaction mixtures.

**Registry No.**—1a, 36914-18-8; 1b, 36914-19-9; 1c, 36914-20-2; 1d, 36914-21-3; 1e, 36914-22-4; 1f, 36914-23-5; 2a, 36914-24-6; 2b, 36914-25-7; 2e, 36914-42-8; 3a, 36914-26-8; 3b, 36914-27-9; 3c, 36914-28-0; 3d, 36914-29-1; 3e, 36914-30-4; 3f, 36914-31-5; 5f, 36914-32-6; 7, 36914-33-7; 9, 36914-34-8; 10, 36914-35-9; 11, 36914-36-0; 12, 36914-37-1; 13, 36914-38-2; 14, 36914-39-3; 15, 36914-40-6; 16, 36914-41-7; 17, 36895-16-6; $\alpha$-bromoethylbenzene, 585-71-7; nitrosyl chloride, 2696-92-6.

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# The Synthesis of Imenine.   A Route to 4-Oxygenated Oxoaporphines

M. P. CAVA* AND I. NOGUCHI

*Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104*

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The alkaloid imenine (1) has been synthesized.   This work represents the first synthesis of an oxoaporphine base containing a 4-oxygenated function.

The yellow alkaloid imenine occurs in the woody stems of the Amazonian vines *Abuta imene*[1] and *A. rufescens*[2] (Menispermaceae). An X-ray crystallographic analysis has shown that imenine has structure 1,



1
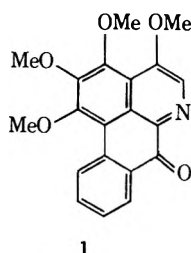
making it the first example of a 4-oxygenated oxoaporphine base.[1] We now report the first synthesis of imenine; this work represents also the only synthesis of any natural 4-oxygenated aporphine.[3]

## Results

Condensation of 3,4,5-trimethoxybenzaldehyde (2) with aminoacetaldehyde diethyl acetal gave the Schiff base 3, which was directly hydrogenated to N-(3,4,5-trimethoxybenzyl)aminoacetaldehyde diethyl acetal (4).   Hydrolytic cyclization of 4 by aqueous hydrochloric acid was carried out according to the general procedure of Bobbitt[4] to give 4-hydroxy-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (5), mp 138–139.5°, in 61% yield based on aldehyde 2. When the alcohol 5 was heated with 10% palladium on charcoal in *p*-

cymene at 140–145°, a fair yield (23%) of the phenolic dehydrogenation product, 4-hydroxy-5,6,7-trimethoxy-isoquinoline (6), mp 116–117°, was obtained; 5,6,7-trimethoxyisoquinoline (7)[5] was also isolated in 18% yield. Methylation of phenol 6 with diazomethane gave 4,5,6,7-tetramethoxyisoquinoline (8), mp 96°.
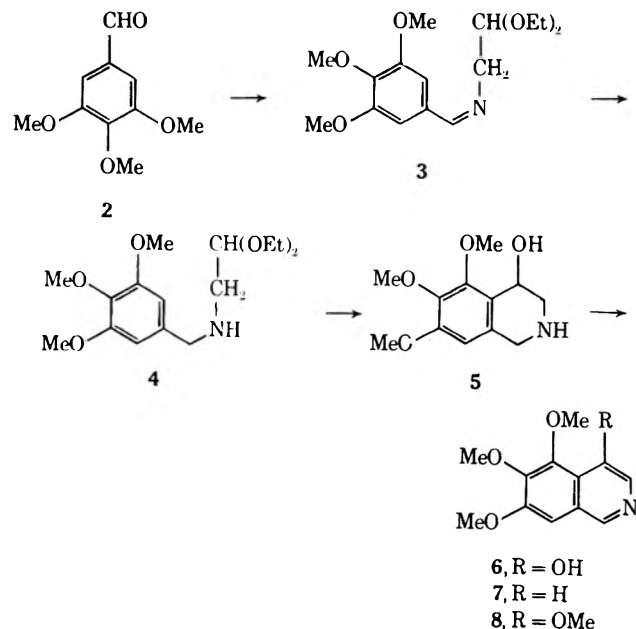
Elaboration of 8 to imenine was effected by use of the Reissert method.[6] Thus, treatment of 8 with benzoyl chloride and potassium cyanide afforded the Reissert compound 9, mp 136–137°, in 51% yield. Alkylation of 9 by *o*-nitrobenzyl chloride, followed by direct Triton B hydrolysis[5,7] of the intermediate 10, afforded 1-(2-nitrobenzyl)-4,5,6,7-tetramethoxyisoquinoline (11), mp 118–119°, in 38% yield; 1-cyano-4,5,6,7-tetramethoxy-isoquinoline (12), mp 138–139°, was obtained as a byproduct in this reaction.

The conventional approach to imenine from 11 required, as the next step, oxidation of 11 to the corresponding ketone. Attempts to carry out this oxidation using chromic acid under varied conditions led to failure; either 11 was recovered unchanged or overoxidation to highly polar products took place. The desired synthesis was completed, however, by reducing 11 to the corresponding amine 13, and then subjecting 13 to the usual Pschorr cyclization conditions. The product directly isolated from the Pschorr reaction was not the expected bisdehydroaporphine 14, but rather imenine



2



3



4



5



6, R = OH
7, R = H
8, R = OMe



8 →

9



10



11, R = NO₂
13, R = NH₂



14



12
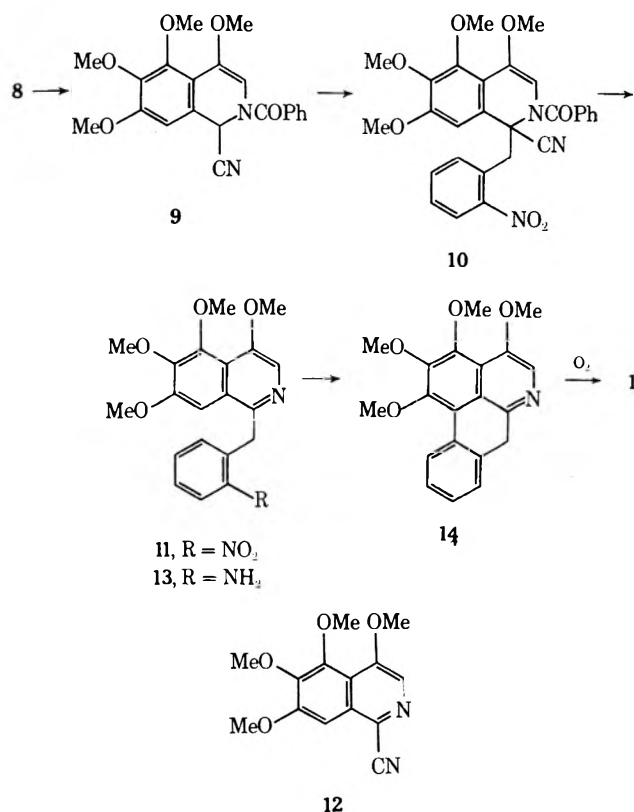
(1) M. D. Glick, R. E. Cook, M. P. Cava, M. Srinivasan, J. Kunitomo, and A. I. daRocha, *Chem. Commun.*, 1217 (1969).

(2) K. T. Buck, unpublished observations.

(3) Only two other natural bases of this type have been reported: (a) J. Kunitomo, Y. Okamoto, E. Yuge, and Y. Nagai, *Tetrahedron Lett.*, 3287 (1969);   (b) I. Ribas, J. Sueiras, and L. Castedo, *ibid.*, 2033 (1972).

(4) J. M. Bobbitt and J. C. Sih, *J. Org. Chem.*, 33, 856 (1968).

(5) M. P. Cava and M. V. Lakshmikantham, *ibid.*, 35, 1867 (1970).

(6) F. D. Popp and W. E. McEwen, *J. Amer. Chem. Soc.*, 79, 3773 (1957).

(7) M. P. Cava and M. Srinivasan, *Tetrahedron*, 26, 4649 (1970).

(1), identical in all respects with the natural alkaloid. The yield of imenine based upon nitro compound 11 was remarkably good (35%).

## Discussion

The imenine synthesis described above contains several novel steps which are worthy of comment.

The direct dehydrogenation of alcohol 5 to phenol 6 illustrates the simplest and most direct synthesis of a 4-hydroxyisoquinoline yet recorded. In view of the ease of preparation of 4-hydroxy-1,2,3,4-tetrahydroisoquinolines,[4] the use of our procedure should make available many hitherto inaccessible 4-hydroxyisoquinolines.

The formation of imenine (1) from the amine 13 represents the first successful example of the Pschorr cyclization starting from a 1-(2-aminobenzyl)isoquinoline. The direct isolation of imenine rather than the expected cyclization product 14 indicates that 14 is extremely susceptible to attack by oxygen. This is not too surprising, since abstraction of a hydrogen from the methylene carbon of ring C would afford a highly delocalized and *planar* radical. The ease of oxidation of 14 to imenine offers a reasonable explanation for the fact that ring B aromatic aporphines related to 14 have neither yet been encountered synthetically nor in nature except as their stable oxidation products, the oxoaporphines.

## Experimental Section

Analyses were carried out by Midwest Microlab, Inc., Indianapolis, Ind. All melting points are uncorrected. Nmr spectra were measured on Varian A-60 and Varian A-100 instruments in CDCl₃ using tetramethylsilane as an internal standard unless noted. Mass spectra were measured on a Perkin-Elmer Model 270 instrument. Ultraviolet spectra were measured on a Perkin-Elmer Model 202 spectrophotometer.

**4-Hydroxy-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (5).**—A mixture of 3,4,5-trimethoxybenzaldehyde (2, 100.0 g), aminoacetaldehyde diethyl acetal (120 ml), and dry benzene (1000 ml) was kept at room temperature for 20 hr, and then refluxed for 6 hr using a Dean-Stark to collect the water which was formed. Evaporation of the solvent afforded the syrupy Schiff base 3, which was dissolved in EtOH (200 ml) and hydrogenated in the presence of platinum at room temperature (45 psi H₂ pressure) for 20 hr. After filtration of the catalyst, evaporation of solvent left the syrupy amino acetal 4, which was dissolved in EtOH (250 ml). Aqueous 6 N HCl (2275 ml) was added dropwise to the stirred and cooled (0–5°) solution of 4, after which the mixture was stirred at room temperature for an additional 20 hr. Basification with ammonia, followed by CHCl₃ extraction and solvent removal, gave, after crystallization from Et₂O, pale yellow needles of 4-hydroxy-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (5, 73.9 g, 61%): mp 138–139°; ir (KBr) 3.05 μ (OH); uv $\lambda_{max}^{EtOH}$ 290 nm (log ε 2.95).

*Anal.* Calcd for C₁₂N₁₇NO₄: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.23; H, 7.40; N, 5.69.

**Dehydrogenation of Alcohol 5.**—A mixture of 2.80 g of alcohol 5, 10% Pd on charcoal (3.0 g), and *p*-cymene (200 ml) was heated at 140–145° for 5 hr in an atmosphere of N₂. The catalyst was removed by filtration, and Et₂O saturated with dry HCl was added. A yellow precipitate formed, which was filtered off and partitioned between 10% aqueous NaOH and CHCl₃ (50 ml). The aqueous phase was neutralized with NH₄Cl and extracted with CHCl₃. The evaporated extract crystallized from CH₂Cl₂–hexane to give colorless needles of 4-hydroxy-5,6,7-trimethoxyisoquinoline (6, 0.613 g, 23%): mp 116–117°; *m/e* 235 (M⁺); uv $\lambda_{max}^{EtOH}$ (log ε) 248 (4.53), 287 (3.77), 298 (3.74), 330 (3.74), 343 nm (3.77).

*Anal.* Calcd for C₁₂H₁₃NO₄: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.55; H, 5.65; N, 5.90.

The CHCl₃ phase from the separation of 6 was dried and evaporated, and the residue was purified by chromatography on alumina (C₆H₆ eluent) to give 5,6,7-trimethoxyisoquinoline (7)

as a yellow syrup[6] (0.503 g, 18%): nmr δ 9.10 (1 H, s, C₁ H), 8.43 (1 H, d, *J* = 6.0 Hz, C₃ H), 7.85 (1 H, d, *J* = 6.0 Hz, C₄ H), 7.07 (1 H, s, C₈ H), 4.03, 3.99, 3.97 (each 3 H, s, 3 OCH₃); uv $\lambda_{max}^{EtOH}$ (log ε) 240 (4.73), 320 (3.72), 335 nm (sh) (3.66). The hydrochloride of 7 formed needles, mp 179–180°, from MeOH–Et₂O.

*Anal.* Calcd for C₁₂H₁₃NO₃·HCl: N, 5.47. Found: N, 5.30.

**4,5,6,7-Tetramethoxyisoquinoline (8).**—An excess of ethereal diazomethane was added to a solution of phenol 6 (2.50 g) in a mixture of MeOH (25 ml), dioxane (15 ml), and ether (10 ml). After 3 days at room temperature, excess diazomethane was destroyed by adding acetic acid. The usual work-up, followed by crystallization from hexane, gave pale yellow needles of 4,5,6,-7-tetramethoxyisoquinoline (8, 2.40 g): mp 96°; nmr δ 8.68, 7.97 (each 1 H, s, C₁ and C₃ H), 7.02 (1 H, s, C₈ H), 4.03, 3.90 (each 3 H, s, 2 OCH₃), 3.98 (6 H, s, 2 OCH₃); *m/e* 249 (M⁺); uv $\lambda_{max}^{EtOH}$ (log ε) 246 (4.61), 285 (3.87), 325 (3.79), 338 nm (3.83).

The hydrochloride of 8 crystallized from EtOAc as colorless prisms, mp 148–150°.

*Anal.* Calcd for C₁₃H₁₅NO₄·HCl; C, 54.64; H, 5.64; N, 4.90. Found: C, 54.72; H, 5.63; N, 5.13.

**2-Benzoyl-1-cyano-4,5,6,7-tetramethoxy-1,2-dihydroisoquinoline (9).**—To a vigorously stirred mixture of 4,5,6,7-tetramethoxyisoquinoline (8, 3.865 g), CH₂Cl₂ (40 ml), potassium cyanide (1.98 g), and water (10 ml) was added dropwise at 0–5° a solution of benzoyl chloride (4.0 g) in CH₂Cl₂ (10 ml). After the solution was stirred for an additional 3 hr at 0–5°, CH₂Cl₂ (200 ml) and water (100 ml) were added, and the organic layer was separated. The washed (H₂O) and dried (Na₂SO₄) solvent was evaporated to afford a gum which, after silica chromatography (CHCl₃ eluent), crystallized from *i*-PrOH to give the Reissert compound 9 (2.93 g, 51%) as colorless prisms: mp 136–137°; nmr δ 7.72–7.33 (5 H, m, C₆H₅), 6.72 (1 H, s, C₈ H), 6.52, 5.98 (each 1 H, s, C₁ and C₃ H), 3.88 (9 H, s, 3 OCH₃), 3.67 (3 H, s, OCH₃); uv $\lambda_{max}^{EtOH}$ (log ε) 240 (4.38), 299 (4.13), 317 nm (4.07).

*Anal.* Calcd for C₂₁H₂₀N₂O₅: C, 66.30; H, 5.30; N, 7.37. Found: C, 66.21; H, 5.28; N, 7.54.

**1-(2-Nitrobenzyl)-4,5,6,7-tetramethoxyisoquinoline (11).**—Sodium hydride (57% in mineral oil, 0.057 g) was added at 0–5° to a stirred mixture of Reissert compound 9 (0.540 g), *o*-nitrobenzyl chloride (0.270 g), sodium iodide (0.010 g), and dry benzene (50 ml). After the solution was stirred for 1.5 hr at 5–10° (N₂ atmosphere), NH₄Cl (0.200 g) and a solution of Triton B (30% in MeOH, 6 ml) in MeOH (10 ml) was added. After the solution was stirred for 20 hr at room temperature, benzene (100 ml) and water (20 ml) were added. The usual work-up of the organic phase gave a gum which was subjected to preparative tlc on silica (CHCl₃–Et₂O, 2:3, as developer) to give two major bands. Elution of the more polar band, followed by crystallization from CHCl₃–hexane, gave 1-(2-nitrobenzyl)-4,5,6,7-tetramethoxyisoquinoline (11, 0.202 g, 38°C): mp 118–119°; uv $\lambda_{max}^{EtOH}$ (log ε) 248 (4.46), 296 (3.80), 300 (3.78), 330 (3.65), 340 nm (3.68).

*Anal.* Calcd for C₂₀H₂₀N₂O₆: C, 62.49; H, 5.24; N, 7.29. Found: C, 62.73; H, 5.35; N, 7.37.

Elution of the less polar band, followed by crystallization from CHCl₃–hexane, gave 1-cyano-4,5,6,7-tetramethoxyisoquinoline (12, 0.064 g): mp 138–139°; ir (KBr) 4.45 μ (CN); nmr δ 8.12 (1 H, s, C₃ H), 7.38 (1 H, s, C₈ H), 4.17, 4.08, 4.03, 3.95 (each 3 H, s, 4 OCH₃); uv $\lambda_{max}^{EtOH}$ (log ε) 260 (4.57), 303 (3.73), 314 (3.75), 353 nm (3.85).

*Anal.* Calcd for C₁₄H₁₄N₂O₄: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.50; H, 5.35; N, 10.27.

**Hydrogenation of 11 and Pschorr Reaction of 13.**—The isoquinoline 11 (0.100 g) was dissolved in tetrahydrofuran (30 ml) and hydrogenated in the presence of Raney nickel (W-2) at atmospheric pressure for 20 hr. The catalyst was removed and the solvent was then evaporated to afford a gum, which was dissolved in ether (30 ml). Ether saturated with HCl gas was added to the solution to give the hydrochloride of amine 13 (0.088 g) as a colorless powder. This hydrochloride was dissolved in a mixture of methanol (12 ml) and 2 N H₂SO₄ (0.7 ml) and then diazotized by the dropwise addition of 10% sodium nitrite (0.48 ml) at 0–5°. After the solution was stirred for a further 20 min at 0–5°, copper powder (0.020 g) was added to the reaction mixture. The mixture was gradually warmed to 40°, stirred at 40–45° for 40 min, basified with ammonia and extracted with CHCl₃. The usual work-up afforded a brown residue, which was purified by preparative tlc on silica (CHCl₃–Et₂O, 1:2, developer) to give, after

crystallization from methanol, yellow needles of imenine (1, 0.032 g, 35%): mp 206–207°; nmr δ 9.12 (1 H, pair of doublets, $J$ = 8.0 and 2.0 Hz, $C_{11}$ H), 8.57 (1 H, s, $C_5$ H), 8.56 and 7.80–7.35 (3 H, m, $C_{10}$, $C_9$, and $C_8$ H), 4.22, 4.12, 4.07, 4.02 (each 3 H, s, 4 OCH₃); $m/e$ 351 (M⁺), 336 (M − 15), 321 (M − 30); uv $\lambda_{max}^{EtOH}$ (log ε) 240 (4.30), 275 (4.38), 335 (3.71), 345 (3.71), 434 nm (4.03); $\lambda_{max}^{EtOH-HCl}$ (log ε) 244 (4.07), 290 (4.11), 360 (3.77), 484 nm (3.67). Its ir (KBr) was superimposible upon that of natural imenine and a mixture melting point (206–207°) with the natural base showed no depression.

# The Reaction of Iodobenzene with Nickel Carbonyl in the Presence of *N*-Benzylidene Alkylamine

MEMBO RYANG,* YOSHIHISA TOYODA, SHINJI MURAI, NOBORU SONODA, AND SHIGERU TSUTSUMI

*Department of Petroleum Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka, Japan*

The intermediate benzoylnickel carbonyl iodide, derived from iodobenzene and nickel carbonyl, was reactive toward *N*-benzylidene alkylamine to give 1-alkyl-2-phenylindolin-3-one in *N*,*N*-dimethylformamide (DMF). On the other hand, the similar reaction in benzene solution proceeded *via* a different course to give coupling products of two of the benzoyl groups to an intervening imine double bond.

Organomonohalides react with metal carbonyls to form unstable acyl or alkyl metal carbonyl derivatives, which exhibit unique reactivities toward unsaturated compounds;[1,2] *i.e.*, the addition of the acyl or alkyl group to carbon–carbon double bonds, carbon–carbon triple bonds, and carbon–oxygen double bonds. Herein, although the carbonation and ring closure reactions of Schiff bases or aromatic ketoximes using dicobalt octacarbonyl had been established as a synthetic reaction of phthalimidine derivatives,[3] the reaction of alkyl or acyl metal carbonyl derivatives with imines which contain carbon–nitrogen double bond has not yet been reported.

In this paper we wish to report two types of novel and synthetically useful reactions, *i.e.*, the benzoylation and cyclization of imines to 1-alkyl-2-phenylindolin-3-one (in DMF) and the coupling reaction of two of the benzoyl groups to an intervening imine double bond (in benzene).

## Results and Discussion

Iodobenzene reacted with nickel carbonyl in DMF at 75° in the presence of *N*-benzylidenemethylamine to give 1-methyl-2-phenylindolin-3-one (I) and *N*,*N*′-

$$\text{PhI} + \text{PhCH}=\text{NCH}_3 \xrightarrow[\text{in DMF}]{\text{Ni(CO)}_4}$$
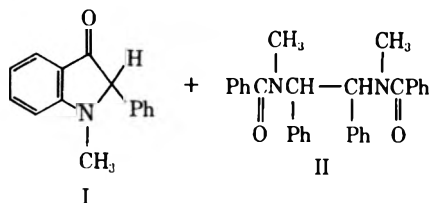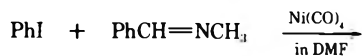
dibenzoyl-*N*,*N*′-dimethyl-1,2-diphenylethylenediamine (II) in 28 and 13% yields, respectively.

To determine whether the initial reaction for the formation of I is C attack of the benzoyl group or N

attack of the phenyl group, a similar reaction was carried out using *p*-methyliodobenzene instead of iodobenzene. The isolated product (60% yield) was determined to be 1,6-dimethyl-2-phenylindolin-3-one (IIIa)

IIIa                                 IIIb
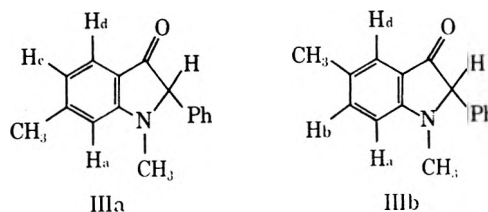
by the elemental analysis and ir, mass, and nmr spectra. The nmr spectrum showed the proton $H_a$ signal at τ 3.07 (singlet), the characteristic proton on the α-substituted aromatic nucleus with amine nitrogen, and the proton $H_d$ signal at τ 2.3 (doublet). Herein in the case of the product by the N attack of the *p*-tolyl group to the imine double bond, 1,5-dimethyl-2-phenylindolin-3-one (IIIb), the $H_a$ proton signal should be a doublet and the $H_d$ proton signal a singlet. The formation of IIa strongly suggests that the attack of benzoyl group to the carbon site of the imine double bond occurs first, followed by cyclization, to give the indolinone derivatives as shown in Scheme I. The 1,2-diphenyl-ethylenediamine derivative VI might be formed by the N-attack of benzoyl group to the imine double bond.

This reaction underwent a remarkable solvent effect. When benzene was used as a solvent instead of DMF, the main product was not the indolinone derivative but the coupling product of two of benzoyl group to an intervening imine double bond, *N*-methyl-*N*-(α-phenylphenacyl)benzamide (VII) (53% yield). Similarly the reaction using *N*-benzylideneethylamine gave *N*-ethyl-*N*-(α-phenylphenacyl)benzamide (VIII) in 59% yield. This remarkable solvent effect was considered to be due to the difference of the structure of the intermediate benzoylnickel carbonyl iodide; that is, the benzoylnickel complex was assumed to be monomeric in DMF solution and dimeric in benzene

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SCHEME I

$$\left[ CH_3{-}\!\!\!\bigcirc\!\!\!-\overset{O}{\underset{\;}{C}}{-}Ni(CO)_{n-1} \atop I \right] + PhCH{=}NCH_3$$

C attack | N attack

IV

V

$$\downarrow cyclization$$

$$\downarrow coupling$$

IIIa

VI
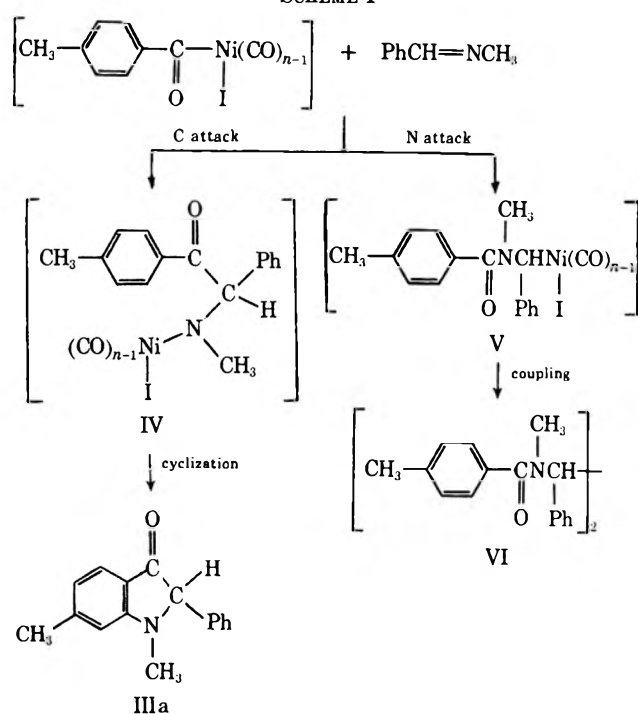
solution.[4] Therefore cis insertion of the imine double bond to the benzoyl–nickel bond may proceed in DMF solution. The benzoyl group adds both to the carbon site and the nitrogen site of the imine double bond, thus yielding the second intermediates (IV and V in Scheme I). However, in benzene solution, the less coordinating solvent, the imine coordinates to the nickel atoms of the dimeric benzoylnickel complex and then coupling of two of benzoyl groups occurs to an intervening imine double bond to form VII or VIII (Scheme II).

SCHEME II

$$\left[ \underset{O}{\overset{\;}{Ph}}{C}{-}Ni(CO)_{n-1} \atop I \right]_2 + PhCH{=}NR \longrightarrow$$

VII, R = CH₃
VIII, R = CH₃CH₂
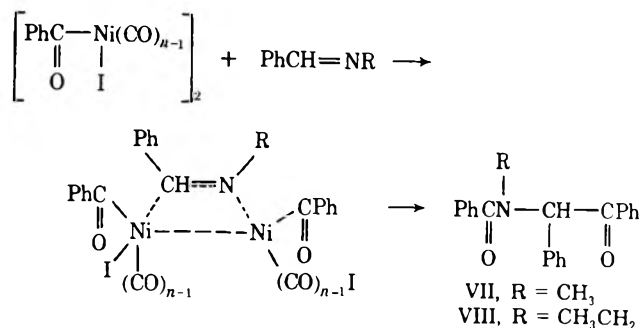
Various types of coupling reactions of alkyl or acyl groups using transition metal complexes have been reported. More recently synthetic interest on coupling reactions has been focused on the coupling of alkyl, acyl, or alkoxy groups intervening the unsaturated bond of the third component, such as carbon monoxide, olefins, dienes, acetylenes, and enamines. For example, the following types of new synthetic reactions have been established: formation of carbonates from alkoxycopper and carbon monoxide,[5] synthesis of 1,4-diketones from the reaction of lithium acylnickel carbonylates with

acetylenes,[6] and the reaction of α,α'-dibromo ketones with dienes or enamines in the presence of diiron nonacarbonyl.[7,8] The formation of VII and VIII from iodobenzene, N-benzylidene alkylamine, and nickel carbonyl in benzene solution presents a new type of coupling reactions of acyl groups, in which the carbon–nitrogen double bond is the third component in coupling.

Furthermore, the formation of indolinone derivatives in DMF solution is also a new type of cyclization reaction and presents a new synthetic route to heterocyclic compounds using organotransition metal complexes.

## Experimental Section

**The Reaction of Iodobenzene with Nickel Carbonyl in DMF in the Presence of N-Benzylidenemethylamine.**—Into a 100-ml, three necked flask equipped with a magnetic stirrer, a thermometer, a reflux condensor attached to a gas bubbler with liquid paraffin, and a gas inlet were placed 6.1 g (0.03 mol) of iodobenzene, 4 ml (0.03 mol) of nickel carbonyl, and 3.6 g (0.03 mol) of N-benzylidenemethylamine in 50 ml of DMF. The mixture was warmed to 75–80° and was stirred for 22 hr. The reaction mixture was poured into 200 ml of 3 N HCl and was extracted with diethyl ether. The ether extract was dried over magnesium sulfate and the ether was evaporated. The precipitated solid was filtered and recrystallized from ethanol to give 0.9 g of white crystals: mp 245–246°; ir 1615 cm⁻¹ (CO); nmr τ 7.36 (s, 6 H), 3.09 (s, 2 H), 2.65 ppm (m, 20 H); mass spectrum *m/e* 448 (M⁺), 224, 105.

*Anal.* Calcd for C₃₉H₂₈O₂N₂: C, 80.33; H, 6.29; N, 6.25. Found: C, 80.50; H, 6.09; N, 6.16.

This compound was confirmed to be N,N'-dibenzoyl-N,N'-dimethyl-1,2-diphenylethylenediamine (II) (13% yield). The filtrate was distilled under reduced pressure to give the following fractions: (1) 3.77 g, bp 65–67° (15 mm); (2) 1.32 g, bp 133–155° (0.3 mm); and (3) residual solid, 1.18 g. Fraction 1 was found to consist of nearly equal amounts of benzaldehyde and unreacted iodobenzene by gas chromatographic analysis. Fraction 2 was recrystallized from petroleum ether (bp 30–60°)–benzene to give white crystals: mp 107°; ir 1673 cm⁻¹ (CO); nmr τ 7.05 (s, 3 H), 4.69 (s, 1 H), 2.73 (m, 9 H); mass spectrum *m/e* 223 (M⁺).

*Anal.* Calcd for C₁₅H₁₃ON: C, 80.69; H, 5.87; N, 6.25. Found: C, 80.70; H, 5.77; N, 6.16. This compound was confirmed to be 1-methyl-2-phenylindolin-3-one (I) (28% yield). Residual solid was recrystallized from petroleum ether–benzene to afford white crystals, mp 220°, which was assumed to be α-(N-benzoyl-N-methyl)aminostilbene (18% yield): ir 1630 (CO), 950 cm⁻¹ (C=CH); mass spectrum *m/e* 313 (M⁺), 105.

**The Reaction of p-Methyliodobenzene with Nickel Carbonyl in DMF in the Presence of N-Benzylidenemethylamine.**—A solution of 6.5 g (0.03 mol) of p-methyliodobenzene, 3.6 g (0.03 mol) of N-benzylidenemethylamine, and 4 ml (0.03 mol) of nickel carbonyl in 50 ml of DMF was stirred at 75–80° for 38 hr. From the reaction mixture, 2.62 g of solids and the following fractions were obtained: (1) 0.74 g, bp 120–160° (1.0 mm); (2) 1.64 g, bp 160–167° (1.0 mm); (3) 0.14 g, bp 167–180° (1.0 mm); and small amounts of residue. The components of solids were isolated by column chromatograph on silica gel. Benzene eluate was recrystallized from petroleum ether–benzene to give white crystals: mp 145°; ir 1670 cm⁻¹ (CO); nmr τ 7.66 (s, 3 H), 7.06 (s, 3 H), 4.75 (s, 1 H), 3.07 (s, 1 H), 2.8 (d, 1 H), 2.6 (m, 5 H), 2.3 (d, 1 H); mass spectrum *m/e* 237 (M⁺). This compound was confirmed to be 1,6-dimethyl-2-phenylindolin-3-one (IIIa) (60% yield). Ethyl ether eluate was recrystallized from ethyl alcohol–ethyl acetate to give small amounts of white crystals, ir 1625 cm⁻¹ (CO), mass spectrum *m/e* 238 (P/2), 119 (p-CH₃C₆H₄CO⁺). This compound was assumed to be N,N'-di-p-toluoyl-N,N'-dimethyl-1,2-diphenylethylenediamine.

**The Reaction of Iodobenzene with Nickel Carbonyl in Benzene in the Presence of N-Benzylidenemethylamine.**—A solution of

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(6) Y. Sawa, I. Hashimoto, M. Ryang, and S. Tsutsumi, *J. Org. Chem.*, **33**, 2159 (1968).

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6.1 g (0.03 mol) of iodobenzene, 3.6 g (0.03 mol) of *N*-benzylidene-methylamine, and 4 ml (0.03 mol) of nickel carbonyl in 50 ml of benzene was stirred at 70–75° for 20 hr. From the reaction mixture, the following fractions were obtained: (1) 0.98 g, bp 90–94° (50 mm); (2) 0.95 g, bp 110–140° (0.4 mm); (3) 0.87 g, bp 140–160° (0.4 mm); and (4) 2.45 g, bp 160–200° (0.4 mm). Fraction 1 was confirmed to be benzaldehyde by gas chromatographic analysis. Fraction 2 and 3 were found to consist of *N*-methylbenzamide and benzil. Fraction 4 was recrystallized from methanol to give white crystals: mp 113°; ir 1695, 1640 cm⁻¹ (CO); nmr τ 7.17 (s, 3 H), 2.65 (m, 15 H), 2.05 (broad, 1 H); mass spectrum *m/e* 329 (M⁺), 224, 105. *Anal.* Calcd for C₂₂H₁₉O₂N: C, 80.36; H, 5.69; N, 4.30. Found: C, 80.22; H, 5.81; N, 4.25. This compound was confirmed to be *N*-methyl-*N*-(α-phenylphenacyl)benzamide (VII) (53% yield), the coupling product of two benzoyl group intervening *N*-benzylidenemethylamine.

**The Reaction of Iodobenzene with Nickel Carbonyl in Benzene in the Presence of *N*-Benzylideneethylamine.**—A solution of 6.1 g (0.03 mol) of iodobenzene, 6 g (0.045 mol) of *N*-benzylidene-ethylamine, and 4 ml (0.03 mol) of nickel carbonyl in 50 ml of benzene was stirred at 70–75° for 24 hr. From the reaction mixture, the following fractions were obtained: (1) 1.0 g, bp 30–35° (0.5 mm); (2) 1.54 g, bp 124–153° (0.6 mm); and (3) 2.91 g, bp 154–210° (0.6 mm). Fraction 1 was confirmed to be benzaldehyde. Fraction 2 was confirmed to consist of 87 parts of *N*-benzyl-*N*-ethylbenzamide and 13 parts of *N*-ethylbenz-amide. Fraction 3 was recrystallized from petroleum ether–benzene to afford white crystals: mp 103°; ir 1685, 1628 cm⁻¹ (CO); mass spectrum *m/e* 333 (M⁺), 228, 105. *Anal.* Calcd for C₂₃H₂₁O₂N: C, 80.69; H, 5.94; N, 4.08. Found: C, 80.44; H, 6.16; N, 3.81. This compound was confirmed to be *N*-ethyl-*N*-(α-phenylphenacyl)benzamide (VIII) (59% yield).

**Registry No.**—I, 36917-63-2; II, 36917-64-3; IIIa, 36917-65-4; VII, 36917-66-5; VIII, 36895-14-4; iodobenzene, 591-50-4; nickel carbonyl, 13463-39-3; *N*-benzylidene, methylamine 622-29-7; α-(*N*-benzoyl-*N*-methyl)aminostilbene, 16151-51-2; *p*-methyliodobenzene, 624-31-7; *N*-benzylideneethylamine, 6852-54-6.

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# The Group VI Metal Carbonyl Catalyzed Reaction of Ethers and Acid Halides

HOWARD ALPER* AND CHE-CHENG HUANG

*Department of Chemistry, State University of New York at Binghamton, Binghamton, New York 13901*

The reaction of acyclic and cyclic ethers with acid halides in the presence of catalytic quantities of Group VI metal carbonyls [M(CO)₆, where M = Cr, Mo, W] was investigated. The catalytic order of effectiveness was found to be Mo(CO)₆ > W(CO)₆ > Cr(CO)₆ with Mo(CO)₆ being a very useful catalyst for the reaction. The group VA substituted molybdenum carbonyls, EMo(CO)₅ [E = (C₆H₅)₃P, (C₆H₅)₃As] and *cis*-[(C₆H₅)₃P]₂Mo-(CO)₄, are also good catalysts for the reaction. These catalytic reactions can be carried out either thermally or photochemically (at room temperature). The effects of temperature, of oxygen, and of variation of the halogen in the acid halide on the thermal reaction are noted. Stereochemical studies show that the reaction occurs with partial or complete retention, or net inversion of configuration, subject to the nature of the ether. An ionic mechanism is proposed for these reactions.

Considerable interest has developed recently in the use of Group VI metal carbonyls [M(CO)₆, M = Cr, Mo, W] as catalysts[1-8] and as stoichiometric reagents[9-11] for organic synthesis. This paper is concerned with the catalysis of the reaction of ethers and acid halides[12] by these metal carbonyls. The primary objectives of this study were the effectiveness of Group VI metal carbonyls as catalysts compared to other catalysts for the ether–acid halide reaction; the relative catalytic effectiveness within Group VI and possible correlations with the metal–carbon bond strength;[13,14] and the stereochemistry and possible mechanism(s) for the reaction.

## Results and Discussion

**Acyclic Ethers.**—Refluxing the acyclic ethers, neat or in hexane or isooctane solution, with acid chlorides in the presence of molybdenum hexacarbonyl gave esters, organic chlorides, and, in some instances, alkenes.

$$\text{ROR} + \text{R'COCl} \xrightarrow{\text{Mo(CO)}_6} \text{RCl} + \text{R'COOR}$$
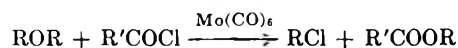
The results are listed in Table I. For unsymmetrical ethers, the alkyl chloride formed is that derived from the more highly substituted alkoxy carbon atom. Only in the case of benzoin methyl ether was a sluggish reaction observed, probably owing to the presence of the electron-attracting benzoyl group in the reactant ether. When dehydrohalogenation occurs, Saytzeff's rule is usually, but not always, followed. Olefins produced in some of these reactions do not arise from Mo(CO)₆-catalyzed dehydrohalogenation of an alkyl chloride, since, for example, 2-chlorooctane was inert to Mo(CO)₆ when refluxed in hexane for 1 day.

The alkyl aryl ether, *n*-butyl phenyl ether, reacted with acetyl chloride in the presence of Mo(CO)₆ to give only traces of *o*- and/or *p-n*-butoxyacetophenone. Here, complexation of the benzene ring of the reactant ether with molybdenum carbonyl may give the less active arene–Mo(CO)₃ catalyst.

**Cyclic Ethers.**—A number of cyclic ethers were subjected to acid halide treatment in the presence of

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TABLE I

REACTION OF ACYCLIC ETHERS WITH ACID CHLORIDES IN THE PRESENCE OF $Mo(CO)_6$

| Ether | $R'COCl$, $R' =$ | Solvent[a] | Reaction time, hr | Products (yield, %) |
|---|---|---|---|---|
| (+)-2-Ethoxyoctane | $CH_3$ | H | 20 | $CH_3C(Cl)HC_6H_{13}$ (62), $CH_3CH=CHC_5H_{11}$ (31), $CH_3COOC_2H_5$ |
|  | $C_6H_5$ | I | 24 | $CH_3C(Cl)HC_6H_{13}$, $CH_3CH=CHC_5H_{11}$, $C_6H_5COOC_2H_5$ (82) |
| n-Butyl ether | $C_6H_5$ | N | 16 | $C_6H_5COOC_4H_9$ (73), $C_4H_9Cl$ |
| Benzoin methyl ether | $C_6H_5$ | I | 48 | $C_6H_5COC(Cl)HC_6H_5$, $C_6H_5COOCH_3$ (37) |
| Ethyl triphenylmethyl ether | $C_6H_5$ | H | 12 | $(C_6H_5)_3CCl$, $C_6H_5COOC_2H_5$ (72) |

[a] H = hexane, I = isooctane, N = neat.

TABLE II

REACTION OF CYCLIC ETHERS WITH ACID HALIDES IN THE PRESENCE OF $M(CO)_6$ (M = Cr, Mo, W)

| Ether | Acid halide | Solvent[a] | Reaction time, hr | M of $M(CO)_6$ | Halo ester (yield, %) | Alkenyl ester (yield, %) |
|---|---|---|---|---|---|---|
| 2-Methyltetrahydrofuran | $CH_3COCl$ | H | 20 | Mo | 4-Chloropentyl acetate (80) | 3-Pentenyl acetate (7) |
|  | $CH_3COCl$ | H | 20 | W | 4-Chloropentyl acetate (61) |  |
|  | $CH_3COCl$ | H | 20 | Cr | 4-Chloropentyl acetate (17) |  |
|  | $C_6H_5COCl$ | H | 60 | Mo | 4-Chloropentyl benzoate (54) | 3-Pentyl benzoate (27) |
|  | $C_6H_5COCl$ | I | 18 | Mo | 4-Chloropentyl benzoate (78) | 3-Pentyl benzoate (12) |
|  | $C_6H_5COCl$ | H | 60 | W | 4-Chloropentyl benzoate (39) | 3-Pentenyl benzoate (trace) |
|  | $C_6H_5COCl$ | H | 60 | Cr | 4-Chloropentyl benzoate (11) | 3-Pentenyl benzoate (3) |
| Tetrahydrofuran | $CH_3COCl$ | H | 23 | Mo | 4-Chlorobutyl acetate (78) |  |
|  | $C_6H_{11}COCl$ | N | 18 | Mo | 4-Chlorobutyl cyclohexanecarboxylate (84) |  |
|  | $C_6H_{11}COCl$ | N | 18 | W | 4-Chlorobutyl cyclohexanecarboxylate (42)[b] |  |
|  | $C_6H_{11}COCl$ | N | 18 | Cr | 4-Chlorobutyl cyclohexanecarboxylate (16) |  |
|  | $C_6H_5COBr$ | N | 23 | Mo | 4-Bromobutyl benzoate (88) |  |
| 2,2,4,4-Tetramethyltetrahydrofuran | $CH_3COCl$ | H | 19 | Mo |  | 2,2,4-Trimethyl-4-pentenyl acetate (48) / 2,2,4-Trimethyl-3-pentenyl acetate (24) |
| 2,5-Dihydrofuran | $CH_3COCl$ | H | 20 | Mo | 4-Chloro-2-butenyl acetate (61) |  |
|  | $CH_3COCl$ | H | 36 | W | 4-Chloro-2-butenyl acetate (12) |  |
|  | $CH_3COCl$ | H | 26 | Cr |  |  |
| 7-Oxabicyclo[2.2.1]-heptane | $CH_3COCl$ | H | 20 | Mo | trans-4-Chlorocyclohexyl acetate (55) | 3-Cyclohexenyl acetate (22) |
|  | $CH_3COCl$ | I | 16 | W | trans-4-Chlorocyclohexyl acetate (57) | 3-Cyclohexenyl acetate (10) |
|  | $CH_3COCl$ | H | 20 | W | trans-4-Chlorocyclohexyl acetate (trace) |  |
|  | $CH_3COCl$ | H | 20 | Cr | trans-4-Chlorocyclohexyl acetate (trace) |  |
|  | $C_6H_5COCl$ | H | 36 | Mo | trans-4-Chlorocyclohexyl benzoate (69) | 3-Cyclohexenyl benzoate (13) |
|  | $C_6H_5COCl$ | I | 16 | Mo | trans-4-Chlorocyclohexyl benzoate (54) | 3-Cyclohexenyl benzoate (23) |
|  | $C_6H_5COCl$ | H | 36 | W | trans-4-Chlorocyclohexyl benzoate (28) | 3-Cyclohexenyl benzoate (12) |
|  | $C_6H_5COCl$ | H | 36 | Cr | trans-4-Chlorocyclohexyl benzoate (9) | 3-Cyclohexenyl benzoate (6) |
|  | $C_6H_5COBr$ | I | 16 | Mo | trans-4-Bromocyclohexyl benzoate (72) | 3-Cyclohexenyl benzoate (13) |
|  | $C_6H_5COF$ | H | 72 | Mo |  | 3-Cyclohexenyl benzoate (67) |
|  | $C_6H_5COF$ | H | 72 | W |  |  |
|  | $C_6H_5COF$ | H | 72 | Cr |  |  |

[a] H = hexane, I = isooctane, N = neat.   [b] $C_6H_{11}COO(CH_2)_4O(CH_2)_4Cl$ was also obtained in 18% yield.

group VI metal hexacarbonyls (Table II). Halo esters and/or elimination products were formed in these reactions. In the reaction of a given acid halide with a specific ether, e.g., tetrahydrofuran (THF) with cyclohexanecarboxylic acid chloride, the yield of halo ester usually decreased in the catalytic order of $Mo(CO)_6$ > $W(CO)_6$ > $Cr(CO)_6$. Molybdenum hexacarbonyl is an excellent catalyst for the ether–acid halide reaction, as the yields in Tables I and II indicate (note that no attempt was made to optimize conditions).

Variable amounts of alkenyl ester were also observed in these reactions.

The catalytic order of effectiveness of $Mo(CO)_6$ > $W(CO)_6$ > $Cr(CO)_6$ is not in accord with the previously mentioned and generally accepted order of $\pi$-back donation of group VI metal carbonyls [Mo–C < Cr–C < W–C].[13,14] This suggests that the cleavage of a metal–carbon bond may not be involved in the rate-determining step of the reaction process.

The presence of an allylic double bond in the reactant ether did not affect the reaction, as 2,5-dihydrofuran gave unrearranged 4-chloro-2-butenyl acetate as the only product on $Mo(CO)_6$- or $W(CO)_6$-catalyzed reaction with acetyl chloride. In contrast, 2,3-dihydropyran, a vinyl ether, reacted with acid chloride and $Mo(CO)_6$ to give no isolable monomeric or dimeric product, but polymeric materials were apparently formed.

The presence of a sulfur atom in the reactant ether resulted in ligand substitution rather than carbon–oxygen bond cleavage; e.g., treatment of 1,4-thioxane (1) with acetyl chloride and $Mo(CO)_6$ gave 2.



**1**                                **2**
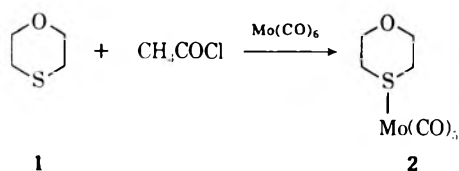
**Effect of Halogen.**—The effect of the halogen, in the acid halide, on the reaction course was determined. Molybdenum carbonyl catalyzed reaction of 7-oxa-bicyclo[2.2.1]heptane with benzoyl bromide or benzoyl chloride in isooctane gave the halo and alkenyl esters in the ratio of 5.5:1.0 and 2.3:1.0, respectively. Only the elimination product was obtained when benzoyl fluoride was used as the acid halide (Table II).

**Temperature Variation.**—Several reactions were run in both hexane (bp 68°) and isooctane (bp 101°) in order to see what effect, if any, change in temperature had on the product ratio for a given reaction. While a 2.0:1.0 ratio of halo ester to alkene resulted from the 2-methyltetrahydrofuran–$C_6H_5COCl$–$Mo(CO)_6$ reaction in hexane, isooctane gave a product ratio of 6.5:1.0. Similarly, carbon–oxygen bond cleavage of 7-oxabicyclo[2.2.1]heptane by $C_6H_5COCl$ in isooctane [Mo(CO)_6 catalyst] gave a 2.3:1.0 halo ester–alkenyl ester distribution, which was different than the 5.3:1.0 ratio observed using hexane as solvent. In essence, then, the total product yield is not markedly altered with a change in reaction temperature but the product ratio is affected.

**Effect of Oxygen.**—It should be emphasized that these $M(CO)_6$ catalyzed reactions can be equally effected in the presence or absence of air (under $N_2$).

**Triphenylphosphine and Triphenylarsine Substituted Molybdenum Carbonyls as Catalysts.**—Group VA substituted metal carbonyls have been shown to be more or less effective reagents or catalysts than the parent metal carbonyls, in different reactions. For example, triphenylphosphineiron tetracarbonyl does not react stoichiometrically with 2-bromo-4'-phenyl-acetophenone in refluxing 1,2-dimethoxyethane, while use of iron pentacarbonyl provides a simple preparation of the coupled 1,4-diketone and $p$-phenylacetophenone.[15]

(15) H. Alper and E. C. H. Keung, *J. Org. Chem.*, **37**, 2566 (1972).

In contrast, $Fe(CO)_5$ is a less active catalyst than triphenylphosphineiron tetracarbonyl in generating the trichloromethyl radical by treatment of methyl methacrylate with carbon tetrachloride.[16]

Acetyl chloride was treated with tetrahydrofuran in the presence of Group VA substituted molybdenum carbonyls, and the results are presented in Table III.

TABLE III
REACTION OF TETRAHYDROFURAN AND ACETYL CHLORIDE IN THE PRESENCE OF SUBSTITUTED MOLYBDENUM CARBONYLS

| Catalyst | Yield of 4-chlorobutyl, acetate, % |
|---|---|
| $Mo(CO)_6$ | 78 |
| $Mo(CO)_5[P(C_6H_5)_3]$ | 62 |
| $cis$-$Mo(CO)_4[P(C_6H_5)_3]_2$ | 79 |
| $Mo(CO)_5[As(C_6H_5)_3]$ | 84 |

Substitution of one carbonyl of $Mo(CO)_6$ by triphenylphosphine results in a modest reduction in the yield of chloro ester. However, triphenylarsinemolybdenum pentacarbonyl is a better catalyst than either $Mo(CO)_6$ or $(C_6H_5)_3PMo(CO)_5$ for ring-opening tetrahydrofuran. The disubstituted carbonyl, $cis$-$[(C_6H_5)_3P]_2Mo(CO)_4$, is as effective a catalyst as $Mo(CO)_6$. On the basis of the generally accepted $\sigma$-donor and $\pi$-acceptor abilities of the ligands, the Mo–C bond strength should decrease in the order $cis$-$Mo(CO)_4[P(C_6H_5)_3]_2$ > $(C_6H_5)_3PMo(CO)_5$ > $(C_6H_5)_3AsMo(CO)_5$ > $Mo(CO)_6$. As in the trend observed within the parent group VI carbonyls, the catalyst effectiveness does not correlate with the metal–carbon bond strength order.

**Stereochemistry of the Reaction.**—(+)-2-Ethoxy-octane, (−)-menthyl methyl ether, and $3\beta$-ethoxy-cholest-5-ene were each treated with acetyl chloride in the presence of $Mo(CO)_6$ in order to gain some insight into the stereochemistry and mechanism of the reaction. Comparison[17] of the optical rotation of 2-chlorooctane, obtained from (+)-2-ethoxyoctane, with the values for pure (+)- and (−)-2-chlorooctane showed that this reaction proceeds with net inversion of configuration, although some racemization does occur. The optical purity of the formed (−)-2-chlorooctane was 75%.

The $Mo(CO)_6$-catalyzed reaction of (−)-menthyl methyl ether and acetyl chloride in refluxing hexane gave a 2:1 ratio of menthyl to neomenthyl chloride (73% yield). Hence this ether cleavage reaction occurs with overall retention of configuration. Isomeric menthenes were also isolated, and no doubt produced but not isolated were the low-boiling by-products, methyl acetate and methyl chloride. Menthyl acetate, formed by cleavage of the methyl C–O bond of the reactant ether, was isolated in 10% yield. All of the products were identified by comparison with authentic materials.

It is worthwhile noting that essentially the same ratio of menthyl to neomenthyl chloride was obtained using $n$-butyl chloride instead of $CH_3COCl$ in $Mo(CO)_6$-catalyzed thermal reaction with (−)-menthyl methyl

(16) C. H. Bamford and W. R. Maltman, *Trans. Faraday Soc.*, **62**, 2823 (1966).

(17) (a) E. D. Hughes, F. Juliusberger, S. Masterman, B. Topley, and J. Weiss, *J. Chem. Soc.*, 1525 (1935); (b) E. D. Hughes, C. K. Ingold, and S. Masterman, *ibid.*, 1196 (1937); (c) H. M. R. Hoffmann, *ibid.*, 1249 (1964).

ether. Furthermore, the same results were obtained when the reaction was repeated under room temperature photolytic (2537 Å) rather than thermal conditions. In fact, the photoreaction is apparently at least as useful as the thermal process for effecting the ether–acid halide reaction. Another illustrative example is the formation of 4-chlorobutyl acetate in 80% yield (78% thermal reaction) by irradiation of a hexane solution of tetrahydrofuran and acetyl chloride in the presence of a catalytic quantity of $Mo(CO)_6$. No 4-chlorobutyl acetate was isolated when the photolysis was carried out in the absence of $Mo(CO)_6$. 4-Chlorobutyl acetate was also formed using $(C_6H_5)_3PMo(CO)_5$ as the catalyst and conducting this irradiation at 3000 Å.

Complete retention of configuration was observed using 3β-ethoxycholest-5-ene as the reactant ether. 3β-Chlorocholest-5-ene was isolated in high yield, accompanied by a small amount of cholesta-3,5-diene.

**Mechanism.**—Extensive work by Bamford, *et al.*,[5,16] on the oxidation of $Mo(CO)_6$ and other metal carbonyls by several organic halides (*e.g.*, $CCl_4$) has established the generation of halo alkyl radicals in these reactions. A radical mechanism is apparently not operative in the $M(CO)_6$ [M = Cr, Mo, W] catalyzed ether–acid halide reaction owing to insensitivity of the reaction to oxygen and to a radical initiator. Specifically, treatment of THF with acetyl chloride in hexane in the presence of $Mo(CO)_6$ proceeded qualitatively at the same rate and gave the same product yield whether the reaction was executed under a nitrogen atmosphere, in air, or with added azobisisobutyronitrile.

The disappearance of the ir carbonyl stretching absorption of the acid halide and/or appearance of the same type of band for the formed ester was followed for most reactions. Qualitatively, the reaction rate decreased in the order tertiary > secondary > primary carbon (*i.e.*, cleavage of a tertiary carbon–oxygen bond is most facile). For example, the time necessary for complete reaction of acetyl chloride [$Mo(CO)_6$ catalyst] with tetrahydrofuran, 2-methyltetrahydrofuran, and 2,2,4,4-tetramethyltetrahydrofuran was 540, 450, and 105 min, respectively. In addition, the yield of elimination products decreased in the order tertiary > secondary > primary for the same three ethers.

An ionic mechanism is proposed for the reaction (Scheme I). Initial acid halide–$M(CO)_6$ interaction would give the alkyl or aryloxocarbenium[18] ion (3) and metal pentacarbonyl halide anion (4).[19] Addition of an ether to 3 would give 5. For primary and some secondary R', R'' groups in 5, $S_N2$ type displacement by 4 (path a) would give the ester and the alkylated pentacarbonyl halide (6), which would collapse to organic halide and metal pentacarbonyl. Disproportionation of the latter would regenerate $M(CO)_6$. Alternatively, $M(CO)_6$ may add initially generated CO (dissolved) to give $M(CO)_6$. When 5 contains tertiary or some secondary R', R'' groups, $S_N1$ type cleavage (path b) would likely occur to give the ester and a carbenium ion, the latter undergoing elimination and/or attack by 4 to eventually produce the alkyl halide.

(18) G. A. Olah, *J. Amer. Chem. Soc.*, **94**, 808 (1972).
(19) E. W. Abel, I. S. Butler, and J. G. Reid, *J. Chem. Soc.*, 2068 (1963).

SCHEME I
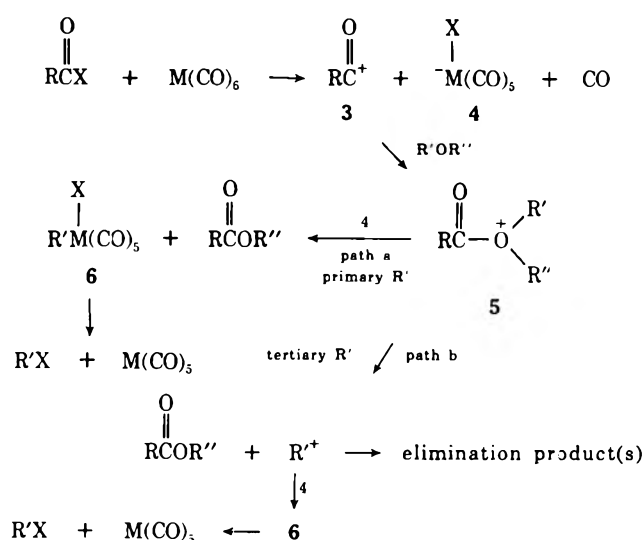


It is also conceivable that $M(CO)_6$ initially interacts with an ether to give 7[20,21] which could then form 4
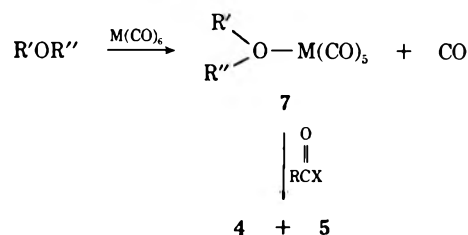


and 5 by reaction with acid halide (5 would then react *via* path a or b of Scheme I). Unsuccessful attempts were made to isolate, in a pure state, substitution products of type 7 by irradiation of tetrahydrofuran and either $Mo(CO)_6$ or $(C_6H_5)_3PMo(CO)_5$. Similar results have been noted by other investigators.[20,21]

Scheme I can account for the (a) reactivity pattern of the ether carbons (tertiary > secondary > primary); (b) tendency to form elimination products (tertiary > secondary > primary R'+); (c) effect of halogen (a metal–fluorine bond would be most difficult to break in 4 or 6); and (d) some of the stereochemical results. Concerning the latter, solvolysis of cholesteryl *p*-toluenesulfonate (carbenium ion generation) and related reactions of cholesteryl derivatives[22] proceed with complete retention of configuration owing to participation of the 5,6-double bond (8). Complete retention



8
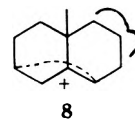
observed in the 3β-ethoxycholest-5-ene–$CH_3COCl$–$Mo(CO)_6$ reaction is in accord with these other results and hence suggests the occurrence of pathway b (Scheme I).

It was previously noted that (−)-2-chlorooctane, of 75% optical purity, was obtained by reaction of

(20) I. W. Stolz, G. R. Dobson, and R. K. Sheline, *Inorg. Chem.*, **2**, 323 (1963).
(21) P. H. Pettit, Jr., Ph.D. Thesis, Lehigh University, Bethlehem, Pa., 1969.
(22) (a) S. Winstein and R. Adams, *J. Amer. Chem. Soc.*, **70**, 838 (1948); (b) S. Winstein and A. H. Schlesinger, *ibid.*, **70**, 3528 (1948); (c) C. W. Shoppee, *J. Chem. Soc.*, 1147 (1946).

(+)-2-ethoxyoctane with $CH_3COCl$ and $Mo(CO)_6$. In a definitive paper on solvolysis reactions at secondary carbon atoms, Weiner and Sneen[23] reported that optically pure 2-octyl brosylate, on solvolysis in a 75% dioxane–25% water mixture, gave inverted 2-octanol of 77% optical purity. Here, dioxane participates as a nucleophile in reaction with the brosylate, a process quite analogous to addition of (+)-2-ethoxyoctane to **3**. In Weiner and Sneen's system, the intermediate undergoes displacement by SOH while in the acid halide reaction, displacement occurs on **5** by **4** (path a).

Smith and Wright[24] were able to convert (−)-menthol into retained menthyl chloride of reasonably high optical purity by reaction with Lucas reagent. Huckel and Pietrzok[25] had earlier shown that the same conversion, effected by phosphorus pentachloride, in the presence of ferric or aluminum chloride, also proceeded with partial retention of configuration. These reactions likely occur by an SNi type mechanism. It is possible that an analogous process could take place in the (−)-menthyl methyl ether reaction. Another possibility is that pathways a and b are occurring simultaneously and that the "equatorial"[26] carbenium ion formed *via* path b undergoes preferential equatorial attack by **4**.

When Group VA substituted metal carbonyls are employed as catalysts, either CO or E[16] [E = $P(C_6H_5)_3$ or $As(C_6H_5)_3$] displacement could occur in the first step in Scheme I.

$$\underset{\text{RCX}}{\overset{O}{\underset{\|}{R}C}X} + M(CO)_6 \longrightarrow R\overset{O}{\underset{\|}{C}}{}^+ + {}^-M(CO)_5 + E$$

or

$$R\overset{O}{\underset{\|}{C}}{}^+ + {}^-\underset{\underset{X}{|}}{\overset{\overset{E}{|}}{M}}(CO)_4 + CO$$

E = $P(C_6H_5)_3$, $As(C_6H_5)_3$
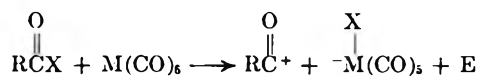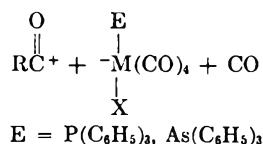
Anions of different nucleophilicities [*e.g.*, $(C_6H_5)_3$-AsMo$(CO)_4X^- > {}^-MoX(CO)_5$] would accompany CO or E generation. Consequently, the direction of cleavage (E and/or CO) may govern the efficiency of the catalyst.

Since **4** is a proposed intermediate of the ether–acid halide reaction, $(n-C_4H_9)_4N^+Mo(CO)_5Br^-$ was prepared[21] and used as a catalyst for the neat reaction of benzoyl bromide with tetrahydrofuran. 4-Bromobutyl benzoate was formed in 83% yield, similar to the yield of halo ester (88%) obtained under identical reaction conditions using $Mo(CO)_6$ as the catalyst. Therefore, **4** appears to be an intermediate in the reaction. It may be generated from acid halide or **7**, possibly itself serving as a source for $Mo(CO)_6$ by disproportionation.

We can offer no rationalization for the order of catalytic effectiveness [$Mo(CO)_6 > W(CO)_6 > Cr(CO)_6$].

(23) H. Weiner and R. A. Sneen, *J. Amer. Chem. Soc.*, **87**, 287 (1965).

(24) J. G. Smith and G. F. Wright, *J. Org. Chem.*, **17**, 1116 (1952).

(25) W. Huckel and H. Pietrzok, *Justus Liebigs Ann. Chem.*, **540**, 250 (1939).

(26) M. Hanack, "Conformation Theory," Academic Press, New York, N. Y., 1965, p 267.

## Experimental Section

**General.**—Infrared spectra (ir) were recorded using a Perkin-Elmer 457 or 521 infrared spectrometer. Nuclear magnetic resonance spectra were recorded on Varian Associates A-60 or HA-100 spectrometers, with tetramethylsilane as internal standard. Optical rotations were determined using a sodium D line polarimeter. Irradiation experiments were carried out in a Rayonet photochemical reactor at 2537 or 3000 Å. Elemental analyses were performed by Par-Alexander Labs, S. Daytona, Fla., Meade Microanalytical Laboratory, Amherst, Mass., and PCR, Inc., Gainesville, Fla. Melting points were determined using Fisher-Johns melting point apparatus and are uncorrected. Boiling point measurements are also uncorrected.

Solvents were purified by standard techniques. All liquid ethers were dried using lithium aluminum hydride (except tetrahydrofuran, where sodium and benzophenone were used). After fractional distillation from the drying agent, the ether was percolated through a column of Woelm neutral alumina (activity grade I). Acid halides were distilled from $MgSO_4$. Chromium hexacarbonyl was purchased from Pressure Chemical Co. Climax Molybdenum Co. provided molybdenum and tungsten hexacarbonyls. Starting materials which were not commercially available were prepared as follows.

**(+)-2-Ethoxyoctane.**—Finely cut sodium (6.25 g) was added to a stirred solution of naphthalene (32.00 g, 0.25 mol) in dry 1,2-dimethoxyethane (250 ml). The solution was stirred for 2 hr, followed by addition of (+)-2-octanol (34.10 g, 0.30 mol). Ethyl bromide (32.70 g, 0.30 mol) was added dropwise to the mixture at *ca.* 5°. The solution was stirred at room temperature overnight. The solvent was removed by flash evaporation, water was added to the residue, and the product was extracted with ethyl ether. The ether extract was dried over anhydrous $MgSO_4$. The residue obtained by removal of ethyl ether was treated with 12 g of phthalic anhydride to react with any unreacted alcohol (the mixture was heated for 8 hr). Distillation of the oil gave (+)-2-ethoxyoctane (9.50 g, 23% yield), bp 45–48° (4.5 mm) [lit.[27] bp 57–58° (10 mm)]; $[\alpha]^{23}D +17.80°$ ($C_2H_5OH$, 2.510 g/100 ml) (lit.[17b] $[\alpha]^{20}D +17.10°$].

**(−)-Menthyl Methyl Ether.**—The ether, bp 82–84° (12 mm), $[\alpha]^{23}D -96.6°$ [lit.[28] bp 83° (12 mm), $[\alpha]^{25}D -95.6°$], was prepared from (−)-menthol in 82% yield following the procedure of Tarbell and Paulson.[23]

**Triphenylphosphine Molybdenum Pentacarbonyl.**—A mixture of triphenylphosphine (10.03 g, 38.3 mmol) and $Mo(CO)_6$ [11.62 g, 88.0 mmol] in dry diglyme (100 ml) was refluxed with stirring under nitrogen for 4 hr. The mixture was cooled, and the solvent was distilled under reduced pressure. The crude product was chromatographed on Florisil using methylene chloride as the eluent. Recrystallization from chloroform–petroleum ether (bp 38–52°) gave 12.47 g (65%) of $(C_6H_5)_3PMo(CO)_5$, mp 134.5–135.5° (lit.[29] mp 138–139°). The ir spectrum was in accord with that reported by Magee, *et al.*[29]

**Triphenylarsine Molybdenum Pentacarbonyl.**—A mixture of triphenylarsine (6.13 g, 20.0 mmol) and $Mo(CO)_6$ (6.07 g, 23.0 mmol) in diglyme (50 ml) was refluxed with stirring under nitrogen for 4.5 hr. The reaction mixture was worked up as for triphenylphosphine molybdenum pentacarbonyl (except for the use of 1:1 chloroform–benzene as chromatographic eluent), and the product was recrystallized from petroleum ether. White crystals, mp 143–145°, of triphenylarsine molybdenum pentacarbonyl were obtained in 65% yield, ir $\nu_{CO}$ (hexane) 2080 (s), 1990 (m), 1955 (vs), and 1925 cm$^{-1}$ (sh).

***cis*-Bis(triphenylphosphine)molybdenum Tetracarbonyl.**—A mixture of triphenylphosphine (5.20 g, 17.0 mmol), $Mo(CO)_6$ (2.03 g, 7.70 mmol), and sodium borohydride (0.8 g) in methanol was refluxed for 4 hr. The reaction mixture was then stirred overnight at room temperature. The solution was filtered and the crystals were washed several times with water and finally with ethanol. Recrystallization from methylene chloride–ethanol gave 1.25 g (22%) of product, mp 155° dec. The product

(27) A. Streitwieser, Jr., and A. C. Waiss, Jr., *J. Org. Chem.*, **27**, 290 (1962).

(28) D. S. Tarbell and M. C. Paulson, *J. Amer. Chem. Soc.*, **64**, 2842 (1942).

(29) T. A. Magee, C. N. Matthews, T. S. Wang, and J. H. Wotiz, *ibid.*, **83**, 3200 (1961).

was assigned the cis configuration on the basis of its ir spectrum[30] [$\nu_{CO}$ (CH$_2$Cl$_2$) 2025 (s), 1910 (vs), 1885 cm$^{-1}$ (sh)]. No trans isomerr was isolated in contrast to the claim by Chatt and coworkers[31] that *only* the trans isomer is produced following essentially the same procedure.

**Tetrabutylammonium Bromopentacarbonyl Molybdenate(0).**— The yellow salt was prepared in 80% yield following the general procedure described by Abel, Butler, and Reid.[19] The salt decomposed at 90° (lit.[21] mp 91° dec), ir [($\nu_{CO}$ (CH$_2$Cl$_2$)] 2070 (w), 1930 (vs), 1850 cm$^{-1}$ (m) [lit.[21] $\nu_{CO}$ (CHCl$_3$) 2063, 1927, 1854 cm$^{-1}$].

**Reaction of Acetyl Chloride with 2-Methyltetrahydrofuran in the Presence of M(CO)$_6$ (M = Cr, Mo, W).**—A mixture of 2-methyltetrahydrofuran (31.0 mmol), acetyl chloride (32.2–34.0 mmol), and Mo(CO)$_6$ (2.3 mmol) in hexane (40 ml) was refluxed for 20 hr. The mixture was cooled and concentrated using a flash evaporator. Metal hexacarbonyl was removed by sublimation. Fractional distillation of the sublimation residue gave (a) 4-chloropentyl acetate (80% yield), bp 135–136° (65 mm) [lit.[32] bp 82° (10 mm)]; ir $\nu_{CO}$ (CCl$_4$) 1736 cm$^{-1}$; nmr (CCl$_4$) $\delta$ 4.06 (m, 3 H, >CHCl and –CH$_2$O–), 1.97 (s, 3 H, CH$_3$COO–), and 1.49 (d, 3 H, CH$_3$CClH–); (b) 3-pentenyl acetate (7% yield), bp 105–108° (78 mm) [lit.[33] bp 48° (12 mm)]; ir $\nu_{CO}$ (CCl$_4$) 1741 cm$^{-1}$; nmr (CCl$_4$) $\delta$ 5.43 (m, 2 H, CH=CH–), 4.01 (t, 2 H, –OCH$_2$–), 2.07 (s, 3 H, CH$_3$COO–). The results using Cr(CO)$_6$ and W(CO)$_6$ as catalysts are given in Table II.

**Reaction of Benzoyl Chloride with 2-Methyltetrahydrofuran in the Presence of M(CO)$_6$ (M = Cr, Mo, W).**—A mixture of 2-methyltetrahydrofuran (46 mmol), benzoyl chloride (36 mmol), and metal carbonyl (2.3 mmol) was refluxed in hexane (35 ml) for 60 hr. The solvent and unreacted ether were removed under reduced pressure, while sublimation recovered M(CO)$_6$. Fractional distillation gave (a) 4-chloropentyl benzoate, bp 129–132° (0.45 mm); ir $\nu_{CO}$ (neat) 1716 cm$^{-1}$; nmr (CCl$_4$) $\delta$ 3.8–4.5 (m, 3 H, >CHCl and –CH$_2$O–), 1.8 (m, 4 H, the remaining methylene protons), 1.47 (d, 3 H, CH$_3$CHCl–) (*Anal.* Calcd for C$_{12}$H$_{15}$ClO$_2$: C, 63.57; H, 6.67. Found: C, 62.98; H, 6.47); (b) 3-pentenyl benzoate, bp 103.5–106.0° (0.55 mm); ir $\nu_{CO}$ (CCl$_4$) 1718 cm$^{-1}$; nmr (CCl$_4$) $\delta$ 5.46 (m, 2 H, –CH=CH–), 4.27 (t, 2 H, –CH$_2$O–), $\delta$ 2.42 (m, 2 H, –CH$_2$CH=CH–), and 1.62 (m, 3 H, CH$_3$CH=CH–) (*Anal.* Calcd for C$_{12}$H$_{14}$O$_2$: C, 75.79; H, 7.37. Found: C, 75.88; H, 7.05).

**Thermal and Photolytic Reactions of Acetyl Chloride with Tetrahydrofuran in the Presence of Mo(CO)$_6$.**—The reaction was carried out as described for 2-methyltetrahydrofuran (reflux 23 hr in hexane) to give 4-chlorobutyl acetate: bp 59–60° (1.8 mm) [lit.[34] bp 92–93° (22 mm)]; ir $\nu_{CO}$ (neat) 1740 cm$^{-1}$; nmr (CCl$_4$) $\delta$ 4.05 (s, 2 H, –CH$_2$O–), 3.55 (t, 2 H, CH$_2$Cl), 1.99 (s, COCH$_3$). A 42% yield of 4-chlorobutyl acetate has been reported when the reaction was carried out in the absence of a catalyst.[34]

An 80% yield of 4-chlorobutyl acetate was obtained by irradiation of a hexane solution of the CH$_3$COCl–THF–Mo(CO)$_6$ mixture at 2537 Å for 28 hr at room temperature. Repetition of the photoreaction in the absence of Mo(CO)$_6$ gave no 4-chlorobutyl acetate.

**Reaction of Cyclohexanecarboxylic Acid Chloride with Tetrahydrofuran in the Presence of M(CO)$_6$ (M = Cr, Mo, W).**—A mixture of the acid chloride (15.5 mmol) and M(CO)$_6$ (1.14 mmol) in THF (25 ml) was refluxed for 18 hr. The solution was cooled and filtered, and unreacted tetrahydrofuran was removed from the filtrate by flash evaporation at room temperature. Distillation at 1.3 mm gave 4-chlorobutyl cyclohexanecarboxylate: bp 139–141°; ir $\nu_{CO}$ (neat) 1735 cm$^{-1}$; nmr (CCl$_4$) $\delta$ 4.06 (t, 2 H, CH$_2$O), 3.55 (t, 2 H, –CH$_2$Cl), 2.25 (m, 1 H, >CHC(=O)O), and 1.20–2.00 (m, 10 H, methylene protons of cyclohexane ring). *Anal.* Calcd for C$_{11}$H$_{19}$ClO$_2$: C, 60.40; H, 8.76. Found: C, 60.22; H, 9.05. Halo ester yields are given in Table II. In the absence of a catalyst, a reaction run

under identical conditions gave a 9% yield of 4-chlorobutyl cyclohexane carboxylate.

**Reaction of Acetyl Chloride with 2,2,4,4-Tetramethyltetrahydrofuran in the Presence of Mo(CO)$_6$.**—Reaction and work-up following the procedure used for 2-methyltetrahydrofuran gave a 2:1 mixture (based on nmr) of (a) 2,2,4-trimethyl-4-pentenyl acetate and (b) 2,2,4-trimethyl-3-pentenyl acetate (72% total yield): bp 78–79° (13 mm) [lit.[35] bp (a) 71.5–73.0° (10 mm), lit.[36] bp (b) 69.0–70.0° (9 mm)]; ir $\nu_{CO}$ (neat) 1710 cm$^{-1}$; nmr (CCl$_4$) $\delta$ 5.06 (m, 2 H, olefinic proton of b), 4.87 and 4.63 (m, 2 H, olefinic protons of a), 3.83 [s, 2 H, –CH$_2$O (b)], 3.76 [s, 2 H, –CH$_2$O (a)]. A mass spectrum showed the expected fragments.

**Reaction of 2,5-Dihydrofuran with Acetyl Chloride in the Presence of M(CO)$_6$ (M = Cr, Mo, W).**—A mixture of 2,5-dihydrofuran (2.42 g, 34.6 mmol), acetyl chloride (5.50 g, 70.0 mmol), and M(CO)$_6$ (2.7 mmol) was refluxed in hexane (20 ml) for 20 or 36 hr (Table II). Metal hexacarbonyl was precipitated in a Dry Ice–acetone bath and filtered. The filtrate was evaporated under reduced pressure. Distillation of the residue at 8 mm afforded 4-chloro-2-butenyl acetate: bp 85–86° [lit.[37] bp 82.0–84.5° (9 mm)]; ir $\nu_{CO}$ (CCl$_4$) 1744 cm$^{-1}$; nmr (CCl$_4$) $\delta$ 5.78 (m, 2 H, olefinic protons), 4.63 (m, 2 H, –CH$_2$O–), 4.14 (m, 2 H, CH$_2$Cl), 2.01 (s, 3 H, CH$_3$CO–).

**Reaction of Acetyl Chloride and 7-Oxabicyclo[2.2.1]heptane in the Presence of M(CO)$_6$ (M = Cr, Mo, W).**—The hexane or isooctane solution containing the acid chloride, the ether, and metal hexacarbonyl was allowed to react and worked up following the procedure described for 2-methyltetrahydrofuran. One or both of the following products were obtained: (a) *trans*-4-chlorocyclohexyl acetate, bp 133.0–135.0° (40 mm) [lit.[38] bp 83.5–83.7° (4.5 mm)]; ir $\nu_{CO}$ (neat) 1736 cm$^{-1}$; nmr (CCl$_4$) $\delta$ 4.75 (m, 1 H, >CHO–), 4.05 (m, 1 H, >CHCl), 1.96 (s, 3 H, CH$_3$C=O), and 1.3–2.4 (m, 8 H, methylene protons); (b) 3-cyclohexenyl acetate, bp 112–114° (40 mm) [lit.[39] bp 75° (25 mm)]; ir $\nu_{CO}$ (neat) 1730 cm$^{-1}$; nmr (CCl$_4$) $\delta$ 5.58 (m, 2 H, olefinic protons), 4.87 (m, 1 H, >CHO–), and 1.96 (s, 3 H, CH$_3$C=O). The product yields are given in Table II.

**Reaction of Benzoyl Chloride and 7-Oxabicyclo[2.2.1]heptane in the Presence of M(CO)$_6$ (M = Cr, Mo, W).**—The procedure for 2-methyltetrahydrofuran was followed. Distillation at 0.15 mm afforded 3-cyclohexenyl benzoate: bp 93–95° [lit.[40] bp 149–150° (12 mm)]; ir $\nu_{CO}$ (neat) 1713 cm$^{-1}$; nmr (CCl$_4$) $\delta$ 5.62 (m, 2 H, olefinic protons), 5.21 (q, 1 H, >CHO), 1.6–2.5 (m, 6 H, methylene protons). *Anal.* Calcd for C$_{13}$H$_{14}$O$_2$: C, 77.20; H, 6.97. Found: C, 77.53; H, 6.87.

The distillation residue was chromatographed on Florisil. Elution with petroleum ether and subsequent recrystallization gave *trans*-4-chlorocyclohexyl benzoate: mp 52.5–54.0°; ir $\nu_{CO}$ (KBr) 1708 cm$^{-1}$; nmr (CCl$_4$) $\delta$ 5.04 (m, 1 H, >CHO–), 4.08 (m, 1 H, >CHCl), 1.5–2.5 (m, 8 H, methylene protons). *Anal.* Calcd for C$_{13}$H$_{15}$ClO$_2$: C, 65.39; H, 6.33. Found: C, 65.64; H, 6.32. Pertinent data for these reactions are given in Table II.

**Reaction of Benzoyl Bromide with 7-Oxabicyclo[2.2.1]heptane in the Presence of Mo(CO)$_6$.**—A mixture of benzoyl bromide (3.70 g, 20.0 mmol), ether (2.16 g, 22.0 mmol), and Mo(CO)$_6$ (1.9 mmol) in isooctane (25 ml) was refluxed for 16 hr. Work-up of the reaction in the usual manner gave (a) *trans*-4-bromocyclohexyl benzoate (72% yield), mp 63.5–64.0° [lit.[41] bp 170° (1 mm)]; ir $\nu_{CO}$ (KBr) 1714 cm$^{-1}$; nmr (CCl$_4$) $\delta$ 5.05 (m, 1 H, >CHO), 4.25 (m, 1 H, >CHBr), and 1.3–2.4 (methylene protons) (*Anal.* Calcd for C$_{13}$H$_{15}$BrO$_2$: C, 55.15; H, 5.34; Br, 28.22. Found: C, 55.24; H, 5.21; Br, 28.55); (b) 3-cyclohexenyl benzoate (13% yield).

**Reaction of Benzoyl Fluoride and 7-Oxabicyclo[2.2.1]heptane in the Presence of M(CO)$_6$ (M = Cr, Mo, W).**—Under standard conditions, Mo(CO)$_6$ as catalyst gave 3-cyclohexenyl benzoate in 67% yield. No reaction occurred when Cr(CO)$_6$ or W(CO)$_3$ were employed as catalysts.

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**Reaction of Benzoyl Chloride and 2,3-Dihydropyran in the Presence of Mo(CO)₆.**—A mixture of benzoyl chloride (4.36 g, 31.0 mmol), dihydropyran (3.87 g, 46.0 mmol), and Mo(CO)₆ (2.3 mmol) in hexane (40 ml) was refluxed for 3 days. The solution was cooled and filtered, and the filtrate was evaporated *in vacuo* to remove solvent and unreacted ether. The residue from evaporation could not be distilled at temperatures as high as 230° and a pressure of 0.2 mm. Intense ir absorption was observed at 1720 cm⁻¹ (neat), presumably due to a carbonyl stretching vibration. The nmr spectrum (CCl₄) gave only a broad singlet absorption at δ 4.2. The product seemed to be polymeric.

**Reaction of Acetyl Chloride and 1,4-Thioxane in the Presence of Mo(CO)₆.**—A mixture of 1,4-thioxane (3.23 g, 31.0 mmol), acetyl chloride (2.85 g, 36.3 mmol), and Mo(CO)₆ (8.14 g, 31.0 mmol) in hexane (30 ml) was refluxed under nitrogen for 84 hr. Unreacted Mo(CO)₆ was removed by filtration. The filtrate was concentrated under reduced pressure. The residue was dissolved in ether–petroleum ether, filtered, and chromatographed on Florisil (under N₂). Elution with ether gave a very air-sensitive yellow solid,[21,42] ir $\nu_{CO}$ (neat) 2075 (m), 1940 (s), 1920 cm⁻¹ (sh). Under catalytic conditions, thioxane–molybdenum pentacarbonyl was also produced along with recovered starting materials.

**Reaction of Acetyl Chloride with n-Butyl Phenyl Ether in the Presence of Mo(CO)₆.**—Using standard reaction (24 hr) and work-up conditions, trace amounts of *o*- and/or *p*-*n*-butoxyacetophenone were obtained.

**Reaction of Benzoyl Chloride and n-Butyl Ether in the Presence of Mo(CO)₆.**—A mixture of benzoyl chloride (4.36 g, 31.0 mmol) and Mo(CO)₆ (2.3 mmol) in *n*-butyl ether (25 ml) was refluxed for 16 hr. Fractional distillation afforded the unreacted ether and 4.02 g (73%) of *n*-butyl benzoate, bp 120° (4 mm) (lit.[43] bp 250.3°). The ir and nmr spectra of the product were identical with spectra for authentic material. No attempt was made to isolate *n*-butyl chloride.

**Reaction of Ethyl Triphenylmethyl Ether and Benzoyl Chloride in the Presence of Mo(CO)₆.**—Standard reaction conditions gave, on work-up, ethyl benzoate in 72% yield and triphenylmethyl chloride. Identification was made by comparison with authentic samples.

**Reaction of Benzoyl Chloride with Benzoin Methyl Ether in the Presence of Mo(CO)₆.**—Methyl benzoate (37% yield) and desyl chloride were obtained by treating benzoyl chloride (10 mmol), benzoin methyl ether (10 mmol), and Mo(CO)₆ (1.3 mmol) in refluxing isooctane (25 ml) for 48 hr.

**Reaction of Acetyl Chloride with Tetrahydrofuran in the Presence of Mo(CO)₅E [E = P(C₆H₅)₃ or As(C₆H₅)₃] or cis-Mo(CO)₄[P(C₆H₅)₃].**—A mixture of acetyl chloride (3.93 g, 50.0 mmol), tetrahydrofuran (2.16 g, 30.0 mmol), and group VA substituted molybdenum carbonyl (2.0 mmol) in hexane (30 ml) was refluxed for 22–23 hr. The solution was filtered, and the filtrate was evaporated at ca. 30 mm. Distillation of the residue from evaporation of the filtrate gave 4-chlorobutyl acetate. See Table III for yields using different catalysts. 4-Chlorobutyl acetate was also obtained when the reaction [(C₆H₅)₃PMo(CO)₅ as catalyst] was effected photolytically at 3000 Å.

**Reaction of Acetyl and Benzoyl Chlorides with (+)-2-Ethoxyoctane in the Presence of Mo(CO)₆.**—Reaction (acetyl chloride) in hexane (20 hr) under standard conditions gave ethyl acetate, 2-octene (31%), and (−)-2-chlorooctane (62%), bp 61.0–63.0° (14 mm) [lit.[43] bp 75° (28 mm)], [α]D −23.5° (ethanol). Using benzoyl chloride as the acid chloride and isooctane as solvent (24 hr) gave the same three products. Yields are given in Table I.

**Reaction of Acetyl Chloride with (−)-Menthyl Methyl Ether in the Presence of Mo(CO)₆.**—A mixture of acetyl chloride (2.34 g, 30.0 mmol), (−)-menthyl methyl ether (2.55 g, 15.1 mmol), and Mo(CO)₆ (1.2 mmol) was refluxed in hexane (20 ml) for 24 hr. The solution was cooled and flash evaporated, and Mo(CO)₆ was recovered by sublimation. The residue was chromatographed on Florisil. Elution with petroleum ether and subsequent distillation afforded (a) menthenes, bp 62.0–65.0° (4.9 mm) (lit.[43] bp 168°); nmr (CCl₄) δ 5.33 and 5.50 (m, 2 H, olefinic protons); (b) menthyl and neomenthyl chloride (1.85 g, 73%), bp 53–55°

(4.9 mm) (lit.[24] bp 101.0–101.5° (21 mm)]. The nmr spectrum of the mixture was superimposable with the spectra published by Glaze and Selman[44] for menthyl and neomenthyl chlorides. Based on nmr integration, the ratio of menthyl to neomenthyl chloride is 2:1.

Elution with ether gave menthyl acetate to (0.22 g, 10%) which was identified by comparison of physical properties with those of authentic material prepared by treating (−)-menthol with acetyl chloride.

**Reaction of n-Butyryl Chloride with (−)-Menthyl Methyl Ether in the Presence of Mo(CO)₆.**—Menthene, menthyl and neomenthyl chlorides, and menthyl *n*-butyrate were obtained following the previous procedure. The ratio of menthyl to neomenthyl chloride was 2:1. Menthyl *n*-butyrate was identified by comparison with an authentic sample prepared by treating (−)-menthol with *n*-butyryl chloride.

A 2:1 ratio of menthyl to neomenthyl chloride also resulted when the same reaction was effected photolytically (2537 Å, hexane solution, 41 hr).

**Reaction of 3β-Ethoxycholest-5-ene and Acetyl Chloride in the Presence of Mo(CO)₆.**—A mixture of the steroidal ether (4.15 g, 10.0 mmol), acetyl chloride (1.26 g, 16.0 mmol), and Mo(CO)₆ (0.8 mmol) in hexane (20 ml) was refluxed with stirring for 21 hr. The solution was cooled and flash evaporated at room temperature, and Mo(CO)₆ was recovered by sublimation. The sublimation residue was chromatographed on Florisil. Elution with petroleum ether gave a small amount of cholesta-3,5-diene, mp 77.5–79.0° (lit.[43] mp 80°). Elution with benzene gave 4.01 g of crude 3β-chlorocholest-5-ene, which was recrystallized from ethanol to give pure material, mp 95–96° (lit.[43] mp 96°), identical with an authentic sample.

**Reaction of Benzoyl Bromide with Tetrahydrofuran in the Presence of Mo(CO)₆ or (C₄H₉)₄N⁺Mo(CO)₅Br⁻.**—A mixture of benzoyl bromide (5.55 g, 30.0 mmol) and metal carbonyl (5 mmol) in tetrahydrofuran (12 ml) was heated at 60° for 23 hr. After standard work-up, 4-bromobutyl benzoate, bp 128–130° (1.5 mm) [lit.[34] bp 155–157° (9 mm)], was isolated in 88% yield using Mo(CO)₆ and in 83% yield using (C₄H₉)₄N⁺Mo(CO)₅Br⁻: ir $\nu_{CO}$ (neat) 1723 cm⁻¹; nmr (CCl₄) δ 4.25 (m, 2 H, –CH₂O), 3.38 (t, 2 H, CH₂Br), and 1.89 (m, 4 H, other methylene protons).

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# Selective Metalations of Methylated Pyridines and Quinolines. Condensation Reactions[1a]

EDWIN M. KAISER,* GREGORY J. BARTLING, WILLIAM R. THOMAS, SUSAN B. NICHOLS,[1b] AND DIANE R. NASH[1b]

*Department of Chemistry, University of Missouri—Columbia, Columbia, Missouri 65201*

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Interactions of 2,4-lutidine, 2,4,6-collidine, and 2,4-dimethylquinoline with *n*-butyllithium in ether–hexane results in exclusive metalation of their 2-methyl groups. In contrast, treatment of these active hydrogen compounds with alkali amides in ammonia or with lithium diisopropylamide in ether–hexane gives exclusive metalation of their 4-methyl groups. Such differences are interpreted in terms of metallic cations and their relative ability to complex with nitrogen atoms, either of the heterocycles or of the solvent or coreagent. Similar selective metalations are not realized on 2,6- or 2,7-dimethylquinolines, presumably because of lack of resonance delocalization of carbanions on the 6- and 7-methyl groups, respectively. All of the carbanions formed, particularly those on the 4-methyl groups, have been condensed with various electrophiles in fair to excellent yields.

2- and 4-picolyl organometallic reagents, prepared from interaction of the parent picolines with a variety of bases, have been studied rather extensively.[2a,b] However, the related carbanions derived from 2,4-lutidine (**1a**) and 2,4,6-collidine (**1b**) have but rarely been prepared and their reactions are thus relatively unknown. For example, 2-lithiomethyl derivatives **2a,b** have been obtained in a few cases by treatment of **1a,b** with lithiohydrocarbons like phenyllithium; subsequent condensations with various carbonyl compounds are known.[3a–c] On the other hand, 4-alkalimethyl derivatives **3a,b** have been realized only upon treatment of **1a,b** with alkali metal amides in liquid ammonia.[4a,b] Compound **3a** has been methylated in unspecified yield,[4a] and both **3a,b** have been nitrated



|  |  |  |
|---|---|---|
| **1a**, R = H | **2a**, R = H | **3a**, R = H |
| **b**, R = CH₃ | **b**, R = CH₃ | **b**, R = CH₃ |

by alkyl nitrates in good yields to afford the corresponding nitromethyl derivatives.[4b]

However, the picture is far from clear, as illustrated by the report by Chichibabin that **1b** is converted to **2b**, not **3b**, by various alkali metal amides.[5] Thus, our involvement with compounds **1a,b** arose not only because of the paucity of data on the 4-lutidyl (**3a**) and 4-collidyl (**3b**) anions, but also on our initial skepticism (and confusion) concerning the above purported different sites of metalation within these molecules (4-methyl *vs.* 2-methyl) as a function of the base (alkali amides *vs.* organolithiums). To our knowledge, such a remarkable dependence upon base had previously not been recognized. Usually, of course, ionization of molecules containing more than a single kind of similarly activated hydrogen atom has resulted in the same hydrogen atom being abstracted regardless of the base employed, though the relative rates of reaction have often been different.

First, to unequivocally ascertain the site of metalation as a function of the base, **1a,b** were allowed to react with three different base systems and the resulting carbanions were subsequently identified by condensations with certain electrophiles. Thus, interaction of **1a,b** with sodium or potassium amides in liquid ammonia (method A) or with lithium diisopropylamide in ether (or THF)–hexane (method B) afforded the 4-alkali methyl derivatives **3a,b** since methylation with methyl iodide gave methylethylpyridines **4a,b** respectively. Similar treatment of



|  |  |
|---|---|
| **4a**, R = H | **5a**, R = H |
| **b**, R = CH₃ | **b**, R = CH₃ |

**1a,b** with *n*-butyllithium in ether–hexane (method C) gave the 2-metallomethyl derivatives **2a,b**, since methylation afforded the isomeric methylethylpyridines, **5a,b** respectively. Incidentally, authentic **4b** was prepared by an unequivocal ring closure, thereby providing a standard compound for nmr spectroscopic determinations of other structures.

Methods A and B were then employed to synthesize various other substituted pyridines arising from alkylation of the 4-methyl groups of **1a,b**. Thus, **3a** was *n*-propylated, *n*-butylated, and benzylated to

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give **6a**, **7a**, and **8a**, respectively, in fair to good yields. Also, **3b** was n-propylated, n-butylated, benzylated and caused to enter into a bis alkylation to afford **6b**, **7b**, **8b**, and **9**, respectively. Parenthetically, a similar bis alkylation on **2b** likewise gave a dipyridyl derivative (**10**).
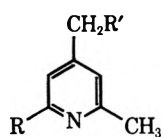


**6a**, R = H; R' = n-C₃H₇
**b**, R = CH₃; R' = n-C₃H₇
**7a**, R = H; R' = n-C₄H₉
**b**, R = CH₃; R' = n-C₄H₉
**8a**, R = H; R' = CH₂C₆H₅
**b**, R = CH₃; R' = CH₂C₆H₅



**9**



**10**
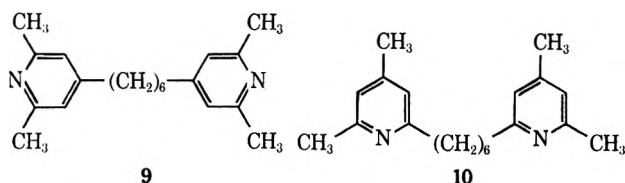
Next, attention was directed toward condensation of the above salts with electrophiles other than alkyl halides. For example, the 4-lutidyl (**3a**) and 4-collidyl (**3b**) anions were condensed with a few aldehydes and ketones to give the expected β-hydroxypyridine derivatives. Thus, **3a,b** were treated with benzophenone and fluorenone by means of method A to afford alcohols **11a–b** and **12a–b**, respectively; adducts **11a–b** were also obtained in THF-hexane (Method B) but in poorer yields. A similar condensation of **3b** with anisaldehyde gave alcohol **13**.



**11a**, R = H
**b**, R = CH₃

**12a**, R = H
**b**, R = CH₃



**13**
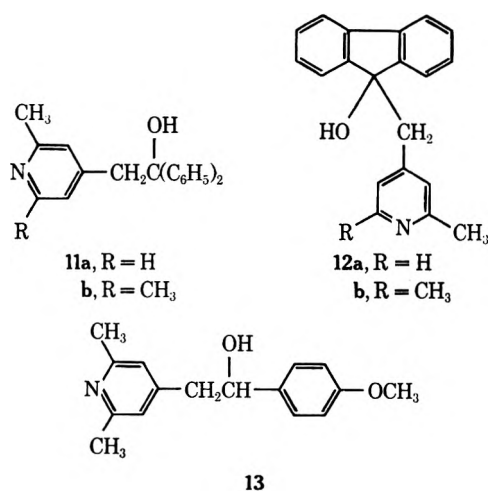
Also, an oxidative dimerization[6] of **3b** was effected by means of potassium permanganate in ammonia to give hydrocarbon **14** in fair yield. It should be mentioned that the 2-lithio derivative **2b** has previously been dimerized by molecular oxygen to give **15**.[7]

Finally, carbanions **2a,b** and **3a,b** were condensed with azobenzene to afford substituted hydrazobenzenes. The specifics of these reactions are reported elsewhere.[8]
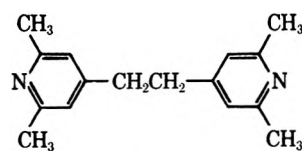


**14**
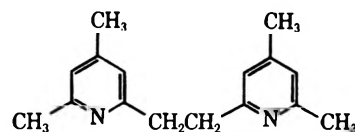


**15**

Next, attention was directed toward the related base-catalyzed chemistry of three isomeric quinolines, namely the 2,4-, 2,6-, and 2,7-dimethyl isomers. As will be seen, selective metalations were realized on the 2,4-dimethyl system, but not on the others.

First, treatment of the 2,4-dimethyl isomer with sodium amide in ammonia (method A) or lithium diisopropylamide in ether–hexane (method B) resulted in exclusive ionization of the 4-methyl group to give **16**, since subsequent condensations with benzophenone afforded alcohol **17**. Anion **16**, prepared by method A, was also treated with p-chlorobenzaldehyde, chalcone, 1,4-dibromobutane, and potassium permanganate to give derivatives **18–21**, respectively.



**16**



**17**



**18**



**19**



**20**



**21**
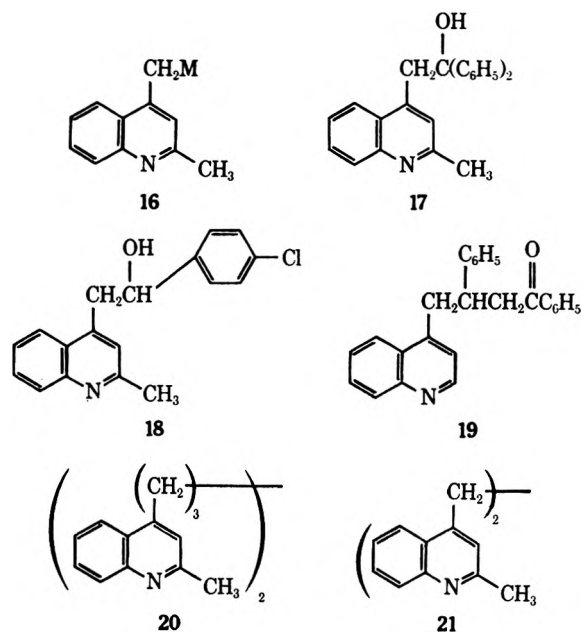
In contrast, treatment of the 2,4-dimethyl isomer with n-butyllithium (method C) gave rise only to anion **22** resulting from metalation of the 2-methyl group. Formation of **22** was confirmed by reactions with benzophenone, p-chlorobenzaldehyde, and chalcone to give **23**, **24**, and **25**, respectively. Interestingly, in contrast with the chalcone condensation with **16**, which occurs *via* a conjugate addition reaction, that with **22** arises from a 1,2-nucleophilic acyl addition; the importance of metallic cations in such reactions is of course, well known.[9] Compound **22** has previously been dimerized in low yield by molecular oxygen.[7]

Disappointingly, treatment of 2,7-dimethylquinoline with any of the bases described above gave metalation

(6) E. M. Kaiser, *J. Amer. Chem. Soc.*, **89**, 3659 (1967).
(7) A. M. Jones and C. A. Russell, *J. Chem. Soc. C*, 2246 (1969).
(8) E. M. Kaiser and G. J. Bartling, *J. Org. Chem.*, **37**, 490 (1972).

(9) For example, see E. E. Royals, "Advanced Organic Chemistry," Prentice-Hall, Englewood Cliffs, N. J., 1954, pp 635–637.
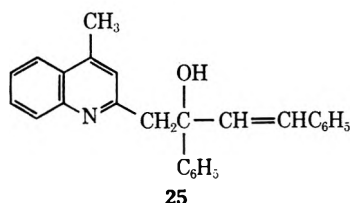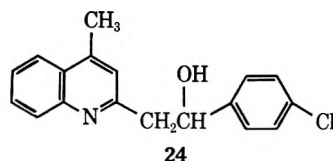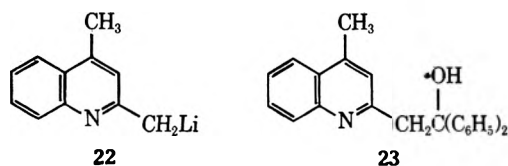
only on the 2-methyl group. Thus, treatment of this isomer by methods A, B, or C afforded only 26,
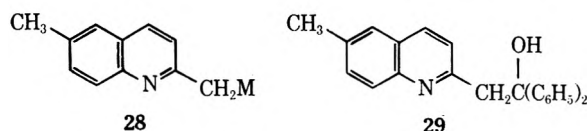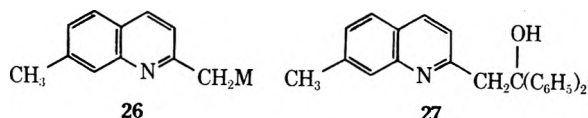
since condensation with benzophenone gave only 27 in high yields. Similar results were obtained with the 2,6-dimethyl isomer using methods B and C giving anion 28; addition of benzophenone yielded only alcohol 29.

## Discussion

The surprising aspect of the above work is not that methyl groups substituted in the 2 and/or 4 positions of pyridine and quinoline moieties undergo facile metalation, since it is well known that the resulting anions are highly resonance stabilized. In fact, even relatively weakly acidic alkyl groups substituted on the 3 position of such molecules can be ionized provided the proper choice of base is made.[10] What is surprising, of course, is that such highly selective metalations can be achieved on these systems at all. This is particularly so if it is realized that the 4-methyl groups are presumably more acidic than those in the 2 position,[11] and thus should undergo exclusive ionization with single molecular equivalents of bases. That n-butyllithium (and other lithiohydrocarbons) promotes only ionization of 2-methyl groups can be ascribed to prior complexation of the lithium cation with the ring nitrogen, thereby effectively "locking in" the basic butyl group near that particular methyl group. Metalation then can proceed by a favorable six-membered-ring process (30). Similar complexes of organolithium reagents with tertiary amines are well known.[2a]

Metalation of 4-methyl groups in these molecules,
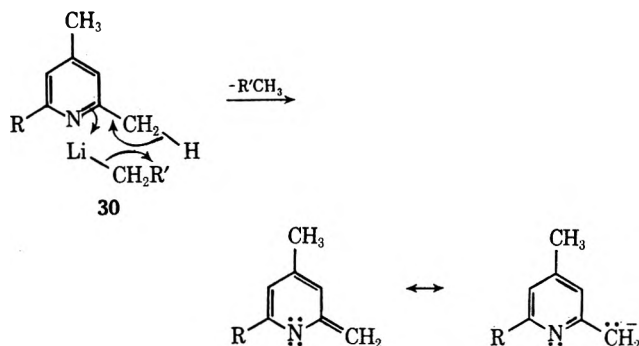
then, can be expected to occur when metallic cations (for example, sodium) are used that are not as effective as lithium in coordinating with nitrogen, or when solvents or coreagents (for example, ammonia or diisopropylamine, respectively) are employed which are more strongly basic, and thus more strongly coordinating, than pyridine or quinoline. For example, in method B, even the use of lithium as cation does not promote lithiation of the 2-methyl groups, since the metal is complexed with the nitrogen of diisopropylamine rather than that of the ring nitrogen. Therefore, the basic reagent is "free" to ionize the more strongly acidic 4-methyl group.

That the 6-methyl group of 2,6-dimethylquinoline is not ionized under any of the conditions described above can be rationalized simply—an anion formed at this position cannot be delocalized onto the nitrogen atom. Thus, in this case, only the more acidic 2-methyl group is metalated in this compound. More surprisingly, however, is the fact that the 7-methyl group of 2,7-dimethylquinoline is also unaffected by our systems. Presumably, an anion formed on such a methyl group could be delocalized onto nitrogen provided the aromaticity of the nonheterocyclic ring is destroyed (for example, 31). Apparently, though,
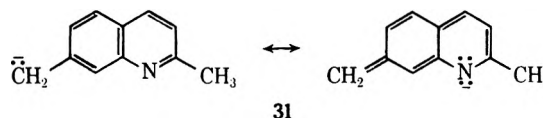
this loss of aromaticity offsets the energy gained by delocalizing the charge, so 31 cannot be realized.

The condensations of all the carbanions prepared above seem to be general and could be easily extended to other electrophiles. The structures of the products, most of which are new, were supported by elemental analyses, nmr spectroscopy, and in some cases by the preparation of known picrate or methiodide derivatives (see Table I).

Work is currently in progress to ascertain if other polymethylated heterocycles will similarly be selectively metalated by different bases. Of particular interest is the possible formation of 1,1[12] and other kinds of multiple anions derived from these systems.

## Experimental Section[13]

**Preparation of Pyridine and Quinoline Derivatives by Means of Alkali Amides in Ammonia (Method A).**—In Table I are listed

(10) For example, see A. D. Miller, C. Osuch, N. N. Goldberg, and R. Levine, *J. Amer. Chem. Soc.*, **78**, 674 (1956).

(11) H. C. Brown and X. R. Mihm, *ibid.*, **77**, 1723 (1955).

(12) E. M. Kaiser, L. E. Solter, R. A. Schwarz, R. D. Beard, and C. R. Hauser, *ibid.*, **93**, 4237 (1971).

(13) Infrared spectra were measured on a Perkin-Elmer Model 237 grating infrared spectrometer. Nmr spectra were obtained on a Varian Associates A-60 spectrometer using tetramethylsilane as internal standard. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

## Table I
### Products Prepared from Condensations of Alkali Derivatives of Alkylated Pyridines and Quinolines with Electrophiles

| Product | Method[a] | Yield, %[b] | Mp or bp, °C (mm) | C | H | N | Nmr spectra, δ |
|---|---|---|---|---|---|---|---|
| | | | | | Analyses (calcd/obsd) | | |
| 4a | A | 37 | 180–182 (760)[c] | | | | 8.4[d] (d, 1, ArH), 6.9 (d, 2, ArH), 2.56 (m, 5, CH$_2$, CH$_3$), 1, 2 (t, 3, CH$_3$) |
| 4b | A | 47 | 177–180 (760)[e] | | | | 6.7[d] (s, 2, ArH), 2.45 (q, 2, CH$_3$CH$_2$), 2.4 (s, 6, CH$_3$), 1.1 (t, 3, CH$_3$) |
| 5a | C | 40 | 173–175 (760)[f] | | | | 8.0[g] (d, 1, ArH), 6.67 (d, 2, ArH), 2.18 (m, 5, CH$_2$, CH$_3$), 0.83 (t, 3, CH$_3$) |
| 5b | C | 60 | 174–176 (760)[h] | | | | 6.7[d] (s, 2, ArH), 2.7 (q, 2, CH$_3$CH$_2$), 2.4 (s, 3, CH$_3$), 2.1 (s, 3, CH$_3$), 1.2 (t, 3, CH$_3$CH$_2$) |
| 6a | A | 27 | 89.5–90 (10) | 80.54[i] | 10.06 | 9.40 | 7.98[d] (d, 1, ArH), 6.04 (d, 2, ArH), 1.93 (m, 5, CH$_2$, CH$_3$), 0.79 (m, 7, CH$_2$, CH$_3$) |
| | B | 37 | 89.5–90 (10) | 80.37[j] | 10.19 | | |
| 6b | A | 57 | 92–94 (11) | 80.98[i] | 10.43 | 8.59 | 6.25[d] (s, 2, ArH), 1.94 (m, 8, CH$_2$, CH$_3$), 0.75 (m, 7, CH$_2$, CH$_3$) |
| | | | | 80.72[j] | 10.36 | | |
| 7a | A | 44 | 89–90 (7.5) | 80.98[i] | 10.43 | 8.59 | 7.99[d] (d, 1, ArH), 6.48 (d, 2, ArH), 1.97 (m, 5, CH$_2$, CH$_3$), 0.70 (m, 9, CH$_2$, CH$_3$) |
| | | | | 80.70[j] | 10.62 | 8.73 | |
| 7b | B | 42 | 128–130 (10) | 81.35[i] | 10.73 | 7.91 | 6.26[d] (s, 2, ArH), 1.91 (m, 8, CH$_2$, CH$_3$), 0.76 (m, 9, CH$_2$, CH$_3$) |
| | | | | 81.16[j] | 10.81 | 7.69 | |
| 8a | B | 47 | 149–151 (8) | 85.27[i] | 7.61 | 7.11 | 7.97[g] (d, 1, ArH), 6.79 (m, 5, ArH), 6.35 (m, 2, ArH), 2.35 (m, 4, CH$_2$), 2.05 (s, 3, CH$_3$) |
| | | | | 84.91[j] | 7.81 | 6.76 | |
| 8b | A | 34 | 184–185 (9) | 85.30[i] | 8.05 | 6.63 | 6.80[g] (m, 5, ArH), 6.30 (s, 2, ArH), 2.40 (t, 4, CH$_2$), 2.08 (m, 6, CH$_3$) |
| | | | | 85.41[j] | 8.34 | 6.48 | |
| 9 | A | 53 | 186–192 (0.25)[k] | 81.03[i] | 9.52 | 9.45 | 6.77[l] (s, 4, m, ArH), 2.47 (m, 15.9, CH$_2$, CH$_3$) 1.4 (m, 8.1, CH$_2$) |
| | | | | 80.79[j] | 9.62 | | |
| 10 | C | 21 | 266–271 (1.5) | 81.03[i] | 9.52 | 9.45 | 6.75[l] (s, 4, ArH), 2.69 (m, 4, benzyl, CH$_2$), 2.23 (s, 6, benzyl, CH$_3$), 1.55 (m, 8, CH$_2$) |
| | | | | 81.26[j] | 9.83 | | |
| 11a | A | 47 | 175–177[m] | 83.04[i] | 6.57 | 4.84 | 8.19[l] (d, 1, ArH), 7.35 (m, 10, ArH), 6.67 (d, 2, ArH), 3.58 (s, 2, CH$_2$), 2.41 (s, 3, CH$_3$) |
| 11a | B | 26 | 175–176[m] | 83.20[j] | 6.47 | 4.85 | |
| 11b | A | 96 | 141–142[m,n] | 78.50[i] | 7.17 | 4.36 | 7.5[l] (m, 10, ArH), 6.81 (s, 2, ArH), 6.04 (s, 1, OH), 3.8 (s, 2, OH), 3.63 (s, 2, CH$_2$), 2.28 (s, 6, CH$_3$) |
| 11b | B | 51 | 141–142[m,n] | 78.60[j] | 7.16 | 4.26 | |
| 12a | A | 23 | 174–175[p] | 83.62[i] | 5.92 | 4.88 | 7.91[l] (d, 1, ArH), 7.41 (m, 8, ArH), 6.64 (d, 2, ArH), 3.57 (m, 1, OH), 3.24 (s, 2, CH$_2$), 2.22 (s, 3, CH$_3$) |
| | | | | 83.50[j] | 5.93 | 4.79 | |
| 12b | A | 24 | 219–221[m] | 83.72[i] | 6.31 | 4.65 | 6.85[g] (m, 10.9, ArH, vinyl), 2.2 (s, 6, CH$_3$) |
| | | | | 83.49[j] | 6.33 | | |
| 13 | A | 60 | 148–149[m] | 74.71[i] | 7.39 | 5.49 | 7.15[l] (q, 4, ArH), 6.86 (s, 2, ArH), 4.91 (t, 1, HCOH), 3.83 (s, 3, OCH$_3$), 2.89 (m, 3, CH$_2$, OH), 2.45 (s, 3, CH$_3$) |
| | | | | 74.82[j] | 7.41 | | |
| 14 | A | 38 | 144–146 (2.5)[q] | 79.95[i] | 8.39 | 11.66 | 6.7[l] (s, 4, ArH), 2.8 (s, 4, CH$_2$), 2.48 (s, 12, CH$_3$) |
| | | | | 79.58[j] | 8.28 | 11.29 | |
| 17 | A | 32 | 170.5–172[m] | 84.95[i] | 6.19 | 4.13 | 7.34[l] (m, 15, ArH), 4.0 (s, 2, CH$_2$), 2.48 (m, 4, CH$_3$, OH) |
| 17 | B | 57 | 169–171[m] | 85.22[j] | 6.23 | | |
| 18 | A | 54 | 192.5–194[r] | 72.60[i] | 5.38 | 4.71 | 7.8[s] (m, 4, ArH), 7.33 (m, 1, ArH), 6.95 (s, 4, ArH), 5.07 (t, 0.90, CH), 3.6 (m, 1.9, CH$_2$), 2.6 (s, 3, CH$_3$) |
| | | | | 72.61[j] | 5.47 | 4.90 | |
| 19 | A | 80 | 107.5–109[m,t] | 85.48[i] | 6.30 | 3.83 | 7.5[g] (m, 14, ArH), 6.48 (s, 1, ArH), 3.35 (m, 5, CH$_2$, CH), 2.35 (s, CH$_3$) |
| | | | | 85.36[j] | 6.39 | 3.80 | |
| 20 | A | 51 | 146.5–148[r] | 84.78[i] | 7.60 | 7.61 | 8.2[s] (m, 8, ArH), 7.8 (m, 2, ArH), 3.44 (m, 4, CH$_2$), 3.05 (s, 6, CH$_3$) |
| | | | | 84.90[j] | 7.45 | | |
| 21 | A | 37 | 199–200.5[r] | 84.61[i] | 6.41 | 8.97 | 8.25[s] (m, 10, ArH), 4.06 (s, 4, CH$_2$), 3.15 (s, 6, CH$_3$) |
| | | | | 84.90[j] | 6.37 | | |
| 23 | C | 75 | 157–159[m] | 84.95[i] | 6.19 | 4.13 | 7.3[l] (m, 15, ArH), 3.98 (s, 2, CH$_2$), 2.65 (s, 3, CH$_3$) |
| | | | | 85.06[j] | 6.22 | | |
| 24 | C | 45 | 98.5–100[u] | 72.60[i] | 5.38 | 4.71 | 7.54[g] (m, 8, ArH), 6.89 (s, 1, ArH), 5.7 (broad s, 0.8, OH), 5.1 (t, 1, OCH), 3.03 (d, 2, CH$_2$) |
| | | | | 72.46[j] | 5.33 | 4.78 | |
| 25 | C | 36 | 120–121.5[m,v] | 85.48[i] | 6.30 | 3.83 | 7.19[g] (m, 18, ArH, OH, vinyl), 3.42 (s, 2, CH$_2$), 2.44 (s, 3, CH$_3$) |
| | | | | 85.26[j] | 6.20 | | |
| 27 | A | 89 | 145.5–148[m] | 84.95[i] | 6.19 | 4.13 | 7.72[l] (m, 15, ArH), 3.86 (s, 2, CH$_2$), 2.4 (s, 3, CH$_3$) |
| 27 | B | 83 | 145.5–148[m] | 84.61[j] | 6.44 | | |
| 27 | C | 96 | 145.5–148[m] | | | | |
| 29 | B | 87 | 150–152[m] | 84.95[i] | 6.19 | 4.13 | 7.7[l] (m, 15, ArH), 3.83 (s, 2, CH$_2$), 2.33 (s, 3, CH$_3$) |
| 29 | C | 88 | 150–152[m] | 85.02[j] | 6.40 | | |

[a] Method A refers to alkali amides in ammonia, method B to lithium diisopropylamide in ether–hexane, and method C to n-butyllithium in ether–hexane.  [b] Though material balances are not reported, they were found to usually be high; for example, in the preparation of 4b, s-collidine was recovered in 46% yield.  [c] Picrate mp 140–141° [lit. mp 141–142°: E. Bamberger and O. Baudisch, *Chem. Ber.*, 42, 3578 (1909)].  [d] No solvent.  [e] Methiodide mp 205° (lit. mp 205°; see ref 15).  [f] Picrate mp 116–117° (lit. mp 116–117°; see ref 15).  [g] In carbon tetrachloride.  [h] Picrate mp 113–115° [lit. mp 117°; F. Engelmann, *Justus Liebigs Ann. Chem.*, 231, 44 (1885)].  [i] Calculated.  [j] Found.  [k] Solidified upon standing, mp 47–50°.  [l] In deuteriochloroform.  [m] Recrystallized from 95% ethanol.  [n] This compound was obtained as a monohydrate. All attempts to remove the water were fruitless.  [o] In DMSO-$d_6$.  [p] Recrystallized from benzene.  [q] Solidified upon standing, mp 103–104°.  [r] Recrystallized from methanol.  [s] In trifluoroacetic acid.  [t] Ir (Nujol) 1675 cm$^{-1}$ (C=O), no OH; 2,4-DNP mp 223–226.5°.  [u] Recrystallized from ether.  [v] Ir (Nujol) 3100 (broad, OH), 1355 (OH), and 1175 (OH) cm$^{-1}$; no carbonyl band.

the derivatives of pyridines and quinolines prepared by method A. The following specific examples illustrate the general procedures for alkylations, aldol condensations, and dimerizations, respectively.

**A. Preparation of 2,6-Dimethyl-4-ethylpyridine (4b).**—To a suspension of 0.3 mol of potassium amide in 700 ml of anhydrous liquid ammonia, prepared from 11.7 g (0.3 g-atom) of potassium metal,[14] was added dropwise a solution of 36.4 g (0.3 mol) of 2,4,6-collidine in 75 ml of anhydrous ether. The dark green mixture was stirred for 30 min; then it was treated with a solution of 42.6 g (0.3 mol) of methyl iodide in 50 ml of ether added during 10 min. After 30 min, the black mixture was neutralized by the addition of excess solid ammonium chloride and the solvents were allowed to evaporate. The residue was treated with 500 ml of water, and the solution was made basic with sodium hydroxide and extracted with ether. The extracts were combined, dried ($Na_2SO_4$), and concentrated to give crude product which, upon fractionation, afforded 19.5 g (47%) of 2,6-dimethyl-4-ethylpyridine (4b), bp 177–181° (760 mm), methiodide mp 205° (lit.[15] mp 205°).

**B. Preparation of 2-Methyl-4-(diphenylhydroxymethyl)methylpyridine (11a).**—To 0.053 mol of sodium amide in 250 ml of liquid ammonia[14] was added during 5 min a solution of 5.35 g (0.05 mol) of 2,4-lutidine in 50 ml of ether. After 30 min, the mixture was treated with a solution of 9.1 g (0.05 mol) of benzophenone in 50 ml of ether added during 5 min. The resulting mixture was stirred for 5 min, and then it was poured into 250 ml of magnetically stirred ammonia containing 20 g of ammonium chloride. Upon evaporation of the solvents, the residue was hydrolyzed by 100 ml of water. Some product, collected by vacuum filtration, was combined with that obtained by extracting the aqueous phase several times with ether and concentrating the combined extracts. There was thus obtained, after recrystallization from 95% ethanol, 6.4 g (47%) of 11a, mp 175–177°.

**C. Preparation of 4,4′-Bis-γ-collidine (14).**—To 0.05 mol of potassium amide in 350 ml of liquid ammonia[14] was added dropwise a solution of 6.1 g (0.05 mol) of s-collidine in 30 ml of ether. After 1 hr, the mixture was treated with 7.9 g (0.05 mol) of solid potassium permanganate added in small portions. The resulting blue-green mixture was stirred for 1 hr, then neutralized with excess solid ammonium chloride. The solvents were allowed to evaporate and the residue was extracted overnight with benzene in a Soxhlet extractor. The crude product was recrystallized from aqueous ethanol to give 2.3 g (38%) of 4,4′-bis-γ-collidine (14). Distillation of the compound provided the analytical sample, bp 144–146° (2.5 mm), mp 103–104°.

**Preparation of Pyridine and Quinoline Derivatives by Means of Lithium Diisopropylamide (Method B).**—Table I lists compounds synthesized from alkylated pyridines and quinolines with various electrophiles effected by means of lithium diisopropylamide (method B). Two specific examples follow which may be considered general.

**A. Preparation of 2,6-Dimethyl-4-n-pentylpyridine (7b).**—To a solution of 5.0 g (0.05 mol) of diisopropylamine in 150 ml of anhydrous THF was added via a syringe 32.0 ml (0.05 mol) of 1.6 M n-butyllithium in hexane.[16] After 15 min, the solution was treated during 6 min with a solution of 6.1 g (0.05 mol) of s-collidine in 25 ml of THF. The resulting orange mixture was stirred for 1 hr, then treated with a solution of 6.85 g (0.05 mol) of n-butyl bromide in 40 ml of THF added during 6 min. After

1 hr, the mixture was cooled to 0° by an ice bath and hydrolyzed by the slow addition of 100 ml of water. Work-up of the reaction mixture and purification of the product were accomplished as described in Part A above.

**B. Preparation of 2-(Diphenylhydroxymethyl)methyl-6-methylquinoline (29).**—To 0.05 mol of lithium diisopropylamide in 150 ml of THF, prepared as in Part A, was added during 5 min a solution of 7.85 g (0.05 mol) of 2,6-dimethylquinoline in 50 ml of THF. After 1 hr, the resulting intense red solution was cooled to −78° by a Dry Ice–acetone bath, then treated with a solution of 9.1 g (0.05 mol) of benzophenone in 50 ml of THF added during 5 min. After 5 more min, the now green solution was poured into 300 ml of water and the reaction mixture was worked up as in Part B above to afford, after recrystallization from 95% ethanol, 12.1 g (72%) of 29, mp 150–152°.

**Preparation of Pyridine and Quinoline Derivatives by Means of n-Butyllithium (Method C).**—Table I lists compounds prepared by interacting lithio derivatives of pyridine and quinoline with electrophiles (method C). Except for the absence of diisopropylamine and the use of ether instead of THF, the mechanics of this method are the same as those of Method B. The following preparation of alcohol 23 is illustrative.

Ethyl ether (125 ml) was treated via a syringe with 32.0 ml (0.05 mol) of 1.6 M n-butyllithium in hexane[16] followed immediately with a solution of 7.85 g (0.05 mol) of 2,4-dimethylquinoline in 50 ml of ether added during 5 min. After 1 hr, the mixture was cooled to −78° by a Dry-Ice–acetone bath, then treated during 5 min with a solution of 9.1 g (0.05 mol) of benzophenone in 50 ml of ether. After 5 min, the mixture was poured into 300 ml of water and worked up as above to give 12.0 g (75%) of 2-(diphenylhydroxymethyl)methyl-4-methylquinoline (23), mp 158–159.5°.

**Preparation of Authentic 2,6-Dimethyl-4-ethylpyridine (4b).**—The method of Balaban and Nenitzescu was employed.[17] Acetyl chloride (314.0 g, 4.0 mol), cooled to 0°, was treated with 267.0 g (2.0 mol) of aluminum chloride added with stirring. The thick mass was mixed with 140.3 g (2.0 mol) of 2-methyl-2-butene at 0–10° and stirred for 2 hr while warming to room temperature. The reaction mixture was poured into 2 l. of ice-water and the aqueous solution was made strongly basic with concentrated ammonium hydroxide. The resulting gelatinous yellow mass of aluminum salts was extracted several times with benzene, the combined extracts were concentrated, and the resulting dark red residue was distilled to afford 6.7 g (2.5%) of 2,6-dimethyl-4-ethylpyridine (4b): bp 180–183° (760 mm); methiodide mp 205° (lit.[15] mp 205°); nmr (neat) δ 6.75 (s, 2, ArH), 2.45 (q, 2, $CH_3CH_2$), 2.4 (s, 6, $CH_3$), and 1.1 (t, 3, $CH_3CH_2$).

**Registry No.**—1a, 108-47-4; 1b, 108-75-8; 4a, 536-88-9; 4b, 36917-36-9; 5a, 2150-18-7; 5b, 1124-35-2; 6a, 28973-18-4; 6b, 3044-78-8; 7a, 36917-41-6; 7b, 36917-42-7; 8a, 36917-43-8; 8b, 36917-44-9; 9, 36917-45-0; 10, 36917-46-1; 11a, 36917-47-2; 11b, 36917-48-3; 12a, 36917-49-4; 12b, 36917-50-7; 13, 36917-51-8; 14, 36917-52-9; 17, 36917-53-0; 18, 36917-54-1; 19, 36917-55-2; 20, 36917-56-3; 21, 36917-57-4; 23, 36917-58-5; 24, 36917-59-6; 25, 36917-60-9; 27, 36917-61-0; 29, 36917-62-1; 2,4-dimethylquinoline, 1198-37-4.

(14) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. React.*, **8**, 122 (1954).

(15) A. Eckert and S. Loria, *Monatsh. Chem.*, **38**, 226 (1917).

(16) Supplied by the Foote Mineral Co., Exton, Pa.

(17) A. T. Balaban and C. D. Nenitzescu, *Justus Liebigs Ann. Chem.*, **625**, 74 (1959).

# Palladium-Catalyzed Syntheses of Aromatic Coupling Compounds

HIROSHI IATAAKI* AND HATAAKI YOSHIMOTO

*Ube Industries, Ltd., Polymer Research Laboratory, 8-2 Minamikaigan, Goi, Ichiharashi, 290, Japan*

The oxidative coupling of aromatic compounds is catalytic under oxygen pressure in the presence of palladium acetate. The addition of acetylacetone or EDTA to the system remarkably promoted the yield of coupling products, whereas acids, bases, lithium chloride, polar solvent, and certain metal ions inhibited the reaction. The steric and polar effects of substituents were also observed in the coupling reaction. The procedure described in this publication would provide a convenient method for preparation of biphenyltetracarboxylic acids from o-xylene, dimethyl phthalate, and naphthalene. The separation of the isomers was achieved by recrystallization.

Palladium on charcoal is generally known to be a highly effective catalyst for dehydrogenation of hydrocarbons, but not for the coupling reaction of aromatic compounds. The conversion of *o*-terphenyl to triphenylene[1] is one of the examples of a dehydrogenation reaction. In 1965, Helden and Verberg[2] reported the coupling of benzene in acetic acid in the presence of palladium chloride and sodium acetate. They also found that no reaction occurred without sodium acetate and the yield of biphenyl was low because palladium metal was precipitated during the reaction. In subsequent studies by Davidson and Triggs,[3] a profound effect of molecular oxygen upon the reactivity of palladium acetate was found, by which the acetoxylation was almost completely inhibited and biphenyl was mainly produced. They also stated a possibility of catalytic oxidative coupling under 50 atm pressure of oxygen since palladium was retained in the solution without cocatalyst ions. In our earlier work,[4] we found that the coupling reactions between aromatic compounds and olefins were catalyzed by oxygen with the pressure higher than 3 kg/cm². Also, we later observed[5] that aromatic coupling compounds were obtained in high yields in the absence of acetic acid by using palladium acetate as a catalyst.

In an extention of our research on the coupling reaction, the effect of oxygen pressure on the coupling of toluene was examined under various pressures of a gaseous mixture of nitrogen and oxygen (molar ratio of 1:1). Table I shows that the yields of bitolyl increase with increasing oxygen pressure. If the pressure is higher than 50 kg/cm², the yield does not remarkably increase. Therefore, further experiments were designated to be carried out under 50 kg/cm² of the gaseous mixture. Although oxygen can be used in the pure state, it is preferable, for prevention of explosions, to use a gaseous mixture of oxygen and an inert gas such as nitrogen or a rare gas. In addition, special care must be taken not to use excess cumene, anisole, tetralin, 1-butanol, or sulfuric acid. Otherwise, an explosion may occur during the reaction.

The effect of the additives on the coupling of dimethyl phthalate is shown in Table II. By adding

### TABLE I
#### EFFECT OF THE PRESSURE OF A GASEOUS MIXTURE OF N₂ AND O₂ (1:1) ON THE YIELD OF BITOLYL[a]

| Pressure,[b] kg/cm² | Yield of bitolyl, %[c] |
|---|---|
| 6 | 110 |
| 12.5 | 500 |
| 25 | 760 |
| 50 | 1800 |
| 75 | 1800 |

[a] Toluene (50 ml), Pd acetate (0.5 mmol), 120°, 4 hr. [b] Pressure filled at room temperature before reaction. [c] Based on Pd acetate used.

### TABLE II
#### EFFECT OF ACETYLACETONE OR EDTA ON THE COUPLING OF DIMETHYL PHTHALATE

| Dimethyl phthalate, mmol | 300[b] | | 100[c] | |
|---|---|---|---|---|
| Pd acetate, mmol | 3 | | 1 | |
| | In glass[d] | In stainless[e] | In glass[d] | In stainless[e] |
| Blank | 4600 | 1700 | 2100 | 1900 |
| Acac | 6900 | 8000 | 5000 | 5200 |
| EDTA[a] | | 4400 | | 2800 |
| Acac + EDTA | | 4400 | | |

[a] EDTA stands for ethylenediaminetetraacetic acid. [b] The autoclave of 1-l. capacity, acetylacetone (3 mmol), EDTA (3 mmol), 150°, 23 hr. [c] The autoclave of 300-ml capacity, acetylacetone (1 mmol), EDTA (1 mmol), 150°, 6 hr. [d] The reaction was carried out in a glass vessel. [e] The reaction was carried out without a glass vessel.

an equimolar amount of acetylacetone to palladium acetate, the yield of coupling products is greatly improved. In a stainless steel vessel where certain metal ions such as iron, nickel, and chromium ions may be contaminated in the reaction medium, the coupling reaction is remarkably suppressed. However, the yields of coupling products are increased by addition of ethylenediaminetetraacetic acid. This effect is probably due to the formation of inactive complexes between ethylenediaminetetraacetic acid and certain metal ions. We have also found that by the addition of hydrochloric acid, sulfuric acid, sodium acetate, triphenylphosphine, bipyridyl, pyridine, lithium chloride, cyclooctadiene, and certain metal ions to the reaction mixture, or using a polar solvent such as dimethylformamide or acetonitrile, the yield of coupling products was extremely small or none at all. Catalytic activity of palladium acetate decreased gradually during the reaction, since water is formed.

(1) P. G. Copeland, R. E. Dean, and D. McNeil, *J. Chem. Soc.*, 1687 (1960).

(2) R. van Helden and G. Verberg, *Recl. Trav. Chim. Pays-Bas*, **84**, 1263 (1965).
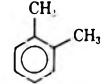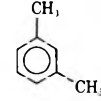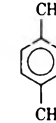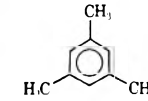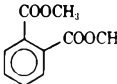
(3) J. M. Davidson and G. Triggs, *Chem. Ind. (London)*, 457 (1966); 1361 (1967); *J. Chem. Soc. A*, 1324, 1331 (1968).

(4) (a) Japanese Patent Application No. 92041 (1968). (b) Symposium of Homogeneous Catalytic Reactions Involving Palladium, American Chemical Society, Minneapolis, Minn., April 13-18, 1969, p 172.

(5) H. Itatani and Y. Yoshimoto, *Chem. Ind. (London)*, 674 (1971).

Table III

Coupling of Aromatic Compounds (50 ml) with
Palladium Acetate (0.5 mmol) and Acetylacetone (0.5 mmol) at 150° for 4 hr

| Compd | benzene | toluene (CH₃) | o-xylene (CH₃, CH₃) | m-xylene (CH₃, CH₃) | p-xylene (CH₃ / CH₃) | mesitylene (H₃C, CH₃, CH₃) | naphthalene |
|---|---|---|---|---|---|---|---|
| Yield,[a] % | 3100 | 7400 | 5700 | 4100 | 400 | 0 | 4500 |

| Compd | COOCH₃ | COOCH₃, COOCH₃ | CF₃ | Cl | F | OCOCH₃ | NO₂ |
|---|---|---|---|---|---|---|---|
| Yield,[a] % | 8500 | 5200 | 700 | 400 | 2300 | 5700 | 2500 |

[a] Mole per cent yield based on palladium acetate used, but the possible isomers were not separated for analysis.

Coupling of toluene gives bitolyl in 20,600% yield based on palladium acetate used, indicating reoxidation of reduced palladium. Bitolyls formed consisted of six isomers, the composition of which is reaction temperature dependent. From the composition of bitolyl formed, the relative reactivities of ortho to meta and para to meta can be calculated to be 0.27 and 0.70 in palladium-catalyzed coupling of toluene, and 0.07 and 0.61 in aluminum-catalyzed isomerization of 4,4'-dimethylbiphenyl. These facts indicate that both reactions are favored meta and para substitutions. The system of mercury acetate and palladium acetate[6] shows the relative reactivities of ortho to meta and para to meta as 0.29 and 3.04, indicating preferable para substitution.

Table III shows the yield of the coupling products of substituted benzenes. The coupling products of methyl-substituted benzenes decrease in the order toluene > o-xylene > m-xylene > p-xylene, probably owing to the steric effect of the methyl group. No coupling occurs in the case of mesitylene, which has two methyl groups ortho to a hydrogen on benzene nucleus. Halogenated benzenes give low yields of coupling products, since the presence of halogen causes precipitation of palladium black during the reaction. No coupling product could be obtained under the present reaction conditions from aromatic compounds containing amino, cyano, and acid anhydride groups. Phenyl acetate and methyl benzoate give high yields of coupling products with a small amount of by-products.

Coupling of o-xylene gives mainly 3,4,3',4'-tetramethylbiphenyl, while the coupling of dimethyl phthalate gives tetramethyl 2,3,3',4'- and 3,4,3',4'-biphenyltetracarboxylates. The coupling of naphthalene gives 43% of α,α'-, 50% of α,β'-, and 7% of β,β'-binaphthyls. There is a drastic change in the isomer distribution of the coupling products. o-Xylene is preferably converted to β isomers whereas naphthalene is converted to α isomers. This may be rationalized by assuming that the former is controlled mainly by steric requirements of the methyl group while the latter is influenced by a polar effect depending on self-polarizability at the α position of naphthalene.

For understanding the present results, we consider the reaction process. Helden and Verberg[2] first considered a coupling process via σ–π palladium complex. Later, Davidson and Triggs[3] proposed an intermolecular coupling through σ-phenyl palladium(II) complex which was reduced partially to palladium(I). On the basis of isomer distributions affected by substituents, an intramolecular coupling of σ-diaryl palladium-(II) complexes[6] has been postulated. In the present study, however, the reaction process is catalytic under oxygen pressure in the absence of acetic acid. Although discussion in detail concerning a reaction mechanism will be described in a subsequent publication, the overall reaction in the formal way can be expressed as follows.

$$2RH + Pd^{2+} \longrightarrow RPdR + 2H^+$$
$$RPdR \longrightarrow RR + Pd$$
$$RH + Pd + O_2 \longrightarrow RPdOOH$$
$$RPdOOH + RH \longrightarrow RPdR + HOOH$$
$$RPdR \longrightarrow RR + Pd$$
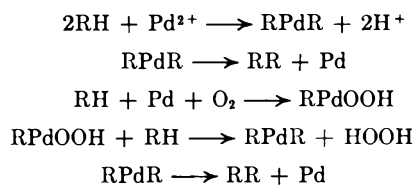
Palladium(0) complex formed can be reoxidized to σ-phenyl palladium(II) hydrogen peroxide by molecular oxygen under pressure, and thus the coupling reaction can be cycled. A similar mechanism[7] has been postulated in the cumene autoxidation catalyzed by oxygen-coordinated palladium complex. The formation of cresol and benzoic acid with bitolyl may be explained by the reactions of toluene and hydroxy radical which would be formed by the decomposition of hydrogen peroxide.

The palladium-catalyzed coupling is highly applicable to the organic syntheses of biphenyltetracarboxylic acid and its dianhydride, which have hitherto been prepared only by cumbersome multistep syntheses. In addition, a new compound, tetramethyl 2,3,3',4'-biphenyltetracarboxylate, was obtained in the coupling of dimethyl phthalate. Figure 1 shows the characteristic nmr spectrum, different from those of known isomeric tetramethyl biphenyltetracarboxylates. Attempts to separate the two isomeric esters were unsuccessful either by fractional distillation or recrystallization. After hydrolysis of the esters, how-

(6) M. O. Unger and R. A. Fouty, *J. Org. Chem.*, **34**, 18 (1969). The sum of the mole per cent of isomers at 90° is written to be 110.9. This raises the question.

(7) E. W. Stern, "Homogeneous Metal Catalyzed Oxidation of Organic Compounds, Transition Metals in Homogeneous Catalysis," Marcel Dekker, New York, N. Y., 1971, p 140.
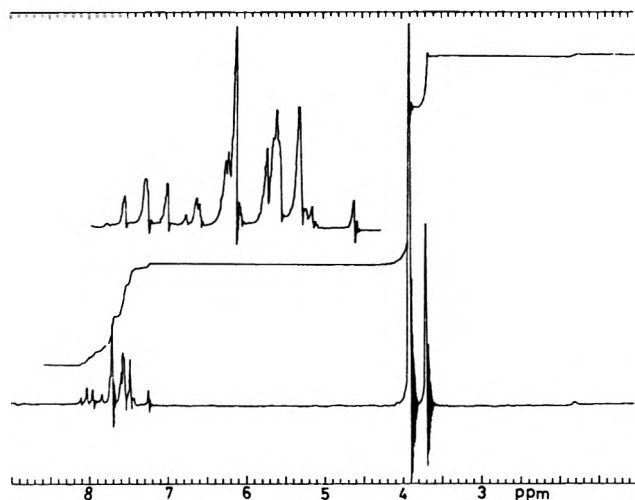
Figure 1.—Nmr of tetramethyl 2,3,3',4'-biphenyltetracarboxylate in CDCl$_3$.

ever, a mixture of 2,3,3',4'- and 3,4,3',4'-biphenyltetracarboxylic acids was able to be separated by recrystallization from water owing to marked differences in the solubility of the two acids. A mixture of acid dianhydrides was also separated by recrystallization from acetic anhydride or acetone.

Finally it is worth noticing that from the product distribution due to substituents, 3,4,3',4'-biphenyltetracarboxylic acid can be conveniently produced from o-xylene or dimethyl phthalate as starting material, while the 2,3,3',4'-isomeric acid can be produced from dimethyl phthalate or naphthalene, and the 2,3,2',3'-isomeric acid can be produced from naphthalene, respectively. Biphenyltetracarboxylic acid dianhydrides obtained from their tetracarboxylic acids have chemical properties similar to those of pyromellitic acid dianhydride, which has been applied in various commercial fields.

## Experimental Section[8]

1.—All chemicals were reagent grade and used without further purification. Benzene, toluene, and o-xylene were purified by distillation and dried over sodium ribbons. Palladium acetate was prepared according to the literature.[9]

The products separated were identified by elemental analysis, ir, nmr, and mass spectra. The coupling products listed in Table III were identified by a combination of gas chromatographic separation and analysis by mass spectrometry, but the possible isomers were not separated.

Unless otherwise indicated, all reactions were carried out in an autoclave which contained a glass vessel bored with a pin hole. A gaseous mixture of oxygen and nitrogen in the molar ratio of 1:1 was introduced into an autoclave until the inner pressure reached 50 kg/cm² at room temperature. The autoclave was shaken (35 times/min) and the temperature was elevated. After the reaction, the solution was analyzed by glc using both a 2-m stainless steel column packed with 5% Apiezon L on Diasolid and a 1-m column with 20% SE-30 using helium as carrier gas. For the determination of yields, the following internal standards were used: dibenzyl for the coupling of benzene, o-xylene, mesitylene, and chlorobenzene; stilbene for p-xylene and methyl benzoate; 3,5-diisopropyltoluene for trifluoromethylbenzene; pyrene or α,α'-binaphthyl for dimethyl phthalate; triphenylethylene for naphthalene.

2. Coupling of Toluene.—A mixture of palladium acetate (0.224 g, 1 mmol), acetylacetone (0.20 g, 2 mmol), and toluene (300 ml) was shaken at 160° for 5 hr under 65 kg/cm² of the gaseous mixture. The reaction mixture was concentrated on an oil bath at 130°, precipitates being separated from it. The filtrate was distilled at 105–125° (2 mm) to give 37.38 g of bitolyl (20,600% based on palladium acetate). The ratio of six bitolyl isomers was determined by glc (Apiezon, 170°) and the result showed as following: 2% of 2,2'-, 13% of 2,3'-, 10% of 2,4'-, 27% of 3,3'-, 35% of 3,4'-, and 13% of 4,4'-bitolyls. The products obtained were characterized by comparison of glc retention time with that of an authentic specimen.[10] The residue remaining in the flask was extracted with aqueous sodium hydrogen carbonate, giving sodium benzoate. Extraction of the residue with aqueous potassium hydroxide afforded the sodium salt of cresols, which structures were identified by comparison of their ir and glc retention times with those of authentic samples.

3. Separation of 4,4'-Dimethylbiphenyl.—To the mixture of bitolyls (50 g) was added a few milligrams of 4,4'-dimethylbiphenyl, and then the mixture was cooled in a Dry Ice–acetone bath with vigorous stirring. The mixture became viscous, and crystals precipitated out. On standing at the temperature of −12° overnight, crystals precipitated and were filtered quickly, giving 0.97 g (15%) of 4,4'-dimethylbiphenyl, mp 120–121°.

Anhydrous aluminum chloride (1.33 g, 10 mmol) and toluene (50 ml) were added to the filtrate. After heating and stirring at 120° for 10 hr, the reaction mixture was diluted with ice water (100 ml) and then extracted with toluene (3 × 50 ml). The toluene was distilled off from the extracts to give dimethylbiphenyls (38.2 g) which were then worked up with aluminum chloride as described in the above procedure; 2.2 g (40%) of 4,4'-dimethylbiphenyl was thus isolated.

4. Isomerization of Bitolyl with Aluminum Chloride.—Isomerization of 4,4'-dimethylbiphenyl (1 mmol) with aluminum chloride (0.1 mmol) in toluene (2 ml) was carried out at 120°. The isomer distribution of bitolyls approached a constant after 3 hr. Similarly, bitolyls (10 mmol) obtained by palladium catalysis (expt 2) were isomerized with aluminum chloride, resulting in the same distribution as that obtained from 4,4'-dimethylbiphenyl. Bitolyls in equilibrium consist of 1% of 2,2'-, 2% of 2,3'-, 4% of 2,4'-, 36% of 3,3'-, 39% of 3,4'-, and 14% of 4,4'-dimethylbiphenyls. The remains contain phenyltolylmethane and a slight amount of dibenzyl.

5. Coupling of o-Xylene.—In a 1-l. capacity autoclave, o-xylene (300 ml) and palladium acetate (0.672 g, 3 mmol) were shaken at 150° for 5 hr under 65 kg/cm² of the gaseous mixture. After the mixture had cooled to room temperature, the autoclave was degassed and refilled with 50 kg/cm² of hydrogen, then allowed to stand overnight. Palladium black (0.31 g, 97%) precipitated and was filtered off, washed with water, and dried. o-Xylene was removed by distillation from the filtrate and subsequently the fraction boiling between 148 and 167° (4 mm) was collected. The yield of bixylyl is 32.8 g (5200% based on Pd acetate). Glc (20% SE, 180°) analysis showed the isomer distribution of 1% of 2,3,2',3'-, 24% of 2,3,3',4'- and 75% of 3,4,3',4'-tetramethylbiphenyls. The distillation residue was black tarry solid (33.1 g) which was dissolved in acetone and precipitated by addition of methanol. High-resolution mass spectrometry[11] showed that the residues contained coupling dimers, trimers, and tetramers of o-xylene, 2-methylbenzaldehyde, 2-methylbenzoic acid, and also their coupling products. The distilled bixylyl (32.8 g) was recrystallized from methanol (80 ml) to give 13.5 g of pure 3,4,3',4'-tetramethylbiphenyl whose ir, nmr, and mass spectra were identical with those of an

(8) Melting points measured were uncorrected. Infrared spectra were recorded using a Hitachi EP 1-G2 spectrophotometer. A JNM-C-60 HL was used for nmr measurement with tetramethylsilane as internal standard. Mass spectra were obtained by a Hitachi RMU-6 and gas chromatographic analyses were performed by a Shimazu GC 4-APT gas chromatograph.

(9) T. A. Stephenson, S. M. Morehouse, A. R. Powell, J. P. Heffer, and G. Wilkinson, *J. Chem. Soc.*, 3636 (1965).

(10) 3,3'-Dimethylbiphenyl boiling at 125–129° (3 mm) was prepared from o-tolidine according to the literature ("Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 295). 2,2'-Dimethylbiphenyl boiling at 110–114° (3 mm) was synthesized by the procedure reported [M. S. Kharasch and E. K. Fields, *J. Amer. Chem. Soc.*, 63, 2319 (1941)] using 2-bromotoluene as starting material. By the same manner, 4-bromotoluene was converted to 4,4'-dimethylbiphenyl, mp 121–122° (recrystallized from ethanol). The coupling reaction between 3-methylcyclohexanone and 4-methylphenylmagnesium bromide was carried out by the modified procedure [M. Orchin, *J. Amer. Chem. Soc.*, 68, 571 (1946)], followed by dehydrogenation with sulfur to give 3,4'-dimethylbiphenyl boiling at 134–136° (6 mm). By the same procedure, 2,3'- [bp 104–106° (4 mm)] and 2,4'-dimethylbiphenyl [bp 101–103° (3 mm)] were prepared from the reactions of 2-methylphenylmagnesium bromide with 3- and 4-methylcyclohexanones, respectively.

(11) A JEOL, JM S-01SG-2 mass spectrometer was employed.

authentic sample. The mixture melting point with an authentic sample showed no depression.

**6. Coupling of Dimethyl Phthalate to Tetramethyl Biphenyltetracarboxylate (TMBT).**—Dimethyl phthalate (2.5 1., 3 kg), palladium acetate (3.36 g, 0.015 mol), and acetylacetone (1.50 g, 0.015 mol) were placed into an electromagnetically agitating typed stainless autoclave (5-l. capacity) equipped with a sampling tube. The autoclave under 50 kg/cm² pressure of the gaseous mixture was stirred (500 rpm) and heated in an oil bath at 130–134° for 1 hr, 130–150° for 1 hr, and then at the constant temperature of 150° for 12 hr. The temperature of the oil bath should be carefully elevated since the reaction was exothermic. During the reaction, the reaction mixture (200 g) was withdrawn periodically for glc (20% SE, 260°). After reaction, the autoclave was cooled to room temperature, degassed, and refilled to 50 kg/cm² of hydrogen and then allowed to stand overnight. Palladium black (1.55 g, 97%) precipitated and was removed by filtration and washed with water. The combined filtrates were concentrated on an oil bath (below 200°) under reduced pressure (3 mm) to remove a mixture of water and low-boiling products (37 g) and also dimethyl phthalate (2140 g). The residue (I, 594 g) was recrystallized from 1 l. of methanol to give 120 g of white crystals (II). From the mother liquor, white crystals (III, 10 g) were collected. Distillation of methanol gave the residue, which was distilled on a salt bath under reduced pressure. The fraction (IV, 306 g) boiling at 200–280° (1 mm) and tarry residue (105 g) were collected. The total yield of crude tetramethyl biphenyltetracarboxylate (II + III + IV) was 436 g (72.50% based on Pd acetate). Fraction IV was treated with charcoal in methanol (200 ml). The charcoal was filtered off and washed with hot methanol (100 ml). On cooling the combined solution, crystals (V, 219 g) were collected.

The fractional distillation of 140 g of the product V afforded the following fractions: 1st fraction, bp 184–242° (1 mm), 77.6 g; 2nd fraction, bp 242–252° (1 mm), 27.0 g; 3rd fraction, bp 253–260° (1 mm), 25.2 g; the residue, 11.7 g. Each fraction was recrystallized from 100, 30, 40, and 30 ml of methanol, respectively, to give white crystals of VI (66.4 g), VII (23.6 g), VIII (20.7 g), and IX (2.0 g). Glc analysis of the marked compounds shows the compositions of 2,3,2′,3′-, 2,3,3′,4′-, and 3,4,3′,4′-TMBT as 3, 57, 40 for I; 0, 97, 3 for II; 1, 46, 53 for V; 0, 60, 40 for VI; 0, 38, 62 for VII; 0, 5, 95 for VIII; and 0, 11, 89 for IX, respectively.

**7. Identification of TMBT. A.**—The crystals II were treated with charcoal and recrystallized from methanol to give 2,3,3′,4′-TMBT: mp 109–111°; nmr (CDCl₃) δ 3.70 (s, 3, 2-COOCH₃), 3.91 (s, 9, 3,3′,4′-COOCH₃), 7.50–7.55 (m, 3, 5,6,6′-H), 7.72 (s, 1, 2′-H), 7.75–7.85 (d, 1, 5′-H), 7.96–8.12 (t, 1, 4-H); ir (KBr) 3000 (w), 2950 (w), 1720 (s), 1420 (s), 1280 (s), 1200 (m), 1160 (m), 1120 (m), 1080 (w), 1060 (m), 960 (m), 920 (w), 860 (w), 820 (m), 795 (w), 780 (m), 760 (w), 750 (m), 700 (m), 680 cm⁻¹ (w).

*Anal.* Calcd for C₂₀H₁₈O₈: C, 62.17; H, 4.70. Found: C, 62.29; H, 4.87.

**B.**—The compound VIII was recrystallized from methanol to give 3,4,3′,4′-TMBT: mp 105–106° (lit.[12] mp 99–100°); nmr (CDCl₃) δ 3.93 (s, 12, 3,4,3′,4′-COOCH₃), 7.84 (s, 2, 2,2′-H), 7.88 (d, 2, J = 6 Hz, 6,6′-H), 7.90 (d, 2, J = 6 Hz, 5,5′-H); ir (KBr) 2950 (m), 1720 (s), 1600 (m), 1430 (s), 1280 (s), 1190 (m), 1160 (m), 1120 (m), 1080 (m), 1040 (w), 950 (m), 890 (w), 840 (m), 820 (m), 780 (m), 760 (m), 700 cm⁻¹ (w).

*Anal.* Calcd for C₂₀H₁₈O₈: C, 62.17; H, 4.70. Found: C, 62.20; H, 4.80.

**C. Preparation of 2,3,2′,3′-TMBT.**[13]—This compound showed

(12) Beilstein's Handbuch der Organischen Chemie," Vol. 9, 438 (1942).

(13) 3-Nitrophthalic acid was esterified with methanol and sulfuric acid, followed by hydrogenation with Raney Ni to dimethyl 3-aminophthalate, which was coupled by a modification of the reported procedure ("Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 222) to give 2,3,2′,3′-TMBT, mp 163–164° [167°, Beilstein's "Handbuch der Organischen Chemie," Vol. 9, 437 (1942)].

nmr (CDCl₃) δ 3.60 (s, 6, 2,2′-COOCH₃), 3.91 (s, 6, 3,3′-COOCH₃), 7.35–7.54 (d, 4, 5,5′, 6,6′-H), 7.93–8.10 (t, 2, 4,4′-H).

*Anal.* Calcd for C₂₀H₁₈O₈: C, 62.17; H, 4.70. Found: C, 62.41; H, 4.62.

**8. Preparation of Biphenyltetracarboxylic Acid Dianhydride (BTDA). A.**—The crystals V (10 g), water (25 ml), acetic acid (25 ml), and sulfuric acid (5 ml) were refluxed for 6 hr. On cooling, the crystals formed were filtered, washed with water, and dried, giving 4.4 g (51.4%) of 3,4,3′,4′-biphenyltetracarboxylic acid, mp 295–302,° which was then esterified with methanol and sulfuric acid to tetramethyl ester. Glc analysis of the ester showed a single peak.

Concentration of the filtrate gave crystals, which were collected and recrystallized from hot water to afford 3.7 g (43.3%) of 2,3,3′,4′-biphenyltetracarboxylic acid, mp 193–204°. After esterification with methanol and sulfuric acid, the ester showed a single peak in glc analysis.

**B.**—2,3,3′,4′-TMBT (65 g), sulfuric acid (30 ml), acetic acid (160 ml), and water (160 ml) were refluxed for 5 hr. On concentrating the reaction mixture afforded 49.2 g (88.5%) of the crude 2,3,3′,4′-biphenyltetracarboxylic acid. Recrystallization of the crude acid from water gave 2,3,3′,4′-biphenyltetracarboxylic acid (31.7 g), mp 193–204°. This acid was then refluxed with acetic anhydride (400 ml) for 3 hr. On cooling, 83 g (80%) of 2,3,3′,4′-BTDA was isolated: mp 195–205°; ir (KBr) 1840 (s, –COOCO–), 1770 cm⁻¹ (s, –COOCO–).

*Anal.* Calcd for C₁₆H₆O₆: C, 65.31; H, 2.07. Found: C, 65.08; H, 2.07.

**C.**—A solution of 3,4,3′,4′-TMBT (18.6 g), concentrated hydrochloric acid (10 ml), and acetic acid (50 ml) in water (50 ml) was refluxed for 4 hr. On cooling with ice water, the crystals precipitated were filtered, washed with water, and dried to give 14.3 g (93%) of 3,4,3′,4′-biphenyltetracarboxylic acid, mp 295–305°. This acid (75 g) was then refluxed with acetic anhydride (250 ml) for 5 hr. On cooling, crystals precipitated and were filtered and dried to afford 52 g (78%) of BTDA: mp 295–308°; ir (KBr) 1820 (sh, –COOCO–), 1760 cm⁻¹ (s, –COOCO–).

*Anal.* Calcd for C₁₆H₆O₆: C, 65.31; H, 2.07. Found: C, 65.45; H, 2.00.

# Selective Hydrogenation of 1,5,9-Cyclododecatriene to Cyclododecene Catalyzed by Ruthenium Complexes

DARRYL R. FAHEY

*Phillips Petroleum Company, Research and Development Department, Bartlesville, Oklahoma 74004*

Ruthenium complexes have been found to catalyze the selective homogeneous hydrogenation of 1,5,9-cyclododecatriene (CDT) to cyclododecene (CDE). The most useful complex, $(Ph_3P)_2(CO)_2RuCl_2$, when employed in the presence of a suitable Lewis base between 125 and 160° at 100–200 psig of hydrogen, affords yields of CDE as high as 98.5% along with 1.0% cyclododecadiene (CDD) and 0.5% cyclododecane (CDA). Upon repeated recyclization of the catalyst, after solvent and products were removed from reaction mixtures by distillation under diminished pressure, an equivalent of 32,100 mol of CDT was selectively hydrogenated per gram-atom of ruthenium metal without any apparent diminuation in catalyst activity. The ruthenium catalyst could be conveniently formed directly from $RuCl_3$, $PPh_3$, and CO under the CDT hydrogenation conditions, thereby obviating its prior synthesis. Rate measurements indicate that the hydrogenation is first order in olefin and catalyst. In the presence of $PPh_3$, the rate of CDE hydrogenation is considerably slowed, whereas the rates of CDT and CDD hydrogenations are not so greatly affected. The rates of *cis*-CDE to *trans*-CDE double bond isomerization and its reverse are $10^{2.8}$ and $10^{2.5}$ times faster, respectively, than the rate of CDE hydrogenation in the presence of $PPh_3$. These results are interpreted in terms of an increased steric crowding in a cyclododecylruthenium intermediate, in the presence of $PPh_3$, favoring metal–hydride elimination over hydrogenolysis.

Catalysts capable of effecting the selective hydrogenation of 1,5,9-cyclododecatriene (CDT) to cyclododecene (CDE) are of considerable practical importance. The CDE finds use as an intermediate to the polyamide monomers 1,12-dodecanedioic acid, 1,12-diaminododecane, and 12-aminododecanoic acid lactam. A high selectivity of CDT hydrogenation is especially desirable since CDE, CDT, cyclododecadiene (CDD), and cyclododecane (CDA) cannot be effectively separated by distillation owing to the close proximity of their boiling points. Any CDT and CDD present as impurities in the product mixture must be removed at later processing stages to prevent contamination in the end product.

In view of the high selectivities which may be achieved in homogeneous catalytic hydrogenations,[1] soluble coordination complexes are obvious choices as catalysts for the desired reaction. A soluble tertiary phosphine cobalt carbonyl catalyst has been found to accomplish the highly selective hydrogenation of CDT affording 98.7% CDE along with 1.3% CDA.[2] However, increasing the ratio of CDT to catalyst over that reported results in decreased selectivity and catalyst decomposition.[3] Subsequent to the completion of the work described herein, additional catalysts based on nickel[4a] and iridium[4b] were disclosed which also are effective for the selective hydrogenation of CDT.

In this paper, the use of ruthenium coordination complexes as catalysts for the selective hydrogenation of CDT is presented, and the catalytic behavior of the complex $(Ph_3P)_2(CO)_2RuCl_2$ under varying reaction conditions is described in detail. In the following discussion, selectivity is defined as [CDE]/([CDE] + [CDA]) and is determined at the point where CDE reaches its maximum concentration during a hydrogenation reaction. At higher conversions, the selectivity

will be less since the CDE concentration is lower while the CDA concentration is higher. Lower conversions may show higher selectivities, but these are of little practical value.

## Results

**Ruthenium Complexes as Catalysts.**—Ruthenium complexes possessing triphenylphosphine, diethyl sulfide, carbon monoxide, methanol, pyridine (Py), 1,2-bis(diphenylphosphino)ethane (diphos), chloride, and hydride ligands were prepared by published methods. Their catalytic activities were examined by gradually increasing the temperature of their solutions with CDT under ~200 psig of hydrogen until gas absorption began. The temperature was further increased 10° and then held constant until gas absorption ceased. For several complexes, the hydrogenation activity was vastly improved when $NaBH_4$ was employed as a cocatalyst. All complexes surveyed were active hydrogenation catalysts under appropriate conditions, and those affording the most selective catalysts are arranged at the top under each solvent in Table I. Two distinct types of behavior were observed regarding the selectivities of the catalysts. The catalysts derived from the formally zero-valent complexes $(Ph_3P)_2(CO)_3Ru$ and $[(CO)_4Ru]_3$ were more active and generally more selective in benzene solutions (expt 1 and 2), while the higher-valent ruthenium complexes gave more selective catalysts in *N,N*-dimethylformamide (DMF) solutions (expt 4–7 and 9–14). The results obtained with a representative example from each class of complexes, *i.e.*, $(Ph_3P)_2(CO)_3Ru$ and $(Ph_3P)_3RuCl_2$, are given in both solvent categories for comparison. Most of the complexes gave catalysts which decomposed under the reaction conditions. Of those that did not decompose, $(Ph_3P)_2(CO)_2RuCl_2$ was selected for more detailed study, and the latter portion of the report is devoted to a description of its characteristics. The catalyst derived from $(Ph_3P)_3$-$RuCl_2$ is presumably the $(Ph_3P)_3RuHCl$ hydrogenation catalyst previously described by Hallman, *et al.*[5] When

(1) J. E. Lyons, L. E. Rennick, and J. L. Burmeister, *Ind. Eng. Chem. Prod. Res. Develop.*, **9**, 2 (1970).

(2) I. Ogata and A. Misono, *Discuss. Faraday Soc.*, **No. 46**, 72 (1968); A. Misono and I. Ogata, *Bull. Chem. Soc. Jap.*, **40**, 2718 (1967).

(3) (a) M. Morita, Y. Iwai, J. Itakura, and H. Ito, U. S. Patent 3,567,790 (1971); (b) D. R. Fahey, unpublished studies (1968).

(4) (a) L. W. Gosser, U. S. Patent 3,499,050 (1970); M. T. Musser, U. S. Patent 3,631,210 (1971); (b) L. W. Gosser, U. S. Patent 3,513,210 (1970).

(5) P. S. Hallman, B. R. McGarvey, and G. Wilkinson, *J. Chem. Soc. A*, 3143 (1968).

TABLE I

HYDROGENATION OF CDT CATALYZED BY RUTHENIUM COMPLEXES[a]

| Expt | Ru complex | Temp, °C | Reaction time, hr | Dec[b] | Yield, % CDA | CDE | CDD | CDT |
|------|-----------|---------|-----------|------|-----|-----|-----|-----|
| | | | In Benzene Solution | | | | | |
| 1 | $(Ph_3P)_2(CO)_3Ru$ | 158 | 1.2 | p | 2.7 | 94.6 | 2.3 | 0.4 |
| 2 | $[(CO)_4Ru]_3$ | 158 | 1.2 | p | 11.2 | 85.0 | 2.9 | 0.9 |
| 3 | $(Ph_3P)_3RuCl_2$ | 85 | 4.0 | | 42.3 | 29.6 | 15.6 | 12.4 |
| | | | In N,N-Dimethylformamide Solution | | | | | |
| 4 | $(Et_2S)_3RuCl_3$ | 135 | 3.5 | p | 2.8 | 92.6 | 3.2 | 1.4 |
| 5 | $(Ph_3P)_2(CO)_2RuCl_2$ | 140 | 4.0 | | 13.3 | 84.7 | 1.8 | 0.3 |
| 6 | $(Ph_3P)_2(CH_3OH)RuCl_3$ | 140 | 4.5 | p | 14.3 | 80.4 | 4.2 | 1.1 |
| 7 | $(Ph_3P)_3(CO)RuH_2$ | 140 | 5.0 | c | 5.3 | 74.8 | 13.2 | 6.7 |
| 8 | $(Ph_3P)_2(CO)_3Ru$ | 140 | 4.0 | c | 1.3 | 51.0 | 27.4 | 20.3 |
| 9 | $[(CO)_2RuCl_2]_n$ | 145 | 3.3 | c | 0.2 | 22.8 | 38.4 | 38.6 |
| 10 | $(Py)_4RuCl_2$ | 145 | 3.0 | c | 2.3 | 36.0 | 30.2 | 31.5 |
| 11 | $(Py)_4RuCl_2-NaBH_4{}^c$ | 110 | 1.8 | p | 36.0 | 59.8 | 2.4 | 1.7 |
| 12 | $(Py)_2(CO)_2RuCl_2-NaBH_4{}^d$ | 125 | 2.2 | p | 21.8 | 47.2 | 15.5 | 15.5 |
| 13 | $(Diphos)_2RuCl_2-NaBH_4{}^d$ | 105 | 2.1 | c | 8.6 | 29.0 | 22.5 | 39.9 |
| 14 | $(Ph_3P)_3RuCl_2$ | 125 | 5.0 | | 31.4 | 51.1 | 8.4 | 9.1 |

[a] Solutions were composed of 0.10 g of complex, 2.0 g (1.2 mmol) of CDT, and 20 ml of solvent. [b] p denotes partial catalyst decomposition during reaction and c denotes complete catalyst decomposition. [c] 0.10 g of NaBH₄. [d] 0.050 g of NaBH₄.

complexes decomposed, they formed black particles and a ruthenium mirror on the wall of the vessel. The ruthenium metal in this form was inactive as a hydrogenation catalyst.

**Preparation and Structure of $(Ph_3P)_2(CO)_2RuCl_2$.**— The $(Ph_3P)_2(CO)_2RuCl_2$, mp 309–312° dec, was synthesized by treating a solution of $[(CO)_2RuCl_2]_n$, prepared by bubbling CO through a refluxing ethanolic solution of $RuCl_3$, with $PPh_3$ according to the method of Stephenson and Wilkinson.[6] Alternately, the catalyst was more conveniently formed directly from $RuCl_3$ in a CDT hydrogenation reaction. For example, when $RuCl_3$, $PPh_3$, CDT, 4 psig of CO, and ethanol were stirred at 140° under hydrogen, the hydrogenation reaction proceeded in the usual manner, and a 98.0% yield of CDE was obtained along with 2.0% CDA. When the solution was cooled to 25°, colorless crystals precipitated which possessed an ir spectrum and C, H, Cl analyses identical with those of $(Ph_3P)_2(CO)_2RuCl_2$. The crystals were obtained in an essentially quantitative yield based on $RuCl_3$. The amount of CO employed is important. If too little is used, the conversion into the dicarbonyl complex is not complete, and with too much, the hydrogenation may cease before complete conversion of the polyenes. This presents no problem when the reaction vessel is pressured with greater than 4 psig of CO, and, after heating the mixture to the reaction temperature, the excess CO is vented. Repressuring the system with hydrogen allows the reaction to proceed normally. This technique has afforded CDT product yields of 1.0% CDA, 98.8% CDE, and 0.2% CDD. The $(Ph_3P)_2(CO)_2RuCl_2$ recovered from these reactions is recyclable.

Most syntheses[6-12] of $(Ph_3P)_2(CO)_2RuCl_2$ produce a white solid having two C≡O stretching vibrations,

one between 2065 and 2050 cm⁻¹ and the other between 2001 and 1990 cm⁻¹. Configurations **1a**[6-11] and either **1b** or **1c**[13] have been assigned to the complex.
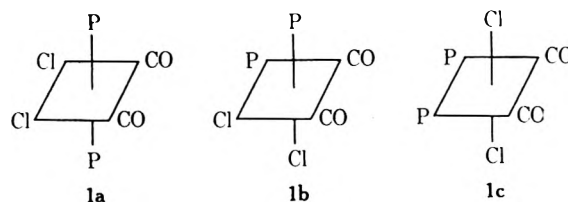


A comparison of the ir spectrum of our $(Ph_3P)_2(CO)_2RuCl_2$ complex with that of cis-$Cl_2$-trans-$(MePh_2P)_2$-cis-$(CO)_2Ru$ (see Experimental Section) very strongly suggests that both have the same configuration, namely **1a**.[13a]

**Effect of Solvent.**—The selectivity of the hydrogenation of CDT catalyzed by $(Ph_3P)_2(CO)_2RuCl_2$ is dependent on the nature of the solvent as shown in Table II. In most solvents, the rates of reaction were about the same with the exceptions being dimethyl sulfoxide and sulfolane. The stability of the catalyst seemed to correlate with its selectivity in the solvents listed. In expt 15–19 where the catalyst selectivity was highest, each homogeneous pale yellow solution retained its physical appearance throughout the course of the reaction. However, in expt 20–23 where the catalyst was less selective, each solution acquired an orange coloration which became more pronounced as the reaction progressed. The ruthenium catalyst apparently undergoes a change in these latter solvents.

(6) T. A. Stephenson and G. Wilkinson, *J. Inorg. Nucl. Chem.*, **28**, 945 (1966).

(7) J. P. Collman and W. R. Roper, *J. Amer. Chem. Soc.*, **87**, 4008 (1965).

(8) M. I. Bruce and F. G. A. Stone, *J. Chem. Soc. A*, 1238 (1967).

(9) J. D. Cotton, M. I. Bruce, and F. G. A. Stone, *ibid.*, 2162 (1968).

(10) W. Hieber and P. John, *Chem. Ber.*, **103**, 2161 (1970); P. John, *ibid.*, **103**, 2196 (1970).

(11) S. Cenini, A. Fusi, and G. Capparella, *J. Inorg. Nucl. Chem.*, **33**, 3579 (1971).

(12) N. Ahmad, S. D. Robinson, and M. F. Uttley, *J. Chem. Soc. Dalton Trans.*, 843 (1972).

(13) B. R. James and L. D. Markham, *Inorg. Nucl. Chem. Lett.*, **7**, 373 (1971).

(13a) NOTE ADDED IN PROOF.—Configuration **1a** has now been confirmed for $(Ph_3P)_2(CO)_2RuCl_2$ by examination of its proton-decoupled ¹³C nmr spectrum. The substituted, ortho, and meta carbon resonances of the phenyl groups are apparent 1:2:1 triplets with $(J_{CL} + J_{CP'})$ of 47.6, 9.8, and 9.2 Hz, respectively, indicative that the PPh₃ groups are mutually trans [see B. E. Mann, B. L. Shaw, and R. E. Stainbank, *J. Chem. Soc., Chem. Commun.*, 151 (1972)]. I thank Dr. J. C. Randall for recording this spectrum.

## TABLE II
### EFFECT OF SOLVENT ON THE HYDROGENATION OF CDT CATALYZED BY $(Ph_3P)_2(CO)_2RuCl_2$[a]

| Expt | Solvent | Reaction time, hr | Yield, % | | | |
|---|---|---|---|---|---|---|
| | | | CDA | CDE | CDD | CDT |
| 15 | Dimethyl sulfoxide[b] | 29 | 1.0 | 97.8 | 0.9 | 0.5 |
| 16 | N-Methylpyrrolidone | 2.5 | 1.0 | 94.6 | 3.2 | 1.2 |
| 17 | Sulfolane | 7 | 0.1 | 27.1 | 28.2 | 44.7 |
| 18 | N,N-Dimethylformamide | 3 | 9.0 | 85.6 | 3.7 | 1.7 |
| 19 | N,N-Dimethylacetamide | 3 | 16.2 | 75.7 | 5.4 | 2.7 |
| 20 | Tetrahydrofuran | 2.5 | 11.3 | 55.1 | 16.5 | 17.0 |
| 21 | Ethyl acetate | 2 | 34.2 | 48.4 | 9.3 | 8.1 |
| 22 | 1-Butanol | 2 | 39.0 | 47.1 | 8.6 | 5.3 |
| 23 | Benzene | 2 | 24.1 | 45.2 | 12.3 | 18.4 |
| 24 | Acetonitrile | 3 | 0 | 0.1 | 3.9 | 96.0 |

[a] Solutions were composed of 0.10 g (0.13 mmol) $(Ph_3P)_2(CO)_2RuCl_2$, 2.0 g (1.2 mmol) of CDT, and 30 ml of solvent. The reaction temperatures were 140–160°. [b] *Caution.* In two of four reactions, a vigorous decomposition of the reaction solution occurred causing the reaction vessel to burst.

Acetonitrile as solvent severely inhibited the activity of the catalyst.

**Effect of Added Lewis Bases.** —The selectivity of the hydrogenation is also influenced by the presence of certain Lewis bases which may coordinate to ruthenium as a ligand. This dependence for several common ligands is given in Table III. The greatest selectivity

### TABLE III
### EFFECT OF ADDED LEWIS BASES ON THE HYDROGENATION OF CDT CATALYZED BY $(Ph_3P)_2(CO)_2RuCl_2$[a]

| Expt | Lewis base | Concentration, M | Yield, % | | | |
|---|---|---|---|---|---|---|
| | | | CDA | CDE | CDD | CDT |
| 23 | None | | 24.1 | 45.2 | 12.3 | 18.4 |
| 25 | PPh₃ | 0.017 | 10.5 | 88.9 | 0 | 0.6 |
| 26 | PPh₃ | 0.034 | 4.4 | 95.6 | 0 | 0 |
| 27 | PPh₃ | 0.068 | 1.9 | 98.1 | 0 | 0 |
| 28 | PPh₃ | 0.13 | 0.6 | 97.8 | 1.5 | 0.5 |
| 29[b] | CO | 0.007 | 30.0 | 66.9 | 3.1 | 0 |
| 30 | CO | <6 psig | 0.1 | 45.7 | 30.2 | 24.0 |
| 31 | HNEt₂ | 0.050 | 36.1 | 63.0 | 0.7 | 0.2 |
| 32 | AsPh₃ | 0.015 | 26.6 | 53.7 | 9.7 | 10.0 |
| 33 | PBu₃ | 0.01 | 29.8 | 51.6 | 9.5 | 7.9 |
| 34 | OPPh₃ | 0.016 | 97.4 | 2.5 | 0 | 0.1 |
| 35 | OP(octyl)₃ | 0.01 | 96.7 | 3.3 | 0 | 0 |

[a] Solutions (except expt 29) were 0.006 M (0.10 g, 0.13 mmol) $(Ph_3P)_2(CO)_2RuCl_2$ and 0.55 M (1.8 g, 1.1 mmol) CDT in 20 ml of benzene. [b] 0.007 M in $(Ph_3P)_2(CO)_2RuCl_2$ prepared by the treatment of a 0.007 M $(Ph_3P)_2(CO)_3Ru$ solution with HCl.

was obtained with PPh₃. The yield of CDE increased with increasing PPh₃ concentration to a maximum of about 98%. Other experiments have shown the selectivity to be dependent on the *relative* concentrations of CDT and PPh₃. The introduction of small amounts of gaseous CO in precise quantities proved to be difficult, and, in expt 30, the actual concentration of CO is unknown. Although this quantity of CO did enhance the selectivity of the hydrogenation, perceptible hydrogen absorption ceased before completion of the hydrogenation. Treatment of $(Ph_3P)_2(CO)_3Ru$ with HCl evolves 1 equiv of CO along with $(Ph_3P)_2(CO)_2RuCl_2$.[7] Utilizing this reaction in expt 29, an improved selectivity over expt 23 was obtained, but it is not high as that obtained in reactions with added PPh₃. Added AsPh₃, PBu₃, and HNEt₂ were less effective than PPh₃, and the phosphine oxides had no effect on the selectivity. Other PR₃ compounds with at least one R more electronegative than carbon and

chelating ligands destroyed the activity of the catalyst. No hydrogenation was observed with P(OPh)₃, P(OEt)₃, P(OMe)Ph₂, P(morpholino)₃, 1,2-bis(diphenylphosphino)ethane, 1,2-bis(diphenylarsino)ethane, or pyridine.

**Effect of Reducing Agents.** —Since a ruthenium hydride or a reduced ruthenium complex is likely the actual catalytic species, the use of reducing agents as cocatalysts were investigated. The effect of several reducing agents upon the hydrogenation of CDT catalyzed by $(Ph_3P)_2(CO)_3RuCl_2$ is shown in Table IV. The only reducing agents which did not impair catalyst activity were SnCl₂ and N₂H₄. None allowed the reaction to occur at a lower temperature. The slightly shorter reaction times of expt 36 and 37 compared to expt 18 most likely result from an increased reaction temperature. Any beneficial effect these reagents may have had on the reaction is not obvious.

**Effect of Hydrogen Pressure.** —The hydrogenation was studied at pressures up to 600 psig, although high pressures are not necessary. If the hydrogen absorbed is not replenished during reactions, the pressure will drop to 0 psig, indicating that the reaction occurs even at very low pressures. The selectivity of the reaction is also dependent on the hydrogen pressure. In comparable reactions in benzene solution containing 0.036 M PPh₃, carried out at 100 and 200 psig hydrogen pressures, the maximum yields of CDE were 98.5 and 91.0%, respectively.

**Effect of Temperature.** —The temperature range 135–160° has been found to be most suitable for the reaction. Below 135°, the reaction occurs only very slowly or not at all. In fact, lowering the temperature of an initiated reaction to below 125° results in a cessation of hydrogen absorption. The hydrogenation may be resumed by increasing the temperature above 125–135°. As the temperature is increased above 135°, the rate of hydrogenation becomes very rapid and the selectivity is also enhanced. At 170°, a hydrogenation equivalent to expt 5 afforded a maximum yield of CDE of 91.6%. Above 160°, a side reaction occurs which affords undesirable by-products. At 170°, a 5.6 glpc area % yield of these by-products was obtained. The influence of temperature on this side reaction has been previously described elsewhere.[14] The hydrogenation reaction is exothermic, and the reaction tempera-

(14) C. G. McAlister, U. S. Patent 3,400,164 (1968); R. Levine, U. S. Patent 3,400,165 (1968); C. G. McAlister, U. S. Patent 3,400,166 (1968).

TABLE IV

EFFECT OF REDUCING AGENTS ON THE HYDROGENATION OF CDT CATALYZED BY $(Ph_3P)_2(CO)_2RuCl_2$[a]

| Expt | Reducing agent | Concn, M | Solvent | Reaction temp, °C | Reaction time, hr | Added PPh₃ | Yields, % CDA | CDE | CDD | CDT |
|------|---------------|----------|---------|-------------------|-------------------|-----------|-----|-----|-----|-----|
| 36 | SnCl₂ | 0.02 | DMF | 148 | 2 | No | 3.2 | 95.1 | 1.4 | 0.3 |
| 37 | N₂H₄ | 0.02 | EtOH | 145 | 2 | Yes | 0 | 98.1 | 1.6 | 0.3 |
| 38 | Electrochemical reduction[b] | | CH₃OCH₂CH₂OCH₃ | 140 | ~3 | No | 0 | 0.4 | 10.9 | 88.7 |
| 39 | AlEt₃[c] | 0.03 | Benzene | 140 | 1.5 | Yes | 0 | 18.2 | 35.5 | 46.3 |
| 40 | NaBH₄[c] | 0.33 | EtOH | 150 | 3 | Yes | 0 | 0.4 | 2.8 | 96.8 |
| 41 | NaBH₄[c] | 0.07 | DMF + benzene (1:1) | 130 | 2 | No | 2.3 | 30.7 | 30.7 | 36.3 |

[a] Solutions (except expt 38) were composed of 0.006 $M$ (0.10 g, 0.13 mmol) $(Ph_3P)_2(CO)_2RuCl_2$, 2.0 g (1.2 mmol) of CDT, and 20 ml of solvent. [b] 25 ml of a 0.010 $M$ $(Ph_3P)_2(CO)_2RuCl_2$ solution containing $[Bu_4N][ClO_4]$, as a supporting electrolyte, was subjected to controlled potential electrolysis at $-2.5$ V until the current dropped to 0 mA. The resulting solution was combined with 1.0 g of CDT, and the hydrogenation was carried out in the typical fashion. [c] The catalyst became inactive.
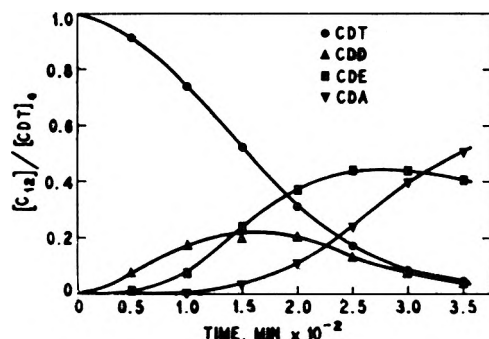


Figure 1.—Plot of relative concentrations of $C_{12}$ compounds *vs* time for the hydrogenation of CDT by $2.48 \times 10^{-3}$ $M$ $(Ph_3P)_2(CO)_2RuCl_2$ without added PPh₃.
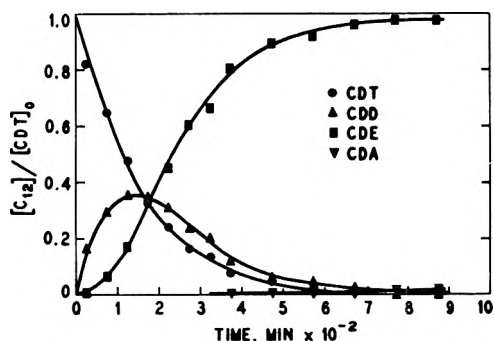


Figure 2.—Plot of relative concentrations of $C_{12}$ compounds *vs.* time for the hydrogenation of CDT by $2.48 \times 10^{-3}$ $M$ $(Ph_3P)_2(CO)_2RuCl_2$ with 0.0356 $M$ PPh₃.

tures sometimes rapidly increased during large batch reactions. For this reason, it was necessary to monitor the temperature very closely on large-scale reactions.

**Productivity of Catalyst–Catalyst Recycle.**—A productivity determination was conducted by hydrogenating seven 50-g samples of CDT with 0.050 g of $(Ph_3P)_2(CO)_2RuCl_2$ in benzene solution with PPh₃ present under 500 psig of hydrogen. After each hydrogenation reaction was completed, the reaction mixture was distilled to dryness at reduced pressure, and the residue (Ru catalyst and PPh₃) was dissolved in benzene and recycled. No diminution in activity of the catalyst was observed. The first hydrogenation required over 6 hr and the remaining six lasted between 1 and 1.5 hr. The yield of CDE was 83–94% for each sample, but additional PPh₃ was occasionally added to maintain the selectivity. Subsequent experiments have shown that the PPh₃ is oxidized to Ph₃PO when no precautions are taken to exclude atmospheric oxygen from reaction solutions. This study demonstrated that a *minimum* of 32,100 mol of CDT can be selectively hydrogenated per mole of $(Ph_3P)_2(CO)_2-RuCl_2$. The maximum productivity of the catalyst certainly significantly exceeds this figure.

**Rate Studies.**—A brief kinetic study was undertaken to enable a greater insight into the origin of catalyst selectivity. A detailed kinetic treatment of this reaction would, of course, be vital to a mechanistic study, but would not significantly amplify the arguments presented here.

Reaction rates were determined at 140° in solutions containing $0.62$–$2.48 \times 10^{-3}$ $M$ $(Ph_3P)_2(CO)_2RuCl_2$ and 0.254 $M$ CDT, while a constant 200 psig hydrogen pressure was maintained above the reaction solution.

The reaction solutions containing all reagents except CDT were equilibrated for 60 min under 60 psig of hydrogen at 140°. The reaction was initiated by the addition of CDT from a reservoir, and samples were withdrawn through a dip tube at regular intervals.

Plots of relative concentrations of the $C_{12}$ intermediates *vs.* time for the hydrogenation in benzene solution without and with added PPh₃ are illustrated in Figures 1 and 2, respectively. The CDT and CDD concentration *vs.* time profiles are similar in both figures, but the CDE concentration attains a much higher maximum value and the CDA concentration increases more slowly in Figure 2. The collection of curves in each figure is typical of a consecutive first-order reaction. A linear relationship between the ln $[CDT]_0/$ $[CDT]$ and time exists for these reactions (Figures 3 and 4) as well as the hydrogenation in DMF solution (not shown), neglecting any induction periods which are believed to involve formation of an active ruthenium hydride catalyst. Thus, a simple first-order dependence of the rate on olefin concentration is experimentally observed. Data from experiments with varying $(Ph_3P)(CO)_2RuCl_2$ concentrations are most consistent with the rate of CDT hydrogenation being first order in catalyst (Figure 5). Thus, the data can be accommodated by rate eq 1. Assuming the hydrogenation of CDD is also first order in both Ru and alkene, the rate of formation of CDD is that shown in eq 2. By invoking the steady-state approximation at the point where CDD reaches its maximum concentration during the reaction, i.e., when $d[CDD]/dt = 0$, eq 2 reduces to eq 3 and the rate constant for the hydrogenation of CDD can be calculated. Equation 4 can be derived in a similar manner, and the rate con-
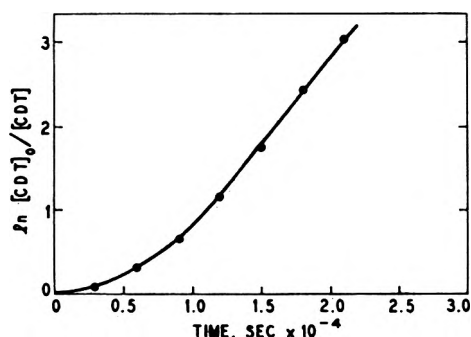
Figure 3.—First-order plot of ln [CDT]₀/[CDT] *vs.* time for the hydrogenation of CDT by $2.48 \times 10^{-3}$ $M$ $(Ph_3P)_2(CO)_2RuCl_2$ without added $PPh_3$.
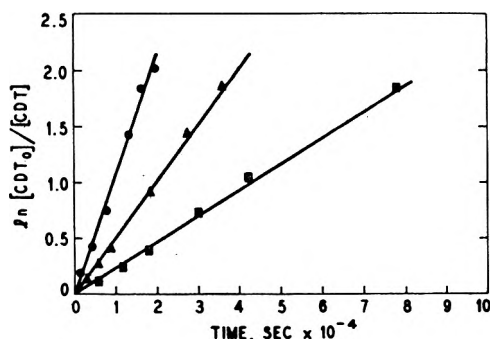


Figure 4.—First-order plot of ln [CDT]₀/[CDT] *vs.* time for the hydrogenation of CDT by (●) $2.48 \times 10^{-3}$ $M$, (▲) $1.55 \times 10^{-3}$ $M$, and (■) $0.62 \times 10^{-3}$ $M$ $(Ph_3P)_2(CO)_2RuCl_2$ with 0.0356 $M$ $PPh_3$.

$$-d[CDT]/dt = K'[Ru][CDT] \tag{1}$$

$$d[CDD]/dt = K'[Ru][CDT] - K''[Ru][CDD] \tag{2}$$

$$K'' = K'[CDT]/[CDD] \text{ at } [CDD]_{max} \tag{3}$$

$$K''' = K''[CDD]/[CDE] \text{ at } [CDE]_{max} \tag{4}$$

stant for CDE hydrogenation, $K'''$, is determined from this equation at the point where CDE attains its maximum concentration. The three rate constants $K'$, $K''$, and $K'''$ undoubtedly contain terms for hydrogenation concentration (which was maintained constant) and for $PPh_3$ and DMF concentrations (which may account for some of the variation in each rate constant between the three systems in Table V).

TABLE V

SECOND-ORDER RATE CONSTANTS FOR THE HYDROGENATION
OF CDT CATALYZED BY $(Ph_3P)_2(CO)_2RuCl_2$[a]

| Solvent system | K'[b] | K''[b] | K'''[b] |
|---|---|---|---|
| Benzene | 83 | 189 | 43 |
| N,N-Dimethylformamide | 58 | 78 | 2.5 |
| Benzene + 0.0356 M PPh₃ | 43 | 66 | 0.58 |

[a] Rate constants presumably include terms for hydrogen, DMF, and PPh₃ concentrations. [b] Units of $mol^{-1}$ l. $sec^{-1} \times 10^3$.

In Table V, the rate constants determined in the two reactions illustrated in Figures 1 and 2 along with a reaction in N,N-dimethylformamide (DMF) solution are tabulated, and their relative values can be directly compared. As the table is descended, the values of $K'$ and $K''$ decrease slightly while $K'''$ greatly diminishes. Thus, the presence of DMF or $PPh_3$ in the system only slightly affects the rates of
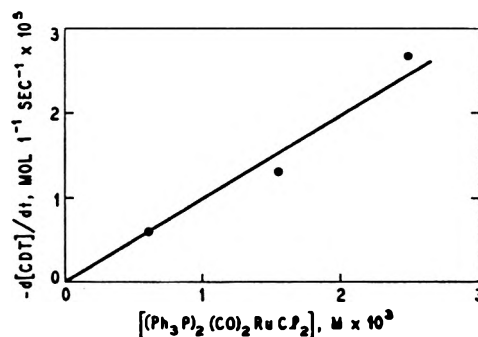


Figure 5.—Rate dependence of CDT hydrogenation on $(Ph_3P)_2(CO)_2RuCl_2$ concentration.

hydrogenation of CDT and CDD, but greatly slows the rate of CDE hydrogenation.

**Hydrogenation–Isomerization of *trans*-CDE.**—If a ruthenium hydride intermediate is the actual catalytic species, as it is for related soluble ruthenium hydrogenation catalysts,[5,15,16] the rate of metal hydride addition–elimination to and from the olefin would be reflected in the rate of olefin isomerization. The rate of isomerization of *trans*-CDE to the equilibrium trans/cis mixture and the rate of CDE hydrogenation were determined using the same solvent system and conditions as the third entry in Table V except that the *trans*-CDE concentration was 0.125 $M$ and the $(Ph_3P)_2(CO)_2RuCl_2$ concentration was $6.36 \times 10^{-4}$ $M$. In the earlier study, the CDT concentration was 0.254 $M$ and the $(Ph_3P)_2(CO)_2RuCl_2$ was $6.20 \times 10^{-4} M$.

The rate of isomerization of the olefin in this reaction was very fast. Within 25 min, the isomerization had progressed 50% toward the equilibrium trans/cis mixture. Yet, after 1200 min, only 3.9% of the CDE was hydrogenated to CDA. The isomerization reaction under consideration is shown in eq 5 with the rate constants $k'$ and $k''$ to be determined. These constants were evaluated from eq 6 which is the expression for a reversible first-order reaction adapted to our pseudo-first-order reaction; where [*trans*-CDE] at time 0 is $A_0$, at time $t$ is $A$, and at equilibrium is $A_e$. The equilibrium trans/cis ratio of CDE is 2.05. A plot of ln $(A_0 - A_e)/(A - A_e)$ *vs.* time was linear, and a value of 0.80 $mol^{-1}$ l. $sec^{-1}$ was obtained for the sum of the rate constants $k' + k''$. Since at equilibrium, $k'' = 2.05k'$, the values of $k'$ and $k''$ are 0.26 and 0.54 $mol^{-1}$ l. $sec^{-1}$, respectively.

$$RuH + \textit{trans}\text{-CDE} \underset{k''}{\overset{k'}{\rightleftharpoons}} \textit{cis}\text{-CDE} + RuH \tag{5}$$
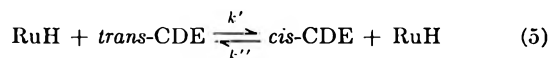
$$\ln (A_0 - A_e)/(A - A_e) = (k' + k'')[Ru]t \tag{6}$$

Employing a pseudo-second-order rate equation equivalent to eq 1 for the hydrogenation of CDE, the rate constant $K''' = 0.80 \times 10^{-3}$ $mol^{-1}$ l. $sec^{-1}$ was calculated. This value should be compared with $K''' = 0.58 \times 10^{-3}$ $mol^{-1}$ l. $sec^{-1}$ reported in Table V. The agreement is fair, and a greater level of confidence should be placed with the $0.80 \times 10^{-3}$ figure since the glpc integration error was greater in the determination of the very small concentration of CDD

(15) D. Rose, J. O. Gilbert, R. P. Richardson, and G. Wilkinson, *J. Chem. Soc. A*, 2610 (1969).
(16) B. R. James, *Inorg. Chim. Acta Rev.*, **4**, 73 (1970).

for use in calculating the $0.58 \times 10^{-3}$ figure. The above figures clearly indicate that, for CDE, the rate of isomerization, and thus metal hydride addition–elimination, is much faster than hydrogenation.

**Hydrogenation–Isomerization of 1,5-COD.**—It is of interest to know if the double bonds become conjugated in the $C_{12}$ polyunsaturated intermediates prior to their hydrogenation. This has been claimed as the mechanism by which CDT is hydrogenated in the presence of the cobalt carbonyl catalyst.[2] The glpc chromatograms of the CDT hydrogenation mixtures at intermediate stages of the reaction are the same when either the ruthenium catalyst or the cobalt carbonyl catalyst is employed indicating that the same $C_{12}$ intermediates are formed in both reactions.

In the hydrogenation of 1,5-cyclooctadiene (1,5-COD) to cyclooctene catalyzed by the ruthenium complex, the 1,5-COD was isomerized to 1,4-COD and then to 1,3-COD faster than cyclooctene was formed. These observations, along with the knowledge that double bond isomerization is faster than hydrogenation (at least for CDE), are consistent with, but do not require, conjugated diolefins as intermediates in the ruthenium-catalyzed hydrogenation of CDT.

## Discussion

The mechanism of the reaction undoubtedly parallels that of other ruthenium hydride complex hydrogenations[5,15,16] and follows the course shown in eq 7, 8, and 9 where the hydrogenation steps are rate determining.

$$\text{RuH} + \text{CDT} \underset{K_1}{\overset{K_1}{\rightleftharpoons}} \text{Ru(dienyl)} \overset{k_1}{\underset{H_2}{\longrightarrow}} \text{RuH} + \text{CDD} \quad (7)$$

$$\text{RuH} + \text{CDD} \underset{K_2}{\overset{K_2}{\rightleftharpoons}} \text{Ru(alkenyl)} \overset{k_2}{\underset{H_2}{\longrightarrow}} \text{RuH} + \text{CDE} \quad (8)$$

$$\text{RuH} + \text{CDE} \underset{K_3}{\overset{K_3}{\rightleftharpoons}} \text{Ru(alkyl)} \overset{k_3}{\underset{H_2}{\longrightarrow}} \text{RuH} + \text{CDA} \quad (9)$$
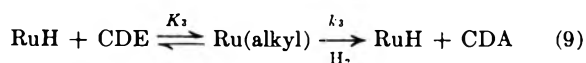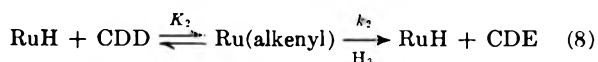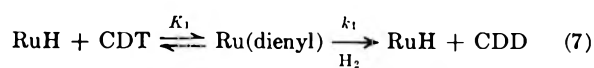
Unfortunately, the true identity of the active ruthenium catalyst remains unknown. The absence of an induction period in rate studies with added $PPh_3$ suggests that $PPh_3$ acts as a base to accept HCl generated from the reaction of $(Ph_3P)_2(CO)_2RuCl_2$ with hydrogen in forming a RuH species as catalyst. The conversion of $(Ph_3P)_3RuCl_2$ into the active catalyst $(Ph_3P)_3RuHCl$ is similarly accelerated in the presence of certain bases such as $NEt_3$.[5] The induction period which occurs in the absence of added $PPh_3$ cannot be due to a slow dissociation of the neutral ligands. Since $(Ph_3P)_2(CO)_2RuCl_2$ was isolated from several hydrogenations after the reaction was completed, it is likely in equilibrium with the catalyst. Therefore, the composition of the catalyst must be only slightly different from $(Ph_3P)_2(CO)_2RuCl_2$ and is envisioned as $(Ph_3P)_2(CO)_2RuHCl$ or possibly $(Ph_3P)_2(CO)_2RuH_2$ with easily dissociated $PPh_3$ ligands. Complexes of these compositions are known.[9,13,17] To comply with the mechanism of related ruthenium-catalyzed hydrogenations,[5,15,16] both $PPh_3$ ligands must readily dissociate.

In the selective hydrogenation of olefin mixtures catalyzed by $RhCl(PPh_3)_3$, the degree of selectivity

(17) F. L'Eplattenier and F. Calderazzo, *Inorg. Chem.*, **7**, 1290 (1968).

achieved is enhanced by the addition of polar solvents.[18] In Table VI, selectivities to CDE in several solvents

### TABLE VI
CDE SELECTIVITIES AND SOLVENT DIELECTRIC CONSTANTS FOR THE HYDROGENATION OF CDT CATALYZED BY $(Ph_3P)_2(CO)_2RuCl_2$

| Solvent | $\epsilon$ | Selectivity[a] |
|---|---|---|
| Dimethyl sulfoxide | 48.9 | 0.99 |
| *N,N*-Dimethylacetamide | 37.8 | 0.82 |
| *N,N*-Dimethylformamide | 36.7 | 0.91 |
| 1-Butanol | 17.8 | 0.55 |
| Ethyl acetate | 6.0 | 0.59 |
| Benzene | 2.3 | 0.65 |

[a] Selectivity = [CDE]/([CDE] + [CDA]) at the point of maximum yield of CDE during the hydrogenation.

are listed (taken from data in Table II) with the dielectric constant, $\epsilon$, of each solvent. There appears to be no correlation of selectivity with solvent $\epsilon$ in the hydrogenation of CDT catalyzed by $(Ph_3P)_2(CO)_2$-$RuCl_2$.

The selectivity dependence on solvent and added Lewis bases could also arise from a competition between the solvent or added Lewis bases and the intermediate olefins for complexation to ruthenium, where CDE does not compete so well as does CDD and CDT. Related to this, previous workers have found that the relative hydrogenation rates of olefins catalyzed by $(Ph_3P)_3RuHCl$ are determined by the respective "coordinating power of the alkene."[19] Alternatively, RuH addition to the coordinated olefin may be more sterically hindered for CDE than for CDD or CDT when Lewis bases or solvents occupy coordination sites about ruthenium. This explanation has been put forth to explain rate differences in the hydrogenation of internal *vs.* terminal olefins catalyzed by $(Ph_3P)_3$-$RuH(OAc)$.[15] The results of the present study eliminate both of the above in the selective hydrogenation of CDT. Since the isomerization of *trans*-CDE is very much faster than its hydrogenation, the RuH addition to the coordinated CDE is very facile in the presence of $PPh_3$. The increased selectivity of the hydrogenation when $PPh_3$ is added must result from either a slowed hydrogenation step or an increased RuH elimination rate for the Ru(alkyl) intermediate. The present data do not allow elimination of either possibility. We speculate that the cycloalkylruthenium intermediate formed by the addition of RuH to CDE is so sterically crowded in the presence of coordinated $PPh_3$ that the intermediate undergoes rapid RuH elimination before reaction with hydrogen. In the intermediates formed by the RuH addition to CDD or CDT, a double bond in the cycloalkenyl ligand displaces a coordinated $PPh_3$ to form a $\sigma,\pi$-bonded chelate structure or a $\pi$-allylic complex. The extra stability gained by chelation and by relief of steric crowding (from loss of coordinated $PPh_3$) allows the intermediate a sufficient lifetime to react with hydrogen. In solutions without added $PPh_3$, the $PPh_3$ ligands remain largely dissociated from the catalyst, and differences in the stabilities of the inter-

(18) J. P. Candlin and A. R. Oldham, *Discuss. Faraday Soc.*, **No. 46**, 60 (1968).

(19) I. Jardine and F. J. McQuillin, presented at the British Chemical Society Annual Meeting, Nottingham, April 1969, and highlighted in *Chem. Brit.*, **5**, 321 (1969); *Tetrahedron Lett.*, 5189 (1968).

mediates formed from CDT, CDD, and CDE due to steric crowding would not be so important. Thus, these hydrogenations are less selective.

In summary, CDT can be selectively hydrogenated in 98–99% yield to CDE by the catalyst derived from $(Ph_3P)_2(CO)_2RuCl_2$ in the presence of certain solvents or added Lewis bases, e.g., N,N-dimethylformamide or $PPh_3$. The ruthenium catalyst exhibits a remarkable stability under the reaction conditions as well as a resistance to attack by oxygen, water, or poisons present as impurities in the reagents used. Two precautions are suggested to obtain the maximum utility from the catalyst system: (1) atmospheric oxygen should be excluded from solutions to avoid the oxidation of $PPh_3$ to $OPPh_3$, and (2) the reaction temperature should be held below 160° to prevent by-product formation.

## Experimental Section[20]

**Materials.**—CDT and 1,5-COD were purchased from the Columbian Carbon Co. The CDT was a mixture of the all trans and the trans,trans,cis isomers in a 3:2 ratio. Smaller amounts of compounds believed to be the trans,cis,cis and the all cis isomers were also present. The CDT was routinely filtered through alumina prior to its use, although no noticeable differences in reactivity were observed with untreated samples. The 1,5-COD was used as commercially supplied. Pure *trans*-CDE was obtained by preparative glpc on a tris-1,2,3-(2-cyanoethoxy)propane column from a mixture comprised of 54% *trans*-CDE along with *cis*-CDE and other compounds. Hydrogen, CO, ligands, and solvents were all obtained commercially and were generally used without further purification. For the kinetic studies, benzene and DMF were distilled from $CaH_2$ before use.

$RuCl_3$ was purchased from Englehard as a hydrate containing 39 wt % Ru. The complex $[(CO)_4Ru]_3$ was purchased from Strem Chemical Co. Literature procedures were used in the preparation of $(Ph_3P)_3(CO)RuH_2$,[5] $[(CO)_2RuCl_2]_n$,[6] $(Ph_3P)_3RuCl_2$,[6] $(Ph_3P)_2(CO)_2RuCl_2$,[6] $(Py)_2(CO)_2RuCl_2$,[6] $(Ph_3P)_2(CH_3OH)RuCl_3$,[6] $(Ph_3P)_2(CO)_3Ru$,[7] $(Py)_4RuCl_2$,[21] $(Et_2S)_3RuCl_3$,[22] and $(diphos)_2RuCl_2$.[23] The complex $(MePh_2P)_2(CO)_2RuCl_2$ was prepared in the same manner as $(Ph_3P)_2(CO)_2RuCl_2$. The configuration of $(MePh_2P)_2(CO)_2RuCl_2$, mp 223–228° [lit.[24] mp 220–224°], is assigned 1a based on infrared absorptions for $\nu_{CO}$ at 2055 and 1989 cm$^{-1}$ ($CH_2Cl_2$) (therefore CO groups) and for $\nu_{RuCl}$ at 308 and 284 cm$^{-1}$ (CsI wafer) (therefore cis Cl groups) along with the appearance of a well-defined apparent 1:2:1 triplet at $\tau$ 7.70 ($J_{PH} + J_{P'H}$) = 10.7 Hz, for the methyl protons in its pmr spectrum (CDCl$_3$) (therefore trans P groups).

Purification of $(Ph_3P)_2(CO)_2RuCl_2$ was achieved by filtering its $CH_2Cl_2$ solution through alumina followed by recrystallization from $CH_2Cl_2$–MeOH mixtures. It melts to a red liquid at 309–312° (lit. mp 233–236°,[12] 257,[6] and 310°[10]) and exhibits $\nu_{CO}$ at 2058 and 1993 cm$^{-1}$ ($CH_2Cl_2$) and $\nu_{RuCl}$ at 300 and 275 cm$^{-1}$ (CsI wafer) (lit.[11] $\nu_{RuCl}$ 300 and 275 cm$^{-1}$) in its infrared spectrum.[25] The relative intensity of the phenyl ir absorption at 1570 cm$^{-1}$ is greater than that at 1583 cm$^{-1}$. This relationship appears to be general for platinum(II) complexes bearing *trans*-$PPh_3$ groups while, for cis complexes, the reverse is true.[26] *Anal.* Calcd for $C_{38}H_{30}Cl_2O_2P_2Ru$: C, 60.65; H, 4.02; mol wt, 752. Found: C, 60.34; H, 3.99; mol wt, 720 ± 35.

**Hydrogenations.**—Reactions at pressures below 250 psig were carried out in thick-walled glass vessels fitted with a stainless-steel cap and sealed by a neoprene rubber O-ring. The bottles had a 3-oz capacity and are referred to as aerosol compatibility tubes by the Fisher-Porter Co. The cap was fitted with a pressure gauge, a hydrogen line, and in some cases, a dip tube through which aliquots of the solution could be withdrawn. Reaction temperatures were controlled by immersing most of the tube and a thermometer in an oil bath heated by a stirrer–hot-plate. Stirring was accomplished by a magnetic stirring bar. Reaction mixtures were usually composed of 0.10 g of ruthenium complex, 2.00 g of CDT, 20 ml of solvent, and any additional reagent. After sealing the reaction vessel charged with reagents, hydrogen was pressured into the tube, and the reaction was initiated by increasing the temperature of the oil bath. When hydrogen absorption began, the temperature was increased an additional 10° and then held constant. Hydrogen absorption was detected by a decrease of pressure in the system. Each time the pressure dropped to 150–180 psig, the system was re-pressured with hydrogen to 210–220 psig. When hydrogen absorption stopped, the mixture was cooled and the reaction solution was analyzed by glpc. In some experiments where the catalysts were not very selective, samples were withdrawn from the dip tube at selected intervals, and the composition of the sample with the highest percentage of CDE is reported. When reactions were conducted in ethanol, colorless crystalline precipitates usually formed when the reaction solutions were cooled. The ir spectra (Nujol) of these precipitates exhibited $\nu_{CO}$ at 1985 and 2058 cm$^{-1}$ [the same $\nu_{CO}$ as in $(Ph_3P)_2(CO)_2RuCl_2$] and occasionally additional absorptions between 1950 and 2058 cm$^{-1}$ which we were unable to assign.

*In Situ* **Preparation of Catalyst.**—A 3-oz tube containing 0.10 g (0.38 mg-atom of Ru) of $RuCl_3 \cdot (H_2O)_n$, 0.40 g (1.5 mmol) of $PPh_3$, 2.0 g (12.3 mmol) of CDT, and 20 ml of ethanol was pressured to 4 psig with CO and then to 180 psig with hydrogen. The hydrogenation was conducted as usual at ∼140° until the gas absorption ceased. Upon cooling the solution to 25°, white crystals of $(Ph_3P)_2(CO)_2RuCl_2$ (ca. 0.30 g, 103%) precipitated and were collected by suction filtration, washing with pentane. Analysis of the mother liquors by glpc revealed the presence of CDA (2.0%), CDE (98.0%), and CDD and CDT (0%).

**Catalyst Recycle.**—A 300-ml Magnedash autoclave was charged with 0.050 g (0.065 mmol) of $(Ph_3P)_2(CO)_2RuCl_2$, 1.00 g (3.82 mmol) of $PPh_3$, 50.3 g (310 mmol) of CDT, and 20 ml of benzene. The autoclave was flushed with nitrogen, pressured to 500 psig with hydrogen, and heated as its contents were rapidly stirred. Hydrogen absorption was noted by the pressure decrease in the system. Each time the pressure dropped to 400–500 psig, the system was repressured to 600 psig with hydrogen. This large-scale reaction was markedly exothermic making the reaction temperature difficult to maintain between 145 and 150°. At times, the temperature approached 165–170°. After completion of the hydrogen absorption, the contents of the autoclave were cooled and transferred to a distillation flask, and the mixture was distilled at 6 mm. The colorless liquid distilling at 56–58° was collected as the product (49.9 g, 96.9%), and it was composed of CDA (5.6%), CDE (91.0%), CDD (3.4%), and CDT (0%). The dark yellow residue in the distillation flask was dissolved in 20 ml of benzene and recycled with another 50 g of CDT, repeating the operations described above. In this manner, the catalyst was recycled six times, with the occasional addition of $PPh_3$ to compensate for its loss by oxidation to $Ph_3PO$. The first hydrogenation lasted 6.3 hr, and the last six required slightly over 1 hr to be completed. A total of 343.3 g of CDT was reduced to CDE in yields of 83–94%, usually 91–93% in each batch.

**Rate Studies.**—Solutions composed of $(Ph_3P)_2(CO)_2RuCl_2$, 40.0 ml of solvent, and $PPh_3$, when desired, were equilibrated in a 140° constant temperature oil bath under 60 psig of hydrogen for 60 min. The bath temperature fluctuated less than ±0.4° during each run. The reaction was initiated by the addition of 1.77 g (10.9 mmol) of CDT and 1.0 ml of benzene from a reservoir in the hydrogen line. The pressure in the system was increased to 200 psig and maintained constant by the regulator on the hydrogen tank. After the addition of CDT, aliquots were withdrawn from the dip tube at selected intervals. A 2-ml forerun was discarded before each aliquot was collected, and the composition of each sample was determined by glpc.

**Product Analysis.**—Samples were routinely analyzed by glpc on a 20 ft × 0.25 in. tris-1,2,3-(2-cyanoethoxy)propane (TCEP)

(20) Infrared and nmr spectra were obtained on Perkin-Elmer Model 621 and Varian T-60 instruments, respectively. The ir spectra are accurate to within ±2 cm$^{-1}$. Glpc measurements were made using a Hewlett-Packard Model 5750 chromatograph employing a flame ionization detector. Electrochemical reduction of $(Ph_3P)_2(CO)_2RuCl_2$ was accomplished by controlled-potential electrolysis by Dr. W. B. Hughes.

(21) E. W. Abel, M. A. Bennett, and G. Wilkinson, *J. Chem. Soc.*, 3178 (1959).

(22) J. E. Fergusson, J. D. Karran, and S. Seevaratnam, *ibid.*, 2627 (1965).

(23) J. Chatt and R. G. Hayter, *ibid.*, 896 (1961).

(24) R. Burt, M. Cooke, and M. Green, *J. Chem. Soc. A*, 2645 (1969).

(25) Very weak far-ir absorptions were also noted at 283 and 258 cm$^{-1}$.

(26) W. J. Bland and R. D. W. Kemmitt, *J. Chem. Soc. A*, 2062 (1969).

column at 140°. Pure samples of each $C_{12}$ product analyzed were not available thus precluding a determination of their relative response factors. The results reported are based only on the relative peak area. The assignment of glpc peaks is as follows: CDA (10.8 min), *trans*-CDE (12.9 min), *cis*-CDE (14.3 min), CDD (15.1 min), CDD (16.4 min), *trans,trans,trans*-CDT (17.2 min), CDD (18.4 min), CDD (19.7 min), *cis,trans-trans*-CDT (21.2 min), CDD (22.5 min), *cis,cis,trans*-CDT (24.7 min), and *cis,cis,cis*-CDT (26.4 min). As a check on this procedure, samples were occasionally reanalyzed by glpc on a 150-capillary squalane column at 120°. The relative yields obtained with this column were always within 3% of those obtained with the TCEP column. For hydrogenations carried out at temperatures over 160°, by-products were formed which had

retention times very close to *cis*- and *trans*-CDE on the TCEP column. This interference did not occur with the capillary column, and the yields were obtained with this procedure.

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# Silicon Heterocyclic Compounds. Ring Closure by Hydrosilation[1,2]

RALPH J. FESSENDEN* AND WILLIAM D. KRAY

*Department of Chemistry, University of Montana, Missoula, Montana 59801*

The hydrosilation reaction has been utilized for the synthesis of silicon heterocyclic compounds. With an appropriately substituted silane, the ring-closure reaction results in a silacyclopentane rather than the expected silacyclohexane. 5-(Dimethylsilyl)-1-hexene, upon treatment with chloroplatinic acid, yields equal amounts of *cis*- and *trans*-1,1,2,5-tetramethylsilacyclopentane.

The principal methods for the preparation of silicon heterocyclic compounds utilize some type of organometallic ring-closure reaction. For example, the standard method for the preparation of silacycloalkanes is the reaction of a di-Grignard reagent with a dichlorosilane.[3] The major disadvantage of this method is the limited number of functional groups that can be introduced into the ring system.

$$BrMg(CH_2)_5MgBr + SiCl_4 \longrightarrow$$
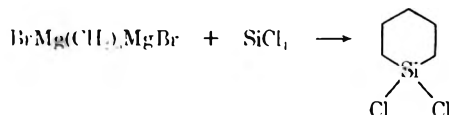


The present study was aimed at the exploration of the use of the hydrosilation reaction for a ring-closure method with particular emphasis on ring systems that contain an $\alpha$-alkyl substituent.

Silicon hydrides add cleanly across terminal double bonds to yield *n*-alkylsilanes in the presence of both free-radical catalysts[4] (dibenzoyl peroxide) and ionic catalysts[5] (chloroplatinic acid). If the olefin contains

$$Cl_3SiH + CH_2=CHCH_2CH_2CH_3 \xrightarrow{H_2PtCl_6}$$
$$Cl_3SiCH_2CH_2CH_2CH_2CH_3$$
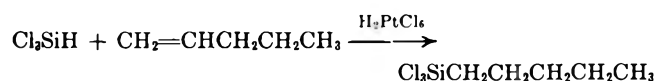
an internal double bond and with chloroplatinic acid as catalyst, the double bond migrates to a terminal position before the addition occurs. For example, 2-pentene yields only *n*-pentylsilane.[5]

$$Cl_3SiH + CH_3CH=CHCH_2CH_3 \xrightarrow{H_2PtCl_6}$$
$$Cl_3SiCH_2CH_2CH_2CH_2CH_3$$
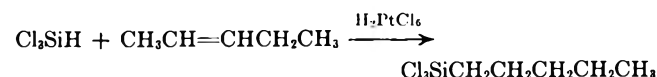
Ring closure reactions involving hydrosilation have been reported.[6]

$$2 \ (CH_3)_2SiHCH_2CH=CH_2 \longrightarrow$$



$$+ \quad polymer$$
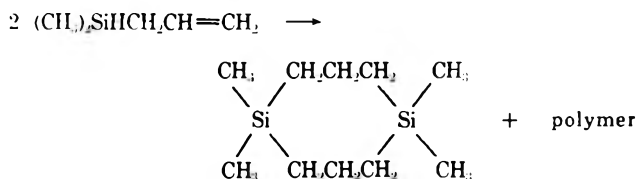
## Results and Discussion

Syntheses of the appropriate starting materials are presented in the Experimental Section. Treatment of 5-(dimethylsilyl)-1-hexene with chloroplatinic acid in pentane yields a mixture principally composed of *cis*- and *trans*-1,1,2,5-tetramethylsilacyclopentane (2) (73% yield) and only a trace of the expected 1,1,2-trimethylsilacyclohexane (1). The five-membered ring was also observed as the major product when 5-(methylchlorosilyl)-1-hexene was used as the starting material.
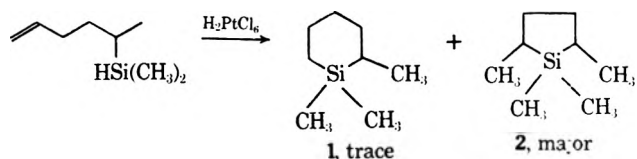


This unexpected path of ring closure finds probable explanation in the mechanism for hydrosilation as proposed by Chalk and Harrod.[7] In their proposed mechanism, a seven-membered ring would be required as the key intermediate in the formation of 1, whereas a six-membered ring intermediate would lead to 2.

Using the hydrosilation ring-closure reaction, 1,1-dimethylsilacyclopentane was obtained in 60% yield from dimethyl(3-butenyl)silane. The hydrosilation

(1) This work was supported in part by Grant AM 12794 from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service.

(2) Taken in part from the Ph.D. Thesis of William D. Kray, University of Montana.

(3) R. West, *J. Amer. Chem. Soc.*, **76**, 6012 (1954).

(4) C. Eaborn, "Organosilicon Compounds," Academic Press, New York, N. Y., 1960, p 45.

(5) J. L. Speier, J. A. Webster, and G. Barnes, *J. Amer. Chem. Soc.*, **79**, 974 (1957).

(6) J. W. Curry and G. W. Harrison, *J. Org. Chem.*, 1219 (1958).

(7) A. J. Chalk and J. F. Harrod, *J. Amer. Chem. Soc.*, **87**, 16 (1965).

compares very favorably to dilithium reagent ring-closure reactions (54–76% yield).[8]

To obtain an authentic sample of 1, an organometallic ring closure was employed. 1-(Trichlorosilyl)-5-chlorohexane was prepared; however, all attempts to ring close this compound met with failure.

When the silyl group was placed at the secondary position and ring closure was attempted to the primary position, the desired compound was obtained in 23% yield.

$$BrCH_2CH_2CH_2CH_2CHCH_3 + Mg \longrightarrow 1$$
$$| $$
$$ClSi(CH_3)_2$$
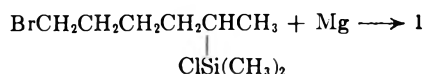
**Structure Assignments.**—The assignment of structures to 1, cis-2 (2a), and trans-2 (2b) is based principally upon their comparative spectral data. The carbon–hydrogen analyses of 1 and 2 were consistent with the empirical formulas. Compound 1 contained only one peak in glpc analysis. However, glpc analysis of compound 2 showed that it was a mixture of two components. These two compounds, 2a and 2b, were separated using preparative glpc and spectral data was obtained on all three compounds.

The main distinguishing feature in the ir was that 1 showed a band at 11.4 $\mu$ while 2a and 2b were clear in this region. Oshesky and Bentley[9] have assigned a band in the 10.93–11.00-$\mu$ region as being characteristic of silacyclohexanes. However, the ring systems in their study were all without alkyl substituents on the ring.

In the mass spectra, all three compounds showed a parent peak at $m/e$ 142. The mass spectra of 2a and 2b were identical and differed from that of 1 by an $m/e$ peak at 114, which appeared in the spectrum of 1 but not in those of 2a and 2b. This P − 28 peak can be interpreted as the loss of ethylene from the unsubstituted side of the silacyclohexane.[10]

In the nmr, the SiCH$_3$ signal for 1 and 2b was a singlet but was a doublet for 2a. This allows assignment of the cis structure to 2a and the trans structure to 2b.



2a　　　　　　　　　　2b
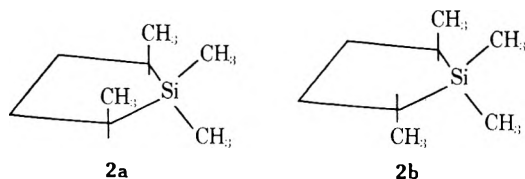
## Experimental Section

The ir spectra were obtained either with neat samples or with 7–10% solutions in CHCl$_3$ using a Beckman IR-5a spectrophotometer. Nmr spectra were obtained with 10% solutions in CCl$_4$ using a Varian HA-60 instrument with either TMS or benzene as the internal standard. Mass spectra were obtained using a modified CEC-103 instrument.

*cis-* and *trans*-1,1,2,5-Tetramethyl-1-silacyclopentane (2). 5-Chloro-1-hexene.—To 82 g (1.0 mol) of biallyl[11] was added 300 ml of concentrated HCl. The mixture was stirred at room temperature for 16 hr. The product (bp 121°, $n^{30}$D 1.4308) was isolated by distillation. The yield was 18 g (14%). Unreacted biallyl (80%) was recovered.

(8) R. J. Fessenden and M. D. Coon, *J. Org. Chem.*, **26**, 2530 (1961).

(9) G. D. Oshesky and F. F. Bentley, *J. Amer. Chem. Soc.*, **79**, 2057 (1957).

(10) N. Y. Chernyak, R. A. Khmel'nitskii, T. V. D'yakova, and V. M. Vdovin, *Zh. Obshch. Khim.*, **36**, 96 (1966); *Chem. Abstr.*, **64**, 13524e (1966).

(11) A. Turk and H. Chanan, *Org. Syn.*, **27**, 7 (1947).

*Anal.* Calcd for C$_{11}$H$_6$Cl: C, 60.75; H, 9.35. Found: C, 60.48; H, 9.49.

5-(Dimethylchlorosilyl)-1-hexene.—A Grignard reagent was prepared from 40 g (0.33 mol) of 5-chloro-1-hexene and 12 g (0.5 g-atom) of Mg. To this was added 50 g (0.4 mol) of dimethyldichlorosilane, and the mixture was heated at reflux overnight. The mixture was filtered through Celite, and the product, bp 118° (12 mm), was isolated by distillation. The yield was 10 g (18%). A sample of the product was reduced with LiAlH$_4$ in ether and characterized as the hydride, 5-(dimethylsilyl)-1-hexene (see below).

5-(Chloromethylsilyl)-1-hexene.—To a slurry of 12 g (0.5 g-atom) of Mg powder in 400 ml of ether was added 24 g (0.19 mol) of 5-chloro-1-hexene. After the addition was complete, 45 g (0.40 mol) of methyldichlorosilane was added, and the mixture was heated at reflux overnight. After filtration through Celite and distillation, there was obtained 23 g (72%), bp 110° (15 mm). A sample of this material was converted to 5-(dimethylsilyl)-1-hexene with methylmagnesium bromide for characterization (see below).

5-(Dimethylsilyl)-1-hexene.—To excess LiAlH$_4$ in 100 ml of ether was added 5 g (0.03 mol) of 5-(dimethylchlorosilyl)-1-hexene. The mixture was heated at reflux overnight, then poured over cracked ice. The ether layer was decanted, and the aqueous layer was extracted with 100 ml of ether. The product, bp 70° (12 mm), $n^{25}$D 1.4411, was isolated by vacuum distillation. The yield was 3.6 g (75%): ir 3.3, 6.1, 10.0, 10.9 (monosubstituted ethylene), 4.45 (SiH), and 8.0 $\mu$ (SiCH$_3$); nmr $\delta$ 5.1–6.0 (monosubstituted ethylene pattern, 3 protons), 3.8 (m, 1 proton, assigned as the SiH), 2.1 (vinyl methylene, 2 protons), 1.1–1.8 (m), 0.95 (d, 6 protons), and 0.05 (d, $J$ = 7 Hz, 6 protons, SiCH$_3$).

*Anal.* Calcd for C$_8$H$_{18}$Si: C, 67.51; H, 12.74. Found: C, 67.60; H, 12.58.

**Ring Closure. Method A.**—A catalytic amount of chloroplatinic acid was placed in 100 ml of olefin-free hexane and heated to reflux. Then 10 g (0.071 mol) of 5-(dimethylsilyl)-1-hexene in 100 ml of hexane was added dropwise over a 4-hr period. The mixture was heated at reflux for an additional 4 hr, and then the solvent was removed by distillation. The product mixture, 7.3 g (73%), bp 145–150°, was isolated by distillation. Glpc analysis showed that the mixture contained three components, later shown to be *cis-* and *trans*-1,1,2,5-tetramethyl-1-silacyclopentane (48%, each isomer) and 1,1,2-trimethyl-1-silacyclohexane (4%). The two silacyclopentanes were separated using preparative glpc (see below).

**Method B.**—Into 200 ml of olefin-free pentane were placed 5.0 g (0.02 mol) of 5-(chloromethylsilyl)-1-hexene and a catalytic amount of chloroplatinic acid. The mixture was placed in a pressure bottle and shaken at 60° for 24 hr. The product mixture, 2.1 g (55%), was isolated by distillation. The product ratios were the same as in method A. Of several catalysts tried, only chloroplatinic acid was effective. With other catalysts, either starting material or polymeric material (in the case of dibenzoyl peroxide) was obtained.

*Anal.* Calcd for C$_8$H$_{18}$Si: C, 67.51; H, 12.74. Found: C, 67.75; H, 12.59.

**Separation of *cis-* and *trans*-1,1,2,5-Tetramethyl-1-silacyclopentane (2a and 2b).**—The mixture of cis and trans silacyclopentanes was separated by preparative glpc using a 20 ft × 0.5 in. SE-30 column at 110° with a flow rate of 80 ml/min He. The trans (2b) and cis (2a) isomers had retention times of 3.7 and 4.4 min, respectively. The refractive indices of the trans and cis isomers were $n^{25}$D 1.4364 and 1.4399, respectively.

The mass spectra of the two isomers were identical: $m/e$ (rel intensity) 27 (38), 31 (12), 43 (15), 58 (12), 59 (22), 67 (20), 72 (15), 73 (20), 85 (base peak), 86 (35), 99 (35), 100 (99), 127 (15), 142 (25); ir (both isomers) 3.4, 6.9, 8.05, 14.5 $\mu$; ir (cis isomer) four symmetrical bands at 11.05 (s), 12.3 (w), 13.05 $\mu$ (s); ir (trans isomer) three symmetrical bands at 12.05, 12.6, 13.2 $\mu$, equal intensity; the 12.05-$\mu$ band had two shoulders at 11.8 and 12.2 $\mu$. In the nmr, the cis isomer showed a doublet (SiCH$_3$) at $\delta$ 0 ($J$ = 7 Hz), and the trans isomer showed a singlet (SiCH$_3$) at $\delta$ 0. Both isomers showed an unresolved multiplet at $\delta$ 1.

1,1-Dimethyl-1-silacyclopentane.—To 150 ml of pentane were added 5 g (0.044 mol) of dimethyl(3-butenyl)silane, bp 95°, $n^{30}$D 1.4190 [lit.[12] bp 98.5° (735 mm), $n^{25}$D 1.4161], and a catalytic

(12) A. D. Petrov, N. P. Smetankina, and G. I. Nikishin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1468 (1958); *Chem. Abstr.*, **53**, 8117 (1959).

amount of chloroplatinic acid. The mixture was stirred for 16 hr at room temperature. The pentane was removed by distillation through a 24-in. spinning-band column yielding the product, 3.1 g (60%), bp 102°, $n^{30}$D 1.4288 (lit [8] bp 103–105°, $n^{22}$D 1.4340).

**1,1,2-Trimethyl-1-silacyclohexane (1). 1-(Trichlorosilyl)-5-chlorohexane.**—To 20 g (0.16 mol) of 5-chloro-1-hexene in 250 ml of cyclohexane were added 60 g (0.50 mol) of trichlorosilane and 3.6 g of dibenzoyl peroxide catalyst. The temperature of the mixture was maintained at 65° for 90 hr. The solvent and excess trichlorosilane were removed by atmospheric distillation, and the product, bp 110–112° (0.12 mm), was isolated by vacuum distillation. The reaction yield was 21 g (87%). The product was converted to trimethyl-*n*-hexylsilane for characterization (see below).

**Trimethyl-*n*-hexylsilane.**—To 50 g of 1-(trichlorosilyl)-5-chlorohexane was added 50 ml of 3 *M* methylmagnesium bromide in ether. The mixture was stirred at ambient temperature for 1 hr, then poured over cracked ice, and extracted with two 50-ml portions of ether. The ether was removed by distillation, and the product, bp 195–197°, $n^{25}$D 1.4125, was distilled. The 1-(trimethylsilyl)-5-chlorohexane was treated with magnesium in ether, and the resulting Grignard reagent was hydrolyzed with $H_2O$. The product was distilled and shown to be trimethyl-*n*-hexylsilane by comparison of its spectra (nmr, ir) with those of an authentic sample prepared from the reaction of *n*-hexylmagnesium bromide and trimethylchlorosilane.[13]

**Attempted Ring Closure of 1-(Trichlorosilyl)-5-chlorohexane.**—To a large excess of Mg in 500 ml of ether was added 20 g (0.063 mol) of 1-(trichlorosilyl)-5-chlorohexane. The mixture was heated at reflux overnight, and then 35 g (0.25 mol) of methyl iodide was added. The mixture was again heated at reflux for

(13) F. C. Whitmore. L. H. Sommer. P. A. DiGiorgio, W. A. Strong. R. E. Van Strien, D. L. Bailey. H. K. Hall, E. W. Pietrusza, and G. T. Kerr, *J. Amer. Chem. Soc.*, **68**, 475 (1946).

24 hr. Water (100 ml) was then added and the organic material was extracted. The ether was removed by careful fractionation, and the volatile product was distilled. This material was shown to be trimethyl-*n*-hexylsilane by comparison of its spectra (nmr, ir) with those of an authentic sample.[13]

**1-Bromo-5-(dimethylchlorosilyl)hexane.**—Anhydrous HBr was bubbled through a mixture of 20 g (0.11 mol) of 5-(dimethylchlorosilyl)-1-hexene and 0.5 g of dibenzoyl peroxide in cyclohexane for 6 hr. During the reaction period, an oil separated from the cyclohexane solution. The ir of this oil showed a strong band at 9.5 μ (SiO). After separation of the oil and removal of the solvent, distillation yielded 18 g of product mixture, bp 80–100° (3 mm). Glpc analysis of this material showed it to be composed of equal amounts of two components. The material was taken into the ring-closure step without further purification.

**Ring Closure.**—A solution of 18 g of crude 1-bromo-5-(dimethylchlorosilyl)hexane in 500 ml of ether was added to an excess of Mg turnings, and the mixture was heated at reflux overnight. Water was then added and the ether phase was decanted and dried ($Na_2SO_4$). The ether was removed by distillation, and the product (bp 150–153°, $n^{25}$D 1.4410) was distilled. The product yield of the reaction was 3.8 g [23.6% from 5-(dimethylchlorosilyl)-1-hexene]: ir 8.0 (SiCH₃), 7.25 (-CH₃), 11.4 μ (silacyclohexane[9]); nmr δ 1.1 (d, α-Me), 1.0–2.2 (m), 0.1 (SiCH₃); there was no olefinic signal; mass spectrum *m/e* (rel intensity) 26 (19), 43 (12), 59 (35), 72 (25), 73 (25), 85 (35), 86 (25), 87 (11), 99 (base), 101 (15), 114 (35), 114 (35), 127 (60), 142 (65).

*Anal.* Calcd for $C_8H_{18}Si$: C, 67.51; H, 12.74. Found: C, 67.27; H, 12.59.

**Registry No.**—**1**, 30102-80-8; **2a**, 36982-63-5; **2b**, 36982-64-6; 5-chloro-1-hexene, 927-54-8; 5-(chloromethylsilyl)-1-hexene, 36982-66-8; 5-(dimethylsilyl)-1-hexene, 36982-67-9.

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# One-Electron *vs.* Two-Electron Oxidations.
# The Vanadium(V) and Manganese(III) Oxidations of Cyclobutanol

JAN ROČEK*[1] AND ANNETTE E. RADKOWSKY

*Department of Chemistry, The Catholic University of America, Washington, D. C.*

Vanadium(V) oxidizes cyclobutanol in high yields to the ring cleavage product, γ-hydroxybutyraldehyde. The observations that 1-methylcyclobutanol reacts about nine times faster than cyclobutanol, that the oxidation of 1-deuteriocyclobutanol is accompanied by a low deuterium isotope effect ($k_H/k_D$ = 1.21), and that cyclobutanol is about 1000 times more reactive than cyclohexanol, all support the mechanism consisting of a rate-limiting ring opening reaction leading to the ·CH₂CH₂CH₂CHO radical as the first reaction product. The presence of manganese(II) in chromic acid oxidations of cyclobutanol has a strong accelerating effect on the reaction, and leads to a large decrease in the deuterium isotope effect and to a large increase in the reactivity of 1-methylcyclobutanol. The yield of cyclobutanone decreases and that of hydroxybutyraldehyde increases with increasing concentration of manganese(II) in the system. These observations are consistent with a mechanism in which the effective oxidant is manganese(III), formed probably by the reaction Cr(VI) + Mn(II) ⇌ Cr(V) + Mn(III), reacting *via* the same free radical intermediate as vanadium(V). Both results strongly indicate that cyclobutanol reacts rapidly and smoothly with one-electron oxidizing agents under ring cleavage, and can be successfully employed as a probe for one-electron oxidants.

Cyclobutanol reacts with chromium(VI), which is a two-electron oxidant, to yield, by carbon–hydrogen bond breaking, the corresponding ketone, cyclobutanone[2] (eq 1), while cleavage of the carbon–carbon bond occurs in the reaction with one-electron oxidants like chromium(IV)[2] or cerium(IV)[3] (eq 2 and 3). It has been proposed[3] that the property of cyclobutanol to react by either carbon–hydrogen or carbon–carbon cleavage could make it a valuable tool for determining the ability of oxidants to react as either one- or two-electron re-

(1) Inquiries should be addressed to J. Roček, Graduate College, University of Illinois at Chicago Circle, Box 4348, Chicago, Ill. 60680.
(2) J. Roček and A. E. Radkowsky, *J. Amer. Chem. Soc.*, **90**, 2986 (1968).
(3) K. Meyer and J. Roček, *ibid.*, **94**, 1209 (1972).

$$\text{Cr(VI)} \ + \ \underset{\text{OH}}{\square}\!\!-\!\text{H} \ \longrightarrow \ \text{Cr(IV)} \ + \ \square\!\!=\!\!O \quad (1)$$

$$\text{M}^{n+} \ + \ \underset{\text{OH}}{\square}\!\!-\!\text{H} \ \longrightarrow \ \text{M}^{(n-1)+} \ + \ \cdot\text{CH}_2(\text{CH}_2)_2\text{CHO} \quad (2)$$

$$\cdot\text{CH}_2(\text{CH}_2)_2\text{CHO} \ \longrightarrow \ \text{HO(CH}_2)_3\text{CHO} \quad (3)$$
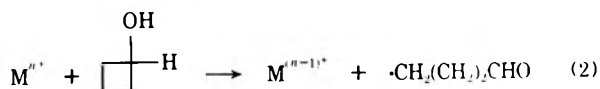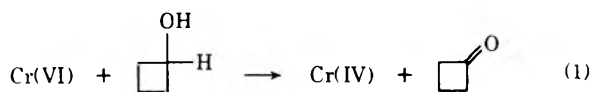
agents. However, before one can use cyclobutanol oxidations as a diagnostic tool, one has to gain more confidence that the observed pattern is indeed generally valid.
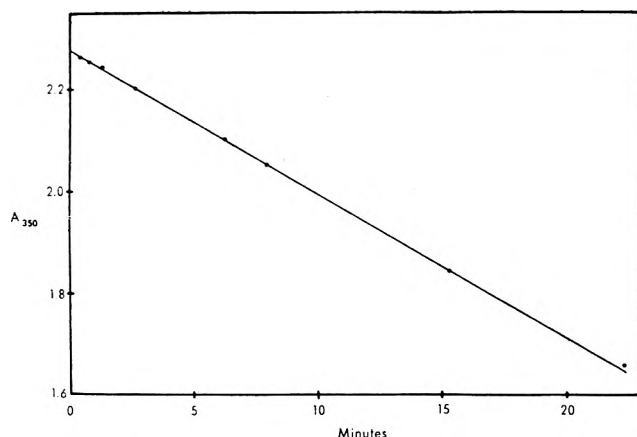
Figure 1.—Example of zero-order plot for the chromic acid oxidation of cyclobutanol in the presence of manganese(II) at 30°: cyclobutanol = 0.0128 $M$, chromium(VI) = 2.09 × 10$^{-3}$ $M$, MnSO$_4$ = 3.35 × 10$^{-3}$ $M$, Na$_2$SO$_4$ = 0.196 $M$.

Both vanadium(V)[4] and manganese(III)[4] are one-electron oxidants. They are known to oxidize unstrained alcohols, like cyclohexanol, to the corresponding ketones in a reaction in which the breaking of the carbon–hydrogen bond occurs in the rate-limiting step. We have therefore examined their reaction with cyclobutanol in order to determine whether this strained alcohol would react differently.

## Experimental Section

**Materials.**—The preparation and/or purification of the organic compounds used in this work will be described elsewhere.[5]

A solution of manganic sulfate, Mn$_2$(SO$_4$)$_3$, in 6.3 $M$ sulfuric acid was prepared from potassium permanganate and manganese sulfate, using an excess of the latter.[6] The solution was diluted to lower acidities with a manganese sulfate solution. With decreasing acidity, a shift[7] of the absorption maximum to shorter wavelengths was observed.

Commercially available ammonium vanadate (Fisher Certified Reagent) was used without purification.

**Kinetic Measurements.**—The reaction rates were followed spectrophotometrically[8] at 350 nm for both the vanadium(V) and the chromium(VI)-manganese(II) oxidation systems. In all cases at least a threefold excess of substrate over oxidant was employed. For the vanadium(V) oxidations, pseudo-first-order rate constants were calculated from the slopes of the plots of the logarithm of the absorbance *vs.* time. In the chromium(VI)-manganese(II) system good straight line plots were obtained for absorbance *vs.* time plots (Figure 1). The slopes of the lines were used to compute reaction rates and pseudo-zero-order rate constants. Only at very low manganese concentrations, the absorbance *vs.* time plots were curved and better straight line plots could be obtained from log (absorbance) *vs.* time plots. The pseudo-first-order constants obtained from the logarithmic plots were converted to initial rates by multiplication with the initial chromium(VI) concentration. The agreement between the rate data obtained from the two types of treatment of the experimental data was usually within 10%, with the logarithmic plots leading to somewhat higher figures. In view of the large amount of kinetic data investigated, only random duplicate runs were made. The deviations from the multiple results were within 3%. For the chromium(VI)-manganese(II)-cyclobutanol system, the molar absorptivity of chromium(VI) at 350 nm was 1.090 × 10$^3$.

(4) For an extensive review of vanadium(V) and manganese(III) oxidations, *cf.* W. A. Waters and J. S. Littler in "Oxidation in Organic Chemistry," Part A, K. B. Wiberg, Ed., Academic Press, New York, N. Y., 1965, pp 185–241.

(5) J. Roček and A. Radkowsky, to be published; *cf.* also A. E. Radkowsky, Ph.D. Thesis, The Catholic University of America, Washington, D. C., 1967.

(6) A. R. J. P. Ubbelohde, *J. Chem. Soc.*, 1605 (1935).

(7) R. G. Selim and J. J. Lingrove, *Helv. Chim. Acta*, **21**, 536 (1959).

(8) J. Roček and Sr. A. Riehl, *J. Amer. Chem. Soc.*, **89**, 6691 (1967).

In determining the rate dependence on the various components of the reaction medium, corrections were made to account for the uncatalyzed chromic acid oxidation of cyclobutanol. The $\Delta v_0$ referred to in all cases is the difference between the observed overall rate and the rate of the uncatalyzed chromium(VI) oxidation, and is therefore equivalent to the rate attributable to the manganese-catalyzed chromium(VI) oxidation. However, rate determinations were not made for chromium(VI) oxidations in which all the variations in substrate and chromium(VI) concentrations of the manganese(II) studies were duplicated. The contributions of the uncatalyzed oxidation were estimated, assuming a first-order dependence.

**Reaction Products. Gravimetric Determinations.**—In a typical experiment, 0.0795 g (0.680 mmol) of ammonium metavanadate, 0.0224 g (0.3114 mmol) of cyclobutanol, and 1 ml of 5 $M$ sulfuric acid were diluted with water to 5 ml and allowed to react at room temperature in the dark. After completion of the reaction, the solution was allowed to react overnight with a slight excess of a solution of 2,4-dinitrophenylhydrazine. The precipitate was collected, washed, dried, and weighed. The aqueous layer was extracted three times with chloroform, which was then neutralized, dried, and evaporated. The residue and precipitate were analyzed by tlc (ether–benzene, 3:1). The major product, 4-hydroxybutraldehyde 2,4-dinitrophenylhydrazone, was isolated by preparative tlc and further identified by ir and nmr comparisons with an authentic sample.

**Glpc Determination of Cyclobutanone.**—Isoamyl alcohol (0.01592 g, 0.1806 mmol) was added to a reaction mixture obtained as indicated above. Aliquots (0.2 ml) were extracted under standardized conditions (2 min extraction time) with carbon disulfide (0.2 ml) and analyzed by glpc (Aerograph Hy-Fi Model 600D, 0.125 × 60 in. Carbowax column). A calibration curve was used to determine cyclobutanone yields.

## Results and Discussion

**Vanadium(V).**—Table I gives the results of the kinetic study of the vanadium(V) oxidation of cyclobutanol, 1-deuteriocyclobutanol, and 1-methylcyclobutanol. The vanadium(V) oxidation of all alcohols was found to be first order in both the oxidant and the alcohol.

The data for cyclobutanols can be compared with those obtained for vanadium(V) oxidations of a nonstrained alcohol, cyclohexanol, by earlier investigators.[9] Littler and Waters obtained for somewhat different conditions (50°, 5.59 $M$ HClO$_4$, $\mu$ 6) a second-order rate constant, $k$ = 5.85 × 10$^{-4}$ $M^{-1}$ sec$^{-1}$. Comparing this figure with the figure for cyclobutanol given in Table I, one can estimate that cyclobutanol is about 1000 times more reactive than cyclohexanol toward vanadium(V) oxidation. This huge difference in reactivity clearly suggests that the two alcohols are oxidized by different mechanisms. As cyclohexanol is oxidized with carbon–hydrogen cleavage to the corresponding carbonyl compound, cyclohexanone, the much higher reactivity of cyclobutanol suggests that it undergoes a carbon–carbon cleavage, facilitated by the release of ring strain in the rate-limiting step.

The high reactivity of the tertiary 1-methylcyclobutanol (Table I) provides strong additional evidence

TABLE I

SECOND-ORDER RATE CONSTANTS FOR VANADIUM(V)
OXIDATIONS IN 1.0 $M$ PERCHLORIC ACID AT 30°[a]

| Substrate | 10$^2$ $k$, $M^{-1}$ sec$^{-1}$ | $k/k_{cyclobutanol}$ |
|---|---|---|
| Cyclobutanol | 0.458 | |
| 1-Deuteriocyclobutanol | 0.377 | 0.82 |
| 1-Methylcyclobutanol | 4.22 | 9.22 |

[a] [VO$_2$$^+$] = 5.8 × 10$^{-3}$ $M$; [alcohols] = 0.056–0.065 $M$.

(9) J. S. Littler and W. A. Waters, *J. Chem. Soc.*, 4046 (1959).

TABLE II

PRODUCTS OF VANADIUM(V) OXIDATION OF CYCLOBUTANOLS AT 30°

| Substrate | Mmol | [V(V)], mmol | Cyclobutanone | Yield, %[a] HO(CH₂)₃CR (O‖) | HC(CH₂)₂CR (O‖ O‖) | Total |
|---|---|---|---|---|---|---|
| Cyclobutanol[b] | 0.311 | 0.678 | 0.3 | 57.0[d] | 14.0[d] | 71.0 |
| Cyclobutanol[c] | 0.647 | 0.640 | 1.5 | 93.7[d] | | 95.2 |
| Cyclobutanol-1-d[b] | 0.323 | 0.673 | ~0 | 80.0[e] | 11.0[e] | 91.0 |
| 1-Methylcyclobutanol[b] | 0.260 | 0.658 | | 43.0[f] | | 43.0 |
| 1-Methylcyclobutanol[c] | 0.619 | 0.644 | | 76.0[f] | 4.9[f] | 80.4 |

[a] Calculated on basis of available V(V).  [b] [H₂SO₄] = 0.97 *M*.  [c] [HClO₄] = 1 *M*.  [d] R = H.  [e] R = D.  [f] R = CH₃.

for a mechanism involving carbon–carbon bond cleavage. The nine times higher reactivity of the tertiary alcohol makes it obvious that the presence of an α-hydrogen atom is entirely unnecessary for an oxidation to take place. Also, the low value[10] of the deuterium isotope effect ($k_H/k_D$ = 1.22), which is within the range usually observed for secondary isotope effects,[11] indicates that no carbon–hydrogen bond cleavage is taking place in the rate-limiting step.

Table II gives the result of the product analysis. Except for a minute amount of cyclobutanone, all products result from carbon–carbon bond cleavage. In the experiments in which a slight excess of the oxidant was used, the total yield is lower, and a substantial amount of higher oxidation products was identified. As we analyzed only for carbonyl compounds, substantial amounts of products, *e.g.*, hydroxy acids and lactones, were not determined, and their formation may account for the lower yields.

The nature of the products clearly confirms the conclusion reached from rate studies, that the oxidation proceeds by carbon–carbon bond cleavage. In particular, it should be noted that in this case the secondary cyclobutanol and the tertiary 1-methylcyclobutanol yield the same type of product, and thus obviously react by the same mechanism. This is quite different from the mechanism observed in chromium(VI) oxidations.[12]

All these results indicate that the vanadium(V) oxidation of cyclobutanols proceeds by a carbon–carbon bond cleavage (Scheme I).

SCHEME I



$$\text{·CH}_2\text{CH}_2\text{CH}_2\text{COR} + \text{V(V)} \longrightarrow$$
$$\text{HOCH}_2\text{CH}_2\text{CH}_2\text{COR} + \text{V(IV)} \quad (5)$$

**Manganese(III).**—The oxidation of cyclobutanol by manganese(III) was observed, unexpectedly, during an attempt to carry out a chromic acid oxidation of cyclobutanol in the presence of manganese(II).

When a chromic acid oxidation of a simple alcohol like isopropyl alcohol is carried out in the presence of manganese(II), a precipitate of manganese dioxide is formed, and the rate of oxidation may be reduced to a limiting value of one-half of its normal magnitude. This is due to the following set of reactions (Scheme II),

SCHEME II

$$\text{Cr(VI)} + \text{S} \longrightarrow \text{Cr(IV)} + \text{P}_6 \quad (6)$$
$$\text{Cr(IV)} + \text{Mn(II)} \longrightarrow \text{Mn(III)} + \text{Cr(III)} \quad (7)$$
$$2\text{Mn(III)} \longrightarrow \text{Mn(II)} + \text{MnO}_2 \quad (8)$$

where S represents the substrate and $P_6$ the product formed by its oxidation with chromium(VI).

In the oxidation of cyclobutanol in the presence of manganese(II) entirely different results were obtained. Neither precipitate formation nor the transient appearance of the cherry red color of manganese(III), clearly noticeable in control experiments with cyclohexanol, could be observed. Further, the oxidation rate in the presence of manganese(II) increased rather than decreased. Table III shows the effect of the con-

TABLE III

OXIDATION RATES[a] OF CYCLOBUTANOL AS A FUNCTION OF [Mn(II)]/[Cr(VI)] RATIO[b] AT 30°

| [Mn(II)]/[Cr(VI)] | $10^7 v_0$, *M* sec⁻¹ | $10^7 \Delta v_0$, *M* sec⁻¹ |
|---|---|---|
| 0 | 3.85 | 0 |
| 0.65 | 3.98 | 0.13 |
| 3.23 | 4.45 | 0.60 |
| 16.30 | 6.60 | 2.75 |
| 50.20 | 22.80 | 18.95 |
| 82.30 | 47.70 | 43.85 |
| 99.40 | 69.40 | 65.55 |

[a] $v_0$ oxidation rates extrapolated to the starting time of the reaction; $\Delta v_0$ is the rate increase caused by the presence of manganese(II).  [b] Conditions: [Cr(VI)] = 2.037 × 10⁻³ *M*, [H₂SO₄] = 0.954 *M*, [cyclobutanol] = 0.0127 *M*, [MnSO₄] + [Na₂SO₄] = 0.1998 *M*.

centration of manganese(II) sulfate on the oxidation rate of cyclobutanol at constant ionic strength. As the rate law of the oxidation changes as the concentration of manganese(II) is increased, initial rates ($v_0$) are used.

Table IV shows the effect of added manganese(II) on (a) the magnitude of the kinetic isotope effect and (b) the relative reactivity of 1-methylcyclobutanol and cyclobutanol.

The magnitude of the deuterium isotope effect decreases rapidly as the concentration of manganese(II) in the solution is increased. At high manganese(II): chromium(VI) ratios it reaches a value which is much closer to those typically associated with secondary rather than with primary isotope effects. This decrease in the value of the isotope effect is thus highly indicative of a change in mechanism. It is obvious that the transfer of the α-hydrogen atom which takes place in the rate-limiting step of the chromium(VI) oxidation of cyclobutanol does not take place during the rate-limiting step of the oxidation in the presence of manganese-(II).

(10) This low value stands in strong contrast to the value of $k_H/k_D$ = 3.6, which was obtained for the oxidation of cyclohexanol to cyclohexanone.⁹
(11) E. A. Halevi, *Progr. Phys. Org. Chem.*, **1**, 109 (1963).
(12) J. Roček and A. E. Radkowsky, *Tetrahedron Lett.*, 2835 (1968).

## Table IV

### Comparative Rates[a] in the Manganese(II) Catalyzed Chromic Acid Oxidation of Cyclobutanols[b]

| [MnSO$_4$], $M$ | [Mn(II)]/[Cr(VI)] | Cyclobutanol | 1-Deuterio-cyclobutanol[c] | 1-Methyl-cyclobutanol | $(v_0)_H/(v_0)_D$ | $(v_0)_{CH_3}/(v_0)_H$ |
|---|---|---|---|---|---|---|
| | | | 10$^7 v_0$, $M$ sec$^{-1}$ | | | |
| 0[d] | 0 | 5.43 | 0.88 | | 6.2 | 0.0046[e] |
| 0.0267[d,f] | 12.3 | 6.13 | 1.37 | 0.60 | 4.5 | 0.1 |
| 0.099 | 49 | 20.98 | 14.32 | 17.35 | 1.46 | 0.83 |
| 0.1332 | 66 | 32.6 | 23.8 | 32.3 | 1.37 | 1.0 |
| 0.1998 | 99 | 67.5 | 54.8 | 76.2 | 1.23 | 1.13 |

[a] $v_0$ oxidation rates extrapolated to the starting time of the reaction. [b] Conditions: [Cr(VI)] = 1.971–2.175 × 10$^{-3}M$; [alcohol] = 0.01217–0.01396 $M$; [H$_2$SO$_4$] = 0.954 $M$ 30°. [c] Uncorrected for actual deuterium content. [d] $v_0$ from logarithmic plots of absorbance. [e] In 1 $M$ HClO$_4$. [f] 25°.

The effect of manganese(II) on the relative oxidation rate of 1-methylcyclobutanol leads to the same conclusion. While in the absence of manganese(II) cyclobutanol is oxidized by chromium(VI) about 200 times faster than 1-methylcyclobutanol, the tertiary alcohol actually becomes more reactive than the secondary alcohols at high manganese(II) concentrations. Again, this clearly demonstrates that the breaking of the carbon–hydrogen bond in the rate-limiting step is replaced by another process, most probably the breaking of a carbon–carbon bond.

The conclusions about the effect of added manganese-(II) on the nature of oxidation of cyclobutanol by chromic acid which were derived from the rate studies discussed above are fully supported by the product studies, which are summarized in Table V. The yield

## Table V

### Product Composition in Manganese(II)–Chromium(VI) Oxidation of Cyclobutanols[a]

| R | [Mn(II)]/[Cr(VI)] | Cyclobutanone, % yield[b] | HO(CH$_2$)$_3$C(R)=O, % yield[c] |
|---|---|---|---|
| H | 0 | 38.1 | |
| H | 3.2 | 27.7 | |
| H | 9.5 | 11.5 | 73 |
| H[d] | 12.6 | 18.3 | |
| H | 25.4 | 3.7 | 88 |
| D | 12.7 | 3 | 95 |
| CH$_3$ | 12.7 | | 68 |

[a] Conditions: [H$_2$SO$_4$] = 1 $M$; K$_2$Cr$_2$O$_7$ = 0.0263 mmol; alcohol (R = H, 0.312 mmol; R = D, 0.310 mmol; R = CH$_3$, 0.255 mmol); 30°. [b] Analyzed by glpc. [c] Gravimetric determination. [d] 0°.

of cyclobutanone, which corresponds to about 40% of the products in the chromic acid oxidation in the absence of manganese, decreased to the low value of 3.7% when a Mn(II):Cr(VI) ratio of 25:1 was reached. At the same time, the yield of the cleavage product, γ-hydroxybutyraldehyde, increased considerably. In the presence of less than a 13-fold excess of manganese(II) over chromium(VI), the oxidation of cyclobutanol-1-d gives a 95% yield of the deuteriohydroxyaldehyde and the oxidation of 1-methylcyclobutanol gives an almost 70% yield of the corresponding hydroxy ketone, whereas no identifiable products could be isolated from the oxidation of the latter alcohol in the absence of manganese(II).[12]

The results of both kinetic studies and product studies thus show that in the presence of manganese(II) the oxidation of cyclobutanol assumes a completely

different character than corresponds to a rate-limiting two-electron oxidation of chromium(VI) and becomes in all respects very similar to one-electron oxidations by oxidants like vanadium(V) or cerium(IV).[3] We therefore conclude that the actual oxidant in the chromic acid–manganese(II) system is manganese(III) and not chromium(VI), and that the rate-limiting step of the oxidation consists in a carbon–carbon bond cleavage leading to a free radical intermediate (reaction 2). This conclusion can be made with a great deal of confidence, even though a fully satisfactory detailed reaction mechanism cannot be offered at the present time and further work will be required before the reaction can be fully understood.

The conclusion that manganese(III) is very reactive toward cyclobutanol and is in all probability responsible for the observed oxidation cleavage reaction is also supported by the observation of an instantaneous reduction, upon the addition of cyclobutanol, of a manganese(III) solution in 1.1 $M$ sulfuric acid. Strain-free alcohols react only slowly under these conditions.

A more detailed investigation of the oxidation of cyclobutanol by chromic acid in the presence of manganese(II) led to the following results.

(1) The order of the reaction in chromium(VI) decreases to zero order with increasing manganese(II) concentrations, although in the absence of manganese(II) the oxidation is strictly first order in chromium(VI). Individual runs gave fairly good zero-order plots over almost the entire range of manganese(II) concentrations studied (Figure 1). The dependence of the experimental pseudo-zero-order rate constants on the initial chromium(VI) concentrations is more complex, but a decrease of the order with respect to chromium-(VI) down to zero is clearly evident, particularly at higher concentrations of manganese(II) (Figure 2).

(2) The rate increase, $\Delta v_0$, is proportional to [Mn-(II)] at lower manganese(II) concentrations and to [Mn(II)]$^2$ at higher manganese(II) concentrations (Figure 3).

(3) The reaction is first order in cyclobutanol throughout the whole set of conditions, regardless of the manganese(II) concentration (Figure 4).

(4) The rate is independent of the concentration of chromium(III) (Table VI).

For the regions in which the reaction is first order in manganese(II), these findings, together with the convincing evidence that a one-electron oxidation involving manganese(III) is taking place, can be accommodated by Scheme III.

Reaction 9 is typical for the oxidation of metal ions which can undergo a one-electron reaction, for ex-

Figure 2.—Dependence of the manganese(II) catalyzed oxidation of cyclobutanol on the concentration of chromium(VI) at 30°: ■, [MnSO₄] = 0.1332 $M$, [cyclobutanol] = 0.03621–0.1300 $M$; O, [MnSO₄] = 0.0999 $M$, [cyclobutanol] = 0.0752–0.2103 $M$; ●, [MnSO₄], = 0.0333 $M$, [cyclobutanol] = 0.072 $M$; [H₂SO₄] = 0.954 $M$, $\Delta k_1 = \Delta v_0/[\text{CB}]$.

TABLE VI

DEPENDENCE OF THE MANGANESE(II) CATALYZED OXIDATION
OF CYCLOBUTANOL ON CHROMIUM(III)[a]

| Chromium(III), $M$ | $10^3 v_0$, $M$ sec$^{-1}$ |
|---|---|
| 0 | 0.851 |
| 0.0520 | 0.874 |
| 0.1039 | 0.864 |

[a] Conditions: [MnSO₄] = 0.1996 $M$, [Mn(II)] + [Cr(III)] + [Na₂SO₄] = 0.3038 $M$, [Cr(VI)]$_{avg}$ = 2.02 × 10$^{-3}$ $M$, [cyclobutanol] = 0.0133 $M$, [H₂SO₄] = 0.954 $M$, 30°.

SCHEME III

$$\text{Cr(VI)} + \text{Mn(II)} \rightleftharpoons \text{Cr(V)} + \text{Mn(III)} \qquad (9)$$

$$\text{Mn(III)} + \text{S} \xrightarrow{\text{rate-limiting}} \text{R·} + \text{Mn(II)} \qquad (10)$$

$$3[\text{R·} + \text{Cr(VI)} \longrightarrow \text{P} + \text{Cr(V)}] \qquad (11)$$

$$2[2\text{Cr(V)} \longrightarrow \text{Cr(IV)} + \text{Cr(VI)}] \qquad (12)$$

$$2[\text{Cr(IV)} + \text{S} \longrightarrow \text{Cr(III)} + \text{R·}] \qquad (13)$$

$$\overline{2\text{Cr(VI)} + 3\text{S} \longrightarrow 2\text{Cr(III)} + 3\text{P}}$$

ample, vanadium(IV), iron(II), and neptunium(IV).[13] We assume that the oxidation of the substrate by manganese(III) (reaction 10) constitutes the rate-limiting step. The free radical formed in this reaction can be oxidized further by any of the oxidants which are available, chromium(VI), chromium(V), chromium-(IV), or manganese(III). In Scheme III we assume that the most likely reaction of the free radical is its oxidation by the oxidant which is present in the highest concentration. However, reaction with other oxidants would not alter the overall results. Since chromium(V) is a product of both reactions 9 and 11 in the above sequence, a reaction in which it is consumed has to be included in the scheme. We propose that chromium(V) may undergo a disproportionation reaction into chromium(IV) and chromium(VI) (reaction 12). We have shown earlier[14] that this reaction should have an equilibrium constant of about 2.5 × 10$^{13}$, and should thus be thermodynamically highly favored. Con-

(13) J. K. Beattie and G. P. Haight, Jr., in "Mechanisms of Inorganic Relations," J. A. Edwards, Ed., Wiley, New York, N. Y., 1972.
(14) M. Rahman and J. Roček, *J. Amer. Chem. Soc.*, **93**, 5462 (1971).



Figure 3.—Dependence of the manganese(II) catalyzed oxidation of cyclobutanol on the concentration of manganese(II): [Cr(VI)] = 2.073 × 10$^{-3}$ $M$, [cyclobutanol] = 0.0127 $M$, [MnSO₄] + [Na₂SO₄] = 0.1998 $M$, [H₂SO₄] = 0.954 $M$.



Figure 4.—Dependence of the manganese(II) catalyzed oxidation on cyclobutanol concentration at 30°: $\Delta k_1 = \Delta v_0/[\text{Cr(VI)}]$; [Cr(VI)]$_{avg}$ = 2.07 × 10$^{-3}$ $M$, [H₂SO₄] = 0.954 $M$, [MnSO₄] + [Na₂SO₄] = 0.1332 $M$; □, [MnSO₄] = 0.0333 $M$; ■, [MnSO₄] = 0.0666 $M$; O, [MnSO₄] = 0.0999 $M$; ●, [MnSO₄] = 0.1332 $M$.

siderable evidence that reaction 12 does indeed play an important role in the chromic acid oxidation is now becoming available.[15,16] Reaction 13 represents the chromium(IV) oxidation of cyclobutanol, which is discussed in detail elsewhere.[2,5,17]

The rate of the reaction, according to Scheme III, is governed by step 10, and is therefore given by eq 14.

$$v = k_{10}[\text{S}] \, [\text{Mn(III)}] = k_{10}K_9[\text{S}] \, [\text{Mn(II)}] \frac{[\text{Cr(VI)}]}{[\text{Cr(V)}]} \qquad (14)$$

If one can make the fairly plausible assumption that the steady-state concentration of chromium(V) which will be established rapidly during the reaction

(15) P. M. Nave and W. S. Trahanovsky, *ibid.*, **92**, 1120 (1970).
(16) J. C. Drozd, Ph.D. Thesis, University of Illinois at Chicago Circle, Chicago, Ill., 1971.
(17) M. Rahman and J. Roček, *J. Amer. Chem. Soc.*, **93**, 5455 (1971).

Figure 5.—Determination of rate constant for manganese(II) catalyzed oxidation of cyclobutanol at low manganese(II) concentrations at 30°: [cyclobutanol] = 0.0127 $M$, [Cr(VI)] = 2.073 × 10$^{-3}$ $M$, [Mn(II)] = 0–0.0333 $M$, [MnSO$_4$] + [Na$_2$SO$_4$] = 0.1998 $M$, [H$_2$SO$_4$] = 0.954 $M$; $\Delta v_0 = (v_0)_{expt} - k_A[Cr(VI)]$·[alcohol].

will be approximately proportional to the concentration of chromium(VI), then the reaction should be first order in both the substrate and manganese(II) and approximately zero order in chromium(VI). This is indeed observed at higher manganese concentrations.[18]

At high manganese(II) concentrations, the steady-state concentration of chromium(V) would increase, and an additional reaction (eq 15) may become important.

$$Cr(V) + Mn(II) \overset{\longrightarrow}{\underset{\longleftarrow}{}} Cr(IV) + Mn(III) \qquad (15)$$

This reaction may be responsible for the shift from first- to second-order dependence on the concentration of manganese(II) at high concentrations (Figure 3).

The oxidation rates for cyclobutanol by chromium(VI) and manganese(II) can be expressed very crudely by an empirical rate law (eq 16). The first term corresponds to the oxidation of cyclobutanol in the absence of manganese(II). The second and third terms reflect the dependence of the oxidation rate on manganese(II) at low and high manganese(II) concentrations, respectively. The values of the rate constants in eq 16 as estimated from the experimental data from the appropriate plots (Figures 5 and 6) are

$$v_0 = [\text{alcohol}]\{k_A[Cr(VI)] + k_B[Mn(II)] + k_C[Mn(II)]^2\} \qquad (16)$$

$$k_A = 1.49 \times 10^{-2}\ M^{-1}\ \text{sec}^{-1}$$
$$k_B = 6.5 \times 10^{-4}\ M^{-1}\ \text{sec}^{-1}$$
$$k_C = 9.2 \times 10^{-3}\ M^{-2}\ \text{sec}^{-1}$$

One can attempt to estimate the magnitude of $k_{10}$, the second-order rate constant for the manganese(III) oxidation of cyclobutanol. From the reduction potentials of the Cr(VI)/Cr(V) couple (0.55 V)[19] and the Mn(III)/Mn(II) couple (1.51 V)[20] one can estimate the value of the equilibrium constant of reaction 9: $k_9 \cong 5 \times 10^{-17}$. At the beginning of the reaction, when [Mn(III)] = [Cr(V)], the concentration of manganese(III) will be approximately 10$^{-16}$ $M$ {for [Mn(II)] = 0.1, [Cr(VI)] = 10$^{-3}M$} and will in the course of the reaction decrease further as the concentration of chrom-

(18) At low manganese(II) concentrations, the dependence on chromium(VI) is not reduced to zero but is of an apparent one-half order (Figure 2). No reasonable interpretation for this observation can be offered at this time. It is unfortunate that an attempt to derive a more precise rate law for Scheme III leads to a fourth-order equation, which is too complex to permit direct experimental verification.

(19) L. J. Csanyi, *Magy. Kem. Foly.*, **65**, 415 (1959).

(20) W. M. Latimer, "Oxidation Potentials," 2nd ed, Prentice-Hall, Englewood Cliffs, N. J., 1952.

Figure 6.—Determination of rate constant for manganese(II) catalyzed oxidation of cyclobutanol at high manganese(II) concentrations at 30°: [cyclobutanol] = 0.0127 $M$, [Cr(VI)] = 2.03 × 10$^{-3}$ $M$, [Mn(II)] = 0.0333–0.1998 $M$, [MnSO$_4$] + [Na$_2$SO$_4$] = 0.1998 $M$, [H$_2$SO$_4$] = 0.954 $M$; $\Delta v_0 = (v_0)_{expt} - k_A[Cr(VI)][\text{alcohol}] - k_B[Mn(II)][\text{alcohol}]$.

ium(V) increases. As $k_B = k_{10}[Mn(III)]/[Mn(II)]$ the value of $k_{10}$ must be at least 10$^5$ $M^{-1}$ sec$^{-1}$. Manganese(III) thus appears to be an extremely reactive oxidant toward cyclobutanol. This reactivity, which is clearly by many orders of magnitude higher than the reactivity toward unstrained secondary alcohols,[4] strongly supports the assumption that cyclobutanols react by a completely different mechanism, namely, by way of carbon–carbon cleavage.

Kemp and Waters[21] have described a study of the effect of manganese(II) on the chromic acid oxidation of α-hydroxyisobutyric acid. Their results parallel our findings in many respects, and it is therefore quite probable that a similar mechanism may be operative in both cases. However, these authors proposed a mechanism (Scheme IV) in which the rate-limiting step is the decomposition of a reversibly formed manganese(III)–substrate complex.

This mechanism would lead to the rate law (eq 20),

$$\frac{-d[Cr(VI)]}{dt} = \frac{-d[Mn(III)-S]}{dt} =$$
$$\frac{kK^{1/3}[Cr(VI)]^{1/3}[Mn(II)](S)}{[Cr(III)]^{1/3}} \qquad (20)$$

where $K$ is the overall equilibrium constant for the formation of Mn(III)–S from the substrate, manganese(II) and chromium(VI) (reactions 17 and 18). This rate law requires that chromium(III) should have a retarding effect on the reaction. Kemp and Waters did not examine the effect of added chromium(III).

(21) T. J. Kemp and W. A. Waters, *J. Chem. Soc.*, 3193 (1969).

SCHEME IV

$$Mn(II) + S \rightleftharpoons Mn(II)\text{-}S \qquad (17)$$

$$Cr(VI) + 3Mn(II)\text{-}S \rightleftharpoons Cr(III) + 3Mn(III)\text{-}S \qquad (18)$$

$$Mn(III)\text{-}S \xrightarrow{k} Mn(II) + P \qquad (19)$$
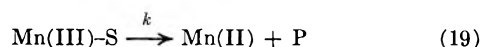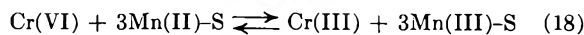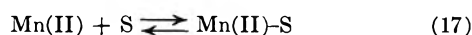
However, in our study chromium(III) definitely did not exhibit any influence on the reaction rate. Therefore, any mechanism which would require an equilibrium involving chromium(III) to be established prior to the rate-limiting step of the oxidation has to be rejected, and we therefore cannot apply the mechanism proposed by Kemp and Waters to rationalize our results. Further, while the formation of a complex

between manganese and an $\alpha$-hydroxy acid was an entirely plausible assumption, it would be much less justified to propose the formation of an intermediate complex in the case of the oxidation of cyclobutanol.

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# The Synthesis of Substituted Hydroazulenes

RICHARD A. KRETCHMER* AND W. MICHAEL SCHAFER

*Department of Chemistry, Illinois Institute of Technology, Chicago, Illinois   60616*

The conversion of 1(9)-octalin-2-one derivatives to isomeric 9-octalin-2-one derivatives by way of ketal formation and subsequent acid hydrolysis has been examined. Construction of substituted diketo hydroazulenes from these 9-octalin-2-one derivatives has been studied, and the chemistry of the resulting compounds investigated.

A large variety of techniques are currently available for the stereoselective construction of substituted decalins and hydrindanes. In addition, conformational analysis is useful in predicting the relative stability of isomers in such systems.[1] Unfortunately, a similar body of information is not available for the stereoselective construction of substituted hydroazulenes, and the application of conformational analysis to substituted seven-membered rings is relatively difficult.[2] Recently, a large and relatively important group of sesquiterpenes, the pseudoguaianolides, has been shown to possess the hydroazulene ring system.[3] Damsin (1) is a typical representative of this family of



1
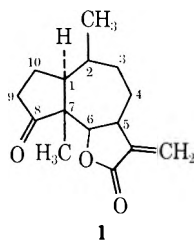
compounds.[4] As a result of our interest in these sesquiterpenes, this work was initiated to develop stereoselective methods for the preparation of substituted and functionalized hydroazulenes, with particular reference to the substitution patterns typical of the pseudoguaianolides.

In order to provide a method for direct introduction of oxygen functionality at C-6 and C-8 of the hydroazulene ring system, we have examined the transannular condensation of two unstable 1,3,6-cyclodecatriones 5a and 5b, which are conveniently prepared by ozonolysis of the corresponding $\beta,\gamma$-unsaturated ketones 4a and 4b[5] (Scheme I).

The methods available in the literature for construction of $\beta,\gamma$-unsaturated ketones, such as 4, are essentially twofold: kinetic protonation of the enolate anion derived from the corresponding $\alpha,\beta$-unsaturated ketone[6] and Birch reduction of a suitably substituted 6-methoxytetralin followed by careful hydrolysis.[7] Unfortunately, these methods require vigorous and strongly basic reaction conditions, which are not compatible with a variety of functional groups. It is well known, however, that conversion of an $\alpha,\beta$-unsaturated ketone to a ketal affords a product in which the double bond has moved to a $\beta,\gamma$ position.[8] We, therefore, chose to examine the possibility of careful hydrolysis of such a ketal to the corresponding $\beta,\gamma$-unsaturated ketone.

Treatment of octalone 2a with ethylene glycol in the presence of $p$-toluenesulfonic acid afforded ketal 3a as the only product. Careful hydrolysis of 3a with oxalic acid in aqueous methanol then afforded an 81% yield of 4a. Ozonolysis of 4a followed by a reductive work-up would be anticipated to yield triketone 5a. This compound proved to be extremely reactive, however, and could not be isolated. Hydroazulene 6a was obtained instead, presumably by way of spon-

(1) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962.

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(3) J. Romo and A. R. de Vivar, *Progr. Chem. Org. Natur. Prod.*, **25**, 90 (1967).

(4) (a) L. Bernardi and G. Büchi, *Experientia*, **13**, 466 (1957); (b) W. Herz, H. Watanabe, M. Miyazaki, and Y. Kishida, *J. Amer. Chem. Soc.*, **84**, 2601 (1962); (c) M. Suchy, V. Herout, and F. Šorm, *Collect. Czech. Chem. Commun.*, **28**, 2257 (1963).

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(6) (a) H. J. Ringold and S. K. Malhotra, *Tetrahedron Lett.*, 669 (1962); (b) J. A. Marshall and S. F. Brady, *ibid.*, 1387 (1969); (c) J. Meinwald and L. Hendry, *J. Org. Chem.*, **36**, 1446 (1971).

(7) *Cf.* A. J. Birch, *J. Chem. Soc.*, 593 (1946).

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SCHEME I



2a, R₁ = R₂ = H → 3a, R₁ = R₂ = H

4a, R₁ = R₂ = H → 5a, R = H

6a, R = H → 7a, R₁ = R₂ = H + 8a, R = H

12 was then alkylated[9] with 3,5-dimethyl-4-chloro-methylisoxazole[10] in the presence of hexamethylphosphoramide to give stereospecifically keto isoxazole 13 in 41% overall yield. Hydrogenolysis of 13 followed by treatment with sodium methoxide and finally aqueous base[11] afforded 5-methyl-1(9)-octalin-2-one (2b), which contained 12% of the β,γ-unsaturated isomer 4b.



Acid-catalyzed ketalization of this equilibrium mixture with ethylene glycol gave 3b as the only product. Subsequent hydrolysis with oxalic acid in aqueous methanol yielded a 12:3:85 mixture of 2b, 3b, and 4b, respectively, from which pure 4b was obtained by column chromatography. Ozonolysis of 4b also failed to produce a stable 1,3,6-cyclodecatrione. Spontaneous condensation of the presumed intermediate 5b afforded the enolic diketo hydroazulene 6b directly in 80% yield. Alkylation of 6b with methyl iodide and potassium carbonate then afforded 7b as the only isolable product. In contrast with 6a, the C-2 methyl group of 6b apparently provides enough additional stabilization of the intermediate enolate anion so that 7b is obtained to the complete exclusion of 8b.

Since C-5 of 7b is activated by a carbonyl group, in principle an additional substituent could be introduced at this position by alkylation. This, however, requires a method for differentiation between the two carbonyl groups. This was accomplished by monoketalization of 7b with ethylene glycol to give a 4:6

taneous transannular bond formation followed by loss of water. Subsequent alkylation of 6a with methyl iodide and potassium carbonate then afforded a 68:32 mixture of 7a and 8a, from which pure 7a could be obtained by fractional crystallization.

Catalytic hydrogenation of an intermediate such as 7 offers a potential method for control of the relative stereochemistry at C-1 and C-2 of the hydroazulene ring, if hydrogen is delivered in a cis fashion from the catalyst surface. Since all of the known pseudo-guaianolides appear to possess a trans ring junction at C-1 and C-7,[3] there is also an additional requirement that hydrogen be delivered from the side of the molecule opposite the C-7 methyl group. Unfortunately, hydrogenation of 7a over platinum afforded the cis-fused compound 9 in 67% yield, while none of the trans-fused compound 10 could be isolated. It appears likely, how-

7a →
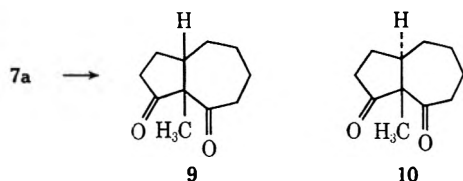


ever, that additional substituents on the ring system may be utilized to control the stereochemistry of this reaction.[4b]

The introduction of a C-2 methyl group on the hydroazulene ring system was next examined. Cuprous chloride catalyzed conjugate addition of methylmagnesium iodide to 2-cyclohexenone (11) in ether solution was carried out to give magnesium enolate 12. Enolate

7b →

(9) *Cf.* (a) G. Stork, *Pure Appl. Chem.*, **17**, 383 (1968); (b) G. Stork, G. L. Nelson, F. Rouessac, and O. Gringore, *J. Amer. Chem. Soc.*, **93**, 3091 (1971).

(10) (a) N. K. Kochetkov, E. D. Khomutova, and M. V. Bazilevskii, *J. Gen. Chem. USSR*, **28**, 2762 (1958); (b) J. E. McMurry, Ph.D. Thesis, Columbia University, New York, N. Y., 1967.

(11) *Cf.* (a) G. Stork, S. Danishefsky, and M. Ohashi, *J. Amer. Chem. Soc.*, **89**, 5459 (1967); (b) G. Stork and J. E. McMurry, *ibid.*, **89**, 5463 (1967); (c) *ibid.*, **89**, 5464 (1967).

mixture of 14 and 15, respectively, which was separated by column chromatography. Although monoketal formation was very facile, diketal 16 was not observed as a product. Relief of the unfavorable interaction between the dipoles of the carbonyl groups of **7b**, whose orientation is fixed by the hydroazulene ring system, may be responsible. In addition, hydrogenation of **7b** over platinum resulted in reduction of the C-8 carbonyl group to give **17** in 36% yield. None of the isomeric product **18** could be isolated.

In an effort to introduce substitution at C-5 of the hydroazulene ring system, without resorting to alkylation of an intermediate such as **14**, an attempt was made to construct **4c**. Reaction of pyrrolidine with **13** afforded the corresponding enamine **19**, which was
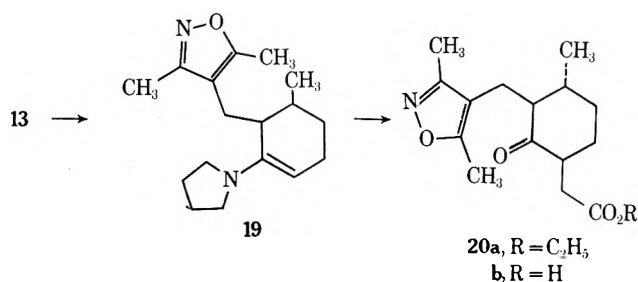


treated with ethyl bromoacetate to give **20a**. Saponification then gave the crystalline acid **20b**, which presumably possesses the more stable all-equitorial configuration. Utilization of the isoxazole annelation procedure[11] permitted conversion of **20b** to **2c**, and subsequent Fischer esterification with methanol afforded **2d**. Ketalization of **2d** with ethylene glycol proceeded smoothly to give a product which contained no vinyl protons in the nmr. Therefore, this represents either **3c**, **21**, or a mixture of the two. Careful hy-



drolysis of this product with oxalic acid afforded a 58% recovery of α,β-unsaturated ketone **2d**. In addition, an inseparable 23:77 mixture of ketal and β,γ-unsaturated ketone was also obtained. On the assumption that the unconjugated ketone thus obtained possessed structure **4c**, the ketone-ketal mixture was ozonized, and the crude product was treated with methyl iodide and potassium carbonate. The anticipated product, **7c**, would be expected to show infrared absorption near 1745 cm$^{-1}$ for the carbonyl group contained in a five-membered ring. This was not observed in the crude product. The implication appears to be that the β,γ-unsaturated ketone obtained in this series of reactions was **22** and not the desired **4c**.[12]
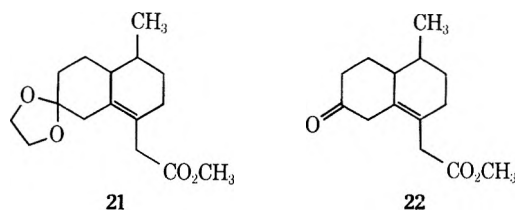
(12) The preparation of β,γ-unsaturated ketone 4c has been accomplished by an alternate route. A manuscript describing its synthesis and conversion to substituted hydroazulenes is in preparation.

**2,2-Ethylenedioxy-9-octalin (3a).**—To a solution of 9.595 g (63.9 mmol) of enone **2a**[14] and 0.1022 g (0.54 mmol) of *p*-toluenesulfonic acid monohydrate in 75 ml of benzene was added 25 ml of ethylene glycol. The resulting mixture was heated at reflux in a nitrogen atmosphere under a Dean-Stark water separator for 25 hr. After cooling, the mixture was diluted with 150 ml of benzene and washed once with 50 ml of saturated NaHCO$_3$ solution and three times with 50-ml portions of water, then dried. Concentration *in vacuo* followed by distillation afforded 11.317 g (91%) of pure ketal **3a** as a colorless liquid: bp 75.5–80.0° (0.10–0.20 mm); nmr (CCl$_4$) δ 3.84 (4 H, s, OCH$_2$CH$_2$O).

*Anal.* Calcd for C$_{12}$H$_{18}$O$_2$: C, 75.76; H, 7.42. Found: C, 75.58; H, 7.53.

**9-Octalin-2-one (4a).**—To a solution of 1.000 g (5.15 mmol) of ketal **3a** in 50 ml of methanol was added a solution of 0.852 g (9.46 mmol) of oxalic acid in 30 ml of water, and the resulting mixture was allowed to stir at room temperature for 4 hr. The mixture was then diluted with 200 ml of half-saturated NaCl solution and extracted with 200 ml of ether. The ether extract was washed twice with 50-ml portions of water, once with 25 ml of saturated NaHCO$_3$ solution, once with 50 ml of water, and once with 25 ml of saturated NaCl, and dried. Concentration *in vacuo* afforded 0.748 g of oil, which was put on a 20-g column of silica gel. Elution with 400 ml of benzene afforded 0.627 g (81%) of **4a**, which was identified by spectroscopic comparison with an authentic sample.[7]

**Bicyclo[5.3.0]dec-1(7)-ene-6,8-dione (6a).**—A solution of 6.217 g of β,γ-unsaturated ketone **4a** in a mixture of 40 ml of dichloromethane and 40 ml of absolute methanol was cooled at Dry Ice–acetone bath temperature and treated with a stream of ozone in oxygen for 2.1 hr (until the blue coloration of excess ozone developed). After the solution was purged with nitrogen, 20 ml of trimethyl phosphite[15] was added and the mixture was allowed to stir at room temperature for 21.3 hr. Concentration *in vacuo* followed by distillation afforded 4.896 g (72%) of **6a** as a yellow liquid, bp 89.5–97.0° (0.4 mm). Redistillation afforded the analytical sample: bp 86–87° (0.6 mm); uv max (CH$_3$OH) 234 nm (ε 8380); ir (neat) 1720, 1668, and 1611 cm$^{-1}$.

*Anal.* Calcd for C$_{10}$H$_{12}$O$_2$: C, 73.14; H, 7.37. Found: C, 72.95; H, 7.23.

**7-Methylbicyclo[5.3.0]dec-1-ene-6,8-dione (7a).**—To a solution of 2.66 g (16.2 mmol) of **6a** in 100 ml of acetone was added 108 g (761 mmol) of methyl iodide and 2.38 g (17.2 mmol) of potassium carbonate. After reflux for 23 hr, the mixture was filtered and the filtrate was concentrated *in vacuo*. Chromatography of the residue on silica gel with 2:98 ether–benzene elution afforded 0.571 g (20%) of a mixture of **7a** and **3a**, which was obtained as a colorless liquid after short-path distillation (121° bath at 0.50 mm). Integration of nmr signals (CCl$_4$ solution) at δ 1.23, 1.30, and 2.96 indicated a 32:68 ratio of **8a** and **7a**.

*Anal.* Calcd for C$_{11}$H$_{14}$O$_2$: C, 74.13; H, 7.92. Found: C, 74.31; H, 7.77.

Crystallization of the isomer mixture from ether–hexane at −20° afforded 0.165 g of oily, white solid. Two recrystallizations yielded pure **7a** as colorless prisms: mp 49.5–50.0°; ir (KBr) 1739 (five-membered ring C=O), 1697 (seven-membered ring C=O), and 1672 cm$^{-1}$ (C=C); nmr (CCl$_4$) δ 1.30 (3 H, s, CH$_3$) and 5.84 (1 H, t, *J* = 6 Hz, vinyl H).

*Anal.* Calcd for C$_{11}$H$_{14}$O$_2$: C, 74.13; H, 7.92. Found: C, 74.02; H, 8.02.

***cis*-7-Methylbicyclo[5.3.0]decane-6,8-dione (9).**—To a solution of 0.0593 g of enedione **7a** in 6.0 ml of absolute ethanol was added 0.0216 g of 83% platinum oxide, and the mixture was stirred under a hydrogen atmosphere for 3 hr. Catalyst was then filtered off and washed with ethanol. Concentration *in vacuo*

(13) Melting points are uncorrected. Unless otherwise stated, magnesium sulfate was employed as a drying agent. Uv spectra were determined either on a Cary Model 11PM or a Beckman DB-G spectrophotometer. The infrared spectra were determined with a Beckman IR-8 infrared spectrophotometer. Nmr spectra were determined with a Varian A-60 spectrometer using tetramethylsilane as internal standard. The mass spectra were obtained with a Varian MAT CH7 mass spectrometer. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich. Baker reagent silica gel, 60–200 mesh, was used as adsorbent for column chromatography.

(14) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

(15) W. S. Knowles and Q. E. Thompson, *J. Org. Chem.*, **25**, 1031 (1960).

of the combined filtrate and washings afforded 0.0598 g of colorless oil, which was chromatographed on 10.0 g of silica gel. Elution with 1:9 ether–benzene afforded 0.0399 g (67%) of 9, identical with an authentic sample[16] by comparison infrared and nmr spectra and also by comparison thin layer chromatography (silica gel G, elution with 2:8 ethyl acetate–benzene).

**3-Methyl-2-(3,5-dimethyl-4-isoxazolylmethyl)cyclohexanone (13).**—A solution of methylmagnesium iodide was prepared under nitrogen by dropwise addition of a solution of 31.248 g (0.220 mol) of methyl iodide in 400 ml of anhydrous ether into a flask containing 5.596 g (0.230 g-atom) of magnesium turnings, over a period of 1.9 hr with mechanical stirring, and at ice-bath temperature. After addition was completed, stirring was continued at room temperature for 1 hr. The resulting mixture was cooled at ice-bath temperature, and 0.991 g (0.010 mol) of cuprous chloride was added. A solution of 19.228 g (0.200 mol) of 2-cyclohexenone in 400 ml of anhydrous ether was then added dropwise over a period of 3.25 hr with stirring. When addition was complete, a solution of 29.136 g (0.200 mol) of 3,5-dimethyl-4-chloromethylisoxazole[10] in 90 ml of hexamethylphosphoramide (distilled from CaH₂) was added rapidly at ice-bath temperature. After the mixture was stirred at ice bath temperature for 1 hr and at room temperature for an additional 13 hr, the mixture was decomposed with 400 ml of saturated NH₄Cl solution. The ether layer was separated, washed nine times with 200-ml portions of water and once with 200 ml of saturated brine, and dried. Concentration *in vacuo* followed by distillation through a 10-cm Vigreux column afforded 18.202 g (41%) of keto isoxazole 13 as a pale yellow oil: bp 128.0–133.0° (0.15–0.27 mm); ir (neat 1712 cm⁻¹ (C=O). Redistillation afforded the analytical sample as a colorless, viscous liquid which partially crystallized after prolonged storage at 0°, bp 129.0–130.0° (0.25 mm).

*Anal.* Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.73; H, 8.71; N, 6.33.

**5-Methyl-1(9)-octalin-2-one (2b).**—A solution of 16.924 g (0.0765 mol) of keto isoxazole 13 in 200 ml of absolute ethanol was stirred with 23 g of W-4 Raney nickel[17] under a hydrogen atmosphere and at room temperature. After 5.6 hr, an additional 20 g of W-4 Raney nickel[17] was added and stirring at room temperature under hydrogen was continued for 19.4 hr (the reaction was monitored by following disappearance of the isoxazole uv band at 224 nm). Catalyst was filtered off and the nickel residues were washed well with absolute ethanol. Concentration *in vacuo* of the combined filtrate and washings afforded a yellow resin, which was dissolved in 250 ml of anhydrous methanol. After the solution was purged with nitrogen, 40.0 g (0.740 mol) of sodium methoxide was added, and the mixture was heated at reflux under nitrogen for 5 hr. The mixture was then diluted with 350 ml of water, and refluxing under nitrogen was continued for an additional 14.5 hr. After cooling, the mixture was diluted with 500 ml of water and extracted four times with 250-ml portions of ether. The combined ether extracts were washed once with 250 ml of water, three times with 100-ml portions of 3 *M* HCl, once with 250 ml of water, once with 100 ml of saturated NaHCO₃, once with 250 ml of water, and once with 100 ml of saturated NaCl, and dried. Concentration *in vacuo* followed by distillation through a 10-cm Vigreux column afforded 7.633 g (61%) of an equilibrium mixture of 2b and 4b as a colorless oil which partially crystallized on standing at 5°: bp 71.0–76.0° (0.12–0.15 mm); ir (neat) 1708 (C=O), 1669 (conjugated C=O), and 1619 cm⁻¹ (C=C); nmr (CCl₄) δ 5.68 (1 H, s, CH=C). Integration of a small signal in the nmr at δ 2.61 indicated the presence of *ca.* 12% β,γ-unsaturated ketone 4b. This material was characterized by conversion to the 2,4-dinitrophenylhydrazone, which crystallized from ethyl acetate–ethanol as small red needles, mp 188.0–189.0°.

*Anal.* Calcd for $C_{17}H_{20}N_4O_4$: C, 59.29; H, 5.85; N, 16.27. Found: C, 59.21; H, 6.08; N, 16.22.

**5-Methyl-9-octalin-2-one (4b).**—To a solution of 2.263 g (13.8 mmol) of enone 2b and 0.100 g (0.53 mmol) of *p*-toluenesulfonic acid monohydrate in 75 ml of benzene was added 25 ml of ethylene glycol. The resulting mixture was heated at reflux in a nitrogen atmosphere under a Dean–Stark water separator for 20 hr. After cooling, the mixture was diluted with 200 ml of benzene, washed once with 50 ml of saturated NaHCO₃ and three times with 50-ml portions of water, and dried. Concentration *in vacuo* followed by distillation afforded 2.498 g (87%) of ketal

(16) R. A. Kretchmer and W. J. Frazee, *J. Org. Chem.*, **36**, 2855 (1971).
(17) A. A. Pavlic and H. Adkins, *J. Amer. Chem. Soc.*, **68**, 1471 (1946).

3b as a colorless liquid: bp 77.0–79.0° (0.14 mm); nmr (CCl₄) δ 1.00 (3 H, d, *J* = 6.5 Hz, CHCH₃) and 3.88 (4 H, s, OCH₂CH₂O).

To a solution of 2.415 g (11.6 mmol) of ketal 3b in 75 ml of absolute methanol was added a solution of 1.272 g of oxalic acid in 45 ml of water. After it was stirred at room temperature for 3.5 hr, the solution was diluted with 200 ml of half-saturated NaCl solution and extracted with 200 ml of ether. The ether extract was washed twice with 50-ml portions of water, once with 50 ml of saturated NaHCO₃, once with 50 ml of water, and once with 50 ml of saturated NaCl, and dried. Concentration *in vacuo* afforded 1.908 g of pale yellow oil. Integration of the nmr signals at δ 2.63, 3.86, and 5.68 indicated the presence of 2b, 3b, and 4b in a ratio of 12:3:85. The crude product was put on a 40-g column of silica gel and eluted with 840 ml of benzene. Concentration *in vacuo* followed by distillation afforded 1.532 g (80%) of pure 4b as a colorless oil: bp 59.5–64.5° (0.12 mm); ir (neat) 1720 cm⁻¹ (C=O); nmr (CCl₄) δ 1.02 (3, H, d, *J* = 6.5 Hz, CHCH₃) and 2.63 (2 H, br, $W_H$ = 5 Hz, $R_2C$=CRCH₂CO).

*Anal.* Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.21; H, 9.85.

**2-Methylbicyclo[5.3.0]dec-1(7)-ene-6,8-dione (6b).**—A solution of 1.464 g (8.91 mmol) of β,γ-unsaturated ketone 4b in a mixture of 10 ml of absolute methanol and 10 ml of methylene chloride was cooled at Dry Ice–acetone bath temperature and treated with a stream of ozone in oxygen for 52 min (until the solution became blue in color from the presence of excess ozone). After the solution was purged with nitrogen, 5.0 ml of trimethyl phosphite[15] was added and the mixture was allowed to stir at room temperature for 19 hr. Concentration *in vacuo* followed by short-path distillation (110° bath at 0.07 mm) afforded 1.268 g (80%) of 6b as a yellow liquid which crystallized on standing at −12° overnight and gave a purple color with ferric chloride. Material from a similar preparation was redistilled to give the analytical sample: bp 107–108° (1.0 mm); uv max (CH₃OH) 233 nm (ε 13,300); ir (neat) 1715, 1637, and 1605 cm⁻¹; nmr (CCl₄) δ 1.68 (3 H, s, vinyl CH₃).

*Anal.* Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.08; H, 7.94.

**2,7-Dimethylbicyclo[5.3.0]dec-1-ene-6,8-dione (7b).**—To a solution of 2.99 g (16.8 mmol) of 6b in a mixture of 30 ml of acetone and 5.25 ml (84.3 mmol) of methyl iodide was added 2.68 g (19.4 mmol) of potassium carbonate (dried overnight at 140°). After reflux under nitrogen for 5 hr, the mixture was diluted with 40 ml of ether and filtered. Concentration *in vacuo* afforded 3.10 g of tan oil, which partially crystallized on standing at −12°. Chromatography on 60 g of silica gel afforded 2.81 g of solid on elution with benzene. Recrystallization from hexane yielded 1.68 g (52%) of 7b as a white solid, mp 68.5–70.0°. Repeated recrystallization from hexane afforded the analytical sample: mp 70.0–71.0°; ir (KBr) 1744 (five-membered ring C=O) and 1696 cm⁻¹ (seven-membered ring C=O); nmr (CCl₄) δ 1.25 (3 H, s, CH₃) and 1.85 (3 H, s, vinyl CH₃).

*Anal.* Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.18; H, 8.25.

**Preparation of Monoketals 14 and 15.**—To a solution of 0.1681 g (0.874 mmol) of 7b in 35 ml of benzene was added 5 ml of ethylene glycol and 0.0525 g of *p*-toluenesulfonic acid monohydrate. The resulting mixture was heated at reflux under a Dean–Stark water separator for 1.5 hr. After cooling, the mixture was diluted with 65 ml of benzene and washed once with 50 ml of saturated NaHCO₃ solution and three times with 50-ml portions of water, then dried. Concentration *in vacuo* afforded 0.2111 g of pale yellow oil which was chromatographed on 19 g of silica gel. Elution with 5:95 ether–benzene afforded 0.0462 g (22%) of monoketal 14 as a white solid, mp 90.5–93.0°. Recrystallization from hexane afforded the analytical sample: mp 92.0–93.0°; ir (KBr) 1696 cm⁻¹ (seven-membered ring C=O); nmr (CCl₄) δ 1.15 (3 H, s, CH₃), 1.71 (3 H, s, vinyl CH₃), and 3.77 (4 H, multiplet, OCH₂CH₂O).

*Anal.* Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.14; H, 8.60.

Continued elution with 5:95 ether–benzene afforded 0.0810 g (39%) of monoketal 15 as a white solid: mp 60.0–63.0°; ir (KBr) 1742 cm⁻¹ (five-membered ring C=O); nmr (CCl₄) δ 1.21 (3 H, s, CH₃), 1.75 (3 H, s, vinyl CH₃), and 3.75 (4 H, s, OCH₂CH₂O); mass spectrum (70 eV) *m/e* (rel intensity) 236 (M⁺, 29), 100 (25), 99 (100).

Elution with ether afforded 0.0546 g of pale yellow oil which appears to be a ketal ester derived from cleavage of the β-diketone system of 7b: ir (neat) 3410 (OH) and 1733 cm⁻¹ (ester C=O);

nmr (CCl$_4$) δ 1.13 (3 H, d, $J$ = 7 Hz, CHCH$_3$), 1.70 (3 H, s, vinyl CH$_3$), 3.5–4.3 (8 H, multiplet, OCH$_2$), and 7.31 (1 H, s, OH); mass spectrum (70 eV) $m/e$ (rel intensity) 298 (M$^+$, 6), 100 (13), 99 (100).

**2,7-Dimethylbicyclo[5.3.0]dec-1-en-8-ol-6-one (17).**—To a solution of 0.1520 g of **7b** in 10.0 ml of absolute ethanol was added 0.0306 g of 81% platinum oxide, and hydrogenation was allowed to proceed at atmospheric pressure for 3 hr. Catalyst was then removed by filtration and washed well with ethanol. Removal of solvent *in vacuo* from the combined filtrate and washings afforded 0.1588 g of colorless resin, which was chromatographed on 10.0 g of silica gel. Elution with 1:9 ether–benzene afforded 0.0705 g of white solid, which was recrystallized from hexane to give 0.0552 g (36%) of **17**, mp 101.5–102.5°. Two recrystallizations from ether–hexane afforded the analytical sample: mp 103.0–104.0°; ir (KBr) 3306, 1108 (OH), and 1681 cm$^{-1}$ (seven-membered ring C=O); nmr (CCl$_4$) δ 1.08 (3 H, s, CH$_3$), 1.66 (3 H, s, vinyl CH$_3$), and 4.07 (1 H, multiplet, $W_H$ = 20 Hz, CH$_2$CHOH); mass spectrum (70 eV) $m/e$ (rel intensity) 194 (M$^+$, 10), 176 (58), 161 (65), 123 (100), 98 (26), 97 (43).

*Anal.* Calcd for C$_{12}$H$_{18}$O$_2$: C, 74.19; H, 9.34. Found: C, 74.55; H, 9.83.

**3-Methyl-2-(3,5-dimethyl-4-isoxazolylmethyl)cyclohexan-1-one-6-acetic Acid (20b).**—A solution of 55.21 g (0.249 mol) of keto isoxazole **13** and 0.0732 g of *p*-toluenesulfonic acid monohydrate in a mixture of 70 ml of pyrrolidine and 200 ml of benzene was heated at reflux under a Dean-Stark water separator in a nitrogen atmosphere for 65 hr. Concentration *in vacuo* afforded the crude product as a viscous amber oil (a weak carbonyl band at 1714 cm$^{-1}$ indicated incomplete conversion to the enamine).

The oil was dissolved in 200 ml of benzene, 64 6 g (0.387 mol) of ethyl bromoacetate was added, and the resulting mixture was heated at reflux in a nitrogen atmosphere for 40 hr. A solution of 5.0 ml of glacial acetic acid in 75.0 ml of water was then added and refluxing was continued for an additional 2 hr. After cooling, the mixture was extracted with 1 l. of ether. The ether extract was washed four times with 100-ml portions of 3 *M* HCl. The combined aqueous washes were then extracted with 250 ml of ether. The combined ether extracts were washed twice with 100-ml portions of saturated NaCl, dried, and concentrated *in vacuo*. The residual amber oil was dissolved in 600 ml of 10% ethanolic KOH and allowed to stir at room temperature for 21.5 hr. After the resulting mixture was concentrated *in vacuo*, the residue was taken up in 3 l. of water and extracted four times with 500-ml portions of ether. The combined ether extracts were washed once with 250 ml of water and once with 250 ml of saturated NaCl, dried, and concentrated *in vacuo* to give 22.42 g (41%) of recovered **13**. The combined aqueous layers were acidified with 100 ml of concentrated HCl and extracted four times with 500-ml portions of benzene. The combined benzene extracts were washed once with 200 ml of saturated NaCl, dried, and concentrated *in vacuo* to give 21.01 g of crude **20b** as a dark amber resin which partially crystallized on standing at room temperature for several days. Crystallization from ether–hexane afforded 9.23 g (13%) of **20b** as a yellowish-brown solid, mp 127.5–131.5°. Repeated recrystallization and treatment with activated carbon afforded the analytical sample as small white prisms: mp 135.0–135.5°; ir (KBr) 1707 cm$^{-1}$ (carboxyl and ketone C=O); nmr (CDCl$_3$) δ 11.57 (1 H, s, COOH).

*Anal.* Calcd for C$_{18}$H$_{21}$NO$_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.63; H, 7.64; N, 4.75.

**Methyl 5-Methyl-1(9)-octalin-2-one-8-acetate (2d).**—To a solution of 16.607 g (59.5 mmol) of crude acid **20b** in 100 ml of absolute ethanol was added 2.0 ml of concentrated H$_2$SO$_4$, and the mixture was heated at reflux for 5 hr. After cooling, the mixture was diluted with 300 ml of water and extracted three times with 75-ml portions of benzene. The combined benzene extracts were washed once with 100 ml of water, twice with 100-ml portions of 5% Na$_2$CO$_3$, and once with 100-ml portions of water, and dried over anhydrous Na$_2$SO$_4$. After concentration *in vacuo*, the residue was chromatographed on a 50-g column of silica gel. Elution with 400 ml of benzene and 500 ml of 1:9 ether–benzene afforded 13.895 g of ester **20a** as a viscous, amber oil: ir (neat) 1734 (ester C=O) and 1713 cm$^{-1}$ (ketone C=O); nmr (CCl$_4$) δ 2.12 (3 H, s, CH$_3$) and 2.30 (3 H, s, CH$_3$).

A solution of 13.627 g (44.3 mmol) of **20a** in 200 ml of absolute ethanol was stirred with 8.6 g of W-4 Raney nickel[17] under a hydrogen atmosphere at room temperature. After 25.7, 40.2, and 67.1 hr, additional 6.7-, 11.4-, and 9-g quantities of W-4 Raney nickel[17] were added. After a 71.1-hr reaction period (the

reaction was monitored by following disappearance of the isoxazole uv band at 229 nm), the mixture was filtered, and the nickel residues were washed well with absolute ethanol. Concentration *in vacuo* of the combined filtrate and washings afforded an amber-colored resin, which was dissolved in 100 ml of absolute ethanol. The solution was diluted with 500 ml of 10% NaOH solution, purged with nitrogen, and heated at reflux under nitrogen for 4 hr. After cooling, the mixture was diluted with 1.5 l. of water and washed twice with 250-ml portions of ether, then acidified with 150 ml of concentrated HCl and extracted four times with 250-ml portions of ether. The combined ether extracts were washed once with 250 ml of saturated NaCl, dried over anhydrous Na$_2$SO$_4$, and concentrated *in vacuo* to give 7.509 g of **2c** as a viscous, amber resin: ir (CHCl$_3$) 1714 (carboxyl C=O) and 1670 cm$^{-1}$ (ketone C=O).

The crude acid **2c** was dissolved in 80 ml of absolute methanol, 4.0 ml of concentrated H$_2$SO$_4$ was added, and the resulting mixture was heated at reflux for 3 hr. After cooling, the mixture was diluted with 250 ml of water and extracted three times with 75-ml portions of benzene. The combined benzene extracts were washed once with 100 ml of water, twice with 100-ml portions of 5% K$_2$CO$_3$, and once with 100 ml of water, and dried over anhydrous Na$_2$SO$_4$. Concentration *in vacuo* followed by distillation of the residue afforded 4.413 g (31% overall) of **2d** as a pale yellow liquid, bp 128–138° (0.2 mm). Redistillation afforded the analytical sample: bp 144.0–144.5° (0.45 mm); ir (neat) 1736 (ester C=O), 1675 (ketone C=O), and 1619 cm$^{-1}$ (C=C); nmr (CCl$_4$) δ 5.58 (0.5 H, s, C=CH) and 5.78 (0.3 H, s, C=CH); mass spectrum (70 eV) $m/e$ 236 (M$^+$).

*Anal.* Calcd for C$_{14}$H$_{20}$O$_3$: C, 71.16; H, 8.53. Found: C, 71.32; H, 8.44.

**Methyl 2,2-Ethylenedioxy-5-methyl-8-octalin-8-acetate (21).**—To a solution of 1.982 g (8.39 mmol) of α,β-unsaturated ketone **2d** in 75 ml of benzene was added 20 ml of ethylene glycol and 0.077 g (0.40 mmol) of *p*-toluenesulfonic acid monohydrate. The resulting mixture was heated at reflux in a nitrogen atmosphere under a Dean-Stark water separator for 2 hr. After cooling, the mixture was diluted with 75 ml of benzene, washed once with 50 ml of saturated NaHCO$_3$ and five times with 50-ml portions of water, and dried. Concentration *in vacuo* afforded 2.253 g of pale yellow oil which was chromatographed on 50 g of silica gel. Elution with benzene and 2:98 ether–benzene afforded 1.686 g (72%) of **21**. Short-path distillation (160° bath, 0.55 mm) afforded the analytical sample as a colorless liquid: ir (neat) 1738 cm$^{-1}$ (ester C=O); nmr (CCl$_4$) δ 1.01 (3 H, br, $W_H$ = 5.5 Hz, CHCH$_3$), 3.60 (3 H, s, OCH$_3$), and 3.86 (4 H, br, $W_H$ = 2.3 Hz, OCH$_2$CH$_2$O).

*Anal.* Calcd for C$_{16}$H$_{24}$O$_4$: C, 68.54; H, 8.63. Found: C, 68.75; H, 8.81.

**Hydrolysis of Ketal 21.**—To a solution of 0.537 g (1.92 mmol) of ketal **21** in 40 ml of methanol was added a solution of 0.700 g (7.77 mmol) of oxalic acid in 25 ml of water. After the mixture was stirred at room temperature for 2.5 hr, it was diluted with 150 ml of half-saturated NaCl solution and extracted with 200 ml of ether. The ether extract was washed once with 75 ml of saturated NaHCO$_3$ solution, twice with 75-ml portions of water, and once with 50 ml of saturated NaCl solution, and dried. Concentration *in vacuo* afforded 0.444 g of pale yellow oil, which was chromatographed on 30 g of silica gel. Elution with 5:95 ether–benzene afforded 0.1578 g of a mixture of ketal **21** and β,γ-unsaturated ketone **22**, which was homogeneous by thin layer chromatography (silica gel G, elution with 2:8 ethyl acetate–benzene). Integration of nmr signals (CCl$_4$ solution) at δ 3.86 and 3.62 indicated the presence of **21** and **22** in a ratio of 23:77. The mass spectrum (70 eV) showed $m/e$ (rel intensity) 280 (10), 236 (19), and 99 (100).

Further elution with 5:95 ether–benzene and 1:9 ether–benzene afforded 0.260 g (57%) of α,β-unsaturated ketone **2d**.

**Attempted Preparation of Methyl 2,7-Dimethylbicyclo[5.3.0]-dec-1-ene-6,8-dione-5-acetate (7c).**—A solution of 0.062 g of the crude β,γ-unsaturated ketone, prepared by ketalization and hydrolysis of **17b**, in a mixture of 5.0 ml of methylene chloride and 5.0 ml of methanol was cooled at Dry Ice–acetone bath temperature and treated with a stream of ozone in oxygen for 4 min (until a blue coloration developed from the presence of excess ozone). After the solution was purged with nitrogen, 0.50 ml of trimethyl phosphite[15] was added and the resulting mixture was allowed to stir at room temperature for 23 hr. The mixture was then concentrated at water-pump pressure, and the remaining volatile material was removed by short-path distillation (107°

bath, 0.20 mm) to give 0.091 g of residual yellow oil. This was dissolved in a mixture of 5.0 ml of acetone and 1.0 ml of methyl iodide, 0.0438 g of anhydrous K$_2$CO$_3$ was added, and the mixture was heated at reflux for 3 hr. After cooling, the mixture was diluted with 15 ml of ether and filtered. Removal of solvent *in vacuo* then afforded 0.094 g of yellow oil which showed infrared absorption at 1734, 1716, 1652, and 1607 cm$^{-1}$.

# Mechanism for the Peracetic Acid Oxidation of *trans*-α-Iodo-α'-acetoxystilbene to Benzil[1]

YOSHIRO OGATA* AND IWAO URASAKI

*Department of Applied Chemistry, Faculty of Engineering, Nagoya University, Chikusa-ku, Nagoya, Japan*

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The mechanism for the reaction of *trans*-α-iodo-α'-acetoxystilbene (*trans*-IAS) with peracetic acid to form benzil has been studied by means of its kinetics and the examination of related reactions. The rate is expressed as $v = (k_2 + k_2'h_0)[trans\text{-}IAS][CH_3CO_3H]$. The reaction is accelerated in a more acidic solvent, but it is retarded by addition of sodium acetate and stopped in strongly basic solvents. *trans*- and *cis*-α,α'-diacetoxystilbene (DAS) are stable against peracetic acid alone, but they are oxidized to benzil by a mixture of peracetic acid and iodine or alkyl iodide. *trans*-IAS gives on treatment with peracetic acid in the presence of anisole *trans*-DAS, benzoin and its acetate together with other products. The reaction of *trans*-α,α'-diiodostilbene (*trans*-DIS) with peracetic acid in propionic acid gives *trans*-α-iodo-α'-propionyloxystilbene (*trans*-IPS) by introduction of solvent carboxylate group. These results suggest a mechanism involving a rate-determining electrophilic attack by peracetic acid on the iodine atom of IAS to give vinylic cation, which yields DAS by the reaction with solvent acetic acid. Then DAS reacts with produced acetyl hypoiodite, the adduct being further oxidized and hydrolyzed to give benzil.

In our previous paper,[2] we reported that *trans*-α-iodo-α'-acetoxystilbene (*trans*-IAS), a product by iodoacetoxylation of tolan, gave benzil on oxidation with peracetic acid (eq 1). The mechanism of this reaction

$$\text{Benzil}$$
(1)
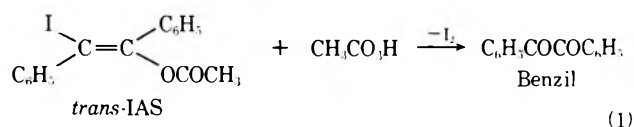
is of interest in comparison to the solvolysis of vinyl halides, since a vinyl cation may be an intermediate in the oxidation. There are many examples of solvolysis of a vinyl halide involving an intermediary vinyl cation.[3-7] Thus, acetolyses of both *cis*- and *trans*-1-iodo-1-cyclopropylpropenes in the presence of silver acetate at 25° gave equal amounts of stereoisomeric acetates as major products, pointing to the conclusion that the products arising from both cis and trans iodides are formed from the same intermediate, which is most likely a linear vinyl cation.[7] The calculations on 1-cyclopropylvinyl cations by means of the extended Hückel molecular orbital method also suggest that the ions are most stable in the linear, bisected conformation.[8]

There are some obscurities in the mechanism for oxidation of *trans*-IAS to benzil (eq 1). (1) Where is the initial attacking site of peracid? (2) Is the attacking

species an electrophile? (3) Is a vinyl cation involved? (4) Is α,α'-diacetoxystilbene (DAS) an intermediate in analogy with the formation of IAS from *trans*-α,α'-diiodostilbene (*trans*-DIS)? For the elucidation of these questions, we carried out the kinetic studies and then examined the related reactions, *i.e.*, oxidations of DAS and DIS with peracetic acid in the presence or absence of iodine or alkyl iodide. Further, we attempted to detect a hypothetical intermediate, DAS. The present paper describes a probable mechanism for the oxidation of *trans*-IAS with peracetic acid as well as of related reactions.

## Results and Discussion

**Stoichiometry.**—The reaction of *trans*-IAS with peracetic acid gives benzil together with iodine.[2] Since the main products are benzil (based on tlc analysis) and iodine, the stoichiometry may be as follows.

$$2C_6H_5COCOC_6H_5 + I_2 + 5CH_3CO_2H \quad (2)$$
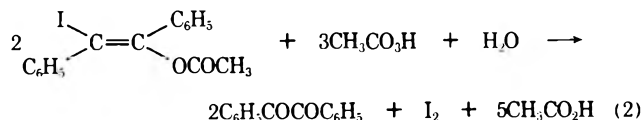
However, it must be taken into account that peracetic acid is consumed also by the further oxidation of iodine and/or hypoiodous acid probably present in the reaction mixture, and by the decomposition of peracid itself. Hence, for the examination of the stoichiometry, the conversion of IAS to benzil, the consumption of peracetic acid, and the formation of iodine should be studied simultaneously at appropriate time intervals. Figure 1 shows conversion curves, which indicate that more than 2 mol of peracetic acid is consumed and less than 0.5 mol of iodine is formed by consuming 1 mol of IAS (or by formation of benzil). This result means that more than 0.5 mol of peracetic acid is consumed by further oxidation of iodine compounds or by decomposition.

(1) Contribution No. 185.

(2) Y. Ogata and I. Urasaki, *J. Org. Chem.*, **36**, 2164 (1971).

(3) C. A. Grob and G. Cseh, *Helv. Chim. Acta*, **47**, 194 (1964).

(4) L. L. Miller and D. A. Kaufman, *J. Amer. Chem. Soc.*, **90**, 7282 (1968); Z. Rappoport and A. Gal, *ibid.*, **91**, 5246 (1969); Z. Rappoport and Y. Apeloig, *ibid.*, **91**, 6734 (1969).

(5) S. J. Huang and M. V. Lessard, *ibid.*, **90**, 2432 (1968).

(6) S. A. Sherrod and R. G. Bergman, *ibid.*, **91**, 2115 (1969); **93**, 1925 (1971); T. C. Clarke, D. R. Kilsey, and R. G. Bergman, *ibid.*, **94**, 3626 (1972); M. Hanack and T. Bässler, *ibid.*, **91**, 2117 (1969).

(7) D. R. Kelsey and R. G. Bergman, *ibid.*, **92**, 228 (1970); **93**, 1941 (1971).

(8) D. R. Kelsey and R. G. Bergman, *ibid.*, **93**, 1953 (1971).
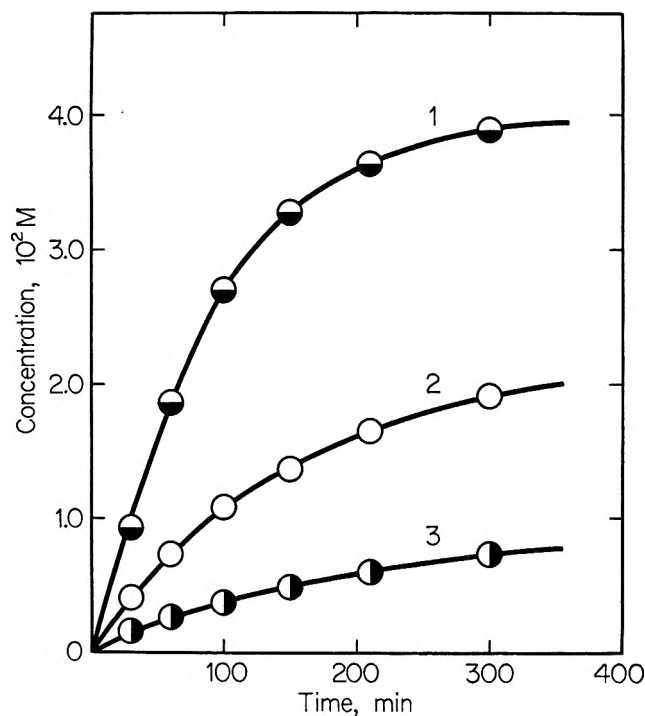
Figure 1.—Stoichiometric examination for the reaction of *trans*-IAS with peracetic acid in acetic acid at 50°. Initial concentration: [IAS] = 0.040 $M$, [CH₃CO₃H] = 0.060 $M$. 1, consumption of peracetic acid; 2, consumption of IAS or formation of benzil; 3, formation of iodine.

## Rate Law.

**Rate Law.**—Because of the excess consumption of peracetic acid as stated above, the rate of the consumption of peracetic acid is complicated. Therefore, the rate of the conversion of *trans*-IAS to benzil with excess peracetic acid was measured by means of uv spectrophotometry, and the obtained pseudo-first-order rate constants at 50° are listed in Table I. The plots of

TABLE I

PSEUDO-FIRST-ORDER RATE CONSTANTS FOR THE REACTION
OF *trans*-IAS WITH PERACETIC ACID IN ACETIC ACID AT 50°

| ——Initial concn, $M$—— | | | |
|---|---|---|---|
| [IAS] | [CH₃CO₃H] | Added iodine, $M$ | $10^5$ $k_1$, sec$^{-1}$ |
| 0.005 | 0.10 | | 10.4 |
| 0.010 | 0.10 | | 9.3 |
| 0.015 | 0.10 | | 10.1 |
| 0.020 | 0.10 | | 9.0 |
| 0.010 | 0.05 | | 5.3 |
| 0.010 | 0.15 | | 15.3 |
| 0.010 | 0.20 | | 18.9 |
| 0.010 | 0.10 | 0.005 | 9.9 |
| 0.010 | 0.10 | 0.010 | 10.4 |

log $k_1$ vs. log [CH₃CO₃H] gave a straight line with a slope of 0.98 and an intercept of −3.01. Hence, the rate law is expressed as eq 3.

$$v = k_2[\text{trans-IAS}][\text{CH}_3\text{CO}_3\text{H}] \qquad (3)$$

Here $k_2$ was calculated to be 9.7 × 10⁻⁴ $M^{-1}$ sec⁻¹. The rate is nearly equal to that of the reaction of iodine with peracetic acid (1.25 × 10⁻³ $M^{-1}$ sec⁻¹ at 50°).[9] As shown in Table I, the rate is not affected by addition of iodine.

## Effect of Sulfuric Acid.

**Effect of Sulfuric Acid.**—As shown in Table II, the addition of sulfuric acid increases the rate, and the

(9) Y. Ogata and K. Nakajima, *Tetrahedron*, **20**, 43 (1964).
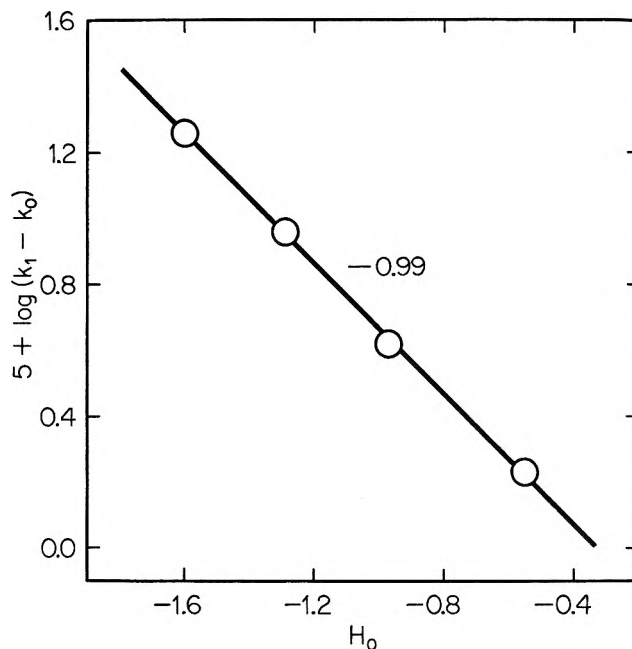
Figure 2.—Plots of log $(k_1 − k_0)$ vs. $H_0$ for the reaction of *trans*-IAS with peracetic acid in acetic acid at 50°. Initial concentration: [IAS] = 0.010 $M$, [CH₃CO₃H] = 0.10 $M$.

TABLE II

EFFECT OF ADDED SULFURIC ACID ON THE REACTION OF
*trans*-IAS WITH PERACETIC ACID IN ACETIC ACID AT 50°[a]

| [H₂SO₄], $M$ | $H_0^{10}$ | $10^5$ $k_1$, sec$^{-1}$ | $10^5(k_1 − k_0)$, sec$^{-1}$ | 5 + log $(k_1 − k_0)$ |
|---|---|---|---|---|
| 0 | | 9.3 | | |
| | | $(= k_0)^b$ | | |
| 0.010 | −0.55 | 11.0 | 1.7 | 0.23 |
| 0.025 | −0.97 | 13.5 | 4.2 | 0.62 |
| 0.050 | −1.29 | 18.5 | 9.2 | 0.96 |
| 0.100 | −1.60 | 27.7 | 18.4 | 1.26 |

[a] Initial concentration: [IAS] = 0.010 $M$, [CH₃CO₃H] = 0.10 $M$. [b] $k_0$ is obtained by extrapolation of $k_1$ to [H₂SO₄] = 0.

plots of log $(k_1 − k_0)$ vs. Hammett's acidity function $(H_0)^{10}$ gave a straight line with a slope of −0.99 as indicated in Figure 2. Thus, the rate is expressed as eq 4, where $k_2$ and $k_2'$ represent uncatalyzed and acid-catalyzed oxidations, respectively.

$$v = (k_2 + k_2'h_0)[\text{trans-IAS}][\text{CH}_3\text{CO}_3\text{H}] \qquad (4)$$

**Effect of Sodium Acetate.**—The addition of sodium acetate to an acetic acid solution of the reaction mixture decreased the rate, as shown in Table III. However, at

TABLE III

EFFECT OF SODIUM ACETATE ON THE REACTION OF
*trans*-IAS WITH PERACETIC ACID IN ACETIC ACID AT 50°

| ——Initial concn, $M$—— | | | |
|---|---|---|---|
| [IAS] | [CH₃CO₃H] | [CH₃CO₂Na] | $10^5$ $k_1$, sec$^{-1}$ |
| 0.010 | 0.10 | 0 | 9.3 |
| 0.010 | 0.10 | 0.005 | 3.6 |
| 0.010 | 0.10 | 0.010 | 1.9 |

higher concentration of sodium acetate, side reactions seem to occur, because fairly large amounts of unidentified products were formed on the basis of tlc analysis.

**Solvent Effect.**—The yield of benzil in the reaction of *trans*-IAS with peracetic acid was determined at 50° in

(10) N. F. Hall and W. F. Spengeman, *J. Amer. Chem. Soc.*, **62**, 2487 (1940).

various solvents. The results are listed in Table IV,
indicating that the reaction is accelerated in a more

| Solvent[b] | Dielectric constant | p$K_a$ (25°) | Yield of benzil, % |
|---|---|---|---|
| Dioxane | 2.21 | | ~0 |
| Ethanol | 24.3 | | ~0 |
| Methanol | 32.6 | 16 | |
| Acetonitrile | 37.5 | 25 | ~0 |
| Carbon tetrachloride | 2.24 | | 13.4 |
| 85% Aqueous propionic acid | | | 13.6 |
| Propionic acid | 3.44 | 4.87 | 17.3 |
| 85% Aqueous acetic acid | | | 27.3 |
| Acetic acid | 6.15 | 4.76 | 35.4 |
| Chloroform | 4.81 | | 44.5 |
| 85% Aqueous formic acid | | | 50.6 |
| Formic acid | 58.5 | 3.74 | |

[a] Initial concentration: [IAS] = 0.020 $M$, [CH$_3$CO$_3$H] = 0.030$M$.   [b] In all cases about 1.5% of acetic acid is also contained because the acetic acid solution of ca. 2 $M$ peracetic acid was used.

acidic solvent except in chloroform and almost stops
in basic solvents. The reactivity is independent of the
dielectric constant of solvent. The fairly fast rate of
reaction in chloroform may be an artifact due to the
generation of hydrogen chloride from the solvent in
a radical reaction. In fact, chloride ion was detected
as silver chloride even by mixing of chloroform and
peracetic acid alone under the same conditions. In
view of these results as well as the effect of sulfuric
acid, it may be said that the reaction is general acid
catalyzed, suggesting the electrophilic nature of the
attacking species. The appreciable rate enhancement
in carbon tetrachloride may be due to a catalysis by
acetic acid existing in peracetic acid. Basic solvents
must annul this catalysis.

**Temperature Effect.**—The rate of the reaction of
*trans*-IAS with peracetic acid was measured in acetic
acid at various temperatures with initial concentrations
of IAS and peracetic acid of 0.01 and 0.10 $M$, respectively. The pseudo-first-order rate constants ($10^5$ $k_1$,
sec$^{-1}$) were 6.4 at 45°, 9.9 at 50°, 15.0 at 55°, and 23.0
at 60°. The plot of log $k_1$ vs. 1/$T$ afforded a straight
line, giving the values of 17.8 kcal mol$^{-1}$ and −23.8
eu for the energy and entropy of activation, respectively.

**Intermediacy of DAS.**—The oxidation of *trans*-DIS
with peracetic acid in acetic acid affords IAS as well as
benzil.[2] Therefore, it is expected that DAS may be
formed similarly as an intermediate in the reaction of
*trans*-IAS with peracetic acid in acetic acid. However,
no DAS was detected in the reaction mixture according to
tlc analysis. Hence, if DAS is truely an intermediate,
it must be oxidized to benzil rapidly under the reaction
conditions. Thus, the reactivity of DAS under similar
reaction conditions was investigated to examine the
intermediacy of DAS.

Both *trans*- and *cis*-DAS are hardly oxidized with
peracetic acid alone, but they are oxidized to benzil in
the presence of iodine. Table V shows the results on
the rate for *trans*-DAS with excess peracetic acid. As
apparent from Table V, the rate law can be expressed
as eq 5.

$$v = k_3[trans\text{-DAS}][I_2][CH_3CO_3H] \qquad (5)$$

| | Initial concn, $M$ | | |
|---|---|---|---|
| [DAS] | [CH$_3$CO$_3$H] | [I$_2$] | $10^5$ $k_1$, sec$^{-1}$ |
| 0.010 | 0.10 | 0 | 0 |
| 0.010 | 0.10 | 0.002 | 2.3 |
| 0.010 | 0.10 | 0.005 | 4.8 |
| 0.010 | 0.10 | 0.010 | 10.2 |
| 0.010 | 0.10 | 0.005 | 3.6[a] |

[a] Reaction rate for *cis*-DAS.

Here, the value of $k_3$ is 1.02 × 10$^{-1}$ $M^{-2}$ sec$^{-1}$,
which is a little smaller than the value for the oxidation
of *trans*-IAS at 0.005 $M$ iodine concentration. It can
easily be seen that this rate behavior for the reaction
of DAS with a mixture of iodine and peracetic acid
is the general one for iodoacetoxylation of olefins,[11-13]
though the rate is slow compared with that of propylene.[12] This slow rate may be due to the low electron
density at the double bond of DAS by the conjugation
with two phenyl groups, so that the π-complex formation between iodine and the double bond of DAS
may be difficult.

Here, it seems likely that the original iodine compound formed in the reaction of IAS with peracetic
acid is not a molecular iodine but an iodine compound
like hypoiodous acid or acetyl hypoiodite. Consequently, it is necessary to examine the reaction of
DAS with hypoiodous acid or acetyl hypoiodite.

The reaction of alkyl iodides with peracetic acid
in the presence of aromatic and olefinic compounds has
been reported to give aromatic iodides[14] and iodoacetoxylated products,[13] respectively, where acetyl hypoiodite has been suggested to be an attacking species as
shown in eq 6-9, because it is more electrophilic than

$$RI + CH_3CO_3H \xrightarrow{\text{slow}} HOI + CH_3CO_2R \qquad (6)$$

$$HOI + CH_3CO_2H \underset{}{\overset{\text{fast}}{\rightleftharpoons}} CH_3CO_2I + H_2O \qquad (7)$$

$$ArH + CH_3CO_2I \xrightarrow{\text{fast}} ArI + CH_3CO_2H \qquad (8)$$

(9)
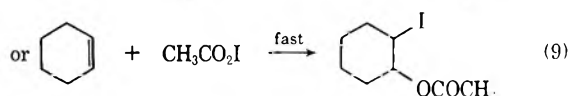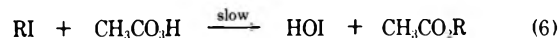
hypoiodous acid. Since the oxidation of alkyl iodide
with peracetic acid is much (ca. 30 times with *n*-butyl iodide) faster than that of iodine,[14] the reaction
of *trans*-DAS with peracetic acid in the presence of
alkyl iodide was examined. The pseudo-first-order
rate constants are listed in Table VI, which suggests

| Iodide | Concn, $M$ | $10^5$ $k_1$, sec$^{-1}$ |
|---|---|---|
| *n*-Butyl | 0.010 | 3.7 |
| *n*-Propyl | 0.010 | 1.3 |
| Isopropyl | 0.010 | 0.40 |
| Molecular iodine | 0.005 | 0.24 |

[a] Initial concentration: [DAS] = 0.010 $M$, [CH$_3$CO$_3$H] = 0.10 $M$.

(11) Y. Ogata, K. Aoki, and Y. Furuya, *Chem. Ind.* (London), 304 (1965).
(12) Y. Ogata and K. Aoki, *J. Org. Chem.*, **31**, 1625 (1966).
(13) Y. Ogata and K. Aoki, *ibid.*, **34**, 3978 (1969).
(14) Y. Ogata and K. Aoki, *ibid.*, **34**, 3974 (1969).

that DAS reacts considerably faster with acetyl hypoiodite to form benzil. This means that acetyl hypoiodite formed by the peracetic acid oxidation of IAS may react rapidly with DAS to form benzil, so that DAS cannot be detected in the reaction mixture irrespective of the intermediacy of DAS. Hence, it is probable that DAS is an intermediate in the present reaction. In this connection, the addition of acetyl hypoiodite to IAS seems to be difficult because of the steric hindrance.

**Attempted Detection of DAS.**—If DAS is truely an intermediate in the peracetic acid oxidation of IAS, then it may be detected by trapping acetyl hypoiodite with electron-rich compounds such as *m*-xylene or anisole which can easily react with acetyl hypoiodite.[15]

Although DAS could not be detected in the presence of *m*-xylene by means of tlc, the products in the presence of anisole gave tlc spots identical with those of benzoin, benzoin acetate, and *trans*-DAS as well as several other unidentified products which may be iodinated or oxidized anisoles.[15,16] It is interesting that benzil could not be detected from the reaction mixture by the tlc analysis. These results also support the intermediacy of DAS, though there still remains some uncertainty in the tlc analysis. The formation of benzoin and its acetate may be due to the hydrolysis of DAS followed by keto–enol tautomerization (eq 10). The fact that



(10)
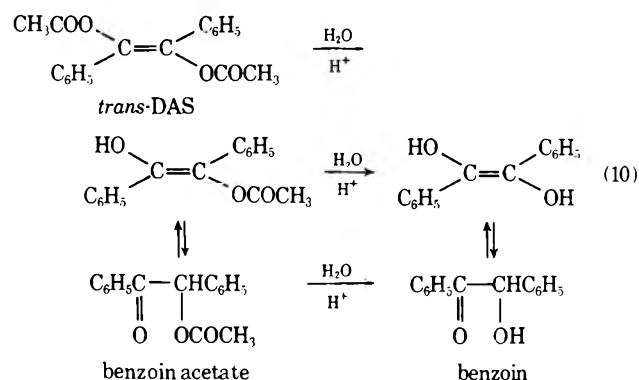
no *cis*-DAS could be detected is probably due to the steric interaction between two phenyl groups, but the possibility of the formation of a little *cis*-DAS cannot be denied.

Benzoin and its acetate are also detected from the reaction of *trans*-IAS with peracetic acid in the presence of sulfuric acid (*ca.* 0.5 *M*), which also suggests the intermediacy of DAS, for the hydrolysis of DAS to form benzoin acetate or benzoin may be catalyzed by sulfuric acid, so that hydrolysis of DAS becomes competitive with the reaction of DAS with acetyl hypoiodite at high concentration of sulfuric acid. Besides, benzoin and particularly its acetate are found to be fairly stable under these conditions.

**Peracid Oxidation of DIS.**—The above discussion shows that DAS may be an intermediate in the reaction of *trans*-IAS with peracetic acid. The next questions are the stereochemistry of the DAS formation and the intermediacy of a vinyl cation. The DAS formed consisted mostly of trans isomer on the basis of tlc analysis. Here, the analogous reaction of *trans*-DIS with peracetic acid was examined as described below,

(15) Y. Ogata and K. Aoki, *J. Amer. Chem. Soc.*, **90**, 6187 (1968).

(16) J. Böeseken and C. F. Metz, *Recl. Trav. Chim. Pays-Bas*, **54**, 345 (1935).

because the intermediate IAS can easily be isolated from the reaction mixture.

Firstly, more detailed examination of the reaction of DIS with peracetic acid in acetic acid showed the formation of *cis*-α-iodo-α'-acetoxystilbene (*cis*-IAS) as well as the trans isomer and benzil, though the amount of *cis*-IAS was very small (eq 11). Thus, the IAS frac-



(11)
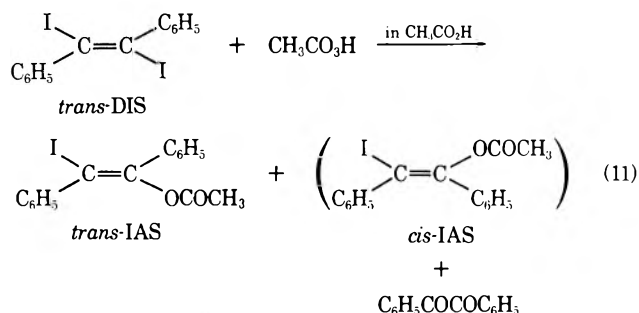
tion, which was isolated by column chromatography of the products, showed a melting point lower than that of pure *trans*-IAS, and its nmr spectrum gave another small singlet signal at τ 7.77 in addition to a singlet signal of the acetoxyl proton of *trans*-IAS at τ 8.21. The signal at τ 7.77 may correspond to the acetoxyl proton of *cis*-IAS, because it is very close to the signal of the acetoxyl proton of *cis*-α-bromo-α'-acetoxystilbene (τ 7.79).[17]

The reaction of DIS with peracetic acid in propionic acid gave *trans*-α-iodo-α'-propionyloxystilbene (*trans*-IPS) (identified by ir and nmr spectra and elemental analysis) and benzil (eq 12), and virtually no IAS



(12)
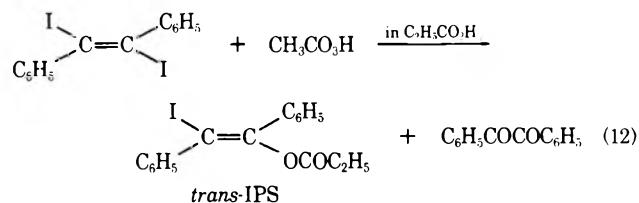
(tlc) or *cis*-IPS (nmr) was detected. Further, the reaction of DIS with peracetic acid in a mixture of equal volumes of acetic and propionic acids gave nearly equal amounts of IAS and IPS (tlc).

In the above reactions, the catalytic amount of sulfuric acid (*ca.* $10^{-3}$ *M*) contained in the solution was preliminarily neutralized with an equivalent amount of sodium acetate to prevent the transfer of an active oxygen from peracetic acid to propionic acid. In fact, the transfer of an active oxygen from peracetic acid to hexahydrobenzoic acid was prevented by the addition of sodium acetate equivalent to the sulfuric acid contained. Otherwise, the active oxygen was transferred a little, the second-order rate constant being *ca.* $6 \times 10^{-7}$ $M^{-1}$ sec$^{-1}$ at 50° in the presence of $3.9 \times 10^{-3}M$ sulfuric acid.

Therefore, for the formation of IAS by peracid oxidation of DIS, the acetoxyl group of IAS does not come from peracid, but from the solvent, acetic acid. Hence, a cyclic transition state such as I is improbable, but a



I         II         III
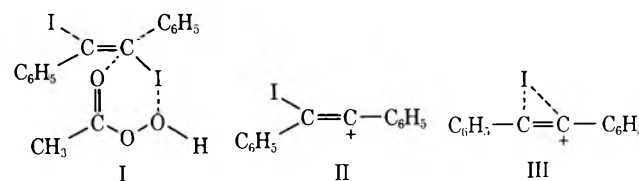
(17) A. Jovtscheff and S. L. Spassov, *Monatsh. Chem.*, **98**, 2272 (1967).

vinyl cation, II, or a cyclic one, III, may be formed by the oxidative elimination of iodide ion from DIS with peracetic acid. Assuming III, a preferential formation of *trans*-IAS can be understood; such a cyclic vinyl cation was also proposed for $\beta$-thiovinyl cations.[18] Of course, the steric interaction between two phenyl groups is also expected to cause a little formation of *cis*-IAS, as described for the formation of DAS from IAS.

**Oxidation Mechanism for IAS.**—All of the above findings suggest the following mechanism for the peracetic acid oxidation of *trans*-IAS to form benzil, which is similar to that of DIS. The effects of sulfuric acid, sodium acetate, and solvent imply that the reaction proceeds with an electrophilic attack by peracetic acid, but no nucleophilic attack by peracetate ion, which is also supported by the fact that *trans*-IAS is stable even on 5-hr refluxing with sodium acetate in acetic acid. The nucleophilic substitution at a vinylic carbon is known to be difficult.[8]

Thus the rate-determining electrophilic attack by peracetic acid on IAS allows the oxidative abstraction of iodide ion from IAS to form hypoiodous acid and a vinyl cation, IV (eq 13), where peracetic acid is activated by hydrogen bonding of solvent acetic acid to the carbonyl group of peracetic acid and activated more effectively by the protonation of peracetic acid with mineral acids. A rapid nucleophilic attack by solvent acetic acid on IV yields DAS, most of which is

$$ \text{IV} + \text{CH}_3\text{CO}_2\text{H} \xrightarrow{-\text{H}^+} $$

$$ \text{VI} + 2\text{H}_2\text{O} \longrightarrow \text{C}_6\text{H}_5\text{COCOC}_6\text{H}_5 + 4\text{CH}_3\text{CO}_2\text{H} \quad (17) $$

$$ \text{V} + \text{CH}_3\text{CO}_3\text{H} \longrightarrow $$

(18) G. Capozzi, G. Melloni, G. Modena, and U. Tonellato, *Chem. Commun.*, 1520 (1969); G. Capozzi, G. Melloni, and G. Modena, *J. Chem. Soc. C*, 2625 (1970).
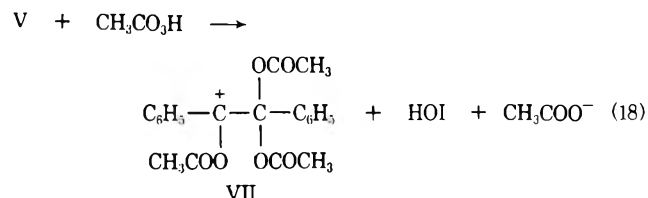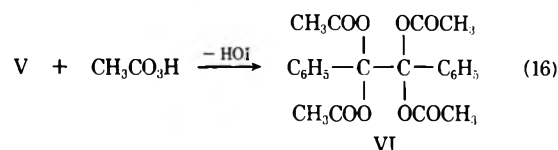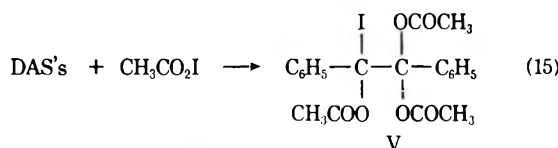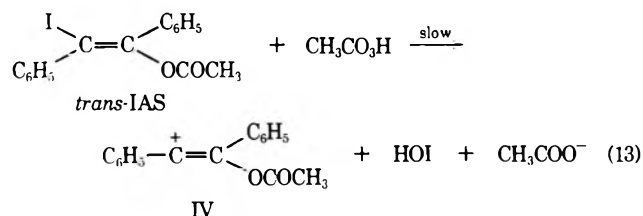
expected to be *trans* isomer (eq 14). Furthermore, DAS is subject to the rapid electrophilic addition of acetyl hypoiodite which is formed from hypoiodous acid with acetic acid (eq 7), to give the adduct V (eq 15), followed by the further oxidation with peracetic acid to provide $\alpha,\alpha'$-tetraacetoxybibenzyl, VI (eq 16), which may easily be hydrolyzed with water[19] yielding benzil (eq 17). Oxidation of V with peracetic acid forming VI may involve a carbonium ion VII (eq 18).

Since acetyl hypoiodite is a good electrophile, its attack on V or even on IAS is expected to give VII or IV accompanied by the formation of molecular iodine (eq 19 and 20).

$$ \text{V} + \text{CH}_3\text{CO}_2\text{I} \longrightarrow \text{VII} + \text{I}_2 + \text{CH}_3\text{COO}^- \quad (19) $$

$$ \text{IAS} + \text{CH}_3\text{CO}_2\text{I} \longrightarrow \text{IV} + \text{I}_2 + \text{CH}_3\text{COO}^- \quad (20) $$
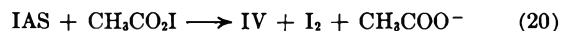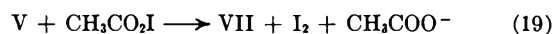
In analogy with the formation of IPS in the peracetic acid oxidation of DIS in propionic acid, which excludes a cyclic transition state I, the reaction of IAS may also deny a cyclic one VIII.
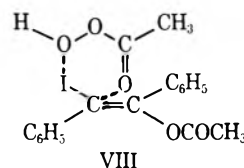
The mechanism described above agrees with the stoichiometry as indicated below. (a) When reaction 19 alone is considered for the formation of iodine, the following steps are probable.

$$ 2\,\text{trans-IAS} + 2\text{CH}_3\text{CO}_3\text{H} \longrightarrow $$

$$ 2\text{IV} + 2\text{HOI} + 2\text{CH}_3\text{COO}^- \quad (13) $$

$$ 2\text{IV} + 2\text{CH}_3\text{CO}_2\text{H} \longrightarrow 2\text{DAS} + 2\text{H}^+ \quad (14) $$

$$ 2\text{HOI} + 2\text{CH}_3\text{CO}_2\text{H} \rightleftharpoons 2\text{CH}_3\text{CO}_2\text{I} + 2\text{H}_2\text{O} \quad (7) $$

$$ 2\text{DAS} + 2\text{CH}_3\text{CO}_2\text{I} \longrightarrow 2\text{V} \quad (15) $$

$$ \text{V} + \text{CH}_3\text{CO}_3\text{H} \longrightarrow \text{VII} + \text{HOI} + \text{CH}_3\text{COO}^- \quad (18) $$

$$ \text{HOI} + \text{CH}_3\text{CO}_2\text{H} \rightleftharpoons \text{CH}_3\text{CO}_2\text{I} + \text{H}_2\text{O} \quad (7) $$

$$ \text{V} + \text{CH}_3\text{CO}_2\text{I} \longrightarrow \text{VII} + \text{I}_2 + \text{CH}_3\text{COO}^- \quad (19) $$

$$ 2\text{VII} + 2\text{CH}_3\text{CO}_2\text{H} \longrightarrow 2\text{VI} + 2\text{H}^+ \quad (21) $$

$$ 2\text{VI} + 4\text{H}_2\text{O} \longrightarrow 2\text{C}_6\text{H}_5\text{COCOC}_6\text{H}_5 + 8\text{CH}_3\text{CO}_2\text{H} \quad (17) $$

$$ 4\text{H}^+ + 4\text{CH}_3\text{COO}^- \longrightarrow 4\text{CH}_3\text{CO}_2\text{H} \quad (22) $$
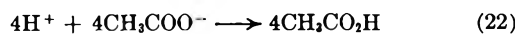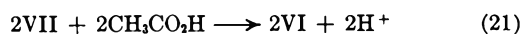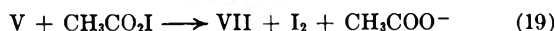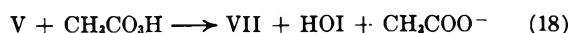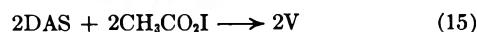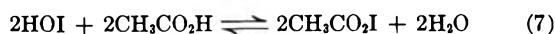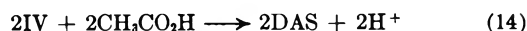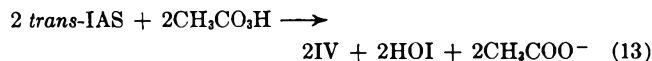
Summing up leads to eq 2, which is the stoichiometry described above. (b) When reaction 20 alone is considered for the formation of iodine, the following steps are possible.
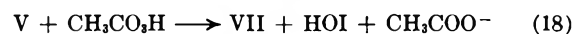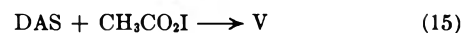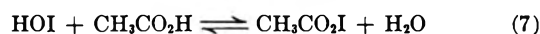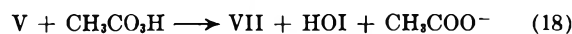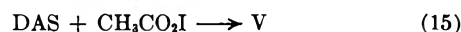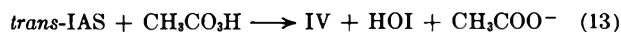
$$ \text{trans-IAS} + \text{CH}_3\text{CO}_3\text{H} \longrightarrow \text{IV} + \text{HOI} + \text{CH}_3\text{COO}^- \quad (13) $$

$$ \text{IV} + \text{CH}_3\text{CO}_2\text{H} \longrightarrow \text{DAS} + \text{H}^+ \quad (14) $$

$$ \text{HOI} + \text{CH}_3\text{CO}_2\text{H} \rightleftharpoons \text{CH}_3\text{CO}_2\text{I} + \text{H}_2\text{O} \quad (7) $$

$$ \text{DAS} + \text{CH}_3\text{CO}_2\text{I} \longrightarrow \text{V} \quad (15) $$

$$ \text{V} + \text{CH}_3\text{CO}_3\text{H} \longrightarrow \text{VII} + \text{HOI} + \text{CH}_3\text{COO}^- \quad (18) $$

$$ \text{HOI} + \text{CH}_3\text{CO}_2\text{H} \rightleftharpoons \text{CH}_3\text{CO}_2\text{I} + \text{H}_2\text{O} \quad (7) $$

$$ \text{trans-IAS} + \text{CH}_3\text{CO}_2\text{I} \longrightarrow \text{IV} + \text{I}_2 + \text{CH}_3\text{COO}^- \quad (20) $$

$$ \text{IV} + \text{CH}_3\text{CO}_2\text{H} \longrightarrow \text{DAS} + \text{H}^+ \quad (14) $$

$$ \text{DAS} + \text{CH}_3\text{CO}_2\text{I} \longrightarrow \text{V} \quad (15) $$

$$ \text{V} + \text{CH}_3\text{CO}_3\text{H} \longrightarrow \text{VII} + \text{HOI} + \text{CH}_3\text{COO}^- \quad (18) $$

$$ \text{HOI} + \text{CH}_3\text{CO}_2\text{H} \rightleftharpoons \text{CH}_3\text{CO}_2\text{I} + \text{H}_2\text{O} \quad (7) $$

(19) J. Jovtscheff and S. L. Spassov, *Monatsh. Chem.*, **98**, 2326 (1967).

$$2VII + 2CH_3CO_2H \longrightarrow 2VI + 2H^+ \qquad (21)$$

$$2VI + 4H_2O \longrightarrow 2C_6H_5COCOC_6H_5 + 8CH_3CO_2H \quad (17)$$

$$4H^+ + 4CH_3COO^- \longrightarrow 4CH_3CO_2H \qquad (22)$$
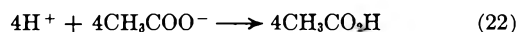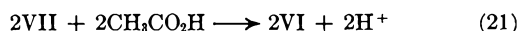
The total equation is the same (eq 2) as that in a, indicating that the mechanism should agree with the stoichiometry whatever the ratio of reaction 19 to 20 may be.

## Experimental Section

**Materials.**—*Ca.* 2.5 *M* peracetic acid in acetic acid was used, which was prepared by the reaction of acetic anhydride with 60% $H_2O_2$ in the presence of a catalytic amount of $H_2SO_4$.[20] The concentration of $H_2SO_4$ in the solution was about 0.039 *M*. *trans*-IAS was prepared by the reaction of tolan with a mixture of iodine and peracetic acid in acetic acid,[2] yield 59%, mp 146–146.5° (from methanol) (lit.[2] mp 146–146.5). *trans*-DIS was prepared by the addition of iodine to tolan in acetic acid at room temperature under irradiation of light for 4 hr, yield 88%, mp 191° dec in a sealed tube (lit.[21] mp 199° dec). DAS (a mixture of cis and trans isomers) was prepared by the reductive acetylation of benzil with zinc dust and acetic anhydride in the presence of sulfuric acid.[22] *trans*-DAS was purified by fractional crystallization and recrystallized from methanol, mp 157° (lit.[22] mp 155°). *cis*-DAS was separated by chromatography on silica gel in benzene–chloroform–ethyl acetate (20:2:1), and recrystallized from ligroin, mp 119.5° (lit.[22] mp 119°). Benzoin acetate was prepared by the acetylation of benzoin with acetic anhydride,[23] mp 82° (from ethanol) (lit.[23] mp 81.5–82.5°). Alkyl iodides were prepared by refluxing respective alcohols with a mixture of iodine and red phosphorus:[24] n-propyl, bp 101.7–102.3°; isopropyl, bp 88.7–89.0°; and n-butyl iodide, bp 63° (80 mm). Acetic acid used as a solvent for kinetic study was purified by rectification, bp 118–119°. All the other commercial solvents were used without further purification.

**Product Analyses.**—Products were analyzed by means of tlc using a 200 × 200 mm plate dragged with silica gel G according to Stahl ∼ 0.3 mm thick. The $R_f$ values of various compounds for several developing solvents are listed in Table VII.

### TABLE VII
$R_f$ VALUES ON TLC USING SILICA GEL *ca.* 0.3 MM THICK

| | Developing solvents | | |
|---|---|---|---|
| Compd | Benzene | Benzene–ethyl acetate (20:1) | Benzene–chloroform–ethyl acetate (20:2:1) |
| Tolan | 0.87 | 0.88 | |
| *trans*-IPS | 0.74 | | |
| *trans*-IAS | 0.69 | 0.72 | |
| Benzil | 0.64 | 0.67 | 0.73 |
| *trans*-DAS | 0.42 | 0.51 | 0.58 |
| Benzoin acetate | | 0.47 | |
| *cis*-DAS | 0.34 | 0.43 | 0.46 |
| Benzoin | | 0.34 | 0.38 |

**Procedure for Stoichiometric Examination.**—The conversion of *trans*-IAS to benzil and the consumption of peracetic acid along with the formation of iodine were measured simultaneously by uv spectroscopy and by iodometric titration, respectively. Separate acetic acid solutions of IAS and peracetic acid were mixed at 50° to start the reaction, giving the solution of 0.04 *M* IAS and 0.06 *M* peracetic acid. Aliquots (each 2 ml) were pipetted out at appropriate intervals of time and poured into a separatory funnel containing CCl₄ (15 ml) and water (40 ml), the funnel being shaken rapidly to extract iodine. After one more extraction (5 ml), the combined extracts were washed with water and separated. The content of iodine in CCl₄ and that of per-

(20) Y. Ogata and I. Urasaki, *J. Chem. Soc. C*, 1689 (1970).

(21) H. Suzuki, *Bull. Chem. Soc. Jap.*, **33**, 396 (1960).

(22) L. F. Fieser, "Experiments in Organic Chemistry," Maruzen, Tokyo, 1956, p 169.

(23) B. B. Corson and N. A. Saliani, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 69.

(24) R. Adams and V. Voorhees, *J. Amer. Chem. Soc.*, **41**, 789 (1919).

acetic acid in the combined aqueous layer were measured iodometrically with 0.01 *N* thiosulfate solution. The titrated CCl₄ layer was then washed with water and dried (Na₂SO₄). After CCl₄ was removed, the residue was then dissolved in methanol, and the composition between IAS and benzil was measured by means of uv spectrophotometry.

**Ultraviolet Spectrophotometry.**—Methanolic solutions containing known concentrations of *trans*-IAS and benzil were prepared, and extinctions at 230 and 260 mμ were measured by a Hitachi double-beam spectrophotometer, Model 124. The compositions calculated from the extinctions and molecular absorption coefficient of each component agreed with the theoretical within 1% error. Hence, the component of the reaction mixture can be measured by uv spectrophotometry, since the only main product is benzil.

When the composition between *trans*-DAS and benzil was measured, the extinctions at 250 and 280 mμ were used, and the extinctions at 258 and 290 mμ were used for the measurement of the composition between *cis*-DAS and benzil.

**Typical Procedure for the Rate Measurements.**—The rate of the conversion of *trans*-IAS to benzil under the existence of excess peracetic acid was measured by means of uv spectrophotometry. A 0.02 *M* acetic acid solution of IAS (5 ml) and acetic acid (4.55 ml) were mixed in a sample tube and allowed to stand at 50° to reach temperature equilibrium. Another solution (0.45 ml) of 2.25 *M* peracetic acid in acetic acid at 50° was added quickly to the above solution to start the reaction, giving the solution of 0.01 *M* IAS and 0.10 *M* peracetic acid. Aliquots (each 1 ml) were pipetted out at known intervals of time and placed in a separatory funnel containing CCl₄ (5 ml), water (5 ml), K₂CO₃ (1.4 g), and KI (0.15 g) to liberate I₂. Aqueous 0.2 *N* Na₂S₂O₃ (2 ml) was then added to the funnel. The funnel was shaken and the two layers were separated. The CCl₄ layer was dried (Na₂SO₄), an aliquot (0.2 ml) was pipetted out, CCl₄ was removed under reduced pressure, the residue was dissolved in methanol (7–8 ml), and then the composition between IAS and benzil was measured by means of uv spectrophotometry. The reactions were usually followed until 30–60% conversion was attained. The rate of the reaction of *trans*- or *cis*-DAS with a mixture of iodine and peracetic acid to form benzil was measured by the same method.

**Reaction of DAS with Peracetic Acid in the Presence or Absence of Iodine.**—An acetic acid solution (5 ml) of DAS (0.05 *M*), peracetic acid (0.05 *M*), and iodine (0.01 *M*) was kept standing at 70° for 3 hr. The reaction mixture was diluted with water and extracted with ether. The extract was treated successively with aqueous KI, Na₂S₂O₃, and NaHCO₃, and washed with wat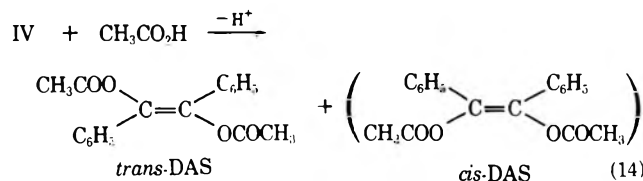er. The mixture was analyzed by means of tlc in benzene, giving two spots corresponding to DAS and benzil. The yield of benzil was 29% from *trans*-DAS and 24% for the cis isomer (spectrophotometry).

When the same reaction of DAS was carried out in the absence of iodine, the reaction gave only recovered DAS.

**Oxidation of IAS in the Presence of Anisole.**—The solution of *trans*-IAS (0.04 *M*) and peracetic acid (0.04 *M*) in the mixture of acetic acid (1 ml) and anisole (1 ml) was kept standing at 50° for 3 hr. The reaction mixture was diluted with water, being neutralized with K₂CO₃, and extracted with CCl₄. CCl₄ and most of anisole were removed from the dried (Na₂SO₄) extract under reduced pressure, giving a yellow liquid. The analysis on tlc in benzene–ethyl acetate (20:1) gave about eight spots, $R_f$ 0.33, 0.38, 0.45, 0.48, 0.51, 0.56, 0.72, and 0.90. Four of them were identical with those of benzoin (0.34), benzoin acetate (0.47), *trans*-DAS (0.51), and IAS (0.72). However, spots of *cis*-DAS ($R_f$ 0.43) and benzil ($R_f$ 0.67) could not be detected.

**Reaction of DIS with Peracetic Acid in Propionic Acid.**—Peracetic acid (1.5 mmol) in propionic acid (5 ml) containing 0.75 ml of acetic acid was added dropwise to the suspension of *trans*-DIS (1.2 mmol) in propionic acid (25 ml) at 70° over a period of 2 hr, and kept standing with stirring for 1 hr. After unreacted DIS was recovered by filtration (0.55 mmol, 46%), the filtrate was diluted with water and extracted with CCl₄. The extract was worked up as above, giving a yellow mixture, whose tlc in benzene showed three spots, $R_f$ 0.63, 0.74, and 0.87. Two of them correspond to benzil (0.64) and tolan (0.87). A compound with $R_f$ 0.74 was isolated by means of tlc in benzene, yielding 0.063 g of pale yellow solid, mp 77.5° (from n-hexane). The uv spectrum of this material was very similar to that of IAS. The ir spectrum (KBr), which was also similar to that of IAS, showed absorption bands at 1190, 1270, and 1750 cm⁻¹ characteristic of

vinyl ester. The nmr spectrum (10% in CCl₄, standard TMS) showed signals at τ 2.34-3.00 (multiplet, C₆H₅), 8.00 (quartet, CH₂), and 9.16 (triplet, CH₃), their intensity ratio being 10:2:3. These data indicate that the compound is *trans*-α-iodo-α'-propionyloxystilbene *(trans*-IPS).

*Anal.* Calcd for $C_{17}H_{15}IO_2$: C, 53.98; H, 4.01; I, 33.55. Found: C, 53.7; H, 3.99; I, 33.7.

**Rate Measurement for the Transfer of Active Oxygen from Peracetic Acid to Hexahydrobenzoic Acid.**—Hexahydrobenzoic acid (9 ml) and 2 *M* peracetic acid in acetic acid (1 ml) were separately allowed to stand at 50° to reach temperature equilibrium, and then they were mixed quickly to start the reaction. Aliquots (each 1 ml) were pipetted out at known intervals of time and poured into a separatory funnel containing water (20 ml) and

CCl₄ (5 ml). The funnel was shaken rapidly to extract hexahydrobenzoic and hexahydroperbenzoic acids. The extract was again washed with water (20 ml) and separated. The content of hexahydroperbenzoic acid in CCl₄ and that of peracetic acid in the combined aqueous layer were measured by iodometric titration with 0.02 *N* Na₂S₂O₃.

**Registry No.**—*trans*-IAS, 29478-23-7; *trans*-DAS, 35855-69-7; *trans*-DIS, 20432-11-5; *trans*-IPS, 36872-18-1; peracetic acid, 79-21-0; benzil, 134-81-6; sulfuric acid, 7664-93-9; sodium acetate, 127-09-3; iodine, 7553-56-2; anisole, 100-66-3; hexahydrobenzoic acid, 98-89-5.

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# CIDNP from Diffusive Encounters of Free Radicals.   The Reaction of Trichloromethyl with Tetramethylethylene

HALVAR Y. LOKEN,[1] RONALD G. LAWLER,[2] AND HAROLD R. WARD*[2]

*Metcalf Research Laboratories, Brown University, Providence, Rhode Island 02912*

The trichloromethyl radical, formed by thermal decomposition of trichloroacetyl peroxide, reacts with tetramethylethylene predominantly by addition rather than by abstraction of an allylic hydrogen atom. The reaction between the adduct radical and another trichloromethyl radical proceeds primarily by donation of a hydrogen atom to form chloroform and 4,4,4-trichloro-2,3,3-trimethyl-1-butene. CIDNP emission signals with enhancement factors greater than 200 are observed for both products. At high tetramethylethylene concentration, radical pair substitution occurs.

The first observations[3] of chemically induced dynamic nuclear polarization (CIDNP) were tentatively explained[4,5] by an adaptation of the Overhauser effect. Free radicals were assumed to form with electron spin states equally populated and subsequent electron-nuclear cross relaxation was supposed to give rise to a nuclear polarization which could be retained in rapidly formed radical products. With this model it was difficult to explain polarization resulting from the diffusive encounter of free radicals, although a "reverse" Overhauser effect was suggested for this purpose.[6] It was at this point in the evolution of CIDNP that we began a study of the enhanced spectra taken during the thermolysis of trichloroacetyl peroxide, a system in which any proton polarization must necessarily result from the reactions of secondary radicals.[7] During the time that this study was underway, it was pointed out[6,8] that very large nuclear polarizations may be generated in the radicals reacting in and escaping from both geminate and diffusive encounter radical *pairs*. The results of our studies of the trichloroacetyl peroxide system are entirely in accord with the radical pair model, and, in addition, offer confirmation that proton polarization is not destroyed during hydrogen atom transfer from one radical to another. In the course of these studies, the reaction of tetramethylethylene (TME) with the trichloromethyl radical (·CCl₃) has been examined in detail.

## Results and Discussion

**Reactions of ·CCl₃ with TME. Products.**—TME was selected as a radical trap for ·CCl₃ because only one primary abstraction and one addition reaction are possible, and only a narrow region of the nmr spectrum (δ 1.5-1.7) is obscured by the allylic methyl absorption. The TME–·CCl₃ reaction does not appear to have been investigated previously, and the ratio of addition to abstraction (*X*) is not known. Huyser[9] has, however, measured this ratio for *cis*- and *trans*-2-butene, for which it is found that *X* = 34 and 26, respectively, at 99° in the liquid phase. The additional methyl groups in TME should favor abstraction by a statistical factor of two, and also possibly enhance the polar character of the abstraction process, which has been suggested to involve a transition state with some electron transfer from the olefin to ·CCl₃.[10] Addition should also be accelerated by both the increased nucleophilicity of the double bond and the greater stability of the tertiary adduct radical, but decreased by steric crowding in the radical. The balancing of these effects is difficult to predict since one can find grounds on which to expect *X* to be both greater than and less than that for 2-butene.

Analyses of the products of the thermolysis of trichloroacetyl peroxide (0.08 *M*) in carbon tetrachloride were made as a function of TME concentration (Table I). Since the purpose of the product determinations was to support the CIDNP studies, reactions were run under the conditions used for recording CIDNP spectra; *e.g.*, an nmr tube containing the reagents at < −10° was dropped into an nmr probe held at 60°. Under these conditions the reaction was complete in

(1) National Center for Air Pollution Control, Special Fellow (Predoctoral), 1967-1970.

(2) Alfred P. Sloan Foundation Research Fellow.

(3) J. Bargon, H. Fischer, and U. Johnsen, *Z. Naturforsch.*, **22a**, 1551 (1967); H. R. Ward, *J. Amer. Chem. Soc.*, **89**, 5517 (1967); H. R. Ward and R. G. Lawler, *ibid.*, **89**, 5518 (1967).

(4) R. G. Lawler, *ibid.*, **89**, 5519 (1967).

(5) J. Bargon and H. Fischer, *Z. Naturforsch.*, **22a**, 1556 (1967).

(6) G. L. Closs, *J. Amer. Chem. Soc.*, **91**, 4552 (1969).

(7) For another system where polarization must take place in a random encounter, see S. R. Fahrenholtz and A. M. Trozzolo, *ibid.*, **94**, 283 (1972).

(8) R. Kaptein and L. J. Oosterhoff, *Chem. Phys. Lett.*, **4**, 195 (1969).

(9) E. S. Huyser, *J. Org. Chem.*, **26**, 3261 (1961).

(10) E. S. Huyser, *J. Amer. Chem. Soc.*, **82**, 394 (1960).

| Initial [TME] | C₂Cl₆ | HCCl₃ | 1 | 4 | 6 |
|---|---|---|---|---|---|
| 0.0 | 100 | | | | |
| 0.078 | 75 | 13 | 11 | 0.001 | |
| 0.16 | 47 | 20 | 19 | 3 | |
| 0.26 | 35 | 25 | 23 | 9 | |
| 0.39 | 22 | 25 | 25 | 9 | |
| 0.65 | 22 | 21 | 46 | 20 | 7 |
| 3.25 | 9 | 18 | 17 | 31 | 5 |

[a] The initial concentration of peroxide was always 0.08 *M*. Product yields are given as per cent of initial peroxide concentration. For most points several determinations were made with a precision of approximately 2.5%. TME concentrations are in moles/liter.

*ca.* 5 sec after the onset of reaction.[11] At TME concentrations of less than 0.6 *M*, the major products derived from the olefin were chloroform and 4,4,4-trichloro-2,3,3-trimethyl-1-butene (1). Scheme I shows

SCHEME I
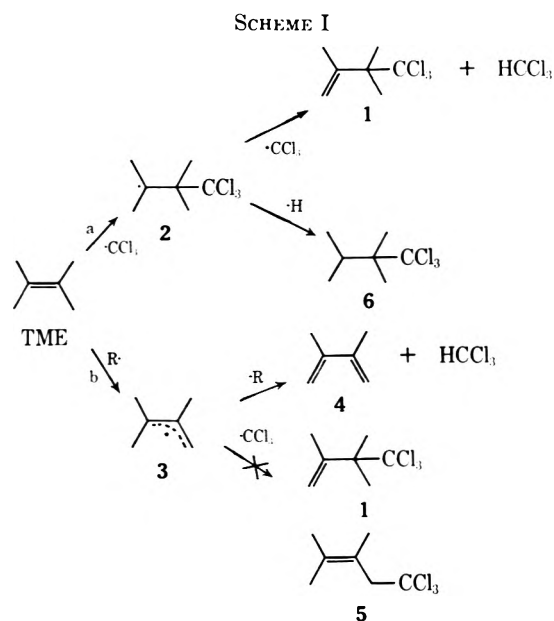


the addition–disproportionation (a) and the abstraction–combination (b) reactions which are reasonable candidates for the route to these products.

There are two pieces of chemical evidence which seem to favor path a.

(1) There is an optimum TME concentration (~0.3 *M*) for chloroform formation, apparently the point where the product of [·CCl₃] and [2] is maximized. In path b, chloroform formation should continue to increase with increasing TME concentrations. Furthermore, nearly equal amounts of HCCl₃ and 1 are formed

at all concentrations up to 0.4 *M* even though reaction of 3 with ·CCl₃ to product 2,3-dimethylbutadiene (4) at high TME concentrations would have simultaneously produced an additional molecule of HCCl₃. The maximization of 1 at 0.65 *M* TME without a corresponding maximum in HCCl₃ is probably due to a peak in the concentration of the radical 2 near this concentration. Disproportionation of two 2 radicals would give 1 and 6. The dimeric radical resulting from the addition of 2 to TME may also react with 2 to give more 1 without producing either HCCl₃ or 6.

(2) Decomposition of trichloroacetyl peroxide in 3.25 *M* TME at temperatures obtained by immersing the nmr tube in a beaker of ice water and letting the system react as it warms to room temperature gives no detectable amount (<2%) of chloroform, although the same reaction mixture at 60° gives 20% chloroform. Most probably, the difference results from a much lower steady-state concentration of ·CCl₃, which decreases the probability of the encounter of 2 and ·CCl₃. The half-life of trichloroacetyl peroxide in carbon tetrachloride solution at 0° is about 10 min,[12] while at least 90% of the decomposition takes place in 3 sec in the heated reaction,[11] giving a difference in the rate of ·CCl₃ formation of at least 10³ under the two conditions.

At higher TME concentrations the radicals 2, formed by addition of ·CCl₃ to TME, are less likely to encounter a ·CCl₃. Consequently, self-disproportionation reactions (giving 1 and 6) and hydrogen abstraction from TME by 2 (leading to 3 and eventually to 4) become more probable. The measured amount of 4 is probably low since it should efficiently trap ·CCl₃ and other radicals. Indeed, in a reaction run with a mixture of TME (0.39 *M*) and 4 (0.13 *M*), chloroform and 1 were decreased by 80% (compared to the reaction in TME alone), and a new unidentified monoadduct of trichloromethyl was formed in trace amounts. The main product of the reaction in the presence of 4, however, appeared to be a highly chlorinated polymer.[13] Even when 4 was not added, substantial polymerization occurred. The presence of chlorine in this polymer helps to account for the low material balance of CCl₃ groups in the volatile products. There is no evidence of atom transfers involving radicals resulting from TME (*i.e.*, 2,3-dimethylbutane and 2,3-dimethyl-2-chlorobutane could not be detected by gas chromatography).

**CIDNP Spectra.**—The radical-pair theory first proposed by Kaptein and Oosterhoff[8] and by Closs[7] and modified by Adrian[14] offers the most satisfying explanation of the CIDNP phenomena. The sign of enhancement of lines in a CIDNP spectrum can be consistently predicted from a knowledge of only the signs of hyperfine splitting, the relative magnitudes of the *g* factors of the two radical fragments, and the initial electron spin multiplicity of the radical pair. Several reviews of the theory are available,[15] as well as simplified

(11) The onset of reaction was about 5 sec after insertion into the probe owing to a lag in heating. If the tube was heated in a block designed to simulate a heated probe [H. R. Ward, R. G. Lawler, H. Y. Loken, and R. A. Cooper, *ibid.*, **91**, 4929 (1969)] for 10 sec and then rapidly transferred to the probe, no polarization was observed, indicating a completed reaction. The block was similarly used to monitor reaction progress, since reaction taking place after transfer from block to probe would result in polarization. This method of running an exothermic reaction leads to kinetics that are almost impossible to quantify. However, an advantage is that the sudden rise in temperature, which can be monitored by inserting a miniature thermocouple into the nmr tube, counteracts the drop in rate that would otherwise take place as the reactants drop in concentration. At peroxide concentrations below about 0.1 *M*, the heat capacity of the solvent moderates the temperature increase enough to prevent the sample from boiling.

(12) J. E. Leffler and H. H. Gibson. Jr., *J. Amer. Chem. Soc.*, **90**, 4117 (1968).

(13) Analysis of a sample of the polymeric material yielded C, 18.9; H, 2.1; Cl, 78.8. This corresponds to a Cl content even higher than the empirical formula (CCl₃)₄C₆H₁₀ (C, 21.6; H, 1.9; Cl, 76.5) expected for addition of four CCl₃ groups to the two double bonds in 4. This apparent excess of Cl was not investigated further.

(14) F. J. Adrian, *J. Chem. Phys.*, **53**, 3374 (1970).

(15) (a) R. G. Lawler, *Accounts Chem. Res.*, **5**, 25 (1972); (b) G. L. Closs, *Spec. Lect. XXIIIrd Int. Congr. Pure Appl. Chem.*, **4**, 19 (1971); (c) H. Fischer, *Top. Curr. Chem.*, **24**, 1 (1971); (d) R. Kaptein, Doctoral Dissertation, University of Leiden, 1971.
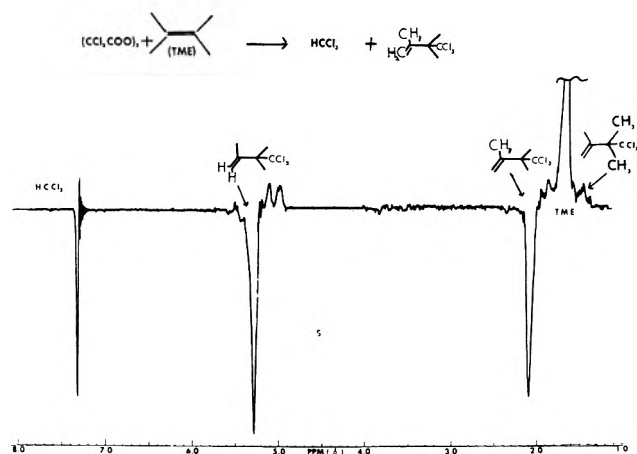
Figure 1.—CIDNP spectrum taken during the thermolysis of trichloroacetyl peroxide in carbon tetrachloride solutions of TME. The spectrum is a composite of three scans.



Figure 2.—Repeated scans of the CIDNP spectrum, taken at 19.3 MHz, during the thermolysis of trichloroacetyl peroxide in carbon tetrachloride solution of TME. The strong absorption peak is TME. Sweeps were from low to high field with flyback from 1 to 8 ppm.

approaches to the predictions of the spectral characteristics.[15a,16,17] The spectrum observed in the system at hand can be predicted by these methods, and is an example of pure net polarization, resulting from the substantial difference in precessional frequencies for the two electrons in radical pairs composed of $\cdot CCl_3$ and 2. This precessional frequency difference is reflected in the $g$ factors ($\cdot CCl_3$, 2.0091;[18] 2, 2.0025[19]). The only protons in the intermediate radical pair that will affect electron precessional rates (*i.e.*, are coupled to an electron) are the $\beta$-methyl protons in 2, for which the hyperfine coupling has a positive sign. Consequently, 1 and $HCCl_3$ which are combination products arising from a diffusively formed radical pair, should both give emission lines.[16,17]

During the decomposition of trichloroacetyl peroxide in carbon tetrachloride with added TME (0.3 $M$), strong nmr emission signals are observed at $\delta$ 7.3 (chloroform) and 5.25 and 2.15 (vinyl and allyl protons of 1) and weak enhanced absorption at $\delta$ 5.04 and 4.93 (vinyl protons of 4) (Figure 1).[20] At the completion of the reaction, these peaks become weak absorption signals. The singlet at $\delta$ 1.54 is from the 3-methyls of 1, and shows no polarization during the reaction. Since the protons exhibiting emission are all equivalent in the intermediate free radical, it would be expected that all three of the observed lines should have the same enhancement factor. When the reaction was run and the spectrum was obtained in times comparable to the shortest $T_1$ ($T_1$ for chloroform $\cong$ 40 sec; $T_1$ for the allyl and vinyl protons in 1 $\cong$ 8 sec), this expectation is realized (Figure 2). The intensities for chloroform, vinyl, and allyl protons appear in approximately the statistical ratios 1:2:3. Nuclear relaxation times were estimated directly from the rapidly reacted sample by following the decay of the polarization of the various
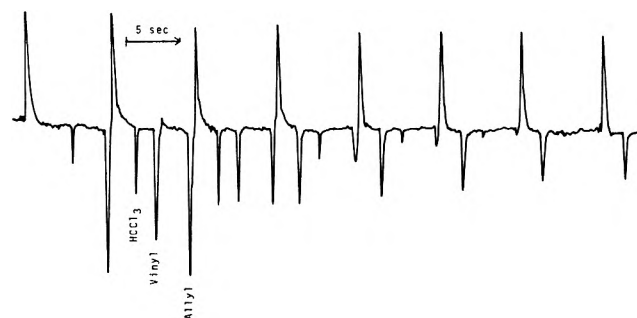
lines as a function of time after the reaction was complete.

The enhancement factor calculated for the chloroform proton was $-220 \pm 20$ at 60 MHz and $-300 \pm 50$ at 19.3 MHz. These measurements were made by a cancellation method. Enough chloroform was added to exactly cancel out the emission signal resulting from the reaction that was over in a time less than the relaxation time. The reaction was then repeated adding inert solvent ($CCl_4$) in an amount equal to the amount of chloroform needed to cancel the emission peak, and the amount of chloroform formed was measured. The observed enhancement factor is then simply the ratio of the amount of $HCCl_3$ needed to cancel the CIDNP emission to the amount formed in the reaction. Chloroform was not consumed under the reaction conditions.

The weak positive enhancement of the signal assigned to the vinyl protons of 4 is probably a result of the partial cancellation of the polarization developed in encounters of 3 with $\cdot CCl_3$. Two of the protons in 3 which appear in the vinyl position of 4 have a negative hyperfine coupling, while the methyl group protons which also become vinyl protons in 4 have a positive coupling. Further, using methallyl radical as a model, the magnitude of the coupling for the two positions should be nearly equal.[21] Since enhanced absorption is observed, apparently the *gem*-methyl hyperfine coupling in 3 dominates.

At very high TME concentrations (about 5 $M$) the sign of the chloroform polarization reverses (and, as expected, very little chloroform is formed). This change of polarization is probably due to the interception of one partner of the radical pair. (After leveling off at intermediate TME concentrations, the hexachloroethane yield drops again at the highest TME concentration. This constitutes independent confirmation of this interception.) Since the $\cdot CCl_3$ geminate pair is in a singlet state, this process of pair substitution[22] leads to a $\cdot CCl_3$-2 pair which is predominantly *singlet* in character. This change in the starting multiplicity of the pair necessarily results in a change in the sign of polarization.[16]

**Reactions of $\cdot CCl_3$ with Isobutylene.**—CIDNP spectra taken of decomposing trichloracetyl peroxide

(16) H. R. Ward, *Accounts Chem. Res.*, **5**, 18 (1972).

(17) R. Kaptein, *Chem. Commun.*, 732 (1971).

(18) A. Hudson and H. A. Hussain, *Mol. Phys.*, **16**, 199 (1969).

(19) R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.*, **39**, 2147 (1963).

(20) Some other unexplained enhanced nmr lines, apparently from otherwise undetectable minor products, were observed at high gain for short periods in fast reactions with high TME concentrations. The weak lines were mostly enhanced absorption, which is expected for radicals that are captured after escaping a cage where reaction leads to emission. The enhanced absorption for the vinyl protons of 4 was more intense than predicted if all $\cdot CCl_3$ that did not dimerize was assumed to react as in Scheme I to form 4.

(21) J. K. Kochi and P. J. Krusic, *J. Amer. Chem. Soc.*, **90**, 7157 (1968).

(22) For a more complete discussion of pair substitution see R. A. Cooper, R. G. Lawler, and H. R. Ward, *ibid.*, **94**, 552 (1972); and R. Kaptein, F. W. Verheus and L. J. Oosterhoff, *Chem. Commun.*, 877 (1971).

in carbon tetrachloride solutions of isobutylene can in most important respects be explained by analogy to reactions with TME. Addition of ·CCl₃ at the terminal position of isobutylene forms **7**, which, on encountering
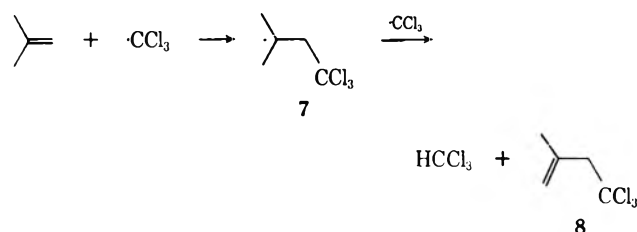


another ·CCl₃, leads to a spin selective interaction giving emission in the proton of chloroform and all of the protons of **8** (vinyl protons at δ 5.1 and the allylic protons just downfield of those in isobutylene).

At higher concentrations of isobutylene (equal volume with carbon tetrachloride), pair substitution occurs and the chloroform proton shows enhanced absorption.

The only substantial difference in the TME and the isobutylene reactions is the appearance in the latter case of a strong emission line for pentachloroethane at δ 6.1. The same emission is observed for reactions with a variety of acetylene and diacetylenic compounds with enhancement factors of up to 10³. Although the source of this emission, identified through its cancellation by added pentachloroethane, is uncertain, two possible sources were eliminated.

(1) A trace of dichloroacetyl chloride in the trichloroacetyl chloride used in the triacetyl peroxide preparation would provide a route to a ·CCl₃–·CHCl₂ pair, which, on combination would show emission for pentachloroethane. Since this is a reaction occurring in a geminate pair, however, the polarization should also be observable in TME reactions, and so does not provide a suitable explanation.

(2) The formation of ·C₂Cl₅ by a chlorine abstraction from C₂Cl₆ and its subsequent encounters with **7** also would lead to a negative sign of enhancement. The addition of C₂Cl₆ to the reaction mixture, however, had no effect on the emission intensity. Further, in reactions of trichloroacetyl peroxide with 2-butyne, pentachloroethane exhibits strong emission while chloroform is unenhanced.

Owing to the strong signal enhancement caused by CIDNP, minor products formed by radical–radical mechanisms can often appear to be very important, while other products, which are not so spectacularly polarized, may tend to be ignored. The pentachloroethane emission, where it occurred, was very prominent in the spectrum during the reaction but there was no detectable absorption from the unenhanced product in the final scans. The pentachloroethane peak is there-

fore a striking example that a polarized peak need not come from a major reaction product.

## Experimental Section

**Trichloroacetyl Peroxide Solution.**—Trichloroacetyl peroxide was prepared by a modification of the method of Leffler and Gibson.[12]

A mixture of 12 g of sodium chloride, 50 g of chipped ice, 20 ml of water, and 2.8 g of sodium peroxide was cooled by a −21° bath and stirred vigorously. Trichloroacetyl chloride (9.0 g) was added by syringe. The addition was stopped for about 45 sec whenever the reaction temperature reached −15°. About 30 sec after the addition was completed, 15–30 ml of carbon tetrachloride (cooled to about −10°) was added and 20 sec later the stirrer was stopped and the carbon tetrachloride layer was removed with a syringe. The solution was stored at Dry Ice temperature.

**Volumetric Determination of Trichloroacetyl Peroxide Concentration.**—The following operation was carried out in its entirety in a 6° cold room. Acetic acid (20 ml, cooled almost to its freezing point) was added to a 125-ml glass-stoppered erlenmeyer flask. Sodium bicarbonate (1.5 g) was added and the contents were stirred magnetically. Potassium iodide in water (40%, 5 ml) was added, followed by 0.5 g of the carbon tetrachloride solution of the peroxide. The contents of the flask were titrated to a starch end point with standardized sodium thiosulfate. A typical peroxide concentration measurement was 0.23 M with a precision of better than 3% (average deviation). Satisfactory results were obtained for a benzoyl peroxide standard. With the benzoyl peroxide it was necessary to wait for about 40 min at room temperature for the peroxide to react completely. With the trichloroacetyl peroxide, 5 min at the cold room temperature was more than adequate.

**Reaction of TME with ·CCl₃.**—Frozen trichloroacetyl peroxide solution was warmed just to the melting point and 0.3- to 0.5-ml quantities were transferred to clean, dry nmr tubes fitted with serum stoppers and precooled with Dry Ice. To run a reaction, a tube was taken from the cooling bath, filled with the correct amount of TME and inert solvent (carbon tetrachloride or chloroform), and repeatedly inverted until the last crystal disappeared. At this point, the tube (with the spinner turbine taped in place) was placed in a variable-temperature probe.

Product concentrations at the end of the reaction were measured by gas chromatography. Nmr was not suitable because of low product concentration. A 15-ft 15% SF-96 column was used at 65° for the low-boiling products and at 180° for the higher boiling hexachloroethane and 4,4,4-trichloro-2,3,3-trimethylbut-1-ene. The high temperature did not cause decomposition of these products, since duplicate analysis on a 5-ft 5% SE-30 column at 65° gave the same yields. However, there were products that decomposed at 180°, with production of chloroform, since the apparent amount of chloroform could be increased simply by raising the injector temperature.

# Intramolecular Addition of Hydroxy Groups to the
# Carbonyl Groups of Trihaloacetate Esters[1]

JACK HINE,* DANIÈLE RICARD, AND ROBERT PERZ

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

The monoesters of trifluoroacetic acid (and, in the first two cases, trichloroacetic acid) with ethylene glycol, pinacol, and isobutylene glycol have been examined by ir and pmr measurements.  In the case of the pinacol esters, but not the other esters, significant amounts of both the hydroxy ester and a cyclic tautomer (a 2-trihalomethyl-1,3-dioxolan-2-ol) are detected at equilibrium.  The presence of small amounts of the cyclic tautomer in all cases, however, is indicated by reaction of all the esters with diazomethane to give derivatives of 2-methoxy-2-trihalomethyl-1,3-dioxolane.

In an earlier paper correlations of rate constants and equilibrium constants for elementary reactions involving coordination of a base with an electrophilic carbon atom were discussed.[2] The reactions considered included a number of nucleophilic attacks on the carbonyl carbon atom of aldehydes and ketones.  In order to extend this work to ester interchange and hydrolysis reactions, we need to know more about the stabilities of the immediate products of nucleophilic attack on esters.  The immediate products are ordinarily protonated and deprotonated forms of the mono- and diesters of ortho acids, RC(OH)$_3$.  Although triesters of ortho acids are well known, we are aware of no reports of direct observations on monoesters in any state of protonation and only a few reports concerning diesters.  The only diester for which we have found good evidence is the product of the internal cyclization of the mono(trifluoroacetate) of *cis*-3,4-dihydroxytetrahydrofuran.[3]  In the reported cyclization of *o*-benzoyloxybenzyl alcohol[4] no spectral measurements were described.  The reaction of diazomethane with 2-hydroxyethyl trichloroacetate (1) yields the cyclic ortho ester 3, presumably *via* the intermediate formation of 2.[5]  However, Meerwein and



Sönke concluded, on the basis of density and refractive index measurements, that the equilibrium between 1 and 2 lies far on the side of 1, as do the analogous equilibria involving the mono- and dichloroacetate esters.[6]

Since a dialkyl ester of an ortho acid must be much more acidic than an ordinary alcohol, it might be easier to make direct observations on its salt than on the un-ionized ester.  In fact, Swarts concluded that

ethyl trifluoroacetate and sodium ethoxide give a solid isolable salt of diethyl 2,2,2-trifluoroorthoacetate.[7]  Bender obtained infrared evidence for this conclusion.[8]  Subsequently, tetrodotoxin has been found to be the inner salt of the diester of an ortho acid.[9,10]

We have extended some of the preceding observations in an attempt to learn whether we could make direct observations on equilibria between ordinary esters and dialkyl esters of ortho acids or their salts.

## Results and Discussion

Treatment of pinacol with trifluoroacetic anhydride gave a crystalline product with the correct elemental analysis for the monoester.  The proton magnetic resonance (pmr) spectrum (in carbon tetrachloride) showed a small peak at $\tau$ 6.5 ppm, attributed to the hydroxylic protons, and four larger peaks at 8.37, 8.61, 8.71, and 8.73 ppm.  In benzene the difference in chemical shift between the last two peaks was 0.05 ppm and the four larger peaks were resolved enough to make it clear that the two middle peaks were of equal size and the outside peaks were each about 38% as large.  It was presumed that one pair of peaks arose from the two different types of methyl groups in the monoester 4 and the other pair from the two types of methyl groups in its cyclic tautomer 4,4,5,5-tetramethyl-2-trifluoromethyl-1,3-dioxolan-2-ol (5).  Since the two types of methyl groups in 4 seem



to differ more in their environment than do those in 5, the two inner peaks were tentatively assigned to 5 and the outer ones to 4.  Since the hydroxy group in 5 must be tremendously more acidic than that in 4, it should hydrogen bond much more strongly to oxygen and nitrogen atoms with unshared electron pairs.  Hence, the pmr spectrum was run in dioxane and acetonitrile, where the lower field outer peak (the only outer peak that was clearly visible) was only about

(1) This investigation was supported in part by Grants GP-7629 and GP-14697 from the National Science Foundation.

(2) J. Hine, *J. Amer. Chem. Soc.*, **93**, 3701 (1971).

(3) P. Bladon and G. C. Forrest, *Chem. Commun.*, 481 (1966).

(4) B. Helferich and H. Liesen, *Chem. Ber.*, **83**, 567 (1950); B. Helferich and H.-O. M. von Blumencron, *ibid.*, **86**, 1058 (1953).

(5) H. Meerwein and G. Hinz, *Justus Liebigs Ann. Chem.*, **484**, 1 (1930).

(6) H. Meerwein and H. Sönke, *J. Prakt. Chem.*, **137**, 295 (1933).

(7) F. Swarts, *Bull. Soc. Chim. Belg.*, **35**, 414 (1926).

(8) M. L. Bender, *J. Amer. Chem. Soc.*, **75**, 5986 (1953).

(9) T. Goto, Y. Kishi, S. Takahashi, and Y. Hirata, *Tetrahedron Lett.*, 779, 1831 (1964).

(10) R. B. Woodward and J. Z. Gougoutas, *J. Amer. Chem. Soc.*, **86**, 5030 (1964).

5% as large as an inner peak. This change in relative peak sizes is attributed to stabilization of **5** by hydrogen bonding to the solvent. The data in Table I show

<div style="text-align:center">

TABLE I

AMOUNTS OF 2-TRIHALOMETHYL-1,3-DIOXOLAN-2-OL
PRESENT IN MONOTRIHALOACETATES OF PINACOL

</div>

| Ester | Solvent | Dioxolan-2-ol, % |
|---|---|---|
| Trifluoroacetate | CCl$_4$ | 60 |
| Trifluoroacetate | Benzene | 72 |
| Trifluoroacetate | 1,4-Dioxane | 95 |
| Trifluoroacetate | MeCN | 95 |
| Trichloroacetate | CCl$_4$ | 7 |
| Trichloroacetate | MeCN | 13 |

that such hydrogen bonding is probably significant even in benzene, where there is significantly more **5** present than in carbon tetrachloride. Addition of the base Dabco (1,4-diazabicyclo[2.2.2]octane) to carbon tetrachloride solutions gave pmr evidence that the equilibrium was shifted toward the cyclic tautomer **5**, which must form a salt or hydrogen-bonded complex with the base. Infrared measurements on the same solutions showed a decrease in the intensity of the absorption peak at 1780 cm$^{-1}$, attributed to the carbonyl group of **4**. Methylation of the mixture of **4** and **5** gave 2-methoxy-4,4,5,5-tetramethyl-2-trifluoromethyl-1,3-dioxolane (**6**), whose pmr spectra showed methyl



**6**
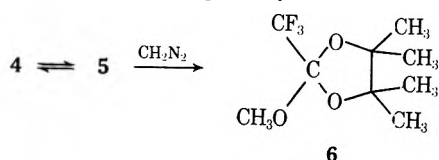
peaks at the same chemical shifts as those of **5** and a methoxy peak split into a quartet by the trifluoromethyl group.

The trichloroacetate of pinacol,[11] like the trifluoroacetate, had a pmr spectrum with two pairs of singlets for the methyl protons, but there was much less cyclic tautomer present (*cf.* Table I). Larger areas could be obtained for the inner peaks by addition of Dabco. Methylation of the mixture of tautomers gave 2-methoxy-4,4,5,5-tetramethyl-2-trichloromethyl-1,3-dioxolane, whose pmr spectrum showed methyl peaks with essentially the same chemical shifts as those in **6**.

In the case of the trifluoroacetate of isobutylene glycol, which consisted largely of the isomer in which the primary alcohol group was esterified, none of the cyclic tautomer was detected. However, in this case, too, treatment with diazomethane gave the cyclic O-methylated derivative **7**, whose methyl groups had about the same chemical shifts as those of **5** and **6**.



**7**
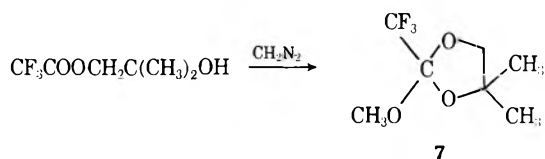
In the case of the trichloroacetate and the trifluoroacetate[12] of ethylene glycol, none of the cyclic tautomer was detected by examination of the pmr spectra. Treatment with diazomethane gave the O-methylated

(11) W. J. Hickinbottom and D. R. Hogg, *J. Chem. Soc.*, 4200 (1954).
(12) S. D. Ross and M. Finkelstein, *J. Org. Chem.*, **22**, 847 (1957).

cyclic derivatives, each of which showed a broadened singlet for the methylene protons, which had given A$_2$B$_2$ patterns in the starting esters.

Studies of the trifluoroacetate of ethylene glycol in ethylene glycol containing the sodium salt of ethylene glycol gave some evidence for the formation of the salt of the cyclic tautomer **8**. Following the reaction in the presence of phenolphthalein by use of a stopped flow spectrophotometer showed that much of the base (in the presence of excess ester) was used up in a reaction with a half-life of less than a second. The remaining base was used up in a reaction that took place over a period of several minutes. We hypothesize that the rapid reaction is the reversible transformation of much of the reactant to **8** and that the slower reaction



**8**
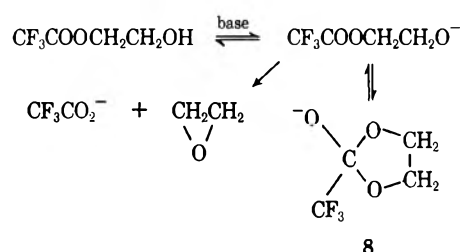
is at least partly a neighboring group displacement reaction to yield ethylene oxide and trifluoroacetate ions. About 70% of sodium trifluoroacetate was found (by ir measurements) to be in the product mixture, but in spite of many experiments we could never detect more than about 10% ethylene oxide.

The strongly electron-withdrawing trihalomethyl group attached to the carbonyl group of our esters must greatly increase the equilibrium constants for addition of hydroxy groups to the carbonyl groups. Addition is further favored by the possibility of forming a five-membered ring. Even so, the fraction of cyclic tautomer present at equilibrium in the case of 2-hydroxyethyl trifluoroacetate was too small to detect directly. Only when there were several methyl groups present to favor ring formation still more (or when the hydroxy and trifluoroacetoxy groups are held next to each other, as in the case of the trifluoroacetate of *cis*-3,4-dihydroxytetrahydrofuran) is the stability of the cyclic dialkyl ortho ester comparable to that of the open-chain hydroxy ester. Examination of the steric and polar substituent constants of trichloromethyl and trifluoromethyl groups suggests that the smaller tendency of the trichloroacetate of pinacol to cyclize is probably largely the result of steric hindrance.

## Experimental Section

**Trifluoroacetylation of Pinacol.**—Various methods of treating pinacol with trifluoroacetic acid gave only pinacolone. Reaction of 10.5 g (50 mmol) of trifluoroacetic anhydride and 5 g (49 mmol) of pinacol in 10 g of benzene at about 25° for 2.5 hr was found by glpc on diethylene glycol succinate (DEGS) to give a major amount of a new product, almost as much pinacolone, and about 15% as much pinacol. The combined products of two such reactions were rid of pinacol by fractional distillation at 35–78° (9.5 mm). Refractionation of the latter fractions from this distillation gave material that showed only one peak on glpc on DEGS: bp 40° (2.5 mm); mp 45–52°; ir[13] (CCl$_4$) 1200, 1780, 1360, 2990, 3010, 1380, 3600, and 1450 cm$^{-1}$.

*Anal.* Calcd for C$_8$H$_{13}$O$_3$F$_3$: C, 44.86; H, 6.11; F, 26.60. Found: C, 45.01; H, 6.12; F, 26.54.

(13) In order of decreasing intensity.

**2-Methoxy-4,4,5,5-tetramethyl-2-trifluoromethyl-1,3-dioxolane.**—The product of the trifluoroacetylation of pinacol (a mixture of 4 and 5) was added to a solution of diazomethane in ether and the resultant mixture was separated by glpc on DEGS. The product that had given the only major new glpc peak had a pmr spectrum (CCl₄) consisting of a quartet ($J_{FH} \cong 1.3$ Hz) at $\tau$ 6.65 and two singlets, each with an area twice that of the quartet, at 8.63 and 8.70 ppm. The ir showed no absorption band in the carbonyl region.

**Trichloroacetate of Pinacol.**—The product [bp 75–78° (0.05 mm); ir (CCl₄) 1760 (C=O) and 3590–3000 cm⁻¹ (OH)] of the reaction of trichloroacetic acid with tetramethylethylene oxide[11] had a pmr spectrum (CCl₄) consisting of a slightly broadened hydroxy peak at $\tau$ 7.50, two methyl peaks, each almost six times as large, at 8.37 and 8.71, and two more methyl peaks, each about 8% as large as the larger methyl peaks, at 8.55 and 8.66 ppm. The pmr spectrum in acetonitrile was quite similar except that the peaks at 8.55 and 8.66 were about 15% as large as those at 8.37 and 8.71 ppm.

**2-Methoxy-4,4,5,5-tetramethyl-2-trichloromethyl-1,3-dioxolane.**—The trichloroacetate of pinacol was added to a solution of diazomethane in ether and the resultant mixture was separated by glpc on DEGS. The material from the only new glpc peak had no carbonyl band in its ir spectrum and a pmr spectrum consisting of three singlets with a ratio of 1:2:2.

**Trifluoroacetates of Isobutylene Glycol.**—Reaction of 9.5 g of trifluoroacetic acid and 8 g of isobutylene glycol in 10 g of benzene was allowed to proceed for 20 hr at 25°. Distillation gave 6 g of colorless liquid, bp 65° (20 mm), ir 1780 cm⁻¹ (C=O). The pmr spectrum showed singlets at $\tau$ 8.68 and 5.80 ppm (areas, 3:2) attributed to the methyl and methylene groups of the primary ester 2-hydroxy-2-methylpropyl trifluoroacetate and two more singlets ($\tau$ 8.45 and 6.24 ppm) 3% as large attributed to the methyl and methylene groups of the tertiary ester 1,1-dimethyl-2-hydroxyethyl trifluoroacetate. This mixture reacted with diazomethane in ether to give, after separation by preparative glpc, 2-methoxy-4,4-dimethyl-2-trifluoromethyl-1,3-dioxolane: ir[13] (CCl₄) 2990, 1360, 1240, 1370, 1450, and 2950 cm⁻¹; pmr (CCl₄) $\tau$ 6.09 (s, 2, CH₂), 6.62 (s, 3, OCH₃), 8.53 (s, 3, CCH₃), and 8.61 ppm (s, 3, CCH₃).

**Trifluoroacetate of Ethylene Glycol.**—A mixture of the mono- and diesters, prepared by the literature procedure,[12] was separated by preparative glpc on DEGS to give 2-hydroxyethyl

trifluoroacetate, whose pmr spectrum (CCl₄) showed two approximate triplets of equal size at $\tau$ 5.34 and 6.02 ppm plus the hydroxyl peak. Methylation by diazomethane gave 2-methoxy-2-trifluoromethyl-1,3-dioxolane: ir[13] (CCl₄) 2910, 2990, 2950, 1430, 1450, 1310, 1360, 1270, 1340, and 2850 cm⁻¹; pmr (CCl₄) $\tau$ 5.77 (s, 4, CH₂), 6.60 ppm (s, 3, OCH₃).

**Reaction of 2-Hydroxyethyl Trifluoroacetate with Sodium 2-Hydroxyethoxide.**—The same results were obtained in this reaction when the diester 1,2-bis(trifluoroacetoxy)ethane was used as when the monoester 2-hydroxyethyl trifluoroacetate was used. Presumably the diester is very rapidly transformed to the monoester under the reaction conditions. Since the diester is more easily obtained in a pure form it was more commonly used. In a typical experiment, 0.2 g of sodium was dissolved in 2.5 ml of anhydrous ethylene glycol under nitrogen. The mixture was cooled to 0° and excess diester was added. After 30 min the pmr of the reaction mixture showed the presence of monoester and ethylene oxide. In other experiments the reaction mixture was evacuated through a trap cooled in liquid nitrogen, which was subsequently found to contain ethylene oxide. The identity of the epoxide was established by glpc on DEGS and SE-30 as well as by pmr. However, in some experiments it was not found, and in no case was its yield greater than about 10%.

Known amounts of the diester were added to standard solutions of sodium 2-hydroxyethoxide in ethylene glycol and absorbance measurements made at the 1680 cm⁻¹ absorption maximum for the trifluoroacetate ion. Comparison of standard solutions of sodium trifluoroacetate in ethylene glycol containing the same concentration of sodium 2-hydroxyethoxide as that found by titration to remain in the reaction solution showed that about 1.4 mol of sodium trifluoroacetate had been formed per mole of diester used.

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# Stereochemistry of Medium-Sized-Ring Cyclopropylcarbinyl Radical Rearrangement[1]

RICHARD W. THIES* AND D. D. McRITCHIE

*Department of Chemistry, Oregon State University, Corvallis, Oregon 97331*

*tert*-Butyl *anti*-bicyclo[7.1.0]decane-2-percarboxylate (1) was prepared and assigned stereochemistry by conversion to *anti*-bicyclo[7.1.0]decan-2-ol. Photolytic or thermal decompositions gave complex product mixtures. The formation of both cis and trans cyclodecenes indicates that the cyclopropylcarbinyl radical does not give a stereospecific ring expansion.

Previous work[2] has shown that *anti*-bicyclo[7.1.0]-decan-2-ol undergoes an acid-catalyzed, stereospecific ring expansion to *trans*-cyclodec-3-en-1-ol (eq 1) and
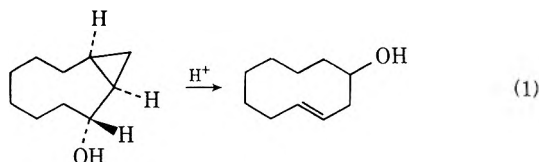


that the syn isomer stereospecifically gives the cis ring expanded product. These results suggest the intermediacy of nonclassical carbonium ions capable of maintaining stereochemistry. However, an argument

could be made for classical ions that maintain stereochemistry because of some property of the medium-sized ring system. For example, the stereospecific ring expansions could result from the least motion rearrangements of two classical ions that do not readily undergo conformational interconversion.[3]

The behavior of the corresponding radical is interesting in this regard because radicals do not generally show nonclassical behavior.[4] If the radicals were to

(1) We thank the Research Corporation for support of this work.

(2) C. D. Poulter and S. Winstein, *J. Amer. Chem. Soc.*, **92**, 4282 (1970).

(3) L. E. Friedrich and F. R. Wight, *ibid.*, **92**, 1807 (1970).

(4) (a) S. J. Cristol and A. L. Noreen, *ibid.*, **91**, 3969 (1969), and references cited therein; (b) J. K. Kochi, P. J. Krusic, and D. R. Eaton, *ibid.*, **91**, 1877 (1969); (c) T. A. Halgren, M. E. H. Howden, M. E. Medorf, and J. D. Roberts, *ibid.*, **89**, 3051 (1967); (d) for a review of earlier work of cyclopropylcarbinyl radicals, see L. K. Montgomery, J. W. Matt, and J. R. Webster, *ibid.*, **89**, 923 (1967).

undergo the same type of stereospecific ring expansion as the carbonium ions, there would be little need to invoke nonclassical ions for this case. The present work reports the stereospecific generation of the anti radical and the stereoselectivity of rearrangement.

## Results

The title compound, 1, was prepared from cyclonon-2-en-1-ol (2) as shown in Scheme I. The stereochemistry

**SCHEME I**
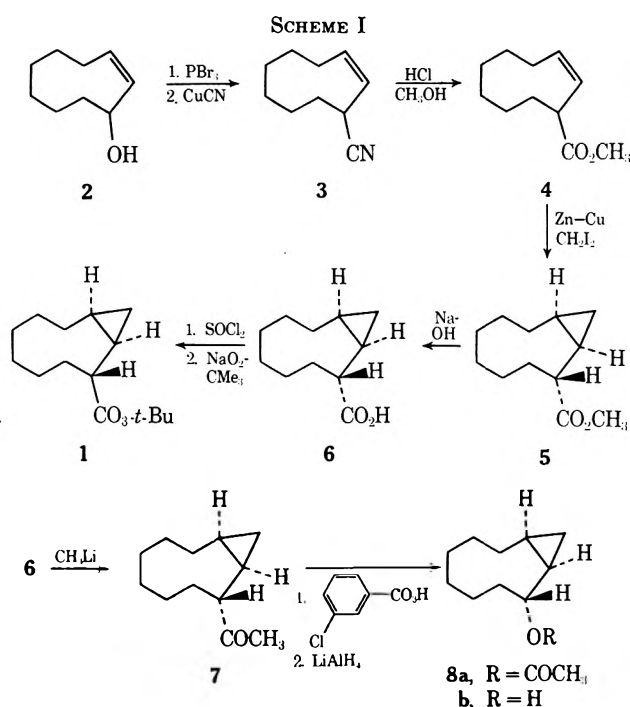


was assigned by converting 6 to the ketone 7, which was degraded by Baeyer–Villiger oxidation to the known alcohol,[2] *anti*-bicyclo[7.1.0]decan-2-ol (8b >99% anti). The Baeyer–Villiger reaction is known[5] to proceed with retention of stereochemistry, which means that the Simmons–Smith reaction gives highly stereoselective formation of the anti isomer 5. This suggests the same sort of directive effect[6] as seen with compound 2, which gives the anti isomer, 8b, under Simmons–Smith conditions. On the other hand, the stereospecificity could be due to steric effects, since the trimethylsilyl derivative 9b also gives only the anti isomer.
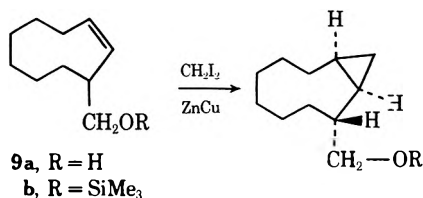


mer. Efforts to epimerize the ester 5 were unsuccessful, as were the other attempts to generate the epimer by alternative synthetic routes.

Photolytic or thermal decomposition of 1 in pentane[7]

(5) J. A. Berson and S. Suzuki, *J. Amer. Chem. Soc.*, **81**, 4088 (1959), and references cited therein.

(6) C. D. Poulter, E. C. Friedrich, and S. Winstein, *ibid.*, **91**, 6892 (1969).

(7) Photolysis in cyclohexane gave similar products except that no C₁₀H₁₇–solvent products were observed and solvent dimer (bicyclohexyl) was formed.

gave a complex set of products that could be separated into four groups by gas chromatography (Table I).

**TABLE I**

VARIATION OF PRODUCT COMPOSITION[a] WITH TIME OF PHOTOLYSIS OF *anti*-BICYCLO[7.1.0]DECANE-2-PERCARBOXYLATE (1) IN PENTANE SOLVENT

| Compd type[b] | Separable components | Time, min | | | |
|---|---|---|---|---|---|---|
| | | 2 | 10 | 20 | 40 | 80 |
| $C_{10}H_{18}$ and $C_{10}H_{16}$[c] | 6 | 3 | 6 | 11 | 17 | 19 |
| $C_{10}H_{17}$–O-*t*-Bu[d] | 4 | 2 | 10 | 8 | 9 | 10 |
| $C_{10}H_{17}$–$C_5H_{11}$ | 4 | 5 | 13 | 17 | 21 | 25 |
| $C_{10}H_{17}$–$C_{10}H_{17}$ | 6 | 1 | 15 | 23 | 44 | 46 |
| 1 | 1 | 90 | 57 | 42 | 9 | |

[a] The composition is presented as moles of "$C_{10}H_{17}$" in that product group, normalized to 100; *i.e.*, the numbers represent the relative peak areas on gc divided by the molecular weight (or the molecular weight/2 for the $C_{20}$ dimer). Corrections were not made for relative response to the flame ionization detector but it was determined that the corrections are small for these compounds. Internal gc standard indicated that the material balances based on the ten carbon radical were 80–90%. [b] A 2% unknown component is not shown. [c] The cyclodecenes represent 56% of this group. [d] Part of this group is either a contaminent in 1 or is formed during LiAlH₄ reduction of 1. The 2-min sample was a different batch of starting peresters.

Further separation of the components within each group required capillary gas chromatography, which precluded collecting each component, so that detailed structures for most of the products could not be readily assigned. A gas chromatograph–mass spectrometer combination was used to obtain mass spectra for most of the individual components. The compound types shown in Table I were assigned from these mass spectra and infrared and nmr spectra of each group.

The *trans*- and *cis*-cyclodecenes, 10 and 11, were intermingled with four compounds that contained two less hydrogens. The gas chromatographic peak for each cyclodecene was enhanced by coinjection of an authentic sample. The mass spectrum for the cis isomer was superimposable with that of authentic *cis*-cyclodecene. The mass spectrum for the trans isomer was similar to that for the authentic sample but showed additional peaks throughout the spectrum that indicated a contaminant with two less hydrogens. The mass spectra for the trans isomer obtained by photolysis of 1 in cyclohexene (see below) was superimposable with that of an authentic sample.

A search was made for two other likely $C_{10}$ products, *cis*-bicyclo[7.1.0]decane (12) and 3-methylcyclononene (13). Coinjection of authentic 12 enhanced the gas
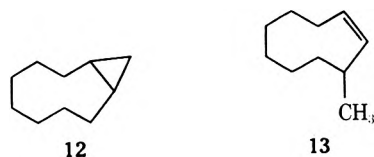


chromatographic peak assigned to the trans isomer but the mass spectra is quite different at high mass; *viz.*, 12 gives a much weaker molecular ion peak and a much stronger $M - 15$ peak than the cyclodecenes. A small amount of 12 could be hidden in the 10 peak but it could not be a major component. The methyl compound, 13, has a much shorter retention time than

any of the $C_{10}$ group and would be easily seen if it were formed. No **13** was detected.[8]

The photolytic decomposition in cyclohexene (Table II) gives a similar set of products but the cyclodecenes

TABLE II

VARIATION IN PRODUCT COMPOSITION[a] WITH TIME OF PHOTOLYSIS OF *anti*-BICYCLO[7.1.0]DECANE-2-PERCARBOXYLATE (**1**) IN CYCLOHEXENE SOLVENT[a]

| Compd type[b] | Separable components | Time, min 7 | 40 | 90 |
|---|---|---|---|---|
| $C_{10}H_{18}$ and $C_{10}H_{16}$[c] | 6 | 2 | 20 | 22 |
| $C_{10}H_{17}$–O-*t*-Bu | 4 | 1 | 9 | 15 |
| $C_{10}H_{17}$–$C_6H_9$[d] | 4 | <1 | 20 | 53 |
| $C_{10}H_{17}$–$C_{10}H_{17}$ | 6 | | 2 | 10 |
| **1** | | 97 | 49 | |

[a] See footnote *a*, Table I. [b] Solvent dimers are also formed. [c] The cyclodecenes make up 68% of this group. [d] This group contains components with mass 220, presumably $C_{10}H_{17}$–$C_6H_{11}$ resulting from addition of radicals from **1** to solvent.

are slightly enhanced, certain decadienes nearly disappear, and $C_{10}H_{17}$–$C_6H_9$ products supplant the dimeric products almost completely.

In pentane, the *cis*- to *trans*-cyclodecene ratio is 75:25 ± 1 from 10% to 58% conversion. The latter two times in Table I give a slightly increased ratio (78:22 and 79:21, respectively), indicating a possible slow interconversion of trans to cis. Control experiments showed that, when *trans*-4-trimethylsiloxycyclodecene (**14**) (a model for **10**) is added to the perester solution, it isomerizes slowly to the cis form under the reaction conditions (7% isomerization after 15 min of reaction). Similar results were observed when *tert*-butyl peracetate was decomposed in the presence of **14** (8% isomerization after 10 min, 33% isomerization after 40 min). *cis*-Cyclodecene did not isomerize measurably to the trans isomer under these conditions.

In cyclohexene the *cis*- to *trans*-cyclodecene ratio was 76:24 ± 1 and did not change even at longer times.

### Discussion

The products from photolytic decomposition of **1** are similar to those previously reported for other stabilized radicals.[10,11] Peresters lose carbon dioxide to give the alkyl radical and *tert*-butoxy radical. The alkyl radicals can abstract hydrogen ($C_{10}H_{18}$), undergo hydrogen abstraction by another radical ($C_{10}H_{16}$), dimerize ($C_{10}H_{17}$–$C_{10}H_{17}$), or combine either with *tert*-butoxy radical ($C_{10}H_{17}$–O-*t*-Bu) or solvent radicals ($C_{10}H_{17}$–$C_5H_{11}$). The latter type of product is less common than the others but has been reported in cumene solvent.[11]

If the radical were to behave in the same way as the carbonium ion, the anti perester should lead to a trans double bond in the ring-expanded products. Models suggest that the best conformation for the system is a

(8) Although **13** was not found, related products arising from external cyclopropane bond cleavage cannot be ruled out in the other types of products. Such external cleavage has been observed in certain other systems.[9]
(9) (a) P. K. Freeman F. A. Raymond, J. C. Sutton, and W. R. Kindley, *J. Org. Chem.*, **33**, 1448 (1968); (b) A. L. J. Beckwith and G. Phillipou, *Chem. Commun.*, 658 (1971); (c) E. C. Friedrich and R. L. Holmstead, *J. Org. Chem.*, **36**, 971 (1971); (d) J. K. Crandell, J. P. Arrington, and C. F. Mazer, *ibid.*, **36**, 1428 (1971).
(10) R. A. Sheldon and J. K. Kochi, *J. Amer. Chem. Soc.*, **92**, 5175, 4395 (1970).
(11) J. P. Engstrom and F. D. Greene, *J. Org. Chem.*, **37**, 968 (1972).

crown form (Chart I) which would initially generate a radical that is favorably aligned for internal cyclo-

CHART I

CONFORMATIONAL PREFERENCE FOR TRANS ISOMER



**1**             **10**
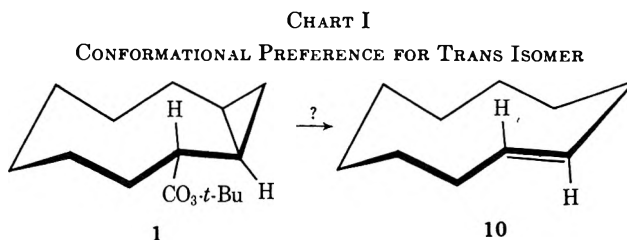
propane bond cleavage leading to a trans double bond. There are no reasonable conformations that would favor the cis isomer.

In pentane and cyclohexene, both *trans*- and *cis*-cyclodecene (**10** and **11**) are formed, the cis isomer predominating 3:1. The other products could not be examined individually, but the trans double bond infrared absorption (a relatively strong band) was not appreciable in any of the other groups of products. Since **10** and **11** only interconvert slowly under the experimental conditions, both must be formed directly from the radical. Thus the radical must interconvert readily between conformations leading to cis and trans ring expanded products (Scheme II). The observed

SCHEME II



trans conformation        cis conformation

↓                  ↓

**10** + other products     **11** + other products
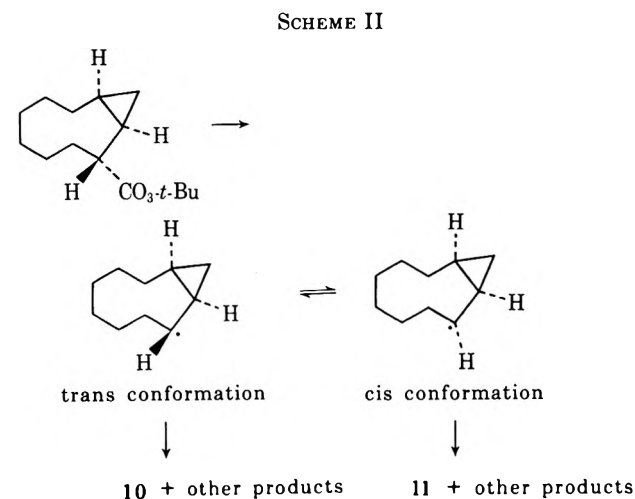
ratio of *cis*- to *trans*-cyclodecene presumably reflects the transition state energy differences leading to the products,[12] although little significance should be placed on the exact ratio because the cyclodecenes represent only 10–15% of the products.

In summary, the present work provides a striking contrast to the medium-sized-ring cyclopropylcarbinyl carbonium ion rearrangements that give stereospecific ring expansion. The corresponding radical reported here gives nonstereospecific rearrangement.

### Experimental Section

The infrared spectra were measured on a Beckman IR-8 or Perkin-Elmer Model 621. Nmr spectra were measured on a Varian Associates HA-100 instrument. Mass spectra were obtained on a Varian MAT CH7 mass spectrometer. Elemental analyses were done by Alfred Bernhardt Analytical Laboratory. Analytical gas–liquid chromatography (gc) utilized a Varian

(12) Acid-catalyzed equilibration of the cyclodecenes give a 94:6 ratio of *cis*- to *trans*-cyclodecenes at 79.9°; A. C. Cope, and P. T. Moore, *J. Amer. Chem. Soc.*, **82**, 1744 (1960).

Model 1200 with flame ionization detector. The following columns were used: column A,0. 01 in. × 125 ft, UCON Polar LB550X capillary; column B, 0.01 in. × 75 ft, DEGS (diethylene glycol succinate) capillary; column C, 0.01 in. × 100 ft, Apiezon N capillary; column D, 0.125 in. × 15 ft, 5% SF-96 on 110/120 Anachrom. The flow through the capillaries was approximately 2 ml/min and the temperature range was 100–140°. The flow through the 0.125-in. column was normally 25 ml/min and the temperature was usually 140°. Gas chromatographic separation with collection was accomplished on a Varian A-90 instrument equipped with column E, ¹/₄ in. × 6 ft, 33% SF-96 on 80/90 Chromasorb A. Photolysis was done in a Rayonet Srinivasan-Griffin photochemical reactor RPR-100 (The Southern New England Ultraviolet Co.).

**cis-Cyclonon-2-en-1-ol (2)** was prepared by the method of Santelli, *et al.*,[13] bp 72° (0.5 mm) (lit.[13] bp 62° (0.5 mm)].

**cis-3-Bromocyclononene.**—A solution containing 16.8 g of cis-8-cyclononenol, 60 ml of dry ether, and 1.0 g of dry pyridine was cooled in an ice bath under a nitrogen atmosphere. To the cooled solution was added, with magnetic stirring, a solution of 10.4 g of phosphorus tribromide in 50 ml of dry ether. The addition required 30 min, after which the ice bath was removed and the solution was stirred further at room temperature for 4 hr and then poured into 100 ml of ice water. The ether layer was separated and washed successively with 3 × 50 ml of cold 5% sodium carbonate and 3 × 50 ml of cold water, dried (MgSO₄), concentrated, and distilled, which gave 22.7 g (93%) of the bromide: bp 54° (0.4 mm); ir (neat) 3350 (OH), 740 (cis C=C), 690 cm⁻¹ (CBr); nmr (CCl₄) δ 5.5 (m, 2), 4.9 (m, 1), 2.1 (m, 4), 1.7 (m, 2), 1.4 (m, 6).

*Anal.* Calcd for C₉H₁₅Br: C, 53.21; H, 7.42. Found: C, 53.05; H, 7.61.

**cis-3-Cyanocyclononene (3).**—In a typical preparation, 10 g of cis-3-bromocyclononene was mixed well with 4.7 g of cuprous cyanide and 20 ml of cyclohexane in a 250-ml flask equipped with an efficient reflux condenser and mechanical stirrer. The mixture was refluxed and moderated when the reaction became vigorous. Refluxing was maintained for an additional 1 hr. The reaction was diluted with 50 ml of cyclohexane and allowed to stir overnight at room temperature. The insoluble portion was separated by filtration, ground with additional cyclohexane, and filtered. The combined organic phase was diluted with an equal volume of cyclohexane and decanted from an ether-insoluble yellow polymer precipitate. The solvent was removed and the resulting yellow oil was vacuum distilled, bp 69–70° (0.5 mm), giving 5.6 g (75%) of 3: ir (neat) 735 (cis C=C), 2240 cm⁻¹ (CN); nmr (CCl₄) δ 5.72 (d of t, *J* = 11, 6 Hz, 1), 5.38 (t, *J* = 11 Hz, 1), 3.50 (t of d, *J* = 11, 4 Hz, 1), 2.10 (m, 2), 1.2–1.9 (m, 10).

**3-Carbomethoxycyclononene (4).**—Dry AR methanol (400 ml) was chilled in an ice bath and anhydrous hydrogen chloride was passed in until the solution was saturated. To this was added 29 g of 3 and the reaction was refluxed. The solution was cooled, poured into 500 ml of saturated ammonium chloride solution, and extracted with 3 × 100 ml of ether. The ether extracts were combined and washed successively with 3 × 50 ml of sodium bicarbonate and 3 × 50 ml of water, and dried over anhydrous sodium sulfate. Solvent was removed and the colorless liquid was distilled, bp 80° (1 mm), which gave 32 g (90%) of 4: ir (neat) 730 (cis C=C), 1725 cm⁻ (C=O); nmr (CCl₄) δ 5.5 (m, 2), 3.57 (s, 3), 3.4 (m, 1), 2.1 (m, 2), 1.3–1.8 (m, 10).

*Anal.* Calcd for C₁₁H₁₈O₂: C, 72.40; H, 9.95. Found: C, 72.19; H, 9.99.

**Methyl Bicyclo[7.1.0]decane-2-carboxylate (5).**—A mixture of 31 g of zinc–copper couple,[14,15] 100 ml of anhydrous ether, and 40 g of methylene iodide was refluxed under nitrogen for 30 min. To this was added 30 g of methyl cyclononene-3-carboxylate in 125 ml of ether. The mixture was refluxed for 1 hr and then an additional 40 g of methylene iodide in 40 ml of ether was added dropwise over a 2-hr period while maintaining reflux. The reaction was monitored by gc (column A) and found to be about 85% complete at the end of the addition. An additional 2-hr reflux gave complete reaction. The reaction was quenched at

room temperature with 150 ml of saturated ammonium chloride solution. The ether layer was separated and washed successively with 1 × 50 ml of saturated ammonium chloride, 3 × 50 ml of 10% sodium carbonate solution, and 3 × 50 ml of water, dried (Na₂SO₄), concentrated, and distilled to yield 29 g (90%) of ester, bp 78° (0.7 mm). The ester eluted as a single peak on columns A, B, and D, indicating that only one isomer had been obtained. The ester was reduced with lithium aluminum hydride in ether solution and the TMS ether 9b was prepared from the resulting alcohol 9a and TriSil Concentrate. The ether eluted as a single peak on columns A, B, C, and D. Compound 5 showed the following characteristics: ir (neat) 3060 (cyclopropyl H), 1725 cm⁻¹ (C=O); nmr (CCl₄) δ 3.36 (s, 3), 2.2–0.9 (m, 12), 0.9–0.2 (m, 4), −0.38 (q, *J* = 4 Hz, 1).

*Anal.* Calcd for C₁₂H₂₀O₂: C, 73.42; H, 10.23. Found: C, 73.26; H, 10.32.

**Bicyclo[7.1.0]decane-2-carboxylic Acid (6).**—The methyl ester 5 was hydrolyzed by refluxing for 1 hr in 50 ml of methanol and 50 ml of 5% sodium hydroxide. Recrystallization of the acid from ethanol–water gave 12.3 g (97%) of acid 6: mp 77–78°; ir (KBr) 2700 (broad CO₂H), 1700 cm⁻¹ (C=O); nmr (CCl₄) δ 11.4 (s, OH), 2.2–1.1 (m, 12), 1.1–0.5 (m, 4), −0.14 (q, *J* = 4 Hz, 1).

*Anal.* Calcd for C₁₁H₁₈O₂: C, 72.40; H, 9.95. Found: C, 72.29; H, 9.97.

The acid was reduced with an ether solution of lithium aluminum hydride and the resulting alcohol, 9a, was treated with TriSil Concentrate. The resulting TMS ether 9b eluted as a single peak on columns A, B, C, and D. Coinjection of this ether with the ether obtained from ester 5 still produced only a single peak on column A. Conditions for the saponification do not cause observable epimerization.

**Bicyclo[7.1.0]decane-2-carboxylic Acid Chloride.**—A solution of 5 g of 6 in 5 ml of thionyl chloride was carefully heated to reflux in an oil bath. When the evolution of acid gases had stopped, usually 1 hr or less, the excess thionyl chloride was removed with the aid of a water aspirator, and the residual yellow oil was distilled, bp 66° (0.2 mm), which gave 5.0 g (90%) of the acid chloride: ir (neat) 3060 (cyclopropyl H), 1780 cm⁻¹ (C=O); nmr (CCl₄) δ 2.3–2.6 (m, 1), 2.3–1.1 (m, 11), 0.7–1.1 (m, 4), −0.02 (m, 1).

**tert-Butyl exo-bicyclo[7.1.0]decane-2-percarboxylate (1)** was prepared from the acid chloride and sodium tert-butyl peroxide as described by Bartlett, *et al.*[16] Chromatography on Florisil gave 1: ir (neat) 3060 (cyclopropyl H), 1770 (C=O), 1194, 1365, 1390 cm⁻¹ (tert-butyl); nmr (CCl₄) δ 2.4–1.1 (m, 12), 1.1 (s, 9), 0.5–1.0 (m, 4), −0.15 (m, 1). Lithium aluminum hydride reduction of 1 gave 9a contaminated with *ca.* 8% of a material that is probably tert-butyl bicyclo[7.1.0]decan-2-yl ether: ir (neat) 3060 (cyclopropyl H), 1052 (COC), 1197 1363, 1386 cm⁻¹ (tert-butyl). The retention time of this contaminent corresponds to the major component of the C₁₀H₁₇-O-*t*-Bu group of products.

**Methyl Bicyclo[7.1.0]decane 2-Ketone (7).**—A solution of 2.7 g of the acid 6 in 5 ml of dry ether was stirred under a nitrogen atmosphere while 21 ml of a 1.8 *M* methyllithium solution was added at a rate to maintain gentle reflux. When addition was complete, the reaction mixture was quenched with ammonium chloride, extracted into ether, washed with water, dried (MgSO₄), concentrated, and distilled, bp 75° (0.4 mm), which gave 2.2 g (80%) of 7. Chromatographic analysis on column A indicated that the compound was contaminated with about 20% of the alcohol resulting from addition of a second molecule of methyllithium. Preparative gas chromatography on column E at 150° gave pure 7, ir (neat) 1700 (C=O), 3060 cm⁻¹ (cyclopropyl H).

*Anal.* Calcd for C₁₂H₂₀O: C, 80.00; H, 11.18. Found. C, 80.20; H, 10.98.

**Bicyclo[7.1.0]decane-2-acetate (8a).**—A solution containing 0.5 g of ketone 7 in 5 ml of chloroform was mixed with 0.5 g of m-chloroperbenzoic acid dissolved in 10 ml of chloroform. The solution was left in the dark for 1 week at room temperature. The reaction mixture was concentrated and extracted into ether solution which was washed successively with 2 × 30 ml of cold 1 N sodium hydroxide, 3 × 30 ml of cold water, and 1 × 30 ml of brine, and dried over magnesium sulfate. Purification by gas chromatography on column E at 180° gave 8a: ir (neat) 3060 (cyclopropyl H), 1725 (C=O), and 1245 cm⁻¹ (COAc).

*Anal.* Calcd for C₁₂H₂₀O₂: C, 73.42; H, 10.23. Found: C, 73.30; H, 10.11.

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**Simmons-Smith[15] Reaction of the Trimethylsilyl Derivative of *cis*-Cyclonon-2-enylmethanol (9).**—Ester 4 was reduced (LiAlH$_4$) and silylated (TriSil, Pierce Chemical Co) to give 9. The Simmons-Smith reaction, conducted in the same way as for compound 6, gave two products: *anti*-bicyclo[7.1.0]decyl-2-methanol (9a) and its trimethylsilyl derivative 9b (approximately 50:50). The alcohol 9a was identical with that obtained by reduction (LiAlH$_4$) of 5. Silylation of the mixture of 9a and 9b gave only 9b: ir 3060 (cyclopropyl H), 1253 cm$^{-1}$ [Si(CH$_3$)$_3$].

*Anal.* Calcd for C$_{13}$H$_{26}$SiO: C, 69.93; H, 11.73. Found: C, 70.04; H, 11.57.

*cis*-**Cyclodecene (11).**—An authentic sample (95% pure) of 11 was prepared by azeotroping water from a solution of cyclodecanol in benzene with *p*-toluenesulfonate catalyst. The spectrum agrees with that reported previously.[17]

*trans*-**Cyclodecene (10).**—A mixture of 4 g of *cis,anti*-bicyclo-[7.1.0]decan-2-ol and 7.1 g of triphenylphosphine in 25 ml of dry dimethylformamide was treated with bromine in dimethylformamide until the orange color persisted. The reaction mixture was distilled under reduced pressure, yielding an oil that was dissolved in ether, washed (5 × 50 ml of water), and dried. The infrared showed that *trans*-3-bromocyclodecene had been produced: no 3060-cm$^{-1}$ band (cyclopropyl H) and a strong absorption at 980 cm$^{-1}$ (trans C=C). Reduction of the bromide by refluxing for 24 hr with excess ethereal lithium aluminum hydride followed by purification on column E gave 10, whose properties coincide with those reported previously.[17]

**Bicyclo[7.1.0]decane (12)** was obtained by hydrogenation over Adams catalyst of bicyclo[7.1.0]deca-3,6-diene.[18] The spectral properties agree with those previously reported.[19] The mass spectrum gave the following data (70 eV): *m/e* (rel intensity) 138 (not measurable), 123 (1), 110 (4), 109 (6), 96 (16), 95 (28), 82 (36), 81 (56), 68 (48), 67 (100).

*cis*-**3-Methylcyclononene (13)** was prepared by reducing (LiAlH$_4$) 4 to the corresponding alcohol, which was then converted to the *p*-toluenesulfonate derivative: mp 77.6–79.0; nmr (CCl$_4$) δ 7.72 (d, *J* = 8 Hz, 2), 7.28 (d, *J* = 8 Hz, 2), 5.57 (q, *J* = 9 Hz, 1), 5.10 (t, *J* = 9 Hz, 1), 3.85 (d, *J* = 6 Hz, 2), 2.83 (m, 1), 2.50 (s, 3), 2.12 (m, 2), 1.55 (m, 10). The *p*-toluenesulfonate was reduced (LiAlH$_4$) to give 13: ir (CS$_2$) 742 cm$^{-1}$ (cis C=C); nmr (CCl$_4$) δ 5.0–5.6 (m, 2), 2.4–2.8 (m, 1), 2.4–2.0 (m, 2), 1.1–1.9 (m, 10), 1.0 (d, *J* = 6 Hz, 3); mass spectrum (70 eV) *m/e* (rel intensity) 138 (4), 123 (5), 110 (9), 109 (10), 96 (19), 95 (25), 82 (25), 81 (54), 68 (64), 67 (100). *Anal.* Calcd for C$_{10}$H$_{18}$: *m/e* 138.141. Found: *m/e* 138.144.[20]

**Photolyses.**—Solutions, 1% of 1 in dry pentane or cyclohexene, were photolyzed in a quartz tube for various times, removed, reduced with ethereal lithium aluminum hydride, and analyzed by gc on column A using a 100 to 180° temperature program. For the cyclohexene case, it was necessary to treat the mixture with TriSil (Pierce Chemical) to prevent serious overlap between the reduced perester and the C$_{10}$H$_7$–C$_6$H$_9$ group. This column was connected to the mass spectrometer inlet, which

allowed mass spectral analysis of the individual components of the mixture. Control studies used 1% of 11 or 14 and 1% of *tert*-butyl peracetate or 0.5% of 14 in the reaction mixture with 1.

**Pyrolyses** used 1% solutions in dry pentene that were warmed at 100° and analyzed as above. The product mixture was similar to photolysis but less C$_{10}$H$_{18}$–C$_{10}$H$_{16}$ products were formed.

**Product Data (Analyzed on Column A). C$_{10}$H$_{18}$–C$_{10}$H$_{16}$ Group.**—In pentane there are six separable components in a ratio of 11:11:11:45:7:15. The second and fourth components were the *trans*- and *cis*-cyclodecenes; mass spectrum (cis) (70 eV) *m/e* (rel intensity) 138 (17), 110 (17), 109 (14), 96 (27), 95 (44), 82 (53), 83 (75), 68 (50), 67 (100); (trans) 138 (11), 110 (11), 109 (10), 96 (17), 95 (34), 82 (43), 83 (71), 68 (57), 67 (100). The other components all gave 136 molecular ion peaks. The infrared spectrum of the group showed a weak band at 980 (*trans* C=C) and a strong band at 708 cm$^{-1}$ (cis C=C). The nmr spectrum showed vinyl protons but no appreciable highfield cyclopropyl protons.

In cyclohexene, there are six separable components in a ratio of 2:16:52:6:17:6. The second and third components were *trans*- and *cis*-cyclodecenes.

**C$_{10}$H$_{17}$–O-*t*-Bu Group.**—The gc analysis showed two poorly resolved doublets in an approximate ratio of 12:8:50:30. The major peak gave a parent ion at *m/e* 210. The group showed the following absorbances: ir 1052 (COC), 1197, 1363, 1386 (*tert*-butyl), 980 cm$^{-1}$ (weak, trans C=C); nmr (CCl$_4$) δ 5.38 (vinyl H), 3.0–3.5 (OCH), 1.15 (O-*t*-Bu), 0.8 and −0.15 (cyclopropyl H). The nmr indicates a 2:1 ratio of cyclopropyl to olefinic compounds.

**C$_{10}$H$_{17}$–C$_5$H$_{11}$ Group.**—The gc analysis gave two poorly resolved doublets in an approximate ratio of 50:30:12:8. The mass spectra of each component gave a molecular ion at *m/e* 208 and a fragmentation pattern similar to that below for the major isomer (70 eV): *m/e* (rel intensity) (fragment lost) 207 (69) (−H), 193 (6) (−CH$_3$), 179 (25) (−Et), 165 (44) (−Pr), 137 (100) (−C$_5$H$_{11}$). The group showed characteristic absorbances: nmr (CCl$_4$) δ 5.3 (m, vinyl H), 1.4 (m, −CH$_2$−), 0.86 (m, CH$_3$).

**C$_{10}$H$_{17}$–C$_6$H$_9$ Group.**—The gc analysis gave five peaks in a ratio of 5:59:19:5:12. The mass spectra gave molecular ion peaks at *m/e* 218 and strong peaks at *m/e* 137, 95, and 81. Part of this group gave molecular ion peaks at *m/e* 220 and strong peaks at *m/e* 137, 95, and 81 (see Table II, footnote *d*).

**C$_{10}$H$_{17}$–C$_{10}$H$_{17}$ Group.**—The mass spectra was characteristic for dimers, *i.e.*, molecular ions at *m/e* 274 with the next prominent mass at *m/e* 137.

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# A Total Stereoselective Synthesis of *myo-*, *allo*, *neo-*, and *epi*-Inositols[1]

Chana R. Kowarski* and Shalom Sarel

*School of Pharmacy, Hebrew University, Jerusalem, Israel*

A total stereoselective synthesis of 1,4-anhydroinositols and *myo-*, *allo-*, *neo-*, and *epi*-inositols was effected. The adducts, *exo-* and *endo*-oxabicyclo[2.2.1]-hept-5-ene carbonate, were epoxidized and upon alkaline hydrolysis yielded 1,4-anhydro-D-*allo*- and -*cis*-inositols, respectively. Upon additional mild acidic hydrolysis, the above mentioned inositols were obtained. Methods of preparations and identification were considered.

The inositols are well-known natural products.[2-4] Although numerous attempts to synthesize them were made in the past,[5-12] none of them were stereoselective. This approach was applied by Criege[13] and by Sarel and Kowarski.[14,15] Their method was to build a well-structured, sterically built, six-membered ring and introduce the missing hydroxyl groups in a well-defined steric position. This paper will describe a total stereoselective synthesis of 1,4 anhydroinositols and inositols. The plan of work is outlined. Vinylene carbonate[16] was condensed *via* Diels–Alder addition with furan and the *endo-* and *exo*-oxabicyclo[2.2.1]-hept-5-ene-2,3-diol carbonate adducts were obtained (eq 1, **1a**, **1b**).
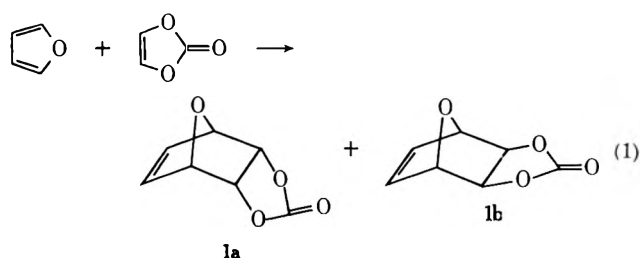


Trans hydroxylation of the olefinic center in endo adduct **1a** was effected *via* epoxide **4**, which was prepared with peracetic acid. (See Scheme I.) After alkaline hydrolysis of **4**, the D-1,4-anhydroinositol was obtained and isolated as the tetraacetate (**5**). Hydrolysis of this substance with acetic acid and minute amounts of sulfuric acid resulted in *myo-* (**7**) and *allo*-inositol (**6**).

Cis hydroxylation of endo adduct **1b** was effected with osmium tetroxide to give 1,4-anhydro-*allo*-inositol, which was isolated as tetraacetate **2**. Treatment with HOAc–H₂SO₄ as described above gave *neo*-inositol (**3**).

### Scheme I



Similar transformation was carried out with the exo adduct **1b**. (See Scheme II.) Epoxidation with peracetic acid gave peroxide **8**. Acid hydrolysis of this substance, or of the derived 1,4-anhydrotetrol, gave *allo-* (**6**) and *myo*-inositol (**7**). Cis hydroxylation as described for the endo adduct and subsequent acid treatment afforded *epi*-inositol, characterized as the hexaacetate (**11**).

## Experimental Section

**Monochloroethylene Carbonate.**[16]—A stream of chlorine was passed through 250 g (2.8 mol) of freshly distilled ethylene carbonate at 63–70° in the presence of a Mazda lamp of 500 W. After 12 hr, vacuum rectification yielded pure monochloroethylene carbonate, bp 106–107° (10–11 mm), $n^{25}$D 1.4530.

*Anal.* Calcd for $C_3H_3O_3Cl$: C, 29.4; H, 2.5; Cl, 29.0. Found: C, 29.6; H, 2.5; Cl, 29.2.

**Vinylene Carbonate.**[16]—Triethylamine (25.3 g) in 50 ml of ether was added to 30.0 g (0.24 mol) of monochloroethylene

(1) (a) Abstracted from a thesis submitted by C. R. Kowarski to the School of Pharmacy, Hebrew University, Jerusalem. (b) Address correspondence to C. R. Kowarski at the Department of Pharmacy, Temple University, Philadelphia, Pa.

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SCHEME II



carbonate in 100 ml of dry ether at reflux temperature dropwise over a 7-hr period. Following refluxing and stirring overnight, the solids were removed and distillation yielded 12.4 g (59%) of colorless liquid, bp 76–79° (37 mm). Further rectification produced pure vinylene carbonate, bp 73–74° (32 mm), $n^{25}D$ 1.149.

*Anal.* Calcd for $C_3H_2O_3$: C, 41.9; H, 2.3. Found: C, 42.1; H, 2.4.

*exo-* and *endo*-Oxabicyclo[2.2.1]hept-5-ene-2,3-diol Carbonates (1a,b).—The method followed in preparing the adduct was Newman's procedure.[17a] Vinylene carbonate (25.0 g, 0.29 mol) and 4.0 g of furan were sealed into an ampoule of 100 ml volume having a wall thickness of 3 mm. The ampoule was maintained in Dry Ice while the ingredients were mixed together. The sealed ampoule was then placed in a dry heat oven at a temperature of 120° and kept there for 12 hr. Unaffected vinylene carbonate was distilled and reused for further reaction. The residue was distilled at a temperature of 155° (2 mm). Upon distillation, a crystalline product having a melting point range of 95–150° was obtained. According to Newman,[17b] this crystalline white powder was a mixture of endo and exo adducts. These adducts, upon column chromatography separation,[17a] yielded 700 mg of the endo isomer, mp 144–148°, and 150 mg of the exo isomer, mp 137–139°. The total yield of the two isomers was 21% (based on furan).

*Anal.* Calcd for $C_7H_6O_4$: C, 54.6; H, 3.9. Found (137° isomer): C, 54.5; H, 4.1; (149° isomer) C, 54.6; H, 4.1.

*endo*-Epoxyoxabicyclo[2.2.1]hept-5-ene-2,3-diol Carbonate (4).—To 1.5 g (9.7 mmol) of the adduct 1a were added 15 ml of glacial acetic acid, 5 ml of $H_2O_2$ (30%, v/v), and 0.02 ml of concentrated sulfuric acid. The mixture was kept at 40° in a dry heat oven for a period of 48 hr. The oxidized product was filtered off, and the precipitate was boiled in 20 ml of chloroform

(17) (a) M. S. Newman, *ibid.*, **77**, 3789 (1955). (b) The fine structure of stereoisomeric forms endo and exo was not established by Newman.[17a] Additional support was given to Newman's rationale when the authors measured the dipole moments of the adducts. The dipole moments measurements were performed through the use of the Heterodyne method [A. Weisberger. "Physical Methods in Organic Chemistry," Vol. I, Part II, Interscience. New York, N. Y., 1900, p 1617]. The dipole moments found were the following: for exo adduct of mp 139° the $\mu$ = 5.6 D and for endo adduct of mp 149° $\mu$ = 3.6 D. These results are in agreement with Newman's conception of the fine structure of the two adducts.

and rinsed with chloroform, yielding 1.19 g (79%). When 4 was heated, it sublimed into needles which later melted at 205–210°, ir max 1800, 1287, 915, 865 cm⁻¹.

*Anal.* Calcd for $C_7H_6O_5$: C, 49.4; H, 3.5. Found: C, 49.7; H, 3.6.

*exo*-5,6-Epoxybicyclo[2.2.1]heptane-2,3-diol Carbonate (10).—Acetic acid (5 ml), 1.5 ml of hydrogen peroxide (30%, v/v), and 0.45 ml of concentrated sulfuric acid were added to 300 mg (0.02 mol) of the exo adduct, 1b. This solution was maintained at 40° during 48 hr. It was cooled for 24 hr and the precipitate yielding 30 mg (13%) was filtered and washed with chloroform. The filtrate was dried, mp 188–190°, ir max 1800, 1274, 940, 935 cm⁻¹.

1,4-Anhydro-D-inositol (5) and Its Acetate.—An aqueous solution of 2 N sodium hydroxide (10 ml) was added to 1.0 g (5.9 mmol) of 4 dissolved in 3 ml of ethanol. This mixture was heated over a water bath for 4 hr. After the hydrolysis was complete, the solution was neutralized with 2 N sulfuric acid. The water was evaporated, and the residue was dried at 60–80°.

The hydrolyzed product was isolated as the tetraacetate in the following way. The crude residue of 1,4-anhydroinositol was acetylated by adding 50 ml of acetic anhydride. The mixture was warmed slightly for 24 hr in an oven and maintained for 24 hr. After completion of the reaction, the acetic anhydride was removed *in vacuo*, and the waxy residue had mp 155–160°, yielding 60 mg (60%), ir max 1750, 1250, 840 cm⁻¹.

*Anal.* Calcd for $C_{14}H_{18}O_9$: C, 50.9; H, 5.4. Found: C, 50.4; H, 5.8.

*myo*- and *allo*-Inositol (7, 6).—A solution (52 ml) consisting of 80% (v/v) acetic acid, 20% (v/v) water, and 1% (v/v) sulfuric acid was added to 700 mg (4.1 mmol) of 5,6-epoxybicyclo[2.2.1]-heptane-2,3-diol (4, 10). This mixture was heated for 48 hr over a water bath. The hydrolyzed products were tested for the presence of inositols by a Scherer[18] test, which was positive. The paper chromatography[19,20] revealed spots at the same location as authentic samples of the inositols, $R_f$ 0.185 for *myo*-inositol and 0.30 for *allo*-inositol.

The separation of the inositols was effected by using a cellulose column.[7] The separated inositols were collected, and the desired fraction was converted into hexaacetates[7] by adding 10 ml of acetic anhydride and 4–5 drops of concentrated sulfuric acid for 48 hr. A white precipitate was formed which, when mixed with cold ice, yielded a white, crystalline precipitate. The crystals obtained from toluene had mp 215–216°. The yield was 100 mg (14.2%) of *myo*-inositol, ir max 1250, 750, 863, 887, 760, 960 cm⁻¹.

1,4-Anhydro-*allo*-inositol (2).—Cis hydroxylation of the adducts was effected with osmium tetroxide;[13] then 1.2 g (7.8 mmol) of *endo*-oxabicyclo[2.2.1]heptene-2,3-diol carbonate was dissolved in 30 ml of freshly distilled ethyl acetate. To it, 1.54 ml of dry pyridine and 2 g of osmium tetroxide, dissolved in 4 ml of ethyl acetate, were added. Upon addition of osmium tetroxide, a black precipitate was formed. After remaining at room temperature for 24 hr, the black precipitate weighed 4.159 g. This precipitate was refluxed for 7 hr with 14 g of sodium sulfite, and the black precipitate of $Na_4[OS(SO_3)_3]\cdot 6H_2O$ was filtered off. This solution was then concentrated to a small volume, and the pH was adjusted to 9 by adding 20 ml of sodium hydroxide. This solution was left at 20° for 1 hr. After neutralization with sulfuric acid, it was evaporated.

Acetate of 1,4-Anhydro-*allo*-inositol (2).—Acetic anhydride (50 ml) was added to the previously obtained residue. The solution was boiled for 24 hr. After the reaction, the acetic anhydride was removed by distillation and the remaining brown liquid was washed off with cold water. The residue was recrystallized from benzene, which produced a crystalline product, mp 128°, yield 100 mg (8.3%), ir max 1750, 830 cm⁻¹.

*Anal.* Calcd for $C_{14}O_9H_{18}$: C, 50.9; H, 5.4. Found: C, 51.6; H, 5.3.

*neo*-Inositol (3).—A solution (5 ml) composed of 80% (v/v) acetic acid, 20% water, and 1% (v/v) sulfuric acid was added to 10 mg (0.8 mmol) of 1,4-anhydro-*allo*-inositol. The solution was warmed over a water bath for 60 hr, and then tested for Scherer reaction,[18] which was positive. The paper chromatography[19,20] revealed the presence of *neo*-inositol according to its $R_f$ 0.19.[20]

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Tetraacetate of *exo*-Oxabicyclo[2.2.1]hept-5-ene-2,3-diol (8).—Oxabicyclo[2.2.1]-hept-5-ene-2,3-diol carbonate (1b) (600 mg, 3.8 mmol) was dissolved in 15 ml of the ethyl acetate and 0.77 ml of dry pyridine; 1 g of osmium tetroxide dissolved in 2 ml of ethyl acetate was added. This mixture was sealed and left for 24 hr at room temperature. The solution was filtered, and a dry, black precipitate weighing 1.4 g was collected; 60 g of sodium sulfite (Na$_2$SO$_3$), previously dissolved in 300 ml of water, and 300 ml of ethyl alcohol were added to the black precipitate. The mixture was boiled for 7 hr, producing a new, black precipitate, Na$_4$[OS(SO$_3$)$_2$]·6H$_2$O. This solution was concentrated, and its volume was reduced to 50 ml. Sodium hydroxide solution (5 ml), 5% (w/v) was added. This mixture was maintained at room temperature for 1 hr. Once again it was neutralized with acid, then concentrated to dryness, and dried at 60–80° for 4 hr.

Acetylation of the Anhydro *cis*-Inositol 8.—Acetic anhydride (50 ml) was added to the dry residue previously obtained. This mixture was warmed for 24 hr in an electric bath. Then the acetic anhydride was removed *in vacuo*, and the residue resembled needles, mp 188–190°, yield 40 mg (6.6%), ir max 1750, 1250, 840, 820 cm⁻¹.

*epi*-Inositol (9,11).—A solution (5 ml) consisting of 80% (v/v) acetic acid, 20% (v/v) water, and 1% (v/v) sulfuric acid was added to 10 mg (0.061 mmol) of hydroxylated material 8. The mixture was warmed over a water bath for 14 hr, then tested by paper chromatography.[19,20] One spot was revealed which corresponded to *epi*-inositol, $R_f$ 0.20.[20] Also the Scherer reaction[18] was positive. The dry residue was acetylated by adding 5 ml of acetic anhydride and a few drops of concentrated sulfuric acid. This mixture was left at 40° for 24 hr and poured into cold water, and then yielded crystals of 11. Further purification from toluene yielded crystals, mp 186–190°.[7]

## Sterol Metabolism. XX. Cholesterol 7β-Hydroperoxide[1]

Jon I. Teng, Martin J. Kulig, Leland L. Smith,* Gordon Kan, and Johan E. van Lier

*Division of Biochemistry, Department of Human Biological Chemistry and Genetics, University of Texas Medical Branch, Galveston, Texas 77550, and the Biochemistry Laboratories, Department of Nuclear Medicine and Radiobiology, Centre Hospitalier Universitaire, Sherbrooke, P. Q., Canada*

3β-Hydroxycholest-5-ene 7β-hydroperoxide was isolated along with 6β-hydroperoxycholest-4-en-3-one from autoxidation of crystalline cholesterol. Epimerization of 3β-hydroxycholest-5-ene 7α-hydroperoxide also provided the 7β-hydroperoxide in low conversion yield. The structure of 3β-hydroxycholest-5-ene 7β-hydroperoxide was established by sodium borohydride reduction to cholest-5-ene-3β,7β-diol and by spectral means. The 7β-hydroperoxide decomposed thermally to cholest-5-ene-3β,7β-diol and 3β-hydroxycholest-5-en-7-one, thereby accounting for the ubiquitous presence of cholest-5-ene-3β,7β-diol in cholesterol autoxidation products. An alternate pathway of derivation of cholest-5-ene-3β,7β-diol *via* epimerization of cholest-5-ene-3β,7α-diol was also demonstrated. Autoxidation of cholesterol 3β-acetate afforded the acetate derivatives of the cholesterol 7β-, 20α-, and 25-hydroperoxides.

The autoxidation of cholesterol (1a) under a variety of conditions leads to formation of the well-known epimeric cholest-5-ene-3β,7-diols (3b, 4b), 3β-hydroxycholest-5-en-7-one (5a), cholesta-3,5-dien-7-one, cholest-5-ene-3β,25-diol, and 5α-cholestane-3β,5,6β-triol. Chromatographic evidence[2] and isolation work[3] have established that autoxidation proceeds *via* initial hydroperoxide fomation followed by thermal decomposition to give the better known stable autoxidation products mentioned. The numerous stable autoxidation products of cholesterol oxidized in the side-chain are satisfactorily accounted in this manner, arising *via* initial formation of the cholesterol 20α-, 24-, 25-, and 26-hydroperoxides.[3] The well-known B-ring autoxidation products 3b, 5a, and cholesta-3,5-dien-7-one are likewise properly accounted for *via* reduction

and dehydration processes acting on the Δ⁵-7α-hydroperoxide 3a, formed by stereospecific rearrangement[4] of the Δ⁶-5α-hydroperoxide 2a formed by initial attack of oxygen on cholesterol.[5]

Such direct pathways do not account for the ubiquitous presence in autoxidized cholesterol of the 3β,7β-diol 4b in substantial amounts along with the 3β,7α-diol 3b. As established in the present study, the 7β-alcohol 4b may be derived by two pathways, one proceeding *via* the previously unrecognized epimerization of the 7α-alcohol 3b, the other *via* similar epimerization of the 7α-hydroperoxide 3a to give the previously undescribed 7β-hydroperoxide 4a whose thermal decomposition provides the 7β-alcohol 4b and the 7-ketone 5a.

In continued examination of cholesterol autoxidation products[3] we isolated for the first time from crystalline cholesterol samples heated in air 6β-hydroperoxy-

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(2) (a) L. L. Smith and F. L. Hill, *J. Chromatogr.*, **66**, 101 (1972). Chromatographic evidence for cholesterol hydroperoxide derivatives in various autoxidation conditions has previously been provided: (b) F. Neuwald and K. E. Fetting, *Pharm. Ztg.*, **108**, 1490 (1963); (c) C. Horvath, *J. Chromatogr.*, **22**, 52 (1966); (d) L. L. Smith, W. S. Matthews, J. C. Price, R. C. Bachmann, and B. Reynolds, *ibid.*, **27**, 187 (1967).

(3) (a) J. E. van Lier and L. L. Smith, *J. Org. Chem.*, **35**, 2627 (1970); (b) J. E. van Lier and L. L. Smith, *Steroids*, **15**, 485 (1970); (c) J. E. van Lier and L. L. Smith, *J. Org. Chem.*, **36**, 1007 (1971); (d) J. E. van Lier and G. Kan, *ibid.*, **37**, 145 (1972).

(4) (a) G. O. Schenck, O.-A. Neumüller, and W. Eisfeld, *Angew. Chem.*, **70**, 595 (1958); *Justus Liebigs Ann. Chem.*, **618**, 202 (1958); (b) B. Lythgoe and S. Trippett, *J. Chem. Soc.*, 471 (1959); (c) A. Nickon and J. F. Bagli, *J. Amer. Chem. Soc.*, **83**, 1498 (1961). A specific research for cholesterol 7β-hydroperoxide in reactions leading to 3a failed to detect 4a.

(5) (a) G. O. Schenck, K. Gollnick, and O.-A. Neumüller, *Justus Liebigs Ann. Chem.*, **603**, 46 (1957); (b) G. O. Schenck and O.-A. Neumüller, *ibid.*, **618**, 194 (1958).

1a, R = H
b, R = Ac

2a, R = OH
b, R = H

3a, R¹ = H; R² = OH
b. R¹ = R² = H
c. R¹ = Ac; R² = OH
d. R¹ = Ac; R² = H
e. R¹ = R² = Ac

4a, R¹ = H; R² = OH
b. R¹ = R² = H
c. R¹ = Ac; R² = OH
d. R¹ = Ac; R² = H
e. R¹ = R² = Ac

5a. R = H
b. R = Ac

6
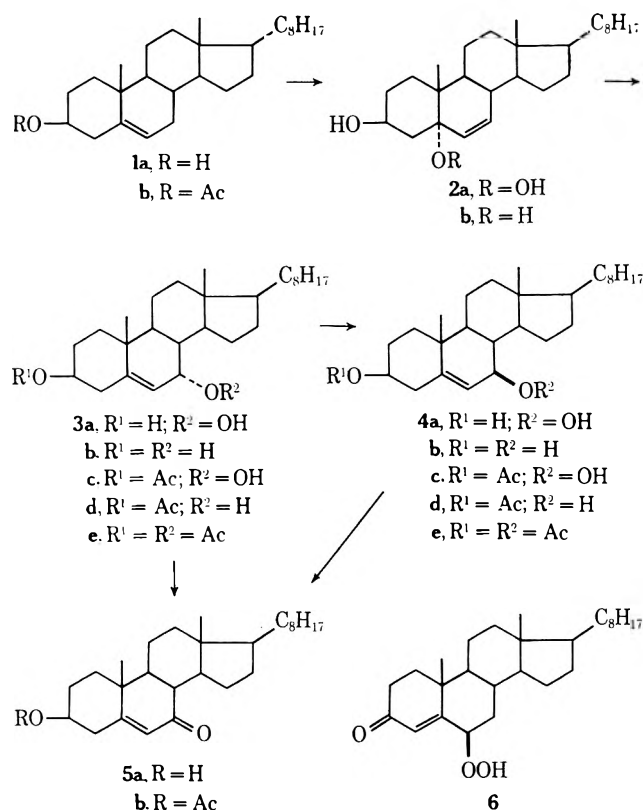
cholest-4-en-3-one (6)[5a,6,7] and the new cholesterol 7β-hydroperoxide 4a. The 7β-hydroperoxide was also isolated from cholesterol autoxidation products enriched in 2a and 3a which had been stored for several months. Notably autoxidation of crystalline cholesterol 3β-acetate (1b) gave a major isolable peroxidic product 3β-acetoxy 7β-hydroperoxide (4c) together with smaller amounts of the 3β-acetates of cholesterol 20α- and 25-hydroperoxides and the secondary products 3d, 4d, and 5b.

The structure of the 7β-hydroperoxide 4a was established by its sodium borohydride reduction to the 3β,-7β-diol 4b obtained as the sole product. Similar borohydride reduction of the epimeric 7α-hydroperoxide 3a yielded the corresponding 3β,7α-diol 3b as the sole product. Molecular rotation of the dextrorotatory 7β-hydroperoxide 4a[8] and proton spectra further support the assigned 7β-hydroperoxide structure of 4a. The 7α-proton signal of 4a appears as a doublet of doublets, coupled with the C-6 vinyl proton ($J_{6,7}$ = 1.5 Hz) and the axial 8β proton ($J_{7,8}$ = 8 Hz), deshielded by 0.3 ppm from its chemical shift in spectra of the 7β-alcohol 4b.[10] Identical B-ring conformations for 4a and 4b and quasiequatorial character for the 7β-hydroperoxide and 7β-hydroxyl groups of 4a and 4b,

respectively, are suggested by these coupling patterns and by the C-19 angular methyl proton signals at 1.04 ppm for 4a and 4b in distinction to a shielded (0.97 ppm) position in the spectrum of the 7α-alcohol 3b.

Attempted acetylation of 4a with acetic anhydride and pyridine afforded the 3β-acetoxy 7-ketone 5b, which reaction finds precedence in the dehydration of cholesterol 24-hydroperoxide by acetic anhydride and pyridine to give 3β-acetoxycholest-5-en-24-one.[3c] Thermal decomposition of 4a gave the 7-ketone 5a as a major product together with the 7β-alcohol 4b.

It is evident that the 7β-hydroperoxide 4a in some autoxidized cholesterol preparations is formed from the 7α-hydroperoxide 3a, which is formed in turn from the 5α-hydroperoxide 2a initially formed from cholesterol. The indicated derivation of 4a from 2a via 3a was established by direct chromatographic observation of solutions of 2a and 3a. In these experiments the facile stereospecific rearrangement of 2a to the 7α-hydroperoxide 3a previously reported[4] was confirmed, and the epimerization of 3a to the 7β-hydroperoxide 4a was established.

The 7β-hydroperoxide 4a was not epimerized under the conditions which epimerized 3a. Epimerization of the quasiaxial 3a to the quasiequatorial 4a accordingly appears to be under thermodynamic control, the 1,3-diaxial interactions associated with a B-ring chair conformation for 3a being dominant over 1,3 interactions with the syn-parallel C-15 methylene group of the product quasiequatorial 7β-hydroperoxide bond of 4a. Under conditions epimerizing 3a, the 7β-hydroperoxide 4a decomposed to the 3β,7β-diol 4b and to the 7-ketone 5a. In general the 7β-hydroperoxide 4a appears to be more labile toward thermal decomposition than its 7α epimer 3a, and isolation of pure samples of 3a free of its decomposition products 3b and 5a is considerably easier than is isolation of 4a free from 4b and 5a.

A rearrangement and epimerization sequence was similarly observed which linked the 5α-alcohol 2b through the 7α-alcohol 3b to the 3β,7β-diol 4b. Although epimerization of the allylic alcohol 3b is unexceptional,[11] the reaction has not been previously recorded. However, the cholest-5-ene-3β,7-diol diacetates 3e and 4e are interconverted in hot acetic acid[12a] but not in refluxing benzene solutions of lead diacetate.[12b]

To our knowledge the conversion of 3a to 4a constitutes the first recorded instance of secondary hydroperoxide epimerization. However, cases of allylic hydroperoxide epimerization may have been involved in other prior studies without being recognized as such. Whereas photosensitized oxidation of lanost-8-en-3β-ol acetate afforded the 7α-hydroperoxide,[13] extended autoxidation in ethyl acetate at 50° gave the epimeric 7β-hydroperoxide.[14] Although no evidence for B-ring conformation in these derivatives is available, a B-ring modified chair conformation is reasonable, giving quasi-

(6) (a) L. F. Fieser, T. W. Greene, F. Bischoff, G. Lopez, and J. J. Rupp, *J. Amer. Chem. Soc.*, **77**, 3928 (1955); (b) A. J. Cox, *J. Org. Chem.*, **30**, 2052 (1965); (c) A. Nickon and W. L. Mendelson, *ibid.*, **30**, 2087 (1965); (d) R. Gardi and A. Lusignani, *ibid.*, **32**, 2647 (1967).

(7) Identity of 6 rests on its physical and chemical properties, including sodium borohydride reduction to the known cholest-5-ene-3β,6β-diol.

(8) Molecular rotational increments (Δ[M]D) for the 7α-hydroperoxide 3a and the 7β-hydroperoxide 4a compared with cholesterol are −427 and +322, respectively; for the 7α-alcohol 3b and the 7β-alcohol 4b, −204 and +168, respectively, calculated using [M]D values for 1a, −154;[9] 3a, −581;[4] 4a, +168; 3b, −358;[9] 4b, +14.[9]

(9) Physical data from J. Jacques, H. Kagan, and G. Ourisson, "Tables of Constants and Numerical Data," Vol. 14, S. Allard, Ed., Pergamon Press, Oxford, 1965, pp 472, 475.

(10) Comparison proton spectra of the 7β-alcohol 4b revealed the 7α proton as a doublet of doublets, $J_{6,7}$ = 1.5, $J_{7,8}$ = 7 Hz; of the 7α-alcohol 3b, as a doublet of doublets, $J_{6,7}$ = 5.5, $J_{7,8}$ = 1.5 Hz.

(11) Ready epimerization of $C_{19}$-Δ[5-7] alcohols in acidic systems has been reported; cf. (a) R. Hampl and L. Stárka, *J. Steroid Biochem.*, **1**, 47 (1969); (b) L. Stárka and R. Hampl, "Hormonal Steroids," V. H. T. James and L. Martini, Ed., Excerpta Medica, Amsterdam, 1971, pp 150–157; (c) P. Morand and A. Van Tongerloo, *Chem. Commun.*, 7 (1972).

(12) (a) L. Ruzicka, V. Prelog, and E. Tagmann, *Helv. Chim. Acta*, **27**, 1149 (1944); (b) M. Stanfanović, A. Jokić, Z. Maksimović, L. Lorenc, and M. L. Mihailović, *ibid.*, **53**, 1895 (1970).

(13) J. E. Fox, A. I. Scott, and D. W. Young, *Chem. Commun.*, 1105 (1967); *J. Chem. Soc., Perkin Trans. 1*, 799 (1972).

(14) (a) D. H. S. Horn and D. Ilse, *J. Chem. Soc.*, 2280 (1957); (b) J. Scotney and E. V. Truter, *J. Chem. Soc. C*, 1911 (1968).

axial 7α and quasiequatorial 7β substituents, thereby implying potential epimerization of the 7α- to the 7β-hydroperoxide in analogy to our own findings with **3a** and **4a**. Furthermore, our isolation of the 6β-hydroperoxide **6** but not its 6α epimer and the variable recovery under other conditions by other investigators of either the 6β-hydroperoxide **6** alone[5a,7a] or of both the 6β-hydroperoxide **6** and its 6α epimer,[7b−d] together with the recognized ease with which 6β-hydroxy-Δ[4] 3-ketones are epimerized, suggests that epimerization of the 6β-hydroperoxide **6** might account in part for the presence of its 6α epimer in some studies.[7b−d] In that the 6β-hydroperoxyl group of **6** appears to be axial,[15] its epimerization in parallel with that of **3a** to **4a** might be expected by analogy. Previous evidence indicating that epimerization of **6** does not occur[7b] cannot be considered as conclusive, and, in matters dealing with the mechanisms of allylic hydroperoxide formation,[7c,17] it may be necessary to consider allylic hydroperoxide epimerization as well as allylic alcohol epimerization as possible complicating features.

## Experimental Section[18]

**Cholesterol Autoxidation.**—Cholesterol (1 kg), recrystallized several times from methanol to remove autoxidation products, was held at 70° in air but in the dark. After 4 weeks the material was recrystallized from ethanol and the crystalline cholesterol therefrom recovered was heated again at 70° for 4 weeks, after which time the sample was recrystallized from ethanol, etc. The ethanol mother liquors were evaporated directly, and a 3-

(15) Axial character of the 6β-hydroperoxyl group in **6** is suggested by the hypsochromic shift (4–6 nm) in the absorption spectrum maximum of **6** and by strong 1,3-diaxial effects (a paramagnetic shift of 0.17 ppm) on the C-19 methyl protons chemical shift, both in comparison with the parent cholest-4-en-3-one. Furthermore, the singlet character of the C-4 proton resonance signal[16] and the absence of 1,2-trans-diaxial coupling between the 6α and 7β protons of **6** exclude a B-ring boat conformation and an equatorial 6β-hydroperoxyl group. Rather, weak coupling ($J$ = 2 Hz) exhibited in the doublet signal of the 6α proton support a B-ring chair conformation for **6** in which an equatorial 6α proton is coupled equally with both vicinal 7-protons.

(16) (a) K. Tori and K. Kuriyama, *Chem. Ind. (London)*, 1525 (1963); (b) T. W. Wittstruck, S. K. Malhotra, and H. J. Ringold, *J. Amer. Chem. Soc.*, **85**, 1699 (1963); (c) D. J. Collins, J. J. Hobbs, and S. Sternhell, *Tetrahedron Lett.*, 197 (1963); *Aust. J. Chem.*, **16**, 1030 (1963).

(17) A. Nickon, V. T. Chuang, P. J. L. Daniels, R. W. Denny, J. B. DiGiorgio, J. Tsunetsugu, H. G. Vilhuber, and E. Werstiuk, *J. Amer. Chem. Soc.*, **94**, 5517 (1972).

(18) Solvents used in this study were redistilled prior to use. All evaporations were conducted under vacuum in all glass rotary evaporator units. Melting points were taken on a Fisher-Johns melting point apparatus. Optical rotations at 578 nm were taken on chloroform solutions of steroids using a Zeiss digital readout polarimeter. Infrared absorption spectra were recorded on 1.5-mm pressed KBr disks incorporating the samples and on solutions in CCl₄ (1.0 mm path), using Perkin-Elmer Model 337 and Model 357 spectrophotometers. Proton nmr spectra were recorded in deuteriochloroform solutions using a Varian T-60 spectrometer, with tetramethylsilane as an internal standard. Mass spectra were obtained using an AEI MS-30 double beam instrument, using heptacosafluorobutylamine in the reference beam. The sample beam was connected *via* a membrane separator operated at 215° to a Pye Unicam Model 104 gas chromatograph equipped with a 5-ft-long 3-mm-i.d. coiled glass column packed with 3% QF-1 on 80–100 mesh Gas-Chrom Q (Applied Science Laboratories, State College, Pa.). Oven temperature was 244°; helium at 30 ml/min was used as a carrier gas. Spectra of resolved sterol components were obtained at 24 eV with a resolution of 1000 and a scanning speed of 10 sec per decade.

Thin layer chromatography was conducted using previously described procedures.[2a,d,3] Mobility data are given for triple ascending irrigation of silica gel HF₂₅₄ 0.25-mm-thick chromatoplates using toluene–ethyl acetate (3:2), except where other solvent systems are designated. *N,N*-Dimethyl-*p*-phenylenediamine[2a] and 50% aqueous sulfuric acid[2d] were used for visualization. Gas chromatography was conducted on 3% SE-30 and 3% QF-1 phases as previously described.[19a] Preparative and analytical liquid chromatography on Sephadex LH-20 columns was carried out as previously described.[19b] Thin layer chromatographic mobilities ($R_c$), gas chromatographic retention times ($t_R$), and liquid chromatographic void volumes on Sephadex LH 20 ($R_v$) were all measured *vs.* cholesterol as unity.

(19) (a) J. E. van Lier and L. L. Smith, *Anal. Biochem.*, **24**, 419 (1968); (b) J. E. van Lier and L. L. Smith, *J. Chromatogr.*, **41**, 37 (1969).

month collection of mother liquor residues (stored in a deep freezer until processed) was chromatographed on silica gel to give five major fractions, fractions A–E, as previously described.[3]

**6β-Hydroperoxycholest-4-en-3-one (6).**—Fraction A contained compounds more mobile than **1a** on thin layer chromatography, including the 6β-hydroperoxide **6**. Rechromatography of fraction A on Sephadex LH-20 developed with methylene chloride gave retarded fractions enriched in **6**, which was recovered by evaporation and crystallization from methanol, thus giving 64 mg of **6** as colorless needles: mp 177–180° (lit. mp 180°,[6a] 177 and 181°,[5a] 180–181°[6b]); $\lambda_{max}^{CH_3OH}$ 237 nm [lit. $\lambda_{max}^{C_2H_5OH}$ 236 nm ($\epsilon$ 16,850),[6a] 235 nm[6b]]; $\bar{\nu}_{max}^{KBr}$ 3300 (broad), 1670 cm⁻¹; $\bar{\nu}_{max}^{CHCl_3}$ 3515 cm⁻¹; $R_c$ 1.25 (yellow color with sulfuric acid); positive Wurster red color with *N,N*-dimethyl-*p*-phenylenediamine; $R_v$ 1.45; nmr δ 0.72 (s, 3 H, C-18 protons), 0.82 (d, 6 H, $J$ = 5 Hz, C-26, C-27 protons), 0.92 (d, 3 H, $J$ = 5 Hz, C-21 protons), 1.35 (s, 3 H, C-19 protons), 4.50 (d, $J$ = 2 Hz, 1 H, 6α proton), 6.00 ppm (s, 1 H, C-4 vinyl proton); mass spectrum $m/e$ (rel intensity) 416 (2, M), 400 (100, M − O), 398 (24, M − H₂O), 382 (10, M − H₂O₂), 385 (17, M − CH₃O), etc.

**Cholest-4-ene-3β,6β-diol.**—Excess sodium borohydride was added to a solution of 10 mg of **6** in 5 ml of methanol. After 15 min a few drops of acetic acid was added, followed by 20 ml of water. The product was extracted with diethyl ether, evaporated, and crystallized from methanol. Thus was obtained 6 mg of cholest-4-ene-3β,6β-diol: mp 257–258° (lit. mp 257–258°,[20a,b] 254°,[20c] 256–257°,[20d]); $R_c$ 0.24; $t_R$ (as the trimethylsilyl ether) 0.70 (3% QF-1), 1.50 (3% SE-30);[21] mass spectrum $m/e$ (rel intensity) (of the trimethylsilyl ether) 546 (20), 531 (24), 519 (9), 457 (32), 404 (100), etc.; identical in all respects with an authentic sample of cholest-4-ene-3β,6β-diol.

**3β-Hydroxycholest-5-ene 7β-Hydroperoxide (4a). A. From Cholesterol.**—Fraction D from the initial chromatography on silica gel of autoxidized cholesterol which contained **4a**, cholest-5-ene-3β,25-diol, and other sterols of similar polarity was chromatographed on 60-cm-long, 2.5-cm-diameter columns of Sephadex LH-20 irrigated with methylene chloride containing 1% (v/v) ethanol. The retarded fractions containing **4a**, well separated from other sterols in fraction D, were evaporated and the hydroperoxide **4a** was recrystallized from methanol–diethyl ether. Thin layer chromatographic analysis of the purification showed contaminant 3β,7β-diol **4b**, formed apparently during processing. Rechromatography on Sephadex LH-20 and recrystallization gave the same contamination of the 7β-hydroperoxide with 3β,7β-diol **4b**. The analytical sample of 7β-hydroperoxide **4a** was prepared by rechromatography a third time on Sephadex LH-20, with the eluates most concentrated in **4a** taken to dryness and subjected to immediate analysis. Thus was obtained pure **4a**: mp 148–150°; [α]₃₇₈ +40.2°; $R_c$ 0.60 (blue color with sulfuric acid; positive Wurster red color with *N,N*-dimethyl-*p*-phenylenediamine); $\bar{\nu}_{max}^{KBr}$ 3350 (OH), 1625 (C=C), 1430, 1340, 1040, 945, 590 cm⁻¹ (distinguished from spectra of the 7α-hydroperoxide **3a**, $\bar{\nu}_{max}^{KBr}$ 3325, 1640, 1425, 1350, 1045, 945, 635 cm⁻¹, by small frequency differences); nmr (CDCl₃) δ 0.69 (s, 3 H, C-18 protons), 0.85 (d, 6 H, $J$ = 5 Hz, C-26, C-27 protons), 0.92 (d, 3 H, $J$ = 5 Hz, C-21 protons), 1.04 (s, 3 H, C-19 protons), 3.58 (broad, 1 H, $W_{1/2}$ = 12 Hz, 3α proton), 4.15 (q, 1 H, $J_{6,7}$ = 1.5 Hz, $J_{7,8}$ = 8 Hz, 7α proton), 5.61 ppm (d, 1 H, $J_{6,7}$ = 1.5 Hz, C-6 vinyl proton).

*Anal.* Calcd for C₂₇H₄₆O₃: C, 77.46; H, 11.07. Found: C, 77.29; H, 11.07.

A separate isolation of **4a** from a preparation enriched in **2a**, **3a**, and other autoxidation products of cholesterol but free from cholesterol and not initially containing **4a** was accomplished after inadvertent storage of the mixture for several months at room temperature. Chromatography on silica gel gave a fraction eluted with 10% ethyl acetate in benzene enriched in **4a**, which was rechromatographed on Sephadex LH-20 developed with benzene. The **4a** fraction, 12 mg, was chromatographed on a 0.25 mm thick silica gel HF₂₅₄ plate irrigated twice with acetone–chloroform (1:4) thereby affording 7 mg of **4a**, identified by thin layer and gas chromatographic properties, infrared absorption spectra, and sodium borohydride reduction to **4b**.

(20) (a) O. Rosenheim and W. W. Starling, *J. Chem. Soc.*, 377 (1937); (b) V. A. Petrow, O. Rosenheim, and W. W. Starling, *ibid.*, 679 (1938); (c) V. Prelog, L. Ruzicka, and P. Stein, *Helv. Chim. Acta*, **26**, 2222 (1943); (d) L. F. Fieser, J. E. Herz, M. W. Klohs, M. A. Romero, and T. Utne, *J. Amer. Chem. Soc.*, **74**, 3309 (1952).

(21) The epimeric cholest-4-ene-3β,6-diols are readily distinguishable by both thin layer and gas chromatography.[19a]

B. **From the 7α-Hydroperoxide 3a.**—A sample of 3a (15.4 mg) meticulously freed from 4a and other detectable sterols was dissolved in 7 ml of ethyl acetate and warmed at 40° in a water bath. The extent of epimerization of 3a to 4a was followed directly by thin layer chromatography and by sodium borohydride reduction and thin layer chromatography of the better resolved alcohols 3b and 4b. After 48 hr epimerization had proceeded to about 25–30%. The solution was concentrated to 0.5 ml and applied to a 0.25 mm thick silica gel HF₂₅₄ chromatoplate. The applied sample was converged into a fine line with acetone, and the prepared chromatoplate was irrigated with benzene–ethyl acetate (18:7) three times. The more mobile 4a zone was eluted with acetone, and dilution of the concentrated solution with petroleum ether (bp 30–60°) gave 3.2 mg of 4a, mp 147–149°, with thin layer and gas chromatographic properties and infrared absorption spectra identical with those of authentic 4a. Sodium borohydride reduction of the sample gave 4b, mp 176–178°, with thin layer and gas chromatographic properties and infrared absorption spectra identical with those of authentic 4b.

Epimerization of 3a to 4a was also achieved using acetone, benzene, carbon tetrachloride, and methanol as solvents, the product 4a being recovered and identified by the means described for the epimerization in ethyl acetate. At slightly higher temperatures (50°) or after 72–120 hr at 40° thermal decomposition of both 3a and 4a occurred, giving thin layer chromatograms bearing 3b, 4b, and 5a as well as 3a and 4a.

Separation of small amounts of 4a in the presence of larger amounts of the more polar 3a required careful attention. Resolution was not achieved when chromatoplates thicker than 0.25 mm were employed. Multiple irrigations were routinely used with the solvent system benzene–ethyl acetate (17:8), in which system the hydroperoxides had the relative mobilities: 4a, 1.00; 3a, 0.96 (2a, 0.96; 2b, 0.71; 3b, 0.48; 4b, 0.54). Repeated thin layer chromatography was necessary for complete purification of 4a free from 3a and thermal decomposition products.

**Autoxidation of Cholesterol Acetate.**—Crystalline cholesterol acetate (1b) (35.5 g) was stirred and exposed to a stream of air in a flask heated in an oil bath at 90–100° in the dark. After 3 days the material became sticky and stirring was difficult. After 2 weeks the light yellow syrup obtained was cooled to room temperature and dissolved in 50 ml of diethyl ether, and 100 ml of methanol was then added to the ether solution. Crystals of 1b (18 g) were removed by filtration, and the mother liquor was concentrated, yielding a second crop of 1b (4.3 g). The mother liquor was evaporated, and the solids (9.2 g) were chromatographed on silica gel using toluene containing 5% (v/v) diethyl ether. Using thin layer chromatographic analyses of individual column fractions, five major fractions (fractions A–E) were collected.

Fraction A on evaporation yielded 3.8 g of 1b, $R_c$ 1.63 (magenta color with sulfuric acid), identified by melting point and nmr with an authentic sample. Fraction B yielded 0.1020 g of 5b, $R_c$ 1.48 (yellow-green color with sulfuric acid), identified by melting point, nmr, and sodium borohydride reduction to the characteristic mixture of epimeric 3β,7-diols 3b and 4b.

Fraction C containing peroxidic components of thin layer chromatographic mobility $R_c$ 1.40–1.48 was rechromatographed on Sephadex LH-20 using methylene chloride containing 1% methanol. Four subfractions with thin layer chromatographic mobilities of 1.40, 1.41, 1.44, and 1.48 were taken.

**3β-Acetoxycholest-5-en-7-one (5b).**—The $R_c$ 1.48 subfraction from fraction C from autoxidation of 1b was evaporated to give 0.058 g of 5b: $R_c$ 1.48; $t_R$ 7.1 (3% QF-1), 2.7 (3% SE-30); nmr δ 0.68 (s, 3 H, C-18 protons), 0.85 (d, $J$ = 5 Hz, 6 H, C-26, C-27 protons), 0.92 (d, $J$ = 5 Hz, 3 H, C-21 protons), 1.21 (s, 3 H, C-19 protons), 2.05 (s, 3 H, 3β-acetyl protons), 4.70 (broad, 1 H, 3α proton), 5.70 ppm (s, 1 H, C-6 vinyl proton), identical in every respect with an authentic sample of 5b.

Samples of 5b isolated on attempted acetylation of 4a and of 4c were crystallized from methanol and identified by the same physical methods in comparison with an authentic sample.

**3β-Acetoxycholest-5-ene 20α-Hydroperoxide.**—The $R_c$ 1.44 subfraction from fraction C from autoxidation of 1b was evaporated and crystallized from methanol to give 0.032 g of 3β-acetoxycholest-5-ene 20α-hydroperoxide: mp 92–95°; $R_c$ 1.44 (brown color with sulfuric acid, positive Wurster red color with $N,N$-dimethyl-$p$-phenylenediamine); nmr δ 0.82 (s, 3 H, C-18 protons), 0.92 (s, 3 H, C-19 protons), 0.95 (d, $J$ = 5 Hz, 6 H, C-26,

C-27 protons), 0.96 (s, 3 H, C-21 protons), 2.05 (s, 3 H, 3β-acetoxyl protons), 4.50 (broad, 1 H, 3α proton), 5.35 ppm (d, $J$ = 5 Hz, 1 H, C-6 vinyl proton).

Reduction with sodium borohydride and hydrolysis with 5% sodium methoxide in methanol gave cholest-5-ene-3β,20α-diol: $R_c$ 0.88; $t_R$ 2.13 (3% QF-1), 2.09 (3% SE-30); mass spectrum $m/e$ (rel intensity) 384 (100), 369 (20), 366 (18), 351 (43), 317 (8), 299 (52), 281 (20), 271 (44), 258 (12), 253 (22), etc., identical with similar physical properties of an authentic sample of cholest-5-ene-3β,20α-diol.

**3β-Acetoxycholest-5-ene 25-Hydroperoxide.**—The $R_c$ 1.41 subfraction from fraction C from autoxidation of 1b was evaporated to give 0.029 g of 3β-acetoxycholest-5-ene 25-hydroperoxide as a syrup: $R_c$ 1.41 (brown color with sulfuric acid, positive Wurster red color with $N,N$-dimethyl-$p$-phenylenediamine); nmr δ 0.66 (s, 3 H, C-18 protons), 0.90 (d, $J$ = 5 Hz, 3 H, C-21 protons), 1.00 (s, 3 H, C-19 protons), 1.20 (s, 6 H, C-26, C-27 protons), 2.05 (s, 3 H, 3β-acetoxyl protons), 4.50 (broad, 1 H, 3α proton), 5.35 ppm (d, $J$ = 5 Hz, 1 H, C-6 vinyl proton).

Sodium borohydride reduction and hydrolysis with 5% sodium methoxide in methanol gave cholest-5-ene-3β,25-diol: $R_c$ 0.60; $t_R$ 2.40 (3% QF-1), 1.60 (3% SE-30); mass spectrum $m/e$ (rel intensity) 402 (7), 384 (75), 382 (16), 370 (35), 367 (60), 351 (52), 299 (32), 273 (47), 271 (100), 255 (30), 253 (25), etc., identical in these properties with an authentic sample of cholest-5-ene-3β,25-diol.

**3β-Acetoxycholest-5-ene 7β-Hydroperoxide (4c).**—The $R_c$ 1.40 subfraction from fraction C from autoxidation of 1b was evaporated to give 0.249 g of 4c: mp 80–82°; $[α]_{573}$ +91.1°; $R_c$ 1.40 (blue color with sulfuric acid, positive Wurster red color with $N,N$-dimethyl-$p$-phenylenediamine); nmr δ 0.68 (s, 3 H, C-18 protons), 0.84 (d, 6 H, $J$ = 5 Hz, C-26, C-27 protons), 0.92 (d, 3 H, $J$ = 5 Hz, C-21 protons), 1.05 (s, 3 H, C-19 protons), 2.10 (s, 3 H, 3β-acetate protons), 4.15 (m, 1 H, $W_{1/2}$ = 12 Hz, 7α proton), 4.65 (m, 1 H, $W_{1/2}$ = 16 Hz, 3α proton), 5.82 ppm (d, 1 H, $J$ = 5 Hz, C-6 vinyl proton).

Sodium borohydride reduction of 4c followed by hydrolysis with 5% sodium methoxide in methanol gave 4b, identified by thin layer and gas chromatographic properties and proton nmr spectra.

**Cholest-5-ene-3β,7β-diol (4b). A. From the 7β-Hydroperoxide 4a.**—A solution of 50 mg of 4a in methanol was reduced with an excess of sodium borohydride. Thin layer chromatographic analysis of the reduction mixture established that no 3b was present and that 4b only had been formed. The crude product was recrystallized from diethyl ether–hexane, yielding 23 mg of 4b: mp 176–179° (lit.⁹ mp 172–179°); $[α]$D +3.3° (lit.⁹ $[α]$D +3.5°); $R_c$ 0.33 (blue color with sulfuric acid); $t_R$ 2.3 (3% QF-1), 1.6 (3% SE-30); $R_v$ 1.6; nmr δ 0.70 (s, 3 H, C-18 protons), 0.86 (d, $J$ = 5 Hz, 6 H, C-26, C-27 protons), 0.92 (d, $J$ = 5 Hz, 3 H, C-21 protons), 1.04 (s, 3 H, C-19 protons), 3.53 (broad, 1 H, 3α proton), 3.86 (q, $J$ = 1.5, 7 Hz, 7α proton), 5.30 ppm (d, $J$ = 1.5 Hz, 1 H, C-6 vinyl proton); mass spectrum $m/e$ (rel intensity) 402 (1), 384 (48), 382 (14), 366 (100), etc.; identical in these respects with an authentic sample of 4b.

B. **From Cholest-5-ene-3β,7α-diol.**—Pure 3b, mp 185–186°, free from 4b and other detectable sterols, was dissolved in acetone (10 mg/5 ml) and warmed at 50° in a water bath. Aliquots (80 μg) were withdrawn at intervals for thin layer chromatographic analysis using benzene–ethyl acetate (3:7). After 72 hr sufficient 4b was present to warrant isolation. The sample was chromatographed on 0.25 mm thick silica gel HF₂₅₄ chromatoplates using benzene–ethyl acetate (3:7) with triple ascending irrigation. The 4b was eluted from the chromatoplate and crystallized from diethyl ether–hexane to yield 4b: mp 176–177° (lit.⁹ mp 172–179°); $\bar{ν}_{max}^{KBr}$ 3320, 1664 cm⁻¹, identical with spectra obtained from an authentic sample of 4b. Full identity of the sample with an authentic sample of 4b was also demonstrated using thin layer and gas chromatographic properties.

C. **From 5α-Cholest-6-ene-3β,5-diol-4-¹⁴C.**—A sample of cholesterol-4-¹⁴C was converted by photosensitized oxidation in pyridine⁴ᶜ,⁵ to 2a-4-¹⁴C of specific activity 9700 dpm/mg. Sodium borohydride reduction of 20 mg of 2a-4-¹⁴C in methanol gave 16 mg of 2b-4-¹⁴C (9200 dpm/mg) purified by repeated thin layer chromatography. The pure 2b-4-¹⁴C, 4 mg, was dissolved in 2 ml of acetone and warmed at 50° for 72 hr, after which time the 2b, 3b, and 4b zones were excised from the chromatoplate and the associated radioactivity was measured by scintillation counting methods. The amount of radioactivity recovered in each fraction was as follows: 2b, 80%; 3b, 14.2%; 5.8%.

**Cholest-5-ene-3β,7α-diol (3b). A. From the 7α-Hydroperoxide 3a.**—A solution of 1 mg of **3a** in methanol was reduced with an excess of sodium borohydride. Thin layer chromatographic analysis of the reduction mixture established that only **3b** was present and that no **4b** had been formed. Pure **3b** was recovered by preparative thin layer chromatography and identified by thin layer and gas chromatographic means.

**B. From 5α-Cholest-6-ene-3β,5-diol.**—Pure **2b**, mp 148–149° (lit. mp 147–150°,[4c] 170–175, 166–171, and 134–135°,[5] 181°[22]), prepared by sodium borohydride reduction of **2a**, free from **3a** and all other detectable sterols, was dissolved in acetone (10 mg/5 ml) and warmed at 50° on a water bath. Aliquots (80 μg) were removed at intervals for thin layer chromatographic analysis. The intensity of the **3b** spot on chromatograms increased over the period 24–72 hr. After 72 hr the sample was chromatographed using benzene–ethyl acetate (3:7) with triple ascending irrigation. The **3b** zone was eluted and the pure product was crystallized from diethyl ether–hexane, thus yielding pure **3b**: mp 185–186° (lit.[9] mp 158–161 and 176–187°); $\nu_{max}^{KBr}$ 3350, 1630 cm$^{-1}$, identical with spectra of an authentic sample. The **3b** preparation was also identical in thin layer and gas chromatographic properties with an authentic sample of **3b**.

(22) H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 1792 (1948). It appears that **2b** may exist in different crystalline modifications depending on conditions of recrystallization and drying.

**C. From Cholesterol Acetate (1b).**—Fraction D, 2.994 g, obtained from autoxidation of **1b**, characterized by thin-layer chromatographic mobility $R_c$ 1.11 with an intense blue color with sulfuric acid spray, was composed of **3c** and **4c** in the proportion 3:2. Hydrolysis of the material with 5% sodium methoxide in methanol followed by chromatography on Sephadex LH-20 and crystallization several times from methanol gave pure **3b**: mp 182–184° (lit.[9] mp 158–161 and 176–187°); [α]D −75.8° (lit.[9] [α]D −89°); $R_c$ 0.28 (blue color with sulfuric acid); $t_R$ 2.2 (3% QF-1), 1.6 (3% SE-30); $R_v$ 1.5; nmr δ 0.68 (s, 3 H, C-18 protons), 0.86 (d, $J$ = 5 Hz, 6 H, C-26, C-27 protons), 0.92 (d, $J$ = 5 Hz, C-21 protons), 0.99 (s, 3 H, C-19 protons), 3.50 (m, $W_{1/2}$ = 12 Hz, 1 H, 3α proton), 3.85 (q, $J_{6,7}$ = 5.5, $J_{7,8}$ = 1.5 Hz, 1 H, 7β proton), 5.60 ppm (d, $J$ = 5.5 Hz, 1 H, C-6 vinyl proton); mass spectrum identical with that of the 3β,7β-diol **4b**. In addition to **3b** thus recovered there was obtained from the Sephadex LH-20 column a pure sample of **4b**, identified by melting point, chromatographic, and spectral properties with an authentic sample.

# Syntheses of 2,5-Dimethyl-4-hydroxy-2,3-dihydrofuran-3-one (Furaneol), a Flavor Principle of Pineapple and Strawberry

GEORGE BÜCHI*[1] AND EDOUARD DEMOLE

*Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139*

ALAN F. THOMAS

*Firmenich et Cie, Laboratoire de Recherche, Geneva*

Three syntheses of furaneol, a flavor component of strawberry and pineapple, are described. Oxidation of the known 2,5-dimethyl-2,5-dimethoxy-2,5-dihydrofuran with potassium chlorate in the presence of catalytic amounts of osmium tetroxide in aqueous solution gave *erythro*-3,4-dihydroxyhexane-2,5-dione, while hydrodimerization of methylglyoxal with zinc yielded the threo isomer. Both dihydroxy diketones on exposure to mildly basic reagents were converted to furaneol. Acidic reagents did not lead to furaneol but its aliphatic isomer 3-hydroxy-3-hexene-2,5-dione and 3-acetyl-2,5-dimethyl-4,5-dihydrofuran-4-one, the latter originating from cleavage to pyruvic acid followed by condensation with starting material. In a third synthesis hexane-3,4-dione was transformed to the symmetrical dibromide and then to furaneol by hydrolysis.

Among the many hundreds of compounds isolated from the volatile portions of fruit aromas,[2] furaneol [2,5-dimethyl-4-hydroxy-2,3-dihydrofuran-3-one (5)] occupies a central position. It was isolated at the same time from the organoleptic principle of pineapple[3] and from strawberry flavor.[4] Since this flavor principle with a powerful caramel-like odor has found many applications in the food and beverage industry, its chemical synthesis has become of some interest. Furaneol was first prepared accidentally, in unspecified yield, from rhamnose and piperidine acetate in hot ethanol solution.[5] Two rational syntheses[6,7] of furaneol have been described, but both seem unpractical for production purposes. In this paper we describe

syntheses of furaneol from three different, readily available starting materials. Oxidation of 2,5-dimethyl-2,5-dimethoxy-2,5-dihydrofuran (2) prepared by bromination of 2,5-dimethylfuran (1) in methanol solution,[8] with potassium chlorate and a catalytic amount of osmium tetroxide[9] in aqueous tetrahydrofuran containing sodium bicarbonate, gave the diol **3** in 10% yield. Since we suspected that most of the diol **3** was lost by hydrolysis the oxidation was performed in a more aqueous reaction medium and in the absence of bicarbonate. The dihydroxy diketone **4** was thus obtained in nearly quantitative yield. The diol **3** is formed also upon oxidation of the olefin with potassium permanganate and we concluded that it has cis stereochemistry and the resulting dihydroxy diketone **4** the erythro configuration. Parenthetically, infrared measurements indicate the presence of only one intramolecular hydrogen bond in the erythro isomer, suggesting the preferred conformation **4**. Efforts to convert the cis diol **3** to furaneol by elimina-

(1) To whom correspondence should be addressed.

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(3) J. O. Rodin, C. M. Himel, R. M. Silverstein, R. W. Leeper, and W. A. Gortner, *J. Food Sci.*, **30**, 280 (1965).

(4) B. Willhalm, M. Stoll, and A. F. Thomas, *Chem. Ind. (London)*, 1629 (1965). The physical properties of furenidones were described by A. Hofmann, W. v. Philipsborn, and C. H. Eugster, *Helv. Chim. Acta*, **48**, 1322 (1965).

(5) J. E. Hodge, B. E. Fisher, and E. C. Nelson, *Amer. Soc. Brew. Chem. Proc.*, 84 (1963).

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(7) D. W. Henry and R. M. Silverstein, *J. Org. Chem.*, **31**, 2391 (1966).

(8) J. Levisalles, *Bull. Soc. Chim. Fr.*, 997 (1957).

(9) *Cf.* H. Muxfeldt and G. Hardtmann, *Justus Liebigs Ann. Chem.*, **669**, 113 (1963).
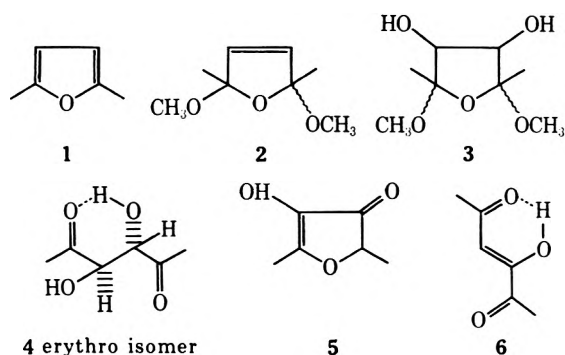
tion of two molecules of methanol under the agency of
p-toluenesulfonic acid, sulfanilic acid, and other
acidic reagents failed, although a faint odor of furaneol
was noticed frequently during these experiments.
Dehydration of the erythro dihydroxy diketone 4 in
the presence of acidic catalyst or by thermolysis, again,
did not yield furaneol (5), but its aliphatic isomer 3-
hydroxy-3-hexene-2,5-dione (6). Attempts to effect
cyclization under basic conditions were more encour-
aging. Eventually, both sodium hydrogen carbonate
and disodium hydrogen phosphate were found to be
useful catalysts, yielding furaneol in over 50% yield.

We next turned to exploring alternate methods for the
preparation of the aliphatic precursor 4. Hydrodimeri-
zation of methylglyoxal (7) with zinc in aqueous acetic
acid solution furnished a new dihydroxy diketone which
turned out to be the threo isomer 8 with two intramo-
lecular hydrogen bonds. Predominant formation of the
threo isomer can be attributed to dimerization within
conformation 9 or 10 with minimum steric interference
between large substituents. Condensation of the
threo epimer 8 with acetone gave two products sepa-
rable by chromatography. The major compound
was the 1,3-dioxolane 11, whose nmr spectrum ex-
hibited a single signal[10] for the geminal dimethyl group-
ing confirming the stereochemistry already assigned.
Elemental composition and mass spectrum of the minor
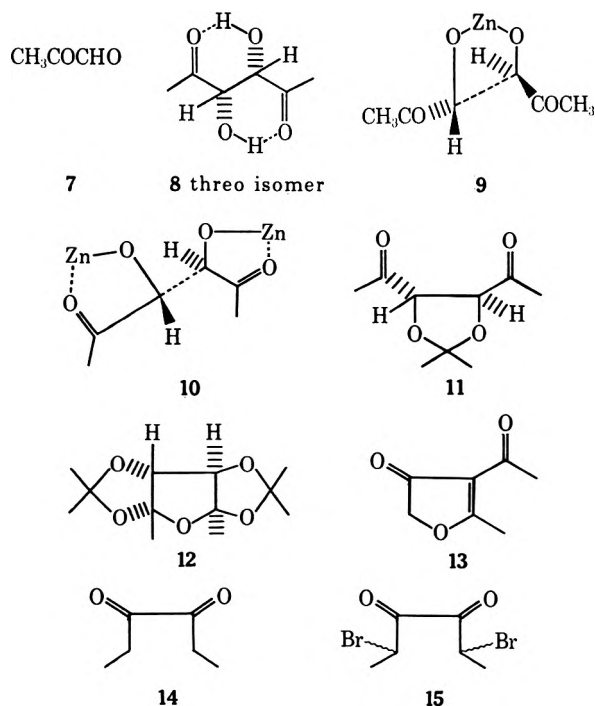


compound demonstrated that it resulted from com-
bination of the threo dihydroxy diketone 8 with two
molecules of acetone, and the nmr spectrum is in agree-
ment with structure 12. Since the enol forms of the
erythro and threo dihydroxy diketones 4 and 8 are
identical, base-catalyzed cyclization of the threo
isomer 8 should also lead to furaneol (5), and this was
confirmed by experiment.

In view of our experience with the erythro isomer 4
we had doubts about the ability of acids to catalyze
the transformation of the threo dihydroxy ketone 8
to furaneol (5), and these were confirmed by experi-
ments. The threo isomer on treatment with acids is
transformed to a mixture of 3-hydroxy-3-hexene-2,5-
dione (6) and a new compound in varying amounts
depending on conditions used. Based on spectral
properties (see Experimental Section) the unknown
was assigned the furenidone structure 13. The ap-
pearance of this product seemed puzzling until it
was realized that the triketone 6 could hydrolyze to
pyruvic acid, which in turn could condense with the
starting material to give the β-hydroxycarboxylic acid A.
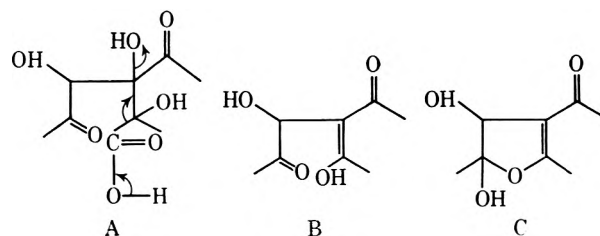


Decarboxylation with concomitant elimination of
water could yield B. Cyclization to C followed by
loss of water could give the furenidone 13. In support
of this hypothesis condensation of pyruvic acid with
the dihydroxy diketone 8 does indeed furnish the
furenidone 13.

Finally, the conversion of hexane-3,4-dione (14) to
furaneol (5) was studied. The symmetrical dibromide
15 as a mixture of threo and erythro forms was avail-
able in nearly quantitative yield by straightforward
bromination in ether–dioxane solution. Hydrolysis
of the dibromide 15 at reflux gave furaneol (5) in 46%
yield based on hexane-3,4-dione (14). After this
last synthesis of furaneol (5) had been completed we
became aware of a German patent application de-
scribing the same sequence of chemical operations.[11]

## Experimental Section

Microanalyses were performed in the laboratory of Dr. E.
Palluy, Firmenich et Cie, Geneva. Boiling points and melting
points are uncorrected. Nmr spectra were measured in CCl₄
solution.

**2,5-Dimethyl-2,5-dimethoxy-3,4-*cis*-dihydroxytetrahydrofuran
(3).   A.**—A heterogeneous mixture of 2,5-dimethyl-2,5-di-
methoxy-2,5-dihydrofuran (2)[8] (2.5 g, 15.8 mmol), potassium
chlorate (2.8 g, 22.8 mmol), osmium tetroxide (0.09 g, 0.3 mmol),
sodium bicarbonate (1.9 g, 22.6 mmol), tetrahydrofuran (25
ml), and water (35 ml) was stirred at 30° for 63 hr and concen-
trated to approximately one quarter of its volume under reduced
pressure, and the residue was extracted twice with ethyl acetate.
The organic layer was washed with brine, dried (Na₂SO₄), and
evaporated under vacuum, leaving 0.32 g (10%) of 3 as colorless
crystals, mp 95–99°.

(10) *Cf.* F. I. Carroll, *J. Org. Chem.*, **31**, 366 (1966).

(11) W. J. Evers, German Offenlegungsschrift 2,105,014 (1971); Belgian
Patent 762,686 (1971); U. S. Patent 3,629,292 (1971).

**B.**—A solution of 47.4 g (0.3 mol) of **2** in 300 ml of butanol was cooled to −8°, and a solution of 31.6 g (0.2 mol) of potassium permanganate and 45 g (0.183 mol) of magnesium sulfate (hydrate) in 750 ml of water was added over a period of 40 min, during which the temperature was maintained below −2°. After storage at room temperature for 4 hr the mixture was filtered and concentrated to 100 ml. The concentrate was extracted with butanol, dried (MgSO$_4$), and evaporated to give 9 g of product. Two crystallizations from hexane gave a product, mp 95–99° which was raised to 104–106° on sublimation, nmr (CCl$_4$ + CD$_3$COCD$_3$) δ 1.29 (6 H, s), 3.22 (6 H, s), 4.00 (4 H, m).

*Anal.* Calcd for C$_8$H$_{16}$O$_5$: C, 49.99; H, 8.39. Found: C, 50.10; H, 8.18.

*erythro*-3,4-Dihydroxyhexane-2,5-dione (4).—A mixture of **2** (7.16 g, 45.2 mmol), potassium chlorate (7.9 g, 64.5 mmol), osmium tetroxide (0.25 g, 1.0 mmol), tetrahydrofuran (50 ml), and water (100 ml) was heated for 18 hr to 45–50° in an oil bath. The resulting yellow solution was evaporated to dryness under reduced pressure and the residue was taken up in successive portions of ethyl acetate. The combined extracts were dried (Na$_2$SO$_4$) and evaporated, giving 6.9 g (∼100%) of crude dihydroxy diketone **4** which was recrystallized from CCl$_4$/CHCl$_3$: mp 59–61°; $R_f$ 0.73 (silica gel G, ethyl acetate); ir (KBr) 3320 cm$^{-1}$; (CHCl$_3$, dilute) 3450–3550, 1705–1710 cm$^{-1}$; mass spectrum (70 eV) *m/e* 128, 43; nmr (CDCl$_3$, CCl$_4$) δ 2.32 (6 H, s), 3.85 (2 H, s), 4.34 (2 H, s).

*Anal.* Calcd for C$_6$H$_{10}$O$_4$: C, 49.31; H, 6.90. Found: C, 49.68; H, 6.84.

**Furaneol (5).** **A.**—Erythro dihydroxy diketone **4** (5.4 g, 36.9 mmol) was dissolved in 100 ml of a freshly prepared saturated solution of NaHCO$_3$ in H$_2$O (pH ∼8.0) and extracted at room temperature with pentane in a continuous extractor. After 1 week the extract contained 0.61 g of crystalline furaneol (**5**). The extraction process was continued for a second week using ethyl ether containing 10–15% of pentane. Evaporation gave a second crop of furaneol (**5**) (1.81 g), total yield 51%. The furaneol obtained was recrystallized at low temperature from a saturated solution in petroleum ether (bp 30–50°) and identified with authentic furaneol[4] by melting point (78–80° dec) and ir and nmr spectra. The latter showed signals (CDCl$_3$) at δ 1.45 (3 H, d, $J = 7$ Hz), 2.30 (3 H, s), 4.55 (1 H, q, $J = 7$ Hz), 7.65 (1 H, broad).

**B.**—A solution of erythro dihydroxy diketone **4** (10.0 g, 68.5 mmol) in 200 ml of 1 *M* Na$_2$HPO$_4$ (pH 8.12) was sealed in an ampoule at 10 mm and then maintained at 75° for 24 hr. Continuous extraction with a mixture of ether–petroleum ether, 1:1 (v/v), during 24 hr followed by drying and evaporation gave 4.545 g (52%) of furaneol (**5**) judged to be pure by nmr spectroscopy. The threo isomer **8** when treated under identical conditions yielded furaneol (**5**) in identical yield.

*threo*-3,4-Dihydroxyhexane-2,5-dione (8).—A solution of 25 g of methylglyoxal (**7**) (50% aqueous solution, commercially available) was further diluted with water (25 ml) and stirred under nitrogen while 11 g of zinc dust was added in one lot. The temperature rose to 50° within 3 min and as it began to fall (6 min) 100 ml of acetic acid (10% aqueous) was added dropwise over 1 hr. Three extractions with ethyl acetate gave, after concentration, 7.0 g of crude material that crystallized at 0° from ethyl acetate–petroleum ether. Two recrystallizations from the same solvent mixture gave the threo compound **8**: mp 89–90°;[12] $R_f$ 0.77 (silica gel G, ethyl acetate); ir (KBr) 3470 (unchanged in CHCl$_3$), 1705–1715 cm$^{-1}$; mass spectrum (70 eV) *m/e* 128, 43; nmr (CDCl$_3$, CCl$_4$) δ 2.33 (6 H, s), 3.72 (2 H, d, $J = 6.5$ Hz), 4.56 (2 H, d, $J = 6.5$ Hz).

*Anal.* Calcd for C$_6$H$_{10}$O$_4$: C, 49.31; H, 6.90. Found: C, 49.35; H, 7.05.

**Reaction of *threo*-3,4-Dihydroxyhexane-2,5-dione (8) with Acetone.**—A solution of the threo compound **8** (10 g) in 50 ml of dry acetone and 0.6 ml of concentrated sulfuric acid was shaken at room temperature for 4 hr, 10 g of dry potassium carbonate

was added, and after stirring for 15 min the mixture was filtered and concentrated. The residue (11 g) showing two peaks in glc (Carbowax column), was chromatographed on silica gel. The less polar compound **12** (40% of the mixture) had mp 54–55°; ir, neither OH nor C=O absorptions; mass spectrum (70 eV) (rel intensity) 43 (100), 87 (23), 229 (M$^+$ − 15) (13), 101 (12), 107, and 171 (9); nmr δ 1.29 (6 H, s), 1.43 (6 H, s), 1.57 (6 H, s), 4.18 (2 H, s).

*Anal.* Calcd for C$_{12}$H$_{20}$O$_5$: C, 59.00; H, 8.25. Found: C, 59.20; H, 8.08.

The more polar compound **11** (60% of the mixture) was obtained as a liquid: mass spectrum (70 eV) *m/e* (rel intensity) 43 (100), 143 (23), 171 (M$^+$ − 15) (1); nmr (CCl$_4$) δ 1.38 (6 H, s), 2.23 (6 H, s), 4.47 (2 H, s).

*Anal.* Calcd for C$_9$H$_{14}$O$_4$: C, 58.05; H, 7.58. Found: C, 58.02; H, 7.66.

**Reaction of Threo Dihydroxy Ketone 8 with Acids.**—When heated with acids or water, compound **8** is transformed to two new compounds whose relative proportions depend on the reaction conditions. In a typical experiment the solution obtained after heating 10 g of **8** with 10 g of oxalic acid in 100 ml of water for 22 hr at reflux was extracted with ethyl acetate. The organic layer was dried and concentrated to yield 8 g of residue, bp 60–61° (10 mm). A sample of **6** was purified further by semipreparative vpc (silicone rubber column, 6 ft, 150°): nmr (CCl$_4$) δ 2.20 (3 H, s), 2.35 (3 H, s), 6.1 (1 H, s) and a low-field enol proton; mass spectrum (70 eV) *m/e* (rel intensity) 43 (100), 85 (53).

*Anal.* Calcd for C$_6$H$_8$O$_3$: C, 56.24; H, 6.29. Found: C, 56.22; H, 6.15.

The yield of **6** is estimated to have been 85%. Heating 5 g of the dihydro diketone **8** in 50 ml of water containing 0.5 ml of concentrated HCl (resulting pH ∼3) at reflux for 48 hr gave 66% of **6**, 16% of **13**, and 17% of starting material **8**.

**Condensation of the Dihydroxy Diketone 8 with Pyruvic Acid.**—A solution of **8** (15 g) and pyruvic acid (15 g) in 150 ml of water was heated at reflux for 10 hr and the product was isolated by extraction with ethyl acetate. Evaporation gave a crude product (15 g). Distillation, bp 42–45° (0.1 mm), yielded **13** judged to be 95% pure by glc: ir (neat) 1702, 1673, 1568 cm$^{-1}$; uv (hexane) 223 nm (ε 9350), 266 (10,000); mass spectrum (70 eV) *m/e* (rel intensity) 43 (100), 67 (76), 139 (52), 154 (47); nmr (CCl$_4$) δ 1.47 (3 H, d, $J = 7$ Hz), 2.33 (3 H, s), 2.58 (3 H, s), 4.60 (1 H, q, $J = 7$ Hz).

*Anal.* Calcd for C$_8$H$_{10}$O$_3$: C, 62.32; H, 6.54. Found: C, 62.10; H, 6.60.

**Bromination of Hexane-3,4-dione (14).**—To a solution of hexane-3,4-dione (**14**) (25 g, 0.219 mol) in 100 ml of dioxane and 100 ml of ether was added with stirring during 90 min 72 g (0.45 mol) of bromine at 15–20°. After storage at 20° during 15 hr the reaction mixture was evaporated at 40° and finally attached to a vacuum system at 0.001 mm. The residue (57.3 g, 96%) consists of the dibromide **15**, nmr (CCl$_4$) δ 1.81 (6 H, d, $J = 7$ Hz), 5.20 (2 H, q, $J = 7$ Hz).

**Hydrolysis of the Dibromide 15 to Furaneol (5).**—A mixture of the dibromide **15** (57.3 g, 0.211 mol) and 500 ml of water was heated under reflux during 2 hr with stirring. After cooling to room temperature the reaction mixture was adjusted to pH ∼4 by addition of solid Na$_2$CO$_3$. After addition of sufficient sodium acetate to buffer the solution (to pH ∼5) it was extracted twice with petroleum ether. Evaporation of the organic layer gave 3.2 g of uncharacterized material. The aqueous phase was saturated with NaCl and extracted three times with ethyl acetate. After drying and evaporating 23.8 g of crude furaneol (**5**) were obtained. Glc indicated a purity of 55%. Purification by distillation at 0.001 mm gave 12.4 g of pure furaneol (**5**).

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(12) A 3,4-dihydroxyhexane-2,5-dione, mp 74°, of unknown configuration was described by F. Micheel, *Justus Liebigs Ann. Chem.*, **496**, 77 (1932).

# The Synthesis of N-Acyl-α-mercaptoalanine Derivatives[1]

S. M. PATEL, JAMES O. CURRIE, JR., AND RICHARD K. OLSEN*

*Department of Chemistry and Biochemistry, Utah State University, Logan, Utah 84321*

N-Acyl-α-mercapto-DL-alanine derivatives have been prepared by the reaction of hydrogen sulfide with the corresponding N-acyl-α-halo-DL-alanines. In a similar manner, reaction of N-acyl-α-haloalanine derivatives with thiolacetic acid or benzhydryl mercaptan gave the corresponding α-acetylthiol and α-benzhydrylmercapto-alanines, which upon removal of the S-acetyl and S-benzhydryl groups yielded α-mercaptoamino acid derivatives. Reaction of N-acyl-2,3-dihaloalanines with hydrogen sulfide or thiolacetic acid effected displacement of the α-halo group to yield 3-halo-2-mercapto- and 3-halo-2-acetylthioalanine derivatives, respectively. Deprotection of N-benzyloxycarbonyl-α-mercaptoalanine gave α-mercapto-DL-alanine hydrobromide, which proved to be quite unstable.

α-Mercapto-α-amino acids (1) are of interest in relationship to certain antibiotics, *i.e.*, gliotoxin,[2a] sporidesmin,[2b] aranotin,[2c] chaetocin,[2d] and the quinomycins,[3] which contain amino acid moieties possessing a sulfur function in the α position. The synthesis of 3,6-dimercaptopiperazine-2,5-dione derivatives 3[4] and 4[5] has been reported; these α-mercapto-α-amino acid derivatives are known to possess antiviral activity.[4a] Recently, Pojer and Rae reported[6] the preparation of N-benzoyl-2-mercapto-DL-alanine (2). We wish to



1, R' = H
2, R = methyl;
    R' = benzoyl

3

4

report in this paper a convenient synthesis of N-acyl-α-mercaptoalanine derivatives.

Treatment of the α-chloroalanine 7, formed *in situ* by the addition[7] of hydrogen chloride to 2-acetamidoacrylic acid (5), with hydrogen sulfide in acetic acid gave N-acetyl-2-mercapto-DL-alanine (9) as a crystalline, readily isolable material. The nmr spectrum of 9 in dimethyl sulfoxide-$d_6$ consisted of three singlets, in a relative intensity of 3:4:1, at δ 1.68 due to the β protons, 1.84 due to the acetyl group superimposed upon the mercapto proton, and 7.50 assignable to the amide proton. Addition of deuterium oxide effected hydrogen-deuterium exchange of the mercapto proton, as evidenced by equal relative intensities, following exchange, of the peaks at δ 1.68 and 1.84.

In a similar manner, 2-benzamidoacrylic acid (6)

was converted to the mercaptoalanine 10; the physical and spectral properties of 10 corresponded in all respects with data reported[6] for this compound.



5, R = CH₃
6, R = C₆H₅

7, R = CH₃
8, R = C₆H₅



9, R = CH₃
10, R = C₆H₅
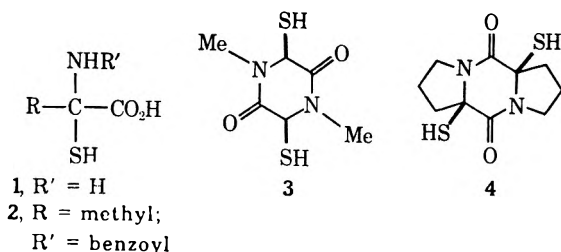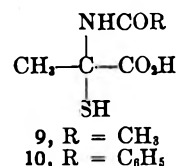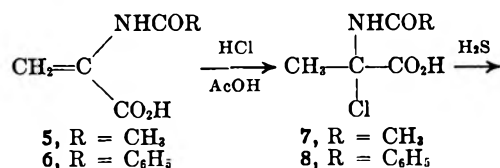
The α-mercaptoalanine 9 also was prepared by treatment of the α-chloro compound 7 with thiolacetic acid to give the α-acetylthioalanine 11. Removal of the S-acetyl group in 11 by methanolysis[6] gave 9.



11

12

Likewise, the α-benzhydrylmercapto derivative 12, prepared by reaction of benzhydryl mercaptan with 7, yielded 9 upon cleavage[8] of the benzhydryl moiety with trifluoroacetic acid.

Addition[9] of chlorine to 5 gave N-acetyl-2,3-dichloro-DL-alanine (13). Treatment of 13 with hydrogen sulfide yielded the 3-chloro-2-mercaptoalanine 15. Similarly, the dibromo compound 14 yielded the 2-acetylthio-3-bromoalanine 16 upon treatment with



5

13, X = Cl
14, X = Br



15, R = H;  X = Cl
16, R = acetyl;  X = Br

(1) Presented in part at the 27th Annual Northwest Regional Meeting of the American Chemical Society, Corvallis, Ore., June 1972.

(2) (a) M. R. Bell, J. R. Johnson, B. Wyldi, and R. B. Woodward, *J. Amer. Chem. Soc.*, **80**, 1001 (1958). (b) J. Fridrichson and A. McL. Mathieson, *Tetrahedron Lett.*, 1265 (1962); R. Hodges, J. W. Ranaldson, A. Taylor, and E. P. White, *Chem. Ind. (London)*, 42 (1963). (c) R. Nagarajan, N. Neuss, and M. M. Marsh, *J. Amer. Chem. Soc.*, **90**, 6518 (1968); D. B. Cosulich, N. R. Nelson, and J. H. van den Herde, *ibid.*, **90**, 6519 (1968). (d) D. Hauser, H. P. Weber, and H. P. Sigg, *Helv. Chim. Acta*, **53**, 1061 (1970).

(3) W. Keller-Schierlein, M. Lj. Mihailovic, and V. Prelog, *Helv. Chim. Acta*, **42**, 305 (1959); H. Otsuka and J. Shōji, *Tetrahedron*, **23**, 1535 (1967).

(4) (a) P. W. Trown, *Biochem. Biophys. Res. Commun.*, **33**, 402 (1968); (b) H. Poisel and U. Schmidt, *Chem. Ber.*, **104**, 1714 (1971).

(5) H. Poisel and U. Schmidt, *ibid.*, **105**, 625 (1972); E. Öhler, H. Poisel, F. Tataruch, and U. Schmidt, *ibid.*, **105**, 635 (1972).

(6) P. M. Pojer and I. D. Rae, *Tetrahedron Lett.*, 3077 (1971).

(7) A. L. Love and R. K. Olsen, *J. Org. Chem.*, **37**, 3431 (1972).

(8) I. Photaki, J. Taylor-Papadimitriou, C. Sakarellos, P. Mazarakis, and L. Zervas, *J. Chem. Soc. C*, 2683 (1970).

(9) O. V. Kil'disheva, L. P. Rasteikene, and I. L. Kunyants, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 231 (1955); *Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk*, 260 (1955).

excess thiolacetic acid. These reactions, which lead only to displacement of the α-halo group, are in contrast to the reported[10] displacement of both the 2- and 3-halo groups by alkyl mercaptans.

An interesting phenomenon was observed in the nmr spectra of the 2,3-disubstituted alanine derivatives **13** and **15**. The β-methylene protons appeared as an AB pattern when the spectra were recorded in trifluoroacetic acid; however, in dimethyl sulfoxide-$d_6$ or deuterium oxide as solvent, the β-methylene protons were observed to occur as a singlet. The acetylthiolalanine **16**, however, maintained the expected AB pattern in both trifluoroacetic acid and dimethyl sulfoxide.

Efforts to prepare N-benzyloxycarbonyl-2-mercapto-DL-alanine (**18**) and to effect subsequent deprotection of **18** to yield 2-mercapto-DL-alanine ·hydrobromide (**19**) proved to be unsatisfactory. Unstable oils were obtained in each case; however, nmr spectra provided evidence for the predominant presence of **18** and **19** in the product mixtures. Thus, the nmr spectrum of
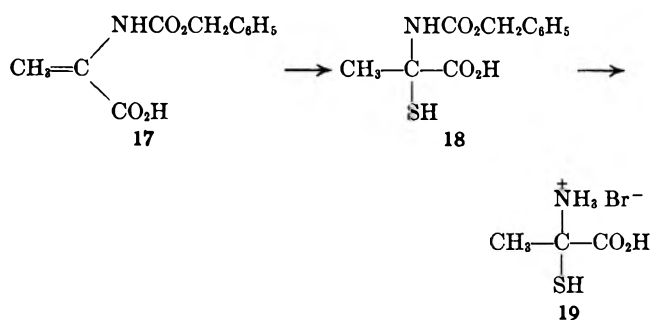


an impure sample of **19**, obtained by deprotection of **18** with hydrogen bromide in acetic acid, showed the β protons as a singlet at δ 1.58, the mercapto proton as a singlet at 2.38, and the ammonium protons as a triplet at 7.40 ($J$ = 51 Hz). Attempts to purify **19** lead only to the isolation of ammonium bromide. Treatment of a solution of **19** in pyridine with acetic anhydride lead to a multicomponent mixture in which none of the possible acetylated products **9** or **11** were detected.

The studies reported herein establish that reaction of appropriate sulfur nucleophiles with α-haloalanines affords a convenient method for the preparation of α-mercapto-α-amino acid derivatives. Further studies on the chemistry of this novel class of amino acids are underway.

## Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-20A spectrophotometer. Nmr data were obtained with a Varian A-60 nmr spectrometer at 60 MHz. Mass spectra were measured on a Hitachi Perkin-Elmer RMU-6E mass spectrometer. Tlc data were measured on Brinkmann precoated silica gel plates in the following solvents: solvent A, chloroform:methanol:acetic acid (10:5:1); solvent B, chloroform:methanol:acetic acid (85:10:5); solvent C, chloroform:methanol:acetic acid (7:2:1). The nmr spectral data recorded in trifluoroacetic acid (TFA) were measured relative to an external TMS standard. Evaporation in vacuo was carried out with a Buchler rotary evaporator. Elemental analyses were performed by M-H-W Laboratories, Garden City, Mich.

(10) O. V. Kil'disheva, M. G. Lin'kova, V. M. Savina, and I. L. Kunyants, Izv. Akad. Nauk. SSSR; Otdel. Khim. Nauk, 1348 (1958).

**N-Acetyl-2-mercapto-DL-alanine (9).**—To a solution of 2-acetamidoacrylic acid[9] (**5**) (0.30 g, 2.33 mmol) in 3 ml of trifluoroacetic acid and 25 ml of glacial acetic acid was added 0.70 ml (2.57 mmol) of 4 N hydrogen chloride in dioxane. After 5 min, hydrogen sulfide gas was passed into the solution for 10 min, following which the reaction mixture was stirred overnight at room temperature. The solvent was evaporated in vacuo; the solid obtained was recrystallized from ethyl acetate to give 0.24 g (63%) of **9**: mp 154–156°; a sodium nitroprusside test[11] on **9** was positive; tlc $R_{fA}$ 0.46; ir (KBr) 3320, 2650, 1705, 1605, 1520, 1430, 1360, 1295, 1250, 1165, 1125, 1100, 1015, 975, 935, 860, 780, 720, 690, 640, 570, 500, and 365 cm$^{-1}$; nmr (DMSO-$d_6$) δ 1.68 (s, 3 H, β-methyl), 1.84 (s, 4 H, acetyl, SH); nmr (DMSO-$d_6$ + D$_2$O) 1.72 (s, 3 H), 1.90 (s, 3 H); nmr (TFA) 1.47 (s, 3 H), 1.80 (s, 4 H), 7.50 (s, 1 H); mass spectrum m/e (rel intensity) 163 (3.5), 130 (22), 129 (16), 88 (36), 87 (26), 59 (75), 58 (28), 45 (27), 44 (62), 43 (97), 42 (100), 41 (52), 36 (13), 34 (100), 33 (50).

*Anal.* Calcd for C$_5$H$_9$NO$_3$S (163.2): C, 36.8; H, 5.53; N, 8.59; S, 19.5. Found: C, 36.6; H, 5.80; N, 8.76; S, 19.6.

**N-Benzoyl-2-mercapto-DL-alanine (10).**—Following the same procedure as described above for **9**, 2-benzamidoacrylic acid[9] (**6**) (0.40 g, 2.1 mmol) was converted to **10** (0.25 g, 53%): mp 146–148° from chloroform (lit.[6] mp 146–147°): tlc $R_{fB}$ 0.20; nmr δ 1.78 (s, 3 H, β-methyl), 3.80 (br s, 1 H, SH), 7.50–8.20 (m, 6 H, phenyl plus amide), 9.20 (s, 1 H, carboxyl proton).

**N-Acetyl-2-acetylthio-DL-alanine (11).**—2-Acetamidoacrylic acid[9] (**5**) (1.20 g, 9.32 mmol) was dissolved in 10 ml of trifluoroacetic acid and an additional 100 ml of glacial acetic acid was added. To this solution was added 3.0 ml (11 mmol) of 4 N hydrogen chloride in dioxane. After approximately 5 min, an excess of thiolacetic acid was added and the reaction mixture was stirred for 2 hr. The solvent was removed in vacuo and the solid obtained was triturated with diethyl ether and collected by filtration (1.42 g, 74%), mp 145–146°. Recrystallization from ethyl acetate yielded 1.0 g (53%) of **11**: mp 150–151°; tlc $R_{fA}$ 0.55; ir (KBr) 3330 and 3280 (NH and OH), 2650 (acid dimer), 1715 (carboxyl), 1675 cm$^{-1}$ (amide); nmr (trifluoroacetic acid) δ 1.60 (s, 3 H, β-methyl), 1.80 (s, 3 H, acetyl), 1.95 (s, 3 H, acetyl), 7.94 (s, 1 H, amide).

*Anal.* Calcd for C$_7$H$_{11}$NO$_4$S (205.3): C, 41.0; H, 5.36; N, 6.83. Found: C, 41.3; H, 5.15; N, 6.63.

**N-Acetyl-2-benzhydrylmercapto-DL-alanine (12).**—2-Acetamidoacrylic acid[9] (**5**) (1.20 g, 9.32 mmol) was treated as above with hydrogen chloride, following which an excess of benzhydryl mercaptan[12] was added to the reaction mixture. After the solution was stirred for 1.5 hr at room temperature, the solvent was evaporated in vacuo to yield, after trituration with diethyl ether, 2.80 g (92%) of a white solid. Recrystallization of this material from 95% ethanol gave 2.10 g (70%) of **12**: mp 166–167°; tlc $R_{fA}$ 0.74; nmr (DMSO-$d_6$) δ 1.55 (s, 3 H, β-methyl), 1.65 (s, 3 H, acetyl), 5.27 (s, 1 H, benzhydryl proton), 7.27 (br s, 10 H, aromatic), 8.17 (s, 1 H, amide proton).

*Anal.* Calcd for C$_{18}$H$_{19}$NO$_3$S (329.4): C, 65.7; H, 5.77; N, 4.25. Found: C, 66.1; H, 5.98; N, 3.98.

**Preparation of N-Acetyl-2-mercapto-DL-alanine (9) from 11.**—**11** (0.3 g, 1.5 mmol) was allowed to stir for 4 hr at room temperature in 5 ml of a solution prepared by the addition of 5 ml of concentrated hydrochloric acid in 15 ml of water and 15 ml of methanol. Evaporation of the solvent in vacuo gave a white solid; recrystallization of this material from acetone–ligroin (bp 60–90°) yielded 0.10 g (41%) of **9**, mp 154–156°. This material was indistinguishable (tlc, ir, mixture melting point) from a sample of **9** as prepared above.

**Preparation of N-Acetyl-2-mercapto-DL-alanine (9) from 12.**—A solution of **12** (0.33 g, 1.0 mmol) in 12 ml of a 2.5% solution of phenol in trifluoroacetic acid was allowed to stir for 18 hr at room temperature. The solvent was removed in vacuo to obtain an oil. After trituration of the oil with diethyl ether, 0.10 g (60%) of **9** was collected by filtration, mp 154–156°. This material was indistinguishable (ir, mixture melting point) from a sample of **9** as prepared above using hydrogen sulfide.

**N-Acetyl-3-chloro-2-mercapto-DL-alanine (15).**—A solution of 0.50 g (3.8 mmol) of 2-acetamidoacrylic acid[9] in 10 ml of trifluoroacetic acid was stirred while a saturated solution of chlorine in carbon tetrachloride was added slowly until a faint green color

(11) K. Shinohra and M. Kilpatrick, J. Biol. Chem., 106, 241 (1934).

(12) M. M. Klenk, C. M. Suter, and S. Archer, J. Amer. Chem. Soc., 70, 3846 (1948).

remained. The dichloroalanine 13 thus obtained showed the following nmr spectral data: nmr (TFA) δ 1.79 (s, 3 H, acetyl), 3.73 and 4.41 (AB doublets, $J$ = 12 Hz, 2 H, CH₂); nmr (DMSO-$d_6$) 1.90 (s, 3 H, acetyl), 3.93 (s, 2 H, CH₂). After the solution was stirred for 10 min, hydrgen sulfide was bubbled in rapidly for 10 min. After an additional 10 min, the solvent was removed *in vacuo.* Trituration four times with small portions of diethyl ether gave 0.65 g (85%) of a white solid: mp 113–114° dec; nmr (TFA) δ 2.36 (s, 4 H, acetyl, SH), 4.36 and 4.74 (AB doublet, $J$ = 12 Hz, 2 H, CH₂), and 7.80 (broad s, 1 H, NH); nmr (DMSO-$d_6$) δ 1.87 (s, 4 H, acetyl, SH), 3.89 (s, 2 H, CH₂).

*Anal.* Calcd for C₅H₈ClNO₃S (197.7): C, 30.39; H, 4.07; N, 7.09. Found: C, 30.39; H, 4.07; N, 7.04.

Similar results, as evidenced by nmr spectral data, were obtained when the dibromo compound 14 was treated with hydrogen sulfide in trifluoroacetic acid. However, the product was an unstable oil and attempts to effect purification were unsuccessful.

*N*-Acetyl-2-acetylthio-3-bromo-DL-alanine (16).—2-Acetamidoacrylic acid (5) (0.30 g, 2.33 mmol) was suspended in 9 ml of glacial acetic acid. A solution of bromine in acetic acid was added until the bromine color was no longer discharged. An excess of thiolacetic acid was added and the reaction mixture was stirred at room temperature for 1.5 hr. The solvent was evaporated *in vacuo* and the solid residue was triturated with diethyl ether to yield 0.47 g (70%) of crystalline material. Recrystallization from ethyl acetate gave material melting at 127–129° dec: tlc $R_{fA}$ 0.62; nmr (trifluoroacetic acid) δ 1.80 (s, 3 H, acetyl), 1.95 (s, 3 H, acetyl), 3.43 and 4.27 (AB doublet, $J$ = 11 Hz, CH₂, 2 H), 7.70 (s, 1 H, amide proton).

*Anal.* Calcd for C₇H₁₀BrNO₄S (284.2): C, 29.6; H, 3.53; N, 4.94. Found: C, 29.5; H, 3.71; N, 4.91.

*N*-Benzyloxycarbonyl-2-mercapto-DL-alanine (18).—2-(Benzyloxycarbonylamino)acrylic acid (17)[9] (500 mg, 2.26 mmol) was stirred in 3 ml of trifluoroacetic acid while hydrogen chloride gas was passed in for 10 min. After the solution was stirred for an additional 10 min, hydrogen sulfide was introduced into the reaction mixture for 15 min. The solvent was removed at reduced pressure followed by a vacuum of <1 mm. Ether was added slowly to the resulting oil until no more solid precipitated (~20 ml). Filtration and removal of solvent gave an oil with a structure apparently that of an impure sample of the thiol 18: nmr (CDCl₃) δ 1.86 (s, 3 H, CH₃), 2.35 (s, 0.8 H, SH), 5.10 (s, 2.5 H, CH₂), and 7.60 (s, 8.5 H, phenyl). The instability of the product precluded further purification; however, tlc showed a major component ($R_{fC}$ 0.60) with only minor impurities.

2-Mercapto-DL-alanine Hydrobromide (19).—A solution of *N*-benzyloxycarbonyl-2-mercaptoalanine (18) was prepared as above but in acetic acid. To this solution was added 6 ml of a saturated solution of hydrogen bromide in acetic acid. Within 5 min, gas evolution began. After the solution was stirred for 1 hr, the mixture was filtered and the solvent was reduced *in vacuo* to ¹/₃ its original volume. The slow addition of 40 ml of diethyl ether, while cooling the mixture, gave a small amount of white solid (NH₄Br) which was filtered off. Removal of the solvent from the filtrate gave a viscous and somewhat unstable oil: nmr (DMSO-$d_6$) δ 1.58 (s, CH₃), 2.38 (s, SH), and 7.40 (t, $J$ = 51 Hz, NH₃⁺). Further attempts at purification of 19 led to loss of ammonium bromide.

An impure sample of freshly prepared 19 in pyridine cooled to 0° was treated with acetic anhydride and allowed to stand in a refrigerator for 2 days. Following work-up of the reaction mixture, no evidence for the presence of 9 or 11 was detected by tlc or nmr. The crude product obtained consisted of several components as shown by tlc.

# Reaction of Hexafluoroacetone with Certain Simple Peptides and Related Compounds

CHARLES A. PANETTA,* TRAVIS G. CASANOVA, AND CHIA-CHI CHU

*Department of Chemistry, The University of Mississippi, University, Mississippi 38677*

Hexafluoroacetone in dimethyl sulfoxide reacts with simple *N*-glycyl peptides and glycine esters to form fluorinated derivatives which contain an oxazolidine ring. When the N-terminal residue of the peptide is α-methylalanyl, the product is a polyfluorinated imidazolidinyl peptide.

For the last four years, our research group has been concerned with the interaction of aldehydes and ketones with amino acids and simple peptides and their derivatives. Thus far, we have studied a fairly general reaction between carbonyl compounds (acetone, cyclohexanone, cyclopentanone, or isobutyraldehyde) and dipeptides[1] which has afforded novel imidazolidine ring systems. In general, polyhalogenated ketones react quite differently from other carbonyl compounds with amino acids, peptides, and their derivatives. Hexachloroacetone and *sym*-trichlorotrifluoroacetone afforded *N*-trichloroacetyl[2] and *N*-trifluoroacetyl[3] derivatives, respectively. Hexafluoroacetone condenses with amino acids to yield 2,2-bistrifluoromethyl-5-oxazolidones (1).[4] All of the foregoing reactions of polyhalogenated ketones were run with dimethyl sulfoxide as the solvent. The interaction of hexafluoroacetone with certain low-molecular-weight peptides in dimethyl sulfoxide is the subject of the present paper.

Hexachloroacetone and *sym*-trichlorotrifluoroacetone both suffered facile cleavage during reactions with simple peptides. In both cases, the trichloromethyl-to-carbonyl carbon bond was ruptured and chloroform was the by-product. Under identical reaction conditions, the cleavage of a carbon–carbon bond of hexafluoroacetone was never observed. Instead, one or two molecules of hexafluoroacetone condensed with the peptides studied in this work and produced relatively nonpolar and volatile peptide derivatives.

When glycylglycine was treated with hexafluoroacetone in dimethyl sulfoxide at −28 to +25°, a crystalline product was obtained, the solubility of which indicated that it was less polar than the parent dipeptide. Elemental analysis indicated that two hexafluoroacetone molecules condensed with one molecule of glycylglycine with the loss of a molecule of water.

(1) C. A. Panetta and M. Pesh-Imam, *J. Org. Chem.*, **37**, 302 (1972).
(2) C. A. Panetta and T. G. Casanova, *ibid.*, **35**, 2423 (1970).
(3) C. A. Panetta and T. G. Casanova, *ibid.*, **35**, 4275 (1970).
(4) F. Weygand, K. Burger, and K. Engelhardt, *Chem. Ber.*, **99**, 1461 (1966).

Spectral data (ir and nmr) provided evidence for carboxyl and amide carbonyl groups and for amine, amide, methylene, and methine hydrogen atoms. The acidity of the product and its apparent carboxyl carbonyl stretching absorption ruled out involvement of the carboxyl moiety (which was involved in the case of the reaction of hexafluoroacetone with amino acids[4] referred to above). The observation of an amide NH deformation absorption band[5] was strong proof that the amide group was not affected during the reaction. The only sites remaining on the dipeptide for the attachement of the two hexafluoroacetone molecules were the amino and methylene groups. Both of these groups, when present in separate molecules, are known to add to hexafluoroacetone.[6] Using the above information and other data which we obtained on similar fluorinated products derived from ethyl glycylglycinate and methyl and ethyl glycinate (see below), the structure of the condensation product



1

2, R = -CONHCH₂CO₂H
3, R = -CONHCH₂CO₂Et
4, R = -CONHCH₂CONHCH₂CO₂Me
5, R = -CO₂Et
6, R = -CO₂Me
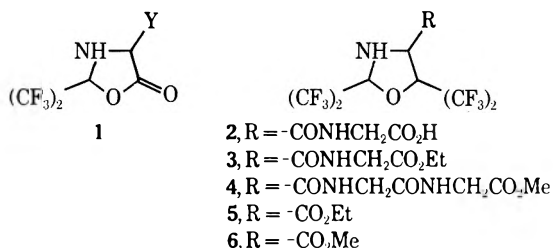
was established as that of 2. The polytrifluoromethylated oxazolidine ring probably resulted from the loss of water from the two hexafluoroacetone adduct moieties in 7. The location of one of the hexafluoroacetone

$$(CF_3)_2CNHCHCONHCH_2CO_2H$$



7

$$(CF_3)_2COH$$

$$(CF_3)_2C=NCHCONHCH_2CO_2Et$$

8
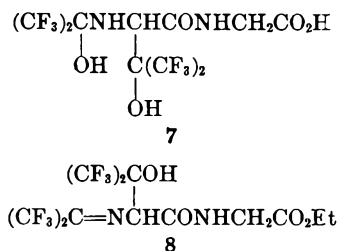
residues on what was originally the amino-end rather than the carboxyl-end methylene group was deduced from the mass spectral fragmentation patterns obtained on the ethyl glycylglycinate–hexafluoroacetone condensation product.

The condensation of glycylglycine ethyl ester with hexafluoroacetone afforded two isomeric products which were distillable, but were actually separated by chromatography on a column of silicic acid. An elemental analysis of a mixture of these isomers showed, as in the case of glycylglycine, that two molecules of hexafluoroacetone had condensed with a molecule of the dipeptide ester and that a molecule of water was lost. The major product (80% of the isomeric mixture) was very similar in its spectral properties with 2. A mass spectrum of it confirmed the structural relationship and resulted in the assignment of structure 3 to this product. The minor (~20%) constituent of the isomeric mixture was tentatively assigned structure 8. This was established mainly from infrared

(5) L. J. Bellamy, "Advances in Infrared Group Frequencies," Methuen and Co. Ltd., London, 1968, pp 286, 287.

(6) For a review of these and other reactions see C. G. Krespan and W. J. Middleton, *Fluorine Chem. Rev.*, **1**, 145 (1967).

(C=N stretching band), nmr (alcohol proton), and mass spectral data.

Triglycine methyl ester has also been treated with hexafluoroacetone under conditions which are identical with those described above for glycylglycine ethyl ester. Elemental analysis and spectral evidence indicated that the fluorinated product also had the oxazolidine structure, 4.

To obtain further support for the polyfluorinated oxazolidinyl peptide structures (2, 3, and 4) proposed above, we undertook the investigation of the action of hexafluoroacetone on the ethyl and methyl esters of glycine. Originally, we assumed that these reagents, when dissolved in DMSO, would combine to form 5-oxazolidones (1) similar to the reaction of zwitterionic amino acids with hexafluoroacetone.[4] However elemental analysis showed that, as with the peptides, two molecules of hexafluoroacetone condensed with each molecule of ethyl or methyl glycinate with the concomitant loss of a molecule of water. The spectral data on the oily products were in complete accord with structures 5 and 6.

Imidazolidinyl peptides are commonly formed from the interaction of dipeptides and nonhalogenated aldehydes and ketones.[1] With hexafluoroacetone, an imidazolidinyl peptide was formed when the α-carbon atom at the amino end of the peptide was completely substituted. This fact was demonstrated in the reaction of α-methylalanyl-α-methylalanine (9) with hexa-

$$CF_3\overset{\displaystyle O}{\overset{\displaystyle \|}{C}}CF_3 + H_2NC(CH_3)_2CONHC(CH_3)_2CO_2H \xrightarrow{\text{DMSO}}$$

9



10
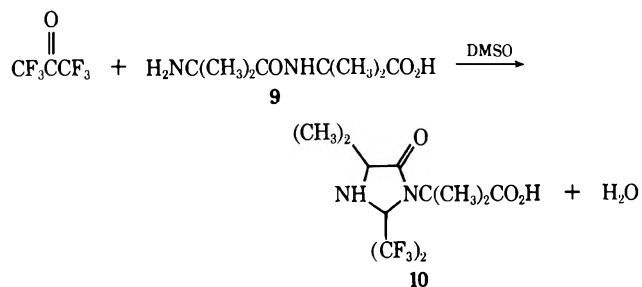
fluoroacetone. The two reactants condensed in a 1:1 molar ratio to afford an acidic, but relatively nonpolar, product the infrared spectrum of which lacked the amide NH deformation absorption band[5] that was present in the spectrum of the parent dipeptide. The polyfluorinated imidazolidinyl peptide product, 10, was characterized by elemental analysis and by its infrared and proton magnetic resonance spectra.

Thus, hexafluoroacetone in dimethyl sulfoxide condenses with N-terminal glycyl peptides and glycine esters in a 2:1 ratio to afford fluorinated products which contain an oxazolidine ring. When the N-terminal residue is α-methylalanyl, equimolar amounts of reactants combine to yield a polyfluorinated imidazolidinyl peptide.

## Experimental Section

**Reaction of Glycylglycine with Hexafluoroacetone. Preparation of 2.—**A solution of 0.698 g (5.3 mmol) of glycylglycine in 15 ml of DMSO was placed in a dry flask which was equipped with a drying tube containing Drierite, a Dry Ice cooled condenser, and a magnetic stirrer. Anhydrous hexafluoroacetone gas was introduced to the flask in a steady stream; this was continued until a persistent reflux rate of the condensed gas was obtained. The reaction mixture soon froze. The entire apparatus was left unattended (in a hood, and usually overnight),

during which time the Dry Ice sublimed and the reaction mixture slowly warmed to ambient temperature. The resultant yellow solution was poured into about 100 ml of ice-water. The aqueous solution was extracted thrice with 30-ml portions of $n$-BuOH, and the butanol solvent was removed by distillation under reduced pressure. The residue weighed 0.573 g and was chromatographed on silicic acid (160 g, Mallinckrodt, 100 mesh) using MeOH as the solvent. This procedure removed the last traces of DMSO from the product, and the resultant homogeneous oil (0.379 g, 16%) crystallized during storage. The product, 2, was soluble in 1 $N$ NaOH, acetone, or methyl isobutyl ketone, but was insoluble in water, benzene, or hexane. It was recrystallized from methyl isobutyl ketone and benzene: mp 135.0–135.5°; ir (Nujol) 3400, 3260 (NH,OH), 1743–1715 (carboxyl C=O), 1670 (amide C=O), 1538 (amide NH); nmr (acetone-$d_6$) 4.12 (m, 2, methylene H), 5.1 (m, 2, methine H and amide H), 6.9 (broad, 1, amine H), 8.0 (broad, 1, carboxyl H).

*Anal.* Calcd for $C_{10}H_8F_{12}N_2O_4$ (2): C, 26.92; H, 1.36; F, 51.10; N, 6.28. Found: C, 26.88; H, 1.47; F, 48.47; N, 6.32.

**Reaction of Glycylglycine Ethyl Ester with Hexafluoroacetone. Preparation of 3 and 8.**—A solution of 0.983 g (5.0 mmol) of the hydrochloride of glycylglycine ethyl ester in 25 ml of DMSO was treated with 0.535 g (5.3 mmol) of triethylamine. This mixture was then treated with an excess of hexafluoroacetone in exactly the same manner as that described above for glycylglycine. An oil was obtained which weighed 0.444 g (18.8%), bp 96–110° (0.23 mm).

*Anal.* Calcd for $C_{12}H_{10}F_{12}N_2O_4$ (3 or 8): C, 30.40; H, 2.13; F, 48.08; N, 5.91. Found: C, 30.60; H, 2.27; F, 47.08; N, 5.81.

In a later run, the above oily product was found to contain two isomers, 3 and 8. The minor product (8) was obtained in only 2.8% yield, tlc $R_f$ 0.8 [$C_6H_6$-EtOAc (9:1), silica gel]. The major oily product (3) was isolated in 12.7% yield, $R_f$ 0.4 [$C_6H_6$-EtOAc (9:1), silica gel]. The ir, nmr, and mass spectra of both of these isomers were consistent with the proposed structures.

**Reaction of Glycylglycylglycine Methyl Ester Hexafluoroacetone. Preparation of 4.**—The hydrochloride of glycylglycylglycine methyl ester[7] (mp 196–197°) was treated with hexafluoroacetone according to the same procedure that was used on glycylglycine ethyl ester hydrochloride (see above). The yield of crystalline product (4) was 27.8%: mp 150.5–151.0° (from hot $CH_2Cl_2$ or benzene); ir (Nujol) 3484, 3356, 3165 (NH), 1757 (ester C=O), 1689, 1667 (amide C=O), 1536 (amide NH), 1227

(C–F), 1183 (C–O–C); nmr (acetone-$d_6$) 2.8 (s, 2, amide, $H_2O$), 3.67 (s, 3, methyl), 4.02 (m, 4, methylene), 4.95 (broad, ~1, methine), 5.2 (broad, ~1, NH, partly exchanged); mass spectrum $m/e$ (rel intensity) 517 (3, M$^+$), 486 (26, M$^+$ − OCH$_3$), 448 (60, M$^+$ − CF$_3$), 429 (7, M$^+$ − NHCH$_2$CO$_2$CH$_3$), 402 (100, M$^+$ − CONHCH$_2$CO$_2$CH$_3$), 351 (4, M$^+$ − hexafluoroacetone), 344 (21, M$^+$ − CONHCH$_2$CONHCH$_2$CO$_2$CH$_3$), 173 (100, CONH-CH$_2$CONHCH$_2$CO$_2$CH$_3$), 88 (29, NHCH$_2$CO$_2$CH$_3$), 85 (25, NH=CHCONH=CH$_2$).

*Anal.* Calcd for $C_{13}H_{11}F_{12}N_3O_5$ (4): C, 30.12; H, 2.14; F, 44.08; N, 8.12. Found: C, 29.98; H, 2.08; F, 43.82; N, 8.14.

**Reaction of Glycine Ethyl and Methyl Esters with Hexafluoroacetone. Preparation of 5 and 6.**—The hydrochlorides of glycine ethyl and methyl esters were treated with hexafluoroacetone in separate experiments according to the procedure used on glycylglycine ethyl ester hydrochloride. The ethyl ester product, 5, was obtained in 16.3% yield, bp 84° (23 mm).

*Anal.* Calcd for $C_{10}H_7F_{12}NO_3$ (5): C, 28.79; H, 1.69; F, 54.65; N, 3.36. Found: C, 28.60; H, 1.79; F, 54.44; N, 3.54.

The methyl ester product, 6, was obtained in 44.5%, bp 78° (25 mm). The ir and nmr spectra of both of these products were consistent with the proposed structures.

**Reaction of α-Methylalanyl-α-methylalanine (9) with Hexafluoroacetone. Preparation of 10.**—A mixture of 0.37 g (1.80 mmol) of α-methylalanyl-α-methylalanine[8] and 5 ml of DMSO was treated with an excess of hexafluoroacetone in the same manner as that described above for glycylglycine. A solid precipitated when the reaction mixture was poured into ice-water. It weighed 0.31 g and was crystallized from aqueous acetone to afford 25 mg (4.1%) of pure 10, mp 88.5°. The ir and nmr spectra supported structure 10 for this product. It was insoluble in water, but soluble in 1 $N$ NaOH solution.

*Anal.* Calcd for $C_{11}H_{14}F_6N_2O_3$ (10): C, 39.29; H, 4.20; F, 33.90; N, 8.33. Found: C, 39.05; H, 4.13; F, 34.15; N, 8.32.

**Registry No.**—2, 36871-69-9; 3, 36871-70-2; 4, 36901-03-8; 5, 36871-71-3; 6, 36871-72-4; 8, 36871-73-5; 10, 36871-74-6; hexafluoroacetone, 684-16-2.

(8) M. T. Leplawy, D. S. Jones, G. W. Kenner, and R.C. Sheppard, *Tetrahedron*, 11, 39 (1960).

(7) H. N. Rydon and P. W. G. Smith, *J. Chem. Soc.*, 2542 (1955).

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# Crystal and Molecular Structure of 5a,11a-Dibromojanusene

WALTER M. MACINTYRE* AND ALAN H. TENCH

*Chemistry Department, University of Colorado, Boulder, Colorado 80302*

The crystal structure of 5a,11a-dibromojanusene has been solved by the heavy-atom method. The strain between the apposed aromatic rings results in corresponding carbon atoms in the two rings being separated by amounts ranging from 2.99 Å for 11b and 12b to 4.09 Å in the case of 14 and 19. The dihedral angle between the apposed rings is 26.6°. The molecular geometry is discussed in detail.

Janusene (5,5a,6,11,11a,12-hexahydro-5,12:6,11-di-*o*-benzenonaphthacene) was first synthesized by Cristol and Lewis in 1967.[1] The compound was synthesized in order to study the physical and chemical effects arising from the π-electron interactions between two apposed aromatic rings, forced by the rigidity of the system to approach each other very closely. The structural formula, and the atom numbering system, are shown in Figure 1. A Dreiding model of janusene shows that the apposed or face (F) rings (in the terminology of Cristol and Lewis) would be parallel to each other and separated by about 2.5 Å, in the absence of any repulsion between the two π-electron clouds. Considerable

repulsion is, of course, to be expected. The X-ray analysis of 5a,11a-dibromojanusene (DBJ) (Figure 2) was undertaken in order to determine how the molecular structure accommodates the strains imposed by the π-electron interaction.

## Discussion

The bond lengths and angles in DBJ, as determined in this analysis, are given in Tables I and II, respectively, together with the corresponding standard deviations. Since none of the hydrogen atoms was located, data are given only for the bonds involving the carbon atoms and the bromine atoms.

The carbon–carbon bond lengths are all well within the expected limits. The carbon–bromine bond length

(1) S. J. Cristol and D. C. Lewis, *J. Amer. Chem. Soc.*, 89, 1476 (1967).

## TABLE I

### BOND LENGTHS IN DIBROMOJANUSENE AND THEIR ESTIMATED STANDARD DEVIATIONS $(\sigma)^a$

| Bond | | Length | $\sigma$ | Bond | | Length | $\sigma$ |
|------|------|--------|----------|------|------|--------|----------|
| C8 | C9 | 1.388 | 0.020 | | | | |
| C9 | C10 | 1.401 | 0.019 | C1 | C2 | 1.402 | 0.019 |
| C10 | C10a | 1.407 | 0.016 | C1 | C12a | 1.396 | 0.016 |
| C6a | C10a | 1.392 | 0.016 | | | | |
| C10a | C11 | 1.518 | 0.015 | C12 | C12a | 1.523 | 0.015 |
| C11 | C11b | 1.526 | 0.015 | C12 | C12b | 1.510 | 0.015 |
| C11 | C11a | 1.557 | 0.014 | C11a | C12 | 1.568 | 0.015 |
| C11b | C20 | 1.380 | 0.017 | C12b | C13 | 1.383 | 0.017 |
| C6b | C11b | 1.406 | 0.015 | | | | |
| C19 | C20 | 1.401 | 0.021 | C13 | C14 | 1.418 | 0.021 |
| C18 | C19 | 1.402 | 0.023 | | | | |
| C5a | C11a | 1.572 | 0.014 | | | | |
| C11a | Br | 1.992 | 0.010 | | | | |

$^a$ Data are presented in ångstroms.

## TABLE II

### BOND ANGLES IN DIBROMOJANUSENE AND THEIR ESTIMATED STANDARD DEVIATIONS $(\sigma)^a$

| Atoms defining angle | | | Angle | $\sigma$ | Atoms defining angle | | | Angle | $\sigma$ |
|------|------|------|-------|----------|------|------|------|-------|----------|
| 8 | 9 | 10 | 120.8 | 1.1 | 1 | 2 | 3 | 121.3 | 1.0 |
| 9 | 10 | 10a | 118.3 | 1.1 | 12a | 1 | 2 | 117.8 | 1.1 |
| 10 | 10a | 6a | 120.3 | 0.9 | 1 | 12a | 4a | 121.5 | 0.9 |
| 6a | 10a | 11 | 113.5 | 0.8 | 12 | 12a | 4a | 113.4 | 0.8 |
| 10 | 10a | 11 | 126.1 | 0.9 | 12 | 12a | 1 | 125.1 | 0.9 |
| 11 | 11b | 6b | 113.0 | 0.8 | 12 | 12b | 5b | 113.5 | 0.8 |
| 11 | 11b | 20 | 125.2 | 0.8 | 12 | 12b | 13 | 125.3 | 0.8 |
| 6b | 11b | 20 | 121.3 | 0.9 | 5b | 12b | 13 | 121.0 | 1.0 |
| 11b | 20 | 19 | 118.5 | 1.0 | 12b | 13 | 14 | 118.0 | 1.2 |
| 20 | 19 | 18 | 120.6 | 1.2 | 13 | 14 | 15 | 120.5 | 1.3 |
| 10a | 11 | 11a | 106.4 | 0.8 | 11a | 12 | 12a | 106.3 | 0.8 |
| 11b | 11 | 11a | 110.1 | 0.8 | 11a | 12 | 12b | 109.7 | 0.8 |
| 11b | 11 | 10a | 104.0 | 0.8 | 12b | 12 | 12a | 104.5 | 0.8 |
| 11 | 11a | Br | 104.1 | 0.7 | 12 | 11a | Br | 102.9 | 0.7 |
| 11 | 11a | 5a | 109.5 | 0.7 | 5a | 11a | 12 | 109.0 | 0.7 |
| 11 | 11a | 12 | 116.1 | 0.8 | | | | | |
| 5a | 11a | Br | 115.2 | 0.6 | | | | | |

$^a$ Values are given in degrees.

is somewhat longer than might be expected. The average value of the length of the bond between a bromine atom and an aliphatic carbon atom has been quoted as 1.94 Å.[2] The value found by us, 1.99 Å ($\sigma$ 0.018), is larger by an amount that is possibly significant. The slight lengthening of the C–Br bond probably is one result of the considerable steric hindrance between the two bromine atoms. The distance between the two bromine atoms (Table III) is 3.269 Å ($\sigma$ 0.0028),

## TABLE III

### SOME INTRAMOLECULAR DISTANCES IN DIBROMOJANUSENE AND THEIR ESTIMATED STANDARD DEVIATIONS $(\sigma)^a$

| Atoms | | Distance | $\sigma$ | Atoms | | Distance | $\sigma$ |
|------|------|----------|----------|------|------|----------|----------|
| C10a | C12a | 4.920 | 0.015 | C16 | C20 | 4.424 | 0.018 |
| C11 | C12 | 2.651 | 0.015 | C5b | C11b | 3.247 | 0.015 |
| C11b | C12b | 2.987 | 0.015 | C6b | C12b | 3.353 | 0.015 |
| C13 | C20 | 3.513 | 0.019 | C6 | C11 | 2.604 | 0.015 |
| C14 | C19 | 4.094 | 0.023 | C10a | C11a | 2.461 | 0.015 |
| C15 | C19 | 4.283 | 0.025 | C10a | Br11a | 3.097 | 0.011 |
| C14 | C18 | 4.371 | 0.023 | C11 | Br11a | 2.812 | 0.011 |
| C13 | C17 | 4.603 | 0.019 | Br5a | Br11a | 3.269 | 0.002 |

$^a$ Data are in ångstroms.

(2) "Tables of Interatomic Distances and Configuration in Molecules and Ions," Special Publication No. 18, The Chemical Society, London, 1965.
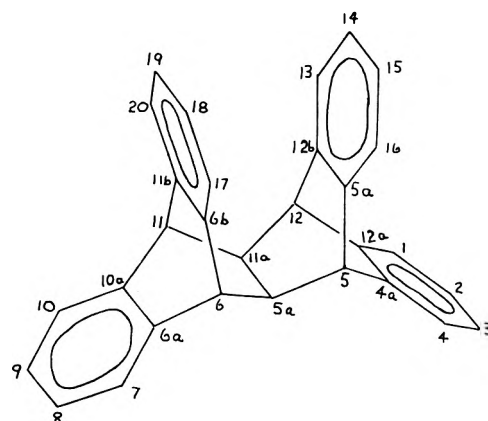


Figure 1.

compared with a nonbonded van der Waals contact of $\sim 4$ Å. The bond angles around C-11a and C-5a reflect this hindrance also. For example, the angle C-5a–C-11a Br, at 115° ($\sigma$ 0.6°), is much larger than the tetrahedral value, whereas the angle C-11–C-11a Br is only 104° ($\sigma$ 0.7°). The mutual repulsion of the bromine atoms leads to an increase in the C-5a–C-11a Br angle relative to the strict tetrahedral angle. This in turn causes a decrease in the C-11–C-11a Br and C-12–C-11a Br angles.

The major effects of intramolecular overcrowding are apparent not so much in the bond lengths and angles, but in the selected intramolecular distances listed in Table III. The closest approach of two nonbonded carbon atoms in the molecule is the 2.461 Å ($\sigma$ 0.015 Å) found between C-10a and C-11a and between C-4a and C-5a. A nonbonded distance of 2.651 Å ($\sigma$ 0.015 Å) separates C-11 and C-12, and C-6 and C-5, which are substituents on the apposed face rings of the mole. The rings themselves are bent outwards, away from each other, as indicated by the increase in distance between corresponding atom from 2.987 Å ($\sigma$ 0.015 Å) for C-11b and C-12b to 4.094 Å ($\sigma$ 0.023 Å) for C-19 and C-14.

It should be observed that the aromatic systems retain their planarity, despite the severe intramolecular overcrowding. The least-squares plane through atoms C-11b, C-6b, C-17, C-18, C-19, and C-20 has the equation $-0.06558X - 0.23031Y + 0.97090Z + 4.72903 = 0.0$, where $X$, $Y$, and $Z$ are coordinates in ångstroms relative to an orthogonal system of axes. These coordinates are related to the fractional atomic coordinates $(xyz)$, relative to the crystallographic axes, given in Table V, by the transformation

$$X = x \cdot a \sin \beta$$
$$Y = y \cdot b$$
$$Z = z \cdot c + x \cdot a \cos \beta$$

where $a$, $b$, $c$, and $\beta$ are the unit cell dimensions of the crystal. The deviations of the ring atoms, and of some other selected atoms, are listed in Table IV. The six atoms in the ring are coplanar. The substituents, C-11 and C-6, are significantly out of the plane, in the same direction.

The two face rings have a dihedral angle of 26.6° ($\sigma \sim 1°$).

The side rings are also planar with the substituents C-6 and C-11 lying in the plane. This plane has the
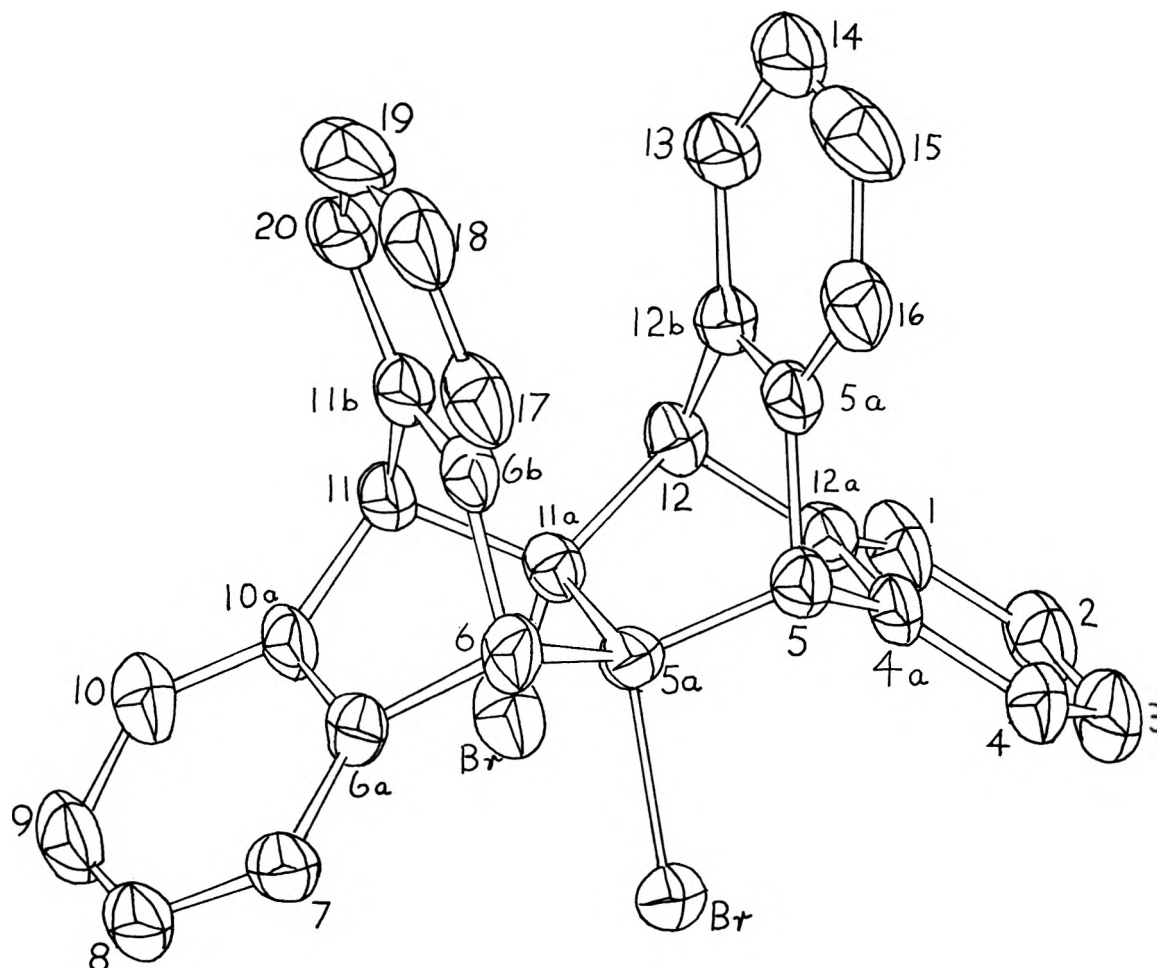
Figure 2.—An ORTEP plot showing the anisotropic thermal ellipsoids in dibromojanusene.

TABLE IV

LEAST-SQUARES PLANE THROUGH THE FACE
RING OF DIBROMOJANUSENE

| Atom | Distance from plane, Å | Atom | Distance from plane, Å |
|------|------|------|------|
| C11b | −0.004147 | C6b | 0.010930 |
| C20 | −0.006369 | C17 | −0.007174 |
| C19 | 0.010096 | C18 | −0.003339 |
| C11 | 0.162718 | C6 | 0.157287 |
| C11a | −0.964632 | C5a | −0.996286 |

equation $-0.66354X + 0.81534Y + 0.57517Z - 1.94107 = 0.0$, where $X$, $Y$, and $Z$ are the coordinates in Å relative to the orthogonal system of axes defined above.

Intermolecular distances in DBJ are not remarkable. The smallest distance between two atoms on neighboring molecules is 3.60 Å between C-2 on one molecule and C-10 on another molecule, related to the first by the *c* glide. The shortest intermolecular distance involving bromine is 3.74 Å (σ 0.002 Å), which is the distance between the bromine atoms and C-19 and C-14 on the molecule down the *b* axis in the next cell.

The molecule in Figure 1 has three elements of symmetry. There is a twofold axis normal to the C-5a–C-11a bond, bisecting it. Furthermore, the axis lies in the plane defined by C-5a, C-11a, and the hydrogen atoms on these two carbon atoms. This plane is a plane of symmetry in the molecule. Another plane of symmetry includes the twofold axis and is normal to the C-5a–C-11a bond. DBJ should possess the same

symmetry, provided that the strain resulting from the eclipsed bromine atoms is not too great.

The crystal does not make use of all the molecular symmetry. The molecular twofold axis coincides with a crystallographic twofold axis. However, there is no crystallographic mirror plane corresponding to either of the molecular planes of symmetry. It is important, therefore, to establish from the bond lengths and angles whether the molecule has the expected symmetry.[3] The data in Tables I and II are arranged such that those bond lengths and bond angles are opposite each other which should be equal if the molecule has a plane of symmetry defined by the twofold axis and the C-5a–C-11a bond. Inspection of the tables indicates at once that the corresponding bond lengths and angles are equal within experimental error. It would appear, then, that the dibromojanusene molecule possesses that plane of symmetry. The other symmetry plane normal to the C-5a–C-11a bond, is generated automatically by the combination of the twofold axis and the first plane of symmetry.

Curiously, other observations can be made which are at variance with this highly symmetrical picture. In Table V the atomic coordinates are arranged so that the coordinates of atoms, related by the symmetry plane including the C-5a–C-11a bond, are grouped together. Such pairs of atoms should have the same *y* coordinates. The *y* coordinates are different, how-

(3) Crystallographic theory does not require that the symmetry of a crystal reflect the full symmetry of the constituent molecules.

TABLE V
ATOMIC COORDINATES FOR DIBROMOJANUSENE[a]

| Atom | $x$ | $y$ | $z$ |
|------|------|------|------|
| C9 | 3070 (74) | 29490 (80) | 3374 (45) |
| C2 | 7998 (67) | 29193 (75) | 50651 (41) |
| C10 | 9362 (58) | 37176 (76) | 10733 (39) |
| C1 | 13254 (61) | 36579 (72) | 47522 (37) |
| C10a | 4138 (52) | 44793 (60) | 13850 (34) |
| C12a | 6975 (50) | 44264 (61) | 40200 (33) |
| C11 | 9516 (48) | 53607 (59) | 21716 (33) |
| C12 | 11294 (50) | 53137 (65) | 36005 (33) |
| C11b | 4395 (50) | 68687 (61) | 18998 (34) |
| C12b | 6846 (51) | 68291 (62) | 35256 (34) |
| C20 | 9763 (63) | 81397 (72) | 19608 (40) |
| C13 | 12901 (65) | 80751 (73) | 38821 (41) |
| C19 | 3749 (91) | 94038 (73) | 15849 (48) |
| C14 | 7446 (84) | 93842 (83) | 38252 (48) |
| C11a | 6275 (44) | 46308 (57) | 27270 (32) |
| Br11a | 13044 (5) | 26627 (7) | 29692 (4) |

[a] The standard deviations in the coordinates are given in parentheses. All values are expressed as fractions of the corresponding cell edge $\times 10^5$.

ever, the differences ranging from three standard deviations in the case of C-2 and C-9 and of C-14 and C-19 to nine standard deviations in the case of C-10a and C-12a. Such differences are significant and indicate that the molecule does depart somewhat from the perfect $2mm$ symmetry indicated by the bond lengths and angles. However, the maximum difference in $y$ coordinates of nine standard deviations corresponds to a difference of only 0.1 Å in the $y$ coordinates of atoms C-10a and C-12a. This is a relatively small effect, probably arising from the effects of the mutual repulsion of the bromine atoms being transmitted through the length of the molecule.

Thus dibromojanusene must be regarded as having very slightly distorted $2mm$ symmetry.

The question arises as to why this distortion does not appear in the bond length and bond angle data. The most probable answer is that at any one atomic center the effect is too small to be significant. However, the effects at each atomic center should be additive and should begin to be noticeable in quantities, such as atomic coordinates, which represent vector sums, but not in quantities such as bond lengths, which represent differences in vectors and where the effects will tend to subtract out.

## Experimental Section

**Crystal Data.**—Crystals of DBJ were supplied by D. C. Lewis. They were recrystallized from an alcohol–acetone mixture. The crystals were colorless and prismatic in habit.

The unit cell is monoclinic. The cell dimensions, determined from Weissenberg and precession photographs, are $a = 14.900$ Å ($\sigma$ 0.012 Å), $b = 9.157$ Å ($\sigma$ 0.011 Å), $c = 19.500$ Å ($\sigma$ 0.051 Å), and $\beta = 123.2°$ ($\sigma$ 0.4°), where $\sigma$ means standard deviation. The cell volume is 2227 Å$^3$.

The density of the crystals was determined by flotation in potassium iodide solution and found to be 1.626 g/cm$^3$. This density, together with the above cell volume, implies that the cell contains four DBJ molecules. The density calculated assuming four molecules per cell is 1.615 g/cm$^3$, in satisfactory agreement with the observed value.

The X-ray photographs showed the following systematic extinctions: $hkl$ absent with $l + k$ odd; $h0l$ absent with $h$ odd or with $l$ odd; $0k0$ absent with $k$ odd. In the monoclinic system these extinctions are consistent with two space groups, $Cc$ and $C2/c$. The space group $C2/c$ has a center of symmetry while $Cc$ does not. The crystal was shown to contain a center of symmetry by the Foster–Hargreaves test[4] and so the space group $C2/c$ was chosen. This assignment of space group was confirmed during the structure refinement. The space group $C2/c$ has eight equivalent positions. The asymmetric unit contained therefore one-half molecule, or 15 carbon atoms, 1 bromine atom, and the associated hydrogen atoms.

Intensities were collected on our automatic single crystal diffractometer CASCADE,[5] operated in the manual mode. Cu K$\alpha$ radiation was used. There were 2380 independent reflexions accessible to the copper radiation. Of these 1770 had intensities higher than twice background and were regarded as being observed. The data were corrected for Lorentz and polarization effects. An absorption correction, based on a program by Moseley,[6] was also applied and resulted in increases of intensity of up to 30%. The crystal used in the intensity collection had dimensions $0.35 \times 0.17 \times 0.14$ mm.

**Structure Analysis.**—The position of the bromine atom in the cell was determined from Harker sections to be (0.129, 0.250, 0.295). With a $y$ coordinate of 0.25, bromine atom contributes nothing to the intensity of any plane with $(k - l)$ odd. Thus the first Fourier synthesis, using the phases of the bromine atoms only, was calculated using as coefficients only those structure factors with $(k - l)$ even. The electron density distribution, so calculated, showed spurious lattice-centering, giving twice the number of peaks which would have been obtained otherwise. It was rather difficult to select from the electron density distribution that set of peaks corresponding to the carbon atoms. However, once the carbon atoms had been correctly identified, Fourier refinement proceeded smoothly. During the refinement, the bromine atom moved slightly away from $y = 0.25$ and began therefore to contribute to the phases of the planes with $k - l$ even. This contributed to the convergence of the Fourier refinement.

The Fourier refinement was followed by several cycles of least squares refinement, using, for the first three cycles, individual isotropic temperature factors, and thereafter individual anisotropic temperature factors. The function minimized was $\Sigma \omega(|F_o| - k|F_c|)^2$. The final value of the $R$ factor over the 1770 observed planes was 0.05. The atomic coordinates, anisotropic thermal parameters, and their corresponding estimated standard deviations, from the final cycle of refinement, are given in Tables V and VI.[7] The estimated radial standard deviation in the position of each of the atoms in the asymmetric unit are listed in Table VII.[7]

The least squares refinement was carried out on the CDC 6400 computer at the University of Colorado Computing Center, using the ORFLS program of Busing, Martin, and Levy.[8] The other calculations were carried out on our IBM 1620 computer in our laboratory.

(4) F. Foster and A. Hargreaves, *Acta Crystallogr.*, **16**, 1124 (1963).

(5) J. P. Cowan, W. M. Macintyre and G. J. Werkema, *ibid.*, **16**, 221 (1963).

(6) J. D. Moseley, M.S. Thesis, University of Colorado, 1964.

(7) Tables VI and VII will appear following these pages in the microfilm edition of this journal. In addition there will be included in the microfilm edition a diagram showing the contents of the unit cell of the crystal projected down the $b$ axis, a diagram illustrating the distortion of the molecule from 2-mm symmetry, and a table of observed and calculated structure factors. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to ccde number JOC-72-130. Remit check or money order for $5.00 for photocopy or $2.00 for microfiche.

(8) W. R. Busing, K. O. Martin, and H. A. Levy, ORNL-TM-305, Oak Ridge National Laboratory, Tenn., 1962.

# Chair–Twist Differentiation by Vibrational Spectroscopy

DAVID S. BAILEY AND JOSEPH B. LAMBERT*[1]

*Department of Chemistry and Materials Research Center, Northwestern University, Evanston, Illinois 60201*

The infrared and Raman spectra of 1,4-dimethylenecyclohexane (**1**), dispiro[2.2.2.2]decane (**2**), and cyclohexane-1,4-dione-$d_8$ (**3**-$d_8$) have been measured in the range 4000–400 cm$^{-1}$. The centrosymmetric chair form is confirmed for **1** and **2** (liquid phase) and the noncentrosymmetric twist boat for **3**-$d_8$ by the mutual exclusion rule, by the total number of fundamentals, and by the proportion of polarized Raman bands.

Vibrational spectroscopy offers a rich and, for the most part, untapped source of conformational information in the form of molecular symmetry determinations. This information is obtained from infrared and Raman spectra by application of two rules of group theory.[2] The principle of mutual exclusion states that, for molecules with a center of symmetry, all bands that are symmetry allowed in the infrared are symmetry forbidden in the Raman, and vice versa. As applied to six-membered rings, this rule allows a differentiation to be made between the centrosymmetric chair form A and the noncentrosymmetric boat forms B and C. A chair molecule would be expected to show no coincidences
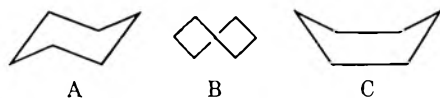


in the infrared and Raman spectra, whereas a boat or twist boat would exhibit only coincident bands. This method has been discussed in a recent application to the structure of cyclobutane photodimers,[3] and has previously been used to make a chair–boat distinction in cyclohexane-1,4-dione.[4,5]

The second rule states that bands from totally symmetrical vibrations are polarized in the Raman spectrum. The depolarization ratio $\rho$ is defined as the intensity of scattered light perpendicular to the xy plane ($I_\perp$), divided by the intensity of light parallel to the xy plane ($I_{||}$) (eq 1). For totally symmetrical

$$\rho = \frac{I_\perp}{I_{||}} \qquad (1)$$

vibrations arising from laser excitation, $\rho$ is less than 0.75, and sometimes nearly zero, whereas, for all other Raman-active vibrations, $\rho$ is close to 0.75. The number of polarized Raman bands depends on the symmetry group of the molecule. More symmetrical molecules have fewer allowed vibrations of the totally symmetrical class, and consequently fewer polarized Raman bands. Thus the symmetrical twist form ($D_2$) would have fewer polarized bands than the canted twist form ($C_2$, *vide infra*). The total number of fundamentals is also a predictable function of the symmetry group of the molecule, so that conformational information can be obtained from this source as well.

The compounds to which we have applied these techniques are 1,4-dimethylenecyclohexane (**1**), dispiro[2.2.2.2]decane (**2**), and cyclohexane-1,4-dione (**3**). Our interest in the methylene compound (**1**) arose from an *R*-value analysis that showed the molecule to be extremely flattened, but did not differentiate between the flattened chair and twist boat forms.[6] The spiro
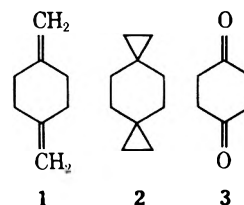


compound was of interest because of the formal similarity between the hybridization of cyclopropyl and ethylenic systems. *R*-Value analysis, however, demonstrated that this analogy does not hold up in a conformational sense.[7] The dione was included as a model compound for a twist boat. X-ray studies clearly showed the molecule to be in the unsymmetrical ($C_2$) twist-boat form in the solid phase,[8] and vibrational experiments[4,5] have confirmed the results in solution. More recent results in the gas phase, however, have cast some doubt on the solution work;[9,10] so we have gathered further vibrational data on the wholly deuterated derivative in order to confirm the previous conformational determination.[11]

## Results

The infrared and Raman spectra of compounds **1**, **2**, and **3**-$d_8$ were obtained as described in the Experimental Section. Neat liquids were used for the spectra of **1** and **2**, whereas the spectra of **3**-$d_8$ were obtained from methylene chloride solutions (infrared and Raman) and from a KBr pellet (infrared only). No data have been reported previously for the methylene and spiro compounds. The one existing vibrational study[5] of **3**-$d_8$ utilized a method of exchange[12] that would have produced only a mixture of incompletely deuterated materials. The present method ensured complete re-

(1) This work was supported by the National Science Foundation (Grant GP-22942), the Advanced Research Projects Agency of the Department of Defense through the Northwestern University Materials Research Center, and the Petroleum Research Fund, administered by the American Chemical Society (Grant 2970-AC4).

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(11) Recent conformational infrared–Raman work has also been reported for cyclohexane, K. B. Wiberg and A. Shrake, *Spectrochim. Acta, Part A*, **27**, 1139 (1971); for 1,4-dioxane, O. H. Ellestad, P. Klaboe, and G. Hagen, *ibid.*, **27**, 1025 (1971); for 1,4-dithiane, O. H. Ellestad, P. Klaboe, and G. Hagen, *ibid.*, **28**, 137 (1972); and for 1,4-diselenane, O. H. Ellestad, P. Klaboe, G. Hagen, and T. Stroyer-Hansen, *ibid.*, **28**, 149 (1972).

(12) G. Wood, E. P. Woo, and M. H. Miskow, *Can. J. Chem.*, **47**, 429 (1969).

placement of the hydrogens with deuterium. Tables I–III present the vibrational data in such a way as to

## TABLE I

INFRARED AND RAMAN SPECTRAL FREQUENCIES (CM$^{-1}$) AND INTENSITIES FOR 1,4-DIMETHYLENECYCLOHEXANE (1)

| Infrared | | Raman | |
|---|---|---|---|
| Frequency | Intensity | Frequency | Intensity |
| | | 182 | 20 (dp) |
| 402 | 80 | 401 | 50 (p) |
| | | 442 | 16 (dp) |
| | | 552 | 40 (p) |
| 695 | 90 | | |
| | | 703 | 2 |
| | | 757 | 100[a] (p) |
| 789 | 50 | 790 | 4 (dp) |
| 893 | 100[a] | 894 | 12 (p) |
| 945 | 10 | | |
| 983 | 40 | | |
| | | 996 | 31 (p) |
| 1015 | 10 | | |
| | | 1061 | 10 (p) |
| 1067 | 10 | | |
| | | 1134 | 8 (dp) |
| 1167 | 50 | | |
| 1188 | 40 | | |
| | | 1216 | 20 (p) |
| | | 1261 | 2 |
| 1313 | 50 | 1311 | 50 (p) |
| | | 1389 | 16 (p) |
| 1406 | 50 | | |
| | | 1420 | 16 (p) |
| | | 1436 | 2 (dp) |
| 1442 | 90 | | |
| 1455 | 50 (sh) | | |
| | | 1467 | 1 |
| 1524 | 10 | | |
| 1540 | 10 | | |
| | | 1589 | 2 |
| 1595 | 20 (sh) | | |
| 1628 | 20 (sh) | | |
| | | 1651 | 84 (p) |
| 1659 | 100[a] | | |
| | | 1671 | 15 (p) |
| 1680 | 30 (sh) | | |
| 1721 | 20 | | |
| 1735 | 10 | | |
| | | 1772 | 1 |
| 1791 | 40 | | |
| (2410)[b] | 10 | | |
| | | (2433)[b] | 1 |
| | | (2473) | 1 |
| | | (2557) | 1 (p) |
| | | (2587) | 1 (p) |
| | | (2601) | 3 (p) |
| (2618) | 10 | | |
| | | (2635) | 1 (p) |
| (2656) | 10 | | |
| (2711) | 10 | | |
| | | (2722) | 1 |
| | | (2778) | 1 |
| | | 2843 | 32 (p) |
| 2851 | 40 | | |
| | | 2888 | 16 (p) |
| 2913 | 40 | | |
| 2942 | 80 | 2944 | 30 (p) |
| 2989 | 40 | 2986 | 35 (p) |
| 3079 | 40 | 3075 | 8 (dp) |
| | | (3287) | 1 (p) |

[a] Base peak. [b] Numbers in parentheses are assumed not to be fundamentals; see text.

## TABLE II

INFRARED AND RAMAN SPECTRAL FREQUENCIES (CM$^{-1}$) AND INTENSITIES FOR DISPIRO[2.2.2.2]DECANE (2)

| Infrared | | Raman | |
|---|---|---|---|
| Frequency | Intensity | Frequency | Intensity |
| | | 184 | 6 (p) |
| | | 302 | 4 (dp) |
| | | 352 | 19 (p) |
| | | 469 | 16 (p) |
| 583 | 40 | | |
| 691 | 80 | 688 | 69 (p) |
| 779 | 12 | 783 | 4 (dp) |
| | | 802 | 3 (dp) |
| | | 854 | 25 (dp) |
| 870 | 12 | | |
| 894 | 95 | | |
| 934 | 100 | 933 | 60 (p) |
| | | 948 | 4 (dp) |
| 997 | 70 | | |
| 1010 | 100[a] | 1011 | 12 (p) |
| 1041 | 47 | 1039 | 4 (p) |
| | | 1091 | 55 (p) |
| | | 1144 | 3 (dp) |
| 1153 | 12 | | |
| | | 1169 | 7 (dp) |
| 1174 | 30 | | |
| | | 1193 | 22 (p) |
| | | 1278 | 4 (p) |
| 1291 | 80 | | |
| | | 1332 | 3 (p) |
| 1339 | 17 | | |
| | | 1353 | 60 (p) |
| 1383 | 55 | | |
| 1426 | 85 | 1428 | 29 (dp) |
| 1441 | 85 | 1437 | 25 (dp) |
| | | 1457 | 23 (p) |
| | | 1458 | 20 (p) |
| 1465 | 53 | | |
| (2041)[b] | 17 | | |
| (2077) | 8 | | |
| 2847 | 90 | 2849 | 27 (p) |
| | | 2874 | 10 (p) |
| 2888 | 72 | 2891 | 42 (p) |
| 2910 | 70 | | |
| 2922 | 100 | | |
| | | 2931 | 65 (p) |
| 2995 | 86 | 2994 | 100[a] (p) |
| 3065 | 83 | 3060 | 27 (dp) |
| | | 3071 | (sh) (dp) |

[a] Base peak. [b] Numbers in parentheses are assumed not to be fundamentals; see text.

emphasize spectral coincidences. Infrared and Raman bands that fall within 5 cm$^{-1}$ of each other are placed on a single line. Noncoincident lines are given separate entries. Polarized Raman lines ($\rho$ <0.75) are labeled "p" and lines exhibiting no polarization are labeled "dp."

## Discussion

In applying the rule of mutual exclusion, it has been customary to make comparisons only below 2000 cm$^{-1}$.[3] Above this value, overtones and combination bands are too common to make meaningful comparisons. The lower limit of infrared observations was 400 cm$^{-1}$; so our full range of comparisons is 2000–400 cm$^{-1}$.

Examination of the vibrational spectra of dimethylenecyclohexane (1) reveals 4 coincident bands out of a total of 21 possibilities. The limiting figure in this case is the number of bands (21) observed (2000–400 cm$^{-1}$)

TABLE III

INFRARED AND RAMAN SPECTRAL FREQUENCIES (CM$^{-1}$) FOR CYCLOHEXANE-1,4-DIONE-$d_8$ (3-$d_8$)

| Infrared[a] | Raman[b] | Infrared[a] | Raman[b] |
|---|---|---|---|
| | 395 (p) | 1043 (m) | 1047 |
| 417 (vs) | | 1065 (w) | |
| 429 (m) | 434 (dp) | 1074 (m) | 1074 |
| 450 (vs) | | 1089 (w) | 1089 |
| | 468 (dp) | 1125 (w) | |
| 541 (m) | 541 (p) | 1143 (m) | |
| 655 (s) | | 1188 (s) | |
| 675 (m) | 673 (vs, p) | 1226 (s) | 1225 |
| 686 (w) | 687[c] (s) | 1263 (m) | |
| 706 (m) | | 1297 (w) | |
| 759 (vs) | | 1712 (s) | 1712 (m, p) |
| 779 (vs) | 776 (p) | | 1728 (s, p) |
| | 786 (p) | | 2060 |
| 818 (w) | 814[c] | 2068 (w) | |
| 839[d] | 842 | | 2078 |
| 859[d] | | 2106 (w) | |
| | 890 | 2123 (w) | 2123 (m, p) |
| 929 (m) | 926 (m) | 2130 (m) | |
| 938[d] | 937 (m) | 2146[d] (w) | 2144 (vs, p) |
| 975 (m) | | 2165 (m) | |
| 1008 (m) | | 2186[d] (w) | |
| 1031 (m) | | | 2220 (s, p) |
| 1037 (m) | | 2228 (w) | 2233 (s, dp) |
| | | | 2245 (s, p) |
| | | | 2266 (m, p) |

[a] KBr pellet unless otherwise noted.  [b] CH$_2$Cl$_2$ solution unless otherwise noted: because of the strong solvent bands at about 730 and 1160 cm$^{-1}$, intensity and polarization measurements were difficult to obtain.  [c] CH$_3$OH solution.  [d] CH$_2$Cl$_2$ solution.

in the Raman spectrum; the corresponding number for the infrared spectrum is 23. The infrared and Raman spectra were obtained under identical conditions (neat liquid); so no problems due to solvent need be considered. This low ratio of coincidence (4 out of 21) is similar to that reported for cyclohexane (2 out of 14);[13] so the compound must be in the centrosymmetric chair conformation. The vibrational data, in conjunction with the nmr coupling constants,[6,14] are sufficient to describe the molecule as an extremely flattened chair. This conclusion is in agreement with the observation that a rate process ($\Delta G^{\ddagger} = 7.5$ kcal/mol) can be frozen out at extremely low temperatures.[15]

For the dispirodecane 2, 7 coincidences were observed out of 17 possibilities in the 400–2000-cm$^{-1}$ range. The number of infrared bands is limiting in this case. Although the coincidence ratio is higher than in the previous case, it is still consistent with a centrosymmetric chair conformation. The $R$-value analysis[7,16] shows that there is no flattening of the ring; so the conformation is best described as an undistorted chair. The barrier to ring reversal ($\Delta G^{\ddagger} = 10.9$ kcal/mol), in agreement with this conclusion, is very close to that of cyclohexane (10.2 kcal/mol).[17]

The 14 observed coincidences out of a possible 18 (the number of Raman bands) in the vibrational spectra of the deuterated dione 3 provide strong evidence for the

noncentrosymmetric boat or twist-boat conformation. The coincidence ratio is impressively large when it is considered that the infrared spectrum was measured from a KBr pellet, and the Raman spectrum was obtained from CH$_2$Cl$_2$ and CH$_3$OH solutions. The conclusion that the molecule lacks a center of symmetry is in agreement with previous vibrational work,[4,5] but does not support the recent suggestion (appropriate only to the vapor phase)[9] that the molecule is in a chair.

The total number of infrared and Raman fundamentals can be calculated by group theory from knowledge of the symmetry class of the molecule. The symmetry of each vibration can also be determined in order to calculate the number of polarized Raman bands expected for each symmetry type. These calculations are summarized in Table IV for the three molecules under study. To determine the approximate number of observed fundamentals for 1 and 2, all bands except those between 2000 and 2800 cm$^{-1}$ and certain obvious overtones were counted. Because the C–D stretch fundamentals fall between 2000 and 2200 cm$^{-1}$, all observed bands except those above 2300 cm$^{-1}$ were used for 3-$d_8$. The bands assumed not to be fundamentals are rendered in parentheses in Tables I–III.

For 1,4-dimethylenecyclohexane, approximately 28 infrared bands and 27 Raman bands are considered to be fundamentals, and 16 of the Raman bands are polarized. Because of the absence of infrared data below 400 cm$^{-1}$, the count of infrared fundamentals may be short. On the other hand, some of the counted bands may be overtones or combinations. Any conclusions we make should therefore be based on large differences in the numbers of fundamentals. The Raman data should be given greater weight, since our range of observation is larger and overtones are much lower in intensity. Happily, the diene 1 presents a very straightforward case. The number of observed infrared and Raman vibrations, and the number of polarized Raman bands are very close to the expectation for the $C_{2h}$ chair (Table IV): 28, 27, 16 observed *vs.* 27, 27, 15 predicted. The less symmetrical boat and twist forms predict a much larger number of fundamentals. The planar form, though not eliminated on the basis of number of fundamentals, is inconsistent with the number of polarized Raman bands (9 predicted *vs.* 16 observed).

The same ground rules, when applied to the dispiro compound 2, give 23 infrared fundamentals (out of 25 observed peaks) and 30 Raman fundamentals (out of 30), of which 19 are polarized. The chair form predicts 36 infrared and Raman fundamentals and 20 polarized Raman bands, whereas the boat and twist forms again have a much larger expected number of bands. The infrared count is probably low because of the unobserved region below 400 cm$^{-1}$. The data, particularly from the more important Raman spectra, are consistent with the chair form.

The data for the dione 3-$d_8$ are more difficult to treat in this manner. Only overtones and combination bands should be expected above about 2300 cm$^{-1}$. Below this point, 33 infrared peaks were observed from the KBr pellet, and a possible additional 5 from the CH$_2$Cl$_2$ solution. This number is far in excess of that possible for a chair, but it cannot differentiate between the $D_2$ (31) and $C_2$ (42) twist boats and the $C_{2v}$ boat (32).

(13) F. A. Miller and H. R. Golob, *Spectrochim. Acta*, **20**, 1517 (1964).

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TABLE IV
PREDICTED AND OBSERVED NUMBERS OF VIBRATIONAL FUNDAMENTALS

| Symmetry group | 1 | | | 2 | | | 3-$d_8$ | | |
|---|---|---|---|---|---|---|---|---|---|
| | Ir | R | P[a] | Ir | R | P[a] | Ir | R | P[a] |
| $C_s$ ($3n - 6$) | 54 | 54 | 54 | 72 | 72 | 72 | 42 | 42 | 42 |
| $C_{2h}$ (chair) | 27 | 27 | 15 | 36 | 36 | 20 | 21 | 21 | 12 |
| $D_2$ (symmetrical twist) | 40 | 54 | 14 | 53 | 72 | 19 | 31 | 42 | 11 |
| $C_2$ (tilted twist) | 54 | 54 | 28 | 72 | 72 | 37 | 42 | 42 | 22 |
| $C_{2v}$ (boat) | 41 | 54 | 15 | 55 | 72 | 20 | 32 | 42 | 12 |
| $D_{2h}$ (planar) | 22 | 27 | 9 | 28 | 36 | 11 | 17 | 21 | 7 |
| Observed | 28 | 27 | 16 | 23 | 30 | 19 | 33/38[b] | 25/27[c] | >12 |

[a] Number of polarized (totally symmetrical) Raman bands. [b] The first figure refers to data from the KBr pellet alone; the second includes additional bands observed in $CH_2Cl_2$ solution. [c] The first figure refers to data from $CH_2Cl_2$ solution alone; the second includes additional bands observed in $CH_3OH$ solution.



$D_2$          $C_2$
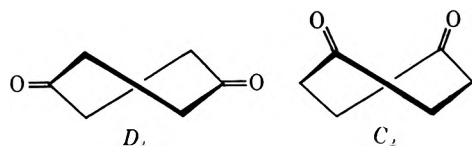
The Raman data are not so useful in this context, because the solvent bands mask too many peaks. Of the 25 peaks observed in $CH_2Cl_2$ (27 when the two additional bands in $CH_3OH$ are included) at least 12 are definitely polarized. Because polarization ratios could not be measured on some 10 peaks owing to solvent interference, the total number of polarized bands should greatly exceed the maximum number possible for the $C_{2v}$ boat or the symmetrical $D_2$ twist boat. More reliable data on crystalline material was not possible because of fluorescence. Because the number of polarized peaks expected for the $D_2$ (11) or $C_{2v}$ (12) forms and the $C_2$ form (22) is quite different, the method is potentially able to make the differentiation. We believe that our data point to the $C_2$ form, but a firm conclusion cannot yet be made.

**Summary.**—All evidence points to chair conformations for 1,4-dimethylenecyclohexane (1) and dispiro-[2.2.2.2]decane (2). The diene exhibits 4 coincidences out of 21 possibilities, the dispiro compound 7 out of 17. The total number of fundamentals and the number of polarized Raman bands are consistent with the chair rather than with any of the less symmetrical boat or twist forms. Cyclohexane-1,4-dione-$d_8$ (3) has 14 coincidences out of a possible 18, so that a non-centrosymmetric boat or twist form is indicated. This conclusion is confirmed by the total number of infrared fundamentals. The number of polarized Raman bands points toward the tilted twist form ($C_2$), rather than the symmetrical twist ($D_2$) or the classic boat ($C_{2v}$). The present data are not unambiguous in this latter conclusion because many of the Raman bands are masked by solvent peaks. These conclusions refer to the dominant conformational form of each molecule. The presence of minor forms cannot be excluded.

## Experimental Section

Infrared spectra were determined on a Beckman IR-9 spectrophotometer. Survey spectra were recorded at 200 cm$^{-1}$/min, and the frequency measurements were subsequently carried out at 8 cm$^{-1}$/min. The instrument was calibrated with a polystyrene film for each individual run. The liquids 1 and 2 were run as thin films on KBr plates. The dione 3 was run in a KBr pellet or in dilute $CH_2Cl_2$ solution. Frequencies of individual bands are accurate to ±1 cm$^{-1}$.

Raman spectra were determined on a laser Raman spectrophotometer described elsewhere,[18] using the 5141.7-Å emission of a 90-mW Argon ion Carlson Laboratory laser. Survey spectra were recorded initially, followed by redetermination of the frequency of each emission line at a slower scan rate or by manual variation of the monochrometer to determine maximum emission. Depolarization ratios were determined by maximizing the emission through a polarizing filter (parallel orientation) and then recording the spectrum again with the lens rotated 90° (perpendicular orientation). Intensities were determined either by photon counting at the emission maxima or by integration of the recorded spectra. The liquids 1 and 2 were examined without solvent in a 1-cm-diameter cell. The dione 3 was run as a 30% solution in $CH_2Cl_2$ and as a 25% solution in $CH_3OH$. The Raman spectra of the pure solvents were run prior to the determination of the dione spectrum. A solid disc of the dione gave only intense fluorescence. Frequencies of individual bands are accurate to ±1 cm$^{-1}$.

1,4-Dimethylenecyclohexane (1) was purchased from Chemical Samples Co. and used without further purification.

Dispiro[2.2.2.2]decane (2) was kindly supplied to us by Dr. J. L. Gosnell, Jr.[7]

Cyclohexane-1,4-dione-$d_8$ (3) was obtained by the acid-catalyzed exchange of the protons in cyclohexane-1,4-dione (Aldrich Chemical Co.) with $D_2O$ according to the procedure of Wood, *et al.*[12] By this method, 0.3 g of $PCl_5$ was dissolved in 15 ml of $D_2O$, and the solution was added to 6.0 g of the dione. The reaction was stirred at room temperature for 8 days and extracted into $CH_2Cl_2$. The solution was dried ($MgSO_4$) and evaporated to dryness. The recovered product was subjected to four such exchanges. The final product was 98.2% deuterated (85% $d_8$, 15% $d_7$ by mass spectrometry), mp 78–79° (lit.[12] mp 78–79°).

**Registry No.**—1, 4982-20-1; 2, 24518-94-3; 3-$d_8$, 23034-25-5.

(18) I. Wharf and D. F. Shriver, *Inorg. Chem.*, 8, 914 (1969).

# Some Observations on the Conductometric Method for Determining Solvolytic Rate Constants

Richard N. McDonald* and Gerald E. Davis[1]

*Department of Chemistry, Kansas State University, Manhattan, Kansas 66502*

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A number of observations and criteria on the use of the conductometric method for determining solvolytic rate constants are described and illustrated with several substrates. The solvents systems examined are 60% (v/v) aqueous dioxane, 60% (v/v) aqueous acetone, acetic acid, and buffered acetic acid. In general, our experiences show that this method gives smaller variances (factor of 2–3) in rate constants determined from duplicate kinetic runs than those obtained from the titrimetric method.

The present study was undertaken as part of our investigation into the solvolyses of derivatives of certain strained ring systems and substituted 2-azulylethanols. Since only limited amounts of these compounds were available due to time and costs of synthesis, a procedure was needed for determining their solvolysis rates with good accuracy and precision in a number of solvent systems with various leaving groups and using only a few milligrams of substrate. To this end, it was felt that the conductometric method with appropriate modifications would meet these requirements.

**Background of the Conductometric Method and Attended Errors.**[2]—Logically, the determination of reaction rates by changes in conductance of the reaction solution should be applicable to any unimolecular or bimolecular solution process where conducting (nonconducting) species are produced or consumed from nonconducting (conducting) substrates (SN1 and pseudo-first-order solvolyses) or different conducting species are produced compared to those consumed (most SN2 reactions). The fact that the rates can be followed by continuous monitoring of a single solution of substrate makes the conductometric technique potentially more desirable than the more standard titrimetric methods requiring aliquot sampling; the total volume of solution required per run should be potentially smaller in the former method. The precision of results from the conductometric method should also be better than those expected from titrimetric data in terms of the specifications and significant figures for data read-out on "research grade," commercially available conductance bridges.

Conductivity measurements have been used in determination of the acidity or basicity of weak acids or bases[3a] and the rates of ionic reactions occurring in ionizing solvents such as water.[3b] Many examples of saponification, diazotization, esterification, and molecular rearrangement have been investigated in this way. Despite the success of the conductometric method in such cases, it has found only limited use in following the rates of first-order and pseudo-first-order solvolyses.

In calculating reaction rate constants from conductivity measurements, the approximation is usually made that the change in conductance is a linear function of the concentration. The error this introduces depends on the solvent, the electrolyte, and the concentration range over which measurements are made.[4] An error of only 0.2% using this conductivity–concentration approximation was reported in the hydrolysis of methyl p-toluenesulfonate.[5] In determining the rates of solvolysis of some arylmethyl tosylates in various dioxane–water mixtures (60, 70, and 79.5%), it was shown that conductance was proportional to concentration below about $10^{-4}$ $M$; duplicate runs agreed within 3% of the mean value.[6] Similarly, a linear correlation was found for the conductance of aqueous acetone or aqueous ethanol solutions below $10^{-3}$ $N$ hydrochloric acid; an error of $\pm 0.2\%$ was obtained for triplicate determinations of the rates of solvolysis of some alkyl chloides from 0 to 35° in both media.[7] The conductance parameters for hydrochloric acid and p-bromobenzenesulfonic acid in various 2,2,2-trifluoroethanol–water mixtures were reported to follow the limiting conductance law in the concentration range below $2 \times 10^{-3}$ $M$ for solvents containing 3% or more water. The precision in the determination of rate constants in these solvents was $\pm 0.1\%$.[8]

Although work in the above polar solvents containing strong electrolytes has given good precision in the rate data, the results involving less polar solvents and/or weaker electroytes have been less satisfactory. In dimethylformamide at 30° errors of only $\pm 1\%$ were observed in the pseudo-first-order kinetics of certain bimolecular elimination reactions without the use of concentration–conductance corrections.[9] However, rate constants for the solvolyses of several arylmethyl chlorides in moist formic acid at 25° were considered to be accurate to $\pm 5\%$ even using concentration–conductance calibration curves.[10] The results reported for the unbuffered acetolyses of some alkyl nosylates showed that the errors averaged about $\pm 6\%$ for the conductometric rate constants without concentration–conductance correction compared to the results from titrimetric data.[11] Another report of unbuffered acetolyses gave $\pm 3\%$ errors in the conductometric rate constants compared to the rate constants obtained from titrimetric studies, but averages of rate

(1) NASA Research Fellow, 1967–1968.

(2) The references included in this section are not intended to be a comprehensive review of the literature on the conductometric method. Rather, they are given to illustrate uses of the technique.

(3) (a) G. Kortum, "Treatise on Electrochemistry," Elsevier, Amsterdam, 1965, p 265; (b) R. Livingston, "Technique of Organic Chemistry," Vol. 8, A. Weissberger, Ed., Interscience, New York, N. Y., 1951, p 65.

(4) B. L. Murr and V. J. Shiner, *J. Amer. Chem. Soc.*, **84**, 4672 (1962).

(5) R. E. Robertson, *Can. J. Chem.*, **33**, 1536 (1955).

(6) M. D. Bentley and M. J. S. Dewar, *J. Amer. Chem. Soc.*, **92**, 3991 (1970).

(7) W. M. Schubert and R. G. Minton, *ibid.*, **82**, 6188 (1960).

(8) (a) V. J. Shiner, W. Dowd, R. D. Fisher, S. R. Hartshorn, M. A. Kessick, L. Milakofsky, and M. W. Rapp, *ibid.*, **91**, 4838 (1969); (b) V. J. Shiner, R. D. Fisher, and W. Dowd, *ibid.*, **91**, 7748 (1969).

(9) W. M. Jones, T. G. Squires, and M. Lynn, *ibid.*, **89**, 318 (1967).

(10) M. J. S. Dewar and R. J. Sampson, *J. Chem. Soc.*, 2789 (1956).

(11) P. D. Bartlett and G. D. Sargent, *J. Amer. Chem. Soc.*, **87**, 1297 (1965).

constants from replicated run (2–12) by the conductometric method agreed with those determined by other methods.[12]

It is interesting that, when good precision in rate constants is required in solvolysis studies, such as in the determination of secondary deuterium isotope effects, the conductometric method is the one most successfully utilized.[4,13]

**Discussion of the Experimental Technique.**[14]—The conductivity cell used throughout this investigation was the M-D Mini-Cell[15] owing to its small (3 ml) working volume and cell constant of about 0.075 cm$^{-1}$. The cell was connected to a Beckman RC-18A conductivity bridge with external capacitance supplied by a Heath Model EUW-29 capacitance substitution box. A 2:1 sulfuric–nitric acid mixture was used to clean the cell;[16] the use of chromic acid causes contamination and should be avoided.[17] The shiny platinum electrodes in the cell gave a system with good stability at reasonably elevated temperatures and were readily cleanable when the solvent system was changed. Conditioning of the cell to the solvent under study was imperative for precise results.

The solvents used in this investigation were generally distilled twice in all-glass apparatus under nitrogen, and all manipulations involving these solvents were then carried out in a glove box in a nitrogen atmosphere. This was critical since simply transferring a solvent from one container to another in the laboratory atmosphere would drastically increase the observed conductance of that solvent; carbon dioxide is a probable culprit. The purity of the solvents was ascertained from their specific conductance values which are given in Table I. Water showed the largest deviation

### TABLE I
### SOME PHYSICAL PROPERTIES OF SOLVENTS AT 25°[a]

| Solvent | L (obsd), mhos/cm | L (lit.), mhos/cm |
|---|---|---|
| Water | $6.1 \times 10^{-7}$ | $5.8 \times 10^{-8}$ |
| Acetone | $5.5 \times 10^{-8}$ | $5.5 \times 10^{-8}$ |
| Dioxane | $<10^{-10}$ | $5.0 \times 10^{-15}$ |
| Acetic acid | $5.9 \times 10^{-9}$ [b] | $1.1 \times 10^{-8}$ |
| Acetic anhydride[c] | | $4.8 \times 10^{-7}$ |

[a] B. E. Conway, "Electrochemical Data," Elsevier, Amsterdam, 1952, p 12. [b] Measurement taken at 24.0°. Professor S. G. Smith (private communication) has found a similar result of 6.39 × 10$^{-9}$ mhos/cm at 25°. [c] This solvent was never measured by itself, but only in acetic acid solution.

from the literature value, but this difference was not large enough to interfere with the measured conductance readings during a run in a mixed solvent containing water.

The stability of the cells and solvent systems at elevated temperatures was determined to see what range of temperatures could be used. Table II lists

### TABLE II
### STABILITY OF SOLVENT SYSTEMS AT ELEVATED TEMPERATURES

| Solvent | Temp, °C | Reading, mhos/cm | % drift/hr[a] |
|---|---|---|---|
| 60% (v/v) aqueous acetone[b] | 25.00 | $4.146 \times 10^{-5}$ | 0.00 |
| | 50.00 | $5.515 \times 10^{-5}$ | 0.05 |
| | 70.00 | $6.620 \times 10^{-5}$ | 0.67 |
| | 90.00 | $7.502 \times 10^{-5}$ | 2.59 |
| Unbuffered acetic acid | 25.00 | $5.9 \times 10^{-9}$ | 0.00 |
| | 50.00 | $2.86 \times 10^{-8}$ | 0.71 |
| Buffered acetic acid[c] | 25.00 | $5.77 \times 10^{-7}$ | 0.00 |
| | 50.00 | $1.223 \times 10^{-6}$ | 0.00 |
| | 75.00 | $3.667 \times 10^{-6}$ | 0.00 |
| | 90.00 | $4.302 \times 10^{-6}$ | 0.00 |
| | 95.00 | $4.872 \times 10^{-6}$ | 0.02 |

[a] Per cent change in reading per hour. [b] Contained 1.198 × 10$^{-3}$ M 3,5-dinitrobenzoic acid. [c] Contained 1.227 × 10$^{-3}$ M potassium acetate.

the solvents and the temperatures investigated. Unbuffered acetic acid has presented many problems to workers[11,12,18] who have used this solvent in conductometric rate studies at elevated temperatures.[19]

The purity of the compounds to be studied was as important as the purity of the solvents. Since there was no convenient method of detecting trace amounts of conducting impurities in substrate samples, the standard methods of purification and analysis had to be employed. Solid derivatives were recrystallized repeatedly after reaching a constant melting point. This procedure generally ensured sufficient purity of the compound for it to be used in a kinetic determination.

The use of conductivity measurements in the determination of first-order rate constants requires that the conductivity precisely measure the concentration of starting material and/or product formed in the reaction at any time. Murr and Shiner[4] used an Onsager-type equation to represent the data on the conductance of hydrochloric acid in their ethanol–water mixtures. They found that the most time consuming aspect of this technique was the independent determination of the conductance parameters. This was avoided in the present study by simply constructing a correlation curve of specific conductance (L) vs. concentration (c) of the conjugate acid of the leaving group from about $1 \times 10^{-5}$ to $1 \times 10^{-3}$ M. One curve had to be constructed for each change in solvent, leaving group, and temperature. Figure 1 gives some representative plots for p-nitrobenzoic acid in 60% (v/v) aqueous acetone and 60% (v/v) aqueous dioxane. The data produced smooth curves indicating considerable ion pairing of the electrolyte.[20] Similar curved lines were found for p-toluenesulfonic acid in unbuffered acetic acid, and 3,5-dinitrobenzoic acid in 60% aqueous acetone. These correlation curves were used directly to determine the concentration of acid which corresponded to each specific conductance obtained during a kinetic run.

(12) H. A. Hammond and A. Streitwieser, *Anal. Chem.*, **41**, 2032 (1969).

(13) For example, see V. J. Shiner and R. D. Fisher, *J. Amer. Chem. Soc.*, **93**, 2553 (1971), and J. M. Harris, R. E. Hall, and P. v. R. Schleyer, *ibid.*, **93**, 2551 (1971), and references therein.

(14) B. L. Murr (Ph.D. Thesis, Indiana University, 1961) outlined the precautions and procedures necessary to obtain a precision of ±0.03% in conductometric rate constants in solvolysis studies with certain alkyl chlorides in aqueous ethanol at or near room temperature. These guidelines were very beneficial to the present study.

(15) Available from R-M Research Products, Inc., Manhattan, Kan.

(16) F. C. Mathers, *Chemist-Analyst*, **54** [13], 10 (1965).

(17) E. P. Laug, *Ind. Eng. Chem., Anal. Ed.*, **6**, 111 (1934).

(18) P. D. Bartlett, S. Bank, R. J. Crawford, and G. H. Schmid, *J. Amer. Chem. Soc.*, **87**, 1288 (1965).

(19) The point at which the stability of a solvent system should no longer be considered adequate depends on several factors including the rate of the reaction at that temperature and the magnitude in the spread of the points observed during the course of the reaction. Generally, a solvent system was not considered useful if the per cent drift per hour exceeded 1%.

(20) R. M. Fouss and F. Accascina, "Electrolytic Conductance," Interscience, New York, N. Y., 1959.

<div align="center">

Table III

Effect of the Use of Correlation Curves on Rate Constants[a]

</div>

| Compd | Registry no. | $10^4k$,[b] sec$^{-1}$ | Av $10^4k$,[c] sec$^{-1}$ | $10^4k$,[b] sec$^{-1}$ | Av $10^4k$,[c] sec$^{-1}$ | Error,[d] % |
|---|---|---|---|---|---|---|
| | | *——With correlation——* | | *——Without correlation——* | | |
| | | 60% (v/v) Aqueous Dioxane, 25.0° | | | | |
| α-(p-Tolyl)-γ-methylallyl p-nitrobenzoate | 36740-13-3 | 8.481 ± 0.012 | | 9.757 ± 0.047 | | |
| | | | 8.512 ± 0.032 | | 9.795 ± 0.038 | 15 |
| | | 8.544 ± 0.010 | | 9.833 ± 0.058 | | |
| | | 60% (v/v) Aqueous Acetone, 25.0° | | | | |
| α-(p-Tolyl)-γ-methylallyl p-nitrobenzoate | | 16.25 ± 0.02 | | 18.86 ± 0.09 | | |
| | | | 16.28 ± 0.04 | | 18.93 ± 0.07 | 17 |
| | | 16.32 ± 0.02 | | 18.99 ± 0.08 | | |
| | | 60% (v/v) Aqueous Acetone, 50.0° | | | | |
| α-Methyl-γ-(p-tolyl)allyl 3,5-dinitrobenzoate | 36740-14-4 | 7.560 ± 0.009 | | 9.294 ± 0.073 | | |
| | | | 7.512 ± 0.047 | | 9.135 ± 0.159 | 21 |
| | | 7.465 ± 0.010 | | 8.976 ± 0.090 | | |
| | | Unbuffered Acetic Acid, 49.8° | | | | |
| exo-Bicyclo[2.2.1]hept-2-yl tosylate | 959-42-2 | 4.405 ± 0.020 | | 5.677 ± 0.020 | | |
| | | | 4.402 ± 0.003 | | 5.596 ± 0.082 | 27 |
| | | 4.399 ± 0.018 | | 5.514 ± 0.019 | | |
| | | Buffered Acetic Acid, 50.0° | | | | |
| exo-Bicyclo[2.2.1]hept-2-yl tosylate | | 4.573 ± 0.009 | | 4.559 ± 0.010 | | |
| | | | 4.565 ± 0.008 | | 4.552 ± 0.007 | 0 |
| | | 4.558 ± 0.006 | | 4.545 ± 0.004 | | |

[a] Reference 22.   [b] Errors are standard deviations.   [c] Errors are maximum deviations from the average.   [d] Difference in av $10^4k$'s divided by av $10^4k$ with correlation.
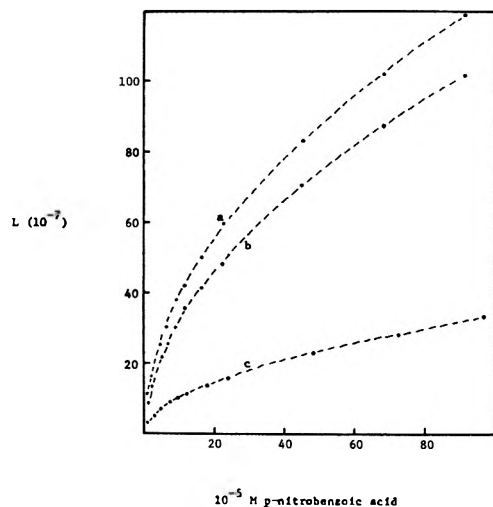


Figure 1.—Specific conductance of p-nitrobenzoic acid in (a) 60% (v/v) aqueous acetone at 35°, (b) 60% (v/v) aqueous acetone at 25.0°, and (c) 60% (v/v) aqueous dioxane at 25.0°.

Figure 2 shows the data for specific conductance *vs.* concentration of a potassium acetate–acetic acid solution with added increments of p-tolenensulfonic acid. No correlation curves were needed between $1 \times 10^{-5}$ and $5 \times 10^{-3}$ M acid in $6 \times 10^{-3}$ M buffer since conductance was directly proportional to concentration under these conditions.

Table III lists the rate constants calculated with and without the use of concentration–conductance correlation curves for five compounds in four different solvent systems. As can be seen, the only solvent system which gave acceptable results without the use of a correlation curve was buffered acetic acid.

**Discussion of Kinetic Data Obtained by the Conductometric Method.**—In Table IV the results of pairs of
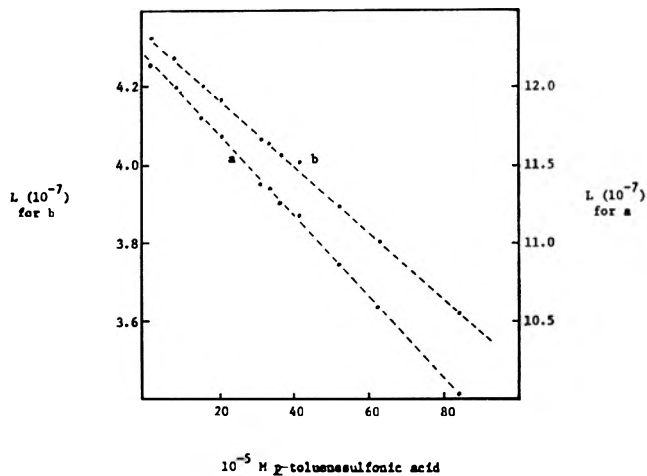


Figure 2.—Specific conductance of $6 \times 10^3$ M KOAc–HOAc with added p-toluenesulfonic acid at (a) 50.0° and (b) 25.0°.

kinetic runs determined conductometrically and titrimetrically on the substrate, but at different concentrations, are compared. The conductometric runs were prepared with $1 \times 10^{-3}$ M substrate and the titrimetric runs with $5 \times 10^{-3}$ M substrate. The runs in aqueous acetone and aqueous dioxane averaged about 1.5% higher than their corresponding titrimetric values. The single comparison in unbuffered acetic acid is not considered reliable since the titrimetric work was a single determination obtained several years ago prior to the use of the automatic titrator (see Experimental Section). The first three comparisons in buffered acetic acid gave an average difference of 0.5% with the conductometric rates generally being higher. These results are in agreement with the fact that the conductometric method generally gives higher rates than those observed titrimetrically.[4,7] The average per cent error for all except the last comparison

TABLE IV

COMPARISON OF CONDUCTOMETRIC AND TITRIMETRIC METHODS[a]

| Compd | Registry no. | Temp, °C | Conductometric $10^4k$,[b] sec⁻¹ | Av $10^4k$,[c] sec⁻¹ | Titrimetric $10^4k$,[b] sec⁻¹ | Av $10^4k$,[c] sec⁻¹ | Error,[d] % |
|---|---|---|---|---|---|---|---|
| | | | **60% (v/v) Aqueous Dioxane** | | | | |
| α-(p-Tolyl)-γ-methyl-allyl p-nitrobenzoate | | 25.0 | 8.481 ± 0.012 | 8.512 ± 0.032 | 8.538 ± 0.102 | 8.409 ± 0.129[f] | 1.2 |
| | | | 8.544 ± 0.010 | | 8.280 ± 0.111 | | |
| | | | **60% (v/v) Aqueous Acetone** | | | | |
| α-(p-Tolyl)-γ-methyl-allyl p-nitrobenzoate | | 25.0 | 16.25 ± 0.02 | 16.28 ± 0.04 | 16.60 ± 0.26 | 16.24 ± 0.37 | 0.3 |
| | | | 16.32 ± 0.02 | | 15.87 ± 0.24 | | |
| α-Methyl-γ-(p-tolyl)-allyl 3,5-dinitro-benzoate | | 50.0 | 7.560 ± 0.009 | 7.512 ± 0.047 | 7.338 ± 0.182 | 7.379 ± 0.041 | 3.1 |
| | | | 7.465 ± 0.010 | | 7.420 ± 0.201 | | |
| | | | **Unbuffered Acetic Acid** | | | | |
| exo-Bicyclo[2.2.1]hept-2-yl tosylate | | 49.8 | 4.405 ± 0.020 | 4.402 ± 0.003 | 4.494 ± 0.050[e] | | −2.1 |
| | | | 4.399 ± 0.018 | | | | |
| | | | **Buffered Acetic Acid** | | | | |
| exo-Bicyclo[2.2.1]hept-2-yl tosylate | | 25.0 | 0.2325 ± 0.0009 | 0.2330 ± 0.0006 | 0.2325 ± 0.0027 | 0.2315 ± 0.0010 | 0.6 |
| | | | 0.2336 ± 0.0010 | | 0.2305 ± 0.0030 | | |
| 2-(1-Azulyl)ethyl tosylate–TNB complex | 36740-15-5 | 35.0 | 1.926 ± 0.001 | 1.943 ± 0.017 | 1.950 ± 0.020 | 1.932 ± 0.018 | 0.5 |
| | | | 1.960 ± 0.001 | | 1.915 ± 0.010 | | |
| exo-Bicyclo[2.2.1]hept-2-yl tosylate | | 50.0 | 4.559 ± 0.010 | 4.552 ± 0.007 | 4.571 ± 0.075 | 4.562 ± 0.008 | −0.2 |
| | | | 4.545 ± 0.004 | | 4.554 ± 0.043 | | |
| 2-(3-Nitro-1-azulyl)-ethyl tosylate | 26154-61-0 | 90.0 | 0.9519 ± 0.0024 | 0.9515 ± 0.0005 | 1.029 ± 0.010 | 1.024 ± 0.005 | −7.6 |
| | | | 0.9510 ± 0.0014 | | 1.019 ± 0.010 | | |

[a] Reference 22. [b] Rate constants given with their standard deviations. [c] Average rate constants given with the maximum deviation from average. [d] Per cent error based on the conductometric value being correct. Sign of number is positive when conductometric value is higher. [e] C. E. Reineke, Ph.D. Thesis, Kansas State University, 1966; a value of $4.67 \times 10^{-4}$ sec⁻¹ was reported in ref 27. [f] Reference 21.

in Table IV was 1.1% indicating that this method gives results in close agreement with those obtained by the titrimetric method.

The major discrepancy in Table IV is the results for 2-(3-nitro-1-azulyl)ethyl tosylate whose difference in the conductometric and titrimetric rate constants is −7.6%. The difference in the results between the two methods is believed due to the smaller concentrations of substrate and buffer used in the conducto-metric determinations compared to those used in the titrimetric method and has been attributed to the presence of a special salt effect by potassium acetate.[23] This is similar though smaller in magnitude to the special salt effect by potassium acetate in the buffered acetolysis of 2-(p-anisyl)ethyl tosylate.[23] The data listed in Table V lists the buffered acetolysis data on 2-(p-anisyl)ethyl tosylate which we believe readily establishes this effect.[24]

Generally, the precision in obtaining rate constants increases when the spread in the observed bridge readings is increased during a kinetic run.[22] In Table VI are listed the spreads in conductance readings observed in kinetic runs using exo-bicyclo[2.2.1]hept-2-yl tosylate. The precision found in the runs in unbuffered acetic acid with this substrate is unusually good when compared to the precision obtained with other compounds under similar conditions.

In addition to the compounds listed in Tables III–V, we have determined the solvolysis rate constants for several other substrates (Table VII) by this conductometric technique to demonstrate the overall applicability of the method. Only three pairs of runs on two different compounds had a negative sign for the direction of the drift after 10 solvolytic half-lives. It is interesting to note that two of these compounds, 2-(5-methyl-1-azulyl)ethyl and 2-(4-methyl-1-azulyl)-ethyl tosylates, were comparatively unstable and difficult to work with even as their sym-trinitrobenzene complexes.[25,26] The remainder of the compounds were relatively stable and easily handled. The average drift for all determinations in this study was 0.8%. The higher temperature runs with 3-(4-azulyl)propyl nosylate probably indicate that we are close to the temperature limit of buffered acetic acid in the absence of better temperature control since they showed the largest per cent drift. It should also be noted

(21) R. A. Sneen, *J. Amer. Chem. Soc.*, **82**, 4261 (1960), reports $k = 7.40 \times 10^{-4}$ sec⁻¹ in 60 vol. % aqueous dioxane for α-(p-tolyl)-γ-methylallyl p-nitrobenzoate.

(22) All kinetic data in Tables III–VII are given to four significant figures even though in several cases the latter figures are statistically meaningless due to the errors involved.

(23) R. N. McDonald and J. R. Curtis, *J. Amer. Chem. Soc.*, **93**, 2530 (1971).

(24) Most electrolytes have a temperature coefficient of conductivity of about 2.5%/°C at around room temperature which increased with increasing temperature. The temperature effect on equilibria involving free ions and ion pairs and higher aggregates is difficult to approximate in unstudied systems. While a temperature control of ±0.01° was adequate for runs involving $1 \times 10^{-2}$ M substrate, kinetic runs with $5 \times 10^{-3}$ M substrate will require better bath temperature control to minimize errors at elevated temperatures.

(25) H. E. Petty, Ph.D. Thesis, Kansas State University, 1971.

(26) N. L. Wolfe, Ph.D. Thesis, Kansas State University, 1972.

## TABLE V
### BUFFERED ACETOLYSIS RATE DATA OF 2-(p-ANISYL)ETHYL TOSYLATE[a,b]

| Substrate (buffer), $10^{-3}$ M | Temp, °C | $10^4k$,[c] sec$^{-1}$ | Av $10^4k$,[d] sec$^{-1}$ | Error,[e] % |
|---|---|---|---|---|
| | | 1.361 ± 0.030[f] | | |
| 5.00 (6.00) | 95.00 ± 0.08 | | 1.412 ± 0.052 | |
| | | 1.464 ± 0.060[f] | | |
| | | 1.123 ± 0.002 | | |
| 1.02 (1.23) | 95.00 ± 0.01 | | 1.134 ± 0.012 | −24.3 |
| | | 1.146 ± 0.003 | | |
| | | 1.360 ± 0.004 | | |
| 4.94 (5.93) | 95.00 ± 0.01 | | 1.319 ± 0.041 | −7.1 |
| | | 1.278 ± 0.004 | | |

[a] Registry no. 5107-52-8.   [b] Reference 22.   [c] Rate constants given with their standard deviations.   Conductometric determinations unless otherwise specified.   [d] Average rate constants given with the maximum deviation from the average.   [e] Per cent error based on the titrimetric value being correct.   The sign of the per cent error is negative when titrimetric value is higher.   [f] Titrimetric determination.

## TABLE VI
### COMPARATIVE CONDUCTANCE ACETOLYSIS RATE DATA FOR exo-BICYCLO[2.2.1]HEPT-2-YL TOSYLATE[a]

| Substrate, $10^{-3}$ M | Buffer, $10^{-3}$ M | Temp, °C | $10^5L$,[b] mhos/cm | $10^5\Delta L$, mhos/cm | Av $10^4k$,[c] sec$^{-1}$ | Precision,[d] % |
|---|---|---|---|---|---|---|
| 1.06 | | 49.84 ± 0.01 | 8.21–16.27 | 8.06 | 4.402 ± 0.003 | 0.07 |
| 1.00 | 1.15 | 25.00 ± 0.01 | 42.76–35.23 | 7.53 | 0.2330 ± 0.0006 | 0.26 |
| 1.00 | 1.15 | 50.00 ± 0.01 | 119.5–100.8 | 18.7 | 4.552 ± 0.007 | 0.15 |
| 4.94 | 5.93 | 50.00 ± 0.01 | 307.5–250.8 | 56.7 | 4.618 ± 0.004 | 0.09 |

[a] Reference 22.   [b] Specific conductance range of kinetic runs.   [c] Average rate constants from duplicate runs given with the maximum deviation from the average.   [d] The error in the average rate constants (in c) expressed as per cent.

that specific conductance increased rather than decreased (see Table VI) during the course of the reaction with this nosylate ester.

The four sets of runs made with p-fluoro- and p-methylbenzyl tosylates in unbuffered acetic acid were carried out since these compounds appeared to be particularly problematical acetolyses.[12]   However, as can be seen in Table VII, the data for these compounds are excellent with the present technique.

In summary, we have found that the conductometric method for the determination of solvolytic reaction rate constants yields more readily duplicable values by a factor of better than 2 than are obtained, on the average, by titrimetric methods with a smaller sample size of substrate required and a reduced problem with substrate solubility if the solvent and sample are pure. As the kineticist's experience increases with this technique so should the precision of the kinetic data.

In all of the work here described, rough, "thumbnail" rate constants were determined for "new" substrates in a selected solvent system by titrimetric determinations on one or two sealed ampoules to establish reasonable solvolytic temperatures.   Solvent systems and leaving groups could then be varied to achieve the desired kinetic result.

## Experimental Section

**Substrate Preparation.**—The following section gives the known substrates prepared by literature procedures from the corresponding alcohols:   α-(p-tolyl)-γ-methylallyl OPNB, mp 42–44° (lit.[21] mp 44.5–46.5°);   exo-bicyclo[2.2.1]hept-2-yl OTs, mp 54–55° (lit.[27] mp 53.7–54.6°);   p-methylbenzyl OTs, mp 47–48° (lit.[28]

mp 57.9–58.5°);[29]   p-fluorobenzyl OTs, mp 42–42.5° (lit.[30] mp 48.5–52.5°);[29]   and 2-(p-anisyl)ethyl OTs, mp 38.5–39.0° (lit.[31] mp 35.5–36.6°).   The nmr spectra of these esters were in agreement with their assigned structures.

**α-Methyl-γ-(p-tolyl)allyl 3,5-Dinitrobenzoate.**—To a stirred, cooled solution of 300 mg (1.83 mmol) of α-methyl-γ-(p-tolyl)-allyl alcohol[21] in 3 ml of pyridine was added 428 mg (1.85 mmol) of 3,5-dinitrobenzoyl chloride (recrystallized from benzene) in small portions.   After stirring for an additional 1.5 hr, the mixture was poured into ice–water, extracted with ether which was washed with saturated sodium bicarbonate solution and water, and then dried (MgSO$_4$).   Evaporation of the solvent gave a yellow oil which crystallized from ether–hexane.   Recrystallization fron this solvent mixture gave 528 mg (80%) of the desired product as a white, waxy solid:   mp 77.5–78.5°;   ir (Nujol) 5.80 μ (C=O);   nmr (CDCl$_3$, internal TMS) τ 0.78 (s, ODNB H's, 3), 2.71 (m, Ar H's, 4), 3.39 (m, vinyl H's, 2), 4.02 (m, methine, 1), 7.66 (s, tolyl CH$_3$, 3), and 8.38 (d, CH$_3$, 3).

*Anal.*   Calcd for C$_{18}$H$_{16}$N$_2$O$_6$:   C, 60.67;   H, 4.53.   Found:   C, 60.70;   H, 4.71.

**exo- and endo-Bicyclo[2.2.0]hex-2-yl 3,5-Dinitrobenzoates.**—Using the above procedure, 50 mg (0.51 mmol) of a mixture of exo- and endo-bicyclo[2.2.0]hexan-2-ol (64:36) and 324 mg (1.53 mmol) of 3,5-dinitrobenzoyl chloride in 1 ml of dry pyridine yielded 111 mg (75%) of fine white needles of product after recrystallization from ether–pentane:   mp 89–92°;   ir (Nujol) 5.81 μ (C=O);   nmr (CDCl$_3$, internal TMS) τ 0.87 (s, ODNB H's, 3), 4.49 (m, C$_2$ H's, 1), and 6.30–8.53 (m, 8).

*Anal.*   Calcd for C$_{13}$H$_{12}$N$_2$O$_6$:   C, 53.43;   H, 4.14.   Found:   C, 53.31;   H, 4.20.

Although we were unable to determine the exact composition of this mixture of derivatives due to the similarities of the C$_2$ H's chemical shifts of the exo and endo isomers, this is of little consequence kinetically since $k_{endo}/k_{exo} > 10^7$.[32]   The rate constant was calculated using the infinity "titer" and was linear through 2 half-lives.

(27) P. von R. Schleyer, M. M. Donaldson, and W. E. Watts, *J. Amer. Chem. Soc.*, **87**, 375 (1965).

(28) J. K. Kochi and G. S. Hammond, *ibid.*, **75**, 3443 (1953).

(29) As was previously pointed out by Streitwieser, *et al.*,[30] melting points of these benzylic tosylates are difficult to reproduce and are not a good criterion of purity.

(30) A. Streitwieser, H. A. Hammond, R. H. Jagow, R. M. Williams, R. G. Jesaitis, C. J. Chang, and R. Wolf, *J. Amer. Chem. Soc.*, **92**, 5141 (1970).

(31) S. Winstein, C. R. Lindgren, H. Marshall, and L. L. Ingraham, *ibid.*, **75**, 147 (1953).

(32) R. N. McDonald and G. E. Davis, *ibid.*, **94**, 5078 (1972).

TABLE VII

OTHER COMPOUNDS SOLVOLYZED BY THE CONDUCTOMETRIC METHOD[a]

| Compd | Registry no. | Temp, °C (±0.01°) | $10^4k$,[b] sec$^{-1}$ | Av $10^4k$,[c] sec$^{-1}$ | Precision,[d] % | Drift,[e] % |
|---|---|---|---|---|---|---|
| *60% Aqueous Acetone* | | | | | | |
| *endo*-Bicyclo[2.2.0]hex-2-yl 3,5-dinitro-benzoate | 36736-32-0 | 50.00 | 2.539 ± 0.015 | | | |
| | | | | 2.524 ± 0.015 | 0.59 | 1.46 |
| | | | 2.509 ± 0.007 | | | |
| | | 70.00 | 19.42 ± 0.08 | | | |
| | | | | 19.52 ± 0.10 | 0.51 | 1.00 |
| | | | 19.62 ± 0.01 | | | |
| *Unbuffered Acetic Acid* | | | | | | |
| *p*-Methylbenzyl tosylate | 4606-98-8 | 49.84 | 24.80 ± 0.04 | | | |
| | | | 24.65 ± 0.04 | 24.70 ± 0.10[f] | 0.40 | 1.57 |
| | | | 24.61 ± 0.06 | | | |
| | | | 24.74 ± 0.02 | | | |
| *p*-Fluorobenzyl tosylate | 3859-77-6 | 49.84 | 1.257 ± 0.008 | | | |
| | | | 1.260 ± 0.011 | 1.256 ± 0.006[g] | 0.48 | 1.82 |
| | | | 1.258 ± 0.012 | | | |
| | | | 1.250 ± 0.012 | | | |
| *Buffered Acetic Acid* | | | | | | |
| Mixture of 2-(5- and 2-(7-methyl-1-azulyl)ethyl tosylate–TNB complex | 36740-18-8 (5-) 36826-33-2 (7-) | 25.00 | 1.986 ± 0.005 | | | |
| | | | | 2.020 ± 0.035 | 1.73 | −1.35 |
| | | | 2.055 ± 0.005 | | | |
| 2-(4-Methyl-1-azulyl)ethyl tosylate–TNB complex | 36740-19-9 | 25.00 | 1.100 ± 0.004 | | | |
| | | | | 1.113 ± 0.013 | 0.92 | −1.45 |
| | | | 1.126 ± 0.006 | | | |
| | | 45.00 | 10.96 ± 0.01 | | | |
| | | | | 10.94 ± 0.02 | 0.18 | −0.20 |
| | | | 10.93 ± 0.01 | | | |
| 2-(6-Methyl-3-nitro-1-azulyl)ethyl tosylate | 36740-20-2 | 70.00 | 0.2519 ± 0.0003 | | | |
| | | | | 0.2512 ± 0.0007 | 0.28 | 0.60 |
| | | | 0.2505 ± 0.0004 | | | |
| | | 90.00 | 1.888 ± 0.002 | | | |
| | | | | 1.886 ± 0.002 | 0.11 | 0.35 |
| | | | 1.884 ± 0.004 | | | |
| 3-(4-Azulyl)propyl nosylate | 36740-21-3 | 100.00 | 1.757 ± 0.007 | | | |
| | | | | 1.725 ± 0.032 | 1.86 | 2.75 |
| | | | 1.693 ± 0.008 | | | |
| | | 120.00 | 12.35 ± 0.06 | | | |
| | | | | 12.54 ± 0.19 | 1.52 | 2.30 |
| | | | 12.73 ± 0.08 | | | |

[a] Reference 22. [b] Rate constants given with their standard deviations. [c] Average rate constants given with the maximum deviation from the average. [d] The error in the average rate constants expressed as per cent. [e] Observed drift expressed as a per cent of the infinity conductance. The sign is positive if the value proceeded in the same direction the points were changing during the run. [f] $k = 2.54 \times 10^{-3}$ sec$^{-1}$; ref 12. [g] $k = 1.23 \times 10^{-4}$ sec$^{-1}$; ref 12.

ω-(1-Azulyl)alkyl Tosylates.—The syntheses of these tosylates were carried out by standard procedures from the corresponding ω-(1-azulyl)alkanols[23,33] and will be reported in detail elsewhere. Each of these tosylate esters gave a satisfactory elemental analysis and the expected, characteristic nmr spectrum.

The inseparable mixture of 2-(5- and 2-(7-methyl-1-azulyl)-ethyl OTs was prepared by tosylation of the mixture of the corresponding ethanols obtained by β-hydroxyethylation of 5-methylazulene.[33] No deviation from linearity of the solvolysis rate was observed through 2 solvolytic half-lives which is the result expected from very similar methyl group effects at these two ring positions.

Titrimetric Method.—The rates for such solvolytic reactions were followed by potentiometric titrations of aliquots removed from sealed ampoules using a Metrohm E436D automatic titrator. In general, 12–15 points were determined through 2 solvolytic half-lives with two to three infinity ($10t_{1/2}$) points. Rate constants were calculated by a computer program RATSOL2 written in PL/I language for the IBM 360/50 computer by Professor K. Conrow, which gives essentially identical results as those from the LSKIN1 program,[34] and utilized experimental infinity titers.

Conductometric Method.—All of the rate measurements made using this method utilized a Beckman RC-18A conductivity

bridge operating at 3000 Hz using shielded cables to connect the bridge to the M-D Mini-Cell;[15] added capacitance, when needed for low conducting solutions, was provided by a Heath EUW-29 capacitance substitution box. Bath control was ±0.01° using a bath oil.

All solvent handling, solution preparations, and cell loading were carried out in a nitrogen atmosphere glove box (dry conditions for nonaqueous solvents). The cell was rinsed five to eight times with the solvent to be used in the kinetic run and then two to three times with 2-ml portions of the substrate solution, filled, and sealed. (Filling and emptying of the cell were accomplished using a 12-in. flexible Teflon needle attached to a 5-ml all-glass syringe.) The cell was removed from the glove box, attached to the arm of the stirring apparatus, and lowered into the bath, and the stirrer was started. After allowing a few minutes for temperature equilibration, the first conductance reading was recorded as time zero. All further readings were made by setting the bridge at a value further along in the direction that the readings were changing and recording the time when the bridge was balanced with the conductance of the solution in the cell. In general, these bridge values were chosen to give 90–100 equally spaced points over the first 2 solvolytic half-lives. After this time, stirring was discontinued. To obtain the infinity point, stirring was begun 5 min before this point was to be taken.

To determine the amount of drift which occurred during a kinetic run, the cell was left in the constant temperature bath for a further convenient number of half-lives (2–4) and the conduc-

(33) R. N. McDonald and H. E. Petty, *J. Org. Chem.*, **37**, 2957 (1972).

(34) D. F. DeTar and C. E. DeTar in "Computer Programs for Chemistry," Vol. I, D. F. DeTar, Ed., W. A. Benjamin, New York, N. Y., 1968.

tance reading recorded. By noting the direction of any drift and its magnitude, and assuming the drift to be constant throughout the run, the corrected infinity point was calculated. Rate constants were then calculated using the RATSOL2 computer program (see above). In several runs, we have plotted the concentrations of substrate from the computer output and found excellent first-order behavior over the 2 half-lifes examined.

Using the above procedure with the M-D Mini-Cell,[15] 30 ml of $10^{-3}$ $M$ substrate solution is adequate to produce *duplicate* rate constants at *two* temperature and potentiometrically determined infinity titer checks at *both* temperatures.

# Preparation of 3-(Hydroxymethyl)-4,4-dimethylpentanoic Acid γ-Lactone

Andrew DeBoer* and John A. Hunter[1]

*Department of Chemistry, University of Wyoming, Laramie, Wyoming 82070*

*Received July 14, 1972*

3-(Hydroxymethyl)-4,4-dimethylpentanoic acid γ-lactone can be prepared in 62% overall yield in four steps from ethyl 3-hydroxy-3,4,4-trimethylpentanoate. The latter was dehydrated to give a mixture of α,β- and β,γ-unsaturated esters which upon bromination with NBS yielded ethyl (Z)-3-(bromomethyl)-4,4-dimethyl-2-pentenoate. Thermal cyclization of the bromo ester produced 3-*tert*-butyl-2-buten-1,4-olide, which was hydrogenated to give the γ-lactone.
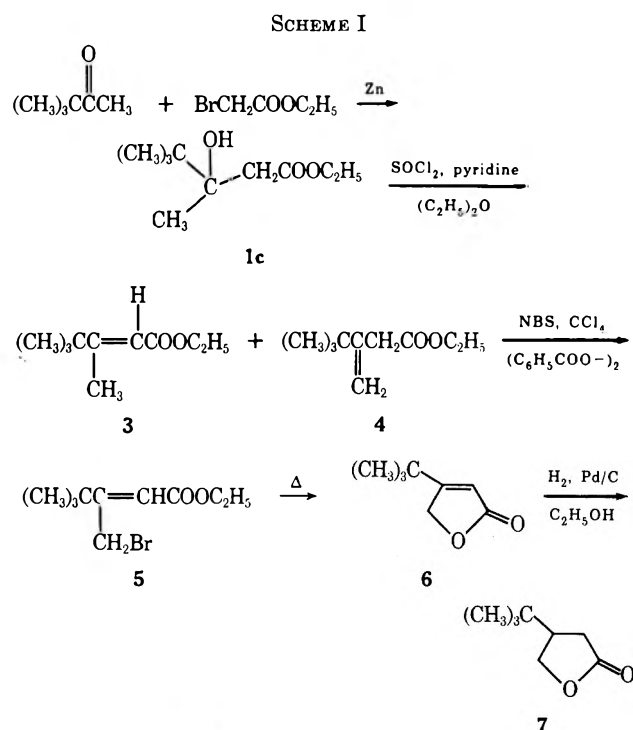
While preparing a number of conformationally biased compounds, 3-(hydroxymethyl)-4,4-dimethylpentanoic acid γ-lactone (7) was required as part of a synthetic scheme. It has been shown on several occasions[2a–c] that the material obtained from the dehydration of ethyl 3-hydroxy-3,4,4-trimethylpentanoate (1c) gives



1a, R = H
b, R = CH₃
c, R = C₂H₅

2
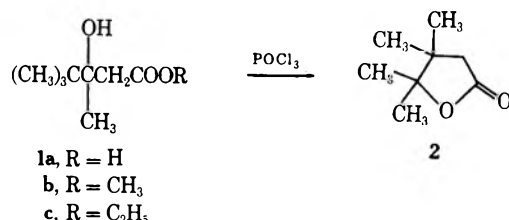
4-hydroxy-3,3,4-trimethylpentanoic acid γ-lactone (2) rather than 7 as originally thought.[2d] We have synthesized 7 in 62% yield from 1c and now summarize our work.

The lactone 7 was prepared by the route shown in Scheme I. Using the procedure of Newman[2] and Heilman,[3] the hydroxy ester 1c was dehydrated in good yield to give the two unsaturated esters 3 and 4 in equal amounts. After separation by preparative glc, ir, mass spectrum, and nmr analysis readily identified the compounds as 3 and 4. This result agrees with the structural revision offered by Newman and Patrick[4] for the products which were obtained from the dehydration of 1b.

The mixture of unsaturated esters 3 and 4 obtained by the dehydration of 1c gave only 5 upon free-radical bromination using NBS. Compounds similar to 5 have been converted into 2-buten-1,4-olides by treating them with concentrated HCl under reflux.[5] Our pre-

(1) NSF Undergraduate Research Participant.
(2) (a) A. W. Burgstahler and D. E. Wetmore, *J. Org. Chem.*, **26**, 3516 (1961); (b) C. Metzger, D. Borrmann, and R. Wegler, *Chem. Ber.*, **100**, 1817 (1967); (c) T. B. Patrick and M. S. Newman, *J. Org. Chem.*, **34**, 3714 (1969); (d) M. S. Newman and R. Rosher, *J. Org. Chem.*, **9**, 221 (1944).
(3) R. Heilmann and R. Glenat, *Bull. Soc. Chim. Fr.*, 1586 (1955).
(4) M. S. Newman and T. B. Patrick, *J. Amer. Chem. Soc.*, **92**, 4312 (1970).
(5) M. U. S. Sultanbawa, P. Veeravagu, and T. Padmanathan, *J. Chem. Soc.*, 1262 (1960).

**Scheme I**



liminary studies indicated that the allylic bromide 5 could be converted into the unsaturated lactone 6 simply by heating for a few minutes at 220°. In addition, 80% of the theoretical amount of bromoethane was isolated, but the volatile distillate from the pyrolysis reaction (see Experimental Section) fumed when exposed to the air, undoubtedly because of the HBr present. Ethene was not looked for in this reaction but presumably was also formed.

The bromo ester 5 was assigned the Z configuration. The structural assignment is by no means definitive, since it is possible that the conditions of the thermal reaction or the HBr produced could cause isomerization from (E)-5 to (Z)-5 before ring closure.

The thermal reaction then provided an excellent route to 5 and subsequently to 6. The lactone 7 was finally obtained by low-pressure hydrogenation of 6.
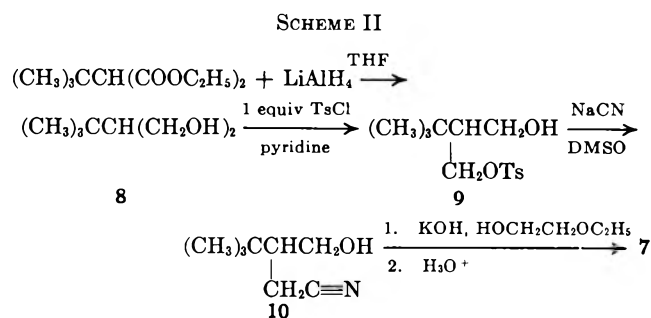
The lactone **7** was also prepared by the route shown in Scheme II. It is more laborious but does serve as a check on the proposed structure.

SCHEME II

$$(CH_3)_3CCH(COOC_2H_5)_2 + LiAlH_4 \xrightarrow{THF}$$

$$(CH_3)_3CCH(CH_2OH)_2 \xrightarrow[\text{pyridine}]{\text{1 equiv TsCl}} (CH_3)_3CCHCH_2OH \xrightarrow[\text{DMSO}]{\text{NaCN}}$$
$$\underset{\text{8}}{} \qquad \underset{\underset{\text{9}}{CH_2OTs}}{}$$

$$(CH_3)_3CCHCH_2OH \xrightarrow[\text{2. } H_3O^+]{\text{1. KOH, HOCH_2CH_2OC_2H_5}} \mathbf{7}$$
$$\underset{\underset{\text{10}}{CH_2C\equiv N}}{}$$

The lactone **7** was reduced with $LiAlH_4$ to give 2-*tert*-butyl-1,4-butanediol, which was identical in all respects

$$\mathbf{7} + LiAlH_4 \xrightarrow{THF}$$

$$HOCH_2\overset{+}{C}HCH_2CH_2OH \longleftarrow H_5C_2OOC\overset{+}{C}HCH_2COOCH_5$$
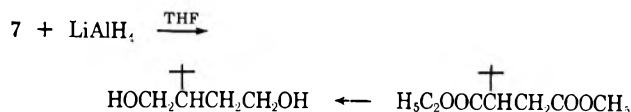
with the product obtained by $LiAlH_4$ reduction of diethyl 2-*tert*-butylsuccinate.[6]

There have been several cases in which **7** has been postulated in addition to those already cited. In two instances **2** was actually isolated.[7]

A more recent reference suggests that **7** can be prepared by allowing allyl alcohol and *tert*-butyllithium to react and treating the adduct with $CO_2$.[8]

## Experimental Section

Boiling points are uncorrected and unless otherwise noted were observed at 580 mm. Melting points were determined using a Mel-Temp melting point apparatus and are corrected. Ir spectra were obtained using a Perkin-Elmer Model 621 spectrophotometer. The nmr spectra were run on a Varian HA-100 spectrometer using $CDCl_3$ or $CCl_4$ as solvents and tetramethylsilane as an internal standard. The nmr data are reported as chemical shifts in δ units followed by s = singlet, d = doublet, t = triplet, q = quartet, or m = multiplet, and the relative number of protons attributable to the particular signal is reported. Mass spectra were determined on a Varian-MAT CH-5 spectrometer. The mass spectral data are reported as $m/e$ (for $M^+$ and major fragment ions) followed by per cent relative abundance. Varian Aerograph Models A90-P3 and 1200 were used for the glc analysis. Reagents were obtained from regular commercial sources unless otherwise noted. $MgSO_4$ was used as the drying agent.

**Ethyl 3-Hydroxy-3,4,4-trimethylpentanoate (1c).**—The synthesis was carried out in 77% yield according to the procedure of Newman and Rosher,[2] bp 47° (0.05 mm) [lit.[2] bp 104–107° (18 mm)].

**Dehydration of Ethyl 3-Hydroxy-3,4,4-trimethylpentanoate.**— The mixture of unsaturated esters **3** and **4** was prepared in 90% yield, bp 65–73° (6 mm) [lit.[3] bp 80–83° (12 mm)], by the $SOCl_2$–pyridine dehydration of **1c** using the method outlined by Heilman and Glenat.[3] The product mixture was analyzed on an 8 ft × 0.25 in. column packed with 15% SE-30 on 60/80 Chromosorb P at 150°. Compounds **3** and **4** were present in equal amounts with **4** having the shorter retention time. Preparative gc gave pure **3** and **4**. The spectral properties of **3** are as follows: ir, $\nu_{C=O}$ 1718, $\nu_{C=C}$ 1633 cm$^{-1}$ (liquid film); nmr δ 1.06 (s, 9 H), 1.21 (t, 3 H), 2.09 (d, 3 H, $J$ = 1.8 Hz), 4.00 (q, 2 H), 5.59 (q, 1 H, $J$ = 1.8 Hz); mass spectrum $m/e$ (rel intensity) 170 (7), 128 (36), 126 (36), 109 (32), 97 (58), 81 (44), 47 (33), 55 (85), 43

(46), 41 (100), 39 (81), 29 (84). The spectral properties of **4** are as follows: ir $\nu_{C=O}$ 1740, $\nu_{C=C}$ 1638 cm$^{-1}$ (liquid film); nmr δ 1.02 (s, 9 H), 1.20 (t, 3 H), 2.90 (m, 2 H), 4.02 (q, 2 H), 4.78 (m, 1 H), 4.02 (m, 1 H); mass spectrum $m/e$ (rel intensity) 170 (6), 109 (19), 96 (28), 83 (60), 82 (15), 81 (37), 69 (19), 67 (24), 57 (22), 55 (90), 43 (27), 41 (82), 39 (44), 29 (100). For ir and nmr data of the corresponding methyl esters see ref 4. Pure **3** can be prepared by the condensation of sodium diethyl carboethoxymethylphosphonate and pinacolone.[9]

**Ethyl (Z)-3-(Bromomethyl)-4,4-dimethyl-2-pentenoate (5).**— Both pure **3** and the mixture, **3** and **4**, gave **5** after reaction with NBS in the presence of $(C_6H_5COO-)_2$ in $CCl_4$ under reflux. A typical experiment is given. A mixture of **3** and **4** (41 g, 0.24 mol), NBS (43 g, 0.24 mol), and $(C_6H_5COO-)_2$ (1 g) in 250 ml of $CCl_4$ was heated under reflux for 48 hr. The succinimide was removed by filtration and the filtrate was concentrated by rotary evaporation to give crude **5**. Distillation of the crude product gave 49.5 g (82%) of **5**: bp 68° (0.04 mm); ir $\nu_{C=O}$ 1720 cm$^{-1}$ (liquid film); nmr δ 1.18 (s, 9 H), 1.26 (t, 3 H), 4.10 (q, 2 H), 4.49 (s, 2 H), 5.76 (s, 1 H); mass spectrum $m/e$ (rel intensity) 250 (12), 248 (12), 205 (21), 203 (18), 155 (54), 127 (38), 123 (25), 109 (22), 95 (38), 57 (66), 55 (33), 43 (44), 41 (79), 39 (43), 29 (100), 27 (38).

**3-*tert*-Butyl-2-buten-1,4-olide (6).**—The bromo ester **5** (49.5 g, 0.198 mol) was placed in a 250-ml flask equipped with a reflux air condenser. A take-off head attached to a water-cooled condenser was placed on top of the air condenser. The water condenser was in turn connected to an adapter and flask which was cooled in an ice-water bath. The entire system was purged with $N_2$ and the reaction flask was then heated at 220° for 30 min. During the heating period the reaction was monitored by ir by periodically removing a drop and examining the C=O region of the ir spectrum. In addition, the rate at which $C_2H_5Br$ collected in the receiver flask was an indication of the progress of the reaction. After cooling the crude product, it was distilled to give 23.1 g (84%) of **6**: bp 60° (0.02 mm); ir $\nu_{C=O}$ 1789 and 1757 (characteristic of 2-buten-1,4-olides[10]), $\nu_{C=C}$ 1630 cm$^{-1}$ (liquid film); nmr δ 1.17 (s, 9 H), 4.71 (d, $J$ = 2 Hz, 2 H), 5.62 (t, $J$ = 2 Hz, 1 H); mass spectrum $m/e$ (rel intensity) 140 (4), 125 (19), 110 (12), 96 (23), 95 (58), 81 (27), 67 (79), 57 (46), 41 (100), 39 (67).

**3-(Hydroxymethyl)-4,4-dimethylpentanoic Acid γ-Lactone (7).** —The butenolide **6** (10 g, 0.072 mol) was hydrogenated at 45 psi in 100 ml of ethanol using 1.5 g of 5% Pd/C as the catalyst. The reaction mixture was diluted with petroleum ether (bp 30–35°), the catalyst was removed by filtration, and the filtrate was diluted with $H_2O$ and continuously extracted with petroleum ether. The petroleum ether extract was dried and concentrated to give 11.2 g of crude product. Distillation gave 9.8 g (98%) of **7**: bp 45° (0.02 mm) (mp between 0 and 10°); ir $\nu_{C=O}$ 1785 cm$^{-1}$; nmr δ 0.88 (s, 9 H), 2.28 (m, 3 H), 4.06 (m, 2 H); mass spectrum $m/e$ (rel intensity) 142 (8), 127 (7), 97 (4), 86 (100), 69 (28), 57 (87), 41 (40).

**Reduction of 7 with $LiAlH_4$.**—A solution of the lactone (2.0 g, 0.0141 mol) in 2 ml of THF was added dropwise to a slurry of $LiAlH_4$ (0.402 g, 0.011 mol) in 10 ml of THF under an atmosphere of $N_2$ while keeping the reaction vessel immersed in an ice-water bath. After the addition had been completed, the reaction mixture was allowed to warm to room temperature and stirred for an additional 18 hr. Water was added to destroy excess $LiAlH_4$ followed by acidification with 10% $H_2SO_4$. The product was extracted with ether. The ether extract was dried and concentrated. The crude product was distilled to give 1.8 g (87%) of 2-*tert*-butyl-1,4-butanediol, bp 85° (0.02 mm), which was identical (ir and nmr) with material obtained from the $LiAlH_4$ reduction of diethyl 2-*tert*-butylsuccinate.[6]

**2-*tert*-Butyl-1,3-propanediol (8).**—Diethyl *tert*-butylmalonate[11] (25 g, 0.116 mol) in 60 ml of THF was added dropwise to a suspension of $LiAlH_4$ (5.3 g, 0.142 mol) in 100 ml of THF at 5° under $N_2$. After the addition had been completed, the reaction mixture was stirred at room temperature for 4 hr. The excess $LiAlH_4$ was destroyed by the addition of ethanol. Ether was added and the mixture was acidified with 10% aqueous $H_2SO_4$. NaCl was added and the layers were separated. The aqueous layer was extracted three times with ether. The organic solutions were combined,

(6) V. K. Andersen and J. Munch-Petersen, *Acta Chem. Scand.*, **16**, 947 (1962).

(7) (a) Y. Maroni-Barnaud and J. E. DuBois, *Bull. Soc. Chim. Fr.*, C-27 (1953); (b) W. J. Hickinbottom, A. A. Hyatt, and M. B. Sparke, *J. Chem. Soc.*, 2529 (1954).

(8) J. K. Crandall and A. C. Clark, *Tetrahedron Lett.*, 325 (1969).

(9) M. J. Jorgenson and T. Leung, *J. Amer. Chem. Soc.*, **90**, 3769 (1968).

(10) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962, p 45.

(11) (a) H. F. Van Woerden, *Recl. Trav. Chim. Pays-Bas*, **82**, 920 (1963); (b) E. L. Eliel, R. O. Hutchins, and M. Knoeber, *Org. Syn.*, **50**, 38 (1970).

washed with saturated NaCl solution, dried, and concentrated on the rotary evaporator to give 12.5 g (80%) of white crystals. Recrystallization from CCl₄ gave 7.0 g of 8, mp 58–58.5° (lit.[11a] mp 58–59°). A second crop was obtained from the mother liquors.

**2-*tert*-Butyl-3-*p*-toluenesulfonoxy-1-propanol (9).**—The diol 8 (7 g, 0.053 mol) and *p*-toluenesulfonyl chloride (10.05 g, 0.053 mol) were dissolved in 100 ml of pyridine. The solution was placed in the refrigerator for 3 days. The reaction mixture was poured onto ice–water and the product was extracted with ether. The ether extract was washed successively with dilute HCl, saturated NaHCO₃, and H₂O. The ether solution was dried and concentrated on the rotary evaporator to give 14 g (92%) of crude monotosylate 9, which contains some ditosylate: nmr of 9, δ 0.86 (s, 9 H), 2.44 (m, 1 H), 2.40 (s, 3 H), 3.60 (m, 2 H), 4.04 (m, 2 H), 7.26 (m, 2 H), 7.66 (m, 2 H).

**3-*tert*-Butyl-4-hydroxybutyronitrile (10).**—Sodium cyanide (2.9 g, 0.059 mol) was added to a solution of the crude monotosylate 9 (14 g) in 50 ml of DMSO. The mixture was stirred at room temperature for 6 days and was then poured on ice–water. The product was extracted with ether. Concentration of the ether extract yielded 6.1 g (88%, assuming that the 14 g of crude tosylate was all 9) of crude 10, which was distilled to give 4.9 g of product: bp 72° (0.08 mm); ir ν_OH 3500, ν_C≡N 2255 cm⁻¹ (liquid film); nmr of 10, δ 0.95 (s, 9 H), 1.6 (m, 1 H), 2.46 (m, 2 H), 3.00 (s, OH), 3.68 (m, 2 H). The nmr spectrum suggests the presence of about 20% of 3-*tert*-butylglutaronitrile. The dinitrile undoubtedly arose from the ditosylate impurity in 9. The presence of the ditosylate in 9 could not be unequivocally established from the nmr spectrum of crude 9. 3-*tert*-Butyl-1,5-pentanedioic acid is, however, isolated from the hydrolysis of the nitrile mixture, confirming the presence of the dinitrile in the hydroxynitrile 10. See the preparation of 7 from 10 which follows.

**3-(Hydroxymethyl)-4,4-dimethylpentanoic Acid γ-Lactone (7) from 3-*tert*-Butyl-4-hydroxybutyronitrile (10).**—The procedure for the basic hydrolysis of nitriles outlined by Sandler and Karo[12] was used. The product was isolated by extraction with ether. The ether extract was washed with H₂O and then dried and the ether was removed on the rotary evaporator. The crude product was dissolved in ether–pentane and cooled. 3-*tert*-Butyl-1,5-pentanedioic acid (1 g) precipitated and was removed by filtration. The mother liquors were concentrated to give 2.5 g of 7 which had physical properties, *i.e.*, boiling point and ir and nmr spectra, identical with those obtained for 7 synthesized by another route (*vide supra*).

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# Rearrangement of Dihalocyclopropanes Derived from Some 6,7-Dihydrobenzo[b]thiophenes

CLAUDE V. GRECO* AND VINCENT G. GROSSO[1]

*Department of Chemistry, St. John's University, Jamaica, New York 11432*

1,1-Dihalocyclopropanes 10 have been prepared from 6,7-dihydrobenzo[b]thiophenes 4 derived from 4-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene (2) through formation of either enol ethers 4a and 4b or dehydration of the tertiary alcohols 5. These alcohols were obtained by reduction of 2 with sodium borohydride or Grignard reagents. The dihalocarbene adducts 10 rearranged with or without an organic base to afford 8H-cyclohepta[b]-thiophenes 11.

The 1-thiaazulenium cation (the thienotropylium cation 1, Scheme I) was reported[2a] to possess unusual stability relative to tropylium and the isoelectronic benzotropylium cations.[2b] Since this discovery, the expected publications describing other representatives of 1 have not appeared.[3] These two factors led us to consider the synthesis of substituted 1-thiaazulenium cations. The preparation of some 8H-cyclohepta[b]-thiophenes as possible precursors of such cations constitutes the subject of this report.

The 4,4-dialkoxy-4,5,6,7-tetrahydrobenzo[b]thiophenes 3a and 3b (Scheme I) were obtained by heating 4-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene (2)[4] under reflux with the appropriate alcohol, a twofold molar excess of trialkyl orthoformate, and a catalytic amount of *p*-toluenesulfonic acid (TsOH). These ketals, un-stable in air at room temperature, slowly eliminated alcohol to produce the respective 4-alkoxy-6,7-dihydrobenzo[b]thiophenes, 4a and 4b. The rate of conversion of 3a,b to 4a,b was enhanced by heating 3a,b with TsOH for 10 min. The enol ethers 4a,b required refrigeration under nitrogen to prevent reversion to the ketone 2.

Treatment of 2 with sodium borohydride in ethanol gave an 81% yield of the alcohol 5a, which readily underwent acid-catalyzed dehydration to 6,7-dihydrobenzo[b]thiophene (4c). Alkenyl-substituted thiophenes are known to exhibit instability leading to polymerization.[5] Likewise, 4c polymerized so rapidly that a correct elemental analysis was prevented. The initial report[6] on the reduction of 2 with methylmagnesium bromide stated that only 4-methyl-6,7-dihydrobenzo[b]thiophene (4d) or the exocyclic isomer, 4-methylene-4,5,6,7-tetrahydrobenzo[b]thiophene (6) were produced. Subsequent publications[7,8a] described

(1) Taken, in part, from the doctoral dissertation of V. G. G., St. John's University, 1971.

(2) (a) R. G. Turnbo, D. L. Sullivan, and R. Pettit, *J. Amer. Chem. Soc.*, 86, 5630 (1964); see also D. L. Sullivan and R. Pettit, *Tetrahedron Lett.*, 401 (1963); (b) H. H. Rennhard, G. Modica, W. Simon, E. Heilbronner, and E. Eschenmoser, *Helv. Chim. Acta*, 40, 957 (1957).

(3) Derivatives of the isomeric 2-thiaazulenium cation have been prepared by M. Winn and F. G. Bordwell, *J. Org. Chem.*, 32, 1610 (1967), from the precursor, 2-thiaazulen-6-ones, and were found to be more stable than 1.

(4) L. F. Fieser and R. G. Kennelly, *J. Amer. Chem. Soc.*, 57, 1611 (1935).

(5) P. Cagniant and G. Merle, *C. R. Acad. Sci., Ser. C*, 267, 156 (1968).

(6) D. A. H. Taylor, *J. Chem. Soc.*, 2767 (1959).

(7) M. Kloetzel, J. Little, and D. Frisch, *J. Org. Chem.*, 18, 1511 (1953).

(8) (a) M. Maillet and M. Sy, *C. R. Acad. Sci., Ser. C*, 264, 1193 (1967). (b) For a detailed study on this type of disproportionation with dihydronaphthalenes, see J. P. Quillet, A. Duperrier, and J. Dreux, *Bull. Soc. Chim. Fr.*, 255 (1967), and J. Jaques and H. B. Kagan, *ibid.*, 128 (1956).

SCHEME I

**1**

**2**

$\xrightarrow{\text{HC(OR)}_3}$
$\overline{\text{TsOH, ROH}}$

**3a**, R = CH₃
**b**, R = CH₃CH₂

NaBH₄
or
RMgX

−ROH

**5a**, R = H
**b**, R = CH₃
**c**, R = Ph

$\xleftarrow[-H_2O]{H^+}$

**4a**, R = OCH₃
**b**, R = OCH₂CH₃
**c**, R = H
**d**, R = CH₃
**e**, R = Ph

**5b** $\xrightarrow{\text{SOCl}_2}$ **7** $\xrightarrow{\text{KOH, EtOH}}$ **6** + **4d**

**6** $\xrightarrow{\text{S, heat}}$

**4e** $\xrightarrow{\text{S, heat}}$ **9**    **8**
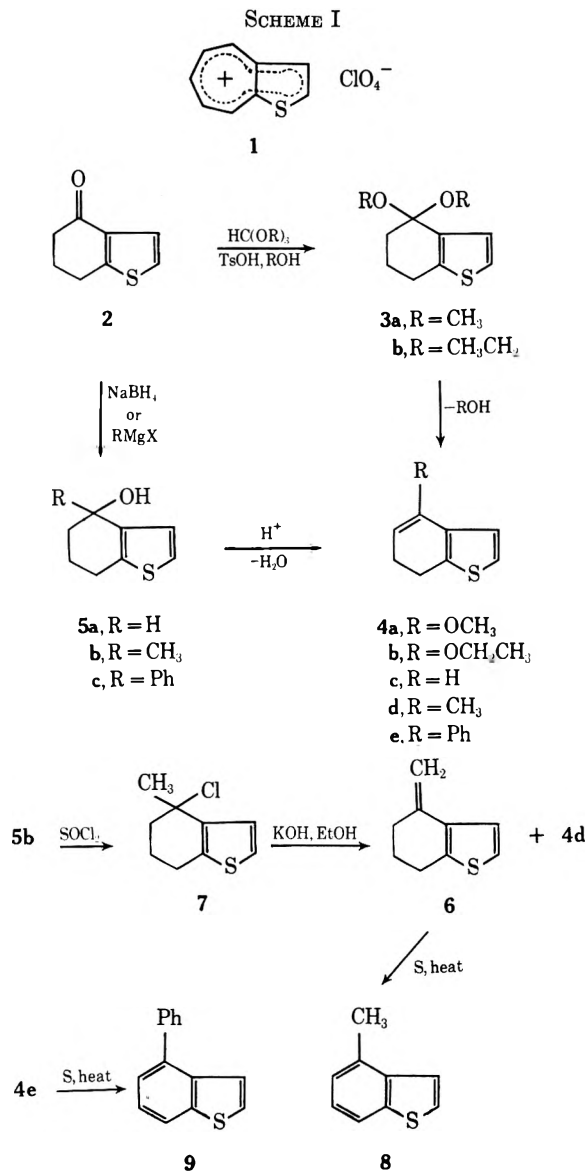
only the isolation of alcohol **5b**. This discrepancy simply resulted from the decomposition of the magnesium bromide complex of the alcohol **5b**, which we found afforded a 90% yield of **5b** if decomposed below 0° while at room temperature the alkenes **4d** and **6** were the only products. Dehydration of **5b** with hot glacial acetic acid gave **4d** and **6** in the isomer ratio of 2.3 (glc determination). Our attempt to minimize the vinylidene olefin **6** through conversion of **5b** to 4-chloro-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene (**7**) with thionyl chloride followed by dehydrohalogenation also resulted in a mixture of **4d** and **6** with an isomer ratio of 1.9. Any of these mixtures could be separated by preparative gas chromatography. Either the separated components or the mixture of isomers **4d** and **6** gave 4-methylbenzo[b]thiophene (**8**) upon dehydrogenation with sulfur.[7] 4-Hydroxy-4-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene (**5c**) was obtained essentially as described,[7] again if the Grignard complex was decomposed below 0°. At room temperature a subsequent dehydration produced the cycloalkene **4e**.

The dehydration of **5c** with acidic reagents was reported[8a] to yield five products. We isolated only two of these, namely, the dihydrobenzothiophene **4e** and 4-phenylbenzo[b]thiophene (**9**). These products prob-

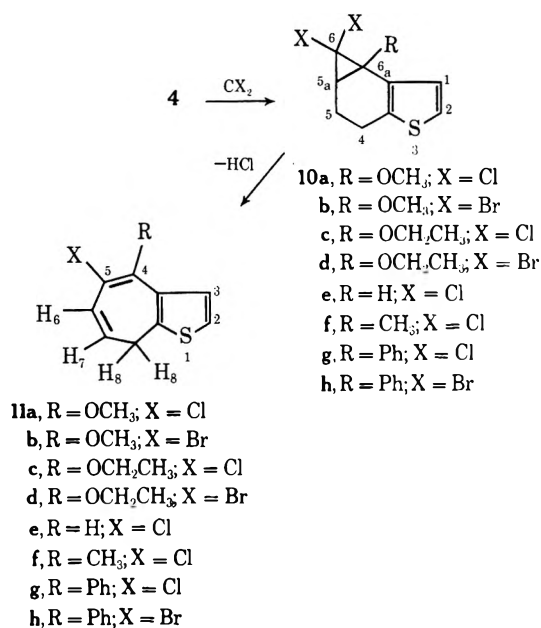ably arise from a disproportionation between two molecules of **4e** or **4e** and the carbonium ion generated from **5c**.[8b] Dehydrogenation of **4e** with sulfur gave the benzothiophene **9**.

The use of carbene intermediates for the synthesis of a variety of carbocyclic and heterocyclic systems is well documented.[9,10] The work of Parham and his co-workers[11] with cyclic enol ethers was especially pertinent to our study as well as rearrangements of other 7,7-dihalobicyclo[4.1.0]heptanes.[12-14] The stereospecific cis addition[15] of dichlorocarbene (sodium methoxide and ethyl trichloroacetate[16] or potassium *tert*-butoxide and chloroform[15,17]) to the cyclic vinyl ethers **4a** and **4b** readily afforded the crude 6,6-dichloro-5,5a,6,6a-tetrahydro-6a-alkoxy-4*H*-cyclopropa[e][1]benzothiophenes, **10a** and **10c**, as dark brown oils (see Scheme II).[18]

SCHEME II

**4** $\xrightarrow{\text{CX}_2}$

$\xrightarrow{-\text{HCl}}$

**10a**, R = OCH₃; X = Cl
**b**, R = OCH₃; X = Br
**c**, R = OCH₂CH₃; X = Cl
**d**, R = OCH₂CH₃; X = Br
**e**, R = H; X = Cl
**f**, R = CH₃; X = Cl
**g**, R = Ph; X = Cl
**h**, R = Ph; X = Br

**11a**, R = OCH₃; X = Cl
**b**, R = OCH₃; X = Br
**c**, R = OCH₂CH₃; X = Cl
**d**, R = OCH₂CH₃; X = Br
**e**, R = H; X = Cl
**f**, R = CH₃; X = Cl
**g**, R = Ph; X = Cl
**h**, R = Ph; X = Br

Their thermolability prevented purification and characterization. Likewise, the adducts **10b** and **10d** were obtained with bromoform and potassium *tert*-butoxide[17] but proved to be less stable[19] and offered no advantage in the rearrangements (*vide infra*). The addition of dichlorocarbene to the very unstable cycloalkene **4c** *possibly* yielded the adduct **10e**, which we were unable to characterize because of its instability. This was contrasted with the adduct of **10f**, which was sufficiently stable to be purified by fractional distillation. With the phenyl substituent in **4e**, a very stable adduct **10g** formed which was purified by distillation and subse-

(9) W. E. Parham and E. E. Schweizer, *Org. React.*, **13**, 55 (1956).

(10) W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1964, Chapter 8.

(11) W. E. Parham, R. W. Soeder, J. R. Throckmorten, K. Kuncl, and R. M. Dodson, *J. Amer. Chem. Soc.*, **87**, 321 (1965), and preceding papers in this series.

(12) D. G. Lindsay and C. B. Reese, *Tetrahedron*, **21**, 1673 (1965).

(13) H. E. Wynberg, *J. Org. Chem.*, **24**, 264 (1959).

(14) G. C. Robinson, *ibid.*, **29**, 3433 (1964).

(15) P. S. Skell and A. Y. Garner, *J. Amer. Chem. Soc.*, **78**, 5430 (1956).

(16) W. E. Parham and E. E. Schweizer, *J. Org. Chem.*, **24**, 1733 (1959).

(17) W. v. E. Doering and A. K. Hoffmann, *J. Amer. Chem. Soc.*, **76**, 6162 (1954).

(18) For a preliminary account of our effort in this area, see V. G. Grosso and C. V. Greco, *Chem. Commun.*, 771 (1970).

(19) This difference in stability between dichloro- and dibromocarbene adducts was first observed with the 7,7-dihalobicyclo[4.1.0]heptanes.[11,12]

quent recrystallization from pentane. Both compounds **10f** and **10g** were completely characterized by elemental and spectral analysis (see Experimental Section). It is of interest to note that the corresponding dibromocyclopropane, **10h**, was found thermally unstable and could not be purified.

The dichlorocyclopropanes described here showed no precipitation with alcoholic silver nitrate[20] at room temperature and failed to react with methanolic sodium methoxide.[21]

The rearrangement of the dihalocyclopropane adducts **10a–d** with or without an organic base gave 8*H*-cyclohepta[b]thiophenes **11a–d**. The results and conditions for these reactions are summarized in Table I. The ring expansions of **10a** and **10c** were accompanied by large amounts of polymerization products. In order to suppress this undesirable side reaction and increase the yield of the cyclohepta[b]thiophenes we took advantage of the increased thermolability of adducts **10b** and **10d** to facilitate the rearrangements at lower temperatures.[22] However, a study of the rearrangement of adducts **10a–d** at constant temperature with pyridine or triethylamine (see Table I) showed that the dichloro-

TABLE I

REARRANGEMENT OF DIHALOCYCLOPROPANES
10 TO 8*H*-CYCLOHEPTA[b]THIOPHENES 11

| Dihalo adduct | R | X | Base[a] | Temp, °C | Time, hr | Yield,[b,c] % |
|---|---|---|---|---|---|---|
| 10a | CH₃O | Cl | A | 150–155 | 0.5 | 58.9 |
|  |  |  | B | 115–116 | 6 | 57.4 |
|  |  |  | C | 89–91 | 48 | 50.2 |
|  |  |  | D | 120–125 | 0.25 | 40.0 |
| 10b | CH₃O | Br | A | 120–130 | 0.5 | 26.4 |
|  |  |  | B | 115–116 | 4 | 38.1 |
|  |  |  | C | 89–91 | 24 | 34.2 |
|  |  |  | D | 70–80 | 0.25 | 21.7 |
| 10c | CH₃CH₂O | Cl | A | 190–200 | 0.5 | 20.0 |
|  |  |  | B | 115–116 | 5 | 48.0 |
|  |  |  | C | 89–91 | 48 | 45.0 |
|  |  |  | D | 125–140 | 0.25 | 40.0 |
| 10d | CH₃CH₂O | Br | A | 125–135 | 0.5 | 30.3 |
|  |  |  | B | 115–116 | 3 | 35.4 |
|  |  |  | C | 89–91 | 24 | 31.7 |
|  |  |  | D | 70–75 | 0.25 | 25.9 |
| 10f | CH₃ | Cl | A | 190–200 | 0.5 | 34.7 |
|  |  |  | D | 240–250 | 0.5 | 17.1 |
| 10g | C₆H₅ | Cl | A | 150–170 | 0.5 | 62.2 |
|  |  |  | D | 190–200 | 0.5 | 38.6 |
| 10h | C₆H₅ | Br | A | 150–160 | 0.5 | 25.1 |
|  |  |  | D | 200–210 | 0.5 | 16.5 |

[a] A, quinoline; B, pyridine; C, triethylamine; D, neat oil. [b] Per cent yields of cycloheptathiophenes **11a–d** are based on the original alkenes **4a** and **4b**, since the adducts were not purified. The yields of **11f–h** are based on the pure adducts **10f–h**. The products 11 turn dark if exposed to air. [c] Boiling points for products at 0.10 mm: **11a**, 111–115°; **11b**, 120–124°; **11c**, 87–91°; **11d**, 101–105°; **11f**, 104–106°; **11g**, 130–134°; **11h**, 135–140°.

carbene adducts **10a** and **10c** were better precursors for preparing the alkoxycycloheptathiophenes.

The freshly distilled 5-chloro-4-alkoxy-8*H*-cyclohepta[b]thiophenes **11a** and **11c** are stable for long periods if refrigerated under nitrogen; otherwise they polymerize at room temperature on exposure to air. The analytical samples, obtained by preparative glc, showed the confirmatory spectral data (see Experimental Section). The structures of **11a–d** were particularly evident from the nmr spectra, which showed, in addition to alkoxy group and thiophene ring absorptions, a sharp doublet ($\delta$ 6.00–6.08) for the 6-methine proton, a multiplet (5.40–5.47) for the 7-methine hydrogen, and a sharp doublet (3.08–3.16) for the two methylene protons at position eight. The observed shift in absorption of these latter protons compared to the cycloheptatriene methylene hydrogens ($\delta$ 2.20)[23] can be ascribed to paramagnetic shielding by the adjacent thiophene ring.

Our initial synthetic plan envisioned hydrolysis of **11a** to the $\alpha$-halo ketone **12** (Scheme III) which after

SCHEME III
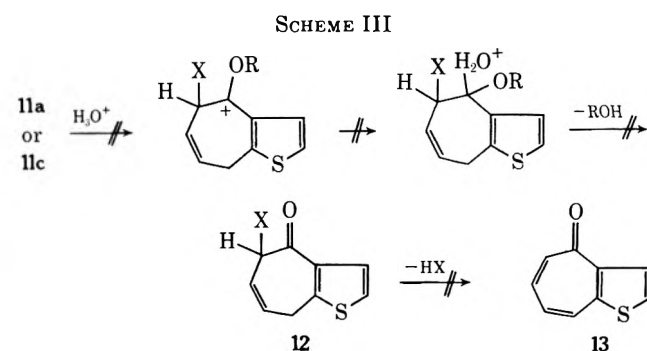


dehydrohalogenation would yield 1-thiaazulen-4-one (**13**). Derivatives of **1** would have been obtained by applying the procedure of Winn and Bordwell[3] to the ketone **13**. While no reports on the hydrolysis of cyclic $\beta$-haloalkenyl ethers are available, the acyclic analogs do undergo hydrolysis.[24] Neither **11a** or **11c** responded to mild acid hydrolysis and more drastic conditions led to polymers. Also, the 2,4-dinitrophenylhydrazone of **12** could not be obtained from either **11a** or **11c**.[25] This resistance to hydrolysis may be attributed to conjugation of the enol ether with the thiophene ring.

Our attention was then directed to the rearrangement of adducts **10e–h**. The inability to observe any change of adduct **10e** to **11e**, by either neat thermal degradation or by refluxing with an organic base below 300°, left doubt as to whether adduct **10e** formed at all (*vide supra*) or if the product **11e** was unstable. At temperatures above 300°, decomposition to polymeric products resulted.[26] The rearrangements of **10f–h** are summarized in Table I. These adducts would not rearrange in refluxing pyridine or triethylamine.[26] This

(20) It was reported[11] that 1-ethoxy-7,7-dichlorobicyclo[4.1.0]heptane failed to respond to silver nitrate.

(21) A 3% yield of 1-ethoxy-1,3,5-cycloheptatriene and methyl phenetole were isolated[11] from a complex mixture obtained after treating 1-ethoxy-7,7-dichlorobicyclo[4.1.0]heptane with sodium methoxide.

(22) The 7,7-dibromobicyclo[4.1.0]heptanes[12] were reported[12] to expand more readily than the dichloro adducts and thus were better preparative precursors for ring-expanded products.

(23) G. Frankel, R. E. Carter, A. McLachlan, and J. H. Richards, *J. Amer. Chem. Soc.*, **82**, 5846 (1960).

(24) M. Shostakovskie and A. Bogdanova, *J. Gen. Chem. USSR*, **17**, 565 (1947); *Chem. Abstr.*, **42**, 4519 (1948).

(25) A dinitrophenylhydrazone was reported[11] isolated from 2-ethoxy-3-chloro-1,3-cycloheptadiene. However, a hydrolysis which formed the corresponding ketone was described only for the dibromobicycloheptane on reaction with alcoholic silver nitrate.

(26) In quinoline at 140–150°, 2-oxa-7,7-dichlorobicyclo[4.1.0]heptane gave 2,3-dihydro-6-chlorooxepin [E. E. Schweizer and W. E. Parham, *J. Amer. Chem. Soc.*, **82**, 4085 (1960)] while 1-ethoxy-7,7-dichlorobicyclo[4.1.0]-heptane required 160° with quinoline or refluxing pyridine. This is contrasted with the rearrangement of 7,7-dihalobicyclo[4.1.0]heptane, which required temperatures of 500°[13] or 444° with calcium oxide.[14]

depressed reactivity compared to the accelerating effect of the alkoxy group in 10a–d clearly reflects the importance of such groups in stabilizing the transition state, which must be essentially polar in nature.[27] The lone-pair electrons on oxygen increased the electron density of the cyclopropane ring, thereby polarizing the carbon–chlorine bond; *i.e.*, the electronic effect of the alkoxy group was transmitted through the cyclopropane ring.[27] The contribution from hyperconjugation by the methyl group in 10f and from the resonance effect by the phenyl group in 10g relative to the effect of the alkoxy groups in 10a–d clearly follows the usual order of activation found in the formation of such incipient cationic transition states, *i.e.*, OR > $C_6H_5$ > $CH_3$. Our interpretation of the fate of such transition states is similar to that described by others.[27,28] With ionization of the carbon–chlorine bond trans to the $C_{5a}$ and $C_{6a}$ substituents,[29] the formed cyclopropyl cation underwent a concerted electrocyclic transformation to an alkyl cation by a disrotatory process,[30] the $C_{5a}$ and $C_{6a}$ substituents moving outward. Finally, the alkyl cation lost a proton from the 7 position to afford the 8*H*-cyclohepta[*b*]thiophenes.

Treatment of compounds 11 with either trityl perchlorate or fluoroborate[31] to obtain the substituted 1-thiaazulenium cations resulted in unstable products which have not yet been fully characterized.

## Experimental Section

All melting points (uncorrected) were determined on a Mel-Temp melting point apparatus. Combustion analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and Childers Microanalytical Laboratories, Milford, N. J. Infrared spectra were determined on a Perkin-Elmer Model 137. Ultraviolet absorption spectra were determined with a Bausch and Lomb Spectronic 505 spectrophotometer. Nmr spectra were obtained on a Varian A-60A spectrometer. Chemical shifts are given in $\delta$ (parts per million) downfield from Me$_4$Si as an internal standard. Gas chromatographic analyses were obtained on a A-700 Varian Aerograph gas chromatography apparatus using helium as a carrier gas and equipped with a thermal conductivity detector. A 6 ft × 0.25 in. i.d. stainless steel column of 5% Apiezon L supported on 60–80 mesh Chromosorb G was used for all separations and purifications.

All reactions were performed under dry nitrogen unless indicated otherwise. The *p*-toluenesulfonic acid was dried by azeotroping off the water by refluxing with benzene and collecting the distillate in a Dean-Stark trap. Sodium methoxide was purchased from Fisher Chemical Co. Trityl perchlorate and fluoroborate were prepared as described.[31] The pentane, bromoform, chloroform, methanol, and ethanol were purified by the procedure of Perrin, Armarego, and Perrin.[32]

**4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene (2).**—This compound was prepared according to the procedure of Fieser and Kennelly,[4] bp 81–84° (0.25 mm) [lit.[4] bp 102–110° (2.00 mm)].

**4,4-Dimethoxy-4,5,6,7-tetrahydrobenzo[*b*]thiophene (3a).**—Into a 200-ml flask was added 15.2 g (0.10 mol) of 2, 44 g (0.41 mol) of trimethyl orthoformate, 50 ml of dry methanol, and 0.50 g of *p*-toluenesulfonic acid. This mixture was stirred at room temperature for 24 hr and refluxed for 5 hr. The solution gradually changed from light yellow to a dark purple. The

reaction was cooled to room temperature and neutralized with alcoholic sodium methoxide, whereupon the color of the solution changed from dark purple to light yellow. After concentration of the solution under reduced pressure, the yellow oil was distilled (6-in. Vigreux), giving 17.1 g (86%) of 3a as a colorless oil, bp 69–72° (0.10 mm). The oil, which solidified upon standing (mp 52–57°), was recrystallized twice from pentane to yield 15 g (75.8%) of 3a: mp 58–60°; ir (KBr) disappearance of carbonyl absorption at 1690 cm$^{-1}$, ketal bands at 1055, 1100, and 1160 cm$^{-1}$; uv max (95% EtOH) 235 nm ($\epsilon$ 4100); nmr (CDCl$_3$) $\delta$ 7.05 (d, 2, thiophene), 3.24 (s, 6, $-$OCH$_3$), 2.78 (t, 2, $-$CH$_2-$), 2.00 (m, 4, $-$CH$_2$CH$_2-$).

*Anal.* Calcd for C$_{10}$H$_{14}$O$_2$S: C, 60.57; H, 7.11; S, 16.17. Found: C, 60.49; H, 7.21; S, 16.37.

**4,4-Diethoxy-4,5,6,7-tetrahydrobenzo[*b*]thiophene (3b)** was prepared by the same method as 3a using ethanol, triethyl orthoformate, and sodium ethoxide to yield 19.2 g (85%) of the diketal 3b, bp 70–74° (0.10 mm). In seven runs the average yield was 80%. The purified oil, which solidified upon standing (mp 62–66°), was recrystallized from methanol to give a white solid: mp 66–67°; ir (neat) disappearance of carbonyl band at 1690 cm$^{-1}$; uv max (95% EtOH) 236 nm ($\epsilon$ 4090); nmr (CDCl$_3$) $\delta$ 7.10 (d, 2, thiophene), 3.62 (m, 4, $-$OCH$_2-$), 2.78 (m, 2, $-$CH$_2-$), 2.01 (m, 4, $-$CH$_2$CH$_2-$), 1.15 (t, 6, CH$_3-$).

*Anal.* Calcd for C$_{12}$H$_{18}$O$_2$S: C, 63.68; H, 8.00; S, 14.16. Found: C, 63.76; H, 8.01; S, 14.29.

**4-Methoxy-6,7-dihydrobenzo[*b*]thiophene (4a).**—Into a 100-ml round-bottom flask fitted with a magnetic stirrer was added 19.8 g (0.10 mol) of 3a and 0.10 g of *p*-toluenesulfonic acid. The reaction was heated to 80°, the methanol was distilled off, and the dark oil that remained was distilled (6-in. Vigreux) to give 10.1 g (60.2%) of a colorless oil, bp 74–76° (0.10 mm). Gas chromatography showed only one component (conditions: column temperature 175°, helium flow 80 ml/min, retention time 4.2 min): ir (neat) doublet at 1695, 1680 (C–C stretch in vinyl ether), 1255 cm$^{-1}$ (=COC); uv max (95% EtOH) 225 nm ($\epsilon$ 14,800), 288 (1800); nmr (neat) $\delta$ 7.00 (q, 2, thiophene), 4.50 (t, 1 =CHCH$_2-$), 3.49 (s, 3, $-$OCH$_3$), 2.50 (m, 4, $-$CH$_2$CH$_2-$).

*Anal.* Calcd for C$_9$H$_{10}$OS: C, 65.02; H, 6.06; S, 19.28. Found: C, 65.21; H, 6.13; S, 19.20.

**4-Ethoxy-6,7-dihydrobenzo[*b*]thiophene (4b)** was prepared in the same manner as described for 4a to afford 9.0 g (50%) of a colorless oil 4b, bp 57–59° (0.10 mm). In seven preparations the average yield was 40%. Gas chromatography showed the product to contain only one component (conditions: column temperature 175°, helium flow 60 ml/min, retention time 6.2 min): ir (neat) 1685 (C–C stretch of vinyl ether), 1250 cm$^{-1}$ (=COC); uv max (95% EtOH) 225 nm ($\epsilon$ 14,700), 288 (1820); nmr (neat) $\delta$ 6.99 (q, 2, thiophene), 4.52 (t, 1, =CHCH$_2-$), 3.68 (q, 2, $-$OCH$_2$CH$_4$), 2.50 (m, 4, $-$CH$_2$CH$_2-$), 1.24 (t, 3, $-$OCH$_2$CH$_3$).

*Anal.* Calcd for C$_{10}$H$_{12}$OS: C, 66.73; H, 6.70; S, 17.78. Found: C, 66.81; H, 6.88; S, 17.98.

**4-Hydroxy-4,5,6,7-tetrahydrobenzo[*b*]thiophene (5a).**—Into a 250-ml round bottom flask was added 10.0 g (0.065 mol) of 2, 150 ml of absolute ethanol, and 2.66 g (0.07 mol) of sodium borohydride. After the solution was stirred at room temperature for 24 hr, 100 ml of water was added and the ethanol was evaporated at reduced pressure. The remaining aqueous solution was extracted with ether (2 × 25 ml). The ether extract was washed with water (2 × 10 ml) and dried (MgSO$_4$) overnight, and the ether was evaporated at reduced pressure. The remaining 9.2 g of colorless oil was dissolved in 100 ml of pentane and placed in the refrigerator overnight to deposit white crystals, 8.2 g (81%), mp 63–64°. The reaction was run four times with an average yield of 75%: ir (KBr) 3400 cm$^{-1}$ (OH); nmr (CDCl$_3$) $\delta$ 6.84 (s, 2, thiophene), 4.65 (m, 1, HCOH), 2.70 (m, 2, $-$CH$_2-$), 2.10 (s, 1, OH), 1.92 (m, 4, $-$CH$_2$CH$_2-$). Upon shaking with D$_2$O the band at $\delta$ 2.10 disappeared.

*Anal.* Calcd for C$_8$H$_{10}$OS: C, 62.31; H, 6.53; S, 20.78. Found: C, 62.18; H, 6.45; S, 20.95.

**4-Hydroxy-4-methyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene (5b)** was prepared according to the procedure of Kloetzel, Little, and Frisch:[7] yield 83.5%; mp 74–76° (lit.[7] yield 91% mp 75–76°); ir (KBr) 3400 cm$^{-1}$ (OH); nmr (CDCl$_3$) $\delta$ 7.00 (s, 2, thiophene), 2.74 (m, 2, $-$CH$_2-$), 2.31 (s, 1, OH), 1.85 (m, 4, $-$CH$_2$-CH$_2-$), 1.48 (s, 3, $-$CH$_3$). The band at $\delta$ 2.31 disappeared when the compound was shaken with D$_2$O.

**4-Hydroxy-4-phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene (5c)** was prepared according to the procedure of Kloetzel, Little, and

(27) L. Skattebøl, *J. Org. Chem.*, **31**, 1554 (1966).

(28) W. E. Parham and R. J. Sperley, *ibid.*, **32**, 926 (1967). See also W. E. Parham and R. J. Sperley, *ibid.*, **32**, 924 (1967).

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Frisch:[7] yield 77%; mp 64–66° (lit.[7] yield 89%, mp 65–67°); ir (KBr) 3400 cm$^{-1}$ (OH); nmr (CDCl$_3$) $\delta$ 7.25 (s, 5, phenyl), 6.78 (q, 2, thiophene), 2.83 (m, 2, –CH$_2$–), 2.35 (s, 1, OH), 2.01 (m, 4, –CH$_2$CH$_2$–). The proton at $\delta$ 2.35 disappeared when the compound was shaken with D$_2$O.

*Anal.* Calcd for C$_{14}$H$_{14}$OS: C, 73.01; H, 6.13; S, 13.91. Found: C, 72.90; H, 6.22; S, 14.01.

**6,7-Dihydrobenzo[b]thiophene (4c).**—In a 100-ml round-bottom flask was added 15.4 g (0.10 mol) of 5a and 0.10 g of *p*-toluenesulfonic acid. The mixture was heated on a steam bath with stirring for 15 min. The dark blue solution was distilled, giving 3.2 g (23.5%) of a colorless oil, bp 68–71° (0.10 mm), ir (neat) 1625 cm$^{-1}$ (C=C), disappearance of OH band at 3400 cm$^{-1}$.

The oil polymerizes very rapidly upon standing in air and less rapidly under nitrogen or with refrigeration. However, it had to be used immediately for the carbene insertion reactions.

**4-Methyl-6,7-dihydrobenzo[b]thiophene (4d). A. Dehydration of 5b.**—Into a 100-ml round-bottom flask was added 16.8 g (0.10 mol) of 5b and 30 ml of glacial acetic acid. The mixture was heated on a steam bath overnight, during which the solution turned dark yellow. The acetic acid was evaporated at reduced pressure to give 14 g of a yellow oil. Distillation of the crude oil gave 13 g (86.6%) of a colorless oil, bp 51–53° (0.25 mm). Gas chromatography showed two components in a ratio of 70:30. Preparative gas chromatography (conditions: column temperature 170°, helium flow 75 ml/min, retention time 4.10 min for major component, 4.18 min for minor component) separated 4-methyl-6,7-dihydrobenzo[b]thiophene (4d) (70%) from the exocyclic isomer (30%) 6: ir of 4d (neat) 1625 cm$^{-1}$ (C=C) and the disappearance of OH at 3400 cm$^{-1}$; nmr (neat) $\delta$ 6.75 (s, 2, thiophene), 5.35 (m, 1, HC=C), 2.60 (m, 2, –CH$_2$–), 2.25 (m, 2, –CH$_2$–), 1.90 (s, 3, CH$_3$–).

*Anal.* Calcd for C$_9$H$_{10}$S: C, 71.94; H, 6.71; S, 21.34. Found: C, 71.76; H, 6.51; S, 21.28.

**B. From 4-Chloro-4-methyl-4,5,6,7-tetrahydrobenzo[b]thiophene (7).**—Into a 250-ml round-bottom flask was added 50 ml of dry benzene and 8.4 g (0.05 mol) of 5b. To this solution was added, over a 1-hr period, 11.9 g (0.10 mol) of thionyl chloride. The solution turned dark yellow after the addition and was then refluxed for 1 hr. Upon cooling to room temperature the excess thionyl chloride and benzene were removed at reduced pressure to yield 8.8 g of a yellow oil. This oil was dissolved in 40 ml of absolute ethanol and 2.5 g of potassium hydroxide was added. The mixture was stirred at room temperature overnight (12–15 hr), then refluxed for 1 hr. The potassium chloride was filtered off and the ethanol filtrate was evaporated at reduced pressure to yield 4.8 g of an oil distilling at 50–52° (0.10 mm). Gas chromatography (conditions: column temperature 170°, helium flow 75 ml/min, retention time 4.10 min for major component, 4.18 min for minor component) showed this to be a 65:35 mixture of 4d and 6.

**4-Phenyl-6,7-dihydrobenzo[b]thiophene (4e).**—Into a 300-ml round-bottom flask was added 23 g (0.10 mol) of 5c and 100 ml of glacial acetic acid. This solution was heated on a steam bath for 12 hr, during which it turned dark yellow. The acetic acid was evaporated at reduced pressure to give 20 g of a yellow oil. Distillation gave 3 g of 4-phenylbenzo[b]thiophene (9), bp 55–70° (0.10 mm), and 18.2 g (86%) of a colorless oil, bp 115–120° (0.10 mm). This oil solidified upon standing and was recrystallized from pentane to give 17 g of white crystals of 4e: mp 54–55°; average yield for five preparations was 80%; ir (KBr) 1620 cm$^{-1}$ (C=C); nmr (CDCl$_3$) $\delta$ 7.22 (s, 5, phenyl), 6.80 (d, 2, thiophene), 5.77 (t, 1, CH$_2$=CHC$_6$H$_5$), 2.58 (complex m, 4, –CH$_2$CH$_2$–).

*Anal.* Calcd for C$_{14}$H$_{12}$S: C, 79.20; H, 5.69; S, 15.10. Found: C, 79.41; H, 5.66; S, 15.28.

**4-Methylbenzo[b]thiophene (8).**—To 1.5 g (0.01 mol) of 4d was added 0.36 g of elemental sulfur and the mixture was heated in a test tube to 250° and kept there for 5 min. The black mixture was distilled to give 0.8 g (54%) of a colorless oil, bp 50–53° (1.00 mm), picrate mp 133–136° (lit.[7] mp 135–136°).

**4-Phenylbenzo[b]thiophene (9).**—To 4.2 g (0.02 mol) of 4e was added 0.61 g (0.02 mol) of elemental sulfur. The mixture was heated in a bomb at 240–250° for 20 min and cooled, and the black oil was distilled to give 3.1 g of a light yellow oil, bp 65–75° (0.10 mm). The purified oil solidified and was recrystallized from 95% ethanol to give 2.5 g (60%) of white crystals, mp 45–47° (lit.[7] mp 48°).

*Anal.* Calcd for C$_{14}$H$_{10}$S: C, 79.96; H, 4.79. Found: C, 79.90; H, 4.79

The sulfone had mp 137–139° (lit.[7] mp 139°).

**General Procedure for the Preparation of 6,6-Dihalo-5,5a,6,6a-tetrahydro 6a-Substituted 4H-Cyclopropa[e][1]benzothiophenes. A. Haloform–Potassium *tert*-Butoxide Method. 10a–e.**—A solution of the appropriate cycloalkene 4 (0.05 mol) in 50 ml of dry pentane was cooled to 0° and treated with an equimolar amount of potassium *tert*-butoxide. The appropriate haloform (1.5 molar equiv) was added dropwise over 1 hr, which gave a dark brown solution. After stirring overnight (12–15 hr), initially in an ice bath and then at room temperature, the precipitated salts were filtered off and washed with 10 ml of dry pentane. The combined pentane filtrates were evaporated (30°) at reduced pressure to afford the crude dihalocarbene adducts 10a–e.

**B. Ethyl Trichloroacetate–Sodium Methoxide Method with 4b.**—To 4.5 g (0.02 mol) of 4b in 40 ml of dry pentane cooled to 0–10° was added 1.3 g (0.024 mol) of sodium methoxide and 4.7 g (0.025 mol) of ethyl trichloroacetate, which gave a yellow mixture. After 4 hr stirring in an ice bath followed by 12–15 hr at room temperature the dark brown solution was filtered and the residue was washed with 10 ml of pentane. The combined pentane filtrates were evaporated (25°) at reduced pressure to afford 6 g of crude 6,6-dichloro-6a-ethoxy-5,5a,6,6a-tetrahydro-4H-cyclopropa[e][1]benzothiophene (10c) as a dark orange oil.

**6,6-Dichloro-5,5a,6,6a-tetrahydro-6a-methyl-4H-cyclopropa[e]-[1]benzothiophene (10f).**—Into a 100-ml round-bottom flask fitted with a magnetic stirrer was added 4.5 g (0.03 mol) of 4d and 50 ml of dry pentane. The reaction flask was placed in an ice bath and 3.4 g (0.03 mol) of potassium *tert*-butoxide was added followed by dropwise addition over a 1-hr period of 6.0 g (0.05 mol) of purified chloroform, whereupon the mixture turned dark brown. The reaction was stirred at room temperature overnight (12–15 hr), then filtered and the residue was washed with 10 ml of pentane. The pentane filtrates were combined and evaporated at reduced pressure, yielding 4.7 g of a dark brown oil. Distillation (6-in. Vigreux) gave 2.3 g (36.4%) of a colorless oil, bp 80–85° (0.10 mm), ir (neat) 1010 (cyclopropane), 815 cm$^{-1}$ (CCl).

*Anal.* Calcd for C$_{10}$H$_{10}$Cl$_2$S: C, 51.51; H, 4.32; Cl, 30.41; S, 13.75. Found: C, 51.79; H, 4.24; Cl, 30.20; S, 13.84.

**6,6-Dichloro-5,5a,6,6a-tetrahydro-6a-phenyl-4H-cyclopropa[e]-[1]benzothiophene (10g).**—Into a 100-ml round-bottom flask fitted with a magnetic stirrer was added 6.3 g (0.03 mol) of 4e, 50 ml of dry pentane, and 1.62 g (0.03 mol) of sodium methoxide. The reaction was cooled in an ice bath and 5.8 g of purified ethyl trichloroacetate was added in one portion. The reaction mixture turned dark yellow. It was stirred in an ice bath for 4 hr and then at room temperature overnight (12–15 hr). The solution was filtered and the residue was washed with 10 ml of pentane. The pentane filtrates were combined and evaporated at reduced pressure to give 7.0 g of a dark, thick, orange oil. The oil was dissolved in 100 ml of hot pentane and cooled in the refrigerator to give 1.8 g (20.4%) of a white solid: mp 110–112°; ir (KBr) 1020 (cyclopropane), 810 cm$^{-1}$ (CCl); nmr (CDCl$_3$) $\delta$ 7.31 (m, 5, phenyl), 6.82 (s, 2, thiophene), 2.85 (m, 2, –CH$_2$–), 2.34 (m, 2, –CH$_2$–), 1.00 (m, 1, HCCCl).

*Anal.* Calcd for C$_{15}$H$_{12}$Cl$_2$S: C, 61.03; H, 4.09; Cl, 24.02; S, 10.86. Found: C, 60.95; H, 4.03; Cl, 24.05; S, 10.93.

**6,6-Dibromo-5,5a,6,6a-tetrahydro-6a-phenyl-4H-cyclopropa[e]-[1]benzothiophene (10h).**—Into a 200-ml round-bottom flask fitted with a magnetic stirrer was added 10.6 g (0.05 mol) of 4e, 100 ml of dry pentane, and 5.6 g (0.05 mol) of potassium *tert*-butoxide. The reaction was cooled to 0° in an ice bath and 12.6 g (0.05 mol) of bromoform was added dropwise over a 1-hr period. The reaction turned black and was stirred at 0° for 5 hr and then at room temperature overnight (12–15 hr). The reaction was filtered and the residue was washed with 10 ml of pentane. The pentane filtrates were combined and evaporated at reduced pressure to give 11.5 g of a dark brown oil which would not be further purified.

**General Procedure for the Rearrangement of Dihalocyclopropanes 10 to the 8H-Cyclohepta[b]thiophenes 11. A. Pyrolysis in Base.**—The dihalocarbene adduct 10 was added to an excess of freshly distilled organic base and heated for the stated time at the designated temperature (consult Table I), then cooled to room temperature, and the amine hydrohalide salt was filtered off. The residue was washed with ether and the combined ether-organic base filtrate was evaporated at reduced pressure. The residual dark oil was vacuum distilled.

**B. Neat Pyrolysis.**—The adduct 10 was heated at atmospheric pressure at the designated temperature and time (Table I), cooled to room temperature, and vacuum distilled. An alternate method was to heat the adduct under a slight vacuum, during which the exothermic rearrangement evolved a gas (vacuum decrease observed), and then to raise the temperature gradually until distillation of the colorless oil commenced.

In all cases, analytical samples were obtained by preparative glc. The conditions required, spectral data of the products, and their elemental analyses, respectively, are described below for the individual cyclohepta[b]thiophenes.

**5-Chloro-4-methoxy-8H-cyclohepta[b]thiophene** (11a) (column temperature 175°, helium flow rate 80 ml/min, retention time 18.2 min) had ir (neat) 1625 (C=C), 1225, 1025 cm$^{-1}$ (=COC); uv max (95% EtOH) 225 nm ($\epsilon$ 21,000), 278 (8200), 360 (650); nmr (neat) $\delta$ 7.02 (s, 2, thiophene), 6.00 (d, 1, H-6), 5.40 (m, 1, H-7) 3.62 (s, 3, -OCH$_3$), 3.08 (d, 2, H-8).

*Anal.* Calcd for C$_{10}$H$_9$ClOS: C, 56.46; H, 4.26; Cl, 16.67; S, 15.07. Found: C, 56.38; H, 4.10; Cl, 16.40; S, 15.00.

**5-Bromo-4-methoxy-8H-cyclohepta[b]thiophene** (11b) (column temperature 170°, helium flow 140 ml/min, retention time 20 min) had ir (neat) 1630 (C=C), 1225 and 1025 cm$^{-1}$ (=COC); uv max (95% EtOH) 225 nm ($\epsilon$ 20,700), 278 (7800), 365 (645); nmr (CDCl$_3$) $\delta$ 7.00 (s, 2, thiophene), 6.02 (d, 1, H-6), 5.47 (m, 1, H-7), 3.67 (s, 3, -OCH$_3$), 3.16 (d, 1, H-8).

*Anal.* Calcd for C$_{10}$H$_9$BrOS: C, 46.70; H, 3.53; Br, 31.08; S, 12.47. Found: C, 46.48; H, 3.40; Br, 30.77; S, 12.30.

**5-Chloro-4-ethoxy-8H-cyclohepta[b]thiophene** (11c) (column temperature 200°, helium flow 100 ml/min, retention time 20.2 min) had ir (neat) 1620 (C=C), 1225, and 1050 cm$^{-1}$ (=COC); uv max (95% EtOH) 228 nm ($\epsilon$ 20,900), 282 (8000), 362 (690); nmr (neat) $\delta$ 7.00 (s, 2, thiophene), 5.95 (d, 1, H-6), 5.42 (m, 1, H-7), 3.85 (q, 2, -OCH$_2$CH$_3$), 3.11 (d, 2, H-8), 1.24 (t, 3, -OCH$_2$-CH$_3$).

*Anal.* Calcd for C$_{11}$H$_{11}$ClOS: C, 58.28; H, 4.89; Cl, 15.64; S, 14.14. Found: C, 58.30; H, 4.73; Cl, 15.50; S, 14.42.

**5-Bromo-4-ethoxy-8H-cyclohepta[o]thiophene** (11d) (column temperature 200°, helium flow 140 ml/min, retention time 22 min) had ir (neat) 1625 (C=C), 1220, and 1025 cm$^{-1}$ (=COC); uv max (95% EtOH) 232 nm ($\epsilon$ 20,850), 280 (7500), 365 (680); nmr (CDCl$_3$) $\delta$ 7.05 (s, 2, thiophene), 6.08 (d, 1, H-6), 5.45 (m,

1, H-7), 3.92 (q, 2, -OCH$_2$CH$_3$), 3.15 (d, 2, H-8), 1.30 (t, 3, OCH$_2$CH$_3$).

*Anal.* Calcd for C$_{11}$H$_{11}$BrOS: C, 48.72; H, 4.08; Br, 29.46; S, 11.82. Found: C, 48.65; H, 4.21; Br, 29.20; S, 11.71.

**5-Chloro-4-methyl-8H-cyclohepta[b]thiophene** (11f) (column temperature 200°, helium flow 140 ml/min, retention time 18.6 min) had ir (neat) 1630 (C=C), 3060 cm$^{-1}$ (=CH); uv max (CH$_3$CN) 225 nm ($\epsilon$ 20,000), 280 (7500); nmr (CDCl$_3$) $\delta$ 7.02 (s, 2, thiophene), 6.08 (d, 1, H-6), 5.59 (m, 1, H-7), 3.12 (d, 2, H-8), 2.40 (s, 3, -CH$_3$).

*Anal.* Calcd for C$_{10}$H$_9$ClS: C, 61.06; H, 4.61; Cl, 18.02; S, 16.30. Found: C, 61.28; H, 4.71; Cl, 17.90; S, 16.27.

**5-Chloro-4-phenyl-8H-cyclohepta[b]thiophene** (11g) (column temperature 200°, helium flow 180 ml/min, retention time 21 min) had ir (neat) 1630 (C=C), 3060 cm$^{-1}$ (=CH); uv max (CH$_3$CN) 230 nm ($\epsilon$ 22,000), 270 (8600); nmr (CDCl$_3$) $\delta$ 7.18 (s, 5, C$_6$H$_5$), 6.52 (q, 2, thiophene), 6.10 (d, 1, H-6), 5.55 (m, 1, H-7), 3.18 (d, 2, H-8).

*Anal.* Calcd for C$_{15}$H$_{11}$ClS: C, 69.62; H, 4.28; Cl, 13.70; S, 12.38. Found: C, 69.69; H, 4.39; Cl, 13.87; S, 12.40.

**5-Bromo-4-phenyl-8H-cyclohepta[b]thiophene** (11h) (column temperature 200°, helium flow 200 ml/min, retention time 16 min) had ir (neat) 1625 (C=C), 3060 cm$^{-1}$ (=CH); uv max (CH$_3$CN) 230 nm ($\epsilon$ 22,200), 275 (8500); nmr (CDCl$_3$) $\delta$ 7.28 (s, 5, C$_6$H$_5$), 6.60 (d, 2, thiophene), 6.30 (d, 1, H-6), 5.53 (m, 1, H-7), 3.15 (d, 2, H-8).

*Anal.* Calcd for C$_{15}$H$_{11}$BrS: C, 59.41; H, 3.65; Br, 26.36; S, 10.57. Found: C, 59.68; H, 3.89; Br, 26.04; S, 10.33.

# Notes

## New Phenolic Hasubanan Alkaloids from *Stephania abyssinica*[1]

S. Morris Kupchan,* Andris J. Liepa, and Tetsuro Fujita

*Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901*

*Stephania abyssinica* Walp. is a creeping plant indigenous to southern and eastern Africa which is reputed to possess a variety of medicinal uses.[2] An examination of *S. abyssinica* from Natal revealed the presence of an alkaloid[3] subsequently characterized as metaphanine (1b).[4] Earlier studies in this laboratory of roots and rhizomes from Ethiopia resulted in isolation and structural elucidation of the alkaloids oxoxylopine[5] ("lanuginosine"[6]) and stephavanine.[7] We report herein the isolation and structure elucidation of three new phenolic hasubanan alkaloids, stephabyssine (1a), stephaboline (2), and prostephabyssine (3a).

A concentrated ethanolic extract of *S. abyssinica* roots and rhizomes was partitioned between 5% hydrochloric acid and chloroform (fraction A). The acid solution was partially basified to pH 5 with ammonium hydroxide and extracted with chloroform to yield fraction B. Further basification with excess am-

(1) This investigation was supported by Public Health Service Grant No. HE-02952 and CA-12059 from the National Institutes of Health.

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monium hydroxide and extraction with chloroform yielded fraction C.

Fraction C was absorbed on silica and the alkaloids were eluted with chloroform containing methanol. The material eluted with 1% methanol in chloroform was crystallized from aqueous ethanol to give stephabyssine (1a) as colorless needles: $C_{18}H_{21}NO_5$; mp 178–180°; $[\alpha]^{25}D$ −58.9° (c 0.87, CHCl$_3$); m/e 331 (M$^+$), 316, 231, 198; $\lambda_{max}^{MeOH}$ 284 nm ($\epsilon$ 3300). The ir spectrum of 1a showed absorption at 5.77 $\mu$, indicative of a saturated ketone, while in the nmr spectrum signals were observed at $\tau$ 3.32 (2 H, s, aromatic H), 3.98 (s) and 4.87 (s) (2 OH), 4.98 (1 H, d, J = 6 Hz), 6.11 (3 H, OCH$_3$), and 7.41 (3 H, NCH$_3$). The presence of a phenolic hydroxyl group with an unsubstituted para position was suggested by a positive reaction of the compound with Gibbs reagent and supported by a 0.3 ppm shift of one aromatic proton in the nmr spectrum (MeOH) upon formation of the phenoxide ion.[8] This alkaloid was further characterized as the hydrochloride: mp 247–250° dec; $[\alpha]^{25}D$ − 32.5° (c 0.41, 60% aq EtOH).

Methylation of 1a with methyl iodide in the presence of potassium carbonate gave metaphanine (1b), identified by comparison of physical constants (mass spectrum, melting point, $[\alpha]D$, ir) observed for the product with reported values.[9] This conversion established the structure of stephabyssine as 4-demethylmetaphanine (1a).

Further elution with an increase in the proportion of methanol in the eluting solvent gave, after additional chromatography on neutral alumina, a crystalline alkaloid hydrochloride: $C_{18}H_{24}NO_5Cl$; mp 230–232° dec (MeOH–CHCl$_3$); $[\alpha]^{25}D$ +23.1° (c 0.44, MeOH), −45° (c 0.8, pyridine). Treatment with potassium carbonate liberated stephaboline (2): $C_{18}H_{23}NO_5$; mp 186–188° dec (aq MeOH); $[\alpha]^{25}D$ +34.7° (c 0.47, MeOH); $\lambda_{max}^{MeOH}$ 281 nm ($\epsilon$ 2760).

The close relationship of stephaboline with 1a was indicated by similarities in their nmr spectra as well as the positive reaction shown by each compound to ferric chloride and to Gibbs reagent. The presence of an additional hydroxyl proton signal at $\tau$ 5.24 in the nmr spectrum of 2, when considered together with the absence of carbonyl absorption in its ir spectrum, suggested 2 was a dihydro derivative of 1a. This proposal was readily confirmed by the high yield (78%) conversion of 1a into 2 by reduction with sodium borohydride. The stereoselective hydride delivery observed in the course of the reduction is noteworthy but not unexpected in view of the previously demonstrated[7,10] influence exerted by steric effects during the reduction of other hasubanan ketones.

This conversion of 1a into 2 established the structure and absolute stereochemistry of 2 as well as the relative stereochemistry at all centers with the exception of C-7. The relative inflexibility of the C ring in the molecule of 2 associated with the hemiketal superstructure permitted the stereochemistry at C-7 to be assigned on the basis of nmr measurements. The nmr spectrum of 2 (pyridine-$d_5$) showed an isolated diffuse multiplet centered at $\tau$ 5.6, assignable to the C-7

proton [–CH$_2$CH(OH)–], which was resolved into a pair of doublets by addition of deuterium oxide. Coupling constant values of $J_{AX}$ = 5 Hz and $J_{BX}$ = 11 Hz were associated with this signal. The high value of $H_B$–$H_X$ coupling constant indicates involvement of the C-7 proton in axial-axial coupling and consequently favors assignment of equatorial ($\beta$) orientation to the hydroxyl group.

Chromatography of extract B upon silica succeeded by preparative layer chromatography upon silica gave an amorphous base, shown to be homogeneous by tlc in a variety of solvent systems. The alkaloid (prostephabyssine, 3a) showed M$^+$ 345 ($C_{19}H_{23}NO_5$) in its mass spectrum, and ir absorption at 2.84 (OH), 5.98 (C=O), and 6.10 (broad, enolic C=C). A positive reaction with Gibbs reagent suggested the presence of a phenolic function with an unsubstituted para position. The alkaloid formed a crystalline methiodide: $C_{20}H_{24}INO_5$; $[\alpha]^{24}D$ − 105° (c 1.98, MeOH); $\lambda_{max}^{KBr}$ 2.96 (OH), 5.94 (C=O) $\mu$. Upon brief treatment of 3a with aqueous hydrochloric acid, the crystalline product which was obtained in high yield was shown to be identical with 1a by nmr, ir, melting point, and mixture melting point measurements. This facile hydrolysis of 3a with loss of the elements of methanol to give 1a demonstrated the presence of a labile enol ether located at C-6–C-7 and consequently supported assignment of the prostephabyssine structure 3a. Determinations of the nmr spectra of prostephabyssine in a variety of solvents gave complex patterns indicative of the presence of the hemiketal 3a and ketone 4 forms in equi-



1a, R = H
b, R = CH$_3$

2

3a, R = H
b, R = CH$_3$

4, R = H
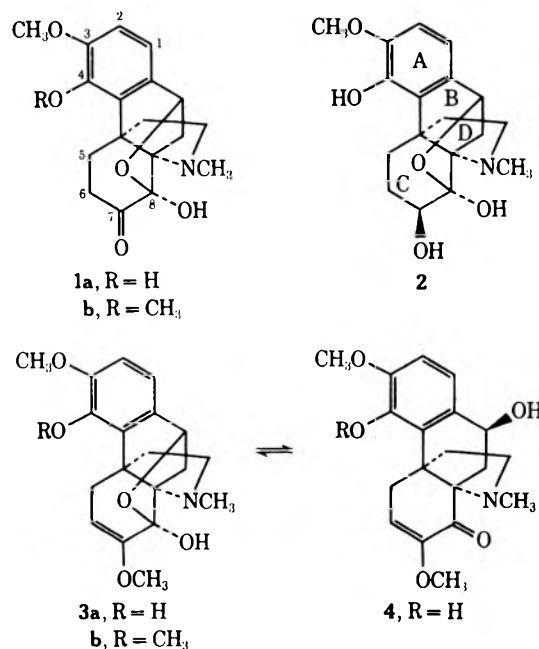
libria similar to the solvent-dependent equilibria observed by Tomita, et al.,[11] for prometaphanine 3b.[12]

### Experimental Section

Melting points were determined on a Mettler FP2 melting point apparatus. Ir spectra were determined on a Perkin-Elmer 337 double beam recording spectrophotometer. Uv spectra were determined on a Beckman DK-2A recording spectrophotometer.

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(12) We have also isolated prostephabyssine (3a) from *Stephania hernandifolia*.

Nmr spectra were determined on a Varian Associates HA-100 spectrometer on solutions in $CDCl_3$ with TMS as internal standard. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Mass spectra were measured on a Hitachi-Perkin-Elmer RMU-6E spectrometer.

**Extraction and Preliminary Fractionation.**—The dried ground roots and rhizomes (5.5 kg) of *S. abyssinica* were continuously extracted with hot 95% ethanol during 24 hr, and the extract was concentrated *in vacuo* to 1 l. The concentrate was dissolved in chloroform and extracted twice with 5% HCl (total of 4 l.). The organic phase was separated and evaporated to yield fraction A (74 g). The acid solution was decanted from an insoluble tar (101 g), adjusted to pH 5.0 with $NH_4OH$, and extracted twice with chloroform (1 l.). The resultant chloroform solution of weak bases yielded fraction B (73 g) upon evaporation. An excess of $NH_4OH$ added to the remaining aqueous phase precipitated the strong bases which were extracted twice with chloroform (1 l.) to give fraction C (25 g).

**Stephabyssine (1a).**—A portion of extract C (15 g) was chromatographed over 400 g of silica gel (0.05–0.2 mm, Merck) in chloroform. Elution was begun with 1% methanol-chloroform, and subsequent to a dark-colored forerun, eluate (2 l.) was collected and evaporated. The residue was twice crystallized from aqueous ethanol to give stephabyssine (1a) (271 mg): mp 178–180°; $[\alpha]D$ −58.9° (*c* 0.87, $CHCl_3$); $\lambda_{max}^{KBr}$ 2.82, 5.77 $\mu$; $\lambda_{max}^{MeOH}$ 284 nm ($\epsilon$ 3300); *m/e* (%) 331 ($M^+$, 26), 316 (2.5), 231 (100), 198 (19); nmr $\tau$ 3.32 (s, 2 H, aromatic), 3.98 (s) and 4.87 (s) (2 OH), 4.98 (d, 1 H, $J$ = 6 Hz), 6.11 (s, 3 H, $OCH_3$), 7.41 (s, 3 H, $NCH_3$).

*Anal.* Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.15; H, 6.29; N, 4.43.

**Stephabyssine Hydrochloride.**—Stephabyssine (40 mg) was stirred with 10% hydrochloric acid (1 ml) for 4 hr, the mixture evaporated to dryness *in vacuo*, and the residue crystallized twice from chloroform–carbon tetrachloride to give the hydrochloride (41 mg) as colorless plates: mp 247–250° dec; $[\alpha]^{25}D$ −32.5° (*c* 0.41, 60% aq EtOH); $\lambda_{max}^{KBr}$ 3.05, 3.99, 5.79, 7.78, 8.73 $\mu$.

*Anal.* Calcd for $C_{18}H_{21}NO_5 \cdot HCl$: C, 58.78; H, 6.03; N, 3.81. Found: C, 58.77; H, 6.03; N, 3.81.

**Methylation of Stephabyssine (1a) to Metaphanine (1b).**—Anhydrous potassium carbonate (200 mg) was added to a suspension of stephabyssine (50 mg) in methanol (1.5 ml) containing methyl iodide (0.3 ml). The mixture was allowed to stand 18 hr and then filtered and the solid washed thoroughly on the filter with water followed by a little methanol. Recrystallization from chloroform–ether gave colorless prisms (24 mg), mp 230–232° dec, charactarized by melting point, optical rotation, and ir, nmr, and mass spectrum as metaphanine by comparison with reported values.[9]

**Stephaboline (2) Hydrochloride.**—Elution was continued with 2, 3, 4, 5, and 6% methanol–chloroform (2 l. each); the eluates containing 5 and 6% methanol were combined and after evaporation the residual material was rechromatographed on 80 g of neutral alumina (activity I, Merck) overlaid with 10 g of basic alumina (activity I, Merck). After preliminary elution with chloroform (300 ml), 300-ml portions of chloroform containing 2, 4, and 5% ethyl acetate were passed through the column. The ethyl acetate containing eluates were combined and the solvents evaporated; the residue was taken up in 50% benzene-chloroform (20 ml) and allowed to stand overnight. Recrystallization of the precipitate from methanol–chloroform gave stephaboline hydrochloride (48 mg): mp 230–232° dec; $[\alpha]^{25}D$ +23.1 (*c* 0.44, MeOH), −45° (*c* 0.8, pyridine); $\lambda_{max}^{KBr}$ 2.92, 2.99, 3.10, 3.71, 7.82 $\mu$; $\lambda_{max}^{MeOH}$ 283 nm ($\epsilon$ 2940).

*Anal.* Calcd for $C_{18}H_{23}NO_5 \cdot HCl$: C, 58.46; H, 6.54; N, 3.79; Cl, 9.59. Found: C, 58.58; H, 6.47; N, 3.64; Cl, 9.39.

**Stephaboline (2).**—Potassium carbonate (100 mg) was added to a solution of stephaboline hydrochloride (20 mg) in 50% aqueous methanol (2 ml), the mixture stirred 10 min, and 10 ml of water added. After 16 hr the precipitate was collected and crystallized from aqueous methanol to give stephaboline (11 mg): mp 186–188° dec; $[\alpha]^{25}D$ +34.7° (*c* 0.47, MeOH); $\lambda_{max}^{EtOH}$ 281 nm ($\epsilon$ 2760); $\lambda_{max}^{KBr}$ 2.79, 3.07, 6.64, 9.15, 9.57 $\mu$; *m/e* (%) 333 ($M^+$, 17), 257 (12), 230 (100), 215 (9), 198 (33), 196 (16); nmr $\tau$ (pyridine-$d_5$) 3.34 (s, 2 H, aromatic), 4.06 (s), 4.81 (s), and 5.24 (s), (3 × 1 H, OH), 5.04 (d, 1 H, $J$ = 6 Hz), 5.62 (dd, 1 H, $J$ = 5 Hz, $J$ = 11 Hz), 6.32 (s, 3 H, $OCH_3$), 7.23 (s, 3 H, $NCH_3$).

*Anal.* Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.84; H, 7.02; N, 3.98.

**Stephaboline Methiodide.**—A suspension of stephaboline (60 mg) in chloroform (8 ml) containing methyl iodide (2 ml) was stirred for 24 hr. The colorless prisms were filtered and recrystallized from methanol–ethyl acetate (42 mg): mp 230–232° dec; $[\alpha]^{25}D$ +19.6° (*c* 0.51, MeOH); $\lambda_{max}^{KBr}$ 2.98, 6.20, 7.81, 9.42 $\mu$.

*Anal.* Calcd for $C_{18}H_{23}NO_5 \cdot CH_3I$: C, 48.01; H, 5.51; N, 2.95. Found: C, 48.02; H, 5.59; N, 3.04.

**Borohydride Reduction of Stephabyssine.**—Sodium borohydride was added in eight portions (50 mg each) during 2 hr to a stirred suspension of stephabyssine (450 mg) in 50% aqueous methanol (15 ml). After a further 0.5 hr, 20% aqueous methanol (10 ml) was added and the mixture stirred 2 hr. The crystalline precipitate was collected, washed with 10% aqueous methanol, and recrystallized from methanol to give colorless needles (330 mg) of **2**, characterized by melting point, mixture melting point, and nmr comparison with stephaboline.

**Prostephabyssine (3a).**—Extract B (48 g) was stirred with 80% ethyl acetate–chloroform (500 ml) until no further material dissolved. After removal of the insoluble components the solvents were evaporated, and the residue was chromatographed over 1.5 kg of silica gel (0.2–0.05 mm, Merck). After elution with chloroform (4 l.), followed by chloroform containing 1, 2, and 4% methanol (4 l. of each), chromatography was continued with chloroform containing 6% methanol (8 l.). After evaporation of the solvents from the latter eluate, the residue was stirred with ethyl acetate (100 ml), the mixture filtered, and the filtrate evaporated. The residue in chloroform was applied to preparative layer silica gel plates (20 × 20 cm, 0.2 cm absorbent layer, Merck $F_{254}$) which were subsequently eluted with 4% methanol–chloroform. The principal low $R_f$ band was collected and then extracted with 20% methanol–chloroform, and the filtered extract was evaporated to dryness to give prostephabyssine (3a) (200 mg) as a pale yellow glass, $\lambda_{max}^{CHCl_3}$ 2.84, 5.98, 6.10 $\mu$.

**Prostephabyssine Methiodide.**—A solution of prostephabyssine, (3a, 80 mg) in benzene (1 ml) containing methyl iodide (0.5 ml) was refluxed 20 min and allowed to stand overnight at room temperature. Recrystallization of the precipitate from methanol–benzene gave colorless prisms (47 mg): mp 196–198° dec; $[\alpha]^{25}D$ −105° (*c* 1.98, MeOH); $\lambda_{max}^{MeOH}$ 282 nm ($\epsilon$ 3810); $\lambda_{max}$ 2.95, 5.90 $\mu$.

*Anal.* Calcd for $C_{19}H_{23}NO_5 \cdot CH_3I$: C, 49.29; H, 5.34; N, 2.87. Found: C, 49.04; H, 5.22; N, 2.84.

**Acid Hydrolysis of Prostephabyssine (3a) to Stephabyssine (1a).**—A solution prostephabyssine (3a, 41 mg) in 50% acetone–methanol (2 ml) containing 5% hydrochloric acid (0.6 ml) was warmed on the steam bath for 5 min. After removal of the volatile materials *in vacuo* the residue was basified with ammonium hydroxide and extracted with chloroform (20 ml). After evaporation of the chloroform, the residue was twice crystallized from methanol–acetone to give colorless needles of 1a (24 mg), characterized as stephabyssine by melting point, mixture melting point, and ir and nmr comparison with an authentic sample.

**Registry No.**—1a, 36871-84-8; 1a HCl, 36871-85-9; 2, 36871-86-0; 2 HCl, 36921-52-5; 2 MeI, 36871-87-1; 3a, 36871-88-2; 3a MeI, 36921-53-6.

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# The West Synthesis of Hexabromocyclopentadiene

Gary A. Ungefug

*Hydrocarbons and Monomers Research Laboratory, The Dow Chemical Company, Midland, Michigan 48640*

Carleton W. Roberts[*1]

*Textile Department, Clemson University, Clemson, South Carolina 29631*

Until the publication of the West procedure for the synthesis of hexabromocyclopentadiene (II) from

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(1) To whom inquiries should be directed.

hexachlorocyclopentadiene (I) by an exchange reaction,[2,3] the standard synthesis of II involved the bromination of cyclopentadiene using sodium hypobromite.[4] The West procedure has been modified[5-7] and clarified and we wish to describe these modifications.

The original literature procedure[2,3] gives a low-melting product with chlorinated impurities; the modified procedure described here is a convenient laboratory synthesis of a high-purity product with residual chlorine levels less than 0.2%.
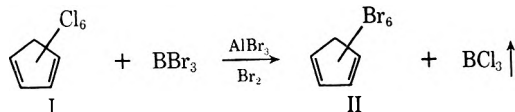


Some of the minor products were isolated from the above reaction to gain a further understanding of their formation and to help determine the best way to purify the crude product. Their amounts varied with the source of starting material (I), suggesting that the minor products may arise from impurities in I.

The most abundant side product (5%) is a colorless ketone $C_5Br_6O$, mp 185–188° dec. Structure IIIa, X = Br, is proposed on the basis of its failure to react with ethanol after 1 hr of reflux and on the similarity of its infrared spectrum with that of IIIa, X = Cl. Structure IIIb would be expected to give an enol ether on heating in ethanol.

Further confirmation is found in the uv of IIIa. The uv spectrum of III does not have the absorption for a conjugated ketone which is found at 270 nm for the Diels–Alder dimer of tetrabromocyclopentadienone (VIII). The two spectra are quite different, while the uv spectrum of IIIb, X = Cl, is very similar to the
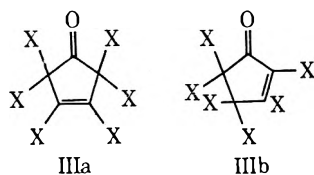


X = Cl
X = Br

spectrum of the Diels–Alder dimer of tetrachlorocyclopentadienone.[8,9]

A product formed in lesser amounts ($C_5HBr_7$, mp 136–140°) is formally the result of addition of HBr to $C_5Br_6$. Either structure IVa or IVb is consistent with the present data.
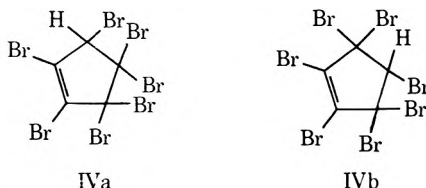
(2) P. T. Kwitowski and R. West, *J. Amer. Chem. Soc.*, **88**, 4541 (1966).
(3) R. West and P. T. Kwitowski, *ibid.*, **90**, 4697 (1968).
(4) F. Straus, L. Kollek, and W. Heyn, *Chem. Ber.*, **63B**, 1868 (1930).
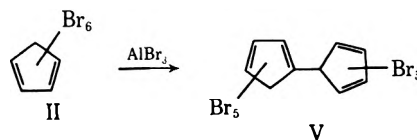(5) R. G. Pews and C. W. Roberts, *J. Org. Chem.*, **34**, 2029 (1969).
(6) S. D. McGregor and C. W. Roberts, *ibid.*, **35**, 3576 (1970).
(7) G. A. Ungefug, S. D. McGregor, and C. W. Roberts, *ibid.*, **36**, 352 (1971).
(8) E. T. McBee, D. K. Smith, and H. E. Ungnade, *J. Amer. Chem. Soc.*, **77**, 559 (1955).
(9) R. G. Pews, *Org. Prep. Proceed. Int.*, **3**, 37 (1971).

A dimer $C_{10}Br_{10}$, mp 139–141° (V), was isolated in less than 1% yields. Compound V was isolated by



McGregor from the reaction of II with aluminum bromide and from the cuprous bromide coupling of II.[6]

Hexabromoindone (VI)[9] and ester VII were isolated in less than 1% yields. Both VI and VII probably arise from dimer VIII. Pews has shown that dimer
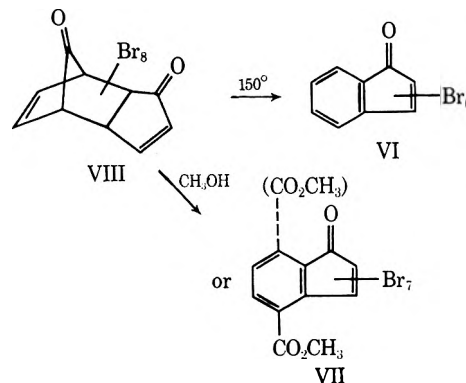


VIII can be pyrolyzed to VI at 150° and ester VII is produced by reaction of VII with methanol.[10] Methanol was used as a recrystallization solvent during product separation.

### Experimental Section

Infrared spectra were obtained with Beckman IR-9 and Perkin-Elmer 137 spectrometers. The mass spectra were obtained on a CEC-21-110B( direct probe) instrument. Nuclear magnetic resonance spectra were obtained on Varian A-60 and HA-100 spectrometers. Thin layer chromatography (tlc) plates were prepared from silica gel G containing 0.04% of Rhodamine 6G.

Preparation of Hexabromocyclopentadiene (II) from Hexachlorocyclopentadiene (I).[2]—(Caution: Run this reaction in a well-ventilated hood. All of the reagents and the exhaust gases are toxic. On two occasions this reaction has become so vigorous that the mixture foamed out of the flask. A large bucket of ice water was kept on hand while mixing the reagents and adding the catalyst. A dish was placed under the reaction pot so that ice water could be poured over the sides of the flask if the temperature should rise too rapidly. A large bulb (2 l.) was placed on top of the condenser to help contain foam. The two runaways occurred when the catalyst was added faster than directed by the procedure below. Reactants were mixed cautiously since impure I will react violently with boron tribromide.)

Hexachlorocyclopentadiene (474 g, 1.73 mol, Hooker Chemical Co.), boron tribromide (1108 g, 4.70 mol, Trona Division, American Potash and Chemical Corp.), and bromine (420 ml) were added via an additional funnel to a 2-l., three-necked flask equipped with magnetic stirring, a reflux condenser, a thermometer, and a dry nitrogen inlet. The nitrogen flow was adjusted to a rate that would sweep out evolved gases with a minimum loss of bromine. Aluminum bromide (10 g) was preweighed in 1-g lots into rubber-stoppered vials under a nitrogen atmosphere in a glove bag. The vials were stored in a desiccator. Five 1-g aluminum bromide samples were added one at a time to the reaction mixture at about 20-min intervals. The temperature was watched closely during addition of catalyst. If a rapid increase in temperature occurred, ice water was poured on the sides of the flask. If the temperature rose steadily without decreasing during the 20-min period after addition of catalyst,

(10) R. G. Pews, personal communication.

the next catalyst addition was delayed until the reaction cooled to 35°. The mixture was stirred for 20 hr at 20–25°; the remaining five 1-g samples of aluminum bromide were added one at a time at 20-min intervals. The mixture was heated at 50° for 13 days.

The mixture was cooled to room temperature. Solvent and excess boron tribromide were removed by vacuum distillation into a series of two Dry Ice–acetone cooled traps. Vacuum was produced by a water aspirator connected to a large safety trap. Solvent removal was speeded by warming the flask with an oil bath set no higher than 40°. The residual reaction mixture was poured on ice, stirred, and then dissolved in methylene chloride. The organic solution was washed with water, 5% sulfuric acid, and water, and then dried with magnesium sulfate.[11] The solvent was removed under vacuum. Hexane was added and the solvent was removed under vacuum to force out remaining bromine and methylene chloride. Although not all of the material dissolved at this point, the mixture was not filtered. The methylene chloride insoluble and hexane insoluble material was mostly $C_5Br_6O$. The crude yield of II was 851 g.

The crude II was dissolved in 3.5 l. of hot hexane and cooled to room temperature to give a dark solution and additional $C_5Br_6O$. The solution was split into two equal fractions and each was absorbed on a 3-kg silica gel column (Davison, 200 mesh) and eluted with hexane. The hexane eluent was poured back into the column until the yellow product band began to come off. Six 2-l. fractions were collected from each column. The solvent was removed under vacuum. All of the fractions were combined, since their ir spectra were identical.

Recrystallization from methanol gave 734 g (78%) of high-purity hexabromocyclopentadiene (II), mp 88–90°, with total chlorine 0.05% by X-ray fluorescence.

**Hexabromo-3-cyclopentenone (IIIa).**—Ketone IIIa, $C_5Br_6O$ (9 g), was separated from the hexane solution of crude II prepared above as nearly colorless crystals, and after elution of II from the silica gel column with hexane, the remaining material was eluted with benzene. The benzene was evaporated under vacuum, and the residue was recrystallized from chloroform to yield 33 g of white crystals. An analytical sample was prepared by three recrystallizations from chloroform: mp 185–188° dec; tlc (carbon tetrachloride with wick) one spot, $R_f$ 0.49; uv $\lambda_{max}^{cyclohexane}$ 241 nm ($\epsilon$ 14,700), no other max to 400 nm; ir (split mull) C=O at 1841 (w), 1789 (s), 1768 (m), C=C at 1563 $cm^{-1}$ (s).

*Anal.* Calcd for $C_5Br_6O$: C, 10.81; Br, 86.31. Found: C, 10.80; Br, 86.70.

**Isolation of Other By-products.**—Crude II prepared as indicated above was absorbed on silica gel for purification. After elution of II with hexane the remaining material was eluted with hexane–benzene by slowly increasing the percentage of benzene to 50%. Fifteen fractions of 1–2 l. were collected from each column, and the solvent was removed under vacuum. Each fraction was analyzed by tlc. Those fractions having only one or two components were purified further. The only compounds isolated were those which were separated by chance. Many unknown mixtures were discarded.

Fractions 1–9, 2–9, and 2–10 were absorbed on a 350-g silica gel column and eluted with hexane. Nine fractions with a volume increasing from 250 to 2000 ml were collected. Fractions 6–9 were combined. Recrystallization from hexane gave clumps of brown crystals and of off-white crystals. The crystals were separated by hand.

Two recrystallizations of the brown crystals from hexane–methylene chloride gave 0.9 g of V as amber crystals, mp 139–141° dec, tlc (hexane with wick) one spot, $R_f$ 0.35. This material was identical with a sample of $C_{10}Br_{10}$ previously described.[6]

Recrystallization of the off-white crystals from hexane–methylene chloride gave 0.4 g of IV as off-white crystals: mp

(11) Chlorine-containing impurities in earlier preparations from halogen exchange with methylene chloride during work-up. Slow work-up can drive the product back to very high values of chlorine-containing impurities if the aluminum bromide is not destroyed. A volatile solvent that does not react with aluminum bromide is desired. Benzene gives brominated benzene impurities which are very difficult to remove. Bromine was added as a solvent when early runs at room temperature set up solid. Excess boron tribromide is used on the assumption that $BBrCl_2$ is vented along with $BCl_3$. When high-purity starting material [purified by vacuum distillation, center cut, bp 108° (10 mm); $n^{25}D$ 1.5625; glc indicated 98% purity] I was used, the crude product could be passed through a single 3-kg column for purification.

135–137° dec; tlc (hexane with wick) one spot, $R_f$ 0.35; ir ($CCl_4$) CH at 2961 (w), C=C at 1566 (m), max at 1152 $cm^{-1}$ (s); nmr ($CDCl_3$) single line at $\delta$ 5.56; mass spectrum, weak P+ at $m/e$ 614; uv $\lambda_{max}^{cyclohexane}$ 244 nm ($\epsilon$ 13,000).

*Anal.* Calcd for $C_5HBr_7$ (620.5): C, 9.68; H, 0.16; Br, 90.16. Found: C, 10.0; H, <0.3; Br, 90.4.

Column fractions 1–15, 2–14, and 2–16 were combined and recrystallized from hexane–methylene chloride. The first crop (0.5 g) was eluted from a 12 × 2.5 cm silica gel column with benzene to give 0.4 g of brown solid. Two recrystallizations from methylene chloride–carbon tetrachloride gave 0.2 g of VI as yellow crystals, mp 190–192°, identical with a sample of VI prepared by Pews.[9]

Column fractions 1–16, 17, 18, and 2–17, 18, 19 were recrystallized from methanol–methylene chloride to give a mixture of colorless and yellow crystals. Two recrystallizations from methylene chloride–carbon tetrachloride gave 0.3 g of VII as white crystals, mp 172–174° with decomposition and formation of a solid remelting about 215° dec, tlc (benzene with wick) one spot, $R_f$ 0.47. This material was identical with a sample of VII prepared by Pews.[10]

**Registry No.**—II, 14310-17-9; IIIa (X = Br), 36976-60-0; IVa, 36976-61-1; IVb, 36976-62-2.

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# The Synthesis of Cyclic *N*-Cyanoguanidines
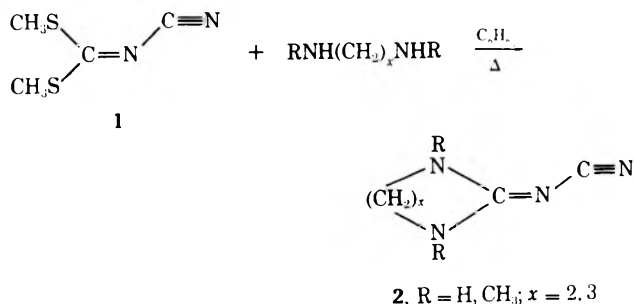
C. M. Baltzer and C. G. McCarty*

*Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506*

The observation that dimethyl cyanoimidodithiocarbonate (1) reacts readily with primary and secondary amines to give *N*-cyanoguanidines[1] prompted us to examine the possible use of 1 with diamines for the synthesis of cyclic *N*-cyanoguanidines. Such cyclic guanidines, not previously reported in the literature, may prove to be as interesting as some of their acyclic analogs which have been studied as hypotensive agents[2] and potential antimalarials.[3]

The reactions of 1 with the various primary and secondary diamines proceed quite readily at the reflux temperature of dry benzene to yield cyclic guanidines with the general formula 2 (Table I).

**2.** R = H, $CH_3$; x = 2.3

(1) C. G. McCarty, J. E. Parkinson, and D. M. Wieland, *J. Org. Chem.*, **35**, 2067 (1970).

(2) S. M. Gadekar, S. Nibi, and E. Cohen, *J. Med. Chem.*, **11**, 811 (1968).

(3) E. L. May, *J. Org. Chem.*, **12**, 437 (1947).

TABLE I

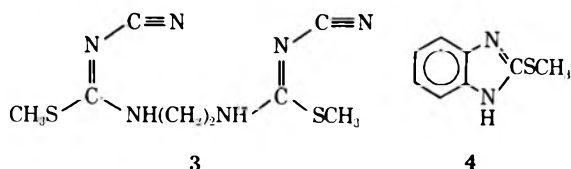CYCLIC *N*-CYANOGUANIDINES FROM 1[a]

| Diamine | Yield, % | Mp, °C | Registry no. |
|---|---|---|---|
| H₂N(CH₂)₂NH₂ | 41 | 215–216 | 36982-79-3 |
| CH₃NH(CH₂)₂NHCH₃ | 58 | 93–94 | 36982-80-6 |
| H₂N(CH₂)₃NH₂ | 85 | 186–188 | 36982-81-7 |
| CH₃NH(CH₂)₃NHCH₃ | 59 | 34–35 | 36982-82-8 |

[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all compounds listed.

Five- and six-membered rings have been prepared using ethylenediamine, *N,N*'-dimethylethylenediamine, 1,3-propanediamine, and *N,N*'-dimethyl-1,3-propanediamine in yields of 41–85%.

The products all show three distinct bands in the infrared region: 2195–2175 (C≡N), 1630–1550 (C=N), and 1290 cm⁻¹ (CN). Their respective nmr spectra are consistent with the assigned structures.

In the case of the reactions using ethylenediamine, the total yield of products was divided between the expected cyclic guanidine (41%) and a compound which proved to be 3 (31%). The reaction gave 3 under a variety of conditions using different solvents, high dilution, inverse addition, etc. Such a side product was not found in any of the reactions with the other diamines. The structure assigned to 3 is consistent with the ir and mass spectral data obtained for it plus the correct microanalysis. Also consistent is the observation that 3 eliminated methyl mercaptan (trapped as the silver mercaptide) when heated to 360°.[1]



3                                        4

The reaction of 1 with *o*-phenylenediamine did not yield the expected cyclic *N*-cyanoguanidine. The product obtained was found to be a benzimidazole (4) as reported by D'Amico and coworkers[4] during the course of our investigation.

It is interesting to compare our results with those reported recently by others for the synthesis of cyclic *N*-tosylguanidines from diamines and the *N*-tosyl derivative of 1. Rodricks and Rapaport[5] apparently observed no product similar to 3 in reactions with ethylenediamine. Also they reported the formation of the expected cyclic guanidine from reactions with *o*-phenylenediamine. On the other hand, their reactions were limited to the synthesis of cyclic guanidines with R = H, since dimethyl *N*-tosylimidodithiocarbonate is unreactive toward secondary amines.

### Experimental Section

Melting points were determined with a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Nmr spectra were recorded on a Varian T-60 spectrometer using tetramethylsilane as an internal standard (δ 0.0) and solvents as specified. Ir spectra were recorded on Perkin-Elmer Model 137B and Beckman

(4) J. J. D'Amico, K. Boustany, A. B. Sullivan, and R. R. Campbell, presented at the 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 13–17, 1971.

(5) J. V. Rodricks and H. Rapaport, *J. Org. Chem.*, **36**, 46 (1971).

IR-8 spectrophotometers. Mass spectra were obtained with a Nuclide 12-90-G high resolution. single-focusing spectrometer.

**General Procedure.**—The reaction involving 1,3-propanediamine will be described. The reactions involving the other diamines were carried out in a similar fashion.

To 20 mmol (1.48 g) of the freshly distilled diamine was added 20 mmol (2.92 g) of dimethyl cyanoimidodithiocarbonate (1)[6] in 250 ml of benzene (previously dried over CaH₂). The reaction mixture turned cloudy immediately upon combination of starting materials and the evolution of methyl mercaptan was apparent. The mixture was heated under reflux with stirring for about 6 hr. The white precipitate was filtered from the reaction mixture and air dried. Reduction of the volume of the filtrate yielded no additional material. The crude product was recrystallized from acetone to yield 2.1 g (85%) of white crystals: mp 186–188°; ir (KBr) 3270 (NH), 2150 (C≡N), 1630 (C=N), and 1290 cm⁻¹ (CN); nmr (DMSO-*d₆*) δ 7.5 (s, 2, NH), 3.2 (t, 4, *J* = 6 Hz, -CH₂CH₂CH₂-), 1.8 (quintet, 2, *J* = 6 Hz, -CH₂CH₂CH₂-).

*Anal.* Calcd for C₅H₆N₄: C, 48.4; H, 6.44; N, 45.1. Found: C, 48.1; H, 6.41; N, 44.9.

This reaction (and the others) was successfully repeated several times to establish the reproducibility of the results.

Formation of 3 along with the expected cyclic guanidine from 1 plus ethylenediamine was observed under a variety of conditions, including different solvents (benzene, acetone, absolute ethanol), high dilution, and inverse addition. For example, when 40 mmol (5.48 g) of 1 was added to 40 mmol (2.40 g) of ethylenediamine in 250 ml of dry benzene the mixture immediately turned cloudy. After 4 hr at reflux temperature, the mixture was cooled and the white solid was collected by vacuum filtration. The crude material (4.0 g, mp 203–205°) was separated by fractional crystallization from hot water into 1.62 g of cyclic guanidine (mp 215–216°) and 1.62 g of 3 (mp >350° dec): ir (KBr) 3260 (NH), 2180 (C≡N), 1545 cm⁻¹ (C=N); mass spectrum (70 eV) *m/e* 208 (M⁺ − CH₃SH), 161 (208 − CH₃S·).

*Anal.* Calcd for C₈H₁₂N₆S₂: C, 37.5; H, 4.7; N, 32.8; S, 25.0. Found: C, 37.6; H, 4.6; N, 32.9; S, 24.9.

A sample of 3 was heated to 360° in a test tube in a Wood's metal bath while the vapors evolved were led through a trap filled with 5% aqueous AgNO₃. The precipitate which formed in the trap (AgSCH₃) was collected by filtration. Treatment of this material with a few drops of dilute HCl resulted in the evolution of a gas which was unmistakably methyl mercaptan.

**Benzimidazole 4** was formed from the reaction of 20 mmol (2.92 g) of 1 with 20 mmol (2.16 g) of *o*-phenylenediamine in 250 ml of 95% ethanol. After the mixture was heated under reflux for 48 hr the solvent was removed on a rotary evaporator. The brown residue was recrystallized from ethanol–water (3:2) to yield 2.05 g of white crystals: mp 203–205°; ir (KBr) 3060 (CH), 740 cm⁻¹ (ortho-disubstituted benzene); nmr (DMSO-*d₆*) δ 2.7 (s, 3, CH₃), 7.0–7.6 (m, 4, C₆H₄). Further analysis of 4 was not pursued since the report on its identity[5] appeared at this time.

**Registry No.**—3, 36994-48-6; 4, 7152-24-1.

(6) A. Hantzsch and M. Wolvekamp, *Justus Liebigs Ann. Chem.*, **331**, 265 (1904).

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### Reaction of *tert*-Butylcyanoketene with Tertiary Amines. Synthesis of 1,3-Di-*tert*-butyl-1,3-dicyanoallene

HAROLD W. MOORE* AND WARREN G. DUNCAN

*Department of Chemistry, University of California, Irvine, California 92664*

Reported here is the high-yield conversion of *tert*-butylcyanoketene (1) to 1,3-di-*tert*-butyl-1,3-dicyano-

allene (**3**) induced by the action of triethylamine at ambient temperature or below. The β-lactone **2** is shown to be an intermediate which subsequently reacts with the amine to give the allene **3**.
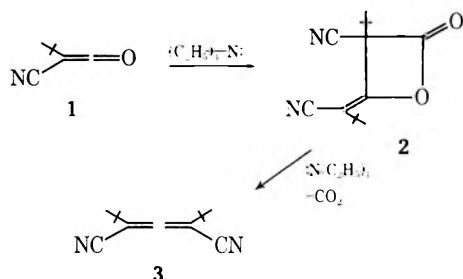


The above transformation, accomplished under the reaction conditions reported here, appears to be unique in the chemistry of ketenes. A variety of dimerization pathways for ketenes have been investigated. Farnum and coworkers[1] have proposed that all spontaneous dimerizations of ketenes, except for the parent itself, give 1,3-cyclobutanediones as the major primary products. England and Krespan[2] have investigated the cycloaddition of bis(trifluoromethyl)ketene with a variety of other ketenes to form mixed dimers. Ketene and methylketene were shown to react with bis(trifluoromethyl)ketene giving, respectively, the β-lactones **4** and **5**. Dimethylketene, however, gave a mixture of the β-lactone **6** and the cyclobutanedione **7**. The
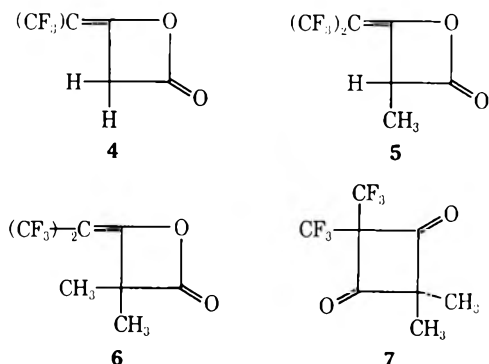


authors have interpreted these reactions as most likely involving a two-step nonconcerted cycloaddition of the electron-deficient fluoroketene to the carbon–carbon bond of the other cumulene component. *In situ* preparation and dimerization of aliphatic aldoketenes by dehydrohalogenation of the corresponding acid chlorides *via* the action of triethylamine in ether give principally the β-lactone dimers.[1,3–5]

Spontaneous dimerization of *tert*-butylcyanoketene has not been observed. This cumulene is conveniently prepared by the thermal cleavage of 2,5-diazido-3,6-di-*tert*-butyl-1,4-benzoquinone (**8**) in refluxing benzene.[6] The ketene is stable to self-condensation in benzene solution, even at the refluxing temperature for a prolonged period of time (7 days). However, the β-lactone
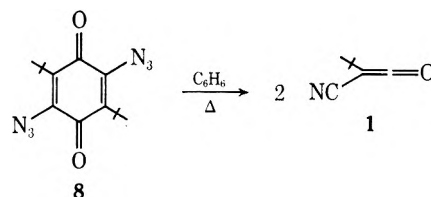


dimer **2** was readily obtained from the ketene **1** by the action of a catalytic amount of triethylamine. It was found that 0.01 equiv of the tertiary amine induced the slow dimerization (8–12 hr) of the ketene in benzene solution giving the β-lactone **2**.

The structure of the β-lactone dimer **2** is in accord with its spectral and chemical properties. Its infrared spectrum (Nujol) showed characteristic carbonyl and alkene absorptions[2,7,8] at 1923, 1865, and 1670 cm$^{-1}$. The nmr spectrum (CDCl$_3$) showed absorptions for the *tert*-butyl groups at δ 1.32, and the mass spectrum showed a molecular ion at $m/e$ 246 corresponding to 3% of the base peak at $m/e$ 108, which represents the loss of a methyl group from *tert*-butylcyanoketene itself (25% of the base peak). The uv spectrum of **2** in 95% ethanol showed λ$_{max}$ 262 nm. Upon standing in air or upon chromatography over silica gel, hydrolytic decarboxylation takes place, giving the ketone **9**. Analogous transformations have been reported for the β-lactone dimers of diphenylketene[8] and *n*-butylketene.[9] Sodium borohydride reduction of **2** in THF gave a 10% isolated yield of the expected product **10**. Analogous reductions have been reported for tetramethyl-β-propiolactone.[10,11]
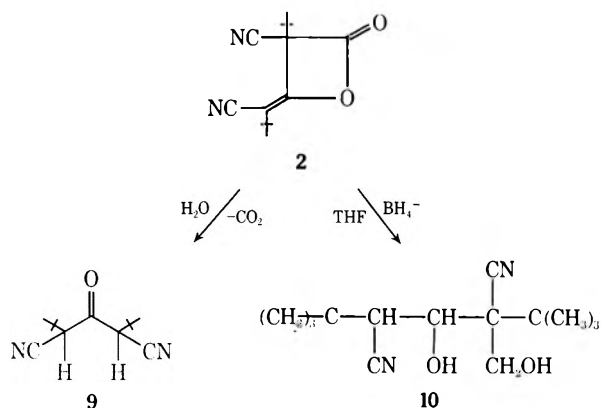


A most interesting and, to our knowledge, unprecedented reaction takes place when the β-lactone **2** is treated with 0.1 equiv of triethylamine at ambient temperature. It reacts immediately to give 1,3-di-*tert*-butyl-1,3-dicyanoallene (**3**) in 68% isolated yield. The same allene could be efficiently generated by reacting a benzene solution of *tert*-butylcyanoketene (**1**) with 0.1 equiv of triethylamine (50%) or upon dehydrohalogenation of α-*tert*-butyl-α-cyanoacetyl chloride with the tertiary amine (95%). All of these results are consistent with the following possible mechanism.

The infrared spectrum (Nujol) of the allene **3** shows characteristic absorptions at 2220 (C≡N) and 1945 cm$^{-1}$ (C=C=C). The chemical shift of the *tert*-butyl

(1) D. G. Farnum, J. R. Johnson, R. E. Hess, T. B. Marshall, and B. Webster, *J. Amer. Chem. Soc.*, **87**, 5191 (1965).

(2) D. C. England and C. G. Krespan, *J. Org. Chem.*, **35**, 3322 (1970).

(3) J. C. Sauer, *J. Amer. Chem. Soc.*, **69**, 2444 (1947).

(4) C. M. Hill and G. W. Senter, *ibid.*, **71**, 364 (1949).

(5) For further discussion of the dimerization of ketenes, see H. Ulrich, "Cycloaddition Reactions of Heterocumulenes," Academic Press, New York, N. Y., 1967; R. N. Lacey in "The Chemistry of the Alkenes," S. Patai, Ed., Interscience, New York, N. Y., 1964.

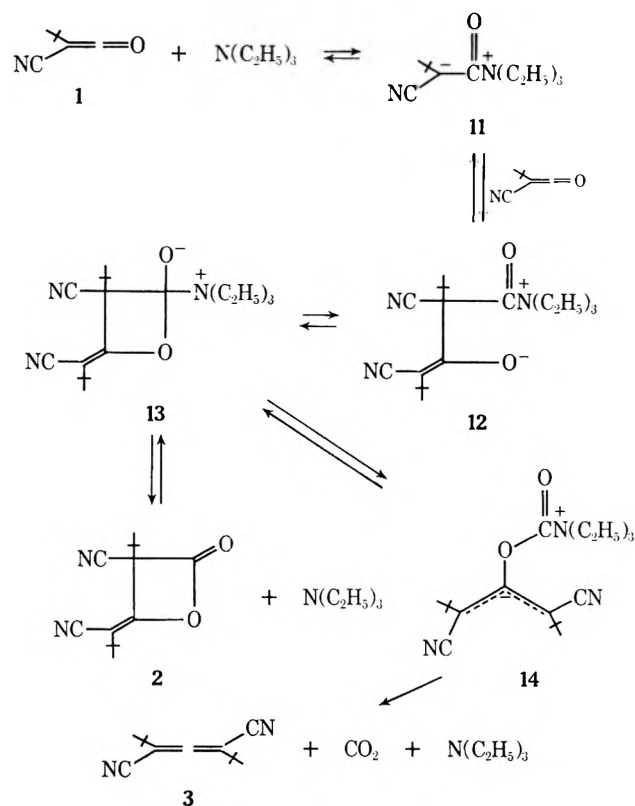(6) H. W. Moore and W. Weyler, *J. Amer. Chem. Soc.*, **92**, 4132 (1970); **93**, 2812 (1971).

(7) C. J. Pauchert, "The Aldrich Library of Infrared Spectra," Aldrich Chemical Co., Milwaukee, Wis., 1970, pp 206, 310.

(8) R. Anet, *Chem. Ind. (London)*, 1313 (1961).

(9) C. M. Hill and M. E. Hill,[1] *J. Amer. Chem. Soc.*, **75**, 4591 (1953).

(10) G. Natta, G. Mazzanti, G. Pregaglia, and M. Binaghi, *ibid.*, **82**, 5511 (1960).

(11) R. L. Wear, *ibid.*, **73**, 2390 (1951).

groups appear at δ 1.23 (s) in the nmr spectrum (CCl₄), and the mass spectrum shows a molecular ion at $m/e$ 202.

Allenes have been generated from β-lactone dimers of certain ketenes by high-temperature pyrolysis (150–650°).[12] However, there are no reports in the literature analogous to the facile hydrolytic decarboxylation reported here. Thus, the triethylamine-catalyzed conversion of **2** to **3** appears to be a new reaction. The ease with which this cleavage takes place may be a reflection of the stability of the proposed dicyanoallylcarbanionic intermediate **14**, and thus may be a general reaction for the asymmetrical dimers of cyanoketenes.[13]

### Experimental Section

**Reaction of *tert*-Butylcyanoketene (1) with 0.01 Equiv of Triethylamine. β-Lactone 2.**—A solution of 13.3 mmol of *tert*-butylcyanoketene (1) was prepared by refluxing 2.0 g (6.67 mmol) of 2,5-diazido-3,6-di-*tert*-butyl-1,4-benzoquinone (8) in 20 ml of anhydrous benzene for 2 hr. The benzene solution was cooled to room temperature and 13 mg (0.13 mmol) of triethylamine was added. After 21 hr, an ir spectrum of the reaction solution showed no ketene absorption. The solvent was removed *in vacuo* at 0°, leaving a yellow solid which resisted further purification and recrystallization. It slowly decomposed upon heating and thus showed a broad melting range, 69–79°. However, all of the spectral data for this compound are in agreement with the β-lactone structure **2** (*vide supra*).

**3,5-Dicyano-2,2,6,6-tetramethyl-4-heptanone (9).**—The ketone **9** was prepared in 45% yield by subjecting 0.8 g (3.3 mmol) of the β-lactone **2** to chromatography over silica gel. The same ketone could be prepared by allowing a small sample of **2** to stand exposed to the laboratory air for several days. Hexane recrystallization of the 0.35 g of white solid obtained from the silica gel chromatography gave an analytical sample of **9**, mp 108–109°.

(12) J. C. Martin, U. S. Patent 3,131,234 (1964); *Chem. Abstr.*, **61**, 2969*f* (1964).

(13) The relaxation of possible steric interactions between the two *tert*-butyl substituents in going from the β-lactone to the allene may also be of major importance in this reaction.

*Anal.* Calcd for C₁₃H₂₀N₂O: C, 70.86; H, 9.15; N, 12.71. Found: C, 71.31; H, 8.89; N, 12.67.

Spectral data for **9** follow: ir (Nujol) 2260 (CN) and 1730 cm⁻¹ (C=O); nmr (CDCl₃) δ 1.19 (s, 18, (CH₃—C), 3.57 (s, 2, CH).

**3,5-Dicyano-4-hydroxy-3-hydroxymethyl-2,2,6,6-tetramethyl-heptane (10).**—To a solution of 0.5 g (2.2 mmol) of **2** in 25 ml of THF was added 0.18 g (4.8 mmol) of sodium borohydride. This mixture was stirred for 24 hr at room temperature. It was then diluted with water and extracted with dichloromethane. Removal of the solvent gave an oil which partially solidified upon addition of carbon tetrachloride. Filtration gave 50 mg (10% yield) of **10** as a white solid which was recrystallized from chloroform-hexane (1:1) to give the analytical sample, mp 226–227°.

*Anal.* Calcd for C₁₄H₂₄N₂O₂: C, 66.63; H, 9.59; N, 11.10. Found: C, 66.69; H, 9.55; N, 11.10.

Spectral data for compound **10** follow: ir (Nujol) 3350 (OH) and 2265 cm⁻¹ (CN); nmr (DMSO-d₆) δ 1.05 (s, 9), 1.15 (s, 9), 3.00 (s, 1), 3.67 (d, 2, $J$ = 4 Hz), 4.18 (d, 1, $J$ = 7 Hz), 5.35 (t, 1, $J$ = 4 Hz), 5.77 (d, 1, $J$ = 7 Hz).

**1,3-Di-*tert*-butyl-1,3-dicyanoallene (3). Method A.**—To 10 ml of a benzene solution containing 6.7 mmol of the β-lactone **2** was added 50 mg (0.5 mmol) of triethylamine. An infrared spectrum taken immediately after addition of the amine showed the disappearance of all bands associated with the β-lactone. Thin layer chromatography showed only one spot. Removal of the solvent and purification of the resulting white solid by chromatography gave 0.923 g (68% yield) of the allene **3**, mp 50.5–51.5°.

*Anal.* Calcd for C₁₃H₁₈N₂: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.29; H, 8.90; N, 13.88.

**Method B.**—To a solution of 10.0 mmol of *tert*-butylcyanoketene (1) in 15 ml of benzene was added 30 mg (0.3 mmol) of triethylamine. An infrared spectrum taken immediately showed no ketene absorption. The solvent was removed *in vacuo* and the residue was purified by column chromatography over silica gel. There was collected 0.5 g (50% yield) of the allene **3** which was shown to be identical in all respects with that obtained by method A.

**Method C.**—A solution of 6.6 mmol of *tert*-butylcyanoketene (1) in 10 ml of benzene was cooled in an ice bath and anhydrous hydrogen chloride gas was passed through the solution for 30 min. A solution infrared spectrum showed the absence of ketene absorption and the presence of a carbonyl absorption corresponding to an acyl chloride at 1780 cm⁻¹. Nitrogen gas was then passed through the reaction solution in order to remove the excess hydrogen chloride. The resulting solution was stirred at 0° while adding, dropwise, 0.66 g (6.6 mmol) of triethylamine. The reaction mixture was then extracted with water and the benzene solution was separated and dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* gave 0.63 g (95% yield) of the allene **3**.

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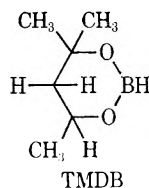## Relative Rates of Hydroboration of Several Olefins with 4,4,6-Trimethyl-1,3,2-dioxaborinane

RICHARD H. FISH[1]

*U. S. Borax Research Corporation,*
*Anaheim, California*

Recently we have demonstrated the utility of 4,4,6-trimethyl-1,3,2-dioxaborinane (TMDB) as a stable,

(1) Address correspondence to the Western Regional Research Laboratory, USDA, Berkeley, Calif. 94710.

CH₃, CH₃

(TMDB structure)

TMDB

monomeric hydroborating agent.[2,3] It was found that TMDB could be added to olefins[2] and 1,2- and 1,3-dienes[3] at temperatures of 100–130° in 24–48 hr.

In this note we report the relative rates of hydroboration of several olefins with TMDB and compare the reactivity of TMDB with that of disiamylborane (DSB)[4] and 1,3,2-benzodioxaborole (BDB).[5] Table I

TABLE I

RELATIVE RATES OF HYDROBORATION UTILIZING TMDB

| Olefin | $K_{rel}^a$ at 98 ± 0.1° |
|---|---|
| 1-Octene | 7.18 |
| cis-2-Octene | 1.19 |
| trans-2-Octene | 1.07 |
| Cyclohexene | 1.0 |

*a* See Experimental Section for the procedure and calculations involved in these studies.

shows the results when cyclohexene was allowed to compete with three other olefins separately for a deficiency of TMDB.

It is evident that the range of magnitudes of the relative rates is not large, since 1-octene is only 7.18 times more reactive than cyclohexene toward TMDB. In contrast to this result, 1-octene reacts 8400 times faster than cyclohexene toward DSB at 0°.[4] Also, cis-2-pentene was 161 times more reactive than cyclohexene (DSB) at 0°,[4] while cis-2-octene was only 1.19 times more reactive than cyclohexene (TMDB) at 98°. Interestingly enough, cis-2-pentene was 3.0 times more reactive than trans-2-pentene (DSB)[4] at 0°, while cis-2-octene was 1.1 times faster than trans-2-octene (TMDB) at 98°. It is quite obvious from these results that the effect of the oxygens on the boron–hydrogen bond moment is such that electron donation by oxygen 2p electrons to the vacant 2p orbital of boron makes the B–H bond moment of TMBD larger, and hence TMDB is less reactive in hydroboration. This effect raises the activation energy for hydroboration and makes any change in olefin structure (i.e., 1-octene to 2-octene) with respect to the rate of reaction extremely small, as is observed. Although we have not done any quantitative relative rate measurements comparing TMDB with other stable dialkyloxy or diaryloxyboranes, we can qualitatively compare 1,3,2-benzodioxaborole (BDB),[5,6] a stable, benzene-substituted dioxaborane, with TMDB in their reactivity with several olefins. It is evident from Brown's data[5] that terminal olefins react reasonably well with BDB at 100° for 2 hr to give high yields (>95%) of adducts. Brown[5] also found that internal olefins such as cyclohexene and norbornene reacted well at 100° for 4 hr to also give >95% yields of hydroboration products. In contrast to this, TMDB reacts very slowly with 1-octene in diethyl

ether to give a 28% isolated yield of adduct after heating for 3 days at 100° (sealed tube) and similarly with cyclohexene at higher temperatures (2 days at 100° and 1 day at 210°) to give a 57% yield of adduct.[2] In a comparion using a bicyclic olefin [norbornadiene (TMDB) vs. norbornene (BDB)] we found that TMDB adds to norbornadiene in 16% yield (92% exo, 8% endo) after heating for 50 hr at 130°, while Brown[5] can add BDB to norbornene at 100° for 4 hr in >95% yield. These results point up the fact that in BDB, where oxygen is bonded to a benzene ring, a dramatic increase in hydroboration rates is observed, since the oxygen 2p electrons can resonate into the benzene ring, thus making the B–H bond moment much weaker and hence more reactive. Steric factors must also enter into this rate decrease for TMDB, since its reactivity with the more reactive norbornadiene (as compared to norbornene in addition reactions) was inordinately slow as compared to cyclohexene. This apparent steric factor in TMDB does not seem important with BDB, as evidenced from the latter's reactivity.

Although TMDB reacts more slowly with olefins as compared to DSB or BDB, its stability and that of its adducts allow one to isolate the hydroboration product for direct identification.[2,3]

## Experimental Section

**Procedure for Determining the Relative Rates of Hydroboration for TMDB with Several Olefins.**—The method entails the use of an internal standard along with the two olefins, which compete for a deficiency of TMDB. The internal standard and the calibration curves are used to determine the concentration of the olefins after a given time. Thus a typical competitive experiment was run as follows.

In an ampoule was accurately weighed 1.7953 g (0.016 mol) of 1-octene, 1.3142 g (0.016 mol) of cyclohexene, 2.0520 g (0.016 mol) of nonane (internal standard), and 1.0157 g (0.008 mol) of TMDB.[3] The gas–liquid chromatography (glc) was done on a 20 ft × 0.375 in. silicone nitrile column at 50° (50 ml/min) with a sample of 6 μl. The ampoule was sealed and placed in a constant-temperature bath at 98 ± 0.1° for 78 hr. The ampoule was removed and the contents were analyzed again by glc using the above described conditions. The ratio of areas of each olefin to the area of the internal standard (nonane) was then measured by the height times half-width method. This ratio was then found on a calibration curve of known concentration vs. area. The ratio of concentration of olefin to internal standard was found and a simple calculation gave the concentration of the olefin after a certain period of time.

The calculation for $K_{rel}$ was carried out using the following equation.

$$K_{rel} = \frac{k_1}{k_2} = \frac{\log\left[\dfrac{\text{concn initial (octene)}}{\text{concn final}}\right]}{\log\left[\dfrac{\text{concn initial (cyclohexene)}}{\text{concn final}}\right]}$$

**Reaction of TMDB with Norbornadiene.**—In an ampoule was placed 8.0 g (0.084 mol) of norbornadiene, 5.4 g (0.042 mol) of TMDB, and 2 ml of anhydrous ether. The ampoule was sealed and then heated at 130° for 50 hr. Distillation gave 1.5 g (16%), bp 64–67° (0.15 mm), of product. Analysis by glc on a 5 ft × 0.25 in. silicone nitrile column at 100° (40 ml/min) gave two peaks, the first being the endo isomer (8%) and the second the exo isomer (92%) with the same retention times as those of authentic samples.[7]

**Registry No.**—TMDB, 23894-82-8; 1-octene, 111-66-0; cis-2-octene, 7642-04-8; trans-2-octene, 13389-42-9; cyclohexene, 110-83-8; norbornadiene, 121-46-0.

(2) W. G. Woods and P. L. Strong, *J. Amer. Chem. Soc.*, **88**, 4667 (1966).
(3) R. H. Fish, *ibid.*, **90**, 4435 (1968).
(4) H. C. Brown and A. W. Moerikofer, *ibid.*, **85**, 2063 (1963).
(5) H. C. Brown and S. K. Gupta, *ibid.*, **93**, 1816 (1971).
(6) H. C. Newsom and W. G. Woods, *Inorg. Chem.*, **7**, 177 (1968).

(7) W. G. Woods and I. S. Bengelsdorf, *J. Org. Chem.*, **31**, 2769 (1966).

# Proton Magnetic Resonance Spectra and Stereochemical Assignments in 5-Benzyl-2,4,6-triphenyl-1,3,5-dioxaphosphorinane 5-Oxides

Armand B. Pepperman, Jr.*

*Southern Regional Research Laboratory,[1]
New Orleans, Louisiana 70179*

Thomas H. Siddall, III

*Louisiana State University in New Orleans,
New Orleans, Louisiana 70122*

It has been reported by Buckler[2] that the reaction of benzaldehyde with phosphine in the presence of HCl proceeds with the transfer of oxygen from carbon to phosphorus to yield benzylbis($\alpha$-hydroxybenzyl)phosphine oxide 1.

$$C_6H_5C=O \ (H) \quad + \quad PH_3 \quad \xrightarrow{HCl} \quad \left( C_6H_5C(H)(OH)- \right)_2 PCH_2C_6H_5 \ (O)$$

**1**
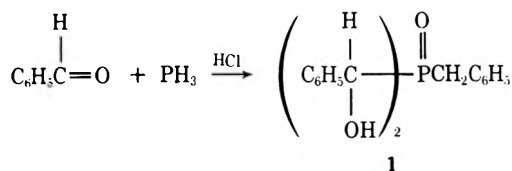
It was further shown that the reaction of 1 with benzaldehyde under conditions suitable for acetal formation led to the title compounds which are represented by the general structure 2.

$$1 \quad + \quad C_6H_5C=O \ (H) \quad \xrightarrow[\text{catalytic amount}]{p\text{-toluenesulfonic acid}} $$



**2**
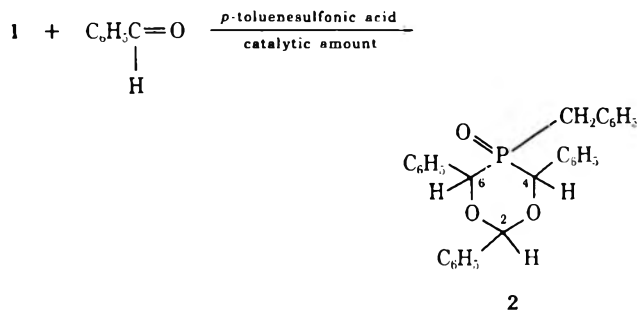
2 was obtained as a mixture of stereoisomers, two of which were isolated in pure form by fractional crystallization. 2 represents one of only several examples of 1,3,5-dioxaphosphorinanes which have been prepared.[3,4] To our knowledge there have been no reports on the stereochemistry of these products. Furthermore, there has been a great deal of interest in recent years in the preparation and stereochemistry of 1,3,2-dioxaphosphorinanes.[5-7] This interest has prompted us to report our studies on the title compounds.

(1) One of the facilities of the Agricultural Research Service, U. S. Department of Agriculture.

(2) S. A. Buckler, *J. Amer. Chem. Soc.*, **82**, 4215 (1960).

(3) (a) S. A. Buckler and V. P. Wystrach, *ibid.*, **83**, 168 (1961); (b) V. Ettel and J. Horak, *Collect. Czech. Chem. Commun.*, **25**, 2191 (1960).

(4) M. Epstein and S. A. Buckler, *Tetrahedron*, **18**, 1211, 1231 (1962).

(5) (a) A. R. Katritzky, M. R. Nesbit, J. Michalski, Z. Tuhmowski, and A. Zwierzak, *J. Chem. Soc. B*, 140 (1970); (b) R. S. Edmundson and E. W. Mitchell, *J. Chem. Soc. C*, 752 (1970).

(6) (a) R. S. Edmundson and E. W. Mitchell, *ibid.*, 2091 (1968); (b) D. W. White, G. K. McEwen, R. D. Bertrand, and J. G. Verkade, *J. Chem. Soc. B*, 1454 (1971).

(7) W. G. Bertrand, H. W. Tan, and K. C. Yee, *J. Amer. Chem. Soc.*, **94**, 3264 (1972).

## Discussion and Results

An examination of 1 revealed the possibility of two meso forms and one *d,l* pair. These are shown in Figure 1. Ph stands for phenyl and Bz for benzyl, and the configuration about each carbon is designated.[8] The nmr spectra for 1 showed it to be the *d,l* form as the benzyl methyne protons appeared as a doublet of doublets and the benzyl methylene protons as the AB portion of an ABX pattern. The meso form of 1 would be expected to show doublets for both the benzyl methyne and benzyl methylene protons. Raising the temperature of 1 to 100° caused no change in its nmr spectra.

For 2 there is the possibility of 16 isomers. Assuming rapid ring inversion, these can be reduced to eight sets of different nmr signals. Furthermore, since there are two sets of mirror pairs, only six sets of nmr signals are potentially observable. Table I lists the eight pos-

### Table I

#### Isomeric Possibilities of 2

| Isomer no. | Configuration (equatorial) | |
|---|---|---|
| I | O, Ph, Ph, Ph | |
| II | O, H, Ph, Ph | |
| III | O, H, H, Ph | |
| IV | O, H, H, H | *d,l* pair |
| V | O, Ph, H, Ph | *d,l* pair |
| VI | O, Ph, H, H | |
| VII | O, Ph, Ph, H | |
| VIII | O, H, Ph, H | |

sibilities; the groups shown are in the equatorial positions. The groups are taken in order moving clockwise from phosphorus.

Preparation of 1 and 2 and fractional crystallization of 2 proceeded essentially as described by Buckler.[2] Two isomers were obtained and shown to have markedly different ir and nmr spectra. Table II shows the

### Table II

#### Infrared Bands for Both Isomers

| Spectral region, $\mu$ | Bands for 2a | Bands for 2s |
|---|---|---|
| 2.5–3.0 | | |
| 3.0–4.0 | 3.28 (m), 3.45 (m) | 3.28 (m), 3.45 (m) |
| 4.0–5.0 | | |
| 5.0–6.0 | | |
| 6.0–7.0 | 6.25 (m), 6.7 (s), 6.9 (s) | 6.25 (m), 6.7 (s), 6.9 (s) |
| 7.0–8.0 | 7.32 (s), 7.85 (m) | 7.26 (s) |
| 8.0–9.0 | 8.22 (vs), 8.33 (vs), 8.60 (s), 8.99 (vs) | 8.4 (vs) |
| 9.0–10.0 | 9.09 (vs), 9.37 (s), 9.8 (vs), 9.92 (s) | 9.20 (vs), 9.39 (vs), 9.72 (s) |
| 10.0–11.0 | 10.6 (m), 10.85 (m) | 9.8–10.1 (vs), 10.68–10.96 (vs) |
| 11.0–12.0 | 11.48 (m) | 11.48 (m) |
| 12.0–13.0 | 12.41 (m) | |
| 13.0–14.0 | 13.10 (vs), 13.20 (s), 13.62 (m) | 13.0 (vs), 13.2 (s), 13.85 (s) |
| 14.0–15.0 | 14.15 (s), 14.4 (vs) | 14.3 (vs) |

important ir bands for the two isomers. The ir spectra were essentially identical up to the 7.0-$\mu$ region, but

(8) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 92.
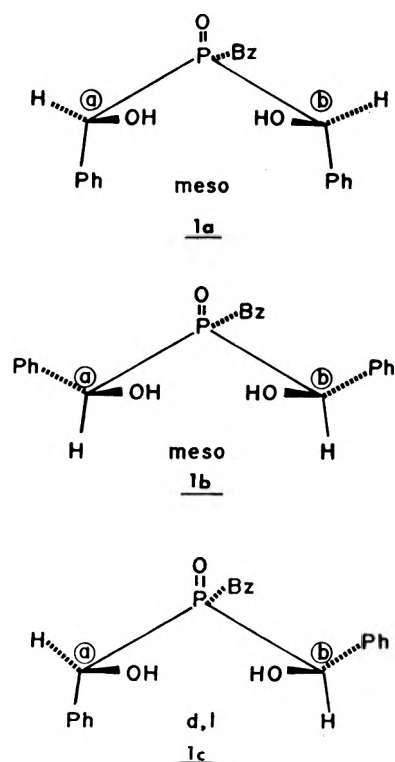
Figure 1.—Isomeric possibilities for 1: 1a, $C_a$ has $S$ and $C_b$ $R$ configuration; 1b, $C_a$ has $R$ and $C_b$ $S$ configuration; 1c, $C_a$ has $S$ and $C_b$ $S$ configuration. In mirror image of 1c both carbons have $R$ configuration.



Figure 2.—Nmr spectra of isomeric 1,3,5-dioxaphosphorinanes.

from there to 17 $\mu$ they differed dramatically. Of particular interest were the numerous differences in the 8–10-$\mu$ region where the P=O and C–O–C absorptions are expected. There were no differences in the >C–H stretching or aromatic >C=C< and >C–H bending regions but minor differences could be seen in the substituted benzene region.

The nmr spectra of the two isomers are shown in Figure 2. 2a exhibited a relatively complex spectrum with different protons at $C_4$ and $C_6$ (two overlapping AX patterns). The proton at $C_2$ appeared as a singlet. The benzylic protons at phosphorus appeared as the AB portion of an ABX pattern. Analysis of this portion of the spectrum gave values of 15 Hz for $J_{AB}$, 22.5 Hz for $2D_+$, 30.5 Hz for $2D_-$, and 13 Hz for $^1/_2|J_{AX} + J_{BX}|$.[9,10]

Solving simultaneously the equations

$$D_+ = {}^1/_2\{[(V_A - V_B) + {}^1/_2(J_{AX} - J_{BX})]^2 + J_{AB}{}^2\}^{1/2}$$

$$D_- = {}^1/_2\{[(V_A - V_B) - {}^1/_2(J_{AX} - J_{BX})]^2 + J_{AB}{}^2\}^{1/2}$$

yields values for $(J_{AX} - J_{BX})$ of $\pm 43.3$ and $\pm 9.8$. Solving for $J_{AX}$ and $J_{BX}$ gives one set of values in which $|J_{AX}|$ or $|J_{BX}|$ is 34.65 which is unrealistically high. The other solution $[(J_{AX} - J_{BX}) = \pm 9.8)]$ gives values of $\pm 17.9$ and $\pm 8.1$ for $J_{AX}$ and $J_{BX}$. Neither value can be assigned to a particular coupling constant as 2a was not soluble enough for a $^{31}P$ nmr spectra to be obtained. Thus the X portion of the spectra could not be observed. However, the values of $\pm 17.9$ and $\pm 8.1$ are what would
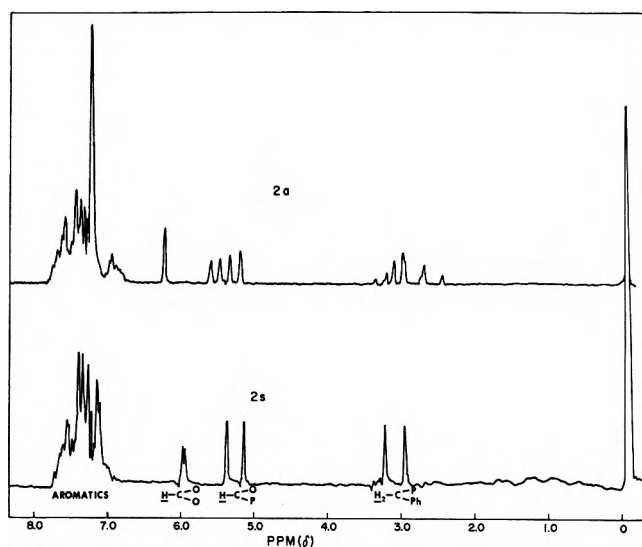
be expected for P–CH coupling in phosphorus–methylene compounds.[11–14]

The spectra showed conclusively that 2a was one of the $d,l$ pairs II–VII or III–VI since the benzyl protons were nonequivalent. This could occur only if there was no symmetry plane between the benzyl protons[15] as is the case in the $d,l$ pairs. All of the other isomers have a symmetry plane through the 2,5 positions and of course through the benzyl methylenes.

Studies of 1,3,2-dioxaphosphorinanes[5–7] and very recent studies on phosphacyclohexane[16] and its derivatives have shown that the favorable position for substituents on phosphorus is axial while the electron pair (phosphines), oxygen (oxides), or sulfur (sulfides) occupy the equatorial position.

Alkyl and aryl substituents on phosphorus exhibit this strong preference for the axial conformation despite the fact that severe 1,3 interactions are possible. In the 1,3,5-dioxaphosphorinane system there is no possibility of 1,3 interactions involving the substituent on phosphorus. For this reason the preference for the axial conformation by the substituent on phosphorus should be more pronounced and the benzyl group on phosphorus should be axial.

The proton at $C_2$ shows no discernible coupling to phosphorus. If the proton were in the equatorial position, a coupling of about 1–2 Hz would be expected as a planar zigzag arrangement[17] exists between the phosphorus and the equatorial proton. The phosphorus coupling to the axial proton would be expected to be less than 1 Hz.[18] The structure of 2a can therefore be designated as shown which is the $d,l$ pair II–VII. Thus, two of the three phenyl groups attached to carbon occupy the favored equatorial positions.

2s exhibits a highly symmetrical nmr indicating that the phenyl groups at $C_4$ and $C_6$ are either both axial or both equatorial. Isomers I, IV, V, and VIII would be

(9) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. I, Pergamon Press, Oxford, 1965, pp 357–363.

(10) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, pp 105–113.

(11) K. J. Coskran and J. G. Verkade, *Inorg. Chem.*, **4**, 1655 (1965).

(12) R. G. Laughlin, *J. Org. Chem.*, **30**, 1322 (1965).

(13) K. Moedritzer, L. Maier, and L. C. D. Groenweghe, *J. Chem. Eng. Data*, **7**, 307 (1962).

(14) R. A. Y. Jones and A. R. Katritzky, *Angew. Chem.*, **74**, 60 (1962).

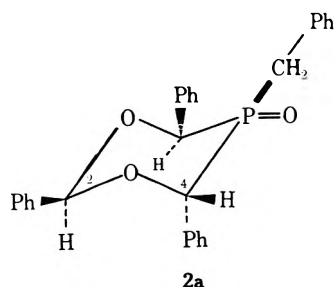(15) T. H. Sidall, III, *J. Phys. Chem.*, **70**, 2050 (1966).

(16) J. D. Lambert and W. L. Oliver, Jr., *Tetrahedron*, **27**, 4245 (1971).

(17) K. C. Raney and J. Messick, *Tetrahedron Lett.*, 4423 (1965).

(18) L. D. Hall and R. B. Malcolm, *Chem. Ind. (London)*, 92 (1968).

**2a**

expected to give symmetrical nmr spectra since they each have a plane of symmetry through the 2,5-ring positions. However, an examination of molecular models showed isomers IV and VIII to be extremely crowded with severe 1,3 interactions between the phenyl groups at $C_4$ and $C_6$. These interactions would favor the diequatorial configuration at $C_4$ and $C_6$. The proton at $C_2$ shows a doublet ($J = 2$ Hz). The only coupling which would give a doublet would be to phosphorus. This long-range coupling would be expected to be greater than 1 Hz only if the proton were equatorial.[17,18] Thus, the structure of **2s** is that of



**2s**
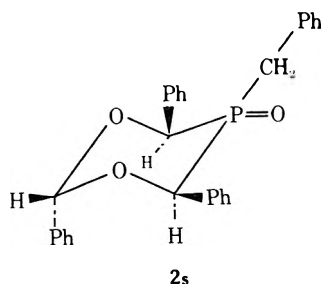
isomer V. Again two of the three phenyl groups attached to carbon are in the equatorial positions.

The two isomers isolated are the only ones which have two bulky groups equatorial and two axial. All the rest have three bulky groups, either axial or equatorial.

The reasons for obtaining only these two isomers and the mechanism necessary to produce the meso ring system from *d,l* starting material are now under investigation and will be reported in a subsequent publication.

### Experimental Section

Reagent grade chemicals were used as supplied. Phosphine was generated by addition of water to a suspension of aluminum phosphide in dioxane. The benzene and benzaldehyde were dried over Linde Molecular Sieve 4A. Ir spectra were run as KBr disks on a Perkin-Elmer 137 with NaCl optics; nmr spectra were run in $CDCl_3$ on a Varian A-60.

**Benzylbis(α-hydroxybenzyl)phosphine Oxide.**—The preparation was carried out identically with Buckler's work.[2] However, after running the experiment several times, the maximum yield of crystalline solid was 35%: mp 150–152°; nmr (DMSO-$d_6$) δ 3.18 (m, 2 H, PCH$_2$Ph), 5.17 (d, $J = 9$ Hz, 1 H, HC(O)P), 5.3 (d, $J = 12$ Hz, 1 H, HC(O)P), 6.48 (m, 2 H, OH), 6.73–7.78 (m, 15 H, aromatics).

**5-Benzyl-2,4,6-triphenyl-1,3,5-dioxaphosphorinane 5-Oxide (2).**—A solution of 35 ml of benzaldehyde, 120 ml of dry benzene, and a crystal of *p*-toluenesulfonic acid was prepared and 17.6 g (0.05 mol) of 1 was added. The mixture was heated under reflux until the water in the Dean–Stark trap did not increase over several hours reflux. Only 0.55 ml of water was collected (theoretical, 0.90 ml), and this took 7 days of reflux (Buckler reported 20 hr). The resulting solution was dried *in vacuo* and the residue mixed with 150 ml of anhydrous ether. The white solid present was collected (11.6 g, 52.8% yield), mp 158–200°, as a mixture of isomers **2**. The pure isomers were obtained by mixing **2** with 450 ml of ethyl acetate, heating, and filtering.

The ethyl acetate soluble material after crystallization was recrystallized further from 2-propanol (three times) to yield 2.32 g of a white solid: mp 198–200° (**2a**); nmr (CDCl$_3$) δ 2.9 (m, 2 H, PCH$_2$Ph), 5.36 (d, $J_{P-H} = 17$ Hz, 1 H, eq HC(O)P), 5.50 (d, $J_{P-H} = 16$ Hz, 1 H, ax HC(O)P), 6.25 (s, 1 H, HC(O)O), 7.87–6.78 (m, 20 H, aromatics).

The ethyl acetate insoluble portion was then recrystallized four times from dioxane to yield 0.3 g of a white solid: mp 216–220° (**2s**); nmr (CDCl$_3$) δ 3.5 (d, $J_{P-H} = 16$ Hz, 2 H, PCH$_2$Ph), 5.32 (d, $J_{P-H} = 14$ Hz, 2 H, HC(O)P), 6.02 (d, $J_{P-H} = 2$ Hz, 1 H, HC(O)O), 7.85–6.88 (m, 2 OH aromatics).

**Registry No.** —**1**, 36871-68-8; **2a**, 36871-89-3; **2s**, 36871-90-6.

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## Use of Polymethylhydrosiloxane as a Selective, Neutral Reducing Agent for Aldehydes, Ketones, Olefins, and Aromatic Nitro Compounds

JONATHAN LIPOWITZ* AND SHERYL A. BOWMAN

*Research Department, Dow Corning Corporation, Midland, Michigan 48640*

Several reports of the reductions of a variety of functional groups by silyl hydrides under mild conditions and in high yields prompted this work. The present study was aimed at determining the scope and utility of siloxane hydrides as general reducing agents for organic compounds under mild, neutral conditions.

Recently Grady and Kuivila[1] reported reductions of halocarbons and a ketone by tin hydrides, generated *in situ* from reaction of polymethylhydrosiloxane (PMHS) and organostannoxanes. Stoichiometric quantities of stannoxane were required. Earlier work

$$SnOSn + \frac{2}{n}[MeHSiO]_n \longrightarrow \frac{2}{n}[MeSiO_{1.5}]_n + 2SnH$$
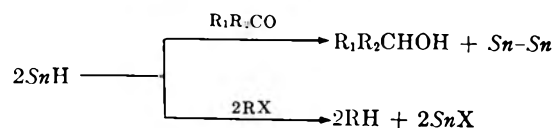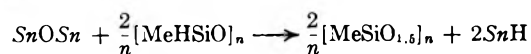


$$Sn = \text{organotin}$$

of Nitzsche and Wick[2] had described reductions of several ketones and aromatic nitro compounds with methylhydrosiloxanes and catalytic quantities of dialkyltin diacylates or other organometallics in protic solvents. In view of Grady and Kuivila's work[1] and earlier reports of the reactions of stannoxanes and alkoxystannanes with silyl hydrides,[3] it is likely that tin hydrides are the active reducing agents, being rapidly consumed and regenerated *in situ*.

The organotin hydrides are versatile reagents which reduce a variety of functional groups.[4] However,

(1) G. L. Grady and H. G. Kuivila, *J. Org. Chem.*, **34**, 2014 (1969).

(2) S. Nitzsche and M. Wick, *Angew. Chem.*, **69**, 96 (1957); U. S. Patent 3,061,424 (1962).

(3) (a) K. Hayashi, J. Iyoda, and I. Shiihara, *J. Organometal. Chem.*, **10**, 81 (1967); (b) K. Itoi and S. Kumano, *Kogyo Kogoku Zasshi*, **70**, 82 (1967); (c) B. Bellegarde, M. Pereyre, and J. Valade, *Bull. Soc. Chem. Fr.*, 3082 (1967).

(4) (a) H. G. Kuivila, *Advan. Organometal. Chem.*, **1**, 47 (1964); (b) *Synthesis*, **2**, 499 (1970), and references cited therein; (c) W. P. Neumann, "The Organic Chemistry of Tin," Interscience, New York, N. Y., 1970, Chapter 10, and references cited therein; (d) R. C. Poller, "The Chemistry of Organotin Compounds," Academic Press, New York, N. Y., 1970, Chapter 7.

difficulty in the preparation and storage of tin hydrides, especially the reactive dihydrides, and the use of stoichiometric quantities of reagent have hindered widespread use of this unique class of reducing agent. Some examples of marked selectivity are known. Thus, progesterone is reduced to the carbinol preferentially at the 3-carbonyl by tin hydrides whereas sodium borohydride reduces preferentially at the 20-carbonyl.[4a]

We find that PMHS[5] and an organotin catalyst, bis(dibutylacetoxytin) oxide (DBATO),[6] in a protic solvent functions as a mild, convenient reagent for the specific reduction of aldehydes and ketones to carbinol in high yield.

$$R_1R_2CO + \frac{1}{n}[MeHSiO]_n + ROH \xrightarrow{\ DBATO\ }$$

$$R_1R_2CHOH + \frac{1}{n}[MeSi(OR)O]_n$$
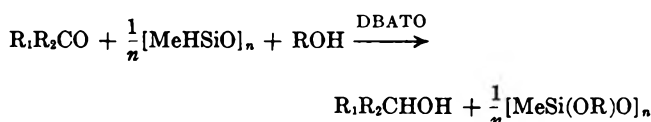
One equivalent of siloxane hydride per mole of substrate is required, with the solvent contributing a proton to complete reduction to the carbinol. Reduction takes place under mild, neutral conditions during reaction and work-up.[8] Exclusion of air and water is not necessary. Table I lists reductions which have

TABLE I

PMHS REDUCTIONS WITH 2 MOL % DBATO[a]

| Substrate | Registry no. | Product | Yield, % |
|---|---|---|---|
| Ph$_2$CO | 119-61-9 | Ph$_2$CHOH | 80[b] |
| PhCOMe | 98-86-2 | PhCHOHMe | 81[b,d] |
| PhCHO | 100-52-7 | PhCH$_2$OH | 100[c] |
| Me$_2$CO | 67-64-1 | Me$_2$CHOH | 100[c] |
| CH$_2$=CHCOMe | 78-94-4 | CH$_2$=CHCHOHMe | 65[c] |
| | | EtCOMe | 35[c] |
| 4-tert-Butylcyclohexanone | 98-53-3 | trans-4-tert-Butylcyclohexanol | 65[b] (100[c]) |
| p-Benzoquinone | 106-51-4 | Hydroquinone | 81[b] |

[a] At 80° in refluxing 95% ethanol. [b] Isolated yield. [c] Glc yield, using an internal standard. [d] 1-Hr reflux was required after PMHS addition.

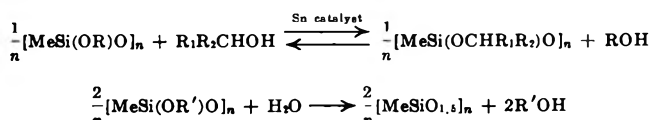been carried out in refluxing 95% ethanol (80°) using 2 mol % DBATO and a 10% excess of PMHS.

Table II lists representative esters, lactones, amides, carboxylic acids, nitriles, alkyl halides, and nitro com-

(5) PMHS (Dow Corning® XZ8-5486 chemical reducing agent) is distributed by Aldrich Chemical Co., Inc. PMHS is an easily handled, chemically inert liquid in uncatalyzed form; the structure is Me$_3$SiO(MeHSiO)$_n$-SiMe$_3$, where $n \approx 35$.

(6) DBATO, mp 57°, is the stable hydrolysis product of dibutyltin diacetate under neutral or mildly basic conditions and is readily prepared by alkaline hydrolysis of dibutyltin diacetate,[7] by reaction of dibutyltin diacetate and dibutyltin oxide,[7] or most conveniently by reaction of dibutyltin oxide and acetic acid (cf. Experimental Section). DBATO is a more active catalyst than dibutyltin diacetate for the reduction of ketones and is more resistant to reduction to metallic tin.

(7) D. L. Alleston, A. G. Davies, M. Hancock, and R. F. M. White, *J. Chem. Soc.*, 5469 (1963).

(8) Nitzsche and Wick[2] worked up reactions using aqueous mineral acid to hydrolyze carbinol product which had been incorporated in the siloxane as alkoxysiloxane. We find that hydrolysis of product which has been in-

$$\frac{1}{n}[MeSi(OR)O]_n + R_1R_2CHOH \underset{}{\overset{Sn\ catalyst}{\rightleftarrows}} \frac{1}{n}[MeSi(OCHR_1R_2)O]_n + ROH$$

$$\frac{2}{n}[MeSi(OR')O]_n + H_2O \longrightarrow \frac{2}{n}[MeSiO_{1.5}]_n + 2R'OH$$

corporated in the polysiloxane and formation of an easily filtered, granular, methylsilsesquioxane gel will take place simply by addition of water with heating and stirring. The DBATO which is present functions as a hydrolysis catalyst.

TABLE II

UNSUCCESSFUL REDUCTIONS WITH PMHS AND
2 MOL % DBATO[a]

PhNO$_2$[b]
EtCHNO$_2$CH$_2$OH[b]
m-NO$_2$C$_6$H$_4$COMe[b]
PhCN[b]
EtCN[b]
PhCH$_2$Cl[b]
MeCO$_2$Et
MeCO$_2$Bu
γ-Butyrolactone
n-BuCHEtCO$_2$H
HCONMe$_2$

[a] Little or no reduction at 80 (in ethanol) or 130° (in 2-ethylhexanol). [b] Reduction is approximately stoichiometric with catalyst at 130°.
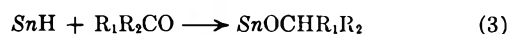
pounds which are not reduced. In some cases, noted in Table II, reduction takes place approximately stoichiometrically with catalyst, especially in 2-ethylhexanol at 130°. Thus, 2 mol % catalyst gave about 2% amine (or ammonia) with nitriles and nitro compounds at 130°. Benzyl chloride reduction gave a 2% yield of toluene. Nitzsche and Wick[2] reported quantitative reductions of nitrobenzene and p-dinitrobenzene to the amines at higher temperature in refluxing 2-ethylhexanol (bp 184°).

The following reaction scheme appears likely for reduction of carbonyl groups using catalytic stannoxane.

Catalyst formation

$$SnOSn + SiH \longrightarrow SnH + SiOSn \qquad (1)$$

$$SiOSn + ROH \longrightarrow SiOH + SnOR \qquad (2)$$

Reductive cycle

$$SnH + R_1R_2CO \longrightarrow SnOCHR_1R_2 \qquad (3)$$

$$SnOCHR_1R_2 + ROH \rightleftarrows SnOR + R_1R_2CHOH \qquad (4)$$

$$SnOR(SnOCHR_1R_2) + SiH \longrightarrow$$
$$SnH + SiOR(SiOCHR_1R_2) \qquad (5)$$

Reactions of PMHS with stannoxanes (reaction 1) and alkoxystannanes (reaction 5) are rapid and exothermic.[3,9] Solvolyses of siloxystannanes (reaction 2) are well known.[10] Reaction of tributyltin hydride with ketones in methanol has recently been reported to lead directly to the carbinol *via* reactions 3 and 4.[11]

The active reducing agent in the system is either dibutylacetoxytin hydride or dibutyltin dihydride. The acetoxytin hydride is known to undergo rapid disproportionation, favoring the dihydride and the diacetate.[12] Evidence for the presence of dihydride is obtained by ir spectroscopy. A mixture of PMHS and DBATO leads to rapid formation of an ir band at 1830 cm$^{-1}$.[13] The presence of dibutylacetoxytin hydride in the reaction mixture is indicated by slow formation of 1,1,2,2-tetrabutyl-1,2-diacetoxyditin, the

(9) Siloxystannanes also react with PMHS.[3a] Addition of PMHS too rapidly during reaction leads to an increase in PMHS concentration. The excess PMHS may then react with siloxystannane in a reaction competitive with reaction 2, leading to methylsilsesquioxane gel formation before reduction is complete: SiOSn + SiH → SiOSi + SnH.

(10) P. G. Harrison, *Organometal. Chem. Rev.*, **4**, 415 (1969), and references cited therein.

(11) M. Pereyre and J. Godot, *Tetrahedron Lett.*, 3653 (1970); M. Pereyre, J. Quintard, J. Godot, and J. Valade, *Organometal. Chem. Syn.*, **1**, 269 (1971).

(12) A. K. Sawyer and H. G. Kuivila, *J. Org. Chem.*, **27**, 613 (1962).

(13) Dibutyltin dihydride exhibits an ir band, $\nu$(SnH), at 1832 cm$^{-1}$.[12]

thermal decomposition product of the acetoxytin hydride.[12] Evidence for the intermediacy of dibutylacetoxytin hydride was provided by formation of dibutylacetoxychlorotin and chloroform in the reaction of PMHS and DBATO in CCl₄. Tin hydrides are known to react rapidly and exothermally with CCl₄.[4,14] It is possible, however, that dibutyltin dihydride was trapped by CCl₄ to give dibutyltin dichloride, which can subsequently undergo exchange with diacetate.[15]

Differences are observed between our results and previous reductions using dibutyltin dihydride. Reduction of methyl vinyl ketone gives 65% methyl vinyl carbinol and 35% methyl ethyl ketone (Table I). The latter product arises by 1,4 addition of a tin hydride followed by solvolysis.[16] However, Kuivila and Beumel[17] reported reduction only to methyl vinyl carbinol in 31% yield by dibutyltin dihydride. We obtained exclusively *trans*-4-*tert*-butylcyclohexanol in reduction of 4-*tert*-butylcyclohexanone whereas Kuivila and Beumel[17] obtained a 7:1 trans–cis mixture using dibutyltin dihydride. The differences observed between reductions with dibutyltin dihydride and the PMHS–DBATO reagent, although not pronounced, are considered to be great enough to suggest that the reactive intermediate in the present case is dibutylacetoxytin hydride. This tin hydride seems to be somewhat more reactive towards carbonyl groups than the dihydrides,[16,17] although its selectivity and stereospecificity remains largely unexplored.

Hydrogenations using a Pd-on-charcoal catalyst provide additional examples of the versatility of PMHS as a reducing agent under mild conditions. High yields have been reported in room temperature hydrogenolyses of aryl chlorides and bromides and reactive alkyl chlorides.[18,19] We find that hydrogenations of

$$R_3SiH + R'X \xrightarrow{\text{Pd/C}} R_3SiX + R'H$$
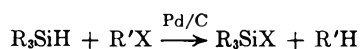
terminal and cis olefins, aromatic nitro compounds and aromatic aldehydes proceed readily in ethanol with Pd on charcoal (Table III). Similar reductions

### TABLE III
### HYDROGENATION WITH PMHS AND Pd/C IN EtOH, 40–60°

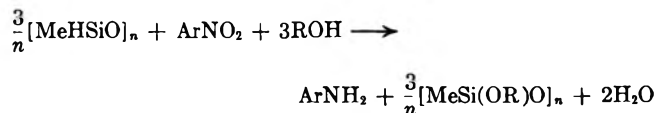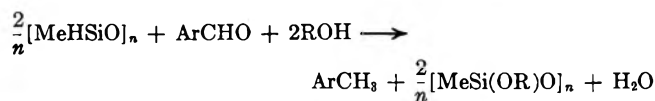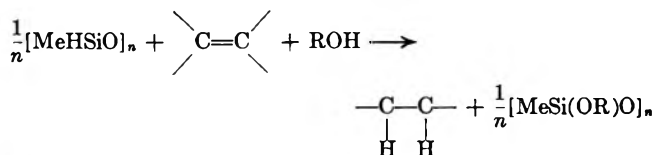| Compound | Registry no. | Time, (hr) | Product | Yield, % |
|---|---|---|---|---|
| PhNO₂ | 98-95-3 | 1 | PhNH₂ | 89[a] |
| PhCHO | | 1 | PhCH₃ | 84[a] |
| 1-Octene | 111-66-0 | 1 | *n*-Octane | 88[b] |
| 2-Nonene | 6434-77-1 | 1 | *n*-Nonane | 25[a,c] |
| Cyclohexene | 110-83-8 | 1 | Cyclohexane | 100[a] |
| CH₂=CHCOMe | | 2 | EtCOMe | 100[a] |

[a] Glc yield, using an internal standard. [b] Distilled yield. [c] 100% cis isomer reduction, no trans isomer reduction.

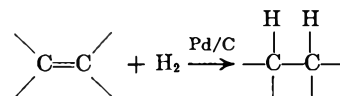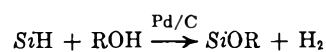by trialkylsilyl hydrides and siloxane hydrides have been observed in aqueous dioxane.[20]

(14) D. H. Lorenz and E. I. Becker, *J. Org. Chem.*, **27**, 3370 (1962).

(15) A. K. Sawyer and H. G. Kuivila, *Chem. Ind. (London)*, 260 (1961).

(16) A. J. Leusink and J. G. Noltes, *Tetrahedron Lett.*, 2221 (1969).

(17) H. G. Kuivila and O. F. Beumel, Jr., *J. Amer. Chem. Soc.*, **83**, 1246 (1961).

(18) J. D. Citron, J. E. Lyons, and L. H. Sommer, *J. Org. Chem.*, **34**, 638 (1969).

(19) Hydrogenolyses by siloxane hydrides with Pd/C proceed in high yield in hydrocarbons or without solvent; private communication from Dr. G. H. Barnes, Jr.

(20) Private communication from Dr. G. H. Barnes, Jr.

$$\frac{1}{n}[\text{MeHSiO}]_n + \diagdown\text{C}=\text{C}\diagup + \text{ROH} \longrightarrow$$

$$-\underset{\underset{H}{|}}{\text{C}}-\underset{\underset{H}{|}}{\text{C}}- + \frac{1}{n}[\text{MeSi(OR)O}]_n$$

$$\frac{2}{n}[\text{MeHSiO}]_n + \text{ArCHO} + 2\text{ROH} \longrightarrow$$

$$\text{ArCH}_3 + \frac{2}{n}[\text{MeSi(OR)O}]_n + \text{H}_2\text{O}$$

$$\frac{3}{n}[\text{MeHSiO}]_n + \text{ArNO}_2 + 3\text{ROH} \longrightarrow$$

$$\text{ArNH}_2 + \frac{3}{n}[\text{MeSi(OR)O}]_n + 2\text{H}_2\text{O}$$

Reductions using PMHS and Pd/C constitute a safe, convenient form of low-pressure hydrogenation. Although the observed pattern of hydrogenations are similar to those obtained with hydrogen and Pd/C at 1 atm and room temperature,[21] reaction *does not* proceed simply by the known[22] Pd/C catalyzed solvolysis of silyl hydride, followed by olefin hydrogenation. Thus, in the reduction of 2-nonene containing

$$Si\text{H} + \text{ROH} \xrightarrow{\text{Pd/C}} Si\text{OR} + \text{H}_2$$

$$\diagdown\text{C}=\text{C}\diagup + \text{H}_2 \xrightarrow{\text{Pd/C}} -\underset{\underset{|}{|}}{\overset{\overset{H}{|}}{\text{C}}}-\underset{\underset{|}{|}}{\overset{\overset{H}{|}}{\text{C}}}-$$

a 75:25 ratio of trans/cis isomers, only the cis isomer is reduced. No hydrogen evolution is observed even though 77% of the silyl hydride remains unreacted. However, hydrogenation of 1-octene proceeds with vigorous hydrogen evolution throughout even though reduction if rapid and 91% complete (9% isomerized octenes are obtained). The absence of a correlation between the extent of hydrogen evolution and the extent of reduction indicates that reaction does not take place *via* the above scheme.

The versatility of the PMHS reagent is illustrated by quantitative reduction of methyl vinyl ketone to methyl ethyl ketone with Pd/C catalyst whereas catalysis by DBATO gives a 65% yield of methyl vinyl carbinol. Additional reactions in which the utility of silyl hydrides have been demonstrated include the Pd/C catalyzed reduction of acid chlorides to aldehydes.[23] Reductions of phosphine oxides, and phosphoric acid esters to phosphines by PMHS are also known.[24]

### Experimental Section

Melting and boiling points are uncorrected.

**Bis(dibutylacetoxytin) Oxide (DBATO).**—A mixture of 10.0 g of dibutyltin oxide (40 mequiv) and 2.4 g of acetic acid (40 mmol) in 15 ml of ethanol was heated at 60° with stirring. In 30 min, the solution had become homogeneous and functioned as well as recrystallized DBATO in reduction of acetophenone. Evaporation of solvent and recrystallization from acetone at −20° gave DBATO, 10.3 g (86%), mp 54–57° (lit.[7] mp 56–60°), ir (CCl₄) 1570, 1640 cm⁻¹ (C=O).

(21) R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, New York, N. Y., 1965.

(22) G. H. Barnes, Jr., and N. E. Daughenbaugh, *J. Org. Chem.*, **31**, 885 (1966); L. H. Sommer and J. E. Lyons, *J. Amer. Chem. Soc.*, **89**, 1521 (1967).

(23) J. D. Citron, *J. Org. Chem.*, **34**, 1977 (1969).

(24) H. Fritzsche, U. Hasserodt, and F. Korte, *Chem. Ber.*, **97**, 1988 (1964); *ibid.*, **98**, 1681 (1965).

Dibutylacetoxychlorotin was prepared[15] by heating 3.5 g of dibutyltin diacetate and 3.0 g of dibutyltin dichloride at 80–90° for 5 min. Recrystallization from pentane gave 5 g of the acetoxytin chloride, mp 59–62° (lit.[15] mp 63–65°), ir (CCl$_4$) 1590 cm$^{-1}$ (C=O).

**PMHS Reduction with DBATO.**—A solution of the organic substrate (1 mol) and 12 g of DBATO (0.02 mol) in 700 ml of 95% ethanol was heated to reflux (80°).[25] PMHS,[5] 70 g (1.1 equiv), was added dropwise slowly enough to maintain gentle reflux.[26] In most cases, reduction was complete when all the PMHS was added. Completion of reduction was determined by disappearance of carbonyl absorption using ir analysis. Water, 800 ml, was added and the reaction mixture was stirred at 80° until a granular methylsilsesquioxane gel was obtained (about 1 hr). The gel was filtered and the filtrate and gel were extracted with chloroform. The combined chloroform extracts were distilled, recrystallized, or analyzed by glc with addition of toluene or xylene as an internal standard. Products on which glc yields are reported were identified by tandem glc–mass spectroscopy. Isolated products were characterized by melting point or boiling point, and ir spectroscopy. Isomeric purity of *trans*-4-*tert*-butylcyclohexanol was determined by ir spectroscopy.[27] *p*-Hydroquinone was isolated as the quinhydrone.[17] Reductions that failed were carried out similarly, using 700 ml of 2-ethylhexanol as solvent in the 130° runs. The reductions of nitro compounds and nitriles at 130° gave traces of amines (or ammonia) as evidenced by alkalinity during attempted distillation. In addition, approximately 2% yields of aniline and toluene were obtained, by glc mass spectroscopy, in reductions of nitrobenzene and benzyl chloride, respectively.

**Reaction of Polymethylhydrosiloxane and Bis(dibutylacetoxytin) Oxide.**—A solution of 0.19 g of PMHS (3 mequiv) and 1.8 g of DBATO (3 mequiv) in 25 ml of dry cyclohexane was prepared under dry N$_2$. An ir spectrum, obtained immediately, showed a band at 1830 cm$^{-1}$ attributable to ν(SnH) of dibutyltin dihydride [lit.[12] ν(SnH) 1832 cm$^{-1}$]. After storage overnight, a band appeared at 1550 cm$^{-1}$ attributable to 1,1,2,2-tetrabutyl-1,2-diacetoxyditin [lit.[12] ν(C=O) 1553 cm$^{-1}$], which is a decomposition product of dibutylacetoxytin hydride.[12]

A solution of 0.20 g of PMHS and 1.8 g of DBATO in 20 ml of CCl$_4$ was refluxed for 2 hr. Infrared analysis during the reaction showed the disappearance of silyl hydride [ν(SiH) 2160 cm$^{-1}$] and the formation of chloroform [δ(CH) 1210 cm$^{-1}$] and dibutylacetoxychlorotin [ν(C=O) 1590 cm$^{-1}$].

**PMHS Reductions with Pd on Charcoal.** A 10% excess of PMHS was added to a mixture of the organic substrate (0.1 mol) and 0.05 g of 5% Pd on charcoal in 40 ml of 95% ethanol containing 1 drop of concentrated HCl.[28] For reduction of olefins, benzaldehyde, and nitrobenzene, 0.11, 0.22, and 0.33 equiv respectively of PMHS were used. The reaction mixture was swirled occasionally, and the temperature was maintained at 40–60° by cooling or heating, depending on substrate reactivity. Methyl vinyl ketone, which did not exotherm, was heated at 40–60° for 2 hr. Other substrates were heated for about 30 min after the exotherm, which required cooling, had subsided. The catalyst was removed by filtration, 80 ml of water was added, and the product was extracted from the aqueous mixture with pentane. The pentane extract was dried (CaCl$_2$) and products were identified by tandem glc–mass spectrometry. Yields were determined by addition of toluene or xylene as a glc internal standard to the pentane extract. Distillation of the 1-octene reduction product gave *n*-octane, bp 125°, containing 7% isomerized olefins. Isomerized olefins were also detected by glc in the 2-nonene reduction product.

**Registry No.**—1, 9004-73-3; 2, 5967-09-9; Pd, 7440-05-3.

(25) The rate of reduction can be increased by increasing DBATO concentration or by increasing reaction temperature by use of a higher boiling alcohol.

(26) Premature gelation before completion of reduction may occur if PMHS concentration is allowed to build up by too rapid addition.

(27) R. S. Ro, Ph.D. Thesis, University of Notre Dame, 1957; E. L. Eliel and R. S. Ro, *J. Amer. Chem. Soc.*, **79**, 5992 (1957).

(28) *Caution.* PMHS should be added in small portions to reactions run on an appreciably larger scale to control the exotherm.

# Carbonyl Compounds and Secondary Amines from Diarylhydroxylamines *via* Nitroxides

YUL YOST AND H. R. GUTMANN*

*Laboratory for Cancer Research, Veterans Administration Hospital and Department of Biochemistry, University of Minnesota, Minneapolis, Minnesota 55417*

In previous work we have described the preparation of *N*-phenyl-*N*-fluorenylhydroxylamines by the reaction of nitrofluorenes with phenylmagnesium bromide in a nitrogen atmosphere.[1] In the presence of air the hydroxylamines were transformed to products that have now been identified. The work presented here shows that *N*-phenyl-*N*-fluoren-2-ylhydroxylamine in the presence of air gives rise to 2-anilinofluoren-9-one and *N*-phenylfluoren-2-amine and that a nitroxide is the intermediate, as shown in Scheme I. Similarly, *N*-phenyl-*N*-fluoren-3-ylhydroxylamine yielded the corresponding diaryl ketone and diarylamine. 1-Anilinofluoren-9-one and *N*-phenylfluoren-1-amine, isolated from the reaction of 1-nitrofluorene and phenyl Grignard in air, undoubtedly arose from the intermediate *N*-phenyl-*N*-fluoren-1-ylhydroxylamine. The course of these reactions may be rationalized by a mechanism similar to that proposed by Calder and Forrester.[2] According to these workers, *N*,*N*-alkylarylhydroxylamines disproportionate to carbonyl compounds and arylamines *via* intermediate nitroxides. The applicability of this mechanism to diarylhydroxylamines was supported by the oxidation of *N*-phenyl-*N*-biphenyl-4-ylhydroxylamine to a stable nitroxides and by the conversion of the nitroxide to *p*-benzoquinone biphenyl-4-ylimine *N*-oxide and *N*-phenylbiphenyl-4-ylamine.

Another reaction which yields fluoren-9-ones from fluorenes is the oxidation of the methylene group involving intermediate peroxides.[3] This pathway may have contributed to the formation of fluorenones, since 2- and 3-anilinofluoren-9-one were obtained in minor amounts by air oxidation of the respective secondary amines.

## Experimental Section

Melting points were taken with a Fisher-Johns apparatus. Ir spectra were recorded with a Beckman IR-10 spectrophotometer. The uv spectra were taken with a Beckman DK-2 spectrophotometer and the absorbancies at λ$_{max}$ were read with a Gilford digital absorbance meter on a DR Beckman monochromator. Mass spectra were recorded with a Hitachi Perkin-Elmer RMU-6 spectrometer. Silica gel GF$_{254}$ for tlc was obtained from Brinkman Instruments, Inc., Westbury, N. Y.

**2-Anilinofluoren-9-one.**—*N*-Fluoren-2-yl-*N*-phenylhydroxyamine[1] (1.50 g, 5.50 mmol) in ethanol (60 ml) and 2.5 N NaOH (2.5 ml) were stirred in an open flask for 12 hr at 40°. The colorless mixture turned red, then yellow, and finally green. A red precipitate was dissolved by addition of dimethylformamide (25 ml). The solution was treated with gaseous ammonia (9 min) and hydrogen sulfide (20 min) and stirred at room temperature for 1 hr. The volume of the solution was reduced by 50%. Ice–water was added and the resulting red precipitate was collected and washed with water (1.22 g). A portion (80 mg) was chromatographed (tlc) on silica gel with benzene. The

(1) Y. Yost, H. R. Gutmann, and C. Muscoplat, *J. Chem. Soc.*, 2119 (1971).

(2) A. Calder and A. R. Forrester, *J. Chem. Soc. C*, 1459 (1969); A. R. Forrester and S. P. Hepburn, *ibid.*, 1277 (1971).

(3) Y. Sprinzak, *J. Amer. Chem. Soc.*, **80**, 5449 (1958); E. F. Pratt and L. E. Trapasso, *ibid.*, **82**, 6405 (1960).

Scheme I
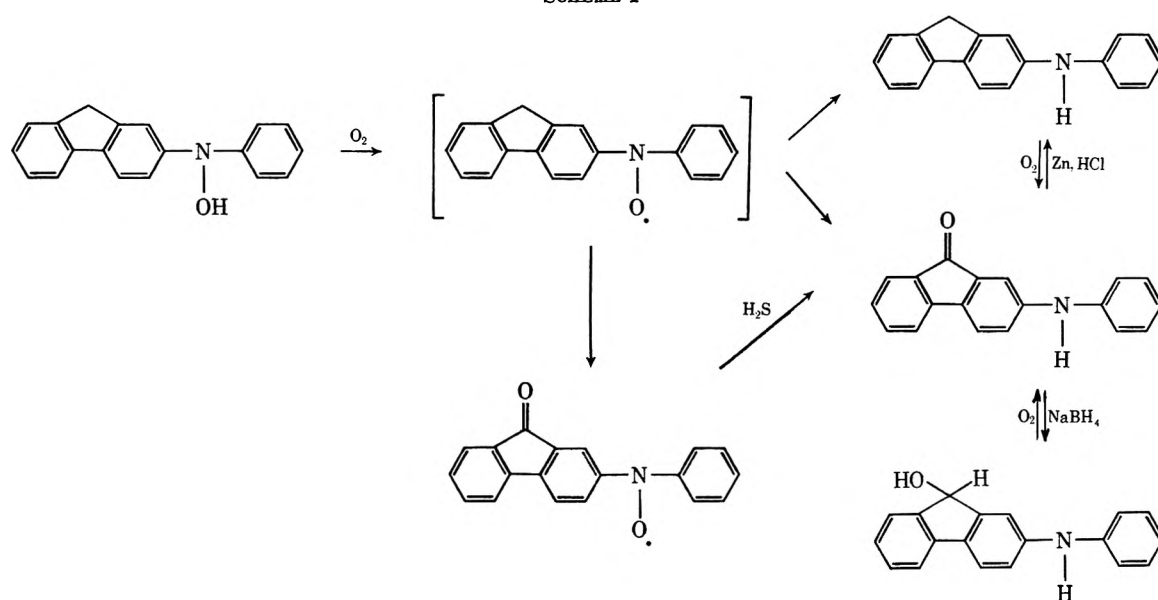


band, $R_f$ 0.7, yielded *N*-phenylfluoren-2-amine (27%) identified by the uv spectrum.[1] The red band, $R_f$ 0.6, yielded the title compound (53%), as a red powder from benzene–*n*-heptane: mp 201–203°; uv max (EtOH) 245 nm (log ε 4.34), 250$^i$ (4.29), 293 (4.59), 343 (4.28), and 506 (3.04); ir max (KBr) 3370 (NH) and 1710 cm$^{-1}$ (C=O); $m/e$ 271 (M$^+$). (Superscript i denotes inflection point.)

*Anal.* Calcd for $C_{19}H_{13}NO$: C, 84.10; H, 4.83; N, 5.16. Found: C, 83.91; H, 4.91; N, 5.16.

In another experiment *N*-phenylfluoren-2-amine (5 mg) in ethanol (2 ml) was exposed to air at room temperature for 6 days. 2-Anilinofluoren-9-one was isolated by tlc and estimated spectrophotometrically (6%).

The ketone in a mixture of acetic acid and HCl was reduced with zinc to the *N*-phenylfluoren-2-amine.[1] The ketone was also reduced to the alcohol as follows. A mixture of 2-anilinofluoren-9-one (80 mg), sodium borohydride (50 mg) in methanol (25 ml), and 0.1 *N* sodium hydroxide (1 ml) were stirred until the red solution was colorless (∼15 min). 2-Anilino-9-hydroxyfluorene was isolated (75%) by extraction with ether and crystallized from ethanol–water: mp 149–150°; uv max (EtOH) 328 nm (log ε 4.48); ir max (KBr) 3505 (OH) and 3310 cm$^{-1}$ (NH); $m/e$ 273 (M$^+$).

*Anal.* Calcd for $C_{19}H_{15}NO$: C, 83.49; H, 5.53; N, 5.13. Found: C, 83.26; H, 5.50; N, 5.43.

The ethanolic solution used for the measurement of the uv spectrum was exposed to sunlight and the uv absorption spectrum was recorded at 10-min intervals. After 1 hr, the solution had turned pale red and the spectrum resembled that of 2-anilinofluoren-9-one. Oxidations of hydroxymethylene groups adjacent to aromatic systems have already been reported.[3]

**Phenyl(9-oxofluoren-2-yl) Nitroxide.**—*N*-Fluoren-2-yl-*N*-phenylhydroxylamine[1] (700 mg, 2.57 mmol) in ethanol (75 ml) and aqueous 2.5 *N* sodium hydroxide (5 ml) was stirred in an open flask for 30 min. A white precipitate (sodium carbonate, 200 mg) was removed by filtration. The red filtrate was stirred for 90 min. A maroon precipitate was collected and washed with water and ethanol (0.27 g), mp 160–170° dec. The material was suspended in hot benzene (10 ml) and the mixture was filtered (gravity). The product crystallized as dark needles after dilution with hot *n*-heptane (110 mg): mp 162° dec; uv max (CHCl₃) 250 nm (log ε 4.59), 304 (4.26), 312 (4.27), 338 (4.20), 380$^i$ (3.72), 405$^i$ (3.52), 470 (3.08), 500 (3.04), and 670$^i$ (2.08); ir max (KBr) NH, OH none, 1715 cm$^{-1}$ (C=O); $m/e$ 286 (M$^+$); esr, a triplet with $a_N$ 9.3 G, characteristic of diaryl nitroxides.[4]

(4) H. Lemaire, A. Rassat, and A. Ravet, *Bull. Soc. Chim. Fr.*, 1980 (1963). Esr spectra of the nitroxide will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-73-165. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

*Anal.* Calcd for $C_{19}H_{12}NO_2$: C, 79.70; H, 4.23; N, 4.89 O, 11.18. Found: C, 79.56; H, 4.46; N, 4.98; O, 11.29.

The filtrate from which the crude product had been obtained was cooled in an open flask and a precipitate was collected every 24 hr over a period of four days. Each precipitate consisted essentially of 2-anilinofluoren-9-one and *N*-phenylfluoren-2-amine. The separations were effected by tlc and the compounds were identified spectrophotometrically. In another experiment in which air was excluded neither nitroxide nor ketone were obtained.

The title compound (10 mg) in dimethylformamide (2 ml) and ethanol (1 ml) was treated successively with NH₃ (5 min) and with H₂S (5 min). After 15 min, the mixture was diluted with water and chloroform. 2-Anilinofluoren-9-one, identified spectrophotometrically, was isolated from the organic phase.

**3-Anilinofluoren-9-one.**—A stream of air was passed for 2 hr through a solution of *N*-fluoren-3-yl-*N*-phenylhydroxylamine[1] (500 mg, 1.85 mmol) and 2.5 *N* sodium hydroxide (2 ml) in ethanol (5 ml). The mixture was kept at room temperature for 2 days. It was then treated with Na₂S (1 g) and NH₄Cl (1 g) and stirred for another 3 hr. The solvents were removed and the residue was triturated with water and chloroform. The organic phase was chromatographed on tlc with benzene–*n*-hexane (2:1). The first band, $R_f$ 0.8, gave *N*-phenylfluoren-3-amine (60 mg): mp 145–147°; uv max (EtOH) 264 nm (log ε 4.45) and 298 (4.25); ir max (KBr) 3380 cm$^{-1}$ (sharp, NH); $m/e$ 257 (M$^+$). *Anal.* Calcd for $C_{19}H_{15}N$: C, 88.68; H, 5.88; N, 5.44. Found: C, 88.96; H, 6.13; N, 5.17. The purple band, $R_f$ 0.7, gave a crimson substance (40 mg) that could not be crystallized and remains unidentified. The orange band, $R_f$ 0.3, gave the title compound (110 mg): mp 201–203°; uv max (EtOH) 252 nm (log ε 4.59), 267 i (4.22), 322 (4.24), 388 (3.80), and 444 (3.92); ir max (KBr) 3300 (NH) and 1690 cm$^{-1}$ (C=O); $m/e$ 271 (M$^+$).

*Anal.* Calcd for $C_{19}H_{13}NO$: C, 84.10; H, 4.83; N, 5.16. Found: C, 84.14; H, 4.89; N, 5.35.

In another experiment *N*-phenylfluoren-3-amine (5 mg) in ethanol (2 ml) was exposed to air at room temperature for 6 days. 3-Anilinofluoren-9-one was isolated by tlc and quantified spectrophotometrically (18% yield).

**1-Anilinofluoren-9-one.**—1-Nitrofluorene[5] (100 mg, 0.4 mmol) in anhydrous tetrahydrofuran (4 ml) was treated with phenylmagnesium bromide as previously described.[1] After addition of water, the organic phase was concentrated to 1 ml and diluted with ethanol (10 ml) and 8 *N* ammonium hydroxide (0.5 ml). The red mixture was stirred at room temperature for 24 hr. Sodium sulfide (0.1 g) and NH₄Cl (0.1 g) were then added and stirring was continued for 4 hr. The mixture was concentrated at reduced pressure, diluted with H₂O (20 ml), and then extracted with chloroform (2 × 3 ml). The extract was chromatographed (tlc) with benzene–*n*-hexane (1:1). The following compounds were isolated: biphenyl, $R_f$ 0.9; *n*-phenylfluoren-1-amine, $R_f$

(5) Y. Yost and H. R. Gutmann, *J. Chem. Soc. C*, 345 (1969).

0.7, mp 130–132°, uv max (EtOH) 266 nm (log $\epsilon$ 4.34), ir max (KBr) 3400 cm$^{-1}$ (NH), $m/e$ 257 (M$^+$). The red band, $R_f$ 0.4, yielded 1-anilinofluoren-9-one. Prior to analysis the product was rechromatographed (tlc) with benzene and recrystallized from methylene chloride–*n*-hexane: 54 mg (46%); mp 187–188°; uv max (EtOH) 257 nm (log $\epsilon$ 4.68), 296 (4.04), and 500 (3.88); ir max (KBr) 3322 (NH), 1705 cm$^{-1}$ (C=O); $m/e$ 271 (M$^+$).

*Anal.* Calcd for C$_{19}$H$_{13}$NO: C, 84.10; H, 4.83; N, 5.16. Found: C, 83.98; H, 4.87; N, 5.38.

**Biphenyl-4-ylphenyl Nitroxide. A. By Oxidation of *N*-Biphenyl-4-yl-*N*-phenylhydroxylamine with Ferric Chloride.**— A 0.93 $M$ ethanolic solution of ferric chloride (4 1 ml, 3.8 mmol) was added to *N*-biphenyl-4-yl-*N*-phenylhydroxylamine (1.00 g, 3.82 mmol) in ethanol–benzene (1:1) (40 ml). The red mixture was stirred for 5 min and was then diluted with water (40 ml). The organic phase was washed with water and dried (MgSO$_4$), and the solvent was removed. One crystallization from dichloromethane–*n*-hexane and two crystallizations from benzene–*n*-heptane gave the title compound: 0.25 g; mp 127–130° dec; uv max (*n*-hexane) 243 nm (log $\epsilon$ 4.00), 294 (4.02), 329 (4.29), and 400 i; uv max (EtOH) 243 nm (log 3.96), 294 (3.96), and 332 (4.27); ir max (KBr) 1477 cm$^{-1}$ (NO); $m/e$ 260 (M$^+$); esr, a triplet with $a_N$ 9.5 G, characteristic of diaryl nitroxides.[4]

*Anal.* Calcd for C$_{18}$H$_{14}$NO: C, 83.05; H, 5.42; N, 5.38; O, 6.15. Found: C, 83.17; H, 5.38; N, 5.44; O, 6.30.

The nitroxide in dimethylformamide and ethanol was treated with gaseous NH$_3$ and H$_2$S for 10 min. The resulting colorless solution was diluted with water and washed with diethyl ether. The organic phase yielded *N*-phenylbiphenyl-4-ylamine.[1]

**B. By Air Oxidation of *N*-Biphenyl-4-yl-*N*-phenylhydroxylamine.**—To an ethanolic solution of *N*-biphenyl-4-yl-*N*-phenylhydroxylamine (54 mg, 0.21 mmol) was added KOH (5 mg) and the solution was flushed with air for 10 min. The yellow color of the solution turned red as soon as the air was admitted, and the red nitroxide precipitated. The compound was collected and washed with water (30 mg, 55%), mp 132–134°. Additional product (19 mg) was obtained from the filtrate by tlc; total yield, 90%. An alkaline ethanolic solution of the hydroxylamine that was flushed with nitrogen remained colorless. This indicated that no nitroxide was formed in the absence of air.

***p*-Benzoquinone Biphenyl-4-ylimine *N*-Oxide.**—Biphenyl-4-ylphenyl nitroxide (30 mg) in CHCl$_3$ was applied to a plate coated with silica gel (1 mm) and developed after 30 min with benzene–ethyl acetate (1:1). The band, $R_f$ 0.8, gave *N*-phenylbiphenyl-4-ylamine (10%); the red band, $R_f$ 0.6, yielded starting material (41%). The orange band, $R_f$ 0.3, gave the *N*-oxide (7 mg, 22%): mp 200°; uv max (EtOH) 250 nm (log $\epsilon$ 4.21) and 378 (4.36); ir max (KBr) NH, OH none, 1623 cm$^{-1}$ (C=O); $m/e$ 275 (M$^+$). The tlc was intended to purify the nitroxide. In addition, the nitroxide was converted in part to the *N*-oxide on the chromatogram as indicated by the fact that additional bands containing *N*-oxide and amine, respectively, appeared when the chromatogram was developed a second time. The strong absorption bands of the *N*-oxide at 250 and 378 nm are evidence for the biphenyl system and for the *p*-benzoquinone imine *N*-oxide, respectively.[2,6] The structural assignment of the compound was confirmed by reduction to 4-hydroxy-4'-phenyldiphenylamine.[7] An ethanolic solution of the *N*-oxide was treated with ammonium chloride and sodium sulfide (hydrated). The mixture was stirred for 15 min and the solvent was removed. The residue was dissolved in a mixture of water and chloroform. The organic phase was chromatographed on silica gel with benzene–ethyl acetate (4:1). The major band, $R_f$ 0.2, gave 4-hydroxy-4'-phenyldiphenylamine as pale tan needles from benzene–*n*-heptane: mp 149–150° (reported[7] mp 148–149°); ir max (KBr) 3420 (sharp, NH), 3300 (broad, OH), 815 (4 × 2 adjacent H), and 750 and 680 cm$^{-1}$ (phenyl); $m/e$ 261 (M$^+$).
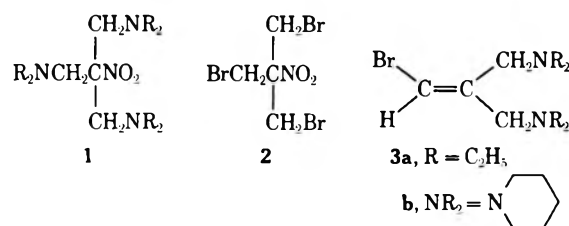
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# Reactions of Amines with 1,3-Dibromo-2-(bromomethyl)-2-nitropropane

DAVID A. KLEIN[1] AND J. E. FERNANDEZ*

*Chemistry Department, University of South Florida, Tampa, Florida 33620*

The object of this research was to prepare compounds of type **1** utilizing the appropriate secondary amines and



the tribromide **2**. We find that these reactions do not lead to the desired compound **1**. Instead, compounds of structure **3** result.

The reaction of **2** with diethylamine gave only one product, **3a**. The reaction with *tert*-butylamine did not give a pure product, and *N*-methylaniline did not react at all. Three products were obtained from the reaction of piperidine with **2**: *N*-(2-nitroethyl)piperidine (**4**), di(*N*-piperidino)methane (**5**), and **3b**. The formation of **4** and **5** in this reaction suggests that the desired triamine, **1**, was formed and then converted to **4** and **5** *via* two reverse Mannich reactions according to the mechanism of Spoerri, *et al.*[2] On the other hand, **2** could alternately have undergone aminomethylation and the reverse Mannich reaction to form the same products in a stepwise manner (Scheme I) without ever having formed the triamine **1**. Thus no conclusion can be drawn as to whether or not the desired compound **1** was ever formed.

Each of the reaction mixtures in which compound **3** was formed gave a positive test for the nitrite ion.[3] Dehydrobromination of **3** did not occur in any of these denitrations because there were no protons $\beta$ to the bromine atom.

The loss of HNO$_2$ has been observed previously in

(6) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," Wiley, New York, N. Y., 1963, p 101.

(7) J. C. Conner, U. S. Patent 2,661,375 (1953); *Chem. Abstr.*, **49**, 375i (1955).
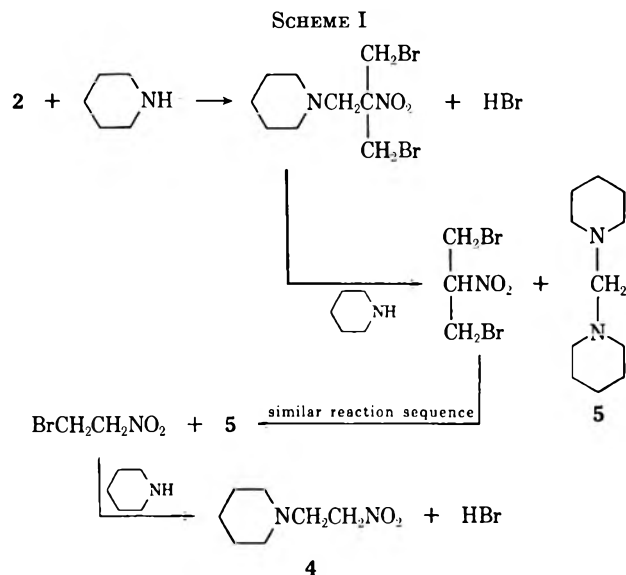
(1) Taken in part from the M.S. Thesis of David A. Klein, University of South Florida, 1971.

(2) D. Taber, E. I. Becker, and P. E. Spoerri, *J. Amer. Chem. Soc.*, **76**, 776 (1954).

(3) The test used for the detection of nitrite ion is described by G. Charlot, "Rapid Detection of Cations and Anions," translated by R. E. Oesper, Chemical Publishing Co., New York, N. Y., 1965, p 80.

SCHEME I



similar reactions of 2 with sodium amalgam[4] and with KOH in alcohol.[5]

The major products of these reactions, 3a and 3b, were probably formed in two steps: first the denitration similar to that observed by Kleinfeller, *et al.*, to form 6, followed by substitution of amine groups for



6
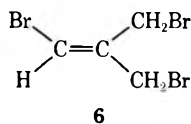
the allylic bromine atoms. The vinyl bromine atom is so unreactive that it is not replaced by the amine group.

Thus in general the denitration of tertiary nitro alkanes containing vicinal halides can be brought about by amines with a basicity at least as weak as *tert*-butylamine ($K_b = 2.8 \times 10^{-4}$) as well as by strong bases such as KOH and sodium amalgam as observed previously.[4,5]

### Experimental Section

Boiling points are uncorrected. Nmr spectra were recorded on a Varian A-60 nmr spectrometer. Infrared spectra were recorded on a Perkin-Elmer Model 337 grating spectrophotometer. Molecular weights were determined by titrating the products with standard HCl, following the titration with a pH meter.

**Reaction of Diethylamine with $(CH_2Br)_3CNO_2$.**—A solution of 2 (25 g, 0.0735 mol) in methanol (300 ml) was placed in a flask fitted with a reflux condenser protected with a drying tube and an addition funnel. The mixture was heated to reflux, and diethylamine (16.2 g, 0.221 mol) was added dropwise. The mixture was refluxed for 1 week and cooled, and then the solvent was evaporated leaving an oily solid, which was mixed with 50 ml of 10% HCl. The resulting mixture was filtered, leaving 21.5 g of the starting bromide. The filtered solution was saturated with $K_2CO_3$ and extracted with ether. The ether extract was dried ($MgSO_4$), concentrated, and distilled, giving 2.3 g (79%) of 4: bp 68-69° (0.25 mm); ir (film) 3030, 1630 cm$^{-1}$ (CH=C); nmr (neat) δ 0.93 (t, 12), 2.44 (q, 8), 3.05 (s, 2), 3.17 (s, 2), 6.24 (s, 1). The product decolorized Br₂ in CCl₄ and gave a positive Beilstein test but did not react with alcoholic $AgNO_3$.

*Anal.* Calcd for $C_{12}H_{25}BrN_2$: C, 51.98; H, 9.09; Br, 28.82; N, 10.11; mol wt, 277.26. Found: C, 51.52; H, 8.96; Br, 29.49; N, 9.77; mol wt (titration), 278.

(4) H. Kleinfeller, A. Kirsch, and F. Eckert, *Ber.*, **62B**, 1582 (1929).

(5) H. Kleinfeller and H. Stahmer, *ibid.*, **66B**, 1127 (1933).

Similar results were obtained when this reaction was carried out without a solvent.

**Reaction of Piperidine with $(CH_2Br)_3CNO_2$ (2).**—A mixture of 2 (10 g, 0.0294 mol) and piperidine (30 ml) was refluxed for 12 hr, cooled, and diluted with acetone (100 ml). This solution was filtered, yielding 10.8 g of piperidine hydrobromide. The filtered solution was concentrated and distilled into two fractions. The lower boiling fraction [bp 42–44° (0.25 mm)] was shown to be a mixture of 5 and 6 in a ratio of 3:1 by nmr analysis. This fraction weighed 4.0 g; no attempt was made to separate the mixture into its components. The higher boiling fraction, 7, weighed 9.5 g: bp 104–108° (0.25 mm); ir (film) 3050, 1630 cm$^{-1}$ (CH=C); nmr (neat) δ 1.42 (m, 12), 2.30 (m, 8), 2.92 (s, 2), 3.06 (s, 2), 6.25 (s, 1). This product decolorized Br₂ in CCl₄, and gave a positive Beilstein test, but did not react with alcoholic $AgNO_3$.

*Anal.* Calcd for $C_{14}H_{25}BrN_2$: C, 55.81; H, 8.36; Br, 26.53; N, 9.30; mol wt, 301.28. Found: C, 56.01; H, 8.49; Br, 26.34; N, 9.18; mol wt (titration), 297.

Similar results were obtained when methanol was used as a solvent.

**Registry No.**—2, 36809-38-8; 3a, 36809-39-9; 3b, 36809-40-2.

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## The Crystal and Molecular Structure of Dimeric Allyl Azide[1]

J. C. PEZZULLO AND E. R. BOYKO*

*Chemistry Department, Providence College, Providence, Rhode Island 02918*

The dimer of allyl azide was first synthesized by Forster and Fierz[2] from the spontaneous dimerization of the monomer, $C_3H_5N_3$. The resulting prismatic crystals melted with decomposition at 150° but were found to be stable at room temperature. The conclusion that a dimer was present was based on boiling point elevation measurements of chloroform solutions of the compound. Forster and Fierz[2] considered several possible molecular structures and, a number of years later, Boyer and Canter[3] proposed the following as being more consistent with the known chemistry of olefinic azides.
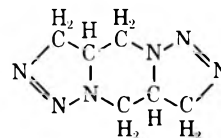


The subsequent X-ray diffraction analysis of the compound shows this molecular structure to be the correct one.

### Experimental Section

Preliminary diffraction photographs showed the crystals to be orthorhombic with systematic absences uniquely determining the space group as *Pbca*. The cell parameters were determined from calibrated photographs to be $a = 7.803$, $b = 10.821$, and $c = 8.819$ Å with standard deviations of 0.006 Å. The density measured by the flotation method was 1.45 g cm$^{-3}$; the density calculated on the basis of four dimer units per unit cell is 1.44 g cm$^{-3}$.

(1) Based on a thesis submitted by J. C. Pezzullo in Feb 1969 in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) M. O. Forster and H. E. Fierz, *J. Chem. Soc.*, **93**, 1178 (1908).

(3) J. H. Boyer and F. C. Canter, *Chem. Rev.*, **54**, 1 (1954).

Equi-inclination Weissenberg photographs (multiple-film technique) were taken of the $h0l$ and $hkh$ zones, and layer lines $hkl$ with $k$ = 1–4, using Cu K$\alpha$ radiation. The intensities were estimated visually with the use of a standard scale. A total of 354 independent reflections was obtained. The dimensions of the crystals employed were approximately 0.5 mm, but, owing to the low linear absorption coefficient of the compound, no correction for absorption was made.

## Structure Determination and Refinement

Since there are four dimer units in the unit cell and *Pbca* is centrosymmetric with an eightfold general position, the dimer must possess a center of symmetry. The problem is therefore reduced to one of determining the positions of the three carbon and three nitrogen atoms in the asymmetric unit. The sign determination technique developed by Sayre[4] and Zachariasen[5] was employed to accomplish this. A three-dimensional electron density map was calculated and a trial structure was developed based on the positions of the largest peaks. A calculation of interatomic distances indicated a bonding arrangement which corresponded to the molecular model proposed by Boyer and Canter.[3] The three positions to which the nitrogen atoms were assigned were chosen so as to be in agreement with the model. It was observed that several reflections with low Bragg angle values had calculated structure factors substantially exceeding the observed values. This was attributed to secondary extinction and the calculated structure factors were corrected according to the relation of Darwin.[6] A full-matrix least-squares program was written specifically for this compound so that the secondary extinction coefficient might be included as an adjustable parameter. Hydrogen positions were also incorporated into the least squares refinement (fixed positions, no temperature factors). The value of $R$, the reliability index, in the final structure was 0.133. The atomic coordinates (fractions of cell edges) and temperature factors, $B$, are given in Table I; the estimated standard errors (hydrogens excluded)

### TABLE I
COORDINATES AND ISOTROPIC TEMPERATURE
FACTORS FOR THE FINAL STRUCTURE

| Atom | $x$ | $y$ | $z$ | $B$ |
|---|---|---|---|---|
| C-1 | 0.2088 | 0.3526 | 0.5205 | 2.8 |
| C-2 | 0.3193 | 0.4718 | 0.5357 | 1.9 |
| C-3 | 0.4621 | 0.4460 | 0.6516 | 2.2 |
| N-1 | 0.6077 | 0.5298 | 0.6193 | 1.8 |
| N-2 | 0.6060 | 0.6514 | 0.6758 | 2.8 |
| N-3 | 0.7078 | 0.7176 | 0.6054 | 3.3 |
| H-1[a] | 0.075 | 0.380 | 0.500 | |
| H-2[a] | 0.215 | 0.300 | 0.625 | |
| H-3[b] | 0.250 | 0.550 | 0.575 | |
| H-4[c] | 0.400 | 0.475 | 0.750 | |
| H-5[c] | 0.535 | 0.370 | 0.625 | |

[a] Attached to C-1. [b] Attached to C-2. [c] Attached to C-3.

are 0.01 Å for the positional coordinates and 0.2 Å$^2$ for the temperature factors.

## Discussion

Bond distances and angles are shown in Figure 1. All bond distances agree well with those previously

(4) D. Sayre, *Acta Crystallogr.*, **5**, 60 (1952).
(5) W. H. Zachariasen, *ibid.*, **5**, 68 (1952).
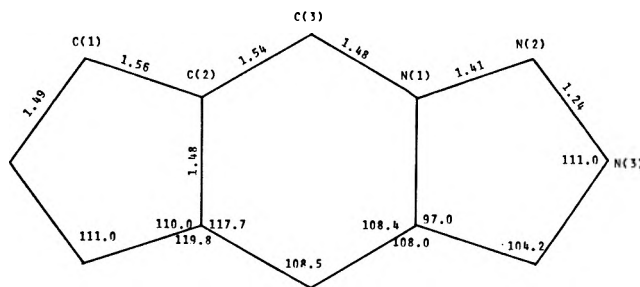(6) C. G. Darwin, *Phil. Mag.*, **43**, 800 (1922).



Figure 1.—Bond distances and angles.

reported for similar bond types. Calculation of intermolecular distances indicates that the nearest-neighbor contacts are of the van der Waals type. The individual five-membered rings are not planar; atom C-2 is 0.42 Å out of the least-squares plane of the other four atoms. The two least squares planes of these rings are stepped with an interplanar distance of 1.90 Å.

The stability of the crystal, as evidenced by the high melting point and somewhat low temperature factors, warrants interest in the conformational aspects of this molecule. Dreiding stereomodels were constructed and manipulation of these models indicated that the conformation was strongly influenced by the nitrogen atom, N-1, at the junction of the five- and six-membered rings. With a tetrahedral atom (sp$^3$) at this position, the model closest to the observed structure corresponds to a cis–cis attachment of the five-membered rings to the six-membered ring having the CH$_2$ groups equatorial (C-1–C-2 bonds) and the N=N groups axial (N-1–N-2 bonds). This model, however, is not stable with respect to a noncentrosymmetric conformation in which the six-membered ring is a boat and both five-membered rings are planar. The introduction of a trigonal atom (sp$^2$) at the N-1 position produces a stable centrosymmetric model, but with planar five-membered rings which are stepped with an interplanar distance of only 1.2 Å. In the actual case, the bridgehead nitrogen is found to be 0.30 Å out of the plane of the atoms to which it is bonded, whereas a value of 0.48 Å would correspond to sp$^3$ hybridization. Consequently, neither extreme satisfactorily describes the hybridization.

**Registry No.**—Dimeric allyl azide, 36895-17-7.

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## On the Reaction of
## α-Bromo-ε-caprolactam with Methoxide

H. K. REIMSCHUESSEL

*Corporate Chemical Research Laboratory,
Allied Chemical Corporation,
Morristown, New Jersey 07960*

In a recent paper, Kondeliková, Králíček, and Křivinkova asserted that they were successful in preparing α-methoxy-ε-caprolactam by a nucleophilic substitution reaction entailing sodium methoxide and α-bromo-ε-caprolactam.[1] This assertion, however, did not

(1) J. Kondeliková, J. Králíček, and D. Křivinková, *Collect. Czech. Chem. Commun.*, **36**, 3391 (1971).
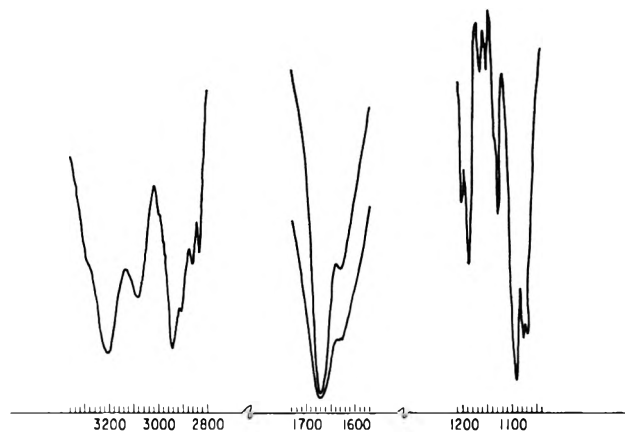
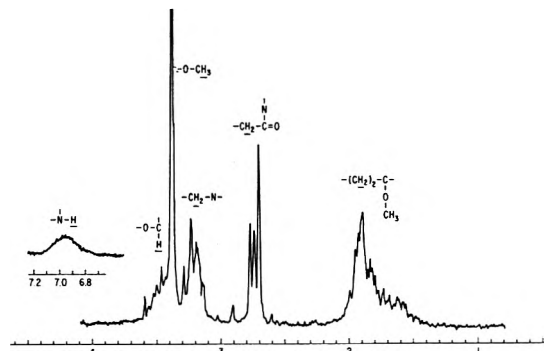Figure 1.—Infrared spectrum of β-methoxy-ε-caprolactam.

appear to be well founded in light of results obtained in studies on caprolactam derivatives carried out in our laboratory. Although it had been shown that substituted caprolactams can be obtained from α-bromocaprolactam by nucleophilic substitution,[2,3] the reaction between the latter and a strong base such as sodium alkoxide was found to be governed by a quite different mechanism. Nevertheless, to verify the available information, α-bromocaprolactam and sodium methoxide were allowed to react according to both the procedure given in ref 1 and a modified one which gave the same reaction product but in a higher yield (60%). The modified procedure resembled one reported earlier[4] and differed from that given in ref 1 mainly by eliminating the vacuum distillation of the reaction product. Purification was achieved by crystallization from a chloroform–petroleum ether (bp 30–50°) system. An analytically pure sample, mp 62°, was obtained in either case by recrystallization from petroleum ether. A melting point of 54–55° was reported in ref 1. *Anal.* Calcd for $C_7H_{13}NO_2$: C, 58.68; H, 9.15; N, 9.78. Found: C, 58.68; H, 9.43; N, 9.89.

Considering the results of previous studies[4] on similar compounds, the reaction product was identified by spectroscopic analyses to be not the α-methoxy- but the β-methoxy-ε-caprolactam. The significant bands of the infrared spectrum (KBr, Beckman IR9) are shown in Figure 1. They are 3205, 3080 (NH stretching); 2860, 2830 (methoxy, CH stretching); 1670 (amide I); 1072, 1080, 1090 [C–O asymmetrical stretching, this triplet seems to be characteristic for the isopropyl ether moiety $>(CH_2)_2\,CHOCH_3$].

The 100-MHz nmr spectrum is shown in Figure 2; it consists of four major groups, the integral of which correspond to the proportional relation of 1:6:2:4.

The most significant signal is the triplet centered at about 2.75 ppm which has been attributed to the protons of the methylene group located between a carbonyl group and a carbon linked to an ether oxygen.[4]

The formation of the β derivative may be explained by a mechanism that entails elimination of HBr, followed by nucleophilic addition of the methoxide anion to the formed unsaturated lactam. It was shown earlier[4] that treating α-bromocaprolactam with a strong

(2) H. K. Reimschuessel, *J. Heterocycl. Chem.*, **1**, 193 (1964).

(3) T. G. Bassiri and H. K. Reimschuessel, U. S. Patent 3,331,835 (1967).

(4) H. K. Reimschuessel, J. P. Sibilia, and J. V. Pascale, *J. Org. Chem.*, **34**, 959 (1969).

Figure 2.—Nmr spectrum of β-methoxy-ε-caprolactam.

base can yield both 1,5,6,7- and 1,3,6,7-tetrahydro-2H-azepin-2-one (**1** and **2**, respectively). This can be rationalized by a mechanism such as shown below.
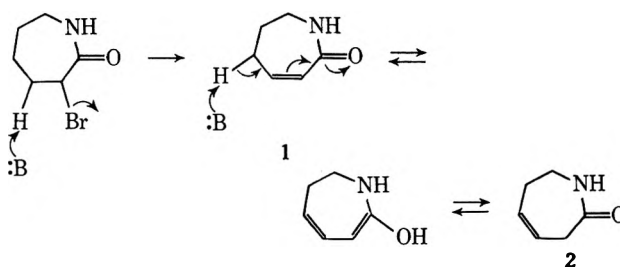


Isomerization of the β,γ-unsaturated lactam **2** into the α,β-unsaturated **1** can easily be visualized for the reaction conditions employed.

Typical 1,4 addition involving **1** yields then as the principal reaction product, the β-methoxy-ε-caprolactam.

There is no disagreement with the phenomenological aspects of the paper by Kondeliková, *et al.;* however, any conclusions regarding the behavior of the lactam as a function of the position of the methoxy group may need revision.

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# Conformational Properties of 2,2′-Disubstituted Diphenyl Ethers and Sulfides by Dipole Moments. A Reexamination

G. MONTAUDO,* P. FINOCCHIARO, AND S. CACCAMESE

*Institute of Industrial Chemistry of the University, Viale A. Doria 8, Catania, Italy*

The conformational properties of diphenyl ethers (DPO) and diphenyl sulfides (DPS) in solution have received continued attention up to recently, and several workers have resorted to dipole moment (DM)
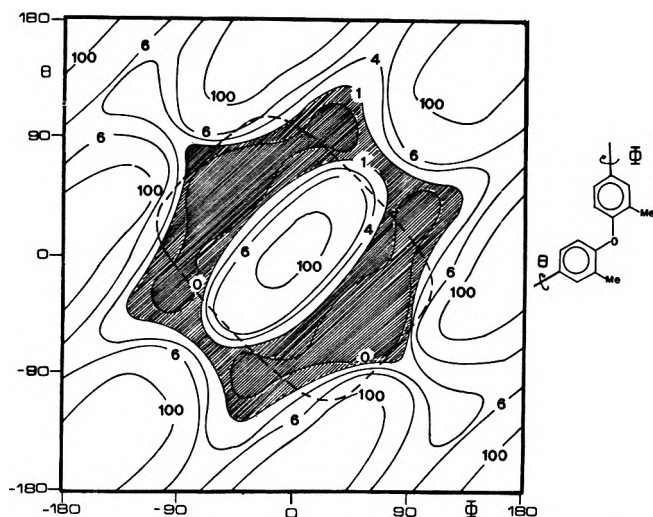
Figure 1.—Energy contour map (kcal/mol) of 2,2'-dimethyldiphenyl ether. Energy values are relative to the conformation of minimum energy. The shaded area corresponds to the energetically allowed region. The dotted superimposed line corresponds to the experimental (0.83 D) isomoment line.
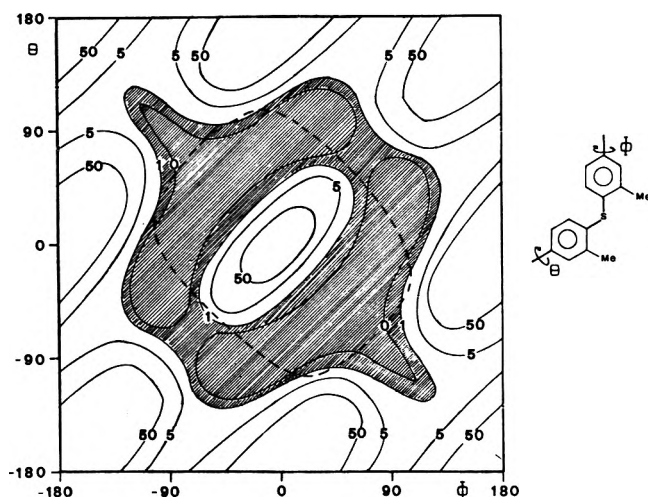


Figure 2.—Energy contour map (kcal/mol) of 2,2'-dimethyldiphenyl sulfide. Energy values are relative to the conformation of minimum energy. The shaded area corresponds to the energetically allowed region. The dotted superimposed line corresponds to the experimental (1.18 D) isomoment line.

measurements of 2,2'-disubstituted derivatives in an attempt to ascertain the conformational properties of these compounds.[1-6]

Dipole moments, being conformation dependent, are very useful in this kind of study, but sometimes do not provide unequivocal information since different conformations may be calculated to have the same DM value.

In spite of this difficulty, definite conformational assignments have been repeatedly reported for several 2,2'-disubstituted DPO and DPS, on the basis of DM data.[1,2,4,6]

During an nmr study[7a,b] of the conformational properties of ortho-substituted DPO and DPS, we have noted that no definite conformational preferences can be associated with the 2,2' derivatives. Therefore, nmr and DM data seem to be in conflict and we have found it opportune to reexamine the problem on energetic grounds.

### Results and Discussion

The contour maps of calculated DM as a function of the two internal rotation angles for compounds in Table I reveal that several different conformations have the same calculated DM value.[1,4,6] Furthermore, the experimental DM values (Table I) come surprisingly close to the values corresponding to a thermodynamically unrestricted rotation of the phenyl rings.

(1) K. Higasi and S. Uyeo, *Bull. Chem. Soc. Jap.*, **14**, 87 (1939).

(2) M. Rolla and M. Sanesi, *Ric. Sci.*, **32**, (IIA), 29 (1962), and references cited therein.

(3) F. K. Fong, *J. Chem. Phys.*, **40**, 132 (1964).

(4) C. W. N. Cumper, J. F. Read, and A. I. Vogel, *J. Chem. Soc.*, 5860 (1965).

(5) J. E. Anderson and C. P. Smyth, *J. Chem. Phys.*, **42**, 473 (1965).

(6) G. C. Pappalardo and S. Pistarà, *Tetrahedron*, **28**, 1611 (1972).

(7) (a) G. Montaudo, P. Finocchiaro, E. Trivellone, F. Bottino, and P. Maravigna, *ibid.*, **27**, 2125 (1971). (b) G. Montaudo, F. Bottino, and E. Trivellone, *J. Org. Chem.*, **37**, 504 (1972). (c) By this term we indicate the conformations which are likely to be populated because of their low energy content. This applies at the equilibrium and should not be confused with the kinetic process (height of the energy barrier to internal rotation). Accordingly, the shaded area in Figures 1 and 2 is extended to the 1 kcal/mol contour line, since a definite fraction of the overall population is likely to be present up to that level.

### TABLE I

EXPERIMENTAL AND CALCULATED DM VALUES FOR 2,2' DERIVATIVES OF GENERAL FORMULA I
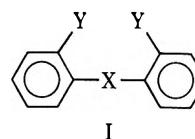
| No. | X | Y | $\mu_{exptl}$ | $\mu^a_{free\ rotation}$ |
|-----|---|------|---------|---------|
| 1 | O | CH₃ | 0.83[b] | 1.07 |
| 2 | O | I | 2.72[b] | 2.40 |
| 3 | O | NO₂ | 6.64[b] | 5.80 |
| 4 | S | CH₃ | 1.18[c] | 1.40 |
| 5 | S | Cl | 3.33[c] | 3.15 |
| 6 | S | NO₂ | 6.89[d] | 6.20 |

[a] Calculated for the free rotating molecules according to reference 1. [b] Reference 1. [c] Reference 4. [d] Reference 6.

Based exclusively on such data, it appears hazardous to speculate about possible conformational preferences of these compounds, as the previous authors have done.

On the other hand, the existence of a specific preferred conformation cannot be excluded *a priori*, if it happens to have a DM value coincident with the experimental one (Figures 1 and 2).

This ambiguity can be removed by complementing the DM with energetic considerations, and we have used semiempirical conformational energy calculations to build contour maps of relative conformational energy as a function of the two internal rotation angles for 2,2'-dimethyl DPO and DPS (Figures 1 and 2, respectively).

Inspection of the contour maps in Figures 1 and 2 reveals that large regions of the conformational space are "energetically allowed"[7c] shaded area in Figures 1 and 2), so that the molecular population becomes distributed over a wide range of torsional angles and the experimentally observed DM values can be properly interpreted as a weighted average of the DM contributions of separate species.

The experimental DM values of the chloro and nitro derivatives (Table I) are so close to those calculated for the free rotating molecules that their energy con-

tour maps are likely to resemble those of the methyl derivatives, as should be expected by comparing only their relative van der Waals radii. Accordingly, also for these compounds the observed DM should be interpreted as a weighted average of the DM contributions from the overall range of allowed conformations.

The situation is similar in 2,2',4,4'-tetranitrodiphenylmethane,[8] for which the experimental DM value (4.25 D) comes close to that calculated for the free rotating molecule (5.25 D).

Under these circumstances, it appears incorrect to associate the experimental DM values in Table I with a specific conformation,[1,4,6] and the situation seems to be best rationalized by considering these molecules as experiencing an almost complete thermodynamically unrestricted rotation.

On evaluating our results, it appears that the comparison of experimental and calculated DM is insufficient to reach unequivocal conclusions about the conformational properties of the title compounds and that a knowledge of the potential energy–internal rotation profiles is necessary to evaluate the DM data properly. More specifically, when the energy contour maps show a lack of conformational preference, immaterial of the technique employed, one should not try to interpret the experimental data in terms of specific preferred conformations.

## Calculations

Calculations were performed with the help of a microcomputer, Hewlett-Packard Model 9100 B.

The starting conformation ($\Phi = \theta = 0°$) for the compounds studied was taken with both rings planar, and the origin of the axes was placed at the bridge atom. Interatomic distances and natural bond angles were taken from pertinent literature data.[9,10]

Distances among all the atoms were computed for each pair of $\Phi$ and $\theta$ values calculating first (trigonometrically) the atomic coordinates for each atom for a fixed conformation and then applying the usual rotation matrix method.[11]

The energy for nonbonded interactions was obtained from the calculated distances using the Lennard–Jones potential.[12]

Torsional energies were not taken into account because they were found to be negligible.[13] Individual energy values for each one of the interacting pairs considered were added together, obtaining the total strain energy (unminimized) for each pair of $\Phi$ and $\theta$ values from 0 to 360°, with a stepwise 10° increment.

The strain energies found were minimized according to a procedure described in a previous paper[14] and the necessary bending constants were taken from the literature.[15-17]

Dipole moments were calculated, for each pair of $\Phi$ and $\theta$ values, adding vectorially the $x$, $y$, and $z$ components of the individual bond moments. The individual moments and bond angles used were the same as reported in the references.[1,4,6] The values of the dipole moment for the free rotating molecules were calculated according to the literature.[1]

**Registry No.**—2,2'-Dimethyldiphenyl ether, 4731-34-4; 2,2'-dimethyldiphenyl sulfide, 4537-05-7.

(8) G. Montaudo, S. Caccamese, and P. Finocchiaro, *J. Amer. Chem. Soc.*, **93**, 4202 (1971).

(9) L. E. Sutton in "Tables of Interatomic Distances and Configuration in Molecules and Ions," Supplement 1956–59, Burlington House, London, 1965.

(10) J. Toussaint, *Bull. Soc. Chim. Belg.*, **54**, 319 (1945).

(11) H. A. Elliot, K. D. Fryer, J. G. Garden, and N. J. Hill in "Vectors and Matrices," Holt, Toronto, Canada, 1966, p 254.

(12) R. A. Scott and H. A. Scheraga, *J. Chem. Phys.*, **45**, 2091 (1966); **46**, 4410 (1967); H. A. Scheraga in "Advances in Physical Organic Chemistry," Vol. 6, V. Gold, Ed., Academic Press, New York, N. Y., 1968, p 103.

(13) J. F. Yan, G. Vanderkooi, and H. A. Scheraga, *J. Chem. Phys.*, **49**, 2713 (1968).

(14) G. Montaudo and P. Finocchiaro, *J. Amer. Chem. Soc.*, **94**, 6745 (1972).

(15) A. Mannschreck and L. Ernst, *Chem. Ber.*, **104**, 228 (1971).

(16) N. C. Cohen, *Tetrahedron*, **27**, 789 (1971).

(17) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 447.

## N-Hydroxypyrroles and Related Compounds

*Summary:* 2-Azidopyridine 1-oxides and 2-azidopyrazine 1-oxide undergo thermal decomposition accompanied by ring contraction to give 2-cyanopyrroles or 1-hydroxy-2-pyrrolones, and 2-cyano-1-hydroxyimidazole, respectively.
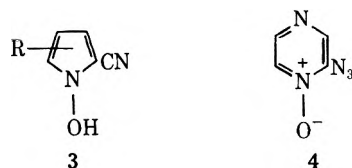
*Sir:* While the thermal and photochemical decomposition of 3- and 4-azidopyridine 1-oxides have been studied,[1,2] the chemistry of 2-azidopyridine 1-oxide (**1a**) has received little attention.[3] In principle, the nitrene derived from **1a** could either behave as a 1,4 dipole (**2**) or undergo ring contraction as do some other cyclic azides.[4] We have now prepared a series of 2-azidopyridine 1-oxides (**1**) and studied their thermal



**1a**, R = H
**b**, R = 4-CH₃
**c**, R = 5-CH₃
**d**, R = 6-CH₃
**e**, R = 5-Cl

**2**
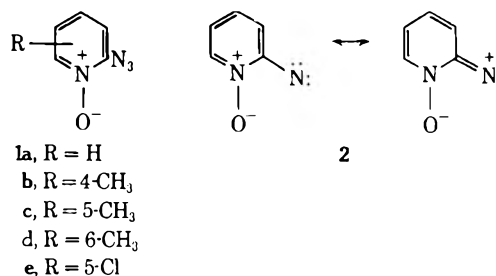
decomposition. To date we have not found any 1,4-dipolar behavior but have observed ring contraction leading to the desirable but otherwise unavailable 2-cyano-N-hydroxypyrroles (**3**). We report on the generality and possible mechanism of this reaction.

Direct oxidation to 2-aminopyridine 1-oxides by a modification of Pentimalli's procedure[5] was followed by diazotization of the hydrochlorides and treatment with sodium azide to give **1a–e** (60–80%). The structure of the azides were confirmed by their spectral properties and by microanalysis. 2-Azidopyrazine 1-oxide (**4**, 25%, mp 86–88° dec) was prepared analogously.

Thermolysis of **1** to give **3** in good yield occurred smoothly at 90° in benzene solution. This temperature is appreciably lower than that at which aryl azides usually decompose (>*ca.* 120°) and this suggests that an arylnitrene is not an intermediate but that nitrogen



**3**

**4**

elimination is concerted with ring opening. Thus, thermolysis of **1a** (mp 84°) gave **3** (R = H), 90%, bp 80° (0.5 mm), M⁺ calcd *m/e* 108.0324, found 108.0326. Compounds **3** could exist in a number of tautomeric modifications, *e.g.*



A          B          C

Only the N-hydroxy form (A) was observed as indicated by the ir and nmr spectra of **3**. The following, *e.g.*, were found for **3a** (R = H): ir (film) 3400–2800 (v br, NOH), 2225 cm⁻¹ (C≡N); nmr (CDCl₃) δ 7.56 (1 H, s, NOH, exchanges with D₂O), 6.90 (1 H, d of d, $J_{4,5}$ = 2.5, $J_{3,5}$ = 1.5 Hz, H₅), 6.55 (1 H, d of d, $J_{3,4}$ = 3.5, $J_{3,5}$ = 1.5 Hz, H₃), 5.96 (1 H, d of d, $J_{4,5}$ = 2.5, $J_{3,4}$ = 3.5 Hz, H₄). **3a** gave an O-p-toluenesulfonate, mp 79.5–80.5° dec, and O-p-nitrobenzyl derivative, mp 69–70° dec, and an O-benzoate, mp 77–79° dec, all of which exhibited the expected spectral features for O-substituted derivatives. The other compounds **3** behaved similarly.

When the thermolysis of **1a** was carried out in MeOH at 95°, 2-cyanopyrrole (**5**, 6%)[6] and 3-methoxy-2,3-dihydro-2-pyrrolone (**6**, 26%, mp 52–53°) were obtained. The cyanopyrrole (**5**) may result from the deoxygenation of **3a** in boiling methanol, which reaction was found to occur. The structure of the pyrrolone (**6**) followed from its spectral properties: ir (KBr) 3260 (NH), 1690 (amide C=O), 1103 cm⁻¹ (C—OMe); nmr (CDCl₃) δ 7.78 (1 H, s, NH, exchanges with D₂O), 6.84 (1 H, d of d, $J_{1,5}$ = 1.0, $J_{4,5}$ = 3.5 Hz, H₅), 6.08 (1 H, d of d, $J_{4,5}$ = 3.5, $J_{1,4}$ = 0.5 Hz, H₄), 5.42 (1 H, s, H₃), 3.24 (3 H, s, OCH₃); mass spectrum *m/e* 113 (M⁺), 82 (M⁺ − OCH₃), 31 (OCH₃⁺). It was confirmed by its hydrolysis to α-methoxysuccinic acid (**7**), mp 107–109°.[7]

Similarly, thermolysis of **1a** in aniline gave **5** (22%), 2-aminopyridine 1-oxide (21%),[8] and 3-anilino-2,3-dihydro-2-pyrrolone N-phenylimine (**8**, 26%, mp 137–139° dec).[9] Hydrolysis of the latter under very mild conditions gave the pyrrolone **9**, mp 89°. The other



**8**

**9**

(1) T. Okamoto and S. Hayashi, *Yakugaku Zasshi*, **86**, 776 (1966); *Chem. Abstr.*, **65**, 20116 (1966).
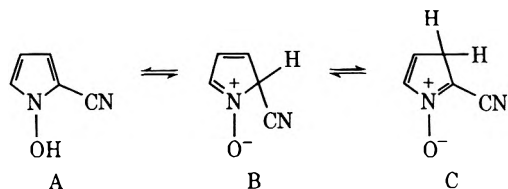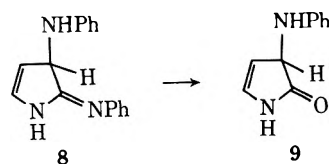
(2) S. Kamiya, *Chem. Pharm. Bull. (Tokyo)*, **10**, 471 (1962).

(3) Attempts to purify crude 2-azidopyridine 1-oxide led to its decomposition: J. H. Boyer, R. Borgers, and L. T. Wolford, *J. Amer. Chem. Soc.*, **79**, 687 (1957).

(4) R. A. Abramovitch and E. P. Kyba, in "The Chemistry of the Azido Group," S. Patai, Ed., Interscience, London, 1971, pp 273, 278.

(5) L. Pentimalli, *Gazzetta*, **94**, 458 (1964).

(6) Identical with an authentic sample prepared from pyrrole-2-carboxaldehyde oxime: H. J. Anderson, *Can. J. Chem.*, **37**, 2053 (1959).

(7) M. A. Khalique and M. D. Ahmed, *J. Org. Chem.*, **19**, 1523 (1954).

(8) Formally, this is the product of hydrogen abstraction by 1-oxido-2-pyridylnitrene from solvent; it could also arise by reduction of the azide function by aniline.

(9) Spectral and microanalytical data consistent with all of the proposed structures were obtained.

azides **1b–e** gave similar products on thermolysis in nucleophilic solvents.

A plausible mechanism which would account for the formation of products **3**, **6**, and **8** involves a nitrogen
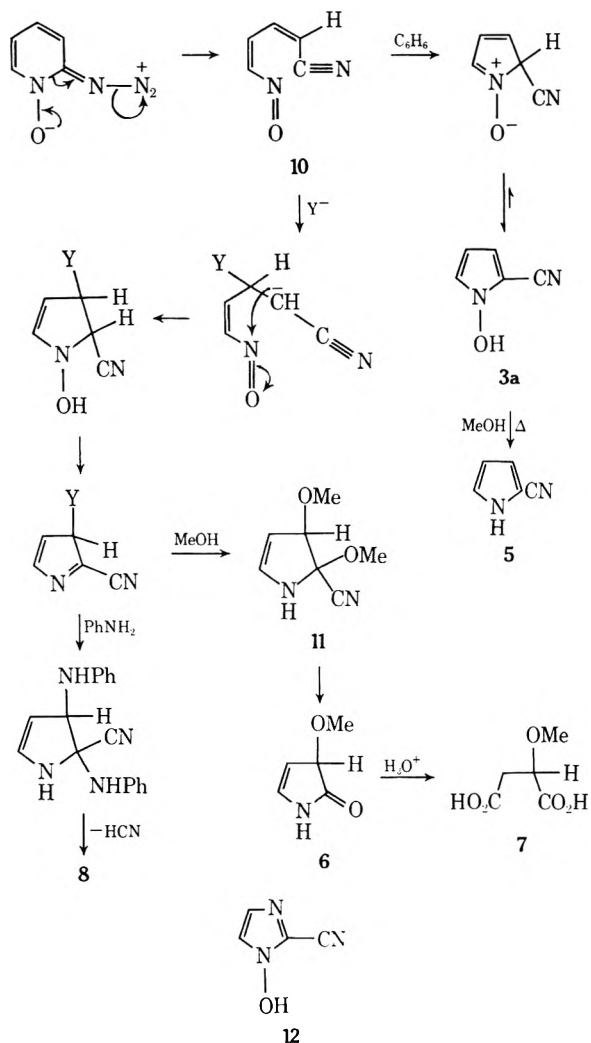


elimination concerted with ring opening to give the unsaturated nitrile (**10**). This can either undergo electrocyclic ring closure and tautomerization to give **3** or a Michael addition of solvent followed by cyclization and dehydration to **6** or **8**. Mechanistic analogy for **11** → **6** exists.[10]

The potential generality of this ring contraction is indicated by the production of 2-cyano-*N*-hydroxy-imidazole (**12**) [83%; mp 169–170° dec; ir (KBr) 2400 (NOH), 2225 cm$^{-1}$ (C≡N); mass spectrum *m/e* 109 (M$^+$), 92 (M$^+$ − OH)] by the thermolysis of **4** in benzene.

Extensions to fused systems and to the azidopyrimidine 1-oxides are now under investigation.

(10) S. M. McElvain and R. L. Clarke, *J. Amer. Chem. Soc.*, **69**, 2657, 2661 (1947); S. M. McElvain and C. L. Stevens, *ibid.*, **69**, 2663 (1947); R. Roger and D. Neilson, *Chem. Rev.*, **61**, 192 (1961).

DEPARTMENT OF CHEMISTRY                 R. A. ABRAMOVITCH*
UNIVERSITY OF ALABAMA                    B. W. CUE, JR.
UNIVERSITY, ALABAMA  35486

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## Stearoyl Methanesulfonate. A Mixed Anhydride from an Isopropenyl Ester

*Summary:* Isopropenyl stearate and methanesulfonic acid react at ambient temperatures in methylene chloride to give the mixed anhydride stearoyl methanesulfonate, a powerful stearoylating agent.

*Sir:* Mixed carboxylic–oxy acid anhydrides have been regarded as highly effective acylating agents. They have been prepared by the reaction of a silver sulfonate with an acid chloride,[1] a sulfonic acid with a ketene,[2] a sulfonic acid with an acid chloride,[3] or a sulfonic acid with a carboxylic anhydride[3] or from a lithium carboxylate and the sulfur trioxide–*N*,*N*-dimethylformamide complex.[4]

Nevertheless, little attention has been given to the facile synthesis of these acylating agents from sulfonic acids and isopropenyl esters. An early report[5] on the reactions of isopropenyl acetate (IPA) acknowledged that IPA reacts with carboxylic acids in the presence of a catalytic amount of sulfuric acid to give mixed carboxylic anhydrides. Another group studied the kinetics of various acid-catalyzed IPA reactions and concluded that the active intermediates are mixed acetic–sulfonic or acetic–sulfuric anhydrides.[6] Isopropenyl esters now may be prepared easily by reaction of a carboxylic acid with propyne in the presence of zinc oxide or the zinc carboxylate,[7] and this opens a new synthetic pathway to the once difficult to obtain mixed anhydrides.

We have isolated the mixed anhydride stearoyl methanesulfonate from the reaction mixture of equimolar amounts of isopropenyl stearate and anhydrous methanesulfonic acid in methylene chloride. Although attempts to recrystallize the white solid led to disproportionation, ir analysis and potentiometric titration demonstrated that the initial product was reasonably pure mixed anhydride. Ir absorptions (in a Nujol mull) occur at 1805 and 1185 cm$^{-1}$ and are typical[1c] for mixed carboxylic–sulfonic anhydrides. Ir analysis also showed that the material was essentially free of stearic acid, stearic anhydride, and isopropenyl stearate. A weighed sample of product was hydrolyzed in a known amount of dilute aqueous sodium hydroxide, and the resulting solution was back-titrated with 0.1 *N* hydrochloric acid. Two potentiometric end points were observed, one corresponding to double the amount of sodium hydroxide of the other; one end point was in the pH 5 region (methanesulfonic acid) and the other at pH 9 (stearic acid). The equivalent weight of the mixed anhydride calculated from the titration was within 3% of the theoretical value. The stearic acid that resulted from the hydrolysis and subsequent acidification was isolated in 93% yield and identified by its melting point and its ir spectrum. Quenching of the

(1) (a) F. Effenberger and G. Epple, *Angew. Chem., Int. Ed. Engl.*, **11**, 299 (1972). (b) A. Baroni, *Atti Acad. Lincei*, **17**, 1081 (1933). (c) C. G. Overberger and E. Sarlo, *J. Amer. Chem. Soc.*, **85**, 2446 (1963).

(2) G. A. Olah and S. J. Kuhn, *J. Org. Chem.*, **27**, 2667 (1962).

(3) M. H. Karger and Y. Mazur, *J. Amer. Chem. Soc.*, **90**, 3878 (1968).

(4) W. L. Garbrecht, *J. Org. Chem.*, **24**, 368 (1959).

(5) H. J. Hagemeyer, Jr., and D. C. Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949).

(6) E. A. Jeffery and D. P. N. Satchell, *J. Chem. Soc.*, 1876, 1887, 1906 (1962).

(7) E. S. Rothman and S. Serota, *J. Amer. Oil Chem. Soc.*, **48**, 373 (1971).

mixed anhydride in methanol produced methyl stearate; *tert*-butyl stearate resulted from quenching in *tert*-butyl alcohol.

Glpc evidence confirms that the isolated material that we have labeled "mixed anhydride" is not merely an IPS-methanesulfonic acid adduct $C_{17}H_{35}CO_2C$-$(CH_3)_2OSO_2CH_3$. The glpc trace of a methylene chloride solution of *isolated* mixed anhydride previously quenched with methanol showed the absence of acetone, whereas repetition of the experiment with *in situ* generated mixed anhydride plus methanol revealed the presence of acetone.

Ir analysis of a mixture of equimolar amounts of isopropenyl acetate and methanesulfonic acid in methylene chloride also suggests the formation of mixed anhydride ($\nu_{max}$ 1800 cm$^{-1}$ *vs.* 1825 cm$^{-1}$ for acetic anhydride). No acetyl methanesulfonate was isolated, however.

This work is part of an extensive study of low temperature acylation procedures using isopropenyl esters in the presence of strong oxy acids. In these applications the mixed anhydride generally is formed *in situ*. Since (1) addition of a stoichiometric quantity of the strong acid is essential for complete acylation to occur, (2) neither the stearic acid–strong acid combination nor the stearic anhydride–strong acid combination is capable of acylation at such ambient temperatures, at reasonable rates, (3) the formation of a mixed anhydride is demonstrated, and (4) the mixed anhydride is shown to be a potent acylating agent, we are confident that the active materials in these ambient temperature acylation reactions are mixed anhydrides. The results of the application studies using the mixed anhydride acylating agents will be published separately.[8]

(8) Detailed experimental data will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D.C. 20036, by referring to code number JOC-73-174. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(9) Agricultural Research Service, U. S. Department of Agriculture.

(10) National Research Council–Agricultural Research Service Postdoctoral Research Associate, 1970–1972. Presently Fats and Proteins Research Foundation Fellow.

EASTERN REGIONAL RESEARCH     WILLIAM N. MARMER*[10]
   LABORATORY[9]            SAMUEL SEROTA
PHILADELPHIA, PENNSYLVANIA   19118    GERHARD MAERKER

RECEIVED SEPTEMBER 22, 1972

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## Dihydro-1,3-oxazines. XVI. A General Synthesis of 2-Alkylcyclopentenones and a Method for Adding CH₂CO₂Me to Electrophilic Olefins. Application to the Synthesis of Methyl Jasmonate[1]

*Summary:* Addition of Grignard reagents to elaborated oxazines **3** gives the keto aldehyde **5** which is readily cyclized to the 2-alkylcyclopentenone **6**; the latter then is transformed into methyl jasmonate by Michael addition of the ketene *N,O*-acetal, **7**.

(1) For the previous paper in this series, see A. I. Meyers and N. Nazarenko, *J. Amer. Chem. Soc.*, **94**, 3243 (1972).

*Sir:* We wish to further illustrate the utility of the dihydro-1,3-oxazine system **2** as a synthetic tool by describing a total synthesis of methyl jasmonate (**1**), an
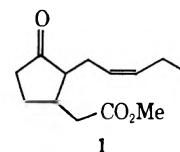


1

essential constituent for the characteristic odor of Jasmine.[2] The carboxylic acid of **1** has recently been reported to be a green plant growth inhibitor.[3] Although the synthesis of **1** has been accomplished,[4] we report a route which, in addition to culminating in (±)-**1**, provides a general method for (a) obtaining 2-alkylcyclopentenones, **6**,[5] and (b) Michael addition of $CH_2CO_2Me$ to electrophilic olefins. Treatment of the 2-methyloxazine **2**[6,7] with 1.0 equiv of butyllithium followed by addition of 1.0 equiv of 2-iodomethyl-1,3-dioxolane afforded the alkylated oxazine **3** in 83% yield (Scheme I). The latter was transformed into its methiodide salt which was utilized with or without isolation[8] in the reaction with the Grignard reagent of *cis*-1-bromo-3-hexene[9] (THF) producing the alkylated oxazine, **4** (51%). Heating **4** in aqueous oxalic acid for 2 hr resulted in the cleavage of both masking groups and provided the keto aldehyde **5** in good yield. The cyclopentenone **6** was efficiently formed (72% yield from **4**) when the keto aldehyde was heated in 1% sodium hydroxide solution for 30 min.[10] This synthesis of 2-substituted cyclopentenones should find considerable utility when one considers the variation of Grignard reagents that could be added to the dioxolane-substituted oxazine, **3**.

The formation of **6** represented a key intermediate in the jasmonic ester synthesis in view of our observation that the ketene *N,O*-acetal **7**[1] behaves as a highly reactive nucleophile toward electrophilic olefins[11]

(2) E. Demole, E. Lederer, and D. Mercier, *Helv. Chim. Acta*, **45**, 675 (1962).

(3) D. C. Aldridge, S. Galt, D. Giles, and W. B. Turner, *J. Chem. Soc. C*, 1623 (1971).

(4) E. Demole and M. Stall, *Helv. Chim. Acta*, **45**, 692 (1962); K. Sisido, S. Kurozumi, and K. Utimoto, *J. Org. Chem.*, **34**, 2661 (1969); G. Büchi and B. Egger, *ibid.*, **36**, 2021 (1971). The absolute configuration is also known [R. K. Hill and A. G. Edwards, *Tetrahedron*, **21**, 1501 (1965)].

(5) Various methods have recently been reported to lead to substituted cyclopentenones: W. D. Woessner and R. A. Ellison, *Tetrahedron Lett.*, 3735 (1972); *Chem. Commun.*, 529 (1972); P. A. Grieco, *J. Org. Chem.*, **37**, 2363 (1972); W. F. Berkowitz and A. A. Ozario, *ibid.*, **36**, 3787 (1971); G. Stork, G. L. Nelson, F. Rouessac, and O. Gringore, *J. Amer. Chem. Soc.*, **93**, 3091 (1971); J. E. McMurray and J. Melton, *ibid.*, **93**, 5309 (1971).

(6) Commercially available from Columbia Organic Chemical Co., Columbia, S. C.

(7) Complete experimental details on all compounds described in this communication will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N. W., Washington, D. C. 20036, by referring to code number JOC-73-175. Remit check or money order for $4.00 for photocopy or $2.00 for microfiche.

(8) A. I. Meyers and E. M. Smith, *J. Amer. Chem. Soc.*, **92**, 1084 (1970). The full paper describing this ketone synthesis is currently in press (*J. Org. Chem.*).

(9) F. Sondheimer, *J. Chem. Soc.*, 877 (1950).

(10) In another experiment, *n*-hexylmagnesium bromide was added to the methiodide salt of **3** producing the corresponding *n*-hexyl keto aldehyde and ultimately the 2-*n*-hexylcyclopentenone in good yield.

(11) A variety of electrophilic olefins (esters, nitriles, ketones) have been examined and appear to behave in the fashion described in Scheme II. Certain limitations have been found, however, in highly substituted compounds (*e.g.*, $\Delta^{1,9}$-2-octalone) and unsaturated aldehydes (*e.g.*, $\Delta^1$-cyclopentene carboxaldehyde). Studies are continuing to determine whether or not conditions could be found to implement these transformations successfully.

SCHEME I



**2**    **3**



**4**    **5**



**6**    **7**



**8**
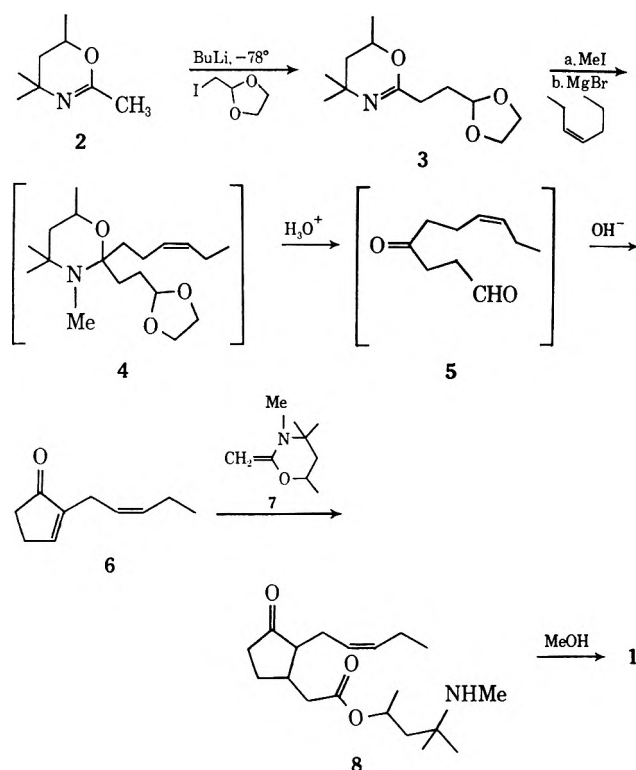
(Scheme II). Thus, $\alpha,\beta$-unsaturated carbonyl compounds are readily homologated to the acetic esters by

SCHEME II



**10**



**11**
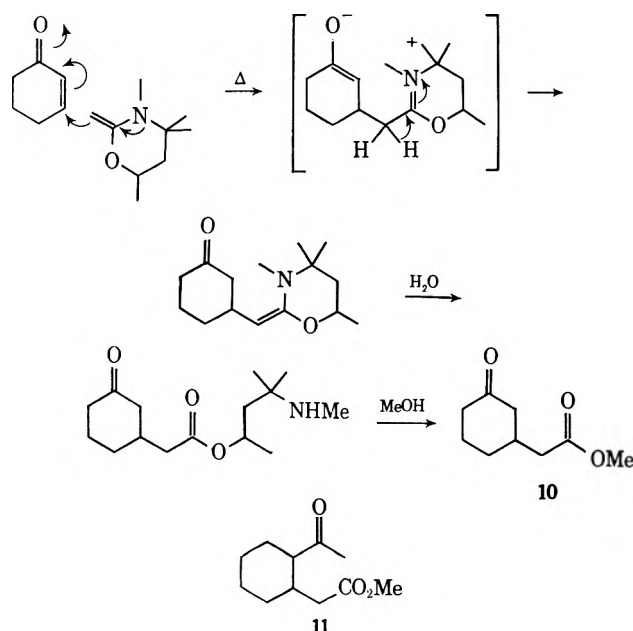
treatment with **7** followed by hydrolysis and transesterification. In this manner, 2-cyclohexenone was converted to the keto ester (benzene, 80°, 3 hr) **10** in 55% yield and 2-acetylcyclohexene was transformed into the keto ester **11** (toluene, 110°, 3 hr) in 62% yield. Although these compounds could conceivably be prepared using sodio malonate, the absence of the hydrolysis–decarboxylation step in the present method is significant.

Addition of the ketene $N,O$-acetal **7** to the cyclopentenone **6** (3 hr, 135°) afforded the keto ester **8** after

quenching in water. Transesterification using methanol and a catalytic amount of $p$-toluenesulfonic acid led to ($\pm$)-methyl jasmonate (**1**) (40% based on **6** recovered) whose properties were identical with those reported.[4]

(12) Address all correspondence to this author at the Department of Chemistry, Colorado State University, Fort Collins, Colo. 80521.

DEPARTMENT OF CHEMISTRY    A. I. MEYERS[*12]
WAYNE STATE UNIVERSITY    NICHOLAS NAZARENKO
DETROIT, MICHIGAN 48202

## The Photochemical Decomposition of Triphenyltriazafulvenes

*Summary:* Dehydrohalogenation of **1a**, **1b**, and **3** at −78° affords the triazafulvenes **2a**, **2b**, and **4**, photolysis of which affords a mixture of products; the intermediacy of the *exo*-methyleneazirine (triphenylazatriafulvene) **10** is strongly implicated.

*Sir:* An elegant approach to the synthesis of the theoretically interesting heterocyclic variant of cyclopropenone, azirinone, *via* decomposition at −30° of $\alpha$-azidophenylketene gave only carbon monoxide and benzonitrile.[1] An analogous reaction an $\alpha$-azidoallene or an isomeric triazafulvene might provide evidence for the presence of an equally interesting azatriafulvene. We now wish to report our observations on the photochemical decomposition of the triphenyltriazafulvenes, **2** and **4**.

The substituted 2-(1,3,4-triazolyl)diphenylcarbinol (**3**, X = OH) and 4-(1,2,3-triazolyl)diphenylcarbinols (**1a**, **1b**, X = OH)[2,3] were converted to the hydrochloride salts of the chlorides (**1a**, **1b**, **3**, X = Cl) by thionyl chloride in benzene at 30°. Dehydrohalogenation of these salts with triethylamine in THF at −78° gave intensely colored solutions of **2a** ($\lambda_{max}$ 463 nm), **2b** ($\lambda_{max}$ 454 nm), and **4** ($\lambda_{max}$ 442 nm) which appeared to be quite stable for a long period of time at this temperature.[4] However, warming the THF solutions to 30° led to rapid dimerization to give the photochemically inert $4H,10H$-ditriazo[1,2-$a$:1′,2′-$d$]pyrazines, **5**, mp 278–280°, and **6**, mp 291–293°, characterized by their acid-catalyzed hydrolysis to **1a** (X = OH) and **3** (X = OH).[3,5] The fulvenes

(1) A. Hassner, R. J. Isbister, R. B. Greenwald, J. T. Klug, and E. C. Taylor, *Tetrahedron*, **25**, 1637 (1969).

(2) These precursors resulted from the addition of excess phenyllithium to the corresponding carbomethoxytriazoles. Complete synthetic details and physical properties will appear in our full paper.

(3) All new compounds reported herein gave satisfactory elemental analyses and displayed structurally consistent ir, nmr, and mass spectra including an exact mass determination.

(4) A phenyl substituent at C-5 appears to be a requirement for stability in **2** based on the observation that when R = H the lifetime of this fulvene was <3 sec at −78°.

(5) Analogous (1,3) cycloadditions of 6,6-diphenyl-1,4-diazafulvene and 6,6-diphenyl-1,2,3,4-tetraazafulvene have been reported: W. Rohr, R. Swoboda, and H. A. Staab, *Ber.*, **101**, 3491 (1968); H. Behringer and M. Matner, *Tetrahedron Lett.*, 1663 (1966).

were further identified by their rapid reaction with methanol at −78° to give the ethers, **1a** (X = OCH₃), mp 101–102°, and **3** (X = OCH₃), mp 134–135°.



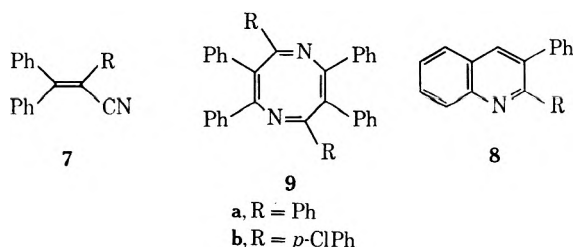**a**, R = Ph
**b**, R = *p*-ClPh
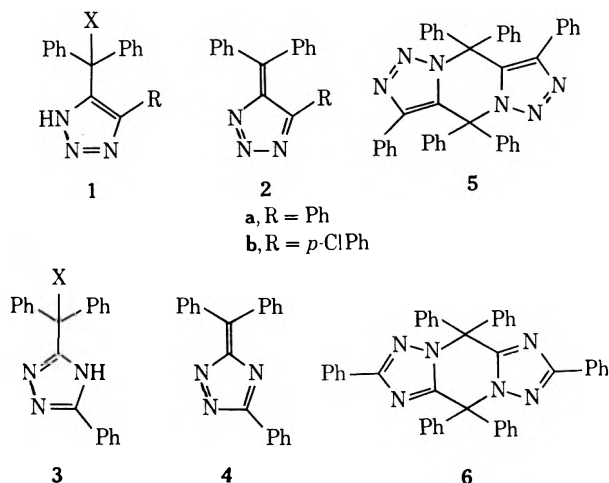
The irradiation[6] of either **2a** or **4** in THF–benzene (1:1) solution (0.025 *M*) at −78° for 4–5 hr led (>95% conversion) to a chromatographically separable mixture (see Table I) of benzonitrile,[7] diphenylacetylene,[7]

**TABLE I**
**RATIOS OF PHOTOLYSIS PRODUCTS**

| Compd | PhCN | PhC≡CPh | 7 | 8 | 9 |
|-------|------|---------|---|---|---|
| **2a** | 7 | 7 | 1 | 1 | 4 |
| **2b** | 13 | 13 | 2 | 1 | 1 |
| **4** | 6 | 6 | 1 | 1 | 1 |
| **14** | 10 | 10 | — | 1 | 2 |

2,3-diphenylquinoline (**8a**),[7,8] triphenylacrylonitrile (**7a**),[7,9] and a yellow crystalline dimer of C₂₁H₁₅N, mp 230–232°. *Anal.* Calcd for C₄₂H₃₀N₂: C, 89.65; H, 5.37; N, 4.98. Found: C, 89.55; H, 5.39; N, 4.99. This latter substance had ir absorbance at 1618 (C=N), 1598 (C=C), and 1577 (C=C) cm⁻¹ and only aromatic proton resonances in the nmr spectrum while the structural symmetry present could be inferred from the mass spectrum (~70 eV) which displayed major ions at *m/e* 562 (C₄₂H₃₀N₂⁺), 281 (C₂₁H₁₅N⁺), and 204 (C₂₁H₁₅N⁺−C₆H₅). The λ_max in EtOH occurred at 258 nm associated with the formation of a cation in concentrated sulfuric acid which had λ_max at 618 nm. This information, coupled with the observation that pyrolysis at 300° gives in >98% conversion only benzonitrile[7]



**a**, R = Ph
**b**, R = *p*-ClPh

and hexaphenylpyridine,[7,10] provides a basis for a *tentative* structural assignment of hexaphenyl-1,5-diazocine (**9a**) to this dimer.[11]

The photolysis of **2b** under the previously described conditions afforded only diphenylacetylene, *p*-chlorobenzonitrile, 1-(*p*-chlorophenyl)-2,2-diphenylacrylonitrile,[7,12] mp 142–143°, 2-(*p*-chlorophenyl)-3-phenylquinoline,[7,13] mp 93–95°, and the diazocine[3] **9b**, mp 243–244°.

The two structurally diverse fulvenes **2** and **4** appear to undergo photochemically fragmentation by loss of nitrogen to common intermediates. This mechanistic symmetrization is best accommodated by the intervention of the triphenylazatriafulvene **10** which rearranges by a (1,2) phenyl shift to **7** and is an *especially* compelling intermediate in the conversion of **4** to **7**.[14] The appearance of **8** and **9** as photoproducts probably represent the ultimate result of further transformations of an intermediate triphenylazete (**13**) which arises from **11** or **12** by phenyl migration
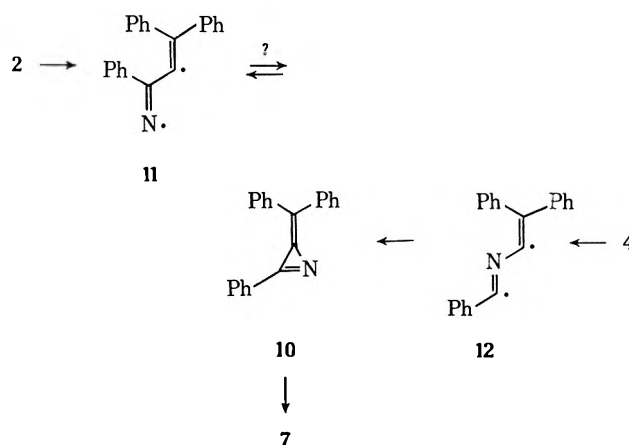


and closure. The hypothesis that **8** and **9** are uniquely derived from **13** is supported by a reexamination[15] of the photochemistry of the triphenyl-*v*-triazine **14** which in benzene–THF (1:1) solution (0.025 *M*) upon irradiation[6] at 30° for 5 hr gave in addition to benzonitrile and diphenylacetylene both **8a** and **9a**. The [ₚ2ₛ + ₚ4ₛ] dimerization[16] of **13** followed by electrolytic[17] opening would yield **9**. The path for conversion of **13** to **8** remains obscure; a *speculative*

(10) We wish to thank Dr. Merle Battiste for an authentic sample of this compound.

(11) The mass spectrum of **9a** resembles that of octaphenylcyclooctatetraene: R. C. Cookson, *et al.*, *J. Chem. Soc.*, 2052 (1965).

(12) G. H. Hitchings, P. B. Russell, and N. Whittaker, *ibid.*, 1019 (1956).

(13) K. Mukherjee, G. B. Behera, and M. K. Rout, *J. Inst. Chem.*, *Calcutta*, **41**, 138 (1969).

(14) Mechanistic interpretation of the photochemical conversion of β-styryl azide to phenylacetonitrile follows a parallel proposal: J. H. Boyer, W. E. Krueger, and G. J. Mikol, *J. Amer. Chem. Soc.*, **89**, 5504 (1967).

(15) Smolinsky and Chandross obtained **14** from the rearrangement of triphenylcyclopropenyl azide and report its photodecomposition to only diphenylacetylene and benzonitrile. A compound of constitution C₄₂H₃₀N₂ with spectral properties similar to **9a** was isolated by Smolinsky from this azide rearrangement reaction: E. A. Chandross and G. Smolinsky, *Tetrahedron Lett.*, 19 (1960). More recently Closs and Harrison reported that the photolysis of trimethyl-*v*-triazine gives 2-butyne and acetonitrile: G. L. Closs and A. M. Harrison, *J. Org. Chem.*, **37**, 1051 (1972).

(16) If the cycloaddition proceeds through a polar transition state, charge development is best accommodated by bond formation at the heteroatom sites. Of course, one other combination is possible to give ultimately a symmetrical diazocine.

(17) The ground-state conrotation required by orbital symmetry for the opening of **15** can avoid the strain of a developing trans bond by inversion at nitrogen: R. B. Woodward and R. Hoffman, "The Conservation of Orbital Symmetry," Verlag Chemie GmbH, Weinheim, West Germany, 1970, p 51.

**a**, R = Ph
**b**, R = *p*-ClPh

(6) Photolyses were conducted using a 450-W Hanovia high-pressure mercury discharge lamp in a Pyrex probe.

(7) Identified by ir spectral comparison with an authentic sample and mixture melting point where applicable.
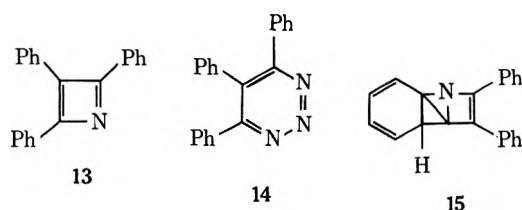
(8) W. Pfitzinger, *J. Prakt. Chem.*, **56**, 304 (1897).

(9) S. Wawzonek and E. M. Smolin, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 387.

proposal might invoke a $[_\pi 2 + _\pi 2]$ intramolecular cyclization to **15** which by suitable hydrogen shift and bond reorganization is transformed into **8**.[18]



13    14    15

**Acknowledgment.**—We wish to thank the National Science Foundation (GP-27956) for support.

(18) An analogous sequence has been proposed for the transformation of tetraphenylcyclobutadiene to 1,2,3-triphenylnaphthalene: G. Büchi, C. W. Perry, and E. W. Robb, *J. Org. Chem.*, **27**, 4106 (1962). Other mechanistic proposals may, of course, be offered for this reaction.

SCHOOL OF CHEMISTRY             EDWARD M. BURGESS*
GEORGIA INSTITUTE OF TECHNOLOGY  JOSEPH P. SANCHEZ
ATLANTA, GEORGIA  30332

## Bruceantin, a New Potent Antileukemic Simaroubolide from *Brucea antidysenterica*[1-3]

*Summary:* Bruceantin and bruceantarin, new antileukemic simaroubolides from *Brucea antidysenterica*, a plant used in Ethiopia in the treatment of cancer, are shown to have structures **1** and **2**, respectively.

*Sir:* *Brucea antidysenterica* Mill. is a simaroubaceous tree which is used in Ethiopia in the treatment of cancer.[4] In the course of a continuing search for tumor inhibitors from plant sources, we found that an alcoholic extract of *Brucea antidysenterica* Mill.[5] showed significant inhibitory activity *in vitro* against cells derived from human carcinoma of the nasopharynx (KB) and against two standard animal tumor systems.[6] We report herein the isolation and structural elucidation of a new potent antileukemic simaroubolide tumor inhibitor, bruceantin (1),[7] and the companion simaroubolide bruceantarin (2), from *Brucea antidysenterica*.

Fractionation of the alcohol extract, guided by assay against KB and P-388, revealed that the inhibitory activity was concentrated, successively, in the chloroform layer of a chloroform–water partition, the methanol layer of a 10% aqueous methanol–petroleum ether partition, the methanol layer of a 20% aqueous

(1) Tumor Inhibitors. LXXXII. Part LXXXI is ref 2.

(2) S. M. Kupchan and G. Tsou, *J. Org. Chem.*, in press.

(3) Supported by grants from the National Cancer Institute (CA-11718) and American Cancer Society (T-275 and IC-57H), and a contract with the National Cancer Institute (NIH-NCI-C-71-2099).

(4) J. L. Hartwell, *Lloydia*, **34**, 221 (1971).

(5) Stem bark was collected in Ethiopia in June 1971. Leaves and the wood of stems from Ethiopia also yielded active extracts. We thank Dr. Robert E. Perdue, Jr., USDA, Beltsville, Md., for supplying the plant material.

(6) Activity was noted against P-388 leukemia in the mouse and Walker 256 intramuscular carcinosarcoma in the rat. Cytotoxicity and *in vivo* activity were assayed as in *Cancer Chemother. Rep.*, **25**, 1 (1962).

(7) Bruceantin showed significant antileukemic activity against P-388 lymphocytic leukemia over a 50–100-fold dosage range at the µg/kg level, and cytotoxicity (ED₅₀) against KB cell culture at 10⁻³ µg/ml. Bruceantarin showed only moderate activity against P-388, and the previously isolated[8] bruceine B showed only marginal activity against this system.

(8) J. Polonsky, Z. Baskevitch, A. Gaudemer, and B. C. Das, *Experientia*, **23**, 424 (1967).

1, R = OC
2, R = OCC$_6$H$_5$
3, R = OCCH$_3$
4, R = H
5, R = OCCH$_2$CH(CH$_3$)CH(CH$_3$)$_2$

methanol–carbon tetrachloride partition and, finally, in the chloroform layer of a chloroform–40% aqueous methanol partition. Column chromatography of the final chloroform-soluble material on SilicAR CC7 yielded two KB cytotoxic fractions (A and B) on elution with 1% methanol in chloroform. Continued elution with 2% methanol in chloroform gave a third cytotoxic fraction (C). Careful rechromatography of fraction A on SilicAR CC7 with 20% ether in benzene gave bruceantin (1, 0.01%): C$_{28}$H$_{36}$O$_{11}$; $[\alpha]^{25}$D −27.7° (c 3.0, pyridine); uv max (EtOH) 280 nm (ε 6450) and 221 (14,100), uv max (EtOH + NaOH) 328 nm (ε 4260) and 221 (15,500); ir (KBr) 2.90, 5.76, 6.05, 6.13, 8.70, and 9.45 µ; mass spectrum m/e 548.222 (M$^+$, calcd 548.225), 438, 420, 402, 297, 151, 111.0819 (calcd, C$_7$H$_{11}$O, 111.0809); nmr (CDCl$_3$) τ 8.88 [6 H, d, $J$ = 6.5 Hz, CH(CH$_3$)$_2$], 8.56 (3 H, s, 10-CH$_3$), 8.11 (3 H, br s, 4-CH$_3$), 7.82 [3 H, s, CH=C(CH$_3$)], 7.29 (1 H, br m, OH), 6.47 (1 H, br s, OH), 6.24 (3 H, s, OCH$_3$), 4.39 [1 H, br s, O$_2$CCH=C(CH$_3$)], 3.87 (1 H, br s, OH), and 3.79 (1 H, d, $J_{15,14}$ = 13 Hz, 15-H).

Rechromatography of fraction B on SilicAR CC7 with 30% ether in benzene gave bruceantarin (2, 0.002%): C$_{28}$H$_{30}$O$_{11}$; mp 182–185°; $[\alpha]^{25}$D −20.7° (c 0.6, pyridine); uv max (EtOH) 278 nm (ε 7000) and 231 (10,500), uv max (EtOH + NaOH) 330 nm (ε 4480) and 230 (9030); ir (KBr) 2.9, 5.78, 6.03, 6.08, 6.12, 7.88, 8.70, 9.0, 9.45, and 13.8 µ; mass spectrum m/e 542 (M$^+$), 437, 420, 402, 297, 151, 105, and 77; nmr (CDCl$_3$) τ 8.63 (3 H, s, 10-CH$_3$), 8.20 (3 H, br s, 4-CH$_3$), 6.56 (3 H, s, OCH$_3$), 3.58 (1 H, d, $J_{15,14}$ = 13 Hz, 15-H), 2.60 (3 H, m, B$_2$X portion of A$_2$B$_2$X, m and p-benzoate protons), and 2.07 (2 H, d of d, A$_2$ part of A$_2$B$_2$X system, $J_{AB}$ = 7.5, $J_{AX}$ = 1.5 Hz, o-benzoate protons).

Rechromatography of fraction C on SilicAR CC7 using 2:1 ether in benzene gave the known bruceine B (3, 0.002%), characterized by comparison of its melting point, $[\alpha]$D, and ir, nmr, uv, and mass spectra with those previously reported.[8]

Bruceantin (1) and bruceantarin (2) gave a positive ferric chloride test, and displayed in their uv spectra the large bathochromic shift with alkali characteristic of diosphenols. In addition, acetylation of bruceantin (1) gave a triacetate which displayed neither the uv absorption at 280 nm nor the associated bathochromic shift. The mass spectra of 1 and 2 displayed as primary fragmentations peaks corresponding to a

loss of $C_7H_{10}O$ (m/e 438) and $C_7H_5O$ (437) and base peaks corresponding to $C_7H_{11}O$ (111) and $C_7H_5O$ (105), respectively. Except for the above-mentioned base peaks in the mass spectra of **1** and **2**, peaks in the region from m/e 438 to 69 were almost identical with those present in the mass spectrum of bruceine B (**3**). Inspection of the nmr spectra of bruceantin (**1**), bruceantarin (**2**), and bruceine B (**3**) revealed that all three displayed peaks corresponding to an angular methyl group in the region of τ 8.3–8.6, a vinyl methyl at 8.0–8.2, a methoxyl at 6.2–6.5, and a sharp one-proton doublet (J = 13 Hz) between 3.2 and 3.6 [assigned to H-15 in bruceine B (**3**)[8]]. The major differences between the nmr spectra of bruceantin (**1**) and bruceine B (**3**) were the additional signals for **1** of a six-proton doublet (J = 6.5 Hz) at τ 8.88, a vinyl methyl signal at 7.82, and a vinyl proton singlet at 4.39. These data and the presence of the base peak at m/e 111 in the mass spectrum supported formulation of bruceantin (**1**) as the 3,4-dimethylpent-2-enoic acid ester of bruceolide[8] (**4**). Hydrogenation of bruceantin (**1**) gave dihydrobruceantin (**5**): $C_{28}$-$H_{38}O_{11}$; mp 137–140°; $[\alpha]^{25}D$ −64.5° (c 2.9, pyridine); mass spectrum m/e 550 (M+), 438, 297, 151, and 113. That only the side-chain ester of **1** had been reduced was indicated by the uv spectrum, which still showed the diosphenol absorption and alkaline shift, and by the nmr spectrum, which showed no olefinic proton but a new three-proton doublet (J = 6.5 Hz) at τ 9.06. Mild alkaline hydrolysis of **5** gave bruceolide (**4**). In addition, alkaline hydrolysis of bruceantin (**1**) and esterification of the steam-distillable acid with diazoethane gave ethyl trans-3,4-dimethyl-2-pentenoate.[9] In the nmr spectrum of ethyl cis-3,4-dimethyl-2-pentenoate the vinyl methyl signal appeared at τ 8.25, whereas the corresponding peak for the trans isomer occurred at 7.90. The peak attributed to the ester vinyl methyl in **1** appeared at τ 7.82, indicative of trans stereochemistry in bruceantin (**1**).

The sharp one-proton doublet at τ 3.79 (J = 13 Hz) in the nmr spectrum of **1** indicated C-15 as the point of attachment of the ester side chain. The corresponding peak in the spectrum of dihydrobruceantin (**5**) appeared at τ 3.14 (J = 13 Hz) and in that of bruceine B (**3**) at τ 3.28 (J = 13 Hz).

In the nmr spectrum of bruceantarin (**2**), a complex $A_2B_2X$ system centered at τ 2.3 was indicative of the presence of a benzoate group. In addition, the sharp one-proton doublet (J = 13 Hz) at τ 3.58 and the base peak at m/e 105 in the mass spectrum supported for bruceantarin (**2**) the C-15 benzoate ester structure. The postulated structure was confirmed by mild alkaline hydrolysis of bruceantarin (**2**) to benzoic acid and bruceolide (**4**).

The observed potent antileukemic activity of bruceantin confirms and extends an earlier report of antitumor activity of a simaroubolide.[10] The markedly higher potency of bruceantin (**1**),[7] compared with that of bruceantarin (**2**) and bruceine B (**3**), may be attributable to the role of the α,β-unsaturated ester.[11] Investigations are in progress to determine the significance of the unsaturated ester, the diosphenol, and

(9) M. J. Jorgenson and T. Leung, *J. Amer. Chem. Soc.*, **90**, 3769 (1968).
(10) M. E. Wall and M. Wani, *Int. Symp. Chem. Nat. Prod., 7th*, Abstracts E138, 614 (1970).
(11) *Cf.* S. M. Kupchan, *Pure Appl. Chem.*, **21**, 227 (1970).

of other structural features in relation to the tumor-inhibitory activity of bruceantin.

DEPARTMENT OF CHEMISTRY     S. MORRIS KUPCHAN*
UNIVERSITY OF VIRGINIA     RONALD W. BRITTON
CHARLOTTESVILLE, VIRGINIA 22901     MYRA F. ZIEGLER
    CARL W. SIGEL

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## Intramolecular Electrostatic Stabilization of an SN1 Transition State

*Summary:* o-Carboxybenzal chloride hydrolyzes at about the same rate as the para isomer in water but 110 times as fast as in 60% aqueous dioxane.

*Sir:* The mechanism proposed for the hydrolytic action of lysozyme[1] involves at least two essential features. The first of these is the suggestion that Glu-35 acts as a general acid[2] effecting intracomplex protonation of the acetal linkage. It seems to be well established that a carboxyl group can function as an intermolecular general acid in acetal hydrolysis.[3] Intramolecular general acid catalysis has also recently been observed in the hydrolysis of 2-(o-carboxyphenoxy)tetrahydropyran in aqueous dioxane.[4] The second feature of the proposed enzymatic mechanism is that the ionized form of Asp-52 functions either as a nucleophile forming a glycosyl enzyme intermediate or electrostatically stabilizes the transition state leading to the oxocarbonium ion intermediate. In a very careful study Dunn and Bruice[5] have provided evidence that an ortho carboxylate ion can electrostatically stabilize the transition state in the A-1 cleavage of acetals and that this type of stabilization can provide substantial rate enhancements. To obtain additional information concerning the role of an ionized carboxyl group in stabilizing an ionic transition state uncomplicated by a proton-transfer step we have studied the hydrolysis of o- and p-carboxybenzal chlorides.

The mechanism of hydrolysis of benzal chlorides has been the subject of numerous reports.[6] It is clear that the mechanism involves rate-determining formation of a chlorocarbonium ion followed by a series of rapid steps leading to the product aldehyde (Scheme I). For example, $\rho^+$ calculated from published[6a] data is −5.2 ± 0.3. Also the rate is completely unaffected by external nucleophiles[6b,c,e] and the value

(1) Reviews: P. Jolles, *Angew. Chem., Int. Ed. Engl.*, **3**, 28 (1964); P. Jolles, *ibid.*, **8**, (1969); B. Capon, *Chem. Rev.*, **69**, 434 (1969); (a) R. E. Canfield, *J. Biol. Chem.*, **238**, 2699 (1963); (b) C. C. F. Blake, D. F. Koenig, G. A. Mair, A. C. T. North, D. C. Phillips, and V. R. Sarma, *Nature (London)*, **206**, 757 (1965); (c) L. N. Johnson and D. C. Phillips, *ibid.*, **206**, 761 (1965); (d) J. B. Howard and A. N. Glazier, *J. Biol. Chem.*, **244**, 1399 (1969); (e) J. A. Rupley, *Proc. Roy. Soc. Ser. B.* (*London*), **167**, 416 (1967); (f) D. C. Phillips, *Sci. Amer.*, **215**, 78 (1966); (g) J. A. Rupley and V. Gates, *Proc. Nat. Acad. Sci. U. S.*, **57**, 496 (1967); (h) T. Osawa and Y. Nakasawa, *Biochem. Biophys. Acta*, **130**, 56 (1966); (i) M. A. Raftery and T. Rand-Meir, *Biochemistry*, **7**, 3281 (1968).
(2) C. C. F. Blake, L. N. Johnson, G. A. Mair, A. C. T. North, D. C. Phillips, and V. R. Sarma, *Proc. Roy. Soc. B* (*London*), **167**, 378 (1967).
(3) T. H. Fife, *Accounts Chem. Res.*, **5**, 264 (1972).
(4) T. H. Fife and E. Anderson, *J. Amer. Chem. Soc.*, **93**, 6610 (1971).
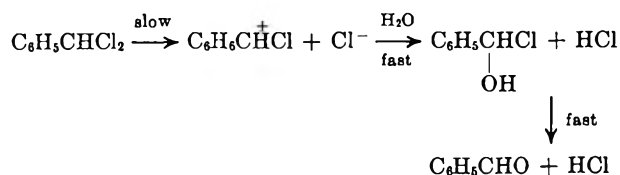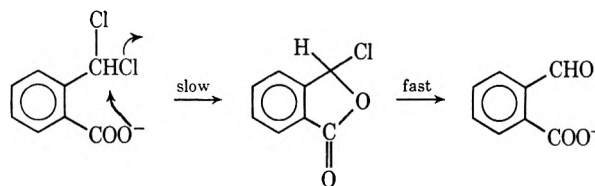(5) B. M. Dunn and T. C. Bruice, *ibid.*, **93**, 5725 (1971).
(6) (a) F. Asinger and G. Lock, *Monatsh. Chem.*, **62**, 323 (1933); (b) S. C. T. Olivier and A. Weber, *Recl. Trav. Chim. Pays-Bas*, **53**, 869 (1934); (c) L. J. Andrews and W. W. Kaeding, *J. Amer. Chem. Soc.*, **73**, 1007 (1951); (d) B. Bensley and G. Kohnstam, *J. Chem. Soc.*, 287 (1956); (e) K. Tanabe and T. Ido, *J. Res. Inst. Catal., Hokkaido Univ.*, **12**, 223 (1965).

SCHEME I

$$C_6H_5CHCl_2 \xrightarrow{slow} C_6H_5\overset{+}{C}HCl + Cl^- \xrightarrow[\text{fast}]{H_2O} \underset{OH}{C_6H_5CHCl} + HCl$$

$$\downarrow \text{fast}$$

$$C_6H_5CHO + HCl$$

SCHEME II



of $m$ measured in aqueous ethanol solutions for benzal chloride is large $(1.31 \pm 0.02)$[7] indicative of an $S_N1$ transition state.[8]

We have measured the hydrolysis rates of $o$-carboxybenzal chloride (1) and $p$-carboxybenzal chloride (2) in water and mixtures of water and dioxane in the
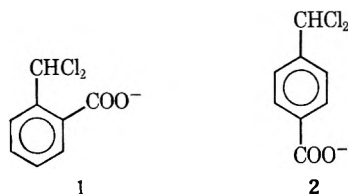


presence of excess base and these results are collected in Table I. These results show that in water an ortho

TABLE I

RATES OF HYDROLYSIS OF CARBOXY
SUBSTITUTED BENZAL CHLORIDES AT $25.2 \pm 0.2°$ [a]

| $10^7 k_{ortho}^{obsd}$, sec$^{-1}$ | $10^7 k_{para}^{obsd}$, sec$^{-1}$ | $k_{ortho}/k_{para}$ | Solvent[b] |
|---|---|---|---|
| 2210 | 2640 | 0.83 | A |
| 563 | 11.2 | 50.3 | B |
| 276 | 2.52 | 110 | C |

[a] Rate constants were determined by following the increase of absorbance at 257 nm due to the aldehyde product. The slower reactions were studied using an initial rate method and the rate constants thus obtained are considered accurate to $\pm 10\%$. The results are the average of at least three separate determinations. [b] A, 0.2 $N$ NaOH in water; B, 50% dioxane–50% 0.2 $N$ NaOH (v/v); C, 60% dioxane–40% 0.2 $N$ NaOH (v/v).

carboxylate ion does *not* facilitate the reaction and, in fact, has a slight rate-retarding effect. Presumably in water (a highly polar solvent) the ortho carboxylate ion does not compete effectively with the solvent in stabilizing the ionic transition state. However, increasing the amount of dioxane present in the solvent results in a dramatic increase in $k_{ortho}/k_{para}$ (Table I). Thus, as the solvent becomes less able to stabilize the transition state electrostatic stabilization by the ortho carboxylate ion becomes more pronounced. In fact, extrapolation of the data in Table I give $k_{ortho}/k_{para} = 7600$ in 90% aqueous dioxane.

An alternative mechanism involving intramolecular nucleophilic displacement by the ortho carboxylate function (Scheme II) cannot rigorously be excluded at the present time.[9]

However, if intramolecular displacement was responsible for the high $k_{ortho}/k_{para}$ values in aqueous dioxane solutions, one would expect an even large value of $k_{ortho}/k_{para}$ in aqueous DMSO (*cf.* the large

rate accelerations observed[10] for $S_N2$ reactions in DMSO and the increased rate of anhydride formation from phenyl hydrogen phthalate in aqueous DMSO).[11] On the other hand, electrostatic catalysis ought to be favored in media of low dielectric constant and, since DMSO has a higher dielectric constant ($\sim 50$) than dioxane ($\sim 2$), a lower value of $k_{ortho}/k_{para}$ is expected in aqueous DMSO. Since $k_{ortho}/k_{para} = 12$ in 50% aqueous DMSO it would seem that the ortho carboxylate ion enhances the solvolysis rate of benzal chloride by electrostatically stabilizing the ionic transition state rather than effecting an intramolecular nucleophilic displacement.

In conclusion, we feel that the results described in the communication support the suggestion that, under certain conditions, a properly oriented carboxylate ion can stabilize a transition state leading to a resonance stabilized carbonium ion.

(10) J. J. Delpuech, *Bull. Soc. Chim. Fr.*, 1624 (1966).

(11) T. C. Bruice and A. Turner, *J. Amer. Chem. Soc.*, **92**, 3422 (1970).

DEPARTMENT OF CHEMISTRY      V. P. VITULLO*
UNIVERSITY OF MARYLAND      N. R. GROSSMAN
  BALTIMORE COUNTY
BALTIMORE, MARYLAND 21228

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# A Reinvestigation of
# 3,5′-Anhydro-2′,3′-$O$-isopropylideneinosine

*Summary:* Nmr studies have shown that 3,5′-anhydro-2′,3′-$O$-isopropylideneinosine (II), previously described, is actually the ring-opened compound 5′,$N^5$-anhydro-1-(2,3-$O$-isopropylidene-$\beta$-$D$-ribofuranosyl)-5-formamidoimidazole-4-carboxamide (I); the preparation and characterization of authentic II is described.

*Sir:* The formation of cyclonucleosides from purine nucleoside derivatives is well established.[1] The first reported synthesis[2] of 3,5′-anhydro-2′,3′-$O$-isopropylideneinosine used thermal cyclization of the appropriate 5′-$O$-$p$-toluenesulfonyl derivative in an inert solvent, a procedure first used in the synthesis of 3,5′-anhydro-2′,3′-$O$-isopropylideneadenosine.[3] The inosine cyclonucleoside was isolated as the $p$-toluenesulfonate salt[2] which was converted to a product described as the monohydrate of 3,5′-anhydro-2′,3′-$O$-isopropylideneinosine. Three subsequent reports have described the formation of the same final product by the following

(7) N. Grossman, unpublished work.

(8) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," Vol. X, McGraw-Hill, New York, N. Y., 1962, pp 45–47.

(9) An additional mechanism suggested by a reviewer involving the intramolecular deprotonation of the dichloromethyl group followed by $\alpha$ elimination to generate a carbene seems unlikely in view of the fact that the rate is independent of the concentration of HO$^-$ (a much stronger base) for both **1** and **2** if pH > p$K_A$.

(1) C. A. Dekker and L. Goodman in "The Carbohydrates," Vol. IIA, 2nd ed, W. Pigman and D. Horton, Ed., Academic Press, New York, N. Y., 1970, Chapter 29.
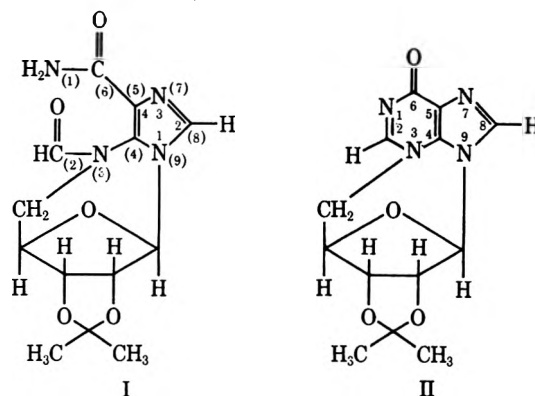
(2) R. E. Holmes and R. K. Robins, *J. Org. Chem.*, **28**, 3483 (1963).

(3) V. M. Clark, A. R. Todd, and J. Zussman, *J. Chem. Soc.*, 2952 (1951).

TABLE I

$^1$H (PMR) AND $^{13}$C (CMR) NUCLEAR MAGNETIC RESONANCE DATA



A. Pmr[a]

| Compd | H$_8$ | H$_2$ | NH$_2$ | H$_1'$ | H$_2'$ | H$_3'$ | H$_4'$ | H$_{5',5''}$ | CH$_3$ |
|---|---|---|---|---|---|---|---|---|---|
| I | 7.94 | 8.32 | 7.34 | 6.23 | 4.97 | 4.54 | 4.73 | 4.76 | 1.48 |
|  |  |  | 7.26 |  |  |  |  | 2.93 | 1.33 |
| II | 8.20 | 8.12 |  | 6.56 | 5.04 | 4.54 | 4.94 | 4.84 | 1.52 |
|  |  |  |  |  |  |  |  | 4.26 | 1.30 |

Vincinal coupling constants, Hz

| Compd | 1'–2' | 2'–3' | 3'–4' | 4'–5' | 4'–5'' | 5'–5'' |
|---|---|---|---|---|---|---|
| I | <1 | 6.0 | b | 1.7 | 2.7 | 14.0 |
| II | <1 | 6.0 | b | 2.0 | 3.0 | 14.8 |

B. Cmr[c]

Chemical shifts, ppm

| Compd | C$_2$ | C$_4$ | C$_5$ | C$_6$ | C$_8$ | C$_1'$ | C$_2'$ | C$_3'$ | C$_4'$ | C$_5'$ | *C(CH$_3$)$_2$ | *CH$_3$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I | −35.7 | −4.06 | 1.40 | −35.7 | −6.36 | 37.4 | 42.8 | 45.8 | 42.8 | 82.6 | 15.7 | 101.1 |
|  |  |  |  |  |  |  |  |  |  |  |  | 102.9 |
| II | −20.7 | −11.5 | 2.30 | −36.3 | −7.95 | 37.3 | 43.1 | 46.9 | 41.9 | 71.3 | 15.1 | 101.1 |
|  |  |  |  |  |  |  |  |  |  |  |  | 102.8 |

C–H coupling constants, Hz

| Compd | $^1J_{C_2-H_2}$ | $^1J_{C_8-H_8}$ | $^3J_{C_4-H_8}$ | $^3J_{C_6-H_2}$ | $^3J_{C_8-H_1'}$ |
|---|---|---|---|---|---|
| I | 209 | 215 | d | 0 | ca. 3 |
| II | 208 | e | 11 | 11 | ca. 3 |

[a] 60-MHz spectra were taken on Perkin-Elmer R20A, probe temperature 34°. Samples were 10% w/v in DMSO-$d_6$. Shifts were measured in parts per million from internal 2,2-dimethylsilapentanesulfonic acid sodium salt. [b] Not resolved. [c] 22.6-MHz spectra were taken on Bruker HX-90 using the Fourier Transform mode. Samples were 20–40% w/v in DMSO-$d_6$. Chemical shifts (parts per million) were taken from noise-decoupled spectra (16,000–40,000 accumulation) measured from external hexafluorobenzene and converted to benzene using the experimentally determined relationship $\delta_{C_6H_6} = \delta_{C_6F_6 \,(ext)} - 9.9$ ppm. C–H coupling constants (hertz) were taken from undecoupled spectra (40,000–200,000 accumulations). Probe temperature was 40–45° for noise-decoupled spectra and ~30° for undecoupled spectra. [d] Unresolved multiplet. [e] One leg of doublet obscured by C$_6$F$_6$.

routes: (1) treatment of 2',3'-*O*-isopropylideneinosine with phosphoryl chloride,[4] (2) interaction of methyltriphenoxyphosphonium iodide with 2',3'-*O*-isopropylideneinosine,[5] and (3) treatment of 5'-deoxy-5'-iodo-2',3'-*O*-isopropylideneinosine with aqueous ammonia.[6] Each of these reports characterizes the inosine cyclonucleoside as a monohydrate identical with the product of Holmes and Robins.[2]

We have recently reexamined the product described as 3,5'-anhydro-2',3'-*O*-isopropylideneinosine by $^1$H (pmr) and $^{13}$C (cmr) nmr spectroscopy and have determined that this compound is instead the ring-opened derivative 5',$N^5$-anhydro-1-(2,3-*O*-isopropylidene-$\beta$-D-ribofuranosyl)-5-formamidoimidazole-4-carboxamide (I). The preparation of the intact 3,5'-anhydro-2',3'-*O*-isopropylideneinosine (II) was accomplished by careful neutralization of the corresponding *p*-toluenesulfonate salt[2] on a column of Amberlite IR-45 (OH)

(4) K. Kusashio and M. Yoshikawa, *Bull. Chem. Soc. Jap.*, **41**, 142 (1968).
(5) J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, **35**, 2319 (1970).
(6) A. Hampton, M. Bayer, V. S. Gupta, and S. Y. Chu, *J. Med. Chem.*, **11**, 1229 (1968).

at 5°. The water was removed from the solution by freeze drying and the product was crystallized from methanol to provide II: mp 314–315° dec; uv max (H$_2$O) 258 nm ($\epsilon$ 12,000), at pH 1 253 (10,400), at pH 11 250–256 (unstable) (7200). Calcd for C$_{13}$H$_{14}$N$_4$O$_4$·0.5 H$_2$O: C, 52.17; H, 5.05; N, 18.72. Found: C, 51.98; H, 5.16; N, 18.98. The presence of 0.5 mol of water in the sample was confirmed by the pmr spectrum. The pyrimidine ring of the inosine cyclonucleoside II was readily opened in aqueous solution at room temperature as shown by tlc (silica gel, 4:1 chloroform–methanol). After several days at room temperature, a solution of the inosine cyclonucleoside II in water deposited crystals of the imidazole cyclonucleoside I. Also, tlc of a solution of the *p*-toluenesulfonate salt of II,[2] after neutralization to pH 7, showed the presence of II with the gradual formation of the imidazole cyclonucleoside I.

Pertinent nmr data is contained in Table I. The parenthetical numbering in I is used for data comparison and corresponds to the same positions in II. Important features in the pmr spectra of I are the peaks

at δ 7.34 and 7.26, characteristic of amide $NH_2$ protons, and the doublet at high field, 2.93, due to one of the 5' protons. Contrarily, II displays both 5' doublets at low field and no exchangeable $NH_2$ protons. The closely spaced singlets of the purine base protons are arbitrarily assigned with $H_8$ at lowest field in the spectrum of II.

Natural abundance cmr measurements are even more revealing. The decoupled spectrum of II has one resonance, $C_6$, in the carbonyl region of inosine at −36.3 ppm.[7] On the other hand, the decoupled spectrum of I contains two peaks superimposed at −35.7 ppm, indicating two carbonyl carbons, $C_6$ and $C_2$. In addition, the loss of the conjugated purine ring is noticed in the upfield shift of $C_5$, from 71.3 in II to 82.6 ppm in I.

Perhaps the most succinct structural information is derived from the undecoupled cmr spectra. The vicinal $^3J_{C_6-H_2}$ of the usual magnitude ($\sim$9–12 Hz[8−10]) is observed in II, but is completely absent in I, indicative of no bond between $N_1$ and $C_2$.

This report illustrates the utility of cmr in nucleoside structural analysis.

(7) A. J. Jones, D. M. Grant, M. W. Winkley, and R. K. Robins, *J. Amer. Chem. Soc.*, **92**, 4079 (1970).

(8) F. J. Weigert and J. D. Roberts, *ibid.*, **90**, 3543 (1968).

(9) R. U. Lemieux, T. L. Nagabhushan, and B. Paul, *Can. J. Chem.*, **50**, 773 (1972).

(10) G. P. Kreishman and M. P. Schweizer, unpublished work.

ICN Nucleic Acid Research          Joseph T. Witkowski*
   Institute                     George P. Kreishman
Irvine, California   92664        Martin P. Schweizer
                                  Roland K. Robins

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# An Unusually Powerful Directive Effect in the Hydroboration of Representative Olefins with Monochloroborane–Ethyl Etherate

*Summary:* Hydroboration–oxidation of alkenes with monochloroborane ($BH_2Cl$) in ethyl ether gives the anti-Markovnikov alcohols in >99.5% isomeric purity, revealing a directive effect in the addition stage far stronger than that exhibited by borane–tetrahydrofuranate itself.

*Sir:* The hydroboration of representative olefins with monochloroborane–ethyl etherate ($BH_2Cl–OEt_2$) reveals a powerful directive effect which greatly reduces the yield of the minor isomer formed in hydroborations with borane itself. Consequently, hydroboration with monochloroborane ($BH_2Cl$) makes possible the synthesis of the major product in purities which often exceed 99.5%.

A difficulty in using hydroboration–oxidation for the anti-Markovnikov hydration of olefins[1] is the

(1) (a) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **82**, 4708 (1960); (b) H. C. Brown, "Hydroboration," W. A. Benjamin, New York, N. Y., 1962; (c) H. C. Brown and R. L. Sharp, *J. Amer. Chem. Soc.*, **88**, 5851(1966).

formation of significant amounts of the minor isomer in the hydroboration stage (eq 1 and 2). This phe-

$$CH_3(CH_2)_3CH=CH_2 \xrightarrow{BH_3 \atop THF}$$



$$2 \text{ (cyclopentene)} + BH_2Cl \xrightarrow[0°, 1hr]{EE} \text{(cyclopentyl)}_2BCl \quad (3)$$
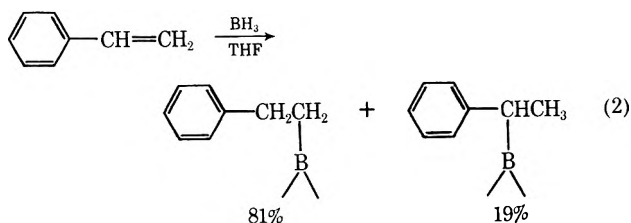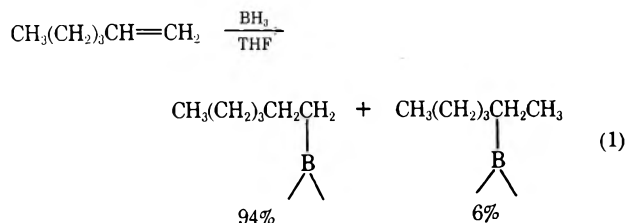
nomenon often makes necessary a tedious purification to remove the minor component. Hydroboration with disiamylborane has been recommended as a means of overcoming this difficulty. However, the reagent hydroborates internal and cyclic olefins only very sluggishly.[2] Moreover, here also it is necessary to separate the desired product from the *sec*-isoamyl alcohol resulting from the oxidation of the disiamylborane moiety. We wish to report here a new more readily and generally applied procedure to avoid these difficulties.

We recently discovered that monochloroborane in ethyl ether (EE) in contrast to monochloroborane in tetrahydrofuran (THF) readily hydroborates a wide variety of olefins to give the corresponding dialkylchloroboranes[3] (eq 3). The reaction in THF proceeds to give a mixture of products, $R_3B$, $R_2BCl$, and $RBCl_2$.[3]
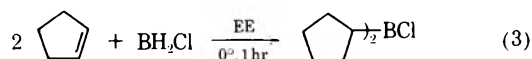
It has been reported that in THF chloroborane had little, if any, advantage over $BH_3$ in the directive effects achieved. Thus Zweifel found that the hydroboration–oxidation of 1-hexene gave 94% 1-hexanol with 6% 2-hexanol.[4] Similarly, Pasto and Balasubramaniyan observed a 96:4 distribution of the two products.[5]

We discovered that hydroboration with $BH_2Cl$ in ethyl ether exhibits a far more powerful directive effect. Thus 1-hexene yields >99.5% 1-hexanol with <0.5% 2-hexanol. Styrene (eq 2) gives 96% primary derivative with 4% secondary. Norbornene gives >99.8% exo alcohol. 1-Methylcyclopentene gives >99.8% the *trans*-2-methylcyclopentanol, with no cis isomer and only <0.2% tertiary isomer indicated.

The following procedure for the hydroboration–oxidation of 1-methylcyclopentene with $BH_2Cl–OEt_2$ is representative. In a dry 50-ml flask under nitrogen was taken 5 mmol of $BH_2Cl$ in ethyl ether[6] (3.7 ml)
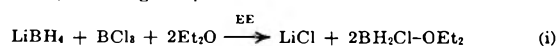
(2) H. C. Brown and G. Zweifel, *ibid.*, **83**, 1241 (1961).

(3) H. C. Brown and N. Ravindran, *ibid.*, **94**, 2112 (1972).

(4) G. Zweifel, *Organometal. Chem.*, **9**, 215 (1967).

(5) D. J. Pasto and P. Balasubramaniyan, *J. Amer. Chem. Soc.*, **89**, 295 (1967).

(6) The $BH_2Cl$ solution in ethyl ether was prepared by adding stoichiometric quantity of $LiBH_4$ in ethyl ether solution to a solution of $BCl_3$ in ethyl ether at 0°, according to eq i.

$$LiBH_4 + BCl_3 + 2Et_2O \xrightarrow{EE} LiCl + 2BH_2Cl–OEt_2 \quad (i)$$

at 0°. The hydroboration was done by adding 10 mmol of 1-methylcyclopentene and stirring for 2 hr at 0°. For the oxidation 15 ml of ethanol was added, followed by 5 ml of $\sim3$ $N$ NaOH, and 2 ml of 30% $H_2O_2$ added dropwise (vigorous reaction). The completion of the oxidation was ensured by maintaining the reaction mixture at 50° for 15 min. The absolute and relative yields of the alcohols were determined by glpc using undecane as the internal standard. (The amount of the internal standard was chosen such that its peak size was closer to that of the minor component. The reliability of the instrument in determining the minor component present in such small quantities was checked by analyzing known synthetic mixtures of the two components in the proportions expected from the reaction.) *trans*-2-Methylcyclopentanol were obtained in 94% yield. There was present <0.2% tertiary alcohol and no cis isomer.

The results are summarized in Table I together with comparable data for hydroboration with $BH_3$ in THF.

TABLE I

PRODUCTS FROM HYDROBORATION–OXIDATION OF
REPRESENTATIVE OLEFINS WITH $BH_2Cl$ IN ETHYL ETHER AND
$BH_3$ IN TETRAHYDROFURAN

| Olefin | Products | Relative yield of products, % $BH_2Cl-$ $OEt_2{}^a$ | $BH_3-$ $THF{}^b$ |
|---|---|---|---|
| 1-Hexene | 1-Hexanol | >99.5 | 94 |
|  | 2-Hexanol | <0.5 | 6 |
| 2-Methyl-1-butene | 2-Methyl-1-butanol | >99.9 | 99 |
|  | 2-Methyl-2-butanol | <0.1 | 1 |
| Norbornene | *exo*-2-Norbornanol | >99.8 | 99 |
|  | *endo*-2-Norbornanol | <0.2 | 1 |
| 2-Methyl-2-butene | 3-Methyl-2-butanol | 99.7 | 98 |
|  | 2-Methyl-2-butanol | 0.3 | 2 |
| 1-Methylcyclo-pentene | *trans*-2-Methylcyclo-pentanol | >99.8 | 98.5 |
|  | 1-Methylcyclopentanol | <0.2 | 1.5 |
| Styrene | 2-Phenylethanol | 96 | 81[c] |
|  | 1-Phenylethanol | 4 | 19[c] |
| α-Methylstyrene | 2-Phenyl-1-propanol | 100 | 100 |
|  | 2-Phenyl-2-propanol | 0 | 0 |
| 2-Pentene | 2-Pentanol | 58[d] | 55[d] |
|  | 3-Pentanol | 41[d] | 45[d] |
| 4-Methyl-2-pentene | 4-Methyl-2-pentanol | 60[d] | 57[e] |
|  | 2-Methyl-3-pentanol | 40[d] | 43[e] |
| 4,4-Dimethyl-2-pentene | 4,4-Dimethyl-2-pentanol | 79[d] | 58[e] |
|  | 2,2-Dimethyl-3-pentanol | 21[d] | 42[e] |

<sup>a</sup> Total yields were 95 ± 5%.  <sup>b</sup> Reference 1a,b.  <sup>c</sup> Reference 1c.  <sup>d</sup> Cis olefin.  <sup>e</sup> Trans olefin.

The results with olefins, such as 2-pentene, 4-methyl-2-pentene, and 4,4-dimethyl-2-pentene, reveal a slightly greater directive effect compared to $BH_3$, but very minor compared to disiamylborane. Consequently, disiamylborane remains the hydroborating agent of choice when it is desirable to use steric effects to control the direction of addition. The results with the 2-pentenes show that the direction of addition of $BH_2Cl$ is not significantly influenced by steric effects. Therefore, the powerful directive effects observed with the other olefins must be due to electronic (polar) effects.

The question arises as to why the results for the directive effects are so different in ethyl ether from those reported for THF. The reaction in THF is relatively slow. In fact, it may be that only a small part of the reaction in THF proceeds through the monochloroborane–tetrahydrofuranate, but proceeds instead through a small equilibrium concentration of borane (eq 4). ($BHCl_2$ in THF does not hydroborate

$$2ClH_2B\text{–}THF \rightleftharpoons Cl_2HB\text{–}THF + H_3B\text{–}THF \qquad (4)$$
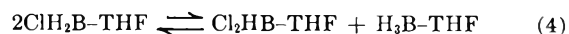
olefins to any significant extent under these conditions[7].) On the other hand, there is little doubt that the hydroboration in ethyl ether must be proceeding through the $BH_2Cl$ entity.

In any case, it is quite clear that hydoboration with monochloroborane–ethyl etherate not only provides a convenient route to dialkylchloroboranes and the corresponding borinic acids and esters, but also provides the anti-Markovnikov alkylborane moiety in far higher isomeric purity than hydroboration with borane itself. This development greatly extends the utility of the hydroboration reaction for the synthesis of regiospecifically and stereochemically pure derivatives.

(7) H. C. Brown and N. Ravindran, unpublished results.
(8) Postdoctoral research associate on National Science Foundation Grant No. 27742X.

RICHARD B. WETHERILL LABORATORY       HERBERT C. BROWN*
PURDUE UNIVERSITY                         N. RAVINDRAN[8]
LAFAYETTE, INDIANA   47907

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## Migrations in Oxidations of Trisubstituted Anilines

*Summary:* Homogeneous oxidations of mesidine in moderately acidic mixtures containing methanol afford the expected azo compound and two anils, one of which, 2,6-dimethyl-3-methoxymethyl-*p*-benzoquinone 4-(2',-4',6'-trimethyl)anil, is formed by an alkyl shift.

*Sir:* The peroxidase-catalyzed oxidative dealkylation of mesidine (**1**) to the quinone anil **3**, was disclosed by Chapman and Saunders in 1941.[1] Subsequently the reaction was repeated with a variety of chemical oxidants.[2] We wish to report that mesidine can be transformed by several oxidizing systems into an anil, **4**, containing a shifted alkyl group. We consider this finding to be the first case of an alkyl shift in a non-enzymatic oxidation of a substituted aniline. Saunders and colleagues[3] have invoked an alkyl shift in the peroxidase oxidation of 2,4-dimethylaniline[4] to explain the formation of a minor product.
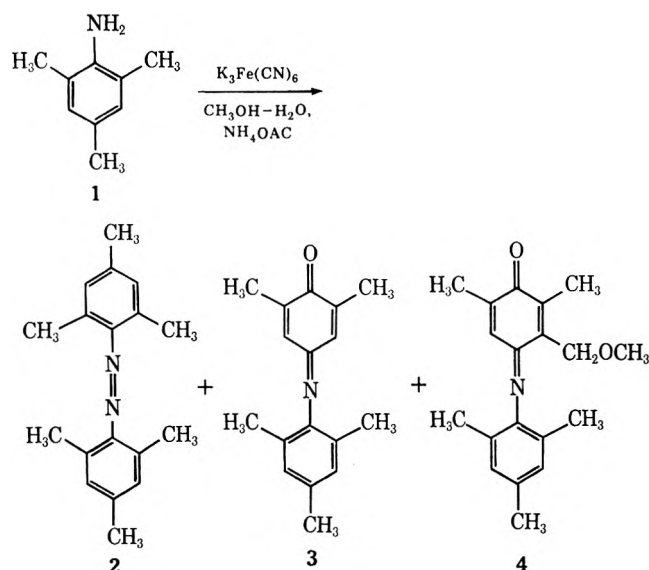
Mesidine, **1**, was oxidized by ferricyanide in a methanol–water mixture to give azo **2**, anil **3**, and a new anil **4** [2,6-dimethyl-3-methoxymethyl-*p*-benzoquinone-4-(2',4',6'-trimethyl)anil]. The respective yields were 1.5, 54, and 17%, when a reaction mixture of 0.010 mol of mesidine and 0.076 mol of potassium

(1) N. B. Chapman and B. C. Saunders, *J. Chem. Soc.*, 496 (1941).
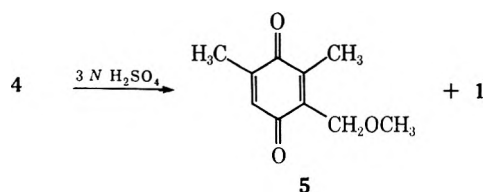(2) A. G. Holmes-Siedle and B. C. Saunders, *Chem. Ind. (London)*, 164 (1959).
(3) V. R. Holland, B. M. Roberts, and B. C. Saunders, *Tetrahedron*, **25**, 2291 (1969).
(4) The shifted product, 2,5-dimethyl-*p*-benzoquinone bis(2,4-dimethyl)-anil, was formed in 3% yield.

and aluminum chloride to give 2,6-dimethyl-3-chloromethylnitrobenzene, mp 61–62°. Sodium methoxide treatment converted this material to 2,6-dimethyl-3-methoxymethylnitrobenzene, mp 46–47°, which was reduced to the corresponding aniline, mp 62–63°, by means of zinc and sodium hydroxide. This aniline was oxidized with Fremy salt to the quinone **5**. This synthesis lends chemical proof for the structural assignment of anil **4**.

A reaction path for the oxidation of mesidine is shown in Scheme I and is consistent with the depen-

ferricyanide in 100 ml of methanol and 600 ml of water containing 80 g of ammonium acetate was maintained at 45° for 10 days. The pH of the reaction was 6.6. If the reactions were run with 1 to 10 g of potassium hydroxide in place of ammonium acetate, the yields of azo **2** were 91–95% and the yields of anils were 0–3%. Separations were accomplished by the use of dry column chromatography.[5] Reaction times were shortened to 4 hr by the use of dichromate- or persulfate-oxidizing systems. Strongly acidic oxidizing agents such as ferric chloride in hydrochloric acid and ammonium persulfate in acetic acid gave little evidence of reaction.

Anil **4** is a purple oil whose ir, uv, and nmr spectra were consistent with the assigned structure: ir (neat) 1639 (C=O), 1109, 1081 cm$^{-1}$ (CH$_2$OCH$_3$); uv max (C$_2$H$_5$OH) 209 nm ($\epsilon$ 22,200), 277 (22,400), 515 (1040); nmr (CDCl$_3$) $\delta$ 6.86 (s, 2), 6.43 (q, 1, $J$ = 1.5 Hz), 4.74 (s, 2), 3.44 (s, 3), 2.32 (s, 3), 2.20 (s, 3), 1.92 ppm (s, 9). Mass spectral data indicated a parent peak at 341.[6] Anil **4** was hydrolyzed with 3 $N$ H$_2$SO$_4$ with concurrent steam distillation. Sublimation of the ether-soluble distillate gave the quinone **5**: mp 33°; ir (KBr) 1667, 1117, 1087 cm$^{-1}$; nmr (CCl$_4$) $\delta$ 6.65 (q, 1, $J$ = 1.5 Hz), 4.36 (s, 2), 340 (s, 3), 2.17 (s, 3), 2.08 ppm (d, 3. $J$ = 1.5 Hz). The acid-soluble portion of the hydrolysate was converted to a benzamide, mp 204°, undepressed on admixture with authentic mesidine benzamide.[7]



The quinone **5** was synthesized *via* a sequence that started with 2,6-dimethylnitrobenzene. The latter compound was alkylated with chloromethyl ether

(5) B. Loew and M. M. Goodman, *Chem. Ind. (London)*, 2026 (1967).
(6) All new compounds were analyzed to give acceptable values.
(7) H. Huebner and E. von Schack, *Chem. Ber.*, **10**, 1711 (1877).

SCHEME I



dence of products on the acidity. Cation radicals are assumed to be formed initially and converted to neutral radicals with increasing basicity of the medium. In strongly acidic media their ability to couple is

limited by charge repulsion. As the solution becomes basic, the concentrations of radicals such as **1c** increase and the nitrogen to nitrogen couplings predominate over disproportionations. At moderate acidities cross-disproportionation between the cation radical and the neutral radical leads to the imino methine **6**, which can add either water or methanol to give intermediates **7** and **8**. These species can couple after oxidation with more mesidine radicals to give **9** and **10**. To achieve aromaticity, formaldehyde can be eliminated from **9**. The methoxymethyl group of **10**, however, cannot be eliminated. Migration ensues in a manner similar to the dieneone–phenol rearrangement. Protonation of the imino nitrogen facilitates the migratory process. The resulting arylamines can be oxidized and hydrolyzed to anils **3** and **4**. Migration is suggested prior to hydrolysis because the corresponding keto forms of **9** and **10** would be expected to cleave in acidic media to a phenol and aniline on the basis of Miller's studies of quinamines.[8]

Intermediate **8**, 2,6-dimethyl-4-methoxymethylaniline, was prepared by an alkaline zinc reduction of the corresponding nitro compound, bp 96–98° (0.65 mm), which was the product of a methoxide displacement of bromide from 2,6-dimethyl-4-bromoethylnitrobenzene. The latter was obtained from the phosphorus tribromide treatment of the benzyl alcohol, mp 39–40°, derived from a diborane reduction of 3,5-dimethyl-4-nitrobenzoic acid. Intermediate **8** was an oil: nmr (CDCl₃) δ 6.86 (s, 2), 4.24 (s, 2) 3.45 (m, 2), 3.25 (s, 3), 2.02 ppm (s, 6); benzamide mp 55.6°; mol wt 165 (mass spectrum, 70 eV).

An equimolar mixture of intermediate **8** and mesidine was oxidized under the original conditions that give product **4**. The anil **4** was formed in 61% yield; no anil **3** was detected. The control run without **8** afforded a 23% yield of anil **4** and a 51% yield of anil **3**. When methanol was replaced by tetrahydrofuran in the reaction mixture containing **8**, product **4** was obtained in 35% yield and the anil **3** in 13% yield. In the control reaction containing mesidine alone, no **4** was formed and the principal product was the anil **3** (61%). Intermediate **7**[9] and mesidine were also oxidized together to give 59% anil **3** and 22% anil **4** under the original conditions. Without methanol in the reaction mixture, the yield of anil **3** was 75%. In all of these cases azo compounds were formed in <5% yields. These experiments with intermediates support the proposed reaction path.

Oxidation reactions involving migrations have been extended to 2,4,6-triethylaniline with a dichromate system[10] and to 2,6-dimethyl-4-benzylaniline with the ferricyanide system. A fuller report of these reactions as well as other mesidine oxidation results will be given subsequently. The scope of oxidative migrations of anilines is broadened by these findings. Heretofore the other authenticated migrations have been the NIH shifts of deuterium or tritium in the oxygenations of amides of aniline and, to a lesser degree, aniline, by

microsomal hydroxylases[11] or peroxytrifluoroacetic acid.[12]

**Acknowledgment.**—We are grateful to the National Science Foundation for partial financial support through an institutional grant program.

(11) S. Udenfriend, P. Zaltzman-Nirenberg, J. Daly, G. Guroff, C. Chidsey, and B. Witkop, *Arch. Biochem. Biophys.*, **120**, 413 (1967).

(12) (a) D. Jerina, J. Daly, W. Landis, B. Witkop, and S. Udenfriend, *J. Amer. Chem. Soc.*, **89**, 3347 (1967); (b) D. Jerina, J. Daly, and B. Witkop, *Biochemistry*, **10**, 366 (1971).

DEPARTMENT OF CHEMISTRY,      STEPHEN L. GOLDSTEIN
NEW YORK UNIVERSITY      EDWARD McNELIS*
NEW YORK, NEW YORK   10003

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### Chromyl Chloride in Acetone. α-Chloro Ketones or Ketones Directly from Olefins

*Summary:* Oxidation of olefins with chromyl chloride in acetone affords the α-chloro ketones in good yield; zinc dust reduction prior to work-up produces the corresponding ketones.

*Sir:* We have found that reaction of disubstituted (R′ = H) and trisubstituted olefins with chromyl chloride in acetone effects the following unique conversion.

$$RHC{=}CR'R^2 \longrightarrow R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}\overset{\overset{\displaystyle Cl}{|}}{C}R'R^2$$
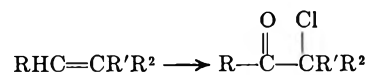
Addition of zinc dust to the crude reaction mixture results in reduction of the α-chloro ketone to the corresponding ketone in high yield. With exception of the recent reports of Freeman and coworkers,[1] the chromyl chloride oxidations of olefins were notorious for producing complex mixtures of little synthetic value.[2] The key to the success of this new procedure appears to be the use of acetone, a relatively polar solvent by comparison with the previously employed halogenated organic solvents.

Two general procedures (A and B), differing only in the temperature during chromyl chloride addition, were employed. The application of these procedures, as described below for the conversion of cyclododecene to α-chlorocyclododecanone, reveals the simplicity of the method.

**Procedure A.**—A solution of 16.6 g (0.10 mol) of cyclododecene (Chemical Samples Co.; glc analysis revealed 91% trans, 7% cis, and 2% diene) in 500 ml of reagent acetone was cooled in a Dry Ice–acetone bath to −70° and then treated with 33.0 g (0.21 mol) of chromyl chloride (Alfa Ventron Co.) which was added *via* a dropping funnel with vigorous stirring of the solution. Addition was controlled so that a temperature of −65° was not exceeded. After addition was complete (∼30 min), the mixture was stirred at −75° for 1 hr, then allowed to warm to room temperature, and stirred at 23–25° for 1 hr. The homogeneous,

(8) B. Miller, *J. Amer. Chem. Soc.*, **86**, 1135 (1964). Quinamines substituted in the ortho and para positions undergo neither a quinamine rearrangement nor a dienone–phenol rearrangement.

(9) B. C. Saunders and J. Wodak, *Tetrahedron*, **23**, 473 (1967).

(10) This system for the oxidation of 10 mmol of amine consists of 10 mmol of K₂Cr₂O₇, 10 ml of acetic acid, 20 ml of methanol, and 100 ml of water. The pH range is 1.8–2.1.

(1) (a) F. Freeman, P. J. Cameran, and R. H. Dubois, *J. Org. Chem.*, **33**, 3970 (1968); (b) F. Freeman, R. H. Dubois, and N. J. Yamachika, *Tetrahedron*, **25**, 3441 (1969).

(2) (a) R. A. Stairs, D. G. M. Diaper, and A. L. Gatzke, *Can. J. Chem.*, **41**, 1059 (1963); (b) S. J. Cristol and K. R. Eilar, *J. Amer. Chem. Soc.*, **72**, 4353 (1950).

dark red-brown mixture was quenched by slowly pouring it into an ice-cold aqueous solution of NaHSO$_3$ [30 g (0.3 mol) of NaHSO$_3$ in 1000 ml of H$_2$O]. The green mixture was stirred for 30 min in an ice bath and then extracted with 2 × 500 ml of ethyl acetate–hexane (1:1). The organic phases were washed with 500 ml of H$_2$O and 500 ml of NaCl (saturated, aqueous), then combined, dried over anhydrous sodium sulfate, filtered, and concentrated to yield a greenish yellow oil weighing 24.0 g (100%). The crude product was distilled to afford 17.1 g (79%) of α-chlorocyclododecanone bp 100–102° (0.075 mm) [lit.[3] bp 117–118° (1.5 mm)] as a yellow liquid which solidified on standing to yield white prisms (from hexane), mp 56–57° (lit.[3] mp 59–60°).

Starting with crude cyclododecene (~65% trans, 25% cis, 6% alkane, 4% diene), lower yields (50–60%) were obtained.

**Procedure B.**—The reaction was run identically as procedure A except that the chromyl chloride was added to the solution cooled in an ice–salt bath such that a temperature of 3° was not exceeded. After addition, the mixture was stirred at −5° for 1 hr, then allowed to warm to room temperature, and stirred at 23–25° for 1 hr. The quench and work-up were carried out as before to yield 69% α-chlorocyclododecanone.

Examination of the table reveals that, although the low temperature procedure (A) gives better yields than B, the yields at the higher temperature (−5 to 3°) are still quite good. The inconvenience of cooling large scale reactions to −70° and the insolubility of many substrates in acetone at such temperatures should make procedure B preferable in certain cases. The improved yields at lower temperatures appear to be due to selective suppression of allylic oxidation which produces α,β-unsaturated ketones, more prominent by-products at higher temperatures. The sensitivity of cyclohexene to allylic attack probably accounts for the below average yield with this olefin.

The reaction is remarkably clean with trans-disubstituted olefins; only trace by-products are visible by glc. However, cis-disubstituted olefins react more slowly and afford poorer yields;[4] the unsaturated ketone is the major by-product. With the trisubstituted olefin 2-methyl-2-heptene a chlorohydrin is the only significant product in addition to the expected chloro ketone.

With a simple change in the work-up, this oxidation process becomes a one-step ketone synthesis.[5]

**Preparation of Cyclododecanone.**—Procedure A was followed with these modifications. After reaction, the mixture was treated with 50 ml of glacial acetic acid, and excess zinc dust while cooling in an ice bath, and then stirred at 23–25° for 3 hr or until the chloro ketone had been completely converted to ketone as determined

by glc analysis of aliquots withdrawn. The mixture was then poured into 500 ml of cold H$_2$O and extracted with 2 × 500 ml of ethyl acetate. After the normal work-up, 18.2 g (95%) of crude cyclododecanone was isolated. Distillation afforded 14.0 g (75%) of pure cyclododecanone, bp 119–121° (9 mm), mp 58–59° [lit.[6] bp 120–125° (12 mm), mp 59–61°].

Unlike Freeman's aldehyde and ketone syntheses[1a,b] this route clearly involves reduction of an intermediate α-chloro carbonyl compound. Following Freeman's procedure for oxidation of *trans*-propenylbenzene (1), and using a bisulfite work-up, the chlorohydrin 2, but none of the chloro ketones 3 and 4, was obtained.
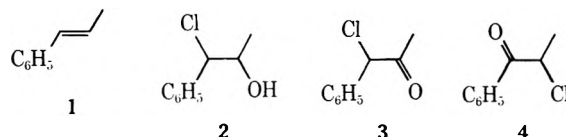


On standing at room temperature chlorohydrin 2 rearranged spontaneously to benzyl methyl ketone, the product which Freeman reports.[1b] Oxidation of olefin 1 in acetone, following procedure B, gave the chloro ketones 3 and 4 (3:1) as the major products.

While studying the effect of solvent polarity on these oxidations, we made several novel observations pertaining to the mechanism of oxidation of olefins by chromyl chloride (Table I);[7] we will report these results shortly.

### TABLE I
#### OXIDATION OF OLEFINS BY CrO$_2$Cl$_2$ IN ACETONE[a]

| Olefin | Yield, % (chloro ketone)[b] | Procedure |
|---|---|---|
| *trans*-cyclododecene | 70 | B |
| *trans*-cyclododecene | 79 (90) | A |
| *trans*-5-decene | (90) | A |
| *trans*-5-decene | (81) | B |
| *cis*-5-decene | (65) | B |
| *cis*-5-decene | (68) | A |
| *trans*-2-octene | 70[c] | A |
| 4,4-dimethyl-*trans*-2-pentene | 60[d] | A |
| 2-methyl-2-heptene | 45[e] | A |
| cyclohexene | 38 | A |
| norbornene | 58 | A |

[a] Generally run using 10 mmol (glc) or 0.1 mol (prep) of the olefin. [b] Yields were determined by isolation or by glc (parentheses). [c] 1:1 mixture of the two possible chloro ketones. [d] 10:1 mixture of 4,4-dimethyl-3-chloro-2-pentanone and 4,4-dimethyl-2-chloro-3-pentanone. [e] 2-Chloro-2-methyl-3-heptanone plus 32% of an unidentified chlorohydrin.

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(8) National Institute of Health Predoctoral Fellow, 1969–1972.

DEPARTMENT OF CHEMISTRY                     K. BARRY SHARPLESS*
MASSACHUSETTS INSTITUTE OF                   ALLAN Y. TERANISHI[8]
TECHNOLOGY
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