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## NOTES



## COMMUNICATIONS



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THE JOURNAL OF Organic Chemistry®

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# Substituent and Solvent Effects on the Rate of Perester Decomposition. The Case for Polar Contributions to the Transition State

JON P. ENGSTROM* AND JOHN C. DUBOSE[1]

*Department of Chemistry, Emory University, Atlanta, Georgia 30322*

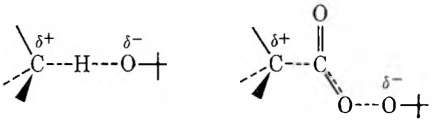
*Received March 26, 1973*

Substituent effects on the rate of decomposition of para-substituted *tert*-butylperoxy α-phenylisobutyrates were measured in three solvents. The rate constants correlated best with $\sigma^+$ to give a $\rho$ value of −0.77 (dodecane), −0.75 (benzene), and −0.91 (acetonitrile). Correlation of the rate constants in alkanes, benzene, and acetonitrile with Brownstein's $S$ values give $R$ values of 2.1–2.6. By choosing suitable reference reactions it is shown that the correlation of the rate constants with substituent and solvent parameters both indicate the formation of a polar transition state.

Partial charge formation in free-radical reactions was first used to explain the alternating effect in copolymerization reactions.[2] Since then a number of radical reactions have been investigated and the results interpreted in terms of a polar effect on the transition state.[3] Many of these reactions were abstraction reactions, principally hydrogen abstraction, occurring in chain reactions.

Substituent effects on *tert*-butylperoxy phenylacetate decomposition have also been interpreted in terms of a polar effect on the transition state.[4] This interpretation was based on the improved correlation of the results for hydrogen-abstraction reactions.[5] Many examples of the effect of polar substituents on perester decomposition have subsequently been presented.[6]

Recently the interpretation of substituent effects on hydrogen abstraction reactions has been challenged and polar effects were termed "inconsistent with experimental observations."[7] Since the interpretation of polar effects in perester decompositions was originally based in part on analogy with hydrogen-abstraction reactions, one may also question the importance of polar effects on perester decompositions. The mechanism for electron transfer in perester transition states is very similar to that for hydrogen abstraction reactions.



The products, the effect of solvent, and the effect of substituents are of primary importance in determining whether a reaction is heterolytic or homolytic. For a reaction that gives typical radical products, substituent effects have generally been the principal criterion for partial charge formation in the transition state. Although the effect of solvent on radical reactions is well known, solvent effects are generally small and are usually considered to have as large an effect on the starting materials as on the transition state.

In this paper we will attempt to show that decompositions of ring-substituted *tert*-butylperoxy α-phenylisobutyrates respond to both substituents and solvent in a manner consistent with partial charge formation in the transition state.

With the exception of *tert*-butylperoxy *p*-nitrophenylacetate, the previously reported rate constants fit the Hammett equation using $\sigma_p^+$ values.[4] The rate constant for the *p*-nitro perester is larger than would be expected on the basis of the Hammett plot. Three tentative explanations have been offered for the faster rate.[4,8,9] We will show that the deviation of the *tert*-butylperoxy *p*-nitrophenylacetate from the Hammett plot is best interpreted by a shift of the mechanism to one-bond homolysis.

## Results and Discussion

The rate constants for decomposition of several *tert*-butylperoxy α-phenylisobutyrates were determined

(1) NDEA Fellow, 1969–1972; Tennessee Eastman Fellow, 1972–1973.
(2) F. R. Mayo and C. Walling, *Chem. Rev.*, **46**, 191 (1950).
(3) R. S. Davidson, *Quart. Rev., Chem. Soc.*, 249 (1967); R. Breslow, "Organic Reaction Mechanisms," Vol. 7, W. A. Benjamin, New York, N. Y., 1967; R. F. Bridger and T. A. Russell, *J. Amer. Chem. Soc.*, **85**, 3754 (1963); J. A. Howard and K. U. Ingold, *Can. J. Chem.*, **41**, 1744 (1963).
(4) P. D. Bartlett and C. Ruchardt, *J. Amer. Chem. Soc.*, **82**, 1756 (1960).
(5) G. A. Russell, *J. Amer. Chem. Soc.*, **78**, 1047 (1956); *J. Org. Chem.*, **23**, 1407 (1958). C. Walling and B. Miller, *J. Amer. Chem. Soc.*, **79**, 4181 (1957).
(6) C. Ruchardt, *Fortschr. Chem. Forsch.*, **6**, 251 (1966); *Angew. Chem., Int. Ed. Engl.*, **9**, 830 (1970).
(7) A. A. Zavitsas and J. A. Pinto, *J. Amer. Chem. Soc.*, **94**, 7390 (1972); A. A. Zavitsas, *ibid.*, **94**, 2779 (1972).
(8) W. A. Pryor and K. Smith, *J. Amer. Chem. Soc.*, **92**, 5403 (1970).
(9) R. C. Neuman, Jr., and J. V. Behar, *J. Org. Chem.*, **36**, 654 (1971).

by the excess scavenger method.[10] For radical initiators giving only free radicals and cage products, the first-order rate constants for scavenger disappearance and initiator decomposition are equal.[10b] We investigated two scavengers, galvinoxyl[11] and BDPA.[12] Comparison of the rate constants determined using these two scavengers is given in Table I. BDPA was

TABLE I

RATE CONSTANTS AND CAGE EFFECTS AS A FUNCTION OF SCAVENGER AND THE SCAVENGER/PERESTER[a] RATIO

| Scavenger | (Scavenger/perester)$_0$ | $k$, sec$^{-1}$ [b] $\times 10^{-4}$ | Fraction cage effect[b] |
|---|---|---|---|
| Galvinoxyl | 1.85 | 3.70 ± 0.03 | 0.54 |
| Galvinoxyl | 1.85 | 3.70 ± 0.06 | 0.53 |
| BDPA | 1.85 | 3.68 ± 0.03 | 0.59 |
| BDPA | 1.85 | 3.91 ± 0.03 | 0.59 |
| BDPA | 1.54[b] | 3.61 ± 0.03 | 0.60 |
| BDPA | 1.96[b] | 4.06 ± 0.05 | 0.60 |
| BDPA | 3.11[b] | 4.01 ± 0.08 | 0.62 |
| BDPA | 3.94[b] | 5.11 ± 0.12 | 0.55 |

[a] The perester was *tert*-butylperoxy α-phenylisobutyrate in dodecane at 60°. [b] Results for these experiments are the average of at least two runs; the kinetic sample were made up from the same stock solution and were run at the same time to minimize variations between the runs. The error limits reported are the standard errors. The 95% confidence limits can be obtained by multiplying the standard error by 2.36 (from a $t$ Distribution Table with $\phi = 7$).

thermally more stable than galvinoxyl and generally gave less fading in blank cells. However, at the concentrations used BDPA did not scavenge the radicals so efficiently as galvinoxyl; the fraction of radicals scavenged by BDPA was generally a few per cent less than the fraction scavenged by galvinoxyl. Galvinoxyl was used for all subsequent determinations.

The reactions were followed in all cases for at least three half-lives, and infinity values were taken after ten half-lives. The absorbance values measured during a kinetic run were corrected for fading of the blank. The correction was made by one of two methods. The absorbance values were either corrected point by point, or the fading of the blank was assumed to be linear and a linear least-squares program was used to determine the correction. The results from both methods were the same within experimental error. Corrected absorbance readings were fit by computer to the Gauss Newton Exponential Function.[13] Values for the rate constant, absorbance at infinite time, and the absorbance change were determined in an iterative manner until the best fit of the absorbance *vs.* time curve was obtained (Table II). The activation parameters for the substituted *tert*-butylperoxy α-phenylisobutyrates are given in Table III.

To ascertain whether the decomposition of all the peresters was proceeding by two-bond homolysis, the rate constants were determined as a function of solvent viscosity. For radical initiators decomposing by one-bond homolysis Pryor and Smith have shown that the rate of decomposition decreases with increasing viscosity, whereas the rates for initiators decomposing by two-bond homolysis are independent of viscosity.[3] Our results clearly show that the rates of decomposition for all the peresters are viscosity independent and thus the peresters are decomposing by two-bond homolysis (Figure 1).

Generally the rates of radical formation reactions are correlated with either $\sigma$ or $\sigma_p^+$.[3] Since recently the relative rates of hydrogen abstraction from substituted toluenes were correlated with $\sigma_p^-$, we have also attempted to correlate our data with this parameter.[7] The Hammett plot for our peresters *vs.* $\sigma$, $\sigma_p^+$, and $\sigma_p^-$ is given in Figure 2, and the results of least squares analysis are summarized in Table IV.

TABLE II

PERESTER RATE CONSTANTS AS A FUNCTION OF SUBSTITUENT, SOLVENT, AND TEMPERATURE[a]

| Substituent | Solvent | Temp,[a] °C | $k$, sec$^{-1}$ [b] $\times 10^{-4}$ |
|---|---|---|---|
| H | Dodecane | 67.0 | 7.13 |
| H | Dodecane | 60.0 | 3.00 |
| H | Dodecane | 50.00 | 0.877 |
| H | Benzene | 50.00 | 2.18 |
| H | Acetonitrile | 50.0 | 3.08 |
| Cl | Octane | 67.0 | 5.95 |
| Cl | Octane | 60.0 | 2.65 |
| Cl | Octane | 50.00 | 0.810 |
| Cl | Dodecane | 67.0 | 6.36 |
| Cl | Dodecane | 60.0 | 2.68 |
| Cl | Dodecane | 50.0 | 0.798 |
| Cl | Hexadecane | 67.0 | 5.96 |
| Cl | Hexadecane | 60.0 | 2.56 |
| Cl | Hexadecane | 50.0 | 0.800 |
| Cl | Benzene | 50.0 | 2.03 |
| Cl | Acetonitrile | 50.0 | 2.55 |
| $CH_3$ | Octane | 60.0 | 5.43 |
| $CH_3$ | Dodecane | 67.0 | 13.20 |
| $CH_3$ | Dodecane | 60.0 | 5.58 |
| $CH_3$ | Dodecane | 50.0 | 1.90 |
| $CH_3$ | Benzene | 50.0 | 3.85 |
| $CH_3$ | Acetonitrile | 50.0 | 6.00 |
| $CH_3O$ | Octane | 50.0 | 4.18 |
| $CH_3O$ | Dodecane | 57.0 | 10.28 |
| $CH_3O$ | Dodecane | 50.0 | 4.21 |
| $CH_3O$ | Dodecane | 40.0 | 1.49 |
| $CH_3O$ | Benzene | 50.0 | 9.96 |
| $CH_3O$ | Acetonitrile | 50.0 | 16.75 |
| $NO_2$ | Octane | 67.0 | 1.98 |
| $NO_2$ | Dodecane | 67.0 | 2.03 |
| $NO_2$ | Dodecane | 60.0 | 0.927 |
| $NO_2$ | Dodecane | 50.0 | 0.263 |
| $NO_2$ | Hexadecane | 67.0 | 2.00 |
| $NO_2$ | Benzene | 50.0 | 0.640 |
| $NO_2$ | Acetonitrile | 50.0 | 0.750 |

[a] Temperature control was accurate to ±0.05° or better for all runs. [b] All rate constants are the average of at least three runs and generally the average of four.

TABLE III

ACTIVATION PARAMETERS FOR SUBSTITUTED *tert*-BUTYLPEROXY α-PHENYLISOBUTYRATES IN *n*-DODECANE

| Registry no. | Substituent | $\Delta H^*$,[a] kcal/mol | $\Delta S^*$,[a] eu |
|---|---|---|---|
| 40919-05-9 | *p*-$CH_3O$ | 22.2 ± 0.6 | −5.3 ± 1.0 |
| 40919-06-0 | *p*-$CH_3$ | 24.0 ± 0.6 | −1.6 ± 1.0 |
| 24161-29-3 | H | 26.1 ± 0.3 | 3.5 ± 0.5 |
| 40919-08-2 | *p*-Cl | 25.8 ± 0.3 | 2.5 ± 0.5 |
| 40919-09-3 | *p*-$NO_2$ | 25.1 ± 0.3 | −1.8 ± 0.5 |

[a] The error limits reported are the standard errors.

(10) (a) R. C. Lamb and J. G. Pacifici, *J. Amer. Chem. Soc.*, **86**, 914 (1964); (b) R. C. Lamb and J. R. Sanderson, *ibid.*, **91**, 5034 (1969).

(11) P. D. Bartlett and T. Funahashi, *J. Amer. Chem. Soc.*, **84**, 2596 (1962).

(12) α,γ-Bis(diphenylene)-β-phenylallyl, also known as Koelsch's radical.

(13) Program was written by Dr. R. C. Johnson, Emory University.

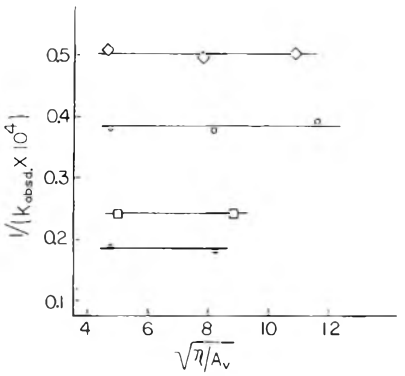



Figure 1.—The effect of viscosity on the rate of perester decomposition.

TABLE IV

TABLE OF RESULTS FROM HAMMETT PLOTS[a]

| Solvent | $\rho$ + SE[b] | $\sigma$ values used | Intercept | Correlation coefficient |
|---|---|---|---|---|
| Dodecane | −0.78 ± 0.04 | Plus | 0.06 | −0.996 |
| Dodecane | −1.02 ± 0.21 | Normal | 0.21 | −0.94 |
| Dodecane | −0.67 ± 0.20 | Minus | 0.24 | −0.88 |
| Benzene | −0.75 ± 0.03 | Plus | 0.04 | −0.997 |
| Acetonitrile | −0.91 ± 0.06 | Plus | 0.05 | −0.994 |

[a] Rate data was taken at 50°. [b] The error limits reported are the standard errors. The 95% confidence limits can be obtained by multiplying the standard error by 2.10 (obtained from a Table for $t$ Distribution with $\phi = 18$).

Hammett correlation of the rates with $\sigma$ and $\sigma_p^-$ is significantly poorer than for $\sigma_p^+$. It has been suggested that the correlation with $\sigma_p^-$ is improved by not including points for substituents that are strongly electron donating, *e.g.*, the *p*-methoxy group.[7] The Hammett plot for perester decomposition *vs.* $\sigma_p^-$ omitting the *p*-methoxy group does give an improved correlation, but one should question this procedure. It is not clear why *p*-methoxy groups should not be considered. The original $\sigma_p^-$ values determined for phenols included these substituents.[14] Recent studies of the ionization of phenols indicate that the $\sigma_p^-$ value for the *p*-methoxy group may be somewhat smaller than the $\sigma$ value ($\sigma_p^- = -0.20$, $\sigma = -0.27$).[14] Nonetheless, a $\sigma_p^-$ value for the *p*-methoxy group would appear to be reasonably well defined.

The improved correlation with $\sigma_p^+$ and the negative sign for $\rho$ indicate a partial positive charge formation on the cumyl radical in the transition state. The absolute value of $\rho$ (0.78) for substituted *tert*-butylperoxy $\alpha$-phenylisobutyrates is smaller than that for substituted *tert*-butylperoxy phenylacetates ($\rho = -1.2$).[4] A smaller absolute value is expected for two reasons. First, the added two methyl groups should stabilize the partial positive charge in the transition state, leaving less charge to be stabilized by the substituents. Second, the two methyl groups may sterically accelerate the reaction, making the transition state occur earlier along the reaction coordinate and consequently less sensitive to substituents.[6] At the present time we know of no way of deciding between these two modes of action.

(14) R. W. Taft, Jr., *J. Amer. Chem. Soc.*, **79**, 1045 (1957); L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1970, Chapter 11; H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1963); R. W. Taft, Jr., and I. C. Lewis, *J. Amer. Chem. Soc.*, **80**, 2436 (1958).

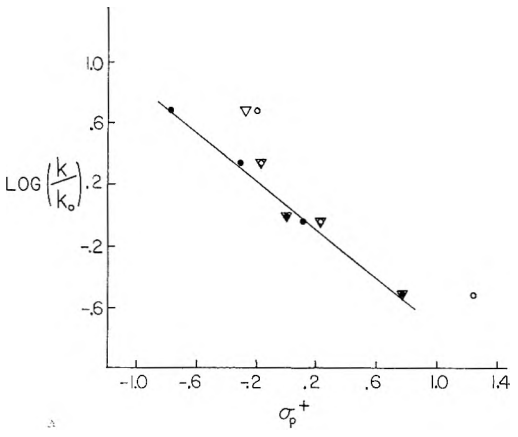



Figure 2.—Hammett plot for perester decomposition in dodecane at 50°: $\sigma^+$ values, ●; $\sigma$ values, ▽; $\sigma^-$ values, ○.

One can now ask what the value of $\rho$ means in terms of how much partial charge is formed in the transition state for perester decomposition. The problem reduces to finding a suitable standard reaction. Solvolysis reactions would be an obvious first choice, but these reactions only occur in solvents capable of strongly stabilizing the ions. What is required is an ionization reaction that occurs in nonpolar solvents. A suitable choice is the gas-phase ionization of benzyl radicals.[15] For this reaction there is no solvent to stabilize the charge and no gegenion; all the stabilization must come from the substituent. The major problem with this choice of a standard reaction is that the substituents also may stabilize the radicals being ionized. Thus one must first be convinced that radical stabilization is of minor importance in determining the ionization potentials of the benzyl radicals. Three different arguments can be used to show that the effect of substituents on the stability of benzyl radicals is small relative to the effect of substituents on the stability of benzyl carbonium ions. First, electron spin resonance spectra of $\alpha$-substituted ethyl radicals show that $\alpha$ substituents remove only a small fraction of the spin density from the radical site.[16] The $\alpha$-methoxy group was the most effective of the substituents examined, and it removed only approximately 17% of the spin density from the radical site. Second, the decomposition of para-substituted azocumenes shows only small variation in the rate of decomposition with substituent.[17] Third, differences in bond dissociation energies for substituted toluenes are so small that the variation with substituent is within experimental error.[18] If radical stability contributes negligibly to the substituent effect in the gas-phase ionization of benzyl radicals, one finds that the decomposition of substituted *tert*-butylperoxy phenylisobutyrates is approximately 0.042 as sensitive to substituents as the gas-phase ionization of benzyl radicals.[19] Comparison of the decom-

(15) A. G. Harrison, P. Kenarle, and F. P. Lossing, *J. Amer. Chem. Soc.*, **83**, 777 (1961).

(16) H. Fischer, *Z. Naturforsch. A*, **20**, 428 (1965); R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.*, **39**, 2147 (1963); H. Fischer, *Z. Naturforsch. A*, **19**, 866 (1964); W. T. Dixon and R. O. C. Norman, *J. Chem. Soc.*, 3119 (1963), 3635 (1964).

(17) J. R. Shelton, C. K. Liang, and P. Kovacic, *J. Amer. Chem. Soc.*, **90**, 354 (1968).

(18) M. Szwarc, *Chem. Rev.*, **47**, 75 (1950).

(19) $\rho_{\text{perester}}/\rho_{\text{ionization}} = -0.78/-19.2 = 0.042$.

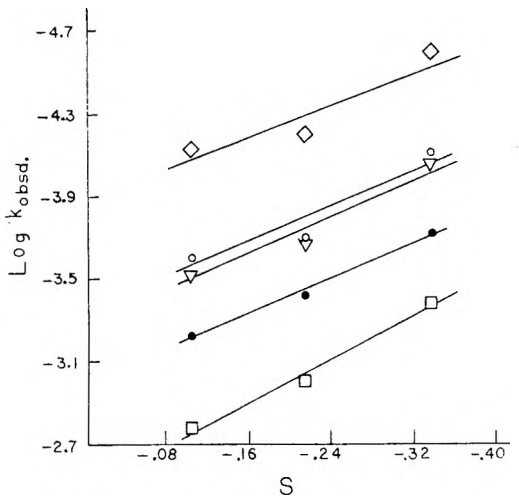



Figure 3.—Plot of log $k_{obsd}$ *vs.* Brownstein's solvent polarity parameter $S$: ◇, *tert*-butylperoxy α-(*p*-nitrophenyl)isobutyrate; ○, *tert*-butylperoxy α-(*p*-chlorophenyl)isobutyrate; ▽, *tert*-butylperoxy α-phenylisobutyrate; ●, *tert*-butylperoxy α-(*p*-tolyl)isobutyrate; □, *tert*-butylperoxy α-(*p*-methoxyphenyl)-isobutyrate.

position of *tert*-butylperoxy phenylacetates to the ionization of benzyl radicals gives a relative sensitivity of 0.063. Thus the amount of partial charge formed in the transition state for perester decomposition is small.

To try to confirm that the ratio of $\rho$ values for the perester decomposition and the ionization of benzyl radicals reflects partial charge formation in the transition state, a comparison was made between the sensitivity of a heterolysis reaction and perester decomposition to changes in solvent polarity. Several scales for measuring the sensitivity of a reaction to changes in solvent polarity are available.[20] However, most of these scales are limited to polar protic solvents and cannot be readily extended to nonpolar aprotic solvents. One system that allows correlation between very polar and nonpolar solvents is the Brownstein scale based on Kosower $Z$ values.[21] Although this scale has been criticized because it cannot be related to an exact model process, it is nonetheless a scale that allows one to compare the sensitivity of solvolysis reactions in polar protic media and the sensitivity of perester decompositions in nonpolar aprotic media to changes in solvent polarity. The Brownstein plots for substituted *tert*-butylperoxy α-phenylisobutyrates are given in Figure 3. The $R$ values for all the peresters are approximately the same, 2.1–2.6. The plots for the *p*-nitro, *p*-chloro, and unsubstituted peresters show a slight upward curvature; however, the plots for the *p*-methyl and the *p*-methoxy peresters are quite good straight lines. The slope, $R$, is a measure of the sensitivity of the reaction to changes in solvent polarity. $R$ values range from 36 for the solvolysis of *tert*-butyl chloride to −3.5 for the keto–enol equilibrium of ethyl acetoacetate.[21] The solvolysis of 1-phenylethyl chloride has an $R$ value of 29.4;[21] the decomposition of *tert*-butylperoxy α-phenylisobutyrates is about 2.3. The ratio of the two $R$ values is 0.078.

A comparison of the sensitivity to substituents (0.042) with the sensitivity to solvent change (0.078) shows that both of these criteria for charge formation are in the same direction and of approximately the same magnitude. The fact that the ratios are not the same is undoubtedly due to the fact that the ideal standard reactions are not available for comparison. However, the major point remains that both criteria for partial charge formation are in agreement, adding confirmatory evidence that the response of perester decomposition to substituents is a response to partial charge formation in the transition state and not a response to changes in radical stability.

The effect of changing the solvent on the Hammett $\rho$ value is just outside experimental error. The higher $\rho$ in acetonitrile may indicate a more polar transition state upon which the substituents can exert a greater influence. This result is the opposite to the effect one would expect for an ionic reaction. For ionic reactions, as one increases the polarity of the solvent the $\rho$ value generally decreases because the more polar solvent is better able to stabilize the charge. However, where only a partial charge develops in the transition state the increased solvent polarity may cause increased polar character in the transition state, making the reaction more sensitive to substituents.

Bartlett and Ruchardt in their study of the decomposition of substituted *tert*-butylperoxy phenylacetates found that the *p*-nitro perester decomposed faster than expected based on the Hammett plot.[4] Three tentative explanations have since been offered for the faster rate: decomposition of the perester partly by a Criegee rearrangement,[4] a shift in the mechanism to one-bond homolysis,[8] and an increase in the rate owing to increasing polar character and solvation of the transition state for peresters with strongly electron-donating substituents.[9]

The change of solvent to acetonitrile should greatly increase the rate of the Criegee rearrangement relative to homolysis.[22] Since the *tert*-butylperoxy α-(*p*-nitrophenyl)isobutyrate fits the Hammett plot in dodecane, benzene, and acetonitrile, Criegee rearrangement cannot be a significant pathway.

If increasing polar character and solvation of the transition state were significant factors, the peresters with strongly electron-donating substituents should be strongly accelerated, especially in acetonitrile, and give curved Hammett plots. Since *tert*-butylperoxy α-(*p*-methoxyphenyl)isobutyrate fits the Hammett plot, increased polar character and solvation of the transition state are not important.

Pryor and Smith have shown that the rate of decomposition of *tert*-butylperoxy (*p*-nitrophenyl)-acetate increases with decreasing solvent viscosity.[8] Two possible explanations were offered to explain the solvent dependence of the rate. First, the homolysis step in the perester decomposition was solvent dependent. Second, the change in viscosity of the solvent was changing the amount of return from the initial radical cage in which only the peroxide bond had been broken. Since the rate of decomposition of *tert*-butylperoxy α-(*p*-nitrophenyl)isobutyrate is independent of solvent (for *n*-alkanes), the homolysis

(20) E. M. Kosower, "An Introduction to Physical Organic Chemistry," Wiley, New York, N. Y., 1968, Chapter 2.6.
(21) S. Brownstein, *Can. J. Chem.*, **38**, 1590 (1960).
(22) R. Criegee and R. Kaspar, *Justus Liebigs Ann. Chem.*, **560**, 127 (1948); H. L. Goering and A. L. Olson, *J. Amer. Chem. Soc.*, **75**, 5853 (1953).

step for this perester is not solvent dependent. One must conclude that the effect of changing solvents (*n*-alkanes) on the rate of decomposition of the *tert*-butylperoxy (*p*-nitrophenyl)acetate is a result of return from the cage from one-bond homolysis.

## Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are corrected. Infrared spectra were taken with a Perkin-Elmer Model 257 grating spectrophotometer. The nuclear magnetic resonance spectra were obtained with a Varian T-60, a Varian A-60, or a JEOL MH100 spectrophotometer using tetramethylsilane as an internal standard.

Benzene and the alkane solvents were purified by washing with concentrated sulfuric acid until the acid layer was clear, followed by washing with water, saturated sodium bicarbonate solution, and water until neutral, dried with magnesium sulfate, filtered, distilled from sodium, and finally redistilled from crude galvinoxyl. Vacuum distillation was used for the alkanes.

**Galvinoxyl** was prepared by the method of Coppinger[23] using the modification of Bartlett and Funahashi.[11] The crude material was recrystallized from pentane under nitrogen. Purity was checked by measuring the absorbance at 772 nm in benzene ($\epsilon$ 607).

***tert*-Butyl hydroperoxide** (Lucidol) was purified by repeated vacuum distillation until the material had the literature value of the refractive index ($n^{25}$D 1.3986)[24] and showed no impurities in the nmr.

**Sodium *tert*-butylperoxide** was prepared by the method of Lorand and Bartlett.[25]

**α-Phenylisobutyric acid** was prepared by the method of Campaigne and Maulding,[26] crude yield 80%, mp 79–80° (lit.[27] mp 80–81°).

**α-Phenylisobutyryl chloride** was prepared by refluxing 5.0 g of the acid in 25 ml of thionyl chloride overnight followed by removal of the excess thionyl chloride by rotary evaporation and vacuum distillation of the crude product, yield 4.96 g (89%), bp 60–61° (0.7 mm) [lit.[28] bp 109° (13 mm)].

***tert*-Butylperoxy α-phenylisobutyrate** was prepared by the method of Herkes, Friedman, and Bartlett.[29] The crude perester, obtained in 60% yield, was purified by dissolving the oil in 20 ml of pentane and passing the solution through a 1 × 10 cm water-cooled column of Woelm activity I alumina. The pentane was removed by rotary evaporation to yield a clear, colorless oil: ir ($CCl_4$) 1770 (C=O); nmr ($CCl_4$) δ 7.29 (m, 5), 1.60 (s, 6), and 1.12 (s, 9).

*Anal.* Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.33; H, 8.51.

**α-(*p*-Chlorophenyl)isobutyronitrile** was prepared by the procedure of Julia and Baillarge,[30] yield 62%, bp 80–84° (0.35 mm) [lit.[30] bp 142–145° (18 mm)].

**α-(*p*-Chlorophenyl)isobutyric acid** was prepared by hydrolyzing 10.7 g of the nitrile in 30 ml of concentrated sulfuric acid and 28 ml of water. The crude acid was recrystallized from a hexane–chloroform mixture (2:1) to give 7.9 g (68%) of white crystals, mp 125–126° (lit.[30] mp 124°).

**α-(*p*-Chlorophenyl)isobutyryl chloride** was prepared by refluxing 8.36 g (0.042 mol) of the acid in 50 ml of thionyl chloride for 7 hr, followed by removal of excess thionyl chloride by rotary evaporation and vacuum distillation of the crude product, bp 82° (0.25 mm), yield 8.58 g (94%).

***tert*-Butylperoxy α-(*p*-chlorophenyl)isobutyrate** was prepared by adding dropwise 11.5 g (0.146 mol) of pyridine to 8.58 g (0.0395 mol) of the acid chloride and 10.16 g (0.114 mol) of *tert*-butyl hydroperoxide in 25 ml of anhydrous ether. The reaction mixture was kept at 0° and stirred with a magnetic stirrer. Stirring was continued for 30 min after addition was complete; the flask was then placed in a refrigerator for 4 days. The reaction mixture was then poured into 40 ml of pentane and 60 ml of ice water, and the layers were separated. The pentane layer was washed with ice-cold 10% $H_2SO_4$, water, ice-cold 10% KOH, and water until neutral and dried ($MgSO_4$), and the solvent was removed by rotary evaporation. The resulting oil, 8.9 g (83%), was chromatographed on a water-cooled 1 × 8 cm alumina column with pentane to remove carbonyl-containing impurities. Other minor impurities, visible in the nmr, were removed by low-temperature recrystallization from pentane: ir (neat) 1767 $cm^{-1}$ (C=O); nmr ($CCl_4$) δ 7.34 (s, 4), 1.56 (s, 6), and 1.17 (s, 9).

*Anal.* Calcd for $C_{14}H_{19}ClO_3$: C, 62.10; H, 7.07; Cl, 13.10. Found: C, 62.08; H, 7.13; Cl, 13.16.

**α-(*p*-Nitrophenyl)isobutyric acid** was prepared by the method of Overberger and Gainer.[31] The crude product was recrystallized from toluene, mp 129–131° (lit.[31] mp 132–133°); the final yield was 39% after four recrystallizations.

**α-(*p*-Nitrophenyl)isobutyryl chloride** was prepared by dissolving 4.2 g of the acid in 50 ml of thionyl chloride and stirring overnight. The reaction mixture was then refluxed for 3 hr, and the excess thionyl chloride was removed by rotary evaporation. The crude acid chloride was recrystallized from petroleum ether (bp 30–60°) to give 3.1 g (68%) of white needles, mp 56–57° (lit.[32] mp 55–56°).

***tert*-Butylperoxy α-(*p*-nitrophenyl)isobutyrate** was prepared by the same procedure as that for the unsubstituted perester, using 2.84 g (0.012 mol) of acid chloride, 3.24 g (0.036 mol) of *tert*-butyl hydroperoxide, and 3.65 g (0.046 mol) of pyridine. Work-up and purification were also the same, yielding a white solid: ir ($CCl_4$) 1764 $cm^{-1}$ (C=O); nmr ($CCl_4$) δ 8.27–7.46 (m, 4), 1.65 (s, 6), and 1.18 (s, 9).

*Anal.* Calcd for $C_{14}H_{19}NO_5$: C, 59.77; H, 6.81; N, 4.98. Found: C, 59.63; H, 6.96; N, 5.00.

**α-(*p*-Methoxyphenyl)isobutyric acid** was prepared by the method of Hauser, Kenyon, and Kaiser.[33] The crude product was recrystallized from hexane and then from water, mp 88–89° (lit.[34] mp 89–90°).

**α-(*p*-Methoxyphenyl)isobutyryl chloride**[35] was prepared by dissolving 4.0 g (0.02 mol) of the acid in 50 ml of dry benzene and adding dropwise 13.1 g (0.10 mol) of oxalyl chloride dissolved in 20 ml of benzene. When the initial reaction subsided, the mixture was refluxed for 5 hr. The benzene and excess oxalyl chloride were removed by distillation, and the crude acid chloride was distilled to give 3.87 g (84%) of a clear liquid, bp 95–96° (0.5 mm).

***tert*-Butylperoxy α-(*p*-Methoxyphenyl)isobutyrate.**—This perester has a half-life of about 30 min at 50°; hence it must be kept cold during synthesis, work-up, and purification to prevent its decomposition. To 1.5 g (0.0135 mol) of sodium *tert*-butylperoxide suspended in 50 ml of methylene chloride was added 1.15 g (0.0063 mol) of the acid chloride in 5 ml of methylene chloride. The reaction mixture was stirred with a magnetic stirrer and kept in a Dry Ice–carbon tetrachloride bath for 5 hr. The flask was then taken into a refrigerated room (approximately 4°) and worked up as follows. The reaction mixture was poured into 40 ml of pentane and 60 ml of ice water. The pentane layer was extracted five times with cold 10% KOH and five times with ice water and dried ($MgSO_4$). The solvent was removed by rotary evaporation, and the resulting oil was dissolved in 10 ml of pentane and passed through a 1 × 2 cm Florisil column. The pentane was removed by rotary evaporation to yield a clear, colorless oil: ir (neat) 1764 $cm^{-1}$ (C=O); nmr ($CCl_4$) δ 7.52–6.83 (m, 4), 3.83 (s, 3), 1.60 (s, 6), and 1.18 (s, 9). This nmr was obtained on a Varian A-60 spectrophotometer at −5°.

*Anal.* Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.78; H, 8.37.

***p*-Methylphenylacetonitrile.**—In a 3-l. three-neck round-bottom flask fitted with a mechanical stirrer and reflux condenser were placed 1600 ml of 50% ethanol, 116 g (1.78 mol) of potassium cyanide, and 250 g (1.78 mol) of *p*-methylbenzyl chloride. The

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(28) O. Wallach, *Chem. Zentr.*, II, 1047 (1899).
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(31) C. G. Overberger and H. Gainer, *J. Amer. Chem. Soc.*, **80**, 4556 (1958).
(32) A. Jonsson, *Acta Chem. Scand.*, **8**, 1203 (1954).
(33) W. G. Kenyon, E. M. Kaiser, and C. R. Hauser, *J. Org. Chem.*, **30**, 2937 (1965).
(34) A. Jonsson, *Acta Chem. Scand.*, **8**, 1211 (1954).
(35) Attempts to prepare this acid chloride from the acid and thionyl chloride gave poor yields.

mixture was stirred and refluxed overnight. The layers were separated, the water layer was saturated with sodium chloride and extracted with ether, and the ether was added to the organic layer. The solvent was removed by rotary evaporation, the crude product was taken up in fresh ether, dried ($MgSO_4$), and filtered, and the ether was removed by rotary evaporation. The crude product was distilled on a spinning band column to yield 99 g (42%) of *p*-methylphenylacetonitrile.

**α-(*p*-Tolyl)isobutyronitrile.**—In a three-neck, 1-l. round-bottom flask fitted with a reflux condenser and glass stoppers were placed 200 ml of benzene and 300 ml of *tert*-butyl alcohol, both dried by distillation from sodium. To this mixture was added 15.6 g (0.4 mol) of potassium metal piecewise, while stirring with a magnetic stirrer. When reaction was complete the solution was cooled to 10°.

In a separate three-neck, 1-l. round-bottom flask fitted with reflux condenser, nitrogen inlet, mecanical stirrer, and addition funnel were placed 26.1 g (0.2 mol) of the nitrile, 85.2 g (0.6 mol) of methyl iodide, and 50 ml of benzene. The alkoxide solution was added dropwise with stirring. The reaction mixture was kept cold for 5 hr, then allowed to warm to room temperature. Stirring was continued overnight, followed by refluxing for 3 hr. The reaction mixture was poured into water and the layers were separated. The water was saturated with sodium chloride and extracted with ether, and the ether was added to the organic layer. After the organic layer was dried ($MgSO_4$) the solvent was removed by rotary evaporation. The crude product was vacuum distilled to yield 26.9 g of material, bp 66–70° (0.25 mm). Analysis of the material by glpc and nmr showed that it was a 50:50 mixture of mono- and dimethylated nitriles. This product mixture was remethylated by the same procedure, using 7.8 g of potassium metal and 42.6 g of methyl iodide.

**α-(*p*-Tolyl)isobutyric Acid.**—In a 100-ml round-bottom flask were placed 12.0 g (0.075 mol) of α-(*p*-tolyl)isobutyronitrile, 12 ml of concentrated sulfuric acid, 12 ml of glacial acetic acid, and 12 ml of water. The mixture was refluxed for 6 hr, allowed to cool, and poured onto 100 g of ice–water. The product was collected by extraction with chloroform and dried ($MgSO_4$), and the chloroform was removed by rotary evaporation. The crude product was repeatedly recrystallized from hexane to give 4.3 g (32%) of white crystals, mp 81.5–82° (lit.[36] mp 82°).

**α-(*p*-Tolyl)isobutyryl chloride** was prepared by dissolving 4.0 g (0.022 mol) of the acid in 25 ml of thionyl chloride and refluxing for 6 hr. The excess thionyl chloride was removed by rotary evaporation and the crude product was vacuum distilled to give 3.77 g (86%) of clear liquid, bp 79–80° (0.65) mm.

***tert*-Butylperoxy α-(*p*-tolyl)isobutyrate** was prepared from 1.0 g of the acid chloride and 1.7 g of sodium *tert*-butylperoxide by the method previously described for the *p*-methoxy perester. Work-up and purification by the same method yielded a white solid (60%): ir (methylene chloride) 1761 $cm^{-1}$ (C=O); nmr ($CCl_4$) δ 7.18 (m, 4), 2.34 (s, 3), 1.56 (s, 6), and 1.13 (s, 9).

*Anal*: Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.96; H, 8.91.

**Procedure for Excess Scavenger Experiments.**—A perester stock solution was prepared by weighing out approximately 20–30 mg of perester in a volumetric flask on a Mettler H20 balance. Kinetic samples were prepared by weighing out about 7 mg of galvinoxyl in a volumetric flask, adding the desired volume of perester stock solution, and diluting to the mark.

Cells used for the thermal decompositions were made from 1-cm-square Pyrex tubing, frosted on two opposite sides and polished on the other two. The cells were fitted with a male 10/30 joint for degassing and a constriction in the neck for sealing off.

The cells were filled with sample solutions using syringes with long hypodermic needles. The cells were degassed with at least five freeze–pump–thaw cycles with a final pressure less than 0.005 mm. Appropriate blanks were also prepared containing galvinoxyl but no perester.

The absorbance was read on a Cary 14 spectrophotometer at 764 nm (ε 540) for the alkane solvents, 769 nm (ε 607) in benzene, and 765 nm (ε 726) in acetonitrile. The cells were then wrapped in aluminum foil and placed in a thermostated oil bath. They were removed periodically and quenched in ice water, and the absorbance was recorded. This procedure was altered for some of the runs with the *p*-methoxy perester owing to its comparatively rapid decomposition. For these runs, the cell compartment of the spectrophotometer was thermostated at 50.0° ± 0.1°, and the absorbance was recorded continuously.

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**Registry No.**—Galvinoxyl, 2370-18-5; BDPA, 2152-02-5; *tert*-butyl hydroperoxide, 75-91-2; sodium *tert*-butylperoxide, 13250-54-9; α-(*p*-chlorophenyl)isobutyric acid, 6258-30-6; α-(*p*-chlorophenyl)isobutyryl chloride, 40919-11-7; α-(*p*-nitrophenyl)-isobutyryl chloride, 40919-12-8; α-(*p*-methoxyphenyl)isobutyric acid, 2955-46-6; α-(*p*-methoxyphenyl)isobutyryl chloride, 40919-14-0; *p*-methylphenylacetonitrile, 2947-61-7; α-(*p*-tolyl)isobutyronitrile, 40119-34-4; α-(*p*-tolyl)isobutyric acid, 20430-18-6; α-(*p*-tolyl)isobutyryl chloride, 40919-17-3.

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# The Nature of the Base-Induced Decomposition of the *p*-Toluenesulfonylhydrazone of Tricyclo[3.2.1.$0^{3,6}$]octan-2-one

PETER K. FREEMAN,* TIMOTHY D. ZIEBARTH, AND V. N. MALLIKARJUNA RAO

*Department of Chemistry, Oregon State University, Corvallis, Oregon 97331, and Department of Chemistry, University of Idaho, Moscow, Idaho 83843*

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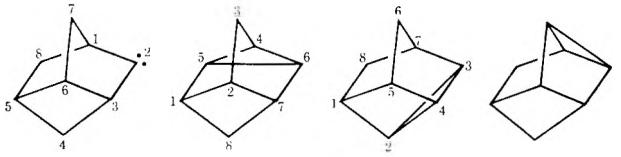
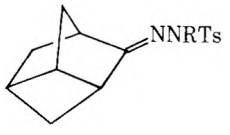
Decomposition of the sodium salt of the tosylhydrazone of tricyclo[3.2.1.$0^{3,6}$]octan-2-one (**5a**) in diglyme in excess sodium methoxide at 145° generates tetracyclo[3.3.0.$0^{2,7}$.$0^{4,6}$]octane (**2**), tetracyclo[3.3.0.$0^{2,4}$.$0^{3,7}$]octane (**3**), and *exo*-2-methoxytricyclo[3.2.1.$0^{3,6}$]octane. Hydrogenolysis of **3** produces tricyclo[3.3.0.$0^{3,7}$]octane (**8**), while similar treatment of **2** results in tricyclo[3.3.0.$0^{2,7}$]octane. Treatment of *exo*-2-chlorotricyclo[3.2.1.$0^{3,6}$]-octane (**10**) with sodium in decane at 85–90° generates a $C_8$ hydrocarbon fraction composed of bicyclo[3.2.1]-octene-2 (**11**), tricyclo[3.2.1.$0^{3,6}$]octane, and tetracyclooctane **2**. Tricyclo[3.2.1.$0^{3,6}$]octan-2-one tosylhydrazone-*N*-*d* (**5b**) decomposes in excess sodium methoxide to provide decreasing ratios of **2**:**3** and decreasing deuterium incorporation as the amount of sodium methoxide is increased. Product composition in the decomposition of **5a** is primarily dependent upon the solvent composition and the base. The decomposition of **5a** is interpreted in terms of competing carbene and ionic pathways.

Our interest in the chemistry of 2-carbenatricyclo-[3.2.1.$0^{3,6}$]octane was stimulated by the interesting possibilities for insertion and the prospects for additional studies on the tetracyclooctane insertion products.[1] If one views bivalent intermediate **1** as an isopropylcarbene intermediate,[2-7] then insertion into C-8, C-4, and C-7 leading to tetracyclooctanes **2**, **3**, and **4** is anticipated.

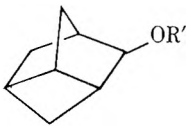


**1** **2** **3** **4**

Thermal decomposition of the tosylhydrazone of tricyclo[3.2.1.$0^{3,6}$]octan-2-one (**5a**), in the presence of 6 equiv of $NaOCH_3$ in diglyme at 145°, resulted in the generation of two hydrocarbons and a methyl ether in a yield ratio of 17:33:22. Infrared and nmr spectral comparisons with an authentic sample demonstrated that the methyl ether component is *exo*-2-methoxy-tricyclo[3.2.1.$0^{3,6}$]octane (**6a**), while elemental and



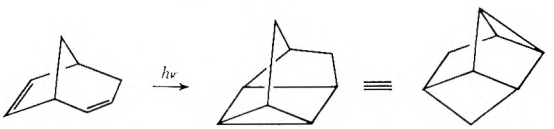
**5a**, R = H
**b**, R = D
**c**, R = Na
**d**, R = Li



**6a**, R′ = $CH_3$
**b**, R′ = $CH(CH_3)_2$

mass spectral measurements ($C_8H_{10}$, *m/e* 106), coupled with infrared and nmr analysis (absorption above 3000 $cm^{-1}$, no absorption in the region 1500–1700 $cm^{-1}$, no absorption below $\tau$ 7.3), indicated that the two hydrocarbon components were tetracyclic hydrocarbons.

Structural identification of the two tetracyclic hydrocarbon components was accomplished by an analysis of spin decoupling at 100 MHz as well as by hydrogenolysis. A consideration of the structures of probable insertion products **2**, **3**, and **4** reveals that **2** possesses three pairs of enantiotopic protons and four unique ones ($C_s$ plane through C-2, C-3, and C-4), tetracyclic **3** possesses four pairs of enantiotopic protons and two unique ones ($C_s$ plane through C-3, C-7, and the midpoint of C-1–C-5), while all the protons of tetracyclic **4** are nonequivalent. Spin decoupling carried out on the 33% component demonstrated the presence of three pairs of equivalent protons, appearing at $\tau$ 7.68–7.80, 8.47–8.57, and 8.60–8.66, and two pairs of nonequivalent protons appearing at $\tau$ 7.90–8.06 and 8.21–8.35, with the largest coupling constant due to the geminal coupling of the protons at C-8 ($J$ = 6.4 Hz), which is consistent with the expectations for structure **2**.[8] Similar decoupling experiments carried out on the 17% hydrocarbon component reveal the presence of four pairs of equivalent protons with absorption bands appearing at $\tau$ 7.56–7.66, 7.95–8.07, 8.58–8.73, and 8.99–9.15, and bands for two unique protons at $\tau$ 7.44–7.56 and 8.21–8.41. Thus, the nmr spectrum fits very nicely that anticipated for tetracyclooctane **3**, and this assignment of structure is reinforced by the fact that the largest coupling constant observed, $J$ = 9.7 Hz, is readily assignable as the geminal splitting constant of the hydrogens in the enantiotopic methylene groups at C-6 and C-8 in structure **3**. Finally, any lingering doubt that asymmetric **4** might be a structural possibility for either of the two hydrocarbons was removed by infrared and nmr spectral comparison with the corresponding data on the photoisomerization product of bicyclo[3.2.1]octa-2,6-diene, which has been assigned the tetracyclo[4.2.0.$0^{2,4}$.$0^{3,8}$]octane structure (**4**).[9]



**4**

(1) An account of the chemistry of bivalent intermediate **1** has been published in preliminary form: P. K. Freeman, V. N. M. Rao, and G. E. Bigam, *Chem. Commun.*, 511 (1965).

(2) W. Kirmse, H. D. von Scholz, and H. Arold, *Justus Liebigs Ann. Chem.*, **711**, 22 (1968).

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(4) W. Kirmse and W. von E. Doering, *Tetrahedron*, **11**, 266 (1960).

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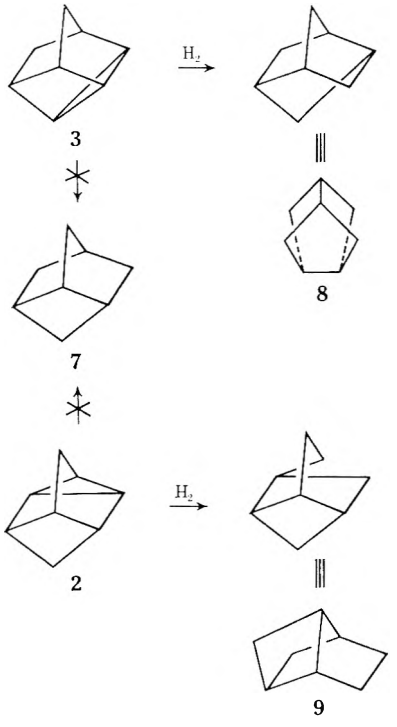
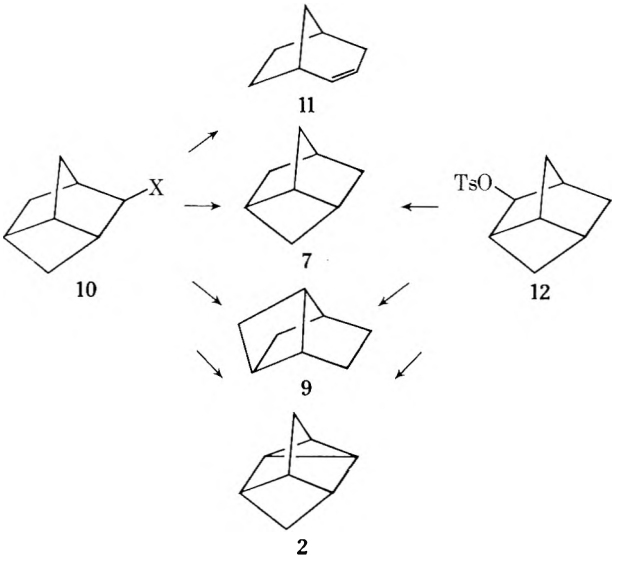
(8) The geminal C-5 protons on the bicyclo[2.1.1]hexane ring system exhibit a similar splitting constant, $J$ = 5.4 Hz: K. B. Wiberg, B. R. Lowry, and B. J. Nist, *J. Amer. Chem. Soc.*, **84**, 1594 (1962).

(9) Professor S. Winstein, private communication.

Hydrogenolysis of the 17% component over platinum in methanol occurred rapidly, yielding only one product, mp 105–105.5°. Elemental and mass spectral analysis ($C_8H_{12}$, *m/e* 108) combined with a consideration of the infrared spectrum, which exhibited no evidence for cyclopropane, methyl, or unsaturation, suggested that the hydrogenolysis product must be tricyclic as a result of fission of a cyclopropane bond. Hydrogenolysis of the enantiotopic bonds C-2–C-3 or C-3–C-4 in **3** does not occur, since the spectral data of the hydrogenolysis product do not agree with the data for tricyclo[3.2.1.$0^{3,6}$]octane (**7**), synthesized by Wolff–Kishner reduction of tricyclo[3.2.1.$0^{3,6}$]octan-2-one. The remaining possibility is fission of the C-2–C-4 bond, which is the transannular bond of a bicyclo[2.1.0]pentane moiety and thus subject to facile cleavage.[10] The nmr spectrum (100 MHz) of this tricyclic hydrocarbon is striking, revealing only two broadened singlets at $\tau$ 7.72 and 8.68 in the ratio of 1:2 and thus is consistent with the $D_{2d}$ symmetry of tricyclo[3.3.0.$0^{3,7}$]octane (**8**). Formation of **8** reinforces the assignment of **3** to the 17% component, since **8** cannot be formed from reductive bond fission of **2** or **4**. Hydrogenation of tetracyclooctane **2** over platinum in methanol proceeds readily to yield a single $C_8H_{12}$ tricyclic hydrocarbon. Reductive bond fission of the C-5–C-6 bond did not occur, as determined by spectral comparison with data of authentic **7**. Since no cyclopropane absorption is evident above 3000 or near 1020 $cm^{-1}$ in the infrared, cleavage of the C-4–C-6 (or C-4–C-5) bond must have occurred, generating tricyclo[3.3.0.$0^{2,7}$]octane. The nmr spectrum (60 MHz) exhibits complex absorption bands at $\tau$ 7.62–7.95 (4 H) and 8.12–8.93 (8 H).




With the structure of the products of the thermal decomposition of the sodium salt of **5a** established, and thus with a tentative view of the reaction routes followed by 2-carbenatricyclo[3.2.1.$0^{3,6}$]octane, or a combination of bivalent **1** and the related carbonium ion, attention was focused on the possibility of generation of a carbenoid intermediate related to **1** by an $\alpha$-elimination pathway. *exo*-2-Chlorotricyclo[3.2.1.$0^{3,6}$]-octane (**10**) was prepared by treatment of the corresponding alcohol[11] with thionyl chloride. Chloride **10** appeared to be homogeneous by vpc and was assigned the exo unrearranged structure on the basis of the appearance of a sharp singlet at $\tau$ 6.00 for the hydrogen $\alpha$ to chlorine in the nmr spectrum. A heart-cut sample of chloride **10**, collected by vapor phase chromatography on a 30-ft Carbowax 20M column, was allowed to react with sodium in decane at 85–90°.[7,12] Distillation of the volatile hydrocarbon fraction directly from the reaction mixture resulted in a 44% yield of $C_8$ hydrocarbons. A combination of vpc and spectral analyses revealed that the $C_8$ hydrocarbon fraction was composed of 72% bicyclo[3.2.1]octene-2 (**11**), 22% tricyclo[3.2.1.$0^{3,6}$]octane (**7**), 3% tetracyclooctane **2**, a 3% unidentified liquid component, and a trace (<1%) of tricyclooctane **9**.




Since an understanding of the base-induced decomposition of tosylhydrazone **5a** as well as the reaction of chloride **10** with sodium depends upon an accurate assessment of the relative importance of carbene as well as carbonium ion pathways in the thermal decomposition of the sodium salt of **5a**, a more detailed analysis of this reaction was undertaken. Tricyclo[3.2.1.$0^{3,6}$]-octan-2-one tosylhydrazone-*N*-*d* (**5b**) was decomposed in the presence of varying amounts of sodium methoxide and the ratio of insertion products **2** and **3**, as well as the deuterium content of **2** and **3**, was measured (Table I). In a second series of decompositions of **5a**, **5c**, and **5d**, thermal reactions were carried out in various solvents and without solvent and a photolytic decomposition in diglyme was investigated (Table II).

(10) K. B. Wiberg in "Advances in Alicyclic Chemistry," Vol. 2, H. Hart and G. J. Karabatsos, Ed., Academic Press, New York, N. Y., 1968, p 185.

(11) R. R. Sauers and R. A. Parent, *J. Org. Chem.*, **28**, 605 (1963); R. R. Sauers, R. A. Parent, and S. B. Danle, *J. Amer. Chem. Soc.*, **88**, 2257 (1966).

(12) P. K. Freeman, D. E. George, and V. N. M. Rao, *J. Org. Chem.*, **29**, 1682 (1964); E. A. Hill, *ibid.*, **37**, 4008 (1972); H. G. Richey, Jr., and E. A. Hill, *ibid.*, **29**, 421 (1964); W. Kirmse and W. von E. Doering, *Tetrahedron*, **11**, 266 (1960); P. S. Skell and A. P. Krapcho, *J. Amer. Chem. Soc.*, **83**, 754 (1961).

TABLE I

DECOMPOSITION OF TRICYCLO[3.2.1.0$^{3,6}$]OCTAN-2-ONE TOSYLHYDRAZONE-*N*-$d^a$ AT 160° IN TETRAGLYME

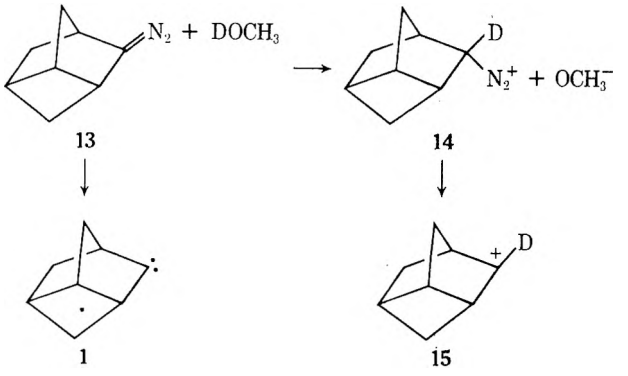
| Run | Equiv of $NaOCH_3$ | % 2 (% $d_1$) | % 3 (% $d_1$) |
|---|---|---|---|
| 1 | 0.48 | 86 (46 ± 4) | 14 (30 ± 6) |
| 2 | 1.07 | 87 (31 ± 2) | 13 (15 ± 2) |
| 3 | 1.97 | 78 (16 ± 2) | 22 (7 ± 2) |
| 4 | 3.16 | 69 (5 ± 1) | 31 (2[b]) |
| 5 | 11.62 | 62 (3 ± 1) | 38 (2 ± 1) |

[a] 68% $d_1$. [b] Only one run.

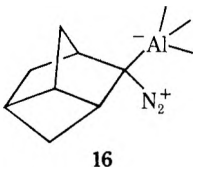
## Discussion

The product ratios and the extent of deuteration found in these experiments listed in Tables I and II provide convincing evidence that 2-carbenatricyclo-[3.2.1.0$^{3,6}$]octane undergoes insertion into the $\gamma$ C–H bonds at C-8 and C-4 to generate tetracyclooctanes **2** and **3** in an approximate ratio of 3:2. Convergence of the 2:3 product ratio with increasing quantities of sodium methoxide (Table I) to that observed in the dry lithium or sodium salt pyrolyses (Table II), as well as the low level recorded for the deterium concentration in 2 and **3** in the high methoxide runs (4 and 5 in Table I), substantiates this view.

One can consider these results in terms of two major competing reaction pathways. Decomposition of sodium salt **5c** yields **13**, which can decompose by loss of nitrogen to form carbene **1** or react with methanol-*d* to give diazonium ion **14**, which, in turn, may generate labeled carbonium ion **15**. Thus with a large excess




of sodium methoxide complete conversion to **5c** is assured and aprotic conditions are achieved with minimum incorporation of deuterium label; carbene **1** is nearly the sole product-determining intermediate. In protic solvents (run 4, Table II), diazoalkane **13** is converted to diazonium ion **14** and either ion **14** or **15** is the major product-determining intermediate. A similar result to that of run 4 is obtained by using Al(*i*-OPr)$_3$ as the base (run 9). Apparently the aluminum alkoxide, acting as a Lewis acid, generates a carbenoid, perhaps similar in structure to **16**, which

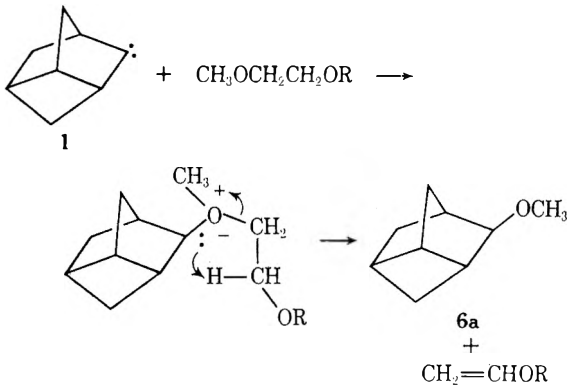



16

undergoes insertion in a pattern similar to that followed by ion **15** (or perhaps diazonium ion **14**). Even though **14** or **15** favors insertion at C-8, the deuterium incorporation at low methoxide concentration (run 1, Table I) suggests that the carbonium ion (or diazonium ion) also undergoes insertion at C-4.

The generation of methyl ether **6a**, in run 1 (Table II), at first glance intrigued us, as one possible route to **6a** is through intermolecular reaction of bivalent **1** with methoxide ion, methyl alcohol, or perhaps diglyme *via* an ylide elimination mechanism[13–16] (Scheme I). The

SCHEME I




ylide mechanism variation was tested by substituting diethylcarbitol for diglyme as the solvent (run 2, Table II). The formation of methyl rather than ethyl ether in this run rules out the ylide mechanism. In run 3, the sodium salt of the tosylhydrazone was formed by treatment with sodium hydride and the decomposition of the sodium salt was run in the presence of 6 equiv of sodium methoxide. The complete lack of methyl ether in this run demonstrates that methyl alcohol is required for the generation of **6a**. One might reasonably anticipate a mild electrophilicity for dialkylcarbene **1**[17] and, therefore, expect that, if bivalent intermediate **1** does not react intermolecularly with methoxide ion, an insertion into methanol would be unlikely. The role of the methanol must be to create a carbonium ion (or diazonium ion) component of the reaction, which then results in ether formation.

The related reaction of chloride **10**-Cl with sodium in decane at 85–90° may be explained in terms of the formation of sodium alkyl **10**-Na, which may undergo cleavage at the C-3–C-6 bond followed by proton abstraction to yield major product **11** or abstract a proton from the $\alpha$ position of **10**-Cl to generate hydrocarbon **7** and a carbenoid related to bivalent **1**, which undergoes insertion to produce tetracyclooctane 2. The trace of tricyclic **9** is believed to be due to the presence of a small amount of Wagner–Meerwein rearranged chloride present in **10**-Cl. Additional evidence pointing to this conclusion is found in the fact that, when a chloride sample prepared in the reaction of **10**-OH with thionyl chloride, but not purified by taking a vpc heart-cut,

(13) G. B. R. deGraaf, J. H. van Dijck-Rothius, and G. van deKolbe, *Recl. Trav. Chim. Pays-Bas*, **74**, 143 (1955); G. B. R. deGraaf and G. Van deKolbe, *ibid.*, **79**, 48 (1960).

(14) V. Franzen, *Justus Liebigs Ann. Chem.*, **627**, 22 (1959); V. Franzen and L. Fikentscher, *ibid.*, **617**, 1 (1958); V. Franzen and H. Kuntze, *ibid.*, **627**, 15 (1959).

(15) M. Saunders and R. W. Murray, *Tetrahedron*, **11**, 1 (1960).

(16) W. Ando, T. Yagihara, and T. Migita, *Tetrahedron Lett.*, 1983 (1969); W. Ando, T. Yagihara, S. Tozune, and T. Migita, *J. Amer. Chem. Soc.*, **91**, 2786 (1969); W. Ando, K. Nakayama, K. Ichibori, and T. Migita, *ibid.*, **91**, 5164 (1969); W. Ando, S. Kondo, and T. Migita, *ibid.*, **91**, 6516 (1969).

(17) W. M. Jones, M. H. Grasley, and W. S. Brey, Jr., *J. Amer. Chem. Soc.*, **85**, 2754 (1963).

TABLE II

DEPENDENCE OF PRODUCT COMPOSITION ON REACTION CONDITIONS IN THE DECOMPOSITION OF TOSYLHYDRAZONE 5a AND TOSYLHYDRAZONE SALTS 5c AND 5d

| Run | R | Solvent, conditions | Equiv base | Temp, °C | Yield, % 2/3 | 2 + 3 | 6a | 6b |
|---|---|---|---|---|---|---|---|---|
| 1 | H | Diglyme, Δ | 6 NaOMe | 145 | 1.96 | 50 | 22 | |
| 2 | H | Diethylcarbitol, Δ | 6 NaOMe | 145 | 2.01 | 29 | 17 | |
| 3 | H | Diglyme, Δ | 1.25 NaH, then 6 $NaOCH_3$ | 145 | 2.07 | 24 | 0 | |
| 4 | H | Ethylene glycol, Δ | 6 NaOMe | 145 | 22.4 | 8 | 3 | |
| 5 | Li | None, Δ | | 200 | 1.64 | 78 | | |
| 6 | Li | None, Δ | | 160 | 1.63 | 76 | | |
| 7 | Na | None, Δ | | 160–175 | 1.50 | 39 | | |
| 8 | Li | Diglyme, $h\nu$ | | 20 | 2.03 | 3 | | |
| 9 | H | Diglyme, Δ | 8 $Al(i\text{-}OPr)_3$ | 145 | 18 | 13 | | 44 |

was employed, a considerably larger fraction of **9**, amounting to 15% of the volatile hydrocarbon fraction, was produced.

In a related experiment solvolysis of the exo tosylate **12** in bis(2-ethoxyethyl) ether at 90° in the presence of lithium aluminum hydride generated a 32% yield of $C_8$ hydrocarbons, which consisted of tricyclic **7**, tricyclic **9**, and tetracyclic **2** in a ratio of 60:27:13. Thus Wagner–Meerwein rearrangement does occur in contrast to the result of acetolysis of **12** at 105°[11] and the reaction pattern of the carbonium ion reveals that insertion into C-8–H is highly favored over C-4–H in accord with the pattern uncovered for the decomposition of **5a** in a protic solvent (run 4, Table II). Carbenoid **16** also exhibits a marked preference for C-8 insertion, but the related species formed by α-proton abstraction from **10**-Cl forms **2** in too low a yield to establish the insertion pattern with certainty.

Assuming a singlet state precursor for the carbene insertion products,[18] it might have been reasonable to expect a similar insertion pattern for both the bivalent and carbonium ion intermediates, since each should be approximately $sp^2$ hybridized at C-2 and interact with the σ bond of the migrating hydrogen by electrophilic attack of an empty C-2 p orbital. The contrasting patterns revealed in the ratios of 2:3 (22 *vs.* 1.5–1.6) suggest that the product-determining intermediates may be rather different.

Nickon and Werstiuk prefer a diazonium ion precursor for the Bamford–Stevens reaction of norcamphor tosylhydrazone in ethylene glycol,[19] and thus it is reasonable to consider endo diazonium ion **14** as the product-determining intermediate in the present case. It turns out that a syn-periplanar transition state for 1,3 elimination in the preferred U-shaped configuration[20] is more easily achieved with the endo C-8 hydrogen than with the corresponding hydrogen at C-4, although the difference is not large. Perhaps the greater selectivity of the diazonium ion is due to a major extent to a greater sensitivity to product strain, which might be expected in a comparison of a diazonium ion with a free carbene. An alternative view in the case of tosylhydrazone decomposition in protic solvent is that the ionic intermediate is indeed a free carbonium ion, but is delocalized, which is consistent with the anchimeric assistance found for acetolysis of **12** ($10^{2.8}$)[11] and the Wagner–Meerwein rearrangement observed in the present study. Such delocalization should provide stabilization and a geometry with a shortened C-2–C-8 distance, which would be expected to enhance insertion at C-8. Such a view would have the advantage of encompassing the ionic pathways of the several variations discussed.

(18) There is no evidence for products derived from the triplet state in the reactions of the closely related 2-carbena-6,6-dimethylnorbornane, generated by pyrolysis of the lithium salt of the tosylhydrazone of 6,6-dimethylnorbornan-2-one: P. K. Freeman and T. A. Hardy, *J. Amer. Chem. Soc.*, submitted.

(19) A. Nickon and N. H. Werstiuk, *J. Amer. Chem. Soc.*, **94**, 7081 (1972); A. Nickon and N. H. Werstiuk, *ibid.*, **88**, 4543 (1966).

(20) A. Nickon and N. H. Werstiuk, *J. Amer. Chem. Soc.*, **89**, 3914, 3915, 3917 (1967).

## Experimental Section

All melting points and boiling points reported are uncorrected. Microanalyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, 5251 Elbach über Engelskirchen, West Germany, or Chemalytics, Inc., Tempe, Ariz. 85282. Infrared spectra were recorded on a Beckman Model IR-8 infrared spectrophotometer and nmr spectra were determined on a Varian Associates A-60 or HA-100 nmr spectrometer. Mass spectra were obtained using an Atlas CH7 mass spectrometer. Vapor phase chromatographic analyses and collections were carried out using either an F & M Model 700 or an Aerograph Model A-90-P chromatograph equipped with thermal conductivity detectors. Columns employed were made with aluminum tubing and contained the following: A, 9 ft × 0.125 in. 5% Carbowax 20M on 70/80 Anakrom ABS; B, 8 ft × 0.25 in. 15% Carbowax 20M and 2% XF-1112 on 30/60 Chromosorb P (AW); C, 20 ft × 0.125 in. 10% β,β′-oxydipropionitrile on 30/60 Chromosorb P (AW); D, 30 ft × 0.125 in. 5% Carbowax 20M on 70/80 Anakrom ABS; E, 25 ft × 0.25 in. 25% Carbowax 20M on 30/60 Chromosorb P. Product ratios and percentage yields calculated from chromatographic data are based on relative peak areas and were corrected, when necessary, for differences in molecular weight by the method of Eastman.[21] Peak areas were determined by electronic integration using a Hewlett-Packard Model 3373-B integrator unless stated otherwise. Solvents used in tosylhydrazone decompositions were distilled from lithium aluminum hydride or calcium hydride and stored over 4-Å molecular sieves, but only for short periods.

**Tricyclo[3.2.1.$0^{3,6}$]octan-2-one *p*-Toluenesulfonylhydrazone (5a).**—A mixture of tricyclo[3.2.1.$0^{3,6}$]octan-2-one (4.08 g, 32.9 mmol) and *p*-toluenesulfonylhydrazine (6.35 g, 34.1 mmol) in 26 ml of pyridine was heated on a steam bath for 1.5 hr. Subsequent dilution with 125 ml of cold water with vigorous stirring yielded 8.05 g (85%) of **5a**, mp 149–160°. A pure product was obtained by effecting solution of the crude solid in a hot 1:1 DMF–$H_2O$ solution (10 g of solution per gram of crude tosylhydrazone), filtering, then allowing the solution to cool slowly to room temperature. The resulting crystals were collected, washed with three aliquots of 1:1 DMF–$H_2O$ and three aliquots of water, and then dried. Recovery gave about 85% of pure **5a**: mp 161–164° dec; ir ($CHCl_3$, 0.1 mm) 3257, 3031, 2994, 2899, 1669, 1600, 1394, 1340, 1164, 1092, 1021, 918, 811, 659 $cm^{-1}$.

*Anal.* Calcd for $C_{15}H_{18}N_2O_2S$: C, 62.04; H, 6.24. Found: C, 61.80; H, 6.02.

**Decomposition of Tricyclo[3.2.1.$0^{3,6}$]octan-2-one *p*-Toluenesulfonylhydrazone (5a) in Sodium Methoxide–Diglyme.**—In a

(21) R. Eastman, *J. Amer. Chem. Soc.*, **79**, 4243 (1957).

dry 25-ml flask fitted with a reflux condenser and nitrogen inlet, a mixture of 1.00 g (3.45 mmol) of tosylhydrazone **5a**, 1.12 g (21.7 mmol, 6 equiv) of sodium methoxide, and 15 ml of dry diglyme was stirred at ambient temperature for 1 hr under a nitrogen atmosphere. The flask was then plunged into a 145° oil bath and held at that temperature for 5 hr. Initially a red-brown color appeared, which dissipated after *ca.* 15 min, leaving a pale milky-pink suspension. Allowing the mixture to cool, followed by dilution with an equal volume of pentane and subsequent extraction with five aliquots of water, yielded a pentane extract which was dried over anhydrous $Na_2SO_4$ and concentrated by distillation of the pentane through a 10-cm Vigreux column. The concentrated solution in the pot was analyzed by vpc on column A, and contained three components. The first two were identified as tetracyclo[3.3.0.0$^{2,7}$.0$^{4,6}$]octane (**2**) and tetracyclo[3.3.0.0$^{2,4}$.0$^{3,7}$]octane (**3**) in a yield ratio of 33:17 (determined by quantitative gas chromatography relative to a norbornane internal standard introduced after product isolation) by the ir and nmr analysis described in the Discussion section. Analytical samples of tetracyclic **2** and **3** were separated by vpc.

*Anal.* Calcd for $C_8H_{10}$ (**2**): C, 90.51; H, 9.49. Found: C, 90.31; H, 9.57.

*Anal.* Calcd for $C_8H_{10}$ (**3**): C, 90.51; H, 9.49. Found: C, 90.31; H, 9.29.

The third component was identified as *exo*-2-methoxytricyclo[3.2.1.0$^{3,6}$]octane (**6a**) by ir and nmr spectral comparison with spectra of an authentic sample.

*Anal.* Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.04; H, 10.09.

A 106-mg sample of tetracyclic hydrocarbon **3** was hydrogenated in methanol over platinum oxide in a semimicro hydrogenation apparatus. Hydrogen take-up was rapid and approximately 1 molar equiv of hydrogen was absorbed in 30 min. Vpc analysis of the product on column E at 90° indicated the presence of only one product. Purification of this product by vapor phase chromatography gave a white solid, mp 105–105.5. The infrared spectrum of this hydrogenated material was very simple, indicating that the product is symmetrical. There are no absorptions above 3000 cm$^{-1}$ or near 1022 cm$^{-1}$, and no evidence of methyl absorptions, thus indicating that the cleavage of the ring must have occurred in one of the cyclopropyl bonds. A parent peak at *m/e* 108 is exhibited in the mass spectrum. The nmr spectrum showed two singlets at $\tau$ 7.72 and 8.68 in the ratio 1:2. The data are consistent with the identification of this hydrocarbon as tricyclo[3.3.0.0$^{3,7}$]octane.

*Anal.* Calcd for $C_8H_{12}$: C, 88.81; H, 11.19. Found: C, 88.93; H, 11.37.

A 106-mg sample of tetracyclic hydrocarbon **2** was hydrogenated in methanol over platinum oxide in a semimicro hydrogenation apparatus. Approximately 1 molar equiv of hydrogen was absorbed. Vpc analysis of the hydrogenated mixture on a 25-ft Carbowax 20M column at 90° indicated the presence of only one product component. An infrared spectrum showed no olefinic absorption and there were no absorptions above 3000 cm$^{-1}$ or near 1020 cm$^{-1}$, indicating the absence of a cyclopropane ring. Absorption corresponding to a methyl group was also absent. The nmr spectrum of this component exhibits complex absorption bands at $\tau$ 7.62–7.95 (4 H) and 8.21–8.93 (8 H), while the mass spectrum reveals a weak parent peak at *m/e* 108. The spectral data of this compound were different from that of tricyclo[3.2.1.0$^{3,6}$]octane; consequently, the hydrogenated product was identified as tricyclo[3.3.0.0$^{3,6}$]octane.

*Anal.* Calcd for $C_8H_{12}$: C, 88.81; H, 11.19. Found: C, 88.95; H, 11.29.

**Preparation of *exo*-2-Methoxytricyclo[3.2.1.0$^{3,6}$]octane (6a).**—In a sealed reaction vessel were stirred 0.15 g (1.23 mmol) of *exo*-tricyclo[3.2.1.0$^{3,6}$]octan-2-ol, 0.56 g (2.4 mmol) of $Ag_2O$, 0.34 g (3.6 mmol) of methyl iodide, and 2 ml of dimethylformamide at ambient temperature for 5 days with exclusion of light. Dilution of the resulting solution with 1:1 pentane–ether (5 ml) followed by extraction with five aliquots of $H_2O$ yielded, after solvent removal at reduced pressure, a residue which contained two components by vpc analysis on column B.

The minor component (30%) was identified as starting alcohol. The major component (70%) had ir and nmr spectra consistent with the assigned structure, *exo*-2-methoxytricyclo[3.2.1.0$^{3,6}$]-octane (**6a**) and was formed in 65% yield based on unreacted alcohol: ir ($CCl_4$) $\nu$ 2959, 2875, 2833, 1449, 1366, 1199, 1120, 1106, 1094, 1078, 971 cm$^{-1}$; nmr (100 MHz, $CCl_4$) $\delta$ 3.24 (s, 1 H), 3.17 (s, 3 H), 2.74 (broad s, $W_{1/2}$ = 9 Hz, 1 H), 2.60 (broad s, $W_{1/2}$ = 7 Hz, 1 H), 2.18 (m, 3 H), 1.80 (doublet of doublets, $J$ = 11, 1.7 Hz, 1 H), 1.56 (doublet of multiplets, $J$ = 11 Hz, 1 H), 1.36 (s, 1 H), 1.23 (s. 1 H), 1.12 (m, 1 H).

**Preparation of Tricyclo[3.2.1.0$^{3,6}$]octan-2-one *p*-Toluenesulfonylhydrazone-*N*-*d* (5b).**—Deuterium exchange was effected by vigorously shaking 3.0 g (10.3 mmol) of tosylhydrazone **5a**, 25 ml of $CHCl_3$, 30 ml of 99.8% $D_2O$, and a catalytic amount of sodium methoxide in a 125-ml separatory funnel. Monitoring the amount of N-*h vs.* N-*d* by observation of the 3.1-$\mu$ band in the infrared revealed that a maximum $d_1$ incorporation occurred after only a few minutes—continued shaking caused a diminution of the amount of N-*d* owing to exchange of the chloroform proton. Precipitation of the tosylhydrazone by pentane addition yielded 1.74 g (6 mmol, 58%) of **5b**, mp 156–157° dec. Quantitative ir analysis using the resolved C=N stretching absorption at 6.0 $\mu$ as an internal standard in comparison to the NH stretching frequency at 3.1 $\mu$ indicated 68% deuterium incorporation at the desired position. Mass spectral analysis at 16 eV likewise revealed 68 ± 3% $d_1$ incorporation, determined from nine scans.

**Preparation of *N*-Lithiotricyclo[3.2.1.0$^{3,6}$]octan-2-one *p*-Toluenesulfonylhydrazone (5d).**—The tosylhydrazone lithium salt was prepared by addition of 1 equiv of methyllithium (1.95 *M* in ether) to tosylhydrazone **5a** in ether under nitrogen in a glove bag, followed by removal of solvent at reduced pressure and at room temperature with swirling of the solution such that the salt forms a thin coat on the inside of the reaction vessel. The last traces of ether were very difficult to remove, but extended subjection of the salt to a pressure of less than 0.01 mm, while warming to 40°, seemed moderately effective. No attempt was made to separate the tosylhydrazone lithium salt from the lithium bromide (1 equiv/mol of methyllithium) present in the commercial methyllithium solution used.

**Decomposition of Tricyclo[3.2.1.0$^{3,6}$]octan-2-one *p*-Toluenesulfonylhydrazone (5a) in Sodium Methoxide–Ethylene Glycol.**—Decomposition of 1.00 g (3.45 mmol) of tosylhydrazone **5a** was effected under conditions in all respects identical with those above, except that ethylene glycol (distilled from sodium) was substituted for diglyme as the solvent. Isolation and analysis of the resulting product mixture was also done in a fashion identical with the diglyme decomposition. Ether **6a** was found in only 2.0% yield, and a mixture of hydrocarbons **2** and **3** in the ratio of 90:4 was found in 7.8% yield using an internal norbornane reference. Two additional peaks, eluting before **2** or **3**, were found in 0.13 and 0.36% yield in order of elution and were not identified.

**Decomposition of *N*-Lithiotricyclo[3.2.1.0$^{3,6}$]octan-2-one *p*-Toluenesulfonylhydrazone (5d) in the Absence of Solvent.**—A reaction vessel containing the lithium salt **5d** was connected to a trap and cooled to −78° in a Dry Ice–2-propanol bath, and the system was evacuated to 0.01 mm. Immersion of the flask in a 200° silicone oil bath for 1 hr yielded a clear pyrolysate which collected in the −78° trap. This product mixture was analyzed in the same manner as the two preceding decomposition product mixtures. Hydrocarbons **2** and **3** were found in a ratio of 59:36 in a 74% yield in addition to an unidentified component, in 4% yield, which eluted after both **2** and **3** on column C (this component was not present when the same reaction was carried out at 160°).

**Photolysis of *N*-Lithiotricyclo[3.2.1.0$^{3,6}$]octan-2-one *p*-Toluenesulfonylhydrazone in Diglyme.**—The lithium salt was prepared by addition of 1.1 equiv of methyllithium (2.13 *M* in ether) to tosylhydrazone **5a** dissolved in diglyme. Irradiation of the resulting suspension in a quartz reaction vessel, equipped with a magnetic stirrer, a cold finger, and $CaCl_2$ drying tube, with a 450-W Hanovia high-pressure mercury lamp for 5 hr at a distance of 1 in., followed by dilution with pentane and extraction several times with water, yielded a solution which was analyzed by vpc as in the above thermal decompositions of **5a**. Both tetracyclic $C_8$ hydrocarbons **2** and **3** were formed, in a ratio of 67:33 but in only 3% yield as determined by an internal norbornane standard. The low yield was attributed to a low conversion of tosylhydrazone salt to hydrocarbon owing to the heterogeneity of the mixture.

**Decomposition of Tricyclo[3.2.1.0$^{3,6}$]octan-2-one *p*-Toluenesulfonylhydrazone (5a) in Aluminum Isopropoxide–Diglyme.**—Decomposition of 0.88 g of tosylhydrazone **5a** was effected under conditions in all respects identical with those for the methoxide–diglyme experiment above, except that 8 equiv of freshly distilled aluminum isopropoxide was substituted for sodium methoxide as the base. Isolation and analysis, also as above, in-

dicated a very low yield (13%) of the two tetracyclic isomers **2** and **3** in the ratio of 18:1. The two volatile peaks observed in the ethylene glycol decomposition were again noticed in similar relative yields.

**Decomposition of Tricyclo[3.2.1.0$^{3,6}$]octan-2-one *p*-Toluenesulfonylhydrazone (5a) in Sodium Methoxide–Bis(2 ethoxyethyl) Ether.**—Decomposition and analysis of 0.68 g of tosylhydrazone **5a** under conditions identical with those for the methoxide–diglyme decomposition above, except for a change in solvent to bis(2-ethoxyethyl) ether, gave ether **6a** in 17% yield, and tetracyclic hydrocarbons **2** and **3** in the ratio of 2:1 in 29% yield.

**Decomposition of Tricyclo[3.2.1.0$^{3,6}$]octan-2-one *p*-Toluenesulfonylhydrazone-*N*-*d* (5b) with Various Equivalents of Sodium Methoxide.**—In a 15-ml round-bottomed flask fitted with nitrogen inlet and condenser were mechanically stirred 0.290 g (1.0 mmol) of tosylhydrazone **5b**, 5 ml of tetraglyme, and various amounts of sodium methoxide at room temperature for 15 min. The entire apparatus was lowered into a 160 ± 5° oil bath and held there for 30 min. After cooling, the pot was diluted with pentane, filtered, washed six times with water, dried over anhydrous $Na_2SO_4$, and reduced in volume by distillation of the pentane through a 10-cm Vigreux column. Vpc analysis on column D connected directly to an Atlas CH-7 mass spectrometer operated at 13 eV gave ratios of **2** to **3** and per cent deuterium incorporation reported in Table I. The values reported are the average and average deviation of three scans of each sample.

***exo*-2-Chlorotricyclo[3.2.1.0$^{3,6}$]octane.**—In a 100-ml, three-necked flask, provided with a magnetic stirrer, a condenser, a pressure-equalizing dropping funnel, and a nitrogen inlet, was placed 9.5 g (0.798 mol) of redistilled thionyl chloride in 20 ml of anhydrous ether. To this mixture was added at ambient temperature with stirring a mixture of 9.0 g (0.725 mol) of *exo*-tricyclo[3.2.1.0$^{3,6}$]octan-2-ol[11] and 1 drop of piperidine in 30 ml of anhydrous ether during 30 min. The ether solution was heated at reflux for 2 hr, at the end of which period the ether was removed by distillation and the product was distilled under reduced pressure. A 43.6% yield of *exo*-2-chlorotricyclo[3.2.1.0$^{3,6}$]-octane (5.1 g), bp 66–67° (15 mm), was obtained: ir (0.025 mm) 2980, 1442, 1319, 1266, 1240, 1058, 920, 874, 799, 759, 748 cm$^{-1}$; nmr ($CCl_4$) δ 3.98 (s, 1 H), 2.92 (broad s, 1 H), 2.67 (broad s, 1 H), 2.55–1.20 (m, 8 H).

*Anal.* Calcd for $C_8H_{11}Cl$: C, 67.36; H, 7.77. Found: C, 67.52; H, 7.90.

**Reaction of *exo*-2-Chlorotricyclo[3.2.1.0$^{3,6}$]octane with Sodium.**—A solution of 4.0 g (0.028 mol) of *exo*-2-chlorotricyclo-[3.2.1.0$^{3,6}$]octane in 15 ml of redistilled *n*-decane was allowed to react with 1.28 g (0.056 g-atom) of sodium in a manner described previously for 5-chloromethylbicyclo[2.2.1]hept-2-ene.[22] When the reaction was complete, the mixture was distilled through a Claisen head at 40 mm and 6.2 g of a distillate was obtained. From the distillate, a total of 1.39 g (42.4%) of $C_8$ hydrocarbons was isolated by redistillation on an 18-in. semimicro spinning band column at 90 mm. The mixture was analyzed on column E and showed the presence of seven components in the ratio 1:15:17:11:46:8:4. A sufficient quantity of the 1% component was not obtained to make a positive identification. The 15% component was a low-melting solid. The infrared and the nmr spectra of the solid were identical with those of an authentic sample of tricyclo[3.3.0.0$^{2,7}$]octane. The 17% component was a white solid at room temperature, mp 120–121.5°. The infrared spectrum showed no evidence of any unsaturation. The absence of a cyclopropyl group was indicated by no absorptions above 3000 cm$^{-1}$ or near 1020 cm$^{-1}$. The nmr spectrum was identical with that of a sample obtained by the Wolff–Kishner reduction of tricyclo[3.2.1.0$^{3,6}$]octan-2-one. Two purifications by vapor phase chromatography raised the melting point of the solid to 140–141°. The 11% component was a liquid at room temperature. The spectral data of this component were identical with those of a sample of tetracyclo[3.3.0.0$^{2,7}$0.$^{4,6}$]octane. The 46% component was a low-melting solid. The infrared and the nmr spectra of this component were identical with those of an authentic sample of bicyclo[3.2.1]octene-2.[23] The 8% component was a liquid at room temperature. The infrared spectrum of this sample exhibited olefinic absorption at 1580 and 1630 cm$^{-1}$. In addition, it also had absorptions at 3045 and 3070 cm$^{-1}$, although there was no absorption corresponding to a nortricyclene type of ring structure near 800 cm$^{-1}$. The nmr spectrum indicated that this component was probably a mixture of more than one constituent. Owing to the paucity of material, further identification of this component was not carried out. The 4% component was a low-melting solid. The infrared spectrum of this component was very simple, suggestive of a symmetrical hydrocarbon. It exhibited characteristic absorptions at 3100 and 1022 cm$^{-1}$, suggestive of a nortricyclene type of ring skeleton. In addition, it also exhibited olefinic absorption at 1610 cm$^{-1}$ and sharp absorptions at 915 and 720 cm$^{-1}$. The nmr spectrum of this compound showed four sets of absorptions, a triplet at τ 4.22, corresponding to two protons, a one-proton multiplet centered at 3.52, a five-proton peak between 8.3 and 8.81, and two singlets at 9.21 and 9.41, whose integrated area corresponded to two protons, and is identical with the spectrum of authentic tricyclo[3.2.1.0$^{2,7}$]oct-3-ene.[24]

When a heart-cut sample of *exo*-2-chlorotricyclo[3.2.1.0$^{3,6}$]-octane was allowed to react with sodium, a 44.2% yield of $C_8$ hydrocarbons was obtained. Analysis of this mixture on column E showed only four peaks in the ratio 22:71:3:3. The 22% component was tricyclo[3.2.1.0$^{3,6}$]octane, the 71% component was bicyclo[3.2.1]octene-2, and the 3% component was tetracyclo[3.3.0.0$^{2,7}$0.$^{4,6}$]octane. The other 3% component was not identified.

**Solvolysis of *exo*-Tricyclo[3.2.1.0$^{3,6}$]octan-2-yl *p*-Toluenesulfonate.**—In a 50-ml three-necked flask provided with a nitrogen inlet, a mechanical stirrer, and a condenser was placed 1.39 g (0.005 mol) of the title tosylate in 10 ml of bis(2-methoxyethyl) ether. To this mixture was added 0.38 g (0.01 mol) of lithium aluminum hydride in 10 ml of dry bis(2-methoxyethyl) ether in one portion. The mixture was heated under a nitrogen atmosphere with stirring at a temperature of 90° for 72 hr. The mixture was cooled; water and wet sodium sulfate were added; and the mixture was extracted with three 25-ml portions of pentane. The pentane solutions were combined, washed with three 50-ml portions of water, and dried over anhydrous magnesium sulfate. The pentane was removed on an 18-in. semimicro spinning band column to leave a residue which weighed 0.17 g (32.2%). Analysis of this residue on column E at 90° showed the presence of three peaks in per cent ratios 27:60:13.

The 27% peak was identified as tricyclo[3.3.0.0$^{2,7}$]octane by comparison of its infrared and nmr spectra with those of a known sample of the same hydrocarbon. The 60% component was likewise identified as tricyclo[3.2.1.0$^{3,6}$]octane and the 13% component was identified as tetracyclo[3.3.0.0$^{2,7}$0$^{4,6}$]octane.

**Acknowledgment.**—The authors gratefully acknowledge the generous support of their research by the National Science Foundation and the Air Force Office of Scientific Research. T. D. Z. thanks the National Science Foundation for an NSF Graduate Traineeship, 1971–1972.

**Registry No.**—**2**, 5078-81-9; **3**, 4582-22-3; **5a**, 41564-15-2; **5b**, 41564-17-4; **5d**, 41564-16-3; **6a**, 41564-18-5; **7**, 250-22-6; **8**, 444-26-8; tricyclo[3.2.1.0$^{3,6}$]octan-2-one, 6239-87-8; *p*-toluenesulfonylhydrazine, 1576-35-8; *exo*-tricyclo[3.2.1.0$^{3,6}$]-octan-2-ol, 6239-90-3; methyl iodide, 74-88-4; *exo*-2-chlorotricyclo[3.2.1.0$^{3,6}$]octane, 41564-23-2.

(22) P. K. Freeman, V. N. M. Rao, D. E. George, and G. L. Fenwick, *J. Org. Chem.*, **32**, 3958 (1967).

(23) D. E. George, Ph.D. Thesis, University of Idaho, 1963.

(24) We thank Professor R. R. Sauers for this identification.

# Tricyclic Ketones *via* Cyclodehydration of Bicyclic Unsaturated Acids[1]

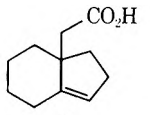
ROBERT L. CARGILL,* A. M. FOSTER, JAMES J. GOOD, AND F. KEITH DAVIS[2]

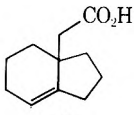
*Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208*

*Received May 30, 1973*

Cyclodehydration of acids **5** and **8** provides a mixture of ketones **6** and **7** in 30% yield. Acids **14** and **19** provide representatives of the tricyclo[6.2.1.$0^{5,11}$]undecane system. Catalytic hydrogenation of the unsaturated ketones derived from **14** and **19** leads to the corresponding all-cis-saturated derivatives. These and other related transformations are discussed.

In a previous paper[3] we reported that cyclodehydration of acids **1** and **2** gave ketone **4**, probably *via*


1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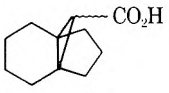
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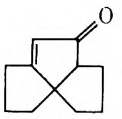
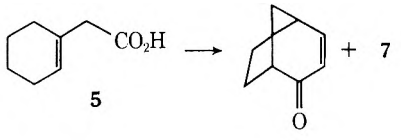
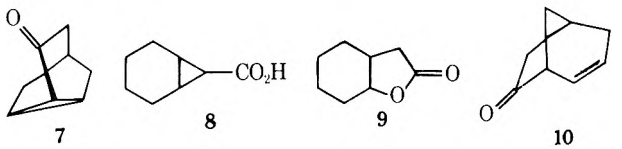

4

intramolecular acylation of acid **3**[3] and subsequent carbonium ion rearrangements. In this paper we describe the cyclodehydrations of a new series of olefinic acids.

Cyclodehydration of acid **5**[4,5] with polyphosphoric acid (PPA) for 1 hr at 100° gave a mixture of ketones **6** and **7** (ratio 2:1, respectively) in 34% yield. Similar cyclization of the cyclopropyl acid **8**[6] provided an identical mixture of **6** and **7** in 10–20% yield. The lower yield in the latter case appears to result from the lower solubility of the solid isomer **8** in PPA compared with that of the liquid acid **5**. The structures of ketones **6** and **7** were established by comparison of their spectra with those of authentic samples.[7,8] Separate treatment of **6** and **7** with PPA gave only recovered starting material; therefore the mixture

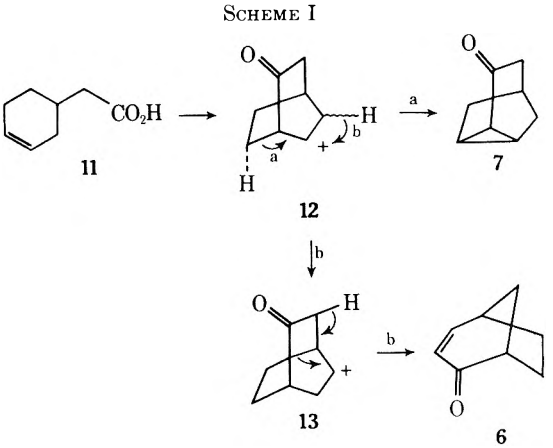

5 6 + 7


7 8 9 10

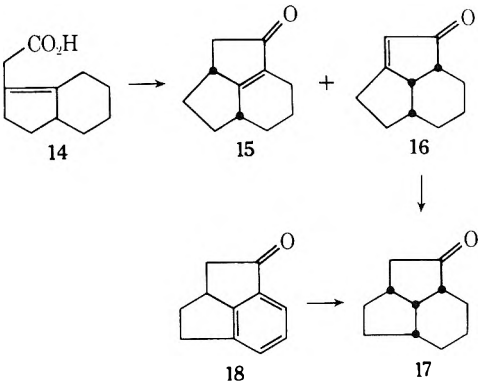
obtained in the cyclodehydration represents a kinetic rather than an equilibrium mixture of ketones.

Ketones **6** and **7** presumably arise *via* isomerization of the starting acid to **11** and cyclization of **11** to yield ion **12**. The latter may yield **7** by loss of a proton (path a), or ion **13** *via* the equivalent of a hydride shift (path b). Formation of **6** from **13** by a Wagner–Meerwein shift and proton loss has ample precedent (Scheme I). These results are essentially the same as those reported recently by Ficini and Maujean,[9] who found that lactone **9** gave **6**, **7**, and a $\beta,\gamma$-unsaturated ketone, **10**.

SCHEME I


11 12 13 6 7

When acid **14** was heated in PPA for 1 hr at 100°, a mixture of ketones **15** and **16** (ratio 85:15, respectively) was obtained in 30% yield. A similar result was obtained when **14** was stirred in methanesulfonic acid–phosphorus pentoxide[10] for 2 days at 25°. The structures of **15** and **16** were established by catalytic hydrogenation of the mixture of $\alpha,\beta$-unsaturated cyclopentenones[11] to yield a single cyclopentanone **17**.


14 15 16 18 17

(1) We thank the National Science Foundation for generous support of this research.

(2) NSF Undergraduate Research Participant, summer, 1969; deceased.

(3) R. L. Cargill and A. M. Foster, *J. Org. Chem.*, **35**, 1971 (1970).

(4) A. C. Cope, A. A. D'Addieco, D. E. Whyte, and S. A. Glickman, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 243.

(5) Having concluded earlier[3] that the position of the double bond in the starting acid is unimportant in these PPA cyclodehydrations, we have not separated double-bond isomers of our olefinic acids.

(6) M. Mousseron, R. Jacquier, and R. Fraisse, *C. R. Acad. Sci.*, **243**, 1880 (1956).

(7) H. L. Goering, R. W. Greiner, and M. F. Sloan, *J. Amer. Chem. Soc.*, **83**, 1391 (1961).

(8) W. R. Moore, W. R. Moser, and J. E. LaPrade, *J. Org. Chem.*, **28**, 2200 (1963). We thank Professor Moore for copies of the ir and nmr spectra of **7**.

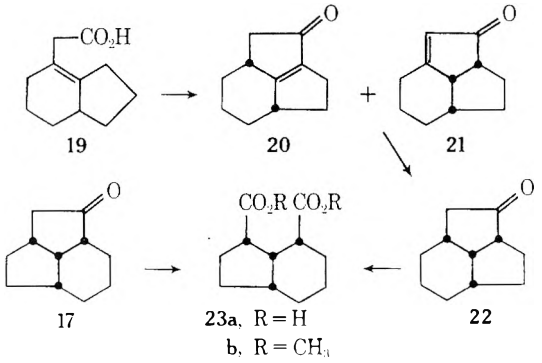
(9) J. Ficini and A. Maujean, *Bull. Soc. Chim. Fr.*, 4395 (1972).

(10) P. E. Eaton and R. H. Mueller, *J. Amer. Chem. Soc.*, **94**, 1014 (1972).

(11) See Experimental Section for spectral data.

The identity of the latter with the saturated ketone obtained from hydrogenation of the strained aromatic ketone **18**[12] confirmed structures **15**, **16**, and **17**.

Cyclization of acid **19** as above again provided a mixture of cyclopentenones[11] for which structures **20** and **21** were assigned. In this case the two new ketones were obtained in almost equal amounts (31% total yield). Catalytic hydrogenation of the mixture of **20** and **21** gave cyclopentanone **22**. Conversion of both **17** and **22** *via* oxidation with nitric acid into diacid **23** es-

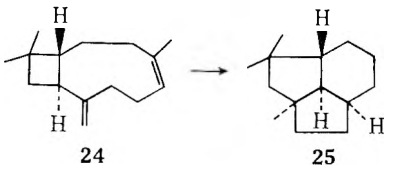



tablished the structural relationship of the two series of tricyclic ketones. The cyclization of both **14** and **19** presumably occur after initial double-bond migration followed by standard acylation processes which need no further elaboration here.

In the mixtures of unsaturated ketones derived from acids **14** and **19** the ratios of trisubstituted *vs.* tetrasubstituted double bonds varied somewhat depending upon the reaction conditions. In each case, the tetrasubstituted isomer may arise directly from deprotonation of the obvious intermediate cation. The trisubstituted isomer must result from isomerization of the initial product(s). If reaction times were sufficiently long, an equilibrium mixture of ketones was produced.

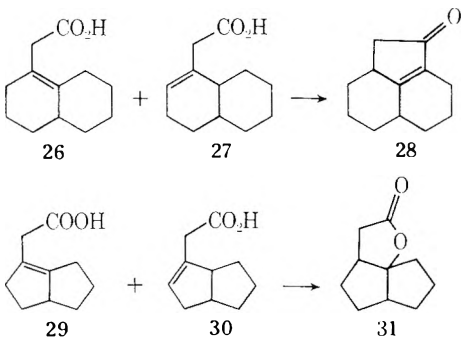
The stereochemical assignments indicated in the structural formulas are based on the reasonable assumption that catalytic hydrogenation of the distorted benzene ring of **18** will occur from the convex face of that molecule, thus providing all-cis **17**. The interrelation of all other tricyclic compounds with **17** confirms that all possess the same relative stereochemistry. Our assumptions were confirmed by a series of lanthanide shift experiments performed with **17**, **22**, and the corresponding alcohols.[13]

The only other known aliphatic tricyclo[6.2.1.$0^{5,11}$]-undecane compound appears to be the product of acid-catalyzed isomerization of isocaryophylene (**24** → **25**). The structure of **25** was determined by X-ray crystallo-




graphic analysis of the corresponding dibromide.[14] In this case, the stereochemistry of **25** reflects the trans ring fusion of the starting material.

Cyclodehydration of the higher and lower homologs of **14** and **19** was carried out with slightly different results. Thus, a mixture of acids **26** and **27** yielded a single cyclopentenone to which structure **28** is assigned, based on spectroscopic analysis[11] and analogy to the previously discussed results. Attempts to cyclodehydrate a mixture of acids **29** and **30** gave only a γ-lactone[11] whose structure is assigned as **31**.




Although the yields of the cyclodehydrations described here are in the 30–40% range, the starting acids are easily prepared; thus the tricyclic systems represented by **17**, **22**, and **28** are now readily available.

## Experimental Section

Melting points were determined on a Büchi apparatus and are uncorrected. Ultraviolet spectra were determined on a Perkin-Elmer Model 202 spectrophotometer, infrared spectra with a Perkin-Elmer Model 337 spectrophotometer, and nmr spectra with a Varian A-60 spectrometer using tetramethylsilane as internal reference. Analyses were performed by Bernhardt Microanalytisches Laboratorium, Elbach über Engelskirchen, West Germany. Mass spectra were determined with a Hitachi Perkin-Elmer RMU-6 spectrometer. An Aerograph Model 1200 Hy-Fi was used for analytical glpc and an Aerograph Model A-90-P3 was used for preparative glpc work.

**Bicyclo[4.3.0]non-6-ene-7-acetonitrile.**—A solution of 13.70 g (0.098 mol) of tetrahydro-1-indanone, 17 g (0.20 mol) of cyanoacetic acid, and 3.85 g (0.05 mol) of dry ammonium acetate in 150 ml of benzene was refluxed for 3 days with removal of water. The mixture was cooled, washed with water, dried ($MgSO_4$), and concentrated at reduced pressure. The residue was then subjected to decarboxylation–distillation to yield two fractions. The first, bp 42–52° (0.8 mm), yielded 4.70 g of the starting ketone, and the second, bp 112° (5.5 mm), yielded 7.12 g (45%) of bicyclo-[4.3.0]non-6-en-7-acetonitrile: ir ($CCl_4$) 2245 $cm^{-1}$; nmr ($CCl_4$) δ 3.0 (s, 2, $-C{=}CCH_2CN$).

*Anal.* Calcd for $C_{11}H_{15}N$: C, 81.93; H, 9.38; N, 8.69. Found: C, 81.83; H, 9.31; N, 8.90.

**Bicyclo[4.3.0]nonene-2-acetonitrile and 4-hydrindanylidine-acetonitrile** were obtained from bicyclo[4.3.0]nonan-2-one according to the general procedure described above in 67% yield: bp 94–96° (0.6 mm); ir ($CCl_4$) 2240 and 2215 $cm^{-1}$; nmr ($CCl_4$) δ 5.70 (br s, 1, $-C{=}CHCN$) and 2.93 (s, 2, $-C{=}CCH_2CN$).

*Anal.* Calcd for $C_{11}H_{15}N$: C, 81.93; H, 9.38; N, 8.69. Found: C, 81.84; H, 9.07; N, 8.90.

**Bicyclo[4.4.0]decene-2-acetonitrile and 1-decalinylideneacetonitrile** were obtained from 1-decalone in 71% yield according to the general procedure described above: bp 106–108° (0.65 mm); ir ($CCl_4$) 2240 and 2210 $cm^{-1}$; mass spectrum (70 eV) *m/e* 175 ($M^+$); glpc (3% SE-30, 8 ft × 0.125 in., 175°, 50 ml/min He) shows two compounds; nmr ($CCl_4$) δ 5.65 (br s, 1, $-C{=}CHCN$), 2.95 (d, 2, $J$ = 1 Hz, $-C{=}CCH_2CN$).

(12) H. Rapoport and J. Z. Parky, *J. Amer. Chem. Soc.*, **78**, 3788 (1956). We thank Professor Henry Rapoport for a sample of the corresponding alcohol.

(13) M. R. Willcott, R. E. Lenkinski, and R. E. Davis, *J. Amer. Chem. Soc.*, **94**, 1742 (1972); R. E. Davis and M. R. Willcott, *ibid.*, **94**, 1744 (1972). These experiments, which were carried out in the laboratory of Professor Willcott, will be reported in detail separately.

(14) K. Gollnick, G. Schade, A. F. Cameron, C. Hannaway, J. S. Roberts, and J. M. Robertson, *Chem. Commun.*, 248 (1970). See also K. Gollnick, G. Schade, A. F. Cameron, C. Hannaway, and J. M. Robertson, *ibid.*, 46 (1971).

*Anal.* Calcd for $C_{12}H_{17}N$: C, 82.28; H, 9.72; N, 8.00. Found: C, 82.17; H, 9.57; N, 7.81.

**Bicyclo[3.3.0]octene-2-acetonitrile and 1-octahydropentalenylidineacetonitrile** were obtained from bicyclo[3.3.0]octan-2-one in 63% yield according to the above procedure: bp 110–114° (5 mm); ir ($CCl_4$) 2260 and 2220 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 5.5 (br s, 1, $-C{=}CHCN$), and 3.0 (br s, 2, $CH_2CN$).

*Anal.* Calcd for $C_{10}H_{13}N$: C, 81.58; H, 8.90; N, 9.52. Found: C, 81.60; H, 8.83; N, 9.43.

**Bicyclo[4.3.0]non-6-ene-7-acetic Acid** (14).—A mixture of 10 g (0.062 mol) of bicyclo[4.3.0]non-6-ene-7-acetonitrile and 100 ml of 30% potassium hydroxide was refluxed overnight. The resulting solution was cooled, washed with pentane, and acidified with 1:1 hydrochloric acid. The resulting cream-colored precipitate was filtered and dried *in vacuo* at 40°. Recrystallization from hexane yielded 6.93 g (62%) of fluffy white crystals (mp 74.1–74.9°) of 14: ir ($CCl_4$) 3200–2500 and 1705 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 3.10 (s, 2, $-C{=}CCH_2CO_2H$) and 10.8 (s, 1, $-CO_2H$).

*Anal.* Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.48; H, 8.90.

**Bicyclo[4.3.0]nonene-2-acetic acid** (19) was obtained from the appropriate mixture of nitriles in 79% yield according to the general procedure described above: mp 66.3–67.2°; ir ($CCl_4$) 3300–2500 and 1700 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 11.4 (s, 1, $-CO_2H$), 2 91 (s, 2, $-C{=}CCH_2CO_2H$).

*Anal.* Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.20; H, 8.72.

**Bicyclo[4.4.0]decene-2-acetic acid** (26) **and bicyclo[4.4.0]dec-2-ene-2-acetic acid** (27) were obtained from the mixture of nitriles in 55% yield according to the general procedure described above: bp 130° (0.30 mm); ir ($CCl_4$) 3300–2500, 1705, and 1645 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 5.45 (m, 1, $HC{=}CCH_2CO_2H$), 2.95 (s, 2, $C{=}C\text{-}CH_2CO_2H$), 2.88 (br s, 2, $C{=}CCH_2CO_2H$), and 11.00 (s, 1, $-CO_2H$). Treatment of the acid mixture with diazomethane gave the methyl esters: glpc (3% SE-30, 8 ft × 0.125 in., 140°, 50 ml/min He) shows two compounds; ir ($CCl_4$) 1740 and 1645 $cm^{-1}$.

*Anal.* Calcd for $C_{12}H_{20}O_2$: C, 75.00; H, 9.62. Found: C, 74.82; H, 9.55.

**Bicyclo[3.3.0]octene-2-acetic acid** (29) **and bicyclo[3.3.0]oct-2-ene-2-acetic acid** (30) were obtained in 70% yield from the nitriles according to the above procedure: bp (bath temperature) 100° (0.02 mm). Treatment of the acids with diazomethane gave the corresponding methyl esters: ir ($CCl_4$) 1735 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 5.25 (br s, 1, $HC{=}CCH_2CO_2CH_3$), 3.55 (s, 3, $-OCH_3$), and 2.90 (br s, 2, $-CH_2CO_2CH_3$).

*Anal.* Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.53; H, 8.72.

**Cyclodehydration of 14.**—A mixture of 2 g (11.2 mmol) of 14 and 40 g of PPA was stirred at 120° for 1 hr, cooled, poured onto ice, and extracted with ether. The ether extracts were combined, washed with aqueous $Na_2CO_3$ and brine, and dried ($MgSO_4$), and the ether was removed under reduced pressure. The residual oil was vacuum distilled [bath temperature 100–150° (0.15 mm)] to yield 0.550 g (30%) of a mixture of 15 and 16, ratio 85:15, respectively.

Preparative glpc (10% Carbowax 1000, 8 ft × 0.25 in., 132°, 300 ml/min He, followed by 10% SE-30, 10 ft × 0.25 in., 172°, 120 ml/min He) gave a pure sample of 15: ir ($CCl_4$) 1710 and 1670 $cm^{-1}$; uv max (95% $C_2H_5OH$) 241 nm ($\epsilon$ 12,150); mass spectrum (70 eV) *m/e* 162 ($M^+$); and 16 slightly contaminated with the major component: ir ($CCl_4$) 3060, 1705, 1670, and 1630 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 5.60 (m, 1, $-CH{=}C-$); uv max (95% $C_2H_5OH$) 241 nm ($\epsilon$ 12,100); mass spectrum (70 eV) *m/e* 162 ($M^+$). Elemental analysis was obtained for the mixture of ketones.

*Anal.* Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.20; H, 8.86.

**Tricyclo[6.2.1.0$^{4,11}$]undec-1(11)-en-2-one** (20) **and tricyclo-[6.2.1.0$^{4,11}$]undec-3-en-2-one** (21) were obtained in 31% yield from 19, ratio 5:3 (nmr), respectively, by the above procedure: bp (bath temperature) 115–135° (0.37 mm). Preparative separation of 20 and 21 was not practical. Therefore, spectral data were obtained for the mixture: ir ($CCl_4$) 1700, 1655, and 1620 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 5.80 (br s, 1, $C{=}CH$); uv max (95% $C_2H_5OH$) 241 nm ($\epsilon$ 13,100); mass spectrum (70 eV) *m/e* 162 ($M^+$). Elemental analysis was obtained for the mixture of ketones.

*Anal.* Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.46; H, 8.70.

**Tricyclo[7.2.1.0$^{5,12}$]dodec-9(12)-en-10-one** (28) was obtained in 38% yield from a mixture of 26 and 27 by the procedure described above: bp (bath temperature) 115–130° (0.13 mm); ir ($CCl_4$) 1700 and 1650 $cm^{-1}$; glpc (10% Carbowax 1000, 6 ft × 0.125 in., 160°, 50 ml/min He) shows a single peak; mass spectrum (70 eV) *m/e* 176 ($M^+$); uv max (95% $C_2H_5OH$) 241 nm ($\epsilon$ 13,600).

*Anal.* Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.78; H, 9.00.

**Lactone 31** was obtained in 70% yield from a mixture of 29 and 30 as described above: bp (bath temperature) 130° (0.2 mm); ir ($CCl_4$) 1770 $cm^{-1}$; mass spectrum (70 eV) *m/e* 166 ($M^+$).

*Anal.* Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.18; H, 8.44.

**Bicyclo[3.2.1]oct-3-en-2-one** (6) **and tricyclo[3.2.1.0$^{2,7}$]octan-3-one** (7) were obtained in 34% yield, ratio 2:1, respectively, according to the above procedure from acid 5: bp (bath temperature) 80° (0.5 mm). Separation of the two compounds was accomplished by preparative glpc (20% DEGS, 5 ft × 0.25 in., 145°, 100 ml/min). The major component was identified as bicyclo[3.2.1]oct-3-en-2-one (6): ir ($CCl_4$) 3025 and 1690 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 7.07 (m, 1, $-CH{=}CHC{=}O$) and 5.62 (d, 1, $J$ = 9 Hz, $-CH{=}CHC{=}O$); uv max (95% $C_2H_5OH$) 230 nm ($\epsilon$ 10,000). The minor component was identified as tricyclo[3.2.1.0$^{2,7}$]octan-3-one (7), ir ($CCl_4$) 3040 and 1700 $cm^{-1}$.

**Ketones 6 and 7** were obtained in 11% yield, ratio 2:1, respectively, according to the above procedure from acid 8.

**Hydrogenation of 15 and 16.**—A mixture of 0.600 g (37 mmol) of 15 and 16 was hydrogenated over 10% Pd/C at 50 psi in methanol to yield 0.590 g (95%) of 17. The crude product was sublimed (bath temperature 60°, 0.1 mm) to give white crystals (mp 55.5–58.2°): ir ($CCl_4$) 1740 $cm^{-1}$; mass spectrum (70 eV) *m/e* 164 ($M^+$).

*Anal.* Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.07; H, 9.55.

**Tricyclo[6.2.1.0$^{4,11}$]undecan-2-one** (22) was obtained in quantitative yield from a mixture of 20 and 21 according to the above procedure: bp (bath temperature) 95° (0.15 mm); ir ($CCl_4$) 1730 $cm^{-1}$; mass spectrum (70 eV) *m/e* 164 ($M^+$).

*Anal.* Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.26; H, 9.94.

**Oxidation of 22.**—A solution of 35 mg (0.21 mmol) of 22, 10 ml of 1:1 nitric acid, and 20 mg of vanadium pentoxide was heated at 70° until the brown fumes disappeared. The solution was cooled and extracted with ether; the combined ether extracts were dried ($MgSO_4$); and the ether was removed under reduced pressure. Esterification of the product with diazomethane gave a yellow oil which was vacuum distilled (bath temperature 85°, 0.3 mm) to yield 20 mg (36%) of 23b: ir ($CCl_4$) 1730 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 3.58( s, 3, $-OCH_3$), 3.47 (s, 3, $-OCH_3$); mass spectrum (70 eV) *m/e* 240 ($M^+$); glpc (10% Carbowax 1000, 6 ft × 0.125 in., 160°, 50 ml/min He) shows a single peak.

*Anal.* Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.66; H, 8.21.

**Oxidation of 17.**—Oxidation of 35 mg of 17 as above, followed by esterification and distillation, gave 18 mg (33%) of ester 23b. The two samples were shown to be identical by glpc and by comparison of ir and nmr spectra.

**Reduction of 28.**—A mixture of 0.425 g (2.4 mmol) of 28, 50 ml of liquid ammonia, and 0.252 g (36 mg-atoms) of lithium was refluxed for 1.5 hr. Ammonium chloride, then water, was added and the excess ammonia was removed. The aqueous layer was extracted with ether, the combined ether extracts were dried ($MgSO_4$), and the ether was removed under reduced pressure. The pure saturated ketone, tricyclo[7.2.1.0$^{5,12}$]dodecan-10-one, was isolated by column chromatography on neutral alumina using a mixture of hexane and benzene (2:1) as the eluting solvent: ir ($CCl_4$) 1745 $cm^{-1}$; mass spectrum (70 eV) *m/e* 178 ($M^+$); glpc (10% Carbowax 1000, 6 ft × 0.125 in., 165°, 50 ml/min He) shows a single peak.

*Anal.* Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.67; H, 10.01.

**Reduction of 17.**—To a suspension of 77 mg (2 mmol) of lithium aluminum hydride in 50 ml of dry ether was added 600 mg (27.4 mmol) of 17. After the mixture had been stirred for 2 hr, a solution of 15% potassium hydroxide was added dropwise. The resulting white precipitate was filtered, the ether was removed under reduced pressure, and the residual semisolid was distilled onto a cold finger (bath temperature 100°, 0.45 mm) to give 0.530 g (88%) of tricyclo[6.2.1.0$^{4,11}$]undecan-3-ol: ir ($CCl_4$) 3590 and 3350 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 4.0 (m, 1, HOCH) and 3.40 (s, 1, HOCH); mass spectrum (70 eV) no $M^+$, peak at *m/e* 148 indicates loss of water from parent ion.

*Anal.* Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.27; H, 10.81.

Tricyclo[6.2.1.$0^{4,11}$]undecan-2-ol was obtained from **22** in 89% yield according to the above procedure: mp 97.1–98°; ir ($CCl_4$) 3590 and 3430 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 4.32 (m, 1, –CHOH) and 1.72 (br s, 1, –OH); mass spectrum (70 eV) no $M^+$, *m/e* 148 results from loss of $H_2O$ from parent.

*Anal.* Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.71; H, 10.69.

Tricyclo[7.2.1.$0^{5,12}$]dodecan-10-ol was obtained as an oil in quantitative yield from tricyclo[7.2.1.$0^{5,12}$]dodecan-10-one by the above procedure: bp (bath temperature) 80° (0.3 mm); ir ($CCl_4$) 3590 and 3350 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 3.70 (m, 1, –CHOH) and 2.90 (br s, 1, –OH); glpc (10% Carbowax 1000, 6 ft × 0.125 in., 160°, 50 ml/min He) shows a single peak; mass spectrum (70 eV) *m/e* 180 ($M^+$).

*Anal.* Calcd for $C_{12}H_{20}O$: C, 79 94; H, 11.18. Found: C, 79.90; H, 11.04.

**Registry No.**—**5**, 18294-87-6; **6**, 3212-77-9; **7**, 39163-38-7; **8**, 41894-76-2; **14**, 41894-77-3; **15**, 41915-67-7; **16**, 41915-68-8; **17**, 41915-69-9; **19**, 41894-78-4; **20**, 41915-70-2; **21**, 41915-71-3; **22**, 41915-72-4; **23b**, 41915-73-5; **26**, 41894-79-5; **26** methyl ester, 41894-80-8; **27**, 41894-81-9; **27** methyl ester, 41894-82-0; **28**, 41894-83-1; **29**, 41894-84-2; **29** methyl ester, 41894-85-3; **30**, 41894-86-4; **30** methyl ester, 41894-87-5; **31**, 41894-88-6; bicyclo[4.3.0]non-6-ene-7-acetonitrile, 41894-89-7; tetrahydro-1-indanone, 22118-00-9; cyanoacetic acid, 372-09-8; bicyclo[4.3.0]nonene-2-acetonitrile, 41894-91-1; 4-hydrinanylidineacetonitrile, 41894-92-2; bicyclo[4.3.0]nonan-2-one, 5686-83-9; bicyclo[4.4.0]decene-2-acetonitrile, 41894-94-4; 1-decalinylidineacetonitrile, 41894-95-5; 1-decalone, 4832-16-0; bicyclo[3.3.0]-octene-2-acetonitrile, 41894-96-6; 1-octahydropentalenylideneacetonitrile, 41894-97-7; bicyclo[3.3.0]octan-2-one, 28569-63-3; tricyclo[7.2.1.$0^{5,12}$]dodecan-10-one, 41894-98-8; tricyclo[6.2.1.-$0^{4,11}$]undecan-3-ol, 41894-99-9; tricyclo[6.2.1.$0^{4,11}$]undecan-2-ol, 41895-00-5; tricyclo[7.2.1.$0^{5,12}$]dodecan-10-ol, 41895-01-6.

# Thermal Cyclization of Substituted Aryl Propargyl Ethers. The Scope and Regioselectivity of the Reaction in the Synthesis of Substituted 3-Chromenes[1]

WAYNE K. ANDERSON* AND EDMOND J. LAVOIE

*Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14214*

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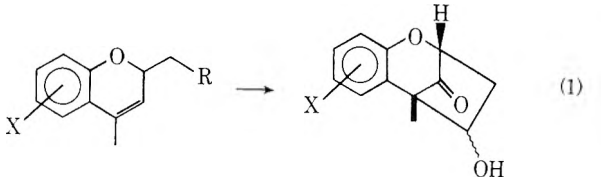
The thermal cyclization of substituted aryl propargyl ethers was examined. Simple 3-aryloxypropynes (**12**, **15a–c**) were cyclized to the corresponding chromenes in ~60% yield. The cyclization of **12** was not regiospecific and two isomeric chromenes (**13** and **14**) were obtained. The thermal cyclizations of C-1 and/or C-3 methyl-substituted 3-aryloxypropynes (**16d–g**) have been shown to proceed in a much higher yield than the corresponding unsubstituted compounds. The influence of water, reaction temperature, and solvent on the cyclization was also studied.

During the course of our research directed toward the synthesis of trichothecan mycotoxins and simpler analogs for antitumor evaluation, we required a simple yet flexible method for the synthesis of chromene precursors. Specifically, we required an efficient synthesis of 2,4-disubstituted chromenes (*cf.* eq 1) which




(1)

could incorporate a variety of substituents in the aromatic ring.

A variety of standard methods for the preparation of 3-chromenes have been described in the literature.[2] More recently, new methods have been developed; some of these newer methods include the reaction of vinylphosphonium salts with *o*-hydroxybenzaldehyde,[3] the oxidative cyclization of *o*-allyl phenols,[4] and the partial reduction of a coumarin followed by alkylation and cyclization.[5] None of these methods, however, appear to be broadly applicable and many suffer from the disadvantage of low yields, difficult and/or expensive reagents, and long procedures or difficult work-up.

The thermal cyclization of aryl propargyl ethers has been reported to yield chromenes and related compounds.[6–8] The general utility and scope of a variety of thermal reactions in organic synthesis (*e.g.*, Diels–Alder reaction, Claisen rearrangement, Cope rearrangement, etc.) prompted us to further examine this method for the synthesis of chromenes.

The Claisen rearrangement of propargyl ethers has been reported in both aromatic and nonaromatic systems.[9] Thermal cyclization of aryl propargyl ethers has been used to prepare naphtho[2,1-*b*]- and -[1,2-*b*]-pyrans,[6] pyranoflavones,[7d] pyranocoumarins,[7d,g] pyranoacridones,[7e] chromenes,[7] pyrano[3,2-*d*]pyrimidines,[8a] and furo[3,2-*d*]pyrimidines.[8a]

The mechanism of the thermal cyclization of aryl propargyl ethers has been studied by Zsindely and Schmid.[8b] The proposed mechanism (Scheme I) involves an initial Claisen rearrangement of the aryl propargyl ether **1** to give the allene intermediate **2**. Enolization of **2** followed by a [1,5] sigmatropic hydrogen shift would give **4**, which can undergo an electrocyclic reaction to give 3-chromene (**5**).[8b]

Otter, *et al.*, have proposed a similar mechanism (Scheme II) for the cyclization of uracil propargyl

(1) This research was supported by Grant 1 R01 CA 11880 from the National Cancer Institute, National Institutes of Health.

(2) (a) S. Wawzonek in "Heterocyclic Compounds," Vol. 2, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1951, pp 277–342; (b) F. M. Dean, "Naturally Occurring Oxygen Ring Compounds," Butterworths, London, 1963, pp 220–250.

(3) E. E. Schweizer, A. T. Wehman, and D. M. Nycz, *J. Org. Chem.*, **38**, 1583 (1973), and references cited therein.

(4) G. Cardill, R. Cricchio, and L. Merlino, *Tetrahedron*, **27**, 1875 (1971).

(5) C. E. Cook and C. E. Twine, Jr., *Chem. Commun.*, 791 (1968).

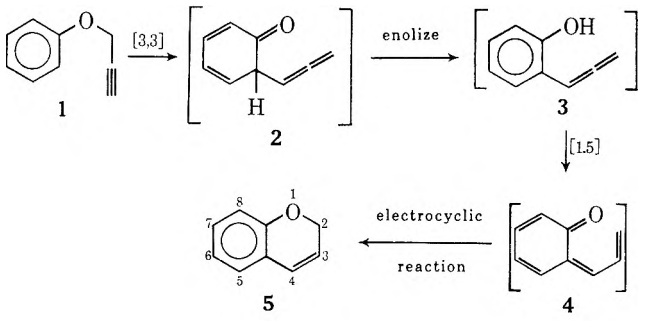
(6) I. Iwai and J. Ide, *Chem. Pharm. Bull.*, **10**, 926 (1962).

(7) (a) K. C. Majumdar and B. S. Thyagarajan, *J. Heterocycl. Chem.*, **9**, 489 (1972); (b) B. S. Thyagarajan, K. K. Balsubramanian, and R. Bhima Rao, *Tetrahedron*, **23**, 1893 (1967); (c) *Tetrahedron Lett.*, 1393 (1963); (d) J. Hlubucek, E. Ritchie, and W. C. Taylor, *Aust. J. Chem.*, **24**, 2347 (1971); (e) J. Hlubucek, E. Ritchie, and W. C. Taylor, *ibid.*, **23**, 1881 (1970); (f) I. Iwai and J. Ide, *Chem. Pharm. Bull.*, **11**, 1042 (1963); (g) J. Nickl, *Chem. Ber.*, **91**, 1371 (1958).

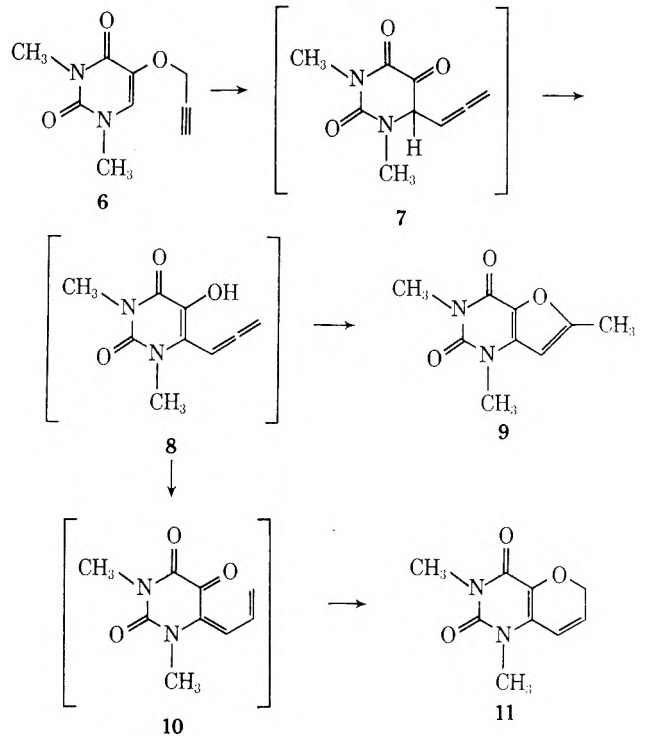
(8) (a) B. A. Otter, S. S. Saluja, and J. J. Fox, *J. Org. Chem.*, **37**, 2858 (1972); (b) J. Zsindely and H. Schmid, *Helv. Chim. Acta*, **51**, 1510 (1968).

(9) A. Jefferson and F. Scheinmann, *Quart. Rev., Chem. Soc.*, **22**, 391 (1968).

SCHEME I




SCHEME II




ethers (*e.g.*, **6**).[8a] In this case, however, both pyrimidopyrans (**11**) and furans (**9**) were formed. The greater electron-withdrawing effect of the uracil, as compared to the phenyl ring, was cited as a possible reason for the formation of the furo[3,2-*d*]pyrimidine (**9**). The electron-withdrawing effect of the uracil ring would make the central allenic carbon in **8** relatively electron deficient (compared to **3**) and hence more susceptible to nucleophilic attack of the enolic hydroxyl to give the furo compound (**9**).[8a] It should be noted that no benzofuran products have been reported from the thermal cyclization of phenyl propargyl ethers.[10]

Steric and electronic effects also appear to play a prominent role in the cyclization of aryl propargyl ethers (**1**) to 3-chromenes (**5**). In this regard aryl phenylpropargyl ethers[6,7f] and aryl 2,2-dimethylpropargyl ethers[7d,e] can be cyclized to the corresponding 4-phenyl-3-chromenes and 2,2-dimethyl-3-chromenes in yields superior to those obtained from simple aryl propargyl ethers.

(10) (a) Small quantities of benzofurans have been isolated in the red mercuric oxide–glacial acetic acid–sulfuric acid cyclization of phenyl propargyl ethers.[8a] The formation of benzo[*b*]thiophenes has been noted in the thermal cyclization of phenyl propargyl sulfides.[10b] (b) H. Kwart and T. J. George, *Chem. Commun.*, 433 (1970). (c) See also ref 9b and 10d. (d) R. Gaertner, *J. Amer. Chem. Soc.*, **73**, 4400 (1951).

With meta-substituted aryl propargyl ethers, cyclization is reported to occur regioselectively para to the substituent[7d,f] and electron-donating meta substituents have been reported to increase the yield of chromenes in the cyclization reaction.[7f,11]

The reported[7f] low yield for the syntheses of **13** (12.5% from **12**), **16a** (11.9% from **15a**), and **16b** (30% from **15b**) initially prompted us to repeat these experiments in an attempt to improve the yield to a point where this cyclization would become a synthetically useful reaction. The reactions were repeated as described in the literature, with the exception that they were carried out under a nitrogen atmosphere. The isolated yield of chromenes was in the range of 50–60%[12] (Table I). Furthermore, the cyclization of **12**

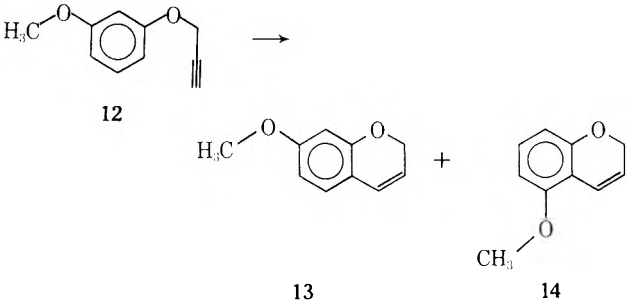
TABLE I

YIELDS OF SUBSTITUTED 3-CHROMENES (16) FROM SUBSTITUTED ARYL PROPARGYL ETHERS (15)

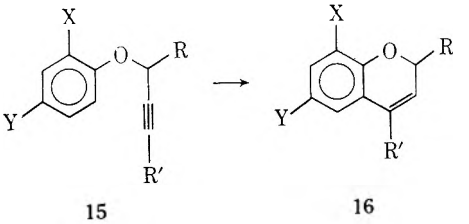
| Compd | X (C-8) | Y (C-6) | R (C-2) | R′ (C-4) | Yield, % |
|---|---|---|---|---|---|
| **16a**[a] | H | $OCH_3$ | H | H | 60 |
| **16b**[a] | $OCH_3$ | H | H | H | 58 |
| **16c**[b] | $COCH_3$ | H | H | H | 65 |
| **16d**[c] | H | $OCH_3$ | H | $CH_3$ | 88 |
| **16e**[b] | $OCH_3$ | H | H | $CH_3$ | 83 |
| **16f**[b] | H | $OCH_3$ | $CH_3$ | H | 90 |
| **16g**[b] | H | $OCH_3$ | $CH_3$ | $CH_3$ | 90 |

[a] See ref 7f. [b] Satisfactory combustion analytical data (±0.4%) were reported: Ed. [c] J. Colonge and A. Guyot, *Bull. Soc. Chim. Fr.*, 325 (1958).

led to the formation of *two* isomeric chromenes, **13** and **14**, in a ratio of approximately 46:54. This is in contrast with previous reports, wherein only **13** was reported as a product in the thermal cyclization of **12**.




In an effort to rationalize the discrepancy between our yields and the reported literature values we examined the effect of water added to the reaction mixture. In this regard *N*,*N*-diethylaniline was thoroughly dried and distilled immediately prior to its use in the reaction. The cyclization of **15a** (2.0 g) was




(11) Electronic effects have also been observed in the Claisen rearrangement of phenylallyl ethers; see ref 8b and 9 and references cited therein.

(12) The cyclization of **15a** was repeated in the absence of nitrogen and gave only slightly lower yield (43%).

carried out under anhydrous conditions and, in separate experiments, with 0.05 and 0.5 ml of water added to the *N,N*-diethylaniline (10 ml). The isolated yields of pure **16a** were 48, 54, and 39%, respectively.

The cyclization of **15a** (2.0 g) was also conducted in anhydrous *p*-diisopropylbenzene (10 ml) at 210–215°[13] and in *p*-diisopropylbenzene with 0.05, 0.25, and 1.0 ml of added water. The isolated yields of pure **16a** were 34, 44, 46, and 27%, respectively.

The effect of water on the cyclization thus appears to be minimal (in the case of either *N,N*-diethylaniline or *p*-diisopropylbenzene). A trace of water appears to facilitate the reaction somewhat. The most critical factor appears to be the reaction temperature. A *constant* bath temperature of 210–215° currently has proven most successful.

The yield of **16** is markedly increased in the cyclization of aryl propargyl ethers where the propargyl moiety is substituted (**15d–g**). These results are consistent with those of Hlubucek, *et al.*,[7d,e] where it was found that 2,2-dimethylchromenes were formed in high yield from the corresponding aryl propargyl ether.

The reasons for the increased yield in the cyclization of **15d–g** are not clear. It would seem unlikely that the methyl substituent(s) would have any reaction-promoting effect on the initial Claisen rearrangement or the subsequent enolization step. If subsequent steps are irreversible and non-rate-limiting the reactivity of either **3** or **4** should be of no consequence to the yield of **5** except as they allow escape from this reaction pathway to form different products.

Increased substitution on the propargyl moiety of **1** could stabilize the s-cis conformation of **4** (*i.e.*, destabilize the s-trans conformation *via* steric interactions) necessary for the final electrocyclic reaction (Scheme I). In this manner a smaller population of **4** in the s-trans conformation could result in fewer side reactions deriving from that non-product-yielding conformation.

Increased methyl substitution could also render the aryl propargyl ether (**1**) or the product chromene (**5**) more stable. In this regard a terminal acetylene, *e.g.*, **16f**, might be expected to exhibit a greater propensity toward polymerization than a less reactive nonterminal acetylene, *e.g.*, **16g**; however, both **16f** and **16g** afforded high yields (90%) of the respective chromenes under identical conditions. Thus the presence or absence of a terminal acetylene cannot be a major determinant of yield insofar as starting material stability is concerned. Similarly, the stability of the product chromenes does not appear to be significantly affected by increased methyl substitution.

If, on the other hand, the Claisen rearrangement or the subsequent enolization step is not rate limiting, then the reactivity of the allene intermediate, **3**, becomes a major determinant. The reactivity of allenes toward central attack by free radicals, nucleophiles, and electrophiles is known to increase with increasing methyl substitution on the allene moiety.[14] While the precise steric and electronic requirements for the hydrogen shift are not known, it would not be unreasonable to presume that this reaction would also be enhanced by increased methyl substitution on the allenic intermediate, **3**.

The thermal cyclization of substituted aromatic propargyl ethers to 3-chromenes can incorporate a variety of substituents at every position except C-3. Highest yields in this cyclization are achieved when the propynyl moiety is monosubstituted either at C-1 or C-3, disubstituted at C-3, and monsubstituted at both C-1 and C-3. The ready availability of a variety of phenols and propargyl halides makes this method a very attractive approach for the synthesis of a great variety of substituted 3-chromenes.

Iwai and Ide have reported that a resonance electron-donating meta substituent facilitated the cyclization of aryl proparyl ethers to 3-chromenes.[7f] In our work it is interesting to note the slightly higher yield obtained in the cyclization of **15c** (*p*-$COCH_3$ substituent) compared to **15b** (*p*-$OCH_3$ substituent). It should be noted that per cent yield cannot justify statements regarding reaction mechanisms, since the yield depends upon many factors including product stability and isolation. Furthermore, one cannot exclude, *a priori*, the possibility that various substituents simply retard competing decomposition reactions.

Further work is in progress to elucidate the effects of electron-donating and electron-withdrawing substituents on the aromatic ring and to study factors which influence the regioselectivity in the reaction.

## Experimental Section

Nmr spectra were determined in $CCl_4$ solution (containing *ca.* 1% TMS as an internal standard) on a Varian T-60 spectrometer; peak positions of multiple signals were confirmed by spin–spin decoupling. Infrared spectra were determined neat using a Perkin-Elmer Model 237 spectrophotometer. The uv data were determined in 95% ethanol solution on a Beckman DB-G grating spectrophotometer. The purity of analytical and spectral samples was confirmed by glc (Varian Aerograph Model 90-P with a thermal conductivity detector) using a 12-ft 30% NPGA column. Elemental analysis were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

**General Procedure for Preparation of Aromatic Propargyl Ethers *via* Direct Williamson Etherification (Method A).**—A mixture of the appropriate phenol (1.0 mol), the acetylenic halide (0.9 mol), and anhydrous $K_2CO_3$ (1.2 mol) in 400 ml of reagent-grade acetone was heated under reflux with vigorous stirring. The cooled mixture was filtered, and the inorganic residue was dissolved in $H_2O$ (500 ml) and extracted with ether (2 × 50 ml). The filtrate was concentrated *in vacuo* and the residue was dissolved in ether (350 ml). The combined ethereal solution was washed with 5% NaOH solution (until pH of the ethereal layer gave a neutral reaction to moist pH paper), then $H_2O$ (200 ml). The ether solution was dried (anhydrous $Na_2SO_4$) and concentrated *in vacuo*. The residue was distilled under vacuum (see Table II).

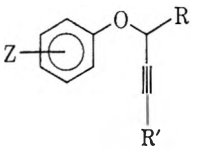
**General Procedure for Preparation of Aromatic Propargyl Ethers *via* Alkylation of the Terminal Acetylene (Method B).**—The appropriate acetylenic ether (0.1 mol) was added over a period of 10 min to a magnetically stirred suspension of $NaNH_2$ (0.1 mol) in liquid $NH_3$ (*ca.* 100 ml). The reaction mixture was stirred for 1 hr before methyl iodide (0.1 mol) was added over a period of 0.5 hr under an argon atmosphere (the argon was bubbled into the reaction mixture through a dispersion tube). The reaction mixture was cooled with a Dry Ice–acetone bath and let stand overnight. The residue was poured onto crushed ice (200 g) and extracted with ether (2 × 125 ml). The ethereal layer was washed with a saturated $NH_4Cl$ solution and dried (anhydrous $MgSO_4$). The ethereal solution was concentrated *in vacuo* and the residue was vacuum distilled (see Table II).

(13) (a) At a temperature of 178–180° **15a** decomposed (polymerization) and no cyclized product was obtained. This is consistent with the results of Powell and Adams,[13b] who were unable to cyclize phenyl propargyl ether or *p*-bromophenyl propargyl ether in refluxing diisoamyl ether (bp 170°). (b) S. G. Powell and R. Adams, *J. Amer. Chem. Soc.*, **42**, 646 (1920).

(14) M. C. Casserio in "Selective Organic Transformations," Vol. 1, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N. Y., 1970, pp 239–299.

TABLE II

PREPARATION OF SUBSTITUTED ARYL PROPARGYL ETHERS 12 AND 15



| Compd | Z | R | R′ | Bp, °C (mm) | Yield,[a] % | Reaction time, hr |
|---|---|---|---|---|---|---|
| 12[b] | *m*-$OCH_3$ | H | H | 86–87 (1.0) | 83 (A) | 17.5 |
| 15a[b] | *p*-$OCH_3$ | H | H | 82.5–83 (0.6) | 89 (A) | 13 |
| 15b[b] | *o*-$OCH_3$ | H | H | 83 (0.8) | 84 (A) | 20.5 |
| 15c[c] | *o*-$COCH_3$ | H | H | 96 (0.7) | 76 (A) | 15 |
| 15d[d] | *p*-$OCH_3$ | H | $CH_3$ | 104 (0.9) | 73 (A) | 14 |
| 15d | *p*-$OCH_3$ | H | $CH_3$ | 97.5–98 (0.8) | 92 (B)[e] | |
| 15e[c] | *o*-$OCH_3$ | H | $CH_3$ | 126 (3.5) | 77 (B)[e] | |
| 15f[c] | *p*-$OCH_3$ | $CH_3$ | H | 93 (1.5) | 67.2 (A) | 15[f] |
| 15g[c] | *p*-$OCH_3$ | $CH_3$ | $CH_3$ | 77.5 (0.1) | 75.1 (B)[e] | |

[a] A or B in parentheses following the yield refers to method A or method B. [b] See ref 7f. [c] Satisfactory combustion analytical data (±0.4% for C, H) were provided: Ed. [d] W. N. White and B. E. Norcross, *J. Amer. Chem. Soc.*, **83**, 1968 (1961). [e] Unreacted terminal acetylene was removed with 5% ethanolic silver nitrate. [f] The reaction stood for 24 hr at room temperature prior to the 15 hr of heating.

**General Procedure for Preparation of 3-Chromenes *via* Aromatic Propargyl Ethers.**—A solution of the appropriate phenyl propargyl ether in *N*,*N*-diethylamine (distilled; 5 ml/g of phenyl propargyl ether) was heated to 210–215° under a nitrogen atmosphere without stirring. The *N*,*N*-diethylaniline was removed by distillation under a 1-mm vacuum, and further distillation under high vacuum yielded the desired chromenes (in the final stages of the distillation the bath temperature was increased *ca.* 80° above the boiling point of the chromene in order to remove last traces of product from the polymeric pot residue). Reported yields are based upon reaction with at least 5.0 g of starting acetylene.

**7-Methoxy-Δ³-chromene (13) and 5-methoxy-Δ³-chromene (14)** had 15-hr reaction time; 51% yield; bp 86–87° (1.0 mm); the isomeric mixture was separated by preparative glc (30% NPGA, 12 ft × 0.375 in. column at 190° with 35-μl injections) to yield **13** and **14** with retention times of 32.5 and 27.5 min, respectively.

**7-Methoxy-Δ³-chromene (13)** had ir 1271 (m), 1026 (m), 981 (s), and 758 $cm^{-1}$; uv max 226 nm (ε 17800), 286 (6640), and 306 (5750); nmr δ 3.67 (s, 3), 4.65 (d of d, 2, $J_{2,4}$ = 1.7, $J_{2,3}$ = 3.3 Hz), 5.52 (pair of t, 1, $J_{3,4}$ = 9.5 Hz), 6.28 (pair of t, 1), and 6.16–6.82 (m, 3). *Anal.* Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.22. Found: C, 74.17; H, 6.29.

**5-Methoxy-Δ³-chromene (14)** had ir 1059 (m), 1014 (m), 885 (w), 763 (m), 740 (s), and 680 $cm^{-1}$ (w); uv max 232 nm (ε 16,900) and 282 (6790); nmr δ 3.72 (s, 3), 4.63 (d of d, 2, $J_{2,4}$ = 1.7, $J_{2,3}$ = 3.3 Hz), 5.58 (pair of t, 1, $J_{3,4}$ = 9.5 Hz), 6.65 (pair of t, 1), and 6.14–7.04 (m, 3).

*Anal.* Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.22. Found: C, 73.67; H, 6.19.

**6-Methoxy-Δ³-chromene (16a)** had 15-hr reaction time; 60.1% yield; bp 72–72.5° (0.18 mm); ir 1047 (s), 1035 (s), 811 (m), 754 (m), 709 (m), and 686 $cm^{-1}$ (m); uv max 241 nm (ε 9920), 269 (2025), and 333 (3910); nmr δ 3.72 (s, 3), 4.71 (q, 2, $J_{2,4}$ = 1.7, $J_{2,3}$ = 3.5 Hz), 5.73 (pair of t, 1, $J_{3,4}$ = 10 Hz), 6.44 (pair of t, 1), and 6.36–6.65 (m, 3).

**8-Methoxy-Δ³-chromene (16b)** had 15-hr reaction time; 58.3% yield; bp 68° (0.1 mm); ir 1037 (m), 1020 (m), 794 (m), 766 (m), and 686 $cm^{-1}$ (m); uv max 228 nm (ε 16,000), 273 (5030), 280 (4800), and 310 (803); nmr δ 3.77 (s, 3), 4.77 (d of d, 2, $J_{2,4}$ = 2, $J_{2,3}$ = 3 Hz), 5.71 (pair of t, 1, $J_{3,4}$ = 10 Hz), 6.34 (pair of t, 1), and 6.20–6.90 (m, 3).

**8-Aceto-Δ³-chromene (16c)** had 15-hr reaction time; 64.6% yield; bp 102° (0.6 mm); ir 1675 (s), 1053 (m), 814 (m), 752 (m), and 706 $cm^{-1}$ (m); uv max 245 nm (ε 10,350) and 334 (3190); nmr δ 2.52 (s, 3), 4.90 (d of d, 2, $J_{2,4}$ = 1.9, $J_{2,3}$ = 3.6 Hz), 5.78 (pair of t, 1, $J_{3,4}$ = 10 Hz), 6.43 (pair of t, 1), 6.67–7.16 (m, 2), and 7.54 (pair of d, 1).

**4-Methyl-6-methoxy-Δ³-chromene (16d)** had 24.5-hr reaction time; 88% yield; bp 112.5° (2.2 mm); ir 1054 (m), 1008 (m), 824 (w), 799 (m), 774 (w), 732 (w), 705 (m), and 693 $cm^{-1}$ (w); uv max 224 nm (ε 4020), 242 (6500), 266 (1400), and 331 (3440); nmr δ 2.00 (d of d, 3, $J_{4',3}$ = 1.8, $J_{4',2}$ = 1.3 Hz), 3.75 (s, 3), 4.63 (m, 2), 5.53 (m, 1), and 6.62 (s, 3).

**4-Methyl-8-methoxy-Δ³-chromene (16e)** had 24.5-hr reaction time; 83.0% yield; bp 114.5° (1.1 mm); ir 1038 (m), 1000 (m), 861 (m), 800 (m), 773 (w), 731 (m), and 661 $cm^{-1}$ (w); uv max 236 nm (ε 7850), 276 (4910), and 316 (1680); nmr δ 1.98 (d of d, 3, $J_{4',3}$ = 2.0, $J_{4',2}$ = 1.4 Hz), 3.78 (s, 3), 4.61–4.81 (m, 2) 5.37–5.67 (m, 1), and 6.76 (s, 3).

**2-Methyl-6-methoxy-Δ³-chromene (16f)** had 12-hr reaction time; 89.5% yield; bp 86° (0.9 mm); ir 1050 (s), 871 (m), 851 (w), 817 (m), and 711 $cm^{-1}$ (w); uv max 238 nm (ε 6270), 265 (1860), and 332 (2560); nmr δ 1.46 (d, 3, $J_{2',2}$ = 6.4 Hz), 3.77 (s, 3, 4.70–5.14 (m, 1), 5.67 (d of d, 1, $J_{3,4}$ = 9.6, $J_{3,2}$ = 3.0 Hz), 6.34 (d, 1), 6.50 (s, 1), and 6.67 (d, 2).

**2,4-Dimethyl-6-methoxy-Δ³-chromene (16g)** had 12-hr reaction time; 89.8% yield; bp 97° (1.1 mm); ir 1042 (s), 1031 (m), 852 (m), 811 (m), 769, and 690 $cm^{-1}$ (m); uv max 239 nm (ε 10,580, 268 (2830), and 332 (3850); nmr δ 1.36 (d, 3, $J_{2',2}$ = 6.8 Hz), 2.00 (apparent t, 3), 3.73 (s, 3), 4.60–5.0 (m, 1), 5.40–5.57 (m, 1), and 6.66 (s, 3).

**Registry No.**—**12**, 41580-72-7; **13**, 18385-89-2; **14**, 41580-69-2; **15a**, 17061-86-8; **15b**, 41580-71-6; **15c**, 41580-73-8; **15d**, 41580-74-9; **15e**, 41580-75-0; **15f**, 33143-82-7; **15g**, 41580-77-2; **16a**, 18385-84-7; **16b**, 16336-25-7; **16c**, 41580-80-7; **16d**, 41580-81-8; **16e**, 41580-65-8; **16f**, 33143-98-5; **16g**, 41580-67-0.

# Cycloadditions of Dienes to Fulvenes[1]

K. N. HOUK*[2a] AND L. J. LUSKUS[2b]

*Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803*

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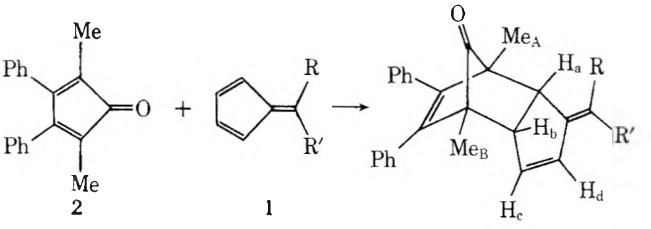
The cycloaddition reactions of 6,6-dimethyl- (**1a**), 6,6-diphenyl- (**1b**), 6-methyl-6-phenyl- (**1c**), 6-methyl- (**1e**), 6-phenyl- (**1g**), 6,6-tetramethylene- (**1i**), 6,6-di-*p*-anisyl- (**1j**), and 6,6-dicyclopropyl- (**1k**) fulvenes with 2,5-dimethyl-3,4-diphenylcyclopentadienone (**2**), cyclopentadiene, $\alpha$-pyrone, and 2,4-cycloheptadienone are reported. In each reaction only Diels–Alder adducts with fulvene as dienophile were isolated. The regioselectivity observed with the unsymmetrical dienes is compatible with the frontier orbital model, where the fulvene HO–diene LU interaction predominates.

The discoveries of reactions of fulvenes as 6-$\pi$-electron cycloaddends with the 4-$\pi$-electron addends tropone,[3,4] diazomethane,[5] and nitrile oxides[6] led us to investigate the cycloadditions of conjugated dienes with fulvenes. After the completion of this work, a frontier orbital analysis of fulvene cycloadditions led to a rationalization of the results reported here.[7]

## Results

The most complete studies reported here involved the reactive diene, 2,5-dimethyl-3,4-diphenylcyclopentadienone (**2**).[8] This compound exists as the endo Diels–Alder dimer in the solid state,[9] but in solution the monomer is reversibly formed. This monomeric cyclopentadienone has been used frequently as a Diels–Alder diene which reacts readily across the 2 and 5 positions.[10] One example of addition across the 2 and 3 positions reported by Paquette, *et al.*,[10e] is most likely the result of a Cope rearrangement of an initial Diels–Alder adduct in which **2** is the diene component.[10b] The cyclopentadienone can react at the 2 and 3 positions, as demonstrated by the dimerization reaction[9] and the [8 + 2] reaction with tropone.[10b] The cycloadditions of **2** with three- to eight-membered cycloalkenes have been reported and, in all cases, crystalline adducts are obtained with stereochemistries corresponding to those predicted from considerations of secondary orbital interactions.[10c,d,j]

The reaction of dimethylfulvene with **2** in refluxing THF gave a single adduct (**3a**) in nearly quantitative

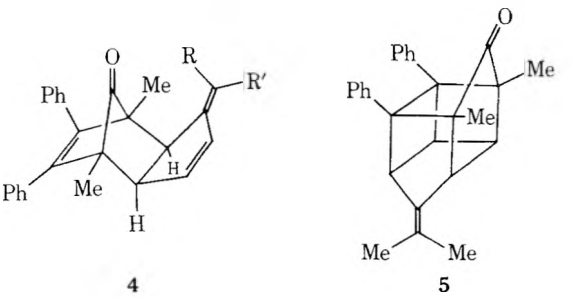



2 1 3

**a**, R = R′ = Me
**b**, R = R′ = Ph
**c**, R = Me; R′ = Me
**d**, R = Ph; R′ = H
**e**, R = Me; R′ = H
**f**, R = H; R′ = Me
**g**, R = Ph; R′ = H
**h**, R = H; R′ = Ph
**i**, R; R′ = $-(CH_2)_4-$
**j**, R = R′ = *p*-MeOPh
**k**, R = R′ = *c*-$C_3H_5$
**l**, R, R′ = H, CHCHPh

yield. The carbonyl stretching absorption at 5.63 $\mu$ in the ir indicated that reaction had occurred across the diene system of **2**, while the nmr spectrum ($CDCl_3$) of **3a** displayed a sharp resonance at 1.37 ppm for the two saturated methyls and a sharp resonance at 1.78 ppm for the two methyls on unsaturated carbon. The two methine protons in the fulvene fragment appeared as an AB pattern in $CDCl_3$ solution at 60 MHz, but these resonances were resolved in $C_6D_6$ solution at 100 MHz. Double-resonance experiments established the coupling constants shown in Table I.

These spectral data are compatible with either endo (**3a**) or exo (**4a**) structures for the adduct. The endo nature of the adduct was established by photolytic intramolecular [2 + 2] cycloaddition. While direct photolysis of **3a** led mainly to decarbonylation, acetone-sensitized photolysis led to formation of a caged adduct **5** in 40% yield. The loss of the stilbene chromophore




4 5

was indicated by the uv spectrum of **5** [$\lambda_{max}$ 261 nm ($\epsilon$ 640)]. The nmr spectrum of this adduct showed

(1) Taken in part from L. J. Luskus, Ph.D. Dissertation, Louisiana State University, Baton Rouge, La., 1971.

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TABLE I

| Compd | Adduct R | Adduct R′ | Chemical shifts (CDCl₃), ppm: $Me_A$ | $Me_B$ | $H_a$ | $H_b$ | $H_c$ | $H_d$ | R | R′ | Coupling constants, Hz: $J_{ab}$ | $J_{bc}$ | $J_{bd}$ | $J_{cd}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **3a** | Me | Me | 1.37 | 1.37 | 3.3 | 3.3 | 5.72 | 6.63 | 1.78 | 1.78 | 7.2 | 1.8 | 1.5 | 5.8 |
| **3b** | Ph | Ph | 0.54 | 1.32 | 3.93 | 3.42 | 6.00 | 6.68 | | | 7.0 | 2.5 | 1.5 | 5.5 |
| **3c** | Me | Ph | 1.47 | 1.56 | 3.50 | 3.50 | 5.75 | 6.46 | 2.20 | | | | | 5.5 |
| **3d** | Ph | Me | 0.50 | 1.38 | 3.72 | 3.42 | 6.12 | 6.6 | | 2.07 | | 2.5 | | 5.5 |
| **3e,f** | Me | H | 1.33 | 1.38 | 3.02 | 3.35 | 5.24 | 6.68 | 1.67 | 6.01 | 7.5 | | | 5.5 |
| **3f,e** | H | Me | 1.38 | 1.38 | 3.18 | 3.40 | 5.75 | 6.35 | 1.75 | 5.59 | 7.5 | | | 5.5 |
| **3h** | H | Ph | 1.45 | 1.54 | 3.28 | 3.48 | 6.23 | 6.9 | 6.38 | | 7.5 | | | 5.5 |
| **3i** | $-(CH_2)_4-$ | | 1.37 | 1.40 | 3.10 | 3.39 | 5.83 | 6.55 | 1.2–1.9 | | 7 | 2.5 | 1.5 | 5.5 |
| **3j** | Ph-*p*-OMe | Ph-*p*-OMe | 0.63 | 1.35 | 3.76 | 3.36 | 5.93 | 6.69 | | | 7.0 | 2.5 | 1.5 | 6.0 |
| **3k** | c-$C_3H_5$ | c-$C_3H_5$ | 1.37 | 1.44 | 3.41 | 3.41 | 5.75 | 6.8 | 0.3–1.3 | | 7 | 2.5 | | 5.5 |

two methyls on saturated carbon at 0.61 and 1.11 ppm and four saturated methine protons ($CDCl_3$, $\delta$): $H_a$, 3.92; $H_b$, 3.44; $H_c$, 2.65; $H_d$, 3.11 ($J_{ab}$ = 4.8 Hz; $J_{bc}$ = 7.2 Hz; $J_{cd}$ = 5.6 Hz; $J_{ac} \cong 1$ Hz; $J_{bd}$ = 1.6 Hz). These spectral data are compatible only with formation of caged adduct **5** by intramolecular [2 + 2] cycloaddition of the endo Diels–Alder adduct **3a**. Although photolyses were not carried out with the remaining adducts of **2** and other fulvenes, the similarity of the nmr spectra of all the adducts (Table I) indicates the identical endo nature of all of these adducts.

Reactions of 6,6-diphenylfulvene, 6,6-tetramethylenefulvene, 6,6-di-*p*-methoxyphenylfulvene, and 6,6-dicyclopropylfulvene proceeded similarly to give adducts **3b**, **3i**, **3j**, and **3k**. An attempt to form the caged adduct corresponding to **5** from the diphenylfulvene adduct (**3b**) by sensitized photolysis in acetone led only to decarbonylation. However, reduction of **3b** with sodium borohydride led to formation of two alcohols in a ratio of 1:1. If the diphenylfulvene adduct had the exo stereochemistry (**4b**), then reduction would have certainly led to only a single alcohol by reduction from the less hindered side of the carbonyl group.[10b]

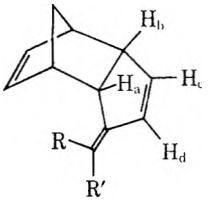
The establishment of the endo stereochemistry in the cases of the dimethylfulvene and diphenylfulvene adducts allows reasonably secure assignment of the endo stereochemistry to the remaining adducts. Thus, the tetramethylenefulvene adduct **3i** and the dicyclopropylfulvene adduct **3k** have nmr resonances for the fulvene ring protons and cyclopentadienone methyls which are nearly identical with those of **3a**. Similarly, the 6,6-di-*p*-anisylfulvene and 6,6-diphenylfulvene adducts have nmr resonances for the skeletal protons nearly identical with each other. The nmr spectra of the arylfulvene adducts (**3b** and **3j**) differ from the spectra of the alkylfulvene adducts (**3a**, **3i**, and **3k**) in the shielding of one of the methyls by about 0.8 ppm in the arylfulvene adducts. Inspection of models indicates that the methyl (A) syn to the fulvene exo methylene will lie in the shielding zone of an exo aromatic group. The only ring proton affected appreciably by the aromatic ring is $H_a$, which is deshielded by about 0.5 ppm. This anisotropic effect of the phenyl group allowed assignments of the structures of the adducts formed from unsymmetrical fulvenes.

Reaction of 6-methyl-6-phenylfulvene with **2** gave a mixture of two 1:1 adducts in a ratio of about 1:1. Fractional recrystallization gave pure **3c** which had saturated methyl resonances at 1.47 and 1.50 ppm in the nmr. By contrast, the isomer **3d**, whose nmr spectrum was obtained from a mixture of **3c** and **3d**, had saturated methyl resonances at 0.50 and 1.38 ppm. Thus, **3c** has the phenyl endo and **3d** has the phenyl exo. 6-Phenylfulvene and **2** gave a single 1:1 adduct in 83% yield. The position of the methyl resonances (1.45 and 1.54 ppm) clearly indicate that the phenyl is endo in this adduct (**3h**).

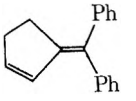
6-Methylfulvene reacts with **2** to give a 3:1 mixture of two 1:1 adducts. Although nmr evidence did not reveal the endo or exo nature of the fulvene methyl in these adducts, steric arguments (see below) indicate that the major isomer has an endo methyl group. Attempted use of the shift reagent $Eu(dpm)_3$ to elucidate the structures of this and related adducts led to exceedingly small chemical shift changes even with a large excess of the shift reagent, indicating little coordination of Eu by the hindered carbonyl.

The reaction of **2** with 6-(2-styryl)fulvene led to a 2:1 mixture of adducts. However, separation of these adducts was not accomplished, and the nmr spectra of the mixture did not clearly indicate which isomer predominated in the reaction.

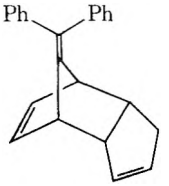
The second diene whose reactions with fulvenes were investigated was cyclopentadiene. Cyclopentadiene might react as a diene in the Diels–Alder reaction or the [6 + 4] cycloaddition with fulvene as dienophile. In the event, reaction of cyclopentadiene and diphenylfulvene at 60° led to formation of a single 1:1 adduct **6a** in 72% yield. The uv spectrum of **6a** [$\lambda_{max}$ 289 nm ($\epsilon$ 6000), sh 240 (3200)] is similar to that of model compound **7** [$\lambda_{max}$ 290 nm ($\epsilon$ 19,500), 250 (7100)].[11] By comparison, exocyclic diphenylmethylene moieties such as that present in the other possible Diels–Alder adduct, **8**, generally have $\lambda_{max}$ at 245–252 nm.[12]




**6a**, R = R′ = Ph
**b**, R = R′ = Me
**c**, R,R′ = Ph,H




**7**




**8**

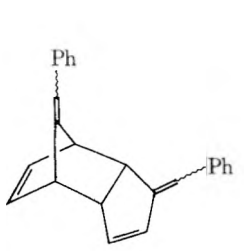
The nmr spectrum of **6a** in $C_6D_6$ gave resonances typical of the methylene group of 4,5-disubstituted norbornenes at 1.07 and 1.40 ppm, coupled by 7.4 Hz.[13] The endo nature of the adduct was verified by

(11) J. L. Rice and F. M. Parham, *J. Amer. Chem. Soc.*, **80**, 3792 (1958).
(12) "The Standard Ultraviolet Spectra," Sadtler Research Laboratory, Inc., 1965, No. 6401.
(13) N. H. Werstiuk, *Can. J. Chem.*, **48**, 2310 (1970).

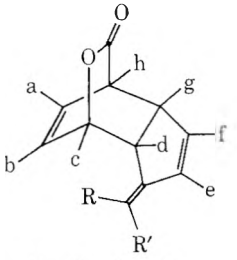
partial analysis of the 100-MHz nmr spectrum. Proton $H_a$ appears as a first-order doublet of doublets at 3.54 ppm. The two vicinal couplings of 4.25 and 6.75 Hz result from coupling of $H_a$ to the bridgehead proton and $H_b$, respectively. The magnitude of the coupling with the bridgehead proton is compatible only with the endo structure of the adduct.[14]

The reaction of cyclopentadiene with dimethylfulvene at 60° gave a single adduct **6b** as a light yellow oil in 23% yield which was isolated by preparative gas chromatography. The uv spectrum [$\lambda_{max}$ 252 nm ($\epsilon$ 2500)] was compatible with the Diels–Alder structure in which cyclopentadiene acts as the diene. The nmr spectrum showed two methyls on unsaturated carbon at 1.68 and 1.81 ppm, but was not sufficiently resolved to make proof of the endo stereochemistry possible. However, the appearance of the methylene protons as a broad multiplet at 1.3–1.4 ppm indicates that the environment of these protons is nearly the same, suggesting the endo stereochemistry for this adduct.

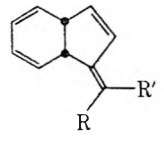
The reaction of 6-phenylfulvene with cyclopentadiene at 40° resulted in formation of a 1:1 adduct (**6c**) in 17% yield along with a mixture of phenylfulvene dimers (**9**) in 31% yield. The latter could also be isolated from a 6-phenylfulvene sample kept at 25° for 3 days. Although not well resolved, the nmr spectrum of **6c** is similar to that of **6a**, suggesting an analogous structure for this adduct. The adduct **6c** appears to be a single isomer, since a sharp doublet at 6.55 ppm ($J$ = 5.5 Hz) due to $H_d$ integrates as one fifth of the total area of the olefinic resonances. Since it is unlikely that a single resonance for proton $H_d$ would be observed in a mixture of adducts with endo and exo phenyls, it is likely that this product consists of a single isomer.



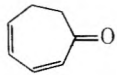

**9**




**11a**, R = R′ = Ph
**b**, R = R′ = Me
**c,d**, R,R′ = Me,H
**e,f**, R,R′ = Ph,H




**12a**, R = R′ = Ph




**13**

The structure of the phenylfulvene dimers in the mixture is of particular interest in light of recent calculations of fulvene reactivities toward different modes of cycloaddition.[15] The dimer mixture proved to be inseparable by tlc, and attempted gas chromatographic analysis led only to isolation of monomeric phenylfulvene. The mixture did not react with dimethyl acetylenedicarboxylate, indicating the absence of [6 + 4] dimers.[3] The nmr spectrum of the mixture revealed aryl, olefinic, and aliphatic proton resonances in a ratio of 10:6:4, in agreement with [4 + 2] or [2 + 2] formulations for the dimers. Furthermore, the spectrum had two doublets at 6.67 and 6.88 ppm in a ratio of 1:2.5. Each of these resonances was split by 5.5 Hz. Assuming these are due to $H_d$ of the dimer, two [4 + 2] dimers are present in a ratio of 2.5:1.

The reactions of $\alpha$-pyrone **10** with fulvenes were briefly investigated. Reaction of **10** with diphenylfulvene at 90° gave a single crystalline adduct, **11a**, in 60% yield. Upon heating at 130°, the adduct lost carbon dioxide to give dihydrobenzofulvene **12a**. The infrared spectrum of **11a** exhibited a carbonyl stretching absorption at 5.71 $\mu$ compatible with the nonconjugated $\delta$-lactone moiety. The uv spectrum [$\lambda_{max}$ 287 nm ($\epsilon$ 16,700), 236 (11,400)] is that expected of the diphenylmethylenecyclopentene moiety.[12] Analysis of the nmr spectrum with and without added $Eu(dpm)_3$ shift reagent led to elucidation of the adduct stereochemistry.

In $CDCl_3$, $H_f$ of the fulvene moiety appeared as a doublet of doublets ($J_{ef}$ = 5.0 Hz; $J_{fg}$ = 2.5 Hz) at 5.89 ppm. The remaining three olefinic resonances appeared as overlapping multiplets between 6.2 and 6.5 ppm. Addition of $Eu(dpm)_3$ caused the resonances due to $H_a$ and $H_b$ to shift downfield, such that the resonance due to $H_e$ could be identified as a doublet of doublets ($J_{eg}$ = 1.5 Hz; $J_{ef}$ = 5.0 Hz) centered at 6.35 ppm before addition of shift reagent (by extrapolation). Protons $H_a$ and $H_b$ appeared as an AB pseudotriplet centered at 6.30 ppm. The resonances due to $H_d$ (4.03 ppm; $J_{dg}$ = 5.0 Hz; $J_{dc}$ = 7.5 Hz) and $H_c$ (4.62 ppm; $J_{cd}$ = 7.5 Hz; $J_{cb}$ = 4.0 Hz) were resolved in $CDCl_3$, while the two-proton multiplet at 3.25–3.70 ppm was resolved into a doublet of doublets arising from $H_h$ ($J_{hg}$ = 7.5 Hz; $J_{ha}$ = 4.0 Hz) and a multiplet due to $H_g$ ($J_{gh}$ = 7.5 Hz; $J_{gd}$ = 5.0 Hz; $J_{gf}$ = 2.5 Hz; $J_{ge}$ = 1.5 Hz) by addition of $Eu(dpm)_3$. The large magnitude of $J_{cd}$ = $J_{hg}$ = 7.5 Hz is compatible only with the endo stereochemistry for this adduct. The anti stereochemistry of the carbonyl and diphenylmethylene groups was revealed by the magnitude of the LIS's. Europium shift reagents are known to complex mainly at the carbonyl oxygen of esters.[16] Since the resonance due to $H_h$ is shifted downfield 12.5 Hz by a concentration of $Eu(dpm)_3$ which shifts $H_g$ and $H_d$ downfield by 7.0 and 6.0 Hz, respectively, the adduct must have the anti stereochemistry.

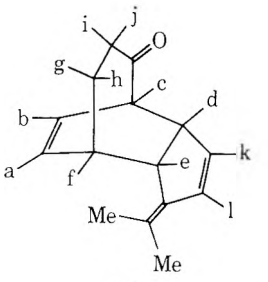
Dimethylfuvene reacts with $\alpha$-pyrone to give a 64% yield of a single adduct whose ir and uv spectra confirmed that the gross structure of the adduct was the same as that of the diphenylfulvene adduct. Although the nmr spectrum of this compound was not fully analyzed, the 7.5-Hz coupling of resonances assigned to $H_c$ (5.38 ppm) and $H_d$ (3.5 ppm) as well an LIS's similar to those for the diphenylfulvene adduct confirm the structure as **11b**. Although exhaustive structure proofs were not carried out, the nmr spectra of the adducts of $\alpha$-pyrone with 6-methylfulvene and 6-phenylfulvene indicated formation of single isomers, **11c** or **11d** and **11e** or **11f**.

(14) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969.

(15) M. N. Paddon-Row, P. L. Watson, and R. N. Warrener, *Tetrahedron Lett.*, 1033 (1973).

(16) H. Hart and G. M. Love, *Tetrahedron Lett.*, 625 (1971).

In connection with the studies of the cycloadditions of tropone with fulvenes,[3] we studied the reaction of 2,4-cycloheptadienone (**13**) with dimethylfulvene. If only the distance between the diene termini were important in causing tropone to add in a [6 + 4] fashion with fulvenes, then **13** might be expected to add in this fashion also. However, reaction of **13**, which is in equilibrium with 3,5-cycloheptadienone at the temperature of the reaction (80°),[17] with dimethylfulvene produced a single 1:1 adduct in 41% yield. The reaction occurred at the 2 and 5 positions of **13** as indicated by nmr and ir (5.85 $\mu$), while the nmr spectrum revealed methyls attached to unsaturated carbon (1.72 ppm). Of the four possible adducts arising from reaction with **13** acting as diene and dimethylfulvene as dienophile, use of the Eu(dpm)$_3$ shift reagent unequivocally established the structure as **14**.




**14**

The olefinic resonances of **14** appeared as resolved multiplets at 5.32 ($H_k$) and 6.27 ppm ($H_l$) in $C_6D_6$, while the olefinic resonances at 5.64 and 5.94 ppm were assigned on the basis of double-resonance experiments to $H_a$ and $H_b$, respectively. $H_b$ was coupled to the doublet of doublets at 3.06 which was shown to be $H_c$ by the fact that this proton shifted downfield most upon addition of Eu(dpm)$_3$. $H_f$, which was coupled to $H_a$ and $H_e$, appeared as a broad multiplet at 2.5 ppm. Addition of shift reagent at maximum concentration in $CCl_4$ caused the following downfield shifts (Hz): $H_a$, 26; $H_b$, 47; $H_c$, 104; $H_d$, 94; $H_e$, 52; $H_f$, 38; $H_g$, $H_h$, 50; $H_i$, $H_j$, 125; $H_k$, 23; $H_l$, 22; Me, 14, 10.

The assignment of resonances was made by incremental addition of Eu(dpm)$_3$ and was as follows. The protons $\alpha$ to the carbonyl should be shifted downfield most ($H_{c,i,j}$). The protons $H_d$ and $H_e$ are shifted downfield much more than protons $H_k$ and $H_l$, indicating the endo nature of the adduct. Furthermore, the small shifts of the methyl resonances are most compatible with the anti arrangement of the dimethylmethylene and carbonyl functions.

The reactions of additional dienes with fulvenes were attempted but not studied in detail. Thus, furan, norbornadiene, and 1,2-dimethylenecyclobutane did not react with dimethylfulvene at temperatures from 25 to 100°.

## Discussion

The reactions of the dienes with fulvenes reported here invariably led to endo [4 + 2] adducts. Although no intermediate adducts were observed, these endo adducts could be the result of Cope rearrangements of the alternative Diels–Alder adducts in which fulvene acts as the diene. Most of the reactions studied here involved reaction temperatures lower than those required for Cope rearrangements of similar adducts,[10c] so that we assume that the observed products are those resulting from kinetic control. Apparently these are also the thermodynamically more stable isomers, since heating did not result in Cope rearrangements.

The periselectivity observed in these reactions was unexpected at the onset of the work. However, in the meantime, a frontier orbital analysis of fulvene cycloadditions has led to a general understanding of the factors which control periselectivity.[7]

The frontier orbitals of dimethylfulvene, along with those derived below for the dienes used in this work, are shown in Figure 1. As noted previously, the HO orbital of fulvene and its alkyl derivatives is antisymmetric, and reactions with dienes in which the fulvene HO–diene LU interaction is predominant will lead to Diels–Alder reactions, while dienes which have high-energy frontier orbitals and have principal interaction of their HO with the fulvene LU will give [6 + 4] addition owing to the large fulvene coefficient at C-6.[7,18]

The estimation of orbital energies and coefficients in Figure 1 follow the methods used earlier.[7,18] The estimates for fulvene have been given earlier,[7] while those for cyclopentadiene follow from the measured ionization potential[19] and electron affinity and coefficient estimates made earlier.[18]

The relative frontier orbital coefficient magnitudes for $\alpha$-pyrone can be qualitatively understood using the generalizations made earlier about substituent effects on diene coefficients.[18] In the LU, electron-releasing groups increase the adjacent coefficient, while electron-withdrawing groups decrease the adjacent coefficient. Thus the coefficient at C-6 in the LU is considerably larger than that at C-3. In the HO, both types of substituents tend to decrease the adjacent coefficient, but the effect of the ether oxygen is larger than that of the carbonyl.[18] Thus, the C-3 coefficient is larger than that of C-6. A CNDO/2 calculation also supports this qualitative conclusion.

The ultraviolet spectrum of $\alpha$-pyrone ($\lambda_{max}^{EtOH}$ 291 nm)[20] indicates an 8.6-eV separation between the HO and LU orbitals using our earlier empirical estimates for electron repulsion in singlet excited states.[18] Although the photoelectron spectrum of $\alpha$-pyrone has not been reported,[20a] a crude estimate can be made on the basis of the known ionization potentials of 1,3-cyclohexadiene (8.30 eV),[19] propene (9.73 eV),[21] methyl acrylate (10.72 eV),[22] and vinyl acetate (~9.2 eV).[21,22a] Since substitution of a carbomethoxy group for a methyl raises the ionization potential of propene by ~1 eV, and substitution of an acetoxy group for a methyl lowers the ionization potential of propene by

(17) A. P. Ter Borg and H. Kloosterziel, *Recl. Trav. Chim. Pays-Bas*, **82**, 1189 (1963).

(18) K. N. Houk, J. Sims, R. E. Duke, Jr., R. W. Strozier, and J. K. George, *J. Amer. Chem. Soc.*, in press; K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *ibid.*, in press.

(19) P. Bischof and E. Heilbronner, *Helv. Chim. Acta*, **53**, 1677 (1970).

(20) E. J. Corey and J. Streith, *J. Amer. Chem. Soc.*, **86**, 950 (1964).

(20a) NOTE ADDED IN PROOF.—The photoelectron spectrum of $\alpha$-pyrone has recently been measured in our laboratories by Mrs. Linda Lambert. The lowest vertical ionization potential is 9.13 ± 0.02 eV.

(21) K. Watanabe, T. Nakayama, and J. Mottl, *J. Quant. Spectrosc. Rad. Transfer*, **2**, 369 (1962).

(22) R. Sustmann and H. Trill, *Tetrahedron Lett.*, 4271 (1972).

(22a) NOTE ADDED IN PROOF.—We have measured the pes spectra[20a] of vinyl acetate and find vertical ionization potentials of 9.85 and 10.73 eV for the $\pi$ and n orbitals, respectively. The estimate for $\alpha$-pyrone becomes 9.41 eV based on this number, closer to the experimental value.

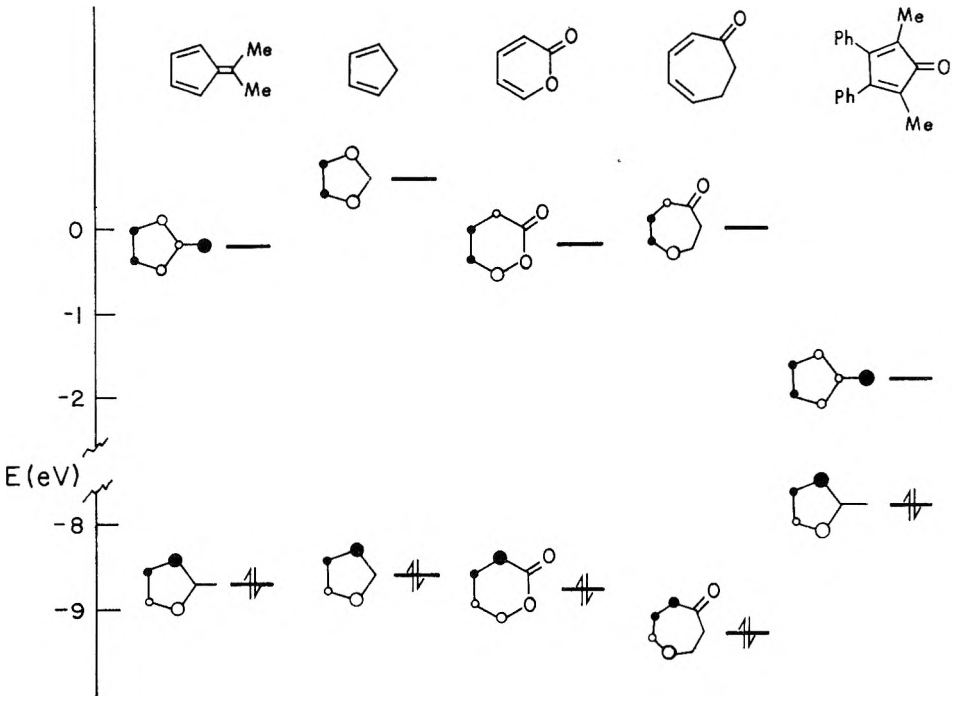



Figure 1.—Estimated frontier orbital energies and coefficients for dimethylfulvene and substituted dienes.

~0.5 eV, α-pyrone is estimated to have an ionization potential of +0.5 eV higher than that of 1,3-cyclohexadiene, or about 8.8 eV. This and the uv data place the $E_a$ at +0.2 eV.

The ionization potential of 2,4-cycloheptadienone can be estimated as 9.31 eV from that of 1,3-cycloheptadiene (8.31 eV),[19] and by comparing the ionization potential of 1-butene (9.6 eV)[21] to that of methyl vinyl ketone (10.60 eV).[22] The LU energy is estimated very roughly from considerations of substituent effects on electron affinities.[18] The coefficients for the type of system were estimated earlier.[18]

Finally, the frontier orbital energies of cyclopentadienones can be estimated in several ways. As a first approximation, cyclopentadienone should have the same ionization potential as fulvene, since their HO orbitals are essentially identical asymmetric orbitals, but the electron affinity of cyclopentadienone should be much higher than that of fulvene, since the LU's of both have large coefficients at atom 6, the site of substitution of the electronegative oxygen atom. CNDO/2 calculations indicate a 0.5-eV lowering of the LU for cyclopentadienone as compared to fulvene. We estimate HO and LU orbital energies of −9 and −1.5 eV for the parent compound. For the heavily substituted derivative whose cycloadditions were studied here, the substituent effects can be estimated only very crudely. The two methyls are expected to raise the HO and LU energies by about 0.6 eV, while the phenyls will raise the HO by about 0.6 eV and lower the LU by about 0.3 eV.[23] The resulting estimates of HO and LU energies are −7.8 and −1.8 eV. This narrow gap is compatible with the long-wavelength absorptions and intense colors of cyclopentadienones.[10a]

In addition to the CNDO/2 calculations performed here, Hückel[24] and extended Hückel[25] calculations have been reported for cyclopentadienone. All of these calculations predict a low-energy LU orbital. In fact, the narrow frontier orbital separation in cyclopentadienones was cited by Garbisch as the source of the high reactivity of cyclopentadienones in dimerization, in one of the first applications of perturbation theory to the study of cycloaddition reactivity.[24] In light of these very low LU energies, cyclopentadienones should be more readily trapped by electron-rich species than by electron-deficient compounds. The latter types of compounds have often been used as cyclopentadienone traps, usually without success.[10a]

The exercise of estimating frontier orbital energies was carried out here in order to test whether the reason for invariable formation of the [4 + 2] adducts in the reactions studied resulted from a narrower fulvene HO–diene LU separation (which favors [4 + 2] cycloaddition) than the opposite frontier orbital separation (which favors [6 + 4] cycloaddition). As can be seen from Figure 1, only in the case of the cyclopentadienone is the fulvene HO interaction clearly much more important than the fulvene LU interaction. For 3,5-cycloheptadienone and α-pyrone, both pairs of frontier orbitals are separated by comparable amounts. However, both pairs of interactions will lead to stabilization of the [4 + 2] transition state, while only the fulvene LU–diene HO interaction can stabilize the possible [6 + 4] transition state. This suggests that only dienes with very high energy frontier orbitals will react in a [6 + 4] sense with fulvenes.

The regiochemistry of both the α-pyrone and 2,4-cycloheptadienone cycloadditions can be rationalized by the coefficients shown in Figure 1. Thus, the fulvene HO–diene LU interaction will be more important in determining the favored regioisomeric transition state due to the larger difference between the coefficients at C-2 and C-3 in the fulvene, as well as due to the larger absolute magnitude of the coefficients at C-2 and C-3 in the fulvene HO than in the fulvene LU. Unit-

(23) These are very qualitative estimates based on substituent effects derived earlier.[18]

(24) E. W. Garbisch, Jr., *J. Amer. Chem. Soc.*, **88**, 3433, 3434 (1966).

(25) W. C. Herndon and L. H. Hall, *Theor. Chim. Acta*, **7**, 4 (1967).

ing the larger LU coefficient of these dienes with that in the fulvene HO[18,26] leads to formation of the observed adducts, that is, **11** from α-pyrone and **14** from 2,4-cycloheptadienone.

Cyclopentadiene represents an anomaly in that the fulvene LU–cyclopentadiene HO interaction must be greatest; yet the [4 + 2] adducts are formed. However, the considerations used for the last two dienes may also be invoked to explain the formation of [4 + 2] adducts, since the diene LU is still not too high in energy for appreciable interaction to occur. It would appear that, if this is the correct explanation, the parent fulvene, which has lower energy frontier orbitals than dimethylfulvene, might undergo [6 + 4] cycloadditions to some extent with cyclopentadiene.

Finally, the secondary stereochemistry observed in cycloadditions of unsymmetrical fulvenes to **2** should be noted. In every case, the adducts formed are endo, compatible with the importance of secondary orbital interactions,[27] but the larger group on the exocyclic carbon of fulvene also is endo oriented. This appears from models to be due to steric repulsion between a methyl of **2** and the substituent which becomes exo on the fulvene exocyclic carbon.

## Summary

The 6-substituted and 6,6-disubstituted fulvenes investigated here react only as dienophiles in the Diels–Alder reaction with several five-, six-, and seven-membered ring dienes. In no cases were [6 + 4] adducts obtained. These results are rationalized by a frontier orbital analysis which also correctly rationalizes the regiochemistry of these cycloadditions.

## Experimental Section

The preparations of 2,5-dimethyl-3,4-diphenylcyclopentadienone,[8] α-pyrone,[28] 3,5-cycloheptadienone,[29] 1,2-dimethylenecyclobutane,[30] and the fulvenes[31] were by literature procedures.

**Cycloadditions of 2,5-Dimethyl-3,4-diphenylcyclopentadienone (2) to Fulvenes (1).** The following procedure is exemplary.

**Preparation of 3a from Dimethylfulvene 1a and 2.**—The dimer of 2,5-dimethyl-3,4-diphenylcyclopentadienone (1.56 g, 6.0 mmol monomer) and 6,6-dimethylfulvene (0.814 g, 7.7 mmol) were dissolved in tetrahydrofuran (10 ml). The solution was refluxed under a nitrogen atmosphere for 24 hr or until thin layer chromatography indicated disappearance of **2**. Evaporation of the solvent and excess dimethylfulvene *in vacuo* gave a solid residue which was recrystallized from methanol to give 2.16 g (98%) of crude **3a**, mp 133–136°. Three recrystallizations from methanol gave colorless blocks, mp 137–139°.

The remaining adducts of **2** and various fulvenes were prepared in the same way. The data are collected in Table II. The only deviations from the procedure described above are described below.

**Preparation of 3h from 6-Phenylfulvene and 2.**—The oily residue formed was purified on plc [5% ethyl acetate, petroleum ether (bp 30–60°) on Merck silica gel PF-254, two elutions] to give 84% of a solid, mp 162–169°. Recrystallization from methanol gave **3h**, mp 172–173°. The nmr spectra of this product and of the crude material were identical. However, gradual formation of a polymeric decomposition product prevented elemetal analysis.

**Preparation of 3c and 3d from 6-Methyl-6-phenylfulvene and 2.**—The procedure described above gave 92% of solid, the nmr spectrum of which had four methyl resonances of equal height, indicating formation of two adducts in equal amounts. Several slow recrystallizations from methanol solutions gave a pure adduct, **3c**, mp 159–161°.

A solution of pure **3c** in tetrachlorethylene was heated at 95° for 38 hr. Nmr spectra taken of this solution before and after heating indicated no change. Similarly, a 60:40 mixture of **3c** and **3d** was unchanged after heat at 95° for 38 hr.

**Preparation of 3e and 3f from 6-Methylfulvene and 2.**—The procedure described above gave a solid, in quantitative yield, mp 121–135°, which was homogeneous on tlc. However, nmr spectra indicated the presence of two adducts, **3e** and **3f**, in a ratio of 3:1 as determined by integration of olefinic resonances. Fractional recrystallization from methanol gave each isomer free of the other, but polymerization prevented acquisition of pure compounds for elemental analyses.

**Preparation of 3l and 3m from 6-(β-Styryl)fulvene and 2.**—The procedure described above gave 76% of a pale yellow liquid after plc (20% ethyl acetate–petroleum ether, one elution). The nmr spectrum of this oil gave methyl resonances at 1.37, 1.44, and 1.50 ppm, indicating two isomers, **3l** and **3m**, in a ratio of 2:1.

**Attempted Reaction of 6-Dimethylaminofulvene and 2,5-Dimethyl-3,4-diphenylcyclopentadienone (2).**—A mixture of 0.121 g (1 mmol) of 6-dimethylaminofulvene, 0.260 g (1 mmol) of 2,5-dimethyl-3,4-diphenylcyclopentadienone dimer, and 5 ml of xylene was heated at reflux under nitrogen and in the dark for 1 week. Only starting materials and a small amount of insoluble decomposition product were found.

**Photolysis of 3a.**—To 150 ml of acetone was added 0.590 g (1.6 mmol) of **3a**. The solution was purged with a nitrogen stream and photolyzed (4 Rayonet RUL lamps, 2537 Å) for 2.5 hr. The solvent was removed *in vacuo* and the resulting oily solid was subjected to plc (5% ethyl acetate–petroleum ether, three elutions) to give four fractions. The slowest fraction gave 0.235 g (40%) of a white solid. Two recrystallizations from methanol yielded colorless needles, mp 136.5°, which were shown to be the caged compound **5**.

*Anal.* Calcd for $C_{27}H_{26}O$: C, 88.48; H, 7.15; O, 4.37. Found: C, 88.35; H, 7.33.

Mass spectrum *m/e* (rel intensity) 366 (48), 323 (100), 260 (71), 196 (72), 115 (68), 102 (85); ir ($CCl_4$) 5.68 μ (C=O); nmr ($CDCl_3$) 0.61 (s, 3 H), 1.11 (s, 3 H), 1.69 (s, 3 H), 1.79 (s, 3 H), 2.65 (dd, $J$ = 5.6, 7.2 Hz, 1 H), 3.11 (dd, $J$ = 1.6, 5.6 Hz, 1 H), 3.44 (dd, $J$ = 4.8, 7.2 Hz, 1 H), 3.92 (br d, $J$ = 4.8 Hz, 1 H), 7.6–8.1 ppm (br m, 10 H); uv $\lambda_{max}$ (hexane) 304 nm (ε 304), sh 261 (640), sh 224 (23,000).

**Preparation of 6a from 6,6-Diphenylfulvene and Cyclopentadiene.**—A solution of 0.360 g (1.56 mmol) of 6,6-diphenylfulvene in 6 ml of freshly distilled cyclopentadiene was heated under nitrogen at 60° (bath temperature) for 18 hr. Excess cyclopentadiene and dicyclopentadiene formed during the reaction were removed by prolonged low-temperature vacuum distillation. The oily, yellow solid remaining was decolorized with activated charcoal and recrystallized from 10 ml of methanol to give 0.332 g (72%) of crystalline **6a**. Three recrystallizations from 50:50 ethyl acetate–methanol gave small, colorless needles, mp 106.5–107°.

*Anal.* Calcd for $C_{23}H_{20}$: C, 93.20; H, 6.80. Found: C, 92.91; H, 6.92.

Spectra: mass *m/e* (rel intensity) 296 (3), 230 (100), 229 (33); uv $\lambda_{max}$ (hexane) 289 nm (ε 6000), sh 240 (3200).

**Preparation of 6b from 6,6-Dimethylfulvene and Cyclopentadiene.**—A mixture containing 0.424 g (4 mmol) of 6,6-dimethylfulvene and 0.528 g (8 mmol) of freshly distilled cyclopentadiene was heated under nitrogen at 60° (bath temperature) for 8 hr. Separation of the components of the yellow solution by preparation vpc on a column of 15% Apiezon L on Chromosorb W (160°) gave 0.160 g (23%) of an impure, viscous, light yellow oil consisting mainly of **6b**. Repeated attempts at vpc and prolonged low-temperature vacuum distillation failed to give the adduct in sufficient purity for elemental analysis.

Spectra: mass *m/e* (rel intensity) 172 (6), 106 (100), 91 (28); nmr ($CDCl_3$) 1.40 (m, 2 H), 1.68 (s, 3 H), 1.81 (s, 3 H), 2.7–3.4 (m, 4 H), 5.6–5.9 (m, 3 H), 6.17 ppm (d, $J$ = 5.5 Hz, 1 H); uv $\lambda_{max}$ (hexane) 252 nm (ε 2500).

(26) K. N. Houk, *J. Amer. Chem. Soc.*, **95**, 4092 (1973).

(27) R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, **87**, 4388 (1965).

(28) H. E. Zimmerman, G. L. Grunewald, R. M. Paufler, and M. A. Sherwin, *J. Amer. Chem. Soc.*, **91**, 2330 (1969).

(29) D. I. Schuster, B. R. Skolnick, and F. H. Lee, *J. Amer. Chem. Soc.*, **90**, 1300 (1968).

(30) W. von E. Doering and W. R. Dolbier, Jr., *J. Amer. Chem. Soc.*, **89**, 4534 (1967).

(31) Reviewed in P. Yates, *Advan. Alicycl. Chem.*, **2**, 70 (1968).

TABLE II[a]

| Adduct | Yield, % | R | R′ | Mp, °C (solvent) | Analysis | m/e (rel abundance) | Ir ($CCl_4$), μ | Uv, $\lambda_{max}$ in hexane (ε) |
|---|---|---|---|---|---|---|---|---|
| **3a** | 98 | Me | Me | 137–139 (methanol) | Calcd for $C_{27}H_{26}O$: C, 88.48; H, 7.15; O, 4.37 | 366 (9) 260 (100) | 5.63 | 247 (29,000) |
| | | | | | Found: C, 88.33; H, 7.31 | 232 (34) 106 (7) | | |
| **3b** | 93 | Ph | Ph | 200–204 dec (ethyl acetate) | Calcd for $C_{37}H_{30}O$: C, 90.57; H, 6.16; O, 3.26 | 490 (1) 260 (35) | 5.62 | 273 (18,000) |
| | | | | | Found: C, 90.37; H, 6.46 | 230 (100) 229 (86) 215 (43) | | |
| **3j** | 89 | *p*-MeOPh | *p*-MeOPh | 192–197 dec (benzene) | Calcd for $C_{39}H_{34}O_3$: C, 85.06; H, 6.22; O, 8.72 | 550 (<1) 290 (55) | 5.62 | 284 (16,000) |
| | | | | | Found: C, 85.16; H, 6.40 | 260 (100) | | |
| **3c** | 46 | Ph | Me | 159–161 (methanol) | Calcd for $C_{32}H_{28}O$: C, 89.68; H, 6.59; O, 3.73 | 428 (44) 260 (100) | 5.63 | 258 (38,600) |
| | | | | | Found: C, 89.57; H, 6.75 | 232 (18) 168 (69) 167 (19) 166 (44) 165 (35) 154 (29) | | |
| **3d** | 46 | Me | Ph | As mixture with **3c** | | Mass spectrum of mixture same as above | | |
| **3h** | 84 | Ph | H | 172–173 (methanol) | | 414 (38) 260 (77) 154 (77) 153 (100) 152 (41) | 5.67 | 278 (19,000) |
| **3e** | | Me | H | See text | | 352 (10) 260 (100) 232 (14) | 5.63 | 247 (23,400) |
| **3f** | | H | Me | See text | | | 5.63 | |
| **3i** | 81 | $(CH_2)_4$ | | 141–143 (methanol) | Calcd for $C_{29}H_{28}O$: C, 88.73; H, 7.19; O, 4.08 | 392 (56) 260 (100) | 5.62 | 253 (20,500) |
| | | | | | Found: C, 88.64; H, 7.32 | 132 (61) | | |
| **3k** | 72 | c-$C_3H_5$ | c-$C_3H_5$ | 159–159.5 (methanol) | Calcd for $C_{31}H_{30}O$: C, 88.95; H, 7.22; O, 3.82 | 418 (10) 260 (85) | 5.63 | 261 (25,000) |
| | | | | | Found: C, 88.72; H, 7.33 | 158 (100) | | |

[a] Satisfactory analytical data (±0.35% for C, H, N, etc.) were reported for all new compounds listed in the table: Ed.

**Preparation of 6c from 6-Phenylfulvene with Cyclopentadiene.**—A mixture of cyclopentadiene (10 ml) and 1.54 g (10 mmol) of 6-phenylfulvene was allowed to stand at 40° under nitrogen for 18 hr, after which the volume of the solution was reduced *in vacuo* and the resulting orange-yellow oil was subjected to plc (2%, three elutions). Two fractions were isolated. The slower moving fraction (0.463 g) gave an nmr spectrum almost identical with that of the product obtained upon keeping 6-phenylfulvene under nitrogen at room temperature (25°) for 3 days or more. The spectrum was complicated and presumably a composite of the spectra of several Diels–Alder dimers, **9**. The faster moving fraction gave 0.389 g (17%) of a pale yellow, heavy oil. Attempted reaction of the oil with dimethyl acetylenedicarboxylate was monitored by nmr; after 5 days at room temperature, only starting materials were detected. Attempts to increase the purity of the oil by vpc (15% Apiezon L on Carbowax W) led only to total isomerization of the oil to an unidentified product(s).

**6c** (fast moving fraction) had mass spectrum *m/e* (rel intensity) 220 (4, $M^+$), 205 (10), 154 (100), 153 (90), 152 (33); **9** (slow moving fraction) had $M^+$ 154, identical pattern with that of 6-phenylfulvene.

**Preparation of 11a from 6,6-Diphenylfulvene and α-Pyrone.**—A mixture containing 0.720 g (3.13 mmol) of 6,6-diphenylfulvene, 0.317 g (3.30 mmol) of α-pyrone, 3 drops of triethylamine, and 2 ml of xylene was heated under nitrogen at 90° for 72 hr. Removal of the solvent under reduced pressure followed by plc (20% ethyl acetate–petroleum ether, one elution) and recrystallization from 5% ethyl acetate–petroleum ether gave 0.591 g (60.3%) of small crystals, **11a**, mp 111–115°. Repeated recrystallization from 5% ethyl acetate–petroleum ether gave colorless blocks, mp 140–141°.

*Anal.* Calcd for $C_{23}H_{18}O_2$: C, 84.64; H, 5.56; O, 9.80. Found: C, 84.35; H, 5.85.

Spectra: mass *m/e* (rel intensity) 326 (3), 282 (100), 230 (79), 205 (24), 204 (24), 203 (38); ir ($CCl_4$) 5.71 μ (C=O); uv $\lambda_{max}$ (ethanol) 287 nm (ε 16,700), 236 (11,800).

**Preparation of 11b from 6,6-Dimethylfulvene and α-Pyrone.**—A solution containing 0.540 g (5.09 mmol) of 6,6-dimethylfulvene, 0.250 g (2.60 mmol) of 2-pyrone, 3 drops of triethylamine, and 1 ml of xylene was heated under nitrogen at 80° for 39 hr. Removal of the volatile components *in vacuo* gave a yellow, oily solid which was subjected to plc (20% ethyl acetate–petroleum ether, one elution). Two recrystallizations of the resulting 0.335 g (64%) of solid from ethyl acetate–petroleum gave **11b** as colorless plates, mp 100–101°.

*Anal.* Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98; O, 15.82. Found: C, 77.07; H, 7.05.

Spectra: mass *m/e* (rel intensity) 202 (2), 158 (7), 143 (15), 125 (15), 106 (100), 91 (30); ir ($CCl_4$) 5.75 μ (C=O); uv $\lambda_{max}$ (ethanol) 246 nm (ε 19,200).

**Preparation of 11c and 11d from 6-Methylfulvene and α-Pyrone.**—A 0.184-g (2 mmol) quantity of 6-methylfulvene was added to a mixture of 0.194 g (2 mmol) of α-pyrone, 3 drops of triethylamine, and 3 ml of benzene. Refluxing under nitrogen for 31 hr gave, after plc (5% ethyl acetate–petroleum ether, two elutions), 0.265 g (70.5%) of a light yellow oil whose nmr spectrum indicated the presence of two isomers, presumably **11c** and **11d**, in the ratio of about 3:1, respectively (based on the relative in-

tensities of the methyl resonances). The mixture had ir ($CHCl_3$) 5.78 $\mu$ (C=O); 11c nmr ($CDCl_3$) 1.82 (d, $J$ = 8.5 Hz, 3 H), 3.2–3.7 (m, 3 H), 5.38 (dd, $J$ = 3.7, 7.0 Hz, 1 H), 5.5–6.4 ppm (m, 5 H); 11d 1.68 (d, $J$ = 8.5 Hz, 3 H), 3.2–3.7 (m, 3 H), 5.15 (dd, $J$ = 3.7, 7.0 Hz, 1 H), 5.5–6.4 ppm (m, 5 H).

**Preparation of 11e and 11f from 6-Phenylfulvene and α-Pyrone.**—A 0.154-g (1 mmol) quantity of 6-phenylfulvene was added to a solution containing 0.096 g (1 mmol) of 2-pyrone, 3 drops of triethylamine, and 3 ml of benzene. Refluxing under nitrogen for 16 hr followed by plc (5% ethyl acetate–petroleum ether, two elutions) resulted in 0.220 g (88%) of a light yellow solid. The nmr spectrum of the crude solid indicated the presence of relatively pure adduct 11e contaminated with what appeared to be a small amount (<10%) of isomeric adduct 11f (no further purification was attempted): ir ($CHCl_3$) 5.76 $\mu$ (C=O); nmr ($CDCl_3$) 3.3–3.7 (m, 3 H), 5.27 (dd, $J$ = 3.5, 7.0 Hz, 1 H), 5.7–6.4 (m, 4 H), 6.70 (d, $J$ = 5.5 Hz, 1 H), 7.3 ppm (m, 5 H).

**Preparation of 14 from 2,4-Cycloheptadienone and 6,6-Dimethylfulvene.**—A solution containing 1.06 g (10 mmol) of 6,6-dimethylfulvene, 0.507 g (4.7 mmol) of 3,5-cycloheptadienone, 50 mg of hydroquinone, and 2 ml of tetrachloroethylene was heated under nitrogen at 85° for 5 days. The solvent and excess fulvene were removed under reduced pressure, and 0.409 g (41%) of a single 1:1 adduct was isolated by plc (5% ethyl acetate–petroleum ether, three elutions). Vacuum distillation of the yellow liquid at 190–205° (0.2 mm) led to increased impurity because of some decomposition. Slow redistillation (2 hr) at a pot temperature of 84° (0.2 mm) gave a deposit of light yellow crystals, mp about 25°, 14, on the condenser. This material was adequate for characterization except elemental analysis: mass spectrum $m/e$ (rel intensity) 214 (30), 106 (100), 91 (30); ir ($CCl_4$) 5.85 $\mu$ (C=O).

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**Registry No.**—**1a**, 29183-07-1; **1b**, 2175-90-8; **1c**, 2320-32-3; **1e**, 3839-50-7; **1h**, 7338-50-3; **1i**, 4727-24-6; **1j**, 15972-55-1; **1k**, 4479-62-3; **1l**, 35516-21-3; **2**, 26307-17-5; **3a**, 41727-87-1; **3b**, 41727-88-2; **3c**, 41762-74-7; **3d**, 41727-89-3; **3e**, 41727-90-6; **3f**, 41727-91-7; **3h**, 41727-92-8; **3i**, 41727-93-9; **3j**, 41727-94-0; **3k**, 41727-95-1; **3l**, 41727-96-2; **3m**, 41727-97-3; **5**, 41718-21-2; **6a**, 41727-98-4; **6b**, 41727-99-5; **6c**, 41728-00-1; **11a**, 41728-01-2; **11b**, 41728-02-3; **11c**, 41728-03-4; **11d**, 41728-04-5; **11e**, 41728-05-6; **11f**, 41728-06-7; **14**, 41728-07-8; cyclopentadiene, 542-92-7; α-pyrone, 504-31-4.

# The [2 + 2] Cycloaddition Dimer from 1,2-Nonadien-4-yne

WALTER J. GENSLER* AND ALAN WHITEHEAD

*Department of Chemistry, Boston University, Charles River Campus, Boston, Massachusetts 02215*

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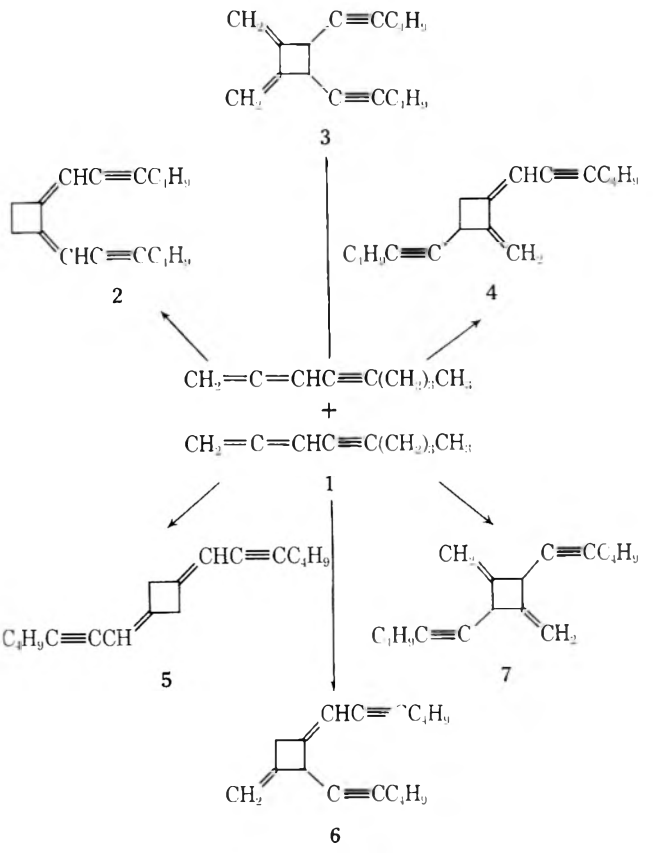
1,2-Nonadien-4-yne, a conjugated acetylenic allene, condenses with itself to form a short-lived dimer, which was not obtained as such but instead was trapped and isolated as a bis adduct with maleic anhydride. The proved structure of the bis adduct derivative provides evidence that the dimer is the product of a thermal [2 + 2] cycloaddition process. The structure of the derivative also serves to limit the allene dimer to two possibilities, namely, 1,2-bis(hexynylmethylene)cyclobutane or 3,4-bis(hexynyl)-1,2-bis(methylene)cyclobutane, with the former preferred.

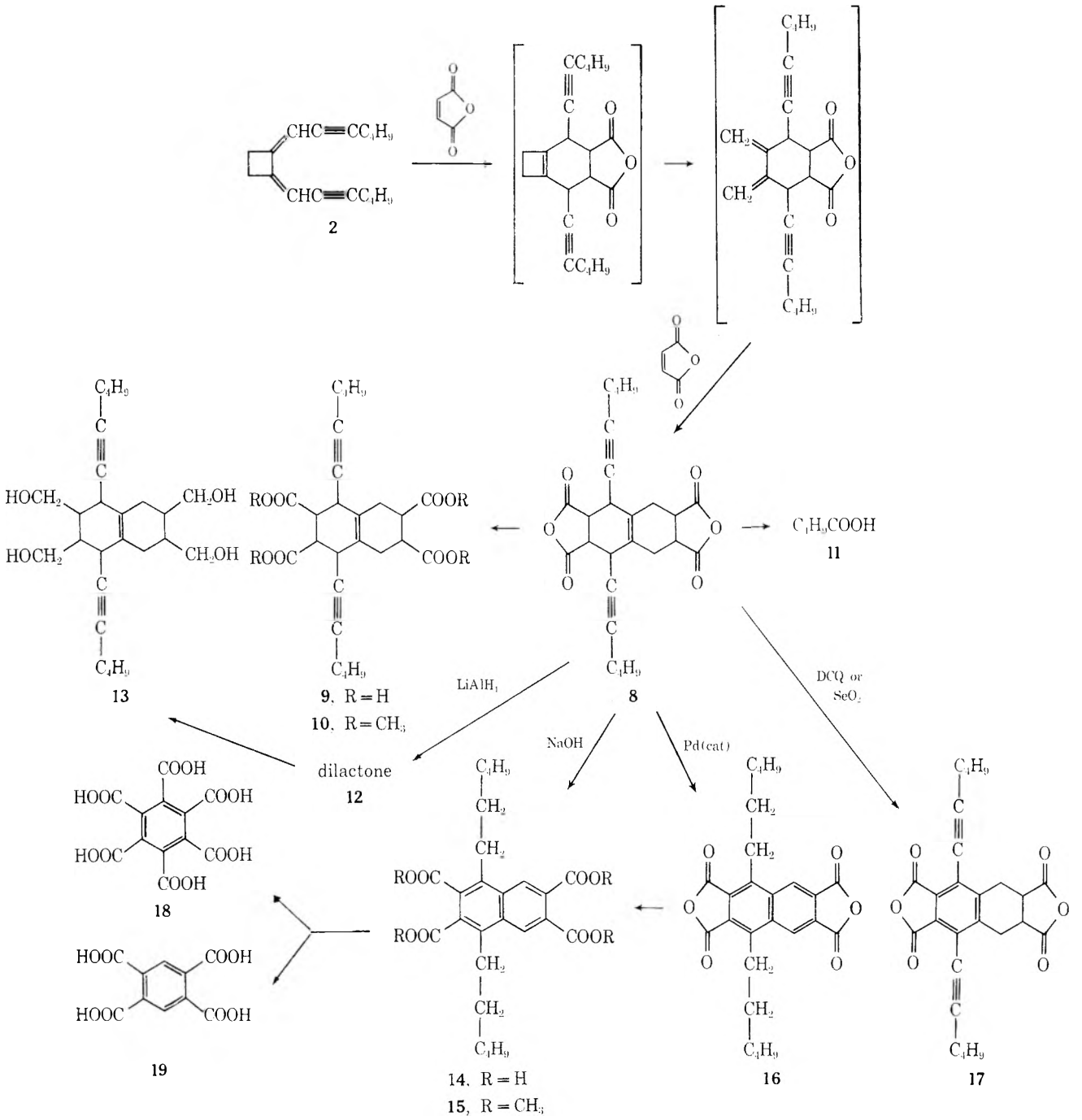
Allenes are known to dimerize by thermal [2 + 2] cycloaddition to give dimethylenecyclobutanes.[1] Among the compounds studied, we could find no example of an allene conjugated to an acetylenic group. To determine whether and how this kind of conjugation might affect the reaction, we undertook to examine the behavior of 1,2-nonadien-4-yne (**1**),[2] an allene that can lead to six *a priori* possible isomeric dimers, **2**–**7**.

1,2-Nonadien-4-yne (**1**) was found to be thermally unstable at temperatures above 100°. A variety of reaction conditions were tried in an effort to isolate dimers, but in every case only mixtures of unchanged starting material with intractable, nondistillable resins were obtained. The high boiling point together with the fact that the product showed no nuclear magnetic resonance signals attributable to vinylic protons suggested that the reaction had gone past the dimer stage, presumably at least to the level of tetramers ($C_{36}H_{48}$; ~4.1% vinylic H's) or pentamers ($C_{45}H_{60}$; 3.4%). Attempts to determine the molecularity of the process by following the decrease in the concentration of 1,2-nonadien-4-yne furnished data that, over the first 40% of the reaction, could be fitted equally well to first- as




(1) Reviews have been published by D. R. Taylor, *Chem. Rev.*, **67**, 317 (1967); T. F. Rutledge, "Acetylenes and Allenes," Reinhold, New York, N. Y., 1969; J. E. Baldwin, *Fortschr. Chem. Forsch.*, **15**, 281 (1970); and D. Seebach, "Methoden der Organischen Chemie (Houben-Weyl)," Vol. IV, 4th ed, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, 1971, p 151. Also see R. Maurin, G. Leandri, and M. Bertrand, *Bull. Soc. Chim. Fr.*, 530 (1971); T. L. Jacobs and O. L. Muscio, Jr., *Tetrahedron Lett.*, 4829 (1970).

(2) W. J. Gensler and J. Casella, Jr., *J. Amer. Chem. Soc.*, **80**, 1376 (1958).




to second-order rate expressions.[3] Thereafter, the data followed no simple kinetic order.

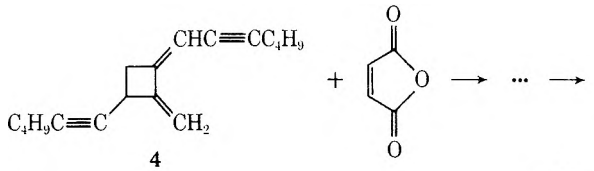
Failing to isolate dimers or lower oligomers, we resorted to trapping the dimer(s) by condensation with maleic anhydride.[4] Taking structure **2** as representing the allene dimer, the anticipated sequence of steps leading to a bis adduct may be formulated as **2** → **8**. This device proved successful, with the desired product **8** isolable in modest yield. Large amounts of gummy products were routinely obtained also; further, when the maleic anhydride was added to the allene reaction not during but immediately after the heating period, no trace of bis adduct **8** was formed. The bis adduct, therefore, must arise by action of maleic anhydride with the reactive, short-lived allene dimer **2** in competition with a more rapid oligomerization to high molecular weight products. The maleic anhydride plays no role in the initial dimerization step, **1** → **2**, since the rate of disappearance of allene was the same in the presence as in the absence of maleic anhydride.

All the properties of the bis adduct can be accommodated by formulation **8**. For example, hydrolysis gives tetraacid **9**, esterification gives the corresponding tetraester **10**, and oxidative cleavage affords more than 1 mol of valeric acid (**11**). Although 1-hexenyl side chains could account for the valeric acid, the absence of vinylic hydrogen signals in the nuclear magnetic resonance spectrum of **8** excludes this possibility.

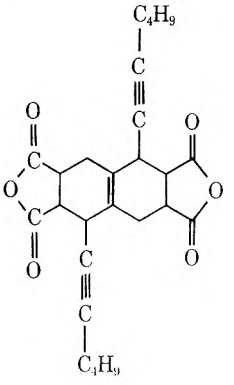
(3) N. Detzer and A. Roedig, *Tetrahedron Lett.*, 5697 (1971), find second-order kinetics for the dimerization of several tetrasubstituted allenes. This paper gives references to other kinetic studies.

(4) This approach has been used with allene itself [K. Alder and O. Ackermann, *Chem. Ber.*, **57**, 1567 (1954); A. T. Blomquist and J. A. Verdol, *J. Amer. Chem. Soc.*, **78**, 109 (1956)] and with a cyclic allene [L. Skattebøl and S. Solomon, *ibid.*, **87**, 4506 (1965)]. Another kind of reaction occurs between maleic anhydride and ethylallene, *sym*-dimethylallene, or *unsym*-dimethylallene [K. Alder and O. Ackermann, *Chem. Ber.*, **90**, 1697 (1957)].

An alternate structure for bis adduct **8** is the one derived from cycloaddition dimer **4**, namely **20**. To



4



20

distinguish between isomers **8** and **20**, we attempted to convert the bis adduct to a recognizable naphthalene bearing substituents either at positions 1, 2, 3, 4, 6, 7 (related to **8**) or at positions 1, 2, 3, 5, 6, 7 (derived from **20**). Although lithium aluminum hydride reduction to an intermediate dilactone **12** and further to the tetrahydroxymethyl compound **13** was possible, the subsequent transformation to the desired tetramethyl compound presented difficulties and was not pursued. In an alternative approach, in which the substituents remained at the carboxylic stage of oxidation, bis adduct **8** was aromatized to naphthalene **14** by the action of alkali. Bis adduct **8** and naphthalene **14** are at the same stage of oxidation, so that the conversion may be regarded as occurring through a series of alkali-catalyzed prototropic shifts.[5] Heating bis adduct **8** in the presence of a palladium catalyst caused disproportionation to naphthalene dianhydride **16**. Esterification converted both **14** and **16** to the same tetraester **15**. Dehydrogenation of bis adduct **8** with dichlorodicyanoquinone or with selenium dioxide gave product **17**, with intact hexynyl side chains attached to a benzene ring. The choice between bis adduct structures **8** and **20** was made possible by oxidatively degrading the naphthalene tetraacid **14** with permanganate to a mixture of 1,2,4,5-benzenetetracarboxylic acid (**19**) and benzenehexacarboxylic acid (**18**). Both of these acids can originate in naphthalene **14**, but only benzenepentacarboxylic acid can come from **20**. With this result, the structure of the maleic anhydride bis adduct could be accepted as **8**.

## Discussion

Although eliminating structure **20** for the bis adduct serves to eliminate structure **4** for the dimer precursor, this still does not permit an unequivocal assignment for the dimer. Inspection will show that the same bis adduct **8** can arise not only from dimer **2** but, by a parallel series of steps, from dimer **3** as well. The reported structures for the cycloaddition dimers from various other monosubstituted allenes[6] suggest that the 1,2–1,2 mode of combination is preferred over the 2,3–2,3 mode;[7] and, in our case, the 1,2–1,2 combination leads to dimer **2** rather than **3**. Further, a special factor may be operating that favors **2** over **3**. Cycloaddition dimer **2** is the only one of the six possible dimers (**2**–**7**) that has an extended chain of conjugation. If the attendant resonance stabilization contributes significantly to the transition state for formation of dimer **2**, it could be produced faster than any of the others.

So far as 1,3-dimethylenecyclobutane structures **5**, **6**, and **7** are concerned, the literature offers little support for allene dimerizations to this kind of product. In fact, the only example of a 1,3-dimethylenecyclobutane from [2 + 2] cycloaddition refers to allene itself.[8]

With these considerations, we conclude that acetylenic conjugation does not change the mode of allene cycloaddition, although it does produce a 1,2-dimethylenecyclobutane dimer of high reactivity.

## Experimental Section

**General.**—Boiling points and melting points are uncorrected. Nuclear magnetic resonance spectra were taken at 60 MHz. Galbraith Laboratories, Knoxville, Tenn., and Scandinavian Microanalytical Laboratories, Herlev, Denmark, performed the analyses for elements.

**1,2-Nonadien-4-yne (1) from 1,4-Nonadiyne.**[9]—A solution of 4 g (0.1 mol) of sodium hydroxide in 5 ml of water and 500 ml of 95% ethyl alcohol through which nitrogen was bubbling was cooled to 0° and was treated with 100 g (0.83 mol) of 1,4-nonadiyne containing less than 1% of the isomeric 2,4-diyne. The tightly stoppered mixture was stored at 0° for 15–18 hr. The cold alkaline mixture was shaken with 10 ml of concentrated hydrochloric acid plus 200 ml of petroleum ether (bp 30–60°), and the separated aqueous layer, after dilution with water to 4 l., was extracted further with petroleum ether. The combined petroleum ether layers were washed with water to pH 6–7, dried, and concentrated under reduced pressures at temperatures no higher than 45°. So far as possible throughout the entire preparation, a protective nitrogen atmosphere was kept above the solutions.

Unchanged 1,4-nonadiyne was removed as its insoluble copper derivative as follows. The product mixture was added to a cold (0°), stirred solution of cuprous chloride (45 g, 0.5 mol) in 200 ml of concentrated aqueous ammonia and 500 ml of ethyl alcohol. After about 15–20 min, when gas–liquid chromatography with a suitably processed small test sample showed that no 1,4-nonadiyne remained in solution, the mixture, diluted with 4 l. of water, was extracted several times with petroleum ether. Filtration through Kieselguhr, drying, and concentration at temperatures below 45° left a residue, which was distilled through a 9-in. vacuum-jacketed Vigreux column to give 44.2 g (44%) of water-white 1,2-nonadien-4-yne (1). Gas–liquid chromatography at 110° through a 4-ft column packed with silicone rubber on diatomaceous earth showed an intense peak at 3.1 min corresponding to the desired product 1 and a trace peak (less than 0.1%) at 4.0 min corresponding to 2,4-nonadiyne. Further exposure of the allene product 1 to alkali easily isomerized it to 2,4-nonadiene.[2] Half the starting material could be recovered from the copper precipitate as pure 1,4-nonadiyne, bp 82–83° (32 mm), by treat-

(5) R. J. Bushby, *Quart. Rev., Chem. Soc.*, **24**, 585 (1970).

(6) See especially the tabulation by D. R. Taylor in ref 1. Also *cf.* J. R. McClenon, *Diss. Abstr.*, **25**, 101 (1964).

(7) The one exception we could find refers to methylallene, which in the gas phase at 170° gives a mixture, including dimers, which consist of about twice as much of the 2,3–2,3 as the 1,2–1,2-isomer [J. J. Gajewski and C. N. Shih, *J. Amer. Chem. Soc.*, **91**, 5901 (1969)].

(8) S.-H. Dai and W. R. Dolbier, Jr., have recently reexamined the thermal dimerization of allene [*J. Org. Chem.*, **37**, 950 (1972); *J. Amer. Chem. Soc.*, **92**, 1774 (1970)].

(9) W. J. Gensler, A. P. Mahadevan, and J. Casella, Jr., *J. Amer. Chem. Soc.*, **78**, 163 (1956); H. Taniguchi, I. M. Mathai, and S. I. Miller, *Tetrahedron Lett.*, **22**, 867 (1966).

ment with cold aqueous hydrochloric acid,[2] so that the yield of allene 1 based on 1,4-nonadiyne consumed came to 86%.

**Polymerization of 1,2-Nonadien-4-yne (1). A. Polymerization without Solvent.**—When a flask provided with a reflux condenser and containing 2 g of 1,2-nonadien-4-yne (1) under a nitrogen atmosphere was lowered into a bath at 165°, the liquid boiled after 15 sec and darkened; after 1 min only a black tar remained. The same experiment at 140° showed bubbling in 30 sec. A black tar resulted even when the flask was removed as soon as boiling began.

Since 2,4-nonadiyne was almost certainly present in the 1,2-nonadien-4-yne (1), although in very low concentration, the possible involvement of the diyne had to be checked. A mixture of allene 1 and 2,4-nonadiyne (92:8) was held at 110°, with 0.5-μl samples analyzed at intervals by gas–liquid chromatography. The only two peaks appearing corresponded to those of the starting mixture, but, while the peak for the allene decreased steadily from 94 to 29 mm in 3 hr and to 3 mm after 17 hr, the diyne peak stayed about the same at about 5–8 mm. Distillation from a short-path still at temperatures gradually raised from 100 to 240° (0.01 mm) gave only a very small amount of distillate, which consisted of the starting components. A solution of the residue in carbon tetrachloride showed a broad nuclear magnetic resonance signal at δ 0.41–2.28 ppm and nothing else downfield as far as 11 ppm. This was also true when the attempted distillation was done with bath temperatures no higher than 110°.

**B. Polymerization in the Gas Phase.**—A sample of 1,2-nonadien-4-yne (1) containing 12% 2,4-nonadiyne was volatilized at 70° (10 mm), and the vapors at the reduced pressure were passed through a 24-in. Pyrex tube heated to 350°. Practically all the starting weight could be recovered as condensate at Dry Ice temperatures. Gas–liquid chromatography with the column temperature programmed to range from 110 to 300° gave only two peaks corresponding to the starting materials still in the same ratio. A similar gas-phase experiment at 420° furnished 65% of water-white condensate, again consisting only of starting materials. The hard yellow gum (30%) remaining in the tube showed no signals between δ 2.3 and 11 ppm.

**C. Polymerizations in Solution.**—The experiments were performed using 4.07 g of allene 1 containing 8.4% of 2,4-nonadiyne dissolved in 50 ml of refluxing pure solvent under a blanket of nitrogen. Aliquots, withdrawn by hypodermic needle through a septum, were analyzed by gas–liquid chromatography (110°) with the stable 2,4-nonadiyne serving as an internal reference. The only other peak observed was that for allene. A sampling of the data follows. In boiling *n*-decane (174°), the allene content dropped from 0.57 to 0.33 *M* after 5 min and to 0.082 *M* after a total time of 15 min. In *p*-xylene (130°), the allene content went from 0.57 to 0.424 *M* in 35 min and to 0.084 *M* in 160 min. In *n*-octane (125°), the change was from 0.57 to 0.49 *M* in 0.5 hr, and to 0.12 *M* in 6 hr. In toluene (110°) the change was from 0.57 to 0.51 *M* in 5 hr, and to 0.10 *M* after 48 hr. Plots of log *C* or of $1/C$ against time were linear before but not after the first 40% of reaction.

When a xylene solution of the allene containing *both* 2,4-nonadiyne (8%) and the skipped 1,4-nonadiyne (8%) was refluxed, the allene content decreased as before while the amounts of the two diynes remained about the same. At no time did gas–liquid chromatography show more than the three peaks corresponding to the initial components.

**D. Exposure to Ultraviolet Light.**—A 0.25 *M* stock solution of 1,2-nonadien-4-yne (1) containing 2,4-nonadiyne (15%) was prepared with oxygen-free pentane as solvent. Samples of this stock solution in 0.5-in. quartz tubes under a nitrogen atmosphere were tightly stoppered with rubber serum caps. The three ultraviolet sources used were a Sylvania blue-black lamp, a Sylvania H37/5KB lamp, and a high-intensity 253.7-nm source. During irradiation periods of up to 66 hr, no gas–liquid chromatography peaks other than the two corresponding to the starting materials were observed. Since the height of the peaks changed little and not regularly, only a minimal amount of photochemistry could have occurred.

**Polymerization of Allene 1 in the Presence of Maleic Anhydride.**—1,2-Nonadien-4-yne (14 g, 0.20 mol) containing about 3% of 2,4-nonadiyne was added over a period of 5 min to a solution of maleic anhydride (19.6 g, 0.20 mol) in pure *p*-xylene (200 ml) refluxing in a nitrogen atmosphere. After 3.5 hr, gas–liquid chromatography showed that no allene 1 remained. Distillation removed the solvent, followed by 11.3 g (56.5% recovery) of unchanged maleic anhydride, bp 100° (5 mm), mp 51–52°. Recrystallizations of the brown, viscous residue from ether–petroleum ether and from ethyl acetate gave 5.8 g (13%) of white, crystalline bis adduct **8**, mp 231–235°. The presence of a small quantity of hydroquinone did not change the yield significantly. Use of an excess of maleic anhydride resulted in a somewhat lower yield. Changing the solvent to *n*-octane gave the same yield (14%), but a longer reaction time in refluxing toluene lowered the yield.

When two parallel reactions were run with 1.2 g (0.01 mol) of allene in 20 ml of refluxing xylene, one with and the other without 0.98 g (0.01 mol) of maleic anhydride, the decrease in allene concentration in each tube followed the same curve to within 4%. Adding maleic anhydride to an octane solution of allene that had been boiled for 9 hr and in which allene could no longer be detected, and then refluxing the mixture gave none of the bis adduct and allowed recovery of 97.5% of the maleic anhydride.

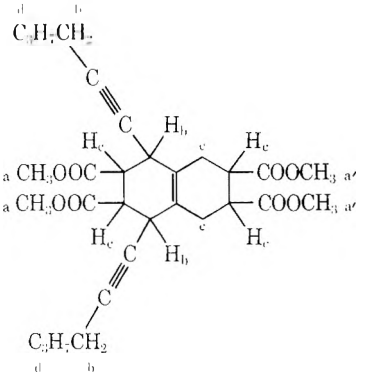
Further crystallization brought the melting point of bis adduct **8** to 235–236°: mass spectrum *m/e* (rel intensity) 436 (37), 364 (84), 279 (100), 45 (90), 42 (100); ir (mineral oil mull) 2220 (C≡C), 1870, 1790 $cm^{-1}$; nmr ($CF_3CCOOH$) δ 2.32–1.90 (m, 14, ring protons plus 2 $CH_2C{\equiv}C$), 1.10–0.55 ppm (m, 14, 2 $C_3H_7$).

*Anal.* Calcd for $C_{26}H_{28}O_6$: C, 71.54; H, 6.47. Found: C, 71.33; H, 6.49.

**Tetracarboxylic Acid 9 and Ester 10 Derived from Bis Adduct 8.**—A mixture of 2.5 g of bis adduct **8** and 10 ml of 2 *N* sodium hydroxide solution was heated at steam-bath temperatures until the solids dissolved. Acidification with 2 *N* hydrochloric acid to pH 2 precipitated a white solid, which after washing with a small volume of cold water and drying *in vacuo* weighed 2.7 g (100%), mp 213–216°. Recrystallization from ethanol gave 1.9 g (70%) of white, needlelike tetraacid **9**, mp 216.5–217.5°, ir (mineral oil mull) 3600, 2500, 2220, 1700 $cm^{-1}$.

*Anal.* Calcd for $C_{26}H_{32}O_8$: C, 66.72; H, 6.71. Found: C, 66.45; H, 6.93.

To form the tetraester **10**, bis adduct **8** (3.0 g, 0.0069 mol) was dissolved in refluxing absolute methanol (25 ml). The solution was cooled to 0°, and diazomethane in ether was added until the yellow color persisted. After a drop of 2 *N* acetic acid was added, the solution was concentrated to a volume of 10 ml and then held at 0–5° for 1 day. The resulting precipitate of colorless cubes of tetramethyl ester **10** (3.2 g, 88%) showed mp 207–209°. One crystallization from methanol gave product with mp 210.5–211° (2.6 g): ir ($CHCl_3$) 2850, 2230, 1735, 1105 $cm^{-1}$; nmr ($CDCl_3$) δ 3.76 and 3.84 (two s, 6 and 6, a and a'), 2.29 (m, 6, b), 1.91 (m, 8, c), 1.06–0.73 ppm (m, 14, d).



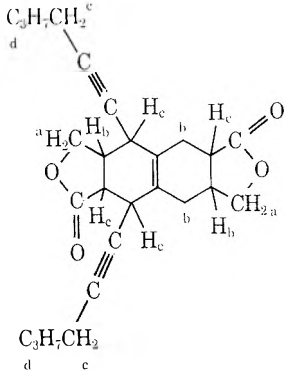
*Anal.* Calcd for $C_{30}H_{40}O_8$: C, 68.15; H, 7.64. Found: C, 68.32; H, 7.79.

**Oxidative Cleavage of Bis Adduct 8. A. Ozonolysis.**—Over a 3-hr period, ozonized oxygen was bubbled into a −78° solution of bis adduct **8** (0.215 g, 0.493 mmol) in methanol (100 ml). After the excess ozone had been swept out with oxygen (1 hr, 0°), the solution was treated with 2 g of zinc dust and 20 ml of ice–water, and the mixture was stirred for 18 hr. Solids were removed, and the filtrate, to which 10 ml of 2 *N* sodium hydroxide was added, was distilled *in vacuo* in a 40–50° heating bath to remove methanol. The remaining aqueous solution was acidified to pH 2, saturated with sodium chloride, and extracted continuously with ether for 24 hr. The dried extract was treated at room temperature with 5 mmol of diazomethane in ether (25 ml). Removal of low-boiling material left 96 mg of a yellow, oily residue. Gas–liquid chromatography (110° column) showed only a single peak even when the column temperature was

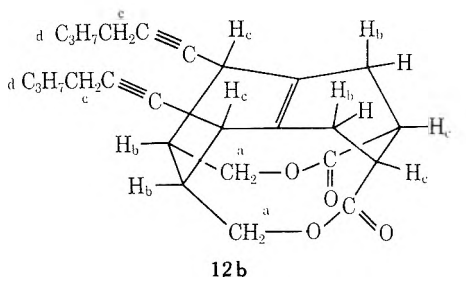
brought to 210°; direct gas–liquid chromatography comparisons with authentic samples of methyl butyrate, methyl valerate, and methyl hexanoate identified this product as methyl valerate. After column chromatography through a silica gel column with ether as eluent, 88 mg (79% assuming a 2-mol yield) of pure methyl valerate was obtained, which was identified by gas–liquid chromatography and by thin layer chromatography (silica gel with 39:1 *n*-pentane–ether) comparisons.

B. **Oxidative Cleavage with Permanganate.**—A solution of 1.00 g (2.29 mmol) of bis adduct **8** in 50 ml of 2% aqueous sodium bicarbonate was titrated at 50° with 0.100 *M* permanganate. A permanent pink color persisted only after adding 125.5 ml of the reagent. If each of the acetylenic carbon atoms in **8** is oxidized to carboxyl, and if the two carbon atoms of the double bond are oxidized to the ketone stage, the equivalence point may be calculated to be 121.8 ml, in good agreement with that found. A steam-volatile acid (3.17 mmol by alkali titration of the steam distillate) could be obtained by processing the oxidation mixture. Further treatment gave pure methyl valerate (3.02 mmol) as assayed by gas–liquid chromatography, so that the yield of valeric acid **11** here too comes to about 70%.

**Dilactone 12 by Lithium Aluminum Hydride Reduction of Bis Adduct 8.**—Over a 5-min period, a solution of 1.5 g (3.4 mmol) of bis adduct **8** in 5 ml of tetrahydrofuran was added to a cooled, stirred suspension of lithium aluminum hydride (0.56 g, 14 mmol) in 10 ml of tetrahydrofuran. After 2 hr, water (1 ml) was carefully added followed by enough 2 *N* hydrochloric acid to dissolve the solids. Product was taken up in ether, and the ether extract was dried and stripped of solvent. Cooling the residue gave a precipitate, which was collected by centrifugation and recrystallized from methylene chloride–benzene. The dilactone **12**, mp 141.5–142.5°, was obtained in this way in 0.24-g yield: ir ($CHCl_3$) 2870, 2230, 1745 $cm^{-1}$; nmr ($CDCl_3$) δ 4.05 (distorted t, 4, a), 2.29 (*ca.* t, 6, b), 1.81 (m, 8, c), 1.09–0.83 ppm (m, 14, d). Formulations **12a** and **12b** are both possible, but, since the



**12a**



**12b**

observed 1745-$cm^{-1}$ lactone carbonyl absorption is low for a five-membered lactone, we favor **12b**.

*Anal.* Calcd for $C_{26}H_{32}O_4$: C, 76.46; H, 7.90. Found: C, 76.59; H, 7.81.

**Naphthalenes from Bis Adduct 8. A. Base-Catalyzed Prototropy.**—A stoppered mixture of 1.5 g (3.44 mmol) of bis adduct **8** and 10 ml of 10% aqueous sodium carbonate was stored at room temperature for 5 weeks. Acidification with 6 *N* hydrochloric acid followed by extraction of organic material into ether, etc., afforded 1.6 g of naphthalenetetracarboxylic acid **14** as a white solid. The corresponding tetraester **15** was formed by refluxing a solution of this solid in 10 ml of methanol containing 1 ml of boron trifluoride etherate. After dilution of the reaction mixture with 20 ml of cold water, shaking with ether extracted the product, which was isolated in the usual way to give 1.71 g of white tetramethyl ester **15**, mp 196–201°, showing a dark thin layer chromatographic spot at $R_f$ 0.37 (2:1 chloroform–ether) and a light spot at $R_f$ 0.42. Recrystallization from methanol afforded 0.95 g (52%) of white, crystalline product **15**: mp 204.5–206°; $R_f$ 0.37 (note, this is slower running than tetramethyl ester **10**, with $R_f$ 0.49); uv ($10^{-3}$–$10^{-5}$ *M* in $CH_3OH$) $\lambda_{max}$ 242 nm (log ε 4.87), 304 (3.82), 342 sh (2.87), 387 (2.25); blue fluorescence under ultraviolet light; ir ($CHCl_3$) 3010, 1725, 1628, 1105 $cm^{-1}$; nmr ($CDCl_3$) δ 7.91 (s, 2, aromatic H), 3.97 (s, 12, $OCH_3$), 2.24 (t, $J$ = 6–7 Hz, 4, benzylic H's), 1.19–0.65 (m, 22, all other H's).

*Anal.* Calcd for $C_{30}H_{40}O_8$: C, 68.15; H, 7.64. Found: C, 68.06; H, 7.49.

The same product was obtained on refluxing a solution of the bis adduct **8** in 1 *N* aqueous sodium hydroxide under nitrogen for 12 days. Exposing the bis adduct to hot sodium methoxide in methanol for 3 days, however, proved not to be particularly effective.

B. **Catalytic Disproportionation.**—A mixture of bis adduct **8** (2.2 g), 50 ml of peroxide-free *p*-cymene (bp 177°), and 5 g of 10% palladium on carbon was refluxed under nitrogen for 3 hr. Removal of solids and then solvent left an off-white solid (2.06 g, mp 272–277°), which on recrystallization from ethyl acetate and tetrahydrofuran furnished white, needlelike bis anhydride **16** (1.5 g, 66%), mp 281–281.5°, ir (mineral oil mull) 3010, 1850, 1780, 1615 $cm^{-1}$.

*Anal.* Calcd for $C_{26}H_{28}O_6$: C, 71.54; H, 6.49. Found. C, 71.63; H, 6.45.

When *p*-cymene was replaced with *p*-xylene (bp 138°), no reaction occurred over a 17-hr period. The process was not simply thermal, since 96% of unchanged starting material could be recovered after refluxing a cymene solution of bis adduct **8** in the absence of palladium catalyst.

To form the tetramethyl ester, a methanol solution of bis anhydride **16** (1.1 g in 15 ml) containing 1 ml of boron trifluoride etherate solution was refluxed overnight. The brown residue, obtained on removing volatiles, could be crystallized from methanol to give 0.91 g (69%) of tetramethyl ester **15**, mp 204.5–205.5°, showing the same properties as those described above.

**Dehydrogenation of Bis Adduct 8 to Tetralin 17.**—Dry dioxane (25 ml) containing 2.2 g (5.0 mmol) of bis adduct **8** plus 4.5 g (20 mmol) of 2,3-dichloro-5,6-dicyanoquinone was refluxed for 6 hr. Filtration gave 2.6 g of insoluble 2,3-dichloro-5,6-dicyanohydroquinone, an amount corresponding to the consumption of 11.4 mmol of reagent. Refluxing the filtrate further for 17 hr precipitated no more hydroquinone. Thin layer chromatography at this point demonstrated the presence of quinone, hydroquinone, and product **17**, but not of starting material **8**. After the remaining 2,3-dichloro-5,6-dicyanoquinone was destroyed by adding 2 ml of tetralin and boiling the mixture, the mixture was cooled and filtered and the filtrate was stripped of volatile materials. The brown residue, crystallized from ethyl acetate, afforded 1.4 g of white, crystalline product **17**: mp 267.5–268.5°; ir (mineral oil mull) 2230, 1870, 1765, 1620 $cm^{-1}$; nmr (DMSO-$d_6$) δ 2.26 (m, 8, benzylic H's plus $C{\equiv}CCH_2$), 1.86 (m, 2, $HCC{=}O$), 1.60 ppm (m, 14, all other H's).

*Anal.* Calcd for $C_{26}H_{24}O_6$: C, 72.20; H, 5.59. Found: C, 72.42; H, 5.80.

The same product **17** was formed when bis adduct **8** was dehydrogenated with selenium dioxide in acetic anhydride. Chloranil failed to effect dehydrogenation.

**Benzenecarboxylic Acids 18 and 19 by Oxidative Degradation of Naphthalene Derivative 14.**—When a mixture of naphthalene **14** (2.2 g, 5 mmol), 5 g of sodium hydroxide, 15 ml of water, and 7.9 g of potassium permanganate was held at 70–80° for 4–5 hr, all the oxidant was converted to manganese dioxide. The filtrate from this mixture was acidified to pH 2 with 25% sulfuric acid, cooled, and filtered to collect solids. Treatment with methanol dissolved the organic material and allowed the inorganics to be separated by decanting. To methylate the carboxylic acid groups, ethereal diazomethane was added until the yellow color persisted. Removing all volatiles left a mixture of white solids (0.49 g).

For separation, the product mixture dissolved in ethyl acetate (50 mg in 0.5 ml) was streaked onto a plate covered with a 2-mm layer of silica gel, and the plate was developed with 1:1 ether–benzene. The resulting three bands were scraped off, each was extracted with ethyl acetate, and the solvent was then removed to isolate the separated compounds. The respective fractions from three such preparative plates (*i.e.*, from a total of 150 mg of

mixed oxidation products) were combined and examined individually. The fastest moving material (22 mg) showed $R_f$ 0.76 on thin layer chromatography (1:2 ether–benzene), melted at 247–249°, and produced a pale-blue fluorescence under ultraviolet light. This product, which could be the naphthalene hexacarboxylate, was not investigated further. The fraction with $R_f$ 0.51 weighed 16 mg and showed mp 138–140°; the fraction with $R_f$ 0.35 weighed 44 mg and showed mp 187–188°. Direct thin layer chromatographic and mixture melting point comparisons with authentic samples of the methyl esters of 1,2,4,5-benzenetetracarboxylic acid, benzenepentacarboxylic acid ($R_f$ 0.44), and benzenehexacarboxylic acid identified the material with $R_f$ 0.51 as the tetraester of acid **19**, and the material with $R_f$ 0.35 as the hexaester of acid **18**. No pentaester could be detected among the oxidation products.

**Acknowledgment.**—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

**Registry No.**—**1**, 41580-44-3; **2**, 41580-45-4; **8**, 41580-46-5; **9**, 41580-47-6; **10**, 41580-48-7; **12b**, 41580-49-8; **14**, 41580-50-1; **15**, 41580-51-2; **16**, 41580-52-3; **17**, 41580-53-4; 1,4-nonadiyne, 6088-94-4.

# Synthesis of DL-Slaframine

WALTER J. GENSLER* AND MAE W. HU

*Department of Chemistry, Boston University, Charles River Campus, Boston, Massachusetts 02215*

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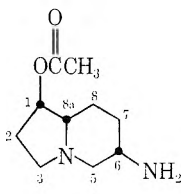
A stereoselective synthesis of slaframine is described. Ethyl *N*-(β-carbethoxyethyl)-5-oxopyrrolidine-2-carboxylate was obtained conveniently from glutamic acid and acrylonitrile. Dieckmann cyclization of this pyrrolidine diester followed by hydrolysis, decarboxylation, and catalytic hydrogenation furnished 2-(β-carbomethoxyethyl)-3-hydroxypyrrolidine hydrochloride. *N*-Alkylation with methyl bromoacetate led to a mixture of the lactone and the methyl ester of *N*-(carbomethoxymethyl)-2-(β-carboxyethyl)-3-hydroxypyrrolidine, which could be cyclized by a second Dieckmann process. Subsequent hydrolysis, decarboxylation, and acetylation gave 1-acetoxy-6-oxoindolizidine, which, after conversion into the oxime, was hydrogenated to DL-slaframine.

Slaframine (**1**), an alkaloid first detected as the result of its property of stimulating excess salivation in live-



**1**

stock foraging on fungus-infected red clover, has been isolated in low yield from cultures of *Rhizoctonia leguminicola*.[1,2] The proposed indolizidine structure **1**,[3,4] as revised in 1968,[5] has been confirmed by synthesis.[6] Since slaframine is of interest as a possible research tool for locating acetylcholine receptor sites and as an agent relieving the symptoms of cystic fibrosis,[7-9] we were led to investigate alternative approaches. The present paper describes our work on a direct and stereoselective synthesis of DL-slaframine (**13**).

The starting point was ethyl *N*-(β-carbethoxyethyl)-5-oxopyrrolidine-2-carboxylate (**3**), which can be prepared conveniently from L-(+)-glutamic acid (**2**) and acrylonitrile.[10] Cyclization with sodium ethoxide produced ethyl 1,5-dioxopyrrolizidine-2-carboxylate (**4**). Although pyrrolidone **3** still showed optical activity, pyrrolizidine **4** was completely racemized. Decarboxylation of the pyrrolizidine **4** in hot hydrochloric acid was accompanied by lactam ring hydrolysis, so that the product was the 3-oxopyrrolidine acid **5**. The corresponding alcohol methyl ester **6** was obtained (46% from **3**) by hydrogenating the keto group over a platinum catalyst in methanol solvent.

To attach the fused six-membered rings as in slaframine (**1**), the sequence continued by alkylating hydroxypyrrolidine **6** on nitrogen with methyl bromoacetate. The expected diester **7** was obtained mixed with the equally useful lactone **8** (40 and 23%, respectively). The relation between the two products was established by allowing lactone **8** to methanolize, whereupon dimethyl ester **7** was produced. Dieckmann cyclization of a mixture of diester **7** and ester lactone **8** gave rise to indolizidine **9**. Although there is no steric barrier to direct ring closure of lactone **8** as a first step, whether this occurs or whether there is prior *in situ* methanolysis that converts the lactone into the diester **7** was not ascertained. The unstable Dieckmann product **9** was decarboxylated with acid to give 1-hydroxy-6-oxoindolizidine hydrochloride (**10**), which was first acetylated to **11** and then converted into the relatively stable oxime **12**.

With the hope of providing milder conditions in the decarboxylation stage (**9** to **10**), *tert*-butyl bromoacetate was substituted for methyl bromoacetate in the *N*-alkylation of pyrrolidine **6**. Although a pair of products analogous to diester **7** and lactone **8** was obtained in good yield, the next two steps with these *tert*-butyl esters was found to offer no advantages over the methyl esters.

The oxime **12** emerged as a mixture of syn and anti forms, which could be separated and characterized. The last step proceeded by hydrogenating the mixed

(1) D. P. Rainey, E. B. Smalley, M. H. Crump, and F. M. Strong, *Nature*, **205**, 203 (1965).
(2) S. D. Aust and H. P. Broquist, *Nature*, **205**, 204 (1965).
(3) S. D. Aust, H. P. Broquist, and K. L. Rinehart, Jr., *J. Amer. Chem. Soc.*, **88**, 2879 (1966).
(4) B. J. Whitlock, D. P. Rainey, N. V. Riggs, and F. M. Strong, *Tetrahedron Lett.*, 3819 (1966).
(5) R. A. Gardiner, K. L. Rinehart, Jr., J. J. Snyder, and H. P. Broquist, *J. Amer. Chem. Soc.*, **90**, 5639 (1968).
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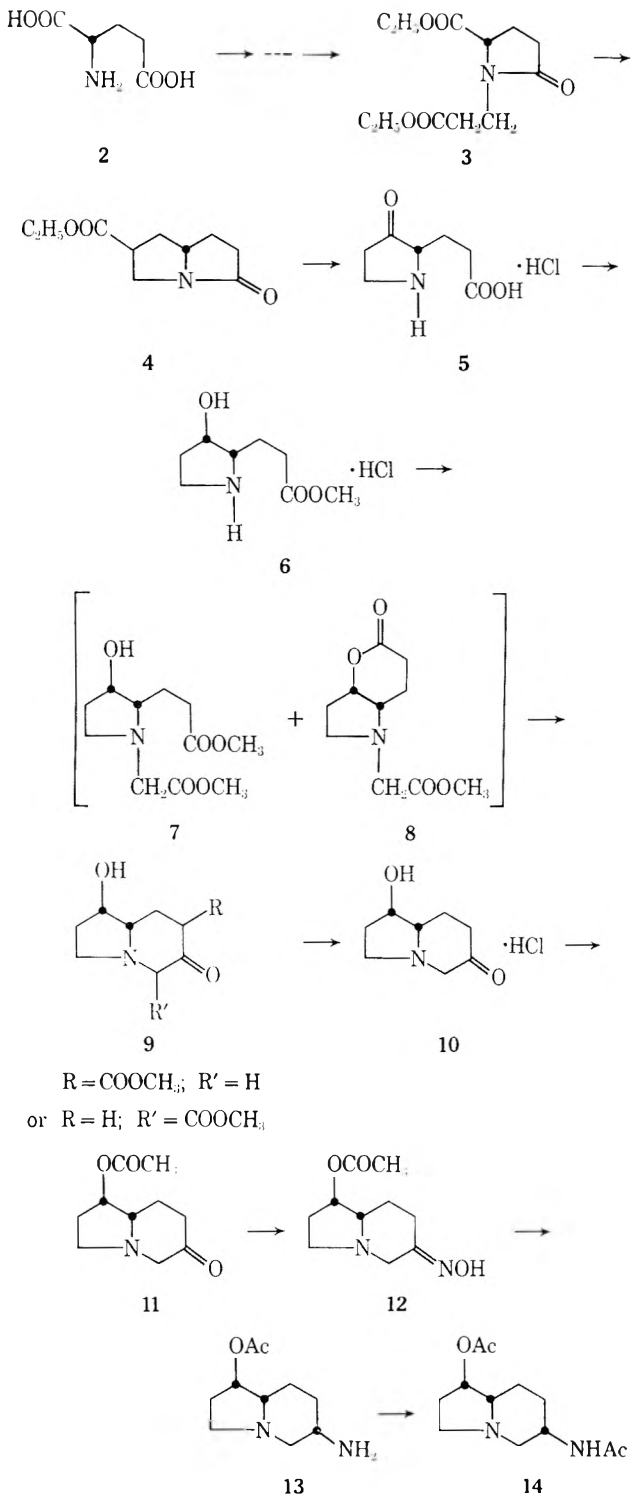
(9) *Cf. Chem. Eng. News*, **46**, 43 (July 15, 1968).
(10) L. L. McKinney, E. H. Uhing, E. A. Setzkorn, and J. C. Cowan, *J. Amer. Chem. Soc.*, **72**, 2599 (1950); J. F. Cavalla, J. Davoll, M. J. Dean, C. S. Franklin, D. M. Temple, J. Wax, and C. V. Winder, *J. Med. Pharm. Chem.*, **4**, 1 (1961).

oximes to the final product, DL-slaframine (**13**). Neither the hygroscopic dihydrochloride of slaframine **13** nor the free base itself was as convenient to work with as the dipicrate, so that we generally relied on the dipicrate for product isolation and for purification. The identity of our product as DL-slaframine was proved by the correspondence in properties of the dihydrochloride, dipicrate, free base, and *N*-acetyl derivative **14**




of the synthetic material with those of the natural alkaloid. Tables I, II, and III give the details.

The two steps in our synthesis that determine the configuration, *i.e.*, **5** to **6** and **12** to **13**, are both platinum-catalyzed hydrogenations in acidic media. In this kind of process the hydrogen generally favors in-

TABLE I

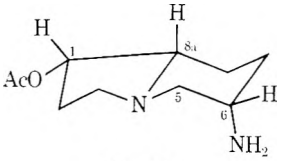
COMPARISON OF DIPICRATES FROM SYNTHETIC AND NATURAL SLAFRAMINE

| | Synthetic, 215–221° dec | Natural, 180–184° |
|---|---|---|
| Mp[a] | | |
| Ir[b] | 3000, 1738, 1634, 1368, etc., $cm^{-1}$ | 3000, 1738, 1634, 1364, etc., $cm^{-1}$ |
| Nmr[c] | δ 8.60, 8.10 (broad), 5.35 ($W_{1/2}$ = 13 Hz), 4.12–2.86 (m), 2.32–1.57 (m) ppm | δ 8.59, 8.12 (broad), 5.35 ($W_{1/2}$ = 13 Hz), 4.12–2.88 (m), 2.30–1.57 (m) ppm |
| Tlc | $R_f$[d] 0.87, 0.66 | $R_f$[d] 0.87, 0.66 |
| | $R_f$[e] 0.63, 0.68 | $R_f$[e] 0.63, 0.68 |

[a] The mixture melting point was 180–195°. The different melting points represent the only discrepancy in properties. We suggest that the racemic derivative is a molecular compound of the two enantiomers. [b] The ir curves, taken with KBr pellets, were superposable. [c] The curves were determined with the dipicrates dissolved in DMSO-$d_6$, with both curves showing a prominent singlet at 2.10 ppm. The low solubility in DMSO made integration difficult. The dipicrate was only slightly soluble in $F_3CCOOH$, $D_2O$, or $CDCl_3$. [d] The solvent system here was 7:7:3 chloroform–methanol–17% ammonium hydroxide. The yellow $R_f$ 0.66 spots were identified as dissociated picric acid and the $R_f$ 0.87 spot as dissociated free base by separate determinations of picric acid and of slaframine on the same plate. The dissociation of amine picrates during thin layer chromatography has been observed by H. B. Henbest, E. R. H. Jones, and G. F. Smith, *J. Chem. Soc.*, 3796 (1953), and by P. A. Plattner and A. S. Pfau, *Helv. Chim. Acta*, **20**, 224 (1937). The slaframine with $R_f$ 0.87 came out as a brown spot with iodine vapor or as an orange-red spot with a spray of aqueous hydrochloric acid containing bismuth subnitrate and potassium iodide (Dragendorff mixture). [e] These results were obtained with 7:7:1 chloroform–methanol–17% ammonium hydroxide, with $R_f$ 0.63 corresponding to the free base and $R_f$ 0.68 to picric acid.

sertion into the unsaturation from the less hindered side,[11] and, since in both substrates scale models suggest clearly which side is the less hindered, we had a good basis from which to predict the stereochemical outcome. This led us to expect the hydrogen atoms at positions 1, 8a, and 6 of slaframine (**1**) to appear on the same side of the molecule. Thus, the earlier assignment for the slaframine configuration, as in **1**,[5] receives independent support.

Several spectroscopic data also agree with this configuration as well as with the conformation shown in **15** for slaframine. So far as the ring fusion in **15** is




**15** = **13**

concerned, the relatively intense infrared absorption peaks observed in the 2800–2700-$cm^{-1}$ region point to the trans arrangements.[12,13] These same peaks are also noted in indolizidine intermediates **9**, **10**, **11**, **12** (syn and anti) as well as in *N*-acetylslaframine (**14**). The relative configurations at positions 1 and 8a are

(11) R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, New York, N. Y., 1965, pp 46, 86, 101; E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 119; S. Siegel, *J. Amer. Chem. Soc.*, **75**, 1317 (1953).

(12) H. S. Aaron, C. P. Radar, and G. E. Wicks, Jr., *J. Org. Chem.*, **31**, 3502 (1966).

(13) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958); H. S. Aaron, *Chem. Ind. (London)*, 1338 (1965); C. P. Rader, R. L. Young, Jr., and H. S. Aaron, *J. Org. Chem.*, **30**, 1536 (1965).

TABLE II

COMPARISON OF SYNTHETIC AND NATURAL SLAFRAMINE BASES

| | Synthetic | Natural |
|---|---|---|
| Ir[a] | 1734, 1242 $cm^{-1}$ | 1734, 1242 $cm^{-1}$ |
| Nmr[b] | $\delta$ 5.22, 2.09 ppm | $\delta$ 5.22, 2.09 ppm |
| Tlc[c] | $R_f$ 0.66,[d] 0.64, 0.12 | $R_f$ 0.66,[d] 0.64, 0.12 |
| Glc,[e,g] retention time (area, appearance) | 7.3 min (3%, broad), 11.1[f] (79, slight distortion), 18.2 (1, broad), 24.8 (12, broad), 31.1 (5, broad) | 7.6 min (3%, broad), 11.1[f] (67, slight distortion), 18.2 (19, broad), 24.8 (5, broad), 31.6 (6, broad) |

[a] The two infrared absorption curves, both taken with $CCl_4$ solutions, were identical. [b] Samples recovered from the infrared determinations were used here. Although all features of the two curves matched very well, the inadequate integration results allowed no comparison on this basis. The solvent used was $CDCl_3$. [c] Different solvent systems gave different $R_f$ values, although in no case was more than one spot noted. Exposure to iodine vapor gave brown spots; exposure to acid bismuth subnitrate plus potassium iodide gave orange-red spots with the same $R_f$ values. [d] The decreasing $R_f$ values were obtained respectively with 7:6:2 chloroform–1-propanol–29% aqueous ammonia, with 7:7:1 chloroform–1-propanol–17% aqueous ammonia, and with 7:7:0.1 chloroform–1-propanol–29% aqueous ammonia. [e] The comparisons utilized a 6-ft column of methyl phenyl silicone supported on an acid-washed calcined diatomite support at 140° (1.5% OV 17 supported on Chromosorb W). [f] Tentatively, the 11.1-min peak is associated with the slaframine; the other peaks may arise as the result of decomposition at the port or on the column. [g] To get some idea of the nature of the synthetic slaframine base *before* purification, it was isolated from its hydrochloride directly out of a hydrogenation run and examined by glc. The following features appeared: 4.2 min (18%, sharp peak), 6.7 (8%, broad), 8.9 (1%, broad), 11.1 (71%, slightly distorted), 25.0 (1%, broad), and 31.5 (1%, broad). The area of the large peak at 11.1 min compared favorably with the purer samples.

TABLE III

COMPARISON OF *N*-ACETYL DERIVATIVES OF SLAFRAMINE

| | Synthetic | Natural |
|---|---|---|
| Mp[a] | 143–146° | 143–146° |
| Ir[b] | 3426, 1735, 1663, 1509 $cm^{-1}$ | 3420, 1735, 1663, 1510 $cm^{-1}$ |
| Nmr[c] | $\delta$ 5.20 ($W_{1/2}$ = 13 Hz), 4.20 ($W_{1/2}$ = 8 Hz) | $\delta$ 5.31 ($W_{1/2}$ = 13 Hz), 4.24 ($W_{1/2}$ = 8 Hz) |
| Mass spectrum[d] | *m/e* 240 (M), 181 (M − $AcNH_2$), 121 (M − $AcNH_2$ − AcOH) | *m/e* 240, 181, 121 |
| Tlc[e] | $R_f$ 0.60,[f] 0.49, 0.25 | $R_f$ 0.60,[f] 0.49, 0.25 |
| Glc,[g] retention time | 4.5, 15.1 min | 4.5, 15.1 min |

[a] The mixture melting point was 143–146°. [b] The curves were taken from chloroform solutions, with the curve for the natural material sent to us by Dr. Aust.[3] The two curves were essentially identical. [c] The nmr spectrum for the natural material as furnished by Aust[3] was essentially the same as the one obtained here with the synthetic material. Data for the nmr absorption of the hydrochloride of *N*-acetylslaframine are also available.[5] [d] The two mass spectra, determined on a Hitachi Perkin-Elmer RMU-6E instrument, were virtually superposable. [e] In each case only one spot was seen. Comparisons performed by Aust in his laboratory, using samples of our synthetic *N*-acetylslaframine, independently established the identify of the synthetic and natural materials. [f] The decreasing $R_f$ values were obtained with the following solvents, in order: 7:6:0.1 chloroforom–1-propanol–29% aqueous ammonia, 7:7:0.1 chloroform–1-propanol–29% ammonia, and 16:4:0.5 ether–ethanol–29% ammonia. [g] Single peaks were noted, with the shorter retention time obtained at 220° and the longer at 185°. Comparisons made by Rinehart in his laboratory using a sample of our synthetic *N*-acetylslaframine independently confirmed the identity.

supported by nuclear magnetic resonance measurements. The curve for indolizidine **9** shows a signal for $H_1$ at $\delta$ 4.12 ppm with $W_{1/2}$ = 11 Hz. The same signal with about the same bandwidth is seen for both oxime acetates **12** ($W_{1/2}$ = 13 Hz) as well as for *N*-acetylslaframine (**14**) ($W_{1/2}$ = 13 Hz). With the help of scale models built according to **15**, the bandwidths can be estimated[14] to be 13 Hz for cis ($H_{8a}$, $H_1$) and 18.4 Hz for trans ($H_{8a}$, $H_1$). Thus the cis geometry is preferred.[15] So far as the configuration at position 6 is concerned, *N*-acetylslaframine (**14**) shows a nuclear magnetic resonance signal for $H_6$ with $W_{1/2}$ = 8 Hz (N–H coupling removed). This value corresponds more closely to the $W_{1/2} \sim 12$ Hz calculated for equatorial $H_6$ (as assigned for slaframine) than for $W_{1/2} \sim 22$ Hz calculated for axial $H_6$.

## Experimental Section

**General Information.**—All proton magnetic resonance spectra were determined at 60 MHz. Temperature readings are uncorrected. The concentrations of solutions used for optical rotation readings are given in grams per 100 milliliters. All thin layer chromatography runs used polyethylene terephthalate supported layers of silica gel 0.1 mm thick. Analyses for elements were reported either by Galbraith Laboratories, Inc., Knoxville, Tenn., or by Werby Laboratories, Inc., Boston, Mass.

**Ethyl *N*-(β-Carbethoxyethyl)-5-oxo-2-pyrrolidinecarboxylate (3).**—*N*-(β-Cyanoethyl)-5-oxo-2-pyrrolidinecarboxylic acid, prepared from 147 g of L-(+)-glutamic acid (**2**) and acrylonitrile,[10] was esterified by refluxing with absolute ethanol (698 ml) containing concentrated sulfuric acid (207 g) for 18 hr. Precipitated inorganic salts were removed from the cooled mixture, and the clear solution was concentrated at 30°. After adjusting the concentrate to pH 5 with 10% bicarbonate, product was collected by repeated extractions with chloroform. The combined extracts were rinsed with small volumes of 10% bicarbonate and saturated salt solution, dried, and concentrated. Distillation afforded 140 g (55% from glutamic acid) of the desired diester **3**: bp 134–135° (0.07 mm); $[\alpha]^{25}D$ −12.3° (c 1.41, $C_2H_5OH$); ir ($CHCl_3$) 1740 (ester C=O) and 1740 $cm^{-1}$ (lactam C=O); nmr ($CDCl_3$) $\delta$ 4.25 (q, *J* = 7 Hz, $OCH_2CH_3$), 3.90–3.60 (m, pyrrolidine no. 2 H), 3.42 (t, *J* = 7 Hz, $N-CH_2CH_3$), 2.56 (distorted t, ring $CH_2C=O$), 2.40–1.80 (m, ring no. 3 $CH_2$ plus acyclic $CH_2C=O$), 1.28 and 1.22 ppm (2 t, *J* = 6–7 Hz, 6, 2 $-OCH_2CH_3$'s). The integration ratio for the signals at $\delta$ 4.25–3.42 and at 2.56–1.84 ppm was 7:6 as required. This ethyl *N*-(β-carbethoxyethyl)-5-oxo-2-pyrrolidenecarboxylate (**3**) was homogeneous according to both thin layer chromatography (2:1 ether–hexane) and gas–liquid chromatography (neopentyl glycol succinate column at 180°).

*Anal.* Calcd for $C_{12}H_{19}NO_5$: C, 56.06; H, 7.59; N, 5.64. Found: C, 56.01; H, 7.46; N, 5.44.

**1,5-Dioxo-2-carbethoxypyrrolizidine (4) from Ethyl *N*-(β-Carbethoxyethyl)-5-oxo-2-pyrrolidenecarboxylate (3).**—A solution of 50.3 g (0.196 mol) of diester **3** in 50 ml of absolute ethanol was added dropwise to a room temperature solution of sodium

(14) R. H. Bible, Jr., "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965; N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 79, 80; also see F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961).

(15) Note that the $H_1$ signal for 1-hydroxyindolizidine itself has been reported with $W_{1/2}$ = 11.5 Hz and $W_{1/2}$ = 21 Hz for the cis and trans forms, respectively.[12]

(6.2 g, 0.27 g-atom) in absolute ethanol (125 ml). With pure nitrogen blanketing the reaction mixture throughout, it was allowed to stand overnight and then concentrated at temperature below 40° under reduced pressure. Adding 280 ml of dry ether transformed the residual yellow oil to the solid sodium enolate of cyclization product **4**, which could then be collected conveniently by filtration. A solution of the solid in 125 ml of water (5°) was brought to pH 5 with hydrochloric acid and then extracted with chloroform. Straightforward processing furnished 42 g of oily pyrrolizidine product **4** showing one spot on a thin layer chromatographic plate (3:8:1 chloroform–methanol–hexane); ir ($CHCl_3$) 1765 (cyclopentanone C=O), 1727 (ester C=O), 1695 ($\gamma$-lactam C=O), and 1614 $cm^{-1}$ (enol). This material was suitable for use in the next step in the preparation of pyrrolidine **5**. A sample was purified by slow short-path distillation at 100–110° ($10^{-3}$ mm); decomposition was noted at 140°. The water-white distillate of 1,5-dioxo-2-carbethoxypyrrolizidine (**4**) moved with exactly the same $R_f$ value as the unpurified material and gave the same infrared absorption curve; the ferric chloride test developed a purple color. The product showed $[\alpha]^{25}D$ 0.0° (*c* 0.5, $C_2H_5OH$); nmr ($CDCl_3$) $\delta$ 5.15 (broad, enol OH), 4.70–3.64 (m, with a quartet evident at 4.26, $J$ = 7 Hz), 2.48–1.82 (m, 4, $\gamma$-lactam ring 2 $CH_2$), 1.32 and 1.28 ppm (two sets of t's, $J$ = 7 Hz, 3, $CH_2CH_3$). Integration of the signals at $\delta$ 5.15 and at 4.70–3.64 ppm totaled to 6 protons, in the ratio 0.5:5.4; the 5.15 signal disappeared when a drop of $D_2O$ was added.

*Anal.* Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63. Found: C, 56.58; H, 6.08; N, 6.40.

**2-($\beta$-Carboxyethyl)-3-oxopyrrolidine Hydrochloride (5).**—Warming the pyrrolizidine product **4** (40 g) in 420 ml of 15% hydrochloric acid at 75° for 6 hr resulted in release of carbon dioxide. After about 10 hr at room temperature, the acid mixture was concentrated *in vacuo* (temperatures no higher than 60°), and the residual light-orange oil was allowed to stand at 5° under a layer of ether. The resulting solid hydrochloride of 2-($\beta$-carboxyethyl)-3-oxopyrrolidine (**5**), after washing on the funnel with a small volume of cold alcohol, weighed 30 g (80%), developed to a single spot on thin layer chromatography (7:3:0.05, chloroform–methanol–acetic acid), and showed ir (mineral oil) 1758 (cyclopentanone C=O) and 1726 $cm^{-1}$ (acid C=O). A sample recrystallized from ethanol plus ether solvent gave a positive silver nitrate test for chloride and melted at 152–157°: $[\alpha]^{25}D$ 0.0° (c 0.5, $C_2H_5OH$); nmr (DMSO-$d_6$) $\delta$ 10.30 (broad, 1, COOH), 3.60 (m, 3, pyrrolidine H's at 2 and 5), 2.52 (m, 6, $CH_2$ at pyrrolidine 4 plus $CH_2COOH$ plus $-N^+H_2-$), 2.05 ppm (m, 2, $CH_2CH_2COOH$). The carboxylic H signal at $\delta$ 10.3 ppm disappeared on addition of $D_2O$; a clear-cut change at 3.60 was difficult to establish.

*Anal.* Calcd for $C_7H_{12}ClNO_3$: C, 43.42; H, 6.25; N, 7.23. Found: C, 43.17; H, 6.18; N, 7.26.

A convenient derivative was prepared by ketalizing the keto group as follows. The oxopyrrolidinium chloride **5** (0.5 g) was added to a solution of thionyl chloride (0.34 mg) in absolute methanol (0.7 g) at 0°, and the mixture was allowed to stand at 35–40° for 2 hr. After removing all volatiles, trituration of the gummy residue with a small volume of cold ethanol afforded a solid, which on recrystallization from ethanol–ether gave the white, crystalline hydrochloride of 2-($\beta$-carbomethoxyethyl)-3,3-dimethoxypyrrolidine: mp 134–135°; ir (mineral oil) 1730 $cm^{-1}$ (ester C=O); nmr ($D_2O$) showed signals at *ca.* $\delta$ 3.23 (two s's, 6, $CH_3O-\underset{}{\overset{}{C}}-OCH_3$) and 3.63 ppm (s, 3, $COOCH_3$).

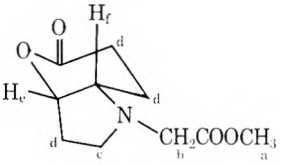
*Anal.* Calcd for $C_{10}H_{20}ClNO_4$: C, 47.33; H, 7.95; N, 5.52. Found: C, 47.37; H, 7.86; N, 5.47.

This ester–ketal could be reconverted into the keto acid **5** by treatment with 10% hydrochloric acid at 95°.

**2-($\beta$-Carbomethoxyethyl)-3-hydroxypyrrolidine Hydrochloride (6) by Hydrogenation of 2-($\beta$-Carboxyethyl)-3-oxopyrrolidine Hydrochloride (5).**—Keto pyrrolidine hydrochloride **5** (20.6 g) in 250 ml of methanol was hydrogenated for 3 days at atmospheric pressure over 1.1 g of platinum oxide catalyst. Removal of solids followed by concentration of the solution *in vacuo* at ~40° left a yellow oil that solidified when scratched under ether at −80°. Crystallization of the product from methanol afforded 12.7 g (61%) of 2-($\beta$-carbomethoxyethyl)-3-hydroxypyrrolidine hydrochloride (**6**) in the form of white needles, melting at 120–125° and showing only one spot on thin layer chromatography (7:3:0.05, chloroform–methanol–acetic acid); ir (KBr) 1726 $cm^{-1}$ (ester C=O); nmr (DMSO-$d_6$) $\delta$ 5.50 (d, $J$ = 3.8 Hz, 1, OH), 4.25 (broad band, $W_{1/2}$ = 12 Hz, 1, H–C–OH), 3.66 (s, $COOCH_3$), 3.23 (m, pyrrolidine ring H's at 2 and 5), 2.53 (m, 4, $CH_2CH_2COOCH_3$ plus $^+NH_2$), 1.95 ppm (m, 4, pyrrolidine H's at 4 plus $CH_2CH_2COOCH_3$) (together, the integration values of the $\delta$ 3.66 and 3.23 ppm signals came to 6 H's as required); nmr ($D_2O$) $\delta$ 4.34 (m, 1, HCOD), 3.68 (s, 1, $COOCH_3$), 3.4 (m, 3, pyrrolidine H's at 2 and 5), 2.48 (q, 2, pyrrolidine H's at 4), 2.12 ppm (t, 4, $CH_2CH_2COOCH_3$). These chemical shifts may be compared with those reported for hydroxyproline.[16] The yield of crystallized hydroxy product **6** over the three steps from the oxo diester **3** came to 46%. A sample of 2-($\beta$-carbomethoxyethyl)-3-hydroxypyrrolidine hydrochloride prepared for analysis by two recrystallizations from methanol showed mp 123–127° and $[\alpha]^{25}D$ 0.0° (*c* 0.5, $CH_3OH$).

*Anal.* Calcd for $C_8H_{16}ClNO_3$: C, 45.78; H, 7.69; N, 6.68. Found: C, 45.65; H, 7.55; N, 6.53.

***N*-Alkylation of Pyrrolidine Derivative 6 with Bromoacetate Esters.**—A solution of 11 g (0.053 mol) of 2-($\beta$-carbomethoxyethyl)-3-hydroxypyrrolidine hydrochloride (**6**) in 200 ml of dry methanol was treated with sodium carbonate (6.7 g, 0.063 mol) and methyl bromoacetate (11.8 g, 0.077 mol), and the mixture was stirred at 60° for 2 days. The reaction mixture was filtered at room temperature, and the filtrate was stripped of volatiles. The residue was triturated with chloroform (200 ml), solids were removed, and the chloroform solution was again freed of solvent. Chromatography of the residual oil through an 80-g column of silica gel with 2:1 hexane–ether as elution solvent allowed the two main constituents to be separated. The faster moving material, which proved to be lactone **8**, was obtained as crystals (2.9 g, 23%), mp 52–55°, homogeneous according to thin layer chromatography (8:1 ether–hexane). The next fraction through the column was taken as diester **7**, an oil (5.5 g, 40%) containing a trace of lactone **8** by thin layer chromatography.




**8**

Lactone **8** showed the following properties: ir ($CHCl_3$) 1730 (ester and lactone C=O's) with no significant absorption above 3100 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 4.84 (q, $J$ = 5 Hz, 1, $H_e$), 3.68 (s, 3, $CH_3$-a), 3.50–2.86 (m for $H_e$ including a pronounced peak at 3.42 for $H_b$, 4), 2.87–1.77 ppm (m, 7, H's at d and f). A single crystallization from ether–hexane brought the melting point of lactone **8** to 58–60°.

*Anal.* Calcd for $C_{10}H_{15}NO_4$: C, 56.32; H, 7.09; N, 6.57. Found: C, 56.07; H, 6.97; N, 6.47.

Dimethyl ester **7** was obtained with ir ($CHCl_3$) 3400 (OH) and 1729 $cm^{-1}$ (ester C=O's); nmr ($CDCl_3$ plus 10% $D_2O$) $\delta$ 4.70–3.90 (m, $W_{1/2}$ = 12 Hz, 1, CHOD), 3.66 and 3.62 (two s's, 6, 2 $COOCH_3$), 3.42 (s) and 3.20 (m) (3, $NCH_2COOCH_3$ plus pyrrolidine H at 2), 2.40 and 1.85 ppm (two sets of m's, 8, pyrrolidine H's at 4 and 5 plus $CH_2CH_2COOCH_3$).

Converting lactone **8** into the dimethyl ester **7** established the relation between the two. Thus, when a solution of homogeneous lactone **8** (27 mg) in 5 ml of methanol was allowed to stand at room temperature for 2 weeks, the resulting product (still with traces of lactone **8** plus an unidentified spot, possibly from the corresponding carboxylic acid) gave $R_f$ values as well as infrared and nuclear magnetic resonance spectra identical with those obtained from dimethyl ester **7**.

When *tert*-butyl bromoacetate was substituted for methyl bromoacetate in the N-alkylation using essentially the same procedure, the homogeneous *tert*-butyl ester lactone analogous to **8** was obtained (49%) as a solid, mp 48–50°; and the *tert*-butyl methyl diester analogous to **7** was obtained in about 30% yield as a colorless oil still containing a trace of lactone. The *tert*-butyl lactone ester showed ir ($CHCl_3$) 1732 (ester and lactone C=O's), no maxima above 3100 $cm^{-1}$; nmr ($CDCl_3$) essentially the same as that of the methyl lactone ester **8** except that the three-proton singlet at $\delta$ 3.68 for $COOCH_3$ has changed to a nine-proton singlet at 1.48 ppm for $COOC(CH_3)_3$. One crystalliza-

(16) R. J. Abraham and K. A. McLauchlan, *Mol. Phys.*, **5**, 195, 513 (1962).

tion from ether–hexane furnished *tert*-butyl lactone ester with mp 50–52°.

*Anal.* Calcd for $C_{13}H_{21}NO_4$: C, 61.66; H, 8.29; N, 5.49. Found: C, 61.22, H, 8.41; N, 5.60.

The oily *tert*-butyl methyl diester showed ir ($CHCl_3$) 3400 (OH), 1734 $cm^{-1}$ (ester C=O's); nmr ($CDCl_3$) δ 4.02 (m, $W_{1/2}$ = 3 Hz, 2, HCOH), 3.65 (s, 3, $COOCH_3$), 3.35 and 3.15 (s and m, 3, $NCH_2COO$ plus pyrrolidine H at 2), 2.40 and 1.87 (two sets of multiplets, 8, pyrrolidine H's at 3 and 4 plus $CH_2CH_2COOCH_3$), 1.46 ppm (s, 9, $COOC(CH_3)_3$). The hydroxyl group of this *tert*-butyl methyl diester could be acetylated at room temperature with acetic anhydride and pyridine. Chromatography followed by a single crystallization from ether–hexane gave the expected *N*-(*tert*-butyloxycarbonylmethyl)-2-(β-carbomethoxyethyl)-3-acetoxypyrrolidine, mp 39–39.5°.

*Anal.* Calcd for $C_{16}H_{27}NO_6$: C, 58.34; H, 8.26; N, 4.25. Found: C, 58.22; H, 8.28; N, 4.35.

**1-Acetoxy-6-oxoindolizidine (11) by Dieckmann Cyclization of Pyrrolidines 7 and 8, Decarboxylation, and Acetylation.**—A mixture of lactone **8** and dimethyl ester **7** was prepared as described above. No separation was attempted; instead, after chromatography through a short column, solvent was removed completely, and the colorless oily mixture was used directly in the Dieckmann process.

Sodium hydride in oil, as a 57% suspension, was rinsed free of heavy solvent with dry ether. A vigorously stirred suspension of this sodium hydride (3.0 g, 0.070 mol) with 20 ml of dry benzene was treated at room temperature over a 1-hr period with a solution of mixed lactone and diester **8** and **7** (8.1 g) in 50 ml of benzene containing 0.05 ml of methanol. Pure nitrogen protected the reaction mixtures throughout. Thin layer chromatography (19:1 chloroform–methanol) of the condensation mixture after 6 hr of stirring at room temperature revealed no unchanged starting materials. Adding 10% hydrochloric acid brought the mixture to pH 5. The resulting two-phase system was used directly for decarboxylation to **10** (see below) or, in a similar run with sodium methoxide in place of sodium hydride, was processed to isolate cyclic keto ester **9**. The latter experiment involved evaporating the aqueous phase, triturating the dry residue with 1:20 methanol–chloroform to separate inorganic salts, and chromatographing the soluble material through silica gel with 1:19 methanol–chloroform as solvent. The pale yellow product (purple color with ferric chloride solution), when crystallized from chloroform–hexane at −80°, was obtained as pale yellow solid keto ester **9**: mp 99–102°; ir ($CHCl_3$) 3608 (sharp, free OH), 3396 (broad, H-bonded OH), 1721, 1666, and 1629 (ester and ketone C=O's and the enolic system), 2806, 2751, 2704 $cm^{-1}$; nmr ($CDCl_3$) δ 9.48 (m, 1, O=C—CH—C=O), 4.12 (broad, $W_{1/2}$ = 11 Hz, 1, HCOH), 3.70 (s, 3, $COOCH_3$), 3.54–2.45 (m, 4), 2.45–1.56 ppm (m, 6). The δ 9.48-ppm signal disappeared when $D_2O$ was added to the tube. Keto ester **9** proved to be very unstable, turning brown after standing a few hours either in air or sealed under argon.

For the decarboxylation of Dieckmann product **9** to hydroxy ketone **10**, the neutralized condensation mixture described above was mixed with concentrated hydrochloric acid (23 g) and water (32 ml) and the two-phase system was stirred and heated at 85°. After 6 hr, when none of the starting material **9** could be detected by thin layer chromatography, the aqueous acid layer was washed twice with benzene and then evaporated at 45° to remove all volatiles. The dark residual hydrochloride of indolizidine **10** was either acetylated directly to **11** (see below) or in other experiments was worked up at this point for the free indolizidine **10** by basification, extraction with chloroform, and preparative layer chromatography of the chloroform-soluble product (1:19, methanol–chloroform). The resulting partially purified still somewhat colored 1-hydroxy-6-oxoindolizine (**10**) was obtained as an unstable material in *ca.* 34% yield calculated from the **7** and **8** reactant mixture: ir ($CHCl_3$) 3410 (OH), 1717 (C=O), 2801, 2742, 2709 $cm^{-1}$. The Dieckmann cyclization with sodium methoxide or with potassium *tert*-butoxide using either the methyl or the *tert*-butyl compounds followed by decarboxylation offered no advantages; nor did decarboxylation in glacial acetic acid containing a trace of *p*-toluenesulfonic acid.

In order to obtain 1-acetoxy-6-oxoindolizidine (**11**), the unpurified hydrochloride of 1-hydroxy-6-oxoindolizidine (**10**) described above was mixed under nitrogen with pyridine (13 ml), acetic anhydride (6.4 g) was added dropwise, and the mixture was allowed to stand at room temperature for 3 hr. After stripping off volatiles, the residue was treated at temperatures below 0° with 10 ml of water followed by 10% sodium hydroxide solution to pH 8. The product was taken up in chloroform, and the chloroform solution was rinsed with aqueous bicarbonate, dried, and freed of all solvent. The acetylated product **11** so obtained weighed 2.6 g (estimated 38% from **7** + **8**) and was suitable for conversion into the oxime **12**.

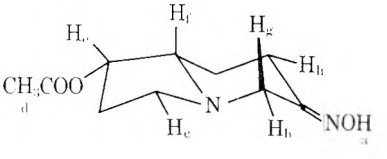
An experiment that was used to prepare pure 1-acetoxy-6-oxoindolizidine (**11**) utilized 5.0 g of the lactone–ester mixture (**8** and **7**) in a cyclization with sodium methoxide. Subsequent acid decarboxylation (**9** to **10**) followed by a 1-day exposure of the 1-hydroxy-6-oxoindolizine (**10**) to the action of acetic anhydride (3 g) plus pyridine (10 ml) as described above gave the unpurified acetyl derivative **11**, which was fractionated by chromatography through 24 g of neutral alumina (1:1, ether–hexane). The light-yellow material emerging as a thin layer chromatographically homogeneous product (8:1, ether–hexane) was taken as the desired 1-acetoxy-6-oxoindolizidine (**11**): mp 32–35°; ir ($CHCl_3$) 2795, 2744, 2721, 1732 (ester C=O) and no maxima at 4000–3500 $cm^{-1}$; nmr ($CDCl_3$) δ 2.03 ppm [s, —C(=O)$CH_3$]. One crystallization from ether–hexane at −80° brought the melting point to 42–44°.

The analysis for elements was performed with minimum delay, since indolizidine **11** deteriorated rapidly at room temperature. It could be stored however at Dry Ice temperature.

*Anal.* Calcd for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.66; N, 7.10. Found: C, 60.72; H, 7.85; N, 6.87.

**Oximes 12 from 1-Acetoxy-6-oxoindolizidine (11).**—A mixture of 1-acetoxy-6-oxoindolizidine (2.6 g) with pyridine (20 ml), ethanol (40 ml), and hydroxylamine hydrochloride (3.1 g) in a nitrogen atmosphere was stirred at 85–95° under a reflux condenser for 4 hr. After standing overnight, the mixture was stripped of volatiles. The residue was brought to pH 8 with 10% aqueous sodium hydroxide, and the mixture was extracted thoroughly with chloroform. The dried combined chloroform extracts were stripped of solvent at temperatures no higher than 40°, and the residual oxime product (two spots on thin layer chromatography) was passed through a 25-g silica gel chromatography column using 50 ml of hexane, 500 ml of 1:7 ether–hexane, and finally 2 l. of 1:1 ether–hexane as developing solvents. A fraction emerging with the 1:1 ether–hexane solvent and showing a single thin layer chromatography spot ($R_f$ 0.47 with 9:0.4 ether–ethanol), when stripped of solvent, appeared as a colorless oil; layered under 1:2 ether–hexane at 0°, the oil crystallized to give colorless oxime **12A** (81 mg), mp 129–132°. This fraction was followed by a mixture of the two oximes **12A** and **12B** ($R_f$ 0.47 and 0.31), mp 68–74°, weighing 230 mg, and finally by the homogeneous oxime **12B** ($R_f$ 0.31), mp 95–97°, weighing 91 mg (total ~14%).

The oxime isomer **A**, mp 129–132°, showed ir ($CHCl_3$), 3590 (free OH), 3304 (H-bonded OH), 1730 (ester C=O), 1657 (C=N), 2800, 2751, 2719 $cm^{-1}$; nmr ($CDCl_3$) δ 8.58 (broad, $H_a$, disappears on addition of $D_2O$), 5.08 (broad d, $J$ = 13 Hz, 1, $H_e$), 4.48 (d, $J$ = 13 Hz, 1, $H_b$), 3.06 (m, 2, $H_c$ + $H_g$), 2.28 (d with




further splitting, $J$ = 12 Hz, $H_h$), 2.02 (s, 3, $H_d$), 2.70–1.60 ppm (m, unlabeled H's). The signals from 2.70–1.60 integrated to 11 H's as required. Crystallization from ether did not change the melting point of oxime **12A**.

*Anal.* Calcd for $C_{10}H_{16}N_2O_3$: C, 56.59; H, 7.60; N, 13.20. Found: C, 56.48; H, 7.62; N, 13.18.

Oxime isomer **B**, mp 95–97°, showed ir ($CHCl_3$) 3590 and 3294 (OH), 1730 (ester C=O), 1658 (C=N), 2800, 2751, 2719 $cm^{-1}$; nmr ($CDCl_3$) δ 8.60 (broad, $H_a$), 5.08 (broad, $W_{1/2}$ = 13 Hz, 1, $H_e$), 3.55 (d, $J$ = 13 Hz, 1, $H_b$), 3.06 (m, 2, $H_g$ + $H_c$), 2.57 (d, $J$ = 12 Hz, 1, $H_h$), 2.02 (s, 3, $H_d$), 2.40–1.60 ppm (unlabeled H's). Signal integration showed 10 H's from δ 2.40–1.60 ppm. Crystallization of this oxime **12B** from ether–hexane raised the melting point to 97–99°.

*Anal.* Calcd for $C_{10}H_{16}N_2O_3$: C, 56.59; H, 7.60; N, 13.20. Found: C, 56.31; H, 7.82; N, 13.07.

The overall yield of oximes **12** obtained in the several steps from 2-(β-carbomethoxyethyl)-3-hydroxypyrrolidine hydrochloride (**6**) was in the order of 3.5%.

**Hydrogenation of Oxime 12 to DL-Slaframine (13).**—A mixture of 81 mg of oxime **12A**, mp 130°, 7.2 ml of absolute ethanol, 0.5 ml of 36.5% aqueous hydrochloric acid, and 96 mg of platinum oxide was shaken at room temperature under hydrogen (40 psi) for 6 hr. Catalyst and solvent were then removed, and the residue was pumped at room temperature (0.1 mm) to give 109 mg of slaframine dihydrochloride (**13** 2HCl) as a foamed, very hygroscopic solid. This dihydrochloride showed ir (KBr) 3120–2500 ($^+NH_3$) and 1732 $cm^{-1}$ (C=O); nmr ($D_2O$) $\delta$ 5.5 (broad, H-C-OAc), 2.16 ppm (s, $OCOCH_3$).[3]

To obtain slaframine base (**13**) the dihydrochloride was stirred at 0° for 15 min in methanol containing solid sodium carbonate. Removal of solids and then solvent left a residue, which was triturated with carbon tetrachloride. The carbon tetrachloride-soluble slaframine, freed of solvent (30°; vacuum), was obtained as an oil homogeneous according to thin layer chromatography ($R_f$ 0.43 with 12:3:5 1-butanol–acetic acid–water and $R_f$ 0.30 with the same solvents in the ratio 4:1:1) using a 1:1 mixture of 1.1% potassium iodide and 0.14% chloroplatinic acid to bring out the spots. The product gave a positive ninhydrin test for primary amine:[3] ir ($CCl_4$) 1734 (ester C=O), 1242 $cm^{-1}$ (acetate); gas–liquid chromatography with a 6-ft column of supported methyl phenyl silicone at 140° indicated a major component (71%) at 11.1 min accompanied by several much smaller peaks.

The minimum yield of slaframine, judging from the yield of pure dipicrate (34%) or *N*-acetyl (40%) derivatives obtained from the hydrogenation product (see below), is in the order of 30–40%.

**Dipicrate and *N*-Acetyl Derivatives of Synthetic Slaframine (13).**—The mixed syn and anti oximes **12** (168 mg) were hydrogenated essentially as described above. A small aliquot of the resulting slaframine dihydrochloride was processed as before to recover the free base **13**, which proved to be homogeneous by thin layer chromatography (with the same $R_f$ value as before) and which gave essentially the same kind of gas–liquid chromatography pattern. The bulk of the dihydrochloride hydrogenation product was diluted with water to 40 ml and used for the preparation of derivatives.

The dipicrate was obtained by removing all solvent from 5 ml of this stock solution, dissolving the residue (31 mg) in 0.5 ml of water, and adding saturated aqueous picric acid dropwise until no more precipitate formed. Crystallization of the solids (35 mg) from 20% aqueous alcohol gave slaframine dipicrate (21.3 mg, 34%) as yellow needles: mp 215–221° dec; ir (KBr) 3000, 2700–2250 ($^+NH_3$), 1738 (ester C=O), 1634, 1609, 1365 $cm^{-1}$.

*Anal.* Calcd for $C_{22}H_{24}N_8O_{16}$: C, 40.28; H, 3.63; N, 16.90; Found: C, 40.24; H, 3.68; N, 17.07.

*N*-Acetylslaframine (**14**) was obtained by stripping solvent from the remaining 35 ml of dihydrochloride stock solution and stirring the residue at room temperature with acetic anhydride (1.2 g) under a nitrogen atmosphere for 18 hr. Water (5 ml) was added at 0°, followed by 10% sodium hydroxide to pH 8. The *N*-acetylslaframine product was extracted repeatedly with chloroform, and the dried extracts ($MgSO_4$) were stipped of solvent to leave 143 mg of a light brown residue. Gas–liquid chromatography results suggested that at this stage the *N*-acetylslaframine (**14**) was 94% homogeneous; thin layer chromatography produced one heavy spot accompanied by two faint spots. Chromatography through a 36-cm column of neutral alumina (14 g) with ether–hexane mixture as solvents (300 ml of 1:4, 300 ml of 3:7; 5 l. of 1:1) furnished a one-spot fraction, which on crystallization from hexane at −80° gave 72 mg (40%) of white, crystalline *N*-acetylslaframine, mp 142–144°. This material showed one spot on thin layer chromatography ($R_f$ 0.41 with 8:1 ether–alcohol) and produced a single peak on gas–liquid chromatography: ir ($CHCl_3$) 3426 (N-H), 1734 (ester C=O), 1663 (amide C=O), 1509 (N-H), 2900, 2750 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 6.28 (m, 1, N-H; disappears when $D_2O$ added), 5.20 (m, $W_{1/2}$ = 13 Hz, 1, H-C-OAc), 4.20 (m, $W_{1/2}$ = 16 Hz before, and 8 Hz, after, adding $D_2O$, 1, H-C-NHAc), 3.00 (m, 2, $H_{eq}$-C-N-C-$H_{eq}$), 2.75–1.20 ppm (m, 15, all other protons, including two prominent singlets at 2.02 and 2.10 assigned respectively to $CH_3COO$ and $CH_3CONH$). One crystallization from ethanol–hexane brought the melting point of the *N*-acetylslaframine (**14**) to 143–146°, $[\alpha]^{25}D$ 0.0°.

*Anal.* Calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found: C, 59.81; H, 8.27; N, 11.58.

**Comparison Samples of Slaframine and Derivatives. A. Synthetic Slaframine Dihydrochloride.**—A partially purified sample of the synthetic material was used. Although natural slaframine dihydrochloride was not available for comparison in our laboratories, copies of its infrared absorption curve (KBr) and its nuclear magnetic resonance curve ($D_2O$)[3] were sent to us by Dr. Aust. The corresponding pairs of curves were found to be identical.

**B. Natural Slaframine Dipicrate.**—A sample of the dipicrate from slaframine isolated from *R. leguminicola* was furnished by Dr. Aust. Table I compares this material with the synthetic material described above.

**C. Slaframine Base.**—The synthetic dipicrate (11 mg) in 5 ml of 10% hydrochloric acid was shaken several times with ether to remove the picric acid. Adding 10% sodium hydroxide solution to the aqueous layer until pH 10 released the slaframine, which was extracted thoroughly with chloroform. The dried extracts ($MgSO_4$) were freed of all solvent at reduced pressures at temperatures no higher than 30° to leave *ca.* 2 mg (*ca.* 60%) of oily DL-slaframine (**13**).

Natural slaframine base (3 mg, 64% yield) was obtained in the same way from its dipicrate. Table II gives the comparison results.

**D. *N*-Acetylslaframine from the Natural Material.**—A 0.5-mg sample supplied to us showed mp 138–144°. Purified by sublimation at 100° (0.1 mm), the sample was obtained as white needles, mp 143–146°. The comparison between this material and synthetic *N*-acetylslaframine appears in Table III.

**Acknowledgment.**—We are indebted to Professor Steven D. Aust, Michigan State University, for spectra and for samples of slaframine dipicrate and *N*-acetylslaframine prepared from natural slaframine. His help in other ways, as well as the help of Professor Kenneth L. Rinehart, Jr., of the University of Illinois, is also appreciated.

**Registry No.**—**1**, 6582-81-6; **1** dipicrate, 6582-82-7; **1** *N*-acetyl deriv., 41563-75-1; **3**, 41563-76-2; **4**, 41563-77-3; **5**, 41563-78-4; **6**, 41563-79-5; **7**, 41563-80-8; **7** *N-tert*-butyl ester analog, 41563-81-9; **8**, 41563-82-0; **8** *tert*-butyl ester analog, 41563-83-1; **9** (R = $COOCH_3$, R′ = H), 41563-84-2; **9** (R = H, R′ = $COOCH_3$), 41563-85-3; **10**, 41563-86-4; **11**, 41563-87-5; *syn*-**12**, 41563-88-6; *anti*-**12**, 41563-89-7; **13**, 30591-15-2; **13** 2HCl, 41563-91-1; **13** dipicrate, 41563-92-2; **14**, 41563-93-3; *N*-(β-cyanoethyl)-5-oxo-2-pyrrolidinecarboxylic acid, 41563-94-4; 2-(β-carbomethoxyethyl)-3,3-dimethoxypyrrolidine HCl, 41563-95-5; methyl bromoacetate, 96-32-2; *tert*-butyl bromoacetate, 5292-43-3; *N-tert*-butyloxycarbonylmethyl)-2-(β-carbomethoxyethyl)-3-acetoxypyrrolidine, 41563-97-7.

# The Anodic Reaction of (S)-2-Acetamido-2-(3,4-dimethoxybenzyl)propionitrile. Synthetic and Stereochemical Implications

SEEMON H. PINES

*Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, New Jersey 07065*

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Reaction of the title compound 1 at a Pt anode (1.14 V *vs.* sce) in sodium acetate–acetic acid containing acetic anhydride gives (4*R*,5*S*)- and (4*R*,5*R*)-4-cyano-5-(3,4-dimethoxyphenyl)-2,4-dimethyl-2-oxazoline (**3** and **4**), respectively, in a 3.5:1 ratio as the major products. This stereoselectivity results not from the heterogeneity of reaction of adsorbed species *on* an anode surface, but from the nature of benzylic cation **2**, since the same oxazolines are formed in the homogeneous reaction of 1 with $Mn(OAc)_3$ in similar ratio. Lesser products of reaction, most of which derive from benzylic oxidation, are considered. The hydrolysis of some of them is examined insofar as it bears on stereochemical correlations and reaction work-up.

It has come to mind that the anodic side chain acetoxylation reaction[1] could provide a new means of introducing an oxygen function into a β-arylalanine derivative to form a β-arylserine derivative.

Exploration of this reaction could provide additional benefit. Most of the studies of anodic side chain oxidation have been carried out on reasonably simple molecules, and the majority of them have been concerned with unraveling the mechanism of electron transfer.[1,2] This basic question is now well answered,[3] but experiments on the possible stereochemical consequence of reaction at a solid anode surface are few, and it seemed that some contribution to this important facet of electroorganic chemistry might result.

Eberson previously expressed the hope[4] that stereochemical studies would illustrate some differences between anodic acetoxylation and mechanistically similar electrophilic processes which could be attributed to the heterogeneous nature of the electrode surface. Our substrate for such an electrolysis, (*S*)-2-acetamido-2-(3,4-dimethoxybenzyl)propionitrile[5] (**1**), not only possessed a chiral center, but the differing polarizability of the attached groups suggested that the different conformers might contribute an effect somewhat different from a solely steric one.

## Results and Discussion

(*S*)-2-Acetamido-2-(3,4-dimethoxybenzyl)propionitrile (**1**) was allowed to react at a platinum mesh electrode in acetic acid–sodium acetate containing acetic anhydride under controlled potential conditions (1.14 V *vs.* sce). The major products resulted from an ece-formed benzylic cation,[2-4] and are shown in Chart I with their correct stereochemical representation. These configurations imply that no changes occurred at the original chiral center. The two major products, (4*R*,5*S*)-4-cyano-5-(3,4-dimethoxyphenyl)-2,4-dimethyl-2-oxazoline (**3**) and its diastereomeric 4*R*,5*R* isomer, **4**, were formed in a ratio of about 3.5:1 as judged from nmr integrals. The products of acetate attack, (2*R*,3*S*)-3-acetoxy-2-acetamido-3-(3,4-dimethoxyphenyl)-2-methylpropionitrile (**6**), its 2*R*,3*R* isomer, **7** (not shown), and (4*R*,5*S*)-5-acetoxy-4-cyano-5-(3,4-dimethoxyphenyl)-2,4-dimethyl-2-oxazoline (**8**), amplify the nature of the reactions occurring, especially since **8** is the formal product of two cation formations.

Products **4**, **7**, and **8** were not isolated in pure form, but their presence was amply demonstrated in partially purified fractions by spectral methods and by hydrolysis (of **4** and **8**) to rational, fully characterized, crystalline products (see below).

Aliquots which were analyzed throughout the electrolysis gave results in harmony with the isolations performed at the conclusion of the run. Integrals of the nmr (see Figure 1) permitted product estimation as follows.

| Product | Approx conversion, %[a] |
|---|---|
| **3** | 40 |
| **4** | 11 |
| **6** and **7** | 7.5 |
| **8** | 5 |

[a] Based on 1 charged.

That the true "acetoxylation" products, **6** and **7**, were found in lower yield than the oxazolines, **3** and **4**, is not surprising in view of the proximity of the amide oxygen for attack in cation **2**.[6] The diastereomer of **8** was not found. Intuitively, one would expect **3** to be adsorbed on the anode more readily than **4**, because both the aromatic ring and the polarizable nitrile are cis. Acetoxylation *at the anode* would give the isomer *not* observed. With such a highly stabilized cation as **5**, however, diffusion to the bulk solution can be expected where the veratryl ring would tend toward coplanarity and acetate attack would occur from the less hindered side to give **8**. Such attack might not, however, be predicted to be exclusive.

A small amount (less than 1%) of 3,4-dimethoxybenzaldehyde (**9**)[8] was invariably formed. From some electrolyses, at slightly higher potential, it was pos-

(1) L. Eberson and H. Schäfer, "Organic Electrochemistry," Fortschritte der Chemischen Forschung, No. 21, Springer-Verlag, New York, N. Y., 1971. Chapters 7 and 9 are particularly pertinent.

(2) V. D. Parker and R. N. Adams, *Tetrahedron Lett.*, 1721 (1969).

(3) For a less sanguine view, see A. Bewick and D. Pletcher in "Electrochemistry," Vol. 1, Specialist Periodical Reports, The Chemical Society, Burlington House, London, 1970, p 135; also Vol. 2, 1972, pp 8–10.

(4) L. Eberson, *J. Amer. Chem. Soc.*, **89**, 4669 (1967).

(5) R. A. Firestone, D. F. Reinhold, W. A. Gaines, J. M. Chemerda, and M. Sletzinger, *J. Org. Chem.*, **33**, 1213 (1968).

(6) The experimental evidence does not rule out formation of **6** and **7** by nucleophilic attack of acetate on **4** and **3**, respectively. This seems quite unlikely, however. If **6** and **7** formed by oxazoline ring opening,[7] one would expect their ratios to be reversed on two counts: first, there is more **3** to start with; and second, the transition state for **4** to **6** suggests greater nonbonded interaction (aryl–methyl) than **3** to **7** (aryl–nitrile).

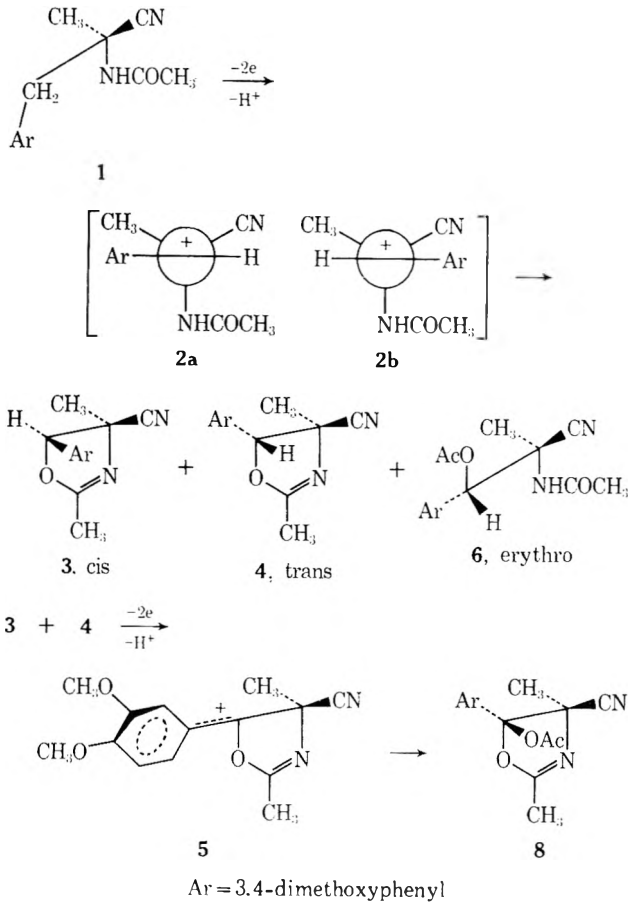
(7) S. H. Pines, M. A. Kozlowski, and S. Karady, *J. Org. Chem.*, **34**, 1621 (1969).

(8) The formation of aldehydes at the anode has frequently been attributed to traces of water and/or overoxidation. Here, formation of **9** requires cleavage of a C–C bond. A recent paper[9] describes conditions for preparation of aldehydes from $ArCH_2X$ compounds in good yields; however, ketones were formed from ArCHXR starting materials.

(9) E. A. Mayeda, L. L. Miller, and J. F. Wolf, *J. Amer. Chem. Soc.*, **94**, 6812 (1972).

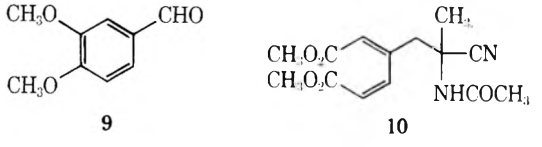
CHART I

ANODIC OXIDATION OF 1



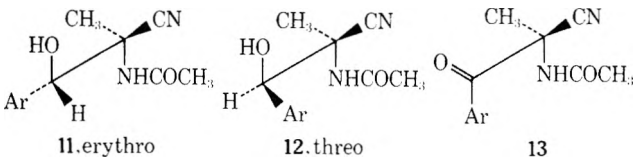

Ar = 3,4-dimethoxyphenyl

sible to isolate traces of (*S*)-3-[3-(2-cyano-2-acetamido)-propyl]-*cis*,*cis*-2,4-hexadienedioic acid dimethyl ester (**10**). The latter results from oxidative cleavage of the




veratryl moiety, a type reaction which has both conventional reagent[10] and electrochemical[11] precedent.

The configurations of **3**, **4**, and **8** were assigned mainly by nmr. With similar isomeric oxazolines, it has been established that the isomer with both the aryl and methyl groups on the same side possesses the distinctly higher field 4-methyl signal.[12] Since **3** and **6** gave, upon aqueous hydrolysis, the same (2*R*,3*S*)-2-acetamido-3-(3,4-dimethoxyphenyl)-3-hydroxy-2-methylpropionitrile (**11**), the erythro configuration of **6** is assured. Hydrolysis of the mixture of **4** and **8** gave threo isomer **12** and keto nitrile **13**, thus confirming both




(10) R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, and K. Schenker, *Tetrahedron*, **19**, 247 (1963).

(11) B. Belleau and N. L. Weinberg, *J. Amer. Chem. Soc.*, **85**, 2525 (1963).

(12) S. H. Pines, S. Karady, M. A. Kozlowski, and M. Sletzinger, *J. Org. Chem.*, **33**, 1762 (1968).

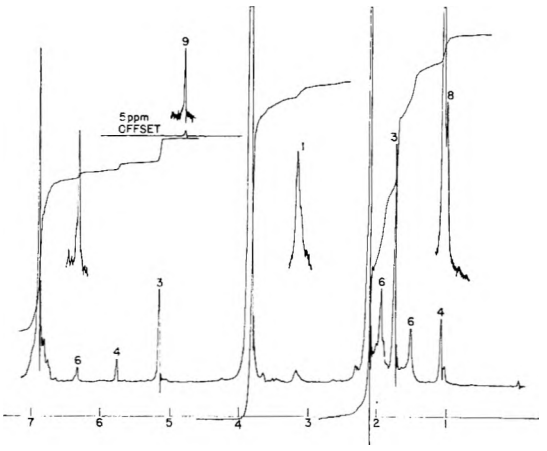
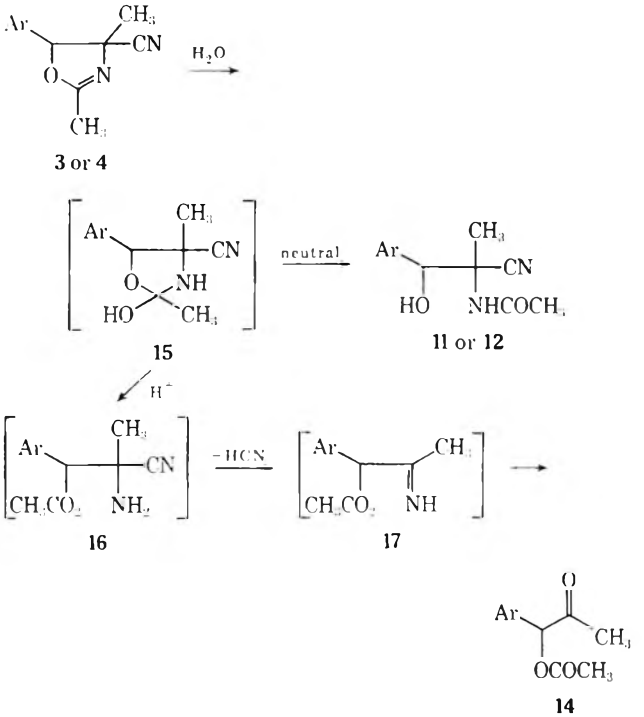



Figure 1.—60-MHz nmr spectrum of the total organic product of electrolysis. The numbers at several of the signals refer to the structures to which those signals have been assigned.

the structures of **4** and **8**, and the stereochemistry of **4**. The structure **13** emphasizes again that **8** is a product of two oxidation stages.

A trivial product, 1-acetoxy-1-(3,4-dimethoxyphenyl-2-propanone (**14**),[13] was found in some chromatography fractions but was not observed by gas chromatography–mass spectral analysis of the electrolysis reaction *per se*. If hydrolysis of an oxazoline occurred on an adsorbent such as silica, loss of HCN and hydrolysis of the resulting imine, **17**, would lead to formation of **14** (Chart II).

CHART II




Reaction of **1** with manganic acetate in acetic acid–acetic anhydride gave the same oxazolines **3** and **4** in nearly the same ratio, approximately 3:1. This reaction has been cited previously as being mechanistically

(13) **14** was previously reported [H. L. Slates, D. Taub, C. H. Kuo, and N. L. Wendler, *J. Org. Chem.*, **29**, 1424 (1964)] from $Pb(OAc)_4$ oxidation of optically active *N*-acetyl-α-methyl-3,4-dimethoxyphenylalanine without rotational data. In the present instance, **14** is optically active.

similar to anodic acetoxylation.[4,14,15] The overall yield was much lower with $Mn(OAc)_3$, attesting to the advantages of the electrochemical method for synthesis.

Of more significance, the product ratio from the homogeneous reaction, paralleling the ratios obtained *via* electrolysis, discounts any striking steric effect attributable to reaction *at* the anode. One must conclude, therefore, that in the electrolysis either adsorption of the conformers of **2** is not widely disparate, or the product-forming final step occurs after desorption of **2** from the electrode.

Having established that a stereochemical bias does exist in the anodic reaction but that it is not appreciably different from the stereoselectivity of an analogous homogeneous reaction, it is worthwhile asking whether the bias is predictable. If the intermediacy of a benzylic cation can be accepted for both reactions,[1,2,4,14,15] then this cation can be represented by (at least) the two conformers of **2** shown in Chart I. Cyclization of **2b** should be favored over **2a**, since, at the point of bond formation, there is less nonbonded interaction in **2b** (Ar to CN) than **2a** (Ar to $CH_3$).

In the light of these results, and Eberson's recent stereochemical study with 2-*tert*-butylindan,[16] where he concludes with "... several reasons why 2-*tert*-butylindane is not an ideal model system for stereochemical study ...," it is interesting to speculate on what kind of substrate would provide "drastic differences in the cis–trans ratio between the electrochemical and homogeneous reactions ...."[16] In addition to the steric limitations he discusses, perhaps there should be added an electronic limitation. Thus, a "too stable cation" might be too readily desorbed from the anode prior to conversion to product. A "too unstable cation," on the other hand, might require higher electrode potentials for its formation, thereby diminishing the possibilities of reaction selectivity, a great promise of organic electrochemistry.

## Experimental Section[17]

**Cell Assembly.**—The electrolyses were performed in a covered, water-jacketed cell of 250-ml capacity. A dry nitrogen atmosphere was maintained throughout. Unless otherwise specified, the anode consisted of a cylinder of platinum mesh, 2-in. diameter, 2.25 in. high. The cathode was 1 in. × 1 in. platinum foil separated from the anode compartment by a medium-porosity glass frit. Mixing was by a Teflon-covered magnetic stirring bar. A Wenking Model 70HV 1/90 potentiostat was used in conjunction with a saturated calomel electrode to control the potential.

**Analytical Procedures.**—Aliquots of the electrolysis were transferred by syringe into dry flasks and pumped to dryness without applied heat. The residue was taken up in sieve-dried ethyl acetate, separated from the crystalline sodium acetate, and evaporated as before, and the process was repeated with dry benzene. Vapor phase and thin layer chromatography were performed with dry solvents and protection from moisture; nmr spectra were usually run in $CDCl_3$. The vpc column which was used (3% OV-1 on Supelcoport, 5 ft × 0.25 in.) did not permit separation of the isomeric oxazolines **3** and **4**. The tlc systems, $CHCl_3$ with 0.5–4% MeOH, or benzene with 1–3% acetone, did not separate (4*R*,5*R*)-oxazoline **4** from acetoxy oxazoline **8**. All other compounds were resolved; some separations required multiple development.

**Electrolysis.**—The electrolyte was made by warming 200 ml of glacial acetic acid, 12.5 ml of acetic anhydride, and 12 g of anhydrous sodium acetate for 1 hr at 80–90°. To 200 ml of this cooled solution was added 6 g of **1**, and the stirred solution was electrolyzed at 1.14 V (*vs.* sce) and 18–20° with an initial-current of 18 mA. The reaction was continued until the current dropped to 5 mA. Solvent and sodium acetate were removed as described for the aliquots.

**Isolation and Characterization of the Products.**—A 0.5-g portion of the above residue was separated by chromatography on three 2-mm, 20 × 20 (E. Merck) preparative plates with 4% MeOH in $CHCl_3$. Column chromatography (Baker silica gel) was aggravated by continuing hydrolysis throughout (see section on hydrolysis). Seven bands, A to G, were obtained. The products in each are discussed below, in order of increasing polarity.

**Band A** weighed 17 mg. The major constituent was 3,4-dimethoxybenzaldehyde (**9**), identical with (ir, nmr) and inseparable from (tlc, vpc) an authentic sample. A tlc eluate of a second, lesser spot showed significant fragments at *m/e* 209, 167, and 139, suggesting partial structure $(CH_3O)_2C_6H_3CH(OCOCH_3)$–. It was not further characterized.

**Band B** weighed 84 mg. This fraction was a mixture of the (4*R*,5*R*)-oxazoline **4** and acetoxy oxazoline **8** in a ratio of *ca.* 2.5–3 to 1: nmr ($CDCl_3$) δ 6.65–7 (m, 3, aromatic), 5.75 (s, 0.75, CH), 3.9 (s, 6, $OCH_3$), 2.2, 2.15 (s, 4+, $CH_3C{=}$), 1.1, 1.07 (s, 3−, $CH_3C{<}$); gc–mass spectrum *m/e* (rel intensity) peak 1 (**4**) 260 ($M^+$, 50), 233 (<0.5), 218 (29), 167 (13), 139 (5), 94 (100); peak 2 (**8**) 318 ($M^+$, 3), 259 (3), 190 (6), 165 (100), 94 (>100); ir ($CHCl_3$) 1785 (ester C=O) and 1665 $cm^{-1}$ (C=N). The two products were not further separated.

**Band C** weighed 205 mg. This fraction deposited 187 mg of crystalline (4*R*,5*S*)-oxazoline **3** from 1:1 ether–hexane, mp 84–87°. Recrystallization from ether–hexane after filtration in benzene gave an analytical sample: mp 87.5–89°; nmr ($CDCl_3$) δ 6.87 (m, 3, aromatic), 5.1 (s, 1, CH), 3.93, 3.91 (each) (s, 3, $OCH_3$), 2.15 (s, 3, $CH_3C{=}$), 1.77 (S, 3, $CH_3C{<}$); mass spectrum very similar to that of **4** (above); ir (Nujol) 1670 $cm^{-1}$ (C=N); $[\alpha]D$ +90° (*c* 4, $CHCl_3$).

*Anal.* Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.58; H, 6.25; N 10.44.

**Band D** weighed 15 mg and contained mainly the (4*R*,5*S*)-oxazoline **3** and its hydrolysis product **11**, which is characterized below.

**Band E** weighed 146 mg. The benzylic proton at δ 6.2 could be equated with 65% of the total methoxy signal. The starting material, **1**, was also present. Rechromatography on three 1-mm 20 × 20 (Analtech Labs) plates with 3X development, 4% MeOH in $CHCl_3$, gave a fraction which yielded 30 mg of crystalline **6**: mp 171–172.5° from ethyl acetate–hexane; nmr ($CDCl_3$) δ 6.9 (m, 3, aromatic), 6.15 (s, 1, CH), 6.25 (broad s, 1 NH), 3.86 (s, 6, $OCH_3$), 2.2 (s, 3, $CH_3C{=}$), 1.98 (s, 3, $CH_3C{=}$), 1.55 (s, 3, $CH_3$–$C{<}$); mass spectrum 320 ($M^+$, 0.5), 261 (1), 219 (2.5), 209 (12), 167 (100), 139 (28), 112 (13); as its TMS derivative, 392 ($M^+$), 167 (100); ir (Nujol) 3280 (NH), 1760 (ester C=O), 1660 $cm^{-1}$ (amide C=O).

*Anal.* Calcd for $C_{16}H_{20}N_2O_5$: C, 59.99; H, 6.29; N, 8.75. Found: C, 60.17; H, 6.47; N, 8.66.

**Band F** weighed 21 mg. The nmr spectrum was interpretable most readily as that of a pair of isomeric compounds. Since half of the singlets corresponded to **6**, the presence of the isomer **7** was inferred from the others.

| **6**, δ | Assignment | **7**, δ |
|---|---|---|
| 6.15 | CH | 6.23 |
| 2.16 | $CH_3C{=}$ | 2.13 |
| 1.97 | $CH_3C{=}$ | 1.9 |
| 1.5 | $CH_3C{<}$ | 1.68 |

The two isomers were separated by gc and the individual eluates gave almost identical mass spectra ($M^+$ 320, remainder of spec-

(14) P. J. Andrulis, Jr., M. J. S. Dewar, R. Dietz, and R. L. Hunt, *J. Amer. Chem. Soc.*, **88**, 5473 (1966), and succeeding papers in the series.

(15) J. P. Dirlam and L. Eberson, *Acta Chem. Scand.*, **26**, 1454 (1972).

(16) L. Eberson and H. Sternerup, *Acta Chem. Scand.*, **26**, 1431 (1972). This paper, and its companion, ref 15, appeared in print after the completion of the above work. In it, the authors clearly and succinctly trace the background of the stereochemistry *vs.* adsorption postulate.

(17) Melting points are uncorrected. Elemental analyses were performed by Mr. R. N. Boos and his associates of these laboratories. Ir spectra were usually obtained on a Perkin-Elmer 137. Nmr spectra were obtained with a Varian A-60A or Jeolco C-60HL spectrometer. Mass spectra were obtained with an LKB-9000 spectrometer at 70 eV. For brevity, only portions of some spectra are reported. Commerical tlc and preparative silica plates from Analtech Labs, E. Merck, and Quantum Industries were used.

trum as described above for 6). The TMS derivatives were also separable and gave the proper mass spectra. Preparative separation was not attempted.

**Band G** weighed 22 mg. The major constituent was the *erythro*-hydroxyamidonitrile **11** (nmr, tlc). Its characterization is described directly below.

**Hydrolysis of the Oxazoline 3.**—Several milligrams of **3** was left at room temperature overnight in 90% acetic acid. The residue was essentially a single component (tlc, 4% MeOH in $CHCl_3$) of greater polarity than **3**. Crystallization from ethyl acetate–ether and then from ethyl acetate gave pure **11**: mp 127–132°;[18] nmr ($CDCl_3$) δ 6.8–7.1 (m, 3, aromatic), 6.65 (broad s, 1, NH), 4.9 (d, 1, $J$ = 4 Hz, CH), 4.5 (d, 1, $J$ = 4 Hz, OH), 3.85 (s, 6, $OCH_3$), 2.0 (s, 3, $CH_3C$=), 1.45 (s, 3, $CH_3C$<); mass spectrum 278 ($M^+$, <0.01), 203 (1), 167 (100), 139 (70), 112 (2.5); as the bis TMS derivative, 407 ($M^+ - 15$), 239 (100); ir (Nujol) 3550, 3500, 3300, 3250 (NH, OH), 2250 (C≡N), 1650 $cm^{-1}$ (amide C=O); $[\alpha]_D$ −54.4° (*c* 6, $CH_3OH$).

*Anal.* Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.38; H, 6.55; N 10.03.

**Hydrolysis of the Oxazoline 4 and the Acetoxy Oxazoline 8 Mixture.**—Most of the band B mixture was hydrolyzed in 90% acetic acid as with **3**. The residue was chromatographed twice with 4% MeOH in $CHCl_3$ on a 2-mm 20 × 20 (Analtech) preparative plate. Two products were isolated. The first was (*R*)-2-acetamido-2-(3,4-dimethoxybenzoyl)propionitrile (**13**) (17 mg) as crystals from MeOH: mp 163.5–164.5°; nmr ($CDCl_3$) δ 8 (q, 1, $J$ = 9 Hz, aromatic $C_6H$), 6.65 (d, 1, $J$ = 2 Hz, aromatic $C_2H$), 6.93 (d, 1, $J$ = 9 Hz, aromatic $C_5H$), 7.37 (broad s, 1 NH), 3.93, 3.99 (each) (s, 3, $OCH_3$), 2.06, 2.11 (each) (s, 3, $CH_3$); mass spectrum *m/e* 276 ($M^+$, 2), 165 (100), 137 (12), 122 (5); ir (Nujol) 3290, 3250, 3200 (NH), 2250 (C≡N), 1690 (C=O), 1650 $cm^{-1}$ (amide C=O). A second compound was (2*R*,3*R*)-2-acetamido-3-(3,4-dimethoxyphenyl)-3-hydroxy-2-methylpropionitrile (**12**), mp 115–118°[19] (ethyl acetate–ether). On tlc, **12** was separated with difficulty (slower) from **11**: nmr ($CDCl_3$) δ 6.7–7.1 (m, 3, aromatic), 6.35 (broad s, 1, NH), 5.05 (s, 1, CH), 3.85 (s, 6, $OCH_3$), 1.99 (s, 3, $CH_3C$=), 1.55 (s, 1, $CH_3C$<) [the OH signal was not observed until exchange with $CD_3OD$, whereupon the $CD_3OH$ (δ 3.18) signal integrated for 2 H]; mass spectrum *m/e* 278 ($M^+$, <1), 260 (1), 219 (2.5), 210 (1.5), 167 (100), 139 (65), 112 (30). The mono TMS derivative had *m/e* 350 ($M^+$), 335, 239 (100); the bis TMS derivative had *m/e* 407 ($M^+ - 15$), 239 (100).

**Hydrolysis of 6.**—A solution of 2 mg of **6** in 0.2 ml of 85% MeOH–15% saturated sodium bicarbonate was left overnight. Tlc of the organic portion of the residue (4% MeOH in $CHCl_3$) alone and in admixture with **11** showed the hydrolysis product to be *erythro*-hydroxylamidonitrile, **11**. The threo isomer, **12**, was not detected.

**Manganic Acetate Oxidation of 1 to Give 3 and 4.**—A slurry of 1 g of $Mn(OAc)_3 \cdot 2H_2O$[20] in 10 ml of acetic acid and 3 ml of acetic anhydride was warmed at 70° for 2 hr with stirring. To it was added 200 mg of **1** and the reaction mixture was stirred at 65° overnight under $N_2$. The solvent was removed *in vacuo* below 45°, and the residue was dissolved in $CHCl_3$ and filtered to remove inorganics. Final traces of Mn salts were removed by passage through a small bed of silica, followed by ethyl acetate. The nmr spectrum of the residue (~150 mg) showed the presence of about 40% **1** and 20–25% of **9**. Both oxazolines, **3** and **4**, were present.

Separation on a 2-mm 20 × 20 (E. Merck) preparative plate with 2% MeOH in $CHCl_3$ gave about 20 mg of the mixed oxazolines, **3** and **4**, clearly identifiable by nmr, tlc, and mass spectrum.

**(*S*)-3-[3-(2-Cyano-2-acetamido)propyl]-*cis*,*cis*-2,4-hexadienedioic Acid Dimethyl Ester (10).**—Electrolysis of 750 mg of **1** in 150 ml of 0.35 *M* NaOAc–HOAc at 1.7 V in an uncooled, undivided cell overnight gave a gross mixture (tlc). Preparative plate (E. Merck) chromatography (3% MeOH in $CHCl_3$) gave the aldehyde **9** and a crystalline material, uv $\lambda_{max}$ 210 mm, $\lambda_{infl}$ ~250 nm, with an $R_f$ just slightly less than that of **1**. The analytical sample, mp 153–156° (ethyl acetate), was shown to be **10**: nmr ($CDCl_3$) δ 7.1 (d of d, 1, $J$ = 12.5 Hz, $C_4H$), 6.03 (m, 2, $C_2$ and $C_4$ H's), 6.6 (broad s, 1, NH), 3.66, 3.7 (each) (s, 3, $OCH_3$), 3.05 (q, 2, $CH_2$), 2.0 (s, 3, $CH_3C$=), 1.75 (s, 3, $CH_3C$<); mass spectrum *m/e* 294 ($M^+$, 0.5), 263 (1.5), 252 (5), 235 (35), 221 (18), 194 (22), 183 (90), 176 (100), 152 (53), 124 (70); the TMS derivative had *m/e* 366 ($M^+$); ir (Nujol) 3320 (NH), 1735 (ester C=O), 1665 $cm^{-1}$ (amide C=O).

*Anal.* Calcd for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.17; N, 9.52. Found: C, 56.81; H, 6.03; N, 9.44.

The same compound was observed (nmr, tlc) in trace quantities from a "usual" electrolysis of **1** in a divided cell at 1.14 V.

**Isolation of 1-Acetoxy-1-(3,4-dimethoxyphenyl)-2-propanone (14).**—When the least polar fractions from a silica gel column chromatograph were examined by tlc (2.5% acetone in benzene, then 2% MeOH in $CHCl_3$), a new component was observed with an $R_f$ between that of **9** and the **4**–**8** mixture. It was first separated by 3X development on E. Merck tlc plates, 250 μ, with 5% acetone in benzene, and shown to be **14**, an oil: nmr ($CDCl_3$) δ 6.7–7 (m, 3, aromatic), 5.9, (s, 1, CH), 3.85 (s, 6, $OCH_3$), 2.1, 2.17 (each) (s, 3, $CH_3C$=O); ir (neat film) 1735, 1750 $cm^{-1}$; mass spectrum *m/e* 252 ($M^+$, 15), 209 (47), 167 (100), 139 (78); ORD (MeOH) (λ, [α], description) 305, −4900, − trough; 292, 0, cross; 278, +5710, + peak; 267, +5450, + trough; 258, +5950, + peak.

**Acknowledgment.**—Thanks are due to Mr. Jack Smith for mass spectra and assistance in their interpretation and to Mr. R. C. Zerfing and Mrs. E. Maitheny for nmr and ORD spectra. I wish particularly to acknowledge stimulating and helpful discussions with Dr. A. W. Douglas.

**Registry No.**—**1**, 38188-53-3; **3**, 41674-68-4; **4**, 41674-69-5; **6**, 41674-70-8; **7**, 41674-71-9; **8**, 41674-72-0; **10**, 41755-30-0; **11**, 41674-73-1; **12**, 41674-74-2; **13**, 41674-75-3; **14**, 38007-20-4.

(18) Other samples showed a variety of melting points: 121–126°, 168–170°, etc., suggesting polymorphism.

(19) On a hot stage. Dta: endotherm at 128°.

(20) Made by the method of footnote 4, J. B. Bush, Jr., and H. Finkbeiner, *J. Amer. Chem. Soc.*, **90**, 5903 (1968).

# The Synthesis and Spectral Properties of Stereoisomeric β-Bromo Carbamates and 2-Oxazolidinones

RONALD A. WOHL

*School of Chemistry, Rutgers University, The State University of New Jersey, New Brunswick, New Jersey 08903*

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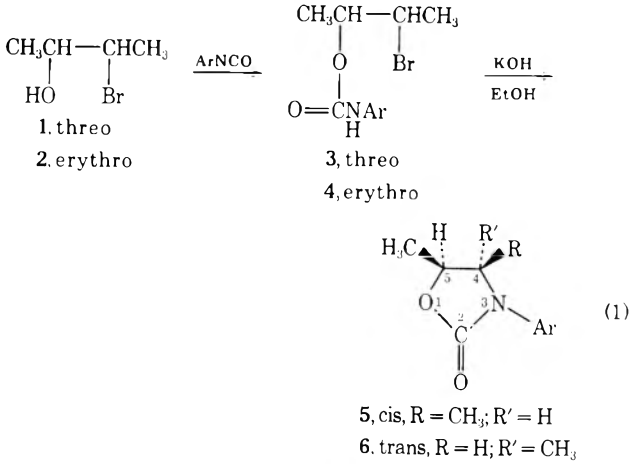
*cis*- and *trans*-4,5-dimethyl-*N*-phenyl-2-oxazolidinone (**5a** and **6a**), as well as *cis*- and *trans*-4,5-dimethyl-*N*-(α-naphthyl)-2-oxazolidinone (**5b** and **6b**), have been prepared from the corresponding threo and erythro β-bromo carbamates **3** and **4** by ring closure through elimination of hydrogen bromide by alcoholic potassium hydroxide. The ir and nmr spectra of the β-bromo carbamates and 2-oxazolidinones are discussed.

For a study about which we will report at a later date we needed stereoisomeric 2-oxazolidinones having substituents at carbon atoms 4 and 5 as well as at the nitrogen atom (see eq 1).

Possible synthetic precursors for such 2-oxazolidinones are β-amino alcohols, β-halo amines, β-halo alcohols, 1,2-glycols, β-halo carbamates, and *N*-(β-halo) carbamates of defined stereochemistry.[1] A number of stereoisomeric 2-oxazolidinones of established configuration around atoms 4 and 5 have been prepared; the early efforts were undertaken in connection with establishing the configurations of ephedrine and ψ-ephedrine.[2] Most of these synthetic pathways have used β-amino alcohols as precursors. Recently, the pyrolysis of *N*-(β-iodo) carbamates has been used for the synthesis of 4,5-disubstituted 2-oxazolidinones.[3,4]

While this reaction is stereospecific in the case of cyclic carbamates, Foglia and Swern found this reaction to be stereoselective only in the case of acyclic carbamates derived from *cis*- and *trans*-2-butenes and -3-hexenes.[4b]

A convenient route for the synthesis of stereoisomeric 4,5-disubstituted 2-oxazolidinones seemed to be the ring closure from the corresponding β-bromo carbamates by elimination of hydrogen bromide with base (see eq 1).



1, threo
2, erythro
3, threo
4, erythro

(1)

5, cis, R = $CH_3$; R′ = H
6, trans, R = H; R′ = $CH_3$
a, Ar = $C_6H_5$
b, Ar = α-naphthyl

The β-bromo carbamates are readily available from the corresponding bromohydrins. This route does not seem to have been used previously for the stereospecific synthesis of 2-oxazolidinones.[1]

## Results and Discussion

*threo*-3-Bromo-2-butanol (1) with phenyl or α-naphthyl isocyanate gave the threo carbamates **3a** and **3b**, respectively. Ring closure by elimination of HBr with potassium hydroxide in ethanol then led in practically quantitative yield to the *cis*-4,5-dimethyl-*N*-aryl-2-oxazolidinones **5a** and **5b** (eq 1).

*erythro*-3-Bromo-2-butanol (2) similarly led *via* the intermediate erythro carbamates **4a** and **4b** to the *trans*-2-oxazolidinones **6a** and **6b**.

Ring closure steps such as the one used for the oxazolidinone ring formation are generally accepted to proceed with inversion at the carbon atom at which the bromine atom is displaced. The stereochemistry of the 2-oxazolidinones **5** and **6** is supported by their nmr spectra (see below).

**Infrared Spectra of β-Bromo Carbamates.**[5]—The infrared spectra of the carbamates **3** and **4** generally agree well with literature data.[6-9] They show $\nu(NH)_{free}$ at *ca.* 3500 $cm^{-1}$, the amide I and II bands at *ca.* 1742 and 1532 $cm^{-1}$, symmetric and asymmetric methyl bending frequencies at *ca.* 1447 and 1384 $cm^{-1}$, skeletal frequencies corresponding to the –CNHC=O group at *ca.* 1335 and 1318 $cm^{-1}$, and skeletal frequencies corresponding probably to the –COO group at *ca.* 1210, 1105, and 1075 $cm^{-1}$.[5]

**Nmr Data and Conformational Analysis of β-Bromo Carbamates**—The nmr data of the β-bromo carbamates **3** and **4** are summarized in Table I. It can be seen from this table that the two threo carbamates on one side and the two erythro carbamates on the other side behave very similarly.

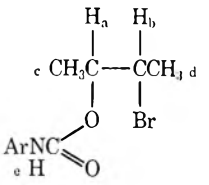
The threo compounds **3** may assume *a priori* the three conformations **3**-I (gauche), **3**-II (gauche), and **3**-III (anti) (and their mirror images). For the erythro compounds **4** the three corresponding conformations are **4**-I (gauche), **4**-II (gauche), and **4**-III (anti) (and their mirror images).

Turning our attention first to the vicinal coupling constant $J_{ab}$, it is seen that the values for the erythro compounds are slightly larger (4.2 Hz) than those for the corresponding threo compounds (3.8 and 4.0 Hz). It has been found in many stereoisomeric series of the

(1) For a recent review on 2-oxazolidinone chemistry see M. E. Dyen and D. Swern, *Chem. Rev.*, **67**, 197 (1967).
(2) See references cited in ref 1.
(3) C. Heathcock and A. Hassner, *Angew. Chem., Int. Ed. Engl.*, **2**, 213 (1963); A. Hassner, M. E. Lorber, and C. Heathcock, *J. Org. Chem.*, **32**, 540 (1967).
(4) (a) T. A. Foglia and D. Swern, *J. Org. Chem.*, **32**, 75 (1967); (b) *ibid.*, **34**, 1680 (1969).
(5) See paragraph at end of paper regarding supplementary material.
(6) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1966.
(7) L. J. Bellamy, "Advances in Infrared Group Frequencies," Methuen and Co., London, 1968.
(8) S. Pinchas and D. Ben-Ishai, *J. Amer. Chem. Soc.*, **79**, 4099 (1957).
(9) A. R. Katritzky and R. A. Jones, *J. Chem. Soc.*, 676 (1960).

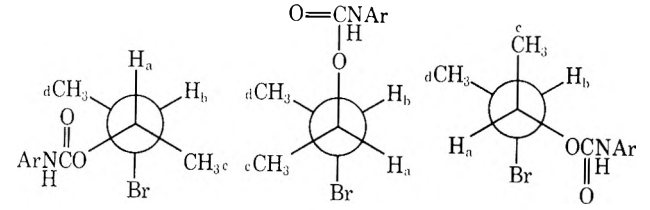
Table I

Nmr Data of β-Bromo Carbamates[a]

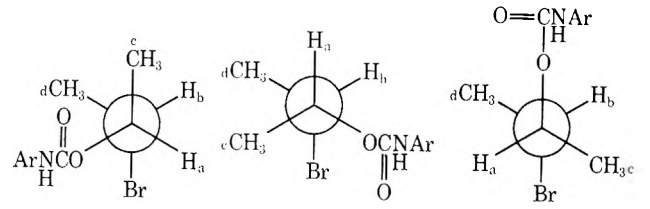


| Carbamate | Nmr in $CCl_4$ | | | | |
|---|---|---|---|---|---|
| | $H_a$ | $H_b$ | $H_c$ | $H_d$ | $H_e$ |
| 2-(*threo*-3-Bromobutyl) carbanilate (**3a**) | 4.95 (oct) $J_{ab}$ = 3.8 | 4.12 (oct) $J_{ba}$ = 3.8 | 1.66 (d) $J_{ca}$ = 6.8 | 1.33 (d) $J_{db}$ = 6.4 | 6.87–7.5 (m) |
| 2-(*threo*-3-Bromobutyl)-*N*-(α-naphthyl) carbamate (**3b**) | 5.02 (oct) $J_{ab}$ = 4.0 | 4.15 (oct) $J_{ba}$ = 4.0 | 1.67 (d) $J_{ca}$ = 6.8 | 1.38 (d) $J_{db}$ = 6.5 | 7.07–8.0 (m) |
| 2-(*erythro*-3-Bromobutyl) carbanilate (**4a**) | 4.85 (oct) $J_{ab}$ = 4.2 | 4.23 (oct) $J_{ba}$ = 4.2 | 1.65 (d) $J_{ca}$ = 6.8 | 1.34 (d) $J_{db}$ = 6.4 | 6.85–7.5 (m) |
| 2-(*erythro*-3-Bromobutyl)-*N*-(α-naphthyl) carbamate (**4b**) | 4.89 (oct) $J_{ab}$ = 4.2 | 4.28 (oct) $J_{ba}$ = 4.2 | 1.69 (d) $J_{ca}$ = 6.8 | 1.40 (d) $J_{db}$ = 6.3 | 6.90–8.0 (m) |
| | Δ*H*(erythro–threo) | | | | |
| Ar = phenyl | −0.10 | +0.11 | −0.01 | +0.01 | |
| Ar = α-naphthyl | −0.13 | +0.13 | +0.02 | +0.02 | |

[a] With respect to tetramethylsilane as internal standard. *J* values are observed splitting values in hertz.



threo 3-I gauche 3-II gauche 3-III anti



erythro 4-I gauche 4-II gauche 4-III anti

type $CH_3CHXCHYCH_3$ that the vicinal coupling constant is larger in the erythro series than in the threo series. The general interpretation is that the anti conformation is more stable in the erythro series, where it is frequently the dominant conformer, than the anti conformation in the threo series.[10a]

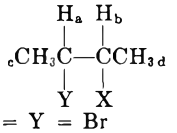
In our case the relatively small value of the vicinal coupling constant precludes this. The percentage of the anti conformation **4**-III for the erythro compounds may be estimated at about 33%, assuming a value of 9.6 Hz for $J_{anti}$ and 1.5 Hz for $J_{gauche}$:[11] $J_{ab}$ = (0.67·1.5 + 0.33·9.6) = 4.2 Hz.

For the threo compounds the estimated percentages of the anti conformation **3**-III are only approximately 2–5% lower, corresponding to a decrease in the coupling constant of 0.2–0.4 Hz.

Addressing ourselves now to the chemical shifts of the methine protons, it can be seen from Table I that the proton $H_a$ appears at lower field in the threo series whereas the proton $H_b$ appears at higher field.

The protons $H_a$ are vicinal to the bromine atom and the observed behavior corresponds to that of the 2,3-dibromobutanes **7a**, where the signal of the DL (corresponding to threo) isomer appears at lower field than that of the meso (corresponding to erythro) compound.[10b,12]

$H_b$, on the other hand, is vicinal to the carbamate group and the behavior is analogous to that of the 2,3-diacetoxybutanes **7b**, where the signal of the DL isomer also appears at higher field than that of the meso compound.[10b,12a]



**7a**, X = Y = Br
**b**, X = Y = $CH_3COO$
**c**, X = NCO; Y = I
**d**, X = NHCOOMe; Y = I

The chemical shift differences in $H_a$ and $H_b$ between the two stereoisomeric series of β-bromo carbamates show that the corresponding protons are in *different* magnetic environments. The difference in the population of the anti conformers **3**-I and **4**-I is too small in the present case to account solely for the magnitude of the chemical shift differences, and we will concentrate therefore on the ratio of the two gauche conformations I:II.

The treatment has to take into account the orientation of all vicinal groups with respect to each other. These orientations are listed in Table II. Not included are the orientations of the two vicinal protons $H_a$ and $H_b$, which have been taken *a priori* to be gauche in the conformations I and II and anti in the conformation III.

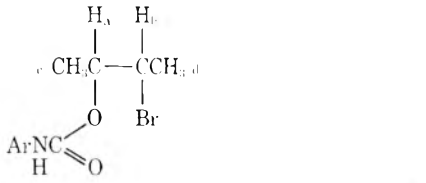
It can be seen from Table II that with respect to the three conformations I, II, and III the environment around $H_a$ is different for both the threo and the erythro

(10) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969: (a) p 291 ff; (b) p 163 ff; (c) p 286 ff; (d) p 234 ff; and references cited therein.

(11) Compare the value of $J_{cis}$ = 8.5 Hz in the *cis*-2-oxazolidinones **5** discussed in this paper as well as the value of $J_{anti}$ in compounds of similar structure known to exist preferentially in the anti conformation. The estimated value of 33% is presumably close to the upper limit considering the perhaps somewhat low estimates for both $J_{gauche}$ and $J_{anti}$.

(12) (a) A. A. Bothner-By and C. Naar-Colin, *J. Amer. Chem. Soc.*, **84**, 743 (1962); (b) F. A. L. Anet, *ibid.*, **84**, 747 (1962).

TABLE II
ORIENTATION OF VICINAL SUBSTITUENTS IN THE CONFORMATIONS OF THREO AND ERYTHRO β-BROMO CARBAMATES



| Orientation of | With respect to | threo 3-I | threo 3-II | threo 3-III | erythro 4-I | erythro 4-II | erythro 4-III |
|---|---|---|---|---|---|---|---|
| | | Conformation[a] | | | | | |
| Br | $H_a$ | a | g | g | g | a | g |
| $CH_3$ (d) | $H_a$ | g | a | g | a | g | g |
| ArNHCOO | $H_b$ | a | g | g | a | g | g |
| $CH_3$ (c) | $H_b$ | g | a | g | g | a | g |

[a] a = anti; g = gauche.

series, but that the environment of $H_b$ is identical for the two series.

The observed chemical shift difference of $H_b$ then leads us to the conclusion that the ratio I:II must be quite *different* in the threo and the erythro series. While it is not possible, unfortunately, to evaluate any of the ratios I:II in the two stereoisomeric series, the implication follows that *at least* three of the four gauche conformations or at least five out of the total of six conformations are present in significant proportions in the conformational equilibria discussed.

Foglia and Swern have investigated β-iodo isocyanates **7c** and *N*-(β-iodo) carbamates **7d**.[4b] The general behavior found is similar to that of our compounds, with slightly smaller vicinal coupling constants of 3.0 and 3.5 Hz for the threo and erythro series, except that the chemical shifts $H_b$ (in formulas **7c** and **7d**) are practically identical in both the threo and erythro compounds. Foglia and Swern concluded that their compounds existed only in the two gauche conformations **3-I** and **4-I**, respectively (iodo in place of bromo, NCO or NHCOOMe in place of OCONHAr). As can be seen from Table II, another interpretation is compatible with their data. Namely, the compounds can exist in all four gauche conformations, provided that the ratios I:II are accidentally very similar but not close to 1 in both stereoisomeric series.[13]

No explanation is readily apparent why in all the carbamates discussed as well as in the 2,3-diacetoxybutanes **7b**[12a] the anti conformation **4-III** is not the dominant conformer in the erythro series, as in so many other erythro or meso compounds studied.[10a,12]

**Infrared Spectra of 2-Oxazolidinones.**[5]—The value of the C=O stretching frequency (amide I band) lies at *ca.* 1750 $cm^{-1}$ in the typical region of other 2-oxazolidinones, specifically *N*-aryl-2-oxazolidinones and similar five-membered lactams.[7,8,14,15] Mecke, Mecke, and Lüttringhaus have, in a detailed examination of the parent compound, 2-oxazolidinone, listed five skeletal frequencies.[16] All 2-oxazolidinones examined show corresponding bands at *ca.* 1215, 1078, 1060, 915, and 765 $cm^{-1}$. It appears that these five skeletal bands, perhaps besides the band around 915 $cm^{-1}$ which, being less intense, seems only marginally useful, are suitable as a diagnostic tool for recognizing the 2-oxazolidinone structure.

The band around 1050 $cm^{-1}$ has also been pointed out by Pinchas and Ben-Ishai.[7]

**Nmr Spectra of 2-Oxazolidinones.**[17]—The nmr data of the 2-oxazolidinones examined agree well with those of similar oxazolidinones reported by other authors.[4b,15] The two cis oxazolidinones **5a** and **5b** thus have a 4-H–5-H coupling constant of *ca.* 8 Hz, whereas the corresponding trans compounds **6a** and **6b** have a coupling constant of *ca.* 6.0 Hz.[4b] Generally, cis proton coupling is larger than trans proton coupling in five-membered rings, which cannot deviate appreciably from planarity as expected from the Karplus rule.[10c,18,19] The 4 and 5 methyl groups absorb at higher field in the cis oxazolidinones (δ *ca.* 1.12 and 1.45 ppm, respectively) than in the corresponding trans isomers (δ *ca.* 1.24 and 1.52 ppm, respectively). The 4 and 5 methine protons, on the other hand, appear at lower field in the cis compounds (δ *ca.* 4.43 and 4.93 ppm, respectively) than in the trans isomers (δ 3.98 and 4.24 ppm, respectively). This effect can be attributed mainly to the diamagnetic anisotropy of the *C*-methyl bond and is found in many cis–trans isomer pairs of planar three- to five-membered ring compounds.[10d] A more detailed discussion has been given elsewhere.[19]

**The Boiling Points of the Oxazolidinones.**—The stereoisomeric 2-oxazolidinones were analyzed by glc on a QF-1 column. For both the *N*-phenyl compounds **5a** and **6a** (column temperature 220°) and the *N*-(α-naphthyl) compounds **5b** and **6b** (column temperature 250°) the *trans*-2-oxazolidinones **6a** and **6b** had a lower retention time, indicating a lower boiling point than the cis isomers. We have observed the same relationship with numerous other heterocyclic three- to five-membered rings possessing two vicinal alkyl substituents.[19b,20] This behavior is reminiscent of the von Auwers' rule, or rather of the "extended von Auwers' rule",[21] originally applied (occasionally with erroneous conclusions) to cis–trans isomeric cyclohexane derivatives, according to which the cis compound has the higher boiling point, refractive index, and density, but the lower molar refraction. Recent modifications of the von Auwers' rules have been called the "Allinger rule" and the "conformational rule."[22–24] According

(13) A ratio I:II of 1 would make the magnetic environment around $H_a$ equal for both the threo and erythro series and should therefore result in practically equal values of $H_a$.

(14) H. K. Hall, Jr., and R. Zbinden, *J. Amer. Chem. Soc.*, **80**, 6428 (1958).

(15) J. E. Herweh, T. A. Foglia, and D. Swern, *J. Org. Chem.*, **33**, 4029 (1968).

(16) (a) R. Mecke, R. Mecke, and A. Lüttringhaus, *Chem. Ber.*, **90**, 975 (1957); (b) R. Mecke, Jr., and R. Mecke, Sr., *ibid.*, **89**, 343 (1956); (c) see also A. R. Katritzky and A. P. Ambler in "Physical Methods in Heterocyclic Chemistry," Vol. 2, Academic Press, New York, N. Y., 1963, pp 161, 219 ff.

(17) See paragraph at end of paper regarding supplementary material.

(18) S. Sternhell, *Quart. Rev., Chem. Soc.*, **23**, 236 (1969).

(19) (a) R. A. Wohl and D. F. Headley, *J. Org. Chem.*, **37**, 4401 (1972); (b) R. A. Wohl and J. Cannie, *ibid.*, **38**, 1787 (1973).

(20) R. A. Wohl, unpublished data.

(21) The boiling point, although frequently quoted, is not included in the original von Auwers' rule. See the comments in ref 23. The rule, including the reference to the boiling point, has therefore been called the "extended Auwers' rule".[23]

(22) (a) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 172 ff; (b) M. Hanack, "Conformation Theory," Academic Press, New York, N. Y., 1965, pp 86, 142.

(23) H. van Bekhum, A. van Veen, P. E. Berkaade, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **80**, 1310 (1961).

(24) N. L. Allinger, *Experientia*, **10**, 328 (1954); *J. Org. Chem.*, **21**, 915 (1956); *J. Amer. Chem. Soc.*, **79**, 3443 (1957); **80**, 1953 (1958); **81**, 232 (1959). N. L. Allinger and R. J. Cirby, Jr., *J. Org. Chem.*, **26**, 933 (1961).

to the latter, "the isomer with the smaller molar volume has the greater heat content." The higher boiling point can then be related to the smaller molecular volume, although the origin of the relationship is not very clear. Van Bekhum and coworkers have suggested that the boiling point should be excluded from any statement of the von Auwers' rule since it frequently fails for the boiling point.[23]

The examples where the extended von Auwers' rule fails consist of cyclohexane rings with very bulky or very polar substituents. We have, on the other hand, not been able to find an example where the rule fails in three- to five-membered rings with two vicinal alkyl substituents, such as occur very frequently in heterocyclic compounds. The extended von Auwers' rule in this restricted context has occasionally been of use to us for the tentative assignment of configuration until a more rigorous proof of stereochemistry could be obtained.

## Experimental Section

**General Procedures.**—Melting points were taken on a Fisher-Johns melting point apparatus and are corrected. Infrared spectra were taken on a Perkin-Elmer 137 sodium chloride spectrophotometer. Methylene chloride was used as a solvent. Gas chromatography was done on a Varian Model 90P gas chromatograph. Most of the work was done with an 8-ft column of 10% QF-1 on Gas-Chrom Q. Nmr spectra were taken on a Varian T-60 nmr spectrometer. Tetramethylsilane was used as internal standard. The elemental analyses were performed by Hoffmann-La Roche, Inc., Nutley, N. J., to whom we would like to extend our thanks.

*threo-* **and** *erythro-***3-Bromo-2-butanol.**—**1** and **2**, respectively, were prepared essentially according to the method of Winstein and Lucas,[25] by addition of HOBr to *cis-* and *trans*-2-butene, respectively, using, however, *N*-bromosuccinimide in place of *N*-bromoacetamide. The bromohydrins were found to be >99% pure as judged by ir and nmr data and gc analysis as originally assumed by Winstein and Lucas. **1** and **2** each gave only one peak on gas chromatography on a 6-ft 15% Carbowax 20M on Gas-Chrom R column. A mixture of the two compounds was easily separated at 115°, the compounds having retention times of 8.6 and 10.4 min, respectively, at a flow rate of 100 ml/min.

**Preparation of Carbamates.**[26]—A mixture of bromohydrin (10.0 g, 65 mmol) and phenyl or α-naphthyl isocyanate (64–65 mmol) was kept for 1 hr at 95–100°. After cooling, the mostly solid residue was triturated twice with cold pentane and then extracted with three to five portions of hot petroleum ether (bp 30–60°) or ligroin. The combined petroleum ether or ligroin fractions were evaporated to about 150 ml and then allowed to cool for crystallization. The obtained product was recrystallized from petroleum ether or ligroin.

**2-(*threo*-3-Bromobutyl) carbanilate (3a)** was obtained as white crystals (56%), mp 64.5–65° (from petroleum ether).

*Anal.* Calcd for $C_{11}H_{14}BrNO_2$: C, 48.55; H, 5.19; N, 5.15; Br, 29.36. Found: C, 48.37; H, 5.15; N, 5.15; Br, 29.64.

**2-(*threo*-3-Bromobutyl)-*N*-(α-naphthyl) carbamate (3b)** was obtained as slightly yellowish crystals (71%), mp 99.5–100° (from ligroin, bp 90–120°).

*Anal.* Calcd for $C_{15}H_{16}BrNO_2$: C, 55.92; H, 5.01; N, 4.35. Found: C, 56.32; H, 5.03; N, 4.30.

**2-(*erythro*-3-Bromobutyl) carbanilate (4a)** was obtained as white crystals (62%), mp 56–56.5° (from petroleum ether).

*Anal.* Calcd for $C_{11}H_{14}BrNO_2$: C, 48.55; H, 5.19; N, 5.15; Br, 29.36. Found: C, 48.53; H, 5.11; N, 5.15; Br, 29.59.

**2-(*erythro*-3-Bromobutyl)-*N*-(α-naphthyl) carbamate (4b)** was obtained as white, fluffy crystals (41%), mp 128–129° (from ligroin, bp 90–120°).

*Anal.* Calcd for $C_{15}H_{16}BrNO_2$: C, 55.92; H, 5.01; N, 4.35; Br, 24.80. Found: C, 55.99; H, 4.99; N, 4.20; Br, 25.00.

**Preparation of 2-Oxazolidinones from β-Bromo Carbamates.**—A solution of 840 mg (15 mmol) of potassium hydroxide in 6 ml of absolute ethanol was added to a hot solution of carbamate (15 mmol) in 12 ml of absolute ethanol and the mixture was heated in a 95° water bath for 10 min with occasional shaking. The precipitated potassium bromide was filtered off and the filtrate was evaporated at the rotary evaporator to dryness. The residue was taken up in ether and filtrated again to remove any small additional amount of potassium bromide. The solution was then evaporated again and the residue was distilled and/or recrystallized.

***cis*-4,5-Dimethyl-*N*-phenyl-2-oxazolidinone (5a)** was obtained as an oil (2.84 g, 99%). Distillation at 141–143° (0.2 mm), low-temperature recrystallization from isopropyl alcohol, and washing with petroleum ether yielded colorless crystals, mp 42–42.5°.

*Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.04; H, 6.92; N, 7.23.

Ring closure with aqueous sodium hydroxide gave only about 50% yield beside about 50% of basic compounds.[27]

***cis*-4,5-Dimethyl-*N*-(α-naphthyl)-2-oxazolidinone (5b)** was obtained as colorless crystals (3.57 g, 99%), mp after repeated recrystallization from isopropyl alcohol 138–140°.

*Anal.* Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.89; H, 6.43; N, 5.71.

***trans*-4,5-Dimethyl-*N*-phenyl-2-oxazolidinone (6a).**—Distillation of the crude product (3.67 g, 99%) at 120–122° (0.05 mm) gave a colorless liquid which solidified. After two recrystallizations from isopropyl alcohol, colorless crystals, mp 63–63.5°, were obtained.

*Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.00; H, 6.99; N, 7.23.

***trans*-4,5-Dimethyl-*N*-(α-naphthyl)-2-oxazolidinone (6b).**—Decolorization of the crude material (3.61 g, 100%) with activated charcoal and recrystallization from isopropyl alcohol gave almost colorless crystals, mp 112.5–113°.

*Anal.* Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.59; H, 6.44; N, 5.70.

**Acknowledgment.**—We wish to thank the Rutgers Research Council for financial support.

**Registry No.**—**1**, 19773-41-2; **2**, 19773-40-1; **3a**, 41594-13-2; **3b**, 41594-14-3; **4a**, 41594-15-4; **4b**, 41594-16-5; **5a**, 41594-17-6; **5b**, 41594-18-7; **6a**, 41594-19-8; **6b**, 41594-20-1; phenyl isocyanate, 103-71-9; α-naphthyl isocyanate, 86-84-0; di-α-naphthylurea, 607-56-7.

**Supplementary Material Available.**—Detailed tables showing the ir frequencies of all compounds examined, a table containing detailed nmr data of all 2-oxazolidinones examined, and full details for the preparation of all carbamates described in this paper will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20 × reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-3858.

(25) S. Winstein and H. J. Lucas, *J. Amer. Chem. Soc.*, **61**, 1576 (1939).

(26) See paragraph at end of paper regarding supplementary material.

(27) *Cf.* R. Adams and J. B. Segur, *J. Amer. Chem. Soc.*, **45**, 785 (1923).

# Ring Expansions and Contractions with Diazonium Betaines. I. Synthesis of Ketones by Ring Expansion of Methylenecycloalkanes with Arenesulfonyl Azides

RONALD A. WOHL

*School of Chemistry, Rutgers University, The State University of New Jersey, New Brunswick, New Jersey 08903*

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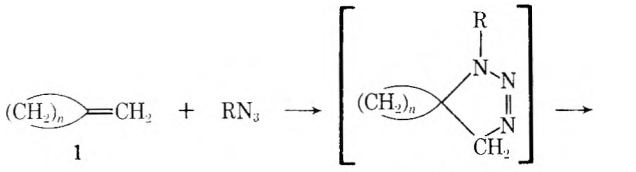
Reactions of methylenecycloalkanes with an aromatic sulfonyl azide proceed practically quantitatively *via* unstable intermediate $\Delta^2$-triazolines **2b** to the ring-expanded arenesulfonimidocycloalkanes **3b** which are then hydrolyzed to the corresponding ketones **4**. The related reaction of 1,2-disubstituted olefins with arenesulfonyl azides provides a convenient route to ketones. Some aspects of the 1,3-dipolar addition of azides to olefins and the thermal decomposition of the resulting $\Delta^2$-triazolines are discussed.

Organic azides react with olefins in a 1,3 cycloaddition to form $\Delta^2$-triazolines **2**, a reaction first reported



**a**, R = NC
**b**, R = $ArSO_2$

by Wolff in 1912.[1,2] McMurry,[3] and recently Hermes and Marsh,[4] have used the reaction between methylenecycloalkane and cyanogen azide as a ring expansion method[5] according to reaction 1 (R = NC). The intermediate $\Delta^2$-triazolines **2a** are unstable in this case and rearrange spontaneously to the ring-enlarged imides **3a** which can be hydrolyzed readily to the corresponding ketones **4**. McMurry obtained cycloheptanone and 2-methylcycloheptanone in this manner from methylenecyclohexane and ethylidenecyclohexane, respectively.[3]

Independently of McMurry's work we have investigated the scope and nature of the analogous reaction using arenesulfonyl azides [reaction 1 (R = $ArSO_2$)] in place of cyanogen azide. The use of arenesulfonyl azides offers the advantages of stability and nonhazardous nature as compared with cyanogen azide.[4]

## Results

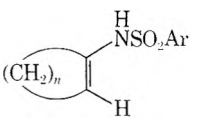
The results obtained are summarized in Table I. All exocyclic olefins examined from methylenecyclobutane to methylenecycloheptane reacted smoothly with aromatic sulfonyl azides to give the corresponding ring-enlarged imides in practically quantitative yield. Of several arenesulfonyl azides tested *o*-nitrobenzenesulfonyl azide was used most extensively because it seemed to give the best crystallizing products.

The identical imidocycloalkane products could also be obtained by the reaction between the corresponding cycloalkene and arenesulfonyl azide. All imides **5–10** show a very strong band around 1600 $cm^{-1}$ in the ir spectrum corresponding to the C=N group (see Table I). This frequency shows a regular decrease when going from the five-membered to the eight-membered ring similar to the conditions found for the corresponding cyclic ketones.[6,7] As expected no band around 3400 $cm^{-1}$ is apparent demonstrating the absence of any NH group.

In the nmr spectra the $\alpha$ protons to the imido function syn and anti to the arenesulfonyl group are generally separately visible with a chemical shift separation between 0.37 and 0.56 ppm. No assignment of these signals with respect to syn and anti was undertaken since no general method for assigning these resonances seems to be available at present.[8] In cyclohexanone oximes and cyclohexanone oxime tosyl esters, the $\alpha$ protons syn to the N substituent are deshielded.[9] It seems perilous, however, to extrapolate from the oxime tosyl esters to the benzenesulfonimido group under consideration.[8]

The sulfonimides **3b**, *i.e.*, **5–10**, were easily hydrolyzed in acidic solution to the corresponding ketones **4** (see reaction 1). The hydrolysis of the related alkylidene cyanamides **3a** has been reported to be catalyzed by silver ion.[4]

From the crude reaction product between cyclohexene and *o*-nitrobenzenesulfonyl azide, in which the imide **7** was the major product as judged by the ir and nmr spectra, an isomeric compound could be isolated in 13% yield to which, on the base of spectral evidence, the enamide structure **11b** was ascribed. The ir spectrum



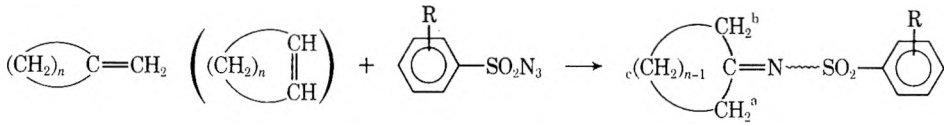
**11a**, Ar = *o*-$NO_2C_6H_4$; *n* = 3
**b**, *n* = 4
**c**, *n* = 5
**d**, *n* = 6

**12**, Ar = *m*-$NO_2C_6H_4$; *n* = 3
**13**, Ar = *p*-$CH_3C_6H_4$; *n* = 6

(1) L. Wolff, *Justus Liebigs Ann. Chem.*, **394**, 23 (1912).
(2) For reviews of this reaction see R. Huisgen, *Angew. Chem.*, **75**, 604, 742 (1963); R. Huisgen, R. Grashey, and J. Sauer in "The Chemistry of Alkenes," Vol. 1, S. Patai, Ed., Interscience, London, 1963, p 835; G. L'Abbé, *Chem. Rev.*, **69**, 345 (1969); T. Sheradsky in "The Chemistry of the Azido Group," S. Patai, Ed., Interscience, New York, N. Y., 1971, pp 359 ff, 373 ff; W. Lwowski, *ibid.*, p 529; see also R. Huisgen, R. Sustmann, and K. Bunge, *Chem. Ber.*, **105**, 1324 (1972).
(3) J. E. McMurry, *J. Amer. Chem. Soc.*, **91**, 3676 (1969).
(4) M. E. Hermes and F. D. Marsh, *J. Org. Chem.*, **37**, 2969 (1972).
(5) For a review of ring-enlargement reactions see C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions," Academic Press, New York, N. Y., 1968.
(6) (a) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1966, p 147 ff.
(7) L. J. Bellamy, "Advances in Infrared Group Frequencies," Methuen and Co., London, 1968, p 132 ff.
(8) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, p 226.
(9) G. J. Karabatsos, R. A. Tiller, and F. M. Vane, *J. Amer. Chem. Soc.*, **85**, 2326 (1963).

TABLE I

*o*-NITROBENZENESULFONIMIDOCYCLOALKANES PREPARED FROM METHYLENECYCLOALKANES AND CYCLOALKENES



| *n* | R | Product | Yield,[a,b] % | Reaction time[a] at 60°, days | Ir ($CH_2Cl_2$), $cm^{-1}$ $\nu$(C=N) | Nmr ($CDCl_3$)[c] $H_a$[d] | $H_b$[d] | $H_c$ |
|---|---|---|---|---|---|---|---|---|
| 3 | *o*-$NO_2$ | 5 | 99 (100) | 4 (1) | 1630 | 2.99 (t)[e] | 2.62 (t)[e] | 1.57-2.3 (m) |
| 3 | *m*-$NO_2$ | 6 | (100) | (1) | 1625 | 3.02 (t)[e] | 2.58 (t)[e] | 1.57-2.3 (m) |
| 4 | *o*-$NO_2$ | 7 | 99 (99.5) | 3 (8) | 1620 | 2.99 (m) | 2.44 (m) | 1.07-2.2 (m) |
| 5 | *o*-$NO_2$ | 8 | 98[f] (100)[f] | 6 (2) | 1605 | 3.10 (m) | 2.67 (m) | 1.40-2.05 (m) |
| 6 | *o*-$NO_2$ | 9 | 100 (99) | 2 (2) | 1595 | 3.33-2.34 (m) | | 1.56 (m), 1.96 (m) |
| 6 | *p*-$CH_3$ | 10 | (100) | (1) | 1598 | 3.03 (m) | 2.47 (m) | 1.10-2.24 (m) |

[a] Yields and reaction time in parentheses refer to the starting olefins in parentheses. [b] Crude weight yields (with respect to the azide component if an excess of olefin was used). Some products contain small amounts of the isomeric enamide **11**–**13** (see Discussion). [c] Chemical shifts $\delta$ with respect to tetramethylsilane as internal standard. [d] See discussion for assignment of $H_a$ and $H_b$ with respect to syn and anti. [e] Major splitting pattern in actually higher multiplet. [f] The crude material contains up to 13% of the isomeric enamide **11b**.

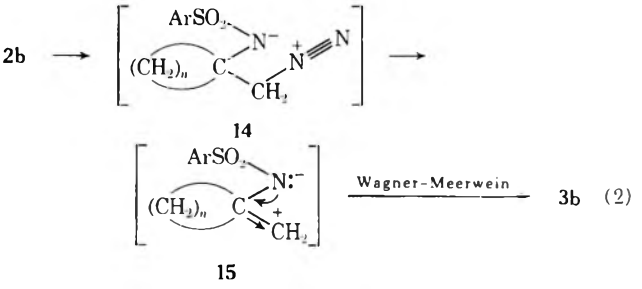
shows a sharp band at 3390 $cm^{-1}$ corresponding to the N–H stretch. There are medium weak bands at 1674 and 1591 $cm^{-1}$ corresponding to the double bond in a monosubstituted cyclohexene and the amide II band.[6] The nmr spectrum shows a pair of one-proton singlets at 6.42 and 5.61 ppm with half-height widths of 6.4 and 7.6 Hz, respectively. The lower field proton is exchangeable with $D_2O$ and can therefore be assigned to the N–H proton. The four $\alpha$- and four $\beta$-methylene protons absorb in two separate signals at 2.00 and 1.52 ppm.

All other crude imide products **5**, **6**, and **8**–**10** also contained small amounts of the isomeric enamides **11**–**13**, as judged by their ir and nmr spectra, although the percentage was in all cases much smaller than in the cyclohexane case **7**. No effort was made to isolate these enamides. The imide–enamide equilibrium is quite slow in the cases studied, since the pure compounds in $CDCl_3$ solution at room temperature are stable for weeks.

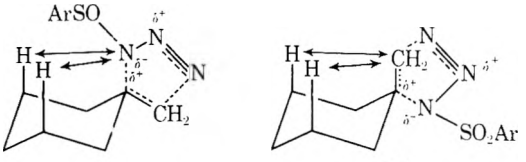
## Discussion

While strong electron-withdrawing substituents (R = NC–, ArCO–, ROCO–, picryl, $ArSO_2$–) on the azide facilitate the 1,3-dipolar addition to electron-rich olefins, the resulting triazolines turn out to be relatively unstable and lose nitrogen spontaneously or with slight heating.[2-4,10-14] For this reason the intermediate 1-arenesulfonyl-$\Delta^2$-triazolines **2b** were, analogously to the corresponding 1-cyano compounds **2a**, not isolable.

The probable reaction mechanism proceeds *via* the betaine intermediates **14** and **15** as depicted in reaction 2.[2-4,11-14] The ring-enlargement step is closely related to the classic Demjanov–Tiffeneau reaction.[5] In the case of the reaction with cycloalkenes a hydrogen shift takes the place of the Wagner–Meerwein shift.



With respect to reaction rates methylenecyclohexene proved to be by far the slowest reacting among the exocyclic olefins. A possible explanation is that the transition state probably looks like **16a** or **16b** with



severe 1,3-diaxial interactions. Such 1,3-diaxial interactions are typical of the rigid cyclohexane chair and comparatively absent in other cycloalkanes.

Transition state **16b** resulting from equatorial attack by the bulky azide reagent appears to be the less unfavorable alternative. Among the cycloalkenes cyclohexene was the slowest reacting olefin as has been observed before in cycloadditions with other azides.[13,15-18] No evidence for any aziridine formation[4,14,18] was observed in any of the reported reactions.[19]

## Experimental Section

**General Procedures.**—Melting points were taken on a Fisher–Johns melting point apparatus and are corrected. Ir spectra were taken on a Perkin-Elmer 137 sodium chloride spectrophotometer. Methylene chloride was used as solvent. Gas

(10) R. Huisgen, L. Möbius, and G. Szeimies, *Chem. Ber.*, **98**, 1138 (1965); R. Huisgen and G. Szeimies, *ibid.*, **98**, 1153 (1965).

(11) R. Fusco, G. Bianchetti, and D. Pocar, *Gazz. Chim. Ital.*, **91**, 849, 933 (1961). R. Fusco, G. Bianchetti, D. Pocar, and R. Ugo, *ibid.*, **92**, 1040 (1962); *Chem. Ber.*, **96**, 802 (1963).

(12) R. M. Schribner, *Tetrahedron Lett.*, **No. 47**, 4737 (1967).

(13) A. S. Bailey, J. J. Merer, J. E. White, *Chem. Commun.*, 4 (1965); A. S. Bailey and J. E. White, *J. Chem. Soc. B*, 819 (1966).

(14) A. C. Oehlschlager and L. H. Zalkow, *J. Org. Chem.*, **30**, 4205 (1965); R. S. McDaniel and A. C. Oehlschlager, *Tetrahedron*, **25**, 1381 (1969).

(15) P. Scheiner, *Tetrahedron*, **24**, 349 (1967).

(16) A. S. Bailey and J. E. White, *J. Chem. Soc. B*, 819 (1966).

(17) R. Huisgen, G. Szeimies, and L. Möbius, *Chem. Ber.*, **100**, 2494 (1967).

(18) K. R. Henery-Logan and R. A. Clark, *Tetrahedron Lett.*, **No. 7**, 801 (1968).

(19) The spirocyclic aziridines under consideration would be derived from the betaine intermediates **14** or **15**. The methylene group of the aziridine ring is expected to absorb at *ca.* $\delta$ 2.5–3 ppm.[4,14]

chromatography was done on a Varian Model 90P gas chromatograph. Most of the work was done with a 8-ft column of 10% QF-1 on Gas-Chrom Q. Nmr spectra were taken on a Varian T-60 nmr spectrometer. Tetramethylsilane was used as internal standard. The elemental analyses were performed by the Hoffmann-La Roche Corp., Nutley, N. J., to whom we would like to extend our thanks.

The methylenecycloalkanes not commercially available were prepared from the corresponding ketones by the Wittig reaction modification of Corey and coworkers.[20] The aromatic sulfonyl azides were prepared according to the procedure of Leffler and Tsuno.[21]

**General Procedure for Reaction with Aromatic Sulfonyl Azide.**—The azide and olefin (1–2 equiv) were combined in a sealed glass pressure tube (Fischer and Porter Co.) and immersed in an oil bath of 60° and protected from light. After all the contents had become liquid, whereby frequently two phases were formed, the contents were stirred magnetically for the time period indicated in Table I, *i.e.*, until an ir spectroscopic analysis indicated that all azide had reacted. The excess olefin was removed *in vacuo* until the sample reached constant weight. Alternatively the reaction may be conducted in acetonitrile as a solvent.

*o*-**Nitrobenzenesulfonimidocyclopentane** (**5**) formed as slightly yellowish crystals from absolute ethanol, mp 91–94°.

*Anal.* Calcd for $C_{11}H_{12}N_2O_4S$: C, 49.25; H, 4.51; N, 10.44; S, 11.95. Found: C, 49.13; H, 4.60; N, 10.28; S, 11.37.

*m*-**Nitrobenzenesulfonimidocyclopentane** (**6**).—Imide **6** was obtained as slightly yellowish oil, which according to ir and nmr spectra (see Table I) was practically pure.

*Anal.* Calcd for $C_{11}H_{12}N_2O_4S$: C, 49.25; H, 4.51; N, 10.44. Found: C, 49.51; H, 4.66; N, 10.65.

*o*-**Nitrobenzenesulfonamidocyclohexane** (**7**).—The crude reaction mixture obtained was recrystallized from ether whereupon 69% of crystalline **7**, mp 72–74°, was obtained. This was taken up in warm benzene and filtrated from impurities and the benzene taken off *in vacuo*. The residual oil was treated with ether and a seed crystal whereupon pure imide **7** crystallized as slightly yellowish crystals, mp 73–74°.

*Anal.* Calcd for $C_{12}H_{14}N_2O_4S$: C, 51.05; H, 5.00; N, 9.92; S, 11.36. Found: C, 51.02; H, 4.90; N, 9.86; S, 11.36.

*o*-**Nitrobenzenesulfonimidocycloheptane** (**8**) formed as slightly yellowish crystals from benzene–petroleum ether, mp 90–90.8°.

*Anal.* Calcd for $C_{13}H_{16}N_2O_4S$: C, 52.69; H, 5.44; N, 9.45; S, 10.82. Found: C, 52.70; H, 5.42; N, 9.33; S, 10.86.

*o*-**Nitrobenzenesulfonimidocyclooctane** (**9**) formed as slightly yellowish crystals from isopropyl alcohol, mp 95.5–97°.

*Anal.* Calcd for $C_{14}H_{18}N_2O_4S$: C, 54.18; H, 5.85, N, 9.03; S, 10.33. Found: C, 53.96; H, 5.79; N, 8.93; S, 10.13.

*p*-**Toluenesulfonimidocyclooctane** (**10**). **A.**—A mixture of tosyl azide (0.59 g, 3.0 mmol) and cyclooctene (1.65, g, 15 mmol) was kept for 5 weeks at room temperature in a tightly stoppered reaction flask with occasional release of pressure. Removal of the olefin *in vacuo* until constancy of weight afforded 892 mg (100%) of a colorless oil. According to the ir and nmr spectra (see Table I) this consisted of practically pure title compound **10**.

**B.**—The same compound was obtained in the same yield by heating the two reagents in a sealed pressure tube at 65° for 24 hr.

*Anal.* Calcd for $C_{15}H_{21}NO_2S$: C, 64.48; H, 7.58; N, 5.01. Found: C, 64.18; H, 7.66; N, 4.82.

*o*-**Nitrobenzenesulfonamido-1-cyclohexene** (**11b**).—A mixture of *o*-nitrobenzenesulfonyl azide (3.42 g, 15 mmol) and cyclohexene (2.46 g, 30 mmol) was treated as described in the general procedure, for 8 days at 60°. Evaporation *in vacuo* yielded 4.20 g of a yellowish oil, which was triturated with five 20-ml portions of petroleum ether. After addition of *ca.* 30 ml of cold ether crystals formed. Filtration and washing with ether afforded 553 mg (13%) of yellowish crystals, mp 99–107°. Repeated recrystallization from benzene–petroleum ether raised the melting point to 105–107°: ir ($CH_2Cl_2$) 3390 (N–H), 2905 (C–H), 1674 (C=C), 1591 (amide II), 1538 ($NO_2$, asym), 1361 ($NO_2$, sym), 1328 ($SO_2$, asym), 1171 $cm^{-1}$ ($SO_2$, sym); nmr $\delta$ ($CDCl_3$) 8.08 (m, 1, arom), 7.80 (m, 3, arom), 6.42 (s, 1, N–H), 5.61 (m, 1, >C=C—H), 2.00 (m, 4, $\alpha$-$CH_2$), 1.52 (m, 4, $\beta$-$CH_2$).

*Anal.* Calcd for $C_{12}H_{14}N_2O_4S$: C, 51.05; H, 5.00; N, 9.92; S, 11.36. Found: C, 50.95; H, 4.95; N, 9.78; S, 11.24.

**General Procedure for Hydrolysis.**—The arenesulfonimidocycloalkane was treated with an excess of cold 2 *N* hydrochloric acid. The mixture was kept at room temperature for 24 hr with occasional shaking, and the ketone then was isolated according to methods A or B.

**A.**—The mixture was steam distilled. The distillate was extracted with ether, and the ethereal extracts were dried with magnesium sulfate. After filtration, evaporation of the ether yielded the ketone. For low-boiling ketones the ether was removed through a fractionating column.

**B.**—The mixture was made alkaline with 2 *N* sodium hydroxide and then extracted three times with ether. The subsequent work-up was as described under method A.

Yields for the hydrolysis under methods A or B were better than 80%. The resulting ketones were identified by their ir and nmr spectra and gas chromatographic retention times.

**Acknowledgment.**—We wish to thank the Rutgers Research Council for financial support.

**Registry No.**—**1** ($n$ = 3), 1120-56-5; **1** ($n$ = 4), 1528-30-9; **1** ($n$ = 5), 1192-37-6; **1** ($n$ = 6), 2505-03-5; **5**, 41700-94-1; **6**, 41700-95-2; **7**, 41700-96-3; **8**, 41700-97-4; **9**, 41700-98-5; **10**, 41700-99-6; **11b**, 41701-00-2; cyclopentene, 142-29-0; cyclohexene, 110-83-8; cycloheptene, 628-92-2; cyclooctene, 931-88-4; *o*-nitrobenzenesulfonyl azide, 6655-31-8; *m*-nitrobenzenesulfonyl azide, 6647-85-4; tosyl azide, 941-55-9.

(20) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

(21) J. E. Leffler and Y. Tsuno, *J. Org. Chem.*, **28**, 902 (1963).

# Rearrangements of Azidoquinones. XI. Acid-Catalyzed Rearrangements of 2,5-Diazido-1,4-benzoquinones

WALTER WEYLER, JR., PAUL GERMERAAD, AND HAROLD W. MOORE*[1]

*Department of Chemistry, University of California, Irvine, California 92664*

*Received March 6, 1973*

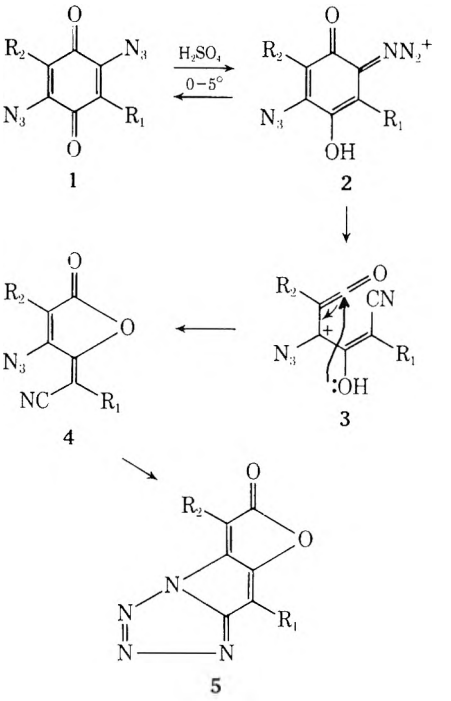
The acid-catalyzed decomposition of 2,5-diazido-1,4-benzoquinones (1) provides a convenient route to β-azido-γ-cyanoalkylidene-$\Delta^{\alpha,\beta}$-butenolides (4). Bulky substituents (*tert*-butyl or *tert*-pentyl) on the butenolide ring cause a subsequent cycloaddition of the β-azido group to the cyano moiety giving the tetrazoles (5). Synthetic uses of these products are also discussed, *e.g.*, the conversion of α-phenyl-β-azido-γ-cyanomethylidene-$\Delta^{\alpha,\beta}$-butenolide (4c) to the indole 10 and the formation of the lactone–lactams (12) from the tetrazoles (5).

Azidoquinones constitute a synthetically versatile class of reagents which can be specifically converted to a large variety of other compounds.[2] Of particular importance regarding the present manuscript is the previously reported stereospecific acid-catalyzed rearrangements of azidoquinones to γ-cyanoalkylidene-$\Delta^{\alpha,\beta}$-butenolides.[2a] This rearrangement is very general, usually proceeding in high yields, and does not seem to depend upon the substitution pattern of the quinone. Even the diazidoquinone, 2,5-diazido-3,6-dimethyl-1,4-benzoquinone (1b), was shown to rearrange in 87% isolated yield to α-methyl-β-azido-γ-cyanoethylidene-$\Delta^{\alpha,\beta}$-butenolide (4b) in cold concentrated sulfuric acid.[2a] Recently, we have observed that 2,5-diazido-3,6-di-*tert*-butyl-1,4-benzoquinone rearranges under the same conditions to the unique tetrazole lactone 5a. This anomalous tetrazole formation, along with the fact that the β-azido-γ-cyanoalkylidene-$\Delta^{\alpha,\beta}$-butenolides provide a most interesting system in their own right, has prompted a more detailed investigation of the acid-catalyzed rearrangements of 2,5-diazido-1,4-benzoquinones. Reported here are the results of such a study.

**Synthetic Scope.**—The synthetic utility of this reaction is summarized in Scheme I. In general, β-azido-γ-cyanoalkylidene-$\Delta^{\alpha,\beta}$-butenolides were formed from all of the 2,5-diazido-1,4-benzoquinones investigated except those having bulky substituents in the 3,6 orientation. Such compounds, 2,5-diazido-2,6-di-*tert*-butyl- and 2,5-diazido-3,6-di-*tert*-pentyl-1,4-benzoquinone, rearranged to the tetrazoles (5a and 5b) which are envisaged as arising *via* an intramolecular 1,3-dipolar cycloaddition of the azido group to the cyano moiety in the intermediate butenolides. Cycloadditions of this kind are well known,[3] and the present case would be expected to be facilitated by the release of steric strain between the bulky α substituent and the β-azido group in 4 [$R_1 = R_2 = C(CH_3)_3$ or $C(CH_3)_2C_2H_5$].

The transformation of the 2,5-diazido-1,4-benzoquinones (1) to the β-azido-γ-cyanoalkylidene-$\Delta^{\alpha,\beta}$-butenolides (4) provides a facile route to γ-lactones which are substituted with the highly reactive azido group in the β position. A number of synthetic possibilities can be envisaged for such compounds, and their subsequent study should be fruitful.

SCHEME I




| Compd | $R_1$ | $R_2$ | Yield, % |
|---|---|---|---|
| 4a | H | H | 47 |
| 4b | $CH_3$ | $CH_3$ | 87 |
| 4c | H | $C_6H_5$ | 90 |
| 4d | $CH_3$ | $CH(CH_3)_2$ | 72 |
| 4e | $CH(CH_3)_2$ | $CH_3$ | 28 |
| 4f | $CH(CH_3)_2$ | $CH(CH_3)_2$ | 95 |
| 5a | $C(CH_3)_3$ | $C(CH_3)_3$ | 76 |
| 5b | $CCH_2CH_2$ \| $(CH_3)_2$ | $CCH_2CH_2$ \| $(CH_3)_2$ | 80 |

The rearrangements reported here were all accomplished by the same general procedure, which constitutes the slow addition of the diazide to cold (0–5°), vigorously stirred, concentrated sulfuric acid. After nitrogen evolution ceased, the reaction solution was poured into ice–water and the product was collected by filtration.

The diazides were conveniently prepared from the corresponding 2,5-dichloro-1,4-benzoquinones by reaction with aqueous ethanolic sodium azide. These azidoquinones are generally obtained in high yield from this reaction as beautifully colored crystalline compounds which decompose (sometimes violently) at their melting points.

(1) The authors are grateful to the National Science Foundation and to the National Cancer Institute of the Public Health Service for financial support of this investigation.

(2) (a) H. W. Moore, H. R. Shelden, D. W. Deters, and R. J. Wikholm, *J. Amer. Chem. Soc.*, **92**, 1675 (1970); (b) W. Weyler, Jr., D. S. Pearce, and H. W. Moore, **95**, 2603 (1973); (c) W. Weyler, Jr., and H. W. Moore, *ibid.*, **93**, 2812 (1971); (d) H. W. Moore and W. Weyler, Jr., *ibid.*, **92**, 4132 (1970); (e) H. W. Moore and H. R. Shelden, *J. Org. Chem.*, **33**, 4019 (1968).

(3) A. I. Meyer and J. C. Sircar in "The Chemistry of the Cyano Group," Z. Rappoport, Ed., Interscience, New York, N. Y., 1970, p 351.

**Structures.**—The structures of the butenolides (**4a–f**) and the tetrazoles (**5a** and **5b**) are based primarily upon spectral properties (Table I). However, for some, chemical data are also provided. The butenolides all show characteristic[2a] azido, nitrile, alkene, and lactone carbonyl absorptions in their infrared spectra. Their nmr spectra all show absorptions with consistent chemical shifts and proton counts for the proposed structures (Table I).

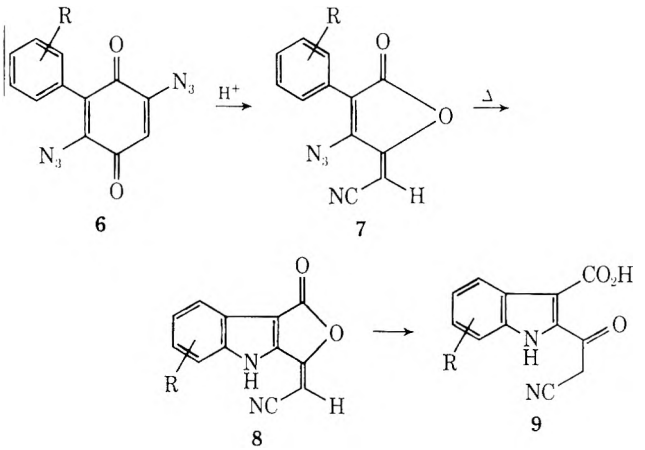
TABLE I
SPECTRAL PROPERTIES OF BUTENOLIDES (4), TETRAZOLES (5), AND LACTONE–LACTAMS (12)

| Compd | Ir (Nujol), $cm^{-1}$ | Nmr ($CDCl_3$), $\delta$ |
|---|---|---|
| 4a | 2230, 2160, 1780, 1650 | 5.31 (d, 1, $J$ = 1.3 Hz), 6.00 (d, 1, $J$ = 1.3 Hz) |
| 4c | 2200, 2130, 1785 | 5.93 (s, 1), 7.08–7.88 (m, 5) |
| 4d | 2210, 2120, 1780, 1640 | 1.13 (d, 6, $J$ = 6 Hz), 2.11 (s, 3), 3.08 (h, 1, $J$ = 6 Hz) |
| 4e | 2210, 2140, 1785, 1640 | 1.25 (d, 6, $J$ = 6 Hz), 2.03 (s, 3), 3.08 (h, 1, $J$ = 6 Hz) |
| 4f | 2210, 2120, 1780, 1640 | 1.13 (d, 6, $J$ = 6 Hz), 1.30 (d, 6, $J$ = 6 Hz), 3.06 (h, 2, $J$ = 6 Hz) |
| 5a | 1785, 1685, 1650 | 1.41 (s, 9), 1.51 (s, 9) |
| 5b | 1780, 1685, 1650 | 0.90 (m, 6), 1.36 (s, 6), 1.46 (s, 6), 1.74 (m, 4) |
| 12a | 3150, 1800, 1725, 1680, 1650 | 1.30 (s, 9), 1.33 (s, 9), 9.16 (s, 1) |
| 12b | 3200, 1800, 1720, 1680, 1655 | 0.83 (m, 6), 1.28 (m, 12), 1.71 (m, 4), 9.50 (s, 1) |

Two quinones studied were unsymmetrically substituted, namely 2,5-diazido-3-methyl-6-isopropyl-1,4-benzoquinone (**1d**) and 2,5-diazido-3-phenyl-1,4-benzoquinone (**1c**). The former gave **4d** and **4e** in a ratio of 2.6:1.0; the latter gave only **4c** isolated in 90% yield. In both instances the major or exclusive products arise *via* an initial protonation on the least hindered carbonyl of the quinone (Scheme I). The orientation of the methyl and isopropyl groups in **4d** was unambiguously established by its borohydride reduction to the known amino derivative, $\alpha$-isopropyl-$\beta$-amino-$\gamma$-cyanoethylidene-$\Delta^{\alpha,\beta}$-butenolide.[1e] In an analogous fashion, using catalytic reduction, **4a** was reduced to $\beta$-amino-$\gamma$-cyanomethylidene-$\Delta^{\alpha,\beta}$-butenolide, a compound of known constitution.[4]

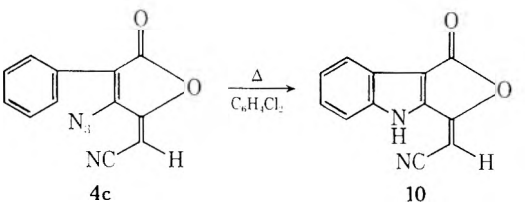
The structure of **4c** did not lend itself to elucidation by such a direct approach. However, on the basis of the spectral data presented below, along with chemical data to be presented later, its structure is firmly documented. The vinyl proton in **4c** absorbs at $\delta$ 5.93 in its nmr spectrum. This chemical shift is best in agreement with a structure having a vinyl proton on the exocyclic methylene group. This is based upon a comparison with other butenolides[2a] having analogous vinyl protons as well as vinyl protons at the $\alpha$ position, which appear respectively at $\delta$ 6.00–6.40 and 5.10–5.67.

**Synthetic Utility. A. Indole Formation.**—The availability[5] of $\alpha$-aryl-$\beta$-azido-$\gamma$-cyanoalkylidene-$\Delta^{\alpha,\beta}$-butenolides, *e.g.*, **4c**, by the method reported here suggests a possible new and general route to $\alpha,\beta$-diacyl substituted indoles. That is, thermal decomposition of such azides could give the indoles (**8**) *via* a nitrenoid insertion reaction.[6] Subsequent hydrolysis would give the diacyl derivatives (**9**), which would be most useful




compounds for the synthesis of a variety of natural products.

In order to test this possible route to indoles, the thermal decomposition of **4c** in refluxing *o*-dichlorobenzene was studied. The indole **10** was formed, but




in low isolated yield (5–10%). In spite of the yield, which was not maximized, these results are encouraging and this reaction is currently being actively pursued.

The structure of **10** is in complete accord with its spectral and analytical properties, which are recorded in the Experimental Section.

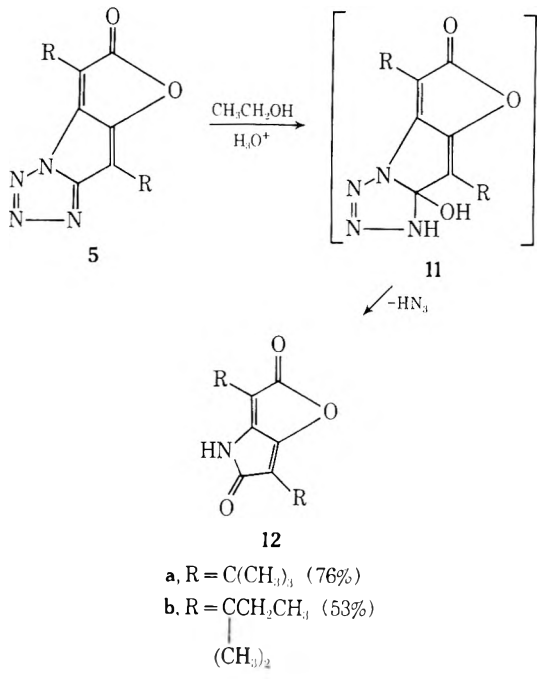
**B. Tetrazole Hydrolysis.**—The tetrazoles (**5a** and **5b**) show a most interesting hydrolytic transformation to the respective lactone–lactams **12a** and **12b**. Simply refluxing **5a** in aqueous ethanol causes its conversion to **12a** in 76% isolated yield. On the other hand, it is necessary to reflux the more hindered *tert*-pentyl homolog in acidic aqueous ethanol in order to accomplish its analogous transformation to **12b** in 53% isolated yield. These reactions are envisaged as arising *via* addition of water to the tetrazoles to give the adducts **11a** and **11b**, which then suffer loss of hydrazoic acid. Subsequent tautomerization would then give the observed products. To our knowledge, the only other example of such compounds in the literature is the corresponding diphenyl analog, generated from 2-amino-5-hydroxy-3,6-diphenyl-1,4-benzoquinone upon dimethyl sulfoxide–acetic anhydride oxidation.[7]

(4) H. W. Moore, H. R. Shelden, and D. F. Shellhamer, *J. Org. Chem.*, **34**, 1999 (1969).

(5) Variously aryl-substituted quinones are available by a number of routes. See, for example, C. S. Rondestvedt, Jr., *Org. React.*, **11**, 189 (1960).

(6) Such insertion reactions are very well documented in the literature. See, for example, P. A. S. Smith in "Nitrenes," W. Lwowski, Ed., Interscience, New York, N. Y., 1970, and references cited therein.

(7) R. J. Wikholm and H. W. Moore, *J. Amer. Chem. Soc.*, **94**, 6152 (1972).




5 11 12

a, R = C(CH3)3 (76%)
b, R = CCH2CH3 (53%) (CH3)2

## Experimental Section

**β-Azido-γ-cyanomethylidene-Δ$^{\alpha,\beta}$-butenolide (4a).**—2,5-Diazido-1,4-benzoquinone[4] (**1a**, 1.5 g, 7.8 mmol) was slowly added to 20 ml of vigorously stirred concentrated sulfuric acid (0–5°) over a period of 45 min. After gas evolution ceased (5 min after addition of the azide) the reaction solution was poured into ice–water. The resulting homogeneous solution was extracted twice with methylene chloride and twice with diethyl ether. The combined organic layers were dried and concentrated *in vacuo*. Upon cooling, 600 mg (47%) of the butenolide **4a** precipitated, mp 116–118°.

**β-Amino-γ-cyanomethylidene-Δ$^{\alpha,\beta}$-butenolide.**—Reduction of the butenolide **4a** with hydrogen and PtO at 40 psi in methanol solvent gave a quantitative yield of β-amino-γ-cyanomethylidene-Δ$^{\alpha,\beta}$-butenolide.[4]

**α-Phenyl-β-azido-γ-cyanomethylidene-Δ$^{\alpha,\beta}$-butenolide (4c).**—2,5-Diazido-3-phenyl-1,4-benzoquinone (**1c**, 3.9 g, 14 mmol) was slowly added to 50 ml of vigorously stirred concentrated sulfuric acid at 0.5°. After gas evolution had ceased, the yellow-brown reaction mixture was poured into 300 ml of ice–water. The resulting light yellow precipitate was collected, dried, and recrystallized from 95% ethanol, giving 2.7 g (90%) of the butenolide **4c**, mp 152–154°. Three more recrystallizations gave the analytical sample.

*Anal.* Calcd for $C_{12}H_6N_4O_2$: C, 60.50; H, 2.52; N, 23.52. Found: C, 60.42; H, 2.39; N, 23.48.

**α-Isopropyl-β-azido-γ-cyanoethylidene-Δ$^{\alpha,\beta}$-butenolide (4d) and α-Methyl-β-azido-γ-(1-cyano-2-methylpropylidene)-Δ$^{\alpha,\beta}$-butenolide (4e).**—2,5-Diazido-3-methyl-6-isopropyl-1,4-benzoquinone[2c] (**1d**, 4.3 g, 17 mmol) was slowly added (40 min) to 60 ml of vigorously stirred concentrated sulfuric acid at 0°. Five minutes subsequent to the addition of the azide, nitrogen evolution ceased and the reaction mixture was poured into 300 ml of water. The resulting mixture was extracted four times with methylene chloride. The combined organic layers were dried and the solvent was removed *in vacuo* to give 3.7 g which by nmr analysis was shown to be a mixture of the butenolides **4d** and **4e** in a ratio of 2.6:1.0, respectively. Three recrystallizations from ethanol gave the major isomer **4d** in pure form, mp 79–81°.

*Anal.* Calcd for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.58; N, 25.68. Found: C, 55.13; H, 4.59; N, 25.75.

**α-Isopropyl-β-azido-γ-(1-cyano-2-methylpropylidene)-Δ$^{\alpha,\beta}$-butenolide (4f).**—2,5-Diazido-3,6-diisopropyl-1,4-benzoquinone[2b] (**1f**, 200 mg, 0.7 mmol) was slowly added to 15 ml of vigorously stirred concentrated sulfuric acid at 0°. After gas evolution ceased, the reaction was worked up in the standard way (above), giving 172 mg (95%) of the butenolide **4f**, mp 62–66°. Recrystallization from ethanol gave the analytical sample, mp 66–68°.

*Anal.* Calcd for $C_{12}H_{14}N_4O_2$: C, 58.53; H, 5.69; N, 22.79. Found: C, 58.48; H, 5.68; N, 22.83.

**Acid-Catalyzed Decomposition of 2,5-Diazido-3,6-di-*tert*-butyl-1,4-benzoquinone. Formation of the Tetrazole 5a.**—2,5-Diazido-3,6-di-*tert*-butyl-1,4-benzoquinone[2d] (4 g, 14 mmol) was slowly added (15 min) to 100 ml of vigorously stirred concentrated sulfuric acid at 0–10°. The reaction solution was stirred for an additional 1 hr, during which time gas evolved. It was then poured into water and the resulting bright yellow, crystalline solid was collected by filtration, yielding 2.9 g (76%) of the tetrazole **5a**. The sample was recrystallized from benzene to give the analytical sample, mp 134–136°.

*Anal.* Calcd for $C_{14}H_{18}N_4O_2$: C, 63.60; H, 7.28; N, 18.54. Found: C, 63.56; H, 7.32; N, 18.23.

**Acid-Catalyzed Decomposition of 2,5-Diazido-3,6-di-*tert*-pentyl-1,4-benzoquinone. Formation of the Tetrazole 5b.**—2,5-Diazido-3,6-di-*tert*-pentyl-1,4-benzoquinone[2d] (3.30 g, 10 mmol) was slowly added (15 min) to 70 ml of vigorously stirred, cold (5°) concentrated sulfuric acid. After 1 hr of stirring no more gas evolution could be detected. The solution was then poured into 300 ml of ice–water and the resulting yellow tetrazole **5b** (2.3 g, 80%) was collected, mp 85–90°. Recrystallization from ethanol gave an analytical sample, mp 92–94°.

*Anal.* Calcd for $C_{16}H_{22}N_4O_2$: C, 63.60; H, 7.28; N, 18.54. Found: C, 63.56; H, 7.32; N, 18.23.

**Reaction of the Tetrazole 5a with Aqueous Ethanol. Formation of the Lactone–Lactam 12a.**—A solution of 1.0 g (3.6 mmol) of the tetrazole **5a** in 30 ml of 95% ethanol was refluxed for 5 min. The reaction solution was then cooled and allowed to stand at room temperature for 12 hr. The solution was then heated to 60° and water was added until the solution became turbid. It was then cooled to 0° and filtered, giving 650 mg (76%) of the white crystalline lactone–lactam **12a**, mp 192–193°.

*Anal.* Calcd for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.62; N, 5.62. Found: C, 67.57; H, 7.66; N, 5.62.

**Reaction of the Tetrazole 5b with Acidic Aqueous Ethanol. Formation of the Lactone–Lactam 12b.**—A solution of 0.5 g (1.7 mmol) of the tetrazole **5b** in 30 ml of 80% ethanol and 1 drop of cencentrated sulfuric acid was refluxed for 15 min and then allowed to stand at ambient temperature for 12 hr. At the end of this time a light yellow precipitate had formed which was collected and recrystallized from 95% ethanol to give 250 mg (53%) of the white crystalline lactone–lactam **12b**, mp 180–181°.

*Anal.* Calcd for $C_{16}H_{23}NO_3$: C, 69.31; H, 8.30; N, 5.05. Found: C, 69.39; H, 8.24; N, 5.13.

**α-Isopropyl-β-amino-γ-cyanoethylidene-Δ$^{\alpha,\beta}$-butenolide.**—A solution of 200 mg (9 mmol) of the butenolide **4d** in 50 ml of methanol was treated with excess sodium borohydride. After 30 min, 10 ml of water was added and the reaction solution was cooled to 0° and left for 48 hr. At the end of this time a white, crystalline precipitate had formed which was collected giving 75 mg of the known 2-isopropyl-β-amino-γ-cyanomethylidene-Δ$^{\alpha,\beta}$-butenolide (**1e**).

**Thermolysis of α-Phenyl-β-azido-γ-cyanomethylidene-Δ$^{\alpha,\beta}$-butenolide (4c). Formation of the Indole 10.**—α-Phenyl-β-azido-γ-cyanomethylidene-Δ$^{\alpha,\beta}$-butenolide (**4c**, 650 mg, 2.7 mmol) was suspended in 1 ml of dry *o*-dichlorobenzene. This suspension was added dropwise over a period of 1 min to 15 ml of refluxing *o*-dichlorobenzene. After the addition was complete, the solution was refluxed for an additional 5 min. Carbon tetrachloride was then added until the solution became turbid and the precipitate which formed upon cooling to 0° was collected. This crude solid was purified by column chromatography over silica gel (eluting with 10% acetone in $CH_2Cl_2$). The second compound which was collected was the colorless crude indole. Recrystallization from *n*-butyl alcohol gave 30 mg (5.2%) of an analytical sample: mp 248–250°; ir (Nujol) 3300 (NH), 2220 (CN), and 1800 cm$^{-1}$ (CO); nmr (DMSO) δ 6.14 (s, 1, CH=C), 7.32–7.96 (m, 4, ArH).

*Anal.* Calcd for $C_{12}H_6N_2O_2$: C, 68.57; H, 2.86; N, 13.33. Found: C, 68.37; H, 3.06; N, 13.03.

**Registry No.**—**1a**, 19462-78-3; **1c**, 41675-57-4; **1d**, 17448-05-4; **1f**, 41675-59-6; **1** ($R_1$ = $R_3$ = *t*-Bu), 29342-21-0; **1** ($R_1$ = $R_3$ = *tert*-pentyl), 41675-60-9; **4a**, 41675-61-0; **4c**, 41675-62-1; **4d**, 41675-63-2; **4e**, 41675-64-3; **4f**, 41753-76-8; **5a**, 41675-65-4; **5b**, 41675-66-5; **10**, 41675-67-6; **12a**, 41675-68-7; **12b**, 41675-69-8.

# Mesoionic Purinone Analogs. V. Synthesis of Mesoionic Thiazolo[3,2-*a*]-*s*-triazine-5,7-diones, Mesoionic 1,3,4-Thiadiazolo[3,2-*a*]-*s*-triazine-5,7-diones, and Their Monothione Derivatives[1]

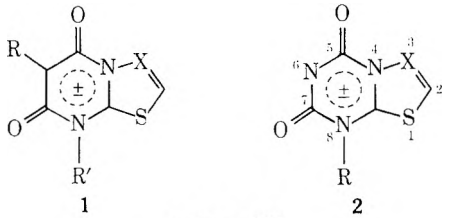
ROBERT A. COBURN* AND BHARAT BHOOSHAN

*Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14214*

*Received June 8, 1973*

Mesoionic 8-alkylthiazolo- and -1,3,4-thiadiazolo[3,2-a]-*s*-triazine-5,7-diones have been prepared by the reactions of 2-alkylaminothiazoles (**3**) or 2-alkylamino-1,3,4-thiadiazoles with phenoxycarbonyl isocyanate. Mesoionic 8-alkylthiazolo[3,2-*a*]-*s*-triazin-5-one-7-thiones and -7-one-5-thiones are obtained from the reaction of **3** with phenoxycarbonyl isothiocyanate and ethoxycarbonyl isothiocyanate, respectively. These mesoionic xanthine analogs react readily with amines and are easily hydrolyzed in water.

We have previously described[2] the formulation and quantum chemical study of a large class of unknown mesoionic heterocycles which are isoconjugate with the purinones: xanthine, hypoxanthine, and purin-2-one. The synthesis and properties of the mesoionic xanthine analogs **1**, which may be viewed as ring-fused derivatives of known mesoionic 1,3-disubstituted pyrimidine-4,6-diones, have been recently reported.[3] We now report the synthesis of the mesoionic xanthine analogs **2** and their monothione derivatives.[4]



**1** **2**

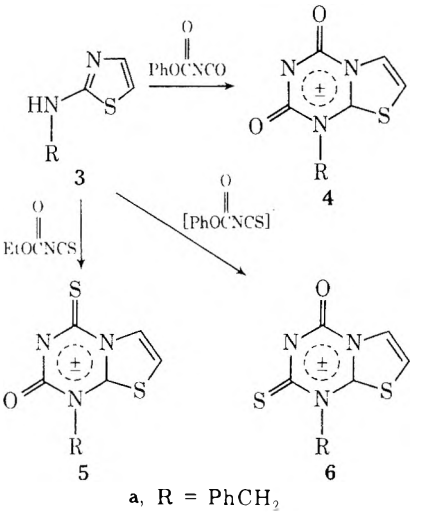
a, X = CH
b, X = N

4-Thiouracils have been prepared by the reaction of enamines with ethoxycarbonyl or phenoxycarbonyl isothiocyanate.[5] Uracils have been synthesized by the reaction of enamines with ethoxycarbonyl isocyanate.[6]

2-Alkylaminothiazoles **3a** and **3b** are acylated by ethoxycarbonyl isocyanate, but cyclization to give **4** was not observed. Phenoxycarbonyl isocyanate, however, reacts with **3a** and **3b** to produce mesoionic 8-substituted thiazolo[3,2,-*a*]-*s*-triazine-5,7-diones[7] (**4a** and **4b**), Scheme I. Structure assignment is based upon spectral evidence, including substantial downfield shift of both thiazole ring proton signals and alkyl group methylene proton signals, pseudocarbonyl group absorption at 1730 and 1669 $cm^{-1}$, and observed parent molecular ions.

Mesoionic thiazolotriazinediones **4** exhibit only low solubility in water and many organic solvents (EtOH, DMF, DMSO, etc). An aqueous solution of **4b** (buffered, pH 7.4) showed spectrophotometric evidence of decomposition after 24 hr at room temperature.

SCHEME I



a, R = $PhCH_2$
b, R = Et

They decompose rapidly when heated in aqueous or alcoholic solution. Compound **4a** reacts readily with ethylamine in ethanol with apparent nucleophilic attack of the 5-position pseudocarbonyl group resulting in ring-opened product **7**. The acylaminothiazole structure **7**, rather than the ring-acyl iminothiazoline structure **8**, is indicated by the ultraviolet absorption spectrum of the product.[8] Confirmation of this structure was obtained by the synthesis of **7** from **3a** as shown in Scheme II. Structure **9** was assigned to the phenylcarbamate ester, produced by the reaction of **3a** with phenylchloroformate, owing to its manner of preparation, and lack of an imino stretching band in its infrared spectrum.[8,9] Treatment of **9** with the sodium salt of ethylurea gives a product, **7**, identical with that obtained by the reaction of **4a** with ethylamine.

Reaction of **3a** and **3b** with phenoxycarbonyl isothiocyanate gives **6a** and **6b** while the analogous reaction employing ethoxycarbonyl isothiocyanate[10] produces the isomeric products **5a** and **5b** (Scheme I). Al-

(1) Taken from the Ph.D. dissertation to be submitted by B. Bhooshan in partial fulfillment of the requirements for the Ph.D. degree.

(2) R. A. Coburn, *J. Heterocycl. Chem.*, **8**, 881 (1971); R. A. Coburn, R. A. Carapellotti, and R. A. Glennon, *ibid.*, **10**, 479 (1973).

(3) R. A. Coburn and R. A. Glennon, *J. Heterocycl. Chem.*, **10**, 487 (1973).

(4) A report describing the preparation and properties of the corresponding monocyclic mesoionic 1,3-disubstituted *s*-triazine-4,6-diones is in preparation.

(5) J. Goerdeler and H. W. Pohland, *Chem. Ber.*, **96**, 526 (1963); J. Goerdeler and J. Gnad, *ibid.*, **98**, 1531 (1965).

(6) R. W. Lamon, *J. Heterocycl. Chem.*, **5**, 837 (1968).

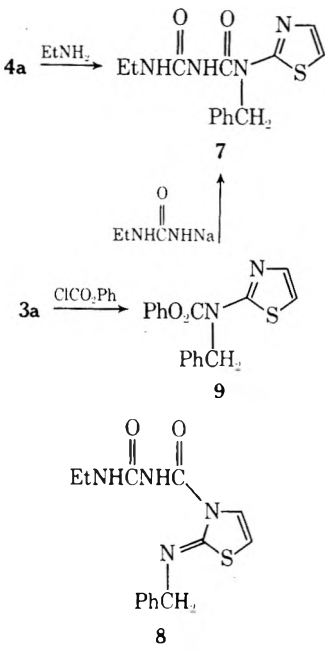
(7) Anhydro 8-substituted 5-hydroxythiazolo[3,2-*a*]-*s*-triazinium-7-one hydroxides.

(8) I. Y. Postovskii and I. B. Ludina, *J. Gen. Chem. USSR*, **29**, 604 (1959); S. G. Bogomolov, Y. N. Sheinker, and I. Y. Postovskii, *Dokl. Akad. Nauk SSSR*, **93**, 277 (1953). Ultraviolet absorption of typical models is as follows: 3-acetyl-2-methylimino-4-methylthiazoline-4, uv max (EtOH) 229 nm (log $\epsilon$ 2.98), 263 (1.95), and 307 (3.14); 2-(*N*-acetylmethylamino)thiazole, uv max (EtOH) 240 nm (log $\epsilon$ 2.45) and 275 (3.8).

(9) W. S. Paul, *Bull. Soc. Chim. Belg.*, **75**, 29 (1966).

(10) The reaction of 2-ethylaminothiazole and ethoxycarbonyl isothiocyanate has been recently reported to give low yields of 1-ethoxycarbonyl-3-ethyl-3-(2-thiazolyl)thiourea and *N*-ethoxycarbonyl-2-ethylaminothiazole. The order of reagent addition, reaction period, and product isolation procedure differ in this work from that previously described. M. Nagano, T. Matsui, J. Tobitsuka, and K. Oyamada, *Chem. Pharm. Bull.*, **21**, 74 (1973).

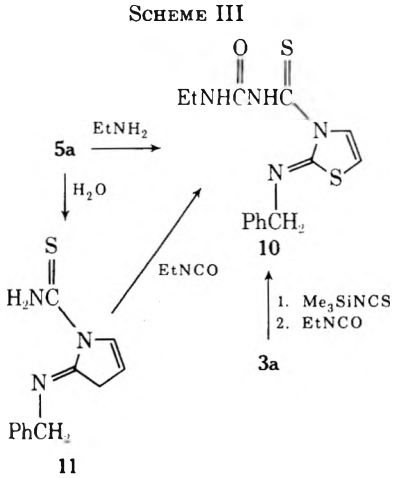
SCHEME II



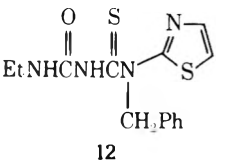
though **5a** and **6a** are easily distinguished, the physical and spectral properties of **5b** and **6b** are quite similar. In the latter case, reaction of the ethyl derivatives **5b** and **6b** with benzylamine gives different products, thus establishing their isomeric relationship.

The structure assignment of the isomeric monothiones **5a** and **6a** was based upon spectral evidence and by the products obtained in their reactions with ethylamine. Structure **10** was assigned to the product of the reaction of **5a** with ethylamine owing to its longest wavelength absorption at 305 nm and the low-field chemical shift of the benzyl methylene protons ($\delta$ 5.88). Heating **5a** with water gives thiourea **11**, whose spectral properties are also consistent with the imino structure. The ring-opened product **10** can be obtained from **11** by reaction with ethyl isocyanate or from **3a** by reaction with trimethylsilyl isothiocyanate followed by ethyl isocyanate, Scheme III.

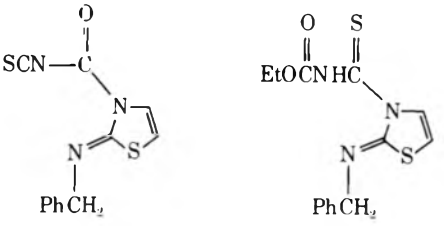
SCHEME III



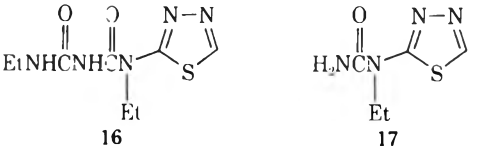
The thiobiuret obtained from **6a** by reaction with ethylamine was shown to be 1-benzyl-1-(2-thiazolyl)-5-ethyl-2-thiobiuret (**12**) based upon its uv and pmr spectra by comparison to those of **10**. It appears probable that the better leaving group leads to initial



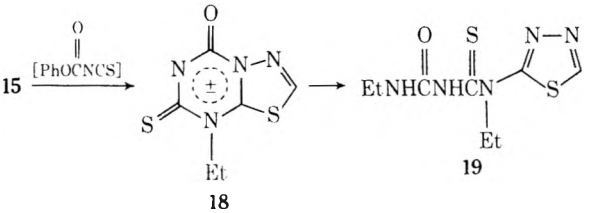
thiazole ring nitrogen acylation in reactions of phenoxycarbonyl isothiocyanate with **3a** and **3b** followed by cyclization of the resulting iminothiocyanate **13**, whereas ethoxycarbonyl isothiocyanate gives initially the thioacyl ester **14**, which then cyclizes to give **6a**.



Reaction of 2-ethylamino-1,3,4-thiadiazole (**15**) with phenoxycarbonyl isocyanate produces mesoionic 8-ethyl-1,3,4-thiadiazolo[3,2-*a*]-*s*-triazine-5,7-dione (**2b**, R = Et). This compound reacts very readily with ethylamine to produce 1-ethyl-1-(1,3,4-thiadiazol-2-yl)-5-ethylbiuret (**16**) and with water to give 1-ethyl-1-(1,3,4-thiadiazol-2-yl)urea (**17**).



Although **15** reacts with phenoxycarbonyl isothiocyanate to give **18**, no cyclized product could be obtained with ethoxycarbonyl isothiocyanate. Structure **18** was assigned based upon analogy to the results obtained in the reactions of **3a** and **3b** with phenoxycarbonyl isothiocyanate and by the structure of thiobiuret **19** obtained by the reaction of **18** with ethylamine. Thiobiuret **19** can be identified as an aminothiadiazole derivative *via* its uv spectrum. The position of the thiocarbonyl group in **19** is indicated by the observation that with mesoionic analogs **5a** and **6a** nucleophilic attack occurs at the pseudocarbonyl group.



## Experimental Section

Pmr spectra were obtained on a Varian T-60 spectrometer and chemical shifts are reported relative to TMS as an internal standard. Ultraviolet spectra were recorded on a Beckman Model DB spectrophotometer. Infrared spectra were obtained on a Perkin-Elmer Model 237 spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. All melting points were determined with a Mel-Temp melting point apparatus and are uncorrected. Mass spectra were obtained with a Hitachi Perkin-Elmer RMC-6 single-focusing mass spectrometer, using a solid sample direct inlet.

*anhydro*-5-Hydroxy-8-benzylthiazolo[3,2-*a*]-*s*-triazinium-7-one Hydroxide (4a).—A solution of **3a** (1.9 g, 10 mmol) in anhydrous ethyl acetate (25 ml) was added dropwise with stirring to a solution of phenoxycarbonyl isocyanate[11] (1.77 g, 11 mmol) in ethyl acetate (30 ml). After 6 hr, the crude product which had precipitated was collected. Recrystallization from glacial acetic acid gave 0.82 g (31.6%) of **4a** as white crystals: mp 205–207° dec; ir (KBr) 1720 and 1669 $cm^{-1}$ (C=O); nmr ($CF_3CO_2H$) $\delta$ 5.53 (s, 2 H), 7.56 (s, 5 H), 7.68 (d, 1 H), and 8.30 (d, 1 H); uv max ($H_2O$) 215 nm ($\epsilon$ 21,169) and 272 (5616); mass spectrum (70 eV) *m/e* (rel intensity) 259 (12), 190 (24), 189 (27), 91 (100), 65 (17), 44 (31).

*Anal.* Calcd for $C_{12}H_9N_3O_2S$: C, 55.60; H, 3.50; N, 16.21; S, 12.34. Found: C, 55.35; H, 3.35; N, 16.13; S, 12.10.

*anhydro*-5-Hydroxy-8-ethylthiazolo[3,2-*a*]-*s*-triazinium-7-one Hydroxide (4b).—A procedure identical with that described for the preparation of **4a** was employed with **3b** (1.28 g, 10 mmol). Recrystallization of the product from glacial acetic acid gave 1.0 g (50.7%) of **4b** as white crystals: mp 232–234° dec; ir (KBr) 1730 and 1669 $cm^{-1}$ (C=O); nmr ($CF_3CO_2H$) $\delta$ 1.58 (t, 3 H), 4.40 (q, 2 H), 7.77 (d, 1 H), and 8.30 (d, 1 H); uv max ($H_2O$) 214 nm ($\epsilon$ 22,232) and 283 (6594); mass spectrum (70 eV) *m/e* (rel intensity) 197 (23), 182 (15), 169 (12), 128 (20), 127 (100), 126 (52), 113 (27), 100 (26), 99 (15), 86 (11), 76 (97).

*Anal.* Calcd for $C_7H_7N_3O_2S$: C, 42.65; H, 3.58; N, 21.31; S, 16.23. Found: C, 42.63; H, 3.54; N, 21.20; S, 16.07.

*anhydro*-7-Hydroxy-8-benzylthiazolo[3,2-*a*]-*s*-triazinium-5-thione Hydroxide (5a).—A solution of **3a** (1.9 g, 10 mmol) in anhydrous ethyl acetate (20 ml) was added to ethoxycarbonyl isothiocyanate (1.44 g, 11 mmol) in ethyl acetate over a period of 10 min. The reaction mixture was refluxed for 6 hr and cooled. The resulting precipitate was collected and washed with absolute ethanol. Recrystallization from trifluoroacetic acid–ether gave 0.85 g (31%) of **5a** as white crystals: mp 209–210° dec; ir (KBr) 1730 $cm^{-1}$ (C=O); uv max ($H_2O$) 229 nm ($\epsilon$ 11,330), 275 (9200), and 320 (12,570); nmr ($CF_3CO_2H$) $\delta$ 5.96 (s, 2 H), 7.53 (s, 5 H), 7.70 (d, 1 H), and 7.26 (d, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 275 (3), 190 (12), 189 (30), 126 (8), 91 (100), 65 (17).

*Anal.* Calcd for $C_{12}H_9N_3OS_2$: C, 52.37; H, 3.30; N, 15.27; S, 23.26. Found: C, 52.20; H, 3.26; N, 15.35; S, 23.15.

*anhydro*-7-Hydroxy-8-ethylthiazolo[3,2-*a*]-*s*-triazinium-5-thione Hydroxide (5b).—A procedure identical with that described for the preparation of **5a** was employed with **3b** (1.28 g, 10 mmol). The product was recrystallized from trifluoroacetic acid–ether to give 1.0 g (46.9%) of **5b** as pale yellow crystals: mp 205–206° dec; ir (KBr) 1690 $cm^{-1}$ (C=O); nmr ($CF_3CO_2H$) $\delta$ 1.56 (t, 3 H), 4.70 (q, 2 H), 7.77 (d, 1 H), and 8.26 (d, 1 H); uv max (EtOH) 225 nm ($\epsilon$ 8400), 274 (9100), and 320 (12,860); mass spectrum (70 ev) *m/e* (rel intensity) 213 (21), 180 (11), 155 (36), 128 (28), 127 (100), 126 (37), 113 (43), 100 (38), 86 (78).

*Anal.* Calcd for $C_7H_7N_3OS_2$: C, 39.42; H, 3.31; N, 19.70; S, 30.07. Found: C, 39.57; H, 3.44; N, 19.58; S, 29.80.

Treatment of **5b** with benzylamine (1 equiv) in tetrahydrofuran gave, after solvent evaporation and recrystallization of the residue from ethanol, a derivative, mp 60–62°.

*anhydro*-5-Hydroxy-8-benzylthiazolo[3,2-*a*]-*s*-triazinium-7-thione Hydroxide (6a).—Phenyl chloroformate (1.56 g, 10 mmol) was added to a suspension of potassium thiocyanate (1.0 g, 10 mmol) in anhydrous ethyl acetate (30 ml). After stirring for 15 min, a solution of **3a** (1.9 g, 10 mmol) in ethyl acetate (30 ml) was added. After 4 hr, the product was collected by filtration. Recrystallization from trifluoroacetic acid–ether gave 2.0 g (72.7%) of **6a** as white crystals: mp 208–209° dec; ir (KBr) 1669 $cm^{-1}$ (C=O); nmr ($CF_3CO_2H$) $\delta$ 5.53 (s, 2 H), 7.58 (s, 5 H), 7.66 (d, 1 H), and 8.36 (d, 1 H); uv max ($H_2O$) 217 nm ($\epsilon$ 36,860), 256 (8500), and 302 (4250); mass spectrum (70 eV) *m/e* (rel intensity) 275 (6), 190 (20), 189 (53), 126 (11), 91 (100), 65 (18), 44 (17).

*Anal.* Calcd for $C_{12}H_9N_3OS_2$: C, 52.37; H, 3.30; N, 15.27; S, 23.26. Found: C, 52.31; H, 3.31; N, 15.09; S, 23.03.

*anhydro*-5-Hydroxy-8-ethylthiazolo[3,2-*a*]-*s*-triazinium-7-thione Hydroxide (6b).—A procedure identical with that described for the preparation of **6a** was employed with **3b** (1.28 g, 10 mmol). Recrystallization of the product from trifluoroacetic acid–ether gave 1.5 g (70.4%) of **6b** as white crystals: mp 201–203° dec; ir (KBr) 1675 $cm^{-1}$ (C=O); nmr ($CF_3CO_2H$) $\delta$ 1.60 (t, 3 H), 4.40 (q, 2 H), 7.74 (d, 1 H), and 8.71 (d, 1 H); uv max ($H_2O$) 216 nm ($\epsilon$ 16,930), 239 sh (11,290), 276 (10,180), and 298 (10,550); mass spectrum (70 eV) *m/e* (rel intensity) 213 (20), 180 (11), 155 (33), 127 (100), 100 (16), 86 (17), 69 (26), 59 (25), 58 (52), 45 (32).

*Anal.* Calcd for $C_7H_7N_3OS_2$: C, 39.42; H, 3.31; N, 19.70; S, 30.07. Found: C, 39.38; H, 3.22; N, 19.68; S, 29.93.

Treatment of **6b** with benzylamine in tetrahydrofuran gave, after solvent evaporation and recrystallization of the residue from ethanol, a derivative, mp 142–143°, easily distinguished from the corresponding product obtained from **5b**.

1-Benzyl-1-(2-thiazolyl)-5-ethylbiuret (7). **Method A.**—To a suspension of **4a** (0.15 g) in ethanol (5 ml) was added ethylamine (0.5 ml, 70% aqueous solution). After stirring for 15 min, a clear solution was obtained. Addition of petroleum ether (bp 30–60°) gave 0.17 g (96%) of **7** as white needles: mp 134.5–135.5°; nmr ($CDCl_3$) $\delta$ 1.21 (t, 3 H), 3.41 (m, 2 H), 5.11 (s, 2 H), 6.95 (d, 1 H), 7.38 (s, 5 H), 7.48 (d, 1 H), 8.3 (broad s, 1 H); uv max (EtOH) 218 nm ($\epsilon$ 8840) and 267 (12,800).

*Anal.* Calcd for $C_{14}H_{16}N_4O_2S$: C, 55.26; H, 5.30; N, 18.41; S, 10.51. Found: C, 55.16; H, 5.32; N, 18.36; S, 10.69.

**Method B.**—To a suspension of sodium hydride (50 mg, 57% oil dispersion) in benzene (10 ml) was added ethylurea (88 mg). The mixture was stirred for 1 hr and a soluton of *N*-benzyl-*N*-(2-thiazolyl)phenylcarbamate (**9**, 310 mg) in benzene (5 ml) was added. The mixture was stirred for 2 hr, washed with water until the washing was neutral, and evaporated to dryness to give a solid (250 mg). Recrystallization from benzene–petroleum ether gave 0.2 g (66%) of **7** as white needles, mp 135–136°, identical (ir spectra and mixture melting point) with that prepared in method A.

Phenyl *N*-Benzyl-*N*-(2-thiazolyl)carbamate (9).—To a solution of **3a** (0.95 g, 5 mmol) in ethyl acetate (20 ml) was added triethylamine (1.0 ml, 7 mmol) and phenyl chloroformate (0.8 g, 5.1 mmol). The reaction mixture was refluxed for 30 min, washed twice with water, and evaporated to dryness. The residue was taken up in benzene and placed on a column (20 g) of silica gel (Woelm). Elution with benzene and recrystallization from benzene–petroleum ether yielded 0.62 g (40%) of **9** as white crystals: mp 91–92°; ir (KBr) 1725 $cm^{-1}$ (C=O); uv max (EtOH) 218 nm ($\epsilon$ 14,300) and 262 (11,530); nmr ($CDCl_3$) $\delta$ 5.61 (s, 2 H), 7.03 (d, 1 H), 7.11–7.48 (m, 10 H), and 7.53 (d, 1 H).

*Anal.* Calcd for $C_{17}H_{14}N_2O_2S$: C, 65.80; H, 4.55; N, 9.03; S, 10.31. Found: C, 66.05; H, 4.53; N, 8.87; S, 10.11.

2-Benzylimino-*N*-ethylaminocarbonylthiazol-4-ine-3-thiocarboxamide (10). **Method A.**—Ethylamine (0.7 ml of 70% aqueous solution) was added to a suspension of **5a** (0.275 g, 1 mmol) in chloroform (10 ml). After 15 min a clear solution was obtained. Solvent was evaporated under reduced pressure and the residual oil (0.33 g) was crystallized from ethanol to give 0.25 g (78%) of **10** as white crystals: mp 114–115°; nmr ($CDCl_3$) $\delta$ 1.26 (t, 3 H), 3.5 (q, 2 H), 5.88 (s, 2 H), 7.06 (d, 1 H), 7.36 (s, 5 H), 7.58 (d, 1 H), 9.88 (broad s, 1 H), 14.15 (broad s, 1 H); uv max (EtOH) 216 nm ($\epsilon$ 8440) and 305 (18,390).

*Anal.* Calcd for $C_{14}H_{16}N_4OS_2$: C, 52.50; H, 5.04; N, 17.49; S, 19.98. Found: C, 52.79; H, 5.15; N, 17.39; S, 19.88.

**Method B.**—Trimethylsilyl isothiocyanate (0.72 g, 5.5 mmol) was added to a solution of **3a** (0.95 g, 5 mmol) in anhydrous tetrahydrofuran. After stirring for 1 hr, methanol (5 ml) was added. The solvent was removed under reduced pressure and the remaining oil (1.25 g) was dissolved in chloroform (10 ml). Ethyl isocyanate (0.47 g, 6 mmol) was added and the mixture was stirred for 4 hr. Chloroform was removed under reduced pressure and the residue was placed on a column (50 g) of silica gel (Woelm). Elution with benzene–ethyl acetate (9:1) and recrystallization from ethanol yielded 0.35 g (20%) of **10** as white crystals, mp 114–115°, identical (ir spectra and mixture melting point) with that prepared by method A.

**Method C.**—Sodium hydride (50 mg of 57% oil dispersion) was added to a solution of **11** (0.25 g, 1 mmol) in anhydrous tetrahydrofuran (15 ml). After stirring for 1 hr, ethyl isocyanate (0.1 g, 1.4 mmol) was added and the mixture was refluxed for 2 hr. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The solution was washed with water until the washing was neutral and evaporated to dryness to give an oil. Crystallization from ethanol gave 0.12 g (37.5%) of **10** as white crystals, mp 114–115°, mmp 114–115°.

2-Benzyliminothiazol-4-ine-3-thiocarboxamide (11).—Water (10 ml) was added to a suspension of **5a** (0.9 g, 3.3 mmol) in tetra-

(11) A. J. Speziale, L. R. Smith, and J. E. Fedder, *J. Org. Chem.*, **30**, 4306 (1965).

hydrofuran (60 ml). After refluxing for 30 min, a clear solution was obtained. The solvent was evaporated under reduced pressure and the residue was recrystallized from 2-propanol to give 0.65 g (79.5%) of **11** as yellowish white crystals: mp 162–163°; nmr ($CDCl_3$) δ 5.90 (s, 2 H), 6.96 (d, 1 H), 7.36 (m, 8 H); uv max (EtOH) 217 nm (ε 10,600) and 293 (19,300); ir (KBr) 3330, 3150 ($NH_2$), and 1610 $cm^{-1}$ (C=N).

*Anal.* Calcd for $C_{11}H_{11}N_3S_2$: C, 53.01; H, 4.45; N, 16.86; S, 25.68. Found: C, 53.22; H, 4.50; N, 16.77; S, 25.78.

**1-Benzyl-1-(2-thiazolyl)-5-ethyl-2-thiobiuret (12).**—To a suspension of **6a** (0.275 g, 1 mmol) in chloroform (10 ml) was added ethylamine (0.7 ml of 70% aqueous solution). After stirring for 30 min, the solvent was removed under reduced pressure. The residual oil was crystallized from ethanol to give 0.26 g (81.3%) of **12** as white crystals: mp 74–75°; nmr ($CDCl_3$) δ 1.43 (t, 3 H), 3.90 (q, 2 H), 5.35 (s, 2 H), 7.15 (d, 1 H), 7.53 (s, 5 H), 7.66 (d, 1 H), 10.45 (broad s, 1 H); uv max (EtOH) 220 nm (ε 13,670) and 269 (22,300).

*Anal.* Calcd for $C_{14}H_{16}N_4OS_2$: C, 52.50; H, 5.04; N, 17.49; S, 19.98. Found: C, 52.36; H, 5.10; N, 17.43; S, 20.20.

***anhydro*-5-Hyroxy-8-ethyl-1,3,4-thiadiazolo[3,2-*a*]-*s*-triazinium-7-one Hydroxide (2b, R = Et).**—To a solution of phenoxycarbonyl isocyanate (3.54 g, 22 mmol) in anhydrous ethyl acetate (50 ml) under nitrogen atmosphere was added a solution of **15** (2.58 g, 20 mmol) over a period of 15 min. The reaction mixture was stirred at room temperature for 2 hr and then refluxed for 4 hr. The crude product, which precipitated on cooling, was filtered and recrystallized from glacial acetic acid to give 3.22 g (81.3%) of **2b** (R = Et) as white crystals: mp 145–146°; ir (KBr) 1667 and 1734 $cm^{-1}$ (C=O); nmr ($CF_3CO_2H$) δ 1.61 (t, 3 H), 4.45 (q, 2 H), and 9.80 (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 198 (17), 174 (11), 173 (11), 172 (12), 156 (12), 128 (28), 127 (12), 124 (12), 97 (26), 76 (29), 70 (100), 69 (46), 60 (32), 59 (33), 56 (20); uv max ($H_2O$) 221 nm (ε 9073) and 267 (28,900).

*Anal.* Calcd for $C_6H_6N_4SO_2$: C, 33.65; H, 2.82; N, 26.16; S, 29.89. Found: C, 33.51; H, 2.91; N, 26.21; S, 29.62.

**1-Ethyl-1-(1,3,4-thiadiazol-2-yl)-5-ethylbiuret (16).**—To a suspension of **2b** (R = Et) (0.2 g, 1 mmol) in chloroform was added ethylamine (0.7 ml of 70% aqueous solution). The reaction mixture became clear after 10 min. The solvent was removed under reduced pressure and the residue was recrystallized from benzene–petroleum ether to give 0.20 g (82%) of **20** as white crystals: mp 160–161°; nmr ($CDCl_3$) δ 1.25 (t, 3 H), 1.43 (t, 3 H), 3.40 (q, 2 H), 4.50 (q, 2 H), 8.40 (broad s, 1 H), 8.86 (s, 1 H), 10.08 (broad s, 1 H); uv max (EtOH) 218 nm (ε 5560) and 254 (11,650).

*Anal.* Calcd for $C_8H_{13}N_5O_2S$: C, 39.51; H, 5.39; N, 28.78; S, 13.15. Found: C, 39.44; H, 5.43; N, 28.66; S, 13.22.

**1-Ethyl-1-(1,3,4-thiadiazol-2-yl)urea (17).**—Water (10 ml) was added to a suspension of **2b** (R = Et) (0.54 g, 2.87 mmol) in tetrahydrofuran (50 ml). The mixture was refluxed for 10 min and solvent was removed under reduced pressure. The residue was recrystallized from tetrahydrofuran to give 0.16 g (34%) of **17** as white crystals: mp 173–174°; nmr (DMSO-$d_6$) δ 1.16 (t, 3 H), 4.15 (q, 2 H), and 9.13 (s, 1 H); uv max (EtOH) 222 nm (ε 4200) and 254 (9200).

*Anal.* Calcd for $C_5H_8N_4OS$: C, 34.87; H, 4.68; N, 32.54; S, 18.62. Found: C, 35.05; H, 4.72; N, 32.45; S, 18.72.

***anhydro*-5-Hydroxy-8-ethyl-1,3,4-thiadiazolo[3,2-*a*]-*s*-triazinium-7-thione Hydroxide (18).**—Phenyl chloroformate (1.56 g, 10 mmol) was added to a suspension of potassium thiocyanate (1.0 g, 10 mmol) in anhydrous ethyl acetate. After stirring for 15 min, a solution of **15** (1.29 g, 10 mmol) in ethyl acetate (25 ml) was added over a period of 15 min. The reaction mixture was stirred at room temperature for 3 hr and then refluxed for 4 hr. The crude product, which precipitated on cooling, was collected by filtration and recrystallized from trifluoroacetic acid–ether to give 1.65 g (77.1%) of **18** as yellow crystals: mp 153–154°; ir (KBr) 1706 $cm^{-1}$ (C=O); nmr ($CF_3CO_2H$) δ 1.60 (t, 3 H), 4.43 (q, 2 H), 9.70 (s, 1 H); uv max ($H_2O$) 217 nm (ε 10,380) and 277 (28,100); mass spectrum (70 eV) *m/e* (rel intensity) 214 (2), 189 (16), 128 (23), 86 (23), 78 (12), 76 (100), 69 (13), 60 (25), 59 (37), 44 (26).

*Anal.* Calcd for $C_6H_6N_4OS_2$: C, 33.65; H, 2.82; N, 26.16; S, 29.73. Found: C, 33.51; H, 2.91; N, 26.21; S, 29.62.

**1-Ethyl-1-(1,3,4-thiadiazol-2-yl)-5-ethyl-2-thiobiuret (19).**—Ethylamine (0.7 ml of 70% aqueous solution) was added to a suspension of **18** (0.21 g, 1 mmol) in chloroform (10 ml). After stirring for 15 min at room temperature, the solvent was removed under reduced pressure and the residue was recrystallized from benzene–petroleum ether to give 0.16 g (62%) of **18** as white crystals: mp 139–140°; nmr ($CDCl_3$) δ 1.37 (q, 6 H), 3.68 (q, 2 H), 4.17 (q, 2 H), 8.91 (s, 1 H), 10.05 (broad s, 1 H), 10.83 (broad s, 1 H); uv max (EtOH) 216 nm (ε 9350) and 264 (19,500).

*Anal.* Calcd for $C_8H_{13}N_5OS_2$: C, 37.07; H, 5.05; N, 27.02; S, 24.68. Found: C, 37.34; H, 5.15; N, 26.98; S, 24.79.

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**Registry No.**—**2b** (R = Et), 39386-54-4; **3a**, 41593-98-0; **3b**, 13472-75-8; **4a**, 39386-60-2; **4b**, 39386-57-7; **5a**, 39386-58-8; **5b**, 39386-55-5; **5b** derivative, 41594-00-7; **6a**, 39386-59-9; **6b**, 39386-56-6; **6b** derivative, 41594-01-8; **7**, 41594-02-9; **9**, 41594-03-0; **10**, 41594-04-1; **11**, 41594-05-2; **12**, 41594-06-3; **15**, 13275-68-8; **16**, 41593-95-7; **17**, 41593-96-8; **18**, 39386-53-3; **19**, 41593-97-9; phenoxycarbonyl isocyanate, 5843-43-6; ethoxycarbonyl isothiocyanate, 16182-04-0; benzylamine, 100-46-9; phenyl chloroformate, 1885-14-9; ethylamine, 75-04-7; ethylurea, 625-52-5; triethylamine, 121-44-8; trimethylsilyl isothiocyanate 2290-65-5; sodium hydride, 7646-69-7.

# The Preparation of 11-Aryl-11*H*-isoindolo[2,1-*a*]benzimidazol-11-ols

MARCEL K. EBERLE,* WILLIAM J. HOULIHAN, AND PAUL SCHIRM

*Research and Development Division, Sandoz-Wander, Inc., East Hanover, New Jersey 07936*

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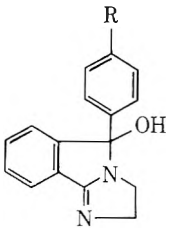
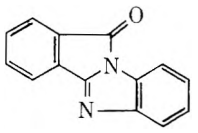
3-(*p*-Chlorophenyl)-3-methoxyphthalimidine was treated with Meerwein salt to yield the imino ether **4a**. Upon treatment with *o*-phenylenediamine **4a** rearranged to **5a**, which hydrolyzed to **5c** in the presence of hydrochloric acid. Compound **5c** was synthesized independently from **5e**, which was prepared from 2-(*p*-chlorobenzoyl)benzaldehyde and *o*-phenylenediamine.

The recent interest in the anorexic and antidepressant properties[1a-c] of 5-(*p*-chlorophenyl)-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ol (**1a**) and the publication of a paper[2] describing the chemistry of the 5-phenyl analog **1b**[3] prompted us to prepare some 11-aryl-11*H*-isoindolo[2,1-*a*]benzimidazol-11-ols, the 2,3-benz analogs of **1**, for similar studies. The only reported method for preparing these compounds[4] consists in treating benzoylenebenzimidazole **2** with phenyl-



**1a**, R = Cl
**b**, R = H



**2**

magnesium bromide. In our studies, we found this procedure to be erratic and unsatisfactory for general use. We therefore wish to report in this work a new method for preparing 11-aryl-11*H*-isoindolo[2,1-*a*]benzimidazol-11-ols.

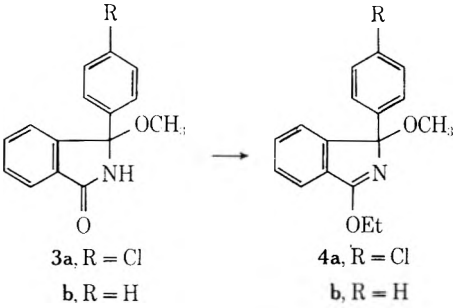
Earlier we had reported[5] the preparation of 1-(*p*-chlorophenyl)-3-ethoxy-1*H*-isoindole and its 1-phenyl analog. Continuing our efforts in this field, we now wish to report the preparation of 1-(*p*-chlorophenyl)-3-ethoxy-1-methoxy-1*H*-isoindole (**4a**) and its 1-phenyl analog **4b**, which served as our starting material.

## Results

The reaction of the known[6] 3-aryl-3-methoxyphthalimidines **3a** and **3b** with triethyloxonium fluoroborate[7] and subsequent treatment with sodium carbonate resulted in the formation of the corresponding imino ethers **4a** and **4b** in 90 and 56% yield, respectively. From the reaction of **4a** with *o*-phenylenediamine in refluxing ethanol, 11-amino-11-(*p*-chlorophenyl)-11*H*-isoindolo[2,1-*a*]benzimidazole (**5a**) was isolated in 64% yield. The structural assignment for this compound is in agreement with the analytical data and supported by spectral information. The nmr spectrum of the compound has a broad signal at $\delta$ 2.75 ppm, integrating for two protons which readily exchanged with $D_2O$ and therefore are assigned to a primary amino group. The compound dissolved readily in 2 *N* hydrochloric acid and after a few minutes a salt of the composition $C_{20}H_{13}ClN_2O \cdot HCl$ precipitated from the solution. Neutralization with base yielded a $C_{20}H_{13}ClN_2O$ compound that was assigned structure **5c** on the basis of the data given below.

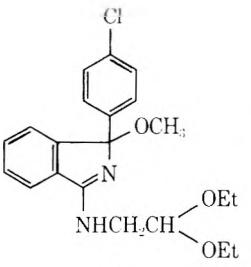
The same sequence of reactions, but starting with 3-ethoxy-1-methoxy-1-phenyl-1*H*-isoindole (**4b**), resulted in the isolation of a free base of the composition $C_{20}H_{14}N_2O$. The properties of this compound compared favorably with those of the known compound **5d**.[4]

To further establish the structure of **5c**, it was synthesized independently by treating 2-(*p*-chlorobenzoyl)-benzaldehyde with *o*-phenylenediamine to give the expected[8] 11-(*p*-chlorophenyl)-11*H*-isoindolo[2,1-*a*]-benzimidazole (**5e**). Oxidation to **5c** was achieved by



**3a**, R = Cl
**b**, R = H

**4a**, R = Cl
**b**, R = H



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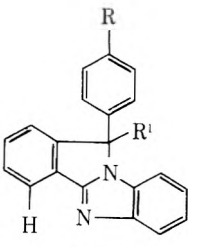


| | R | R' |
|---|---|---|
| **5a** | Cl | $NH_2$ |
| **5b** | H | $NH_2$ |
| **5c** | Cl | OH |
| **5d** | H | OH |
| **5e** | Cl | H |

(1) (a) J. H. Gogerty, W. J. Houlihan, M. Galen, P. Eden, and C. Penberthy, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **27**, 501 (1968); (b) E. A. DeFeliee, S. Bronstein, and A. Cohen, *Curr. Res. Therap.*, **11**, 256 (1969); (c) J. H. Goberty and W. J. Houlihan, Abstracts of Papers, Joint Conference, Chemical Institute of Canada and the American Chemical Society, Toronto, Canada, May 24–29, 1970, No. MEDI-016.

(2) W. Metlesics, T. Anton, M. Chaykovsky, V. Toome, and L. H. Sternbach, *J. Org. Chem.*, **33**, 2874 (1968).

(3) This compound was found[2] to coexist in solution with the tautomeric form 2-(2-imidazolin-2-yl)benzophenone.

(4) J. Arient, L. Havlickova, and J. Knizek, *Collect. Czech. Chem. Commun.*, **31**, 4682 (1966).

(5) M. K. Eberle and W. J. Houlihan, *Tetrahedron Lett.*, 3167 (1970).

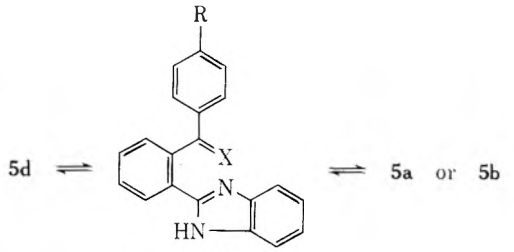
(6) W. Graf, E. Girod, E. Schmid, and W. G. Stoll, *Helv. Chim. Acta*, **42**, 1085 (1959).

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

(8) A similar reaction has been reported by Metlesics, *et al.*, with ethylenediamine and 2-benzoylbenzaldehyde to give 5-phenyl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindole; *cf.* ref 2.

treating **5e** with a stream of air in DMF in the presence of a catalytic amount of sodium hydride.[9] This product was found to be identical in every respect with the compound isolated from hydrolysis of **5a**.

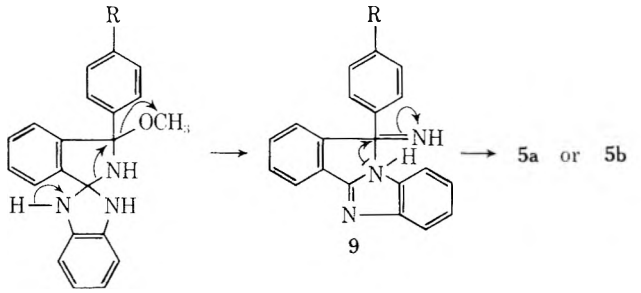
Arient and coworkers[4] have found that compound **5d** displayed an intensive carbonyl band, indicating that the substance exists partly or completely as the benzophenone tautomer **7a**. We have compared the ultraviolet and nmr spectra of amino analogs **5a** and **5b** with those of **5e**, a substance that can only exist in the cyclic form. The similarity of the spectra is in agreement with the cyclic forms **5a** and **5b** and indicates that little or none of the open tautomeric forms **7b** and **7c** are present.




**7a**, R = H; X = O
**b**, R = H; X = NH
**c**, R = Cl; X = NH

## Discussion

We assume that the ethoxy group of compounds **4a** and **4b** is more reactive than the methoxy group toward nucleophiles and conclude that the incoming *o*-phenylenediamine replaces first the ethoxy group. Bond reorganization *via* the possible intermediates **8** and **9**




could lead to the products **5a** and **5b**. Support for the reactivity of the iminoethoxy group in **4a** was obtained when it was treated with aminoacetaldehyde diethyl acetal to give 1-(*p*-chlorophenyl)-3-(β-diethoxyethylamino)-1-methoxy-1*H*-isoindole (**6**) in 60% yield.

2-Benzoylbenzoic acid is reported to react with *o*-phenylenediamine to form 4b-phenyl-4b,5-dihydro-11*H*-isoindolo[2,1-*a*]benzimidazol-11-one.[10] Evidence[10,11] has been cited that the keto group of 2-benzoylbenzoic acid reacts with a diamine *via* a Schiff base to form an imidazolidine. Our compounds **4a** and **4b** may therefore be regarded as modifications of 2-benzoylbenzoic acid with a more reactive equivalent of the carboxy group relative to the equivalent of the keto group without change of the oxidation stage.

(9) P. Aeberli and W. J. Houlihan, *J. Org. Chem.*, **33**, 1640 (1968).
(10) P. Aeberli and W. J. Houlihan, *J. Org. Chem.*, **34**, 165 (1969).
(11) T. S. Sulkowski, M. A. Wille, A. Mascitti, and J. L. Diebold, *J. Org. Chem.*, **32**, 2180 (1967).

## Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting apparatus and have not been corrected. Proton magnetic resonance spectra were obtained on a Varian Associates A-60 spectrometer and are recorded in hertz of δ values (parts per million) relative to tetramethylsilane as internal standard. Infrared spectra were recorded on a Perkin-Elmer spectrophotometer, Model 457. Ultraviolet spectra were determined in 95% ethanol with a Cary recording spectrophotometer, Model 15. Thin layer chromatography (tlc) was carried out on glass plates coated with silica gel HF-254, E. Merck AG.

**3-(*p*-Chlorophenyl)-3-methoxyphthalimidine (3a).**—A solution of 182 g (0.7 mol) of 3-*p*-chlorophenyl-3-hydroxyphthalimidine in 700 ml of anhydrous methanol saturated with hydrogen chloride was stirred at room temperature for 1 hr. The resultant solid was filtered off to give 135 g (71%) of **3a**: mp 161–163° ($CH_2Cl_2$–hexane); ir ($CH_2Cl_2$) 3420 (NH), 1715 $cm^{-1}$ (C=O); nmr ($CDCl_3$) δ 3.12 (3 H, s, $OCH_3$), 7.10–7.65 (8 H, m, arom + NH), 7.7–8.0 (1 H, C-7 H).

*Anal.* Calcd for $C_{15}H_{12}ClNO_2$: C, 65.8; H, 4.4; N, 5.1. Found: C, 65.7; H, 4.5; N, 5.4.

**3-Methoxy-3-phenylphthalimidine (3b).**—A mixture of 36 g (0.16 mol) of 3-phenyl-3-hydroxyphthalimidine and 200 ml of anhydrous methanol, saturated with hydrogen chloride, was stirred at room temperature for 45 min. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel (eluent benzene) to give 10.5 g (27%) of **3b**: mp 139–140° (acetone–hexane); ir ($CH_2Cl_2$) 3430 (NH), 1715 $cm^{-1}$ (C=O); nmr ($CDCl_3$) δ 3.12 (3 H, s, $OCH_3$), 7.10–7.75 (9 H, m, arom + NH), 7.75–8.00 (1 H, C-7 H).

*Anal.* Calcd for $C_{15}H_{13}NO_2$: C, 75.3; H, 5.5; O, 13.4. Found: C, 75.6; H, 5.9; O, 13.7.

**1-(*p*-Chlorophenyl)-3-ethoxy-1-methoxy-1*H*-isoindole (4a).**—A solution of 21.0 g (0.11 mol) of triethyloxonium fluoroborate and 30.0 g (0.11 mol) of **3a** in 100 ml of methylene chloride was stirred at room temperature for 15 hr under an atmosphere of nitrogen. The solution was poured into 100 ml of 2 *N* sodium carbonate solution and extracted with diethyl ether. The organic phase was separated, dried over anhydrous $K_2CO_3$, filtered, and evaporated to yield 30.0 g (90%) of liquid **4a**. Distillation in a Kugelrohr under high vacuum gave pure **4a**: tlc ($CHCl_3$); nmr ($CDCl_3$) δ 1.48 (3, t, $J$ = 7.0 Hz, $CH_2CH_3$), 3.15 (3, s, $OCH_3$) 4.61 (2, q, $J$ = 7.0 Hz, $OCH_2CH_3$), 7.1–7.6 (8, m, aromatic H); ir (film) 1625 $cm^{-1}$ (C=N). *Anal.* Calcd for $C_{17}H_{16}ClNO_2$: C, 67.7; H, 5.3; N, 4.6. Found: C, 67.4; H, 5.5; N, 4.8.

**3-Ethoxy-1-methoxy-1-phenyl-1*H*-isoindole (4b).**—Following the procedure used to prepare **4a**, 10.5 g (0.055 mol) of triethyloxonium fluoroborate, 10.0 g (0.042 mol) of **3b**, and 50 ml of methylene chloride gave 6.3 g (56%) of liquid **4b**: nmr ($CDCl_3$) δ 1.48 (3, t, $J$ = 7.0 Hz, $CH_2CH_3$), 3.16 (3, s, $OCH_3$), 4.61 (2, q, $J$ = 7.0 Hz, $OCH_2CH_3$), 7.1–7.7 (9, m, aromatic H).

**11-Amino-11-(*p*-chlorophenyl)-11*H*-isoindolo[2,1-*a*]benzimidazole (5a).**—A solution of 9.1 g (0.03 mol) of **4a** and 2.8 g (0.026 mol) of *o*-phenylenediamine in 50 ml of absolute ethanol was refluxed for 15 hr under an atmosphere of nitrogen. The solvent was evaporated under reduced pressure and the residue was crystallized from benzene–hexane to give 5.5 g (64%) of **5a**: mp 200–202°; nmr ($CDCl_3$–DMSO-$d_6$) δ 2.75 (2, broad, $D_2O$ exchangeable, $NH_2$), 6.9–7.8 (11, m, aromatic H), 7.8–8.1 (1, m, aromatic H); ir ($CH_2Cl_2$) 3340, 3400 ($NH_2$), 1625 $cm^{-1}$ (C=N); uv $\tau_{max}$ 222 nm (ε 32,800), 295 infl (14,250), 309 (18,100) 321 (13,600). *Anal.* Calcd for $C_{20}H_{14}ClN_3$: C, 72.4; H, 4.3; Cl, 10.7; N, 12.7. Found: C, 72.0; H, 4.6; Cl, 10.9; N, 12.8.

**11-Amino-11-phenyl-11*H*-isoindolo[2,1-*a*]benzimidazole (5b).**—In a similar manner as described above, there was obtained from 5.0 g (0.019 mol) of **4b** and 2.3 g (0.021 mol) of *o*-phenylenediamine in 30 ml of ethanol 2.4 g of **5b**, mp 193–195° (benzene–hexane). Chromatography of the filtrate on silica gel gave an additional 0.61 g of **5b** and 1.4 g of starting material: total yield 3.01 g (75% based on recovered starting material); nmr ($CDCl_3$) δ 2.58 (2, broad, $D_2O$ exchangeable, $NH_2$), 6.8–7.7 (11, m, aromatic), 7.7–8.1 (2, m, aromatic); uv 295 nm infl (ε 14,290), 309 (18,500), 321 (13,990). *Anal.* Calcd for $C_{20}H_{15}N_3$: C, 80.8; H, 5.1. Found: C, 80.5; H, 5.3.

**11-(*p*-Chlorophenyl)-11*H*-isoindolo[2,1-*a*]benzimidazol-11-ol (5c). A. From Hydrolysis of 5a.**—A solution of 0.40 g of **5a** in 10 ml of 2 *N* hydrochloric acid was allowed to stand at room temperature for 1.5 hr. The resulting solid was filtered off to give 0.17 g (38%) of **5c** HCl, mp 244–245° (from ethanol–water,

four times). *Anal.* Calcd for $C_{20}H_{13}ClN_2O \cdot HCl$: C, 64.9; H, 4.1; Cl, 19.2; N, 7.6. Found: C, 64.7; H, 4.0; Cl, 19.0; N, 7.8.

Treatment of 0.090 g of **5c** HCl in ethanol with 2 *N* NaOH gave 0.055 g (68%) of **5c**: mp 222–223° (from ethanol–water); ir (Nujol) 3060 (OH), 1660 $cm^{-1}$ (C=N or C=O); uv $\lambda_{max}$ 248 nm ($\epsilon$ 18,700) 261 (19,690), 305 infl (12,160). *Anal.* Calcd for $C_{20}H_{13}ClN_2O$: C, 72.2; H, 3.9; Cl, 10.7; N, 8.4. Found: C, 71.9; H, 4.1; Cl, 11.0; N, 8.4.

**B. From Oxidation of 5e.**—A solution of 0.30 g (0.0095 mol) of **5e** in 10 ml of anhydrous DMF was added to 0.06 g (0.0025 mol) of sodium hydride and stirred at room temperature. The resultant red solution was treated with a stream of dry air until the color had disappeared. The solution was poured on ice water to give 0.21 g (67%) of **5c**: mp 222–224° (ethanol–water); nmr, uv, and ir identical with spectra obtained from **5c** from **5a**; mmp 224–225°.

**11-Phenyl-11*H*-isoindolo[2,1-*a*]benzimidazol-11-ol (5d).**—A solution of 0.5 g of **5b** in 10 ml of 2 *N* hydrochloric acid was allowed to stand at room temperature for 1.5 hr. The resultant solid was filtered off to give 0.4 g (71%) of **5d** HCl, mp 288–290°. *Anal.* Calcd for $C_{20}H_{14}N_2O \cdot HCl$: C, 71.7; H, 4.5; Cl, 10.6. Found: C, 72.1; H, 4.7; Cl, 10.3.

Treatment of a solution of 0.1 g of **5d** HCl in ethanol with 2 *N* NaOH gave 0.070 g (79%) of **5d**: mp 223–225° (ethanol–water) (lit.[3] mp 220–221°); ir (Nujol) 3060 (OH), 1655 $cm^{-1}$ (C=N); uv $\lambda_{max}$ 242 nm ($\epsilon$ 19,240), 291 (12,300), 305 infl (11,420). *Anal.* Calcd for $C_{20}H_{14}N_2O$: C, 80.5; H, 4.7; N, 9.4. Found: C, 80.9; H, 4.8; N, 9.7.

**11-(*p*-Chlorophenyl)-11*H*-isoindolo[2,1-*a*]benzimidazole (5e).**—To a stirred suspension of 2.16 g (0.02 mol) of o-phenylenediamine in 50 ml of water, sufficient concentrated hydrochloric acid was added to obtain a clear solution. To this a solution of 4.89 g (0.02 mol) of 2-(*p*-chlorobenzoyl)benzaldehyde[12] (mp 108–110°) in 100 ml of acetic acid was added. The resulting solution was held at 80° for 15 min and then concentrated under reduced pressure. The residue was treated first with ethanol followed by ether to give 4.3 g (61%) of **5e** HCl, mp 268–271° (ethanol–ether). Treatment of 1.0 g of **5e** HCl with 2 *N* NaOH gave 0.80 g (89%) of **5e**: mp 207–208° (from ethanol–water); nmr ($CDCl_3$) $\delta$ 6.07 (1, s, $C_{11}$ H), 6.8–8.2 (12, m, aromatic); ir ($CH_2Cl_2$) 1622 $cm^{-1}$ (C=N); uv $\lambda_{max}$ 222 nm ($\epsilon$ 33,420), 242 (14,820), 251 (9660), 306 (22,300), 319 (18,170). *Anal.* Calcd for $C_{20}H_{13}ClN_2$: C, 75.8; H, 4.1; N, 8.8. Found: C, 75.8; H, 4.3; N, 8.8.

**1-(*p*-Chlorophenyl)-3-(β-diethoxyethylamino)-1-methoxy-1*H*-isoindole (6).**—A mixture of 7.1 g (0.023 mol) of **4a** and 11 g (0.053 mol) of aminoacetaldehyde diethyl acetal was refluxed in 250 ml of absolute ethanol for 4 hr under an atmosphere of nitrogen. The solvent was evaporated under reduced pressure to yield 5.5 g (60%) of **6**: mp 113–114° (ether–pentane); nmr ($CDCl_3$) $\delta$ 1.18 (3, t, $J$ = 7 Hz, $CH_2CH_3$), 1.23 (3, t, $J$ = 7 Hz, $CH_2CH_3$), 3.10 (3, s, $OCH_3$), 3.40–4.0 (6, m, 2 $CH_2CH_3$, $NCH_2$), 4.79 (1, t, $J$ = 5 Hz, –CHO), 5.4 (1, broad, NH), 7.1–7.6 (8, m, aromatic); ir ($CH_2Cl_2$) 3440 (NH), 1672 (weak), 1640 $cm^{-1}$; uv $\lambda_{max}$ 227 nm ($\epsilon$ 24,200). *Anal.* Calcd for $C_{21}H_{25}ClN_2O_3$: C, 64.9; H, 6.5; N, 7.2. Found: C, 65.2; H, 6.8; N, 7.2.

**Acknowledgment.**—We would like to thank Dr. S. Barcza and his staff for recording the spectra.

**Registry No.**—**3a**, 730-77-8; **3b**, 28489-08-9; **4a**, 41581-41-3; **4b**, 41581-42-4; **5a**, 41581-43-5; **5b**, 41581-44-6; **5c**, 41581-45-7; **5c** HCl, 41581-46-8; **5d**, 41581-47-9; 5d HCl, 41581-48-0; **5e**, 41581-49-1; **5e** HCl, 41581-50-4; **6**, 41581-51-5; **7a**, 14539-29-8; **7a** HCl, 41581-53-7; 3-*p*-chlorophenyl-3-hydroxyphthalimidine, 956-92-3; 3-phenyl-3-hydroxyphthalimidine, 6637-53-2; 2-(*p*-chlorobenzoyl)benzaldehyde, 23864-94-0.

(12) Prepared in analogy to the known 2-benzoylbenzaldehyde; *cf.* ref 2.

# The Synthesis of the 3a,8a-Dihydrofuro[2,3-*b*]benzofuran-2(3*H*)-one and 1,3,3a,8a-Tetrahydro-2*H*-benzofuro[2,3-*b*]pyrrol-2-one Ring Systems from 4-Formylcoumarin *via* Acyllactone and Iminelactone Rearrangements

DAVID T. CONNOR* AND M. VON STRANDTMANN

*Department of Organic Chemistry, Warner-Lambert Research Institute, Morris Plains, New Jersey 07950*

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Syntheses of 3a,8a-dihydrofuro[2,3-*b*]benzofuran-2(3*H*)-ones and 1,3,3a,8a-tetrahydro-2*H*-benzofuro[2,3-*b*]-pyrrol-2-ones by acyllactone and iminelactone rearrangements, respectively, are described.

The rearrangement of α-acyllactones is a well-known synthetic method which has received considerable attention over the past few years for the synthesis of various heterocyclic systems.[1,2] In contrast, there are only two examples of the rearrangement of β-acyl-δ-lactones. Lawson[3] rearranged 4-acetyl-3,4-dihydrocoumarin to 2-methylbenzofuran-3-acetic acid with 3 *N* hydrochloric acid, and Buchi[4] rearranged 4-formyl-5-benzyloxy-7-methoxycoumarin to 4-benzyloxy-6-methoxy-2-oxo-2,3,3a,8a-tetrahydrofuro[2,3-*b*]benzofuran. The difficulties in synthesizing β-acyl-δ-lactones are the probable[3,5] reason for this disparity.

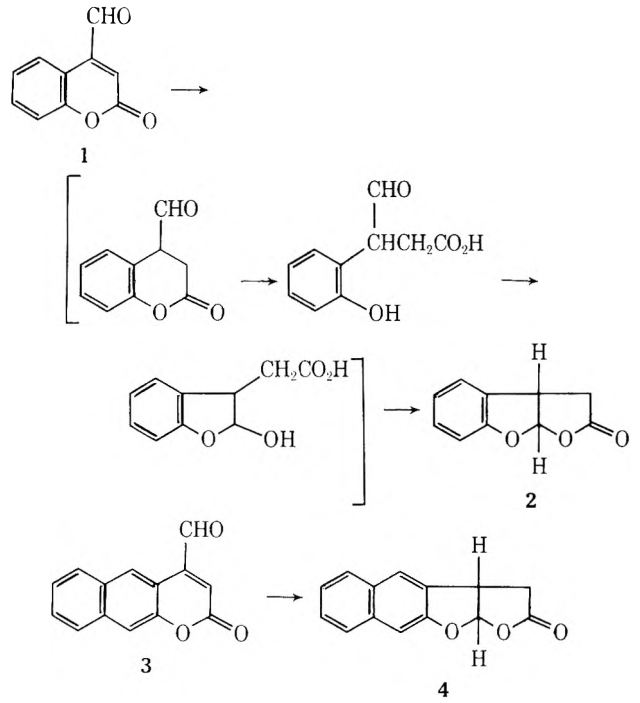
Our earlier work[6] resulted in the first general synthesis of 4-formylcoumarins and made them readily available starting materials to investigate the scope of the rearrangement. The 4-formylcoumarins (**1** and **3** Scheme I) were reduced and rearranged with zinc in acetic acid at 100° to give the expected products (**2** and **4**, respectively). The products are readily converted to benzofuran-3-acetic acids[7] and could also serve as potential intermediates for the synthesis of certain indole alkaloids. Benzofuran derivatives were not detected as by-products from the rearrangement, indicating the ease of formation of the five-membered lactone ring under the reaction conditions.

We were particularly interested in extending the rearrangement to molecules in which the C=O bond of the aldehyde is replaced by C=N. Thus, we subjected imines **5a** and **5b**, oximes **7** and **14**, phenylhydrazone (**16**), and 4-formylcoumarin semicarbazone to the rearrangement conditions.

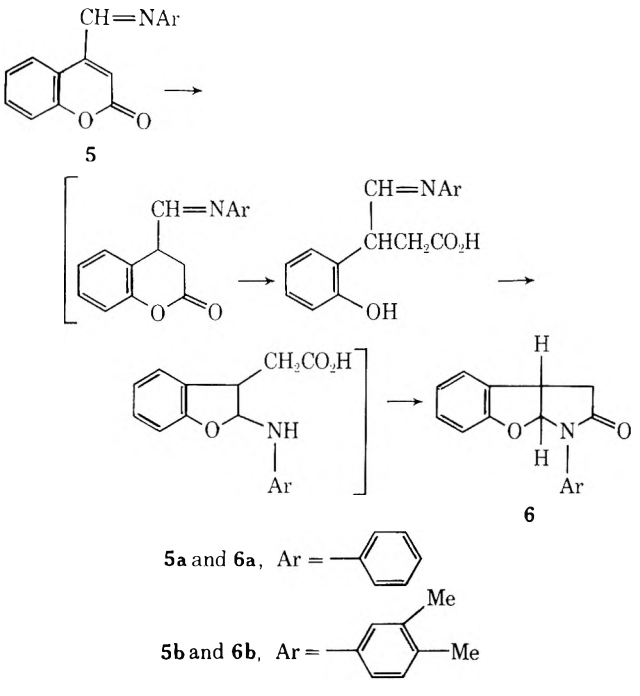
The imines **5a** and **5b** (Scheme II) were reduced and rearranged to give the pyrrolones **6a** and **6b**, respectively. To our knowledge this constitutes the first case

(1) F. Korte and K. H. Buchel in "Newer Methods of Preparative Organic Chemistry," Vol. III, Academic Press, New York, N. Y., 1964, p 199.
(2) H. Wamhoff and F. Korte, *Synthesis*, **4**, 151 (1972).
(3) A. Lawson, *J. Chem. Soc.*, 144 (1957).
(4) G. Buchi, D. M. Foulkes, M. Kurono, G. F. Mitchell, and R. S. Schneider, *J. Amer. Chem. Soc.*, **89**, 6745 (1967).
(5) A. Schiavello and E. Cingolani, *Gazz. Chim. Ital.*, **81**, 717 (1951).
(6) M. von Strandtmann, D. T. Connor, and J. Shavel, Jr., *J. Heterocycl. Chem.*, **9**, 175 (1972).
(7) D. T. Connor and M. von Strandtmann, unpublished work.

SCHEME I



SCHEME II



of an imine–lactone rearrangement and the first synthesis of this ring system. The pyrrolones **6a** and **6b** could also be obtained by the reaction of **2** with corresponding amines, but the overall yields were lower by this route.

The oxime **7** was treated with zinc and acetic acid in the expectation of obtaining hydroxamic acid derivative **8**. The only product isolated was condensation product **13** (Scheme III). Similarly, oxime **14** yielded only condensation product **15**.

Scheme III depicts the probable mechanism for the formation of **13** from **7**. It appears that there is an equal probability for the reduction of either the 3,4 double bond or the C=N double bond resulting in the production of approximately equal amounts of **9** and **10**, which condense to give **11**. The normal cyclization occurs to give **12**, which cyclizes with the net loss of hydroxylamine to give **13**. **8** (or a molecule derived from **8**) would be the major product if the 3,4 double bond were reduced more rapidly than the C=N double bond. **10** would be the major product if the reverse was true.[8] The analytical and spectral data are in agreement with the proposed structure **13**.

The rearrangement of the phenylhydrazone **16** gave a mixture of acetanilide (65%), **20** (6%), and **6a** (25%). The reaction was more complex than in the previous examples. Thin layer chromatography indicated two other compounds present which were not isolated in pure form. It is clear from the products isolated that, as in the case of the oxime **7** rearrangement, the 3,4 double bond and the C=N double bond are competitively reduced. The probable pathway is outlined in Scheme IV.

Reduction of the C=N double bond yields a mixture of aniline and amine **10**, which is acetylated to give the observed products acetanilide and **20**, respectively. Reduction of the 3,4 double bond yields **17**, which condenses with aniline to give **18**. The normal cyclization to give **19**, followed by cyclization with the net loss of phenylhydrazine, yields the observed product **6a**.

4-Formylcoumarin semicarbazone gave an intractable mixture when subjected to the rearrangement conditions.

## Experimental Section

Melting points were measured with a Thomas-Hoover capillary melting point apparatus without correction. Nmr spectra were recorded on a Varian A-60 spectrometer with TMS used as internal standard. Infrared spectra were recorded on a Baird Model 455 spectrophotometer. Ultraviolet spectra were recorded on a Beckman DK-I spectrophotometer. Mass spectra were obtained with an AEI MS-902 instrument.

**General Procedure for the Preparation of Imines.**—A mixture of 4-formylcoumarin (0.01 mol) and the corresponding amine (0.01 mol) in benzene (50 ml) was refluxed under a water separator for 3 hr. The solvent was removed under reduced pressure to give a solid product.

**4-[(Phenylimino)methyl]coumarin (5a).**—Yellow crystals recrystallized from ethyl acetate to give **5a** (80%): mp 148–150°; $\lambda_{max}^{EtOH}$ 240 mμ (ε 15,000), 302 (11,500); $\nu_{max}^{Nujol}$ 1720 cm$^{-1}$ (lactone C=O); nmr ($CDCl_3$) δ 8.66 (d, 1, $J$ = 10 Hz, $C_5$ H), 8.50 (s, 1, HC=N), 7.60–7.10 (m, 8, ArH), and 6.75 (s, 1, $C_3$ H).

*Anal.* Calcd for $C_{16}H_{11}NO_2$: C, 77.09; H, 4.45; N, 5.62. Found: C, 76.80; H, 4.53; N, 5.42.

**4-{[(3,4-Dimethylphenyl)imino]methyl}coumarin (5b).**—Yellow crystals recrystallized from ethyl acetate to give **5b** (85%): mp 146–148°; $\lambda_{max}^{EtOH}$ 245 mμ (ε 12,400), 315 (12,000); $\nu_{max}^{Nujol}$ 1720 cm$^{-1}$ (lactone C=O); nmr ($CDCl_3$) δ 8.70 (d, 1, $J$ = 9 Hz, $C_5$ H), 8.50 (s, 1, HC=N), 7.75–7.10 (m, 6, ArH), 6.82 (s, 1, $C_3$ H), and 2.36 (s, 6, $CH_3$-).

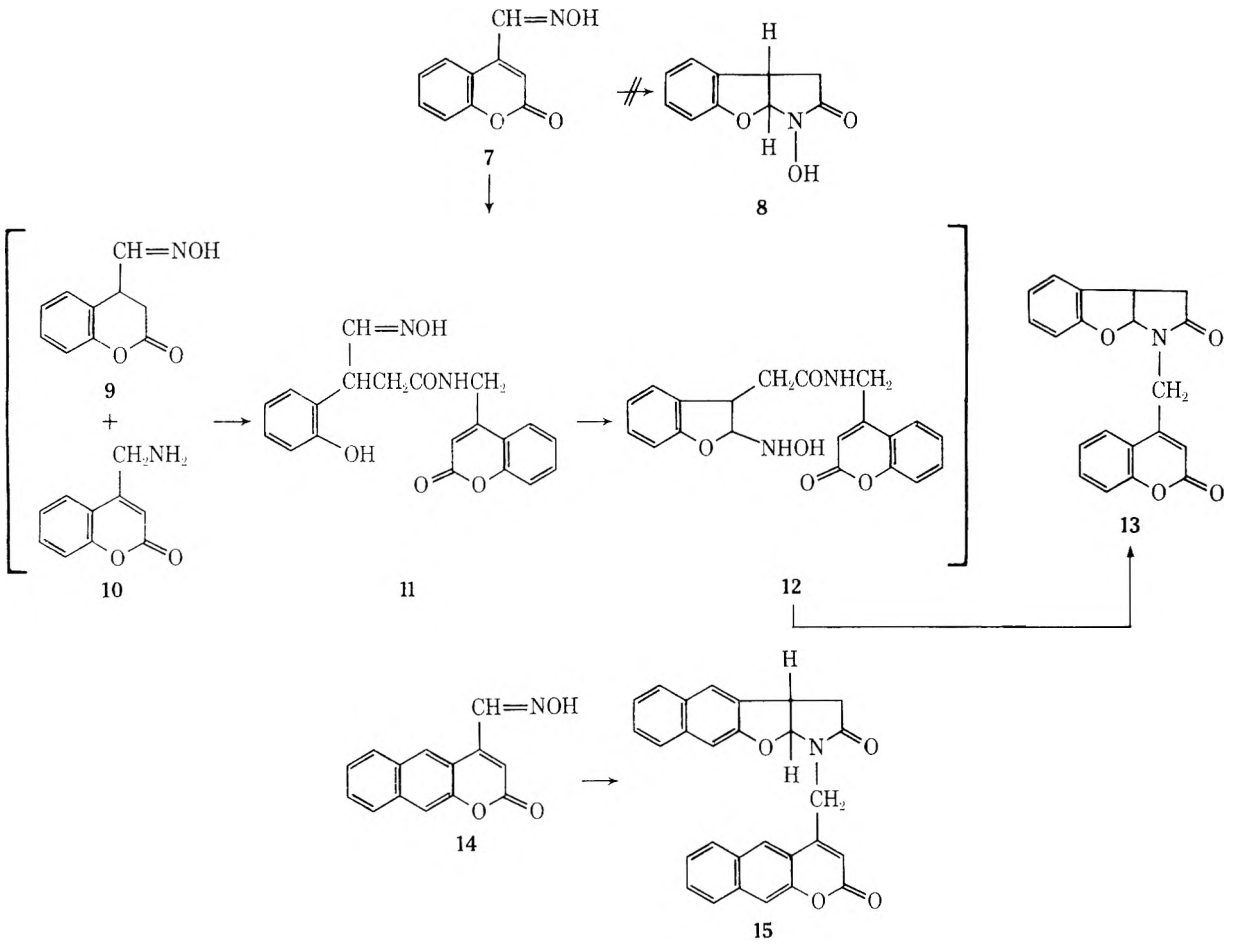
*Anal.* Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.96; H, 5.47; N, 5.14.

**General Procedure for the Preparation of Oximes.**—A mixture of 4-formylcoumarin (0.03 mol), hydroxylamine hydrochloride (0.03 mol), sodium acetate (1 g), water (5 ml), and 95% ethanol (50 ml) was refluxed for 5 hr, cooled, and poured onto ice. The white, crystalline solid which precipitated was filtered and washed with water.

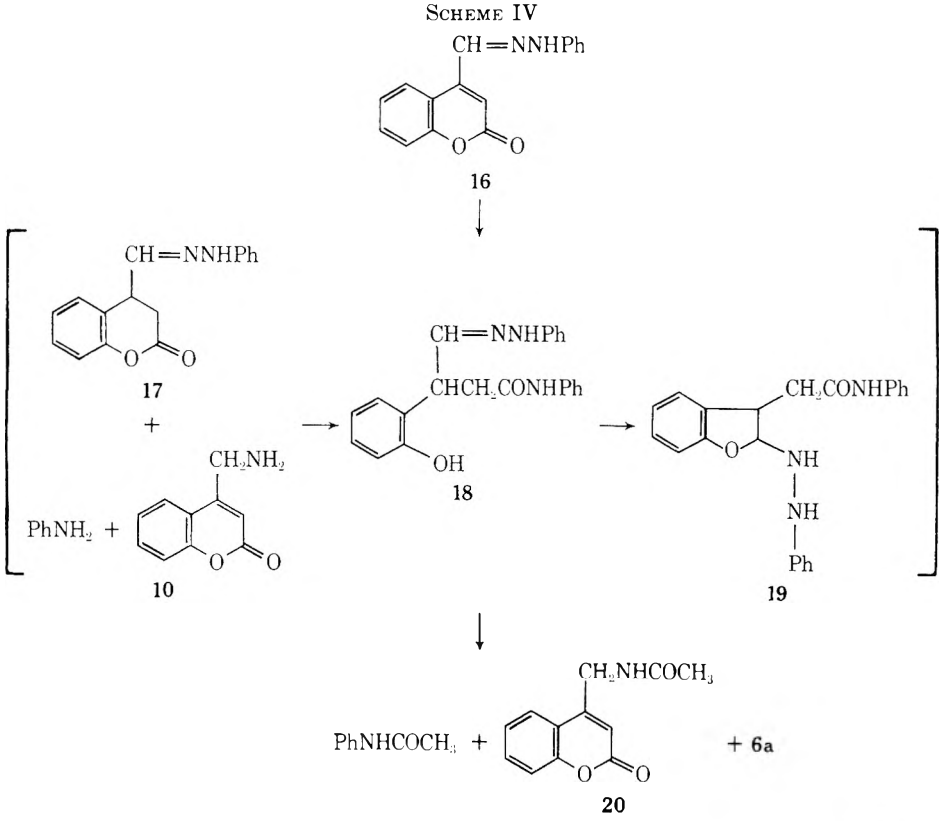
**4-Formylcoumarin Oxime (7).**—White crystals were recrystallized from ethyl acetate–methanol to give **7** (77%): mp 246–248°; $\lambda_{max}^{EtOH}$ 232 mμ (ε 1400), 284 (12,000); $\nu_{max}^{Nujol}$ 1700 cm$^{-1}$ (lactone C=O); nmr (DMSO-$d_6$) δ 12.40 (s, broad, 1, OH, exchanges with $D_2O$), 8.50 (s, 1, HC=N), 8.41 (d, 1, $J$ = 6 Hz, $C_5$ H), 7.70–7.15 (m, 3, ArH), and 6.26 (s, 1, $C_3$ H).

(8) The reduction of 6-chloro-4-formylcarbostyril with zinc and acetic acid yielded 6-chloro-4-(hydroxymethyl)carbostyril as the sole product.

SCHEME III



SCHEME IV



*Anal.* Calcd for $C_{10}H_7NO_3$: C, 63.49; H, 3.73; N, 7.40. Found: C, 63.71; H, 3.71; N, 7.17.

**β-Formyl-3-hydroxy-2-naphthaleneacrylic Acid δ-Lactone Oxime** (14).—Yellow crystals were recrystallized from DMF to give 14 (80%): mp 255–256°; $\lambda_{max}^{EtOH}$ 232 mμ (ε 40,000), 277 (16,000), 330 (12,000); $\nu_{max}^{Nujol}$ 1700 cm$^{-1}$ (lactone C=O); nmr (DMSO-$d_6$) δ 12.75 (s, broad, 1, OH, exchanges with $D_2O$), 9.20 (s, 1), 8.83 (s, 1), 8.35–7.50 (m, 5, ArH), and 6.85 (s, 1, $C_3$ H).

*Anal.* Calcd for $C_{14}H_9NO_3$: C, 70.29; H, 3.79; N, 5.86. Found: C, 70.15; H, 3.90; N, 5.43.

**4-Formylcoumarin Phenylhydrazone** (16).—A mixture of 4-formylcoumarin (5.22 g, 0.03 mol), phenylhydrazine hydrochloride (4.32 g, 0.03 mol), sodium acetate (2 g), water (30 ml), and dioxane (60 ml) was warmed on a steam bath for 1 hr. The reaction mixture was cooled. The crystalline precipitate which formed was filtered and recrystallized from methanol to give orange crystals (5 g, 64%): mp 196–198°; $\lambda_{max}^{EtOH}$ 260 mμ (ε 13,000), 410 (22,500); $\nu_{max}^{Nujol}$ 1720 cm$^{-1}$ (lactone C=O); nmr (DMSO-$d_6$) δ 11.20 (s, 1, NH exchanges with $D_2O$), 8.58 (d, 1, $J$ = 9 Hz, $C_5$ H), 8.10 (s, 1, HC=N), 7.65–7.00 (m, 8, ArH), and 6.60 (s, 1, $C_3$ H).

*Anal.* Calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; 4.58; N, 10.60. Found: C, 72.62; H, 4.45; N, 10.78.

**4-Formylcoumarin Semicarbazone.**—A solution of semicarbazide hydrochloride (1.11 g, 0.01 mol) in water (5 ml) was added to a solution of 4-formylcoumarin (1.74 g, 0.01 mol) in dioxane (20 ml). The resulting mixture was warmed on a steam bath for 30 min. The precipitate which formed was filtered, washed with water, and recrystallized from DMF to give white crystals (1.3 g, 56%): mp 247–249°; $\nu_{max}^{Nujol}$ 1720, 1710, and 1690 cm$^{-1}$; nmr (DMSO-$d_6$) δ 10.67 (s, 1, NH, exchanges with $D_2O$), 8.16 (s, 1, HC=N), 8.07 (d, 1, $J$ = 10 Hz, $C_5$ H), 7.65–7.00 (m, 3, ArH), 6.83 (s, 1, $C_3$ H), and 6.60 (s, 2, $NH_2$ exchanges with $D_2O$).

*Anal.* Calcd for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92; N, 18.17. Found: C, 56.87; H, 4.00; N, 18.09.

**General Procedure for the Rearrangements.**—Zinc dust was added to a solution of the substrate (0.03 mol) in glacial acetic acid (100 ml) at 100°. The reaction mixture was stirred at this temperature for 2 hr, cooled, diluted with chloroform, filtered, and concentrated. The crude oil obtained was dissolved in chloroform. The resulting solution was washed with water, dried over $MgSO_4$, and evaporated to give a colorless gum, which crystallized on standing.

**3a,8a-Dihydrofuro[2,3-*b*]benzofuran-2(3*H*)-one** (2).—White crystals were recrystallized from methanol to give 2 (36%): mp 124–126°; $\lambda_{max}^{EtOH}$ 274 mμ (ε 2600), 281 (2200); $\nu_{max}^{Nujol}$ 1780 cm$^{-1}$ (C=O); nmr ($CDCl_3$) δ 7.30–6.70 (m, 4, ArH), 6.42 (d, 1, $J$ = 6 Hz, $C_{8a}$ H), 4.17 (m, 1, $C_{3a}$ H), 2.94 (d, 1, $J$ = 9 Hz, $C_3$ H), and 2.80 (d, 1, $J$ = 3 Hz, $C_3$ H).

*Anal.* Calcd for $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 68.06; H, 4.54.

**3a,10a-Dihydronaphtho[2′,3′:4,5]furo[2,3-*b*]furan-2(3*H*)-one** (4).—White crystals were recrystallized from ethyl acetate to give 4 (55%): mp 224–226°; $\lambda_{max}^{EtOH}$ 264 mμ (ε 4500), 274 (5000), 285 (3500), 316 (2000), 329 (3000); $\nu_{max}^{Nujol}$ 1780 cm$^{-1}$ (C=O); nmr (DMSO-$d_6$) δ 7.85–7.10 (m, 6, ArH), 6.64 (d, 1, $J$ = 6 Hz, $C_{10a}$ H), 4.30 (m, 1, $C_{3a}$ H), 3.18 (d, 1, $J$ = 9 Hz, $C_3$ H), and 2.90 (d, 1, $J$ = 3 Hz, $C_3$ H).

*Anal.* Calcd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.06; H, 4.40.

**1-Phenyl-1,3,3a,8a-tetrahydro-2*H*-benzofuro[2,3-*b*]pyrrol-2-one** (6a).—White crystals were recrystallized from ethyl acetate to give 6a (50%): mp 105–107°; $\lambda_{max}^{EtOH}$ 276 mμ (ε 4800), 284 (4400); $\nu_{max}^{Nujol}$ 1700 cm$^{-1}$ (C=O); nmr ($CDCl_3$) δ 7.80–6.65 (m, 9, ArH), 6.37 (d, 1, $J$ = 8 Hz, $C_{8a}$ H), 4.05 (m, 1, $C_{3a}$ H), 2.95 (d, 1, $J$ = 9 Hz, $C_3$ H), and 2.80 (d, 1, $J$ = 4 Hz, $C_3$ H).

*Anal.* Calcd for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22; N, 5.57. Found: C, 76.26; H, 5.30; N, 5.60.

**1-(3,4-Dimethylphenyl)-1,3,3a,8a-tetrahydro-2*H*-benzofuro[2,3-*b*]pyrrol-2-one** (6b).—White crystals were recrystallized from ethyl acetate to give 6b (46%): mp 109–111°; $\lambda_{max}^{EtOH}$ 276 mμ (ε 4800), 284 (4000); $\nu_{max}^{Nujol}$ 1700 cm$^{-1}$ (C=O); nmr ($CDCl_3$) δ 7.80–6.65 (m, 7, ArH), 6.30 (d, 1, $J$ = 7 Hz, $C_{8a}$ H), 4.00 (m, 1, $C_{3a}$ H), 2.88 (d, 1, $J$ = 9 Hz, $C_3$ H), 2.73 (d, 1, $J$ = 3 Hz, $C_3$ H), and 2.30 (s, 6, $-CH_3$).

*Anal.* Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.24; H, 6.10; N, 5.06.

**1-[(2-Oxo-2*H*-1-benzopyran-4-yl)methyl]-1,3,3a,8a-tetrahydro-2*H*-benzofuro[2,3-*b*]pyrrol-2-one** (13).—White crystals were recrystallized from ethyl acetate to give 13 (57%): mp 90–93°; $\lambda_{max}^{EtOH}$ 275 mμ (ε 11,200), 312 (5200); $\nu_{max}^{Nujol}$ 1720 (lactone C=O), 1695 cm$^{-1}$ (amide C=O); nmr ($CDCl_3$) δ 7.90–6.65 (m, 8, ArH), 6.23 (s, 1, =CH), 6.00 (d, 1, $J$ = 8 Hz, $C_{8a}$ H), 4.78 (s, 1, $NCH_2$–), 4.55 (s, 1, $NCH_2$–), 4.00 (m, 1, $C_{3a}$ H), 2.92 (d, 1, $J$ = 9 Hz, $C_3$ H), and 2.78 (d, 1, $J$ = 3 Hz, $C_3$ H); mass spectrum (70 eV) $m/e$ 333 (100), 174 (38), 160 (38), 131 (75).

*Anal.* Calcd for $C_{20}H_{15}NO_4$: C, 72.06; H, 4.54; N, 4.20. Found: C, 71.88; H, 4.78; N, 4.03.

**1-[(2-Oxo-2*H*-naphtho[2,3-*b*]pyran-4-yl)methyl]-1,3,3a,10a-tetrahydro-2*H*-naphtho[2′,3′:4,5]furo[2,3-*b*]pyrrol-2-one** (15).—White crystals were recrystallized from DMF to give 15 (73%): mp 263–265°; $\nu_{max}^{Nujol}$ 1725 (lactone C=O), 1694 cm$^{-1}$ (amide C=O).

*Anal.* Calcd for $C_{28}H_{19}NO_4$: C, 77.58; H, 4.42; N, 3.23. Found: C, 77.40; H, 4.46; N, 3.42.

**4-[(Acetamido)methyl]coumarin** (20).—White crystals were recrystallized from methanol to give 20 (6%): mp 185–186°; $\nu_{max}^{Nujol}$ 1710 (lactone C=O), 1665 cm$^{-1}$ (amide C=O); nmr (DMSO-$d_6$) δ 9.00 (t, 1, $J$ = 6 Hz, NH exchanges with $D_2O$), 8.10–7.20 (m, 4, ArH), 6.35 (s, 1, $C_3$ H), 4.60 (d, 2, $J$ = 6 Hz, $-CH_2N$, s after $D_2O$ exchange), and 2.01 (s, 3, $CH_3$–).

*Anal.* Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.32; H, 5.28; N, 6.24.

**Acknowledgment.**—We would like to express our gratitude to Dr. R. C. Greenough for the spectral data and Mrs. U. Zeek for the elemental analyses.

**Registry No.**—1, 35893-95-9; 1 semicarbazone, 41594-38-1; 2, 41594-39-2; 3, 41594-40-5; 4, 41594-41-6; 5a, 41594-42-7; 5b, 41594-43-8; 6a, 41594-44-9; 6b, 41594-45-0; 7, 41594-46-1; 13, 41594-47-2; 14, 41594-48-3; 15, 41594-49-4; 16, 41594-50-7; 20, 41594-51-8; aniline, 62-53-3; 3,4-xylidine, 95-64-7.

# α,β-Unsaturated Lactones. I. Condensation of 5-Bromo-2(5*H*)-furanones with Adenine and Uracil Derivatives[1]

IRIS L. DOERR[2] AND ROBERT E. WILLETTE*[3]

*School of Pharmacy, University of Connecticut, Storrs, Connecticut 06268*

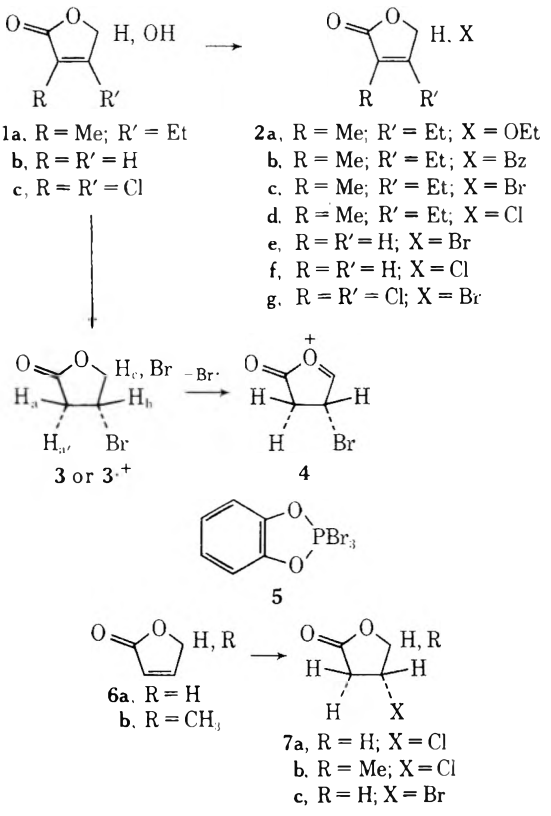
*Received September 1, 1972*

The syntheses of some 5-(pyrimidin-1-yl)- and 5-(purin-9-yl)-2(5*H*)-furanone derivatives, which are nonsugar nucleoside analogs of potential biological interest, are described. 5-Bromo-3-methyl-4-ethyl-2(5*H*)-furanone (**2c**) and its 3,4-unsubstituted and -dichloro analogs **2e** and **2g** were synthesized from the corresponding 5-hydroxy-2(5*H*)-furanone derivatives. Using the Hilbert–Johnson procedure, reaction of 2,4-dimethoxypyrimidine with **2c** and **2e** gave 4-methoxypyrimidinyl intermediates which were hydrolyzed to 5-(uracil-1-yl)-4-ethyl-3-methyl-2(5*H*)-furanone (**9a**) and the unsubstituted analog **9b** in good yields. In the dichlorofuranone series, the pyrimidinyl intermediate **8c**, but not the uracilyl analog **9c**, was prepared. Alkylation of adenine with 5-bromofuranone **2c** in DMF containing $K_2CO_3$ gave 5-(6-amino-9*H*-purin-9-yl)-4-ethyl-3-methyl-2(5*H*)-furanone (**11**) in 22% yield, together with an isomeric product (yield 6%). The proposed structure for the isomer was a tricyclic adenine derivative (**12a**), which contains a diazepine ring. It could be prepared in higher yield by changing the reaction solvent to pyridine. Isomer **12a** was chlorinated with $SOCl_2$ to the 7-chlorodiazepino analog **12b**, which was converted into 7-methoxy and -ethoxy analogs **12c** and **12d**. Uv, ir, mass spectra, pmr, and L1210 screening data are reported and discussed.

In the past decade, it has been demonstrated that certain five- and six-membered α,β-unsaturated lactone derivatives possess, in addition to other pharmacological properties,[4] tumor-inhibitory activity.[5–8] This laboratory was interested in the synthesis and antitumor properties of nonsugar nucleoside analogs where an α,β-unsaturated γ-lactone was substituted for the sugar moiety of nucleosides. The present paper describes the preparation of 5-(uracil-1-yl)-2(5*H*)-furanone (**9b**)[9] and its 4-ethyl-3-methyl analog **9a**, and 5-(6-amino-9*H*-purin-9-yl)-4-ethyl-3-methyl-2(5*H*)-furanone (**11**) and its nonlactonic isomer **12a** (see Schemes II and III). The mycotoxin 5-acetamido-2(5*H*)-furanone[10] is a recently synthesized simple analog of the pyrimidinyl furanone **9b**.

The first part of this study involved the preparation of known and unknown 5-bromofuranones as the desired alkylating agents for the purines and pyrimidines. Three types of furanone moieties were investigated, *i.e.*, where the carbon–carbon double bond was unsubstituted or substituted with alkyl or chloro groups (Scheme I). The obvious precursors of the 5-bromofuranones were the 5-hydroxyfuranones. It should be noted that these derivatives can exist in two open tautomeric forms, *i.e.*, *cis*- and *trans*-β-formylacrylic acid. The lactol tautomer, however, has been established as the predominant form under a variety of conditions.[11–13] As would be expected in reactions involving the hydroxy hemiacetal group, hydroxyfuranones and monosaccharides react similarly. This is exemplified by reactions of the known 4-ethyl-3-methyl-5-hydroxy-2(5*H*)-furanone (**1a**), which was obtained in good yield by the method of Schreiber and Wermuth.[12] Under sugar acetalization conditions,

SCHEME I




(1) (a) Presented in part to the Division of Organic Chemistry at the 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970. (b) Preliminary publication: *Tetrahedron Lett.*, 667 (1970). (c) Taken in part from the Ph.D. Thesis of I. L. D., University of Connecticut, 1971. (d) This investigation was supported in part by funds from the University of Connecticut Research Foundation and The National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 10316).

(2) National Science Foundation Predoctoral Fellow, 1969–1970.

(3) Inquiries should be addressed to R. E. Willette, National Institute of Mental Health, Room 13-15, 5600 Fishers Lane, Rockville, Md. 20852.

(4) Leading references to the extensive literature on the biological activity of unsaturated lactones are given in the following: (a) L. J. Haynes, *Quart. Rev., Chem. Soc.*, **2**, 46 (1948); (b) N. Hellstrom, *Acta Agr. Scand.*, **8**, 285 (1958); (c) K. H. Chemnitus, *Arzneim.-Forsch.*, **11**, 277 (1961); (d) F. Dickens and H. E. H. Jones, *Brit. J. Cancer*, **15**, 85 (1961); (e) *ibid.*, **19**, 392 (1965).

(5) F. Dickens and H. E. H. Jones, *Brit. J. Cancer*, **17**, 100 (1963).

(6) (a) S. M. Kupchan, R. J. Hemingway, and J. C. Hemingway, *J. Org. Chem.*, **34**, 3894 (1969); (b) S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971), and references cited therein.

(7) M. Semonsky, W. Rockova, V. Zikan, B. Kakac, and V. Jelinek, *Collect. Czech. Chem. Commun.*, **28**, 377 (1963).

(8) V. Zikan, M. Semonsky, and V. Jelinek, *Collect. Czech. Chem. Commun.*, **34**, 2157 (1969).

(9) An alternate name for compound **9b**, which is preferred by Chemical Abstracts Service, is 1-(2,5-dihydro-5-oxo-2-furyl)uracil. This nomenclature would also be applicable to analogs **9a**, **8a**, **8b**, and **8c**.

(10) S. G. Yates in "Microbial Toxins," S. Kadis, A. Ciegler, and S. J. Ajli, Ed., Academic Press, New York, N. Y., 1971, pp 191–206, and references cited therein.

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(12) J. Schreiber and C. G. Wermuth, *Bull. Soc. Chim. Fr.*, **8**, 2242 (1965).

(13) S. H. Schroeter, R. Appel, R. Brammer, and G. O. Schenck, *Justus Liebigs Ann. Chem.*, **697**, 42 (1966).

**1a** gave solely the 5-ethoxyfuranone **2a**.[12] We found that reaction of **1a** with benzoyl chloride in pyridine gave the 5 benzoate **2b**. On treatment of **1a** with HBr in glacial acetic acid, a theoretical yield of the 5-bromofuranone **2c** was obtained. The chloro analog **2d** was prepared by the action of titanium tetrachloride on **1a**.

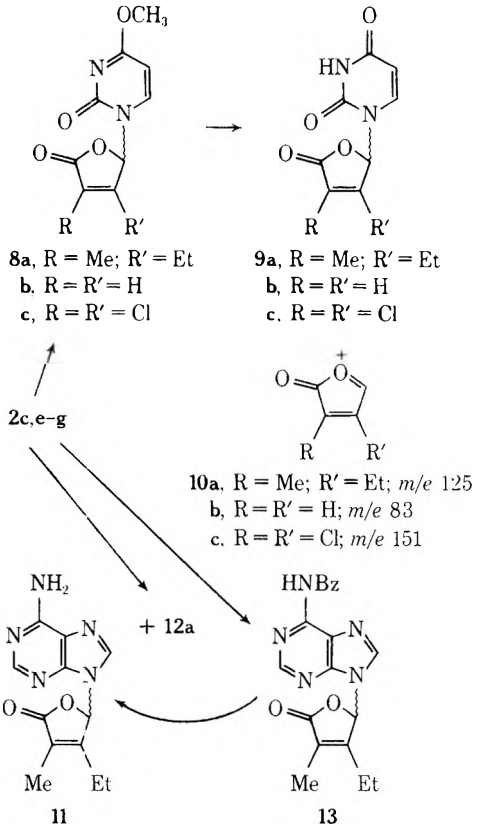
5-Hydroxy-2(5*H*)-furanone[14] has been synthesized in two steps from furfural:[15,16] dye-sensitized photooxygenation of a furfural–ethanol mixture to 5-ethoxy-2(5*H*)-furanone followed by acid hydrolysis of the 5-ethoxy analog to **1b**. In our study, using a modified procedure, photolysis of furfural was rapid in the presence of excess oxygen, and 5-hydroxyfuranone **1b** (not the ethoxy analog) was obtained in one step (yield 43%). Reaction of **1b** with HBr in acetic acid failed to give 5-bromo-2(5*H*)-furanone (**2e**), which had previously been prepared by Elming and Clauson-Kaas[17] using another method. Upon work-up of the reaction, a colorless, HBr-evolving liquid was obtained. The ir, pmr, and mass spectral data suggested that the liquid consisted mostly of *cis*- and *trans*-3,4-dibromobutanolide (**3**, Scheme I). No attempt was made to isolate the isomers **3**. The ir spectrum of the mixture **3** showed lactonic carbonyl absorption at 1825 $cm^{-1}$. In recent studies on the reaction of hydrogen halides with $\alpha,\beta$-unsaturated lactones, Ducher and Michet[18] found that preferential reaction occurred with the conjugated system. Buten-2-olide (**6a**) and $\beta$-angelica lactone (**6b**) reacted with HCl to give the $\beta$-chlorolactones **7a**[18a] and **7b** (cis and trans isomers),[18b] respectively. Reaction of **6a** with HBr gave the $\beta$-bromolactone **7c**.[18a] The pmr data of **7c** reported in deuterated acetone had two multiplet centers due to the methylene protons ($\delta$ 3.10) and $H_\beta$ ($\delta$ 4.78). These values compared closely to the corresponding values for protons a, a′ ($\delta$ 3.13), and b ($\delta$ 4.85) of diastereoisomers **3**. The mass spectral data of **3** showed no peak at *m/e* 242 for the molecular ion $3^{\cdot+}$. However, major even-electron ion peaks were detected, among them the peak at *m/e* 163 due to the [M − Br] ion **4**.

Some exclusion of the formation of addition products **3** was avoided when catecholphosphorus tribromide (**5**)[19] was used as the brominating agent of **1b**. Reaction of 5-hydroxyfuranone **1b** with **5** in methylene chloride gave a crude product containing the 5-bromofuranone **2e** and the addition products **3**. After purification of the crude product, the desired monobromide was obtained in yields that varied from 10 to 20%.

5-Bromo-3,4-dichloro-2(5*H*)-furanone (**2g**) was prepared in 55% yield by bromination of mucochloric acid (**1c**) using the tribromide **5**. When HBr in glacial acetic acid was used as the brominating agent of **1c**, different results were obtained. In addition to the formation of the major monobromo product, a small amount of displacement of the 3- or 4-chloro atom with bromine occurred, producing either of two proposed structures, 4,5-dibromo-3-chlorofuranone or its 3,5-dibromo isomer. This new dibromofuranone was not detected in the **2g**-containing mixture, but its presence was proved in the 2,4-dimethoxypyrimidine-alkylation product discussed below.

The Hilbert–Johnson procedure[20] for the syntheses of 1-substituted uracils was used to prepare the uracilyl furanones (Scheme II). Reaction of 5-bromofuranone

SCHEME II




**2c** with 2,4-dimethoxypyrimidine[20a] in methylene chloride for 7 days at room temperature gave the 4-methoxypyrimidine derivative **8a** (yield 75%). On treatment of an aqueous ethanolic solution of **8a** with 1 *N* HCl, 5-(uracil-1-yl)-4-ethyl-3-methyl-2(5*H*)-furanone (**9a**) was obtained in high yield. The unsubstituted 5-bromofuranone **2e** alkylated 2,4-dimethoxypyrimidine more rapidly than the dialkylated analog **2c**. The 4-methoxy derivative **8b** was obtained in 1 day (yield 53%). Derivative **8b** was also prepared from the 5-chlorofuranone **2f** in 29% yield under more strenuous conditions. Acid hydrolysis of the 4-methoxy compound **8b** gave 5-(uracil-1-yl)-2(5*H*)-furanone (**9b**) in 58% yield. Alkylation of dimethoxypyrimidine with 5-bromo-3,4-dichlorofuranone **2c** gave the 4-methoxy compound **8c** in only 23% yield. The yield of **8c** could not be improved. Preparation of the uracil analog **9c** from **8c** was not achieved because of the ease of N–C bond cleavage in these compounds in aqueous acid. Thus, the reaction of **8c** in dilute acid gave a mixture of products containing predominantly uracil and mucochloric acid (**1c**) as detected by tlc, ir, and uv. Cleavage of the N–C bond also oc-

(14) H. Fecht, *Ber. Deut. Chem. Ges.*, **38**, 1272 (1905).

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(16) M. D. Grove, S. G. Yates, W. N. Tallent, J. J. Ellis, I. A. Wolff, N. R. Kosuri, and R. E. Nichols, *J. Agr. Food Chem.*, **18**, 734 (1970).

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(20) (a) G. E. Hilbert and T. B. Johnson, *J. Amer. Chem. Soc.*, **52**, 2001, 4489 (1930); (b) J. Phiml and H. Prystas, *Advan. Heterocycl. Chem.*, **8**, 115 (1967), a recent review.

TABLE I

PROTON MAGNETIC RESONANCE DATA OF N HETEROCYCLES

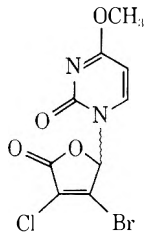
| Compd | Solvent | Chemical shift, δ (J, Hz) $C_{5(7)}H$[a] | $C_{2(9)}CH_3(H)$ | $C_{4(8)}C_2H_5(H)$ | Others |
|---|---|---|---|---|---|
| 8a | $CDCl_3$ | 7.36 (b s) | 1.97 (s) | 2.38 (m),[b] 1.14 (t, 7.5) | 7.12, 6.00;[c] 4.20[d] |
| 8b | $CDCl_3$ | 7.36 (t, 1.8) | 6.47 (dd, 5.5, 1.3) | 7.56 (dd, 5.5, 1.8) | 7.32, 6.00;[c] 4.81[d] |
| 8c | DMSO-$d_6$ | 7.41 (s) | | | 8.28, 6.34;[c] 3.99[d] |
| 9a | P-$d_5$–$D_2O$ | 7.36 (b s) | 1.97 (s) | 2.25 (m),[b] 1.05 (t, 7.5) | 7.50, 6.00[c] |
| 9b | DMSO-$d_6$ | 7.27 (t, 2.0) | 6.77 (dd, 6, 2) | 7.94 (dd, 6, 2) | 7.55, 5.80[c] |
| 11 | TFA | 7.36 (b s) | 2.13 (s) | 2.54 (m),[b] 1.18 (t, 7.5) | 8.68, 8.63[e] |
| 12a | TFA | 6.54 (b s) | 2.13 (s) | 2.47, 1.28 (q, t, 9) | 9.00, 8.95[e] |
| 12c | $CDCl_3$ | 6.56 (b s) | 1.97 (s) | 2.50, 1.30 (q, t, 8) | 8.95, 8.53;[e] 11.50;[f] 3.37[d] |
| 13 | P-$d_5$ | 7.25 (b s) | 1.92 (s) | 2.28 (m),[b] 0.92 (t, 7.5) | 9.03, 8.88;[e] 12.48;[f] 8.33, 7.49[g] |

[a] The broad peak width at half-height ranged from 3.5 to 6 Hz. [b] Multiplet spin decoupled: **8a**, $\Delta\gamma_{AB}$ = 21.1 Hz, $J_{AB}$ = 13 Hz; **9a**, $\Delta\gamma_{AB}$ = 20.2 Hz, $J_{AB}$ = 14 Hz; **11**, $\Delta\gamma_{AB}$ = 28.3 Hz, $J_{AB}$ = 15 Hz; **13**, $\Delta\gamma_{AB}$ = 23.1 Hz, $J_{AB}$ = 14 Hz. For compounds **11** and **13**, the values cited in ref 1b have been corrected. [c] Pyrimidine H-6 and H-5. [d] $OCH_3$. [e] Purine H-8 and H-2. [f] NH proton, disappeared on deuteration. [g] Aryl protons.

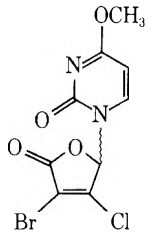
curred when the uracil derivative **9b** was boiled in water for 15 hr. Tlc analysis of the reaction mixture revealed two uv-absorbing spots of equal intensity corresponding to uracil and analog **9b**.

The uv spectra of the five pyrimidinylfuranones in stable solutions were similar to those of their respective 1-substituted 4-methoxypyrimidine and -uracil analogs,[21,22] except for small changes due to the chromophoric furanone moiety. The ir data of pyrimidines **8a**, **8b**, **8c**, and **9b** showed characteristic lactonic carbonyl absorption in the range 1762–1777 $cm^{-1}$.[13,14,23] From the mass spectral data of these derivatives, the furanone moieties were identifiable as abundant peaks due to the appropriate oxonium lactone ion, *i.e.*, **10a**, **10b**, or **10c** (Scheme II). These ions arose from their respective molecular ions *via* an α-cleavage process, which is a common fragmentation route of furanone derivatives reported here and in the literature.[24a] The pmr data (Table I) for derivatives **8a**, **8b**, **8c**, **9a**, and **9b** were consistent with these structures. Interestingly, the methylene protons of the 4-ethyl group in analogs **8a** and **9a** appeared as a multiplet.[25]

As discussed above, reaction of mucochloric acid (**1c**) with HBr in glacial acetic acid gave a mixture containing products 5-bromofuranone **2g** and 3,5- (or 4,5-) dibromo-4- (or 3-) chlorofuranone. The presence of the latter compound in the mixture was implied from physical data on the Hilbert–Johnson product. Reaction of 2,4-dimethoxypyrimidine with the (HBr–acetic acid + **1c**) product gave a mixture of the dichlorofuranone **8c** and a bromo chloro analog with proposed structures **14** or **15**. The mass spectrum of the mixture




**14**




**15**

exhibited a small peak at *m/e* 320 (1.5%) that was attributed to the molecular ion of the product **14** (or **15**). From the elemental analysis the amount of bromo chloro product **14** (or **15**) present in the mixture was calculated to be 12.7%, the remainder being the dichloro product **8c**. From their work on dihalogenofuranones, Wasserman and Precopio[26] have proposed that the reaction of nucleophiles occurs preferentially at the 4 position in all dihalogenofuranones that are exclusively in the cyclic form. By analogy, therefore, the 4-bromofuranone derivative **14** would be favored as a replacement product over the 4-chloro analog **15**.

Alkylations of adenine under basic conditions have been reported to give the 7- or 9-substituted product as the predominating isomer.[27,28] The reaction of adenine with 5-bromofuranone **2c** in DMF containing $K_2CO_3$ gave 5-(6-amino-9*H*-purin-9-yl)-4-ethyl-3-methyl-2(5*H*)-furanone (**11**, yield 22%, Scheme II). In addition to **11**, an isomeric product **12a** was also isolated in 6% yield. The structure of the furanone compound **11** was confirmed as follows. The ir spectrum showed a sharp band at 1773 $cm^{-1}$ due to the lactonic carbonyl. Compound **11** was established as the 9-purinyl and not the 7, 1, or 3 isomer from the uv data.[29] The pmr data for derivative **11** are listed in Table I and showed signals due to the $H_5$ proton, the methyl and ethyl groups, and the adenine moiety. The chemical shift difference for the 2 and 8 position purine protons in DMSO-$d_6$ solution has been used to predict substitution products of the purine ring.[29] In this regard the Δδ of 6 Hz for **11** is consistent with

(21) D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, **9**, 199 (1951).

(22) J. J. Fox and I. Wempen, *Advan. Carbohyd. Chem.*, **14**, 283 (1959).

(23) J. F. Grove and H. A. Willis, *J. Chem. Soc.*, 877 (1951).

(24) (a) Q. N. Porter and J. Baldos, "Mass Spectrometry of Heterocyclic Compounds," Wiley-Interscience, New York, N. Y., 1971, pp 195–198; (b) pp 484–485; (c) pp 313–315.

(25) The protons of the 4-ethyl group in pyrimidine derivatives **8a** and **9a** as well as in purine analogs **11** and **13** constitute an $ABX_3$ spin system (Table I). In these compounds the methyl protons ($X_3$) appeared as a well-resolved triplet, $J_{AX,BX}$ = 7.5 Hz, whereas the methylene protons (AB) showed up as a multiplet having five to six visible lines. Double irradiation of the X resonance position in each compound reduced the multiplet having five to six visible lines. Double irradiation of the X resonance position in each compound reduced the multiplet to an AB quartet from which $\Delta\gamma_{AB}$ and $J_{AB}$ were obtained. The main factors that are considered responsible for the large nonequivalence effect in these compounds are the magnetic anisotropy associated with the N heterocycle and the intrinsic nonequivalence of the $C_4$ methylene adjacent to the chiral $C_5$–N bond. Preferred conformer populations due to restricted rotation about the $C_4$ methylene bond may also contribute. In comparison to the above data, the pmr spectra of 4-ethylfuranones **1a**,[12] **2a**,[12] **2b**, **2c**, and **2d** displayed an $A_2$ pattern for the methylene protons indicating their apparent equivalence.

(26) H. H. Wasserman and F. M. Precopio, *J. Amer. Chem. Soc.*, **76**, 1242 (1954), and references cited therein.

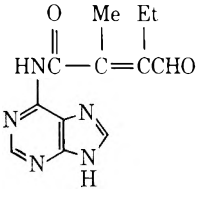
(27) (a) N. J. Leonard and J. A. Deyrup, *J. Amer. Chem. Soc.*, **84**, 2148 (1962); (b) N. J. Leonard and T. Fujii, *ibid.*, **85**, 3719 (1963); (c) M. Rasmussen and N. J. Leonard, *ibid.*, **89**, 5439 (1967).

(28) (a) J. A. Montgomery and H. J. Thomas, *J. Heterocycl. Chem.*, **1**, 115 (1964); (b) *J. Amer. Chem. Soc.*, **87**, 5442 (1965).

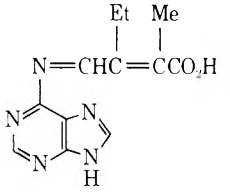
(29) (a) L. B. Townsend, R. K. Robins, R. N. Loeppky, and N. J. Leonard, *J. Amer. Chem. Soc.*, **86**, 5420 (1964); (b) K. R. Darnall and L. B. Townsend, *J. Heterocycl. Chem.*, **3**, 371 (1966).

other 9-substituted adenines. The adenyl furanone **11** was also obtained by the mercury salt method, which has been used to synthesize numerous adenine nucleosides. Condensation of 6-benzamidochloromercuripurine with the 5-bromofuranone **2c** (in refluxing toluene) gave 5-(6-benzamido-9*H*-purin-9-yl)-4-ethyl-3-methyl-2(5*H*)-furanone (**13**, yield 20%, Scheme II). Debenzoylation of **13** with picric acid in methanol gave the picrate of **11**, which was converted into the free base.

**The Tricyclic Purine Side Product 12a.**—As mentioned above, the reaction of adenine and the bromofuranone **2c** in basic DMF yielded furanone **11** and a small quantity of an isomer. Fortunately, it was found that the isomer could be prepared in higher yield (20–40%) from adenine and **2c** merely by changing the solvent to pyridine and omitting the $K_2CO_3$. This study was carried out in order to further explore the chemical reactivities of the bromofuranone with adenine. The 1-, 3- or 7-adenyl furanone isomers of **11** were excluded as structures of isomer **12a** by the following data: (1) the absence of the lactonic carbonyl band in the ir; (2) the absence of the lactonic oxonium ion **10a** in the mass spectrum; (3) the presence in the uv spectrum of a maximum at 290 nm in neutral, acid, and basic solutions; and (4) a $pK_a$[1] of 1.98. Furthermore, isomer **12a** was not an open derivative, such as the amido or aldimine isomers **16** and **17**, because an



**16**



**17**

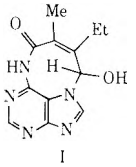
aldehydo or carboxyl group was not detected by either chemical tests[30] or ir and pmr data.

In a preliminary experiment isomer **12a** was found to hydrolyze readily in boiling 1 *N* sodium hydroxide to adenine and unknown product(s). However, certain data given below established the isomer as a tricyclic purine with 8-ethyl-7-hydroxy-9-methyl-3*H*-[1,3]diazepino[2,1-*i*]purin-10(7*H*)-one (**12a**, Scheme III) as the favored structure.[31]

Owing to the low solubility of **12a**, the only suitable solvent for the pmr was TFA. Except for the imino and exchangeable hydroxy protons, all protons of the diazepino structure **12a** were accounted for, *i.e.*, purine protons, 9-methyl, 8-ethyl, and aminal-like proton $H_7$ (Table I). The chemical shift values of these protons were similar to those for the purine, methyl, ethyl, and $H_5$ protons of **11**. In the ir, the carbonyl of the cyclic amide moiety of **12a** absorbed at 1712 $cm^{-1}$. High-resolution mass spectral data also supported structure **12a**, as discussed below.

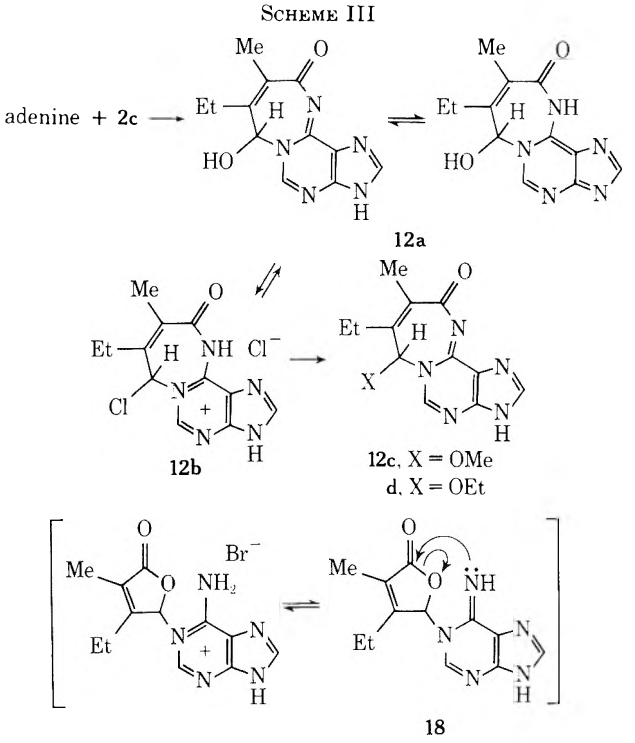
(30) *E.g.*, compound **12a** was insoluble in sodium bicarbonate, did not form phenylhydrazones, and was not reduced with sodium borohydride.

(31) The chemical and physical data do not unequivocally support the 1 to $N^6$ structure **12a** for the isomer. The possibility that the isomer is the diazacino compound I, which contains the hitherto unknown 7 to $N^6$ cyclic system, could not be ruled out.



I

SCHEME III



Consistent with structure **12a**, the hydroxy group underwent certain replacement reactions (Scheme III). On treating **12a** with thionyl chloride, 7-chloro-8-ethyl-3,7,10-tetrahydro-9-methyl-10-oxo[1,3]diazepino-[2,1-*i*]purin-6-ium chloride (**12b**) was obtained (yield 88%). This derivative was readily hydrolyzed back to compound **12a**. The 7-chloro derivative **12b**, upon treatment with anhydrous base in absolute methanol or ethanol, was converted to the respective 7-alkoxy derivative **12c** or **12d**. In the pmr spectrum of the methoxy analog **12c** ($CDCl_3$), all protons were accounted for (Table I). On the addition of $D_2O$, the imino proton ($\delta$ 11.50) disappeared.

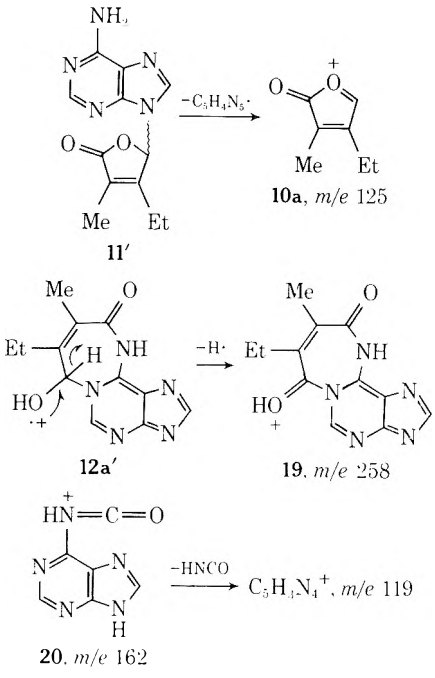
**Mechanism of Formation of 12a.**—$N^6 \rightarrow 1$ cyclization of $N^6$-substituted adenines is by far the most numerous type of ring closure involving the adenine moiety.[32] It should be noted that, although a ring closure of N-7 was also possible, only closure involving N-1 has been observed. There is only one example of a cyclization proceeding $1 \rightarrow N^6$. Chheda and Hall[33] found that alkylation of 9-methyladenine with *tert*-butyl bromoacetate gave *tert*-butyl 6-imino-9-methylpurine-1-acetate. On treatment of this 1,9-disubstituted derivative with alkali, instantaneous intramolecular acylation to 3-methyl-3*H*-imidazo[2,1-*i*]purin-8(7*H*)-one occurred. A possible mechanism for the formation of the diazepino derivative **12a** also may involve an intramolecular $1 \rightarrow N^6$ cyclization as shown in Scheme III. Hence, the first step in the formation of **12a** would be the alkylation of the 1 nitrogen of adenine by the bromofuranone **2c**, yielding the intermediate 6-imino purinyl furanone **18**. The carbonyl end of the lactone moiety then aminoacylates *in situ*, giving the cyclic amide product **12a**.

(32) N. J. Leonard and R. A. Swaringen, *J. Org. Chem.*, **34**, 3814 (1969), and references cited therein.

(33) G. B. Chheda and R. H. Hall, *J. Org. Chem.*, **34**, 3492 (1969).

**Mass Spectra of Isomers 11 and 12a.**—The low-resolution mass spectra of the diazepino derivative **12a** compared to that of its isomer **11** exhibited peaks due to different and common ions. With regard to the high mass common ions, which are listed in Table II, both compounds had peaks at *m/e* 259 (M), 258, 230, 202, 136, 135, 108, and 81. Peaks at *m/e* 136–81 are associated with the mass spectra of adenine and some of its derivatives. The peak at *m/e* 135 is attributable to the molecular ion adenine.[24b,34] The spectra of **11** and **12a** did show notable differences. For example, the spectrum of **11** (but not **12a**) contained a peak at *m/e* 125 due to the oxonium lactone ion **10a**, which resulted from N–C bond cleavage in molecular ion **11′** (Scheme IV). The low-resolution mass spectrum

SCHEME IV




of the diazepino derivative **12a** exhibited many peaks not present in isomer **11**, *e.g.*, at *m/e* 241, 229, 216, 162, and 119. In addition two peaks common to both compounds at *m/e* 258 and 230 had significantly greater abundances in compound **12a**. In isomers **11** and **12a**, the peaks at *m/e* 230 were attributable to [M − $C_2H_5$] and/or [M − CHO] ions (metastable 204.3). The high-resolution mass spectrum of **12a** was determined in order to find the exact mass of fragment ions (see Experimental Section). Most peaks from **12a** are associated with the fragmentation of the diazepino ring. As in the above low-resolution mass spectrum of **12a**, chief fragmentation ions were at *m/e* 258 [M − 1] and 230 [M − 29]. The [M − 1] ion probably resulted from cleavage of the hydrogen atom $\alpha$ to the 7-hydroxy group of molecular ion **12a′**, giving cation **19** (Scheme IV). Two isobaric species contributed to the ion at *m/e* [M − 29]. This ion was due to both the loss of $C_2H_5$ (100%) and CHO (20%). The loss of ethyl may have occurred in a single step or in a two-step process [M − H − $C_2H_4$]. The cation at *m/e* 244 was due to the [M − $CH_3$] ion. The alcoholic nature of **12a** was established by the odd-electron ion at *m/e* 241 [M − $H_2O$] and the strong *m/e* 18 peak. The very abundant peaks at *m/e* 162 and 119 supported the cyclic amide structure of **12a**. These peaks are associated with the following pathway.

$$M\cdot^{+} \xrightarrow[x \text{ steps}]{-C_6H_9O} C_6H_4N_5O^{+},\ m/e\ 162 \xrightarrow[m^*]{-HNCO} C_5H_3N_4^{+},\ m/e\ 119$$

A metastable peak at *m/e* 87.4 (low-resolution mass spectrum) confirmed the fragmentation *m/e* 162 → 119. Structure **20** is proposed for the cation at *m/e* 162. The loss of HNCO from other ionic fragments may be involved in the formation of ions at *m/e* 215 and 199. Other cyclic amides commonly lose HNCO, *e.g.*, 2-pyrrolidone.[24c]

**Screening Data.**—It was hoped that the furanone derivatives would initiate a new series of compounds with antitumor activity. Preliminary L1210 screening data on a few of these derivatives, including the diazepino compound **12a**, have been obtained. Six mice, infected with L1210 lymphoid leukemia, were treated with a single dose of the drug.[35] The uracilyl, diazepino, and adenyl derivatives **8a**, **12a**, and **11** exhibited a weak positive effect on the mean survival time of mice at the 400-mg dose having *T/C* values of 102, 103, and 113%, respectively. The uracilyl analog **9b**, which bore the most chemically reactive furanone moiety, was toxic at the 100-mg dose to five out of six mice, but had a weak positive effect on the surviving mouse (*T/C* 116%). We are currently synthesizing and testing other furanone derivatives to determine if activity can be enhanced.

## Experimental Section

**General.**—Melting points were determined on a Thomas-Hoover apparatus in capillaries and are corrected. Infrared (ir) spectra were obtained using a Beckman Microspec or a Perkin-Elmer Model 21 (P-E) spectrophotometer. Ultraviolet (uv) spectra were determined on a Cary 15 spectrophotometer. The apparent $pK_a'$ of 1.98 for compound **12a** was determined spectrophotometrically using buffers and techniques previously employed.[21,22] Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Proton magnetic resonance (pmr) spectra were determined using a Varian A-60 spectrometer. Spin–spin decoupling studies were carried out using a Jeol JNMC-60HL spectrometer.[36] Chemical shifts ($\delta$) are given in parts per million downfield from internal TMS. The low-resolution mass spectra were obtained with an AEI MS-12 spectrometer using solid probe introduction. High-resolution mass spectra were obtained with a CEC 21-110B double-focusing mass spectrometer,[37a] except in the case of compounds **12c** and **12d**, which were measured on an AEI MS902 spectrometer.[37b] They were all determined at 70 eV. Thin layer chromatography (tlc) was carried out on Eastman silica gel plates (6060) using the following solvent systems: (1) cyclohexane–ethyl acetate (8:2); (2) acetone; (3) ethyl acetate; (4) benzene; (5) acetone–chloroform–water (5:1:1). The products were visualized by uv absorption and/or iodine vapor. Column chromatography was carried out using J. T. Baker silica gel

(34) S. Hanessian, D. C. DeJongh, and J. A. McCloskey, *Biochim. Biophys. Acta*, **117**, 480 (1966).

(35) Assays were performed under the auspices of the Drug Development Branch, National Cancer Institute, National Institutes of Health, using procedures described in *Cancer Chemother. Rep.*, **25**, 1 (1962).

(36) These studies were carried out through the courtesy of Jeol Inc., Cranwood, N. J.

(37) The high-resolution mass spectra were obtained by support of the Division of Research Resources, National Institutes of Health, U. S. Public Health Service; (a) A. D. Little, Cambridge, Mass.; (b) Battelle Columbus Laboratories, Columbus, Ohio.

(3405). Paper electrophoretic data was obtained using a Kenco Model 50 apparatus with an organic pH 3.3 buffer (K-100). The furfural photochemical oxidation was carried out using a 650-W lamp (Sylvania Sungun, DWY), which was contained in an Hanovia quartz immersion well in a 1-l. reaction vessel bearing a circular filter disk (Ace Company) through which $O_2$ was passed.

Furfural was distilled at 20–25 mm immediately before use in the photolysis. DMF was dried over $P_2O_5$, distilled at 15 mm, and stored over molecular sieve. Pyridine was dried over BaO and then distilled. Thionyl chloride was distilled according to the procedure of Rigby.[38] Using the method of Schreiber and Wermuth,[12] 4-ethyl-3-methyl-5-hydroxy-2(5*H*)-furanone (**1a**, mp 50°) was prepared in comparable yield and gave identical pmr and ir data with those reported. 5-Hydroxy-2(5*H*)-furanone (**1b**, 20 mmol) was allowed to react with $SOCl_2$ (56 mmol) to give 5-chlorofuranone **2f** in 30% yield (lit.[13] 45%): pmr ($CCl_4$) $\delta$ 6.73 (t, 1, $J_{3,5} = J_{4,5} = 1.3$ Hz, $C_5$ H), 7.70 (dd, 1, $J_{3,4} = 5.5$, $J_{4,5} = 1.5$ Hz, $C_4$ H), 6.37 (dd, 1, $J_{3,4} = 5.5$, $J_{4,5} = 1.3$ Hz, $C_3$ H). Pyrocatecholphosphorus tribromide (**5**, 100 g),[19] because of its reactivity, was dissolved in methylene chloride and divided into 25-g batches. The solvent was removed and the solid tribromide was kept in the freezer until use.

**5-Ethoxy-4-ethyl-3-methyl-2(5*H*)-furanone (2a).**—Schreiber and Wermuth[12] prepared this compound by another method. Furanone **1a** (0.5 g) was dissolved in absolute ethanol (30 ml) containing HCl gas. The reaction mixture was boiled for 0.5 hr and then cooled. The ethanol was evaporated and the residue was azeotroped with benzene to remove the HCl. The liquid weighed 0.55 g and contained only product **2a**. The pmr data ($CCl_4$) were identical with those reported. Using tlc solvent 1, **2a** had $R_f$ 0.42 (**1a**, $R_f$ 0.15); ir ($CCl_4$) 1754 (s), 1672 $cm^{-1}$ (w) (lit.[12] ir 1785, 1700 $cm^{-1}$).

**5-Benzoyl-4-ethyl-3-methyl-2(5*H*)-furanone (2b).**—Furanone **1a** (2 g, 14.1 mmol) was dissolved in dry pyridine (50 ml) and the solution was cooled to 0°. Benzoyl chloride (1.9 ml, 14.8 mmol) was added. Pyridine hydrochloride precipitated. The reaction was allowed to stand overnight at room temperature and then ethanol (2 ml) was added. The pyridine was evaporated, leaving a syrup. Residual pyridine was removed from the syrup by evaporation with 50% ethanol. The residue was dissolved in methylene chloride and dried ($MgSO_4$). The solvent was evaporated and the residue was crystallized from an ether–petroleum ether (bp 30–60°) mixture. White crystals were obtained: 2.6 g (75%); mp 69–71°; mass spectrum *m/e* (rel intensity) 234 (14). Using tlc solvent 1, **2b** had $R_f$ 0.57 (**1a**, $R_f$ 0.2); ir ($CCl_4$) 1785 (s, lactone C=O), 1710 (benzoyl C=O), 1695 $cm^{-1}$ (w, C=C); pmr ($CCl_4$) $\delta$ 6.92 (b s, 1, $C_5$ H), 1.87 (s, 3, $C_3$ $CH_3$), 2.45 (q, 2, $-CH_2-$), 1.17 (t, 3, $J$ = 7.5 Hz, $CH_3$), 7.95 and 7.43 (m, 5, aryl H).

*Anal.* Calcd for $C_{14}H_{14}O_3$: C, 68.28; H, 5.72. Found: C, 68.23; H, 5.63.

**5-Bromo-4-ethyl-3-methyl-2(5*H*)-furanone (2c).**—Glacial acetic acid (15 ml) containing HBr gas (40% by weight) was added to a small flask containing **1a** (1 g, 7.04 mmol). The flask was sealed for 5 days at room temperature. The solvent was rotary evaporated at 40° and the residue was azeotroped five times with toluene in order to remove residual HBr. The final product contained only **2c** by tlc (solvent 1, $R_f$ 0.7): pmr ($CCl_4$) $\delta$ 6.79 (b s, 1, $C_5$ H), 1.90 (s, 3, $C_3$ $CH_3$), 2.57 (q, 2, $-CH_2-$), 1.20 (t, 3, $J$ = 7.5 Hz, $CH_3$).

**5-Chloro-4-ethyl-3-methyl-2(5*H*)-furanone (2d).**—Furanone **1a** (0.14 g, 0.96 mmol) was dissolved in distilled ethylene dichloride, and a solution of titanium tetrachloride (0.99 mmol) in ethylene dichloride (3 ml) was added. The reaction mixture was refluxed for 5 hr, during which time a white solid precipitated. Methylene chloride and water were added, dissolving the solid. The organic layer was washed with water and dried ($Na_2SO_4$). The solvent was evaporated, giving a liquid product (yield 84%), which was chromatographically pure by tlc (solvent 1, $R_f$ 0.7): ir ($CCl_4$, P-E) 1792 (s, C=O), 1686 $cm^{-1}$ (w, C=C); pmr ($CCl_4$) $\delta$ 6.48 (b s, 1, $C_5$ H), 1.87 (s, 3, $C_3$ $-CH_3$), 2.57 (q, 2, $-CH_2-$), 1.21 (t, 3, $J$ = 7.5 Hz, $CH_3$).

**5-Hydroxy-2(5*H*)-furanone (1b).**—This procedure is a modification of the photooxygenation of furfural as described by Schenck[13,15] and Grove[16] and coworkers. Our procedure gave a different major product, the 5-hydroxy analog **1b** rather than 5-ethoxy-2(5*H*)-furanone.[39]

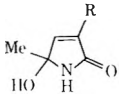
A solution of freshly distilled furfural (90.5 g) in absolute ethanol (850 ml) containing rose bengal (1.3 g)[40] was photolyzed in the presence of a vigorous stream of oxygen. An external ice bath was used to keep the temperature of the reaction between 25 and 32°. The reaction was monitored by removing aliquots and determining the loss of uv absorption at 276 nm. After about 6 hr, a 97% decrease in absorption was observed. The solvent was evaporated and an acidic red syrup was obtained. On the addition of carbon tetrachloride (150 ml), an orange-colored crystalline product (50 g) precipitated and was filtered.[41] Product **1b** was purified on a silica gel column (150 g) using methylene chloride as eluent. The eluate, upon evaporation, gave an almost colorless syrup, which crystallized on addition of chloroform. After recrystallization from chloroform, the yield of **1b** was 43%: mp 56–58° (lit.[13] mp 58–59°); ir ($CCl_4$) shoulder 1786, 1757 $cm^{-1}$ (s) (lit.[13] ir 1795, 1761 $cm^{-1}$); mass spectrum *m/e* (rel intensity) 101 (12), 100 (12), 85 (10), 72 (14), 55 (55), 29 (23), 27 (39), 18 (11). The pmr data of **1b** ($CDCl_3$) agreed with those reported by Catala and Defaye.[42]

**A. 5-Bromo-2(5*H*)-furanone (2e) *via* Pyrocatecholphosphorus Tribromide (5).**—The furanone **1b** (3 g, 30 mmol), dissolved in methylene chloride (20 ml), was placed in a three-necked flask fitted with a condenser and $CaCl_2$ tube. Powdered molecular sieve (3A, 15 g) was added. The suspension was stirred and **5** (12.1 g, 31 mmol) in methylene chloride (20 ml) was added dropwise. The reaction mixture was refluxed for 1.8 hr. (HBr was evolved vigorously near the end of the reaction.) Upon filtration of the reaction mixture, a bright orange filtrate was obtained, which was rapidly washed with 400-ml aliquots of cold, saturated $NaHCO_3$ solution two times and then with water. The organic layer was dried ($MgSO_4$) and evaporated, giving a pale yellow syrup (4.3 g), which was distilled bulb to bulb using a Kugelrohr distilling apparatus and gave a colorless liquid (1.0 g), bp 96–102° (12 mm) [lit.[17] bp 69–70° (0.1 mm)]. The distillate showed two spots at $R_f$ 0.6 and 0.75 (tlc solvent 4) corresponding to product **2e** (92%) and addition products **3** (8%). (The relative per cents of products were determined from pmr integration data.) The yield of **2e** in the mixture was 18%. (The crude product darkens rapidly if not kept under refrigeration.) A pure sample of **2e** was obtained using a silica gel column with cyclohexane–benzene (1:1) as eluent. The ir spectrum of **2e** ($CCl_4$) exhibited a strong band at 1805 $cm^{-1}$ (C=O, lactone); pmr ($CCl_4$) $\delta$ 7.08 (t, 1, $J_{3,5} = J_{4,5} = 1.3$ Hz, $C_5$ H), 7.80 (dd, 1, $J_{3,4} = 5.5$, $J_{4,5} = 1.3$ Hz, $C_4$ H), 6.35 (dd, 1, $J_{3,4} = 5.5$, $J_{3,5} = 1.3$ Hz, $C_3$ H).

**B. Identification of 3,4-Dibromobutanolides 3.**—In other preparations of **2e**, the per cent of 1,4-addition products **3** was higher, varying from 10 to 50%, than in the above distillate. Products **3** were isolated as follows. A silica gel column (20 g) was prepared with benzene. A 50% mixture of **2e** and **3** (2.8 g) was dissolved in benzene and applied to the column. Benzene was used as the eluent and 5-ml fractions, which were monitored by tlc, were taken. Fractions 4 and 5 contained mostly compounds **3**. These fractions were combined and gave, after evaporation, a liquid product (1.4 g), ir ($CCl_4$) 1825 $cm^{-1}$ (s). From pmr integration, the liquid contained 88% of **3** and 12% of **2e**.

(38) W. Rigby, *Chem. Ind. (London)*, **18**, 1508 (1969).

(39) Why the 5-hydroxyfuranone **1b** is the predominant product in our reaction is not clear. However, the presence of **1b** in the photolysis reaction is not wholly unexpected. Recently it has been found that in the photooxygenolysis of 2-methylpyrrole, where intermediates analogous to those in the furan series[13,15] have been proposed, the predominant products are the 5-hydroxylactams II: D. A. Lightner and L. K. Low, *J. Heterocycl. Chem.*, **9**, 167 (1972).




II, R = H, Me

(40) Eosin could be substituted for rose bengal, although the photooxygenation took longer (20 hr, 85% reaction).

(41) The carbon tetrachloride was evaporated from the filtrate and a residue was obtained, which upon distillation gave 1.0 g of 5-ethoxy-2(5*H*)-furanone, bp 95–97° (12–14 mm) [lit.[13] bp 95° (12 mm)]. The pmr data for this derivative were identical with those kindly supplied by Dr. Michael D. Grove, U. S. Department of Agriculture, Agriculture Research Service, Peoria, Ill.

(42) F. Catala and M. J. Defaye, *C. R. Acad. Sci., Ser. C*, 4094 (1964).

The pmr spectrum ($CCl_4$) exhibited multiplet patterns in three regions (disregarding signals due to **2e**): 391–397 (four peaks), 278–300 (eight peaks), and 180–207 Hz (eight peaks). The relative intensity of absorption in the three regions was 1:1:1.7. Other products in the mixture besides **2e** and **3** have not been ruled out. Fractions 6–8 contained mostly **2e** (purity 97%). On evaporation 1.0 g of liquid product was obtained.

**3,4-Dibromobutanolides 3 *via* HBr–Acetic Acid.**—To furanone **1b** (3 g) was added ethylene dichloride (60 ml) and glacial acetic acid containing HBr gas (40%, 16 ml). The flask was sealed and pressure was applied to the glass stopper to prevent escape of HBr. The reaction mixture was allowed to stand at room temperature for 6 hr. Carbon tetrachloride (150 ml) was added and a yellow oil separated. The layers were washed with cold water and saturated $NaHCO_3$ and again with water. After the organic layer was dried and the solvent was evaporated, a colorless residue (3.4 g) was obtained. Distillation of the residue gave dibromobutanolides **3** [0.88 g, bp 69–76° (0.7 mm)], ir ($CCl_4$) 1825 $cm^{-1}$ (C=O). The presence of small amounts of other products in this sample was not ruled out. The sample exhibited a single spot ($R_f$ 0.73) in tlc solvent 4. The pmr spectrum ($CCl_4$) showed multiplets in three regions: 394–400 (five peaks), 287–297 (four peaks), and 186–200 Hz (six peaks); the relative intensity of absorption in the three regions was 1:1:2. In the mass spectrum no parent peak ($m/e$ 242) was observed for **3**. Major even-electron ion peaks were present at $m/e$ (rel intensity) 163 (100, M − Br), 135 (23), 119 (38), 107 (38). According to the intensity of the P + 2 peaks, each of the ions contained one bromine atom. Butanolides **3** gave off HBr and darkened at room temperature and were more stable under refrigeration.

**Method A. 5-Bromo-3,4-dichloro-2(5*H*)-furanone (2g).**—A mixture of mucochloric acid (**1c**, 11.9 mmol), powdered molecular sieve (5 g), and methylene chloride (10 ml) was treated with tribromide **5** (14 mmol) in 20 ml of methylene chloride. The mixture was kept at room temperature for 3 hr and worked up as in the preparation of **2e**. The residual liquid (1.8 g) was distilled [111–116° (12 mm)], giving the bromofuranone **2g** in 55% yield, ir ($CCl_4$) 1815 $cm^{-1}$, pmr ($CCl_4$) $\delta$ 6.92 (s, $C_5$ H).

**Method B. 2g *via* HBr–Acetic Acid.**—The acid **1c** (2.97 mmol) was placed in a small flask and about 1 ml of HBr–acetic acid (40%) was added. The flask was sealed. After 3 days at room temperature, carbon tetrachloride (40 ml) was added to the bright yellow reaction mixture. The organic layer was washed with cold $NaHCO_3$ solution and water and dried ($MgSO_4$). Upon evaporation, a residue (0.39 g) was obtained, which was distilled [60–66° (0.7 mm)] to give 0.29 g of product, ir ($CCl_4$) 1815 $cm^{-1}$ (s). In a latter reaction (see Preparation B for **8c**), this product was shown to contain a dibromofuranone along with the major component **2g**.

**5-(1,2-Dihydro-2-oxo-4-methoxypyrimidin-1-yl)-4-ethyl-3-methyl-2(5*H*)-furanone (8a).**[9]—To furanone **2c** (7.04 mmol) and methylene chloride (10 ml) in a small flask equipped with a $CaCl_2$ tube, 2,4-dimethoxypyrimidine (7.2 mmol) was added. The reaction mixture was stirred for 7 days. Tlc analysis indicated that all starting materials had been consumed. The solvent was removed and the white residue was rubbed with petroleum ether and filtered. The product **8a** (1.6 g) was recrystallized from ethyl acetate and gave colorless needles: mp 188–195° (yield 75%); ir (KBr, P-E) broad 3472 (m), 2941 (m), 1777 (s), broad 1675 (s), 1643 $cm^{-1}$ (s); uv max (50% EtOH) 275 nm ($\epsilon$ 6100), min 246 (3000); pmr, see Table I; high-resolution mass spectrum $m/e$ 250.09460 (calcd 250.09535), selected peaks and assignments $m/e$ 235.07143 (M − $CH_3$), 221.09182 (M − CHO), 125.03459 (M − $C_7H_9O_2$), and 125.05865 (M − $C_5H_5O_2N_2$). Using tlc solvent 3, compound **8a** had $R_f$ 0.79 (2,4-dimethoxypyrimidine, $R_f$ 0.88).

*Anal.* Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.63; N, 11.20. Found: C, 57.76; H, 5.65; N, 10.96.

**5-(Uracil-1-yl)-4-ethyl-3-methyl-2(5*H*)-furanone (9a).**[9]—Compound **8a** (1.8 g, 7.2 mmol) was dissolved in warm 50% ethanol (50 ml). The solution was cooled and 5.5 ml of 1 *N* HCl was added. Precipitation of product occurred immediately. The reaction was refrigerated overnight. Upon filtration 1.0 g of **9a**, mp 162–166°, was obtained. The mother liquor gave additional product, bringing the total yield to 91%. Recrystallization of **9a** from water gave mp 165–168°; ir (KBr, P-E) broad 3380 (m), 3045 (m), 1768 (s), broad 1687 (s), broad 1632 $cm^{-1}$ (s); uv max (pH 3–7) 255 nm ($\epsilon$ 9800), min 229 (7600); mass spectrum $m/e$ (rel intensity) 236 (16), 207 (3), 125 (100), 41 (55); pmr, see Table I. Using tlc solvent 3, **9a** had $R_f$ 0.73 (**8a**, $R_f$ 0.81).

*Anal.* Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.85. Found: C, 55.79; H, 5.00; N, 11.79.

**Method A. 5-(1,2-Dihydro-2-oxo-4-methoxypyrimidin-1-yl)-2(5*H*)-furanone (8b).**[9]—Furanone **2e** (0.9 g, 5.5 mmol) in dry methylene chloride (8 ml) was allowed to react with 2,4-dimethoxypyrimidine (0.8 g, 5.7 mmol) using the method described for analog **8a**. The reaction was completed in 1 day. Washing the solidified reaction mixture with petroleum ether and ethyl acetate gave the product (0.85 g, mp 161–165°). Recrystallization from ethyl acetate gave colorless platelets: mp 168–173° (yield 53%); ir (KBr, P-E) broad 3490 (m), broad 3062 (m), shoulder 1787, broad 1657 (s), broad 1622 $cm^{-1}$ (s); uv max (50% EtOH) 274 nm ($\epsilon$ 5600), min 241 (1800); mass spectrum $m/e$ (rel intensity) 208 (33), 179 (24), 127 (100), 83 (54), 70 (14), 27 (16); pmr, see Table I. Using tlc solvent 3, compound **8b** had $R_f$ 0.52.

**Method B.**—Reaction of 5-chlorofuranone **2f**[13] (0.3 g, 2.6 mmol) with 2,4-dimethoxypyrimidine (0.4 g) at 50–60° under house vacuum for 6 days gave a black residue. The product was purified on a small silica gel column using methylene chloride as eluent, and 15-ml fractions were taken. Tubes 20–30, containing **9b**, were combined and the solvent was evaporated. The white crystals of **9b** were recrystallized from ethyl acetate (yield 29%, mp 165–170°). Uv, ir, pmr, and tlc data were identical with those given under method A.

**5-(Uracil-1-yl)-2(5*H*)-furanone (9b).**[9]—Compound **8b** (0.28 g, 1.4 mmol) in 50% methanol was stirred with 1 *N* HCl (1.4 ml) for 1 day at room temperature. Colorless prisms of **8b** (yield 58%) precipitated and their purity was determined using tlc solvent 3, $R_f$ 0.38 (analog **8b**, $R_f$ 0.47). Product **9b** was recrystallized from water: mp 242–246°; ir (KBr, P-E) broad 3490 (w), 3044 (w), 1803 (s), 1774 (m), broad 1702 (s), 1626 $cm^{-1}$ (m); uv max (pH 3–7) 255 nm ($\epsilon$ 9800), min 229 (3800); at pH 13 compound was unstable, max 240–280 (6200); mass spectrum $m/e$ (rel intensity) 194 (15), 165 (10), 83 (100), 27 (19); pmr, see Table I.

*Anal.* Calcd for $C_8H_6N_2O_4$: C, 49.49; H, 3.12; N, 14.43. Found: C, 49.23; H, 3.06; N, 14.20.

In order to test the stability of the N–C bond, compound **9b** (8 mg) was boiled in water (5 ml) for 15 hr. Using tlc solvents 2 and 3, the reaction revealed two spots of equal intensity corresponding to uracil and starting material **9b**.

**Preparation A. 5-(1,2-Dihydro-2-oxo-4-methoxypyrimidin-1-yl-3,4-dichloro-2(5*H*)-furanone (8c).**[9]—Furanone **2f** (0.92 g, 3.3 mmol) in dry methylene chloride (5 ml) was stirred with 2,4-dimethoxypyrimidine (0.63 g, 4.5 mmol) for 10 days at room temperature, using the method described for compound **8a**. The reaction slowly turned amber-colored and a small amount of solid precipitated. The solvent was evaporated and the dark brown residue was rubbed with ethyl acetate. Filtration gave product **8c** as an off-white, crystalline solid, mp 210–214° dec (yield 23%). Recrystallization of the compound from 95% ethanol gave 123 mg of colorless crystals: mp 219–228° dec; ir (KBr) broad 3550 (m), 3010 (m), 1805 (s), 1686 (s), 1639 $cm^{-1}$ (s); uv max (50% EtOH) 268 nm ($\epsilon$ 6300), 231 (12,900); at pH 0 cleavage of N–C bond occurred, max 231 nm ($\epsilon$ 12,900); high-resolution mass spectrum $m/e$ 275.97070 (calcd 275.97046, 65%), selected peaks and assignments, $m/e$ 246.96256 (M − CHO), 240.99541 (M − Cl), 213.00287 (M − COCl, 100%), 150.93488 (M − $C_5H_5N_2O_2$), and 125.03491 (M − $C_4HO_2Cl_2$); tlc, solvent 3, **8c** had $R_f$ 0.82 (2,4-dimethoxypyrimidine, $R_f$ 0.89).

*Anal.* Calcd for $C_9H_6N_2O_4Cl_2$: N, 10.11; Cl, 25.55. Found: N, 10.05; Cl, 25.66.

**Preparation B. Detection of Bromochlorofuranone Analogs 14 (or 15).**—Furanone **2f** (1.25 mmol), prepared by method B, was stirred with 2,4-dimethoxypyrimidine (1.26 mmol) in methylene chloride (3 ml) as described in preparation A. The reaction gave an off-white solid (0.1 g), which was recrystallized from 95% ethanol. The ir, tlc, and uv data were identical with those reported for compound **8c**. However, the elemental analysis showed the presence of bromine.

*Anal.* Calcd for sample containing $C_9H_6Cl_2N_2O_4$ (87.3%) + $C_9H_6BrClN_2O_4$ (12.7%): C, 38.61; H, 2.15; N, 9.94; Br, 3.16. Found: C, 38.08; H, 2.35; N, 9.81; Br, 3.16.

The mass spectral data supported the $C_9H_6N_2O_4BrCl$ structure **14** (or **15**). The contaminant **14** (or **15**) gave a weak peak at $m/e$ 320 (1.5%) [M]. A weak peak at $m/e$ 195 (8%) was observed and was attributed to the bromochloro analog of ion **10c** ($m/e$ 151). The existence of these bromochloro ions was supported by the relative intensities of the halogen isotope peaks. The

major peaks in the spectrum were due to the dichloro derivative **8c**: mass spectrum *m/e* (rel intensity) 276 (92), 241 (91), 213 (97), 151 (100).

**Acid Hydrolysis of 8c.**—The procedure used for **9b** was followed. Compound **8c** (50 mg) was stirred with 1 *N* HCl (0.2 ml) in 50% methanol (25 ml) for 24 hr. Spectral patterns indicated that N–C bond cleavage had occurred: uv (water) max 252–255 nm, shoulder 235 nm, min 224 nm; uv (acid) max 235 nm, shoulder 255 nm, min 220 nm. The reaction mixture was treated with ion exchange resin (acetate form), which removed most of the mucochloric acid (**1c**). Using the tlc solvent 5, the resin-treated solution showed three uv-absorbing spots at $R_f$ 0.55 (uracil, $R_f$ 0.55), 0.87 (**8c**, $R_f$ 0.89), and 0.67 (**1c**, $R_f$ 0.65). The uracil spot was very intense and the other spots were faint. Upon concentration of the solution to 1 ml, uracil (5 mg) precipitated, mp 330° dec. The melting point, uv, and ir data were identical with those of authentic uracil.

**Method A. 5-(6-Amino-9*H*-purin-9-yl)-4-ethyl-3-methyl-2(5*H*)-furanone (11) and Isomer 12a.**—To a flask containing dry adenine (4.1 g, 30.4 mmol), anhydrous $K_2CO_3$ (4.2 g, 30.1 mmol), dry DMF (190 ml), and a magnetic stirring bar was added furanone **2c** (28.3 mmol) in DMF (10 ml). The reaction mixture, which was protected from moisture by a $CaCl_2$ tube, immediately developed a yellow color. After stirring at room temperature for 3 days, the reaction mixture was filtered. The white solid obtained contained adenine[43] and salts. The yellow filtrate was evaporated and a light orange residue (11.9 g) was obtained. The residue was treated with hot acetone (200 ml) and filtered. The acetone insolubles (2.4 g), a cream-colored solid, contained adenine[43] and salts. Upon evaporation of the filtrate, an orange residue was obtained. This residue was extracted with methylene chloride (35 ml) and filtered. (The methylene chloride filtrate A was saved for later isolation of isomer **12a**.) The methylene chloride insolubles, an off-white solid (2.7 g), contained product **11** contaminated with small amounts of adenine and isomer **12a**, which were removed as follows.

The 2.7-g mixture was dissolved in warm acetone (400 ml) and passed through a 100-g silica gel column. The uv-absorbing fractions were collected and the solvent was evaporated. A white, crystalline solid (2.3 g, mp 210–220° dec) was obtained. By uv spectrometry, the solid was composed of a mixture of **11** (92%) and **12a** (8%). The solid was dissolved in hot methanol (300 ml) and treated with a methanolic solution of picric acid (2.1 g). The picrate of **11** precipitated and was collected, 3.7 g, mp 252–258° dec.

*Anal.* Calcd for $C_{18}H_{16}N_8O_9$: N, 22.73. Found: N, 22.94.

The methanolic filtrate B was saved for the isolation of **12a**. The picrate of **11** was dissolved in aqueous acetone (50%) and the solution was passed through an ion exchange column (acetate form). Evaporation of the uv-absorbing eluate gave a white solid, which was recrystallized from 95% ethanol. Colorless crystals of **11** precipitated (yield 22% based on adenine): mp 187–190°; ir (KBr, P-E) 3289 (m), 3115 (m), 2907 (w), 1773 (s), 1661 (s), 1600 $cm^{-1}$ (s); uv max (pH 7.5) 258 nm ($\epsilon$ 14,600), pH 0 max 257 (14,800); at pH 14 compound decomposed, max 262 (22,000); pmr, see Table I; mass spectrum, see Table II.

TABLE II

COMPARISON OF LOW-RESOLUTION MASS SPECTRAL DATA FOR ISOMERS 11 AND 12a

| Common peaks[a] | Unique peaks, **11** | Unique peaks, **12a** |
|---|---|---|
| 259 (36/47), 258 (2/30) | 125 (32) | 244 (10) |
| 230 (9/36), 202 (11/16) | 124 (33) | 242 (6) |
| 136 (40/11), 135 (21/11) | | 241 (3) |
| 108 (18/6), 97 (11/6) | | 216 (13) |
| 81 (23/8), 53 (21/19) | | 229 (100) |
| 41 (100/62), 39 (20/22) | | 162 (63) |
| 28 (26/37), 18 (8/90) | | 119 (11) |

[a] *m/e* (rel intensity **11**/**12a**).

*Anal.* Calcd for $C_{12}H_{13}N_5O_2$: C, 55.59; H, 5.05; N, 27.01. Found: C, 55.42; H, 5.36; N, 26.87.

Derivative **11** was subjected to rapid paper electrophoresis (200 V, 41 mA) using an organic pH 3.3 buffer. After 2 hr, the spot of **11** was visualized under uv light and had a cathodic migration of +13 mm (adenine, +46 mm). The isolation of isomer **12a** from the above filtrates A and B is discussed below.

Most of the solvent, but not all, was evaporated from the picrate filtrate B. Aqueous acetone (40 ml) was added to the residue. The resulting solution was passed through an ion-exchange column (acetate form). The uv-absorbing fractions were evaporated. The white residue was suspended in ethanol (10 ml) and filtered. White crystals of the diazepino derivative **12a** (0.14 g, 2%) were obtained. The compound was recrystallized from 85% ethanol (yield 0.104 g): mp 236–241° eff; ir (KBr, P-E) 3280 (m), 3004 (m), 2833 (w), 1712 (s), 1682 $cm^{-1}$ (s); high-resolution mass spectrum *m/e* 259.1060 (calcd 259.1042, 70%); selected peaks (assignments, rel intensity) were *m/e* 258.0985 (M − H, 80%), 244.0828 (M − $CH_3$, 40%), 241.0960 (M − $H_2O$, 40%), 230.1032 (M − CHO, 20%), 230.0673 (M − $C_2H_5$, 100%), 216.0890 (M − $C_2H_3O$, 40%), 215.0924 (M − $CH_2NO$, 20%), 162.0410 (M − $C_6H_9O$, 70%) 135.0541 (M − $C_7H_6O_2$, 50%), 119.0360 (M − $C_7H_{10}NO_2$, 60%); uv max (pH 0) 292 nm ($\epsilon$ 21,200), 209 (23,700), min 252 (5700); pH 3–7 max 290 (16,800), 207 (23,400); at pH 13 the compound decomposes slowly, max 295 (10,900); after 24 hr, max 271 (14,300); pmr data, see Table I; low-resolution mass spectral data, see Table II. Using tlc solvent 2, derivative **12a** had an $R_f$ of 0.57 (isomer **11**, $R_f$ 0.78).

*Anal.* Calcd for $C_{12}H_{13}N_5O_2$: C, 55.59; H, 5.05; N, 27.01. Found: C, 55.52; H, 5.14; N, 27.06.

The methylene chloride filtrate A contained derivative **12a** as detected by uv spectrometry: uv (50% ethanol) max 287 nm, min 245 nm. Absorption was also observed at 315–320 nm, suggesting the presence of unknown product(s). Filtrate A was evaporated and an orange glass (2.8 g) was obtained. The glass was dissolved in acetone and the solution was applied to a 100-g silica gel column in an attempt to separate the mixture. Acetone was used as the eluent, and 15-ml fractions were taken. As analyzed by tlc (solvent 2), fractions 13–17 contained two unknown uv-absorbing components at $R_f$ 0.93 (X) and 0.89 (Y). Fraction 18 contained four components, $R_f$ 0.93 (X), 0.89 (Y), 0.77 (**11**), and 0.65 (Z). Fractions 21–27, which contained mostly **12a** ($R_f$ 0.55) with small quantities of compounds **11** and Z, were combined and concentrated to dryness. The white residue was crystallized from acetone and gave 132 mg of compound **12a**. As analyzed by tlc, fractions 27–40 contained only **12a**. These fractions were combined and gave 180 mg of **12a**. The total isolable yield of **12a** was 6%.[44] No attempt was made to determine the structures of unknowns X, Y, Z.

**Method B. Adenyl Compound 11 from 6-Benzamido Analog 13.**—The benzamidopurine analog **13** (0.026 g) was dissolved in ethanol (8 ml) and the solution was refluxed with picric acid (0.050 g) for 2 hr. The picrate of **11** precipitated and was filtered. Yellow crystals (0.029 g, yield 80%) were obtained, mp 250–257° dec. The picrate was converted to the free base (mp 187–189°) in high yield by the resin treatment described in method A. The ir, uv, and tlc properties of the product were identical with those of **11**.

**Hydrolysis of 11 in Alkali.**—The adenyl analog **11** (84 mg) was dissolved in warm 1 *N* sodium hydroxide. The solution was subjected immediately to rapid paper electrophoresis (200 V, 16 mA, 1.25 hr, pH 3.3). After the paper was dried, a single spot was observed under uv light (cathodic migration +47 mm) which corresponded to adenine (+48 mm). A reference sample of analog **11** had a migration of +15 mm. After 0.5 hr the pale yellow reaction mixture[45a] was neutralized with formic acid to pH 7.6. The solution was concentrated to about 3 ml, whereupon 29 mg (66%) of adenine precipitated. (Uv, ir, and melting point data of the sample were identical with those of authentic adenine.) The filtrate from adenine had ultraviolet patterns in water and alkali showing that mostly furanone **1a** was present together with a small amount of adenine: uv (water) max 260 nm (OD 0.80); uv max ($OH^-$) 260 nm (OD 1.46).[45b]

(43) By uv spectrometry, the total amount of adenine recovered was 1.4 g (35%).

(44) In another preparation it was found from the uv extinction that filtrate A contained only a small amount of uv-absorbing material, about 13% of **12a**. Most of the material in filtrate A was either non-uv-absorbing or absorbed below 260 nm, explaining the low yield of **12a** obtained on chromatography of the 2.8 g.

(45) (a) On increasing the reaction time, the solution turned progressively darker yellow. Samples of furanone **1a** behaved similarly in alkaline solutions. (b) Ultraviolet absorptions of compound **1a** in water, max 218 nm ($\epsilon$ 9670); in 1 *N* NaOH, max 256 nm ($\epsilon$ 9730), min 224 nm ($\epsilon$ 4000).

**8-Ethyl-7-hydroxy-9-methyl-3*H*-[1,3]diazepino[2,1-*i*]purin-10-(7*H*)-one (12a).**—To a flask containing adenine (0.49 g, 3.6 mmol) and pyridine (10 ml) was added furanone **2c** (7.04 mmol) in pyridine (1 ml). The reaction mixture turned dark amber in color on heating. After 6 hr of refluxing, the reaction was cooled and quenched with ethanol (1 ml). The pyridine was evaporated, giving a dark amber residue, which was first azeotroped with 50% ethanol to get rid of the residual pyridine, and finally with absolute ethanol to remove the water. The residue was rubbed with chloroform. The procedure gave a pale yellow solid, 0.47 g (50%), mp 230–240°. The crude product was recrystallized from 95% ethanol. Colorless crystals (0.3 g) were obtained, mp 237–243° eff. The compound gave ir, uv, pmr, and tlc data identical with those of compound **12a** isolated in method A.

The mother liquor from the 0.47-g product was spotted in tlc, solvent 2. Five spots were observed at $R_f$ 0.9, 0.77, 0.58, 0.42 and 0.14; the last was the most intense. The compounds with $R_f$ 0.77, 0.58, and 0.14 were probably compounds **11**, **12a**, and adenine, respectively. No attempt was made to determine the structures of the two unknowns.

**Hydrolysis of 12a in Alkali.**[46]—Derivative **12a** (92 mg) was refluxed in 1 *N* sodium hydroxide (6 ml) for 3 hr. During this time, an intense orange color developed. The uv data in water exhibited max 266 nm (ε 11,500), min 231 (5060), shoulder 275. A broad maximum was also observed at 320 nm that had 23% of the absorption of the 266-nm max. The reaction mixture was cooled and subjected to paper electrophoresis (200 V, 18 mA, 0.75 hr, pH 3.3). After the paper was dried, two spots with cathodic migration were observed under uv light. A uv-absorbing spot corresponded to adenine (+22 mm). The other, a fluorescent pink spot (+5 mm), was due to unknown product(s). (In visible light a brown or pink spot was observed at +5 mm. A reference sample of analog **12a** was visualized as a uv spot at the origin.) The pH of the reaction mixture was adjusted to 7.6 with formic acid. An ethanolic solution of picric acid was added. Needles of adenine picrate precipitated (46 mg, 35%, mp 285° dec). The picrate was dissolved in 50% ethanol and treated with ion exchange resin (acetate form). The solution was evaporated to 3 ml, whereupon crystalline adenine (10 mg) precipitated. The mother liquor from adenine picrate was freed of picric acid with acetate resin. The uv spectrum of this solution in water exhibited max 255 nm (OD 0.35), broad shoulder 310–330 (OD 0.10). Attempts made to isolate other products of the reaction failed.

**7-Chloro-8-ethyl-3,7,10,11-tetrahydro-9-methyl-10-oxo[1,3]diazepino[2,1-*i*]purin-6-ium Chloride (12b).**—The diazepino derivative **12a** (91 mg) was added to a flask containing thionyl chloride (2 ml) and fitted with a $CaCl_2$ tube. Solution occurred. The reaction was allowed to stand at room temperature overnight. Colorless, iridescent crystals precipitated, which were filtered and washed with ether. The yield of **12b** was 88%: mp 204–210°, red, partial melting, 265° char; mass spectrum *m/e* (rel intensity) 277 (M − HCl, 100), 242 (100), 239 (51), 214 (100), 119 (25), 38 (100); ir (KBr) 1739 (s), 1603 (s), broad 1468 $cm^{-1}$ (s). The uv spectrum of the compound was very similar to that of precursor **12a** in acid, base, and water. Treatment of the salt **12b** with water immediately converted it back to precursor **12a**.

*Anal.* Calcd for $C_{12}H_{12}ClN_5O \cdot HCl$: N, 22.29; Cl, 22.57. Found: N, 22.20; Cl, 21.29.

**Method A. 8-Ethyl-7-methoxy-9-methyl-3*H*-[1,3]diazepino-[2,1-*i*]purin-10(7*H*)-one (12c).**—To a solution of the salt **12b** (160 mg, 0.51 mmol) in absolute methanol was added 2 equiv of sodium methoxide. (The total volume of the reaction was about 5 ml.) After the reaction mixture was refluxed for 1 hr, the solvent was removed and a white solid was obtained, which was extracted into chloroform. The organic layer was washed with water, dried ($Na_2SO_4$), and evaporated, giving a white solid, which was crystallized from methanol–ether (1:1). The yield of **12c** was 63%: mp 127–146°; ir (KBr) broad 3333 (s), broad 3125 (s), broad 2959 (s), 1724 (s), 1600 (s), 1553 (s), 1458 $cm^{-1}$ (s); high-resolution mass spectrum *m/e* 273.1240 (calcd 273.1226, 13%), 274.1304 (calcd 274.1226, M + H, 100%); uv max (50% EtOH) 289 nm (ε 13,800), 207 (21,600), min 258 (5100); pmr, see Table I.

*Anal.* Calcd for $C_{13}H_{15}N_5O_2$: C, 57.13; H, 5.53; N, 25.64. Found: C, 57.18; H, 5.47; N, 25.55.

**Method B.**—The salt **12b** (175 mg, 0.56 mmol) was refluxed in methanol (5 ml) containing triethylamine (2 equiv) for 2 hr. The solvent was removed and a white solid was obtained. Trituration of the solid with ethyl acetate gave a theoretical yield of crystalline triethylamine hydrochloride. The ethyl acetate was evaporated and product **12c** was crystallized as in the above preparation. The yield of **12c** was 28%, mp 129–146°.

**7-Ethoxy-8-ethyl-9-methyl-3*H*-[1,3]diazepino[2,1-*i*]purin-10-(7*H*)-one (12d).**—The procedure used in method A for the 7-methoxy analog **12c** was followed. An ethanolic solution of the salt **12b** (60 mg, 0.23 mmol) was treated with sodium methoxide (2 equiv). The yield of **12d** was 43%: mp 145–150°; high-resolution mass spectrum *m/e* 287.1382 (calcd 287.1382, 2%), 288.1474 (calcd 288.1460, M + H, 100%); ir (KBr) broad 3195 (s), 2985 (s), 1733 (s), 1597 (s), 1555 (s), 1456 $cm^{-1}$ (s). Using tlc solvent 2, the 7-methoxy (**12c**), -ethoxy (**12d**), and -hydroxy (**12a**) derivatives had $R_f$ 0.7, 0.72, and 0.59, respectively.

**5-(6-Benzamido-9*H*-purin-9-yl)-4-ethyl-3-methyl-2(5*H*)-furanone (13).**—6-Benzamidochloromercuripurine[47] (2.5 g, 5.26 mmol), dried Celite (1 g Manville filtering aid), and dry toluene (210 ml) were added to a three-necked flask equipped with a stirrer, condenser, $CaCl_2$ tube, and take-off head. The suspension was refluxed and 100 ml of toluene was removed. The suspension was cooled to 60° and the furanone **2c** (5.98 mmol) in 10 ml of dry toluene was added. The yellow-colored reaction mixture was refluxed for 3.5 hr, then cooled and filtered. A pale yellow solid was obtained. Evaporation of the filtrate gave a yellow, sticky solid. All the solids from the reaction were combined and extracted with warm chloroform (125 ml). Filtration gave a white, Celite-containing solid (1.68 g), which was discarded. The filtrate was washed with 30-ml portions of a 30% KI solution eight times and then with water twice. The solution was dried ($MgSO_4$) and evaporated, giving a yellow glass. The glass was rubbed with ether and a powdery yellow solid M (1.3 g) was obtained, mp 50–100° eff, uv max (50% ethanol) 280 nm (ε 13,700), shoulder 320 (2850). In solid M three compounds were detected by tlc solvent 2. These were the product **13** ($R_f$ 0.54), the unknown R ($R_f$ 0.8) and 6-benzamidopurine ($R_f$ 0.32). The most intense spot was due to the product **13**. Solid M was purified by using a 60-g silica gel column with benzene–ethyl acetate (85:15) as eluent. Fractions (10 ml) were taken and monitored in tlc solvent 2. In combined fractions 19–39, two compounds, **13** ($R_f$ 0.59) and R ($R_f$ 0.8), were detected. Fractions 40–63 contained only **13** ($R_f$ 0.59). Removal of the solvent from fractions 40–63 gave a colorless syrup. The syrup was dissolved in benzene (15 ml) and cyclohexane was added until turbidity. Colorless, hairlike crystals of **13** precipitated. The crystals were filtered and washed with ether, 129 mg, mp 110°. Fractions 19–39 were evaporated and the residue, crystallized in the above manner, gave **13** (109 mg), mp 105° eff. The total yield of chromatographically pure compound **13** was 16%. The compound was recrystallized from benzene–cyclohexane for analysis. It was found that benzene–cyclohexane solvent was difficult to remove from **13**. The sample was dried at 80° (1 mm): mp 100–130°, 139° eff; ir (KBr, P-E) 3175 (w), 3058, 2900, 1770 (s), 1695, 1613, 1582 $cm^{-1}$; mass spectrum *m/e* (rel intensity) 363 (10), 334 (33), 240 (5), 125 (24), 105 (100), 77 (100), 40 (50), 29 (12); uv max (50% EtOH) 280 nm (ε 23,000), max (pH 1) 290 (26,300).

*Anal.* Calcd for $C_{19}H_{17}N_5O_3$: C, 62.80; H, 4.71; N, 19.27. Found: C, 63.03; H, 4.87; N, 18.80. The low nitrogen and high carbon suggested the presence of a small amount of cyclohexane. The pmr spectrum (Table I) confirmed the presence of cyclohexane.

In connection with the unknown compound R also formed in this reaction, fractions 16–18 from the silica gel column were evaporated and gave a colorless syrup (25 mg). Using tlc solvent 2, this sample gave one spot at $R_f$ 0.8. Attempts to crystallize the compound failed. The uv spectrum of R (95% ethanol) exhibited a maximum at 303 nm and a minimum at 266 nm. These data suggest that the compound is a purine derivative.

**Acknowledgment.**—The authors are indebted to Dr. Robert B. Fairweather for his help in mass spectra interpretation.

(46) It was hoped that this experiment would give unequivocal proof of structure **12a** *via* isolation of diazepino ring cleavage purine product(s). However, adenine was the only product isolable. The experiment does not exclude the possibility that these products may be obtainable under less stringent hydrolysis conditions.

(47) J. Davoll and B. A. Lowy, *J. Amer. Chem. Soc.*, **73**, 1650 (1951).

Registry No.—1a, 3816-83-9; 1b, 14032-66-7; 1c, 766-40-5; 2b, 41473-30-7; 2c, 26212-26-0; 2d, 41473-32-9; 2e, 40125-53-9; 2f, 14032-71-4; 2g, 41473-35-2; 3, 41473-36-3; 5, 3712-44-5; 8a, 41473-38-5; 8b, 41611-40-9; 8c, 41473-39-6; 9a, 41473-40-9; 9b, 41473-41-0; 11, 26212-27-1; 11 picrate, 41473-42-1; 12a, 41473-43-2; 12a isomer, 41473-44-3; 12b, 41473-45-4; 12c, 41611-41-0; 12d, 41473-46-5; 13, 26212-28-2; 2,4-dimethoxypyrimidine, 3551-55-1.

# Reductive Alkylation of Monoaromatic Ketones

MASAYUKI NARISADA* AND FUMIHIKO WATANABE

*Shionogi Research Laboratory, Shionogi and Company, Limited, Fukushima-ku, Osaka, 553 Japan*

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Metal–ammonia reduction of acetophenone in the presence of *tert*-butyl alcohol is shown to proceed in three ways: dimerization to give *dl*-2,3-diphenylbutane-2,3-diol (**3**), nuclear reduction to form 1-(cyclohexa-2,5-dienylidene)ethanolate (enolate) (**4**), and carbonyl carbon reduction to yield 1-phenethyl alcohol. Subsequent *in situ* methylation of **4** generates 1-acetyl-1-methylcyclohexa-2,5-diene (**1**) and/or 1-(cyclohexa-2,5-dienylidene)-ethyl methyl ether (**5**), a hypothetical intermediate; the latter is supposed to isomerize to 1-phenethyl methyl ether. The product composition depends strongly upon the dissolving metal and methylating conditions used, and is controlled by proper selection of them; thus, reduction in ammonia–THF at −78° with potassium in either order of addition gives potassium enoate **4c** and subsequent methylation with methyl iodide in THF of lithium enolate **4b**, prepared by treatment of **4c** with lithium bromide, affords a regioselective preparative method of compound **1** in yields of >80%. Applicability of the method is established in reductive methylation of *o*-methoxyacetophenone (**6a**), *m*-methoxyacetophenone (**6b**), *p*-methylacetophenone (**6d**), and 1-tetralone. Similarly, 1-acetyl-1-ethylcyclohexa-2,5-diene (**10a**), 1-acetyl-1-allylcyclohexa-2,5-diene (**10b**), ethyl 1-acetylcyclohexa-2,5-dienylacetate (**10c**), and 1-acetylcyclohexa-2,5-dienylacetonitrile (**10e**) were prepared by using ethyl iodide, allyl bromide, ethyl bromoacetate, and chloroacetonitrile as the alkylating agent, respectively. HMO calculation suggests that the difference in the regioselectivity of the reduction according to the kind of counterion can be correlated with changes in electron density of the acetophenone dianion **12** on association with the counterion.

A solution of an alkali metal in ammonia combined with a proton source has long been known to provide an efficient reducing system[1] for aromatic rings. Partial nuclear reduction of benzoic acids by this method to give 1,4-dihydro derivatives as the primary products has been well established.[2,3] It has since been found[3,4] that the reduction can proceed without addition of a proton source, the intermediate enolates being subsequently alkylated *in situ* to afford 1-alkyl-1,4-dihydrobenzoic acids.

Metal–ammonia reduction of aromatic ketones takes a different course:[1] the site of reduction is always localized at the carbonyl carbon. Reduction of acetophenone in liquid ammonia with an excess of potassium and *tert*-butyl alcohol gives ethylbenzene,[5,6] while benzophenone is reduced with sodium in ammonia followed by quenching with water to give diphenylmethanol.[7,8] Conversion of benzophenone, 1-tetralones, and 1-indanones into aromatic hydrocarbons by an excess of lithium[8] in liquid ammonia and ammonium chloride quench has been recently reported.[9] Electrophilic reaction on the benzophenone dianion, produced with an equivalent amount of metal in liquid ammonia, resulting in formation of diphenylmethane derivatives has been investigated in detail.[10]

The apparent difficulty of nuclear reduction of aromatic ketones compared with the smooth nuclear reduction in the benzoic acid series attracted our attention and prompted us to investigate the problem.

We now report our findings that under selected conditions metal–ammonia reduction of acetophenone proceeds by the hitherto unknown nuclear reduction[11−13] and that after cation exchange of the counterion the resulting enolate is selectively methylated *in situ*

(1) For general discussions, see (a) A. J. Birch, *Quart. Rev., Chem. Soc.*, **4**, 69 (1950); (b) A. J. Birch and H. Smith, *ibid.*, **12**, 17 (1958); (c) G. W. Watt, *Chem. Rev.*, **46**, 317 (1950); (d) C. Djerassi, Ed., "Steroid Reactions," Holden-Day, San Francisco, Calif., 1963; (e) H. Smith, "Organic Reactions in Liquid Ammonia, Vol. 1, Part 2, Chemistry in Nonaqueous Ionizing Solvents," Wiley, New York, N. Y., 1963; (f) R. L. Augustine, "Reduction: Techniques and Applications in Organic Synthesis," Marcel Dekker, New York, N. Y., 1968; (g) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972; (h) R. G. Harvey, *Synthesis*, 161 (1970); (i) E. M. Kaiser, *ibid.*, 392 (1972).

(2) (a) A. J. Birch, *J. Chem. Soc.*, 1551 (1950); (b) A. J. Birch, P. Hextall, and S. Sternhell, *Aust. J. Chem.*, **7**, 256 (1954); (c) H. Plieniger and G. Ege, *Angew. Chem.*, **70**, 505 (1958); (d) M. E. Kuehne and B. F. Lambert, *J. Amer. Chem. Soc.*, **81**, 4278 (1959); (e) A. P. Krapcho and A. A. Bothner-By, *ibid.*, **81**, 3658 (1959); (f) O. L. Chapman and P. Fitton, *ibid.*, **83**, 1005 (1961); **85**, 41 (1963); (g) F. Camps, J. Coll, and J. Pascual, *J. Org. Chem.*, **32**, 2563 (1967); (h) M. E. C. Biffin, A. G. Moritz, and D. B. Paul, *Aust. J. Chem.*, **25**, 1329 (1972).

(3) (a) M. D. Bachi, J. W. Epstein, Y. Herzberg-Minzly, and H. J. E. Loewenthal, *J. Org. Chem.*, **34**, 126 (1969); (b) H. van Bekkem, C. B. van den Bosch, G. van Minnenpathuis, J. C. de Mos, and A. M. van Wijk, *Recl. Trav. Chim. Pays-Bas*, **90**, 137 (1971).

(4) For similar reductive methylation of biphenyl and polynuclear aromatic compounds, see D. F. Lindow, C. N. Cortez, and R. G. Harvey, *J. Amer. Chem. Soc.*, **94**, 5406 (1972), and the papers in this series.

(5) A. R. Pinder and H. Smith, *J. Chem. Soc.*, 113 (1954).

(6) Metal was added to the ketone solution.

(7) (a) H. Schlubach, *Chem. Ber.*, **48**, 12 (1915); (b) See also W. E. Bachmann, *J. Amer. Chem. Soc.*, **55**, 1179 (1933).

(8) Ketone was added to the solution of metal in ammonia.

(9) (a) S. S. Hall, S. D. Lipsky, F. J. McEnroe, and A. P. Bartels, *J. Org. Chem.*, **36**, 2588 (1971). The accelerating effect of a catalytic amount of cobalt or aluminum was observed. (b) S. S. Hall, S. D. Lipsky, and G. H. Small, *Tetrahedron Lett.*, 1853 (1971).

(10) (a) P. J. Hamrick, Jr., and C. R. Hauser, *J. Amer. Chem. Soc.*, **81**, 493 (1959); (b) S. Selman and J. F. Eastham, *J. Org. Chem.*, **30**, 3804 (1965); (c) E. L. Anderson and J. E. Casey, Jr., *ibid.*, **30**, 3955 (1965); (d) W. S. Murphy and D. J. Buckley, *Tetrahedron Lett.*, 2975 (1969).

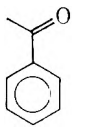
(11) Pinder and Smith[5] have already attempted to prepare 1-acetylcyclohexa-2,5-diene by potassium–*tert*-butyl alcohol–ammonia reduction of the potassium enolate of acetophenone, an equivalent to benzoate, but they recovered acetophenone.

(12) For the lithium–methylamine reduction of acetophenone yielding 1-(cyclohexen-1-yl)ethanol, see (a) R. A. Benkeser, C. Arnold, Jr., R. F. Lambert, and O. H. Thomas, *J. Amer. Chem. Soc.*, **77**, 6042 (1955); (b) R. A. Benkeser, R. K. Agnihotri, M. L. Burrous, E. M. Kaiser, J. M. Mallan, and P. W. Ryan, *J. Org. Chem.*, **29**, 1313 (1964).

(13) Reduction of pivalophenone by magnesium–trimethylsilyl chloride to 1-(*p*-trimethylsilylphenyl)-2,2-dimethylpropane trimethylsilyl ether *via* initial nuclear reduction and subsequent aromatization has been reported. See (a) R. Calas, C. Biran, J. Dunogues, and N. Duffaut, *C. R. Acad. Sci., Ser. C*, **269**, 412 (1969); (b) R. Calas, J. Dunogues, J.-P. Pillot, C. Biran, and N. Duffaut, *J. Organometal. Chem.*, **25**, 43 (1970); (c) J.-P. Pillot, J. Dunogues, R. Calas, and N. Duffaut, *Bull. Soc. Chim. Fr.*, 3490 (1972).

TABLE I

REDUCTIVE METHYLATION OF ACETOPHENONE[a]



1. M/proton source/$NH_3$–THF/−78°, 10 min
2. LiX/$NH_3$–THF/−78°, 40 min
3. $CH_3I$/THF/0–10°, 40 min

→ products

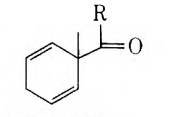
| Item No. | Metal | Proton source | Molar equiv | Lithium halide | Yield of product, %[b] Ethylbenzene | 1-Phenethyl methyl ether | 1 | 2 | Acetophenone | Isobutyrophenone | Propiophenone | 1-Phenethyl alcohol | 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Li | HOAc | 1.0 | | <3[c] | 2 | 41 | 1 | 3 | 1 | 2 | 18 | 19[c] |
| 2 | Li | $H_2O$ | 1.1 | | <3[c] | 1 | 21 | | 4 | 2 | 2 | 47 | 11[c] |
| 3 | Li | *t*-BuOH | 1.2 | | 8[c] | 6 | 26 | 5 | 6 | 6 | <1 | 19 | 8[d] |
| 4 | Li | *t*-BuOH | 6.0 | | 4[c] | 3 | 36 | 2 | 4 | 5 | 12 | 23 | <3[c] |
| 5 | Na | *t*-BuOH | 1.2 | | 3[c] | 23 | 12 | 25 | | 4 | | 8 | 3[d] |
| 6 | Na | *t*-BuOH | 6.0 | | | 34 | 14 | 28 | | 2 | | 9 | <3[c] |
| 7 | Na | *t*-BuOH | 1.2 | LiI | 9[c] | <1 | 53 | | 1 | | | 14 | <3[c] |
| 8 | Na | *t*-BuOH | 1.2 | LiBr | | <1 | 61 | | 4 | | | 21 | <3[c] |
| 9[e] | Na | *t*-BuOH | 6.0 | LiI | 4[c] | <1 | 46 | 1 | 1 | | | 36 | <3[c] |
| 10 | Na | | | LiI | 11[c] | <1 | 26 | | 1 | | | 16 | 35[c] |
| 11 | K | *t*-BuOH | 1.2 | LiBr | 7[c] | <1 | 84 | | 5 | | | 2 | 3[d] |
| 12 | K[f] | *t*-BuOH | 0.5 | | | | 25 | 2 | 22 | 17 | 4 | | 13[d] |

[a] Procedure is described in the Experimental Section. [b] Determined by glpc analysis unless otherwise stated. [c] Based on nmr spectroscopy. [d] Isolated by alumina chromatography. [e] Reduction was carried out at −33°. [f] 1.0 atom equiv of potassium was used.

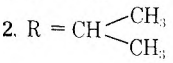
to produce 1-acetyl-1-methylcyclohexa-2,5-diene (**1**). The mechanism of the reaction and application for preparation of derivatives of **1** are also described.

## Results and Discussion

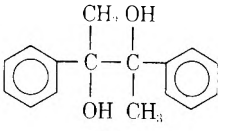
**Reductive Methylation of Acetophenone.**—The product mixture from reductive methylation of acetophenone consists of ethylbenzene, 1-phenethyl methyl ether, 1-acetyl-1-methylcyclohexa-2,5-diene (**1**), 1-isobutyryl-1-methylcyclohexa-2,5-diene (**2**), acetophenone, isobutyrophenone, propiophenone, 1-phenethyl alcohol, and *dl*-2,3-diphenylbutane-2,3-diol (**3**). The



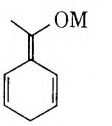
1, R = $CH_3$



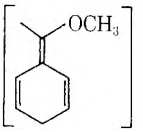
2, R = $CH(CH_3)_2$



3



4a. M = Na
b, M = Li
c. M = K



5

1,4-dihydro structure of **1** is easily assigned, mainly from the presence in the nmr spectrum of proton signals characteristic of a symmetrical diene group (4 H, δ 5.53 and 5.86), an acetyl group (3 H, δ 2.12), and a $CH_3C<$ group (3 H, δ 1.22). Structures of other products were deduced from their nmr spectra and confirmed by identification with authentic samples.

Investigation into the factors influencing product composition gave interesting results (Table I). In each experiment reduction proceeded, giving some amount of **1**, regardless of the nature of the proton source and the kind of metal. It was initially assumed that use of a strongly acidic proton source would be necessary for the reduction, judging from the fact that benzoic acids are reduced smoothly to the 1,4-dihydro derivatives with alkali metal and their own protons.[3,14] However, it turned out that *tert*-butyl alcohol (1.2 or 6.0 molar equiv) behaves as a satisfactory proton source. A significant increase in the amount of **3** was observed when acetic acid was used as the proton source (compare item 1 with 3 and 4). Also, water assisted the preferential formation of 1-phenethyl alcohol (item 2).

A profound effect on the reaction pattern was observed on substitution of sodium for lithium: methylation of **1** was enhanced with an increase in the yield of **2**, recovery of the starting material and its methylated compounds was decreased, production of 1-phenethyl alcohol was suppressed, and dominant formation of 1-phenethyl methyl ether was observed (items 5 and 6). The last fact may be interpreted by assuming that the methyl ether is generated through O-methylation of intermediate sodium trienolate **4a** and subsequent aromatization of the resulting methyl enolate **5**, and this was verified by the fact that methyl ether formation became negligible and the yield of compound **1** was increased when, in order to avoid[15] the O-methylation, an attempt was made to convert sodium enolate **4a** into lithium enolate **4b** by additional treatment with lithium

(14) The authors are grateful to a referee who has called their attention to a report that sodium benzoate very rapidly quenches lithium dissolved in ammonia in the presence of ethanol[2e] (and without a proton source[9]). In fact, sodium benzoate was reduced with 1.9 molar equiv of lithium in ammonia–THF without added proton source at −78° and successively methylated with methyl iodide to give 1-methylcyclohexa-2,5-dienecarboxylic acid in 56% yield after distillation as its methyl ester (unpublished data). However, since base-catalyzed isomerization and further reduction of a 1,4-dihydrobenzoic acid has been reported,[2b,h] we have considered that, in addition to the protonation, quenching of sodium amide may be important in preventing the possible isomerization of 1,4-dihydroacetophenone to phenethyl alcohol.

(15) For general discussion on the problem of O-methylation and C-methylation of ambident anions, see (a) R. Gomper, *Angew. Chem.*, **76**, 412 (1964); *Angew. Chem., Int. Ed. Engl.*, **3**, 560 (1964); (b) W. J. Le Noble, *Synthesis*, 1 (1970); (c) Reference 1g.

iodide (item 7). In addition, the undesirable methylation yielding **2** was also suppressed by this treatment. Lithium bromide showed a similar effect (item 8), while lithium chloride was unsatisfactory.

Several additional factors were also found: reverse order[16] of addition of lithium and sodium caused a slightly dimenished yield of **1**; a significant temperature effect was seen, formation of 1-phenethyl alcohol was increased at an elevated temperature (item 9); and reduction without a proton source resulted in increased accumulation of the pinacol **3** (item 10).

Optimal conditions were obtained when acetophenone was treated in a selected combination of metals (item 11). Thus, compound **1** was isolated in 80% yield after fractional distillation. Contrary to the experiments using lithium and sodium, reverse addition[16] in the reduction with potassium gave a slightly increased yield (90%). Reduction using a twofold excess of potassium (4.0 instead of 2.2 atom equiv in item 11) under more drastic conditions (80 min at −33° in addition to 10 min at −78° in item 11) little affected the product composition.

**Reductive Methylation of Substituted Acetophenone.**—In Table II, examples of reductive methylation

TABLE II

REDUCTIVE METHYLATION OF ACETOPHENONE DERIVATIVES

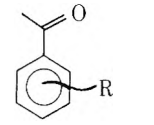
| Substrate | Product | Yield, % |
|---|---|---|
| **6a** | **7a** | 74[a] |
| **6b** | **7b** | 89[a] |
| **6c** | **1** | 33[b] |
| | **8a** | 16[b] |
| | **6c** | 37[b] |
| **6d** | **7c** | 55[b,c] |
| | **8b** | 26[b] |
| 1-Tetralone | **9** | 60,[a] 62[a,d] |
| | Tetralin | 4,[a] 1[a,d] (96[e]) |
| | 1-Tetralone | 13,[a] 14[a,d] |

[a] Isolated yield. [b] Based on glpc analysis. [c] A mixture of cis and trans isomers. [d] By reverse addition.[16] [e] See ref 9.

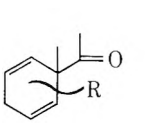
of acetophenone derivatives are listed. All the products gave satisfactory analytical and spectral data and the by-products were identified with authentic samples.

Of the methoxy acetophenones, ortho- and meta-substituted derivatives **6a** and **6b** were converted smoothly into compounds **7a** and **7b**, while the para-substituted compound **6c** suffered elimination resulting in **1**. Successful nuclear reduction of a para-substituted acetophenone was observed only with methyl derivative **6d**, a 1:1 mixture of cis and trans isomers **7c** being obtained. Both of the para-substituted derivatives underwent marked carbonyl reduction, producing alcohols **8a** and **8b**. Effective conversion of 1-tetralone into tetralin by reduction[8] with 5 molar equiv of lithium in ammonia–THF at reflux temperature and ammonium chloride quench has been reported.[9] By our procedure (reduction using 2.5 molar equiv of potassium in either order of addition and 3.0 molar equiv of *tert*-butyl alcohol in ammonia–THF at −78° and *in situ* methylation with methyl iodide in THF after treatment of lithium bromide), the nuclear reduction product **9** was obtained in yields of >60%. The formation of tetralin was substantially suppressed.

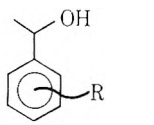
(16) Addition of a solution of ketone and a proton source to a solution of alkali metal in liquid ammonia.



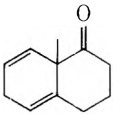
**6a**, R = *o*-$OCH_3$
**b**, R = *m*-$OCH_3$
**c**, R = *p*-$OCH_3$
**d**, R = *p*-$CH_3$



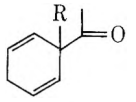
**7a**, R = *o*-$OCH_3$
**b**, R = *m*-$OCH_3$
**c**, R = *p*-$CH_3$
(a mixture of cis and trans isomers)



**8a**, R = *p*-$OCH_3$
**b**, R = *p*-$CH_3$



**9**



**10a**, R = $C_2H_5$
**b**, R = $CH_2CH{=}CH_2$
**c**, R = $CH_2COOC_2H_5$
**d**, R = $CH_2COOH$
**e**, R = $CH_2CN$

**Reductive Alkylation of Acetophenone.**—Utilizing the optimal conditions for the reductive methylation of acetophenone, compounds **10a**, **10b**, **10c**, **10d**, and **10e** were prepared (Table III). Assignment of the structure of each compound was made from analytical and spectral data. Although the reaction conditions were not optimized, it is concluded that the reactive alkylating reagents alkylate lithium enolate **4b** satisfactorily. It is also noteworthy that attempts to alkylate it with chloroacetone, *n*-amyl bromide, and *p*-iodoanisole failed.

TABLE III

REDUCTIVE ALKYLATION OF ACETOPHENONE

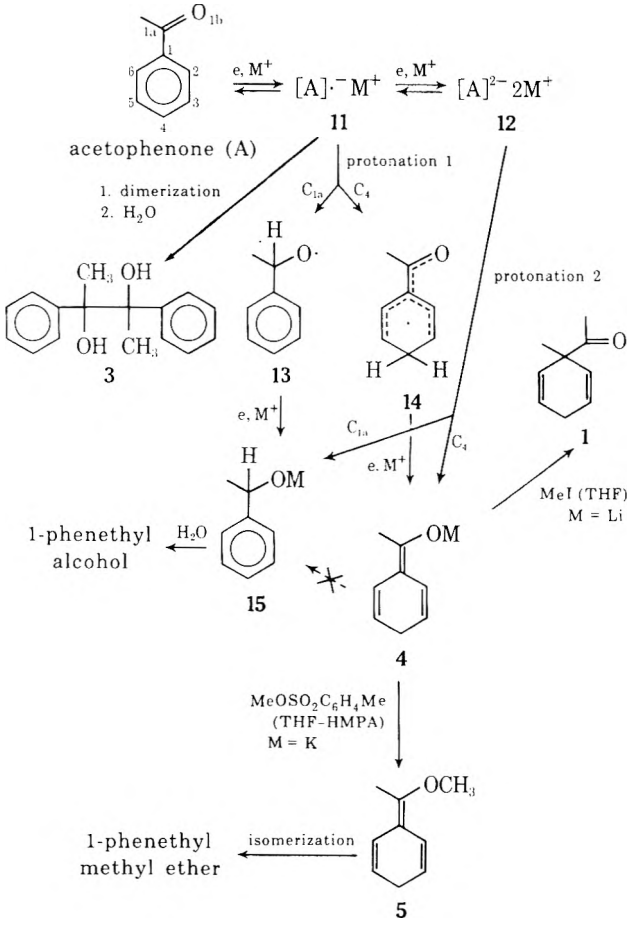
| Alkylating reagent | Product | Yield, % |
|---|---|---|
| $C_2H_5I$ | **10a** | 59[a] |
| $CH_2{=}CHCH_2Br$ | **10b** | 85[b] |
| $BrCH_2COOC_2H_5$ | **10c** | 62[a] |
| | **10d** | 21[b] |
| $ClCH_2CN$ | **10e** | 26[a] |

[a] Based on glpc analysis. [b] Isolated yield.

**Mechanism of Reductive Methylation of Acetophenone.**—Reductive methylation of acetophenone is rather complicated compared with that[3b] of benzoic acid. Scheme I shows a suggested mechanism for the important figures of the reaction.

The anion radical **11** formed by one-electron reduction of acetophenone is consumed in three ways: (1) dimerization to **3**; (2) protonation 1 to produce radicals **13** and **14** and then further reduction to give **15** and **4**; and (3) acceptance of a second electron to form the dianion **12**, which is transformed to alcoholates **15** and **4** by protonation 2. To obtain some idea of the competition between these alternative reactions, an experiment was carried out in which the reduction was stopped halfway (Table I, item 12). This showed a distinct increase in amount of the pinacol **3**. We consider this to imply that the reduction path *via* protonation 1 is not significant, otherwise half of the yield of compound **1** would be retained without any increase in the formation of **3**, and that an insufficiency of metal retards the consumption of **11** through **12**, resulting in formation of **3**. Evidence for the formation of the dianion **12** is also given by the observation of a deep green color in the reaction mixture where no proton source was added

SCHEME I




(Table I, item 10); the low concentration of proton retards the consumption of the dianion, making it observable. These pieces of evidence suggest that protonation 2 is the more important path.[17,18]

Protonation 2 is presumably a kinetically controlled process. Possible isomerization of lithium enolate **4b** to alcoholate **15** is excluded by the observation that almost pure lithium enolate **4b**, prepared by treatment of potassium enolate **4c** with lithium iodide, did not produce any detectable increase in the amount of 1-phenethyl alcohol but gave mainly **1** after prolonged stirring at −33° and subsequent methylation. Thus, the product ratios of compound **1** to 1-phenethyl alcohol are believed to reflect directly the relative rates of $C_4$ to $C_{1a}$ protonations, which increase rapidly in the order Li < Na < K (Table I, items 3, 8, and 11). Protonation during the Birch reduction of aromatic hydrocarbons is known to proceed in accord with HMO theory.[20] So we attempted to interpret the difference in the relative rates of protonation in terms of the changes in electron density of the dianion on association[21] with the counterion. In Table IV, the calculated values of electron densities and spin densities of the radical anion **11** and the dianion **12** are shown. Choice of the parameters is based on the work of Steinberger and Fraenkel,[22] who have shown a very good agreement of the calculated values with the experimental values of the spin densities of the free anion radical **11** in DMF. As parameters for the associated species, we used values[23,24] intermediate between those for the free species and for a hypothetical species which is protonated at the oxygen atom. The electron densities of the free and associated dianions agree[25] well with the observed decreasing trend of relative rates of $C_4$ to $C_{1a}$ protonations in the order K > Na > Li when covalencies of the bond between the oxygen atom and the alkali metals are supposed to increase in the order K < Na < Li.

TABLE IV

SPIN AND ELECTRON DENSITIES OF $[A]\cdot^-$ AND $[A]^{2-}$

| | [A]·⁻ Spin densities[a] Free | [A]·⁻ Spin densities[a] Associated | [A]·⁻ Electron densities Free | [A]·⁻ Electron densities Associated | [A]²⁻ Electron densities Free | [A]²⁻ Electron densities Associated |
|---|---|---|---|---|---|---|
| 1 | 0.095 | −0.037 | 1.156 | 1.052 | 1.270 | 1.077 |
| 2 | 0.164 | 0.170 | 1.049 | 1.039 | 1.178 | 1.167 |
| 3 | −0.046 | −0.062 | 1.031 | 1.005 | 1.052 | 1.008 |
| 4 | 0.270 | 0.182 | 1.148 | 1.059 | 1.345 | 1.199 |
| 5 | −0.057 | −0.062 | 1.021 | 1.005 | 1.034 | 1.008 |
| 6 | 0.183 | 0.170 | 1.082 | 1.039 | 1.222 | 1.167 |
| 1a | 0.260 | 0.564 | 0.895 | 0.985 | 1.131 | 1.439 |
| 1b | 0.131 | 0.076 | 1.618 | 1.816 | 1.768 | 1.935 |

[a] McLachalan modification of Hückel calculation with λ = 1.2; see A. D. McLachalan, *Mol. Phys.*, **3**, 233 (1960).

Methylation of enolate **4** with methyl iodide proceeds in two ways depending on the sort of counterion. With lithium it is methylated exclusively at $C_1$ to afford compound **1**, while the sodium salt is methylated both at the oxygen atom and at $C_1$.[26] The O-methylation product **5** is believed to isomerize into 1-phenethyl methyl ether. Interestingly, potassium enolate **4c** was methylated to yield only a small amount of 1-phenethyl methyl ether. This might be ascribable to the low solubility of the enolate.[15] However, methylation of potassium enolate **4c** with methyl *p*-toluene-

(17) In the reduction employing a strongly acidic proton source, we still retain the possibility of the protonation 1 as a by-path.

(18) Polarographic study on the reduction of acetophenone in dimethylformamide has revealed that at a lower concentration of proton (less than 1 molar equiv of phenol) acetophenone is reduced to the radical anion **11** in a reversible manner and successively to the dianion **12** in an irreversible manner at −1.95 and −2.63 V[19] *vs.* a saturated calomel electrode, respectively, and that at a higher concentration of phenol protonation of the radical anion **11** becomes a diffusion-controlled competitive reaction path. See J. Simonet, *Bull. Soc. Chim. Fr.*, 1533 (1970). The facts are compatible with our suggested mechanism.

(19) The value is in the range −2.9 V or less (*vs.* a saturated calomel electrode) noted for the reduction potential of dissolving metals in ammonia.[1g]

(20) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961.

(21) (a) Zaugg and Schaefer have investigated the effects of cation and solvent on the uv spectra of alkali phenolates and enolates and showed that the $\pi-\pi^*$ transition energies in DMF are proportional to the inverse of the cationic radius. See H. E. Zaugg and A. D. Schaefer, *J. Amer. Chem. Soc.*, **87**, 1857 (1965). (b) Hogen-Esch and Smid observed increasing diametrically opposite cation effects (solvent-induced shifts on the uv spectra) of 9-fluorenyl salts in THF on lowering the temperature to −50°. See T. E. Hogen-Esch and J. Smid, *J. Amer. Chem. Soc.*, **88**, 307 (1966).

(22) N. Steinberger and G. K. Fraenkel, *J. Chem. Phys.*, **40**, 723 (1964).

(23) The values used[22] for the free ion ($\gamma_{CC}^* = 1.1$, $\delta_O = 1.55$, $\gamma_{CO} = 1.7$, and $\delta_{C'} = -0.05$) were modified to the following values for the associated ion: $\gamma_{CC}^* = 1.0$, $\delta_O = 2.05$, $\gamma_{CO} = 1.2$, $\delta_{C_{1a}} = 0.10$, and $\delta_{C'} = 0.00$.

(24) For a more precise treatment of the cation effect on esr spectra of aromatic nitro compounds at various temperatures, see Y. Kawamura, K. Nishikida, and T. Kubota, *Bull. Chem. Soc. Jap.*, **46**, 737 (1973), and references cited therein.

(25) The spin densities and the net charge at $C_{1a}$ of the anion radical are considered to parallel with the experimentally found tendency for dimerization.

(26) A referee kindly informed us of a report describing nmr evidence for the structure (solvent-separated ion pairs *vs.* contact ion pairs) of metal enolates in various solvents. Kinetically controlled acylation of the contact ion pairs gave the C-acylated products while that of solvent-separated ion pairs gave the O-acylated products. See H. O. House, R. A. Auerbach, M. Gall, and N. P. Peet, *J. Org. Chem.*, **38**, 514 (1973). These evidences accord with our mechanism.

sulfonate in a 1:2 mixture of THF–hexamethylphosphoric triamide (HMPA)[27] proceeded almost exclusively to give 1-phenethyl methyl ether in 63% yield and little **1**. The result supports strongly the above-described hypothesis for the formation of 1-phenethyl methyl ether *via* **5**. An alternate path for the formation of 1-phenethyl methyl ether by methylation of **15** cannot be excluded but must be of minor contribution on the basis of the composition change on lithium halide treatment.

The importance of the species of counterion for control of the reductive methylation of acetophenone was revealed. Selecting a suitable species of counterion in each step, an efficient preparative method of compound **1** is established. Synthetic applicability of the method for similar compounds is also shown. The importance in nuclear and the carbonyl reduction of the changes in electron density of the intermediate acetophenone dianion owing to counterion association is also suggested.

## Experimental Section

**Physical Data.**—Gas chromatographic analyses were performed on a Shimazu GC-4A chromatograph employing a 1.5 m × 4 mm 1% Carbowax 20 M on Gas-Chrom Q column at 130° and 1.4 kg/cm² nitrogen pressure. Proton nmr spectra were recorded on a Varian A-60 spectrometer; chemical shifts are reported relative to TMS in $CDCl_3$. Ir spectra were obtained on a Jasco DS-403G grating spectrometer in $CHCl_3$, unless otherwise noted. Mass spectra were measured on a Hitachi RMU-6 mass spectrometer at 70 eV.

**Reductive Methylation of Acetophenone. General Procedure.**—All the reactions were carried out under slight pressure of dry nitrogen.[28] Tetrahydrofuran (THF) was purified by refluxing under nitrogen over sodium hydride and distilled just before use. Dry ammonia[29] (140 ml) was placed in a flask equipped with a ground glass seal stirrer and cooled at −78°. A solution of 5.192 g (43.2 mmol) of acetophenone and a proton source (1.0–6.0 × 43.2 mmol) diluted with 20 ml of THF was introduced, followed by small pieces of alkali metal (2.2–2.5 × 43.2 mg-atoms) with efficient stirring over a period of 1–5 min. The resulting mixture was then stirred for 10 min; usually the initially observed blue color persisted. The resulting blue solution was in some cases (Table I, items 7, 8, 9, 10, and 11) mixed with anhydrous lithium halide (2.2 × 43.2 mmol) and stirred at −78° for 40 min; in other cases (Table I, items 1, 2, 3, 4, 5, 6, and 12) this operation was omitted. The ammonia was evaporated during 1–4 hr and the resulting pasty mixture was methylated by adding methyl iodide (2.0 × 43.2 mmol) and stirring the mixture at 0–10° for 40 min. Saturated salt solution and ether were added to the reaction mixture and the resulting two-phase solution was adjusted to pH 7.5 by cautious addition of hydrochloric acid at 0°. The ether layer was separated and the aqueous layer was extracted with ether. The organic layer was washed with salt solution and dried over sodium sulfate, and the solvent was evaporated under reduced pressure at room temperature. Yields of each component were determined by glpc analysis employing phenethol as internal standard; retention times of 1-phenethyl methyl ether, phenethole, **1**, **2**, acetophenone, isobutyrophenone, and propiophenone were 0.68, 0.78, 1.08, 1.38, 2.65, 3.43, and 3.65 min, respectively. The product ratios of ethyl benzene and **3** relative to 1 were determined by repeated measurements of the integrated areas (on a Varian T-60) of the signals characteristic for each component. The yield of **3** was also confirmed by isolation by alumina column chromatography, the value agreeing well with that obtained by nmr spectroscopy.

*dl*-**2,3-Diphenylbutane-2,3-diol (3)**[30,31] had mp 125–127° (lit.[30] mp 122–124°); ν ($CCl_4$) 3628, 3581, 1603, 1495, 1442, 1373, 1355, and 1143 cm⁻¹ (lit.[30] 1355 and 1143 cm⁻¹ as characteristic bands to the *dl* form). *Anal.* Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.42; H, 7.47. Nmr δ 1.46 (6 H, s), 2.66 (2 H, broad s), and 7.17 (10 H, s).

**1-Acetyl-1-methylcyclohexa-2,5-diene (1).**—Under optimal conditions (Table I, item 11), **1** was isolated in a yield of 80% after fractional distillation of the above-described mixture, bp 72.2° (18 mm), $n^{18.5}$D 1.4802. *Anal.* Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.10; H, 8.75. Ir ν 1707, 1673, 1632, and 1602 cm⁻¹; mass spectrum *m/e* (rel intensity) 136 ($M^+$, 0.2), 94 (100), 92 (66), and 77 (52); nmr δ 1.22 (3, H s), 2.12 (3 H, s), 2.74 (2 H, m), 5.53 (2 H, d of t, $J$ = 10.5, 2.0 Hz), and 5.86 (2 H, d of t, $J$ = 10.5, 3.0 Hz).

**1-Isobutyryl-1-methylcyclohexa-2,5-diene (2).**—An authentic sample was prepared by methylation of **1**. To a solution of 38 ml of a 1.68 *M* solution of sodium *tert*-amylate in benzene diluted with 90 ml of THF, cooled at −10 to −13°, a mixture of 3.967 g of **1**, 9.13 g of methyl iodide, and 100 ml of THF was added dropwise under a nitrogen atmosphere. After introduction of an additional 2.08 g of methyl iodide, the resulting mixture was stirred at room temperature for 75 min. The resulting cloudy solution was poured into ice–water and extracted with ether. The product was shown to be almost pure **2** contaminated with a trace of the monomethylated product by nmr spectrum. After distillation, the sample was analyzed, bp 104° (33 mm). *Anal.* Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.05; H, 9.75. Ir ν 1704, 1671, 1630, and 1602 cm⁻¹; mass spectrum *m/e* (rel intensity) 121 (1.6) and 93 (100); nmr δ 1.00 (6 H, d, $J$ = 7.0 Hz), 1.21 (3 H, s), 2.77 (2 H, m), 3.15 (1 H, septet, $J$ = 7.0 Hz), 5.52 (2 H, d of t, $J$ = 10.5, 1.9 Hz), and 5.88 (2 H, d of t, $J$ = 10.5, 3.0 Hz).

**Reductive Methylation of Acetophenone Derivatives. A. Reductive Methylation of *o*-Methoxyacetophenone (6a).**—The reaction was carried out in a similar way to that described for the reductive methylation of acetophenone. A mixture of 10.026 g (66.6 mmol) of *o*-methoxyacetophenone, 7.55 ml (1.2 × 66.6 mmol) of dry *tert*-butyl alcohol, and 40 ml of THF was added under nitrogen[28] to 270 ml of redistilled ammonia[29] cooled at −78°. Small pieces of potassium (5.75 g, 2.2 × 66.6 mg-atom) were added quickly to the stirred mixture. After 10 min of stirring, 12.8 g (2.2 × 66.6 mmol) of anhydrous lithium bromide was added and the mixture was stirred at −78° for 40 min. The ammonia was evaporated to give a pasty mixture, to which 8.3 ml (2.0 × 66.6 mmol) of methyl iodide was injected and the resulting mixture was stirred vigorously at 0–10° for 40 min. The reaction mixture was diluted with salt solution and extracted with ether. The ether solution was washed with salt solution and dried over sodium sulfate, and the solvent was evaporated under reduced pressure. Distillation produced pure **1-acetyl-1-methyl-2-methoxycyclohexa-2,5-diene (7a)** in a yield of 74%, bp 67–70° (2.0 mm), $n^{25}$D 1.4848, $d^{25}25$ 1.0171. *Anal.* Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.44; H, 8.50. Ir ν 1713, 1683, 1644, and 1597 cm⁻¹; mass spectrum *m/e* (rel intensity) 166 ($M^+$, 4.5), 123 (91), 108 (100), and 91 (66); nmr δ 1.27 (3 H, s), 2.07 (3 H, s), 2.76 (2 H, m), 3.52 (3 H, s), 4.80 (1 H, t, $J$ = 3.5 Hz), 5.27 (1 H, d of t, $J$ = 10.0, 2.0 Hz), and 5.83 (1 H, d of t, $J$ = 10.0, 3.5 Hz).

**B. Reductive Methylation of *m*-Methoxyacetophenone (6b).**—In a way similar to A, *m*-methoxyacetophenone was treated to produce **1-acetyl-1-methyl-3-methoxycyclohexa-2,5-diene (7b)** in a yield of 89%, bp 69.5–71° (2.0 mm), $n^{25}$D 1.4856, $d^{25}25$ 1.0192. *Anal.* Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.97; H, 8.48. Ir ν 1710, 1681, and 1640 cm⁻¹; mass spectrum *m/e* (rel intensity) 166 ($M^+$, 1.5) and 108 (100); nmr δ 1.22 (3 H, s), 2.10 (3 H, s), 2.79 (2 H, m), 3.56 (3 H, s), 4.47 (1 H, $W_{1/2}$ = 3 Hz), 5.51 (1 H, d of q, $J$ = 10.0, 2.0 Hz), and 5.82 (1 H, d of t, $J$ = 10.0, 3.0 Hz).

**C. Reductive Methylation of *p*-Methoxyacetophenone (6c).**—The product of reductive methylation of *p*-methoxyacetophenone (6c) showed two peaks other than those of the starting material in glpc carried out at 180°. One was identified as compound **1** and the other as an authentic sample of ***p*-methoxy-1-phenethyl**

(27) Predominant methylation at the oxygen atom of sodium acetylacetonate and potassium enolate of ethyl acetoacetate by a similar procedure has been reported. See A. L. Kurts, N. K. Genkina, A. Macias, I. P. Beletskaya, and O. A. Reutov, *Tetrahedron*, **27**, 4777 (1971).

(28) J. F. Eastham and D. R. Larkin, *J. Amer. Chem. Soc.*, **81**, 3652 (1959).

(29) H. L. Dryden, Jr., G. M. Webber, R. R. Burtner, and J. A. Cella, *J. Org. Chem.*, **30**, 3985 (1965).

(30) D. J. Cram and K. R. Kopecky, *J. Amer. Chem. Soc.*, **81**, 2748 (1959).

(31) Bands at 1335, 1129, and 1111 cm⁻¹ characteristic of the meso modification[30] were scarcely observable in the ir spectrum of the crude crystalline mass of the pinacol dissolved in $CCl_4$.

alcohol (**8a**), which was prepared by lithium aluminum hydride reduction of **6c**. The results of quantative analysis by glpc are shown in Table II. The nmr spectrum of the crude product also supported the above-described characterization.

D. **Reductive Methylation of *p*-Methylacetophenone (6d).**—The crude product obtained by reductive methylation of *p*-methylacetophenone (**6d**) in the same way as in A was chromatographed on silica gel thick layer plates. Elution with a 4:1 mixture of benzene–ethyl acetate yielded two fractions. The upper fraction was purified by bulb-to-bulb distillation to give a 1:1 mixture of cis and trans isomers of **1-acetyl-1,4-dimethylcyclohexa-2,5-diene (7c)**. On the basis of 100 MHz nmr spectrum, the product was concluded to be a 1:1 mixture of geometric isomers. *Anal.* Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.68; H, 9.26. Ir $\nu$ 1713, 1673, and 1628 $cm^{-1}$; mass spectrum *m/e* (rel intensity) 150 ($M^+$, 0.4), 107 (100), and 91 (96); nmr (100 MHz) $\delta$ 1.12 and 1.13 (3 H, two doublets, $J$ = 7.0 Hz), 1.18 and 1.19 (3 H, two singlets), 2.18 (1 H, m), 5.48 (2 H, overlapped d of d, $J$ = 10.0, 2.5 Hz), and 5.76 (2 H, overlapped d of d, $J$ = 10.0, 3.5 Hz). The lower fraction was shown to be *p*-methyl-1-phenethyl alcohol (**8b**) by comparison with an authentic sample, bp 73° (3 mm), prepared by lithium aluminum hydride reduction of **7c**. Quantitative analysis of the crude product was performed by employing phenylcyclohexane as internal standard at 160° and the result is shown in Table II.

E. **Reductive Methylation of 1-Tetralone.**—The reductive methylation of 1-tetralone was carried out in a way similar to A and the resulting product was chromatographed on silica gel. Continuous elution with benzene yielded successively 4% of tetralin and 60% of **8a-methyl-1,2,3,4,6,8a-hexahydronaphthalen-1-one (9)**. Distillation afforded an analytical sample, bp 62–63° (0.53 mm), $n^{22.5}D$ 1.5207. *Anal.* Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.39; H, 8.65. Ir $\nu$ 1708, 1688, and 1644 $cm^{-1}$; mass spectrum *m/e* (rel intensity) 162 ($M^+$, 10.3), 105 (65), and 91 (100); nmr $\delta$ 1.35 (3 H, s), 1.65–3.00 (8 H, m), 5.55 (1 H, m), 5.71 (1 H, d of t of d, $J$ = 10.2, 2.6, 1.8 Hz), and 5.97 (1 H, d of t, $J$ = 10.2, 1.5 Hz). 1-Tetralone (13%) was eluted last.

**Reductive Alkylation of Acetophenone. General Procedure.**—The method described for the reductive methylation of acetophenone was applied to the preparation of the lithium trienolate **4b**. A solution of 10.000 g (83.1 mmol) of acetophenone and 9.40 ml (1.2 × 83.1 mmol) of dry *tert*-butyl alcohol diluted with 40 ml of THF was introduced to 270 ml of redistilled ammonia.[29] To the stirred solution 7.15 g (2.2 × 83.1 mg-atoms) of small pieces of potassium was added quickly and the resulting solution was stirred at −78° under nitrogen for 10 min. Anhydrous lithium bromide (15.90 g, 2.2 × 83.1 mmol) was introduced into the resulting blue solution and stirring was continued for 1 hr. Removal of the ammonia afforded a viscous mixture, which was mixed with an alkylating reagent (2.0–2.2 × 83.1 mmol). When the reaction was too vigorous, the reagent was added in the form of a THF solution (ethyl bromoacetate). The resulting mixture was stirred at 0–10° for 20–40 min and the reaction mixture was worked up as was done for methylation. The crude product was either purified by fractional distillation (allyl bromide) or analyzed quantitatively by glpc (ethyl iodide, ethyl bromoacetate, and chloroacetonitrile) employing a pure sample obtained by separation using thick layer chromatography (silica gel). Results are listed in Table III.

A. **With Ethyl Iodide. 1-Acetyl-1-ethylcyclohexa-2,5-diene (10a)** had bp 73° (11 mm), $n^{25}D$ 1.4809. *Anal.* Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.65; H, 9.31. Ir $\nu$ 1704, 1673, 1630, and 1601 $cm^{-1}$; mass spectrum *m/e* (rel intensity) 151 (0.3), 150 ($M^+$, 0.3), and 79 (100); nmr $\delta$ 0.77 (3 H, t, $J$ = 7.5 Hz), 1.63 (2 H, q, $J$ = 7.5 Hz), 2.12 (3 H, s), 2.72 (2 H, m), 5.49 (2 H, d of t, $J$ = 7.5 Hz), and 5.95 (2 H, d of t, $J$ = 10.8, 3.0 Hz).

B. **With Allyl Bromide. 1-Acetyl-1-allylcyclohexa-2,5-diene (10b)** had bp 53–56° (0.8 mm), $n^{25}D$ 1.4950, $d^{25}25$ 0.9630. *Anal.* Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.74; H, 8.84. Ir $\nu$ 1705, 1675, 1638, and 919 $cm^{-1}$; mass spectrum *m/e* (rel intensity) 162 ($M^+$, 8) and 43 (100); nmr $\delta$ 2.10 (3 H, 2), 2.38 (2 H, m), 2.72 (2 H, m), 4.86, 5.06 (3 H, m), 5.51 (2 H, d of t, $J$ = 10.5, 2.0 Hz), and 5.91 (2 H, d of t, $J$ = 10.5, 3.0 Hz.

C. **With Ethyl Bromoacetate. Ethyl 1-acetylcyclohexa-2,5-dienylacetate (10c)** had bp 104° (0.9 mm), $n^{25}D$ 1.4822, $d^{25}25$ 1.0686. *Anal.* Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.51; H, 7.93. Ir $\nu$ 1726, 1710, 1674, and 1632 $cm^{-1}$; mass spectrum *m/e* (rel intensity) 210 (0.2), 208 ($M^+$, 0.2), and 91 (100); nmr $\delta$ 1.22 (3 H, t, $J$ = 7.0 Hz), 2.17 (3 H, s), 2.69 (2H, s), 2.76 (2 H, m), 4.10 (2 H, q, $J$ = 7.0 Hz), 5.70 (2 H, d of t, $J$ = 10.5, 1.3 Hz), and 5.95 (2 H, d of t, $J$ = 10.5, 3.0 Hz).

**1-Acetylcyclohexa-2,5-dienylacetic Acid (10d).**—This was obtained as a nonvolatile fraction, crystallized from ether–*n*-pentane, mp 96–98°, and identified with the authentic sample described below. *Anal.* Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.39; H, 6.68. Ir $\nu$ (KBr) 2740, 2660, 1717, 1708, 1673, and 1630 $cm^{-1}$; mass spectrum *m/e* (rel intensity) 181 (0.3), 180 ($M^+$, 0.2), 92 (100), and 91 (53); nmr $\delta$ 2.16 (3 H, s), 2.75 (4 H, m), 5.70 (2 H, d of t, $J$ = 10.3, 1.6 Hz), 5.97 (2 H, d of t, $J$ = 10.3, 3.0 Hz), and 8.51 (1 H, br). An authentic sample was obtained by refluxing a mixture of the ester **10c**, 2 *N* sodium carbonate, and methanol under nitrogen for 1 hr. Crystallization from ether–*n*-pentane produced the acid **10d**, mp 96–98°.

**With Chloroacetonitrile. 1-Acetylcyclohexa-2,5-dienylacetonitrile (10e).**—*Anal.* Calcd for $C_{10}H_{11}ON$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.35; H, 6.83; N, 8.79. Ir $\nu$ 2250, 1711, 1677, and 1633 $cm^{-1}$; mass spectrum *m/e* (rel intensity) 161 ($M^+$, 0.5), 91 (89), and 43 (110); nmr $\delta$ 2.17 (3 H, s), 2.65 (2 H, s), 2.89 (2 H, m), 5.54 (2 H, d of t, $J$ = 10.3, 2.0 Hz), and 6.17 (2 H, d of t, $J$ = 10.3, 3.2 Hz).

**Acknowledgment.**—The authors are very grateful to Dr. K. Takeda and Dr. H. Otsuka for their support and encouragement in this work. Thanks are also due to Dr. W. Nagata for his advice and agreement in alloting the work in this field, and to Dr. S. Uyeo for his helpful discussion.

**Registry No.**—**1**, 41477-77-4; **2**, 41477-78-5; **3**, 22985-90-6; **6a**, 579-74-8; **6b**, 586-37-8; **6c**, 100-06-1; **6d**, 122-00-9; **7a**, 41477-79-6; **7b**, 41477-80-9; *cis*-**7c**, 41477-81-0; *trans*-**7c**, 41477-82-1; **8a**, 3319-15-1; **8b**, 536-50-5; **9**, 41477-84-3; **10a**, 41477-85-4; **10b**, 41477-86-5; **10c**, 41477-87-6; **10d**, 41477-88-7; **10e**, 41477-89-8; acetophenone, 98-86-2.

# The Chemistry of Carbanions. XXV. The Reaction of Various Organocopper Reagents with α,β-Unsaturated Carbonyl Compounds[1a]

HERBERT O. HOUSE* AND MICHAEL J. UMEN[1b]

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

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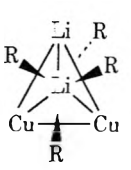
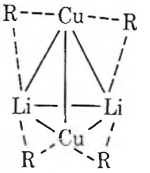
Successful conjugate additions of lithium dimethylcuprate have been effected with the esters, methyl crotonate (**15**) and methyl cinnamate (**17**), and the ketones, benzalacetone (**13**), benzalacetophenone (**19**), 2-methoxy-3,5,5-trimethyl-2-cyclohexenone (**21**), and 4-*tert*-butyl-1-cyclohexenyl methyl ketone (**6**). In the latter case **6**, 92% of the addition product has the added methyl group axial. The more difficultly reduced ester **12b** and ketone **24** failed to react with lithium dimethylcuprate. A new mixed cuprate reagent, *t*-BuC≡C(Li)CuR, is described where R, the group transferred in conjugate additions, is either methyl (**36**) or vinyl (**37**). These mixed cuprate reagents, whose preparation is especially convenient, were used in conjugate additions with isophorone **28**. Other reactions studied included the reaction of lithium dimethylcuprate with the tetraester **25** to give the reduction product **26** and treatment of the unsaturated nitriles **11** and **40** with the same cuprate. No reaction was observed in these latter cases and the unchanged nitriles were recovered.

Previous studies[2,3] of the conjugate addition of organocopper reagents to α,β-unsaturated carbonyl compounds have established this reaction as a useful preparative procedure for the introduction of alkyl, aryl, or alkenyl[3e,4] groups R from the corresponding lithium cuprate reagents $R_2CuLi$. Several lines of evidence[3a,c,e] have established that a free carbon radical R· is not an intermediate in these reactions: particularly compelling evidence arises from the fact that alkyl and alkenyl groups R are transferred from the metal to the enone substrate with retention of configuration. In conjugate additions to unhindered cyclohexenone systems, the group R is usually introduced predominantly from the direction that will form a cyclohexanone with an axial substituent R;[3b,5] with more hindered cyclic enones, the group R is usually added from the less hindered side of the enone.[6]

Although the structures of the commonly used cuprate reagents, $R_2CuLi$, are uncertain, it seems probable that many of these reagents have structures such as **1a** or **1b** with clusters of four metal atoms bonded to the organic ligands at the faces (*e.g.*, **1a**) or the edges




**1a**




**1b**

(*e.g.*, **1b**) of the tetrahedron formed by the four metal atoms. Such structures (especially **1b** in which all R groups are equivalent) are compatible with the structural information available for one relatively stable cuprate reagent[7] and are also analogous to the tetrameric structures indicated for certain stable organocopper compounds[8] as well as certain alkyllithium reagents.[9] Structures of this type **1** (*i.e.*, dimers of the usual cuprate representation $R_2CuLi$) serve readily to explain the oxidation of cuprates with a variety of good oxidizing agents (reduction potentials less negative than *ca.* −1.0 V *vs.* sce, *e.g.*, $O_2$, Cu(II) salts, quinones, nitro compounds) to form dimers R–R (eq A) with

$$\underset{\mathbf{1}}{R_4Cu_2Li_2} \xrightarrow{-e^-} \underset{\mathbf{2}}{[R_4Cu_2Li_2]^+} \xrightarrow{-e^-} (RCu)_x + R\text{–}R + 2Li^+ \quad (A)$$

retention of stereochemistry at the group R.[10] Since it seems likely that this oxidation can occur in two stages involving an intermediate cation **2**,[11] we have been inclined to believe that reaction of cuprates with less powerful oxidizing agents (reduction potential more negative than *ca.* −1.0 V *vs.* sce, *e.g.*, enones) may involve transfer of only a single electron from the cuprate cluster **1** because these less powerful oxidants are unable to remove a second electron from the intermediate cation **2**. Consequently, even in reactions where initial electron transfer steps are involved, oxi-

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(2) For recent reviews, see (a) G. H. Posner, *Org. React.*, **19**, 1 (1972); (b) J. F. Normant, *Synthesis*, 63 (1972); (c) G. Bähr and P. Burba in "Methoden der Organischen Chemie," 4th ed, Vol. 13, Part 1, E. Müller, Ed, Georg Thieme Verlag, Stuttgart, 1970, pp 731–761.

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(4) (a) J. Hooz and R. B. Layton, *Can. J. Chem.*, **48**, 1626 (1970); (b) E. J. Corey and R. L. Carney, *J. Amer. Chem. Soc.*, **93**, 7318 (1971); E. J. Corey, C. U. Kim, R. H. K. Chen, and M. Takeda, *ibid.*, **94**, 4395 (1972); (c) F. S. Alvarez, D. Wren, and A. Prince, *ibid.*, **94**, 7823 (1972); (d) A. F. Kluge, K. G. Untch, and J. H. Fried, *ibid.*, **94**, 7827 (1972); (e) R. Pappo and P. W. Collins, *Tetrahedron Lett.*, **No. 26**, 2627 (1972).

(5) (a) J. A. Marshall and N. H. Andersen, *J. Org. Chem.*, **31**, 667 (1966); J. A. Marshall, N. H. Andersen, and P. C. Johnson, *ibid.*, **35**, 186 (1970); (b) H. O. House, R. W. Giese, K. Kronberger, J. P. Kaplan, and J. F. Simeone, *J. Amer. Chem. Soc.*, **92**, 2800 (1970).

(6) N. T. Luong-Thi and H. Rivière, *C. R. Acad. Sci., Ser. C*, **267**, 776 (1968); *Tetrahedron Lett.*, **No. 19**, 1579, 1583 (1970); H. Rivière and J. Tostain, *Bull. Soc. Chim. Fr.*, 568 (1969); (b) J. A. Marshall, W. I. Fanta, and H. Roebke, *J. Org. Chem.*, **31**, 1016 (1966); J. A. Marshall and H. Roebke, *ibid.*, **33**, 840 (1968); (c) R. G. Carlson and E. G. Zey, *ibid.*, **37**, 2468 (1972).

(7) G. van Koten and J. G. Noltes, *Chem. Commun.*, **No. 16**, 940 (1972).

(8) (a) G. van Koten, A. J. Leusink, and J. G. Noltes, *Chem. Commun.*, **No. 17**, 1107 (1970); J. M. Guss, R. Mason, I. Søtofte, G. van Koten, and J. G. Noltes, *ibid.*, **No. 8**, 446 (1972); (b) M. F. Lappert and R. Pearce, *ibid.*, **No. 1**, 24 (1973); (c) A. Cairncross and W. A. Sheppard, *J. Amer. Chem. Soc.*, **90**, 2186 (1968); **93**, 247 (1971); A. Cairncross, H. Omura, and W. A. Sheppard, *ibid.*, **93**, 248 (1971).

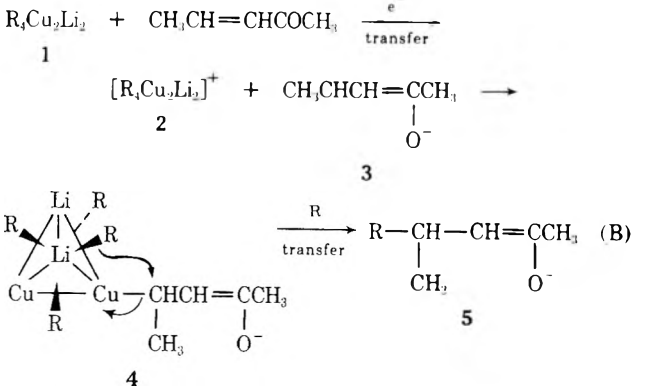
(9) See T. L. Brown, *Accounts Chem. Res.*, **1**, 23 (1968), and references cited therein.

(10) (a) G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe, and H. O. House, *J. Amer. Chem. Soc.*, **91**, 4871 (1969), and references cited therein; (b) G. M. Whitesides, J. San Filippo, Jr., E. R. Stredonsky, and C. P. Casey, *ibid.*, **91**, 6542 (1969).

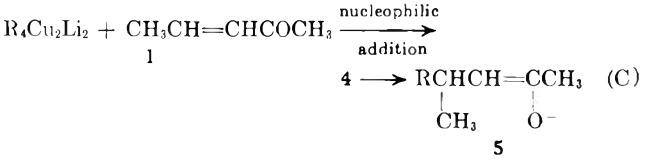
(11) In this species there are formally both the Cu(I) and Cu(II) valence states of copper present. The spectroscopic properties of crystals containing both Cu(I) and Cu(II) species have been discussed previously: P. Day and D. W. Smith, *J. Chem. Soc. A*, 1045 (1967).

dative dimerization (eq A) need not be a competing reaction (*cf.* ref 3c). We hope to resolve this question with studies in progress concerning the electrochemical oxidation of organocuprate reagents.

Meanwhile, we have noted[3f] that reactions of $Me_2CuLi$ with $\alpha,\beta$-unsaturated carbonyl compounds are normally effective for the conjugate addition of a methyl group to the $\beta$ carbon only when the reduction potential of the unsaturated carbonyl compound in an aprotic medium is more negative than *ca.* −1.1 V (*vs.* sce) but less negative than *ca.* −2.4 V (*vs.* sce). This correlation, accompanied by a simple empirical rule[3f] for estimating the reduction potentials of $\alpha,\beta$-unsaturated carbonyl compounds, allows synthetic procedures to be designed to avoid steps where the successful conjugate addition of $Me_2CuLi$ is uncertain. The correlation with reduction potentials is, of course, compatible with (but does not prove) the mechanistic scheme (eq B) proposed[3a,b,f,g] for the conjugate addition of organocuprates *via* an initial electron-transfer process to form the cation **2** and a radical anion **3**. The recombination of these species followed by an intramolecular transfer of the group R as illustrated in structure **4** can account for the formation of the initial reaction product, the enolate ion **5**, and the various stereochemical features of the reaction. We believe that the most reasonable alternative mechanistic path is the direct nucleophilic addition of the cuprate **1** to the enone to form the intermediate **4** is illustrated in eq C. This process, which



(B)

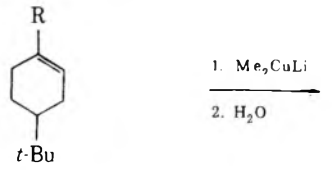


(C)

is analogous to the oxidative addition of an alkyl halide to a cuprate suggested in the first stage of the cuprate–alkyl halide coupling reaction,[10a] differs from the two-stage process (eq B) only in the timing of steps leading to intermediate **4**. Although various $\pi$ complexes of the enone and the cuprate **1** might be envisioned to precede either process, we are aware of no compelling evidence for their presence and have noted previously[3a] that the conjugate addition process is not retarded by the addition of reagents (*e.g.*, trialkylphosphines or trialkyl phosphites) that would certainly compete with the enone for coordination sites on copper. In this manuscript, we will describe the details of certain reactions cited previously[3f] in our correlation of reactivity with reduction potential and also describe reactions involving other cuprate additions. Among these is the use of a mixed cuprate reagent which has proved to be especially useful in synthetic work.

As a background for a synthetic application of cuprate reagents to be described elsewhere,[12] we wished to establish that the conjugate addition of a cuprate reagent to the unhindered cyclohexenyl ketone **6** (Scheme I) would occur in the expected manner (*via* a chair-like

SCHEME I

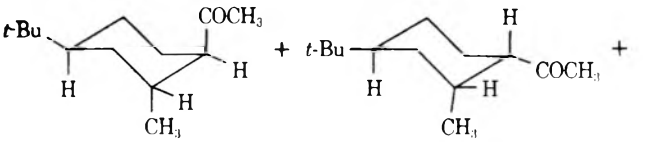


**6**, R = $COCH_3$ ($E_{1/2}$ = −2.24 V)

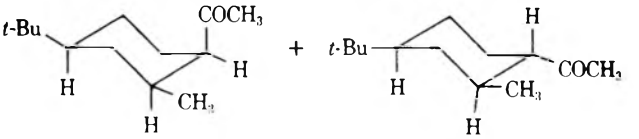
**11**, R = CN ($E_{1/2}$ = −2.55 V)

**12a**, R = $CO_2H$

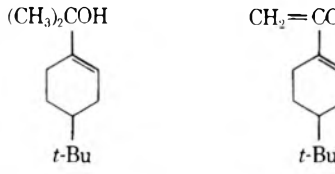
**12b**, R = $CO_2CH_3$ ($E_{1/2}$ = −2.50 V)



**7** (23% of product) **8** (69% of product)



**9** (4% of product) **10** (4% of product)



**I** **II**

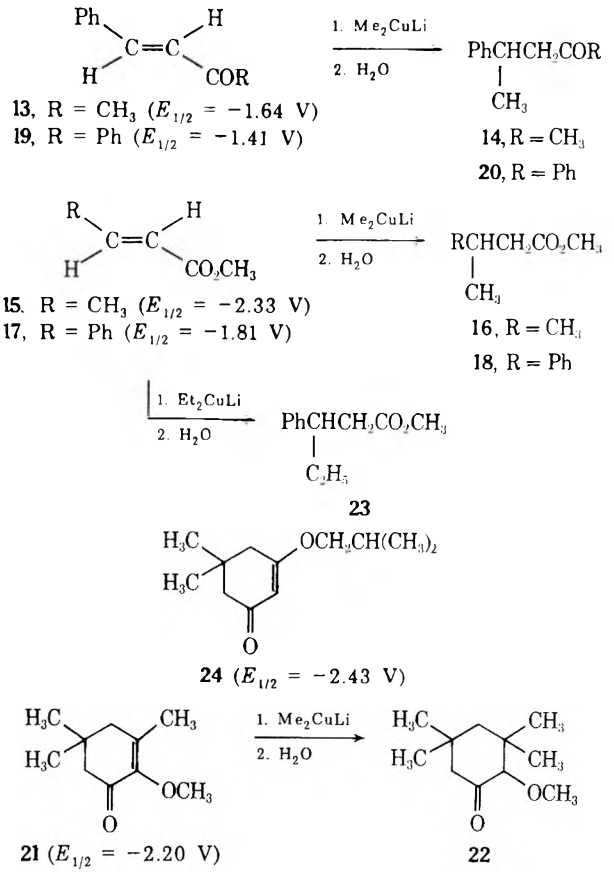
transition state)[3b,5] to form the adducts **7** and **8** with the added group in an axial conformation. As summarized in Scheme I, this expectation was realized with 92% of the conjugate addition product being the ketones **7** and **8** with axial methyl groups.[13] In the course of this work, we found that the more difficultly reduced unsaturated derivatives **11** and **12b** failed to react with $Me_2CuLi$ and were recovered unchanged.

To show that the failure of ester **12b** to react was not attributable to an inherent property of $\alpha,\beta$-unsaturated esters, we demonstrated the successful conjugate addition of $Me_2CuLi$ to both of the more easily reduced esters **15** and **17** (Scheme II) to form esters **16** and **18**. The benzylidene ketones **13** and **19** also reacted normally to form **14** and **20**. The difficultly reduced $\beta$-alkoxy enone **24** failed to react with $Me_2CuLi$, whereas the more easily reduced $\alpha$-alkoxy enone **21** did yield an adduct **22**. Although the $\beta$-diketone enol ether **24** failed to react with $Me_2CuLi_2$ and was recovered, the

(12) H. O. House and M. J. Umen, to be published.

(13) We are most grateful to Professor J. Jacques and M. Dvolaitzky for supplying us with authentic samples of ketones **7**, **8**, and **10** as well as a mixture containing ketone **9** and with nmr spectra for all of these ketones. The preparations of these ketones **7**–**10** are described by A. Heymes, M. Dvolaitzky, and J. Jacques, *Ann. Chim. (Paris)*, 543 (1968).

SCHEME II

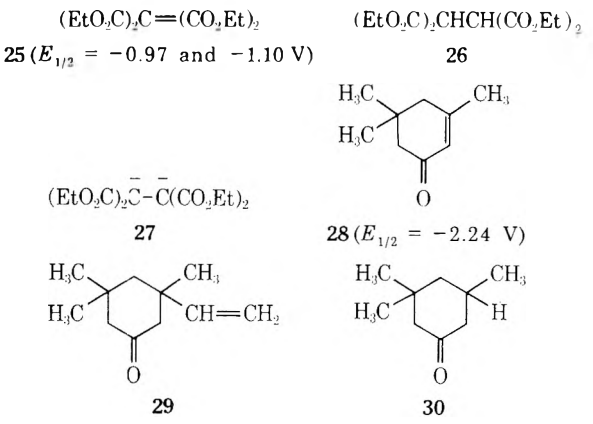



enol acetate of the same β-diketone has been found to react with this reagent.[3h] This difference appears to be consistent with the previously noted reduction potential correlation, since the presence of an electron-donating β-alkoxy substituent (Hammett $\sigma_{para} \sim -0.3$) is known[3f] to make the reduction potential of an α,β-unsaturated ketone more negative whereas an electron-withdrawing β-acetoxyl substituent (Hammett $\sigma_{para}$ +0.31) would be expected to increase the ease of reduction of an enone.

In the course of the foregoing studies two observations of interest were made. Normally, the progress of a $Me_2CuLi$ reaction is easily discerned because addition of a solution of the unsaturated carbonyl compound to the initially cold (0°), colorless $Et_2O$ solution of $Me_2CuLi$ results in an immediate exothermic reaction and polymeric MeCu separates from the cold (0–10°) reaction mixture as a voluminous yellow precipitate within approximately 1 min. These reactions are usually complete within 2–5 min. Also, in many cases the initial reaction mixture exhibits a transient bright red, orange, or violet color which disappears within 15–60 sec followed by the precipitation of MeCu. However, in two of the above cases, the ester **17** and the α-alkoxy ketone **21**, the reaction with $Me_2CuLi$ was unusually slow and complete reaction with the excess $Me_2CuLi$ present was not obtained even after periods of 30–90 min. (Since both the reaction of ester **15** with $Me_2CuLi$ and the subsequently described reaction of ester **17** with $Et_2CuLi$ exhibited normal rapid reaction rates, the reason for the rate difference in only two cases is presently obscure.) In any event, the rather prolonged reaction of ester **17** with $Me_2CuLi$, during which time a transient orange color persisted in the reaction mixture, prompted us to examine these reacting solutions in the probe of an epr spectrometer. Since we were unable to resolve any well-defined signal attributable to a carbon radical, we turned to nmr techniques and examined the nmr spectra of reacting solutions for emission signals arising from CIDNP. Although our experiments with ester **17** and $Me_2CuLi$ were unrewarding, the corresponding reaction of ester **17** with $Et_2CuLi$ produced a clear emission signal in the two highest field lines of the quartet attributable to the ethyl $CH_2$ group bound to a metal. This emission signal persisted for periods of 30 min or more at temperatures in the range −10 to 10°. However, as mentioned above, subsequent investigation revealed that reaction of the ester **17** with $Et_2CuLi$ was complete in <1 min and the prolonged CIDNP emission signal which we observed was arising from decomposition of the excess $Et_2CuLi$ in the reaction mixture. Furthermore, the CIDNP signal was observed only during the decomposition of $Et_2CuLi$ prepared from commercial CuI which was contaminated with traces of iron impurities. When these iron impurities were removed before the preparation of $Et_2CuLi$ (see Experimental Section), no CIDNP emission was observed under any of the above circumstances.[14] A number of pieces of circumstantial evidence have also led us to believe that the amount of iron impurities extracted from imperfectly sealed Teflon-coated magnetic stirring bars may also catalyze the decomposition of various cuprates; as a result, we believe it unwise to use any stirring device not completely encased in glass for organocuprate reactions.

In earlier synthetic studies[15] involving the conjugate addition of aryl Grignard reagents to the easily reduced tetraester **25** (Scheme III), a substantial fraction of the

SCHEME III




ester **25** was reduced to ester **26** unless the Grignard reagent was prepared from triply sublimed, rather than ordinary, Grignard-grade magnesium.[16] These observations suggested that the tetraester **25** might be a sufficiently powerful oxidant to remove two electrons from a cuprate reagent (*cf.* eq A) forming the dianion

(14) A similar complication from the iron-catalyzed decomposition of a Grignard reagent has been observed recently: R. B. Allen, R. G. Lawler, and H. R. Ward, *J. Amer. Chem. Soc.*, **95**, 1692 (1973).

(15) H. O. House, D. G. Melillo, and F. J. Sauter, *J. Org. Chem.*, **38**, 741 (1973).

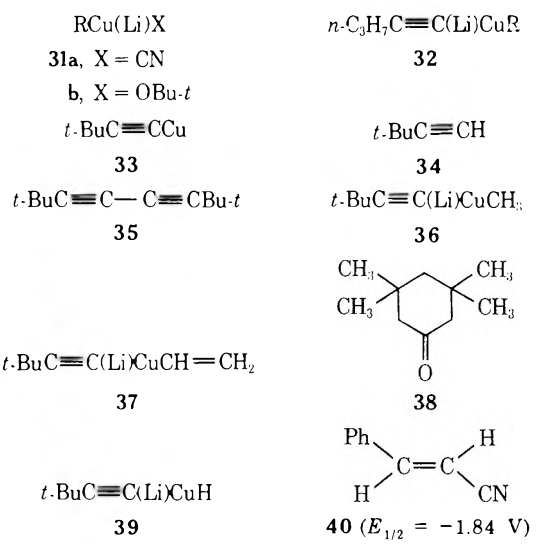
(16) The principal transition metal impurities in ordinary Grignard-grade magnesium are iron, copper, and manganese: D. O. Cowan, J. Hsu, and J. D. Roberts, *J. Org. Chem.*, **29**, 3688 (1964).

27 rather than a conjugate addition product. Reaction of the tetraester **25** with $Me_2CuLi$ confirmed this suspicion by forming, after acidification, the saturated ester **26** in 76–93% yield with no evidence for the formation of a conjugate addition product.

For a synthetic application to be described elsewhere,[12] we needed a reliable procedure for effecting the conjugate addition of a vinyl group in an enone. Although a number of conjugate additions with $(CH_2{=}CH)_2CuLi$[4a,b] and other dialkenylcuprates[3e,4c–e] have been reported, the substantial experimentation required[4d] to apply this reaction to preparative work suggested the need for an improved procedure. Our own experiments involving the preparation of $(CH_2{=}CH)_2CuLi$ from $CH_2{=}CHLi$ and CuI and the subsequent addition of this reagent to the model enone **28** to form adduct **29** also indicated the capricious nature of this procedure. We concluded that our problem arose because of the thermal instability of the vinyl cuprate reagents, which became especially serious as the temperature was raised from *ca.* −20° to 0° or higher. This thermal instability complicated formation of the cuprate because the reaction of $CH_2{=}CHLi$ with the insoluble CuI was relatively slow, especially at temperatures below −40°. Because of these problems various cuprate preparations either contained unchanged $CH_2{=}CHLi$ (which added to the carbonyl group of the enone **28**) or a substantial portion of the cuprate had decomposed, leading either to recovery of the enone **28** or the formation of its reduction product **30**. These difficulties were partially avoided by the use of the $Et_2O$-soluble complex $(MeO)_3PCuBr$ as a source of copper. However, neither the preparation of this complex nor the subsequent removal of $(MeO)_3P$ from the reaction mixtures was convenient and we were led to seek other soluble materials as sources of copper(I) in these reactions. Other recent approaches to this problem have utilized the reaction of CuCN,[17a] $n$-$C_3H_7C{\equiv}CCu$,[17b] or $t$-BuOCu[17c] with an organolithium reagent RLi to form the mixed cuprates **31** and **32** (Scheme IV), which will selectively transfer the group R in conjugate addition reactions.[18] However, neither CuCN nor $n$-$C_3H_7C{\equiv}CCu$ have appreciable solubility in ethereal solvents; although the solubility of the acetylide precursor of cuprate **32** can be increased by the addition of the ligand, $(Me_2N)_3P$,[17b] use of this ligand poses the same inconveniences noted above with $(MeO)_3P$. The mixed cuprate **31b** obtained from $t$-BuOCu appears to be satisfactory for the conjugate addition of alkyl groups; however, use of this reagent (**31b**, R = vinyl) to effect conjugate addition of a vinyl group is reported[17c] not to be a satisfactory procedure.

In exploring other possible copper(I) sources to use for cuprate preparations, we found that copper *tert*-butylacetylide (**33**) was an ideal reagent. This acetylide **33** was available from *tert*-butylacetylene either by reaction with a Cu(I) salt in aqueous ammonia or, preferably, by successive reaction of the acetylene **34** with 1 molar equiv of an organolithium reagent and 1 molar equiv of CuI. The acetylide, an orange-red solid melting with decomposition over the range 80–150°, could either be isolated or used *in situ* and, most important, *the acetylide* **33** *is readily soluble in both ethereal solvents and in saturated hydrocarbons.* Ether solutions of the acetylide **33** were conveniently hydrolyzed by shaking with aqueous $NH_3$ and, even when some competing oxidation occurred during isolation procedures, the product diyne **35** was very volatile and easily removed from reaction products. Employing this acetylide **33**, ether solutions of each of the mixed cuprates **36** (with MeLi at 0–10°) and **37** (with $CH_2{=}CHLi$ at −40°) could be prepared. Treatment of the cold red-orange ether solution of the acetylide **33** with the appropriate lithium reagent produced green solutions of the cuprates **36** and **37**. Each cuprate reacted with isophorone (**28**, 0–10° for **36** and −40 to 10° for **37**) to yield the corresponding adduct **29** or **38**. As the reaction with the cuprate **36** progressed the green color was discharged and the reaction solution again assumed the red-orange color of the acetylide **33**. The reaction of the mixed vinyl cuprate **37** with isophorone (**28**) was still a relatively slow process and some competing thermal decomposition of the cuprate **37** occurred with separation of a brown or black solid (possibly metallic copper). The subsequently described[12] reaction of this mixed cuprate **37** with the enone **6** was more rapid than reaction with isophorone (**28**), and less competing thermal decomposition was observed.

SCHEME IV




An interesting by-product, the reduced ketone **30**, was observed during the reaction of isophorone (**28**) with both $(CH_2{=}CH)_2CuLi$ and the mixed vinyl cuprate **37**. The amount of the by-product formed (typically 7–13%) seemed to be greatest in those reactions where the most thermal decomposition of the vinyl cuprate **37** was occurring, suggesting that one mode of the thermal decomposition of **37** involves transfer of a β-hydrogen atom from the vinyl group to the metal to form a mixed hydride cuprate reagent **39** that has the ability to reduce the C=C double bond of enones. We plan to investigate the formation and possible synthetic utility of such reagents further. It should be noted that a thermal decomposition of the type suggested is compatible both with the pathway followed in the thermal decomposition of alkylcopper

(17) (a) J. P. Gorlier, L. Hamon, J. Levisalles, and J. Wagnon, *Chem. Commun.*, **No. 3**, 88 (1973); (b) E. J. Corey and D. J. Beames, *J. Amer. Chem. Soc.*, **94**, 7210 (1972); (c) G. H. Posner and C. E. Whitten, *Tetrahedron Lett.*, **No. 21**, 1815 (1973).

(18) In general, acetylide or cyanide groups are not transferred from cuprates to unsaturated carbonyl compounds (ref 3b).

derivatives[10a,19] and also with the enhanced thermal stability of $Me_3SiCH_2Cu$,[8b] a compound lacking a $\beta$-hydrogen atom.

The mixed methyl cuprate **36**, although effective for the transfer of a methyl group to the relatively unreactive enone **28** (to form **38**), appeared to be less reactive than $Me_2CuLi$. Thus, with the $\alpha$-methoxy enone **21**, which reacted only very slowly with $Me_2CuLi$ to form **22**, none of the adduct **22** was detected after reaction of the enone **21** with the mixed cuprate **36** for 30 min at 5–18° and 73% of the unchanged enone **21** was recovered.

Finally, we have examined the reaction of the unsaturated nitrile **40** with both $Me_2CuLi$ and with the mixed cuprate **36**. Although the reduction potential (−1.84 V *vs.* sce) of cinnamonitrile is substantially less negative than that of the unsaturated nitrile **11**, in neither case was any evidence of reaction observed and both nitriles **11** and **40** were recovered unchanged. Consequently, it appears that the conjugate addition of cuprates to simple $\alpha,\beta$-unsaturated nitriles is not a useful procedure.

## Experimental Section[20]

**Starting Materials and Reagents.**—Commercial ethereal solutions of MeLi (halide free, Foote Mineral Co.) were standardized by the procedure of Watson and Eastham.[21] An ethereal solution of EtLi, prepared from Li and EtBr, was standardized by the same procedure.[21] A mixture of 22.7 g (100 mmol) of tetravinyltin (M and T Corp.) and 220 mmol of *n*-BuLi in 135 ml of hexane was agitated for 10 min and then the solid vinyllithium was collected on a sintered glass filter.[22] After the solid vinyllithium had been washed with three 50-ml portions of anhydrous hexane, it was dissolved in $Et_2O$ to give 171 ml of a pale yellow solution of ethereal 1.25 *M* vinyllithium (97% yield based on *n*-BuLi). This ethereal solution, standardized by the usual procedure,[21] had nmr absorption corresponding to the published spectrum.[22] Commercial solutions of vinyllithium in THF (a red-brown suspension obtained from Lithium Corporation of America) could be partially purified by removing the THF under reduced pressure followed by extraction of the residue with $Et_2O$ and centrifugation. The resulting orange ethereal solution of vinyllithium contained an extra nmr peak at $\delta$ 7.35 attributable to an unidentified impurity still present. Commercial samples of CuI and CuBr were obtained from Fisher Scientific Co. The colored impurities were removed from these salts by dissolving them in a saturated aqueous solution of the appropriate halide (KI or KBr) followed by treatment with charcoal, filtration, and dilution with water to reprecipitate the Cu(I) halide.[23] Spectrographic analysis of these commercial copper salts indicated them to contain trace amounts (*ca.* 0.005%) of Fe salts, but other common transition metal impurities (Cr, Mn, Ni, Co) were not detected. This iron impurity could be removed by dissolving the Cu(I) salt in at least 2 molar equiv of freshly distilled $Bu_2S$, bp 74–75° (14 mm), to form the $Et_2O$-soluble liquid complexes $ICu(SBu_2)_2$ or $BrCu(SBu_2)_2$. These liquids were filtered through a sintered glass funnel to remove the insoluble iron-containing impurities (spectrographic analysis) and the filtrates were heated to 140–160° under 10–20-mm pressure in a rotary evaporator to leave the copper salts in which the iron-containing impurity was not detected (spectrographic analysis). The copper(I) halides purified in this fashion are subsequently designated as iron-free.

Alternatively, the iron impurity could be removed by forming and then recrystallizing the trimethyl phosphite complexes of these copper(I) halides. After a mixture of 1.897 g (10.0 mmol) of CuI and 1.230 g (9.94 mmol) of $(MeO)_3P$ in 20 ml of PhH had been refluxed for 7.8 hr, it was filtered and concentrated to separate 2.945 g (94%) of the crude phosphite complex as a white solid, mp 179.5–189.5°. Recrystallization ($CHCl_3$–$Et_2O$) afforded 1.066 g of pure $(MeO)_3PCuI$ as white needles, mp 192.5–194° (lit.[24] mp 192–193°).

A mixture of 143.5 g (1.00 mol) of CuBr and 124 g (1.00 mol) of $(MeO)_3P$ in 2 l. of PhH was refluxed for 8.3 hr and then filtered and concentrated. The tan solid that separated was recrystallized ($CHCl_3$–$Et_2O$) to separate 97.9 g (37%) of $(MeO)_3PCuBr$ as white cubes, mp 212–218° dec. Concentration of the mother liquors separated an additional 139 g (total yield 89%) of the same complex: ir ($CCl_4$) 1450, 1180, and 1025 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 3.75 (d, $J_{PH}$ = 12.9 Hz, $CH_3OP$); uv ($CH_3CN$) end absorption at 230 m$\mu$ ($\epsilon$ 10,200).

*Anal.* Calcd for $C_3H_9BrCuO_3P$: C, 13.47; H, 3.39; Br, 29.87; P, 11.58. Found: C, 13.42; H, 3.26; Br, 29.82; P, 11.55.

All ethereal solvents used in organometallic reactions were distilled from $LiAlH_4$ immediately before use. Following a previously described procedure,[25] 200 g (1.30 mol) of 4-*tert*-butylcyclohexanone was treated with 98 g (1.9 mol) of NaCN (95%) and 3.62 mol of HCl in 380 ml of $H_2O$ and 950 ml of $Et_2O$ at 20–29° to form 236 g of the crude cyanohydrin as a pale yellow oil that solidified on standing, mp 56–57° (lit.[25] mp 54–57°). Reaction of 118.5 g (0.655 mol) of this crude cyanohydrin with 200 g (1.30 mol) of $POCl_3$ in 323 ml of pyridine and 150 ml of PhH yielded 107 g (100%) of the crude nitrile **11** that crystallized on standing. Recrystallization (EtOH) afforded the pure nitrile **11** as white plates: mp 44–45° (lit.[25] mp 45–46°); ir ($CCl_4$) 2218 (conjugated C≡N) and 1648 $cm^{-1}$ [C=C]; uv (95% EtOH) end absorption at 210 m$\mu$ ($\epsilon$ 10,600); nmr ($CCl_4$) $\delta$ 6.4–6.7 (1 H, m, vinyl CH), 1.0–2.5 (7 H, m, aliphatic CH), and 0.89 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity), 163 ($M^+$, 69), 148 (63), 108 (47), 107 (100), 106 (75), 92 (63), 84 (44), 79 (38), 77 (34), 69 (50), 57 (84), and 41 (48). Hydrolysis of 32.9 g (0.202 mol) of the nitrile **11** with 41.6 g (0.64 mol) of KOH (85%) in 160 ml of refluxing ethylene glycol yielded 33.5 g (92%) of the crude solid acid **12a**. Recrystallization from aqueous HOAc separated the pure acid **12a** as white needles: mp 188.5–189.5° (lit.[26] mp 182–184°); ir ($CCl_4$) 2850–3300 (broad, associated OH), 1688 (carboxyl C=O), and 1648 $cm^{-1}$ (C=C); uv max (95% EtOH) 213.5 m$\mu$ ($\epsilon$ 12,600); nmr ($CF_3CO_2H$) $\delta$ 7.2–7.5 (1 H, m, vinyl CH), 1.1–2.6 (7 H, m, aliphatic CH), and 0.93 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 182 ($M^+$, 30), 139 (77), 127 (60), 126 (100), 125 (38), 111 (49), 84 (36), 81 (45), 79 (50), 69 (43), 57 (70), and 41 (36). A mixture of 27.7 g (0.152 mol) of the acid **12a**, 14.6 g (0.46 mol) of MeOH, 0.5 ml of concentrated $H_2SO_4$, and 75 ml of $ClCH_2CH_2Cl$ was refluxed[27] for 15 hr and then partitioned between $CH_2Cl_2$ and aqueous $NaHCO_3$. The organic solution was concentrated and an ether solution of the residue was washed with $NaHCO_3$, dried, and concentrated. Distillation of the residue (20.08 g) in a short-path still followed by distillation through a 60-cm spinning band column separated the pure ester **12b** as a colorless liquid which exhibited a single glpc peak: bp 62° (0.3 mm); $n^{25}D$ 1.4758; ir ($CCl_4$), 1721, 1711 (conjugated ester C=O), and 1657 $cm^{-1}$ (C=C); uv max (95% EtOH) 216 m$\mu$ ($\epsilon$ 12,400); nmr ($CCl_4$) $\delta$ 6.7–7.0 (1 H, m, vinyl CH), 3.63 (3 H, s, $OCH_3$), 1.0–2.5 (7 H, m, aliphatic CH), and 0.87 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 196 ($M^+$, 11), 140 (70), 81 (21), 79 (24), 57 (100), 53 (22), and 41 (26).

(19) G. M. Whitesides, E. P. Stredronsky, C. P. Casey, and J. San Filippo, Jr., *J. Amer. Chem. Soc.*, **92**, 1426 (1970).

(20) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated $MgSO_4$ was employed as a drying agent. The ir spectra were determined with a Perkin-Elmer Model 257 infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Perkin-Elmer Model 202 recording spectrophotometer. The nmr spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60 nmr spectrometer or at 100 MHz with a JEOL nmr spectrometer. The chemical shift values are expressed in $\delta$ values (parts per million) relative to a $Me_4Si$ internal standard. The mass spectra were obtained with an Hitachi Perkin-Elmer Model RMU-7 or a Varian Model M-66 mass spectrometer. All reactions involving strong bases or organometallic intermediates were performed under a nitrogen atmosphere.

(21) (a) S. C. Watson and J. F. Eastham, *J. Organometal. Chem.*, **9**, 165 (1967). (b) For a detailed description of the titration procedure, see M. Gall and H. O. House, *Org. Syn.*, **52**, 39 (1972).

(22) The proceedure of D. Seyferth and M. A. Weiner, *J. Amer. Chem. Soc.*, **83**, 3583 (1961); D. Seyferth, C. S. Johnson, Jr., M. A. Weiner, and J. S. Waugh, *ibid.*, **83**, 1306 (1961).

(23) The procedure of G. B. Kauffman and L. A. Teter, *Inorg. Syn.*, **7**, 9 (1963).

(24) H. O. House, W. F. Fischer, Jr., M. Gall, T. McLaughlin, and N. Peet, *J. Org. Chem.*, **36**, 3429 (1971).

(25) R. A. Abramovitch and D. L. Struble, *Tetrahedron*, **24**, 357 (1968).

(26) L. Munday, *J. Chem. Soc.*, 1413 (1964).

(27) The esterification procedure of R. O. Clinton and S. C. Laskowski, *J. Amer. Chem. Soc.*, **70**, 3135 (1948).

*Anal.* Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.32; H, 10.23.

To 110 ml of a cold (0–10°) $Et_2O$ solution containing 0.184 mol of MeLi was added 14.8 g (0.091 mol) of the nitrile **11** in 30 ml of $Et_2O$. After the resulting red-orange solution had been stirred for 20 min, it was partitioned between $Et_2O$ and 500 ml of aqueous 1 *M* HCl. The $Et_2O$ layer was washed with aqueous $NaHCO_3$, dried, and concentrated. The aqueous HCl layer was mixed with 300 ml of hexane and then refluxed for 18 hr to complete hydrolysis of the imine. The combined hexane layer and hexane extract of the aqueous phase were washed with aqueous $NaHCO_3$, dried, concentrated, and combined with the earlier neutral product from $Et_2O$ extraction. Distillation separated 12.95 g (80%) of the pure (glpc) ketone **6** as a colorless liquid: bp 141–143° (19 mm); $n^{25}D$ 1.4844 [lit. bp 137° (18 mm),[13] 135–137° (14 mm)[28]]; ir ($CCl_4$) 1659 (conjugated C=O) and 1643 $cm^{-1}$ (C=C); uv max (95% EtOH) 232 mμ (ε 9150); nmr ($CCl_4$) δ 6.7–6.9 (1 H, m, vinyl CH), 2.17 (3 H, s, $COCH_3$), 1.0–2.7 (7 H, m, aliphatic CH), and 0.90 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 180 ($M^+$, 100), 165 (35), 124 (77), 123 (92), 109 (89), 81 (59), 57 (91), 43 (74), and 41(43).

**Preparation of Copper(I) *tert*-Butylacetylide (33).**—*tert*-Butylacetylene (**34**) was prepared by modification[29] of procedures described previously.[30,31] To 240 g (2.4 mol) of cold (0°) pinacolone was added, portionwise with cooling and stirring during 2 hr, 500 g (2.4 mol) of powdered $PCl_5$. After the resulting brown suspension had been stirred in an ice bath for an additional 9 hr, it was poured onto 1.4 kg of ice and the resulting mixture was allowed to stand in a refrigerator overnight. The resulting purple mixture was extracted with $Et_2O$ and the ethereal extract was dried and concentrated cautiously under reduced pressure on a rotary evaporator until the crude product, 2,2-dimethyl-3,3-dichlorobutane, just began to sublime.[32] The residual yellow semisolid (237.6 g) contained (nmr analysis) *ca.* 60% of the dichloride and *ca.* 40% of 3,3-dimethyl-2-chloro-1-butene. The subsequent dehydrochlorination was effected in a flask fitted with a condenser through which warm (55°) water was circulated so that the intermediate chloro olefin (bp 97–99°)[30] and EtOH would not distil from the reaction mixture. The crude mixture of dichloride and chloro olefin (239 g) was mixed with 1 kg (15 mol) of 85% KOH flakes and 120 ml of EtOH and the mixture was heated under partial reflux until distillation of the acetylene **34** was complete. The acetylene was collected as 43.9 g (*ca.* 20% based on pinacolone) of a fraction, bp 34–38°, containing (nmr analysis) *ca.* 8% $Et_2O$ and 76.01 g (38.6%, total yield *ca.* 58% based on pinacolone) of the acetylene **34**, bp 36–38°. Redistillation afforded the pure acetylene **34** as a colorless liquid: bp 36–38°; $n^{25}D$ 1.3738 [lit. bp 36.4–37.8° (768.3 mm),[30] $n^{20}D$ 1.3736[33]]; ir ($CCl_4$), 3320 (acetylenic CH) and 2110 $cm^{-1}$ (C≡C); nmr ($CCl_4$) δ 1.88 (1 Hs, C≡CH) and 1.25 (9 H, s, *t*-Bu).

A cold (0–5°) solution of 2.50 g (10 mmol) of $CuSO_4 \cdot 5H_2O$ and 10 ml of aqueous 28% $NH_3$ in 40 ml of $H_2O$ was flushed with $N_2$ and then treated with 1.42 g (20.4 mmol) of $HONH_3Cl$. The resulting solution of the copper(I) complex, under an $N_2$ atmosphere, was treated with 0.80 g (10 mmol) of the acetylene **34** and the cold mixture was mixed *vigorously* with a Vibromixer. The acetylide **33** began to separate as an orange solid as soon as the mixing started. After the mixing had been maintained for 10 min, the bulk of the colorless aqueous solution was removed with a cannula and the residual orange solid copper(I) acetylide **33** was extracted from the remaining materials with 100 ml of pentane. The pentane extract was washed with $H_2O$, dried over $Na_2SO_4$, and concentrated to leave 0.77 g (54%) of the acetylide **33** as an orange liquid. A solution of this material in $Et_2O$ was concentrated under reduced pressure to deposit the pure acetylide **33** as an orange solid: mp 80–150° dec (lit.[34] mp 80–140°); ir ($CCl_4$) 2000 $cm^{-1}$ (C≡C); uv (heptane) points of inflection at 235 mμ (ε 5350) and 316 (2680) with gradually diminishing absorption out to *ca.* 600 mμ; nmr ($CCl_4$) δ 1.37 (s, *t*-Bu).

*Anal.* Calcd for $C_6H_9Cu$: C, 49.81; H, 6.27. Found: C, 49.88; H, 6.19.

Although this general procedure is normally very satisfactory for the synthesis of *insoluble* copper(I) acetylides,[35] in the present case the method proved to be very capricious, presumably because the acetylide **33** was soluble in the starting liquid acetylene **34** and, consequently, was not protected from hydrolysis. For example, an $Et_2O$ solution of the acetylide **33** was rapidly hydrolyzed by shaking with aqueous $NH_3$. For this reason, we found it more practical to generate $Et_2O$ solutions of the acetylide **33** by adding the acetylene **34** to an $Et_2O$ solution containing 1 molar equiv of MeLi. The resulting $Et_2O$ solution of *t*-BuC≡CLi was added to a cold (5°) slurry of CuI in $Et_2O$ and the resulting mixture was stirred at 25–30° for 15 min to give an orange solution of the acetylide **33** and an equimolar amount of LiI. Apart from the presence of LiI, we have observed no difference in the physical or chemical properties between these solutions and the solutions obtained by dissolving the pure acetylide **33** in $Et_2O$.

Employing a general procedure for the coupling of terminal acetylenes,[36] a mixture of 5.5 g (28 mmol) of $Cu(OAc)_2 \cdot H_2O$, 10 ml of pyridine, 10 ml of MeOH, and 1.61 g (19.6 mmol) of the acetylene **34** was refluxed with stirring for 1 hr. The resulting mixture was cooled in an ice bath, acidified with 60 ml of 9 *M* $H_2SO_4$, diluted with $H_2O$, and extracted with $Et_2O$. After the $Et_2O$ extract had been washed successively with $H_2O$ and aqueous $NaHCO_3$, it was dried and concentrated to leave 679 mg (43%) of the crude diyne **35** as a white solid. Recrystallization (EtOH) separated 255 mg (16%) of the pure diyne **35** as white cubes: mp 129.5–131.5° (lit. mp 130–131°,[37a] 130–132°[37b]); ir ($CCl_4$) 2160 $cm^{-1}$ (weak, C≡C); uv max (heptane) 215 mμ (ε 152), 226 (245), 238 (284), and 251.5 (186); nmr ($CCl_4$) δ 1.22 (s, *t*-Bu); mass spectrum *m/e* (rel intensity) 162 ($M^+$, 100), 147 (33), 119 (50), 117 (21), 107 (24), 105 (45), 91 (45), 77 (22), 55 (29), 41 (65), 40 (20), and 39 (20).

**Reaction of the Enone 6 with $LiCuMe_2$.**—To a cold (−5°) solution of $Me_2CuLi$ [from 25 mmol of MeLi and 2.37 g (12.5 mmol) of CuI] in 20 ml of $Et_2O$ was added a solution of 1.829 g (10.1 mmol) of the enone **6** in 6 ml of $Et_2O$. The resulting mixture, from which a yellow precipitate of MeCu separated almost immediately, was stirred at −5 to 10° for 10 min and then partitioned between ether and an aqueous solution (pH 8) of $NH_3$ and $NH_4Cl$. The $Et_2O$ solution was washed with aqueous $Na_2S_2O_3$, dried, and concentrated. Distillation separated 1.601 g (81%) of product as a pale yellow liquid, bp 45–59° (0.3 mm), which contained (glpc, silicone fluid $QF_1$ on Chromosorb P) the following components: alcohol **I** eluted as diene **II** (*ca.* 8%, retention time 4.0 min), ketone **9** (*ca.* 4%, 7.6 min), ketone **7** (*ca.* 21%, 10.8 min), ketone **10** (*ca.* 4%, 12.8 min), and ketone **8** (*ca.* 63%, 14.9 min). The product mixture was chromatographed on silica gel with 5% EtOAc in hexane as an eluent. The latter fractions from the chromatograph contained the crude alcohol **I**. Crystallization from hexane and subsequent sublimation afforded the alcohol **I** as white needles: mp 75.3–76.3° (lit.[13] mp 76–78°); ir ($CCl_4$) 3600 $cm^{-1}$ (OH); nmr ($CCl_4$) δ 5.6–5.8 (1 H, m, vinyl CH), 1.0–2.3 (7 H, m, aliphatic CH), 1.37 (1 H, s, OH, exchanged with $D_2O$), 1.23 (6 H, s, $CH_3$), and 0.87 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 196 ($M^+$, 11), 182 (22), 181 (100), 123 (25), 121 (27), 107 (29), 97 (22), 59 (44), 57 (61), 43 (67), and 41 (34). The early fractions from this chromatograph contained a minor liquid component believed to be the diene **II**: ir ($CCl_4$) 1641 and 1610 $cm^{-1}$ (C=C); mass spectrum *m/e* (rel intensity) 178 ($M^+$, 47), 121 (69), 107 (78), 93 (50), 79 (100), 71 (43), 57 (93), 43 (45), and 41 (53). The ketone-containing fractions were rechromatographed on silica gel with 50% PhH in hexane as the eluent to separate pure samples of the ketones **7**, **8**, and **9**. Ketone **7** has the following spectroscopic properties: ir ($CCl_4$) 1704 $cm^{-1}$ (C=O); nmr ($CDCl_3$, 100 MHz) δ 1.0–2.8 (9, H, m, aliphatic CH), 2.10 (3 H, s, $CH_3CO$), 1.03 (3 H, d, $J$ = 7 Hz, $CH_3$), and 0.78 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 196 ($M^+$, 14) 140 (29), 139 (28), 97 (44), 95 (32), 85 (57), 71 (42), 69 (31), 57 (75), 55 (45), 43 (100), and 41 (51).

(28) M. S. Newman and P. H. Goble, *J. Amer. Chem. Soc.*, **82**, 4098 (1960).

(29) These modified procedures were developed in our laboratories by Dr. Norton P. Peet and Mrs. Edith F. Kinloch.

(30) P. D. Bartlett and L. J. Rosen, *J. Amer. Chem. Soc.*, **64**, 543 (1942).

(31) W. H. Puterbaugh and M. S. Newman, *J. Amer. Chem. Soc.*, **81**, 1611 (1959).

(32) It was important to remove as much $Et_2O$ as practical at this stage, since its subsequent separation from the acetylene was difficult.

(33) P. Pomerantz, A. Fookson, T. W. Mears, S. Rothberg, and F. L. Howard, *J. Res. Natl. Bur. Stand., No. 2*, **52**, 51 (1954).

(34) A. E. Favorskii and L. Morev, *J. Russ. Phys.-Chem. Soc.*, **50**, 571 (1920); *Chem. Abstr.*, **18**, 2496 (1924). In accord with our observations, these authors report that the yellow form of the acetylide changes to a red form when it is heated above 80°.

(35) See D. C. Owsley and C. E. Castro, *Org. Syn.*, **52**, 128 (1972), and references cited therein.

(36) I. D. Campbell and G. Eglinton, *Org. Syn.*, **45**, 39 (1965).

(37) (a) H. Bock and H. Seidl, *J. Chem. Soc. B*, 1158 (1968); (b) F. Bohlmann, *Chem. Ber.*, **86**, 657 (1953).

The spectroscopic properties of ketone **8** are ir ($CCl_4$) 1709 $cm^{-1}$ (C=O); nmr ($CDCl_3$, 100 MHz), δ 1.0–2.7 (9 H, m, aliphatic CH), 2.06 (3 H, s, $CH_3CO$), and 0.83 (9 H, s, *t*-Bu) partially resolved from an apparent 3 H doublet ($CH_3$); mass spectrum *m/e* (rel intensity), 196 ($M^+$, 40), 140 (58), 139 (79), 97 (94), 95 (46), 85 (45), 83 (40), 71 (73), 69 (57), 57 (100), 43 (90), and 40 (56). Each of these major products **7** and **8** was identified with an authentic sample[13] by comparison of ir and nmr spectra and glpc retention times. The spectroscopic properties of ketone **9**, identified with an authentic sample[13] by comparison of nmr spectra and glpc retention times, are ir ($CCl_4$) 1708 $cm^{-1}$ (C=O); nmr ($CDCl_3$, 100 MHz) δ 0.9–2.8 (12 H, m, $CH_3$ and aliphatic CH), 2.06 (3 H, s, $CH_3CO$), and 0.82 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 196 ($M^+$, 44), 140 (55), 139 (51), 97 (57), 95 (33), 85 (70), 84 (34), 71 (100), 57 (89), 55 (37), 43 (92), 41 (40), and 40 (68). Treatment of 5.4 mg of ketone **9** with 3.5 mg of NaOMe in 10 ml of refluxing MeOH afforded a mixture containing primarily ketone **10**, ir ($CCl_4$) 1710 $cm^{-1}$ (C=O). This material was identified with an authentic sample[13] by comparison of ir spectra and glpc retention times.

In related experiments, a cold (−10 to −5°) solution of $Me_2CuLi$ [from 9.38 g (48.4 mmol) of CuI and 96.8 mmol of MeLi] in 80 ml of $Et_2O$ was treated with 6.603 g (40.5 mmol) of the nitrile **11** in 20 ml of $Et_2O$. After a 10-min reaction period, the usual isolation procedure separated 6.033 g (92%) of the starting nitrile **11**, mp 44.5–45.5° (identified by a mixture melting point and comparison of ir and nmr spectra), with no evidence for any methylated product. Similarly, treatment of $Me_2CuLi$ [from 2.26 g (11.9 mmol) of CuI and 23.6 mmol of MeLi] in 20 ml of $Et_2O$ with 1.901 g (9.70 mmol) of the ester **12b** in 6 ml of $Et_2O$ resulted in recovery of 1.703 g (90%) of the starting ester **12b**, bp 31–66° (0.5 mm), $n^{25}D$ 1.4750, identified from ir, nmr, and glpc data. Also, treatment of cold (−5°), ethereal (28 ml) $Me_2CuLi$ [from 3.33 g (17.0 mmol) of CuI and 33.8 mmol of MeLi] with 2.695 g (13.8 mmol) of the keto enol ether **24**[38] in 8 ml of $Et_2O$ for 10 min resulted in recovery of 2.425 g (90%) of the starting ketone **24**, bp 88–92° (0.4 mm), $n^{25}D$ 1.4782, identified from ir, nmr, and glpc data.

**Reaction of the Tetraester 25 with $LiCuMe_2$.**—To a cold (−5°) solution of $LiCuMe_2$ [from 49.0 mmol of MeLi and 4.68 g (24.6 mmol) of CuI] in 37.5 ml of $Et_2O$ was added, dropwise and with stirring during 25 min, 6.167 g (19.5 mmol) of the tetraester **25**, mp 52.5–54° (lit.[39] mp 52.5–53.5°), in 20 ml of $Et_2O$. The reaction mixture, from which MeCu separated almost immediately, was maintained at −5 to 10° and stirred for an additional 10 min and then partitioned between $Et_2O$ and aqueous $NH_3$ and $NH_4Cl$. The organic layer was washed with aqueous $Na_2S_2O_3$, dried, and concentrated to leave 4.724 g (76%) of the saturated tetraester **26**, mp 71.3–72.3°. Recrystallization from EtOAc–hexane separated the pure tetraester **26** as white needles: mp 73.3–74.3° (lit. mp 75°,[40b] 75–76°[40a]); ir ($CCl_4$), 1750 and 1740 $cm^{-1}$ (ester C=O); nmr ($CCl_4$) δ 4.18 (8 H, q, *J* = 7 Hz, ethoxyl $CH_2$), 3.95 (2 H, s, CH), and 1.27 (12 H, t, *J* = 7 Hz, ethoxyl $CH_3$); mass spectrum *m/e* (rel intensity) 273 (64), 245 (42), 227 (64), 199 (96), 173 (82), 171 (57), 143 (73), 127 (100), and 99 (85). When this reaction was repeated with 19.5 mmol of the unsaturated tetraester **25** and 22.7 mmol of $Me_2CuLi$ (from iron-free CuI), the yield of the saturated tetraester **26** was 93.5%.

**Reaction of Benzalacetone (13) with $LiCuMe_2$.**—The addition of an $Et_2O$ solution of 1.961 g (13.4 mmol) of the ketone **13** to a cold (−5°) solution of $LiCuMe_2$ [from 32.0 mmol of MeLi and 3.10 g (16.3 mmol) of CuI] in 26 ml of $Et_2O$ resulted in the immediate formation of a red color which rapidly disappeared with the simultaneous separation of MeCu. After a reaction time of 10 min at −5 to 8°, the usual isolation procedure afforded 1.767 g (*ca.* 82%) of liquid product, bp 64–66° (0.45 mm), which contained (glpc, silicone fluid $QF_1$ on Chromosorb P) *ca.* 95% of the ketone **14** (retention time 12.2 min) accompanied by *ca.* 5% of 1-phenyl-3-methyl-1,3-butadiene (6.0 min); no reduced product, 4-phenyl-2-butanone (retention time 11.7 min), was detected by glpc analysis and no starting ketone **13** was detected by glpc or nmr analysis. Collected (glpc) samples of the products, ketone **14**, and the diene, were identified with authentic samples[41] by comparison of ir spectra and glpc retention times. The ketone **14** has nmr ($CCl_4$) peaks at δ 7.16 (5 H, m, aryl CH), 3.22 (1 H, m, benzylic CH), 2.5–2.8 (2 H, m, $CH_2CO$), 1.95 (3 H, s, $COCH_3$), and 1.23 (3 H, d, *J* = 6.5 Hz, $CH_3$).

**Reaction of Methyl Crotonate (15) with $LiCuMe_2$.**—Treatment of a cold (0°) solution of $LiCuMe_2$ [from 35 mmol of MeLi and 3.44 g (18.1 mmol) of CuI] in 30 ml of $Et_2O$ with 1.335 g (13.3 mmol) of the ester **15** in 8 ml of $Et_2O$ resulted in the rapid separation of MeCu. After a reaction time of 10 min at 5–22°, the usual isolation procedure separated 985 mg (63%) of the ester **16**, bp 112–113°, $n^{25}D$ 1.3896, which was contaminated (glpc, silicone fluid $QF_1$ on Chromosorb P) with a small amount of $Et_2O$. An additional 248 mg (16%, total yield 79%) of the ester **16** was recovered from the distillation apparatus. A collected (glpc) sample of the pure ester **16** was identified with an authentic sample by comparison of ir and nmr spectra and glpc retention times. An authentic sample of the ester **16**, prepared in 79% yield by esterification of isovaleric acid with MeOH, $H_2SO_4$, and $CH_2Cl_2$, was obtained as a colorless liquid: bp 115–118°; $n^{25}D$ 1.3918 (lit. bp 115–116°,[42a] $n^{25}D$ 1.3900[42b]); ir ($CCl_4$), 1740 $cm^{-1}$ (ester C=O); nmr ($CCl_4$) δ 3.62 (3 H, s, $OCH_3$) and 1.9–2.3 (3 H, m, CH and $CH_2CO$), and 0.8–1.1 (6 H, m, $CH_3$); mass spectrum *m/e* (rel intensity) 116 ($M^+$, 3), 101 (58), 88 (53), 85 (82), 74 (100), 59 (66), 57 (83), 43 (65), and 41 (49).

**Reaction of Methyl Cinnamate (17) with $LiCuMe_2$.**—Addition of 2.320 g (14.3 mmol) of the ester **17** in 10 ml $Et_2O$ to a cold (−5°) solution of $LiCuMe_2$ [from 85.0 mmol of MeLi and 8.19 g (43.1 mmol) of CuI] in 63 ml of $Et_2O$ formed a yellow-orange solution which was stirred at −5 to 5° for 40 min; the precipitation of MeCu began after approximately 30 min. The usual isolation procedure afforded 2.014 g (79%) of liquid product, bp 35–75° (0.5 mm), which contained (glpc, silicone fluid $QF_1$ on Chromosorb P) the ester **18** (retention time, 5.8 min) accompanied by very minor amounts of two components with the same retention times as the ketone **14** (7.4 min) and the starting ester **17** (9.4 min). A collected (glpc) sample of the ester **18** was identified with an authentic sample by comparison of ir and nmr spectra and of glpc retention times. An authentic sample of the ester **18**, prepared in 89% yield by esterification of 3-phenylbutanoic acid, was obtained as a colorless liquid: bp 74–78° (0.5 mm); $n^{25}D$ 1.4972 [lit. bp 133–134° (22 mm),[43a] $n^{25}D$ 1.4999[43b]]; ir ($CCl_4$) 1740 $cm^{-1}$ (ester C=O); nmr ($CCl_4$) δ 7.15 (5 H, m, aryl CH), 3.47 (3 H, s, $OCH_3$), 2.9–3.7 (1 H, m, benzylic CH), 2.4–2.7 (2 H, m, $CH_2CO$), and 1.23 (3 H, d, *J* = 6.5 Hz, $CH_3$); mass spectrum *m/e* (rel intensity), 178 ($M^+$, 33), 121 (18), 118 (74), and 105 (100).

The same reaction was repeated with 36 mmol of $Me_2CuLi$ and 34.7 mmol of the ester **17** in 57 ml of $Et_2O$ at 25–40° for 30 min, to give 5.48 g of crude liquid product. After addition of a known weight of internal standard (*n*-$C_{12}H_{26}$), glpc analysis (silicone gum SE-52 on Chromosorb P) indicated the presence of *n*-dodecane (retention time 5.9 min at 133°), the saturated ester **18** (56% yield, 11.9 min at 133°), and two unidentified higher boiling components (46.4 and 52.4 min at 230°). Short-path distillation separated a sample of the pure ester **18**, $n^{25}D$ 1.4961, that was identified with the previously described sample by comparison of ir spectra. Analysis (glpc) of the residue from this mixture established the absence of either of the diastereoisomers[5b] of the dihydro dimer **41** among the high-boiling byproducts.

**41**

**Reaction of Methyl Cinnamate (17) with $Et_2CuLi$.**—To a cold (−30°) solution of $Et_2CuLi$, prepared from 4.23 g (22.2 mmol) of CuI, 40.8 mmol of EtLi, and 30 ml of $Et_2O$, was added a solution of 1.616 g (10.0 mmol) of the ester **17** in 10 ml of $Et_2O$. The resulting greenish-purple solution was stirred at −20 to 2° for 75 min and then subjected to the usual isolation procedure to separate 1.741 g of crude product as a yellow liquid. Short-path distillation (100° bath and 0.3 mm) separated 1.253 g 65%) of the pure (glpc, silicone fluid $QF_1$ on Chromosorb P) ester **23**

(38) The preparation and properties of this enone are described elsewhere (ref 3b).

(39) B. B. Corson and W. L. Benson, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 273.

(40) (a) G. C. Buzby, A. J. Castro, and E. B. Reid, *J. Org. Chem.*, **28**, 1082 (1963); (b) J. Tsuji and T. Nogi, *ibid.*, **31**, 2641 (1966).

(41) H. O. House, D. D. Traficante, and R. A. Evans, *J. Org. Chem.*, **28**, 348 (1963).

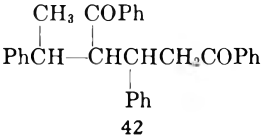
(42) (a) A. Vogel, *J. Chem. Soc.*, 624 (1948); (b) J. C. Munch, *J. Amer. Chem. Soc.*, **48**, 994 (1926).

(43) (a) G. Schroeter, *Ber.*, **40**, 1589 (1907); (b) K. Konno and S. Mitsui, *Nippon Kagaku Zasshi*, **85**, 497 (1964); *Chem. Abstr.*, **62**, 11728 (1965).

as a colorless liquid: $n^{25}D$ 1.4939;[44] ir ($CCl_4$) 1740 $cm^{-1}$ (ester C=O); uv (95% EtOH) series of weak ($\epsilon$ 125–207) maxima in the region 245–265 m$\mu$; nmr ($CCl_4$) $\delta$ 7.0–7.3 (5 H, m, aryl CH), 3.47 (3 H, s, $OCH_3$), 2.7–3.2 (1 H, m, benzylic CH), 2.3–2.6 (2 H, m, $CH_2CO$), 1.3–2.0 (2 H, m, $CH_2$), and 0.77 (3 H, t, $J$ = 7 Hz, $CH_3$); mass spectrum $m/e$ (rel intensity) 192 ($M^+$, 8), 132 (47), 121 (82), 119 (40), 118 (38), 117 (32), 115 (25), 104 (58), 103 (51), 91 (100), 78 (52), 77 (61), 59 (26), 51 (27), 43 (28), 41 (32), and 39 (26). In a similar reaction run at −30°, an aliquot removed after 2.5 min and subjected to glpc analysis indicated that the reaction was essentially complete after 2.5 min at −30°. In an attempt to detect the presence of intermediates in this reaction, reaction mixtures were prepared at −30 to −35° and allowed to warm slowly while the nmr spectra were observed.

**Reaction of Benzalacetophenone (19) with $LiCuMe_2$.**—A solution of 1.799 g (8.65 mmol) of the ketone **19** in 10 ml of $Et_2O$ was added to a cold (−5°) solution of $LiCuMe_2$ [from 19.5 mmol of MeLi and 1.93 g (10.1 mmol) of CuI] in 17 ml of $Et_2O$. This mixing resulted in the immediate formation of a red solution from which the color faded and MeCu began to precipitate within several seconds. The mixture was stirred at −3 to 10° for 10 min and then subjected to the usual isolation procedure. The crude neutral product (1.859 g, 96%, mp 67–70°) contained (glpc, silicone fluid No. 710 on Chromosorb P) the $\beta$-methyl ketone **20** (retention time 37.1 min); none of the reduction product, 1,3-diphenyl-1-propanone (retention time 35.2 min), was detected by glpc or nmr analysis. Recrystallization of the crude product from MeOH afforded 1.08 g (56%) of the pure ketone **20** as either white needles or white plates: mp 70.5–71° (lit.[45] mp 74°); ir ($CCl_4$) 1680 $cm^{-1}$ (conjugated C=O); uv max (95% EtOH) 242.5 m$\mu$ ($\epsilon$ 12,600) and 278 (1190); nmr ($CCl_4$) $\delta$ 7.0–8.5 (10 H, m, aryl CH), 3.0–4.0 (3 H, m, aliphatic CH), and 1.47 (3 H, d, $J$ = 6.5 Hz, $CH_3$); mass spectrum $m/e$ (rel intensity) 224 (83, $M^+$), 210 (21), 209 (100), 120 (36), 106 (29), 105 (78), 91 (26), 77 (48), and 51 (21).

In another experiment in which the $Me_2CuLi$ was generated from 0.91 g (3.4 mmol) of $BrCuP(OMe)_3$ and 6.5 mmol of MeLi in 6.6 ml of $Et_2O$ and then treated with 584 mg (2.81 mmol) of the ketone **19** in 3.3 ml of $Et_2O$, the crude product (528 mg of white solid, mp 112–153°) contained (tlc analysis, $SiO_2$ with an EtOAc–hexane eluent) a mixture of the conjugate addition product **20** and the product **42** resulting from a subsequent Michael



**42**

reaction.[46] Fractional crystallization of this mixture from MeOH separated samples of the ketone **20**, mp 69–70°, and the Michael adduct **42**: mp 161–162° (lit.[46b] mp 161.5–163°); ir ($CCl_4$) 1686 and 1677 $cm^{-1}$ (conjugated C=O); uv max (95% EtOH) 246 m$\mu$ ($\epsilon$ 19,700) with a point of inflection at 280 (2200); mass spectrum $m/e$ (rel intensity) 432 ($M^+$, <1), 329 (25), 328 (100), and 223 (21).

**Reactions of Isophorone (28). A. With the Methyl Cuprate 36.**—A solution of $t$-BuC≡CLi, prepared from 269 mg (3.28 mmol) of the actylene **34** and 3.06 mmol of MeLi in 2.4 ml of $Et_2O$, was added with stirring to a cold (10–13°) slurry of 573 mg (3.02 mmol) of purified[23] CuI in 2.0 ml of $Et_2O$. To the resulting cold (5–7°) red-orange solution of the acetylide **33** was added 1.7 ml of an $Et_2O$ solution containing 2.74 mmol of MeLi. This addition resulted in a progressive color change from red-orange to yellow to green. To the resulting cold (5–7°) solution of the cuprate **36** was added 2 ml of an $Et_2O$ solution containing 2.08 mmol of isophorone (**28**). The color of the reaction mixture changed progressively from green to yellow (1–2 min) to red-orange (20 min), after which the mixture was partitioned between $Et_2O$ and an aqueous solution (pH 8) of $NH_4Cl$ and $NH_3$. The resulting orange $Et_2O$ solution was washed with three 25-ml portions of aqueous 28% $NH_3$ to complete the hydrolysis of the acetylide **33** and the remaining colorless $Et_2O$ solution was washed with $H_2O$, dried, and concentrated. After the residual yellow liquid (288 mg) had been mixed with a known weight of $n$-$C_{14}H_{30}$ (as an internal standard), analysis (glpc, silicone fluid $QF_1$ on Chromosorb P, apparatus calibrated with known mixtures) indicated the presence of $n$-$C_{14}H_{30}$ (retention time 3.8 min), the tetramethyl ketone **38** (5.9 min, 76% yield), and the unchanged enone **28** (8.0 min, 12% recovery). None of the reduced ketone **30** (retention time 5.0 min) was detected. Collected samples of the ketones **28** and **38** were identified with authentic samples by comparison of glpc retention times and ir and nmr spectra.

**B. With Vinylcopper Derivatives.**—A solution of 1.966 g (13.6 mmol) of $t$-BuC≡CCu was cooled to −49° (during which time some of the acetylide **33** separated as an orange solid) and the resulting cold (−40 to −49°) orange slurry was treated, dropwise and with stirring, with 6.8 ml of an $Et_2O$ solution containing 11.6 mmol of $CH_2$=CHLi. In the initial stages of this addition a deep red color developed and the mixture gradually changed to an orange slurry during the time required to complete the addition. The resulting mixture was stirred at −40 to −50° for 5 min, during which time it became an opaque green color, and then 7.2 ml of an $Et_2O$ solution containing 3.65 mmol of isophorone (**28**) was added. The resulting solution was transferred to an ice–salt cooling bath and stirred for 90 min, during which time it slowly warmed to 10°. The resulting brownish-black mixture was added to 50 ml of cold (0°) 1 $M$ HOAc in EtOH and then stirred at 25–40° for 5 min and partitioned between 250 ml of saturated aqueous $NaHCO_3$ and $Et_2O$. The $Et_2O$ layer was washed successively with aqueous 28% $NH_3$, aqueous $Na_2S_2O_3$, aqueous 28% $NH_3$, and $H_2O$, and then dried and concentrated. After the residual liquid (519 mg) had been mixed with an internal standard ($n$-$C_{16}H_{34}$), glpc analysis (silicone fluid $QF_1$ on Chromosorb P, apparatus calibrated with known mixtures) indicated the presence of the reduced ketone **30** (retention time 7.1 min, 7% yield), $n$-hexadecane (9.5 min), the vinyl ketone **29** (10.6 min, 52% yield), the starting enone **28** (11.8 min, 7% recovery), and a minor unidentified component (21.2 min). Collected (glpc) samples of ketones **28** and **30** were identified with authentic samples by comparison of ir spectra and glpc retention times. A collected (glpc) sample of the vinyl ketone **29** was obtained as a colorless liquid with spectral properties corresponding to those reported:[48a] ir ($CCl_4$) 1710 (C=O), 1635 (C=C), and 920 $cm^{-1}$ (CH=$CH_2$); nmr ($CCl_4$) $\delta$ 4.7–6.1 (3 H, m, vinyl CH), a 2 H AB pattern with $J$ = 14.5 Hz for signals at *ca.* 2.50 and 2.05 ($CH_2CO$), 2.07 (2 H, s, $CH_2CO$), 1.65 (2 H, s, $CH_2$), 1.07 (3 H, s, $CH_3$), 1.02 (3 H, s, $CH_3$) and 0.81 (3 H, s, $CH_3$); mass spectrum $m/e$ (rel intensity) 166 ($M^+$, 100), 110 (49), 109 (57), 95 (76), 83 (96), 82 (60), 81 (21), 70 (22), 69 (32), 68 (57), 67 (66), 56 (35), 55 (55), 53 (27), 41 (34), and 39 (28).

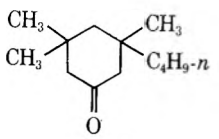
The mixed cuprate **37** could also be prepared without isolation of the copper actylide **33** by the following procedure. To 118 ml of a cold (0°) $Et_2O$ solution containing 186 mmol of MeLi was added, dropwise and with stirring during 30 min, 15.2 g (186 mmol) of the acetylene **34**. The resulting solution of $t$-BuC≡CLi was added, slowly and with stirring, to a cold (8–20°) slurry of 35.42 g (186 mmol) of purified[23] CuI in 210 ml of $Et_2O$. The resulting red-orange solution of the acetylide **33** was cooled to −59° and then treated, dropwise and with stirring while the solution was maintained at −42 to −59°, with 111 ml of an $Et_2O$ solution containing 159 mmol of $CH_2$=CHLi. The resulting opaque green mixture containing the cuprate **37** was stirred for 5 min at −38 to −42° and then treated with a solution of 6.9 g (50 mmol) of isophorone (**28**) in 75 ml of $Et_2O$. The reaction mixture was stirred for 90 min while being cooled in an ice bath and then partitioned between $Et_2O$ and aqueous (pH 8) $NH_4Cl$ and $NH_3$. The resulting $Et_2O$ solution was washed successively with four portions of aqueous 28% $NH_3$ (to complete the hydrolysis of **33**) and aqueous $Na_2S_2O_3$ and then dried and concentrated. After a portion of the residual brown liquid (7.23 g) had been mixed with an internal standard ($n$-$C_{16}H_{34}$), analysis (glpc) showed the presence of the ketones **30** (13% yield), **29** (49% yield), and **28** (14% recovery), as well as a small amount (*ca.* 6%) of the ketone **43**. Short-path distillation (0.5 mm, 95° bath) afforded 6.072 g of colorless liquid products containing the ketones **28** (*ca.* 15%), **29** (*ca.* 65%), **30** (*ca.* 15%), and **43** (*ca.* 5%). Fractional distillation separated 3.70 g of a fraction, bp 104–118°, $n^{25}D$ 1.4643, containing (glpc) **30** (*ca.* 18%), **29** (*ca.* 50%), **28** (*ca.* 30%), and **35** (*ca.* 2%), and 1.51 g of a fraction, bp 118–121°, $n^{25}D$ 1.4662, containing (glpc) **30** (*ca.* 3%), **29**

(44) This ester is reported to boil at 79–80° (0.1 mm): S. Mitsui and Y. Kudo, *Chem. Ind. (London)*, 381 (1965).

(45) R. C. Fuson, R. E. Christ and G. M. Whitham, *J. Amer. Chem. Soc.*, **58**, 2450 (1936).

(46) This by-product **42** has been observed previously: (a) R. A. Kretchmer, *J. Org. Chem.*, **37**, 2744, 2747 (1972); (b) W. Herz and E. Lewis, *ibid.*, **23**, 1646 (1958); (c) G. Wittig and F. Wingler, *Chem. Ber.*, **97**, 2146 (1964).

(*ca.* 79%), **28** (*ca.* 16%), and **43** (*ca.* 2%). The residue (0.692 g) contained (glpc) **29** (*ca.* 31%) and **43** (*ca.* 69%). A collected



**43**

(glpc) sample of the major product, ketone **29**, $n^{25}$D 1.4678, was identified with previously described material by comparison of ir spectra and glpc retention times.

A collected (glpc) sample of the ketone **43** was obtained as a colorless liquid: $n^{25}$D 1.4602; ir ($CCl_4$) 1704 $cm^{-1}$ (C=O); nmr ($CCl_4$) $\delta$ 2.04 (4 H, broad, $CH_2CO$), 1.4–1.6 (2 H, m, $CH_2$), 1.1–2.4 (6 H, m, $CH_2$), and 0.9–1.1 (12 H, m, including a 6 H singlet at 1.02 and a 3 H singlet at 0.98, four $CH_3$ groups); mass spectrum *m/e* (rel intensity) 196 ($M^+$, <1), 181 (5), 139 (42), 83 (60), 58 (45), 55 (42), and 43 (100).

*Anal.* Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.61; H, 12.39.

This ketone by-product **43** was evidently formed from small amounts of *n*-BuLi remaining in the $CH_2$=CHLi [prepared from *n*-BuLi and $(CH_2=CH)_4Sn$].

A cold (−90°) slurry of 1.89 g (7.05 mmol) of $BrCuP(OMe)_3$ in 3 ml of $Et_2O$ was treated with 12.8 mmol of $CH_2$=CHLi in 10 ml of $Et_2O$ and the resulting cold (−65 to −90°), dark, heterogeneous mixture was then treated with 410 mg (2.97 mmol) of isophorone (**28**) in 1 ml of $Et_2O$. After the mixture had been stirred at −50 to −60° for 2.25 hr an aliquot was removed, hydrolyzed (1 *M* HOAc in EtOH at −60°), and found to contain (glpc) the ketones **29** (*ca.* 80%) and **28** (*ca.* 20%). Finally, the remaining solution was warmed to 23° during 30 min and then hydrolyzed. The crude product (439 mg) contained (glpc) the ketones **29** (*ca.* 87%) and **28** (*ca.* 13%).

**Reaction of the Methoxy Ketone 21 with $LiCuMe_2$.**—To a cold (3–9°) mixture of 4.0 mmol of $LiCuMe_2$ and 2.3 mmol of excess MeCu, prepared from 1.19 g (6.27 mmol) of purified[23] CuI and 10.3 mmol of MeLi in 7.7 ml of $Et_2O$, was added 329 mg (1.96 mmol) of the methoxy ketone **21** in 2 ml of $Et_2O$. After the resulting mixture had been stirred at 1–8° for 1.3 hr, it was subjected to the usual isolation procedure. The crude product, 287 mg of a yellow liquid, was mixed with an internal standard (*n*-$C_{14}H_{30}$); it contained (glpc, silicone fluid $QF_1$ on Chromosorb P, apparatus calibrated with known mixtures of authentic samples) the internal standard (*n*-$C_{14}H_{30}$, retention time 4.0 min), the saturated ketone **22** (6.3 min, 26% yield), the starting ketone **21** (9.8 min, 37% recovery), and two or more rapidly eluted peaks (2.8 and 3.3 min) that may be olefins formed by dehydration of an alcohol product. A pure sample of the methoxy ketone product **22** was collected (glpc) as a colorless liquid: ir ($CCl_4$) 1723 $cm^{-1}$ (C=O); uv max (95% EtOH) 268 m$\mu$ ($\epsilon$ 22); nmr ($CCl_4$) $\delta$ 3.28 (3 H, s, $OCH_3$), 3.10 (1 H, s, COCH), a 2 H AB pattern with $J$ = 12 Hz at *ca.* 2.36 and 2.02 ($COCH_2$), a 2 H AB pattern with $J$ = 15 Hz at *ca.* 1.70 and 1.43 ($CH_2$), and a series of partially resolved singlets in the region 0.9–1.1 (12 H, $CH_3$); mass spectrum *m/e* (rel intensity) 184 ($M^+$, 48), 139 (31), 126 (22), 109 (28), 99 (79), 98 (31), 97 (100), 86 (23), 85 (64), 83 (65), 72 (31), 71 (25), 69 (27), 55 (40), 43 (22), and 41 (34).

*Anal.* Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.52; H, 10.85.

A variety of attempts to increase the yield of the saturated ketone **22** formed from the reaction of **21** with $Me_2CuLi$ consistent afforded mixtures of the adduct **22** and substantial quantities of the unchanged enone **21**. A reaction was performed in which the mixed cuprate **36** was prepared by the successive treatment of 283 mg (3.45 mmol) of the acetylene **34** with 3.06 mmol of MeLi, 575 mg (3.02 mmol) of purified[23] CuI, and 2.74 mmol of MeLi. The resulting cold (5–8°) solution of the cuprate **36** in 8.7 ml of $Et_2O$ was treated with 343 mg (2.04 mmol) of the enone **21**. Although color changes (green to yellow to orange) characteristic of reaction were observed during the reaction period (32 min at 5–18°), after following the usual isolation procedure, analysis (glpc) of the crude product (307 mg) indicated a 73% recovery of the unchanged enone **21** (identified by comparison of ir spectra and glpc retention times) and none of the addition product **22** was detected.

**Studies with Cinnamonitrile 40.**—The polarographic reductions of solutions ($2.48 \times 10^{-3}$–$4.27 \times 10^{-3}$ *M*) of the nitrile **40** in DMF containing 0.5 *M* *n*-$Bu_4N^+BF_4^-$ were performed as previously described.[3f] Two reduction waves were observed at −1.84 V *vs.* sce ($\alpha n$ = 1.3, $i_d$ = 13.1–17.5 $\mu$A) and −2.46 V *vs.* sce ($\alpha n$ = 1.2, $i_d$ = 5.8–7.5 $\mu$A). A comparable measurement of a $2.3 \times 10^{-3}$ *M* solution of isophorone (**28**) in DMF containing 0.5 *M* *n*-$Bu_4N^+BF_4^-$ gave the following values: $E_{1/2}$ = −2.24 V *vs.* sce ($\alpha n$ = 1.21, $i_d$ = 17.4 $\mu$A).

To a cold (5–10°) mixture of 13.4 mmol of $Me_2CuLi$ and 4.0 mmol of excess MeCu [from 3.303 g (17.4 mmol) of purified[23] CuI, 30.8 mmol of MeLi, and 27 ml of $Et_2O$] was added a solution of 1.221 g (9.47 mmol) of the nitrile **40** in 5 ml of $Et_2O$. After a reaction period of 20 min at 0–10° (no visible evidence of reaction), the mixture was subjected to the usual isolation procedure and the crude product (1.144 g) was mixed with an internal standard (*n*-$C_{14}H_{30}$). The crude product contained (glpc, silicone fluid $QF_1$ on Chromosorb P, apparatus calibrated with known mixtures) *n*-$C_{14}H_{30}$ (retention time 3.7 min) and the nitrile **40** (11.7 min, 77% recovery, identified by comparison of ir and nmr spectra and glpc retention times).

A comparable result was obtained when a solution of 15.7 mmol of the mixed cuprate **36** and 1.635 g (12.6 mmol) of the nitrile **40** in 43 ml of $Et_2O$ was stirred at 5–10° for 20 min. The recovered nitrile **40** amounted to 85% and no other product was detected (glpc, ir, and nmr analysis).

**Registry No.**—**6**, 37881-09-7; **7**, 22643-00-1; **8**, 22642-99-5; **9**, 22643-02-3; **11**, 7370-14-1; **12a**, 31845-19-9; **12b**, 22173-19-9; I (Scheme I), 41601-70-1; **13** (Scheme II), 1896-62-4; II (Scheme I), 41601-72-3; **14** (Scheme II), 17913-10-9; **15**, 623-43-8; **16**, 556-24-1; **17**, 103-26-4; **18**, 3461-39-0; **19**, 614-47-1; **20**, 1533-20-6; **21**, 5682-76-8; **22**, 41601-77-8; **23**, 30368-22-0; **24**, 15466-96-3; **25**, 6174-95-4; **26**, 632-56-4; **28**, 78-59-1; **29**, 27749-07-1; **33**, 40575-23-3; **34**, 917-92-0; **35**, 6130-98-9; **36**, 41602-02-2; **37**, 41602-03-3; **40**, 1885-38-7; **42**, 41601-83-6; **43**, 41601-84-7; CuBr, 7787-70-4; $(MeO)_3P$, 121-45-9; $(MeO)_3P$-CuBr, 34836-54-9; *t*-BuC≡CLi, 37892-71-0; MeLi, 917-54-4; CuI, 7681-65-4; $CH_2$=CHLi, 917-57-7.

# Relative Migratory Aptitudes in the Rearrangement of N,N-Dichlorocarbinamines by Aluminum Chloride[1]

RONALD E. WHITE,[2] MYRNA B. NAZARENO,[3] MICHAEL R. GLEISSNER,[4] AND PETER KOVACIC*

*Department of Chemistry, University of Wisconsin—Milwaukee, Milwaukee, Wisconsin 53201*

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Rearrangement of a series of N,N-dichlorocarbinamines ($R^1R^2R^3CNCl_2$) at low temperatures with aluminum chloride in methylene chloride, followed by acid hydrolysis, produced carbonyl and amine products in moderate to high yields. The following relative migratory aptitudes were determined: phenyl, 18; *sec*-butyl, 2.4; benzyl, 1.8; *n*-butyl, 1.0; hydrogen, 0.09; methyl, 0.05. These values compare reasonably well with migratory aptitudes observed in the Schmidt and Baeyer–Villiger rearrangements which appear to proceed by concerted processes. Further support for synchronous loss of chloride ion and 1,2 alkyl shift is provided by the low degree of hydrogen migration, indicating the importance of a trans migratory requirement.

Most of the previous work on rearrangement of N,N-dihaloamines by aluminum chloride comprised bi-[5] or tricyclic systems.[6,7] We recently reported[8] the rearrangement of N,N-dichlorotri-*n*-butylcarbinamine, which yielded, after acid hydrolysis, di-*n*-butyl ketone and *n*-butylamine. Migration appeared to involve electron-deficient nitrogen. The present study was concerned with obtaining relative migratory aptitudes for various types of alkyl groups, hydrogen, and phenyl, with the aim of elucidating additional aspects of the reaction mechanism. Useful comparisons are made with related systems entailing 1,2 shifts from carbon to nitrogen, carbon to oxygen, and carbon to carbon.

## Results and Discussion

**Preparation of Starting Materials.**—All the amines except di-*n*-butylcarbinamine were prepared by means of the Ritter reaction or Hofmann degradation as described in the earlier paper.[8] $(n\text{-Bu})_2CHNH_2$ was obtained from reduction of di-*n*-butylketoxime with sodium in ethanol. Acetylation of tri-*n*-butylcarbinamine, followed by $LiAlH_4$ reduction, provided N-ethyltri-*n*-butylcarbinamine. N,N-Dichloroamines **2**–**8** were synthesized by the previous procedure.[8] Treatment of the amine with N-chlorosuccinimide was used to generate N-chloro-N-ethyltri-*n*-butylcarbinamine. Yields of products are calculated[8] on the basis of N-monochloroamine as the impurity in crude N,N-dichloroamine.

**Rearrangement.**—Rearrangement of the N,N-dichlorocarbinamines by aluminum chloride, followed by acid hydrolysis, generally yielded a mixture of two carbonyl compounds, two alkyl amines, recovered parent amine, and intractable material (Table I). The best procedure developed in the previous work[8] was employed in the majority of runs. Rearrangement of $(n\text{-Bu})_2(sec\text{-Bu})CNCl_2$ (**2**) was studied under a variety of conditions. Little change in yield was noted for those reactions in which the amount of solvent was reduced by one third, reaction time was decreased from 90 to 30 min, temperature was in the range of 0 to −50°, or the solvent was methylene chloride or chloroform. A significant feature is the similarity of the ratios, di-*n*-butyl ketone:*n*-butyl-*sec*-butyl ketone and *sec*-butylamine:*n*-butylamine. The figures, which are an index of the relative migratory aptitudes, were 2.2–2.6:1, after statistical correction, over the range of conditions indicated in Table I. The observed relative migratory aptitudes for all groups studied are included in Table II. Ferric chloride, a relatively weak Lewis acid, gave only low yields of rearranged products, emphasizing the role of the catalyst.

In the case of $(Me)_2$-*n*-$BuCNCl_2$ (**3**), since the desired basic products were not separable from a side product, yields could not be ascertained. This problem was circumvented by utilizing the di-*n*-butylmethyl compound, **4**, for determining the migratory aptitude of the methyl group. Although rearrangement of **4** proceeded cleanly, the per cent conversion was somewhat lower than for the cases already discussed. Even when a longer reaction time was employed, the yield of rearrangement products was not appreciably improved. The trimethyl compound, **5**, behaved sluggishly, producing only low yields of acetone and methylamine. Surprisingly (see below), $(n\text{-Bu})_2CHNCl_2$ (**6**) gave very little di-*n*-butyl ketone, which would result from either hydrogen migration or proton elimination. The major product, valeraldehyde, was obtained in conjunction with minor amounts (2–12%) of 2-chloro- and 2,2-dichlorovaleraldehyde. This type of side reaction was also noted in our earlier work.[8] Since both of these compounds are unreported, independent syntheses were carried out for positive identification. 2-Chlorovaleraldehyde was prepared by chlorination of valeraldehyde. Hydride reduction of 2,2-dichlorovaleryl chloride provided the dichloroaldehyde in low yield accompanied by an appreciable amount of material which appeared to be 2,2-dichloro-1-pentanol. Rearrangement of $(n\text{-Bu})_2PhCH_2CNCl_2$ (**7**) was complicated by the aromatic nucleus. Relatively large amounts of tar were formed, and the variation in yields from run to run suggested undesirable side reactions, either during rearrangement or work-up. Thus, the figures for migratory aptitudes from this compound are somewhat less reliable.

With $(n\text{-Bu})_2PhCNCl_2$ (**8**) the reproducibility of yield data and other evidence lead us to believe that one or more competing reactions were taking place

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TABLE I

REARRANGEMENT OF *N,N*-DICHLOROCARBINAMINES BY ALUMINUM CHLORIDE

| | $R^1R^2R^3CNCl_2$ | | | | | | Product, % yield[a] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Registry no. | $R^1$ | $R^2$ | $R^3$ | | Temp, °C | Time, min | $R^1R^2CO$ | $R^1R^3CO$ | $R^1NH_2$ | $R^3NH_2$ | Recovered parent amine[b] | Residue[c] |
| 35329-67-0 | *n*-Bu | *n*-Bu | *n*-Bu | 1[j] | −30 | 45 | 95 | | 92 | | 3 | 3 |
| 35329-68-1 | *n*-Bu | *n*-Bu | *sec*-Bu | 2 | 0 | 90 | 49 | 43 | 43 | 49 | 10 | 7 |
| | *n*-Bu | *n*-Bu | *sec*-Bu | 2[d] | −30 | 90 | 54 | 43 | 46 | 51 | 9 | 5 |
| | *n*-Bu | *n*-Bu | *sec*-Bu | 2 | −30 | 90 | 59 | 47 | 47 | 59 | 4 | 2 |
| | *n*-Bu | *n*-Bu | *sec*-Bu | 2 | −50 | 90 | 56 | 44 | 44 | 56 | 7 | 5 |
| | *n*-Bu | *n*-Bu | *sec*-Bu | 2 | −30 | 30 | 57 | 38 | 41 | 54 | 9 | 8 |
| | *n*-Bu | *n*-Bu | *sec*-Bu | 2[e] | −30 | 90 | 13 | 11 | 11 | 13 | 39 | 9 |
| | *n*-Bu | *n*-Bu | *sec*-Bu | 2[f] | −30 | 90 | 52 | 40 | 41 | 50 | 13 | 9 |
| 41718-24-5 | Me | Me | *n*-Bu | 3 | −30 | 90 | 7 | 42 | | | | |
| 41718-25-6 | *n*-Bu | *n*-Bu | Me | 4 | −30 | 90 | 4 | 75 | 71 | 2 | 12 | <1 |
| | *n*-Bu | *n*-Bu | Me | 4 | −30 | 150 | 1 | 81 | 78 | 2 | 9 | 2 |
| | *n*-Bu | *n*-Bu | Me | 4 | −30 | 90 | 1 | 73 | 81 | 2 | 16 | 3 |
| 2156-72-1 | Me | Me | Me | 5 | −30 | 90 | 32 | | 45 | | 26 | 2 |
| | Me | Me | Me | 5 | −30 | 180 | 38 | | 35 | | 14 | 1 |
| 41718-27-8 | *n*-Bu | *n*-Bu | H | 6 | −30 | 90 | 2 | 53[g] | 55 | | 9 | 2 |
| | *n*-Bu | *n*-Bu | H | 6 | −30 | 150 | 2 | 47[g] | 63 | | 12 | 2 |
| 41718-28-9 | *n*-Bu | *n*-Bu | $PhCH_2$ | 7 | −50 | 30 | 28 | 40 | 42 | 24 | 19 | 20 |
| | *n*-Bu | *n*-Bu | $PhCH_2$ | 7 | −50 | 30 | 29 | 31 | 23 | 12 | 6 | 43 |
| | *n*-Bu | *n*-Bu | $PhCH_2$ | 7 | −50 | 30 | 25 | 24 | 24 | 33 | 17 | 17 |
| 41718-29-0 | *n*-Bu | *n*-Bu | Ph | 8 | −40 | 45 | 36 | 1 | 4 | 36 | 11 | 24 |
| | *n*-Bu | *n*-Bu | Ph | 8 | −40 | 30 | 36 | 1 | 5 | 42 | 12 | 17 |
| | *n*-Bu | *n*-Bu | *n*-Bu | 9[h,i] | 0 | 180 | 70 | | 71 | | 20 | 2 |
| | *n*-Bu | *n*-Bu | *n*-Bu | 9[h,i] | 0 | 180 | 67 | | 68 | | 26 | 2 |

[a] Based on $RNCl_2$. [b] Crude, based on starting amine. [c] Per cent of crude product. [d] 30 ml of solvent. [e] $FeCl_3$ catalyst. [f] $CHCl_3$ solvent. [g] Contained minor amounts of 2-chloro- and 2,2-dichlorovaleraldehyde. [h] *N*-Ethyl; monochloro derivative. [i] The procedure in ref 7 was followed except that the reaction mixture was steam distilled for 7 hr. [j] Reference 8.

TABLE II

RELATIVE MIGRATORY APTITUDES

| | Relative migratory aptitudes | |
|---|---|---|
| R | Range | Average |
| Ph | 17–18 | 18 |
| *sec*-Bu | 2.2–2.6 | 2.4 |
| $PhCH_2$ | 1.0–3.0 | 1.8 |
| *n*-Bu | | 1.0 |
| H | 0.08–0.10 | 0.09 |
| Me | 0.03–0.09 | 0.05 |

which did not affect the rearrangement. Glpc revealed numerous minor products in the neutral fraction. The major component from the side reactions was shown to be 4-phenyl-5-nonanone by comparison with authentic material prepared by propylation of 1-phenyl-2-hexanone. To avoid uncertainty concerning identification, the isomer, 5-phenyl-4-nonanone, was also synthesized. Although nmr and glpc data did not permit differentiation, the ir spectra indicated that no more than 20% of the latter isomer could have been present. Mechanistically, any proposal must be highly tentative because of the paucity of experimental evidence. One possibility entails ionization[9] to $(n\text{-Bu})_2PhC^+(Cl_2NAlCl_3)^-$, followed by synchronous 1,2 shift of hydride and phenyl with the gegenion remaining at the original cationic site. Alternatively, 1,3 hydride shift[10] to electron-deficient nitrogen may take place.

*N*-Chloro-*N*-ethyltri-*n*-butylcarbinamine (**9**) was more reluctant to rearrange, giving only about 70% of rearranged product after 3 hr. The increased basicity of the nitrogen, due to replacement of chlorine by the ethyl group, would promote greater complexation of aluminum chloride with nitrogen, thus retarding rearrangement. Furthermore, increased steric resistance to either approach of a catalyst molecule or migration of an alkyl group, and the reduced statistical factor resulting from the availability of only one chlorine atom, would also retard rearrangement. Previously, *N*-chloro-*N*-ethyl-1-aminoadamantane[7] was found to rearrange to the extent of only 65%, whereas the *N,N*-dichloro derivative gave 79% of rearranged product.[6] Hydrolysis of the rearranged product from **9** was effected only after 7 hr of steam distillation, whereas 1–2 hr was sufficient with the other compounds studied. The slowness of hydrolysis may result from diminished solubility owing to increased molecular weight, and reduced hydrogen bonding capability for $(n\text{-Bu})_2CClNEtBu\text{-}n$ because of absence of the NH group.

The indicated scheme,[8] with **2** as an example, depicts the proposed course of reaction (eq 1). Removal of chloride ion by aluminum chloride and migration of either a *sec*-butyl (path a) or *n*-butyl (path b) group would occur readily to give the corresponding tertiary carbonium ion, **11a** or **11b**, which is stabilized by the two alkyl groups and the neighboring nitrogen. Combination with chloride ion provides the α-chloro-*N*-chloroamines **12a** and **12b**. Treatment with acid effects hydrolysis to the corresponding carbinolamines, **13a** and **13b**, which decompose to ketone and primary amine.

Although evidence presented thus far strengthens the hypothesis that rearrangement proceeds through formation of electron-deficient nitrogen, the question arises as to whether a discrete nitrenium ion intermediate is involved or a somewhat electron-deficient

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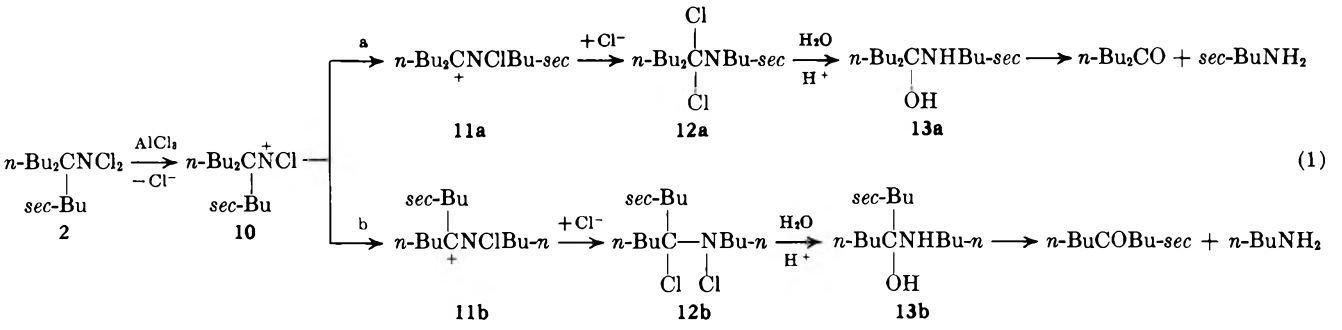

(1)

nitrogen moiety which possesses only transitory existence in a synchronous process. The literature contains examples of carbon to nitrogen migrations which supposedly entail either a concerted process or a two-step pathway with formation of a nitrenium ion. The alternative possibilities will be discussed separately in conjunction with pertinent prior literature. Gassman provided strong evidence[11] for the existence of the nitrenium ion as a distinct entity in either singlet or triplet form. The triplet state on abstraction of hydrogen is converted to the parent amine. In contrast to Gassman's system, most other carbon to nitrogen migrations are postulated to proceed in a concerted fashion. The Schmidt rearrangement comprises a group of reactions resulting from treatment of a carbonyl compound with sodium azide and concentrated acid. A commonly accepted mechanism has been deduced from analogy with the Beckmann rearrangement[12a] and secondary evidence.[12b] In this acid-catalyzed, intramolecular reaction, substituent effects are similar to those in the Hofmann and Lossen processes, and an analogous concerted mechanism is likely.[13] Use of asymmetric ketones enables the detection of a trans-migratory requirement as in the Beckmann reaction. Thus, the tendency for the larger group to migrate in such substrates, *i.e.*, Ph > Me, Et > Me, is a consequence of favored formation of the iminodiazonium ion with the larger group trans.[12c]

There is reason to believe that, in purely aliphatic systems, the iminodiazonium isomers are readily interconverted. As this type of interchange becomes important, so does the role of electronic factors in determining product ratios.[14] Alkyl migration has been shown to be slower than aryl.[15] With phenyl alkyl ketones, the following relative rates of migration of alkyl groups were obtained: methyl, 0.05; ethyl, 0.15; isopropyl, 0.49; *tert*-butyl, 1.0.[16] The group with the largest bulk will migrate preferentially except when electronic effects (chelation or conjugation) come into play.[14]

Another reaction which is relevant to our investigations is the Baeyer–Villiger rearrangement. Mechanistic studies on the oxidation of ketones to esters by peracids suggest that the transformation proceeds in a concerted manner involving a 1,2 shift from carbon to oxygen, with the rate-determining step being the acid-catalyzed decomposition of the peroxy acid–ketone adduct.[17] Several studies have been made to determine the relative migratory aptitudes of alkyl or aryl groups. For example, one group obtained the following sequence: methyl, small; *n*-propyl, 1; isopropyl, 27; benzyl, 19; phenyl, 14; *tert*-butyl, 560.[18]

Although rearrangements which involve 1,2 shift of a saturated alkyl group from carbon to an adjacent, electrophilic carbon are very common, relatively little data are available concerning the effect of structural variation upon migration tendencies. Comparison of intramolecular migratory aptitudes of alkyl groups in the pinacol rearrangement, unlike those for substituted phenyl groups, are unlikely to reflect intrinsic migratory aptitudes because of appreciable variation in the size of the groups. By comparison of absolute rates of migration of different individual groups in the same molecular environment, such as $CH_3CR(OH)C(CH_3)_2^+$, the sequence methyl (1.0), ethyl (17), *tert*-butyl (>4000) has been observed.[19] In carbonium ion rearrangements of bis-*tert*-alkyl ketones,[20,21] recent studies have shown that the relative migratory aptitudes of alkyl groups are a function both of electronic and steric effects (back strain).

It is reasonable to conclude that the rearrangement of *N*,*N*-dichlorocarbinamines proceeds in a concerted manner on the basis of the following evidence. A mechanism involving a free nitrenium ion should be much less susceptible to steric effects than a concerted rearrangement. Since the nitrenium ion would be expected to assume planarity,[22] attack of a migrating group would be possible from two directions, thus decreasing conformational effects. In a concerted rearrangement, on the other hand, much like an internal $S_N2$-type displacement, only the group trans to the leaving chloride is suitably disposed for back-side attack on nitrogen. Since the energetically favored conformation places the bulkiest group as far as possible from the leaving entity (conformers **14** and **15**), the largest substituent will migrate preferentially. The smallest group would be the least likely to migrate on the basis of a trans conformational requirement which places the $AlCl_4^-$ leaving moiety between the more bulky ones (conformer **16**). Hence, evidence for

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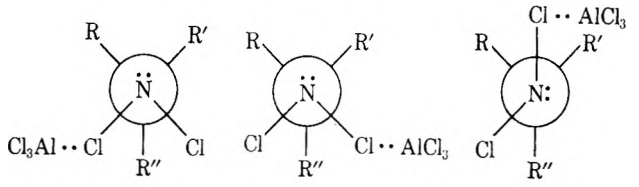

14 15 16

R and R′ > R″

a trans migratory effect weighs against a nitrenium ion intermediate and favors an electron-deficient nitrogen in the transition state.

The relative migratory aptitudes of the groups do not follow the expected order in all cases based on the ability to stabilize an incipient positive charge. Rearrangement of $(n\text{-Bu})_2CHNCl_2$ (**6**) illustrates the importance of stereochemical effects in this system. In related rearrangements, *e.g.*, Schmidt, Beckmann, and Baeyer–Villiger, hydrogen migration or proton elimination comprises the most important process, with alkyl migration usually accounting for only a minor fraction of the product.[12e] Electronically, hydrogen migration in **6** is favored, since *n*-butyl migration would give a secondary carbonium ion, whereas a tertiary type results from the alternate route. Furthermore, it is expected that hydrogen should stabilize an incipient positive charge during migration better than *n*-butyl. However, since hydrogen, in fact, migrates very little, we are led to rationalize this result on the basis of a compelling trans-migration requirement (see **14** and **15**).

On the other hand, acid-catalyzed rearrangement of benzyl azide gave approximately equal amounts of hydrogen and phenyl migration (eq 2), whereas with

$$C_6H_5CH_2N_3 \xrightarrow{-N_2} C_6H_5CH{=}NH\ (30\%) + CH_2{=}NC_6H_5\ (30\%) \quad (2)$$

benzhydryl azide only phenyl migration was observed (eq 3). This result was also rationalized on the basis

$$(C_6H_5)_2CHN_3 \xrightarrow{-N_2} C_6H_5CH{=}NC_6H_5\ (90\%) + (C_6H_5)_2C{=}NH\ (0\%) \quad (3)$$

of conformational factors.[12f] In contrast to **6**, *N,N*-dichloroisopropylamine, when treated with aluminum chloride in methylene chloride at −30°, underwent substantial loss of HCl, producing acetone in 42% yield after work-up.[23] In this case, methyl migrates poorly and the difference in size is less, so that proton elimination becomes important.

One would expect the di-*n*-butylmethyl compound (**4**) to show enhanced *n*-butyl migration compared to that in the *n*-butyldimethyl analog (**3**) because of increased "back strain." This is found to be the case, **3** giving a 0.08 ratio of methyl to *n*-butyl migration, whereas values of 0.05–0.06 are observed with **4**. In the di-*n*-butyl–*sec*-butyl case (**2**), both the electronic and steric effects make *sec*-butyl the preferred group for migration. The resulting carbonium ions **11a** and **11b** are of nearly the same stability. A different situation pertains in the case of the di-*n*-butylbenzyl system (**7**), since benzyl migration produces a standard tertiary carbonium ion, whereas rearrangement entailing *n*-butyl affords a phenonium ion. It is difficult to estimate the relative influence of this consideration in relation to steric and electronic factors. Similarly, rearrangement of $(n\text{-Bu})_2PhCNCl_2$ (**8**) presents two nonequivalent paths, phenyl migration leading to a tertiary ion, while a 1,2 shift of *n*-butyl yields a benzylic cation.

The "back strain" effect also seems to be related to the overall yields of rearranged products (substituents, per cent rearranged product): $(n\text{-Bu})_2$–*sec*-Bu, >95; $(n\text{-Bu})_3$, 95; $(n\text{-Bu})_2Me$, 80; $(n\text{-Bu})_2H$, 55; *n*-$BuMe_2$, 50; $Me_3$, 40. The data indicate that smoothness of reaction is favored by crowding at the carbon affixed to nitrogen.

The small differences in relative migratory aptitudes compare favorably with results from the Schmidt rearrangement and correspond fairly closely to those of the Baeyer–Villiger reaction, both of which are believed to proceed in a concerted fashion. However, in these rearrangements, interpretation is complicated by the possible presence of equilibrium steps prior to the transition state and the existence of nonisolable intermediates, which might influence the kinetics of the reaction. In addition, the alkyl group in the Schmidt reaction apparently migrates across a double bond.

If the rearrangement were a two-step process entailing the nitrenium ion as a discrete intermediate, solvent-catalyzed spin inversion of the singlet to the triplet species should give an increased yield of recovered parent amine when solvent was changed from methylene chloride to chloroform, which has enhanced characteristics of a heavy atom solvent. Furthermore, chloroform could also serve as a good hydrogen atom donor. Gassman and coworkers found a 190-fold reduction in the singlet–triplet product ratio when chloroform was added to methanol.[11] However, with chloroform the yield of recovered amine in the case of **2** was only 13% compared with 4–9% in methylene chloride. We cannot be sure if this small increase is real because of our uncertainty concerning the accuracy of the recovered amine data.

There are various possible reasons for the apparent difference in mechanistic detail between Gassman's work and the present study, although both presumably involve electron-deficient nitrogen. Gassman utilized silver salts as catalysts for *N*-chloroamine ionization, whereas we used aluminum chloride. It is reasonable to suppose that the two catalysts might behave somewhat differently in relation to the degree of ionization induced. Also, there may be differences in the role of the gegenion during rearrangement depending upon the type of catalyst.[11] Sasaki and coworkers[24] reported the virtual absence of rearrangement of *N*-chloro-*N*-acetyl-1-adamantylamine in methylene chloride, in contrast with the formation of 47% of rearranged product in carbon tetrachloride. Since Gassman used methanol, some degree of stabilization of the nitrenium ion by the medium through solvation appears likely. Furthermore, the *ab initio* molecular orbital studies on the structure of the nitrenium ion by Lee and Morokuma stressed the importance of the type of substituents on the ground state of the nitrenium ion.[22]

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There was also the indication that, if the nitrenium ion is formed in a ring structure, the singlet state gains in stability. It is noteworthy that the compounds studied by Gassman generally involved cyclic structures.[11,25,26] In the conversion of *N*-chloroazacyclooctane and *N*-chloroazacyclononane to bicyclic amines by exposure to silver ion, apparently homolytic processes are involved, rather than formation of discrete nitrenium ions.[27]

In summary, the low relative migratory aptitudes, the lack of any convincing evidence for singlet–triplet conversion, and the pronounced steric requirements weaken the case for an intermediate nitrenium ion, but are in accord with concerted loss of chloride with alkyl migration, involving a somewhat electron-deficient nitrogen in the transition state.

## Experimental Section

**Materials.**—In general, high purity commercial chemicals were used directly. Toluene was dried over sodium strips; methylene chloride (Aldrich Chemical Co.) was dried at reflux over calcium hydride.

**Analytical Procedures.**—Infrared spectra were recorded on a Perkin-Elmer 137 spectrophotometer with neat samples and with the 1601.8- and 1028.3-$cm^{-1}$ bands of polystyrene for calibration. Nmr spectra were taken with a Varian Model T-60 (parts per million with tetramethylsilane as internal standard). Gas chromatography was conducted on Varian Aerograph instruments (Hy-Fi 1700 and 1800) by means of the indicated columns (10 ft × 0.25 in.) (column number, packing): (1) 15% Carbowax 20M on Chromosorb W (45/60 mesh); (2) 15% UCON 50HB2000 and 5% NaOH on Chromosorb W, AW-DMCS 45/60 mesh).

Quantitative glpc was accomplished by comparison of peak areas of solutions of crude products with those of solutions of authentic materials or of 4-isopropylcyclohexanone as internal standard. Positive chlorine content in solutions of *N*-chloro compounds was determined by standard iodometric titration.[28] Melting and boiling points are uncorrected. Micro-Tech Laboratories, Skokie, Ill., and Baron Consulting Co., Orange, Conn., performed the elemental analyses.

The analysis of basic products involved a modified Kjeldahl procedure,[8] gas chromatography, and quantitative nmr. About 0.1 g of the hydrochloride salt mixture was dissolved in 50% sodium hydroxide and extracted with ether. The ether extract, dried with sodium sulfate, was analyzed by glpc (column 2). For the quantitative nmr analysis, about 0.1 g of the hydrochloride salt mixture was dissolved in $D_2O$. The signal intensities were compared with those of authentic materials in separate solutions of similar known concentrations.

**1-Bromo-2-methylbutane.**—An available route ($HBr$–$H_2SO_4$)[29a] was used with 2-methyl-1-butanol to yield 59% of bromide, bp 116–118°, $n^{24}D$ 1.4450 (lit.[30] bp 116.5–118°, lit.[31] $n^{20}D$ 1.4452).

**3-Methylvaleronitrile.**—When a published procedure[29b] was followed with 1-bromo-2-methylbutane, the nitrile was obtained in 61% yield, bp 148–150°, $n^{24}D$ 1.4058 (lit.[32] bp 147–149°, lit.[33] $n^{26}D$ 1.4051).

**Di-*n*-butyl-*sec*-butylacetonitrile.**—Use of a prior procedure,[34] with 3-methylvaleronitrile gave 85% of product, bp 84–85° (0.15 mm).

*Anal.* Calcd for $C_{14}H_{27}N$: C, 80.31; H, 13.00. Found: C, 80.53; H, 12.93.

**Di-*n*-butyl-*sec*-butylacetamide.**—A literature method[34] was used to convert di-*n*-butyl-*sec*-butylacetonitrile to the amide in 87% yield, bp 135–136° (0.3 mm). The distillate slowly solidified to a waxy solid, mp 28–30°.

*Anal.* Calcd for $C_{14}H_{29}NO$: C, 73.95; H, 12.85; N, 6.16. Found: C, 73.90; H, 12.79; N, 6.10.

**Di-*n*-butyl-*sec*-butylcarbinamine.**—A known method[35] was used with di-*n*-butyl-*sec*-butylacetamide except that the isocyanate was not isolated. The amine was obtained in 86% yield: bp 75–75.5° (0.28 mm); $n^{25}D$ 1.4474; ir (neat) 3300 (NH), 1615 (NH), 816 (NH), 783, and 732 $cm^{-1}$; nmr ($CDCl_3$) δ 1.6 (m, 2 H, $NH_2$, exchangeable with $D_2O$), 1.27 (m, 14 H, $CH_2$ + CH), 0.92 (m, 12 H, $CH_3$).

*Anal.* Calcd for $C_{13}H_{29}N$: C, 78.31; H, 14.66. Found: C, 78.22; H, 14.75.

The acetamide derivative melted at 62–64°.

*Anal.* Calcd for $C_{15}H_{31}NO$: C, 74.63; H, 12.94; N, 5.80. Found: C, 74.50; H, 13.31; N, 5.73.

***n*-Butyldimethylcarbinol.**—Use of a prior procedure[36] with *n*-butyl bromide and acetone gave 73% of alcohol, bp 138–142°, $n^{23}D$ 1.4171 (lit.[37] bp 141–142°, lit.[37] $n^{20}D$ 1.4175).

***n*-Butyldimethylcarbinamine.**—A published route[38] was followed with *n*-butyldimethylcarbinol to yield 47% of basic product: bp 125–126° (lit.[39] bp 124–127°); $n^{24}D$ 1.4137; phenylurea mp 119–120° (lit.[40] mp 116–117°); ir (neat) 3200 (NH), 1600 (NH), 1370, 1355, 1180, 830 (NH), 790, 760, and 732 $cm^{-1}$; nmr ($CCl_4$) δ 1.27 (m, 6 H, $CH_2$), 1.02 (m, 9 H, $CH_3$), 0.87 (2 H, $NH_2$, exchangeable with $D_2O$).

**Di-*n*-butylmethylcarbinol.**—Use of a prior procedure[35] with *n*-butyl bromide and ethyl acetate provided 68% of the alcohol: bp 52–54° (0.15 mm) [lit.[41] bp 86–87° (5 mm)]; $n^{25}D$ 1.4334 (lit.[41] $n^{20}D$ 1.4330); ir (neat) 3300 (OH), 1150 (CO), 1030 (CO), 950, 910, 795, and 735 $cm^{-1}$; nmr ($CCl_4$) δ 1.87 (s, 1 H, OH, exchangeable with $D_2O$), 1.32 (m, 12 H, $CH_2$), 1.07 (s, 3 H, $CH_3COH$), 0.92 (m, 6 H, $CH_3CH_2$).

**Di-*n*-butylmethylcarbinamine.**—A published procedure[38] was followed with di-*n*-butylmethylcarbinol to yield 67% of basic product: bp 34–35° (0.25 mm); $n^{25}D$ 1.4316; ir (neat) 3250 (NH), 1610 (NH), 1170, 830 (NH), 788, and 732 $cm^{-1}$; nmr ($CCl_4$) δ 1.25 (m, 12 H, $CH_2$), 1.00 (s, 2 H, $NH_2$, exchangeable with $D_2O$), 0.95 (m, 9 H, $CH_3$).

*Anal.* Calcd for $C_{10}H_{23}N$: C, 76.36; H, 14.74; N, 8.90. Found: C, 76.15; H, 14.52; N, 8.61.

The acetamide derivative melted at 60–61°.

*Anal.* Calcd for $C_{12}H_{25}NO$: C, 72.30; H, 12.64; N, 7.03. Found: C, 72.56; H, 12.71; N, 7.01.

**Di-*n*-butylketoxime.**—According to a literature preparation,[42] the oxime was obtained in 88% yield, bp 114–116° (8 mm) [lit.[43] bp 124.5° (15 mm)].

**Di-*n*-butylcarbinamine.**—Modification of a published procedure[44] gave 47% of basic product: bp 70–72° (11 mm) [lit.[45] bp 78° (20 mm)]; $n^{24}D$ 1.4273 (lit.[45] $n^{25}D$ 1.4264); ir (neat) 3300 (NH), 1615 (NH), 816 (NH), 778, and 731 $cm^{-1}$; nmr ($CCl_4$) δ 1.28 (m, 12 H, $CH_2$), 0.92 (t, 6 H, $CH_3$), 2.4–2.9 (m, 1 H, $CHNH_2$).

**Di-*n*-butylbenzylcarbinol.**—A literature method[36] was used with *n*-butyl bromide and ethyl phenylacetate to give a mixture of the alcohol (65% yield) and olefinic material. A pure sample of the alcohol was obtained by preparative glpc: ir (neat) 3400 (OH), 1610, 1494, 1132, 1080, 1034, 906, 727, and 702 $cm^{-1}$; nmr ($CCl_4$) δ 7.18 (s, 5 H, $C_6H_5$), 2.67 (s, 2 H, $PhCH_2$), 1.33 (m, 12 H, $CH_2$), 0.92 (m, 6 H, $CH_3$).

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*Anal.* Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.96; H, 11.08.

**Di-*n*-butylbenzylcarbinamine.**—The Ritter reaction[38] with crude alcohol was employed to obtain the amine: bp 104–106° (0.25 mm); $n^{24}D$ 1.5036; ir (neat) 3200 (NH), 1595 (NH), 1485, 835 (NH), 725, and 703 $cm^{-1}$; nmr ($CCl_4$) δ 7.15 (s, 5 H, $C_6H_5$), 2.55 (s, 2 H, $PhCH_2$), 1.2–1.7 (m, 12 H, $CH_2$), 0.92 (m, 6 H, $CH_3$), 0.67 (s, 2 H, $NH_2$, exchangeable with $D_2O$).

*Anal.* Calcd for $C_{16}H_{27}N$: C, 82.34; H, 11.66; N, 6.00. Found: C, 82.51; H, 11.69; N, 6.00.

The acetamide derivative melted at 106–107°.

*Anal.* Calcd for $C_{18}H_{29}NO$: C, 78.49; H, 10.61; N, 5.09. Found: C, 78.48; H, 10.87; N, 4.88.

**Di-*n*-butylphenylacetonitrile.**—A literature procedure[34] was followed except that the reaction mixture was refluxed for 3 days, giving a 73% yield, bp 93–95° (0.18 mm) [lit.[34] bp 135–140° (1.5 mm)].

**Di-*n*-butylphenylacetamide.**—Conversion of the nitrile to the amide was accomplished *via* a literature method.[34] The crude amide, bp 151–158° (0.05–0.07 mm) [lit.[34] bp 168–170° (0.5 mm)], was used directly in the Hofmann degradation.

**Di-*n*-butylphenylcarbinamine.**—A previous method[35] was employed except that the isocyanate was not isolated. The amine was obtained in 90% yield: bp 82–84° (0.2 mm); $n^{24}D$ 1.5007; ir (neat) 3200 (NH), 1610, 830 (NH), 770, and 713 $cm^{-1}$; nmr ($CCl_4$) δ 7.0–7.5 (m, 5 H, $C_6H_5$), 1.4–1.9 (m, 4 H, $PhCCH_2$), 1.1–1.4 (m, 8 H, $CH_2$), 0.83 (t, 6 H, $CH_3$), 0.83 (s, 2 H, $NH_2$, exchangeable with $D_2O$).

*Anal.* Calcd for $C_{15}H_{25}N$: C, 82.13; H, 11.49; N, 6.38. Found: C, 81.85; H, 11.69; N, 6.09.

The benzamide derivative melted at 151–152°.

*Anal.* Calcd for $C_{22}H_{29}NO$: C, 81.69; H, 9.04; N, 4.33. Found: C, 81.85; H, 8.74; N, 4.06.

***N*-Acetyltri-*n*-butylcarbinamine.**—A literature procedure[35] was used to produce the acetamide, 89% yield, mp 78–80.5° after recrystallization (lit.[35] mp 80.5–81.5°).

***N*-Ethyltri-*n*-butylcarbinamine.**—A previous method[7] was employed to obtain the amine: 98% yield; bp 86–89° (0.45 mm); $n^{24}D$ 1.4419; ir (neat) 1253, 1159, 1124, 1098, 895, and 729 $cm^{-1}$; nmr ($CCl_4$) δ 2.34 (q, 2 H, $CH_2CH_2N$), 1.17 (m, 18 H, $CH_2$), 0.88 (m, 12 H, $CH_3$).

*Anal.* Calcd for $C_{15}H_{33}N$: C, 79.22; H, 14.63; N, 6.16. Found: C, 79.30; H, 14.56; N, 6.28.

***N*-Chloro-*N*-ethyltri-*n*-butylcarbinamine.**—A mixture of *N*-ethyltri-*n*-butylcarbinamine (5.7 g, 25 mmol) and *N*-chlorosuccinimide (3.6 g, 25 mmol) in 15 ml of ether was stirred at room temperature for 1 hr, cooled, and filtered. After the filtrate was washed with water, it was dried with sodium sulfate, the ether was removed, and the residue was dissolved in methylene chloride. Yields of 95–98% of the *N*-chloroamine were obtained, as indicated by titration for positive chlorine.

***N,N*-Dichloroamines.**—Generally, procedure II of the previous work[8] was followed, providing yields of 92–96%, except in the case of di-*n*-butylbenzylcarbinamine (74–84% yield). Iodometric titration was used for analysis.

**Rearrangement of *N,N*-Dichloroamines with Aluminum Chloride.**—General procedure C from the earlier report[8] was used except as otherwise noted. In most cases, products were identified by comparison of the ir and nmr spectra and glpc retention times with those of authentic materials.

**2-Chlorovaleraldehyde.**—A solution of valeraldehyde (10 g, 116 mmol) in 30 ml of methylene chloride in a flask covered with aluminum foil and fitted with a gas-inlet tube was cooled to −15°. Chlorine gas was passed into the solution over a period of 0.5 hr at −15°. The solution was then stirred at −10 to −15° for 5 hr, washed several times with 5% sodium bicarbonate, then with water, and finally dried over sodium sulfate. After removal of solvent, distillation of the residue afforded 7.2 g (49%) of 2-chlorovaleraldehyde: bp 126–130°; 95% pure (glpc); $n^{25}D$ 1.4276 (pure sample); ir (neat) 1725 (C=O), 1050, 892, 762, and 698 $cm^{-1}$; nmr ($CCl_4$) δ 9.42 (d, $J$ = 3 Hz, 1 H, CHO), 4.12 (m, 1 H, CHCl), 1.3–2.2 (m, 4 H, $CH_2$), 0.98 (t, 3 H, $CH_3$).

*Anal.* Calcd for $C_5H_9ClO$: C, 49.81; H, 7.52. Found: C, 50.06; H, 7.31.

**2,2-Dichlorovaleric Acid.**—Procedure B of a literature method[46] provided 73% of 1,2,2-tetrachloropentylphosphorimidic trichloride, bp 109–113° (0.15 mm), $n^{24}D$ 1.5431 [lit.[46] bp 135–136° (3 mm), $n^{20}D$ 1.5450]. Hydrolytic procedure A yielded 76% of 2,2-dichlorovaleric acid: bp 108–110° (6.8 mm); $n^{24}D$ 1.4608 [lit.[46] bp 110–112° (7 mm), $n^{20}D$ 1.4612]; ir (neat) 3600–2200 (COOH), 1725 (C=O), 1265 (CO), 1105, 909, 902, 829, 797, and 756 $cm^{-1}$; nmr ($CCl_4$) δ 12.22 (s, 1 H, COOH, exchangeable with $D_2O$), 2.3–2.7 (m, 2 H, $CH_2CCl_2$), 1.4–2.1 (m, 2 H, $CH_2$), 1.03 (t, $J$ = 6.5 Hz, 3 H, $CH_3$).

**2,2-Dichlorovaleryl Chloride.**—A mixture of 17.1 g (100 mmol) of 2,2-dichlorovaleric acid and 17.9 g (150 mmol) of thionyl chloride was refluxed for 2 days. After removal of excess thionyl chloride, the residue was distilled to yield 7.8 g (41%) of acid chloride: bp 48–50° (7.5 mm); $n^{24}D$ 1.4586; ir (neat) 1780 (C=O), 1085, 979, 877, 811, 750, and 695 $cm^{-1}$; nmr ($CCl_4$) δ 2.3–2.6 (m, 2 H, $CH_2CCl_2$), 1.3–2.1 (m, 2 H, $CH_2$), 1.05 (t, $J$ = 6.5 Hz, 3 H, $CH_3$).

*Anal.* Calcd for $C_5H_7Cl_3O$: C, 31.70; H, 3.72. Found: C, 31.98; H, 3.86.

**2,2-Dichlorovaleraldehyde.**—A solution of 2,2-dichlorovaleryl chloride (5.4 g, 28 mmol) in 15 ml of tetrahydrofuran was cooled to −70° under dry nitrogen. Lithium tri-*tert*-butoxyaluminum hydride[47] (7.4 g, 29 mmol) in 20 ml of tetrahydrofuran was added over a period of 4 hr at −70°. The flask was then allowed to warm to room temperature over a period of 1 hr, water was added, the mixture was extracted with ether, and the organic layer was dried with sodium sulfate. The organic phase contained a low yield of aldehyde. Preparative glpc provided a pure sample: ir (neat) 2690 (CHO), 1750 (C=O), 1111, 992, 758, and 688 $cm^{-1}$; nmr ($CCl_4$) δ 9.17 (s, 1 H, CHO), 2.1–2.5 (m, 2 H, $CCl_2CH_2$), 1.4–2.0 (m, 2 H, $CH_2$), 1.03 (t, 3 H, $CH_3$).

*Anal.* Calcd for $C_5H_8Cl_2O$: C, 38.74; H, 5.20. Found: C, 39.01; H, 5.21.

A large amount of material, apparently 2,2-dichloro-1-pentanol, was also present: ir (neat) 3300 (OH), 1250, 1065, 1000, 905, 763, and 704 $cm^{-1}$; nmr ($CCl_4$) δ 3.80 (s, 2 H, $CH_2OH$), 3.0 (s, 1 H, OH, exchangeable with $D_2O$), 1.9–2.4 (m, 2 H, $CCl_2CH_2$), 1.3–1.9 (m, 2 H, $CH_2$), 1.00 (t, 3 H, $CH_3$).

*Anal.* Calcd for $C_5H_{10}Cl_2O$: C, 38.24; H, 6.42. Found: C, 38.21; H, 6.49.

**4-Phenyl-5-nonanone.**—To a solution of 1-phenyl-2-hexanone (1.8 g, 10 mmol) and *n*-propyl bromide (1.2 g, 10 mmol) in 20 ml of dry benzene was added sodium amide (0.4 g, 10 mmol). After the mixture was heated at reflux overnight, water was added, the layers were separated, and the organic phase was dried with sodium sulfate. Removal of solvent and distillation provided 1.1 g (51%) of ketone: bp 87–89° (0.2 mm) [lit.[48] bp 175° (25 mm)]; $n^{23}D$ 1.4923; ir (neat) 1712 (C=O), 1256, 1132, 1044, 751, and 703 $cm^{-1}$; nmr ($CCl_4$) δ 7.19 (s, 5 H, $C_6H_5$), 3.52 (t, 1 H, PhCH), 2.25 (t, 2 H, $COCH_2$), 1.0–2.1 (m, 8 H, $CH_2$), 0.88 (t, 6 H, $CH_3$); semicarbazone mp 107–109° (lit.[48] mp 109°).

**5-Phenyl-4-nonanone.**—To a solution of 1-phenyl-2-pentanone (4.1 g, 25 mmol) and *n*-butyl bromide (4.3 g, 31 mmol) in 40 ml of dry benzene was added sodium amide (1.2 g, 31 mmol). After the mixture was heated at reflux for 30 hr, water was added, the layers were separated, and the organic phase was dried with sodium sulfate. Removal of solvent and distillation provided 3.1 g (57%) of ketone: bp 73–76° (0.08 mm) (lit.[48] bp 275–277°); $n^{24}D$ 1.4930; ir (neat) 1715 (C=O), 1136, 1025, 899, 751, and 705 $cm^{-1}$; nmr ($CCl_4$) δ 7.19 (s, 5 H, $C_6H_5$), 3.50 (t, 1 H, PhCH), 2.25 (t, 2 H, $COCH_2$), 1.1–2.1 (m, 8 H, $CH_2$), 0.6–1.1 (m, 6 H, $CH_3$).

**Control Experiment for Recovery of Acetone.**—A mixture of 1.45 g of acetone, 60 ml of methylene chloride, and 65 ml of 18% hydrochloric acid was distilled under reduced pressure into cold traps (−78°) until a single phase was present in the distilling flask. The mixture in the flask was then steam distilled into a cooled receiver. Glpc analysis of the collected fractions revealed the presence of 1.36 g of acetone (94% recovery).

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**Registry No.**—Aluminum chloride, 7446-70-0; di-*n*-butyl-*sec*-butylacetonitrile, 41718-30-3; 3-methylvaleronitrile, 21101-88-2; di-*n*-butyl-*sec*-butylacetamide, 41718-32-5; di-*n*-butyl-*sec*-butylcarbinamine, 41718-33-6; di-*n*-butyl-*sec*-butylcarbinamine acetamide derivative, 41718-34-7; *n*-butyldimethylcarbinamine, 2626-64-4; *n*-butyldimethylcarbinol, 625-23-0; di-*n*-butylmethylcarbinol, 33933-78-7; *n*-butyl bromide, 109-65-9; ethyl acetate, 141-78-6; di-*n*-butylmethylcarbinamine, 41718-37-0; di-*n*-butylmethylcarbinamine acetamide derivative, 41718-38-1; di-*n*-butylcarbinamine, 2198-45-0; di-*n*-butylbenzylcarbinol, 41718-40-5; ethyl phenylacetate, 101-97-3; di-*n*-butylbenzylcarbinamine, 41718-41-6; di-*n*-butylbenzylcarbinamine acetamide derivative, 41718-42-7; di-*n*-butylphenylacetamide, 41718-43-8; di-*n*-butylphenylcarbinamine, 41718-44-9; di-*n*-butylphenylcarbinamine benzamide derivative, 41718-45-0; *N*-ethyltri-*n*-butylcarbinamine, 41718-46-1; 2-chlorovaleraldehyde, 41718-47-2; valeraldehyde, 110-62-3; methylene chloride, 75-09-2; 2,2-dichlorovaleric acid, 18240-68-1; 1,1,2,2-tetrachloropentylphosphoimidic trichloride, 18240-56-7; 2,2-dichlorovaleryl chloride, 41718-49-4; 2,2-dichlorovaleraldehyde, 41718-50-7; 2,2-dichloro-1-pentanol, 41718-51-8; 4-phenyl-5-nonanone, 41718-52-9; 1-phenyl-2-hexanone, 25870-62-6; *n*-propyl bromide, 106-94-5; 5-phenyl-4-nonanone, 41718-53-0; 1-phenyl-2-pentanone, 6683-92-7.

# Nucleophilic Reactions of *N*-Hydroxyimide-*O*-triflates

TOBY M. CHAPMAN* AND ELSA ACOSTA FREEDMAN

*Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260*

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Reactions of *N*-hydroxysuccinimide-*O*-triflate (**1**), *N*-hydroxyphthalimide-*O*-triflate (**5**), and *N*-hydroxytetramethylsuccinimide-*O*-triflate (**6**) with various nucleophiles were investigated. Compound **1** reacts with thallous acetate to give *N*-hydroxysuccinimide-*O*-acetate. Sodium thioacetate gives the same product, indicating that the reaction proceeds by initial attack at sulfonate sulfur. Compounds **1** and **5** react with phenoxide and thiophenoxide through attack at imide carbonyl, ring opening, and Lossen rearrangement giving β-alanine and anthranilic acid derivatives, respectively. Compound **6** reacts with phenoxide and thiophenoxide at sulfonate sulfur. In no case was direct nucleophilic displacement at nitrogen or the formation of nitrenium ions indicated.

Nucleophilic substitution reactions at nitrogen are quite rare and the mechanisms are usually in doubt. Although there are several reactions reported in the literature which can be schematically considered nucleophilic displacements at nitrogen, they can be explained by different mechanisms, *e.g.*, nitrene formation, nitrenium ion formation, or addition–elimination.[1-5]

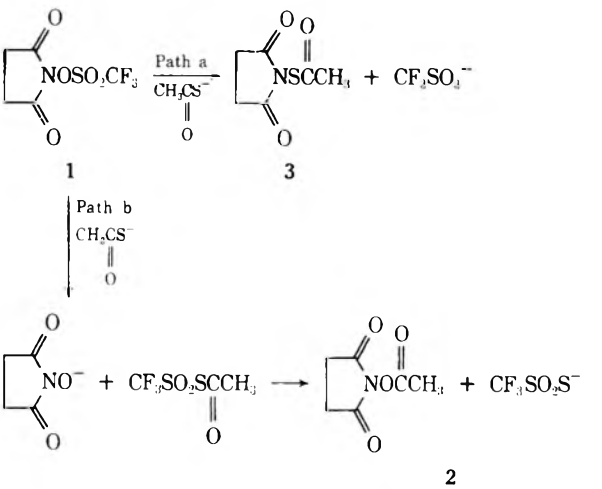
It appeared to us that a compound such as *N*-hydroxysuccinimide-*O*-trifluoromethanesulfonate (triflate)[6] might undergo direct nucleophilic displacement at nitrogen based on the following accounts. First, the group displaced would be triflate anion, considered until recently the most effective leaving group.[7,8] Second, although Gassman and Hartman[9] have shown that the N–O bond in tosyl derivatives of dialkylhydroxylamines is extremely labile, presumably forming nitrenium ion intermediates, related work by Biehler and Fleury[10] showed the proximity of electron-withdrawing groups to stabilize such derivatives.

In an effort to demonstrate the possibility of nucleophilic displacement at nitrogen, the reactivity of compound **1** and two congeners toward nucleophilic reagents was studied.

## Results and Discussion

*N*-Hydroxysuccinimide-*O*-triflate reacted with thallous acetate in dimethylformamide giving a 53% yield of *N*-hydroxysuccinimide-*O*-acetate (**2**). If the reaction occurred by a direct displacement mechanism, it was reasoned that an approach toward the racemization-free formation of peptide active esters might be developed. Compound **2** could have formed from acetate and **1** by two mechanisms, substitution at nitrogen or a double displacement in which carboxylate attacks at sulfonate sulfur giving rise to an activated anhydride which could then acetylate the *N*-hydroxysuccinimidyl anion displaced in the first step. Insight was gained by studying the reaction of sodium thioacetate with **1** under a variety of conditions and solvent media, including dimethylformamide, dimethyl sulfoxide, dimethoxyethane, and methylene chloride. As shown in Scheme I, direct displacement (path a) would give thioacetate **3** whereas double displacement (path

SCHEME I



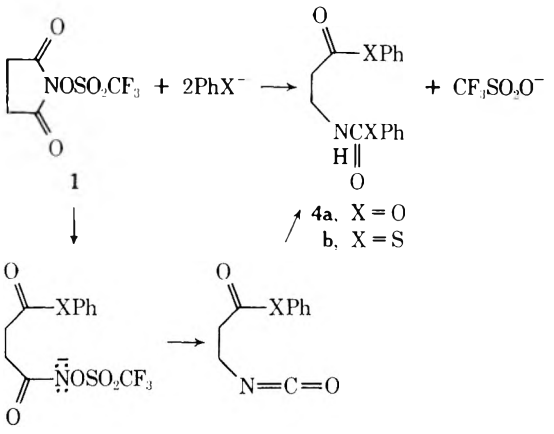

(1) J. W. Cahn and R. E. Powell, *J. Amer. Chem. Soc.*, **76**, 2565 (1954).
(2) L. A. Audrieth and L. H. Diamond, *J. Amer. Chem. Soc.*, **76**, 4869 (1954).
(3) R. Brown and W. E. Jones, *J. Chem. Soc.*, 781 (1948).
(4) (a) A. Nickon and A. Sinz, *J. Amer. Chem. Soc.*, **82**, 753 (1960); (b) A. Nickon and A. Hill, *ibid.*, **86**, 1152 (1964).
(5) D. S. Kemp and R. B. Woodward, *Tetrahedron*, **21**, 3019 (1965).
(6) T. M. Chapman and E. A. Freedman, *Synthesis*, 591 (1971).
(7) (a) R. L. Hansen, *J. Org. Chem.*, **30**, 4322 (1965); (b) A. Streitweiser, Jr., C. L. Wilkins, and E. Kiehlmann, *J. Amer. Chem. Soc.*, **90**, 1598 (1968); (c) T. M. Su, W. F. Sliwinski, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **91**, 5386 (1969).
(8) The "nonaflate" anion has been reported to be an even better leaving group than triflate: L. R. Subramanian and M. Hanack, *Chem. Ber.*, **105**, 1465 (1972).
(9) (a) R. G. Gassman and G. D. Hartman, *Chem. Commun.* 853 (1972); (b) P. G. Gassman and G. D. Hartman, *J. Amer. Chem. Soc.*, **95**, 449 (1973).
(10) J. M. Biehler and J. P. Fleury, *Tetrahedron*, **27**, 3171 (1971).

b) would give acetate **2**. In each case the major product was acetate **2** showing initial attack by nucleophilic acetate at sulfur and not at nitrogen. The resulting mixed anhydride formed at the carboxyl terminus at a peptide would readily racemize the terminal amino acid residue by oxazalone formation or acylium ion formation.[11,12]

Since carboxylate is a weak nucleophile and also forms highly unstable intermediates, it was advisable to study stronger nucleophiles; sodium phenoxide and sodium thiophenoxide were selected.

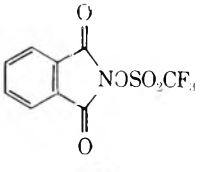
It was expected that sodium phenoxide would react with **1** to give either phenyl succinimidyl ether (attack at nitrogen) or phenyl triflate (attack at sulfur);[13] neither was detected. Instead, equimolar amounts of **1** and phenoxide gave a 54% yield of phenyl *N*-phenoxycarbonyl-β-alanate (**4a**) along with unreacted **1**. The formation of this product is shown in Scheme II.

SCHEME II

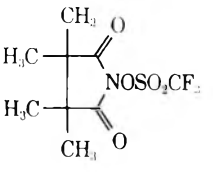



Phenoxide attacks a ring carbonyl leading to ring opening, Lossen rearrangement to an isocyanate, and reaction with a second molecule of phenoxide. Indeed, the ir spectrum of the reaction mixture showed an absorption band at 2250 $cm^{-1}$, characteristic of isocyanates. When thiophenoxide was used as a nucleophile, the reaction with **1** followed a similar path, forming **4b**. It was thus established that the stronger nucleophiles preferentially attack the succinimidyl carbonyl functions rather than sulfur or nitrogen. Acetate and thioacetate may also add to the carbonyl functions with the resulting tetrahedral intermediate reverting back to starting materials in a nonproductive equilibrium. A similar ring opening and rearrangement has been observed by Gross and Bilk, the reaction of dicyclohexylcarbodiimide and *N*-hydroxysuccinimide giving the succinimidyl ester of *N*-(succinimidyloxycarbonyl)-β-alanine.[14a] Also, in 1893 Lengfeld and Stieglitz[14b] observed the reaction of *N*-bromosuccinimide and sodium methoxide to give the methyl analog of **4a**. To optimize the possibility of observing reaction at nitrogen, the reaction at carbonyl had to be suppressed. Conceivably this could be done (i) by introducing conjugation with an aromatic as in *N*-hydroxyphthalimide-*O*-triflate (**5**), (ii) by introducing steric constrictions as in *N*-hydroxytetramethylsuccinimide-*O*-triflate (**6**). Triflate **5** was prepared in good yield by the reaction of the thallium(I) salt of *N*-hydroxyphthalimide with trifluoromethanesulfonic anhydride.[6] Triflate **6** was prepared in analogous fashion from *N*-hydroxytetramethylsuccinimide. The latter was prepared in the following fashion. Using a combination of procedures reported by Rathke and Lindert[15] and by Hudson and Hauser,[16] the lithium enolate of ethyl isobutyrate, prepared *in situ* by reaction of lithium *N*-isopropylcyclohexylamide, was mixed with 0.5 equiv of iodine, giving diethyl tetramethylsuccinate. The anhydride was prepared by acid hydrolysis or by saponification to the acid followed by treatment with acetic anhydride or acetyl chloride.[17] The anhydride was converted to the hydroxysuccimide analog by adapting the Orndorff and Pratt procedure.[18]

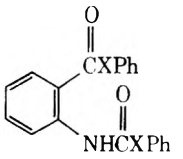
Reaction of phthalimide triflate **5** with 1 equiv of sodium phenoxide gave only ring-opened products identified as phenyl *N*-phenoxycarbonylanthranilate (**7a**), isatoic anhydride, and phenyl anthranilate, all derived from initial nucleophilic reaction at carbonyl. Reaction of **5** with 2 equiv of sodium thiophenoxide gave *S*-phenyl 2-(*S*-phenylthiocarbamyl)thiobenzoate (**7b**),




**5**




**6**




**7a**, X = O
**b**, X = S

anthranilic acid, and a small amount of a third ring-opened product which was only partially characterized. There is some literature precedence for ring-opening attack at phthalimide carbonyl groups. Harpp and Back[19] observed ring opening of *N*-(isopropylthio)-phthalimide while studying sulfenamide synthesis.

Reaction of tetramethylsuccinimide triflate (**6**) with sodium thiophenoxide did not occur in methylene chloride at −8°, but at room temperature some reaction occurred, giving diphenyl disulfide and some *N*-hydroxytetramethylsuccinimide. There was no evidence of ring-opened product and no evidence for

(11) F. Effenberger and G. Epple, *Angew. Chem., Int. Ed. Engl.*, **11**, 299 (1972).

(12) We have observed that the reaction of carbobenzyloxyglycyl-L-phenylalanine with 2,4-dinitrophenyltriflate leads to a 90% recovery of racemic dipeptide starting material.

(13) There is a great deal of precedent for attack by nucleophiles at benzene sulfonate and tosylate sulfur. See, for example, (a) J. Ferns and A. Lapworth, *J. Chem. Soc. Trans.*, **101**, 273 (1912); (b) F. G. Bordwell, B. M. Pitt, and M. Knell, *J. Amer. Chem. Soc.*, **73**, 5004 (1951); (c) J. F. Bunnett and J. Y. Bassett, Jr., *ibid.*, **81**, 2104 (1959); (d) P. G. Gassman, J. M. Hornback, and J. M. Pascone, *Tetrahedron Lett.*, 1425 (1971).

(14) (a) H. Gross and L. Bilk, *Tetrahedron*, **24**, 6935 (1968); (b) F. Lengfeld and J. Stieglitz, *Amer. Chem. J.*, **15**, 504 (1893).

(15) (a) M. W. Rathke and A. Lindert, *J. Amer. Chem. Soc.*, **93**, 2318 (1971); (b) M. W. Rathke and A. Lindert, *Tetrahedron Lett.*, 3995 (1971).

(16) B. E. Hudson, Jr., and C. R. Hauser, *J. Amer. Chem. Soc.*, **63**, 3161 (1941).

(17) P. E. Verkade and H. Hartman, *Recl. Trav. Chim. Pays-Bas*, **52**, 951 (1933).

(18) W. R. Orndorff and D. S. Pratt, *J. Amer. Chem. Soc.*, **47**, 89 (1912).

(19) D. N. Harpp and T. G. Back, *Tetrahedron Lett.*, 4953 (1971).

attack at nitrogen, particularly the formation of tetramethylsuccinimide, which could have been formed from the hypothetical sulfenamide product.[19] The products could be rationalized by nucleophilic attack at sulfonate, giving thiophenyl triflate; thiosulfonates are known to react with mercaptides to give disulfides.[20]

The reaction of 6 with sodium phenoxide gave a 78% yield of phenyl triflate. Although carbonyl attack is suppressed, the site of substitution is shifted to sulfur.

In conclusion, we have demonstrated the difficulty of nucleophilic attack at nitrogen. Of the three electrophic sites in the succinimidyl-based triflates, reaction occurred at carbonyl or sulfonate but never at nitrogen, even though triflate is such as excellent leaving group. Substitution at nitrogen could have been facile in the phthalimide case considering the analogy to phenacyl halides, which readily undergo substitution. The favorable transition state,[21] however, comes at the expense of nitrogen lone-pair delocation.

Of particular interest is the stability of the N–O bond of the triflates, particularly in light of the recent work of Gassman and Hartman.[9] The *N*,*N*-diacyl structure completely suppressed nitrenium ion formation. The rearrangement of the succinimide triflates to the β-alanate compounds could lead to a general synthesis of substituted dihydrouridines if compounds such as **4b** can be cyclized with ammonia. The dicyclohexylcarbodiimide–*N*-hydroxysuccinimide mixture has been shown to have utility in the coupling of peptide fragments[22] but is complicated by the rearrangement reaction discovered by Gross and Bilk;[14a] our results suggest the possible advantage of using *N*-hydroxytetramethylsuccinimide.

## Experimental Section

Melting points were determined on a Kofler micro hot stage melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-8 or Perkin-Elmer 247 spectrophotometer. The nmr spectra were recorded on Varian A-D60 or T-60 spectrometers; mass spectra were obtained on an LKB Type 9000 gas chromatograph–mass spectrometer by use of either the direct probe or analytical glc columns. Elementary analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and by Scandinavian Microanalytical Laboratories, Herlev, Denmark. Column chromatography was carried out using Baker 3405 silica gel and the specified solvents as eluents. Preparative thick layer chromatography was performed on commercial silica gel F-254 precoated plates. All reaction solvents and chromatography eluents were carefully dried and distilled before use.

***N*-Hydroxysuccinimide-*O*-triflate (1).**—*N*-Hydroxysuccinimide-*O*-triflate (1) was prepared as previously reported.[6]

***N*-Hydroxyphthalimide-*O*-triflate (5).**—To *N*-hydroxyphthalimide (4.07 g, 0.025 mol) dissolved in a mixture of ether (200 ml) and acetone (170 ml) was added thallous ethoxide (6.22 g, 0.025 mol). After 15 min the bright orange precipitate was filtered and dried *in vacuo*, affording 8.35 g (90.5%) of the *N*-hydroxyphthalimide thallous salt which was used without further purification.

To a suspension of the salt in methylene chloride (200 ml) was added trifluoromethanesulfonic anhydride (7.7 g, 0.273 mol) in 30 ml of $CH_2Cl_2$. After 13 hr the reaction mixture was filtered and the filtrate was extracted twice with water. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*, affording 5.19 g (78%) of **5**: mp 90° (recrystallization from 2-propanol raised the melting point to 94–96°); ir (KBr) 1810, 1730, 1440, 1340, 1220, 790, and 690 $cm^{-1}$; nmr ($CDCl_3$) δ 7.9 (s, aromatic); mass spectrum *m*/*e* 295 (parent).

*Anal.* Calcd for $C_9H_4F_3NO_5S$: C, 36.6; H, 1.35; F, 19.3; N, 4.75; S, 10.85. Found: C, 36.57; H, 1.49; N, 4.64.

***N*-Hydroxytetramethylsuccinimide-*O*-triflate (6). A. Synthesis of Diethyl Tetramethylsuccinate.**—Lithium *N*-isopropylcyclohexylamide (0.63 mol, from 0.63 mol of *n*-butyllithium and 0.65 mol of isopropylhexylamine) in tetrahydrofuran (200 ml) was cooled to −78°. Ethyl isobutyrate (73.0 g, 63.0 mol) was added dropwise over 15 min followed by the addition of iodine (80 g, 0.63 g-atom) in 400 ml of tetrahydrofuran over 30 min. The reaction mixture was allowed to reach room temperature and after 50 min was quenched with acetic acid (7.6 ml). After filtration and concentration of the organic filtrate, aqueous sodium bicarbonate was added and the mixture was extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$ and concentrated, and the product was distilled, giving 22 g of diethyl tetramethylsuccinate, bp 68–70° (0.3 Torr). Redistillation gave 14.3 g (23.4%) of pure product: ir ($CHCl_3$) 2990, 1720, 1470, 1260, 1130 $cm^{-1}$; nmr (neat) δ 1.21 (s, 12, $CH_3$), 1.25 (t, 6, $J$ = 7 Hz, $OCCH_3$), 4.06 (q, 4, $J$ = 7 Hz, $OCH_2$); mass spectrum *m*/*e* 230 (parent).

**B. Tetramethylsuccinic Anhydride.**—To 6.6 g of diester was added 60 ml of concentrated $H_2SO_4$ and the mixture was heated on a water bath for 3 hr. The reaction mixture was then poured into ice–water, and the precipitate was filtered. Recrystallization from Skelly B gave 2.99 g (57%) of anhydride: mp 140° (lit.[17] mp 152°); ir ($CCl_4$) 2975, 1850, 1750 $cm^{-1}$; nmr ($CDCl_3$) δ 1.23 (s, $CH_3$); mass spectrum *m*/*e* 84, 59 (base). From the aqueous solution, 1.73 g (35%) of diacid could be recovered.

**C. *N*-Hydroxytetramethylsuccinimide.**—To 25 ml of water was added hydroxylamine hydrochloride (1.55 g, 0.0223 mol), tetramethylsuccinic anhydride (2.78 g, 0.0178 mol), and sodium carbonate (1.19 g, 0.0112 mol). The reaction mixture was kept at 81–82° on a water bath for 2 hr. Cooling in an ice bath gave a solid which after crystallization from $CCl_4$ afforded 2.78 g (91%) of *N*-hydroxytetramethylsuccinimide: mp 130–132°; ir ($CHCl_3$) 3200, 2980, 1775, 1700 $cm^{-1}$; nmr ($CDCl_3$) δ 1.2 (s, 12, $CH_3$), 5.23 (broad, 1, OH); mass spectrum *m*/*e* 171 (parent).

*Anal.* Calcd for $C_8H_{13}NO_3$: C, 56.1; H, 7.6; N, 8.2. Found: C, 55.1; H, 7.56; N, 7.99.

**D. Title Compound 6.**—*N*-Hydroxytetramethylsuccinimide thallous salt (4.8 g, 0.0128 mol, prepared from *N*-hydroxytetramethylsuccinimide and thallous ethoxide in ether) was suspended in methylene chloride (65 ml) and cooled to 0°. Trifluoromethanesulfonic anhydride (5.13 g, 0.0182 mol) was added and after 1 hr at 0° the reaction mixture was allowed to come to room temperature and kept for an additional 1.5 hr. After filtration the filtrate was extracted with water, dried over $Na_2SO_4$, and concentrated *in vacuo*. The resulting oil solidified, giving 3.42 g (86%) of triflate **6**. Recrystallization from absolute methanol afforded 2.84 g of white needles (73.5%): mp 37°; ir ($CCl_4$) 2990, 1750, 1440, 1235, 1205 $cm^{-1}$; ir ($CH_2Cl_2$) an additional band at 1800 $cm^{-1}$; nmr ($CDCl_3$) δ 1.28 (s, $CH_3$); mass spectrum *m*/*e* 303 (parent).

*Anal.* Calcd for $C_9H_{12}F_3NO_5S$: C, 35.60; H, 3.97; N, 4.63; S, 10.55. Found: C, 35.79; H, 4.11, N, 4.77; S, 10.86.

**Reaction of Thallium(I) Acetate with 1.**—Thallous acetate (1.64 g, 0.00624 mol) and **1** (0.77 g, 0.00312 mol) were mixed in dimethylformamide (50 ml). After 20 hr the mixture was filtered and the solvent was evaporated *in vacuo*. The resulting residue was titrated with hot benzene and the product was isolated from the benzene extracts after evaporation as an oil which solidified on standing in hexane (0.259 g, 53%), single spot on tlc (silica gel H, 4% acetone in $CH_2Cl_2$ eluent, $R_f$ 0.46, same as authentic **2**). See the next section for further characterization.

**Reaction of Potassium Thioacetate with Triflate 1.**—Potassium thioacetate (0.171 g, 0.0015 mol) and triflate **1** (0.185 g) were suspended in methylene chloride and allowed to stand for 8 days at room temperature. Filtration and evaporation left an oily residue which was chromatographed on silica gel, eluting with chloroform and chloroform–methanol (95:5). Starting material was recovered in 45% yield along with 0.0275 g (23%) of *O*-acetyl-*N*-hydroxysuccinimide (**2**): mp 133° (lit.[23] mp 129–130°); ir ($CHCl_3$) 1820, 1785, 1735, 1370, 1160 $cm^{-1}$; nmr ($CDCl_3$) δ 2.35 (s, 3, $CH_3$) 2.85 (s, 4, $CH_2CH_2$); mass spectrum *m*/*e* 157 (parent), 43 (base). The reaction was repeated in a

(20) H. Gilman, L. E. Smith, and H. H. Parker, *J. Amer. Chem. Soc.*, **47**, 851 (1925).

(21) P. D. Bartlett and E. N. Trachtenberg, *J. Amer. Chem. Soc.*, **80**, 5808 (1958).

(22) (a) E. Wünsch and F. Drees, *Chem. Ber.*, **99**, 110 (1966); (b) F. Weygand, D. Hoffmann, and E. Wünsch, *Z. Naturforsch. B*, **21**, 426 (1966).

(23) LaValle, *Gazz. Chim. Ital.*, **25**, 30 (1895).

variety of solvents (dimethoxyethane, dimethylformamide, dimethyl sulfoxide, thioacetic acid) and cations ($Na^+$, $Tl^+$) always giving **2** but not **3**.

**Reaction of *N*-Hydroxysuccinimidyl Triflate (1) with Sodium Phenoxide.**—Sodium phenoxide was prepared using the method of Kornblum and Lurie.[24] To sodium phenoxide (0.23 g, 0.002 mol) in dimethoxyethane (120 ml) at 0° was added **1** (0.494 g, 0.002 mol). After 26 hr at 0–4° the solvent was evaporated *in vacuo* and ethyl acetate was added. After water extraction the organic layer was dried over $Na_2SO_4$ and evaporated. The resulting solid was subjected to column chromatography on silica gel, which afforded 0.044 g (8.9%) of **1**, 0.020 g (11%) of phenol, and 0.155 g of a solid (mp 74–76°) which was recrystallized from benzene–hexane and identified as compound **4a**: 0.14 g (54%); mp 77°; ir (KBr) 3300, 3050, 1740, 1725, 1695 $cm^{-1}$; nmr ($CDCl_3$)[25] $\delta$ 2.85 (t, 2, $CH_2CO$), 3.61 (d t, 2, $CH_2N$), 5.6 (t, 1, NH), 7.0–7.55 (complex, 10, aromatic); mass spectrum *m/e* 285 (parent).

*Anal.* Calcd for $C_{16}H_{15}NO_4$: C, 67.4; H, 5.27; N, 4.9. Found: C, 67.25; H, 5.35; N, 4.83.

The experiment was repeated at room temperature. After 18 hr an aliquot was removed; ir showed the presence of a band at 2250 $cm^{-1}$. Addition of a second equivalent of sodium phenoxide eliminated this absorption.

**Reaction of Sodium Thiophenoxide with 1.**—To compound **1** (1.86 g, 0.0075 mol) in dimethoxyethane (200 ml) was added sodium thiophenoxide (1.09 g, 0.00825 mol) prepared by the method of Sheehan and Daves.[26] Ir spectra taken after 1 and 21 hr showed the presence of a 2270-$cm^{-1}$ absorption. After 26 hr, thiophenol (0.8235 g, 0.0075 mol) was added and after 5 min the solvent was removed *in vacuo*. Methylene chloride (50 ml) was added and the resulting precipitate was filtered and washed. Combined filtrates were evaporated to a solid residue. Chromatography on silica gel using $CH_2Cl_2$, ethyl acetate, acetone, and acetone–methanol mixtures as eluents gave 0.362 g (21%) of thiophenol and 1.67 g (70%) of compound **4b**, which after recrystallization from cyclohexane had mp 104°; ir (KBr) 3275, 1700, 1680, 1650, 1220 $cm^{-1}$; nmr ($CDCl_3$)[24] $\delta$ 2.9 (t, 2, $J$ = 6 Hz, $CH_2CO$), 3.60 (d t, 2, $J$ = 6 Hz, $CH_2N$), 5.9 (broad triplet, 1, NH), 7.3–7.7 (complex, 10, aromatic); mass spectrum *m/e* 317 (parent).

*Anal.* Calcd for $C_{16}H_{15}NO_2S_2$: C, 60.67; H, 4.81; N, 4.32. Found: C, 60.5; H, 4.74; N, 4.41.

Small amounts of other ring-opened products were also obtained.

**Reaction of Phthalimidyl Triflate (5) with Sodium Phenoxide.**—To sodium phenoxide (0.435 g, 0.00374 mol) in $CH_2Cl_2$ (140 ml) was added **5** (1.00 g, 0.0034 mol) dissolved in $CH_2Cl_2$ (15 ml). After 24 hr at room temperature, the mixture was filtered, the solid was washed with $CH_2Cl_2$, and the combined filtrates were evaporated *in vacuo*. Column separation of the residue afforded **7a**, 0.568 g (40% based on triflate), 0.064 g (8.9%) of anthranilic acid phenyl ester, and 0.284 g (51%) of isatoic anhydride.

Compound **7a** had mp 94–95°; ir (KBr) 3275, 3050, 1740, 1700, 1120–1240 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 7.0–7.7 (complex, 12, aromatic), 8.24 (dd, 1, $J_1$ = 1.5 Hz, $J_2$ = 8 Hz, aromatic), 8.55 (dd, 1, $J_3$ = 1.0, $J_4$ = 7.5 Hz, aromatic); mass spectrum *m/e* 333 (parent).

*Anal.* Calcd for $C_{20}H_{15}NO_4$: C, 72.0; H, 4.50; N, 4.20. Found: C, 71.45; H, 4.52; N, 4.17.

Anthranilic acid phenyl ester had mass spectrum *m/e* 213 (parent), 120 (base).

Isatoic anhydride had mp 243–245° (lit.[27] mp 243° dec); ir (KBr) 1723, 1760 $cm^{-1}$;[28] nmr (acetone-$d_6$) $\delta$ 7.13–7.43 (complex, 2), 7.7 (dd, 1, $J_1$ = 2, $J_2$ = 2 Hz), 8.0 (dd, 1, $J_3$ = 10 Hz, $J_4$ = 2 Hz); mass spectrum *m/e* 163 (parent), 119 (base).

**Reaction of 5 with Sodium Thiophenoxide.**—To sodium thiophenoxide (0.792 g, 0.006 mol) in $CH_2Cl_2$ (100 ml) was added **5** (0.885 g, 0.003 mol) in $CH_2Cl_2$ (40 ml) over 15 min. More $CH_2Cl_2$ (20 ml) was added and the mixture was stirred for 8.5 hr. Thiophenol (0.33 ml, 0.003 mol) was added and stirring was continued overnight. Filtration and evaporation of the filtrate left a residue which was placed on a silica gel column for purification. Elution with benzene, methylene chloride, and acetone, respectively, afforded 0.65 g of crude **7b**, which after recrystallization from hexane was 0.56 g (51%): mp 135–136°, ir (KBr) 3050, 1700, 1630, 1575, 1190, and 900 $cm^{-1}$; nmr (acetone-$d_6$) $\delta$ 7.13–7.73 (m, 12, aromatic), 8.21 (dd, 1, $J_1$ = 10, $J_2$ = 2 Hz), 8.43 (dd, 1, $J_3$ = 10, $J_4$ = 2 Hz), 10.6 (broad s, 1, NH); mass spectrum *m/e* 365 (parent).

*Anal.* Calcd for $C_{20}H_{15}NO_2S_2$: C, 65.75; H, 4.12; N, 3.84; S, 17.5. Found: C, 65.82; H, 4.18; N, 4.0; S, 17.25.

Small amounts of other ring-opened products were obtained.

**Reaction of *N*-Hydroxysuccinimide-*O*-triflate (6) with Sodium Thiophenoxide.**—Compound **6** (0.303 g, 0.001 mol) was dissolved in $CH_2Cl_2$ (25 ml). After cooling to 0°, sodium thiophenoxide (0.132 g, 0.001 mol) was added. The reaction mixture was kept at −8° for 20 hr, but ir showed the presence of starting material. After 24 hr at room temperature the reaction mixture was filtered, the solid (53 mg) was washed with $CH_2Cl_2$, and the organic extracts were concentrated *in vacuo*. The residue was subjected to preparative thick layer chromatography, $CH_2Cl_2$ eluent, and showed two fractions, 0.102 g (94%) of diphenyl disulfide and 0.116 g (38.5%) of recovered starting material. Diphenyl disulfide had mp 60° (lit.[29] mp 60–61°); nmr ($CDCl_3$) $\delta$ 7.37 (complex); mass spectrum *m/e* 218 (parent), 109 (base).

The solid obtained after filtration was dissolved in water, acidified with concentrated HCl, and extracted with ethyl acetate, and the organic layer was dried over $Na_2SO_4$. Evaporation of the solvent afforded 0.044 g (26%) of *N*-hydroxytetramethylsuccinimide.

**Reaction of 6 with Sodium Phenoxide.**—To triflate **6** (0.606 g, 0.002 mol) in $CH_2Cl_2$ (10 ml) was added sodium phenoxide (0.464 g, 0.004 mol). After 21 hr the reaction mixture was filtered and washed with $CH_2Cl_2$, giving 0.659 g of solid. The combined organic filtrates were extracted with water and dried over $CaCl_2$. Evaporation gave 0.375 g of an oil which was subjected to preparative thick layer chromatography, $CH_2Cl_2$ eluent. Recovered was 0.340 g (78%) of phenyl triflate: bp 89–90° (30 mm) [lit.[30] bp 99–100° (60 mm)]; ir ($CHCl_3$) 3070, 1600, 1590, 1490, 1420, 1220, 1120, 880 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 7.3 (s, aromatic); mass spectrum *m/e* 226 (parent, base).

The solid from filtration of the reaction mixture was dissolved in water (5 ml), acidified with concentrated HCl, and extracted with $CH_2Cl_2$. Evaporation left an oil which after preparative thick layer chromatography afforded 0.266 g (79.5%) of *N*-hydroxytetramethylsuccinimide.

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**Registry No.**—**1**, 34684-40-7; **4a**, 41580-56-7; **4b**, 41580-57-8; **5**, 41580-58-9; **6**, 41580-59-0; **7a**, 33067-24-2; **7b**, 41580-61-4; *N*-hydroxypthalimide, 524-38-9; trifluoromethanesulfonic anhydride, 358-23-6; diethyl tetramethylsuccinate, 33367-54-3; lithium *N*-isopropylcyclohexylamide, 32400-20-7; ethyl isobutyrate, 97-62-1; tetramethylsuccinic anhydride, 35046-68-5; *N*-hydroxytetramethylsuccinimide, 41580-64-7; thallium acetate, 563-68-8; potassium thioacetate, 10387-40-3; sodium phenoxide, 139-02-6; sodium thiophenoxide, 930-69-8.

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# Base-Catalyzed Hydrogen–Deuterium Exchange Reactions of Long-Chain Alkyldimethylsulfonium Halides

YUMIHIKO YANO, TSUNEO OKONOGI, AND WAICHIRO TAGAKI*

*Department of Chemistry, Faculty of Technology, Gunma University, Kiryu, Gunma, Japan*

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Base-catalyzed H–D exchange reaction of sulfonium halides, $n$-$C_nH_{2n+1}S(CH_3)_2{}^+X^-$ ($n$ = 1–12), has been studied by nmr technique. The rates of exchange of longer alkyl chain compounds ($n$ = 10, 12) were found to be much larger than those of shorter chain compounds ($n$ = 1–8). Under micellar conditions, the rates for lauryldimethylsulfonium salts ($n$ = 12, X = Cl, Br, I) followed Michaelis–Menten type saturation kinetics with respect to hydroxide ion concentration, and they increase in the order of X = I < Br < Cl.

An enhanced reactivity of a nucleophile on a cationic micellar surface has been well documented for a number of micellar reactions[1] including our previous observations.[2] In most of these cases, except for a few functional micelles,[1a,2b,3,4] a detergent to form micelle is not directly involved in reaction but appears to affect the reactivity of a nucleophile through field effects such as electrostatic and microenvironmental solvent effects.

Direct reaction of micellar component is known in the hydrolysis of primary straight-chain alkyl sulfate in acidic, neutral, and basic aqueous solution.[5] Although this reaction exhibits a typical micellar effect, the detergent decomposes during the reaction. In this report, we describe the H–D exchange reaction of long-chain alkylsulfonium halides catalyzed by sodium deuterioxide in deuterium oxide solution. Such a direct reaction of micellar component with hydroxide ion, without changing the micellar properties during the reaction, may give more insight into the reactivity of a nucleophile on a cationic micelle.

## Results and Discussion

The rate of H–D exchange reaction was followed by determining the relative intensities of the $S$-methyl protons of sulfonium salts and the methyl protons of 2-picoline used as an internal standard in a nmr tube according to our previous method.[6] The methyl protons of 2-picoline do not undergo any detectable exchange under the present reaction conditions. The exchange of the other protons of sulfonium salts are extremely slow and they can also be used as the internal standard. In all the experiments, the rates followed pseudo-first-order kinetics up to more than 90% completion of reaction. The results are shown in Table I and Figure 1.

Table I indicates that the rates for iodides increase slightly by increasing alkyl chain length from $C_1$ to $C_8$, then sharply for $C_{10}$ and $C_{12}$ compounds. It is well known that the $S$-methyl hydrogen of sulfonium salt undergoes ready base-catalyzed H–D exchange reaction[7,8] and the effect of structure of other alkyl portions on the rates is generally small.[8,9] Such a rate change associated with the change of alkyl chain length appears to be explained in terms of micellar effect, since both $C_{10}$ and $C_{12}$ compounds form micelles well below the substrate concentration of kinetics (0.1 $M$) while the micelle formation was not detected for the other shorter alkyl chain compounds. Micellar explanation also appears to be consistent with the effects of a base concentration and counteranion on the rates as described below.

Figure 1 indicates that the rates of $C_1$ and $C_4$ compounds increase in a first-order manner by increasing deuterioxide ion concentration. In addition, these rates are virtually unchanged with the change of counteranions (X = Cl, Br, I), and the slope of the line gives $k_2 = 6.76 \times 10^{-2}\ M^{-1}\ \text{min}^{-1}$. On the other hand, in the case of $C_{12}$ compounds, such a linear plot of $k_{obsd}$ *vs.* $[OD^-]$ was not observed. Rather, the plots gave a saturation curve for each counteranion like in Michaelis–Menten type kinetics. Furthermore, there is an increase of reactivity in the order of X = I < Br < Cl.

For a non-micelle-forming salt, the ion pair can be considered to be fully dissociated in an aqueous media, and abstraction of hydrogen from the cation by deuterioxide ion proceeds through an ordinary bimolecular mechanism without undergoing appreciable interference with the counteranion. Whereas on a cationic micellar surface, the counteranions are thought to be bound to the surface relatively tightly.[1] Effects of ion pairing or micelle formation may be reflected in the chemical shift of $S$-methyl protons ($\delta_{CH_3}$). As indicated in Table I, the $\delta_{CH_3}$ values are substantially larger and constant in $CDCl_3$ than in $D_2O$. The constancy of $\delta_{CH_3}$ in $CDCl_3$ may be reasonable since the ion pairing in less polar $CDCl_3$ should be more complete than in polar $D_2O$, and hence the $\delta_{CH_3}$ may be expected to be insensitive to the change of alkyl chain or the counteranion. The $\delta_{CH_3}$ values of $C_{12}$ compounds in $D_2O$ are intermediate between those in $CDCl_3$ and of $C_4$ compounds in $D_2O$. This suggests in accordance with the accepted view[1,10] that the polarity of the micellar surface of $C_{12}$ compounds is considerably reduced and the ion pairing is more sensitive to the nature of counterion than in the case of a non-micelle-forming salt. Thus, for micelle-

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Table I

Effects of Base Concentration and Counteranion on the H–D Exchange Rates of $n$-$C_nH_{2n+1}S(CH_3)_2{}^+X^-$ [a]

| $n$ | X | Registry no. | Nmr, $\delta_{CH_3}$, ppm [b] $D_2O$ | $CDCl_3$ | $[OD^-] \times 10^2$, $M$ | $k_{obsd}$ [c] $\times 10^2$, $min^{-1}$ |
|---|---|---|---|---|---|---|
| 1 | Cl | 3086-29-1 | 2.92 | *d* | 6.27 | 0.440 |
| | Br | 3084-53-5 | 2.92 | *d* | 6.27 | 0.424 |
| | I | 2181-42-2 | 2.92 | *d* | 3.78 | 0.253 |
| | | | | | 6.27 | 0.460 |
| 4 | Cl | 41580-82-9 | 2.83 | 3.38 | 17.9 | 1.20 |
| | Br | 41580-83-0 | 2.85 | 3.42 | 17.9 | 1.25 |
| | I | 37127-44-9 | 2.86 | 3.42 | 1.31 | 0.118 |
| | | | | | 3.78 | 0.295 |
| | | | | | 4.95 | 0.347 |
| | | | | | 7.15 | 0.493 |
| | | | | | 17.9 | 1.24 |
| 6 | I | 41580-85-2 | 2.90 | 3.42 | 3.78 | 0.312 |
| 8 | I | 41580-86-3 | 3.02 | 3.42 | 3.78 | 0.333 |
| 10 [e] | I | 41619-34-5 | 3.08 | 3.42 | 3.78 | 4.35 |
| 12 | Cl | 41580-87-4 | 2.90 | 3.39 | 1.35 | 5.81 |
| | | | | | 2.65 | 9.66 |
| | | | | | 3.91 | 15.5 |
| | | | | | 5.11 | 19.5 |
| | | | | | 6.27 | 21.1 |
| | | | | | 7.39 | 22.0 |
| | | | | | 9.38 | 29.5 |
| | | | | | 11.2 | 32.5 |
| | | | | | 14.6 | 35.3 |
| | | | | | 17.9 | 41.2 |
| 12 | Br | 41580-88-5 | 2.97 | 3.42 | 1.35 | 4.04 |
| | | | | | 2.65 | 6.86 |
| | | | | | 3.91 | 10.3 |
| | | | | | 5.11 | 11.9 |
| | | | | | 6.27 | 13.6 |
| | | | | | 7.39 | 16.4 |
| | | | | | 11.2 | 25.0 |
| | | | | | 14.6 | 26.9 |
| | | | | | 17.9 | 30.7 |
| 12 | I | 18412-81-2 | 3.10 | 3.42 | 0.792 | 1.95 |
| | | | | | 1.56 | 3.65 |
| | | | | | 2.57 | 5.72 |
| | | | | | 3.78 | 7.66 |
| | | | | | 4.95 | 8.46 |
| | | | | | 5.74 | 9.50 |
| | | | | | 7.15 | 11.7 |
| | | | | | 11.2 | 16.8 |
| | | | | | 14.6 | 17.9 |
| | | | | | 17.9 | 21.0 |

[a] Sulfonium salt = 0.1 $M$, 42 ± 0.5°. [b] From the peak of tetramethylsilane. [c] Mean deviations are less than 6%. [d] Hardly soluble in $CDCl_3$. [e] cmc = $1.72 \times 10^{-2}$ $M$ (in water). For $C_{12}$ salts, see Figure 2.

forming salts, it can be assumed that deuterioxide ion abstracts hydrogen after a fast preequilibrium association with the micellar sulfonium cation, and a halide counteranion acts as an inhibitor in such a way as to occupy the active site for abstraction of hydrogen, competitively or noncompetitively. If the inhibition is competitive, the reaction can be described by eq 1–3,

$$S^+H + OD^- \xrightarrow{k_2} S^+D + OH^- \quad (1)$$

$$S^+H_m + OD^- \overset{K}{\rightleftharpoons} S^+H_m \cdot OD^- \overset{k_m}{\rightleftharpoons} S^+D_m \cdot OH^- \rightleftharpoons S^+D_m + OH^- \quad (2)$$

$$S^+H_m + X^- \overset{K_I}{\rightleftharpoons} S^+H_m \cdot X^- \quad (3)$$

where $S^+H_m$ and $S^+H$ are the micellar and nonmicellar components of sulfonium salt, respectively, $K$ and $K_I$ are the association constants, and $k_m$ and $k_2$ are the rate constants for the hydrogen abstraction from the micellar and nonmicellar salt, respectively. The overall rate is then given by eq 4, where $C_D$ is the initial stoichiometric concentration of substrate. Equation 4 can be transformed to eq 5 based on the assumptions and formulations reported by Bunton,[1b,11] where $[S^+H]$ = cmc, $[S^+H_m]_T = (C_D - \text{cmc})/N$ is the total concentration of micelle, and $N$ is the aggregation num-

$$\text{rate} = k_{obsd}C_D = k_2[S^+H][OD^-] + k_m[S^+H_m \cdot OD^-] \quad (4)$$

$$k_{obsd}C_D = k_2\text{cmc}[OD^-] + \left[\frac{(C_D - \text{cmc})}{N}\right] \cdot \left[\frac{k_mK[OD^-]}{(1 + K_I[X^-] + K[OD^-])}\right] \quad (5)$$

(11) C. A. Bunton and L. Robinson, *J. Amer. Chem. Soc.*, **90**, 5512 (1968). They assume that a micelle and the substrate (here $OD^-$) forms a 1:1 complex and incorporation of substrate in the micelle prevents incorporation of inhibitor competitively. These assumptions are obviously oversimplified for the present case since a micelle should incorporate more than one counteranion.

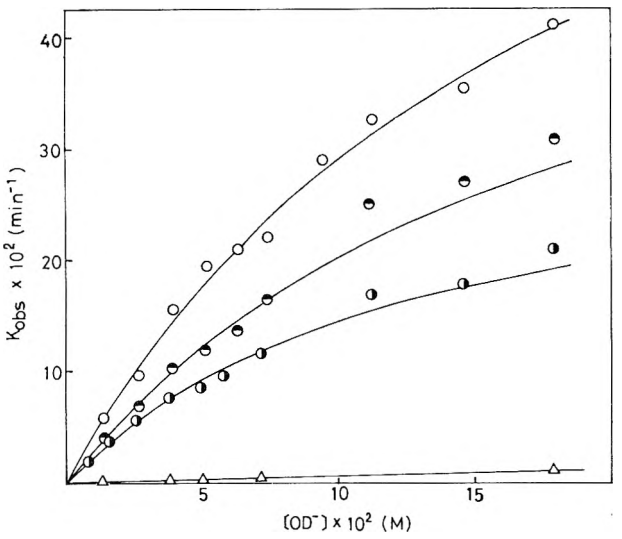


Figure 1.—Plots of $k_{obsd}$ *vs.* base concentration: ○ (X = Cl), ◓ (Br), and ◑ (I) for $n$-$C_{12}H_{25}S(CH_3)_2{}^+X^-$; △, for $n$-$C_4H_9S(CH_3)_2{}^+I^-$. The solid lines are calculated from eq 7 using the intercepts and slopes in Figure 3.

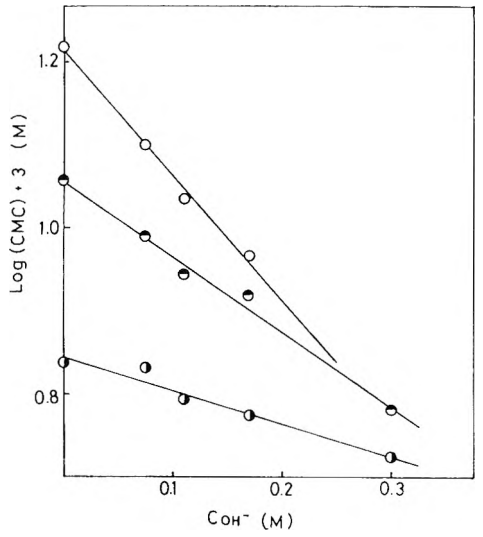


Figure 2.—Plots of log (cmc) *vs.* hydroxide ion concentration for $n$-$C_{12}G_{25}S(CH_3)_2{}^+X^-$: ○ (X = Cl), ◓ (Br), and ◑ (I). The cmc's in water are $1.65 \times 10^{-2}$ $M$ (X = Cl), $1.14 \times 10^{-2}$ $M$ (Br), and $0.689 \times 10^{-2}$ $M$ (I).

ber of micelle. In eq 5, it is difficult to determine the first nonmicellar term because of limitation of the present nmr method to carry out the kinetics with the salt concentration as low as the cmc. Another difficulty was the change of cmc with the change of base concentration. However, as shown in Figure 2, it was found that there is a linear relationship between log (cmc) and the base concentration, $C_{OH^-}$ (eq 6),[12]

$$\log (\text{cmc}) = \log (\text{cmc})_0 - k_s C_{OH^-} \quad (6)$$

which allows the contribution of cmc to the rates to be calculated. Furthermore, if the nonmicellar rate ($k_2$) is assumed to be the same as those of $C_1$ and $C_4$ compounds, the data in Table I and Figure 2 allow the contribution of the first term in eq 5 to be estimated to be negligible (less than 1% of the overall rate).

(12) See also P. Mukerjee, *J. Phys. Chem.*, **69**, 4038 (1965); A. Ray and G. Nemethy, *J. Amer. Chem. Soc.*, **93**, 6787 (1971); A. Hamabata, S. Chang, and P. H. von Hippel, *Biochemistry*, **12**, 1278 (1973).

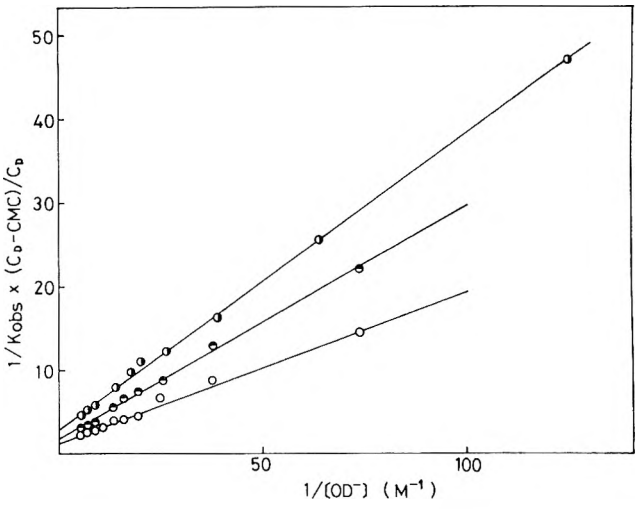


Figure 3.—Plots of data for $n$-$C_{12}H_{25}S(CH_3)_2{}^+X^-$ based on eq 7: ○ (X = Cl), ◓ (Br), and ◑ (I).

Thus, neglect of the first term and rearrangement of eq 5 leads to eq 7. The linearity of the plots based on

$$\left(\frac{1}{k_{cbsd}}\right)\cdot\left(\frac{C_D - \text{cmc}}{C_D}\right) = \frac{N}{k_m} + \frac{N}{k_m K}(1 + K_I[X^-])(1/[OD^-]) \quad (7)$$

eq 7 was confirmed as shown in Figure 3. Figure 3 indicates that the intercepts ($N/k_m$) are almost identical for the three counteranions within experimental error, and the identity may justify the assumption of competitive inhibition, although a small difference can also be argued to indicate other mechanism such as a noncompetitive inhibition. One may suspect that the change of cmc (Figure 2) is the corollary of the change of the size and the aggregation number ($N$) of micelle. The linearity in Figure 3 might indicate that either the change in $N$ is small or $k_m$, $K$, and $K_I$ also change in such a direction to cancel out the change of $N$. The reciprocal values of the slopes $\{k_m K/N(1 + K_I[X^-])\}$ in Figure 3 are 5.47 (X = Cl), 3.57 (Br), and 2.82 $M^{-1}$ min$^{-1}$ (I), and they should be comparable to the $k_2$ values of $C_1$ and $C_4$ compounds ($k_2 = 6.76 \times 10^{-2}$ $M^{-1}$ min$^{-1}$) to give the ratios 81 (X = Cl), 53 (Br), and 42 (I), respectively. These ratios would be raised more if uninhibited rates of micellar reactions ($k_m K/N$) could be compared.[13] Furthermore, the reactivity of deuterioxide ion per one micelle ($k_m K$) should be even more pronounced since the aggregation number $N$ may be expected to be larger than 10 for most $C_{12}$ cationic detergents.[1]

The above results and discussion indicate that the reactivity of deuterioxide ion is enhanced more than 100-fold when bound on a cationic micellar surface of $C_{12}$ sulfonium salt. An increase of local concentration of base near the reaction site may account for a part of rate enhancement. However, a more important factor may be an enhanced basicity of deuterioxide ion bound to a relatively nonpolar cationic micellar sulface.

(13) For such a comparison, one must measure the rates of exchange of the substrate of $X^- = OH^-$, or alternatively the $K_I$ values must be known. However, we have encountered some difficulties in obtaining a pure sample of lauryldimethylsulfonium hydroxide. Furthermore, it may be difficult to obtain a reliable value of $K/(1 + K_I[X^-])$ since it is a ratio of the intercept and slope in Figure 3 which already involves a relatively large error due to the error (~6%) in the rate measurement by the present nmr method.

Table II

Melting Points and Elemental Analyses of Sulfonium Halides [$n$-$C_nH_{2n+1}S(CH_3)_2^+X^-$]

| | | | | Analyses, found (calcd), % | | |
|---|---|---|---|---|---|---|
| $n$ | X | S[a] | Mp,[b] °C (lit.) | C | H | S |
| 1 | Cl | M | 176 (170–173)[d] | | | |
| | Br | M | 196 (198)[e] | 22.49 (22.94) | 5.97 (5.78) | 20.55 (20.41) |
| | I | M | 205 (203–207)[f] | 17.98 (17.66) | 4.45 (4.44) | 15.83 (15.71) |
| 4 | Cl[c] | AE | 120 | | | |
| | Br | MC | 95–98 | 36.12 (36.19) | 7.76 (7.59) | 16.45 (16.09) |
| | I | A | 80 (82)[g] | 29.49 (29.28) | 6.75 (6.14) | 12.92 (13.03) |
| 6 | I | A | 66–67 (68)[h] | 35.20 (35.04) | 7.51 (6.98) | 11.74 (11.69) |
| 8 | I | | *i* | 39.55 (39.74) | 7.98 (7.66) | 11.10 (10.61) |
| 10 | I | | *i* | 43.41 (43.64) | 8.72 (8.23) | 10.03 (9.70) |
| 12 | Cl | A | 64–66 | 62.80 (62.99) | 11.78 (11.71) | 12.03 (12.01) |
| | Br | A | 68–70 | 53.67 (54.00) | 10.16 (10.04) | 10.05 (10.29) |
| | I | A | 87 | 47.31 (46.93) | 8.63 (8.71) | 8.96 (8.95) |

[a] Solvent for recrystallization: M, methanol; AE, acetone–ethanol; MC, methylene dichloride; A, acetone. [b] Uncorrected. [c] Microanalyses have not been done because these salts are very hygroscopic and difficult to weigh. However, chloride titration by silver nitrate and the nmr analyses suppported their purity and structure. [d] Y. Funazukuri, *Japan*, **2**, 173 (1961); *Chem. Abstr.*, **56**, 8566 (1962). [e] R. T. Major and H. J. Hess, *J. Org. Chem.*, **23**, 1563 (1959). [f] S. Miller, *Chem. Ber.*, **56**, 1923 (1923). [g] C. K. Ingold, J. A. Jessop, K. I. Kuriyan, and A. M. M. Mandour, *J. Chem. Soc.*, 533 (1933). [h] J. V. Braun, W. Teuffert, and K. Weissbach, *Justus Liebigs Ann. Chem.*, **472**, 121 (1929). [i] Wax form, no definite melting point.

## Experimental Section

**Materials.**—Deuterium oxide (99.8%) was purchased from Showa Denkko Co. The sodium deuterioxide stock solution in deuterium oxide (0.5 *M*) was prepared by dissolving fresh sodium metal. 2-Picoline was distilled over potassium hydroxide pellets. It boiled at 128° and showed no impurities on vapor phase chromatography.

Sulfonium iodides were prepared by treating sulfides with methyl iodide, and sulfonium bromides were prepared from dimethyl sulfide and alkyl bromide, according to a literature method.[14] Sulfonium chlorides were prepared by the following two methods. (1) A sulfide was treated in a sealed tube with methanol (a large excess) saturated with hydrogen chloride for 15–24 hr at 60°. In the case of lauryl methyl sulfide, the reaction mixture was heterogeneous at the beginning, then became homogeneous at the end of reaction. After removal of excess methanol, the residue was washed with ether, dried, and recrystallized. (2) A sulfonium perchlorate (obtained from the corresponding iodide) was dissolved in methanol containing excess potassium chloride under stirring at room temperature. Potassium perchlorate that formed was removed by filtration, the filtrate was concentrated, and the residue was recrystallized. The solvents for recrystallization, the melting points, and the elemental analyses of these sulfonium halides are listed in Table II. The nmr $\delta_{CH_3}$ values of the salts are also given in Table I.

Critical micelle concentrations (cmc) of $C_{10}$ and $C_{12}$ salts were determined by titration of salt solutions with eosine solution, according to a literature method.[15] The dependency of cmc on base concentration is shown in Figure 2.

**Exchange Kinetics.**—The isotopic composition of solutions of sulfonium salts was determined by nmr spectroscopy with a Varian A-60 spectrometer according to our previous method.[6] 2-Picoline was used as an internal standard which showed the signal from the methyl group at $\delta$ 2.54 in $D_2O$. The control experiments showed no H–D exchange of methyl protons of 2-picoline under the present experimental conditions.

The reaction mixtures for the kinetics were prepared by weighing the sulfonium salt in nmr tubes and by adding 0.5 ml of $D_2O$ containing 2-picoline. After equilibration at the reaction temperature, a calculated volume of the sodium deuterioxide stock solution was added into the tube quickly by a microsyringe and the stoppered tube was shaken by turning upside down. The control experiments using a larger volume of the reaction mixture indicated that the calculated base concentration was the same as that determined by titration and remained constant during the reaction. As the reaction proceeded initial singlet peak for the *S*-methyl proton changed to a small multiplet peak, and the peak area diminished, relative to that for the methyl protons of 2-picoline. The exchange of the other protons was extremely slow and not detected. The rate constants shown in Table I were calculated based on the following equation: $k_{obsd} = (2.303/t \log (r_0 - r_\infty)/(r_t - r_\infty)$, where $r$ = (peak area for *S*-methyl)/(peak area for 2-picoline methyl). As expected, the accuracy of the present method is not high. Kinetic runs which showed more than 6% of mean deviation in $k_{obsd}$ were discarded.

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(15) M. L. Corrins and W. D. Harking, *J. Amer. Chem. Soc.*, **69**, 679 (1947).

# Syntheses and Properties of Molten Tetraalkylammonium Tetraalkylborides

WARREN T. FORD,* ROBERT J. HAURI, AND DONALD J. HART

*The Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801*

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Eight tetraalkylammonium tetraalkyborides have been prepared on a large scale from the corresponding tetraalkylammonium bromides and lithium tetraalkylborides. All melt at <50°, are miscible with most organic materials, and are sufficiently stable to heat, light, oxygen, and water to permit their use as solvents. Their completely filled valence shells of electrons prevent acid–base interactions with each other or with solutes, but their ionic character gives them polarities comparable to many polar organic solvents.

Most investigations of molten salts have concentrated on the thermodynamic, electrochemical, and spectroscopic properties and synthetic uses of inorganic materials.[1] Although the high temperature and ionic nature of fused inorganic salts limit their use as solvents for organic compounds, some organic reactions have been carried out in fused alkali hydroxides, bromides, chlorides, acetates, and thiocyanates.[2,3] Molten tetraalkylammonium salts have shown more promise than fused salts of metals as solvents for organic compounds because of their lower melting points and polarities.[3] Particularly notable are the aromatic substitutions and oxidations in tetraalkylammonium nitrates,[3,4] homogeneous catalysis of olefin hydrogenation and carbonylation in tetraalkylammonium trichlorogermanates and trichlorostannates,[5] solvolysis of *tert*-butyl chloride and electrochemical reductions in tetra-*n*-hexylammonium benzoate hemihydrate,[6] and electrochemical reduction of benzalaniline in tetraethylammonium *p*-toluenesulfonate.[7]

Relative to tetraalkylammonium salts little is known about tetraalkylborides.[8] Isolated reports of lithium and sodium tetraalkylborides[9] preceded the first tetraalkylammonium tetraalkylborides.[10] Damico[10a] found that some tetramethylammonium tetraalkylborides have low melting points (<25 to 112°) and are moderately stable in air. Tetramethylammonium tetra-*n*-butylboride is completely stable in water at pH 10 and 35° for 16 hr but hydrolyzes readily in 20% acetic acid at 60°.[10a] Lithium tetraalkylborides behave similarly in aqueous acid and base but decompose in air.[10a] However, sodium tetraethylboride is reported to be stable in air.[9a] Lithium tetraalkylborides react as hydride donors with alkylating agents.[9e,11] More recent reports of lithium and tetraalkylammonium tetraalkylborides have confirmed the earlier observations of their properties.[12]

The results of Damico[10a] suggested to us that tetraalkylammonium tetraalkylborides which are fluid at or near room temperature might be suitable solvents for organic compounds. As solvents they would possess unique properties. They are ionic, yet less polar than other molten salts because of their alkyl groups; they cannot interact with solutes or with each other as Lewis acids or bases; and they permit only electrostatic, ion dipole, ion-induced dipole, and dispersion forces. Potential obstacles to their use as solvents might be their instability in acids, possible instability in air, thermal decomposition, and other unforseen chemical reactions of tetraalkylboride ions. Tetraalkylammonium ions in general are stable to all but very strong bases at <100°.[13] In this paper we describe an efficient method for preparation of molten tetraalkylammonium tetraalkylborides for use as solvents.

## Results and Discussion

The key to obtaining low-melting tetraalkylammonium tetraalkylborides is the attachment of at least one relatively long alkyl chain to either nitrogen or boron; every such compound we have prepared has melted at <50°. Our general synthetic approach, illustrated in eq 1–3 with $N_{2226}B_{2226}$,[14] is the same one

$$(C_2H_5)_3N + n\text{-}C_6H_{13}Br \longrightarrow N_{2226}Br \quad (1)$$

$$(C_2H_5)_3B + n\text{-}C_6H_{13}Li \xrightarrow{\text{hexane}} LiB_{2226} \quad (2)$$

$$N_{2226}Br + LiB_{2226} \xrightarrow{H_2O} N_{2226}B_{2226} + LiBr \quad (3)$$

used previously.[10] Detailed methods for preparation of eight different salts which are molten at ≤50° appear in the Experimental Section.

By design our molten tetraalkylammonium tetraalkylborides are highly resistant to crystallization. They usually form glasses when cooled to −78°.

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(13) W. K. Musker, *J. Chem. Educ.*, **45**, 200 (1968).

(14) Subscripts refer to the number of carbon atoms in the *n*-alkyl groups.

Instead of purifying the final products we have carried out the syntheses by techniques that exclude the most likely impurities. A variety of tests suggest that they are sufficiently pure for many uses as solvents. They exhibit only end absorption in the ultraviolet. They have correct peak areas and contain no noticeable impurities by pmr spectroscopy. They give reasonable elemental analyses. A limited number of samples tested for lithium and halogens contained $\leq$0.02 ppm lithium and $\leq$0.1 ppm halogen. The most sensitive test of their purity found by us is absorption of visible light. After exposure to air for days to months our tetraalkylammonium tetraalkylborides develop a yellow color due to an absorption maximum at *ca.* 365 nm (in ethanol). These pale yellow samples have pmr and ir spectra and microanalyses indistinguishable from those of the original colorless samples. After extended autoxidation, however, the molten salts become darker and less viscous, and in their ir spectra new peaks appear at 2410 (B–H stretch) and 1565 $cm^{-1}$, and the strong sharp peak at 1095 $cm^{-1}$ (B–C stretch of tetraalkylboride) disappears.[10a,15] Also new broad peaks appear in their pmr spectra at $\delta$ 5–6.

The rate at which tetraalkylammonium tetraalkylborides decompose in air varies greatly from one preparation to the next. Preparations carried out in an inert atmosphere with argon-purged solvents give samples which require months for discoloration in air, but slight exposure to air during preparation at the lithium tetraalkylboride stage leads to molten salts which discolor in air in just a few hours. We suspect that tetraalkylammonium tetraalkylborides of higher purity than we have yet obtained would be indefinitely stable in air, and that the decompositions observed by us are initiated by a trace impurity of some peroxy boron compound. Trialkylboranes autoxidize extremely fast *via* a radical chain sequence in which one propagation step is addition of molecular oxygen to the boron atom,[16] but we see no reason why tetravalent boron should react rapidly with oxygen. The decomposition of tetraalkylborides most likely begins by loss of a hydrogen atom from the $\alpha$ or $\beta$ carbon. Unless the lithium ion plays a role in their decomposition, lithium tetraalkylborides should be as stable in the presence of oxygen as their tetraalkylammonium counterparts. However, we have confirmed Damico's[10a] observation that the lithium tetraalkylborides decompose readily in air. Perhaps most or all of the impurities responsible for initiating decomposition are removed during conversion of the lithium to the tetraalkylammonium tetraalkylborides.

Tetraalkylammonium tetraalkylborides are remarkably stable to light and heat. A sample of $N_{2222}B_{4448}$ in a Pyrex tube showed no visible change after standing for 6 months in direct contact with a 20-W fluorescent lamp. Samples of $N_{1116}B_{1116}$, $N_{2226}B_{2226}$, $N_{3333}B_{3336}$, and $N_{4446}B_{4446}$ in sealed tubes showed no change in their color or pmr spectra after 60 min at 200°.

Our tetraalkylammonium tetraalkylborides are not appreciably soluble in water or aliphatic hydrocarbons, but they are miscible in all proportions with many organic solvents ranging in polarity from benzene to methanol. $N_{2226}B_{2226}$ can be stirred and poured readily at room temperature, but the others are substantially more viscous. $N_{2226}B_{2226}$ is too viscous for high-resolution pmr spectra at 25° but not at 50°, while $N_{4446}B_{4446}$ requires heating to *ca.* 90° to give pmr spectra that do not suffer from viscosity broadening. The densities of three molten tetraalkylammonium tetraalkylborides studied by Grindley and Lind[12c] lie in the range of 0.77–0.80 g/ml at 90–160°, and the density of $N_{2226}B_{2226}$ varies from 0.836 g/ml at 22° to 0.819 g/ml at 65°.

In conclusion, molten tetraalkylammonium tetraalkylborides are suitable for use as solvents which are chemically different from any solvents ever used before. Some are sufficiently low melting and nonpolar to permit organic molten salt chemistry at room temperature. All are reasonably stable to heat, light, oxygen, and water and are miscible with a wide variety of organic materials. In subsequent papers we plan to report uses of these new molten salt solvents.

## Experimental Section[17]

**General.**—Melting points were obtained with a calibrated Du Pont Model 900 thermal analyzer. Pmr spectra were obtained with Varian A-60A, A-56/60, and HA-100 instruments. Uv–visible spectra were obtained with a Cary 14 spectrophotometer. Ir spectra were obtained with Perkin-Elmer Model 137 and 237B instruments. The Vacuum Atmospheres Corp. drybox was argon filled and fitted with a dry train described earlier.[18] Microanalyses were performed by J. Nemeth and associates.

**Materials.**—Hexane and pentane were washed with concentrated sulfuric acid, dried over potassium hydroxide, and distilled from calcium hydride. All other solvents were reagent grade and were used as obtained. Triethylamine, tri-*n*-propylamine, and tri-*n*-butylamine were washed with acetic anhydride and distilled from barium oxide. Tetraethylammonium bromide and tetra-*n*-propylammonium bromide were recrystallized twice from chloroform–diethyl ether. Tetra-*n*-butylammonium iodide was recrystallized twice from methanol–water. 1-Bromohexane, 1-chlorohexane, and 1-chlorooctane were freshly distilled from calcium hydride. Triethylborane and tri-*n*-butylborane (both from Callery Chemical Co.) were distilled shortly before use under argon at 76° and 2 Torr, respectively. Tri-*n*-propylborane was prepared by reaction of *n*-propylmagnesium bromide with boron trifluoride etherate[19] and was vacuum distilled. *Caution: All of these trialkylboranes burn spontaneously in air.* All other reagents were obtained commercially and used without further purification.

**Trimethyl-*n*-hexylammonium Bromide.**—A mixture of 0.50 mol of 1-bromohexane, 100 ml of petroleum ether (bp 30–60°), and excess trimethylamine was held in a flask equipped with a Dry Ice condenser at 25° by day and at −10° by night for 10 days. Periodic additions used a total of 2.5 mol of trimethylamine. The resulting white solid was recrystallized from acetone to give 0.295 mol of $N_{1116}Br$, mp 186° (lit.[20] mp 186°).

**Triethyl-*n*-hexylammonium Bromide.**—A mixture of 0.50 mol of 1-bromohexane, 0.50 mol of triethylamine, and 75 ml of acetonitrile was refluxed for 24 hr. Removal of solvent under vacuum left a pale pink solid which was recrystallized from acetone–ethyl acetate to give 0.464 mol of white $N_{2226}Br$, mp 108° (lit.[21] mp 103.0–104.0°).

**Tri-*n*-butyl-*n*-hexylammonium Bromide.**—A mixture of 0.50 mol of 1-bromohexane, 0.50 mol of tri-*n*-butylamine, and 100 ml

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(17) All new compounds had satisfactory elemental analyses for C, H, and N except when specifically noted. The microanalytical data are compiled in a supplement to this paper prepared for the microfilm edition. See paragraph at end of paper regarding supplementary material.

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(21) J. C. Kellett, Jr., and W. C. Doggett, *J. Pharm. Sci.*, **55**, 414 (1966).

of ethyl acetate was refluxed for 86.5 hr. Removal of solvent under vacuum left a colorless oil which deposited white crystals after 2 months of storage at −20°. Three recrystallizations from chloroform–ether gave 0.245 mol of $N_{4446}Br$, mp 52°, which did not change with further recrystallization. However, microanalyses for C, H, and N failed to conform to calculated values.

*n*-**Hexyllithium in Hexane.**—Small segments of lithium wire (30.5 g, 4.40 g-atoms) were washed with hexane under argon and placed with 100 ml of hexane in an argon-filled flask fitted with mechanical stirrer and addition funnel. A solution of 1.26 mol of 1-chlorohexane in 250 ml of hexane was added with stirring over 3 hr at −10°. The mixture was allowed to warm to room temperature, stirred overnight, and transferred to the drybox, where it was filtered into 250-ml bottles for storage. Titration with 2-butanol in xylene and 1,10-phenanthroline as indicator[22] gave a carbon-bound lithium concentration of 1.05 *M* and a yield of 38%.

*n*-**Octyllithium in Hexane.**—Lithium dispersion (1.48 g-atoms) was washed with benzene and hexane in an argon atmosphere. To the stirred dispersion 0.60 mol of 1-chlorooctane in 250 ml of hexane was added over 2 hr at room temperature. The solution was filtered and stored under argon. It was 0.61 *M* in carbon-bound lithium (25% yield) by a double titration analysis.[23] The method used for *n*-hexyllithium would probably also give a better yield of *n*-octyllithium.

**General Method for Molten Salts. Triethyl-*n*-hexylammonium Triethyl-*n*-hexylboride.**—All glassware was dried at 120° for at least 12 hr. All solvents were purged with a vigorous flow of argon through a gas dispersion tube for at least 30 min immediately before use. All operations were carried out in an argon atmosphere either in the laboratory or in the drybox.

In a 2000-ml flask was placed 0.45 mol of *n*-hexyllithium in hexane, and a solution of 0.46 mol of triethylborane in 300 ml of hexane was added with stirring over 60 min at room temperature. After the triethylborane addition another 800 ml of hexane was added in several portions to prevent caking of the thick solid. The resulting suspension of $LiB_{2226}$ was transferred to the drybox and washed with six 350-ml portions of hexane. The solid $LiB_{2226}$ was removed from the drybox, dissolved in 300 ml of water, and washed with two 100-ml portions of hexane. A solution of 0.47 mol of $N_{2226}Br$ in 120 ml of water was added to the aqueous $LiB_{2226}$ solution and mixed thoroughly. Two phases separated. The heavier aqueous phase was removed, and the lighter molten salt phase was washed with six 150-ml portions of water. The molten salt was dried at $10^{-5}$ Torr and 25° for 12 hr. Yield was 138.6 g of colorless liquid salt.

In some preparations washing of the lithium tetraalkylboride was performed in 250-ml centrifuge bottles by repeated cycles of centrifugation, removal of supernatant hexane solution, and agitation with fresh hexane. In some preparations the wet molten salt was filtered in acetone, benzene, or methanol solution.

Numerous preparations of impure molten salts early in this investigation taught us to (1) avoid contact of stopcock grease with molten salt, (2) carry out all operations under argon, (3) purge all solvents with argon to minimize any possible contact of intermediate solids and solutions with oxygen, and (4) avoid rubber serum caps and molecular sieves, which hasten discoloration of molten salts.

By this general method the following tetraalkylammonium tetraalkylborides were prepared in yields of 75–87%:[17] $N_{2222}B_{4446}$, liquid; $N_{2222}B_{4448}$, liquid; $N_{2226}B_{2226}$, liquid; $N_{2226}B_{4448}$, liquid; $N_{3333}B_{3336}$, liquid; $N_{3333}B_{4446}$, mp 14°; $N_{4446}B_{4446}$, mp 27°. Those designated as liquid formed glasses on cooling to −78° but never crystallized. All had pmr multiplets in acetonitrile at δ 2.8–3.4 ($NCH_3$ and $NCH_2$), −0.5 to 0.2 ($BCH_3$ and $BCH_2$), and 0.5–1.6 (all other $CH_2$ and $CH_3$ groups) which had correct relative areas for the assigned structures. All had ir absorption as neat films at 2930–2950, 2870–2910, 2760–2770, 1455–1480, 1070–1095, 1000–1010, and 780–785 $cm^{-1}$. These spectral properties are similar to those reported earlier[10a,12b] for lithium and tetraalkylammonium tetraalkylborides.

**Trimethyl-*n*-hexylammonium Trimethyl-*n*-hexylboride.**—The following preparation of trimethylborane is modified from the method of Brown.[19] A solution of methylmagnesium bromide was prepared from 1.00 g-atom of magnesium turnings and excess methyl bromide in 200 ml of di-*n*-butyl ether. The flask containing the methylmagnesium bromide was connected with flexible tubing to a second flask containing 0.100 mol of *n*-hexyllithium in hexane. The second flask was fitted with a Dry Ice condenser, mechanical stirrer, and Dry Ice jacket. A solution of 0.40 mol of boron trifluoride in 85 g of di-*n*-butyl ether was added over 40 min to the methylmagnesium bromide solution. The resulting trimethylborane was swept with a stream of argon into the −78° *n*-hexyllithium solution through a tube fixed below the liquid surface. After 60 min the slurry of $LiB_{1116}$ in hexane was warmed to room temperature and converted by the general method to $N_{1116}B_{1116}$, mp 46°, 46% yield based on *n*-hexyllithium. Filtration of the $N_{1116}B_{1116}$ was carried out in methanol, and the methanol was removed at 5 Torr prior to drying under high vacuum. $N_{1116}B_{1116}$ is very hygroscopic; it did not give an acceptable microanalysis.

**Lithium Content of Molten Salts.**—A mixture of 0.5091 g of $N_{2222}B_{4448}$ was heated with 1.80 g of concentrated sulfuric acid and after cooling was diluted to 10.00 ml with water. Comparison to standard lithium chloride solutions by flame photometry[24] indicated that the $N_{2222}B_{4448}$ contained $4.4 \times 10^{-5}$ *M* lithium. Similar analyses of $N_{2222}B_{4446}$ and $N_{2226}B_{2226}$ samples showed that they contained $< 4 \times 10^{-5}$ *M* lithium.

**Halogen Content of Molten Salts.**—A sample of 0.9197 g of $N_{2226}B_{2226}$ and 6.208 g of a 50:50 (w/w) mixture of sodium and potassium hydroxide pellets were melted together in a nickel crucible and heated vigorously for 5 min. The flux was cooled, dissolved in water, acidified with 12 *M* nitric acid, and diluted to 50.0 ml. The halide content relative to standard sodium bromide solutions was determined by a standard mercuric thiocyanate–ferric ammonium sulfate spectrophotometric method[25] using as a blank a sample prepared from the same weight of sodium and potassium hydroxides but no $N_{2226}B_{2226}$. Halogen contents of molten salts determined by this method were $N_{2226}B_{2226}$, $1.42 \times 10^{-4}$ *M*; $N_{3333}B_{4446}$, $9.3 \times 10^{-4}$ *M*; and $N_{4446}B_{4446}$, $8.88 \times 10^{-3}$ *M*. Note that the sodium–potassium hydroxide digestion results in detection of covalently bound halogen in addition to halide ions in the molten salts.

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**Registry No.**—$N_{2222}B_{4446}$, 41724-43-0; $N_{2222}B_{4448}$, 41724-44-1; $N_{2226}B_{2226}$, 41724-45-2; $N_{2226}B_{4448}$, 41724-46-3; $N_{3333}B_{3336}$, 41724-47-4; $N_{3333}B_{4446}$, 41724-48-5; $N_{4446}B_{4446}$, 41724-49-6; $N_{1116}B_{1116}$, 41724-50-9; $N_{1116}Br$, 2650-53-5; $N_{2226}Br$, 13028-71-2; $N_{2222}Br$, 71-91-0; $N_{3333}Br$, 1941-30-6; $N_{4446}Br$, 37026-90-7; triethylborane, 97-94-9; tri-*n*-butylborane, 122-56-5; tri-*n*-propylborane, 1116-61-6; trimethylborane, 593-90-8; 1-bromohexane, 111-25-1; trimethylamine, 75-50-3; triethylamine, 121-44-8; tri-*n*-butylamine, 102-82-9; *n*-hexyllithium, 21369-64-2; 1-chlorohexane, 544-10-5; *n*-octyllithium, 3314-49-6; 1-chlorooctane, 111-85-3.

**Supplementary Material Available.**—Microanalytical data will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20 × reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-3916.

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# Photochemical α-Chlorination of Fatty Acid Chlorides by Thionyl Chloride

R. L. RODIN AND HERMAN GERSHON*

*Boyce Thompson Institute, Yonkers, New York 10701*

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Upon chlorination of long and intermediate chain fatty acid chlorides in refluxing thionyl chloride exposed to visible and ultraviolet light, the orientation of chlorine was primarily to the α position. The more intense the light source, the more rapid the reaction, and the same reaction in the dark or in ambient light affords no more than a trace of α-chloro-substituted products. The rate of α-chlorination is appreciably accelerated in the presence of benzoyl peroxide, whereas mineral acid causes the rate to decrease very little. It is proposed that the reaction is photochemical and takes place in the liquid phase according to the following course. Irradiation of boiling thionyl chloride with intense visible or ultraviolet light causes it to slowly decompose to chlorine along with other products. α-Chloro acid chlorides are subsequently produced by a Hell–Volhard–Zelinsky type chlorination of the enol of the acyl chloride.

Fatty acids can be halogenated by one of two mechanisms: hydrogen abstraction by free radicals[1,2] or addition to the enol[3] form of the acid halide (Hell–Volhard–Zelinsky method[4]). The hydrogen abstraction method leads to the α-halo acid plus halo substitution in various other positions along the carbon chain. Bromination according to the Hell–Volhard–Zelinsky method yields only α-bromo acid,[4] whereas chlorination by the same procedure leads not only to α-chloro acid but to chlorination in various other positions[5] in appreciable amounts. Thionyl chloride is ordinarily employed to convert fatty acids into their acid chlorides or anhydrides and, as a solvent, it is one of a number of reagents used to facilitate α-halogenation of carboxylic acid chlorides. When fatty acid chlorides are treated with thionyl chloride in the presence of tertiary amines, a number of unusual products are obtained: α-chloro, α,β-unsaturated, and α-chlorosulfenyl acids.[6]

We wish to report a new reaction of thionyl chloride on fatty acids. When long and intermediate chain length fatty acids are treated with boiling thionyl chloride in the presence of strong visible or ultraviolet light, in the absence of base, a high percentage of α-chloro fatty acid is formed along with a small amount of α,α-dichloro substituted product.

The more intense the light source, the faster the reaction. The effect of light intensity on the rate of α-chlorination is indicated in Table I. A number of experiments were carried out to show that this reaction was light mediated and not merely brought about by the heat of the system, the results of which are summarized in Table II. When lauroyl chloride was heated under reflux by a heating mantle with thionyl chloride in the dark for 25 hr, only methyl laurate was detected by glc after esterification. In ambient light under the same conditions, 8.0% of α-chlorinated product was found. Upon exposure to a 1000-W tungsten lamp for the same period of time a yield of 84% methyl α-chlorolaurate was obtained. When the reaction flask was kept under reflux and shielded from the light rays of this lamp but not from its heat, 3.2% of α-chlorinated product was formed, whereas 0.2% of α-chlorolauric ester was detected when the reaction flask was not heated and shielded from the light rays of the lamp but not its heat. If a mixture of lauroyl and thionyl chlorides is kept under reflux and exposed to the rays of a 1000-W light source where the air space between the light source and reaction flask is cooled to <40°, 81.2% of methyl α-chlorolaurate is found.

The addition of benzoyl peroxide, a free radical initiator, markedly accelerates the rate of chlorination of lauroyl chloride, whereas the addition of sulfuric acid decreases the rate of reaction very little, as seen in Figure 1. Upon the addition of a catalytic amount of benzoyl peroxide to myristoyl chloride, the rate of α-chlorination was also appreciably accelerated.

It was established that the α-chlorination was not intramolecular, by refluxing lauroyl chloride in the

TABLE I

EFFECT OF LIGHT INTENSITY ON RATE OF α-CHLORINATION OF LAUROYL CHLORIDE BY THIONYL CHLORIDE UNDER REFLUX[a]

| Light source | Time, hr | Methyl laurate, % | Methyl α-chloro-laurate, % | Methyl α,α-dichloro-laurate, % |
|---|---|---|---|---|
| Ambient light | 5 | 100 | | |
| 200 W[b] | 5 | 98.6 | 1.4 | |
| 300 W[b] | 5 | 97.0 | 3.0 | |
| 500 W[b] | 5 | 94.0 | 6.0 | |
| 1000 W[b] | 5 | 63.0 | 37.0 | 1.0 |
| Uv[c] | 0.58 | 0.91 | 90.0 | 4.1 |

[a] Composition of mixture determined by converting acid chlorides into methyl esters followed by glc analysis. [b] Tungsten bulb. [c] Reference 9.

TABLE II

IMPORTANCE OF VISIBLE LIGHT FOR THE α-CHLORINATION OF LAUROYL CHLORIDE IN REFLUXING THIONYL CHLORIDE[a]

| Light source | Methyl laurate, % | Methyl α-chloro-laurate, % | Methyl α,α-dichloro-laurate, % |
|---|---|---|---|
| Dark | 100 | | |
| Ambient light | 92.0 | 8.0 | |
| 1000 W[b,c] | 4.4 | 84.0 | 11.6 |
| 1000 W[b,d] | 86.4 | 3.2 | 10.4 |
| 1000 W[b,e] | 99.8 | 0.2 | |
| 1000 W[b,f] | 4.4 | 81.2 | 14 |

[a] Reaction time, 25 hr; products detected as methyl esters by glc. [b] Tungsten bulb. [c] Vapor temp, 146°. [d] Flask covered to keep out light but not heat of lamp; vapor temp, 94°. [e] Same as *c* without refluxing; vapor temp, 87°. [f] Cool air space between reaction flask and light source, $T < 40°$; vapor temp, 131°.

(1) M. S. Kharasch, and H. C. Brown, *J. Amer. Chem. Soc.*, **62**, 925 (1940).
(2) J. C. Little, Y.-L. C. Tong, and J. P. Heeschen, *J. Amer. Chem. Soc.*, **91**, 7090 (1969).
(3) H. B. Watson, *Chem. Rev.*, **7**, 173 (1930).
(4) C. Hall, *Ber. Deut. Chem. Ges.*, **14**, 891 (1881); N. Zelinsky, *ibid.*, **20**, 2026 (1887); C. Hell and J. Sadomsky, *ibid.*, **24**, 2388 (1891); J. Volhard, *Justus Liebigs Ann. Chem.*, **242**, 141 (1887).
(5) (a) P. Smit, and H. J. den Hertog, *Rec. Trav. Chim. Pays-Bas*, **77**, 73 (1958); (b) Y. Ogata and K. Matsuyama, *Tetrahedron*, **26**, 5929 (1970).
(6) M. S. Simon, J. B. Rogers, W. Saenger, and J. Z. Gougoutas, *J. Amer. Chem. Soc.*, **89**, 5838 (1967); A. J. Krubsack and T. Higa, *Tetrahedron Lett.*, 5149 (1968); A. J. Krubsack, T. Higa, and W. E. Slack, *J. Amer. Chem. Soc.*, **92**, 5258 (1970).

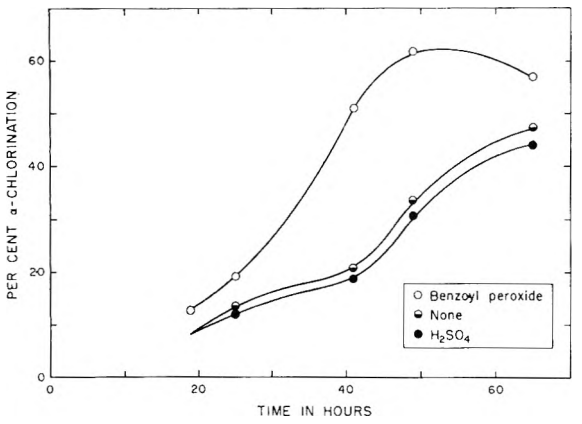



Figure 1.—Effect of benzoyl peroxide and sulfuric acid on the rate of α-chlorination of lauroyl chloride in boiling thionyl chloride illuminated by a 500-W tungsten lamp.

TABLE III
CHLORINATION OF 10-UNDECENOYL CHLORIDE BY REFLUXING THIONYL CHLORIDE[a]

| Time, hr | Methyl undecenoate, % | Methyl 9,10-dichloroundecanoate, % | Methyl 2,9,10-trichloroundecanoate, % | Methyl 2,2,9,10-tetrachloroundecanoate, % |
|---|---|---|---|---|
| 17 | 100 | | | |
| 53 | 64.7 | 35.4 | | |
| 78 | 28.1 | 55.0 | 16.9 | |
| 126 | | 30.4 | 51.8 | 17.8 |

[a] Light source, 500-W tungsten lamp, products detected as methyl esters by glc.

TABLE IV
CHLORINATION OF 9,10-DICHLOROUNDECANOYL CHLORIDE BY REFLUXING THIONYL CHLORIDE[a]

| Time, hr | Methyl 9,10-dichloroundecanoate, % | Methyl 2,9,10-trichloroundecanoate, % | Methyl 2,2,9,10-tetrachloroundecanoate, % |
|---|---|---|---|
| 17 | 100 | | |
| 53 | 69.6 | 16.1 | 14.3 |
| 78 | 57.4 | 20.6 | 18.7 |
| 126 | 33.6 | 44.0 | 22.4 |

[a] Light source, 500-W tungsten lamp; products detected by glc.

presence of strong visible light (500 W) for 48 hr. Only starting material was detected by glc. In order to verify that thionyl chloride does decompose into chlorine, we reacted 10-undecenoyl chloride with thionyl chloride according to our procedure, and a number of products were detected by glc. To identify these different peaks in the chromatograms, the undecenoic acid was chlorinated across the double bond according to standard procedures and subjected to thionyl chloride and light. The principal products were characterized by glc and mass spectrometry. The experiment shows that, when refluxing thionyl chloride is exposed to strong light, it decomposes to significant quantities of chlorine. This is in contrast to the thermal decomposition of thionyl chloride which only begins to dissociate at its boiling point.[7] The initial product formed, when 10-undecenoic acid chloride is exposed to thionyl chloride and light, is the 10,11-dichloro acid chloride and, with time, the 2,10,11-trichloro acid chloride becomes the major product. These data are summarized in Tables III and IV.

(7) N. V. Sidgwick, "The Chemical Elements and Their Compounds," Vol. II, Oxford University Press, London, 1950, p 931.

To demonstrate that the rate of α-chlorination is dependent on the vapor volume, a number of experiments were carried out varying the volume of the vapor phase. The results shown in Table V indicate that the

TABLE V
EFFECT OF VAPOR VOLUME ON RATE OF α-CHLORINATION OF LAUROYL CHLORIDE BY REFLUXING THIONYL CHLORIDE[a]

| Volume of flask, ml | Methyl laurate, % | Methyl α-chlorolaurate, % | Methyl α,α-dichlorolaurate, % |
|---|---|---|---|
| 100 | 78.8 | 9.5 | 11.6 |
| 500 | 74.2 | 15.5 | 10.4 |
| 1000 | 64.3 | 20.4 | 15.2 |
| 5000 | 6.8 | 73.0 | 20.2 |

[a] Light source, 500-W tungsten lamp; reaction time 67 hr; products detected as methyl esters by glc.

greater the vapor volume, the faster the rate of α-chlorination.

That chlorination took place principally in the α position was demonstrated as follows. The mass spectrum of methyl α-chlorolaurate was characterized by peaks at $m/e$ 248 (parent) and $m/e$ + 2 250 (presence of Cl), which was approximately one third of that of the 248 peak. There was also a large 213 peak showing the loss of chlorine (P − 35). The base peak was $m/e$ 108 ($ClCH{=}C(OH)OCH_3$), whereas methyl laurate, or any monochloro methyl laurate other than α, has a base peak of $m/e$ 74 ($CH_2{=}C(OH)OCH_3$). The mass spectrometric data were similarly consistent for the α-chlorinated long chain fatty acid methyl esters of 10,11-dichloroundecanoic, myristic, palmitic, and stearic acids. Nmr data provided confirming evidence of α-chlorination by showing the presence of a triplet at *ca.* δ 4.3 ($J$ = 6 Hz) which integrated for one α proton in the pure product. The nmr spectra of the chlorinated stearic and palmitic acids also showed only one α proton. Methyl laurate and methyl α-chlorolaurate were also identified and quantitated by glc and compared with authentic samples.[8] Elemental analyses and boiling points of some of the chlorinated fatty acids are listed in Table VI. A number of other fatty

TABLE VI
METHYL ESTERS OF α-CHLORO FATTY ACIDS

| Methyl ester | Registry no. | Bp, °C[a] | Formula[c] |
|---|---|---|---|
| α-Chlorolauric | 33422-27-4 | 140 (8 mm)[b] | $C_{13}H_{23}O_2Cl$ |
| α-Chloropalmitic | 41753-98-4 | | $C_{17}H_{33}O_2Cl$ |
| α-Chlorostearic | 41753-99-5 | | $C_{19}H_{37}O_2Cl$ |
| α,α-Dichlorolauric | 33422-25-2 | 262 | $C_{13}H_{24}O_2Cl_2$ |

[a] Analytical sample. [b] Lit.[8] bp 136–139° (8 mm). [c] Satisfactory analytical data (±0.4% for C, H, Cl, O) were reported for all compounds listed in the table: Ed.

acids have been studied under these reaction conditions, and the results are summarized in Table VII. It shows that other long chain fatty acid chlorides, such as myristoyl, palmitoyl, and stearoyl, can be similarly α-chlorinated. By controlling the time of reaction, the rate of formation of side products can be minimized. Upon treating lauroyl chloride for 36 hr, the yield of α-chloro compound decreased while the yield of α,α-dichloro compound increased, and, after 96 hr, the

(8) H. H. Guest and C. M. Goddard, Jr., *J. Amer. Chem. Soc.*, **66**, 2074 (1944).

TABLE VII

α-CHLORINATION OF LONG CHAIN FATTY ACIDS[a]

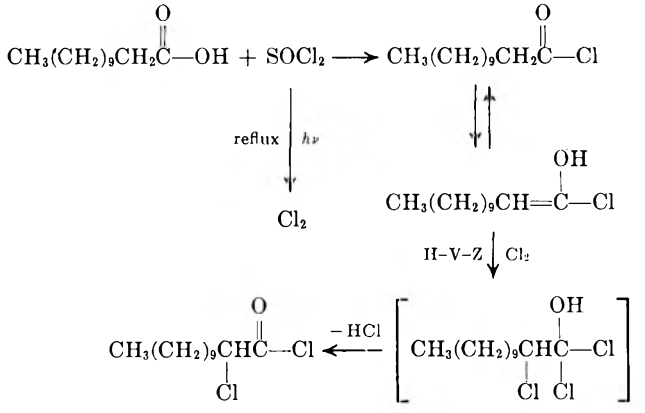
| Fatty acid | Methyl ester, % | Methyl α-chloro ester, % | Methyl α,α-dichloro ester, % |
|---|---|---|---|
| Lauric | 5.3 | 82.1 | 12.6 |
| Myristic | 3.2 | 84.6 | 12.2 |
| Palmitic | 4.3 | 90.0 | 5.7 |
| Stearic | 13.7 | 86.3 | |

[a] Light source, 1000-W tungsten lamp, 14 cm from pot; reaction time, 24 hr; products detected as methyl esters by glc.

yield of α,α-dichloro compound increased to over 60%. If the reaction time was reduced to 18 hr, the per cent of α-chloro product was increased to 91, while the dichloro product decreased to 5.1%.

It appears that the reaction is photochemical and takes place in the liquid phase proceeding by the mechanism shown in Scheme I. Thionyl chloride is

SCHEME I




decomposed in the vapor phase by heat and light into elemental chlorine among other products. The chlorine subsequently adds to the enol form of the acid chloride by a Hell–Volhard–Zelinsky reaction to finally yield α-chloro fatty acid chloride as a principal product. Enolization of fatty acid chlorides is enhanced by the presence of thionyl chloride.[5a] Since benzoyl peroxide is not volatile, its effect on increasing the rate of α-chlorination seems to be in accelerating the decomposition of thionyl chloride in the liquid phase. The increased rate of α-chlorination due to increased head space over the liquid phase is obviously due to the photodecomposition of greater volumes of thionyl chloride vapor in the unit of time, the products of which dissolve in the liquid phase. Finally, since the vapor pressures of the higher fatty acid chlorides are quite low at the boiling point of thionyl chloride, it would be reasonable to expect the chlorination reaction to take place in the liquid phase.

## Experimental Section

Boiling points are uncorrected. Mass spectra were run on a Hitachi RMU-6E single-focusing mass spectrometer. All nmr data were obtained on a Jeolco JMN-C-60HL spectrometer. Separations were carried out on a Varian Aerograph 1200 gas chromatograph, fitted with a flame ionization detector. The column used was 5 ft × 1/8 in. o.d. stainless steel tube packed with 3% QF-10065 on Chromosorb W, with a flow rate of nitrogen of 25 ml/min. The fatty acid esters were chromatographed isothermally at a column temperature of 150° for 2 min and programmed at 12°/min to 210°, and a Varian Aerograph Autoprep Model 700 was used for preparative fractionation.

**Chlorination of Fatty Acids Using Visible Light.**—To a round bottom flask, fitted with a reflux condenser and thermometer, were added 0.5 g of fatty acid and 10 ml of reagent grade thionyl chloride. The mixture was refluxed in the presence of a light source for a given period of time, after which an excess of anhydrous methanol was introduced and refluxing continued overnight. The reaction mixture was evaporated to dryness and the products identified by glc. Preparative samples were obtained using liquid chromatography and preparative glc.

**Chlorination of Lauroyl Chloride Using Ultraviolet Light.**—The reaction was carried out in a reaction vessel fitted with a quartz immersion well and a Hanovia high-pressure quartz mercury 450-W lamp.[9] Lauric acid (0.5 g) in 30 ml of reagent grade thionyl chloride was heated under reflux in the presence of the ultraviolet light. When the quartz immersion well was water cooled, the reaction was completed in 2 hr with the vapor temperature reaching 165°. When the quartz immersion well was not water cooled, the reaction was completed in 35 min, and the vapor temperature reached 230°. The composition of the product of the water-cooled reaction was 2% starting material, 73% α-chloro and 7% α,α-dichloro product, and 18% tarry material. For the reaction that was not water cooled, the composition of products was 0.9% starting material, 88% α-chloro and 4.6% α,α-dichloro product, and 6.5% tarry material.

**Registry No.**—Lauric acid, 143-07-7; thionyl chloride, 7719-09-7.

(9) This lamp emits approximately 30% in the ultraviolet portion of the spectrum, 18% in the visible, and the remainder in the infrared.

# The Photolytically Induced Interconversions of Benzyl Thiocyanates and Isothiocyanates

TERRY E. PARKS[1] AND LANGLEY A. SPURLOCK*[2]

*Metcalf Research Laboratories, Brown University, Providence, Rhode Island 02912*

*Received May 30, 1973*

The photolyses of benzyl thiocyanate (**1a**) and isothiocyanate (**2a**), as well as some of their para-substituted analogs, were found to lead principally to an equilibrium mixture of the two isomers. The equilibrium position was established in several solvents. Rates of photoisomerization were measured. Evidence is presented for the source of several by-products of the reactions.

In the past we[3] and others[4] have devoted considerable effort to the elucidation of the mechanisms of thermally induced thiocyanate–isothiocyanate isomerizations. We now describe some of the few known isomerizations of these compounds which are induced photolytically.[5]

The benzyl thiocyanates were chosen as first objects of study owing to their sluggish uncatalyzed thermal isomerizations[6] and the resultant extensive decomposition prevalent at the required elevated temperatures. It was felt that their photoisomerizations might contrast this and proceed under considerably milder conditions. This indeed proved to be so, as benzyl thiocyanate (**1a**) in an oxygen-free acetonitrile solution at 25° isomerized in 1 hr to a mixture largely composed of isothiocyanate **2a** when irradiated with a medium-pressure Hanovia lamp. Since it was apparent from control studies on **2a** that the isomerization was a

1 2

a. R = H
b. R = $CH_3$
c. R = $OCH_3$
d. R = Cl
e. R = $CF_3$

reversible one, it was undertaken to clarify some aspects of the equilibration process.

Initial efforts centered on investigation of the photoequilibrium position as a function of solvent dielectric. As the equilibrium position of some reversible thermal thiocyanate–isothiocyanate isomerizations had shown a clear influence of this type,[7] we were curious to see if it existed in the photoequilibrium. In actuality, solutions 0.002–0.01 *M* in **1a** or **2a** afforded upon irradiation photoequilibria which varied only from SCN:NCS = 4:96 (cyclohexane) to SCN:NCS = 1:99 (acetonitrile) in the solvents *n*-hexane, cyclohexane, dioxane, and acetonitrile. These ratios were verified as stationary states in each solvent by approach from either isomer. From 0.01 *M* solutions, the photoequilibrium was attained in 3–21 hr from pure **1a** and in 4–10 hr from pure **2a**, depending on the solvent utilized. Photoequilibrium was reached considerably faster (<1 hr) when 0.002 *M* solutions were used.

In a further exploration of possible influences on the photoequilibrium position, photolyses of the various para-substituted isomers, **1b–e** and **2b–e**, were effected in an attempt to ascertain whether any internal electronic influences were involved. For 0.01 *M* cyclohexane solutions of these compounds, however, the photoequilibrium position in every case was SCN:NCS = 4:96, within estimated error limits.

The rates of isomerization for all of these compounds were measured, since we had some evidence from our studies of the equilibrium positions that the attainment of photoequilibrium did not occur in identical time spans. The data from these measurements, made by gc and derived from the initial slopes of concentration *vs.* time plots, are given in Table I.

TABLE I

RATES OF PHOTOISOMERIZATION BY CYCLOHEXANE SOLUTIONS OF BENZYL THIOCYANATES AND ISOTHIOCYANATES

| Para substituent | Concn, *M* | RSCN, $k \times 10^4$ sec$^{-1}$ | RNCS,[a] $k \times 10^6$ sec$^{-1}$ |
|---|---|---|---|
| H | 0.002 | 12.8 ± 3.2 | 3.3 ± 2.0 |
| | 0.01 | 1.1 ± 0.1 | 2.1 ± 1.4 |
| $CH_3O$ | | 3.6 ± 0.8 | 9.2 ± 0.6 |
| $CH_3$ | | 3.7 ± 0.8 | 6.2 ± 2.0 |
| Cl | | 2.5 ± 0.6 | |
| $CF_3$ | | 2.3 ± 0.2 | |

[a] The generally greater error limits given for the isothiocyanates reflect the difficulties in accurately determining the small amounts of thiocyanate generated during the photolyses of the isothiocyanates.

The lack of important electronic influences deducible from these experiments is in accord with the earlier work of Mazzucato, *et al.*,[5] in which homolytic scission of the substrates **1a** and **2a** was indicated by detection of the fluorescence emission of benzyl radical during the isomerization. The principal difference in our findings is the equilibrium position for **1a** and **2a** (the earlier report gave SCN:NCS = 70:30) and the discovery on our part of several by-products of the reaction. When the product mixtures from irradiations of **1a** and **2a** in cyclohexane were subjected to careful gc and mass

(1) Taken in part from the Ph.D. thesis of T. E. Parks, Brown University 1971.

(2) Alfred P. Sloan Fellow, 1973–1975.

(3) See, for example, L. A. Spurlock, R. K. Porter, and W. G. Cox, *J. Org. Chem.*, **37**, 1162 (1972), and references cited therein.

(4) For recent reviews see (a) L. A. Spurlock and T. E. Parks in "Mechanisms of Reactions of Sulfur Compounds," Vol. 3, N. Kharasch, Ed., Intra-Science Research Foundation, Santa Monica, Calif., 1970, p 161; (b) A. Fava in "Organic Sulfur Compounds," Vol. 2, N. Kharasch and C. Y. Meyers, Ed., Pergamon Press, Oxford, 1966, p 85. See also (c) A. Fava, *et al.*, *J. Amer. Chem. Soc.*, **87**, 1045 (1965); (d) A. Ceccon, A. Fava, and I. Papa, *Chim. Ind. (Milan)*, **51**, 53 (1969).

(5) The single earlier report of this type of isomerization [U. Mazzucato, G. Beggiato, and G. Favaro, *Tetrahedron Lett.*, 5455 (1966)] is substantially at odds with our own findings. Possible reasons for this discrepancy will presently be discussed.

(6) (a) L. A. Spurlock and R. G. Fayter, Jr., *J. Org. Chem.*, **34**, 4035 (1969); (b) P. A. S. Smith and D. W. Emerson, *J. Amer. Chem. Soc.*, **82**, 3076 (1960).

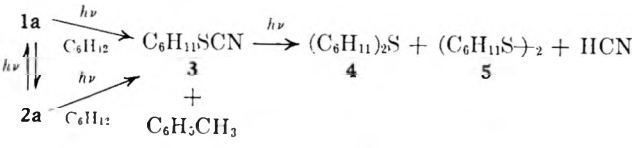
(7) The furfuryl isomers show this effect most clearly. See ref 6a.

spectral analyses, three other products were identified—dicyclohexyl sulfide (4), dicyclohexyl disulfide (5), and toluene. The relative amount of 4 in the product mixture was time dependent and varied from 5% after 4 hr of irradiation to 56% after 36 hr. It was more difficult to accurately analyze for 5 and toluene but it was apparent that their proportions also showed an increase with time of irradiation. No bibenzyl was detected.

As cyclohexyl thiocyanate (3) was the suspected precursor of 4 and 5, despite its absence from the product mixtures, photolysis of an authentic sample of this compound was conducted under conditions identical with those used for the benzyl substrates. This procedure did indeed rapidly afford 4 and 5. In addition, hydrogen cyanide was evolved, and, when reexaminations of the photolysis mixtures from 1a and 2a were undertaken, hydrogen cyanide was also discovered in both samples. This observation allowed a possible explanation for the wide disparity between our photoequilibrium and that of Mazzucato, *et al.* Our recheck of their reported analytical procedure showed that there was no means of distinguishing between 1a and hydrogen cyanide by their methods. Since they seemingly were unaware of the presence of the latter in the products, this seems a likely reason for the contradiction.[8]

The overall reaction shown in Scheme I is most ex-

SCHEME I




plicable as initiated by light-induced homolytic cleavages of the C–S and C–N bonds in the benzyl thiocyanates and isothiocyanates, respectively. Isomerization then results from simple recombination of the benzyl and thiocyanate radicals generated in this fashion.[9] The by-products can be viewed as the results of attack on solvent by the energetic intermediates, probably after they have diffused from the solvent cage in which they were generated.

It was further interesting to note that cyclohexyl thiocyanate (3), unlike its benzyl counterparts, underwent no discernible photoisomerization to isothiocyanate (cyclohexyl radical formation), but rather gave products from cyclohexylthienyl radical. Whether this failure to isomerize reflects the lesser stability of cyclohexyl radical relative to benzyl radicals, or an intramolecular photosensitization by the benzene rings in the benzyl substrates,[10] is not determinable from these results. Whatever the case, however, it is certain that photoisomerization is not a general process for simple, primary, and secondary alkyl thiocyanates and isothiocyanates.

(8) An alternative explanation may lie in their use of a low-pressure Hanovia lamp as compared to our medium-pressure lamp. This appears less likely considering the transparency of 1a [$\lambda_{max}$ 260 nm ($\epsilon$ 470)] and 2a [$\lambda_{max}$ 250 nm ($\epsilon$ 1520)] at wavelengths >280 nm.

(9) The direction of the concentration effect on isomerization rate suggests that a radical-chain reaction is unlikely.

(10) Several examples of intramolecular photosensitization are known. See, for example, R. O. Kan, "Organic Photochemistry," McGraw-Hill, New York, N. Y., 1966, p 14.

## Experimental Section[11]

Benzyl Thiocyanates (1).—All thiocyanates utilized, except the commercially available benzyl derivative, were prepared from the corresponding chlorides or bromides. These precursors were readily available from treatment of the requisite alcohol with concentrated hydrochloric acid or triphenylphosphine dibromide. A typical procedure is that used for synthesis of *p*-trifluoromethylbenzyl thiocyanate (1e).

To 6.0 g (0.025 mol) of *p*-trifluoromethylbenzyl bromide in 35 ml of anhydrous acetone was added 4.85 g (0.05 mol) of dry potassium thiocyanate. This mixture was heated at reflux for 18 hr, diluted with 300 ml of water, and extracted three times with 25-ml aliquots of ethyl ether. Combination of the ether extracts was followed by water washing, drying, and solvent evaporation. Distillation of the residue gave 4.77 g (88%) of 1e: bp 72–74° (0.13 mm); ir (neat) 2147, 1618, 1415, 1320, 1250, 1170–1110, 1065, 1018, 844, 755, 740 cm$^{-1}$; nmr $\tau$ 5.87 (s, 2 H), 2.45 ($A_2B_2$, 4 H); mass spectrum *m/e* (rel intensity) 217 (4.0), 160 (8.9), 159 (100), 109 (18).

*Anal.* Calcd for $C_9H_6F_3NS$: C, 49.76; H, 2.78; F, 26.24; N, 6.45. Found: C, 49.70; H, 2.82; F, 26.37; N, 6.42.

The presence of 1.4% *p*-trifluoromethylbenzyl isothiocyanate (2e) in the product from the above reaction allowed determination of the nmr spectrum of this isomer. The only difference between the spectra of 1e and isothiocyanate 2e was in the methylene protons, where a singlet occurred at $\tau$ 5.24 in 2e. *p*-Chlorobenzyl isothiocyanate (2d), occurring to the extent of 4.0% in the product of an exactly analogous preparation of 1d, showed methylene protons at $\tau$ 5.32 in its nmr spectrum.

The remaining benzyl thiocyanates examined in this study, along with their boiling points and important infrared and nmr absorptions, are given in Table II.

TABLE II

PHYSICAL PROPERTIES OF BENZYL THIOCYANATES AND ISOTHIOCYANATES PHOTOLYZED

| Compd | Bp, °C (mm) | Lit. bp, °C (mm) | Ir, $\nu_{max}$, cm$^{-1}$ | Nmr, $\tau$ Phenyl | Nmr, $\tau$ $-CH_2-$ | Nmr, $\tau$ *p*-$CH_3$ |
|---|---|---|---|---|---|---|
| 2a | 82–85 (0.65) | 126–128 (14)[a] | 2090 | 2.70 (s) | 5.40 (s) | |
| 1b | 85–86 (0.10) | 148–150 (14)[b] | 2140 | 3.00 (s) | 6.00 (s) | 7.70 (s) |
| 2b | 85–87 (0.12) | 94 (1.0)[c] | 2080 | 3.00 (s) | 5.50 (s) | 7.70 (s) |
| 1c | 107–110 (0.15) | 109 (0.5)[d] | 2140 | 3.15 ($A_2B_2$) | 6.03 (s) | 6.32 (s) |
| 2c | 108–110 (0.15) | 160 (2)[c] | 2080 | 3.15 ($A_2B_2$) | 5.51 (s) | 6.32 (s) |
| 1d | 90–91 (0.05) | Mp 17[e] | 2145 | 2.82 (s) | 6.00 (s) | |

[a] D. Martin, E. Beyer, and H. Gross, East German Patent 43,996 (Dec 15, 1965); *Chem. Abstr.*, **65**, 3746*h* (1966). [b] J. von Braun, W. May, and R. Michaelis, *Justus Liebigs Ann. Chem.*, **490**, 189 (1931). [c] K. Antos, A. Stullerova, V. Knoppova, and P. Kristian, *Chem. Zvesti*, **19**, 353 (1965). [d] J. Nosek and V. Janousek, *Chem. Zvesti*, **7**, 676 (1953). [e] C. L. Jackson and A. W. Field, *Amer. Chem. J.*, **2**, 91 (1880).

Benzyl Isothiocyanates (2).—The procedure utilizing carbon disulfide, ethyl chloroformate, and potassium hydroxide as described by Spurlock and Cox[3] afforded the benzyl isothiocyanates listed in Table II in yields varying from 65 to 82%. The crude products from the reaction were purified by elution from a silica gel column (20:1 silica gel to crude isothiocyanate) with pentane. The fractions shown by their infrared spectra to be free of carbonyl-containing impurities were combined and distilled. Gc analyses of the distilled products indicated them to be >99.5% pure isothiocyanate.

(11) Infrared spectra were determined on either a Perkin-Elmer Model 237 or 247 grating infrared spectrometer using sodium chloride optics. Nmr determinations were carried out on a Varian Associates A-60A spectrometer; approximately 20% solutions in $CCl_4$ were employed with tetramethylsilane as the internal standard. Mass spectra were determined at 70 eV on a Hitachi Perkin-Elmer RMU-6D instrument. Analyses were performed by Micro-Analysis, Inc., Wilmington, Del. Practical grade cyclohexane was stirred with concentrated sulfuric acid, the acid was removed, and the remaining cyclohexane was extracted three times with water. This procedure was repeated until the sulfuric acid layer remained colorless after stirring for 24 hr. The recovered cyclohexane was dried and distilled from sodium through a 20-in. Vigreux column. An identical procedure was used for purification of *n*-hexane. Reagent grade acetonitrile was distilled from anhydrous magnesium sulfate. Dioxane was purified by the method of Fieser; see L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath, Boston, Mass., 1955, pp 284–285.

Photolytic Procedures.—The apparatus used in these studies consisted of a Vycor filtered 450-W medium-pressure Hanovia mercury arc lamp placed in a water-cooled quartz jacket fitted with a 45/50 male joint. This assembly was placed in a 700-ml glass finger with a 45/50 female joint. The quartz jacket was of sufficient depth to permit the lamp to be below the surface of 500 ml of liquid contained in the glass finger. The glass portion of the apparatus had a gas inlet tube and a 24/40 side arm to which a water-cooled condenser was attached. All solvents were purified prior to their use.[11] In a typical photolysis, sufficient thiocyanate or isothiocyanate starting material was diluted to 500 ml in solvent to afford the desired concentration. This solution was placed in the glass portion of the apparatus, the lamp assembly was inserted, and argon gas was passed through the solution for a minimum of 1 hr before the lamp was turned on. During argon gas flushing and photolysis the solution was magnetically stirred. At intervals after lamp ignition, aliquots (10 ml for gc analysis and 40 ml for nmr) were removed, the solvent was evaporated, and the residue was analyzed by gc and mass spectrum. Gc was used to analyze the products from the photolyses of **1a**, **2a**, and **3**. On a 2 ft × 0.125 in. 15% diethylene glycol succinate on Chromosorb W column at 150° with a helium carrier gas flow of 75 ml/min, **1a** and **2a** showed retention times of 5.5 and 3.5 min, respectively. In the remaining benzyl systems, nmr analysis was accomplished by comparing the relative peak areas for the benzyl methylene protons of the thiocyanates and isothiocyanates within a given sample. The relative peak areas were measured by integration on the nmr and these results were compared with the relative areas measured with a planimeter. These methods were mutually consistent.

Dicyclohexyl Sulfide (**4**).—To 1.67 g (0.011 mol) of cyclohexanethiol in 15 ml of anhydrous nitrogen-flushed pyridine was added 2.87 g (0.011 mol) of cyclohexyl *p*-toluenesulfonate. The reaction mixture was heated at reflux for 24 hr, cooled, and poured into 100 ml of water. The water solution was extracted three times with 20-ml portions of ether. The ether extracts were combined and washed successively with water, 10% hydrochloric acid solution, and saturated sodium bicarbonate solution. Drying of the resultant ether solution followed by solvent removal afforded 2.4 g of a crude product. Gas chromatographic analysis of this mixture using conditions identical with those used for analysis of the photolysis products from **1a** and **2a** indicated a component with a retention time of 0.80 min. Gc collection of this material afforded dicyclohexyl sulfide: mass spectrum *m/e* (rel intensity) 198 (17), 117 (94), 115 (16), 83 (100), 82 (54), 81 (21), 67 (37), 55 (70), 41 (40), 39 (20).

The mass spectrum and gc retention time of **4** were identical with those shown by the by-product from the photolyses of **1a** and **2a**.

**Acknowledgment.**—We are grateful to the National Institutes of Health (Grant No. F01-GM-38,321) for generous support of this work. We also wish to thank Professor F. W. McLafferty for his assistance in obtaining mass spectral data.

**Registry No.**—**1a**, 3012-37-1; **1b**, 18991-39-4; **1c**, 19927-28-7; **1d**, 2082-64-6; **1e**, 41499-20-1; **2a**, 622-78-6; **2b**, 3694-46-0; **2c**, 3694-57-3; **2d**, 3694-45-9; **2e**, 41499-21-2; **4**, 7133-46-2; *p*-trifluoromethylbenzyl bromide, 402-49-3.

# Perfluorovinyl Isocyanates

WILLIAM J. MIDDLETON

*Contribution No. 2040 from the Central Research Department, E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware 19898*

*Received June 7, 1973*

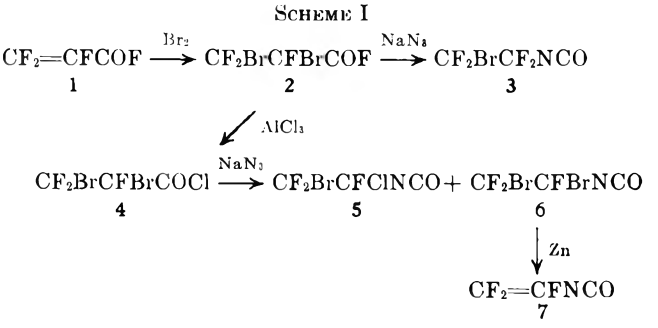
Two new polymerizable monomers, trifluorovinyl isocyanate (**7**) and 2,2-difluoro-1-(trifluoromethyl)vinyl isocyanate (**18**), were prepared by dehalogenation of dichloro- (and dibromo-) trifluoroethyl isocyanates (**6** and **13**) and 1,2-dichloro-2,2-difluoro-1-(trifluoromethyl)ethyl isocyanate (**17**), respectively. The isocyanates **6** and **13** were prepared by the Curtius reaction from the corresponding propionyl chlorides (**4** and **11**) which were in turn prepared by halogenation of trifluoroacryloyl fluoride (**1**) and replacement of the acyl fluorine with chlorine from $AlCl_3$. The isocyanate **17** was prepared in one step by reaction of 1,3-chloropentafluoroacetone imine with oxalyl chloride. Hexafluoroacetone imine and dichlorotetrafluoroacetone imine also gave α-chloro isocyanates with oxalyl chloride. The new vinyl isocyanates, **7** and **18**, add nucleophiles to the isocyanate group in preference to the carbon–carbon double bond.

Although many perfluoroalkyl isocyanates are known,[1] trifluorovinyl isocyanate and other perfluoro isocyanates with α,β double bonds have not been reported previously. Such isocyanates would be expected to polymerize easily and could be used to prepare perfluorinated polymers containing isocyanate groups.

We have prepared trifluorovinyl isocyanate (**7**) in several steps from trifluoroacyloyl fluoride (**1**)[2] (Scheme I). Reaction of **1** with sodium azide to give **7** directly by means of the Curtius reaction failed and gave instead an unidentified, highly explosive material. This explosive material probably resulted from an attack of azide ion on the β-carbon atom of **1**, since it is known that nucleophiles preferentially replace the vinylic β-fluorine atoms of **1** instead of the acyl fluoride.[3]

To circumvent this problem, the double bond was protected by bromination, with the idea that it could be regenerated after the isocyanate was formed by the Curtius reaction. The dibromopropionyl fluoride **2** reacted smoothly with sodium azide, but the major product was the monobromo isocyanate **3**. The sodium fluoride formed in the reaction had apparently replaced the α bromine with fluorine in either the intermediate dibromopropionyl azide or in the expected dibromo isocyanate **6**. It seems most likely that the halogen exchange occurs with **6**, since it could be

SCHEME I



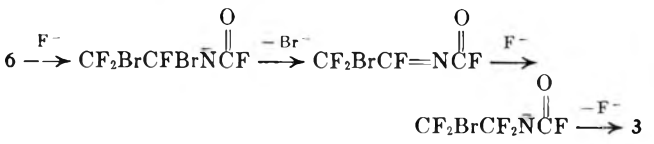

(1) W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry," W. A. Benjamin, New York, N. Y., 1969.

(2) R. E. Banks, J. M. Birchall, T. Clarke, R. M. Haszeldine, M. J. Stevenson, and H. Iserson, *J. Chem. Soc. C*, 266 (1968).

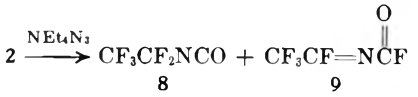
(3) Y. A. Cheburkov and M. D. Bargamova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 833 (1967).

facilitated by a series of addition and elimination reactions as illustrated in Scheme II. More soluble azides,

SCHEME II



such as tetraethylammonium azide, reacted with **2** to give completely fluorinated products, including pentafluoroethyl isocyanate (**8**)[4] and the isomeric carbamoyl fluoride **9**.

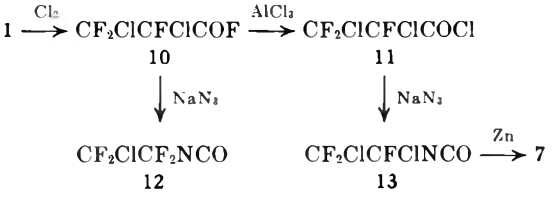


So that no sodium fluoride would be formed in the Curtius reaction, **2** was converted to the corresponding acid chloride **4** by treatment with aluminum chloride in methylene chloride. This dibromo acid chloride (**4**) reacted smoothly with sodium azide to give the dibromo isocyanate **6** as the principal product. Some bromochloro isocyanate **5** was also formed.

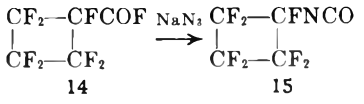
Trifluorovinyl isocyanate (**7**) was formed in 81% yield by debromination of **6** with activated zinc dust in diglyme at room temperature. It is a colorless, low-boiling liquid (bp 19–20°) that polymerizes spontaneously if stored uninhibited at room temperature. The polymerization can be inhibited if small amounts of conventional radical inhibitors such as D-limonene or 2-(trifluoromethyl)phenothiazine are added to the liquid monomer.

Trifluorovinyl isocyanate (**7**) can also be prepared from **1** by protecting the double bond with chlorine, as illustrated in Scheme III.

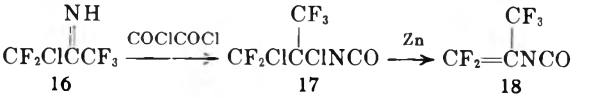
SCHEME III



An attempt to prepare **7** by the pyrolysis of perfluorocyclobutyl isocyanate (**15**) failed, presumably because of the instability of **7** in the presence of radicals generated in the pyrolysis. Isocyanate **15** was prepared by a normal Curtius reaction of the corresponding acyl fluoride **14**.

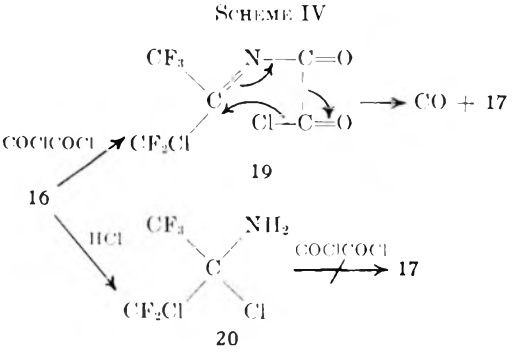


Perfluoroisopropenyl isocyanate (**18**) was also prepared by zinc dehalogenation of the corresponding dichloro isocyanate (**17**) and was obtained in 91% yield as a colorless liquid, bp 42°. Isocyanate **18** does not spontaneously polymerize when stored at room temperature, but it can be polymerized and copolymerized with radical or anionic catalysts.



The dichloro isocyanate (**17**) precursor to **18** was prepared conveniently in one high-yield step by the reaction of oxalyl chloride with chloropentafluoroacetone imine.[5] This reaction is believed to proceed through the oxalyl derivative (**19**) which either undergoes a concerted reaction as illustrated in Scheme IV or adds

SCHEME IV

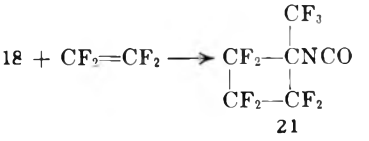


a chloride ion with elimination of CO and chloride to give **17**.

Another possible mechanism would be the addition of hydrogen chloride to **16** to give the α-chloro amine **20**, and then oxalylation of this amine to give **17**. This mechanism appears unlikely, however, since **20**, which can be prepared by the addition of anhydrous hydrogen chloride to the imine **16**, will not react with oxalyl chloride under the same conditions that **16** will react.

The reaction of perhalo ketone imines with oxalyl chloride to give α-chloro isocyanates appears to be a general reaction. Hexafluoroacetone imine[5] and 1,3-dichlorotetrafluoroacetone imine[5] also react with oxalyl chloride to give the corresponding α-chloro isocyanates.[6]

Nucleophiles react with both **7** and **18** preferentially at the isocyanate group instead of the double bond. For example, alcohols add to give carbamates and amines add to give ureas. Bromine, however, adds to the double bond. Tetrafluoroethylene also adds to the double bond of **18** in low yield to give the cyclic isocyanate **21**.



## Experimental Section[7]

**2,3-Dichloro-2,3,3-trifluoropropionyl Fluoride** (**10**).—Chlorine, 60 ml measured at −78° (*ca.* 93 g, 1.31 mol), was slowly distilled into a Pyrex flask containing 100 ml (*ca.* 168 g, 1.31 mol) of trifluoroacryloyl fluoride that was irradiated with a 275-W sun

(4) A. H. Ahlbrecht and D. R. Husted, U. S. Patent 2,617,817 (1952).

(5) W. J. Middleton and C. G. Krespan, *J. Org. Chem.*, **30**, 1398 (1965).

(6) R. F. Swindell and J. M. Shreeve, *J. Fluorine Chem.*, **2**, 191 (1972–1973), describe the preparation of 1-chloro-2,2,2-trifluoro-1-(trifluoromethyl)-ethyl isocyanate by reaction of oxalyl chloride with the lithium salt of hexafluoroacetone imine. L. I. Samarai, V. P. Belaya, O. U. Vishneuskii, and G. I. Derkach, *Zh. Org. Khim.*, **4**, 720 (1968), report that benzophenone imine is converted to chlorodiphenylmethyl isocyanate by treatment with oxalyl chloride.

(7) All boiling points are uncorrected.

lamp at a 6-in. distance. The temperature was kept between 0 and 20°, and the addition required 6 hr. Distillation of the reaction mixture gave 188 g (72%) of 2,3-dichloro-2,3,3-trifluoropropionyl fluoride as a colorless liquid: bp 49–50°; $n^{25}$D 1.3294; ir (liquid) 5.35 μ (COF); $^{19}$F nmr ($CCl_3F$) δ 21.7 (d, $J$ = 15 Hz coupled to d, $J$ = 10.3 Hz coupled to d, $J$ = 10.3 Hz, 1 F) −64.7 (d, $J$ = 173 Hz coupled to d, $J$ = 10.3 Hz coupled to d, $J$ = 8.6 Hz, 1 F), −68.8 (d, $J$ = 173 Hz coupled to d, $J$ = 10.3 Hz coupled to d, $J$ = 10.3 Hz, 1 F), and −123.7 ppm (d, $J$ = 15 Hz coupled to d, $J$ = 10.3 Hz coupled to d, $J$ = 8.6 Hz, 1 F).

*Anal.* Calcd for $C_3Cl_2F_4O$: C, 18.11; Cl, 35.65; F, 38.20. Found: C, 18.20; Cl, 34.87; F, 38.33.

**2,3-Dichloro-2,3,3-trifluoropropionyl Chloride (11).**—A 100-g sample (0.5 mol) of 2,3-dichloro-2,3,3-trifluoropropionyl fluoride was added dropwise to a stirred suspension of 34 g (0.25 mol) of aluminum chloride in 200 ml of methylene chloride. The reaction mixture was stirred for 2 hr, and the volatile portion was distilled under reduced pressure into a Dry Ice cooled trap. Redistillation gave 70.6 g (66%) of 2,3-dichloro-2,3,3-trifluoropropionyl chloride as a colorless liquid: bp 87.5–88°; $n^{25}$D 1.3812; ir (liquid) 5.57 μ (C=O); $^{19}$F nmr ($CCl_3F$) δ −64.2 (d, $J$ = 173 Hz to d, $J$ = 8 Hz, 1 F), −65.7 (d, $J$ = 173 Hz to d, $J$ = 10 Hz, 1 F), and −117.4 ppm (d, $J$ = 10 Hz to d, $J$ = 8 Hz, 1 F).

*Anal.* Calcd for $C_3Cl_3F_3O$: C, 16.73; Cl, 49.38; F, 26.46. Found: C, 16.87; Cl, 49.07; F, 26.56.

**2-Chloro-1,1,2,2-tetrafluoroethyl Isocyanate (12) and 1,2-Dichloro-1,2,2-trifluoroethyl Isocyanate (13).**—A 40-g sample (0.2 mol) of 2,3-dichloro-2,3,3-trifluoropropionyl fluoride was added dropwise to a stirred suspension of 14.3 g (0.22 mol) of powdered sodium azide in 200 ml of xylene. The reaction mixture was stirred for 18 hr at 25° and then warmed slowly to 110°. When the evolution of nitrogen ceased, the volatile portion of the reaction mixture was distilled to give 10.14 g (29%) of 2-chloro-1,1,2,2-tetrafluoroethyl isocyanate as a colorless liquid, bp 31–31.5°, $n^{25}$D 1.3122, $^{19}$F nmr ($CCl_3F$) δ −73.1 (t, $J$ = 4 Hz, 2 F) and −83.6 ppm (broad t, 2 F), and 3.03 g (8%) of 1,2-dichloro-1,2,2-trifluoroethyl isocyanate as a colorless liquid, bp 67–68°, $n^{25}$D 1.3650, $^{19}$F nmr ($CCl_3F$) δ −69.9 (q, 2 F) and −77.9 ppm (broad t, 1 F).

*Anal.* Calcd for $C_3ClF_4NO$: C, 20.30; Cl, 19.98; F, 42.82; N, 7.89. Found: C, 20.69; Cl, 20.23; F, 43.11; N, 7.59.

*Anal.* Calcd for $C_3Cl_2F_3NO$: C, 18.58; Cl, 36.56; F, 29.39; N, 7.22. Found: C, 19.01; Cl, 36.19; F, 29.52; N, 6.96.

**1,2-Dichloro-1,2,2-trifluoroethyl Isocyanate (13).**—A 65-g sample (0.3 mol) of 2,3-dichloro-2,3,3-trifluoropropionyl chloride was added dropwise to a suspension of 21.67 g (0.33 mol) of powdered sodium azide in 300 ml of dry xylene. The reaction mixture was stirred at 25° for 20 hr, and then slowly warmed to 112° over a period of 6 hr. The material boiling below xylene was distilled from the reaction mixture and then redistilled to give 32.2 g (62% yield, 55% conversion) of 1,2-dichloro-1,2,2-trifluoroethyl isocyanate as a colorless liquid, bp 68–69°, $n^{25}$D 1.3654, ir (liquid) 4.40 μ (NCO), and 7.8 g of recovered 2,3-dichloro-2,3,3-trifluoropropionyl chloride.

*Anal.* Calcd for $C_3Cl_2F_3NO$: C, 18.58; Cl, 36.56; F, 29.39; N, 7.22. Found: C, 18.86; Cl, 36.97; F, 28.92; N, 7.32.

**2,3-Dibromo-2,3,3-trifluoropropionyl Fluoride (2).**—A 128-g sample (1 mol) of trifluoroacryloyl fluoride was slowly distilled into 160 g (1 mol) of bromine cooled to 0°. The reaction mixture was stirred for 3 days at room temperature and then distilled to give 261 g (93%) of 2,3-dibromo-2,3,3-trifluoropropionyl fluoride as a colorless liquid: bp 88–89°; $n^{25}$D 1.3938; ir (liquid) 5.33 μ (COF); $^{19}$F nmr ($CCl_3F$) δ 21.3 (d, $J$ = 11.0 Hz to d, 13.3 Hz to d, 14.3 Hz, 1 F), −56.3 ppm (d, $J$ = 177 Hz to d, 15.2 Hz to d, 14.3 Hz, 1 F), 60.9 (d, $J$ = 177 Hz to d, 16.8 Hz to d, 11.0 Hz), and −125.4 ppm (d, $J$ = 16.8 Hz to d, 15.2 Hz to d, 13.3 Hz).

*Anal.* Calcd for $C_3Br_2F_4O$: C, 12.52; Br, 55.52; F, 26.40. Found: C, 12.75; Br, 55.32; F, 26.69.

**2,3-Dibromo-2,3,3-trifluoropropionyl Chloride (4).**—A 163-g sample (0.56 mol) of 2,3-dibromo-2,3,3-trifluoropropionyl fluoride was added dropwise to a mechanically stirred suspension of 76 g (0.56 mol) of aluminum chloride in 282 ml of methylene chloride. The reaction mixture warmed spontaneously to 40°. After cooling, the volatile portion of the reaction mixture was distilled under reduced pressure into a Dry Ice cooled trap. Redistillation gave 97.5 g (57%) of 2,3-dibromo-2,3,3-trifluoropropionyl chloride as a colorless liquid: bp 128–129°; $n^{25}$D 1.4436; ir (liquid) 5.57 μ (COCl); $^{19}$F nmr ($CCl_3F$) δ −55.7 (d, $J$ = 175 Hz to d, $J$ = 14.5 Hz, 1 F), −57.9 (d, $J$ = 175 Hz to d, $J$ = 16 Hz, 1 F), and 116.5 ppm (d, $J$ = 16 Hz to d, $J$ = 14.5 Hz, 1 F).

*Anal.* Calcd for $C_3Br_2ClF_3O$: C, 11.84; Br, 52.52; Cl, 11.65; F, 18.73. Found: C, 12.09; Br, 52.32; Cl, 11.55; F, 18.99.

**1,2-Dibromo-1,2,2-trifluoroethyl Isocyanate (6) and 2-Bromo-1-chloro-1,2,2-trifluoroethyl Isocyanate (5).**—A 27.4-g sample (0.09 mol) of 2,3-dibromo-2,3,3-trifluoropropionyl chloride was added dropwise to a stirred suspension of 6.5 g (0.1 mol) of powdered sodium azide in 100 ml of xylene. The reaction mixture was stirred for several hours at 25°, and then heated gently to reflux until nitrogen evolution ceased. The most volatile portion was distilled out of the reaction mixture and then redistilled to give 2.5 g (12%) of 2-bromo-1-chloro-1,2,2-trifluoroethyl isocyanate as a colorless liquid, bp 89–91°, ir (liquid) 4.43 μ (NCO), $^{19}$F nmr ($CCl_3F$) δ −63.8 (d, $J$ = 10 Hz, 2 F) and −75.7 ppm (broad t, $J$ = 10 Hz, 1 F), and 6.7 g (26%) of 1,2-dibromo-1,2,2-trifluoroethyl isocyanate as a colorless liquid, bp 107–110°, ir (liquid) 4.43 μ (NCO), $^{19}$F nmr ($CCl_3F$) δ −61.3 (d to d, 2 F) and −71.7 ppm (broad t, 1 F).

*Anal.* Calcd for $C_3BrClF_3NO$: C, 15.11; Br, 33.52; Cl, 14.88; F, 23.91; N, 5.87. Found: C, 15.50; Br, 33.60; Cl, 15.01; F, 24.14; N, 5.99.

*Anal.* Calcd for $C_3Br_2F_3NO$: C, 12.74; Br, 56.50; F, 20.15; N, 4.96. Found: C, 13.10; Br, 57.00; F, 20.17; N, 5.30.

**2-Bromo-1,1,2,2-tetrafluoroethyl Isocyanate (3).**—A 25-g sample (0.087 mol) of 2,3-dibromo-2,3,3-trifluoropropionyl fluoride was added dropwise to a stirred suspension of 6.5 g (0.1 mol) of powdered sodium azide in 100 ml of xylene. The mixture was stirred for several hours at about 25°, and then heated gently to about 110° until no further evolution of nitrogen occurred. The most volatile portion was distilled out of the reaction mixture and then redistilled to give 8.35 g (43%) of 2-bromo-1,1,2,2-tetrafluoroethyl isocyanate as a colorless liquid: bp 50°; ir (liquid) 4.40 μ (NCO); $^{19}$F nmr ($CCl_3F$) δ −68.0 (t, $J$ = 5 Hz, 2 F) and −79.3 ppm (broad t, $J$ = 5 Hz, 2 F).

*Anal.* Calcd for $C_3BrF_4NO$: C, 16.23; Br, 36.01; F, 34.24; N, 6.13. Found: C, 16.37; Br, 35.61; F, 34.79; N, 6.39.

**Trifluorovinyl Isocyanate (7). Method A.**—A 35.2-g sample (0.18 mol) of 1,2-dichloro-1,2,2-trifluoroethyl isocyanate was added dropwise to a stirred suspension of 23.5 g of activated zinc dust in 100 ml of diglyme heated to 60°. The temperature was maintained at 60–70°, and stirring was continued at this temperature for 1 hr after the addition was completed. The volatile products (7.8 ml) were distilled from the reaction mixture and then redistilled to give 4 ml (at −78°, about 7 g, 32%) of trifluorovinyl isocyanate, bp 19–20°, and 1.7 g of 2-chloro-1,1,2,2-tetrafluoroethyl isocyanate, bp 31°. The trifluorovinyl isocyanate was identified by its $^{19}$F nmr spectrum in $CCl_3F$: δ −112.6 (d, $J$ = 85 Hz to d, $J$ = 50 Hz, 1 F), −123.0 ppm (d, $J$ = 121 Hz to d, $J$ = 85 Hz, 1 F), and −145.4 ppm (d, $J$ = 121 Hz to d, $J$ = 50 Hz, 1 F).

**Method B.**—A solution of 5.66 g (0.02 mol) of 1,2-dibromo-1,2,2-trifluoroethyl isocyanate in 10 ml of diglyme was added dropwise to a stirred suspension of 2.6 g (0.04 mol) of zinc dust and 0.1 g of zinc chloride in 25 ml of diglyme. The reaction mixture became warm. The most volatile portion was distilled out under reduced pressure (5 mm) into a Dry Ice cooled trap, and the condensate in the trap was redistilled to give 1.2 ml (2.0 g, 81%) of trifluorovinyl isocyanate, bp 19–20° (identified by $^{19}$F nmr).

**Method C.**—A solution of 19.0 g (0.085 mol) of 2-bromo-1,1,2,2-tetrafluoroethyl isocyanate in 20 ml of diglyme was added dropwise to a suspension of 13 g (0.2 mol) of zinc dust and 0.1 g of zinc chloride in 100 ml of diglyme heated to 80°. The reaction temperature was maintained at 80–90° during the addition, and then the most volatile portion was distilled from the reaction mixture and redistilled to give 2.1 ml (*ca.* 3.6 g, 29%) of a colorless liquid, bp 18–21°. The $^{19}$F nmr spectrum indicated that the product was 90% trifluorovinyl isocyanate.

**Spontaneous Polymerization of Trifluorovinyl Isocyanate.**—A sample of trifluorovinyl isocyanate sealed in a glass tube was allowed to remain at room temperature (*ca.* 25°) for 17 days. The tube was broken open, and the polymer was removed as a clear, colorless, flexible rod, mp >250°, ir (film) 4.40 μ (NCO).

*Anal.* Calcd for $(C_3F_3NO)_n$: C, 29.29; F, 46.33; N, 11.38. Found: C, 29.07; F, 45.55; N, 10.75.

The polymerization can be inhibited and the monomer can be stored at room temperature if small amounts of conventional

radical inhibitors such as D-limonene or 2-(trifluoromethyl)-phenothiazine are added to the liquid monomer.

**Curtius Reaction with Tetraethylammonium Azide.**—A 83.65-g sample (0.29 mol) of 2,3-dibromo-2,3,3-trifluoropropionyl fluoride was added dropwise to a stirred mixture of 51.7 g (0.3 mol) of tetraethylammonium azide in 300 ml of diglyme. The mixture was then heated slowly to 110° until nitrogen evolution ceased. The more volatile products were distilled from the reaction mixture and condensed in a cold trap to give 15 ml of a colorless liquid, bp −15 to 30°. Redistillation through a low-temperature still gave 9.1 g (20%) of pentafluoroethyl isocyanate, bp −10 to −5° [identified by its $^{19}F$ nmr spectrum ($CCl_3F$) δ −85.3 (broad singlet, 2 F) and −87.4 ppm (s, 3 F), and by comparison of its ir spectrum with that of an authentic sample] and 6.1 g (13%) of $CF_3CF{=}NCOF$ as a colorless liquid: bp 28–29°; ir (gas) 5.31 (COF) and 5.42 μ (C=N); $^{19}F$ nmr ($CCl_3F$) δ 20.2 (d, $J$ = 20 Hz to q, $J$ = 8 Hz, 1 F), −78.7 (d, $J$ = 9 Hz to d, $J$ = 8 Hz, 3 F), and −136.5 ppm (d, $J$ = 20 Hz to q, $J$ = 9 Hz, 1 F).

*Anal.* Calcd for $C_3F_5NO$: C, 22.37; F, 59.00; N, 9.69. Found: C, 22.67; F, 58.73; N, 8.71.

**1,2-Dichloro-2,2-difluoro-1-(trifluoromethyl)ethyl Isocyanate (17).**—A mixture of 465 g (2.5 mol) of chloropentafluoroacetone imine, 381 g (2.5 mol) of oxalyl chloride, and 2.5 ml of pyridine was refluxed for 3 days. Distillation gave 205 g of a mixture of unreacted starting materials and 17, bp 60–81°, and 315 g (52% conversion) of **17** as a colorless liquid: bp 85–85.5°; $n^{25}D$ 1.3580; ir (liquid) 4.42 μ (NCO); $^{19}F$ nmr ($CCl_3F$) δ −62.9 (q, $J$ = 24 Hz, 2 F) and −75.7 ppm (t, $J$ = 24 Hz, 3 F).

*Anal.* Calcd for $C_4Cl_2F_5NO$: C, 19.69; Cl, 29.07; F, 38.94; N, 5.74. Found: C, 19.39; Cl, 28.81; F, 38.76; N, 5.67.

**1,2-Dichloro-2,2-difluoro-1-(trifluoromethyl)ethylamine (20).**—An 18.2-g sample of chloropentafluoroacetone imine was saturated with dry hydrogen chloride gas and then distilled to give 15.73 g of 1,2-dichloro-2,2-difluoro-1-(trifluoromethyl)ethylamine as a colorless liquid that becomes cloudy on exposure to moist air: bp 65–65.5°; $^{19}F$ nmr ($CCl_3F$) δ −62.0 (q, $J$ = 11 Hz, 2 F) and −75.5 ppm (t, $J$ = 11 Hz, 3 F); ir (liquid) 2.90 and 2.96 μ ($NH_2$).

*Anal.* Calcd for $C_3H_2Cl_2F_5N$: C, 16.53; H, 0.92; Cl, 32.53; F, 43.58; N, 6.42. Found: C, 17.64; H, 0.79; Cl, 32.03; F, 46.68; N, 6.25.

**1-Chloro-2,2,2-trifluoro-1-(trifluoromethyl)ethyl Isocyanate.**—A mixture of 127 g (1 mol) of oxalyl chloride, 165 g (1 mol) of hexafluoroacetone imine, and 5 ml of pyridine was heated in a 600-ml Hastelloy bomb at 100° for 4 hr at 150° for 4 hr, and at 200° for 4 hr. The bomb was cooled and vented, and the contents were filtered to remove the suspended solid. Distillation gave 102.3 g of a 25:75 mixture (by gc and $^{19}F$ nmr) of $(CF_3)_2CClNH_2$ and the isocyanate, bp 46.0–46.5°, and 29.3 g of the pure isocyanate as a colorless liquid: bp 50.5–51.0°; $^{19}F$ nmr ($CCl_3F$) δ −78.0 (s); ir (liquid) 4.40 μ (NCO).

*Anal.* Calcd for $C_4ClF_6NO$: C, 21.12; Cl, 15.58; F, 50.11; N, 6.16. Found: C, 21.11; Cl, 16.01; F, 49.52; N, 6.16.

**2-Chloro-1,1,3,3,3-hexafluoro-2-propylamine (22).**—A 25-ml sample of hexafluoroacetone imine was cooled to 0° and saturated with dry hydrogen chloride gas. The reaction mixture was filtered to remove some white solid, and the filtrate was distilled to give 37.1 g (74%) of **22** as a colorless liquid: bp 51.5–52.5°; $n^{25}D$ 1.3166; $^{19}F$ nmr (neat) δ −77.5 ppm (s); $^1H$ nmr (neat) δ 2.82 ppm.

*Anal.* Calcd for $C_3H_2ClF_6N$: C, 17.88; H, 1.00; F, 56.57; N, 6.95. Found: C, 18.09; H, 1.13; F, 56.59; N, 7.14.

**1,2-Dichloro-2,2-difluoro-1-(chlorodifluoromethyl)ethyl Isocyanate.**—A mixture of 39.6 g (0.2 mol) of 1,3-dichlorotetrafluoroacetone imine and 31.8 g (0.25 mol) of oxalyl chloride was refluxed for 5 days. Distillation of the reaction mixture gave 33.5 g (64%) of the isocyanate as a colorless liquid: bp 121.5–122°; $n^{25}D$ 1.3953; ir (liquid) 4.39 μ (NCO); $^{19}F$ nmr ($CCl_3F$) δ −60.9 ppm (s).

*Anal.* Calcd for $C_4Cl_2F_4NO$: C, 18.45; Cl, 40.85; F, 29.18; N, 5.38. Found: C, 18.50; Cl, 40.61; F, 29.22; N, 5.69.

**2,2-Difluoro-1-(trifluoromethyl)vinyl Isocyanate (18).**—A 244-g sample (1.0 mol) of 1,2-dichloro-2,2-difluoro-1-(trifluoromethyl)ethyl isocyanate was added dropwise to a stirred suspension of 98 g (1.5 g-atoms) of powdered zinc in 1000 ml of diglyme at such a rate that the temperature warmed to 45° and remained between 45 and 50°. The reaction mixture was stirred for 1 hr after the addition, and then the most volatile portion was distilled under reduced pressure (5 mm) into a trap cooled to −78°. The condensate in the trap was redistilled to give 158 g (91%) of 2,2-difluoro-1-(trifluoromethyl)vinyl isocyanate as a colorless liquid: bp 42.3–42.5°; ir (liquid) 4.38 (NCO) and 5.67 μ (=$CF_2$); $^{19}F$ nmr ($CCl_3F$) δ −66.6 (d, $J$ = 9 Hz to d, $J$ = 23 Hz, 3 F), −82.9 (d, $J$ = 21 Hz to q, $J$ = 9 Hz, 1 F), and −89.7 ppm (d, $J$ = 21 Hz to d, $J$ = 23 Hz, 1 F).

*Anal.* Calcd for $C_4F_5NO$: C, 27.76; F, 54.90; N, 8.10. Found: C, 27.70; F, 54.46; N, 7.74.

**Perfluorocyclobutyl Isocyanate (15).**—Perfluorocyclobutanecarbonyl fluoride, 22.6 g (0.1 mol), was added dropwise to a stirred suspension of 7.2 g (0.11 mol) of powdered sodium azide in 100 ml of xylene. The reaction mixture was stirred overnight and then heated to 80–85° until evolution of nitrogen ceased. The volatile portion of the reaction mixture was distilled out under reduced pressure into a cold trap (−78°), and then redistilled to give 10.05 g (45%) of perfluorocyclobutyl isocyanate as a colorless liquid: bp 53°; ir ($CCl_4$) 4.41 μ (NCO); $^{19}F$ nmr ($CCl_3F$) δ −152.8 ppm (m, 1 F) and six other F.

*Anal.* Calcd for $C_5F_7NO$: C, 26.92; F, 59.62; N, 6.28. Found: C, 26.74; F, 59.67; N, 6.26.

**1,2-Dibromo-2,2-difluoro-1-(trifluoromethyl)ethyl Isocyanate.**—A 8.65-g sample (0.05 mol) of 2,2-difluoro-1-(trifluoromethyl)-vinyl isocyanate was mixed with 8.0 g (0.05 mol) of bromine. When the bromine color faded, the sample was distilled to give 13.79 g (83%) of the dibromide as a colorless liquid: bp 45° (39 mm); $n^{25}D$ 1.4056; ir (liquid) 4.40 μ (NCO); $^{19}F$ nmr ($CCl_3F$) δ 55.0 ($ABX_3$, $J_{AB}$ = 165, $J_{AX}$ = 11.6, $J_{BX}$ = 12.6, $\Delta\mu_{AB}$ = 77 Hz) and −72.9 ppm ($ABX_3$).

*Anal.* Calcd for $C_4Br_2F_5NO$: C, 14.43; Br, 48.01; F, 28.54; N, 4.21. Found: C, 14.66; Br, 48.15; F, 29.21; N, 4.20.

**2,2,3,3,4,4-Hexafluoro-1-(trifluoromethyl)cyclobutyl Isocyanate (21).**—A mixture of 34.6 g (0.2 mol) of 2,2-difluoro-1-(trifluoromethyl)vinyl isocyanate, 20 g (0.2 mol) of tetrafluoroethylene, and 0.5 g of hydroquinone was heated at autogenous pressure at 180° for 8 hr in a 80-ml Hastelloy tube. The tube was cooled and vented, and the contents were distilled to give 28.1 g (81%) of recovered vinyl isocyanate, bp 43–43.5°, and 3.05 g (6% conversion, 30% yield) of **21** as a colorless liquid: bp 67–68°; ir (liquid) 4.37 μ (NCO); $^{19}F$ nmr ($CCl_3F$) δ −71.8 (m, 3 F), −125.4 (m, 4 F), and −131.0 ppm (m, 2 F).

*Anal.* Calcd for $C_6F_9NO$: C, 26.4; F, 62.7; N, 5.13. Found: C, 25.8; H, 0.48; F, 62.7; N, 5.33.

**2,2,3,3,4,4-Hexafluoro-1-(trifluoromethyl)cyclobutylamine.**—A 4.6-g sample (0.017 mol) of 2,2,3,3,4,4-hexafluoro-1-(trifluoromethyl)cyclobutyl isocyanate was added to a solution of 1.5 ml (0.017 mol) of concentrated hydrochloric acid in 25 ml of diglyme. To this solution was added 1.5 ml of a 30% sodium hydroxide solution, and the most volatile portion was distilled from the reaction mixture. The lower layer of this distillate was separated and redistilled to give 2.55 g (61%) of 2,2,3,3,4,4-hexafluoro-1-(trifluoromethyl)cyclobutylamine as a colorless liquid: bp 74–75°; $n^{25}D$ <1.3; ir (liquid) 2.90, 2.96, and 6.13 μ ($NH_2$); $^1H$ nmr ($CCl_3F$) δ 2.0 ppm (broad peak); $^{19}F$ nmr ($CCl_3F$) δ −72.8 (m, 3 F), −129.1 (m, 4 F), 131.4 (AB, $J$ = 230 Hz), and −133.1 ppm (AB, $J$ = 230 Hz to q, $J$ = 4 Hz, 1 F).

*Anal.* Calcd for $C_5H_2F_9N$: C, 24.30; H, 0.82; F, 69.21; N, 5.67. Found: C, 24.70; H, 1.21; F, 68.81; N, 5.37.

**Methyl 2,2-Difluoro-1-(trifluoromethyl)vinylcarbamate.**—A 2.05-ml sample (0.05 mol) of methanol was added dropwise to a stirred solution of 8.7 g (0.05 mol) of 2,2-difluoro-1-(trifluoromethyl)vinyl isocyanate in 22 ml of ether. The reaction mixture was distilled to give 8.2 g of methyl 2,2-difluoro-1-(trifluoromethyl)vinylcarbamate as a colorless liquid: bp 67–68° (13.2 mm); $n^{25}D$ 1.3554; ir (liquid) 3.02 (NH), 5.65 (C=$CF_2$), 5.77 (C=O), and 6.55 μ (amide II); $^{19}F$ nmr ($CCl_3F$) δ −66.1 (d, $J$ = 22 Hz to d, $J$ = 9.5 Hz, 3 F), −78.8 (m, 1 F), and −82.3 ppm (m, 1 F); $^1H$ nmr ($CCl_3F$) δ 7.25 (NH) and 3.76 ppm (s, $OCH_3$).

*Anal.* Calcd for $C_5H_4F_5NO_2$: C, 29.43; H, 1.97; F, 46.32; N, 6.83. Found: C, 29.63; H, 2.21; F, 46.30; N, 6.98.

**Hydrolysis of 2,2-Difluoro-1-(trifluoromethyl)vinyl Isocyanate.**—A mixture of 17.3 g (0.1 mol) of 2,2-difluoro-1-(trifluoromethyl)vinyl isocyanate and 50 ml of water was stirred at 25° for 1.5 hr. The white solid that formed was collected on a filter, washed with water, and recrystallized from 50% ethanol to give 10.1 g of 1,3-bis[2,2-difluoro-1-(trifluoromethyl)vinyl]urea as colorless needles: mp 211–213°; ir (KBr) 3.01 (NH), 5.68 (C=$CF_2$), 5.98 (C=O), and 6.30 μ (amide II); $^{19}F$ nmr (acetone) δ −65.2

(d, $J$ = 22.5 Hz to d, $J$ = 10 Hz, 3 F), −78.6 (m, 1 F), and −82.3 ppm (m, 1 F).

*Anal.* Calcd for $C_7H_5F_{10}N_2O$: C, 26.26; H, 0.65; F, 59.35; N, 8.75. Found: C, 26.49; H, 0.84; F, 58.82; N, 8.59.

**Reaction of 18 with 2*H*-Hexafluoroisopropyl Alcohol.**—A solution of 4.33 g (0.025 mol) of **18** in 10 ml of 2*H*-hexafluoroisopropyl alcohol was allowed to remain at room temperature for 5 days. The crystals that precipitated were collected on a filter and dried in air (4.04 g). A second crop was obtained by mixing the filtrate with water (3.22 g). The combined samples were recrystallized from benzene to give 5.3 g of 2,2,2-trifluoro-1-(trifluoromethyl)ethyl 2,2-difluoro-1-(trifluoromethyl)vinylcarbamate as colorless crystals: mp 78–80°; $^{19}$F nmr ($CCl_3F$) δ −69.1 (d, $J$ = 21 Hz to d, $J$ = 10 Hz, 3 F), −73.7 (d, $J$ = 7 Hz, 6 F), −77.3 (m, 1 F), and −81.0 ppm (m, 1 F); ir (KBr) 5.70 μ (C=O).

*Anal.* Calcd for $C_7H_2F_{11}NO_2$: C, 24.65; H, 0.59; F, 61.27; N, 4.11. Found: C, 25.02; H, 0.81; F, 60.71; N, 4.60.

**1-(*p*-Chlorophenyl)-3-(trifluorovinyl)urea.**—A solution of 2.40 g (0.019 mol) of *p*-chloroaniline in 10 ml of ether was added dropwise to a stirred solution of 2.34 g (0.019 mol) of trifluorovinyl isocyanate in 25 ml of ether. The solid that precipitated was collected on a filter and washed with ether. There was obtained 3.77 g (80%) of the urea as colorless plates: mp 170–172° dec; ir (KBr) 3.02 (NH), 5.47 ($CF_2$=C), and 6.00 μ (C=O); $^{19}$F nmr (acetone) δ −106.8 (d, $J$ = 72 Hz to d, $J$ = 44 Hz to m, 1 F), −118.5 (d, $J$ = 72 Hz to d, $J$ = 113 Hz to m, 1 F), and −127.7 ppm (d, $J$ = 113 Hz to d, $J$ = 44 Hz to m, 1 F).

*Anal.* Calcd for $C_9H_6ClF_3N_2O$: C, 43.13; H, 2.42; Cl, 14.15; F, 22.74; N, 11.18. Found: C, 43.24; H, 1.94; Cl, 14.01; F, 22.75; N, 10.86.

**1-(*p*-Chlorophenyl)-3-(1,1,2,2,2-pentafluoroethyl)urea.**—A solution of 2.54 g (0.02 mol) of *p*-chloroaniline in 25 ml of ether cooled to −50° was mixed with 3.22 g (0.02 mol) of pentafluoroethyl isocyanate. The reaction mixture was warmed to 25°, and the white solid that precipitated was collected on a filter, washed with cold ether, and dried to give 4.6 g of the urea as white crystals: mp 133–40° dec; ir (KBr) 5.98 μ (C=O); $^{19}$F nmr (acetone) δ −79.4 (s, 2 F) and −87.4 ppm (s, 3 F).

*Anal.* Calcd for $C_9H_6ClF_3N_2O$: Cl, 12.29; F, 32.91; N, 9.71. Found: Cl, 12.83; F, 32.51; N, 9.51.

**Methyl 1,2-Dichloro-2,2-difluoro-1-(trifluoromethyl)ethylcarbamate.**—Methanol (4.1 ml, 0.1 mol) was added dropwise to a 24.4-g sample (0.1 mol) of 1,2-dichloro-2,2-difluoro-1-(trifluoromethyl)ethyl isocyanate cooled in an ice bath. The reaction mixture solidified. Recrystallization from pentane gave 22.0 g (80%) of the carbamate as colorless crystals: mp 46–47°; $^{19}$F nmr ($CCl_3F$) δ −62.0 (m, 2 F) and −72.1 ppm (d, $J$ = 14 Hz to d, $J$ = 12 Hz, 3 F); ir (KBr) 3.92 (NH), 5.64, and 5.73 μ (CO).

*Anal.* Calcd for $C_5H_4Cl_2F_5NO_2$: C, 21.76; H, 1.46; Cl, 25.69; F, 34.42; N, 5.07. Found: C, 22.17; H, 1.48; Cl, 25.27; F, 34.72; N, 4.79.

**1-(*p*-Chlorophenyl)-3-(2-chloro-1,1,2,2-tetrafluoroethyl)urea.**—A solution of 2.04 g (0.016 mol) of *p*-chloroaniline in 10 ml of ether was added dropwise to a solution of 2.85 g (0.016 mol) of 2-chloro-1,1,2,2-tetrafluoroethyl isocyanate in 25 ml of ether cooled to 0°. The precipitate that formed was collected on a filter, washed with cold ether, and dried in air to give 3.92 g (80% yield) of the urea as colorless crystals: mp 137–138° dec (gas); ir (KBr) 3.02 (NH), 5.97, 6.40, 6.24, and 6.68 μ; $^{19}$F nmr (acetone) δ 71.5 (t, $J$ = 8 Hz, 2 F) and −91.7 ppm (m, 2 F).

*Anal.* Calcd for $C_9H_6Cl_2F_4N_2O$: C, 35.43; H, 1.98; Cl, 23.24; F, 24.91; N, 9.19. Found: C, 35.56; H, 1.75; Cl, 23.22; F, 24.06; N, 8.97.

**Registry No.**—**1**, 667-49-2; **2**, 17773-81-8; **3**, 41594-54-1; **4**, 17773-79-4; **5**, 41594-56-3; **6**, 41594-24-5; **7**, 41594-57-4; **7** polymer, 41588-59-4; **8**, 356-74-1; **10**, 41594-59-6; **11**, 422-43-5; **12**, 41594-60-9; **13**, 41594-61-0; **14**, 710-53-2; **15**, 41594-63-2; **16**, 3749-02-8; **17**, 41594-65-4; **18**, 41594-66-5; **20**, 41594-67-6; **21**, 41594-68-7; **22**, 41594-69-8; tetraethylammonium azide, 993-20-4; hexafluoroacetone imine, 1645-75-6; 1-chloro-2,2,2-trifluoro-1-(trifluoromethyl)ethyl isocyanate, 39095-53-9; 1,2-dichloro-2,2-difluoro-1-(chlorodifluoromethyl)ethyl isocyanate, 41594-25-6; 1,3-dichlorotetrafluoroacetone imine, 1619-97-2; 1,2-dibromo-2,2-difluoro-1-(trifluoromethyl)ethyl isocyanate, 41594-27-8; 2,2,3,3,4,4-hexafluoro-1-(trifluoromethyl)-cyclobutylamine, 41594-28-9; methyl 2,2-difluoro-1-(trifluoromethyl)vinylcarbamate, 41594-29-0; 1,3-bis[2,2-difluoro-1-(trifluoromethyl)vinyl]urea, 41594-30-3; 2*H*-hexafluoroisopropyl alcohol, 920-66-1; 2,2,2-trifluoro-1-(trifluoromethyl)ethyl 2,2-difluoro-1-(trifluoromethyl)vinylcarbamate, 41594-32-5; 1-(*p*-chlorophenyl)-3-(trifluorovinyl)urea, 41594-33-6; *p*-chloroaniline, 106-47-8; 1-(*p*-chlorophenyl)-3-(1,1,2,2,2-pentafluoroethyl)-urea, 41594-34-7; methyl 1,2-dichloro-2,2-difluoro-1-(trifluoromethyl)ethylcarbamate, 41594-35-8; 1-(*p*-chlorophenyl)-3-(2-chloro-1,1,2,2-tetrafluoroethyl)urea, 41594-36-9.

# *syn*-8,16-Difluoro[2.2]metacyclophane-1,9-diene[1]

VIRGIL BOEKELHEIDE* AND PETER H. ANDERSON

*Department of Chemistry, University of Oregon, Eugene, Oregon 97403*

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Normally, syntheses of metacyclophanes lead to the anti conformational isomer. In sharp contrast to this generalization, the condensation of 2,6-bis(bromomethyl)fluorobenzene (**3**) with sodium sulfide gives exclusively the syn isomer of 9,18-difluoro-2,11-dithia[3.3]metacyclophane (**4**) in 37% yield. When **4** is carried through the two-step reaction sequence of a Stevens rearrangement followed by a Hofmann elimination, the corresponding *syn*-8,16-difluoro[2.2]metacyclophane-1,9-diene (**7**) is formed in good yield. Although **7** does not spontaneously undergo valence tautomerization to *cis*-15,16-difluorodihydropyrene (**10**), thermal rearrangement of **7** gives 1-fluoropyrene (**11**), suggesting the intervention of *cis*-15,16-difluorodihydropyrene (**10**) as a transient intermediate.

In previous publications we have indicated the synthetic utility of the two-step reaction sequence—Stevens rearrangement and Hofmann elimination—for transforming sulfide linkages to carbon–carbon double bonds.[2,3] This procedure has been especially useful for preparing derivatives of 15,16-dihydropyrene.[2] One of the striking features of such derivatives is their valence tautomerization, both thermally and photochemically, to the corresponding [2.2]metacyclophane-1,9-diene derivatives (**1** ⇌ **2**). Thus far this valence tautomerization has only been studied for examples where the substituents at the 15 and 16 positions are hydrogen or alkyl.[2,4,5] However, Schmidt, on the basis of an extended Hückel calculation, has made the theoretical prediction that in this valence tautomerization (**1** ⇌ **2**) the *trans*-15,16-dihydropyrene moiety **1** will be preferred for other substituents as well, namely fluoro.[6]

(1) We thank the National Science Foundation for their support of this investigation.

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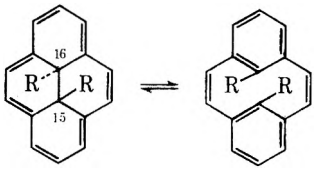


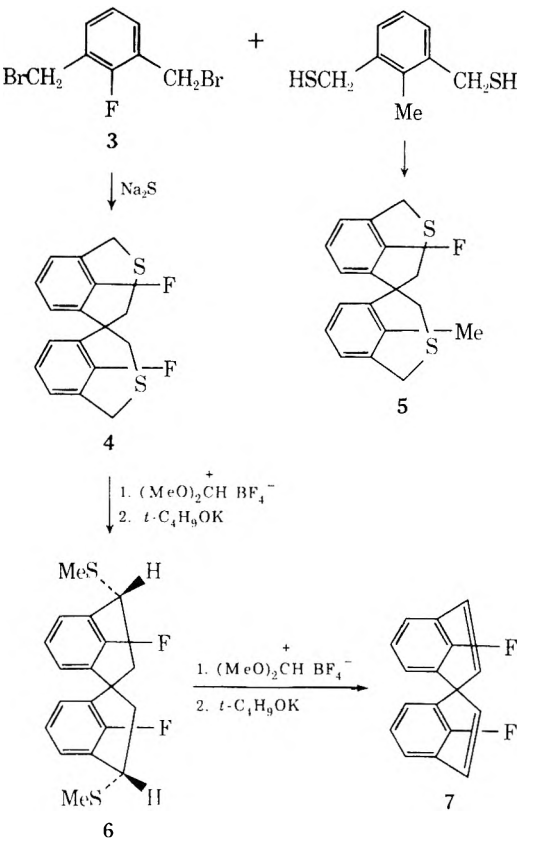
1 2

To test this prediction we undertook the synthesis of *anti*-8,16-difluoro[2.2]metacyclophane-1,9-diene (**2**, R = F) following the general method developed for the corresponding dimethyl derivative (**2**, R = $CH_3$).[2]

Treatment of 2-fluoro-*m*-xylene with *N*-bromosuccinimide gave the necessary starting material, 2,6-bis(bromomethyl)fluorobenzene (**3**), in 41% yield. The reaction of **3** with sodium sulfide gave the corresponding 9,18-difluoro-2,11-dithia[3.3]metacyclophane (**4**) as the pure syn isomer in 37% yield. This is in sharp contrast to the corresponding methyl analog, where the ratio of syn to anti isomers formed is 1:7. Normally the anti isomer in the 2,11-dithia[3.3]metacyclophane series is appreciably more stable than the syn isomer. However, as Vögtle and Schunder have shown,[7] the signals of the methylene protons of **4** appear as an AB pattern which at 60 MHz coalesce at a temperature of 157° ($\Delta\nu$ = 65 Hz; $\Delta G^{\ddagger}_{157}$ = 21.1 kcal/mol). In the case of **4** the assignment of conformation is not obvious from its nmr spectrum and so we resorted to dipole moment measurements to answer the question. The anti conformation of **4** has a center of symmetry so that its dipole moment would be expected to be near zero. On the other hand, the syn conformer of **4** would be expected to have a sizable dipole moment comparable to fluorobenzene. The dipole moment of **4** was measured in benzene following the method of Smith[8a] and was found to be 1.26 D, clearly indicating it to be the syn conformer. For comparison the dipole moment of fluorobenzene is 1.46 D.[8b]

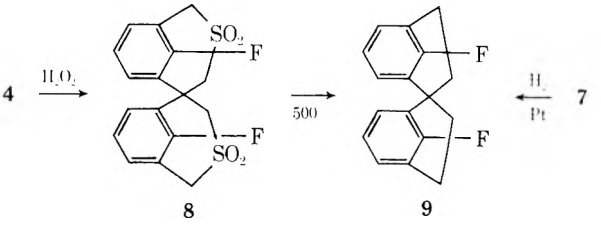
The reasons for the greater thermodynamic stability of the syn conformer of **4** compared to the anti are not clear, but it may be a result of the strong electrostatic repulsion involved in placing a fluorine atom over the aromatic $\pi$-electron cloud as is required in the anti conformer. To see whether a single fluoro substituent would still be effective in stabilizing the syn conformer, we prepared 8-fluoro-16-methyl-2,11-dithia[3.3]metacyclophane (**5**) by the condensation of 2,6-bis(mercaptomethyl)toluene with **3**. In this case **5** was formed with the ratio of syn to anti isomers being 3:2. Similar results have been reported by Vögtle and Neumann.[9] Even in this instance the repulsion of a single fluoro group apparently outweighs the greater strain energy associated with the syn conformation.

The important consequence of the formation of only the syn conformer of **4** was that we were in the wrong series, since syn conformers lead to *cis*-15,16-dihydropyrene derivatives rather than trans. However, in previous examples we had found that the Stevens rearrangement effected a major amount of isomerization from syn to anti conformation.[2] Therefore, we went ahead with the syn isomer. The Stevens rearrangement of **4** gave a mixture of isomers in about 50% yield. From this a pure crystalline isomer was isolated whose nmr spectrum is in accord with structure **6**. Further, measurement of the dipole moment of **6** gave a value of 1.66 D, confirming the syn conformation of the molecule.



3 4 5 6 7

Subjection of **6** to a Hofmann elimination then gave *syn*-8,16-difluoro[2.2]metacyclophane-1,9-diene (**7**) in 80% yield. Again, the dipole moment found for **7** was 1.12 D, in agreement with the assigned syn conformation. Catalytic hydrogenation of **7** readily gave the corresponding *syn*-8,16-difluoro[2.2]metacyclophane (**9**). The synthesis of **9** can also be accomplished by oxidation of **4** to the bis(sulfone) **8** which, on pyrolysis at 500°, gives **9** in 64% yield.[10] Although the accepted mechanism for the pyrolysis of sulfones postulates that the reaction proceeds through an intermediate diradical, a diradical which in this case could isomerize to the anti conformation, we could find no evidence for the formation of the anti conformer in our pyrolysate.



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Even though by the rule of conservation of orbital symmetry the concerted valence tautomerization of **7** to *cis*-15,16-difluorodihydropyrene (**10**) is an allowed process, there is no evidence for the occurrence of such a valence tautomerization of **7** at room temperature. When a sample of **7** was heated in a sealed tube at 120°, it was transformed into a fluoropyrene whose properties

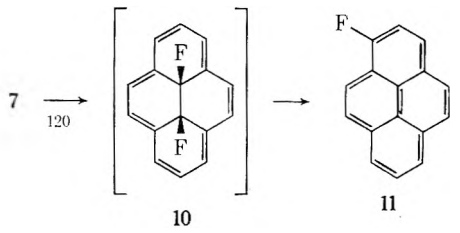
(7) F. Vögtle and L. Schunder, *Chem. Ber.*, **102**, 2677 (1969).

(8) (a) J. W. Smith, *Trans. Faraday Soc.*, **46**, 394 (1950); (b) N. J. Leonard and L. E. Sutton, *J. Amer. Chem. Soc.*, **70**, 1564 (1948).

(9) F. Vögtle and P. Neumann, *Tetrahedron*, **26**, 5299 (1970).

(10) F. Vögtle [*Angew. Chem.*, **81**, 258 (1969)] has also reported the pyrolysis of **8** to give **9**, but only in 15–20% yield.

are in accord with those recorded for 1-fluoropyrene (**11**).[11] Presumably, this thermal rearrangement and elimination involves **10** as a transient intermediate.

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## Experimental Section[12]

**2,6-Bis(bromomethyl)fluorobenzene (3).**—A mixture of 62.1 g of 2-fluoro-*m*-xylene[13] and 178 g of *N*-bromosuccinimide in 900 ml of carbon tetrachloride containing a small quantity of benzoyl peroxide was boiled under reflux for 5 hr. After filtration, the filtrate was concentrated and the residual solid was recrystallized from cyclohexane to give 57.3 g (41%) of white crystals: mp 90.0–91.5°; nmr ($CDCl_3$), triplet at $\tau$ 2.72 (1 H, $J$ = 6 Hz, ArH), a doublet at 2.94 (2 H, $J$ = 6 Hz, ArH), and a singlet at 5.54 (4 H, $-CH_2$).

*Anal.* Calcd for $C_8H_7Br_2F$: C, 34.08; H, 2.50. Found: C, 33.98; H, 2.52.

***syn*-9,18-Difluoro-2,11-dithia[3.3]metacyclophane (4).**—A solution of 2.82 g of 2,6-bis(bromomethyl)fluorobenzene (**3**) in 100 ml of benzene and a solution of 2.40 g of sodium sulfide nonahydrate in 100 ml of 85% aqueous ethanol were added separately, but simultaneously, from two Hershberg funnels to 800 ml of boiling ethanol. When addition was complete (3.5 hr), the solution was concentrated. The residual solid was taken up in benzene and chromatographed over silica gel using a 25% benzene in petroleum ether (bp 30–60°) mixture for elution. The material from the main eluate fraction was recrystallized from carbon tetrachloride to give 575 mg (37%) of white crystals: mp 199–200°; uv (cyclohexane) 218 nm ($\epsilon$ 16,150), 242 (3700, sh), 261 (2440, sh), and 269 (2400); nmr ($CDCl_3$), a multiplet at $\tau$ 2.67–3.20 (6 H, ArH) and an AB quartet at 5.67 and 6.61 (8 H, $J$ = 15 Hz, $-CH_2$); mass spectrum (70 eV) $m/e$ (rel intensity) 308 (93), 185 (23), 154 (24), 123 (100), and 109 (33).

*Anal.* Calcd for $C_{16}H_{14}F_2S_2$: C, 62.31; H, 4.58. Found: C, 62.26; H, 4.52.

**9-Fluoro-18-methyl-2,11-dithia[3.3]metacyclophane (5).**—A solution of 2.82 g of 2,6-bis(bromomethyl)fluorobenzene (**3**) in 200 ml of benzene and a solution of 1.84 g of 2,6-bis(mercaptomethyl)-toluene[2] and 0.8 g of sodium hydroxide in 200 ml of 85% aqueous ethanol were added separately, but simultaneously, from two Hershberg funnels to 750 ml of boiling ethanol. When addition was complete (3.5 hr), the solution was concentrated. The residual solid was taken up in dichloromethane and washed successively with dilute aqueous acid, dilute aqueous base, and water. After the organic extract was dried and concentrated, the residual solid was chromatographed over silica gel using a 20% benzene in petroleum ether mixture for elution. The material from the main fraction of eluate was recrystallized from carbon tetrachloride to give 760 mg (25%) of white crystals; mp 200–205°; nmr ($CDCl_3$), a multiplet at $\tau$ 2.84–3.55 (6 H, ArH), a multiplet at 5.64–6.86 (8 H, $-CH_2$), a doublet at 7.59 (1.8 H, $J$ = 2 Hz, $ArCH_3$), and a singlet at 8.51 (1,2 H, $ArCH_3$). The ratio of the integrated areas of the aromatic methyls at $\tau$ 7.59 and 8.51 is 3:2 and corresponds to the ratio of syn and anti conformers. Attempts to separate this mixture by further crystallization, column chromatography, or thin layer chromatography were to no avail.

*Anal.* Calcd for $C_{17}H_{17}FS_2$: C, 67.07; H, 5.63. Found: C, 66.83; H, 5.60.

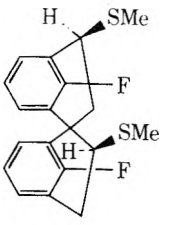
**Bis(sulfonium) Fluoroborate of 4.**—To a solution of 3.0 g of 4 in 150 ml of dichloromethane held at −78° was added with stirring 6.3 g of dimethoxycarbonium fluoroborate.[14] The mixture was then allowed to warm to room temperature and stirring was continued overnight. The solid precipitate was collected, triturated with ethyl acetate, and dried to give 5.0 g (100%) of a white solid. A portion was recrystallized from water to give white crystals, mp 220° dec.

*Anal.* Calcd for $C_{18}H_{20}B_2F_{10}S_2$: C, 42.21; H, 3.93. Found: C, 42.05; H, 4 01.

**Stevens Rearrangement to Give 6.**—To a solution of 4.19 g of potassium *tert*-butoxide in 200 ml of dry tetrahydrofuran there was added with stirring 4.90 g of the bis(sulfonium) fluoroborate of **4**. The mixture was stirred at room temperature under a nitrogen atmosphere for 9 hr. Then the mixture was diluted with 400 ml of dichloromethane, washed successively with dilute aqueous acid and water, and dried. Concentration gave 2.8 g of a yellow oil from which 710 mg of **6** separated as a crystalline solid. This, on recrystallization from cyclohexane, gave 690 mg (22%) of **6** as white crystals: mp 193.5–194°; uv (cyclohexane) 274 nm ($\epsilon$ 910) and 281 (830); nmr ($CDCl_3$), a multiplet at $\tau$ 2.22–2.44 (2 H, ArH next to $-CHSCH_3$), a multiplet at 2.57–2.80 (4 H, ArH), an ABC system at 6.08, 6.96, and 7.42 (6 H, $J_{AB}$ = 4 Hz, $J_{BC}$ = 12 Hz, $J_{AC}$ = 11 Hz, $-CH-$ and $-CH_2$), and a singlet at 7.88 (6 H, $-SCH_3$); mass spectrum (70 eV) $m/e$ (rel intensity) 336 (100), 288 (15), 221 (18), 202 (21), 169 (37), and 168 (16).

*Anal.* Calcd for $C_{18}H_{18}F_2S_2$: C, 64.25; H, 5.39. Found: C, 64.62; H, 5.57.

The mother liquor from which **6** crystallized was taken up in a 10% benzene in petroleum ether mixture and chromatographed over silica gel. The main fraction of eluate gave a second isomer, assigned structure **12** as shown below, as 800 mg (25%) of a color-

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less oil: nmr ($CDCl_3$), a multiplet at 3.0 (2 H, ArH nearest sulfur), a multiplet at 3.6 (4 H, ArH), an ABC system at 5.09, 6.19, and 7.88 (6 H, $J_{AB}$ = 8 Hz, $J_{BC}$ = 12 Hz, and $J_{AC}$ = 8 Hz, $-CH-$ and $-CH_2-$), a singlet at 7.82 (6 H, $-SCH_3$); mass spectrum (70 eV) $m/e$ (rel intensity) 336 (100), 288 (13), 221 (20), 202 (25), 169 (35), and 168 (15).

*Anal.* Calcd for $C_{18}H_{18}F_2S_2$: C, 64.25; H, 5.39. Found: C, 64.35; H, 5.61.

**Bis(sulfonium) Fluoroborate of 6.**—To a solution of 610 mg of **6** in 25 ml of dichloromethane held at −78° was added 730 mg of dimethoxycarbonium fluoroborate with stirring. The mixture was allowed to warm and was then stirred overnight at room temperature. The crystalline precipitate was collected, triturated with ethyl acetate, and dried. This gave 770 mg (95%) of a white solid, of which a portion was recrystallized from water to give white crystals, mp 290° dec.

*Anal.* Calcd for $C_{20}H_{24}B_2F_{10}S_2$: C, 44.47; H, 4.48. Found: C, 44.33; H, 4.47.

***syn*-8,16-Difluoro[2.2]metacyclophane-1,9-diene (7).**—To a solution of 750 mg of potassium *tert*-butoxide in 125 ml of dry tetrahydrofuran there was added 740 mg of the bis(sulfonium) fluoroborate of **6**. After the mixture had been stirred for 2 hr at room temperature, it was diluted with 200 ml of dichloromethane and washed successively with dilute aqueous acid and water. The organic extract was then dried and concentrated. The residual solid was taken up in petroleum ether and chromatographed over silica gel. The material from the main fraction of eluate was recrystallized from a dichloromethane–cyclohexane mixture to give 260 mg (80%) of white crystals: mp 89° dec; uv (cyclohexane) 278 nm ($\epsilon$ 3300) and 337 (830); nmr ($CDCl_3$), a multiplet at $\tau$ 2.86–3.18 (6 H, ArH) and a singlet at 3.59 (4 H, $-CH{=}CH-$); fluorine nmr (acetone-$d_6$) signal at +93 ppm relative to $CFCl_3$ as an internal standard; mass spectrum (70 eV) $m/e$ (rel intensity) 240 (47), 239 (49), 238 (27), 221 (33), 220 (100), 202 (15), and 110 (20).

(11) P. M. G. Bavin and M. J. S. Dewar, *J. Chem. Soc.*, 4486 (1955).

(12) Elemental and mass spectral analyses were determined by Dr. S. Rottschaefer, University of Oregon Microanalytical Laboratories. Infrared spectra were measured with a Beckman IR-5a; visible and ultraviolet spectra with a Cary 15; nmr spectra with a Varian A-60 or HA-100 spectrometer; and mass spectra with a Consolidated Model 21-110 spectrometer.

(13) R. R. Fraser, *Can. J. Chem.*, **38**, 2226 (1960).

(14) R. F. Borch, *J. Org. Chem.*, **34**, 627 (1969).

*Anal.* Calcd for $C_{16}H_{10}F_2$: C, 79.99; H, 4.19. Found: C, 79.85; H, 4.16.

When compound **12**, isomeric to **6**, was converted to the corresponding bis(sulfonium) fluoroborate and subjected to the same conditions for the Hofmann elimination, as described above for the preparation of **7**, the reaction mixture became a deep green but turned colorless during work-up. The material isolated was a complex mixture whose nmr spectrum suggested the presence of pyrene and fluoropyrene derivatives.

**Bis(sulfone) 8.**—A mixture of 25 mg of **7** in 10 mg of glacial acetic acid containing 1 ml of 30% aqueous hydrogen peroxide was boiled under reflux for 24 hr. When the solution was allowed to cool, a crystalline solid separated. This was collected, washed with methanol, and dried to give 30 mg (100%) of a white powder: mp >350°; nmr ($AsCl_3$), a multiplet at $\tau$ 2.68 (4 H, ArH), a triplet at 3.15 (2 H, ArH), and an AB quartet at 5.52 and 5.94 (8 H, $J$ = 14 Hz, $-CH_2SO_2-$).

*Anal.* Calcd for $C_{16}H_{14}O_4F_2S_2$: C, 51.60; H, 3.79. Found: C, 51.56; H, 3.75.

**Pyrolysis of 8 to Give 9.**—The bis(sulfone) **8** (75 mg) was placed in a pyrolysis flow system modeled after that described by Haenel and Staab.[15] The first furnace was at 340° and the second at 500° with the pyrolysis requiring 12 hr. The solid pyrolysate was recrystallized from cyclohexane to give 31 mg (64%) of white crystals: mp 156–158°; uv (cyclohexane) 272 nm ($\epsilon$ 700) and 279 (600); nmr ($CDCl_3$), a multiplet at $\tau$ 2.78–3.10 (6 H, ArH) and a multiplet at 7.26 (8 H, $-CH_2$); fluorine nmr (acetone-$d_6$) signal at +123.1 ppm relative to $CFCl_3$ as an internal standard; mass spectrum (70 eV) $m/e$ (rel intensity) 244 (100), 224 (24), 223 (19), 203 (16), 202 (10), 201 (23), and 122 (32).

(15) M. Haenel and H. A. Staab, *Tetrahedron Lett.*, 3585 (1970).

*Anal.* Calcd for $C_{16}H_{14}F_2$: mol wt, 244.106. Found (high-resolution mass spectrometry): mol wt, 244.104 ± 0.01.

**Hydrogenation of 7 to Give 9.**—A mixture of 9 mg of *syn*-8,16-difluoro[2.2]metacyclophane-1,9-diene (**7**) and 15 mg of a prereduced platinum catalyst in 5 ml of ethyl acetate was subjected to hydrogenation at room temperature and atmospheric pressure. After removal of the catalyst and solvent, the residual solid was recrystallized from cyclohexane to give white crystals, mp 156–158°, identical in all respects with the sample of **9** described previously.

**Thermolysis of *syn*-8,16-Difluoro[2.2]metacyclophane-1,9-diene (7) to Give 1-Fluoropyrene (11).**—A solution of 40 mg of *syn*-8,16-difluoro[2.2]metacyclophane-1,9-diene (**7**) in 5 ml of dry tetrahydrofuran was carefully degassed and sealed in a pyrolysis tube. This was then heated at 120° for 68 hr. The tube was then opened and the contents were concentrated to give a crystalline solid. This was taken up in petroleum ether and chromatographed over silica gel to give 36 mg (98%) of white crystals, mp 136.5–138.0°, nmr ($CDCl_3$), a multiplet at $\tau$ 1.8–2.52.

*Anal.* Calcd for $C_{16}H_9F$: mol wt, 220.069. Found (high-resolution mass spectrometry): 220.067 ± 0.01.

The picrate derived from this material melted at 207–209° [Bavin and Dewar[11] give 135–136° for the melting point of 1-fluoropyrene (**11**) and 208–210° for the melting point of the corresponding picrate].

**Registry No.**—**3**, 25006-86-4; **4**, 25117-62-8; **4** bis(sulfonium) fluoroborate, 41560-37-6; **5**, 30736-36-8; **6**, 41563-60-4; **6** bis(sulfonium) fluoroborate, 41560-38-7; **7**, 41563-61-5; **8**, 41563-62-6; **9**, 22506-31-6; **11**, 1691-65-2; **12**, 41563-65-9; 2-fluoro-*m*-xylene, 443-88-9; *N*-bromosuccinimide, 128-08-5; 2,6-bis(mercaptomethyl)toluene, 41563-67-1; dimethoxycarbonium fluoroborate, 18346-68-4; potassium *tert*-butoxide, 865-47-4.

# Attempted Syntheses of *trans*-15-Methyl-15,16-dihydropyrene[1]

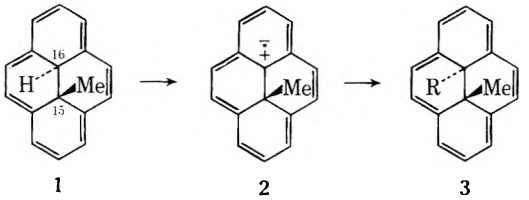
VIRGIL BOEKELHEIDE* AND CHUNG HSIUNG TSAI

*Department of Chemistry, University of Oregon, Eugene, Oregon 97403*

*Received April 10, 1973*

A possible synthesis of the potentially interesting *trans*-15-methyl-15,16-dihydropyrene (**1**) has been investigated by subjecting *anti*-9-methyl-2,11-dithia[3.3]metacyclophane to the two-step reaction sequence of a Stevens rearrangement and a Hofmann elimination. However, the only product isolated was pyrene. When the Hofmann elimination was conducted using a high vacuum train, the green mixture could be shown to contain radicals by esr measurements, and the loss of color accompanying the formation of pyrene resulted in evolution of methane, as shown by mass spectroscopy. Alternatively, the possible photoisomerization of 8-methyl[2.2]metaparacyclophane-1,9-diene (**18**) to **1** was attempted without success, even though the photoisomerization of 8-methyl[2.2]metaparacyclophane (**19**) to 8-methyl[2.2]metacyclophane (**21**) occurs smoothly and in good yield.

Theoretically, *trans*-15-methyl-15,16-dihydropyrene (**1**) is a molecule of high interest because of its possible conversion to the corresponding radical or ions (**2**). Not only would these species be of inherent interest for examination of their physical properties, but they could be valuable synthetic intermediates for preparing dihydropyrenes with substituents at the 16 position as shown by **3**. For these reasons we have studied several

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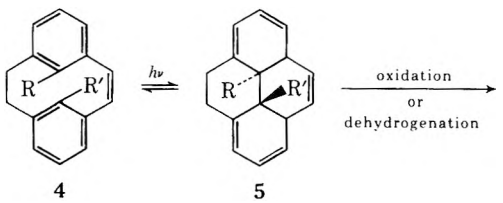
possible approaches which might lead to a synthesis of *trans*-15-methyl-15,16-dihydropyrene (**1**).

In an earlier study,[2,3] we had shown that [2,2]-metacyclophan-1-enes (**4**) are readily photoisomerized to the corresponding 4,5,15,16-tetrahydropyrenes (**5**). With both of the internal substituents being methyl (R = R′ = Me), dehydrogenation of **5** proceeded smoothly to give *trans*-15,16-dimethyldihydropyrene.

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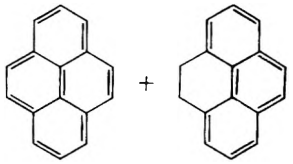

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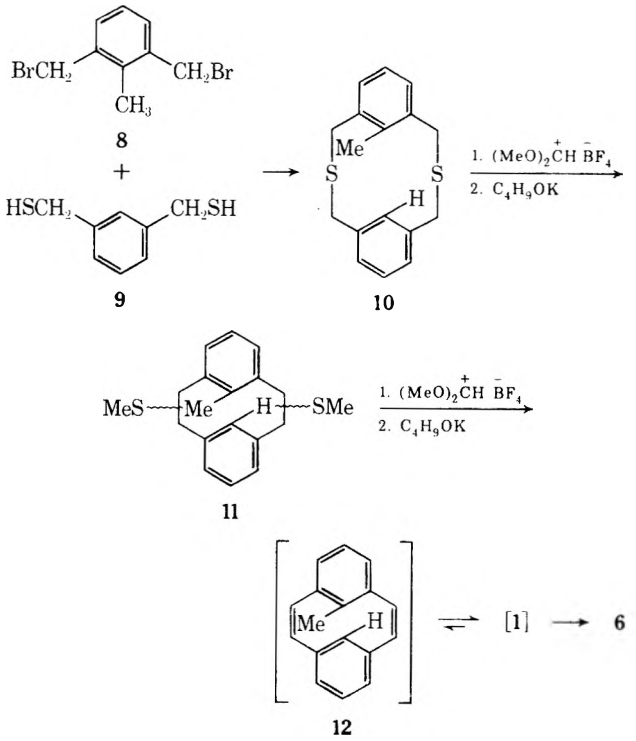
(1) We thank the National Science Foundation for their support of this investigation.

(2) H. Blaschke, C. E. Ramey, I. Calder, and V. Boekelheide, *J. Amer. Chem. Soc.*, **92**, 3675 (1970).

(3) C. E. Ramey and V. Boekelheide, *J. Amer. Chem. Soc.*, **92**, 3681 (1970).

However, when the internal substituents were both hydrogen (R = R′ = H) or hydrogen and methyl (R = H; R′ = Me), dehydrogenation as well as oxidation of **5** gave pyrene (**6**) and 4,5-dihydropyrene (**7**) as the major products. Thus, it was clear that the final step in a synthesis of **1** should be done with rigid exclusion of oxygen and should not require dehydrogenation agents.

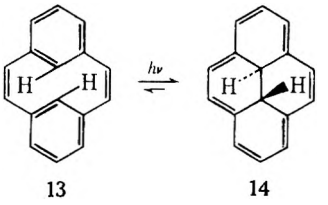
A method which appeared to fulfill these requirements was the two-step Stevens rearrangement and Hofmann elimination sequence developed for the synthesis of 15,16-dialkyldihydropyrenes.[4] For this purpose then, 9-methyl-2,11-dithia[3.3]metacyclophane (**10**) was prepared by the condensation of 2,6-bis(bromomethyl)toluene (**8**) and 1,3-bis(mercaptomethyl)-benzene (**9**).[5] Methylation of **10** using dimethoxycarbonium fluoroborate followed by reaction with potassium *tert*-butoxide in tetrahydrofuran gave the Stevens rearrangement product **11** in 65% yield as a mixture of stereoisomers. Methylation of **11** followed again by treatment with potassium *tert*-butoxide in tetrahydrofuran gave pyrene (**6**), presumably *via* **12** and **1** as intermediates.




In the case of *anti*-[2.2]metacyclophane-1,9-diene (**13**), where both internal substituents are hydrogen, valence tautomerization to *trans*-15,16-dihydropyrene does not occur spontaneously at room temperature and it is possible to isolate the pure compound and study its properties.[4,6] However, when both internal substituents are alkyl, valence tautomerization to the corresponding *trans*-15,16-dialkyldihydropyrene occurs spontaneously at room temperature.[7] In this respect, **12** appears to behave similarly to the *anti*-8,16-dialkyl[2.2]metacyclophane-1,9-dienes rather than to *anti*-[2.2]metacyclophane-1,9-diene (**13**) itself. To investigate whether oxygen was playing a role in the conversion of **12** to pyrene, the Hofmann elimination procedure was repeated using a high-vacuum train with rigid exclusion of oxygen. When the bis(methosulfonium) fluoroborate from **11** was added to potassium *tert*-butoxide in tetrahydrofuran under these conditions, a deep green solution developed, as might be expected for **1**. No useful nmr spectra of this solution were obtained, apparently because of broadening owing to the presence of radicals. An esr spectrum of the solution showed a broad symmetrical peak with a $g$ value of 2.0059. As Bersohn and Thomas have shown,[8] peroxy radicals have $g$ values in the range of 2.0140 to 2.0190, whereas alkyl and alkoxy radicals have $g$ values of less than 2.0100. Although it was not possible to analyze the esr signal in terms of fine structure, the evidence is indicative of the presence of an R′ radical. The green color of the solution faded on standing and introduction of the gases from above the reaction mixture into a mass spectrometer produced an intense signal due to methane.

An attractive interpretation of these data is that **1** is being formed but is undergoing a rapid reaction with base to form the carbanion **2**. The carbanion **2**, in turn, can undergo loss of methyl radical to give the pyrene radical anion. The methyl radical by abstraction of hydrogen from **1** would give methane and the radical **2**, which could complete the cycle by giving pyrene and another methyl radical. Although attempts were made to avoid such a decomposition by using other bases or less than 1 equiv of base, these experiments were unsuccessful.

It would appear that a successful preparation of **1** and a study of its properties requires both the absence of oxygen and base. For the case of *trans*-15,16-dihydropyrene (**14**), a similarly sensitive compound, its synthesis was accomplished by irradiation of [2.2]-metacyclophane-1,9-diene (**13**) in carefully degassed

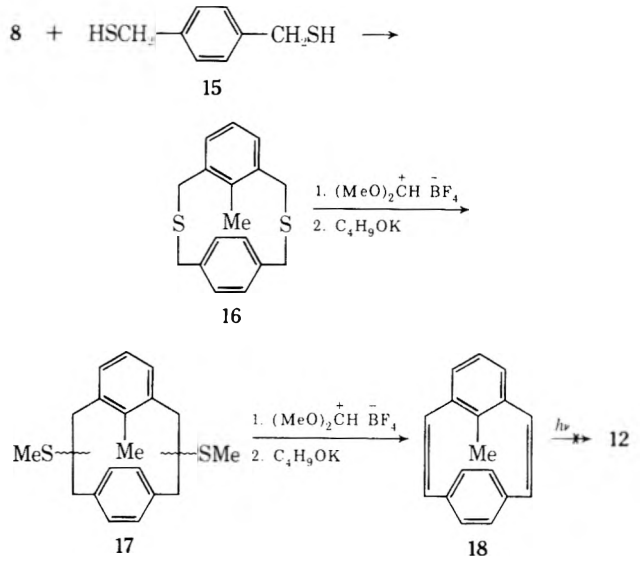



cyclohexane.[4,6] Recently, Cram and his collaborators have reported the photochemical rearrangement of [2.2]metaparacyclophanes to [2.2]metacyclophanes.[9] If a similar photochemical rearrangement of [2.2]metaparacyclophane-1,9-dienes were to occur, this would provide an attractive route to **1**, since the intermediate *anti*-8-methyl[2.2]metacyclophane-1,9-diene (**12**) could be generated under conditions of rigid exclusion of oxygen and base.

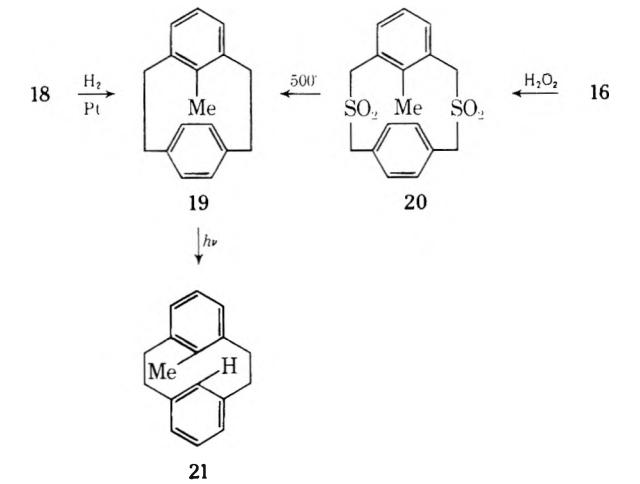
To investigate the possible synthesis of **1** by photochemical rearrangement, the synthesis of 8-methyl-[2.2]metaparacyclophane-1,9-diene (**18**) was undertaken. Condensation of 2,6-bis(bromomethyl)toluene (**8**) with 1,4-bis(mercaptomethyl)benzene (**15**) proceeded smoothly in good yield to give 9-methyl-2,11-

(4) R. H. Mitchell and V. Boekelheide, *Tetrahedron Lett.*, 1197 (1970).
(5) F. Vögtle and P. Neumann [*Tetrahedron*, **26**, 5299 (1970)] have previously reported syntheses of **10** and **16**.
(6) R. H. Mitchell and V. Boekelheide, *J. Amer. Chem. Soc.*, **92**, 3510 (1970).
(7) H.-R. Blattmann and W. Schmidt, *Tetrahedron*, **26**, 5885 (1970).
(8) M. Bersohn and J. R. Thomas, *J. Amer. Chem. Soc.*, **86**, 959 (1964).
(9) R. E. Gilman, M. H. Delton, and D. J. Cram, *J. Amer. Chem. Soc.*, **94**, 2478 (1972).

dithia[3.3]metaparacyclophane (**16**).[5] A Stevens rearrangement of **16** then led to **17**, as a mixture of stereoisomers, and a Hofmann elimination reaction with **17** readily gave the desired 8-methyl[2.2]metaparacyclophane-1,9-diene (**18**). Unfortunately, irradiation of a solution of **18** in carefully degassed cyclohexane with light of 254 nm was entirely without effect.[10]




To make certain that the conditions employed in the photochemical experiments were effective for the photochemical rearrangement of [2.2]metaparacyclophane to [2.2]metacyclophane, the synthesis was extended to prepare 8-methyl[2.2]metaparacyclophane (**19**) and study its behavior on irradiation. Catalytic hydrogenation of **18** readily gave 8-methyl[2.2]metaparacyclophane (**19**) in good yield. However, for preparing larger quantities of **19**, it was more convenient to oxidize **16** to the corresponding bis(sulfone) **20** and subject this to pyrolysis. Thermal decomposition of **20** proceeded smoothly at 500° to give **19** in 90% yield. Irradiation of a solution of **19** in cyclohexane with light of 254 nm for 4 hr readily gave 8-methyl[2.2]metacyclophane (**21**), identical in all respects with




an authentic sample,[2] in 47% yield. It is not clear why the [2.2]metaparacyclophane-1,9-dienes are unaffected by irradiation under conditions which cause a smooth rearrangement of the corresponding [2.2]metaparacyclophane to [2.2]metacyclophane.

(10) V. Boekelheide and P. H. Anderson (unpublished observations) have likewise observed that [2.2]metaparacyclophane-1,9-diene itself is unaffected by irradiation.

## Experimental Section[11]

**9-Methyl-2,11-dithia[3.3]metacyclophane** (**10**).—A solution of 25.0 g of 2,6-bis(bromomethyl)toluene[4] (**8**) in 600 ml of benzene and a solution of 15.3 g of 1,3-bis(mercaptomethyl)benzene[12] (**9**) in 600 ml of 85% aqueous ethanol containing 7.2 g of sodium hydroxide were added separately, but simultaneously, from two Hershberg funnels, to 3 l. of boiling ethanol. When addition was complete (5 hr), the mixture was boiled under reflux for another 28 hr and then concentrated. The residual solid was extracted with dichloromethane and the dichloromethane extract was washed with aqueous base and water. After concentration of the organic extract, the residue was taken up in a 20% chloroform–petroleum ether (bp 30–60°) mixture and chromatographed over silica gel. The main fraction of eluate gave 9.5 g (38%) of white crystals: mp 105–106°; nmr ($CDCl_3$), a multiplet at $\tau$ 2.9–3.2 (6 H, ArH), a broad singlet at 4.50 (1 H, ArH at 18 position), a multiplet at 5.9–6.6 (8 H, $-CH_2-$), and a singlet at 7.82 (3 H, $ArCH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 286 (100), 252 (25), 221 (20), 180 (30), 151 (25), 150 (90), 149 (125), 148 (125), and 147 (120).

*Anal.* Calcd for $C_{17}H_{18}S_2$: C, 71.28; H, 6.33; S, 22.39. Found: C, 71.18; H, 6.28; S, 22.56.

**Bis(methosulfonium) Fluoroborate of 10.**—A solution of 4.0 g of **10** in 100 ml of dichloromethane was added dropwise with stirring to a solution of 5.67 g of dimethoxycarbonium fluoroborate[13] in 50 ml of dichloromethane held at −30°. The mixture was allowed to warm to room temperature and was then stirred overnight. The crystalline precipitate was separated by decantation and triturated with ethyl acetate to give 6.0 g (88%) of a white solid, mp 206° dec.

*Anal.* Calcd for $C_{19}H_{24}S_2B_2F_8$: C, 46.56; H, 4.94. Found: C, 46.33; H, 4.94.

**Stevens Rearrangement to Give 11.**—A mixture of 6.0 g of the bis(methosulfonium) fluoroborate of **10** and 3.0 g of potassium *tert*-butoxide in 200 ml of dry tetrahydrofuran was stirred at room temperature for 5 hr. After addition of dichloromethane and dilute aqueous acid, the organic layer was separated, washed with water, dried, and concentrated. The residual oil was taken up in a 2:3 mixture of dichloromethane in petroleum ether and chromatographed over silica gel. The main fraction of eluate gave 2.87 g (76%) of a colorless oil: nmr ($CDCl_3$), a multiplet at $\tau$ 2.2–3.0 (6 H, ArH), a singlet at 6.0 (1 H, ArH at 16 position), a multiplet at 5.9–6.25 (2 H, $-CHSCH_3$), a multiplet at 6.6–8.1 (4 H, $-CH_2-$), a singlet at 7.9 (6 H, $-SCH_3$), and a narrow doublet at 9.5 (3 H, $ArCH_3$).

*Anal.* Calcd for $C_{19}H_{22}S_2$: C, 72.56; H, 7.05; S, 20.39. Found: C, 72.27; H, 7.13; S, 20.60.

**Bis(methylsulfonium) Fluoroborate of 11.**—A solution of 2.58 g of **11** in 100 ml of dichloromethane was added with stirring to a suspension of 4.4 g of dimethoxycarbonium fluoroborate in 20 ml of dichloromethane held at −30°. After the mixture had been stirred for 5 hr, 50 ml of ethyl acetate was added and the mixture was stirred for an additional 30 min. The crystalline precipitate was collected, triturated with ethyl acetate, and dried to give 3.53 g (84%) of white crystals: mp 260–261°; nmr ($CDCl_3$), a multiplet at $\tau$ 2.4–2.6 (6 H, ArH), a broad singlet at 6.1 (1 H, ArH at 16 position), a singlet at 6.6 (12 H, $-SCH_3$), a multiplet at 7.05 7.20 (6 H, $-CH_2$ and $-CHSCH_3$), and a singlet at 9.4 (3 H; $ArCH_3$).

*Anal.* Calcd. for $C_{21}H_{28}S_2B_2F_8$: C, 48.68; H, 5.45. Found: C, 48.67; H, 5.42.

**Attempted Hofmann Eliminations with the Bis(methosulfonium) Fluoroborate of 11.**—A mixture of 1.04 g of the bis(methosulfonium) fluoroborate of **11** and 667 mg of potassium *tert*-butoxide in 50 ml of dry tetrahydrofuran was stirred at room temperature for 3 hr. Then dilute aqueous acid and petroleum ether were added to the mixture. After the organic layer had been separated, it was washed with water, dried, and concentrated.

(11) Elemental and mass spectral analyses were determined by Dr. S. Rottschaefer, University of Oregon Microanalytical Laboratories. Infrared spectra were measured with a Beckman IR-5a; visible and ultraviolet spectra with a Cary 15; nmr with a Varian A-60 or HA-100 spectrometer; and mass spectra with a Consolidated Model 21-110 spectrometer.

(12) W. Autenreith and F. Beuttel, *Chem. Ber.*, **42**, 4357 (1901).

(13) R. F. Borch, *J. Org. Chem.*, **34**, 627 (1969).

The residual yellow solid was taken up in petroleum ether and chromatographed over silica gel to give 220 mg of pale yellow crystals, mp 156–157°, identical in all respects with an authentic specimen of pyrene.

When the experiment was repeated using various other bases, such as sodium hydride, *n*-butyllithium, or sodium hydroxide, the results were essentially the same. One experiment using potassium *tert*-butoxide as above, but in a high vacuum train, gave a green solution having a strong, broad esr signal ($g$ 2.0059). A mass spectrum of the gases collected in the high-vacuum train showed a strong signal at $m/e$ 16, indicating the presence of methane. The green color of the reaction mixture faded to a pale yellow over a short period of time.

**9-Methyl-2,11-dithia[3.3]metaparacyclophane (16).**—A solution of 12.0 g of 2,6-bis(bromomethyl)toluene (**8**) in 600 ml of benzene and a solution of 7.32 g of 1,4-bis(mercaptomethyl)-benzene (**15**) in 600 ml of 85% aqueous ethanol containing 3.5 g of sodium hydroxide were added simultaneously, but separately, from two Hershberg funnels to 3 l. of boiling ethanol. When the addition was complete, the mixture was boiled under reflux for an additional 30 hr and then concentrated. After the residual solid had been extracted with dichloromethane, the organic extract was washed with dilute base and dried. Concentration of the extract gave a yellow solid which was taken up in a 25% benzene–petroleum ether mixture and chromatographed over silica gel. The main eluate fraction gave 5.35 g (44%) of white crystals: mp 204–205° (lit.[5] mp 202°); nmr ($CDCl_3$), a multiplet at $\tau$ 2.7–3.2 (5 H, ArH), a multiplet at 3.7–3.8 (2 H, ArH), a multiplet at 6.15–6.55 (8 H, $-CH_2$), and a singlet at 8.1 (3 H, $ArCH_3$).

**Bis(methosulfonium) Fluoroborate of 16.**—A solution of 2.86 g of **16** in 50 ml of dichloromethane was added dropwise with stirring to a suspension of 4.55 g of dimethoxycarbonium fluoroborate in 20 ml of dichloromethane held at −30°. After the mixture warmed to room temperature, it was stirred overnight. The crystalline precipitate was collected, triturated with ethyl acetate, and dried. Recrystallization from water gave 4.90 g (100%) of a white powder, mp 200° dec.

*Anal.* Calcd for $C_{19}H_{24}S_2B_2F_8$: C, 46.56; H, 4.94. Found: C, 46.19; H, 5.02.

**Stevens Rearrangement to Give 17.**—A mixture of 3.76 g of the bis(methosulfonium) fluoroborate of **16** and 2.54 g of potassium *tert*-butoxide in 100 ml of dry tetrahydrofuran was stirred at room temperature overnight. Dilute aqueous hydrochloric acid and dichloromethane were then added with stirring and the organic layer was separated. Concentration of the organic extract gave an oily residue which was taken up in a 25% benzene–petroleum ether mixture and chromatographed over silica gel. The main fraction of eluate gave 870 mg (31%) of a colorless oil: nmr ($CDCl_3$), a multiplet at $\tau$ 2.5–3.0 (5 H, ArH), a multiplet at 4.06–4.12 (2 H, ArH), an AB pattern at 5.7–6.62 (4 H, $-CH_2$), a multiplet at 7.4–7.9 (2 H, $-CHSCH_3$), a singlet at 7.95 (6 H, $-SCH_3$), and a singlet at 8.18 (3 H, $ArCH_3$).

*Anal.* Calcd for $C_{19}H_{22}S_2$: C, 72.56; H, 7.05; S, 20.39. Found: C, 72.28; H, 7.04; S, 20.68.

**Bis(methosulfonium) Fluoroborate of 17.**—A solution of 670 mg of **17** in 50 ml of dichloromethane was added dropwise with stirring to a suspension of 1.03 g of dimethoxycarbonium fluoroborate in 50 ml of dichloromethane held at −30°. After the mixture had been stirred for 5 hr, 50 ml of ethyl acetate was added and stirring was continued overnight at room temperature. The crystalline precipitate was collected, washed with ethyl acetate, and dried. Recrystallization from water gave 800 mg (73%) of white crystals, mp 218° dec.

*Anal.* Calcd for $C_{21}H_{28}S_2B_2F_8$: C, 48.68; H, 5.45. Found: C, 48.98; H, 5.50.

**8-Methyl[2.2]metaparacyclophane-1,9-diene (18).**—A mixture of 1.64 g of the bis(methosulfonium) fluoroborate of **17** and 1.08 g of potassium *tert*-butoxide in 25 ml of dry tetrahydrofuran was stirred at room temperature for 24 hr. After addition of dilute aqueous hydrochloric acid and dichloromethane with shaking, the organic layer was separated, dried, and concentrated. The solid residue was taken up in petroleum ether and chromatographed over silica gel. The material from the main fraction of eluate was recrystallized from a benzene–petroleum ether mixture to give 184 mg (26%) of white crystals: mp 157–158°; nmr ($CDCl_3$), a multiplet at $\tau$ 2.9–3.4 (5 H, ArH), a quartet at 3.15 (4 H, $-CH=CH-$), a doublet at 3.9 (2 H, ArH), and a singlet at 8.55 (3 H, $ArCH_3$).

*Anal.* Calcd for $C_{17}H_{14}$: C, 93.54; H, 6.46. Found: C, 93.12; H, 6.61.

**Hydrogenation of 18 to Give 19.**—A solution of 125 mg of **18** in 10 ml of ethyl acetate containing 75 mg of a prereduced platinum catalyst was subjected to hydrogenation at room temperature and atmospheric pressure. After removal of the catalyst and solvent, the residue was recrystallized from a benzene–petroleum ether mixture to give 127 mg (100%) of white crystals: mp 218–219°; nmr ($CDCl_3$), a multiplet at $\tau$ 3.05–3.50 (5 H, ArH), a doublet at 4.28 (2 H, ArH), a multiplet at 6.2–8.2 (8 H, $-CH_2-$), and a singlet at 8.22 (3 H, $ArCH_3$).

*Anal.* Calcd for $C_{17}H_{18}$: C, 91.84; H, 8.16. Found: C, 91.87; H, 8.14.

**9-Methyl-2,11-dithia[3.3]metaparacyclophane Bis(sulfone) (20).**—To a solution of 150 mg of **16** in 30 ml of dichloromethane was added in portions with shaking 450 mg of *m*-chloroperbenzoic acid. When addition was complete, the mixture was stirred overnight. After the mixture was washed with dilute aqueous base and water, it was dried and concentrated to give 182 mg (100%) of a white powder: mp 400° dec; nmr ($CF_3CO_2H$) a multiplet at $\tau$ 2.2–2.8 (5 H, ArH), a broad singlet at 3.25 (2 H, ArH), a multiplet at 5.0–6.1 (8 H, $-CH_2-$), and a singlet at 8.0 (3 H, $ArCH_3$).

*Anal.* Calcd for $C_{17}H_{18}S_2O_4$: C, 58.26; H, 5.17. Found: C, 58.29; H, 5.13.

**Pyrolysis of 20 to Give 19.**—In a pyrolysis flow system, modeled after that described by Haenel and Staab,[14] was placed a 60-mg sample of **20**. The first furnace was set at 300° with the second at 500°, and the flow rate was such that the pyrolysis was complete in 24 hr. There collected on the cold finger 28 mg (90%) of white crystals, mp 218°, identical in all respects with the sample of **19** prepared previously.

**Photoisomerization of [2.2]Metaparacyclophane (19) to [2.2]-Metacyclophane (21).**—A carefully degassed solution of 30 mg of [2.2]metaparacyclophane (**19**) in 5 ml of cyclohexane sealed in a quartz tube was irradiated with 254-nm light for 72 hr. At this stage nmr monitoring indicated that the solution contained about a 50:50 mixture of **19** and **21**. The contents of the tube were then concentrated. The residue was taken up in hexane and chromatographed over silica gel. Analysis of the early fractions of eluate showed only the presence of starting material **19**. The product from the middle eluate fractions was recrystallized from methanol to give 14 mg (47%) of white crystals, mp 91.0–91.5°, identical in all respects with an authentic specimen of 8-methyl-[2.2]metacyclophane (**21**).[2]

When a degassed solution of 10 mg of **18** in 5 ml of cyclohexane was subjected to irradiation in exactly the same way, nmr monitoring showed no change in the spectrum after 43 hr. Work-up of the irradiated solution led to a complete recovery of the starting material (**18**).

**Registry No.**—**8**, 41563-68-2; **9**, 41563-69-3; **10**, 30736-35-7; **10** bis(methosulfonium) fluoroborate, 41560-40-1; **11**, 41583-10-2; **11** bis(methylsulfonium) fluoroborate, 41562-83-8; **15**, 105-09-9; **16**, 27453-78-7; **16** bis(methosulfonium) fluoroborate, 41611-00-1; **17**, 41562-84-9; **17** bis(methosulfonium) fluoroborate, 41562-85-0; **18**, 41563-70-6; **19**, 41563-71-7; **20**, 41563-72-8; **21**, 28746-30-7; dimethoxycarbonium fluoroborate, 18346-68-4; *m*-chloroperbenzoic acid, 937-14-4.

(14) M. Haenel and H. A. Staab, *Tetrahedron Lett.*, 3585 (1970).

# The Reaction of Trimethylsilyl Enol Ethers with Diols

GERALD L. LARSON* AND ANTONIO HERNANDEZ

*Department of Chemistry, University of Puerto Rico, Rio Piedras, Puerto Rico 00931*

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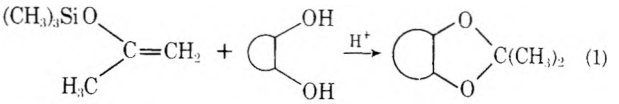
The acid-catalyzed reaction of 2-(trimethylsiloxy)propene (I) (TMSP) with cyclic diols, including the trans 1,2-diols of cyclohexane and cycloheptane and *cis*-1,2-cyclohexanediol, results in the formation of the corresponding acetonides in good yield. Similarly, the reaction of 1-(trimethylsiloxy)cyclohexene (II) with ethylene glycol, 1,3-propanediol, 1,4-butanediol, and 2-mercaptoethanol affords the corresponding ketals of cyclohexanone in good yield. The reactions are exothermic and offer a convenient alternative to other methods of preparing acetonides and ketals.

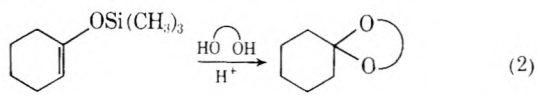
We wish to report that trimethylsilyl enol ethers react with a variety of diols with acid catalysis to give ketals in good yield. The reaction is general and has been used for the preparation of the heretofore unknown *trans*-1,2-cyclohexanediol acetonide.[1] The reactions are exothermic and require from 10 to 30 min for completion. They thus offer an attractive alternative to the more conventional preparations of ketals.[2]

## Results

Two systems were studied, the reaction of 2-(trimethylsiloxy)propene (I) (TMSP) with cyclic 1,2-diols (eq 1) and the reaction of 1-(trimethylsiloxy)cyclohexene (II) with acyclic diols and with 2-mercaptoethanol (eq 2).



I



II

The first efforts were to form acetonides from the reaction of cyclic diols with TMSP using an acid catalyst. The reaction was catalyzed with either concentrated HCl or with trimethylchlorosilane.[3] A variety of solvents were employed, including ether, tetrahydrofuran, acetonitrile, carbon tetrachloride, chloroform, and benzene, with essentially the same results in all cases, although tetrahydrofuran has the advantage of being a better solvent for the diols. The synthesis of TMSP in quantities suitable for large-scale or repeated use presents somewhat of a problem. For this work the method of House and coworkers[4] was used, but there was always about 30% hexamethyldisiloxane present in the distilled product. Redistillation did not improve the product and it was determined that an azeotrope was formed. This problem was apparently also encountered by Krüger and Rochow in their preparation of TMSP.[5] The mixture, however, could be used with good results, since the hexamethyldisiloxane is inert to the reaction conditions and is volatile enough for easy removal under reduced pressure. The amount of TMSP present in the mixture was determined to be about 5 mmol/ml by using nmr spectroscopy with benzene as an internal standard. The exact amount of TMSP varied slightly from batch to batch.

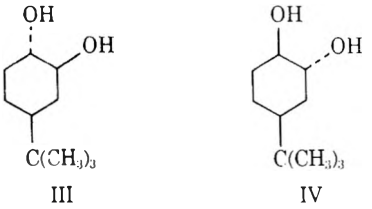
The results of the reaction of TMSP with cyclic 1,2-diols are shown in Table I. The reaction is exothermic with reaction times of 5–10 min sufficient for complete reaction. Of particular interest is the formation of *trans*-1,2-cyclohexanediol acetonide in 80% yield. This compound was shown to be different from the corresponding cis isomer by comparison of their glpc retention times and nmr, ir, and mass spectra. Hydrolysis of this acetonide afforded the trans diol uncontaminated with the cis diol, thus ruling out the possibility of an isomerization occurring during the reaction. The spectral data are recorded in the Experimental Section. A trans acetonide was also formed with 4-*tert*-butyl-*trans*-1,*cis*-2-cyclohexanediol (III), but not from 4-*tert*-butyl-*cis*-1,*trans*-2-cyclohexanediol (IV), consistent with the results of Merkel and coworkers.[6] *trans*-1,2-Cyclopentanediol failed to give an acetonide. The use of a large excess of TMSP resulted in the formation of a considerable amount of 2,2-bis(trimethylsiloxy)propane from the reaction of trimethylsilanol with TMSP.

TABLE I

PRODUCTS FROM THE REACTION OF TMSP (I) WITH CYCLIC 1,2-DIOLS

| Registry no. of diol | Dio. | Registry no. of acetonide | Acetonide yield, % | Bp, °C (mm) | $n^{20}$D |
|---|---|---|---|---|---|
| 1792-81-0 | *cis*-$C_6$ | 41564-26-5 | 80 | 92–96 (22) | 1.4466[a] |
| 1460-57-7 | *trans*-$C_6$ | 24148-95-6 | 80 | 92–96 (22) | 1.4450 |
| 13553-19-0 | *trans*-$C_7$ | 41564-28-7 | 85 | *b* | 1.4536[c] |
| 19793-88-5 | 4-*t*-Bu-*trans*-1,-*cis*-2-$C_6$ | 41564-29-8 | 85 | *b* | 1.4554[d] |

[a] H. G. Derx, *Recl. Trav. Chim. Pays-Bas*, **41**, 331 (1922), gives $n^{17.5}$D 1.4467. [b] Isolated by preparative glpc. [c] H. G. Derx, *Recl. Trav. Chim. Pays-Bas*, **41**, 312 (1922), gives $n^{18}$D 1.45432. [d] See ref 6, which gives $n^{20}$D 1.4572.



III IV

(1) J. Böeseken, *Recl. Trav. Chim. Pays-Bas*, **40**, 553 (1921).

(2) See, for example, O. T. Schmidt in "Methods in Carbohydrate Chemistry," Vol. II, R. L. Whistler and H. L. Wolfram, Ed., Academic Press, New York, N. Y., 1963, p 318.

(3) Other acids were not tried. The trimethylchlorosilane may catalyze the reaction through the generation of HCl by reaction with an OH group or from the HCl present in the chlorosilane.

(4) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).

(5) C. R. Krüger and E. G. Rochow, *J. Organometal. Chem.*, **1**, 476 (1964).

(6) D. Merkel, F. Wolf, and M. Lück, *Z. Chem.*, **8**, 225 (1968).

The results of the reaction of acyclic diols with II are summarized in Table II. It can be seen that the reaction results in the formation of the corresponding ketals of cyclohexanone in good yield. The reactions are exothermic and are complete in 10–30 min. Reaction with 2-mercaptoethanol went cleanly to give 1-oxa-4-thiaspiro[4.5]decane.

TABLE II
PRODUCTS OF THE REACTION OF ACYCLIC DIOLS WITH 1-(TRIMETHYLSILOXY)CYCLOHEXENE (II)

| Registry no. of diol | Diol | Registry no. of ketal | Yield of ketal, % | Bp, °C (mm) | $n^{20}$D |
|---|---|---|---|---|---|
| 107-21-1 | Ethylene glycol | 177-10-6 | 75 | 88–90 (28)[a] | 1.4584 |
| 504-63-2 | Trimethylene glycol | 180-93-8 | 75 | 90–95 (18) | 1.4699[b] |
| 110-63-4 | 1,4-Butanediol | 181-28-2 | 70 | 90–95 (10)[c] | 1.4721[c] |
| 60-24-2 | 2-Mercaptoethanol | 177-15-1 | 75 | 119–120 (25)[d] | 1.5150[d] |

[a] J. Böeseken and F. Telleger, *Recl. Trav. Chim. Pays-Bas*, **57**, 133 (1938), give bp 67–74° (20 mm). [b] E. J. Salmi, *Ber.*, **71**, 1803 (1938), gives $n^{20}$D 1.4692. [c] E. D. Bergamnn and A. Kaluszyner, *Recl. Trav. Chim. Pays-Bas*, **78**, 337 (1959), give bp 117–118° (40 mm), $n^{30}$D 1.4681. [d] C. Djerassi and M. Gorman, *J. Amer. Chem. Soc.*, **75**, 3704 (1953), give bp 47° (0.6 mm), $n^{24}$D 1.5155.

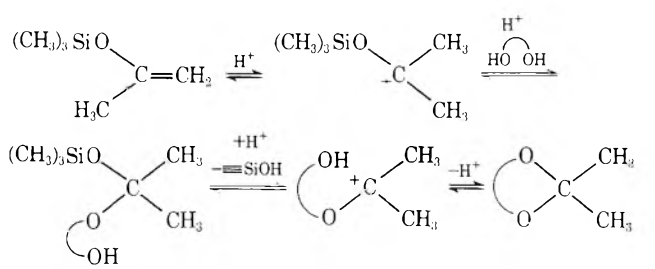
## Discussion

Trimethylsilyl enol ethers are very active reagents with diols under acid catalysis. The advantages of forming ketals using trimethylsilyl enol ethers are found in the short reaction times, the high yields, and the formation of ketals that are not easily realized by other methods (*viz.* *trans*-1,2-cyclohexanediol acetonide and 4-*tert*-butyl-*trans*-1,*cis*-2-cyclohexanediol acetonide).

We have found that the reaction of alcohols with TMSP gives rise to silylation of the alcohol with the elimination of acetone (eq 3).[7] To rule out the possibility that the ketals are being formed by the reaction of silylated diols with the acetone formed, a mixture of *cis*-1,2-cyclohexanediol, acetone, and trimethylchlorosilane was shaken for 10 min and an nmr spectrum was taken. This showed no formation of a peak at about $\delta$ 1.3 for the isopropyl methyl groups of the acetonide, these protons being clearly evident in the spectrum of the reaction mixture of the diol with TMSP. A mechanism analogous to that for ketal formation from ketones and diols with acid catalysis is proposed. This is illustrated in Scheme I.

$$\text{I} + \text{ROH} \xrightarrow{\text{H}^+} \text{ROSi(CH}_3)_3 + (\text{CH}_3)_2\text{CO} \qquad (3)$$

SCHEME I



## Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 237 spectrometer, nmr spectra on a Varian T60, and mass spectra on a Hitachi RMS-4 spectrometer. Melting points are uncorrected. Glpc analyses were carried out using a 12 ft × 0.125 in., 10% Carbowax on Chromosorb W HMDS treated column. All reactions were carried out under an atmosphere of dry nitrogen. Tetrahydrofuran, ether, and benzene were distilled from benzophenone ketyl, acetonitrile from $P_2O_5$. Ethylene glycol (Eastman), 1,3-propanediol (Shell), 1,4-butanediol (Aldrich), and 2-mercaptoethanol (Union Carbide) were used without further purification. Trimethylchlorosilane, generously supplied by Union Carbide, was distilled prior to use. *cis*-1,2-Cyclohexanediol was prepared according to Fieser and Fieser.[8] The trans 1,2-diols of cyclopentane, mp 45–47° (lit.[9] mp 50°), cyclohexane, mp 101–103° (lit.[10] mp 104°), and cycloheptane, mp 56–58° (lit.[11] mp 57–58°), were prepared *via* the hydroboration–oxidation of the trimethylsilyl enol ethers of cyclopentanone, cyclohexanone, and cycloheptanone, respectively.[12] The 4-*tert*-butyl-*trans*-1,*cis*-2-cyclohexanediol (III), mp 101–104° (lit.[6] mp 104–104.5°), and 4-*tert*-butyl-*cis*-1,*trans*-2-cyclohexanediol (IV, mp 139–141° (lit.[6] mp 142–142.5°), were prepared analogously and separated by careful crystallization from ether–pentane.

**Preparation of Cyclic Ketals of Cyclohexanone. A General Procedure.**—Into a 25-ml flask was placed 20 mmol of II, 20 mmol of diol (or mercaptoethanol), and about 10–15 ml of solvent. To this was added 2 drops of concentrated HCl (or about 20 $\mu$l of trimethylchlorosilane). After the exothermic reaction subsided the reaction mixture was stirred for an additional 10–30 min (longer times for the longer chain length of the diol), dried, filtered, and distilled under reduced pressure.

**Preparation of *trans*-1,2-Cyclohexanediol Acetonide.**—Into a 25-ml flask was placed 1.16 g (10 mmol) of *trans*-1,2-cyclohexanediol, 4 ml of $CCl_4$, and 12 mmol of TMSP. Two drops of concentrated HCl were added. An exothermic reaction occurred immediately. The reaction mixture was stirred for 10 min, dried, filtered, and distilled through a short-path distillation apparatus to yield 1.25 g (80%) of the acetonide (*ca.* 96% pure by glpc, bp 92–96° (22 mm). A sample purified by preparative glpc gave $n^{20}$D 1.4450; nmr ($CCl_4$, TMS) 1.30 (s), 1.67 (m), and 3.14 ppm (m); ir (neat) 2950 (s), 1360 (s, doublet), 1210 (s), 1110 (s), 1055 (s), and 835 cm$^{-1}$ (s); mass spectrum (70 eV) *m/e* (rel intensity) 155 (4), 141 (100), 99 (67), 81 (95), 59 (88), 43 (95), and 41 (77).

**Hydrolysis of *trans*-1,2-Cyclohexanediol Acetonide.**—About 10 drops of the acetonide was placed in a vial with 2 ml of ether and 1 ml of 10% HCl. The two-phase system was shaken for 5 min, and the ether layer was removed dried, and evaporated. The resulting solid was sublimed to give a solid, mp 99–101°, whose infrared and nmr spectra were identical with those of an authentic sample of *trans*-1,2-cyclohexanediol.

**Preparation of 4-*tert*-Butyl-*trans*-1,*cis*-2-cyclohexanediol Acetonide.**—A 15-ml flask was charged with 0.43 g (2.5 mmol) of the diol III, 2 ml of $CCl_4$, and 2.8 mmol of TMSP. One drop of concentrated HCl was added. After 10 min the reaction mixture was dried, filtered, and concentrated to give 0.48 g of residue. Glpc analysis of this residue showed the acetonide to be present in about 85% yield. The acetonide was purified by preparative glpc to afford a sample with $n^{20}$D 1.4554; nmr ($CCl_4$, TMS) 0.90 (s), 1.30 (s), 2.00 (m), 3.18 (m), and 3.51 ppm (m); ir (neat) 2950 (s), 1265 (s, doublet), 1230 (s), 1080 (s), and 830 cm$^{-1}$ (s); mass spectrum (70 eV) *m/e* (rel intensity) 197 (60), 137 (83), 81 (57), 59 (91), 55 (40), 43 (100), and 41 (42).

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**Registry No.**—I, 1833-53-0; II, 6651-36-1.

(7) Unpublished work with Antonio Hernandez. It was felt that this reaction involved attack of the alcohol at silicon, but this is now being investigated in view of the present findings.

(8) L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Wiley-Interscience, New York, N. Y., 1961, p 191.

(9) L. N. Owen and P. N. Smith, *J. Chem. Soc.*, 4026 (1952).

(10) "Dictionary of Organic Compounds," Vol. II, Eyre and Spottiswoode, London, 1965, p 783.

(11) A. C. Cope, J. C. Heeren, and V. Seeman, *J. Org. Chem.*, **28**, 516 (1963).

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# α-Diazomercurials. Synthesis and Photochemistry

STEVEN J. VALENTY[1] AND PHILIP S. SKELL*

*Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802*

*Received September 30, 1972*

A general synthesis of alkyl- and arylmercuridiazo compounds is described. By selective control of the experimental conditions, either of two novel intermediates may be studied upon photolysis of the diazomercury compound in the liquid phase: monovalent carbon or α-mercuricarbene. The photochemistry of methylmercuridiazoacetate in methanol is briefly stated.

α-Metallodiazo compounds are of current interest owing to their use as (a) intermediates in the synthesis of substituted diazo compounds,[2] (b) precursors to monovalent carbon,[3] and (c) precursors to metalated divalent carbon.[2c,d,3b,4]

$$\underset{\underset{N_2}{\|}}{RCM} \xrightarrow[R'X]{(a)} \underset{\underset{N_2}{\|}}{RCR'} + MX$$

$$\xrightarrow[h\nu]{(b)} RC + N_2 + M$$

$$\xrightarrow[h\nu]{(c)} RCM + N_2$$

Büchner reported the first synthesis of a diazomercurial compound, diethyl mercuribis(diazoacetate) (**1**).[5] Mercuration has since been extended to include many classes of diazo compounds.[2h,6]

$$\underset{\underset{N_2}{\|}}{2HCCOOEt} + HgO \xrightarrow[ether]{0^\circ} \underset{\underset{N_2}{\|}}{Hg(CCOOEt)_2} + H_2O$$

**1**

During the course of preliminary studies with carboethoxycarbyne, as produced by photolysis of **1**, it became evident that the mercuribis(diazo ester) gave several intermediates rendering mechanistic interpretation difficult. The use of monodiazomercury compounds offered to simplify the chemistry found in these photolysis reactions.

**Synthesis of α-Diazomercurials.**—The following one-flask synthesis was devised to prepare alkyl, or arylmercuridiazo compounds.[7]

$$RHgCl \xrightarrow[EtOH]{KOEt} RHgOEt + KCl \xrightarrow[N_2]{HCY} \underset{\underset{N_2}{\|}}{RHgCY} + EtOH$$

The yields of monodiazomercury compound are high (80–99% based on RHgCl) owing to the insolubility of potassium chloride in ethanol. The method is generally applicable to a wide variety of R and Y substituents. Where RHgOH is available, it can be used directly.

$$RHgOH + \underset{\underset{N_2}{\|}}{HCY} \xrightarrow{EtOH} \underset{\underset{N_2}{\|}}{RHgCY} + H_2O$$

In order to assess the effect of the R group upon the photochemistry of α-mercuridiazo compounds, a series of alkyl- and arylmercury derivatives were synthesized from methyl diazoacetate. The mercurials were characterized by mass spectrum, ir, uv, and nmr. Features common to all the mass spectra were the parent (weak–medium intensity), $PN_2$ and RHg ions. The substitution of a mercury atom for the methine hydrogen of methyl diazoacetate increases the wavelength of both the C=$N_2$ and C=O stretch absorptions by *ca.* 0.1 μ in the infrared spectra. The mercuridiazoacetates possess two absorption bands in the ultraviolet (MeOH): 374–377 nm (ε ~44–59) and 268–274 (8600–10,000). The presence of the mercury atom induces a 20–25-nm red shift of the shorter wavelength absorption maximum and reduces the intensity by *ca.* 40%. The position of the long wavelength absorption maximum changes only slightly (2–3 nm) in the same direction but the intensity is increased threefold.

The amount of carbon–mercury bond fragmentation, as indicated by the yield of mercury precipitated during photolysis in olefin, was a function of R group, wavelength of incident light, and temperature, as shown in Table I.

$$\underset{\underset{N_2}{\|}}{RHgCCOOMe} \overset{h\nu}{\rightleftharpoons} \begin{matrix} RHg\ddot{C}COOMe + N_2 \\ R\cdot + Hg + N_2 + \cdot\ddot{C}COOMe \end{matrix}$$

The increase in fragmentation parallels the order of stability of the carbon radicals (R·) produced: methyl < ethyl < phenyl < isopropyl ≲ benzyl < *tert*-butyl. Second, photolysis in the more intense short-wavelength band (253.7 nm) caused the greatest amount of frag-

(1) General Electric Company, Corporate Research and Development Center, Schenectady, N. Y.

(2) (a) F. Gerhart, U. Schöllkopf, and H. Schumacher, *Angew. Chem., Int. Ed. Engl.*, **6**, 74 (1967); (b) U. Schöllkolf, F. Gerhart, M. Reetz, H. Frasnelli, and H. Schumacher, *Justus Liebigs Ann. Chem.*, **716**, 204 (1968); (c) U. Schöllkopf and N. Rieber, *Angew. Chem., Int. Ed. Engl.*, **6**, 884 (1967); (d) U. Schöllkopf, D. Hoppe, N. Rieber, and V. Jacobi, *Justus Liebigs Ann. Chem.*, **730**, 1 (1969); (e) U. Schöllkopf and H. Frasnelli, *Angew. Chem., Int. Ed. Engl.*, **9**, 301 (1970); (f) U. Schöllkopf and N. Rieber, *ibid.*, **6**, 261 (1967); (g) U. Schöllkopf and N. Rieber, *Chem. Ber.*, **102**, 488 (1969); (h) H. Hartzler, Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, p 205P; (i) M. Regitz, *Synthesis*, 351 (1972); (j) M. F. Lappert and J. S. Polland, *Advan. Organometal. Chem.*, **9**, 397 (1970).

(3) (a) T. DoMinh, H. E. Gunning, and O. P. Strausz, *J. Amer. Chem. Soc.*, **89**, 6785 (1967); (b) O. P. Strausz, T. DoMinh, and J. Font, *ibid.*, **90**, 1930 (1968).

(4) (a) U. Schöllkopf, B. Banhidai, and H. U. Scholz, *Justus Liebigs Ann. Chem.*, **761**, 137 (1972); (b) D. Seyferth, H. Menzel, A. W. Dow, and T. C. Flood, *J. Organometal. Chem.*, **44**, 279 (1972); (c) A. G. Brook and P. F. Jones, *Can. J. Chem.*, **49**, 1841 (1971).

(5) E. Büchner, *Ber. Deut. Chem. Ges.*, **28**, 215 (1895).

(6) (a) P. Yates and F. X. Garneau, *Tetrahedron Lett.*, 71 (1967); (b) T. DoMinh, O. P. Strausz, and H. E. Gunning, *ibid.*, 5237 (1968); (c) A. N. Wright, K. A. W. Kramer, and G. Steel, *Nature (London)*, **199**, 903 (1963); (d) R. Scheffold, private communication to P. S. Skell, June 1968; (e) J. Lorberth, *J. Organometal. Chem.*, **27**, 303 (1971); (f) D. Seyferth, R. S. Marmor, and P. Hilbert, *J. Org. Chem.*, **36**, 1379 (1971); (g) M. Regitz, A. Liedenheger, U. Eckstein, W. Martin, and W. Anschütz, *Justus Liebigs Ann. Chem.*, **748**, 207 (1971).

(7) We learned (June 1968) from R. Scheffold, Universite de Fribourg, that he also had developed synthesis of RHgOR′ and that he had employed these reagents for the replacement of active hydrogen atoms in a variety of systems, including diazo compounds.

TABLE I

MERCURY YIELDS OBSERVED IN THE PHOTOLYSES OF ALKYLMERCURIDIAZOACETATES

| $RHgCCOOCH_3$ ‖ $N_2$ | Hg yield, %[a] 253.7 nm[b] | >280 nm | >355 nm |
|---|---|---|---|
| **Alkyl Group Variation** | | | |
| Methyl | ... | ... | 5 |
| Ethyl | 32 | 15 | 12 |
| Phenyl | ... | 17[c] | 7[d] |
| Isopropyl | 41 | 26 | ... |
| Benzyl | ... | 27 | ... |
| *tert*-Butyl | 64[c] | 37 | ... |
| **Temperature Variation** | | | |
| Ethyl (−48°) | ... | ... | 6 |
| Ethyl (−8°) | ... | ... | 8 |
| Ethyl (1°) | ... | ... | 12 |
| Ethyl (14°) | ... | ... | 13 |

[a] At 100% nitrogen evolution in refluxing *trans*-2-butene (1°). [b] Some mercury may also have come from photolysis of the mercury-containing products. [c] In cyclohexene at 14°. [d] In 2-methylpropene at −8°.

mentation with little occurring when only the long-wavelength band was irradiated ($\lambda > 335$ nm). Third, the amount of mercury obtained in a photolysis decreases slightly as the reaction temperature is lowered. Thus, photolysis of methyl methylmercuridiazoacetate with light of wavelength greater than 335 nm had the least amount of carbon–mercury bond fragmentation (*ca.* 5%). The low yield of mercury was maintained as the Y substituent attached to the methylmercuridiazo group was changed (Y = COMe, CN, $CH_3$, Ph) as shown in Table II. These results indicate that nearly

TABLE II

MERCURY YIELDS OBSERVED IN THE PHOTOLYSIS OF $CH_3HgC(=N_2)Y$

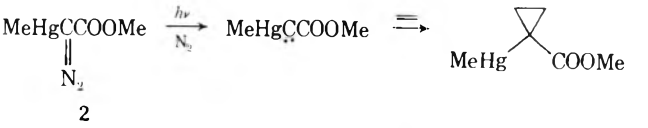
| Y group | Hg yield, %[a] |
|---|---|
| $COCH_3$ ‖ O | 5 |
| $CCH_3$ ‖ O | 4 |
| C≡N | 8 |
| $C_6H_5$ | 9[b] |
| $CH_3$ | 10 |

[a] At 100% nitrogen yield in refluxing 2-methylpropene (−8°), $\lambda > 335$ nm. [b] $\lambda > 400$ nm.

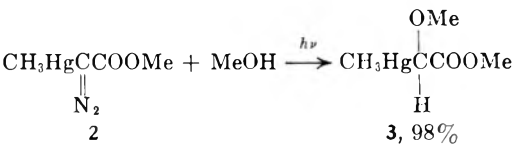
quantitative production of methylmercuricarbene may be obtained upon irradiation of the long-wavelength absorption band of methylmercuridiazo compounds at temperatures below *ca.* 0°. The use of the near-visible light has the further advantage of not causing photodecompositions of the mercury containing products.

The monovalent carbon intermediate resulting from both nitrogen and mercury elimination may be better studied using a *tert*-butylmercuridiazo compound with incident light >280 nm than from the corresponding mercuribisdiazo compound with light of shorter wavelength (~253.7 nm).[8] As a precursor, the *tert*-butylmercuridiazo is superior to the mercuribisdiazo compound since the number of intermediates occurring in its decomposition are reduced and the more ready fragmentation of the carbon–mercury bond allows the use of less energetic light, thus avoiding the photodecompositions of the mercury-containing products.

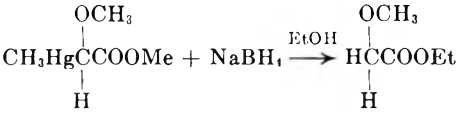
**Photochemistry of Methyl Methylmercuridiazoacetate in Methanol.**—α-Mercuricarbomethoxycarbenes have been shown to react with olefin, yielding cyclopropane almost exclusively, in contrast to non-mercury-containing carbenes which have important competitive pathways of rearrangement and insertion.[9]



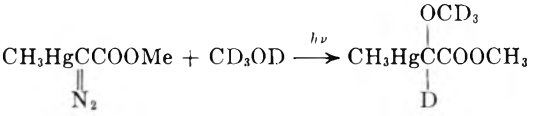
With a similar high selectivity, the photolysis ($\lambda > 335$ nm) of methyl methylmercuridiazoacetate (**2**) in methanol produces a quantitative yield of a single compound, methyl 2-methylmercuri-2-methoxyacetate (**3**).



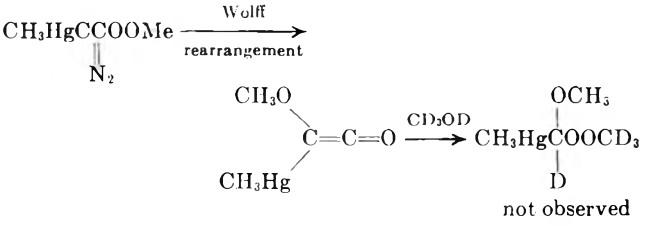
Reduction of methyl 2-methylmercuri-2-methoxyacetate with sodium borohydride in ethanol gives evidence for the position of the carbon–mercury bond. No C–H bond insertion product was detected. Use of methanol-



$d_4$ as substrate for the reaction shows that it is the methyl ether which comes from the alcohol, since the methyl ether proton absorption is absent in the pmr



analysis of the reaction residue. Thus, very little, if any, Wolff rearrangement occurs in the reaction.



Photolysis of mercury-free diazoacetates in alcohol gives rise to products of oxygen–hydrogen and carbon–hydrogen carbene insertion, Wolff rearrangement, and "exchange."[10,11] Thus, the substitution of a mercury

(8) G. J. A. Kennepohl, F. Garneau, T. DoMinh, B. Kim, O. P. Strausz, S. J. Valenty, and P. S. Skell, *J. Amer. Chem. Soc.*, in press.

(9) P. S. Skell and S. J. Valenty, *J. Amer. Chem. Soc.*, **95**, 5042 (1973).

(10) T. DoMinh, O. P. Strausz, and H. E. Gunning, *J. Amer. Chem. Soc.*, **91**, 1261 (1969).

(11) In preliminary experiments, besides the O–H insertion product, a second product was observed (*ca.* 9% yield) in the photolysis of **2** in ethanol which is tentatively identified as ethyl 2-methylmercuri-2-ethoxyacetate on the basis of nmr. This product appears to result from a formal ester exchange as is obtained when methyl diazoacetate is photolyzed in ethanol.[10] Light is required for the exchange, since a "dark" reaction showed no exchange in, or product formation from, the mereuridiazo ester. Further, exchange has been shown not to occur in the products either in the dark or upon irradiation.

atom adjacent to the carbene site enhances the selectivity of the intermediate. Coupled with the nearly quantitative preparation of methylmercuridiazo compounds and this high reaction selectivity, the ready cleavage of the carbon–mercury bond by $NaBH_4$ and electrophilic reagents affords many possibilities for further synthesis.

## Experimental section

**General Information.**—Melting points were determined in a sealed capillary tube using an electrically heated and stirred Thiele-type apparatus and are reported uncorrected. Infrared spectra were obtained with a Beckman IR-5A. Only intense or characteristic absorptions are listed with the position of the maximum reported in microns (μ). Ultraviolet and visible absorption spectra were obtained on solutions in Spectro Grade methanol (1-cm length path) using either a Cary 14 or Cary 15 spectrophotometer. Maxima are reported in wavelength units of nanometers (nm) with the molar extinctions coefficients (ε) following in parentheses. Nuclear magnetic resonance spectra were recorded on a Varian Associates A-60A. The chemical shifts are reported on the δ scale, in parts per million (ppm), downfield from the internal standard tetramethylsilane (TMS). Values of coupling constants (*J* values) are given in hertz (Hz). Low-resolution mass spectra were obtained on an AEI MS-902 instrument. Analysis for covalently bonded mercury was done with a Perkin-Elmer Model 303 atomic absorption spectrometer (AA). Mercurial compounds were analyzed as solutions in 95% ethanol in comparison to standard diphenylmercury solutions. It is to be noted that reproducible and accurate results were obtained only when using the lower temperature flame afforded by a hydrogen (7.0 psi)–argon (9.0 psi)–entrained air mixture in place of the standard acetylene–air mixture.

**Alkylmercuric Halides.**—Alkylmercuric bromides were obtained from the reactions of the corresponding alkyl Grignard reagent with mercuric bromide. The *tert*-butylmercuric chloride was formed from the reaction of *tert*-butyllithium with mercuric chloride. Methylmercuric chloride was used as obtained from Alfa Inorganics, Inc. The alkylmercuric halides were characterized by comparison of their melting points with those reported in the literature and by nmr and mass spectrum.

**Alkylmercuric Ethoxides.**—Alkylmercuric ethoxides were made *via* a two-step synthesis from the corresponding potassium ethoxide and alkylmercuric nitrate which, in turn, was obtained by treating alkylmercuric chloride with silver nitrate in absolute ethanol. The mercuri alkoxides are strong vesicants and must be handled with care. The procedure for methylmercuric ethoxide is typical.

**Methylmercuric Ethoxide.**—Methylmercuric chloride (40.0 mmol, 10.0 g) was added to 150 ml of absolute ethanol freshly distilled from magnesium ethoxide in a foil-wrapped, flame-dried, and nitrogen-purged 250-ml three-necked flask. After the solution was stirred for *ca.* 15 min at 60°, powdered silver nitrate (40.0 mmol, 6.80 g) was added in one portion and the solution was allowed to stir for 3 hr at 60° before suction filtering while hot. After the solid was washed with hot ethanol (3 × 10 ml) and dried, 5.65 g (39.5 mmol, 98.8%) of silver chloride was obtained. The clear, colorless filtrate was returned to the same reaction flask. Cleaned potassium metal (40.0 mmol, 1.56 g) was added in portions to 40 ml of absolute ethanol in a 75-ml dropping funnel (attached to the reaction flask and topped by a water condenser). The potassium ethoxide–ethanol solution was added dropwise to the clear methylmercuric nitrate solution at room temperature, causing a white precipitate to form immediately. After completion of the addition, the solution was allowed to stir for an additional 30 min at room temperature before suction filtering the white solid under nitrogen atmosphere. After the solid was washed with ethanol (2 × 10 ml) and dried, 4.08 g (40.4 mmol, 101%) of potassium nitrate was obtained. The clear, colorless filtrate was evaporated to dryness on a rotary evaporator, using little external heating in the final stages, leaving an off-white, powdery solid. This solid was stirred with hot absolute ether and suction filtered. Additional washes of hot ether were added, stirred with the solid, and the solution was suction filtered until the amount of remaining solid did not appear to decrease. The ethereal solution was evaporated on the rotary evaporator with no external heating, leaving a grayish-white semisolid of methylmercuric ethoxide (9.20 g, 35.4 mmol, 88.5%): mp 24–25°; nmr ($CDCl_3$) δ 1.00 (s, symmetrically disposed $^{199}Hg$–$^1H$ doublet, $J$ = 145 Hz, 3 H), 1.23 (t, $J$ = 7 Hz, 3 H), 3.72 (q, $J$ = 7.0 Hz, 2 H); AA (95% EtOH) mol wt, theory 260, found 264; mass spectrum (70 eV, $^{200}Hg$) *m/e* 260 (very weak), 215, 200, 45 (very strong), 44. *Caution: strong vesicant.*

**Diazo Compounds. Warning.**—By their nature, diazo compounds are thermally unstable and sensitive to conditions where a local temperature rise may cause explosion. Although a wide variation in stability is noted when functional groups are changed in the simple diazo compounds, the safest procedure is to prepare, store, and use the diazo compound in an excess of solvent which will not interfere in later chemical reactions. In this study, explosions have occurred when methyl diazoacetate and diazoacetone were inadvertently heated to >150° at 1 atm. A most violent detonation occurred at room temperature when a drop from a 5-g sample of neat diazoacetonitrile was being removed with a fire-polished glass stirring rod. This sample had been handled often over a two-week period before the explosion occurred, indicating the unpredictable nature of pure diazo compounds.

The diazo compounds were prepared and characterized according to literature procedures: diazomethane,[12] diazoethane,[13] methyl and ethyl diazoacetate,[14] diazoacetone,[15] phenyldiazomethane,[16] and diazoacetonitrile.[17]

**α-Mercuridiazo Compounds. Warning.**—In general, the thermal stability of the mercury derivative parallels that of the parent diazo compound. The only explosion noted with this class of compounds occurred when bis(methylmercuridiazomethane) was isolated as a dry solid at room temperature. *Considering the toxic, light sensitive, and potentially explosive nature of these compounds, the routine use of gloves, shielding, and subdued light is required.*

**Methyl Methylmercuridiazoacetate** (2).—The synthesis of this compound is typical for the preparation of alkylmercuridiazo esters. Methylmercuric chloride (110 mmol, 27.6 g), stirred in 600 ml of absolute ethanol at 60°, was treated directly with alcoholic potassium ethoxide (110 mg-atoms, 4.3 g, of clean potassium metal in 50 ml of absolute ethanol). After 4 hr of additional stirring at 60°, the potassium chloride was filtered and washed with ethanol. Methyl diazoacetate (108 mmol, 10.8 g) was added dropwise to the clear filtrate cooled to 0°. The solution was stirred for 15 min following the completion of the addition, and the ethanol was removed with the rotary evaporator. The yellow solid residue was dissolved in refluxing dry ether (freshly distilled from lithium aluminum hydride) and gravity filtered through a fine filter. After the ether was removed on the rotary evaporator, a powder, yellow solid remained which was used without further purification (93.0 mmol, 29.2 g, 86% based on diazo ester): mp 71–72°; ir ($CCl_4$) 4.85 (C=$N_2$), 6.02 (C=O), 7.9, 8.5 μ; nmr ($CCl_4$) δ 0.83 (s, symmetrically disposed $^{199}Hg$–$^1H$ doublet, 150 Hz, % $^{199}Hg$ ~20, 3 H), 3.68 (s, 3 H); uv (MeOH) 377.0 nm (ε 44), 269.0 (10,000); mass spectrum (70 eV, $^{200}Hg$) *m/e* 314, 286, 283, 243, 215, 200.

**Methyl ethylmercuridiazoacetate** (91% yield) was a yellow oil: ir (neat) 4.85 (C=$N_2$), 6.00 (C=O), 7.8 and 8.5 (conjugated ester), 13.60 μ; nmr ($CCl_4$) δ 1.0–1.8 (m, 5 H), 3.68 (s, 3 H), low-field portion of $^{200}Hg$–$C^1H_2$ coupling centered at 3.0; uv (MeOH) 377.0 nm (ε 50), 272.0 (9410); mass spectrum (70 eV, $^{200}Hg$) *m/e* 328, 300, 257, 229, 200.

**Methyl isopropylmercuridiazoacetate** (97% yield) was a yellow oil: ir (neat) 4.82, 6.01, 7.90, 8.40, 13.5 μ; nmr ($CCl_4$) δ 1.50 (d, $J$ = 7.0 Hz, with symmetrically disposed pair of two doublets, $J_{^{199}Hg-C^1H_3} \cong 194$ Hz, % $^{199}Hg$ = 15, $J_{^1H-^1H}$ = 7.0–7.5 Hz, 6 H), 2.80 (m, 1 H), 3.65 (s, 3 H); uv (MeOH) 376.0 nm (ε 53), 274.0 (8630); mass spectrum (70 eV, $^{200}Hg$) *m/e* 342, 314, 243, 228, 214, 200, 43.

**Methyl *tert*-butylmercuridiazoacetate** (93% yield) was a viscous, yellow oil unstable at 0°: ir (neat) 4.85, 6.0–6.1, 7.8, 8.4, 13.6 μ; nmr ($CCl_4$) δ 1.48 (s, with symmetrically disposed $^{199}Hg$–$^1H$ doublet, $J$ = 173 Hz, % $^{199}Hg$ = 18.6, 10 H), 3.67 (s, 3 H); mass spectrum (70 eV, $^{200}Hg$) *m/e* 356, 328, 300, 200, 57; uv not recorded.

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**Methyl benzylmercuridiazoacetate** (73% yield) was a yellow oil: ir (neat) 4.81, 6.0, 7.75, 8.4, 13.5, 13.15, and 14.35 μ (monosubstituted benzene); nmr ($CCl_4$) δ 2.76 (s, with symmetrically disposed $^{199}Hg$–$^1H$ doublet, $J$ = 192 Hz, % $^{199}Hg$ = 15, 2 H), 3.61 (s, 3 H), 7.08 (m, 5 H); uv (MeOH) 375.5 nm (ε 59), 271.5 (sh, 9080), 250.5 (19,000); mass spectrum (70 eV, $^{200}Hg$) $m/e$ 390, 291, 200, 91.

**Ethyl methylmercuridiazoacetate**[18] (84% yield) was obtained as brilliant yellow needles from $Et_2O$: mp 31–33°; ir ($CCl_4$, $CS_2$) 4.84, 5.99, 7.87, 8.30, 8.49, 9.47, 13.6 μ; nmr ($CDCl_3$) δ 0.80 (s, with symmetrically disposed $^{199}Hg$–$^1H$ doublet, $J$ = 152 Hz, % $^{199}Hg$ = 16.9, 3 H), 1.25 (t, $J$ = 7.0 Hz, 3 H), 4.15 (q, $J$ = 7.0 Hz, 2 H); uv (MeOH) 377 nm (ε 47.7), 269 (11,000); mass spectrum (70 eV, $^{200}Hg$) $m/e$ 328, 300, 283, 215, 200.

Alkyl phenylmercuridiazoacetates were also prepared in an alternative manner by treating phenylmercuric hydroxide with the diazo ester. The following synthetic procedure is typical.

**Methyl Phenylmercuridiazoacetate.**—Methyl diazoacetate (30 mmol, 3.0 g) was dissolved in 50 ml of dry ether and cooled to 0°. Phenylmercuric hydroxide (30 mmol, 8.82 g, Alfa Inorganics) was added in small portions over a period of 60 min. After the addition was completed, the reaction was allowed to stir for 2 hr. The ethereal solution was filtered and concentrated to *ca.* 20 ml with the rotary evaporator, *n*-pentane was added until the solution became cloudy and the solid crystallized at −5°. After suction filtration and drying at room temperature on the filter, an 84% yield of a pale yellow powder was obtained (25.3 mmol, 7.5 g): mp 82–84°; ir ($CCl_4$) 4.85, 5.95, 7.9, 8.4 μ; nmr ($CCl_4$) δ 3.69 (s, 3 H), 7.29 (broadened s, symmetrically placed $^{199}Hg$–$^1H$ broadened doublet, $J$ = 144 ± 10 Hz, 5 H); uv (MeOH) 376.5 nm (ε 59), 268.0 (10,200); mass spectrum (70 eV, $^{200}Hg$) $m/e$ 376, 354, 348, 305, 277, 200.

**Ethyl phenylmercuridiazoacetate** (84% yield) was a yellow oil: ir (neat) 4.85, 6.1 (broad), 7.86, 8.4, 13.6 (sh), 13.8, and 14.4 μ (monosubstituted benzene); nmr ($CCl_4$) δ 1.18 (t, $J$ = 7.0 Hz, 3 H), 4.08 (q, $J$ = 7.0 Hz, 2 H), 7.28 (broadened s, with symmetrically disposed $^{199}Hg$–$^1H$ multiplet, $J$ = 140 ± 10 Hz, 5 H); mass spectrum and uv not recorded.

**Methylmercuridiazoacetone** was prepared from methylmercuric ethoxide and diazoacetone as outlined previously for methyl methylmercuridiazoacetate in 66–79% yield. The reaction was also produced a small amount of a red-yellow solid insoluble in dry ether which might have arisen from a competing mercuration of the carbon adjacent to the carbonyl function. The mercuridiazo compound was characterized as follows: pale yellow solid from ether; mp 94.5–96.0° dec; ir ($CCl_4$, $CS_2$) 4.86, 6.14, 8.47, 12.73, 13.08 μ; nmr ($CCl_4$) δ 0.87 (s, with symmetrically placed $^{199}Hg$–$^1H$ doublet, $J$ = 152 Hz, % $^{199}Hg$ = 12, 3 H), 2.20 (s, 3 H); uv (MeOH) 360.0 nm (ε 71.3), 288.0 (8580), 232.5 (7280); mass spectrum (70 eV, $^{200}Hg$) $m/e$ 298, 270, 215, 200, 43; AA (95% EtOH) mol wt, theory 298, found 304.

**Phenylmercuridiazoacetone** was prepared in methylene chloride at 0° from phenylmercuric hydroxide and diazoacetone as outlined for the synthesis of methyl phenylmercuridiazoacetate: 85% yield; pale yellow powder from $CH_2Cl_2$; mp 119–120° dec; ir ($CCl_4$, $CS_2$) 4.88, 6.18, 7.78, 13.84, 14.44 μ; nmr ($CDCl_3$) δ 2.26 (s, 3 H), 7.36 (broadened s, 5 H) with symmetrically disposed $^{199}Hg$–$^1H$ multiplet ($J_{^{199}Hg-^1H} \cong$ 140 Hz); uv (MeOH) 366 nm (ε 79.6), 288 (8350); mass spectrum (70 eV, $^{200}Hg$) $m/e$ 360 (weak), 332, 277, 200, 77.

**Methylmercuridiazoacetonitrile** was prepared from methylmercuric ethoxide and diazoacetonitrile as outlined for methyl methylmercuridiazoacetate with some modification. After an ethanolic solution of methylmercuric ethoxide (20 mmol) was obtained, the ethanol was removed on the rotary evaporator. The residue was slurried with methylene chloride (20 ml) and added dropwise to a 0.1 *M* diazoacetonitrile solution in methylene chloride (200 ml) stirring at −78° under nitrogen atmosphere. The amber-colored methylene chloride solution was assumed to contain a 100% yield of methylmercuridiazoacetonitrile (0.091 *M*), stored at −78° and used without further purification. A low yield of amber crystals could be obtained upon concentration of a small volume of solution and purified by recrystallization from ether at −10°: mp 107–108° dec; ir ($CCl_4$, $CS_2$) 4.57 (C≡N stretch), 4.86 (C=$N_2$ stretch), 7.98, 12.80, 13.12 μ; nmr ($CDCl_3$) δ 0.95 (s with symmetrically placed $^{199}Hg$–$^1H$ doublet, $J$ = 165 Hz, % $^{199}Hg$ = 15.7); uv (MeOH) 400 nm (65.1), 262 (9370), 208 (21,600); mass spectrum (70 eV, 8 eV, $^{200}Hg$) $m/e$ 281, 253, 215, 200; AA (95% EtOH) mol wt, theory 281, found 289.

**Methylmercuriphenyldiazomethane** was prepared from methylmercuric ethoxide and phenyldiazomethane at −78°. An ethanolic solution of methylmercuric ethoxide (1.0 *M*, 10 ml) was added dropwise over a period of 5 min to a stirring solution of phenyldiazomethane in ethanol (12 mol, 1.4 g in 10 ml) cooled at −78° and stirred for 30 min following completion of the addition. The ethanol was removed at reduced pressure (<5 mm), and the red sludge was taken up in dry ether and gravity filtered. After crystallization at −10°, blood-red crystals (7.5 mmol, 2.5 g, 75%) were obtained following suction filtration, *n*-pentane wash, and rapid vacuum drying at room temperature and must be stored at −78°. Spectral data: ir ($CCl_4$) 2.92, 4.97, 7.74, 8.61, 14.57, 15.00 μ; nmr ($CDCl_3$, −35°) δ 0.79 (s, with symmetrically placed $^{199}Hg$–$^1H$ doublet, $J$ = 145 Hz, % $^{199}Hg$ = 16.2, 3 H), 7.17 (m, 5.6 H); uv (MeOH) 477 (31), 273 (7700), 260 (7360), ~215 (11,000, end absorption); mass spectrum (10 eV, $^{200}Hg$) $m/e$ 332, 304, 89; AA (95% EtOH) mol wt, theory 332, found 356 ± 6. All spectra indicate presence of some phenyldiazomethane impurity.

**Methylmercuridiazoethane** was synthesized from methylmercuric ethoxide and diazoethane at −63°. The low-temperature recrystallization vessel used in this preparation consisted of a Pyrex tube (i.d. ~40 mm) divided into two chambers of 60-ml capacity each by a medium porosity fritted glass filter. The top chamber was surmounted by a 60-ml pressure-equilibrated dropping funnel which in turn was attached to a nitrogen gas–oil bubbler. The bottom chamber was closed at its end but had a separate opening on the side just below the frit which led to a glass tube to a height approximately equal to that of the joint on the top chamber. The apparatus was flushed with nitrogen by applying a positive pressure through the side arm to the lower chamber and flame dried before cooling to −63° (chloroform–liquid nitrogen slush). Isolated methylmercuric ethoxide (11.0 mmol) was dissolved in ~15 ml of absolute ether (freshly distilled from lithium aluminum hydride) and added to the dropping funnel. The positive nitrogen pressure to the bottom chamber was adjusted such that a gentle agitation occurred. Diazoethane in ether (20.2 ml, 0.642 *M*) was then added to the top chamber and allowed to cool to −63°. The ethoxide–ether solution was added over a period of *ca.* 20 min. Since some red crystals precipitated from the deep red-orange solution, the reaction vessel was placed in a −45° bath (chlorobenzene–liquid nitrogen slush) and these crystals were dissolved with vigorous agitation. The reaction mixture was force filtered into the lower chamber by applying a positive pressure to the top, leaving a fine gray layer on the frit. The red-orange solution (−45°) was poured out of the vessel through the side arm of the lower chamber into a tared photolysis vessel cooled at −63° under a nitrogen atmosphere. Crystallization of the red solid began at this temperature and was completed at −78° (60 min) and −120° (30 min). After the orange supernatant (−120°) was poured off, the remaining crystals were washed with 10 ml of trichlorofluoromethane at −78° and excess solvent was removed by evacuation at −45° (<1 mm) for a short time. The reaction vessel was quickly reweighed and the weight of the red crystals obtained was 2.1 g (7.8 mmol, 71% yield based on ethoxide). The mercuridiazoethane is thermally unstable at >−45° and should be stored at −78°. Spectral data: ir ($CFCl_3$), 4.98 μ (C=$N_2$ stretch); nmr ($CDCl_3$, −45°) δ 0.72 (s, with symmetrically placed $^{199}Hg$–$^1H$ doublet, $J$ = 138 Hz, % $^{199}Hg$ = 13, 1.0 H), 2.16 (s, 0.8 H); uv ($Et_2O$, −57°, partial) 465 (10–20), low point in valley between short- and long-wavelength absorptions is at 355 nm.

**Bis(methylmercuridiazomethane)** was prepared from methylmercuric ethoxide and diazomethane in absolute ether at −96°.[19] The same general reaction procedure and apparatus described for the preparation of methylmercuridiazoethane was used here with some modification. A solution of methylmercuric ethoxide (5.0 mmol) in absolute ether (10 ml) was added slowly to a gas-agitated solution containing an excess of diazomethane (5.0 mmol in 20 ml of $Et_2O$) in the vessel's top chamber at −96° (acetone–liquid nitrogen slush). A brilliant yellow solid formed immediately. The reaction was agitated for 10 min following the completion of the addition and then allowed to stand without agitation for 30 min before pressure filtering the solution through the frit. The clear, yellow filtrate was poured out through the

(18) This compound has also been prepared by an alternative route.[6c]

(19) This compound has also been prepared by alternative routes.[6c,7]

side arm, the solid was washed once with ether, and the side arm was closed off with a clamped gum rubber hose. The reaction vessel was evacuated (<1 mm) and warmed to −45° for 15 min. The bright yellow crystals were transferred to a tared vial at −78° and weighed (2.42 mmol, 1.14 g, 96.8% based on ethoxide), mp 99–100° (lit.[6e] mp 98–100°). The solid decomposes rapidly at room temperature and a sample exploded when left on the bench to dry. It is best stored moist with reaction solvent at −78°. At 0°, bis(methylmercuridiazomethane) is insoluble or only slightly soluble in $CHCl_3$, $CCl_4$, $CFCl_3$, DME, $CH_3NO_2$, and *p*-dioxane, slightly more soluble in $Et_2O$, and moderately soluble in DMF and pyridine. Spectral data: ir ($CCl_4$–pyridine) 5.05 μ (C=$N_2$ stretch); nmr ($CDCl_3$, −20°) δ 0.75 (s, with symmetrically disposed $^{199}$Hg–$^1$H doublet, $J$ = 136 Hz; nmr (acetone-$d_6$, −10°) 0.54 (s, 150 Hz), (pyridine, −35°) 0.52 (s, 146 Hz, % $^{199}$Hg = 15); mass spectrum (70 eV, 20 eV, $^{200}$Hg) 442 (parent −$N_2$), 427, 230, 215, 200, no molecular ion at 470; micro $N_2$ analysis, mol wt observed 466 ± 4, theory 470. In several reactions, yellow or yellow-green crystals melting at 82–85° were obtained as well as yellow crystals melting at 99–100°. Both sets of crystals had the same nmr and ir (C=$N_2$) absorptions.

**Monomethylmercuridiazomethane** could not be synthesized by these methods. In the many attempts to prepare this compound, only bis(methylmercuridiazomethane) was isolated. Two typical preparation attempts are presented below.

Methylmercuric ethoxide (5.0 mmol) in absolute ethanol (20 ml) was added very slowly over a 50-min period to excess diazomethane (50.0 mmol, 88 ml of a 0.569 *M* solution in ether) cooled to −96° under a nitrogen atmosphere. A bright yellow solid (1.5 g) was obtained following suction filtration, washing with −96° ether (twice), and vacuum drying (−45°, 1 mm): mp 83–85°; ir (pyridine) 5.07 (C=$N_2$ stretch); nmr (pyridine, −35°) δ 0.52 (s, with symmetrically placed $^{199}$Hg–$^1$H doublet, 146 Hz, % $^{199}$Hg = 20); micro $N_2$ analysis, mol wt 466 (two determinations). Thus, the product was identical with bis(methylmercuridiazomethane).

Methylmercuric ethoxide (5.0 mmol) in absolute ethanol (20 ml) was added slowly to an equimolar amount of diazomethane (5.0 mmol, 8.58 ml of a 0.583 *N* solution in ether) cooled at −96°. A bright yellow solid [1.14 g, 2.42 mmol, 48.8% yield for bis(methylmercuridiazomethane) based on diazomethane] was obtained following suction filtration, washing with −96° ether, and vacuum drying (−45°, 1 mm). The yellow filtrate and ether wash were distilled into a cooled receiver (−110°) at reduced pressure until there was no yellow coloration remaining in the pot. The yellow solution in the receiver was treated with a known amount of benzoic acid and back titrated with standardized sodium hydroxide. Diazomethane was recovered in 42% yield (2.10 mmol).

**Photolysis of Methyl Methylmercuridiazoacetate in Methanol.**—2 (10.0 mmol, 3.14 g) was dissolved in absolute methanol (250 ml distilled from magnesium methoxide) and photolyzed for 80 min at 13–14° with the soft glass-filtered light of a 1000-W A-H6 high-pressure Hg lamp. Nitrogen gas (10.4 mmol, 100 + %) and elemental mercury (0.0342 g, 0.017 mg-atom, 1.7%) were evolved. After distillation of the volatiles (80–100 mm, 25°), a heavy, yellow-brown oil remained (3.12 g). Quantitative nmr analysis of the methylmercury and methyl ester region indicate a *ca.* 100% yield of only one compound, **3**. The compound has the following spectral characteristics: nmr ($CDCl_3$) δ 0.65 (s, with symmetrically placed $^{199}$Hg–$^1$H doublet, $J$ = 124 Hz, % $^{199}$Hg = 17, 3 H), 3.49 (s, 3 H), 3.78 (s, with symmetrically placed $^{199}$Hg–$^1$H doublet, 5 Hz, 3 H), 4.08 (s, with symmetrically placed $^{199}$Hg–$^1$H doublet, 137 Hz, 1 H); nmr (100 MHz, $CDCl_3$) δ 0.63 (s, $^{199}$Hg–$^1$H doublet, 125 Hz), 3.46 (s), 3.74 (s, with shoulders), 4.04 (s, $^{199}$Hg–$^1$H doublet, 137 Hz), the methylmercury absorption at δ 0.65 appears to be composed of two closely spaced signals; ir (neat) 3.42, 5.86, 6.98, 7.49, 7.99, 8.55, 9.10, 10.67, 11.04, 12.83 μ; mass spectrum (70 eV, $^{200}$Hg) *m/e* 318, 303, 259, 215, 200.

The addition of sodium borohydride (6.0 mmol, 0.23 g) to a portion of the oil (3.00 mmol, 0.95 g) dissolved in *ethanol* gave an exothermic reaction precipitating elemental mercury (1.91 mg-atom, 0.382 g, 64%). Quantitative glc analysis (Auto-Prep, Carbowax 1000, 12.5 ft × 0.25 in., 116°, 115 ml/min He) of the residue left after solvent distillation at 1 atm showed only the presence of ethyl methoxyacetate (1.28 mmol, 43%). Ethyl methoxyacetate was prepared independently by the reaction of methoxyacetyl chloride and absolute ethanol.

The postphotolysis solution of a small amount of methyl methylmercuridiazoacetate (0.25 mmol, 0.0792 g) in methanol-$d_4$ (1.0 g, 0.8 ml) gave an nmr spectrum in which the methyl ether (δ 3.49) and methine (δ 4.08) singlets are absent. It is interesting to note that the methyl ester absorption (δ 3.78) is not a singlet but a multiplet with an intensity pattern very similar to that of the partially deuterated methanol-$d_4$ methyl pattern (δ 3.37). Upon addition of the product obtained from the photolysis in methanol-$h_4$, the singlet absorption at δ 3.49 "grew" in while the central absorption of the methyl ester multiplet increased in amplitude as did the methylmercury singlet.

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**Registry No.**—**2**, 41580-12-5; **3**, 41580-13-6; methylmercuric ethoxide, 41580-14-7; methylmercuric chloride, 115-09-3; methyl diazoacetate, 6832-16-2; methyl ethylmercuridiazoacetate, 41580-16-9; methyl isopropylmercuridiazoacetate, 41580-17-0; methyl *tert*-butylmercuridiazoacetate, 41580-18-1; methyl benzylmercuridiazoacetate, 41580-19-2; ethyl methylmercuridiazoacetate, 31787-45-8; methyl phenylmercuridiazoacetate, 41580-21-6; phenylmercuric hydroxide, 100-57-2; ethyl phenylmercuridiazoacetate, 41580-22-7; methylmercuridiazoacetone, 41580-23-8; diazoacetone, 2684-62-0; phenylmercuridiazoacetone, 41580-24-9; methylmercuridiazoacetonitrile, 41580-25-0; diazoacetonitrile, 13138-21-1; methylmercuriphenyldiazomethane, 41580-27-2; phenyldiazomethane, 766-91-6; methylmercuridiazoethane, 41580-28-3; diazoethane, 1117-96-0; bis(methylmercuridiazomethane), 31787-47-0; diazomethane, 334-88-3.

# Synthesis of Certain Cyclopropylpyridines

ROBERT LEVINE* AND GEORGE R. PATRICK[1]

*Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260*

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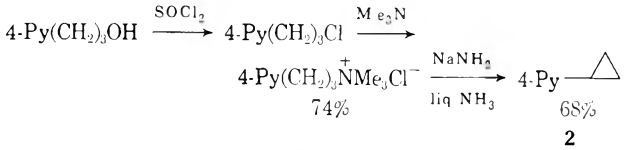
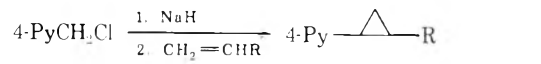
A series of cyclopropylpyridines has been prepared by a new route and their possible participation in nucleophilic ring-opening reactions has been investigated.

Prior to our work the synthesis of 2- and 4-cyclopropylpyridine as well as certain of their ring-substituted derivatives had been reported.[2,3] Mariella, *et al.*,[2] prepared 2-cyclopropylpyridine (1) *via* a six-step process in a 3% overall yield starting with methyl cyclopropyl ketone. Since doubt was expressed[3] as to whether **1** had actually been obtained, an unequivocal synthesis of crude **1** (54%) from 2-(2-pyridyl)-1,3-propanediol was subsequently reported.[4] 4-Cyclopropylpyridine (**2**) has been prepared[3] by the following route.



4-Py = 4-pyridyl group

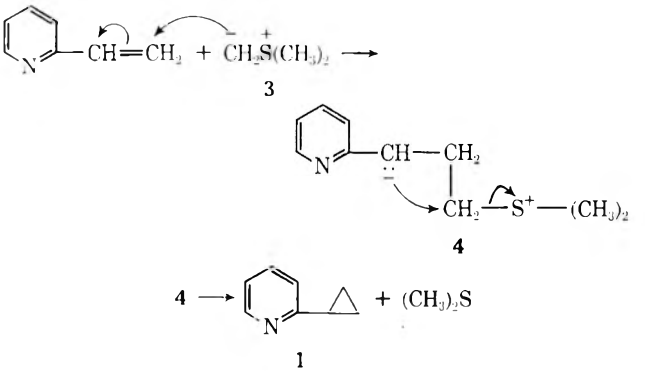
Several 2- and 4-cyclopropylpyridine derivatives have also been reported. Burger, *et al.*,[5] obtained 2-(2-carbethoxycyclopropyl)pyridine (63%) from 2-vinylpyridine and ethyl diazoacetate. More recently[3] a series of 4-cyclopyridine derivatives has been prepared.



R = $CO_2CH_3$ (54%), $CO_2C_2H_5$ (60%), CN (18%)

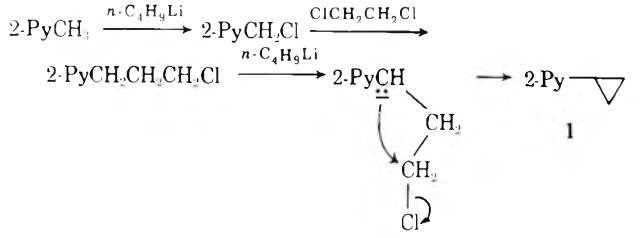
We now report a different route to **1** and **2**, the previously reported 2- and 4-cyclopropylpyridines, and other related systems which are apparently not reported in the literature. Previously, Corey and Chaykovsky[6] observed that dimethylsulfonium methylide (**3**) reacts with activated olefins to give cyclopropanes. Thus, **3** reacts with 1,1-diphenylethylene to give 1,1-diphenylcyclopropane (60%).[6] We have found that **3** reacts with a variety of 2- and 4-vinylpyridines to give the corresponding cyclopropanes (40–91%). Of all the vinylpyridines studied apparently the olefinic bond of only 3-methyl-5-vinylpyridine is too inactive to react with **3**. The cyclopropanes which were prepared appear in Table I.

The reaction of **3** with the 2- and 4-vinylpyridine systems can be envisioned as a Michael-type condensation[7] to give an intermediate carbanion **4**, which



undergoes an intramolecular displacement on carbon with the loss of dimethyl sulfide and the formation of the cyclopropane ring.

Two other methods were attempted as possible routes to cyclopropylpyridines. The Simmons–Smith[8,9] type reaction involving 2-vinylpyridine, methylene bromide, and a zinc–copper couple failed to give any 2-cyclopropylpyridine. The reaction of 1 equiv of 2-picoline and 1,2-dichloroethane with 2 equiv of *n*-butyllithium in THF gave a very low yield (5.3%) of 2-cyclopropylpyridine (**1**), apparently as shown.



2-Py = 2-pyridyl group

Certain activated cyclopropanes, *e.g.*, 1,1-dicarbethoxy-[10] and 1-cyano-1-carbethoxycyclopropane,[11] are susceptible to nucleophilic ring opening. Therefore, it was of interest to determine whether a pyridyl substituent could sufficiently activate cyclopropane so that it would undergo nucleophilic ring opening.

When 4-cyclopropylpyridine was treated with sodiomalonic ester and *n*-butyllithium, ring opening did not occur. The former reaction gave only recovered starting materials, while the latter reaction gave 2-*n*-butyl-4-cyclopropylpyridine (65%), which apparently arises from the addition of *n*-butyllithium to the azomethine linkage of the pyridine ring followed by the loss of lithium hydride. The fact that azomethine addition rather than ring opening occurred may have some interesting synthetic overtones.

(1) Based on the thesis submitted by G. R. P. to the graduate faculty of the University of Pittsburgh in partial fulfillment of the requirements for the Ph.D. degree.

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(6) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).

(7) See, for example, the reaction of 2-vinylpyridine with nucleophiles as reported by M. H. Wilt and R. Levine, *J. Amer. Chem. Soc.*, **74**, 342 (1952); **75**, 1368 (1953).

(8) H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, **81**, 4256 (1959).

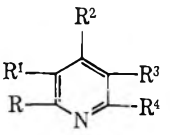
(9) E. LeGoff, *J. Org. Chem.*, **29**, 2048 (1964).

(10) R. W. Kierstad, R. P. Linsted, and B. C. L. Weedon, *J. Chem. Soc.*, 3616 (1952).

(11) J. E. Dolfini, K. Menish, P. Corliss, R. Cavanaugh, S. Danishefsky, and S. Chakrabartty, *Tetrahedron Lett.*, **No. 37**, 442 (1966).

TABLE I

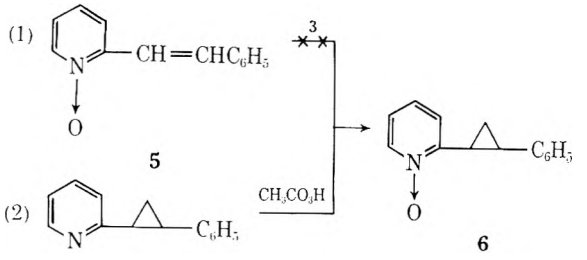
CYCLOPROPYLPYRIDINES AND THEIR *N*-OXIDES



| Registry no. | Compd[a] | R | R¹ | R² | R³ | R⁴ | Bp, °C (mm) | Yield, % | Picrate[a] mp, °C | Picrate registry no. |
|---|---|---|---|---|---|---|---|---|---|---|
| 20797-87-9 | 1 | H | H | H | H | c-$C_3H_5$ | 67–70 (20)[b] | 40.0 | 129.4–130.7 | 41764-98-1 |
| 4904-21-6 | 2 | H | H | c-$C_3H_5$ | H | H | 74–76 (6) | 65.4 | 170.8–171.8[c] | |
| 41765-00-8 | 3 | $CH_3$ | H | H | H | c-$C_3H_5$ | 82–83 (20)[d] | 78.0 | 154.8–156.2 | 41765-01-9 |
| 41765-02-0 | 4 | H | $C_2H_5$ | H | H | c-$C_3H_5$ | 107 (19)[e] | 65.0 | 135.1–135.6 | 41864-64-6 |
| 41765-03-1 | 5 | H | H | c-$C_3H_4$Ph | H | H | 200–202 (20) | 81.0 | 173.6–175.2 | 41765-04-2 |
| 41764-76-5 | 6 | H | H | H | H | c-$C_3H_4$Ph | 175–177 (14)[f] | 70.0 | 201–202.4 | 41764-77-6 |
| 41764-78-7 | 7 | H | H | c-$C_3H_4$Ph | $CH_3$ | H | 139.5–141 (0.5) | 91.0 | 146.6–148.4 | 41764-79-8 |
| 41764-80-1 | 8 | H | H | H | $CH_3$ | c-$C_3H_4$Ph | 133.5–135 (0.7)[g] | 58.0 | 202–203 | 41764-81-2 |
| 41764-82-3 | 9[h] | | | | | | 163.4–164.6[k] | 65.8 | | |
| 41764-83-4 | 10[i] | | | | | | 75–77[k] | 38.4 | | |
| 41764-84-5 | 11[j] | | | | | | 112–8–113.8[k] | 52.2 | | |

[a] Satisfactory analytical data (±0.4% for C and H for the compounds and N for the picrates) were obtained for all the compounds listed in the table. [b] The product was shown to be a mixture of vinylpyridine and 1. The yields were determined by glc, which showed that the product was either a pure cyclopropylpyridine or a mixture of cyclopropylpyridine and recovered pyridylalkene. [c] This is a hydrochloride, lit.[3] mp 170.0–171.0°. [d] Glc showed the product to be a mixture of 2-methyl-6-vinylpyridine and 3. [e] Glc showed the product to be a mixture of 2-vinyl-5-ethylpyridine and 4. [f] Glc showed the product to be a mixture of 2-styrylpyridine and 6. [g] Glc showed the product to be a mixture of 3-methyl-2-styrylpyridine and 8. [h] This is the *N*-oxide of compound 2. [i] This is the monohydrate of the *N*-oxide of compound 5. [j] This is the *N*-oxide of compound 6. [k] Melting point.

The failure of 4-cyclopropylpyridine to undergo nucleophilic ring opening prompted the investigation of an *N*-oxide in such a reaction, since the NO group can act as an electron acceptor.[12] Two possible routes to cyclopropylpyridine *N*-oxides were examined.




It was found that when 2-styrylpyridine *N*-oxide (**5**) was treated with **3** (route 1) none of the desired 1-phenyl-2-(2-pyridyl)-cyclopropane *N*-oxide (6) was obtained using THF as a reaction medium and only a 3.5% yield was obtained in DMSO. By contrast, route 2 (the peracetic acid oxidation of preformed pyridylcyclopropanes) gave fair to good yields of **6** (52.2%) and two other derivatives (Table I, compounds 9–11).

However, refluxing an ethanolic mixture of **6** and sodiomalonic ester for 29 hr gave a quantitative recovery of starting materials. Apparently the *N*-oxide function is not a powerful enough activator to assist in the cyclopropane ring opening, at least with this nucleophile.

## Experimental Section

**Starting Materials.**—The 2-methyl-5-vinylpyridine was supplied through the courtesy of Phillips Petroleum Co., Bartlesville, Okla., while the 2- and 4-picoline, 2,3- and 2,4-lutidine, 2- and 4-vinylpyridine, 2-methyl-6-vinylpyridine, and 2-vinyl-5-ethylpyridine were generously supplied by Dr. F. E. Cislak, Reilly Tar and Chemical Corp., Indianapolis, Ind. The *n*-butyllithium was kindly supplied by Dr. W. T. Barrett, Foote Mineral Co., Exton, Pa. The various styrylpyridines were prepared by the method of Williams, *et al.*[13] Pentimalli's[14] route to 2-styrylpyridine *N*-oxide was used.

**Characterization of Reaction Products.**—Glc analysis of the various product mixtures was carried out on either a 12-ft copper column consisting of 12% Carbowax 20M and 8% Carbowax 1500 on an 80–100 mesh Chromosorb P solid support or a 20 ft × 0.375 in. 30% SE-30 preparative column. Temperatures for the column, injection port, and block were adjusted to give good analyses for the components which were being analyzed.

**General Procedure for the Synthesis of Cyclopropylpyridine Derivatives Using 4-Cyclopropylpyridine (2) as an Example.**—Trimethylsulfonium iodide[15] (0.06 mol, 12.24 g) was added to 100 ml of dry THF in a three-neck, round-bottom flask fitted with a water-cooled condenser (Drierite tube) and a magnetic stirrer. The flask was cooled in an ice–salt bath to 0° or lower and *n*-butyllithium in hexane (0.04 mol, 24.8 ml) was added, under nitrogen, *via* a syringe, to the rapidly stirred suspension of the trimethylsulfonium iodide, maintaining the temperature around 0°. The mixture was stirred for 10 min after the addition of the *n*-butyllithium was completed and then 4-vinylpyridine (0.04 mol, 4.20 g) in 50 ml of THF was added over a 10-min period. The reaction mixture was stirred for 1 hr at 0°, the ice–salt bath was removed, and stirring was continued for 3 hr at ambient temperature. The THF was removed by a rotoevaporator, and the residue was poured into water (tested basic to litmus) and extracted with several portions of $CHCl_3$. The water treatment caused the precipitation of polymerized material, which was filtered. The combined $CHCl_3$ extracts were dried ($Na_2SO_4$), the solvent was removed at atmospheric pressure, and the residue was distilled under vacuum to give 3.08 g of material, bp 74–76° (6 mm). Glc analysis of this material gave one peak with a longer retention time than that of an authentic sample of 4-vinylpyridine. This 3.08 g of material was collected preparatively using glc for characterization and when treated with ethereal hydrogen chloride it gave a hydrochloride, mp 170.8–171.8° (from isopropyl alcohol–ether) (lit.[3] mp 170–171°). A 65.4% yield of 4-cyclopropylpyridine (2) was obtained.

**General Procedure for the Synthesis of Cyclopropylpyridine *N*-Oxides Using 4-Cyclopropylpyridine *N*-Oxide as an Example.**—4-Cyclopropylpyridine (0.02 mol, 2.38 g) was added to glacial acetic acid (25 ml) and 30% hydrogen peroxide (3 ml) and the mixture was stirred for 6 hr at 70–80° followed by the removal of the acid at reduced pressure (rotoevaporator). The mixture was poured into water, and the aqueous phase was made basic

(12) A. R. Katritzky, *Quart. Rev., Chem. Soc.*, **10**, 395 (1956).

(13) J. L. Williams, R. E. Adel, J. M. Carlson, G. A. Reynolds, D. G. Borden, and J. A. Ford, Jr., *J. Org. Chem.*, **28**, 387 (1963).

(14) L. Pentimalli, *Tetrahedron Lett.*, **No. 14**, 151 (1961).

(15) H. J. Emeleus and H. G. Heal, *J. Chem. Soc.*, 1126 (1946).

(aqueous $Na_2CO_3$) and extracted with several portions of $CHCl_3$. The combined extracts were dried ($Na_2SO_4$) and, after the $CHCl_3$ was removed at atmospheric pressure, the residue contained recovered 4-cyclopropylpyridine (0.65 g, 27.4% by comparison of its ir spectrum with that of an authentic sample) and 4-cyclopropylpyridine *N*-oxide (1.75 g, 65.8%, mp 163.4–164.6° from benzene). The structure of the product was confirmed by its elemental analysis, ir spectrum, and nmr spectrum.

**Reaction of 4-Cyclopropylpyridine with *n*-Butyllithium.**—4-Cyclopropylpyridine (0.02 mol, 2.38 g) was added to *n*-butyllithium (0.02 mol, 12.4 ml) and 100 ml of THF. The mixture was refluxed for 6 hr and cooled to room temperature and the THF was removed under reduced pressure (rotoevaporator). The residue was poured into water and extracted with several portions of $CHCl_3$ and the combined extracts were dried ($NaSO_4$). The solvent was removed at atmospheric pressure and the residue was vacuum distilled to give (1) recovered 4-cyclopropylpyridine, bp 74–76° (6.0 mm), 0.19 g, 8%, and (2) 2.06 g of material, bp 119–130° (5.6 mm). Glc analysis of fraction 2 showed three peaks. The peak with the shortest retention time corresponds to the retention time of an authentic sample of 4-cyclopropylpyridine. The smallest peak with an intermediate retention time was not identified. The largest peak with the longest retention time is 2-*n*-butyl-4-cyclopropylpyridine (65% based on glc analysis).

*Anal.* Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78. Found: C, 81.83; H, 9.65.

The picrate had mp 92.4–94.0° (from absolute ethanol). *Anal.* Calcd for $C_{18}H_{20}N_4O_7$: N, 13.86. Found: 13.86.

**Registry No.**—**3**, 6814-64-8; 2-vinylpyridine, 100-69-6; 4-vinylpyridine, 100-43-6; 2-methyl-6-vinylpyridine, 1122-70-9; 2-vinyl-5-ethylpyridine, 5408-74-2; 4-styrylpyridine, 103-31-1; 2-styrylpyridine, 714-08-9; 3-methyl-4-styrylpyridine, 13673-34-2; 3-methyl-2-styrylpyridine, 7433-87-6; 2-*n*-butyl-4-cyclopropylpyridine, 41764-88-9; 2-*n*-butyl-4-cyclopropylpyridine picrate, 41764-89-0.

# Strained Ring Systems. XIV.[1a] Solvolysis of Arenesulfonate Derivatives of Benzobicyclo[2.2.0]hex-5-en-*exo*-2-ol

Richard N. McDonald* and Gary M. Muschik[1b]

*Department of Chemistry, Kansas State University, Manhattan, Kansas 66506*

*Received April 3, 1973*

The buffered acetolysis and formolysis of benzobicyclo[2.2.0]hex-5-en-*exo*-2-yl tosylate (1-OTs) and nosylate (1-ONs) were investigated. Buffered acetolysis of 1-OTs produced only naphthalene while 1-ONs yielded naphthalene (58%) and benzobicyclo[2.1.1]hex-2-en-*exo*-5-yl acetate (2-OAc, 37%). Buffered formolysis of 1-ONs gave exclusively 2-$O_2CH$ in 97% yield. The effects of the benzo group in 1 are discussed.

We recently published the synthesis of benzobicyclo-[2.2.0]hex-5-en-*exo*-2-ol (1-OH) by hydroboration–oxidation of benzobicyclo[2.2.0]hexa-2,5-diene.[2] We now wish to report the preparation and results of solvolytic studies of the tosylate (1-OTs) and nosylate (1-ONs) esters.

Alcohol 1-OH was converted into arenesulfonates 1-OTs and 1-ONs by standard methods. As is our practice with new substrates such as these, approximate rates of buffered acetolysis were determined at two temperatures with two weighed samples (0.005 *M* ROX, 0.006 *M* KOAc) each of 1-OTs and 1-ONs in separate ampoules using the sealed ampoule technique. These approximate rate constants are generally within ±10% of values determined for first-order rate constants from a full kinetic run.[3] These rate constants are listed in Table I.

Table I

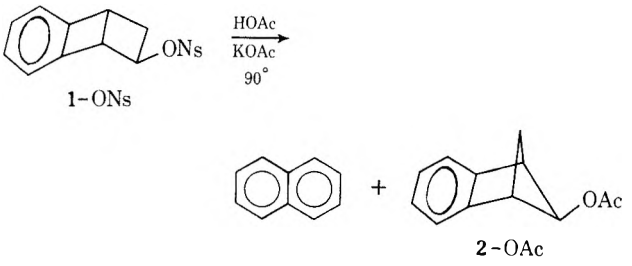
Approximate Buffered Acetolysis Rate Constants for 1-OTs and 1-ONs[a]

| Compd | Temp, °C | $k$,[a] $sec^{-1}$ |
|---|---|---|
| 1-OTs | 90.0 | $1.8 \times 10^{-5}$ |
| | 120.0 | $4.2 \times 10^{-4}$ |
| 1-ONs | 70.0 | $4.6 \times 10^{-6}$ |
| | 90.0 | $4.7 \times 10^{-5}$ |

[a] Determined from only two kinetic points. The instantaneous rate constants from each point based on the initial concentration of substrate agreed within ±3% of these figures.

It was immediately obvious that more than a simple solvolysis reaction was occurring in either 1-OTs or 1-ONs or both from the ratio $k_{1\text{-ONs}}/k_{1\text{-OTs}} = 2.6$. We had previously found the nosylate–tosylate rate ratio to be about 10 for "normal" solvolyses for several primary derivatives,[4] and the same rate ratio was expected for these secondary derivatives.

Isolation of the materials from an interrupted buffered acetolysis of 1-OTs showed the presence of 1-OTs, naphthalene, and decomposition material. A preparative buffered acetolysis of 1-ONs at 90° for approximately 10 solvolytic half-lives (based on approximate $k$, Table I) yielded naphthalene (58%) and benzobicyclo[2.1.1]hex-2-en-*exo*-5-yl acetate (2-OAc, 37%).[5]




The thermal stabilities of 1-OTs and 1-ONs were determined by heating them in hydrocarbon solvents for the time required for approximately 10 buffered acetolysis half-lives of that arenesulfonate. Heating 1-OTs in xylene at 120° and 1-ONs in toluene at 90° produced naphthalene and the corresponding arenesulfonic acid in excellent yields with no recovery of the starting arenesulfonate. From these results it was

(1) (a) Paper XIII: R. N. McDonald and G. E. Davis, *J. Amer. Chem. Soc.*, **94**, 5078 (1972). (b) NDEA Fellow, 1966–1969.

(2) R. N. McDonald, D. G. Frickey, and G. M. Muschik, *J. Org. Chem.*, **37**, 1304 (1972).

(3) R. N. McDonald and G. E. Davis, *J. Org. Chem.*, **38**, 138 (1973).

(4) R. N. McDonald, N. L. Wolfe, and H. E. Petty, *J. Org. Chem.*, **38**, 1106 (1973).

(5) Y. Hata and H. Tanida, *J. Amer. Chem. Soc.*, **91**, 1170 (1969).

TABLE II

BUFFERED FORMOLYSIS DATA FOR BENZOBICYCLO[2.2.0]HEX-5-EN-*exo*-2-YL NOSYLATE (1-ONs)[a]

| Temp, °C | $k$, sec$^{-1}$ | Av $k$, sec$^{-1}$ | $\Delta H^{\pm}$, kcal/mol | $\Delta S^{\pm}$, eu |
|---|---|---|---|---|
| 25.0 | | $1.3 \times 10^{-6}$ [b] | | |
| 50.0 | $(3.91 \pm 0.05) \times 10^{-5}$ | $3.94 \times 10^{-5}$ | $25.4 \pm 0.1$ | $-0.4 \pm 0.4$ |
| | $(3.97 + 0.05) \times 10^{-5}$ | | | |
| 70.0 | $(4.17 \pm 0.05) \times 10^{-4}$ | $4.18 \times 10^{-4}$ | | |
| | $(4.20 \pm 0.07) \times 10^{-4}$ | | | |

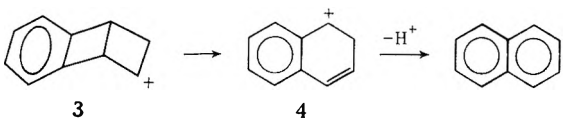
[a] 0.00516 *M* 1-ONs, 0.00646 *M* $HCO_2K$. [b] Extrapolated from data at other temperatures.

obvious that we were not looking at a purely solvolytic reaction in these buffered acetolyses.

We then turned our attention to buffered formolysis, since formolysis kinetic data was available for the parent bicyclo[2.2.0]hex-*exo*-2-yl tosylate.[6] The buffered formolysis data on 1-ONs are listed in Table II. A preparative buffered formolysis (60°, 10 solvolytic half-lives) produced the single formate product, 2-$O_2CH$, in 97% yield; nmr spectral analysis failed to show the presence of naphthalene or 1-$O_2CH$. Formate 2-$O_2CH$ was shown to be stable to the formolysis conditions while 1-$O_2CH$ partially gave naphthalene plus unidentified materials. 1-ONs was shown to be thermally stable in benzene at 70° for 10 formolysis half-lives. The structure of the formolysis product 2-$O_2CH$ was assigned on the basis of close similarities of the pmr chemical shifts and general peak multiplicities of 2-OAc and 2-$O_2CH$ and from spin decoupling of the protons in 2-$O_2CH$.

Two features of the product and kinetic data are evident: (1) the exclusive formation of 2-$O_2CH$ in the buffered formolysis of 1-ONs readily demonstrates the requirement of Wagner–Meerwein rearrangement sometime during the solvolytic processes, and (2) the relatively abnormal effect of olefinic *vs.* arene double bond involvements in such participation compared with those in related bicyclic systems.

Tanida[5] has pointed out that should the classical benzobicyclo[2.2.0]hex-5-en-2-yl cation (**3**) be produced, naphthalene formed *via* benzylic cation **4** would be an




**3** **4**

expected product; we agree. This expectation is given credence from the results of the solvolysis of bicyclo[2.2.0]hex-*endo*-2-yl 3,5-dinitrobenzoate yielding *only* products resulting from disrotatory zero-bridge opening,[7] which we believe would be representative of the classical [2.2.0]-2-yl cation and **3**. Principle sources of naphthalene in the buffered acetic acid media were probably thermal and/or base-induced eliminations.

If we assume that the $k_{RONs}/k_{ROTs}$ ratio for formolysis of derivatives of 1-OH is that found for acetolysis of several primary systems,[4] we calculate that introduction of the 5,6-ethylenic[8] and 5,6-benzo groups depresses the rate of solvolysis of bicyclo[2.2.0]hex-*exo*-2-yl OTs (**5**-OTs) by factors of 28 and $(28)^2$, respectively, with each $\Delta\Delta F^{\pm}$ of about 2 kcal/mol. Even applying an inductive correction factor of 10 for the β-aryl group[9] in 1-ONs leaves us with a rate retardation of 78 for 1-ONs compared to that calculated for 5-ONs. The effects caused by such β-olefinic and β-aryl groups in related systems are listed in Table III.

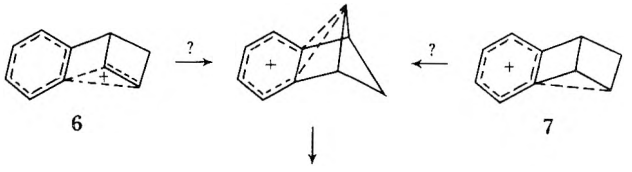
TABLE III

ACETOLYSIS RATE RATIOS OF SATURATED, β-OLEFINIC, AND β-ARYL DERIVATIVES IN BICYCLO[2.2.*n*]ALKYL SYSTEMS[a]

| Structure | $k_{satd}/k_{unsatd}$ | $k_{unsatd}/k_{arene}$ | Ref |
|---|---|---|---|
| *exo*-2-[2.2.0] | 28[b] | 28[c] | 6, 8, this work |
| *exo*-2-[2.2.1][d] | 2.0 | 6.0 | *e*, *f*, *g* |
| *endo*-2-[2.2.1][d] | 44 | 5.7 | *e*, *f*, *g* |
| *exo*-2-[2.2.2][d] | 0.0038 | 100 | *h* |
| *endo*-2-[2.2.2][d] | 0.20 | 5.5 | *h* |

[a] Some rate data were determined in buffered solvent, while others come from unbuffered determinations. [b] Ratio at 90°. [c] Formolysis comparison at 25°. [d] Ratios at 25°. [e] S. Winstein, B. K. Morse, E. Grunwald, H. W. Jones, J. Corse, D. Trifan, and H. Marshall, *J. Amer. Chem. Soc.*, **74**, 1127 (1952). [f] S. Winstein and M. Shatavsky, *ibid.*, **78**, 592 (1956). [g] P. D. Bartlett and W. P. Giddings, *ibid.*, **82**, 1240 (1960). [h] H. Tanida, K. Tori, and K. Kitahonoki, *ibid.*, **89**, 3212 (1967).

It is obvious from the data in Table III that the total rate depression caused by the β-aryl group is largest in the *exo*-2-[2.2.0] system, $k_{satd}/k_{arene} = 780$. At the same time, the exclusive formolysis product from 1-ONs is 2-$O_2CH$, the product of Wagner–Meerwein (σ-bond) rearrangement. The question of whether the formolysis of 1-ONs → 2-$O_2CH$ may involve σ-bond participation in concert with ionization (**6**)[11a] or proceeds by way of initial β-arylethyl type of participation[11b] (**7**) cannot yet be defined with the present limited data.




**6** **7**

2-$O_2CH$

We plan to examine aryl substituent effects in 1-ONs solvolysis. A "plus feature" of such a study is that we can then examine these same effects on derivatives of benzobicyclo[2.1.1]hex-2-en-*exo*-5-ol, the product of rearrangement, where solvolytic participation is *via* the aromatic ring π electrons.[5]

## Experimental Section[12]

**Benzobicyclo[2.2.0]hex-5-en-*exo*-2-yl Acetate (1-OAc).** A.—To 407 mg (2.8 mmol) of 1-OH[2] dissolved in 15 ml of dry pyridine

(6) R. N. McDonald and C. E. Reineke, *J. Org. Chem.*, **32**, 1878 (1967).

(7) R. N. McDonald and G. E. Davis, *J. Amer. Chem. Soc.*, **94**, 5078 (1972).

(8) S. Masamune, E. N. Cain, R. Vukov, S. Takada, and N. Nakatsuka, *Chem. Commun.*, 243 (1969).

(9) A more reasonable value for this inductive correction factor of 4–6 comes from the β-phenyl effects on the rate constants for $k_s$ in 1-phenyl-2-propyl OTs and $k_t$ in isopropyl OTs solvolyses.[10]

(10) C. J. Lancelot, J. J. Harper, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **91**, 4294 (1969); C. J. Lancelot and P. v. R. Schleyer, *ibid.*, **91**, 4296 (1969).

(11) (a) The dashed delocalization indicated in the arene ring of **6** is to show possible arene-$C_1$ p orbital (filled) interaction with the $\pi^*$ $C_1$–$C_2$ olefinic orbital (empty) similar to that suggested by Dewar [*J. Amer. Chem. Soc.*, **92**, 3996 (1970)] for β-arylethyl derivatives. (b) L. A. Paquette and I. R. Dunkin, *ibid.*, **95**, 3067 (1973), concluded that σ-bond participation was *not* involved in the solvolysis of benzobicyclo[2.2.1]hept-5-en-*exo*-2-yl derivatives but that β-arylethyl type participation was "entirely possible" with these substrates.

(12) Melting points were determined on a Kofler hot stage. Spectra were determined on commercial instruments (ir, P-E 137; nmr, Varian T-60). Nmr spectral data are listed as centers except for certain multiplets where the range of the signals is given.

(distilled from barium oxide and kept over potassium hydroxide pellets) at 5° was added 5.0 ml of reagent-grade acetic anhydride. The mixture was stirred for 12 hr and warmed to room temperature. The reaction mixture was dissolved in ether, washed with five 20-ml portions of 10% hydrochloric acid, two 10-ml portions of water, 10 ml of saturated aqueous sodium bicarbonate, and 10 ml of water, and dried ($MgSO_4$). Removal of the ether gave a liquid residue which was short-path distilled [40–60° ($10^{-3}$ mm)] giving 513 mg (98%) of the desired acetate: ir (thin film) 1740 $cm^{-1}$ (C=O); nmr ($CCl_4$, internal TMS) $\tau$ 2.75–3.05 (aromatic $A_2B_2$ pattern, 4), 5.05–5.30 (t, CHOAc, 1), 6.0–6.25 (m, bridgehead H's, 2), 7.50–7.75 (m, $CH_2$, 2), and 7.98 (s, $CH_3$, 3).

*Anal.* Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.44; H, 6.58.

**B.**—To a solution of 11.0 g (98 mmol) of $\Delta^2$-cyclobutenyl acetate[13] and 60 ml of analytical grade ethylene dichloride under nitrogen was added 4.0 g (27 mmol) of benzenediazonium 2-carboxylate. The slurry was stirred at 40–41° for 3 hr. Removal of solvent and recovered $\Delta^2$-cyclobutenyl acetate and short-path distillation gave 1.40 g (28%) of volatile materials [53–100° ($10^{-3}$–$10^{-4}$ mm)]. These volatile materials were chromatographed on silica gel where petroleum ether (bp 30–60°) eluted 0.20 g (4%) of naphthalene, and a 15:85 mixture of benzene–carbon tetrachloride eluted 0.02 g (>1%) of 3-phenyl-$\Delta^1$-cyclobutenyl acetate: ir (thin film) 1750 $cm^{-1}$ (C=O); nmr ($CCl_4$, internal TMS) $\tau$ 2.83 (m, aromatic H's, 5), 4.57 (broadened s, olefinic H, 1), 6.2–6.38 (m, $J_{2,3}$ = 4.5, $J_{2,4}$ = 2.0 Hz, –CHPh, 1), 6.6–7.65 (m, $J_{3,4}$ = 13.0 Hz, $CH_2$, 2), and 7.90 (s, $CH_3$, 3).

A 30:70 mixture of benzene–carbon tetrachloride eluted 200 mg (4%) of 1-OAc, while a 1:1 mixture of benzene–carbon tetrachloride eluted 340 mg (7%) of 4-phenyl-$\Delta^2$-cyclobutenyl acetate: ir (thin film) 1710 $cm^{-1}$ (C=O); nmr ($CCl_4$, internal TMS) $\tau$ 2.87 (m, aromatic H's, 5), 3.58–3.82 (doublet of triplets and doublet of doublets, $J_{2,3}$ = 0.8 Hz, olefinic H's, 2), 4.32–4.47 (doublet of triplets, $J_{1,2}$ = 2.8, $J_{1,3}$ = 1.0, $J_{1,4}$ = 0.7 Hz, CHOAc, 1), and 5.59–5.75 (s, $CH_3$, 3). The 1:1 benzene–carbon tetrachloride also eluted a 0.095-g (2%) mixture of unknown acetates.

To a solution of 11.40 g (0.11 mol) of $\Delta^2$-cyclobutenyl acetate and 80 ml of analytical grade ethylene dichloride under nitrogen was added 7.1 g (0.048 mol) of benzenediazonium 2-carboxylate at 39–40° with another 7.4 g (0.05 mol) added after an additional 2 hr. Removal of solvent and excess $\Delta^2$-cyclobutenyl acetate and distillation [40–100° ($10^{-3}$ mm)] of the remaining residue yielded 4.95 g (38%) of volatile material which gave 493 mg (4%) of 1-OAc.

**Benzobicyclo[2.2.0]hex-5-en-*exo*-2-yl Tosylate (1-OTs).**—To a solution of 200 mg (1.35 mmol) of 1-OH in 25 ml of dry pyridine (distilled from barium oxide) at 5° was added 267 mg (1.4 mmol) of sublimed tosyl chloride. The mixture was stirred for 3 days and warmed to room temperature. Ether was added, and the mixture was washed with five 20-ml portions of water and dried ($MgSO_4$). Removal of solvent gave 279 mg of crude material which was chromatographed on activity 3–4 basic alumina, where carbon tetrachloride eluted 240 mg of product. Recrystallization from pentane–ether gave 185 mg (46%) of 1-OTs: mp 65.5–66°; ir (KBr disk) 1350 (S=O) and 1175 $cm^{-1}$ (CO); nmr ($CCl_4$, internal TMS) $\tau$ 2.5–2.80 ($A_2B_2$, tosyl H's, 4), 2.85–3.10 ($A_2B_2$, aromatic H's, 4), 5.15–5.40 (t, CHOTs, 1), 6.0–6.3 (m, bridgehead H's, 2), 7.4–7.75 (m, $CH_2$, 2), and 7.55 (s, $CH_3$, 3).

*Anal.* Calcd for $C_{17}H_{16}SO_3$: C, 67.98; H, 5.37. Found: C, 67.74; H, 5.19.

**Benzobicyclo[2,2,0]hex-5-en-*exo*-2-yl Nosylate (1-ONs).**—To a solution of 220 mg (1.51 mmol) of 1-OH in 3 ml of anhydrous ether (distilled from lithium aluminum hydride) was added 2.0 ml (3.2 mmol) of a 1.6 *M* solution of methyllithium in pentane at 4°.[14] The mixture was stirred for 15 min at 5° and then 331 mg (1.50 mol) of nosyl chloride (recrystallized from carbon tetrachloride) was added to the alkoxide solution. The solution was stirred at 5° for an additional 1 hr. Ether was added and then the mixture was washed with four 15-ml portions of water and dried ($Na_2CO_3$). Removal of solvent gave a yellow oil (465 mg) which was chromatographed on activity II–III, basic alumina where benzene eluted 0.307 g of crude material. Recrystallization from ether–methylene chloride–pentane gave 262 mg (53%) of 1-ONs: mp 100–101°; ir (KBr disk) 1520 (N=O), 1350 (S=O), and 1175 $cm^{-1}$ (CO); nmr ($DCCl_3$, internal TMS) $\tau$ 1.5–2.0 ($A_2B_2$, nosyl H's, 4), 2.6–3.1 ($A_2B_2$, aromatic H's, 4), 5.0–5.25 (t, CHONs, 1), 5.85–6.20 (m, bridgehead H's, 2), and 7.35–7.65 (m, $CH_2$, 2).

*Anal.* Calcd for $C_{16}H_{13}O_5NS$: C, 58.00; H, 3.95. Found: C, 57.69; H, 3.95.

**Benzobicyclo[2.2.0]hex-5-en-*exo*-2-yl Formate (1-$O_2$CH).**—To a solution of 100 mg (0.675 mmol) of 1-OH in 20 ml of dry pyridine (distilled from barium oxide) at 5° was added 1.50 ml of acetic–formic anhydride.[14] The mixture was stirred for 12 hr at 5–10° and then at room temperature for 2 days. The reaction mixture was poured into ice–water and extracted with two 20-ml portions of ether. The ether extracts were combined and washed with five 15-ml portions of water, three 15-ml portions of cold 10% hydrochloric acid, 15 ml of saturated sodium bicarbonate, and two 15-ml portions of water, and dried ($MgSO_4$). Removal of the ether gave a colorless liquid that was short-path distilled [40° ($10^{-3}$ mm)] yielding 94 mg (78%) of 1-$O_2$CH: ir (thin film) 1730 $cm^{-1}$ (C=O); nmr ($CCl_4$, internal TMS) $\tau$ 2.95 (s, $O_2CH$, 1), 2.6–3.1 (m, aromatic H's, 4), 4.85–5.1 (t, –$CHO_2CH$, 1), 5.9–6.2 (m, bridgehead H's, 2), and 7.4–7.7 (m, $CH_2$, 2).

*Anal.* Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.90; H, 6.16.

**Thermal Stability Check of 1-OTs.**—A solution of 40 mg (0.133 mmol) of 1-OTs in 15 ml of xylene (distilled from sodium) was placed in a bath at 120.0 ± 0.1° for 280 min (approximately 10 $t_{1/2}$ for buffered acetolysis). The solvent was short-path distilled under vacuum, yielding 39 mg (99%) of crude product. The nmr in DMSO-$d_6$ showed the presence of naphthalene and *p*-toluenesulfonic acid which compared identically with spectra of known samples.

**Preparative Buffered Acetolysis of 1-ONs.**—A solution of 80 mg (0.242 mmol) of 1-ONs in 20 ml of 0.013 *M* potassium acetate–acetic acid (2% acetic anhydride) buffer solution was placed in a constant-temperature bath at 90.0 ± 0.1° for 50 hr (approximately 10 $t_{1/2}$ for buffered acetolysis). It was then cooled, placed in a separatory funnel with 20 ml of cold water, and extracted with three 20-ml portions of ether. The ether extracts were combined, washed with five 20-ml portions of water, two 10-ml portions of saturated sodium bicarbonate, two 20-ml portions of water, two 10-ml portions of saturated sodium bicarbonate, and 20 ml of water, and dried ($MgSO_4$). Removal of solvent gave a residue, which was chromatographed on activity II–III, basic alumina where petroleum ether eluted 18 mg (58%) of naphthalene while benzene eluted 17 mg (37%) of 1-OAc.

**Thermal Stability Check of 1-ONs.**—A solution of 40 mg (0.121 mmol) of 1-ONs was dissolved in 15 ml of toluene (analytical reagent) and placed in a constant-temperature bath at 90.0 ± 0.1° for 5 hr (approximately 10 $t_{1/2}$ for buffered acetolysis). The solvent was short-path distilled [50–60° (20 mm)] yielding 36 mg (90%) of a mixture of naphthalene and *p*-nitrobenzenesulfonic acid, as identified by nmr.

**Kinetic Method for Buffered Formolysis.**—The buffered formolysis procedures were modifications of those developed by other workers.[15] All volumetric solutions were prepared in a dry, $N_2$-atmosphere glove box. The sealed ampoule technique was used for formolyses determined above 35°. Substrate solutions were prepared to be 0.005 *M* ROX and 0.006 *M* $KO_2CH$. Approximately 1.5 ml of the formolysis solution was removed per point with a constant-delivery pipette, quenched in 6 ml of purified dioxane, and titrated with $HClO_4$–acetic acid using a Metrohm Herisau E 436D automatic titrator.

The rate constants were calculated using the RATSOL2[23] computer program using experimental infinity titers. Thermochemical data and rate extrapolations were obtained from a computer program which calculated the energy of activation and its maximum error limits.

Using the above procedure, duplicate rate constants for cyclohexyl tosylate (mp 43–44°) were (4.14 ± 0.10) × $10^{-5}$ $sec^{-1}$ and (4.05 ± 0.10) × $10^{-5}$ $sec^{-1}$; average $k$ = 4.1 × $10^{-5}$ $sec^{-1}$. Both determinations had 101 ± 2% infinity titers. The unbuffered formolysis of cyclohexyl tosylate had $k$ = (3.97 ± 0.05) × $10^{-5}$ $sec^{-1}$ at 25°.

(13) K. B. Wiberg, V. Z. Williams, and L. E. Friedrich, *J. Amer. Chem. Soc.*, **92**, 564 (1970).

(14) L. I. Krimen, *Org. Syn.*, **50**, 1 (1970).

(15) S. Winstein and R. Heck, *J. Amer. Chem. Soc.*, **78**, 4801 (1956); S. Winstein and H. Marshall, *ibid.*, **74**, 1120 (1952).

**Preparative Buffered Formolysis of 1-ONs.**—To 30 ml of 0.103 *M* potassium formate–formic acid solution, which had been prepared and kept in a nitrogen atmosphere, was added 82 mg (0.247 mmol) of 1-ONs. The solution was placed in a constant-temperature bath at 60.00 ± 0.05° for 20 hr (approximately 10 $t_{1/2}$). It was then cooled and placed in a separatory funnel with 50 ml of ether. The ether solution was washed with four 20-ml portions of water, two 10-ml portions of 7% sodium bicarbonate solution, and 25 ml of water and dried ($Na_2SO_4$). Removal of solvent gave a residue which was short-path distilled [40–45° ($10^{-3}$ mm)] yielding 40.5 mg (97%) of 2-$O_2$CH: ir (thin film) 1720 $cm^{-1}$ (C=O); nmr ($CCl_4$, internal TMS) $\tau$ 1.95 (s, $O_2CH$, 1), 2.65–3.05 (m, aromatic H's, 4), 5.1–5.2 (d, $CHO_2CH$, 1), 6.4–6.6 (m, *exo*-methylene H, 1), 6.75 (d, bridgehead H's, 2), and 7.5–7.7 (t, *endo*-methylene H, 1); the chemical shifts and peak multiplicities agree closely with those of 2-OAc.[5]

*Anal.* Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.70; H, 5.81.

**Formolysis Stability Check of 2-$O_2$CH.**—To a 25-ml solution of 0.0103 *M* potassium formate–formic acid in a 50-ml round-bottom flask was added 40 mg (0.225 mmol) of 2-$O_2$CH. The solution was placed in a constant-temperature bath at 60.00 ± 0.06° for 20 hr (approximately 10 $t_{1/2}$). At the end of 20 hr, the solution was placed in a separatory funnel with 50 ml of ether, and was washed with five 25-ml portions of water, 10 ml of saturated sodium bicarbonate, and 20 ml of water and dried ($MgSO_4$). Removal of solvent gave a 39.7-mg (99%) recovery of 2-$O_2$CH, as shown by ir and nmr spectroscopy.

**Formolysis Stability Check of 1-$O_2$CH.**—To a solution of 30 ml of 0.0103 *M* potassium formate–formic acid in a 50-ml round-bottom flask was added 43 mg (0.244 mmol) of 1-$O_2$CH. It was placed in a constant-temperature bath at 60.00 ± 0.06° for 20 hr (approximately 10 $t_{1/2}$). The cooled solution was placed in a separatory funnel with 50 ml of ether, and was washed with five 25-ml portions of water, 15 ml of saturated sodium bicarbonate, and 25 ml of water and dried ($MgSO_4$). Removal of the solvent gave 36.3 mg of product. The isolated product was dissolved in 1.0 ml of absolute ethanol and cooled to 5°. To this solution at 5° was added 0.15 ml of a 5% potassium hydroxide in absolute ethanol. The mixture was stirred and warmed to room temperature over 14 hr. The reaction mixture was transferred to a separatory funnel with 20 ml of ether and enough 10% hydrochloric acid to acidify the resulting aqueous solution. This mixture was washed with five 15-ml portions of water, 10 ml of saturated sodium bicarbonate, and 15 ml of water and dried ($MgSO_4$). Removal of solvent gave 28 mg of material which was chromatographed on activity II–III, basic alumina where petroleum ether eluted 5 mg of naphthalene and methylene chloride eluted 22 mg of 1-OH.

**Thermal Stability of 1-ONs.**—A solution of 40 mg (0.12 mmol) of the title compound in 15 ml of benzene (thiophene-free benzene distilled from sodium) was placed in a round-bottom flask and set in a constant-temperature bath at 70.00 ± 0.05° for 5 hr (approximately 10 $t_{1/2}$). Removal of solvent by short-path distillation gave 40 mg (100%) of recovered 1-ONs.

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**Registry No.**—1-OH, 33905-59-8; 1-OAc, 41562-89-4; 1-OTs, 41562-90-7; 1-ONs, 41562-91-8; 1-$O_2$CH, 41562-92-9; 2-$O_2$CH, 41562-93-0; $\Delta^2$-cyclobutenyl acetate, 27238-02-4; benzenediazonium 2-carboxylate, 1608-42-0; 3-phenyl-$\Delta^1$-cyclobutenyl acetate, 41562-96-3; 3-phenyl-$\Delta^2$-cyclobutenyl acetate, 41562-97-4; tosyl chloride, 98-59-9; nosyl chloride, 122-04-3; cyclohexyl tosylate, 953-91-3.

# Notes

## The Preparation of 2-Alkylamino-1,3,4-thiadiazoles

ROBERT A. COBURN,* BHARAT BHOOSHAN, AND RICHARD A. GLENNON

*Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14214*

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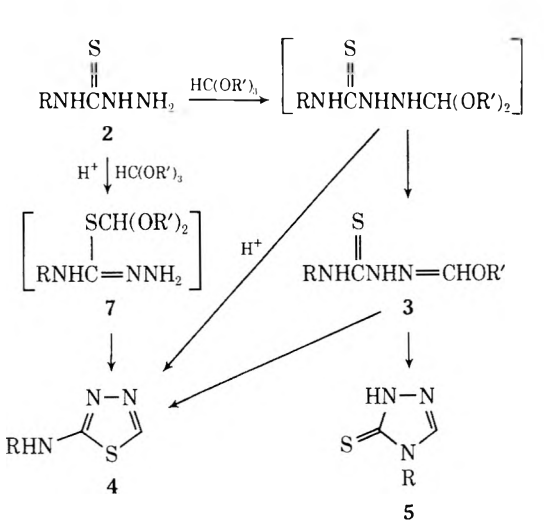
Investigation of the chemical and antimicrobial properties of mesoionic 8-alkyl-1,3,4-thiadiazolo[3,2-*a*]pyrimidine-5,7-diones[1,2] required the preparation of 2-alkylamino-1,3,4-thiadiazoles, unsubstituted in the 5 position, as intermediates. We wish to report an improved procedure for the preparation of these thiadiazole derivatives.

Although 5-substituted 2-acylamino-1,3,4-thiadiazoles can be conveniently reduced to the corresponding amines with lithium aluminum hydride, the 5-unsubstituted amides are base sensitive and undergo extensive decomposition.[3] Formamidate esters undergo thermal rearrangement to *N*-alkylformamides which can be subsequently hydrolyzed to alkylamines.[4] Treatment of 2-amino-1,3,4-thiadiazole with a tenfold excess of trimethyl orthoformate gave as the sole product *N*,*N*′-bis(1,3,4-thiadiazol-2-yl)formamidine (**1**), instead of the desired methyl *N*-(1,3,4-thiadiazol-2-yl)-formamidate. Therefore, this method appears unsuitable for the preparation of the desired 2-alkylaminothiadiazoles.

2-*sec*-Amino-1,3,4-thiadiazoles have been prepared by the treatment of 4-substituted thiosemicarbazides **2** with triethyl orthoformate.[5a-e] Although this is a satisfactory method in the preparation of 2-arylamino derivatives,[5d] 2-alkylamino derivatives are obtained in low yield accompanied by nearly equivalent amounts of 4-alkyl-1,2,4-triazoline-3-thione (**5**). Thus treatment of **2** (R = $CH_3$) with a twofold excess of triethyl orthoformate results in the formation of both **4** (R = $CH_3$) and **5** (R = $CH_3$) in 39 and 34.5% yield, respectively. Heating of the presumed intermediate,[5a,b] ethyl formate 4-methylthiosemicarbazone (**3**, R =

(1) R. A. Coburn and R. A. Glennon, *J. Heterocycl. Chem.*, **10**, 487 (1973).
(2) R. A. Coburn and R. A. Glennon, *J. Pharm. Sci.*, in press.
(3) E. Testa, G. G. Gallo, and F. Fava, *Gazz. Chim. Ital.*, **88**, 1272 (1958); J. Sandstrom, *Advan. Heterocycl. Chem.*, **9**, 165 (1968).
(4) R. M. Roberts and P. J. Vogt, "Organic Syntheses," Collect. Vol. IV, N. Rabjohn, Ed., Wiley, New York, N. Y., 1963, p 420.
(5) (a) C. Ainsworth, *J. Amer. Chem. Soc.*, **78**, 1973 (1956); (b) M. Kanaoka, *J. Pharm. Sci. Jap.*, **75**, 1149 (1955); (c) C. W. Whitehead and J. J. Traverso, *J. Amer. Chem. Soc.*, **77**, 5872 (1955); (d) B. Stanovnik and M. Tisler, *J. Org. Chem.*, **25**, 2234 (1960); (e) J. Goerdeler, J. Ohm, and O. Tegtmeyer, *Chem. Ber.*, **89**, 1534 (1956).

$CH_3$; R′ = $C_2H_5$), obtained in high yield by reducing the reaction period to 1 hr, gave **4** (R = $CH_3$) and **5** (R = $CH_3$) in 24.3 and 27.8% yields, respectively.




It was found that the addition of a small amount of concentrated hydrochloric acid to the reaction of 4-alkylthiosemicarbazides with orthoformate esters gives **4** in high yield with no triazolethione **5** as by-product. Table I gives the yields obtained from the reaction of

TABLE I

ACID-CATALYZED REACTION OF 4-ALKYLTHIOSEMICARBAZIDES (2) WITH TRIETHYL ORTHOFORMATE

| Compd | R | Mp of product 4, °C | Yield of 4, % | Lit. mp of thione 5, °C |
|---|---|---|---|---|
| 2a | $CH_3$ | 66–67[a] | 71.7 | 168[d] |
| 2b | $C_2H_5$ | 71–72[b] | 92.6 | 96–97[e] |
| 2c | $n$-$C_3H_7$ | 42–43 | 91.0 | 74–75[f] |
| 2d | $CH_2Ph$ | 106–107[c] | 87.3 | 121–122[g] |
| 2e | $t$-$C_8H_{17}$ | 127–128 | 92.1 | 182–184[f] |
| 2f | 1-Adamantyl | 155–155.5 | 80.9 | |

[a] Lit. mp 65–66°: G. Werber and F. Massio, *Ann. Chim. (Rome)*, **51**, 944 (1961); *Chem. Abstr.*, **56**, 7305 (1962). [b] Lit.[5c] mp 70°. [c] Lit.[5d] mp 109°. [d] C. F. Kruger, W. Sattler, and H. Beyer, *Justus Liebigs Ann. Chem.*, **643**, 121 (1961). [e] M. Freund, *Chem. Ber.*, **29**, 2487 (1896). [f] S. A. Greenfield, M. C. Seidel, and W. C. Von Meyer, German Patent 1,943,915 (1970); *Chem. Abstr.*, **72**, 100713 (1970). [g] H. Saikachi and M. Kanaoka, *Yakugaku Zasshi*, **81**, 1333 (1961); *Chem. Abstr.*, **56**, 7304 (1962).

4-alkylthiosemicarbazides **2a–f** with triethyl orthoformate in ethanol with an acid catalyst present. The yields of the desired products, **4a–f**, ranged from 72 to 93% and were not affected by the amount of added acid. In addition, it was found that the reaction time could be shortened from 20–36 hr without acid catalyst to 2 hr for the acid-catalyzed reaction.

The use of trimethyl orthoformate in methanol with an acid catalyst was found to give results similar to those described for the acid-catalyzed reactions employing triethyl orthoformate. The reaction was extended to the use of triethyl orthoacetate with **2a** to give, under acid-catalyzed conditions, a 78% yield of 2-methylamino-5-methyl-1,3,4-thiadiazole (**6**).

The thiadiazoles **4a–e** may be distinguished from the previously reported triazoles **5a–e** by a band at 1530–1570 $cm^{-1}$ generally present in the thiadiazoles and absent in the triazoles. In no case could **5** be detected *via* tlc analysis of the reaction product mixtures.

When intermediate **3** (R = $CH_3$; R′ = $C_2H_5$) was heated in ethanol with or without added acid, slow conversion to a mixture of **4a** and **5a** was observed, leading to the conclusion that **3** is not the intermediate leading to the formation of **4a** in the reaction of **2a** and triethyl orthoformate under acid catalysis.

Although it is possible that under acid catalysis 2-alkylamino-1,3,4-thiadiazole is produced *via* 4-alkylthiosemicarbazide 1-acetal, a reviewer has suggested that a different point of attack, possibly by the dialkoxy carbenium ion, on the thiosemicarbazide leads to the formation of **7** which can cyclize only to the observed product. Tlc analysis of the reaction mixture, involving **2a**, prior to heating shows the disappearance of **2a** and the formation of an intermediate (not formed in the absence of ortho ester). During attempted isolation, this intermediate reverts to the thiosemicarbazide following addition of weak base ion-exchange resin and solvent removal *in vacuo*. This behavior is more easily rationalized for the more labile suspected intermediate **7**.

### Experimental Section

Nmr spectra were obtained on a Varian T-60 spectrometer and chemical shifts are reported relative to TMS. Infrared spectra were recorded by a Perkin-Elmer Model 237 spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. All melting points were determined by a Mel-Temp melting point apparatus and are uncorrected.

*N,N′*-**Bis**(1,3,4-thiadiazol-2-yl)**formamidine** (1).—2-Amino-1,3,4-thiadiazole (3.0 g, 30 mmol) and trimethyl orthoformate (31.8 g, 0.3 mol) were heated on an oil bath (120°) for 1 hr. The crystalline material, obtained upon cooling the reaction mixture, was collected and recrystallized from dimethylformamide to yield 2.2 g (94.4%) of 1 as off-white crystals, mp 238–240° dec (lit.[5a] mp 240° dec). The same product was obtained in comparable yield when methanol was employed as a reaction solvent.

4-(*tert*-Octyl)**thiosemicarbazide** (2e).—Hydrazine (0.64 g, 20 mmol) was added dropwise with stirring to a solution of *tert*-octyl isothiocyanate (3.42 g, 20 mmol) in anhydrous ether (25 ml) at 0°. After the reaction mixture was stirred for 3 hr at room temperature, the solvent was removed *in vacuo* to yield a colorless oil which crystallized upon standing. Recrystallization from an ethyl acetate–petroleum ether (bp 30–60°) mixture gave 3.3 g (81.3%) of 2e: mp 94–95°; ir ($CHCl_3$) 3390 and 3300 $cm^{-1}$; nmr ($CDCl_3$) δ 1.0 (s, 9 H), 1.6 (s, 6 H), 2.0 (s, 2 H), 3.8 (broad signal, 2 H), 7.6 (broad signal, 1 H), and 7.8 (broad signal, 1 H).

*Anal.* Calcd for $C_9H_{21}N_3S$: C, 53.16; H, 10.41; N, 20.66; S, 15.77. Found: C, 53.33; H, 10.51; N, 20.52; S, 15.52.

The 4-alkylthiosemicarbazides **2a–d** were prepared according to the method of Jensen, *et al.*,[6] and **2f** according to Oliver and Stokes.[7]

**Reactions of 4-Methylthiosemicarbazide** (2a) **and Ethyl Orthoformate.** A.—4-Methylthiosemicarbazide (**2a**) (1.0 g, 10 mmol) and triethyl orthoformate (3.0 g, 20 mmol) were heated on an oil bath (120°) for 20 hr. Upon cooling, a crystalline product was collected and recrystallized from ethanol to yield 0.38 g (34.5%) of 4-methyl-1,2,4-triazoline-3-thione (**5a**), mp 167–168° (lit.[8] mp 168°). The reaction mother liquid was evaporated *in vacuo* to yield a colorless oil, which was distilled, bp 130–132° (0.35 mm), to give a colorless oil which crystallized

(6) K. A. Jensen, V. Anthoni, B. Kagi, C. Larsen, and C. Pedersen, *Acta. Chem. Scand.*, **22**, 1 (1968).

(7) J. E. Oliver and J. B. Stokes, *J. Med. Chem.*, **13**, 779 (1970).

(8) C. F. Kroger, W. Sattler, and H. Beyer, *Justus Liebigs Ann. Chem.*, **643**, 121 (1961).

upon standing. Recrystallization from ethyl acetate gave 0.42 g (39%) of 2-methylamino-1,3,4-thiadiazole (4a), mp 65° (lit.[9] mp 65–66°).

**B. Ethyl Formate 4-Methylthiosemicarbazone (3, R = $CH_3$; R′ = $C_2H_5$).**—The above reaction was repeated but the period of heating was 1 hr. At this time, the reaction flask was cooled in an acetone–Dry Ice bath and a white, crystalline product was obtained. Recrystallization from ethyl acetate gave 1.5 g (93.3%) of ethyl formate 4-methylthiosemicarbazone (3, R = $CH_3$; R′ = $C_2H_5$): mp 100–101°; ir ($CHCl_3$) 3375, 1645, 1550, 1180 $cm^{-1}$; nmr ($CDCl_3$) δ 1.6 (t, 3 H), 3.5 (d, 3 H), 4.45 (q, 2 H), 6.8 (s, 1 H), 7.6 (broad signal, 1 H), 9.2 (broad signal, 1 H).

*Anal.* Calcd for $C_5H_{11}N_3OS$: C, 37.25; H, 6.88; N, 26.06; S, 19.89. Found: C, 37.44; H, 7.05; N, 26.10; S, 20.09.

This compound (1.6 g, 10 mmol) was heated (neat) at 190° for 5 min. The resultant oil was dissolved in hot absolute ethanol and, upon cooling, 0.32 g (27.8%) of **5a** was obtained, mp 166–167°. The filtrate was evaporated *in vacuo* and the product was distilled to give 0.28 g (24.3%) of **4a** as an oil which crystallized upon standing, mp 63–64°. Similar yields of both products were obtained when ethanol was used as a reaction solvent, with and without acid catalyst. In these cases, the reaction mixture was refluxed for 20 hr.

**C. 2-Methylamino-1,3,4-thiadiazole (4a).**—Triethyl orthoformate (3.0 g, 20 mmol) and **2a** (1.0 g, 10 mmol) were added to absolute ethanol (10 ml). Concentrated hydrochloric acid (0.05 ml) was added and the suspension was stirred until solution was complete (1 hr). After the solution had been refluxed for 1 hr, the solvent was evaporated *in vacuo* and the crystalline product was dissolved in chloroform (10 ml). This solution was filtered and the filtrate was evaporated *in vacuo*. Recrystallization of the residue from ethyl acetate gave 1.65 g (72%) of **4a** as white needles, mp 66–67°.

The 2-alkylamino-1,3,4-thiadiazoles **4b–f** were prepared in the same manner as **4a**, part C, using 10 mmol of 4-alkylthiosemicarbazide, 20 mmol of triethyl orthoformate, and 0.05 ml of concentrated HCl.

**2-*n*-Propylamino-1,3,4-thiadiazole (4c).**—The product **4c** was obtained as low-melting white crystals, mp 37–40°. Distillation, bp 136–138° (0.3 mm), gave a sample which melted at 42–43°: nmr ($CDCl_3$) δ 1.01 (t, 3 H), 1.76 (m, 2 H), 3.36 (t, 2 H), 7.33 (broad s, 1 H), 8.50 (s, 1 H); ir (neat) 3226 and 1530 $cm^{-1}$; hydrochloride salt mp 127–128°.

*Anal.* Calcd for $C_5H_9N_3S \cdot HCl$: C, 33.43; H, 5.61; N, 23.39; S, 17.85; Cl, 19.73. Found: C, 33.58; H, 5.57; N, 23.43; S, 17.92; Cl, 19.66.

**2-*tert*-Octylamino-1,3,4-thiadiazole (4e).**—The product **4e** was recrystallized from ethyl acetate: mp 127–128°; ir ($CHCl_3$) 3400, 1570 $cm^{-1}$; nmr ($CDCl_3$) δ 1.0 (s, 9 H), 1.6 (s, 6 H), 1.8 (s, 2 H), 6.9 (broad signal, 1 H), 8.55 (s, 1 H).

*Anal.* Calcd for $C_{10}H_{19}N_3S$: C, 56.30; H, 8.98; N, 19.70; S, 15.03. Found: C, 56.28; H, 8.84; N, 19.60; S, 14.96.

**2-(1-Adamantylamino)-1,3,4-thiadiazole (4f).**—The product **4f** was recrystallized from ethanol: mp 155–155.5°; ir ($CHCl_3$) 1570 $cm^{-1}$; nmr (DMSO-$d_6$) δ 1.6–2.2 (m), 8.95 (s, 1 H).

*Anal.* Calcd for $C_{12}H_{17}N_3S$: C, 61.24; H, 7.28; N, 17.85; S, 13.62. Found: C, 61.52; H, 7.41; N, 17.94; S, 13.69.

**2-Methylamino-5-methyl-1,3,4-thiadiazole (6).**—A mixture of 4-methylthiosemicarbazide (0.79 g, 7.5 mmol), triethyl orthoacetate (2.43 g, 15 mmol), and 0.05 ml of concentrated hydrochloric acid in ethanol (10 ml) was stirred at room temperature for 1 hr. The resulting clear solution was refluxed for 1 hr and the solvent was removed *in vacuo*. Recrystallization of the residue from ethyl acetate gave 0.75 g (78.1%) of **6** as white crystals, mp 111–112° (lit.[10] mp 112°).

**Registry No.**—**1**, 26907-35-7; **2a**, 6610-29-3; **2b**, 13431-34-0; **2c**, 13431-35-1; **2d**, 13431-41-9; **2e**, 41593-77-5; **2f**, 21126-27-2; **3** (R = $CH_3$; R′ = $C_2H_5$), 21304-97-2; **4a**, 38490-45-8; **4b**, 13275-68-8; **4c**, 41593-82-2; **4c** HCl, 41593-83-3; **4d**, 23289-12-5; **4e**, 41593-85-5; **4f**, 41593-86-6; **5a**, 24854-43-1; **5b**, 32362-78-0; **5c**, 41593-89-9; **5d**, 32362-84-8; **5e**, 41593-91-3; **6**, 38917-35-0; 2-amino-1,3,4-thiadiazole, 4005-51-0; trimethyl orthoformate, 149-73-5; *tert*-octyl isothiocyanate, 17701-76-7; triethyl orthoformate, 122-51-0.

(9) G. Werber and F. Massio, *Ann. Chim. (Rome)*, **51**, 944 (1961); *Chem. Abstr.*, **56**, 7305 (1962).

(10) C. Pulvermacher, *Chem. Ber.*, **27**, 613 (1894).

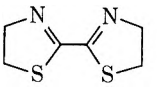
## A Facile Synthesis of 2,2′-Bi-2-thiazolines and -thiazines

DONALD A. TOMALIA* AND J. N. PAIGE

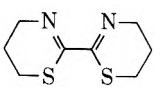
*E. C. Britton Research Laboratory, The Dow Chemical Company, Midland, Michigan 48640*

*Received April 18, 1973*

The first reports of the synthesis of 2,2′-bi-2-thiazolines appeared in 1954. In that year, two groups[1,2] discovered independently that the parent compound **1** could be prepared in poor to modest yield by the reaction of cyanogen with 2-mercaptoethylamine. Subsequent work by Woodburn, *et al.*,[3] has shown that **1** can also be prepared in very good yield by the reaction of dibutyloxamidine 2HCl with 2-mercaptoethylamine HCl. Preparation of its six-membered analogs, **2**,



**1**



**2**

however, has been hindered in that necessary precursors were not readily available. To date, the synthesis of 2,2′-bi-2-thiazine, **2**, or its homologs has not yet been reported.

We wish to describe a general and facile synthesis of **1**, **2**, and their homologs based on the readily available precursors: dithiooxamide (rubeanic acid) and amino alcohols. Heterocycles **1** and **2** are of interest in that they have been found to form dications bearing charge on mutually attached carbon atoms when allowed to react with acylating agents[4a] or Brønsted acids.

The synthetic route involved stirring appropriate amino alcohols with dithiooxamide at room temperature until ammonia evolution ceased, using modified Wallach reaction conditions.[4b] Reaction of the resulting *N*,*N*′-bis(hydroxyalkyl)dithiooxamide with thionyl chloride produced the corresponding bithiazolinium or -thiazinium dications (**1′–4′**) in good to excellent yield. The free bases (**1–4**) were liberated by treatment with sodium bicarbonate since stronger bases generally led to hydrolysis products. (See Scheme I.)

The dications could be stored for several days under anhydrous conditions; however, exposure to moisture led to unidentified hydrolysis products. Samples of the free bases appeared to have long-term stability. The latter compounds were characterized by ir and nmr analyses as well as by elemental analyses.

Dication **5**, as well as its oxygen analog **6**, were of particular interest in that there are relatively few examples of dications bearing positive charges on mutually attached carbon atoms reported in the literature.[5] Dications **5** and **6** were prepared by addition of **1** or 2,2′-bi-2-oxazoline to neat $FSO_3H$. The proton chemical shift assignments for protons a and b were based

(1) R. Kuhn and F. Drawert, *Justus Liebigs Ann. Chem.*, **590**, 55 (1954).

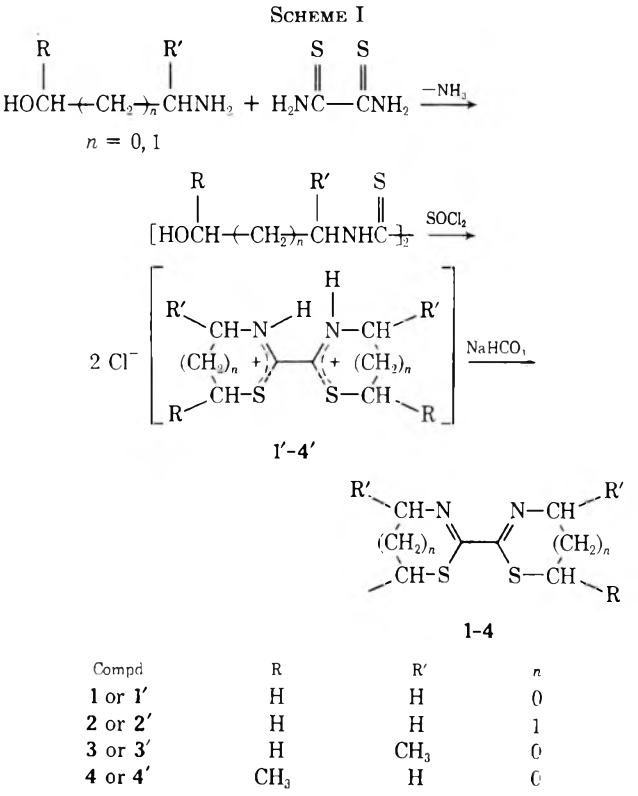
(2) H. M. Woodburn and B. G. Pautler, *J. Org. Chem.*, **19**, 863 (1954).

(3) H. M. Woodburn and W. E. Hoffman, *J. Org. Chem.*, **23**, 262 (1958).

(4) (a) D. A. Tomalia, to be published; (b) O. Wallach, *Justus Liebigs Ann. Chem.*, **262**, 357 (1891).

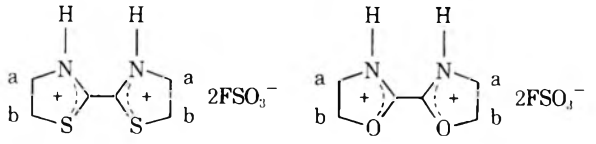
(5) C. U. Pittman, Jr., S. P. McManus, and J. W. Larsen, *Chem. Rev.*, **72**, 376 (1972).

SCHEME I



| Compd | R | R′ | n |
|---|---|---|---|
| 1 or 1′ | H | H | 0 |
| 2 or 2′ | H | H | 1 |
| 3 or 3′ | H | $CH_3$ | 0 |
| 4 or 4′ | $CH_3$ | H | 0 |

on observations made by Weinberger, *et al.*,[6] wherein they noted that methylene protons on carbon attached to the nitrogen in monothiazolines or oxazolines were always at a higher field than those attached to the sulfur or oxygen atom. Previous attempts to prepare the related bis-2,2′-1,3-dioxolenium dication, **7** ($n$ = 0),



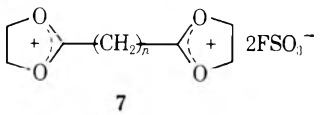
**5**

a, 4.15 (t)
b, 4.78 (t)
(a:b = 1:1)



**6**

a, 4.64 (t)
b, 5.60 (t)
(a:b = 1:1)



**7**

were unsuccessful although the bis-2,2′-methylene-1,3-dioxolenium dication **7** ($n$ = 1) was prepared and characterized by nmr spectroscopy.[7,8]

## Experimental Section

Nmr spectra were obtained with a Varian A-60 spectrometer. Chemical shifts are reported as $\delta$ (parts per million) relative to tetramethylsilane (TMS) or tetramethylammonium tetrafluoroborate (TMA·$BF_4$). The TMA·$BF_4$ signal is assumed to be at 3.10 ppm, relative to TMS.[9] Ir spectra were scanned on a Perkin-Elmer 337 spectrometer. Melting points were determined in a capillary and are uncorrected unless otherwise noted.

Dithiooxamide (rubeanic acid) and $N,N'$-bis(2-hydroxyethyl)-dithiooxamide were available from Mallinckrodt Chemical Co.

**2,2′-Bi-2-thiazoline** (**1**).—To a stirred suspension of $N,N'$-bis-(2-hydroxyethyl)dithiooxamide (104 g, 0.5 mol) in 600 ml of toluene was added a total of 238 g (2.0 mol) of thionyl chloride in two equal portions. After addition of a second portion (119 g) a strong exothermic reaction accompanied by a considerable amount of frothing was observed. A maximum temperature of 55° was attained. After the temperature subsided, the reaction mixture was maintained at 45° for 1.5 hr while stirring. The resulting insoluble, mustard yellow salt was filtered off, slurried with $n$-hexane, and refiltered. After drying, the product weighed 121.7 g (99%) and had a melting point of 140–143° (decomposed to orange oil). The infrared spectrum displayed a broad band centered at ~2220 $cm^{-1}$ (–N=C–) and a medium-intensity band at 1780 $cm^{-1}$ which is characteristic for the thiazolinium ring. An nmr spectrum in DMSO-$d_6$ consisted of two triplets at 4.44 and 3.40 ppm in a ratio of 1:1.

2,2′-Bi-2-thiazolinium dihydrochloride (100 g, 0.41 mol) was added in small portions to a stirred solution of sodium bicarbonate (31 g, 0.41 mol) in 300 ml of water. A grayish-brown precipitate fell out of solution upon neutralization. The precipitate was filtered, washed with two 25-ml portions of water, and dried in a vacuum oven at 60–80°. The gray-brown, powdery product weighed 56.5 g (79.5%) and melted at 124–128° (lit. mp 127–129°).

This material was not very soluble in most common organic solvents. It did dissolve in liquid sulfur dioxide, giving an nmr spectrum (–25°) consisting of triplets at 4.42 (–$SCH_2$–) and 3.46 ppm (=$NCH_2$–) in a ratio of 1:1.

**2,2′-Bi-2-thiazine** (**2**).—$N,N'$-Bis(3-hydroxypropyl)dithiooxamide was prepared by a method similar to that of Jacob and Herman.[9] A mixture of 3-aminopropanol (50 g, 0.66 mol) and dithiooxamide (40 g, 0.33 mol) in 160 ml of absolute ethanol was stirred at room temperature for 16 hr, during which time the reaction became nearly homogeneous. The dark brown solution was filtered and the filtrate was concentrated to a semisolid state. Trituration with water gave a gold-colored solid weighing 47.1 g (60%) which melted at 69–72°. This material was used without further purification for the next step.

To a stirred slurry of $N,N'$-bis(3-hydroxypropyl)dithiooxamide (35.4 g, 0.15 mol) in 200 ml of toluene was added 71.5 g (0.6 mol) of thionyl chloride in two equal increaments over a period of 1.5 hr. A gummy solid appeared as the reaction mixture turned dark. A maximum temperature of 43° was noted during this exothermic reaction. After addition was complete, the reaction temperature was maintained at 45–50° for 2 hr. The beige-colored product which formed was filtered, washed with toluene, and found to weigh 37.1 g (91%). The dication melted at 138–140° and was liberated as the free base without further purification.

A 27.3-g (0.1 mol) sample of the dication intermediate was added in small increments to a stirred solution of sodium bicarbonate (18.6 g, 0.22 mol) in 200 ml of water. The beige-colored product was filtered and found to weigh 21 g (100%). Recrystallization from carbon tetrachloride gave a cream-colored material melting at 161.5–163°. *Anal.* Calcd: C, 48.0; H, 6.00; N, 14.0; S, 32.0. Found: C, 48.0; H, 5.89; N, 13.8; S, 31.9.

The nmr spectrum of **2** in $CDCl_3$ consisted of triplets at 3.87 (–$SCH_2$–) and 3.03 ppm (=$NCH_2$–) as well as a pentet at 1.87 ppm (–$CCH_2C$–).

**4,4′-Dimethyl-2,2′-bi-2-thiazoline** (**3**).—A mixture of *l*-2-amino-1-propanol (10 g, 0.133 mol) and dithiooxamide (8 g, 0.066 mol) was stirred at room temperature for 19 hr. The dark solution was concentrated to a dark-brown semisolid. Trituration with water gave 7.6 g (49%) of a dark-brown powder, mp 113–118°.

To a stirred mixture of 7.5 g (0.032 mol) of $N,N'$-bis(2-hydroxy-1-methylethyl)dithiooxamide in 50 ml of toluene was added 16 g (0.13 mol) of thionyl chloride in four equal portions over a 1.5-hr period. The reaction mixture was then heated at 45–50° for 2 hr. Filtration yielded 6.5 g (75%) of the dication as a gold-colored powder, mp 100–105°.

Neutralization of the dication with a solution of sodium bicarbonate (4.2 g, 0.05 mol) in 50 ml of water gave a beige-colored product which was recrystallized from hexane to give 2.3 g (49%) of a light yellow material which melted at 73–74°. *Anal.* Calcd: C, 48.0; H, 6.00; N, 14.0; S, 32.0. Found: C, 47.96; H, 6.00; N, 14.0; S, not determined.

**5,5′-Dimethyl-2,2′-bi-2-thiazoline** (**4**).—A mixture of dithiooxamide (40 g, 0.33 mol) and 1-amino-2-propanol (50 g, 0.66 mol) in 300 ml of ethanol was stirred at room temperature until

(6) M. A. Weinberger and R. Greenhalgh, *Can. J. Chem.*, **41**, 1038 (1963).
(7) H. Hart and D. A. Tomalia, *Tetrahedron Lett.*, **No. 15**, 1347 (1967).
(8) D. A. Tomalia, Ph.D. Thesis, Michigan State University, 1968.
(9) W. A. Jacob and M. A. Herman, *Anal. Chim. Acta*, **33**, 229 (1965).

ammonia evolution ceased (~5 days). A small amount of solid, which formed during that time, was filtered and the filtrate was reduced to a dark-brown, gummy semisolid by removing solvent under vacuum. This material was stirred with 600 ml of water for 4 hr and filtered to give 33.4 g (43%) of a yellow powder, mp 95–100° (lit.[10] mp 98–101°).

A mixture of *N,N'*-bis(2-hydroxypropyl)dithiooxamide (113.5 g, 0.48 mol) in toluene (575 ml) was treated with four 60-g portions of thionyl chloride over a period of 1.5 hr. The reaction mixture was then heated at 45–50° for 1.5 hr, after which the resulting gold-colored dication was filtered and found to weigh 66.9 g (51%), mp 118–131°.

Neutralization of the dication (66.9 g) with a solution of sodium bicarbonate (42.5 g, 0.5 mol) in 450 ml of water gave 49 g (100%) of a dark-brown solid. Recrystallization from *n*-hexane yielded a cream-colored powder, mp 92–93.5°. *Anal.* Calcd: C, 48.0; H, 6.00; N, 14.0; S, 32.0. Found: C, 48.2; H, 6.22; N, 13.9; S, 31.9.

The nmr spectrum ($CDCl_3$) consisted of a complex multiplet at 4.75–3.80 ppm ($-CH_2CH-$) and a doublet centered at 1.38 ppm ($CH_3-$).

**Registry No.**—**1**, 41601-87-0; 1′ $2Cl^-$, 41601-88-1; **2**, 41601-89-2; 2′ $2Cl^-$, 41601-90-5; **3**, 41601-91-6; 3′ $2Cl^-$, 41601-92-7; **4**, 41601-93-8; 4′ $2Cl^-$, 41601-88-1; *N,N'*-bis(2-hydroxyethyl)-dithiooxamide, 120-86-5; *N,N'*-bis(2-hydroxypropyl)dithiooxamide, 3815-26-7; *l*-2-amino-1-propanol, 35320-23-1; *N,N'*-bis(2-hydroxy-1-methylethyl)dithiooxamide, 41601-97-2; 1-amino-2-propanol, 78-96-6; dithiooxamide, 79-40-3.

(10) R. N. Hurd, G. DeLaMater, G. C. McElheny, R. J. Turner, and V. H. Wallingford, *J. Org. Chem.*, **26**, 3980 (1961).

## Thioimidates and Ketene Mercaptals from Ketenimines

MARVIN W. BARKER,* SUSAN C. LAUDERDALE,[1] AND JOSEPH R. WEST

*Department of Chemistry, Mississippi State University, Mississippi State, Mississippi 39762*

*Received April 2, 1973*

The addition of mercaptans to such heterocumulenes as ketenes, isocyanates, and carbodiimides has been found to occur smoothly and in good yield to produce thio esters,[2] thiocarbamates,[3] and S-substituted isothioureas,[4] respectively. As a continuation of a study of the chemistry of ketenimines[5] and mercaptan addition to heterocumulenes, we have investigated the reactions of mercaptans and ketenimines.

When diphenylketene-*N*-(*p*-bromophenyl)imine (**1a**) is treated with excess thiophenol at the temperature of refluxing benzene, the corresponding thioimidate (**2**) is formed in 72% yield (eq 1). Other *N*-aryl ketenimines behave similarly to produce thioimidates in yields of 44–90%. Structure assignments were based on ir data (loss of the ketenimine absorption at 2000 $cm^{-1}$ and appearance of the imine absorption at approximately 1640 $cm^{-1}$), nmr data (absorption for the benzhydryl proton at $\delta$ 5 ppm), and elemental analyses. All thioimidates produced from thiophenol were crystalline solids and were easily purified. Aliphatic mercaptans as represented by the ethyl and *n*-propyl substituents also add to ketenimines to yield crystalline thioimidates in good yields (Table I).

$$\underset{\mathbf{1a}}{Ph_2C{=}C{=}NAr} + RSH \xrightarrow{80^\circ} \underset{\mathbf{2a}}{Ph_2CHC(SR){=}NAr} \quad (1)$$

TABLE I
THIOIMIDATES FROM KETENIMINES[a]

$$Ph_2C{=}C{=}NAr + RSH \longrightarrow Ph_2CHC(SR){=}NAr$$

| Sample | Ar | R | Yield of **2**, % | Mp, °C |
|---|---|---|---|---|
| a | *p*-Bromophenyl | Phenyl | 72 | 92–93 |
| b | *m*-Bromophenyl | Phenyl | 60 | 82.5–83 |
| c | *p*-Chlorophenyl | Phenyl | 73 | 83.5–84.0 |
| d | *m*-Chlorophenyl | Phenyl | 44 | 75.0–75.5 |
| e | Phenyl | Phenyl | 45 | 80.0–81.0 |
| f | *p*-Tolyl | Phenyl | 64 | 85–85.5 |
| g | *p*-Anisyl | Phenyl | 81 | 106.5–107.5 |
| h | *p*-Fluorophenyl | Phenyl | 61 | 91.5–92.5 |
| i | *p*-Bromophenyl | Ethyl | 71 | 95–95.5 |
| j | *p*-Bromophenyl | *n*-Propyl | 90 | 88.5–89.0 |

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

Although these reactions were first performed with irradiation and presumed to occur by radical addition, it was subsequently found that light is not needed. Furthermore, the same products are obtained in comparable yields if the sodium salt of the mercaptans is employed.

When **1a** was treated with excess thiophenol at 169° (refluxing thiophenol), rather than 80°, no thioimidate was found. Instead, aniline hydrobromide precipitate from solution and work-up of the reaction mixture yielded only diphenylketene diphenylmercaptal[6] (**3**) (eq 2). This reaction is apparently an acid-catalyzed process and the HBr catalyst is produced through a hydrogenolysis reaction of the aryl bromide of **1a**. To test this hypothesis, **1e** was treated with excess thiophenol at 169° with the addition of HCl; **3** was obtained from the reaction in 68% yield. Table II con-

$$\underset{\mathbf{1a}}{Ph_2C{=}C{=}N{-}C_6H_4{-}Br} + PhSH \xrightarrow{169^\circ} PhNH_2{\cdot}HBr + \underset{\mathbf{3}}{Ph_2C{=}C(SPh)_2} \quad (2)$$

TABLE II
KETENE MERCAPTALS FROM KETENIMINES

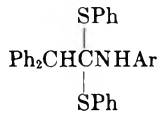
$$Ph_2C{=}C{=}N{-}C_6H_4{-}X + PhSH \xrightarrow{HCl} X{-}C_6H_4{-}NH_2{\cdot}HCl + Ph_2C{=}C(SPh)_2$$

| X | Yield, % |
|---|---|
| H | 67.7 |
| *p*-Cl | 52 |
| *m*-Cl | 64 |
| *p*-$CH_3$ | 42.5 |
| *p*-$OCH_3$ | 42.5 |

(1) NDEA Predoctoral Fellow, 1969–1972.
(2) P. J. Lillford and D. P. N. Satchell, *J. Chem. Soc. B*, 1303 (1970).
(3) S. Ozaki, *Chem. Rev.*, **72**, 457 (1972).
(4) P. Schlack and G. Keil, *Justus Liebigs Ann. Chem.*, **661**, 164 (1963); M. Busch, G. Blume, and E. Pungs, *J. Prakt. Chem.*, **79**, 513 (1909).
(5) For previous reports see M. W. Barker and R. H. Jones, *J. Heterocycl. Chem.*, **9**, 555 (1972); M. W. Barker and J. D. Rosamond, *ibid.*, **9**, 1147 (1972); M. W. Barker, L. L. Combs, and J. T. Gill, *ibid.*, **9**, 77 (1972); and references cited therein.
(6) A. Schonberg and L. V. Vargha, *Justus Liebigs Ann. Chem.*, **483**, 176 (1930).

tains the data for the general reaction of *N*-aryl ketenimines and thiophenol under acid catalysis. Also, it was observed that the thioimidates yield ketene mercaptals when treated with excess thiophenol and HCl.

Several conclusions can be drawn from these observations concerning the mechanism of ketene mercaptal production. The ketenimine presumably undergoes monoaddition to yield the thioimidate, which is converted to the mercaptal with acid catalysis. The intermediate is probably the diadduct **4**. This intermediate would be expected to eliminate aniline at the reaction temperature to yield the mercaptal, a process similar to the preparation of ketene mercaptals by Volger and Arens[7] in which compound **5** undergoes thermal elimination of RSH to produce the ketene mercaptal.

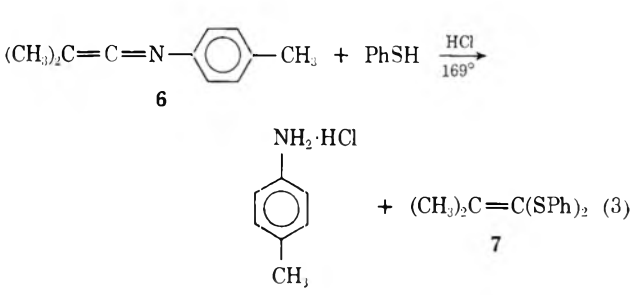


**4**

$R_2CHC(SR)_3$

**5**

In an effort to determine the generality of the synthesis of ketene mercaptals from ketenimines, attempts were made to produce ketene mercaptals containing aliphatic as well as aromatic substituents. When dimethylketene-*N*-(*p*-tolyl)imine (**6**) is treated with excess thiophenol at reflux with added HCl and then the reaction mixture is distilled, a fraction boiling at 168° (0.8 mm) is obtained (86% yield) which has an elemental analysis compatible with **7** and has nmr

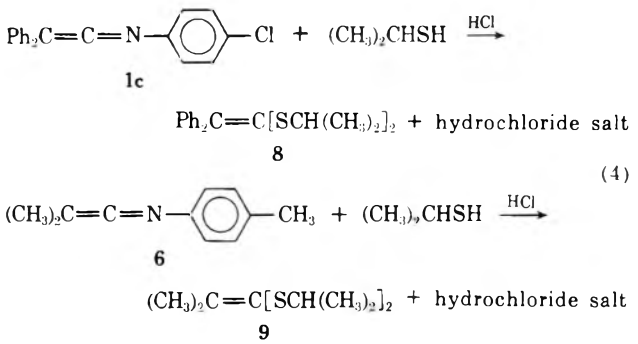


**6**

**7**

absorptions for the methyl protons at δ 1.88 and the phenyl protons at δ 6.2.

Treatment of ketenimine **1c** or **6** with 2-propanethiol and HCl yielded oily liquids (eq 4). The expected



**1c**

**8**

**9**

(4)

product from ketenimine **1c** is **8** and that from **6** is **9**.

The product thought to be **9** was obtained in a crude yield of 24% and possessed nmr absorption at δ 1.22 [d, $-CH(CH_3)_2$], about 2.5 [m, $-CH(CH_3)_2$], and 2.07 [s, $(CH_3)_2C=$]. Likewise, **8** has an nmr spectrum compatible with the proposed structure. However, distillation did not yield analytically pure samples of these two particular ketene mercaptals.[8] Since other preparations are available for these last two ketene mercaptals,[7,9] the additional isolation work was not performed.

In conclusion, the preparation of thioimidates from ketenimines and mercaptans has been shown to be an effective reaction limited only by the availability of ketenimines.[10] The preparation of the synthetically important ketene mercaptals[11] from the reaction of ketenimines and mercaptans under acid catalysis gave insolable products only when thiophenol was employed as the mercaptan. However, the ease of producing these ketene mercaptals by this process makes it potentially useful.

### Experimental Section[12]

**Preparation of Thioimidates.**—The synthesis of phenyl *N*-*p*-chlorophenyldiphenylthioacetimidate (**2c**) is typical for preparation of the thioimidates in Table I prepared from ketenimines and thiophenol. A solution of 5 g (0.017 mol) of diphenylketene-*N*-(*p*-chlorophenyl)imine and 10 g of thiophenol in 50 ml of benzene was heated to reflux for 24 hr. The benzene and excess thiophenol were removed at reduced pressure (aspirator) and the residue was dissolved in 50 ml of hot hexane. Slow cooling of the hexane solution resulted in the precipitation of 5 g (73%) of colorless crystals, mp 81–83°. The product exhibited an ir absorption of 1635 $cm^{-1}$ indicative of the imine stretch and nmr absorptions at δ 5.0 (benzhydryl proton) and centered on 7.1 (aromatic protons). An analytical sample of the crude product from a similar run was prepared by recrystallization from hexane, mp 83.5–84.0°.

The thioimidates from ethyl and *n*-propyl mercaptan were prepared in a similar manner except for the temperature, which was kept compatible with the mercaptan (35° for ethyl and 60° for *n*-propyl).

Thioimidates **2a** and **2j** were also prepared by adding the sodium salt of thiophenol and of *n*-propyl mercaptan, respectively, to **1a**. The products were identical with those produced from the mercaptans and the yield by this procedure for **2a** was 55% and for **2j** was 49%.

**Diphenylketene Diphenylmercaptal. A. From 1a and Thiophenol.**—A solution of 5 g (0.014 mol) of **1a** and 4.7 g of thiophenol was heated to 169° for 24 hr. The excess thiophenol was removed under reduced pressure (aspirator) and the residue was extracted with hot hexane (2 × 15 ml). Concentration and cooling of the hexane solution afforded 4.8 g (84%) of pale yellow needles, mp 92.5–96.5°. Subsequent recrystallization from

(7) H. C. Volger and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **76**, 847 (1957).

(8) The combination of aliphatic mercaptan smell and an inadequate ventilation system prevented in-depth studies on the isolation of these products.

(9) F. A. Carey and A. S. Court, *J. Org. Chem.*, **37**, 1926 (1972).

(10) H. Bestman, J. Lienert, and L. Mott, *Justus Liebigs Ann. Chem.*, **718**, 24 (1968); C. L. Stevens and G. H. Singhal, *J. Org. Chem.*, **29**, 34 (1964).

(11) D. Borrmann, "Sauerstoffverbindungen II," Teil 4, in "Methoden der Organischen Chemie," Band VII, Teil 4, E. Muller, Ed., Georg Thieme Verlag, Stuttgart, 1968, p 404.

(12) Melting points were determined on Fisher-Johns or Mel-Temp apparatus and are corrected. Infrared spectra were determined on a Perkin-Elmer Infracord in KBr, Nujol, and carbon tetrachloride. Nuclear magnetic resonance spectra were determined on either a Jeolco Minimar or a Varian A-60 spectrometer in carbon tetrachloride. Mass spectra were determined on either a Perkin-Elmer Model 270 or Hewlett-Packard Model 5930 mass spectrometer. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

hexane gave a sample melting at 111.0–111.5° (lit.[6] mp 112°). Product identification is based on the nmr (absorptions for aromatic protons at δ 7.2 and 7.35), hydrolysis with concentrated sulfuric acid in glacial acetic acid to diphenylacetic acid, and an elemental analysis which is compatible with the known compound. From the hexane-insoluble residue was obtained 2.05 g (82%) of aniline hydrobromide, mp 283–285°. Identification was made by converting the hydrobromide to aniline and comparing it with an authentic sample.

The other ketenimines listed in Table I did not yield a ketene mercaptal under these conditions.

**B. From Ketenimines, Thiophenol, and Acid Catalysts.**—A solution of 5 g (0.019 mol) of **1e** in 20 ml of thiophenol was heated to reflux for 3 hr. During this period of reflux dry HCl was introduced into the solution continuously. The excess thiophenol was removed under reduced pressure (aspirator), and the residue was extracted with hot hexane (4 × 25 ml). As the hexane solution cooled, 4.8 g (62.7%) of diphenylketene diphenylmercaptal, mp 108–110°, precipitated.

The other ketenimines in Table II were treated in a similar manner to give diphenylketene diphenylmercaptal. Subsequently it was observed that similar yields of **3** could be obtained from these ketenimines, thiophenol, and gaseous HCl in benzene solutions heated to reflux. Thus 80° is sufficient for the synthesis.

**C. From Thioimidates.**—A solution of 4 g (0.01 mol) of **2c** in 20 ml of thiophenol was heated to reflux for 45 min. Dry HCl was introduced continuously into the solution during reflux. Work-up of the reaction mixture as already described gave 2.1 g (53%) of **3**.

**Dimethylketene Diphenylmercaptal.**—A solution of 5 g (0.034 mol) of dimethylketene-*N*-(*p*-tolyl)imine in 30 ml of thiophenol was heated to reflux for 45 min. Dry HCl was introduced into the solution during reflux. The excess thiophenol was removed under reduced pressure (aspirator) and the residue was extracted with hot hexane. Removal of the hexane left 9.4 g (86%) of a yellow, oily liquid which was distilled twice to produce an analytical sample: bp 169° (0.8 mm); nmr ($CCl_4$) δ 1.88 [s, $(CH_3)_2C=$] and 6.2 (m, aromatic protons).

*Anal.* Calcd for $C_{16}H_{16}S_2$: C, 70.59; H, 5.88. Found: C, 70.47; H, 5.86.

**Attempted Synthesis of Dimethylketene Diisopropylmercaptal.**—To a solution of 6.3 g (0.04 mol) of dimethylketene-*N*-(*p*-tolyl)-imine in 20 ml of 2-propanethiol was added dry HCl. The reaction mixture immediately warmed to reflux and maintained reflux for 15 min. The excess 2-propanethiol was removed under reduced pressure (aspirator) and the residue was extracted with hot hexane. Removal of the hexane left 1.9 g (24%) of yellow liquid: nmr ($CCl_4$) δ 1.22 (d, 12), 3.07 (s, 6), and 2.5 (m, 2); mass spectrum (70 eV) *m/e* (rel intensity) 204 (8.6), 161 (6.7), 129 (4.8), 120 (6.7), 119 (9.5), 114 (3.8), 87 (34.3), 86 (53.3), 85 (38.1), 75 (18.1), 72 (20.1), 59 (23.8), 53 (19.1), 43 (94.3), and 41 (100).

**Attempted Synthesis of Diphenylketene Diisopropylmercaptal.**—A solution of 5 g (0.016 mol) of **1c** in 40 ml of 2-propanethiol and 20 ml of benzene was heated to reflux for 4 hr while dry HCl was continuously added. Work-up in the usual manner left 5.3 g (98%) of yellow liquid: nmr ($CCl_4$) δ 1.07 (d, 12). 1.83 (s, 6) and 3.0 (m, 2); mass spectrum (70 eV) *m/e* (rel intensity) 326 (4), 283 (97.7), 190 (19.3), 165 (100), 210 (24.5), 115 (6.8), 89 (13.6), 75 (8.0), 65 (3.2), 43 (9.1), and 41 (12.5).

**Acknowledgment.**—We wish to thank the Vice-President for Research and the Biological and Physical Science Institute of Mississippi State University for partial support of this effort.

**Registry No.**—**1a**, 29376-76-9; **1b**, 41563-33-1; **1c**, 17205-60-6; **1d**, 17518-16-0; **1e**, 14181-84-1; **1f**, 5110-45-2; **1g**, 40012-82-6; **1h**, 41563-37-5; **2a**, 41563-38-6; **2b**, 41563-39-7; **2c**, 41563-40-0; **2d**, 41563-41-1; **2e**, 41563-42-2; **2f**, 41563-43-3; **2g**, 41563-44-4; **2h**, 41563-45-5; **2i**, 41563-46-6; **2j**, 41563-47-7; **3**, 41563-48-8; **6**, 18779-86-7; **7**, 41563-50-2; **8**, 41563-51-3; **9**, 41563-52-4; thiophenol sodium salt, 930-69-8; *n*-propyl mercaptan sodium salt, 6898-84-6; thiophenol, 108-98-5; ethyl mercaptan, 75-08-1; *n*-propyl mercaptan, 107-03-9; aniline hydrobromide, 542-11-0; 2-propanethiol, 75-33-2.

## The Synthesis of 1,3-Dithiolanone Derivatives

SADAYOSHI SATSUMABAYASHI,* HIDEO TAKAHASHI, TOSHIHIRO TANAKA, AND SHINICHI MOTOKI

*Department of Chemistry, Science University of Tokyo, Kagurazaka 1-3, Shinjuku-ku, Tokyo, Japan*

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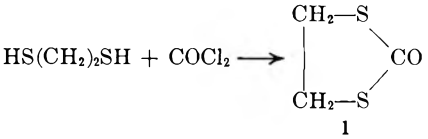
Although 1,3-dithiolan-2-one (**1**) has been prepared by the action of HgO on ethylene trithiocarbonate[1] or COS on ethylene sulfide,[2] the materials used are rather inaccessible. 1,3-Dithiolan-4-one derivatives (**2**) have not appeared in the literature. In this paper, we will describe a simple method of preparation of **1** and the synthesis of new compound **2**.

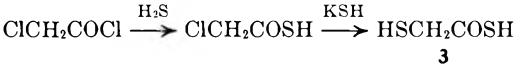
The compound **1** was readily prepared by the reaction of ethanedithiol with phosgene in the presence of




**1**

pyridine in fairly good yield. This reaction was carried out at 0°, but a large amount of polymeric substance was formed above 30°.

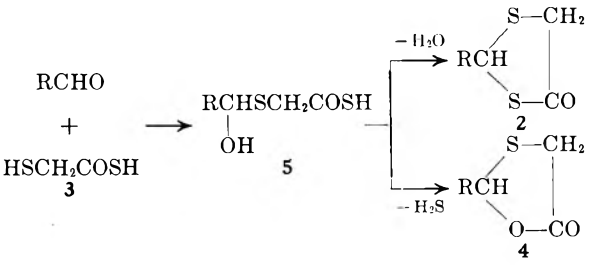
The 4-one derivatives **2** should be obtainable by condensation of mercaptothioacetic acid (**3**) with aldehydes.




**3**

The acid **3**, which has not been reported in the literature, was obtained in a good yield from the reaction of chloroacetyl chloride with hydrogen sulfide, followed by treatment with potassium hydrogen sulfide.

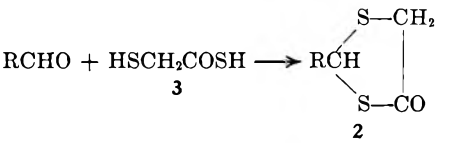
The reactions of **3** with aldehydes were carried out in the presence of *p*-toluenesulfonic acid, and the expected product **2** was obtained in a yield of 25–45%, together with the corresponding 1,3-oxathiolan-5-one (**4**). Considering the formation of these two products, compound **5** was assumed to be the reaction interme-




(1) C. G. Overberger and P. V. Bonsigner, *J. Amer. Chem. Soc.*, **80**, 5427 (1958).

(2) V. S. Etlis, L. N. Grobov, and G. A. Razuvaev, *Zh. Obshch. Khim.*, **32**, 2940 (1962); *Chem. Abstr.*, **58**, 7817a (1963).

TABLE I
1,3-DITHIOLAN-4-ONE DERIVATIVES




| R | Yield, % | Bp, °C (mm) | Nmr ($CCl_4$), δ | Element | Calcd, % | Found, % |
|---|---|---|---|---|---|---|
| $CH_3$ | 27 | 85–86 (6) | 4.95 (q, 1 H) | C | 35.83 | 35.92 |
| | | | 3.71 (s, 2 H) | H | 4.51 | 4.55 |
| | | | 1.76 (d, 3 H) | S | 47.73 | 47.72 |
| $C_2H_5$ | 29 | 86 (2) | 4.74 (t, 1 H) | C | 40.54 | 40.59 |
| | | | 3.63 (s, 2 H) | H | 5.44 | 5.40 |
| | | | 2.28–1.80 (m, 2 H) | S | 43.21 | 43.04 |
| | | | 1.10 (t, 3 H) | | | |
| $n$-$C_3H_7$ | 42 | 96–99 (2) | 4.82 (t, 1 H) | C | 44.44 | 44.56 |
| | | | 3.64 (s, 2 H) | H | 6.22 | 6.09 |
| | | | 2.20–1.23 (m, 4 H) | S | 39.47 | 39.54 |
| | | | 0.98 (t, 3 H) | | | |
| $C_6H_6$ | 31 | 141–143 (2) (mp 50–51) | 7.60–7.17 (m, 5 H) | C | 55.10 | 55.29 |
| | | | 5.93 (s, 1 H) | H | 4.11 | 4.05 |
| | | | 3.74 (s, 2 H) | S | 32.62 | 32.71 |

diate, but attempts to isolate **5** resulted in failure. The structures of the products **2** were confirmed with the elemental analyses and nmr spectra presented in Table I. Identification of the products **4** was made by comparison of their physical properties with reported values.[3]

### Experimental Section

**1,3-Dithiolan-2-one (1).**—To a solution of 1,2-ethanedithiol (9.4 g, 0.1 mol) and pyridine (15.8 g, 0.2 mol) in toluene (150 ml), phosgene (9.9 g, 0.1 mol) dissolved in 35 ml of toluene was added at 0°. The mixture was stirred for 3 hr at the same temperature, and precipitated pyridine hydrochloride was filtered off. The filtrate was washed (10% aqueous $Na_2CO_3$), dried ($Na_2SO_4$), and distilled. A fraction, bp 78–82° (4 mm), was collected, cooled, and recrystallized from $n$-hexane to give **1**: mp 34–35° (lit. mp 34°);[1,2] yield 8.1 g (67.5%); nmr ($CCl_4$) δ 3.69 (s).

*Anal.* Calcd for $C_3H_4OS_2$: C, 30.01; H, 3.36; S, 53.30. Found: C, 30.03; H, 3.32; S, 53.23.

**Mercaptothioacetic Acid (3).**—Hydrogen sulfide was passed into a mixture of chloroacetyl chloride (79 g, 0.7 mol) and anhydrous aluminum chloride (2.0 g) at 0° for 30 hr. The reaction mixture was filtered and the filtrate was distilled to obtain chlorothioacetic acid (56.2 g, 72.7%), bp 34–36° (5 mm).

A solution of KOH (90 g) in ethanol (90%, 270 ml) was saturated with $H_2S$ at 0°, and chlorothioacetic acid (30 g, 0.27 mol) was added slowly at about −5°. After KCl was removed by precipitation, the filtrate was concentrated to about 100 ml, acidified with cold 3 $N$ HCl, and extracted with ether. Distillation gave **3**: bp 61–62° (8 mm); yield 24.6 g (84.5%); nmr ($CCl_4$) δ 5.18 (s, 1 H), 3.60 (d, 2 H), 2.37 (t, 1 H); ir bands at 2550, 1680 $cm^{-1}$.

*Anal.* Calcd for $C_2H_4OS_2$: C, 22.23; H, 3.73; S, 59.23. Found: C, 22.45; H, 3.77; S, 58.97.

**1,3-Dithiolan-4-one (2).**—To a solution of **3** (0.25 mol) and $p$-toluenesulfonic acid (0.5 g) in benzene (250 ml), aldehyde (0.5 mol) was added slowly at room temperature and stirred for 5 hr. The mixture was then refluxed for 10 hr, the water formed in the reaction being removed continuously by azeotropic distillation, washed (10% aqueous $Na_2CO_3$), dried ($Na_2SO_4$), and fractionally distilled to give two fractions and residual tar. The first fraction was the compound **4** (yield 5–15%); the second was redistilled to give **2** (Table I). The ir spectra of **2** showed strong absorption of C=O in the range of 1690–1685 $cm^{-1}$.

(3) S. Satsumabayashi, S. Irioka, H. Kudo, K. Tsujimoto, and S. Motoki, *Bull. Chem. Soc. Jap.*, **45**, 913 (1972).

**Registry No.**—**1**, 2080-58-2; **2** (R = $CH_3$), 41755-28-6; **2** (R = $C_2H_5$), 41755-29-7; **2** (R = $n$-$C_3H_7$), 41701-10-4; **2** (R = Ph), 41701-11-5; **3**, 30298-36-3; acetaldehyde, 75-07-0; propionaldehyde, 123-38-6; butyraldehyde, 123-72-8; benzaldehyde, 100-52-7.

## Raney Nickel Catalyzed Decarbonylation of Formate Esters

M. R. SANDNER* AND D. J. TRECKER

*Union Carbide Corporation, Chemicals and Plastics, South Charleston, West Virginia 25303*

*Received May 14, 1973*

During investigation of a series of formate esters, we had occasion to study the effect of high-temperature treatment in the presence of Raney nickel (activity W2).[1] At reflux the esters were observed to undergo smooth decarbonylation to the corresponding alcohols. Subsequent dehydrogenation to the corresponding aldehydes or ketones also occurred under reaction conditions.[2-5] Typical product distributions for a variety of formate esters are shown in Table I.

$$RR'CHOCH \overset{\text{Raney Ni}}{\underset{\text{reflux (>150°)}}{\longrightarrow}} RR'CHOH + CO + (RR'C{=}O + H_2)$$

Little reaction was observed below 150°, with rates increasing as the boiling points of the higher formates were approached. As indicated in Table I, conversion of low-boiling esters (*e.g.*, $n$-hexyl and cyclohexyl for-

(1) R. L. Augustine, "Catalytic Hydrogenation, Technique and Applications in Organic Synthesis," Marcel Dekker, New York, N. Y., 1965, pp 26–28, 147.
(2) E. J. Badin, *J. Amer. Chem. Soc.*, **65**, 1809 (1943).
(3) E. C. Kleiderer and E. C. Kronfeld, *J. Org. Chem.*, **13**, 455 (1948).
(4) C. Thonon and J. C. Jungers, *Bull. Soc. Chim. Belg.*, **59**, 604 (1950).
(5) S. B. Mahato, S. K. Banerjee, and R. N. Chakravarti, *Tetrahedron*, **27**, 177 (1971).

TABLE I

NICKEL-CATALYZED DECARBONYLATION OF FORMATE ESTERS

| Registry no. | Compd (solvent) | Wt of ester/ wt of Raney Ni | Reaction temp, °C | Reaction time, hr | Products | Distribution[a] |
|---|---|---|---|---|---|---|
| 629-33-4 | *n*-Hexyl formate (neat) | 25 | 150–155 | 30 | *n*-Hexyl formate | 61 |
| | | | | | 1-Hexanol | 30 |
| | | | | | *n*-Hexaldehyde | 9 |
| | *n*-Hexyl formate (diethoxytetraglycol) | 30 | 230–250 | 12[b] | *n*-Hexyl formate | 42 |
| | | | | | 1-Hexanol | 16 |
| | | | | | *n*-Hexaldehyde | 37 |
| | | | | | Hexenes | 5 |
| 4351-54-6 | Cyclohexyl formate (neat) | 50 | 155–160 | 27 | Cyclohexyl formate | 75 |
| | | | | | Cyclohexanol | 9 |
| | | | | | Cyclohexanone | 16 |
| | Cyclohexyl formate (diethoxytetraglycol) | 35 | 230–250 | 11[b] | Cyclohexyl formate | 12 |
| | | | | | Cyclohexanol | 22 |
| | | | | | Cyclohexanone | 62 |
| | | | | | Phenol | 4 |
| 41498-71-9 | 2-*exo*-Norbornyl formate (neat) | 50 | 170–175 | 19 | 2-*exo*-Norbornyl formate | 41 |
| | | | | | 2-*exo*-Norbornanol | 18 |
| | | | | | 2-Norbornanone | 41 |
| 41498-15-1 | 8-*exo*-Tricyclo[5.2.1.$0^{2,6}$]decyl formate (neat) | 37.5 | 220–230 | 2 | 8-*exo*-Tricyclo[5.2.1.$0^{2,6}$]decyl formate | 0 |
| | | | | | 8-*exo*-Tricyclo[5.2.1.$0^{2,6}$]decanol | 20 |
| | | | | | 8-*exo*-Tricyclo[5.2.1.$0^{2,6}$]decanone | 75 |
| | | | | | Others | 5 |
| 5331-67-9 (4) 41498-17-3 (5) | 8-*exo*-Tricyclo[5.2.1.$0^{2,6}$]dec-4- (or 5-) enyl formate (neat) | 50 | 230–235 | 3.2 | 8-*exo*-Tricyclo[5.2.1.$0^{2,6}$]dec-4(5)-enyl formate | 9.5 |
| | | | | | 8-*exo*-Tricyclo[5.2.1.$0^{2,6}$]dec-4(5)-enol | 25 |
| | | | | | 8-*exo*-Tricyclo[5.2.1.$0^{2,6}$]dec-4(5)-anone | 62 |
| | | | | | Others | 13.5 |
| 104-57-4 | Benzyl formate, 80[c] Benzyl acetate, 8 Benzyl alcohol, 12 (neat) | 24 | 180–190 | 9 | Benzyl formate | 18 |
| | | | | | Benzyl acetate | 11 |
| | | | | | Benzyl alcohol | 29 |
| | | | | | Benzaldehyde | 21 |
| | | | | | Toluene | 19 |
| | | | | | Benzene | 2 |
| 100-51-6 | Benzyl alcohol (neat) | 20 | 170–190[d] | 15 | Benzyl alcohol | 15 |
| | | | | | Benzaldehyde | 14 |
| | | | | | Toluene | 35 |
| | | | | | Benzene | 34 |
| | | | | | Others | 2 |

[a] Product distribution determined by ir-glc area per cent (see Experimental Section). [b] Total recycle time, not actual contact time. [c] Benzyl formate was prepared by the method of Stevens and Van Es;[18] composition was that obtained in a refined fraction.[a] [d] Reaction temperature was controlled by periodic removal of volatiles. Volatiles were recomposited with product mixture for analysis.

mates) was enhanced by continuously feeding these materials to a suspension of Raney nickel in a high-boiling solvent. The volatile components were flashed overhead and recycled to increase conversion.

It is noteworthy that *n*-hexaldehyde, formed by *in situ* dehydrogenation of 1-hexanol, was not further oxidized to hexanoic acid or decarbonylated to *n*-pentane, even at 230–250°. The only olefinic product observed was a mixture of hexenes, presumably formed by formate pyrolysis.[6] Of further significance was the observation that the double bond in 8-*exo*-tricyclo-[5.2.1.$0^{2,6}$]dec-4- (or 5-) enyl formate was not hydrogenated under reaction conditions.[7]

Control experiments indicated that the decarbonylation was specific for formate esters. Cyclohexyl acetate and phenyl acetate were unaffected even after prolonged contact with the catalyst.[8]

These results stand in contrast to the work of Matthews, Ketter, and Hall,[9] who observed that alkyl formates were converted to the corresponding alcohols by treatment with palladium on charcoal. Under these conditions benzyl formate was converted primarily to toluene and carbon dioxide with only small amounts of benzene, benzaldehyde, and benzyl alcohol detected. Raney nickel treatment of refluxing benzyl formate, on the other hand, afforded benzyl alcohol, benzaldehyde, and toluene as the principal products (Table I).

The reaction pathway apparently involved formate decarbonylation to benzyl alcohol, which control experiments indicated then underwent dehydrogenation to benzaldehyde. Measurable amounts of benzene were formed from the subsequent nickel-catalyzed decarbonylation of benzaldehyde.[10,11]

Our data suggest that the formate decarbonylation process need not involve discrete free-radical intermediates. The energetics for homolysis of the formyl

(6) A. Maccoll, *J. Chem. Soc.*, 3398 (1958).

(7) F. Bergman and H. Japhe, *J. Amer. Chem. Soc.*, **69**, 1826 (1947).

(8) The stability of phenyl acetate in the presence of Raney nickel obviates the possibility of a hydrolytic pathway resulting from traces of residual caustic in the catalyst. All esters investigated were thermally stable under reaction conditions in the absence of catalyst.

(9) J. S. Matthews, D. C. Ketter, and R. F. Hall, *J. Org. Chem.*, **35**, 1694 (1970).

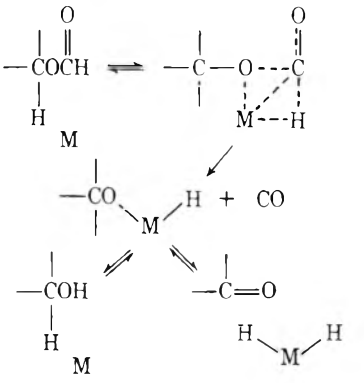
(10) P. Sabatier and J. B. Senderens, *C. R. Acad. Sci.*, **137**, 301 (1903).

(11) T. J. Snen and S. Fan, *J. Amer. Chem. Soc.*, **65**, 1243 (1943).

hydrogen bond would be similar to that of aldehydes[12] and would produce the corresponding alkoxycarbonyl radical. Recent investigations indicated that this radical is quite stable at moderate temperatures and undergoes coupling rather than decarboxylation.[13] Loss of $CO_2$ has been observed[14] in instances where decarboxylation leads to stable alkyl radicals. Products of radical coupling or significant amounts of products derived from loss of $CO_2$ were not observed under our reaction conditions, even with benzyl formate where substantial driving force for formation of the stable benzyl radical might be expected. As indicated in Table I, toluene was likely formed from hydrogenolysis of benzyl alcohol.

A probable mechanism involves initial cleavage of the ester linkage to yield catalyst-bound alkoxy and carbonyl species. Loss of carbon monoxide would produce an adsorbed alcohol intermediate similar to that proposed for hydrogen–deuterium exchange and oxidation of alcohols over metallic surfaces.[15-17] This intermediate could then partition to either or both alcohol and carbonyl products (Scheme I). The product

SCHEME I



composition obtained from treatment of formate esters in the presence of Raney nickel is compatible with the intermediacy of highly polar species. The initial ester cleavage likely involves closely bound ionic or radical moieties which are formed *via* electron transfer with the metal surface.

### Experimental Section

**Materials.**—The chemicals used in this investigation were obtained from suitable commercial sources and checked for purity prior to use or were synthesized using literature methods. Raney nickel was obtained from W. R. Grace, Davison Chemical Division, as Davison Raney nickel, grade 28. The material possessed approximately the same activity as Raney nickel, W2.[1] The following compounds were prepared by the indicated methods and were used as reactants or for comparison purposes: benzyl formate, prepared by the method of Stevens and Van Es;[18] cyclohexyl formate and *exo*-2-norbornyl formate, prepared by addition of formic acid to the corresponding olefins;[19] cyclohexyl acetate, prepared from cyclohexanol by treatment with acetic anhydride–pyridine and product purity confirmed by ir analysis;[20] 8-*exo*-tricyclo[5.2.1.$0^{2,6}$]dec-4- (or 5-) enyl formate and 8-*exo*-tricyclo[5.2.1.$0^{2,6}$]decyl formate, prepared by the method of Bergman and Japhe;[21] and 8-tricyclo[5.2.1.$0^{2,6}$]dec-4- (or 5-) enone, 8-tricyclo[5.2.1.$0^{2,6}$]decanone, and 8-exo-tricyclo[5.2.1.$0^{2,6}$]decanol, prepared by the method of Bruson and Reiner.[22]

**Analyses.**—Glc analyses were performed on an F & M 5750 chromatograph using both a 10 ft × 0.25 in. stainless-steel column of 15% FFAP on Chromosorb W (60/80 mesh) and a similar column of 10% W-98 on Chromosorb G (60/80 mesh). Individual peaks were identified by comparison with authentic materials and by infrared spectral comparisons[20] of the product mixtures. Further confirmation was provided by nmr spectral analyses.

**Typical Procedure.**—In a typical experiment, a 50-ml, three-neck flask was equipped with a distillation head with provision for variable take-off, a thermometer, and a nitrogen inlet tube. Weighed amounts of 2-*exo*-norbornyl formate (15 g) and Raney nickel (0.3 g) were added to the flask. The system was maintained under a positive nitrogen pressure and the contents were stirred magnetically and heated to reflux (170–175°). Reaction progress was followed by glc analysis. When heating was discontinued (19 hr), the reaction vessel was allowed to cool and a small amount of filter aid was introduced. The contents of the flask were then collected by suction filtration and subjected to analysis by ir-glc (Table I). Typical material balances ranged from 85 to 97%.

**Registry No.**—Nickel, 7440-02-0.

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(13) D. E. Zabel and W. S. Trahanovsky, *J. Org. Chem.*, **37**, 2413 (1972).
(14) D. Griller and B. P. Roberts, *Chem. Commun.*, 1035 (1971).
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(16) W. R. Patterson and R. L. Burwell, Jr., *J. Amer. Chem. Soc.*, **93**, 833 (1971).
(17) W. R. Patterson, J. A. Roth, and R. L. Burwell, Jr., *J. Amer. Chem. Soc.*, **93**, 829 (1971).
(18) W. Stevens and A. Van Es, *Recl. Trav. Chim. Pays-Bas*, **83**, 1287 (1964).
(19) D. C. Kleinfelter and P. v. R. Schleyer, *Org. Syn.*, **42**, 79 (1962).
(20) Infrared spectra for comparative purposes were taken from collections of spectra in "Documentation of Molecular Spectroscopy," Butterworths, London, or "Sadtler Standard Spectra," Sadtler Research Laboratories, Inc., Philadelphia, Pa.
(21) F. Bergman and H. Japhe, *J. Amer. Chem. Soc.*, **69**, 1826 (1947).
(22) H. A. Bruson and T. W. Riener, *J. Amer. Chem. Soc.*, **67**, 723 (1945).

## New Lossen Rearrangement Precursors. The Relative Rates of Rearrangement of Nitrophenylbenzhydroxamates in Aqueous Base

J. S. SWENSON,*[1] A. M. DAVIS, R. A. DEYO, B. W. GRAHAM, E. P. JAHN, AND J. D. MATTICE

*Department of Chemistry, Grinnell College, Grinnell, Iowa 50112*

*Received August 2, 1973*

Data in the literature support the theory that the rate of the Lossen rearrangement is directly proportional to the acidity of the leaving group or its conjugate acid where the leaving group is a basic anion.[2-6] However, all of the examples of hydroxamic acid derivatives which have been studied are acylhydroxamates where the leaving group is a carboxylic acid or its conjugate base. Therefore, the data available to test this theory are limited to a relatively narrow range of acidities ($pK_a$ = 2–5) for the leaving group or its conjugate acid. The objective of this study was to prepare Lossen rearrangement precursors where the conjugate acids of the basic anion leaving groups have $pK_a$ values >5 in order to test the classical theory over

(1) Address correspondence to this author at Department of Chemistry, Northern Arizona University, Flagstaff, Ariz. 86001.
(2) R. D. Bright and C. R. Hauser, *J. Amer. Chem. Soc.*, **61**, 618 (1939).
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TABLE I
RATE CONSTANTS AND ACTIVATION ENERGIES FOR THE LOSSEN REARRANGEMENT[a]

| Registry no. | Compd | Temp, °K | $k$, $min^{-1}$ | Av dev, %[b] | $E_a$, kcal | $pK_a$[c] |
|---|---|---|---|---|---|---|
| 41828-26-6 | *p*-Nitrophenylbenzhydroxamate | 342 | 0.00301 | 2.1 | | |
| | | 351 | 0.0108 | 3.7 | 34.5 | 7.14 |
| | | 356 | 0.0193 | 1.6 | | |
| 41828-27-7 | *o*-Nitrophenylbenzhydroxamate | 333 | 0.00895 | 4.3 | | |
| | | 342 | 0.0288 | 2.7 | 30.4 | 7.23 |
| | | 351 | 0.0861 | 4.6 | | |
| 41828-28-8 | 2,4-Dinitrophenylbenzhydroxamate | 303 | 0.0168 | 3.5 | 25.6 | 4.13 |
| | | 313 | 0.0692 | 2.6 | | |
| 7340-13-8 | *m*-Nitrobenzoylbenzhydroxamate | 313 | 0.0216 | 1.0 | 25.4 | 3.5 |
| | | 323 | 0.0685 | 1.2 | | |

[a] All of the rearrangement reactions were run in water at pH 11. [b] These are the average relative deviations from the mean for the rate constants. [c] These are literature values for the conjugate acids of the leaving groups.

a wider range of relative acidities for the conjugate acids of the leaving groups.

Two new nitrophenylbenzhydroxamate derivatives were synthesized where the conjugate acids of the nitrophenoxide leaving groups have $pK_a$ values of 7.14 and 7.23,[7] namely, *p*-nitrophenylbenzhydroxamate and *o*-nitrophenylbenzhydroxamate. In addition to studying the rates for the Lossen rearrangement of these new benzhydroxamic acid derivatives, we undertook to study the rearrangement rate for 2,4-dinitrophenylbenzhydroxamate which had been synthesized by Gallop and Seifter,[8,9] who did not provide data concerning its relative rate of rearrangement. We also studied the rate of rearrangement for *m*-nitrobenzoylbenzhydroxamate in order to relate our data to the previously published data.[2,3]

The Lossen rearrangement reactions were first order and were followed spectrophotometrically to determine the rate constants. The activation energies were determined from the slope $(-E_a/R)$ of the plot of ln $k$ *vs.* $1/T$. The results are summarized in Table I.

The activation energy for the rearrangement of *m*-nitrobenzoylbenzhydroxamate was found to be 25.4 kcal with a rate constant of 0.0216 $min^{-1}$ at 40°. These values are in reasonable agreement with the 26.3 kcal for the activation energy and 0.0231 $min^{-1}$ for the rate constant at 40° reported by Bright and Hauser.[2]

Table I reveals that the classical theory of relating the rate of the Lossen rearrangement directly to the relative acidity of the conjugate acid of the anionic leaving group continues to hold, at least qualitatively, in the higher range of $pK_a$ values for the conjugate acids. However, owing to the fact that only three nitrophenol derivatives of benzhydroxamic acid could be synthesized for study, and that two of them involve phenols with ortho nitro groups which show an "ortho effect," no quantitative correlation between conjugate acid $pK_a$ values and rate constants or activation energies for these rearrangements could be made. Judson and Kilpatrick have shown that the ortho nitro group on *o*-nitrophenol has a definite "acid weakening effect."[10] This effect is most obvious when one compares the $pK_a$ of 7.14 for *p*-nitrophenol, which cannot participate in intramolecular hydrogen bonding, with the $pK_a$ value of 7.23 for *o*-nitrophenol. Therefore, it is not possible to correlate the $pK_a$ values for *o*-nitrophenol and 2,4-dinitrophenol quantitatively with the relative rates of rearrangement for their respective benzhydroxamic acid derivatives.

Despite these limitations it is obvious that there is a correlation between the relative base strengths of the phenoxide anion leaving groups and the rate constants and their related activation energies for the Lossen rearrangement. The *p*-nitrophenoxide anion would be expected to be the strongest base and the conjugate base of the weakest acid in the series of nitrophenylbenzhydroxamates. This would lead one to predict that *p*-nitrophenylbenzhydroxamate would have the highest activation energy (34.5 kcal) and the slowest reaction rate, which is substantiated by the fact that the rearrangement had to be run at the highest temperatures in order to obtain reasonable rates. At the other end of the scale the 2,4-dinitrophenylbenzhydroxamate showed the lowest activation energy (25.6 kcal) and the fastest reactions even at relatively low temperatures. This is to be expected since the 2,4-dinitrophenoxide anion is the weakest base and the conjugate base of the strongest acid. The *o*-nitrophenylbenzhydroxamate falls in between the other two with an activation energy of 30.4 kcal as would be predicted.

## Experimental Section

**Kinetic Measurements.**—The rate studies were carried out using a Beckman DB-G spectrophotometer. The reactions were followed by continuously recording the absorbance of an appropriate concentration of benzhydroxamate in a pH 11.0 water solution at a previously determined wavelength, *i.e.*, $4.0 \times 10^{-5}$ *M* *m*-nitrobenzoylbenzhydroxamate at 250 mμ, $3.6 \times 10^{-5}$ *M* 2,4-dinitrophenylbenzhydroxamate at 400 mμ, $3.0 \times 10^{-5}$ *M* *p*-nitrophenylbenzhydroxamate at 400 mμ, and $9.3 \times 10^{-5}$ *M* *o*-nitrophenylbenzohydroxamate at 420 mμ. Infinite absorbance readings were obtained by allowing the sample to stand overnight at the appropriate temperature to ensure complete reaction.

**Instruments.**—Nmr spectra were determined on a Varian A-60 spectrometer, infrared spectra were run on a Beckman IR-20 A spectrophotometer, and melting points (uncorrected) were taken in open capillary tubes with a Thomas-Hoover melting point apparatus.

Potassium benzhydroxamate was prepared according to the method of Hauser and Renfrow,[11] as was the *m*-nitrobenzoylbenzhydroxamate.[3] The 2,4-dinitrophenylbenzhydroxamate was prepared in a manner analogous to that in the literature.[8,9]

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(10) C. M. Judson and M. Kilpatrick, *J. Amer. Chem. Soc.*, **71**, 3115 (1949).
(11) C. R. Hauser and W. B. Renfrow, Jr., "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 67.

*p*-Nitrophenylbenzhydroxamate.—In a 250-ml flask equipped with a mechanical stirrer, a powder dropping funnel containing 5.80 g (0.0331 mol) of powdered potassium benzhydroxamate, a dropping funnel containing 40 ml of dimethyl sulfoxide, and a thermometer were placed 27 ml (0.338 mol) of dry, freshly distilled pyridine and 55.62 g (0.395 mol) of distilled *p*-fluoronitrobenzene. The system was flushed with dry nitrogen gas and sealed from the atmosphere. The reaction was initiated at room temperature by simultaneously adding small amounts of the powdered potassium benzhydroxamate and dimethyl sulfoxide to the stirred reaction flask. The reaction mixture immediately turned yellow with the color gradually deepening through orange to a dark red as the reaction proceeded. The balance of the potassium benzhydroxamate was added in small increments over a period of 1 hr along with just sufficient dimethyl sulfoxide to dissolve any solid products that formed. The temperature of the reaction mixture rose to 38° in about 15 min and was maintained between 38 and 40° for the balance of the reaction. The reaction mixture was evaporated to dryness in a rotary evaporatory at 40° (0.28 mm). The solid residue was dissolved in a minimum (200–300 ml) of 0.1 *N* sodium hydroxide solution. The solution was acidified with hydrochloric acid to pH 8.4 to precipitate the crude product. Subsequent crops of less pure product may be obtained by further lowering the pH to 7. The crude product was purified by repeated recrystallizations from chloroform to give a 30% yield of white crystals: mp 139.8–141.3°; ir (KBr) 3400, 3100, 2900, 1650 (C=O), 1580 (aromatic C=C), 1510 and 1340 (nitro), 1210 (*O*-phenyl), 1155, 1110, 1020, 910, 852, and 752 (nitro), 710, and 690 $cm^{-1}$; nmr (DMSO-$d_6$) $\delta$ 7.45 (d, 2, $J$ = 9 Hz, H ortho to O), 8.32 (d, 2, $J$ = 9 Hz, H ortho to $NO_2$), 7.55 (d, 1, $J$ = 2 Hz, H para to C=O), 7.64 (d, $J$ = 2 Hz), 7.92 (d, $J$ = 4 Hz), 8.05 (d, $J$ = 2.5 Hz), 3.3 (s, 1, NH); uv max (water, pH 10) 350 nm.

*Anal.* Calcd for $C_{13}H_{10}N_2O_4$: C, 60.44; H, 3.90; N, 10.85. Found: C, 60.37; H, 3.97; N, 10.98.

Further proof for the structure of *p*-nitrophenylbenzhydroxamate was obtained by rearranging a sample of its potassium salt in aniline solution to produce the expected products, *i.e.*, *sym*-diphenylurea and *p*-nitrophenol. The potassium salt was prepared by treating *p*-nitrophenylbenzhydroxamate in absolute ethanol solution with potassium ethoxide in equivalent amounts. The orange potassium *p*-nitrophenylbenzhydroxamate salt was then dissolved in freshly distilled aniline and heated to 120° for 1 hr to ensure complete rearrangement. The insoluble potassium *p*-nitrophenoxide salt was recovered from the reaction mixture and converted to *p*-nitrophenol, which was positively identified by comparison (mixture melting point and ir) with an authentic sample. The diphenylurea was isolated from the aniline solution to yield a sample which was also identical (mixture melting point and ir) with an authentic sample.

*o*-Nitrophenylbenzhydroxamate.—The reaction was run essentially as described for *p*-nitrophenylbenzhydroxamate except that 10.00 g (0.057 mol) of potassium benzhydroxamate, 50.28 g (0.354 mol) of *o*-fluoronitrobenzene, and no pyridine were used. The reaction mixture was dumped into 90 ml of 0.1 *N* sodium hydroxide solution at 0°. The excess *o*-fluoronitrobenzene separated as an oil and was removed. The resulting clear red solution was acidified by the dropwise addition of concentrated hydrochloric acid to precipitate the crude product as a greenish oil which crystallized within 5 min. The crude crystals were purified by recrystallizations from the following solvents in the order listed—chloroform, chloroform–carbon tetrachloride, 1,1,1-trichloroethane, and 4-octyne—followed by several washings with low-boiling petroleum ether to give a 14% yield of cream-colored needles: mp 107–111° dec; ir (KBr) 3440 (NH), 3100 (aromatic CH), 2920 (H-bonded NH), 1680 (C=O), 1615 (aromatic C=C), 1535 and 1367 (nitro), 1300, 1233 (*O*-phenyl), 1172, 1098, 1022, 912, 862, 743, and 705 $cm^{-1}$; uv max (water, pH 11) 357 nm.

*Anal.* Calcd for $C_{13}H_{10}N_2O_4$: C, 60.44; H, 3.90; N, 10.85. Found: C, 60.60; H, 3.91; N, 10.79.

Further proof for the structure of *o*-nitrophenylbenzhydroxamate was obtained by rearranging a sample of its potassium salt in an aniline solution to yield the expected products, *i.e.*, *o*-nitrophenyl and *sym*-diphenylurea, which were identified by comparison with authentic samples.

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**Registry No.**—Potassium benzhydroxamate, 32685-16-8; *p*-fluoronitrobenzene, 350-46-9; *o*-fluoronitrobenzene, 1493-27-2.

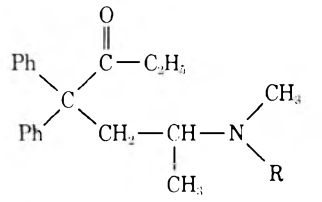
## An Anomalous Reaction of Methadone with Chloroformate Esters

NITHIANANDA CHATTERJIE AND CHARLES E. INTURRISI*

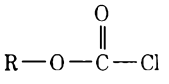
*Department of Pharmacology, Cornell University Medical College, New York, New York 10021*

*Received May 1, 1973*

Current interest in the biotransformations of methadone[1] (4,4-diphenyl-6-dimethylamino-3-heptanone, **1b**), and the identification of its metabolites[2,3] prompted us to investigate the chemical demethylation of this compound. In an attempt to synthesize authentic *N*-demethylmethadone (4,4-diphenyl-6-methylamino-3-heptanone, **1a**), which has not been isolated, the reactions of methadone (**1b**) with ethyl chloroformate (**2a**) and phenyl chloroformate (**2b**) were carried out



**1a**, R = H
**b**, R = $CH_3$
**c**, R = —C(=O)$OC_2H_5$
**d**, R = —C(=O)OPh



**2a**, R = $C_2H_5$
**b**, R = Ph

following essentially the procedure of Abdel-Monem and Portoghese.[4] The product obtained in both instances was a neutral, nitrogen-free compound, 2-ethylidene-5-methyl-3,3-diphenyltetrahydrofuran[5] (**3**), in yields of 25 and 50%, respectively. We did not observe formation of the expected carbamate esters **1c** and **1d**. The conditions employed in our reactions were considerably milder than those employed by other workers,[6] who used cyanogen bromide under reflux in their futile attempts to prepare **1a** by demethylation of **1b**. Our reactions were carried out by suspending the compound **1b** in the form of its hydrochloride in a mixture of tetrahydrofuran and sodium bicarbonate and stirring with **2a** or **2b** for 24 hr at room temperature. The reactions, on usual work-up, showed no evidence of a

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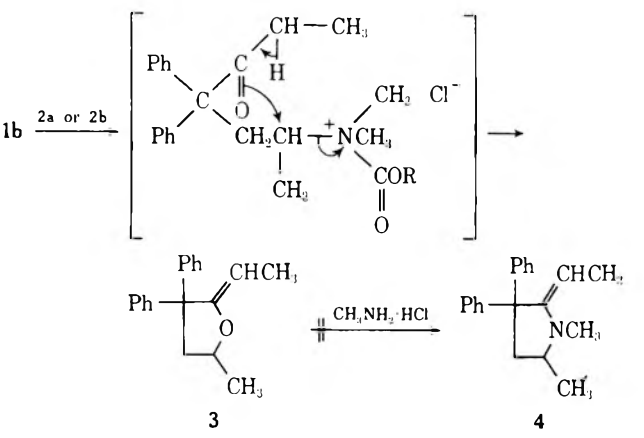
product containing nitrogen. The product **3** (Scheme I) was characterized by it smelting point and ir, nmr,[7] and

SCHEME I



mass spectra, and was found to be identical with the compound obtained by Easton and others on pyrolysis of the methiodide of methadone.[8] An attempt was made by us to convert **3** to **4** (by a variety of conditions; see Scheme I) which was unsuccessful. The compound **4** is a primary metabolite of methadone, which results from demethylation and cyclization.[1,2] However, it is not known whether **3** could result from the biotransformation of methadone, in view of its facile formation, under such mild conditions as employed in our attempted demethylation reaction.

### Experimental Section

Melting points of compounds were determined on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were obtained with a Perkin-Elmer Infracord (KBr disk). Proton magnetic resonance spectra were obtained with a Varian XL 100 instrument ($CDCl_3$, TMS). Mass spectra were obtained with a Du Pont 492 mass spectrometer. Thin layer chromatography was performed on Analtech plates with florescent indicator. Methadone hydrochloride (racemic) was obtained from Eli Lilly and Co., Indianapolis, Ind. Phenyl chloroformate was obtained from Eastman Kodak Co., Rochester, N. Y. Ethyl chloroformate was obtained from J. T. Baker and Co., Phillipsburg, N. J.

**Reaction of Methadone Hydrochloride with Phenyl Chloroformate. Formation of 3.**—To a suspension of racemic **1b** hydrochloride (346 mg, 1 mmol) in 25 ml of tetrahydrofuran was added $NaHCO_3$ (2 g, 6 mmol) and **2b** (1.4 g, 8.9 mmol). The resulting mixture was magnetically stirred at room temperature for 24 hr. The reaction mixture was then treated with NaOH (50% solution) until alkaline in pH (about 11) and the solvent was carefully evaporated *in vacuo*. The residue was extracted with chloroform and aqueous NaOH (pH 11) and the chloroform extract was chromatographed preparatively on precoated silica plates (solvent benzene). Some unreacted methadone was found to be present at the origin.[9] The major band close to the solvent front was eluted with chloroform and the extract was evaporated *in vacuo*. A syrupy residue was obtained. This syrupy residue was treated with the minimum of ethanol and water, and allowed to stand overnight at room temperature. The following day, 132 mg (yield 50%) of white crystals, mp 79–81° (lit.[5] mp 78–80°), of **3** was obtained by filtration.

**Reaction of Methadone Hydrochloride with Ethyl Chloroformate (2a). Formation of 3.**—To a suspension of racemic **1b** hydrochloride (346 mg, 1 mmol) in 20 ml of tetrahydrofuran was added $NaHO_3$ (2 g, 6 mmol) and **2a** (0.8 g, 7.4 mmol). The resulting mixture was magnetically stirred at room temperature for 24 hr. Then the mixture was worked up as in the previous experiment to give 69 mg (25%) of **3**, mp 79–81°.

**Acknowledgment.**—This research was supported in part by the Narcotic Antagonist Research Program of the New York City Department of Health and Grant No. DA-00297.

**Registry No.**—(±)-**1b** HCl, 297-88-1; **2a**, 541-41-3; **2b**, 1885-14-9; **3**, 17494-37-0.

(7) A. F. Casy and M. M. A. Hassan, *Tetrahedron*, **23** (10), 4075 (1967).

(8) We are thankful to Dr. N. R. Easton for kindly sending us the ir and nmr spectra of the compound.

(9) No effort was made to quantitatively estimate the minute amounts of starting material in this reaction.

## Conformations of Carbon-13-Labeled Phenylsuccinic Acid

MICHAEL E. RENNEKAMP*

*Department of Chemistry, Kansas State University, Manhattan, Kansas 66506*

CHARLES A. KINGSBURY

*Department of Chemistry, University of Nebraska, Lincoln, Nebraska 68508*

*Received November 13, 1972*

Various papers have commented upon the apparent relationship between vicinal $^{13}C$–H nmr coupling constants and the geometry of these groups.[1-4] Roughly, the relationship appears to be analogous to the well-known Karplus relationship describing the dependence of H–H coupling constants on dihedral angle.[5] Similar relationships have been postulated for the interaction of $^{31}P$–H, $^{31}P$–$^{13}C$, and F–H pairs of nuclei.[6-13] Recently, the effect of molecular geometry on $^{13}C$–$^{13}C$ coupling constants has been reported.[14]

From the plot of $J_{^{13}CH}$ *vs.* dihedral angle, given by Lemieux and coworkers, a coupling constant of *ca.* 1 Hz would be expected for gauche $^{13}C$–H groups, and *ca.* 8 Hz for trans groups. Somewhat earlier, Perlin and Casu had given values of 0.7 Hz for gauche and 7.8 Hz for trans groups. Lemieux and coworkers caution that $^{13}C$–H couplings are quite sensitive to certain structural parameters, including electronegativity of groups, carbon hybridization, and steric relationships.

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(12) (a) K. L. Williamson, Y. Li, F. Hall, and S. Swager, *J. Amer. Chem. Soc.*, **88**, 5678 (1966); (b) K. L. Williamson, Y. Hsu, F. Hall, S. Swager, and M. Coulter, *ibid.*, **90**, 6717 (1968).

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(14) J. L. Marshall and D. Miller, Abstracts, 165th National Meeting of the American Chemical Society, Dallas, Texas, April 1973.

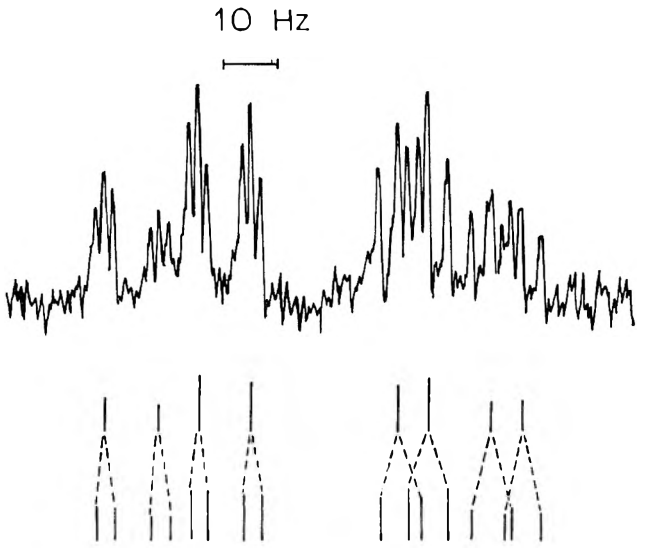
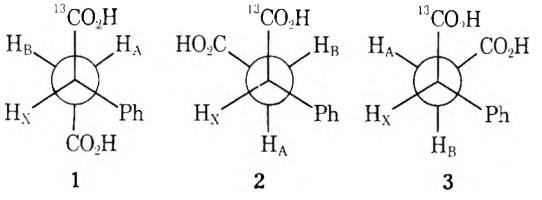



Figure 1.—Partial nmr spectrum of the labeled phenylsuccinic acid in acetone-$d_6$ (protons B and A).

Considering only proton couplings, a common finding in ABX systems might be a large $J_{AX}$ and a small $J_{BX}$. Unfortunately, these findings do not indicate which conformer (*e.g.*, **1** or **2**, Chart I) is predominant, unless

CHART I




some independent means exists of identifying which proton is A and which is B. One technique used to circumvent this difficulty is isotopic labeling.[15] This work describes the use of $^{13}C$ labeling in the molecule of interest, phenylsuccinic acid. Molecular models suggest that the phenyl and carbonyl groups have roughly similar size at their points of attachment to the ethanic skeleton. However, work in other types of molecules has indicated that phenyl is more space demanding than carbonyl.[16] It is of interest to see which group demands the more unhindered position in phenylsuccinic acid, and if the conformation is dependent upon the state of ionization of the carboxylates.[17]

The spectrum of unlabeled phenylsuccinic acid at pH 6 (at which ~30% of the molecules are in the monoanion form)[18] showed the expected ABX pattern, from which the following couplings were calculated: $J_{AB} = -15.1$, $J_{AX} = 9.0$, and $J_{BX} = 6.9$ Hz. A similar spectrum (Figure 1) of the material having about 60% enrichment of $^{13}C$ in one carbonyl group showed that each spectral line of the unlabeled material is almost symmetrically flanked by two new lines, which are the absorptions of the labeled material. Computer simulation of the spectra gave $J_{^{13}C\text{-}A} = 4.3$ and $J_{^{13}C\text{-}B} = 2.5$ Hz Using reasonable values for the limiting coupling constants for trans hydrogens ($J_T = 13.5$ Hz) and gauche hydrogens ($J_G = 2.8$ Hz),[19] the populations of the three conformers are calculated to be 0.58, 0.38, and 0.04. These values are probably good to ±5–8%.[20] Because of large steric effects, conformer **3** probably has the smallest population[21] (4%), but the weights of conformers **1** and **2** cannot be assigned. However, the fact that $J_{^{13}C\text{-}A}$ is larger than $J_{^{13}C\text{-}B}$ suggests that the labeled carbon and proton A are gauche in the major conformer and trans in the next most highly populated conformer, whereas the labeled carbon and proton B are very likely gauche in both principal conformers. This is consistent with **1** being the major conformer and **2** the next most highly populated conformer. For the populations of **1**, **2**, and **3** indicated above, limiting coupling constants for the $^{13}C$–H couplings of $J_T \cong 11$ and $J_G \cong 2$ Hz would be required in order to fit the observed data. The alternate and probably incorrect assignment of conformers (**2**, 58%; **1**, 38%) would demand limiting $^{13}C$–H values of $J_T \cong 1$ and $J_G \cong 4$ Hz, which is quite distant from the data given by Lemieux and Perlin, *et al.*

Varying the pH from 5 or 6 to 9 (at which the dianion form is strongly predominant)[18] had very little effect on the general appearance of the spectra, or the derived parameters (Table I). Thus, the preference for conformer **1** appears quite independent of monoanion or dianion character in this particular case. In contrast, the spectra of malic acid[22] and several halosuccinic acids[23] showed a substantial pH dependence. Erickson[23] assigned a value of 500 cal as an approximate indication of the greater repulsion of gauche carboxylates (dianion form) compared to the corresponding free

TABLE I

100-MHz SPECTRAL PARAMETERS

| | Coupling constants, Hz | | | | | Chemical shifts,[a] ppm | | |
|---|---|---|---|---|---|---|---|---|
| Solvent | $J_{AB}$ | $J_{AX}$ | $J_{BX}$ | $J_{^{13}C\text{-}A}$ | $J_{^{13}C\text{-}B}$ | $\delta_A$ | $\delta_B$ | $\delta_X$ |
| $D_2O$, pH 6 | −15.1 | 9.0 | 6.9 | 4.3 | 2.5 | | | |
| $D_2O$, pH 9 | −15.2 | 9.0 | 7.0 | 4.3 | 2.6 | | | |
| Pyridine[c] | −16.8 | 5.2 | 9.9 | 7.5 | 3.1 | 3.16 | 3.85 | 4.8 |
| Acetone-$d_6$[b] | −17.0 | 5.3 | 10.0 | 7.5 | 3.2 | 2.67 | 3.16 | 4.09 |
| Acetic acid-$d_4$ | −17.3 | 5.4 | 9.9 | 7.5 | 3.0 | 2.76 | 3.25 | 4.14 |

[a] A deuterum lock was used for the $D_2O$ solutions; no internal standard was present. [b] These data are similar to the proton couplings reported by M. Brink, *Tetrahedron*, **24**, 7005 (1968). [c] In the organic solvents, the concentration was 2.5% (w/v), rather than *ca.* 1%, which was used for the aqueous solutions.

(15) (a) G. Whitesides and D. J. Boschetto, *J. Amer. Chem. Soc.*, **91**, 4313 (1969); (b) R. G. Weiss and E. I. Snyder, *Chem. Commun.*, 1358 (1968); (c) C. Kingsbury and W. Thornton, *J. Amer. Chem. Soc.*, **88**, 3159 (1966).

(16) (a) H. E. Zimmerman and W.-H. Chang, *J. Amer. Chem. Soc.*, **81**, 3634 (1959). (b) "*A* values" suggest that phenyl should be more space demanding than carboxyl; however, substantial differences in *A* values occur for COOH and $COO^-$; see J. Hirsch, *Top. Stereochem.*, **1**, 199 (1967).

(17) The dihedral angles in **1** and **2** are shown as 60° purely for convenience. Substantial deviations from this value are probable so that the most comfortable fit of groups may be achieved; see J. E. Mark and C. Sutton, *J. Amer. Chem. Soc.*, **94**, 1083 (1972).

(18) The ratio of the monoanion form to the dianion form is roughly 3.5 at pH 5; see G. Kortum, W. Vogel, and K. Andrussow, "Dissociation Constants of Organic Acids in Aqueous Solutions," Butterworths, London, 1961, p 401.

(19) J. R. Cavanaugh, *J. Amer. Chem. Soc.*, **92**, 1488 (1970).

(20) G. Underwood, A. Chan, T. Green, C. Watts, and C. Kingsbury, *J. Org. Chem.*, in press; this work discusses the errors associated with this type of calculation.

(21) (a) R. A. Newmark and M. A. Miller, *J. Phys. Chem.*, **75**, 505 (1971); (b) P. E. McMahon and W. Tincher, *J. Mol. Spectrosc.*, **15**, 180 (1965).

(22) (a) R. A. Alberty and P. Bender, *J. Amer. Chem. Soc.*, **81**, 542 (1959); (b) O. Gawron, A. Glaid, III, and T. P. Fondy, *ibid.*, **83**, 3634 (1961).

(23) (a) L. E. Erickson, *J. Amer. Chem. Soc.*, **87**, 1867 (1965); (b) E. L. Eliel and M. Reese, *ibid.*, **91**, 1560 (1968).

acids. In other work, very large values for the ratios of the ionization constants of diacids, $K_1/K_2$, were explained by a stabilization of the monoanion by intramolecular hydrogen bonding and by an enhanced coulombic interaction in cases where the $COO^-$ and COOH groups were held near one another.[24,25] In a recent study on the thermodynamics of ionization of dicarboxylic acids, Purdie and Tomson indicated some reservations about the hydrogen-bonding theory.[26] The ionization of several diacids was shown to be dominated by entropy effects, which suggests that solvation of the charged center(s) is of prime importance. "Cooperative solvation" of the $COO^-$ and COOH groups by a set of solvent molecules was mentioned as a possible alternative to intramolecular hydrogen bonding in the monoanion. In phenylsuccinic acid (like succinic acid itself), the magnitudes and the differences between the first and second acid dissociation constants are closer to those of fumaric acid, in which the carboxylates are held remote from one another, than to those of maleic acid. Thus, neither conformation nor acidity of this particular molecule seems to be affected by intramolecular hydrogen bonding or cooperative solvation to any great extent. It is noteworthy, however, that the monoesters of phenylsuccinic acid are between two and four times less acidic than the diacid, and that the COOH group adjacent to phenyl is about two times more acidic than the other COOH group, perhaps owing to the inductive effect of phenyl.[27]

In pyridine solution, the carboxylic acid groups are hydrogen bonded to solvent, but not ionized.[28] Significantly different nmr parameters result in this solvent: $J_{AB} = -16.8$, $J_{AX} = 5.2$, $J_{BX} = 9.9$, $J_{^{13}C\text{-}A} = 7.5$, and $J_{^{13}C\text{-}B} = 3.1$ Hz. These data suggest that conformer **2** is the dominant species in this solvent (~60%). The coupling constants in acetone-$d_6$ were quite similar to those in pyridine. Acetic acid-$d_4$ was tested to see if the coupling constants observed in this solvent would be similar to those found in aqueous solvents, since both are hydroxylic, or similar to the other organic solvents. As Table I indicates, all organic solvents are similar. Thus, the phenyl group prefers the least hindered position, trans to COOH, in the organic solvents tested, but the labeled $COO^-$ group prefers the least hindered position in aqueous solvents.[29]

$^{13}C$ spectra were obtained using the usual Fourier transform technique. The one-bond coupling constant between the labeled carbon and the carbon bearing phenyl was 55 Hz, approximately the same as that observed in acetic acid.[30] No splitting of the methylene carbon resonance was observed, and thus $^2J_{CC} \leq 3$ Hz, which is also close to literature values.

(24) (a) L. Eberson, *Acta. Chem. Scand.*, **13**, 211 (1959); **14**, 641 (1960). (b) L. Eberson and S. Forsen, *J. Phys. Chem.*, **64**, 767 (1960), and references cited therein.

(25) L. L. McCoy, *J. Amer. Chem. Soc.*, **89**, 1673 (1967). This work suggests that intramolecular H bonding may be of less importance in acyclic molecules compared to rigid molecules.

(26) N. Purdie and M. B. Tomson, *J. Amer. Chem. Soc.*, **95**, 48 (1973).

(27) Calculated from data given in ref 18, p 426.

(28) E. J. Corey and G. K. Fraenkel, *J. Amer. Chem. Soc.*, **75**, 1168 (1953).

(29) Intramolecular association of the carboxylates, similar to the well-known acetic acid dimer, is quite unlikely owing to geometric restrictions. A single hydrogen bond between COOH groups could lead to a preference for conformer **2**, although this is unlikely in the powerful hydrogen-bonding solvent pyridine. Carboxyl–phenyl association [*cf.* R. N. MacDonald and R. R. Reitz, *J. Org. Chem.*, **37**, 2703 (1972), and H. S. ElKhadem, D. Horton, and T. F. Page, Jr., *ibid.*, **33**, 734 (1968)] would favor conformer **1**, but its presence in hydrogen-bonding solvents is also problematical.

(30) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley, New York, N. Y., 1972, p 29.

### Experimental Section

The spectra of labeled and unlabeled phenylsuccinic acid were taken on a Varian XL-100 nmr instrument at 500 and at 100 sweep widths, using frequency counter calibration of resonances. The concentration of the solutions was 1.0–1.5% (w/v). Spectra at both sweep widths were simulated using the LAOCOON III program adjusted to provide a computer-generated plot of the spectrum.[31] The parameters were adjusted until the computer-generated plot was superimposable over the observed spectrum. In some cases the iterative operation was used, which led to root mean square errors of 0.08–0.1 between the calculated and observed data sets. Usually the data generated by the iterative procedure required one or two more trial-and-error adjustments before the computer plot and the observed spectrum were identical. The $^{13}C$ spectra were taken on an acetone-$d_6$ solution (2% w/v) using a 1K filter, and a 1500-Hz noise band width at 80% high power operation of the decoupler; 11,000 transients were taken using an acquisition time of 1.3 μsec and a 40-μsec pulse width. Under these conditions, little or no interference of the signal of the labeled carbonyl was observed. The synthesis of the substrate has been reported earlier.[32] In this work, signs of coupling constants are not implied unless expressly stated.

**Acknowledgment.**—Partial funds for the purchase of the XL-100 were provided by NSF Grant GP-10293, which is gratefully acknowledged.

**Registry No.**—Carbon-13 phenylsuccinic acid, 37729-65-0.

(31) S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, **41**, 3863 (1964).

(32) M. E. Rennekamp, W. O. Perry, and R. G. Cooks, *J. Amer. Chem. Soc.*, **94**, 4985 (1972)

## A New Method for the Preparation of 4-Methylene-1-cyclohexenes

BARRY B. SNIDER

*Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138*[1]

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The direct synthesis of 4-methylene-1-cyclohexenes *via* the Diels–Alder reaction, using allene as a dienophile and dienes such as 1,3-butadiene, substituted butadienes, and cyclic dienes, is possible only in special cases.[2,3] 4-Methylene-1-cyclohexenes are usually made by modification of other Diels–Alder adducts. For example, pyrolysis of 3-cyclohexenylmethyl acetate gave a 60% yield of 4-methylene-1-cyclohexene contaminated with toluene.[4] Treatment of the adduct of cyclopentadiene and methyl α-bromovinyl sulfone with sodium methoxide in dimethyl sulfoxide afforded 5-methylene-2-norbornene.[5] Finally, addition of methyllithium to the Diels–Alder adduct of 1,3-butadiene with 3-chloro-2-(trichlorosilyl)propane gave 4-methylene-1-

(1) Address correspondence to Department of Chemistry, Columbia University, New York, N. Y. 10027.

(2) (a) R. Riemschneider, F. Herzel, and H. J. Koetsch, *Monatsh. Chem.*, **92**, 1070 (1961); (b) H. Pledger, Jr., *J. Org. Chem.*, **25**, 278 (1960); (c) S. Kunichika, T. Okamoto, and K. Yoshika, *Bull. Inst. Chem. Res. Kyoto Univ.*, **49**, 109 (1971); (d) D. R. Taylor, *Chem. Rev.*, **67**, 317 (1967), and references cited therein.

(3) Allenes possessing electron-withdrawing groups in conjugation are suitable dienophiles for Diels–Alder reactions. See ref 2d.

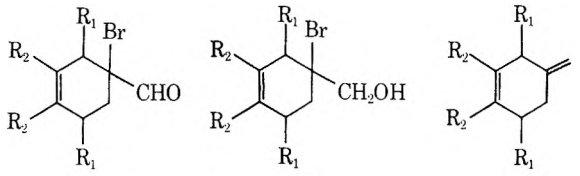
(4) C. G. Overberger and A. E. Borchert, *J. Amer. Chem. Soc.*, **82**, 1007 (1960).

(5) J. C. Philips and M. Oku, *J. Amer. Chem. Soc.*, **94**, 1012 (1972).

cyclohexene.[6] None of these methods is entirely acceptable because of low yields, requirement of harsh conditions, or formation of mixtures of products.

Our experience with α-bromoacrolein (**1**)[7] led us to expect that the Diels–Alder adduct of **1** and various 1,3-dienes could be reduced to the bromohydrin **3**, which upon treatment with zinc in methanol would give the desired 4-methylene-1-cyclohexenes (**4**). As expected, α-bromoacrolein reacted smoothly with a variety of 1,3-dienes. Adducts were formed from cyclopentadiene in 98% yield, from 2,3-dimethyl-1,3-butadiene in 95% yield, from 1,4-*trans*,*trans*-diphenyl-1,3-butadiene in 84% yield, and from anthracene in 69% yield. The order of reactivity of the dienes in the Diels–Alder reaction is as expected: cyclopentadiene > 2,3-dimethylbutadiene > *trans*,*trans*-1,4-diphenylbutadiene ~ anthracene.

The adducts **2** could all be easily converted to the bromohydrin **3** in *ca.* 95% yield by treatment with



**2** **3** **4**

a, $R_1$, $R_1$ = $CH_2$–; $R_2$ = H

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

c, $R_1$ = phenyl; $R_2$ = H

d, $R_1$, $R_1$ =  ; $R_2$, $R_2$ = –CH=CHCH=CH–

excess sodium borohydride in wet tetrahydrofuran at 25° for 2–4 hr. These unusual conditions were found to be very effective in preventing formation of the epoxide or reductive dehalogenation.[8] Dehalohydrination was best carried out by treatment of **3** with excess activated zinc in methanol to give the isomerically pure 4-methylene-1-cyclohexenes in 80–90% yield.

## Experimental Section

**Reaction of Cyclopentadiene with α-Bromoacrolein.**—α-Bromoacrolein[9] (1.6 g, 11 mmol) was dissolved in 5 ml of ether at 0°. Cyclopentadiene (0.9 g, 16 mmol) was added and the solution was stirred for 18 hr at 0°. The solvent was evaporated, giving a 7:3 mixture of exo–endo aldehyde **2a** in quantitative yield, which was used without further purification: ir (neat) 3030, 2940, 2880, 2700, and 1721 $cm^{-1}$; nmr ($CDCl_3$) δ 9.72 (0.7 H, s, exo CHO), 9.48 (0.3 H, s, endo CHO), 6.0–6.8 (2 H, m, CH=), 3.32 1 H, m, CH), 3.00 (1 H, m, CH), 2.1–2.7 (2 H, m, $CH_2CBrCHO$), and 1.2–2.0 (2 H, m, $CH_2$).

**Reaction of 2,3-Dimethylbutadiene and α-Bromoacrolein.**—α-Bromoacrolein[9] (1.35 g, 10 mmol), potassium carbonate (50 mg), hydroquinone (10 mg), and 2,3-dimethylbutadiene (1 g, 12 mmol) were kept at 55° in 5 ml of benzene under nitrogen for 18 hr. Ether (20 ml) was then added and the solution was filtered and evaporated, giving 2.03 g (95%) of bromo aldehyde **2b**: ir (neat) 2985, 2941, 2703, and 1724 $cm^{-1}$; nmr ($CDCl_3$) δ 9.50 (1 H, s, CHO), 2.62 (2 H, br, $CH_2$), 2.13 (4 H, br, $CH_2$), and 1.60 (6 H, br, $CH_3$).

**Reaction of *trans*,*trans*-1,4-Diphenylbutadiene with α-Bromoacrolein.**—*trans*,*trans*-1,4-Diphenylbutadiene (1 g, 5 mmol), α-bromoacrolein[9] (1.35 g, 10 mmol), potassium carbonate (50 mg), and hydroquinone (10 mg) were stirred in 10 ml of toluene under $N_2$ for 72 hr at 100°. The solution was cooled, diluted with ether, filtered, and evaporated giving 2.6 g of brown oil. This was purified by preparative tlc (two developments, pentane–ether 9:1), giving 1.37 g (84%) of bromo aldehyde **2c**. The other compounds present were diphenylbutadiene, α-bromoacrolein, and α-bromoacrolein dimer. The spectral data for **2c** are ir (neat) 3030, 2940, 2860, 2700, 1720, 740, and 700 $cm^{-1}$; nmr ($CDCl_3$) δ 9.64 (1 H, s, CHO), 7.4 (10 H, br, $C_6H_5$), 6.0 (2 H, m, CH=), 4.3 (1 H, br, CH), 3.9 (1 H, m, CH), and 1.6–2.8 (2 H, m, $CH_2$).

**Reaction of Anthracene and Bromoacrolein.**—Anthracene (0.5 g, 2.8 mmol), α-bromoacrolein[9] (0.8 g, 6 mmol), potassium carbonate (50 mg), and hydroquinone (5 mg) were stirred in 5 ml of toluene under nitrogen for 4 days at 100°. The solution was cooled, diluted with ether, filtered, and evaporated to give 1.05 g of brown oil which was purified by preparative tlc (pentane–ether 1:1) to give 0.576 g (69%) of **2d** and 75 mg of 2-formyl-5-bromo-4*H*-pyran. The Diels–Alder adduct **2d** was recrystallized from cyclohexane to give colorless crystals: mp 129–130°; ir (neat) 3030, 2940, 2860, 2700, 1720, and 760 $cm^{-1}$; nmr ($CDCl_3$) δ 9.41 (1 H, s, CHO), 7.2 (8 H, m, $C_6H_4$), 4.67 (1 H, s, CH), 4.3 (1 H, d of d, $J$ = 2.5, 2.5 Hz, CH), 2.94 (1 H, d of d, $J$ = 2.5, 15 Hz, CHH), and 2.12 (1 H, d of d, $J$ = 2.5, 15 Hz, CHH).

**Reduction of 2a.**—The bromo aldehyde mixture **2a** (2.3 g, 11 mmol) was dissolved in 50 ml of THF containing 0.1 ml of water, and sodium borohydride (200 mg) was added. The solution was stirred for 2 hr, and 10 ml of 20% sodium dihydrogen phosphate solution was added to decompose excess borohydride and prevent the halohydrin from forming the epoxide. Water (50 ml) was then added and the solution was extracted with 3 × 30 ml of ether which was extracted with saturated sodium chloride solution, dried over magnesium sulfate, and evaporated to give 2.1 g (95%) of bromo alcohol mixture **3a**: ir (neat) 3400, 2940, and 1110 $cm^{-1}$; nmr ($CDCl_3$) δ 6.0–6.3 (2 H, m, CH=), 3.8 (2 H, m, $CH_2O$), 3.2 (1 H, m, CH), 2.9 (1 H, m, CH), and 1.1–2.1 (4 H, m, $CH_2$).

**Reduction of 2b.**—Bromo aldehyde **2b** (1.68 g) was reduced as for **2a**, giving 1.58 g (93%) of bromo alcohol **3b**: ir (neat) 3400, 2940, 1440, 1090, and 1030 $cm^{-1}$; nmr ($CDCl_3$) δ 3.7 (2 H, s, $CH_2OH$), 2.48 (2 H, br s, $CH_2$), 1.7–2.3 (4 H, m, $CH_2$), and 1.61 (6 H, s, $CH_3$).

**Reduction of 2c.**—Bromo aldehyde **2c** (1.0 g) was reduced as previously described for **2a**, giving 0.92 g (90%) of bromo alcohol **3c**: ir (neat) 3450, 3030, 2970, 1600, 1490, 1450, 760, and 700 $cm^{-1}$; nmr ($CDCl_3$) δ 7.3 (10 H, s, $C_6H_5$), 5.6–6.3 (2 H, m, CH=), 3.6–4.3 (2 H, m, 2 CH), 3.25 (2 H, br s, $CH_2O$), and 1.5–2.4 (2 H, m, $CH_2$).

**Reduction of 2d.**—Bromo aldehyde **2d** (0.4 g) was reduced as previously described for **2a**, giving 370 mg of bromo alcohol **3d** (92%) as colorless crystals. Recrystallization from cyclohexane gave a product melting at 130–132° dec: ir ($CHCl_3$) 3450, 3030, 2940, and 1470 $cm^{-1}$; nmr ($CDCl_3$) δ 7.2 (8 H, m, $C_6H_4$), 4.81 (1 H, s, CH), 4.32 (1 H, d of d, $J$ = 2.5, 2.5 Hz, CH), 3.55 (1 H, d, $J$ = 12 Hz, CHHO), 3.05 (1 H, d, $J$ = 12 Hz, CHHO), 2.50 (1 H, d of d, $J$ = 2.5, 14 Hz, CHH), and 1.93 (1 H, d of d, $J$ = 2.5, 14 Hz, CHH).

**Reaction of Bromo Alcohol 3a with Zinc.**—Bromo alcohol **3a** (3.6 g, 18 mmol) was taken up in 100 ml of methanol and stirred for 18 hr at room temperature with 25 g of activated zinc (prepared by stirring zinc dust for 5 min in glacial acetic acid and then washing with several portions of methanol). The reaction mixture was filtered through sintered glass and the residue was washed with 100 ml of pentane and 100 ml of water. After the filtrate and washings were shaken, the pentane layer was removed and the aqueous layer was extracted with 2 × 25 ml of pentane. The combined pentane extracts were dried and the pentane was distilled, giving 1.3 g (65%) of crude 5-methylene-2-norbornene (**4a**). Evaporative distillation of the residue gave a product which was pure by gc (10 ft 10% TCEP, 50°): ir (neat) 3080, 2940, 2850, 1660, and 880 $cm^{-1}$; nmr ($CDCl_3$) δ 6.05 (2 H, m, CH=), 4.92 and 4.70 (2 H, 2 br s, $CH_2$=), 3.17 (1 H, br, CH), 2.95 (1 H, br, CH), 1.3–2.5 (4 H, m, $CH_2$). The ir and nmr spectra are identical with those of an authentic sample (Aldrich Chemical Co.).

In a similar experiment using cyclohexane as an internal standard, gpc (10 ft 10% TCEP, 50°) indicated the yield to be 90%.

(6) R. F. Cunico and E. M. Dexheimer, *Organometal. Chem. Syn.*, **1**, 253 (1971).

(7) E. J. Corey and B. B. Snider, *J. Amer. Chem. Soc.*, **94**, 2549 (1972).

(8) For a discussion of the reduction of α-halocarbonyl compounds, see E. Schenker in "Newer Methods of Preparative Organic Chemistry," Vol. IV, W. Foerst, Ed., Academic Press, New York, N. Y., 1968, p 126.

(9) R. H. Baker, S. W. Tinsley, Jr., D. Butler, and B. Rigel, *J. Amer. Chem. Soc.*, **72**, 393 (1950).

**Reaction of Bromo Alcohol 3b with Zinc.**—The bromohydrin **3b** (1.04 g, 4.75 mmol) was dissolved in 30 ml of methanol, and 10 g of activated zinc was added. The solution was stirred overnight and filtered through sintered glass, and the residue was washed with pentane and water. After the filtrate and washings were shaken, the pentane was removed and the aqueous layer was extracted with 2 × 25 ml of pentane. The combined pentane layers were dried over magnesium sulfate, and the pentane was evaporated at 1 atm, giving 0.52 g (89%) of 1,2-dimethyl-4-methylene-1-cyclohexane (**4b**). Evaporative distillation gave 0.36 g: ir (neat) 3080, 1670, and 885 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 4.68 (2 H, br s, $=CH_2$), 2.65 (2 H, br, $=CH_2C=$), 2.25 (4 H, m, $=CCH_2$), and 1.62 (6 H, s, $CH_3$).

*Anal.* Calcd for $C_9H_{14}$: mol wt, 122.1095. Found: mol wt, 122.1092.

**Reaction of Bromo Alcohol 3c with Zinc.**—The bromohydrin **3c** (0.407 g, 1.14 mmol) in 10 ml of methanol was treated with 1.5 g of activated zinc. After 2 hr the solution was filtered with suction and the filtrate was evaporated to dryness. The residue was taken up in 2% hydrochloric acid which was then extracted with 3 × 15 ml of pentane, which was dried over magnesium sulfate and evaporated to give 245 mg (86%) of 3,6-diphenyl-4-methylenecyclohexene (**4c**), pure by tlc and gc: ir (neat) 1650 and 870 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 7.36 (10 H, s, $C_6H_5$), 6.03 (2 H, s, CH=), 4.83 and 4.90 (2 H, 2 s, $=CH_2$), 4.16 (1 H, br, CH), 3.62 (1 H, m, CH), and 2.42 (2 H, m, $CH_2$).

*Anal.* Calcd for $C_{19}H_{18}$: mol wt, 246.1408. Found: mol wt, 246.1407.

**Reaction of Bromo Alcohol 3d with Zinc.**—The bromohydrin **3d** (200 mg, 0.53 mmol) was dissolved in 10 ml of methanol, and 1 g of activated zinc was added. After 2 hr the reaction was worked up as described previously for **3c** to give 125 mg (83%) of **4d** as colorless crystals which were recrystallized from hexane: mp 100–101°;[10] ir ($CHCl_3$) 1640 and 880 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 7.2 (8 H, m, $C_6H_4$), 5.07 (1 H, br s, CH), 4.68 (2 H, s, $=CH_2$), 4.27 (1 H, t, $J$ = 3 Hz, CH), and 2.36 (2 H, m, $CH_2$).

*Anal.* Calcd for $C_{17}H_{14}$: C, 93.54, H, 6.46; mol wt, 218.1095. Found: C, 93.20; H, 6.55; mol wt, 218.1092.

**Acknowledgment.**—The author is grateful to the National Science Foundation for financial support and to Professor E. J. Corey for his support and encouragement of this work.

Registry No.—**1**, 14925-39-4; *exo*-**2a**, 28738-84-3; *endo*-**2a**, 28738-83-2; **2b**, 41894-54-6; **2c**, 41894-55-7; **2d**, 41894-56-8; *exo*-**3a**, 41915-51-9; *endo*-**3a**, 41915-52-0; **3b**, 41894-57-9; **3c**, 41894-58-0; **3d**, 42434-74-2; **4a**, 694-91-7; **4b**, 41894-60-4; **4c**, 41894-61-5; 4d, 19978-14-4; cyclopentadiene, 542-92-7; 2,3-dimethylbutadiene, 513-81-5; *trans,trans*-1,4-diphenylbutadiene, 538-81-8; anthracene, 120-12-7.

(10) The olefin **4d** has previously been prepared as a 9:1 mixture of exo–endo double-bond isomers: S. J. Cristol and G. O. Mayo, *J. Org. Chem.*, **34**, 2363 (1969).

## Synthesis and Thermolysis of Thiete 1,1-Dioxide Iron Tetracarbonyl[1,2]

JOHN E. MCCASKIE, PETER L. CHANG, THOMAS R. NELSEN, AND DONALD C. DITTMER*

*Department of Chemistry, Syracuse University, Syracuse, New York 13210*

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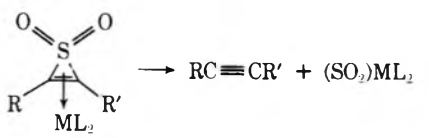
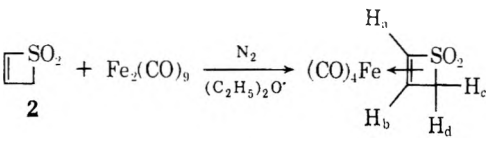
Thermolysis of thiete sulfones (thiete 1,1-dioxides) has been suggested to proceed *via* vinylsulfenes as reactive intermediates.[3] We have observed that thiete sulfone yields sulfur dioxide at elevated temperatures, indicating the possible formation of three-carbon intermediates such as vinylcarbene, cyclopropene, methylacetylene, or allene. Since a number of reactive intermediates have been obtained as stable complexes of transition metals,[4] we investigated the synthesis and properties of thiete sulfone iron tetracarbonyl in which the iron atom conceivably could trap vinylsulfene and reactive intermediates formed during the extrusion of sulfur dioxide. Thermolysis of palladium and platinum complexes (**1**) of thiirene 1,1-dioxides yields an



**1**, M = Pt, Pd; L = $Ph_3P$

acetylene and a complex of sulfur dioxide.[5] Uncomplexed thiirene 1,1-dioxides also yield an acetylene and sulfur dioxide;[6] thus thermolysis of **1** is not fundamentally different from the thermolysis of the uncomplexed sulfone.

Pale yellow crystals of thiete sulfone iron tetracarbonyl (**3**) were obtained (50% yield) either by refluxing a solution of the sulfone **2** in ether with diiron nonacarbonyl or by irradiation of **2** and iron pentacarbonyl in benzene.[7] Under the same conditions no iron complexes could be obtained from 2-sulfolene, 4-phenyl-2*H*-thiete 1,1-dioxide, or 7-thiabicyclo[4.2.0]-1(8)-octene 7,7-dioxide.



**2** **3**

The pmr spectrum of **3** shows all protons shifted to higher field relative to the protons of **2**. The chemical shifts of the protons of the double bond show the greatest displacement: $\Delta\delta_{H_a}$ 1.70, $\Delta\delta_{H_b}$ 2.20, $\Delta\delta_{H_c}$ 0.93, $\Delta\delta_{H_d}$ 0.68 ppm.[8] Sulfone absorption in the infrared is essentially unaltered, as is observed in other sulfone complexes,[8b] and C–H stretching vibrations occur in

(1) Taken in part from the Ph.D. Thesis of P. L. Chang, Syracuse University, 1970.

(2) Reported at the Northeast Regional Meeting of the American Chemical Society, Buffalo, N. Y., Oct 1971, Abstract 166.

(3) J. F. King, P. de Mayo, C. L. McIntosh, K. Piers, and D. J. H. Smith, *Can. J. Chem.*, **48**, 3704 (1970); D. C. Dittmer, R. S. Henion, and N. Takashina, *J. Org. Chem.*, **34**, 1310 (1969).

(4) The following examples are illustrative: Carbenes, E. O. Fischer, *Pure Appl. Chem.*, **24**, 407 (1970); vinyl alcohols, C. H. de Puy, R. N. Greene, and T. E. Schroer, *Chem. Commun.*, 1225 (1968); H. Thyret, *Angew. Chem., Int. Ed. Engl.*, **11**, 520 (1972); cyclobutadienes, G. F. Emerson, L. Watts, and R. Pettit, *J. Amer. Chem. Soc.*, **87**, 131 (1965); cyclohexyne, M. A. Bennett, G. B. Robertson, P. O. Whimp, and T. Yoshida, *ibid.*, **93**, 3797 (1971); trimethylene, G. F. Emerson, K. Ehrlich, W. P. Giering, and P. C. Lauterbur, *ibid.*, **88**, 3172 (1966); vinyl ketenes, A. E. Hill and H. M. R. Hoffmann, *J. Chem. Soc., Chem. Commun.*, 574 (1972).

(5) J. P. Visser, C. G. Leliveld, and D. N. Reinhoudt, *J. Chem. Soc., Chem. Commun.*, 178 (1972).

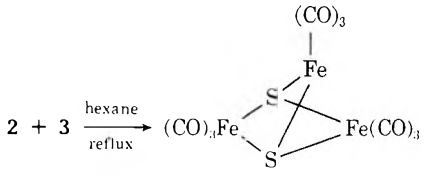
(6) L. A. Carpino and L. V. McAdams, III, *J. Amer. Chem. Soc.*, **87**, 5804 (1965); L. A. Carpino and R. H. Rynbrandt, *ibid.*, **88**, 5682 (1966); L. A. Carpino, L. V. McAdams, III, R. H. Rynbrandt, and J. W. Spiewak, *ibid.*, **93**, 476 (1971).

(7) *Cf.* the preparation of thiophene 1,1-dioxide iron tricarbonyl: Y. L. Chan, J. Fossey, and R. A. Perry, *J. Chem. Soc., Chem. Commun.*, 501 (1972).

(8) (a) Shifts to high fields are typical of olefin–iron tetracarbonyl complexes, shifts of the olefin protons being the greatest: E. Weiss, K. Stark, J. E. Lancaster, and H. D. Murdoch, *Helv. Chim. Acta*, **46**, 288 (1963). (b) A. N. Nesmeyanov, L. V. Rybin, M. I. Rybinskaya, N. T. Gubenko, I. F. Leshcheva, and Y. A. Ustynyuk, *J. Gen. Chem. USSR*, **38**, 1428 (1968).

both the olefinic (3040 $cm^{-1}$) and aliphatic (2950 $cm^{-1}$) region. It is unlikely that the complex involves the ring-opened structure of vinylsulfene ($CH_2$=CHCH=$SO_2$) because the infrared and nmr spectra are not consistent with a structure containing three olefinic protons and one proton of an aldehydic type.

Complex **3** and extra thiete sulfone were refluxed under nitrogen for 1.5 hr in olefin-free hexane. (Thiete sulfone is stable under these conditions.) Within 10 min the heterogeneous mixture became dark red. Sulfur dioxide and carbon monoxide were detected in the effluent gas by infrared analysis. The deep purple solution yielded red-black crystals of $Fe_3S_2(CO)_9$ (19% based on 2 mol of thiete sulfone being consumed per mole of product) and a considerable amount of thiete sulfone (91% of the total amount both complexed and uncomplexed). This inorganic iron–sulfur derivative was identical with the complex **4** obtained by Hieber and Gruber from tetracarbonyl iron ferrate and sulfite ion[9] and whose structure has been determined.[10] Attempts to identify the carbon fragment or fragments from thiete sulfone were unsuccessful. Formally, a $C_3H_4$ fragment must be obtained on extrusion of sulfur dioxide and, in fact, the mass spectra of thiete sulfone and of complex **3** show abundant ions at *m/e* 40 ($C_3H_4^+$) and 39 ($C_3H_3^+$). When complex **3** was subjected to thermolysis in the absence of thiete sulfone, only $^1/_{13}$ of the amount of **4** obtained in the




**4**

regular thermolysis was isolated. Thiete sulfone was recovered in 90% yield, the result of decomposition of the complex into its components.

The reduction of the sulfone group to sulfide (as in **4**) under such relatively mild conditions (69°) is worthy of note. Deoxygenations of nitro, nitroso, and azoxy groups, *N*-oxides, and nitrones by iron pentacarbonyl in refluxing *n*-butyl ether (24 hr) have been observed previously.[11] Equimolar quantities of pure thiete sulfone and complex **3** appear to be required for the formation of **4**. This suggests that a complex containing 2 mol of thiete sulfone may be involved. No **4** was obtained when an equimolar mixture of maleic anhydride iron tetracarbonyl[8a] and thiete sulfone was heated (80–140°, 2 hr); starting materials were recovered.

(9) (a) W. Hieber and J. Gruber, *Z. Anorg. Allg. Chem.*, **296**, 91 (1958); (b) R. Havlin and G. R. Knox, *J. Organometal. Chem.*, **4**, 247 (1965).

(10) L. F. Dahl and P. W. Sutton, *Inorg. Chem.*, **2**, 1067 (1963).

(11) H. Alper and J. T. Edward, *Can. J. Chem.*, **48**, 1543 (1970).

## Experimental Section[12]

**Thiete 1,1-Dioxide Iron Tetracarbonyl. A.**—Diiron nonacarbonyl (1.82 g, 5 mmol) was added to a solution of thiete sulfone[13] (1.04 g, 10 mmol) in dry ether (50 ml). The reaction mixture was refluxed under nitrogen with stirring for 1.5 hr. The brown reaction mixture was filtered and slowly concentrated. Yellow needles of thiete 1,1-dioxide iron tetracarbonyl (1.30 g, 4.78 mmol, 47.8%) separated: mp 99–100°; ir (KBr) 2100 (s, CO), 2050 (s, CO), 2030 (s, CO), 1970 (s, CO), 1275 (m, $SO_2$), 1230 (s, $SO_2$), 1120 $cm^{-1}$ (s, $SO_2$); nmr ($CDCl_3$) $\delta$ 5.10 (d, 1, =$CHSO_2$), 4.50 (m, 1, CH=$CSO_2$), 3.90 (complex d, 1, endo or exo $CH_2$), 3.65 (complex d, 1, endo or exo $CH_2$); mass spectrum (70 eV) *m/e* 272 (parent), 244 (− CO), 216 (− 2CO), 188 (− 3CO), 160 (− 4CO), 104 ($C_3H_4O_2S$).

*Anal.* Calcd for $C_7H_4FeO_6S$: C, 30.96; H, 1.49. Found: C, 31.17; H, 1.70.

**B.**—Iron pentacarbonyl (3.0 g, 14.4 mmol) and thiete sulfone (1.04 g, 10 mmol) were dissolved in benzene (500 ml, dry, degassed) and the solution was irradiated for 1 hr at room temperature under nitrogen with a high-pressure mercury lamp equipped with a Vycor filter. The orange mixture was filtered, concentrated, and triturated with ether to yield the complex (1.36 g, 5 mmol, 50%), mp 99–100°.

**Thermolysis of Thiete 1,1-Dioxide Iron Tetracarbonyl in Presence of Excess Thiete Sulfone.**—A suspension of thiete 1,1-dioxide iron tetracarbonyl (0.824 g, 3.03 mmol) and thiete sulfone (0.312 g, 3.00 mmol) in hexane (25 ml, olefin-free) was refluxed under nitrogen with stirring for 3 hr. After *ca.* 1 hr a deep purple solution was obtained. Sulfur dioxide and carbon monoxide were detected in the effluent gas stream by infrared analysis. Continuous extraction of the solid residue with ether yielded thiete sulfone (0.395 g, 3.79 mmol). The hexane solution was chromatographed on Florisil and elution with ether gave additional thiete sulfone (0.175 g, 1.68 mmol).[14] Elution with hexane gave, after removal of solvent, red-black crystals of $Fe_3S_2(CO)_9$ (0.026 g, 0.054 mmol, 19%):[15] mp 109–110° (lit.[9b] mp 114°); ir (KBr) 2047 (s, CO), 2015 (s, CO), 1996 $cm^{-1}$ (s, CO); uv-visible (hexane) $\lambda_{max}$ 203 nm ($\epsilon$ 190,000), 550 (shallow); mass spectrum (70 eV) *m/e* 484 (parent) and ions resulting from the consecutive loss of nine molecules of carbon monoxide; X-ray analysis, triclinic, $b$ = 9.16 Å (lit.[10] $b$ = 9.22 Å). The compound was identical with a sample of $Fe_3S_2(CO)_9$ prepared according to Hieber and Gruber.[9a] Attempts to trap carbon-containing fragments by passing the effluent gas through bromine in methylene chloride or through cyclopentadiene were not successful. No $Fe_2SO_2(CO)_8$[16] or $Fe_3S_2(CO)_6$[9a] was detected in the reaction mixture.

**Acknowledgments.**—We are grateful to the National Science Foundation (Grant GP 20729) and the National Cancer Institute of the Public Health Service (Grant CA 08250) for financial support of this work. We are indebted to Professor C. E. Pfluger for the X-ray data.

**Registry No.**—**2**, 7285-32-7; **3**, 42116-78-9; **4**, 12287-77-3; diiron nonacarbonyl, 15321-51-4; iron pentacarbonyl, 13464-40-6.

(12) Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrometer. Pmr spectra were obtained on a Varian Associates Model A-60 spectrometer. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU6E spectrometer. Melting points are uncorrected.

(13) D. C. Dittmer and M. E. Christy, *J. Org. Chem.*, **26**, 1324 (1961); D. C. Dittmer, M. E. Christy, N. Takashina, R. S. Henion, and J. M. Balquist, *ibid.*, **36**, 1324 (1971); P. L. Chang and D. C. Dittmer, *ibid.*, **34**, 2791 (1969).

(14) 90.7% of the total amount of thiete sulfone, complexed and uncomplexed, is recovered.

(15) Based on starting material consumed [2 thiete sulfone → $Fe_3S_2(CO)_9$].

(16) D. S. Field and M. J. Newlands, *J. Organometal. Chem.*, **27**, 221 (1971); E. H. Braye and W. Hubel, *Angew. Chem.*, **75**, 345 (1963).

See Editorial, *J. Org. Chem.*, **37**, No. 13, 4A (1972)

## Sulfine and Sulfene Reactivity[1]

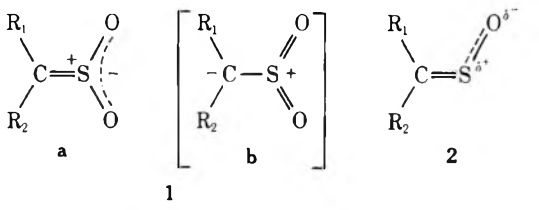
*Summary:* Semiempirical MO calculations provide a rationale for the reactivity differences observed for the title compounds (thiocarbonyl mon- and dioxides, respectively) and suggest that the dioxides may be stabilized by electron-donating substituents.

*Sir:* The *S*-oxides of thiocarbonyl derivatives have recently aroused considerable interest. The dioxides (sulfenes) **1** are highly reactive species which must be generated and used *in situ*. Nonetheless they undergo a remarkable variety of exploitable addition and cycloaddition reactions.[2,3] In the absence of an addend, dimer,[4] tetramer,[5] or polymer[6] is obtained. Verification of transient **1** derives from product analysis,[2] rate studies,[7] and most recently from flash vacuum pyrolysis generation of the parent (**1**, $R_1 = R_2 = H$) followed by trapping at $-196°$.[8] The monoxides (sulfines) **2**, by strong contrast, are often shelf-stable materials[9] which exhibit both a discernible stereochemistry[1,9b,10] and a rich reactivity.[9,11,12]

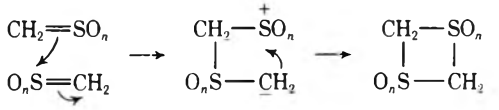
In the present communication we present the results of MO–SCF–CNDO calculations[13] which provide insight into the reactivity differences between *S*-oxides **1** and **2**. Furthermore tactics for producing stabilized sulfenes, essential to structural and spectroscopic studies of the system, are outlined.

Geometry optimization has been carried out for the parent species **1**[14] and **2**[1] ($R_1 = R_2 = H$). The corresponding charge distributions and frontier orbitals are given in Figure 1.

Both systems are predicted to have a full C–S double bond and partial S–O double bonds. Charge distributions, however, are considerably different. Both C and S of dioxide **1** (*i.e.*, **1a**) support exaggerated nega-




tive and positive charges, respectively, in comparison to monoxide **2**. Thus any comparable charge controlled[16] reaction for the two would be predicted to occur more rapidly for sulfene. The same conclusion is reached in the event of a comparable frontier controlled process.[16] For example, consider the dimerization of **1** and **2**. In principle it could proceed by a concerted suprafacial–antarafacial route. The available evidence for the dioxide suggests a two-step pathway initiated by attack of carbon on sulfur. A similar event is reasonably invoked for the onset of the majority of sulfene reactions.




Perturbation MO theory postulates that the $\pi$-frontier orbitals are instrumental in directing the early stages of combination.[16] Accordingly the HOMO of one addend will engage the LUMO of the other. Since the HOMO–LUMO energy differences for dioxide and monoxide in the present case are calculated to be nearly the same [$\Delta E$ (LUMO–HOMO): **1**, 8.41 eV; **2**, 8.40 eV], the magnitude of orbital coefficients should be a major predictor of reaction course and rate. Figure 1 indicates that the sulfene and sulfine LUMO's share a nearly identical electron distribution. By contrast a comparison of the highest occupied MO's suggests a leakage of charge from oxygen onto carbon and sulfur in the formal transformation from monoxide to dioxide. Specifically carbon and sulfur contributions to the HOMO are 36 and 18% less, respectively, for **2** than for **1**.

The calculations agree nicely with the chemistry of **1** and **2**. Thioketone dioxides are highly reactive car-

(1) Organo-Sulfur Mechanisms. II. For part I, see J. P. Snyder and D. N. Harpp, *Chem. Commun.*, 1305 (1972).

(2) Several excellent reviews are available: (a) G. Opitz, *Angew. Chem., Int. Ed. Engl.*, **6**, 107 (1967); (b) T. J. Wallace, *Quart. Rev.*, **20**, 67 (1966); H. Ulrich in "Organic Chemistry," Vol. 9, Academic Press, New York, N. Y., 1967, pp 206–240; L. L. Müller and J. Hamer, "1,2-Cycloadditions," Interscience, New York, N. Y., 1967; N. Kharasch, B. S. Thyagarajan, and A. I. Khodair, *Mech. React. Sulfur Compd.*, **1**, 97 (1967); W. E. Truce and L. K. Liu, *ibid*, **4**, 145 (1969); T. Nagai and N. Tokura, *Int. J. Sulfur Chem., B*, **7**, 207 (1972).

(3) Nitrogen analogs, the iminosulfenes, are under scrutiny as synthetic intermediates: C. R. Johnson and E. U. Jonsson, *J. Amer. Chem. Soc.*, **92**, 3815 (1970).

(4) G. Opitz and H. R. Mohl, *Angew. Chem., Int. Ed. Engl.*, **8**, 73 (1969).

(5) Professor J. S. Grossert, Dalhousie University, personal communication.

(6) (a) L. A. Paguette, J. P. Freeman, and R. W. Houser, *J. Org. Chem.*, **34**, 2901 (1969); (b) J. F. King, P. de Mayo, and D. L. Verdun, *Can. J. Chem.*, **47**, 4509 (1969)

(7) J. F. King and T. W. S. Lee, *J. Amer. Chem. Soc.*, **91**, 6524 (1969).

(8) J. F. King, R. A. Marty, P. de Mayo, and O. L. Verdun, *ibid.*, **93**, 6304 (1971).

(9) *Cf.* (a) B. Zwanenburg and J. Strating, *Quart. Rep. Sulfur Chem.*, **5**,, 79 (1970); (b) B. Zwanenburg, A. Wagenaar, L. Thijs, and J. Strating, *J. Chem. Soc., Perkin Trans. 1*, 73 (1973).

(10) J. F. King and T. Durst, *Tetrahedron Lett.*, 585 (1963); B. Zwanenburg, L. Thijs, and A. Tangerman, *Tetrahedron*, **27**, 1731 (1971); B. Zwanenburg, L. Thijs, and J. Strating, *Recl. Trav. Chim. Pays-Bas*, **90**, 614 (1971); A. Tangerman and B. Zwanenburg, *Int. J. Sulfur Chem. A.*, **2**, 204 (1972); B. F. Bonini, L. Lunazzi, G. Maccagnani, and G. Mazzanti, *ibid.*, 211 (1972).

(11) B. Zwanenburg, L. Thijs, and J. Strating, *Recl. Trav. Chim. Pays-Bas*, **89**, 687 (1970).

(12) B. Zwanenburg, L. Thijs, J. B. Broens, and J. Strating, *Recl. Trav. Chim. Pays-Bas*, **91**, 443 (1972); L. Thijs, J. Strating, and B. Zwanenburg, *ibid.*, **91**, 1345 (1972).

(13) R. J. Boyd and M. A. Whitehead, *J. Chem. Soc., Dalton Trans.*, 73 (1972); 78 (1972); 82 (1972).

(14) Sulfene **1**: all atoms lie in a common plane; $r_{CS} = 1.64$ Å, $r_{SO} = 1.58$ Å, $r_{CH} = 1.09$ Å, $\angle OSO = 129°$, $\angle HCH = 114°$. The predicted geometry in conjunction with representative force constants obtained from the literature permit the ir spectrum of **1** to be computed[15] in reasonable agreement with experiment.[8]

(15) Dr. U. Anthoni, University of Copenhagen, personal communication.

(16) G. Klopman and R. F. Hudson, *Theor, Chim. Acta.*, **8**, 165 (1967); G. Klopman, *J. Amer. Chem. Soc.*, **90**, 223 (1968); R. F. Hudson, *Angew. Chem., Int. Ed. Engl.*, **12**, 36 (1973).

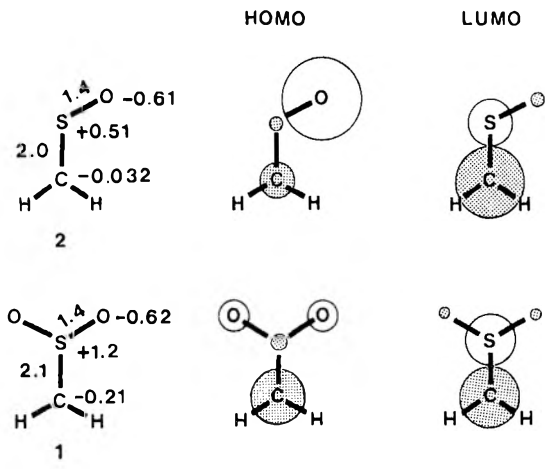



Figure 1.—Computed bond orders [R. J. Boyd, *Can. J. Chem.*, 51, 1151 (1973)], total charge densities, and frontier orbitals for 1 and 2. The MO's are $\pi$ in character. Circle radii represent relative atomic orbital contributions to the HOMO/LUMO eigen functions.

bon nucleophiles and sulfur electrophiles which self-destruct even at low temperatures.[2,8] Thiocarbonyl monoxides on the other hand are isolable,[9] do not to our knowledge oligomerize, and react in certain cases by nucleophilic attack *at carbon*.[11]

Since the chemistry of the sulfene moiety is characterized primarily by carbon nucleophilicity, resonance structure **1b** has frequently been elected the most important contributor to the system.[17] Furthermore, association of the dipolar nature of **1** with ylide properties (**1b**) has stimulated efforts to prepare unreactive sulfenes by the agency of electron-withdrawing substituents,[6a,18] albeit abortive. We would like to suggest that the ylide analogy is misleading and that sulfenes with *electron-donating* groups should be capable of isolation under normal conditions.

To assess reactivity, dimerization will once again serve as reaction model and PMO theory as guide to liability. Three computed reaction indices for a series of substituted *S*-dioxides **1** are detailed in Table I.

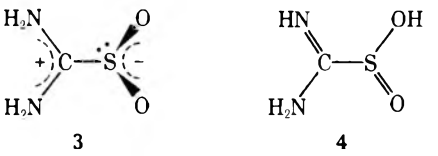
TABLE I
COMPUTED MOLECULAR QUANTITIES FOR SULFENE 1[a]

| $R_1,R_2$ | $\rho_C$[b] | $\rho_S$[b] | $\Delta E$ (LUMO–HOMO), eV | LUMO, $\phi^2$ | HOMO, $\phi^2$ |
|---|---|---|---|---|---|
| CN, CN | −0.12 | +1.3 | 6.70 | 0.38 | 0.22 |
| H, CN | −0.19 | +1.3 | 7.27 | 0.39 | 0.26 |
| H, H | −0.21 | +1.2 | 8.41 | 0.39 | 0.42 |
| H, $NH_2$ | +0.20 | +1.1 | 8.07 | 0.29 | 0.20 |
| $NH_2$, $NH_2$ | +0.65 | +0.91 | 8.34 | 0.04 | 0.07 |

[a] Standard bond lengths and angles have been employed for substituents and the optimized $R_1 = R_2 = H$ geometry has been, maintained around $CSO_2$. The structure having $R_1 = R_2 = NH_2$ supports a 68° angle between the NCN and OSO planes. All other cases are planar.[14] [b] The variation is due almost entirely to changes in $\pi$-electron densities.

As electron-withdrawing substituents are replaced successively with more electron-donating ones, the positive charge on sulfur is diminished while that at carbon undergoes a reversal from negative to positive. Thus for charge-controlled reactions, not only are electron-rich substituents predicted to reduce the electrophilicity of sulfur, but to eliminate altogether the nucleophilicity of carbon. Orbital control for the dimerization requires a concern for both $\Delta E$ (LUMO-HOMO) and the magnitude of frontier MO atomic coefficients at the centers being joined. Electron-pulling groups promote oligomerization by increasing addend interaction energy[19] and by maintaining large S-LUMO and C-HOMO $\pi$ coefficients. The converse is predicted for electron-donating substituents. Thus, strong electron donors should ameliorate sulfene reactivity by introducing electronic properties with sulfine-like character.

There are several pieces of experimental evidence, surprisingly absent from the sulfene literature,[2,20] which lend credence to the calculations. As early as 1910 diaminosulfene **3** (thiourea dioxide) was prepared by the oxidation of thiourea.[21] The substance is an air- and a water-stable material presently used as an industrial reducing agent in dye and photographic processes. Monoalkyl derivatives of **3** have likewise been known for many years.[22] Unfortunately the original report[21] as well as subsequent and current papers[23] have pictured the dioxides as the tautomeric iminosulfinic acids **4**. X-Ray[24,25] and ir[26] studies reveal on the contrary that the parent species in the solid state, although extensively intermolecularly hydrogen bonded, exists as the symmetrical dioxide **3**.[27]




Very recently a series of mono-, di-, and trisubstituted diaminosulfenes have been isolated as crystalline materials.[28] A curious stability pattern as a function of substitution suggests the importance of *intra*molecular

(17) G. Hesse, E. Reichold, and S. Majmudar, *Chem. Ber.*, **90**, 2106 (1957); W. E. Truce and J. R. Norell, *J. Amer. Chem. Soc.*, **85**, 3231 (1963); A. W. Johnson, "Ylide Chemistry," Academic Press, New York, N. Y., 1966, p 353.

(18) G. Opitz, M. Kleeman, D. Bucher, G. Walz, and K. Rieth, *Angew. Chem., Int. Ed. Engl.*, **5**, 594 (1966).

(19) Inversely proportional to $\Delta E$ (LUMO–HOMO).

(20) *Cf.*, however, J. F. King and T. Durst, *J. Amer. Chem. Soc.*, **87**, 5684 (1965); P. H. Laur, in "Sulfur in Organic and Inorganic Chemistry," Vol. 3, A. Senning, Ed., Marcel Dekker, New York, N. Y., 1972, pp 167–168.

(21) E. de Barry Barnett, *J. Chem. Soc.*, **97**, 63 (1910); *cf.* L. Vanino and A. Schinner, *Chem. Ber.*, **47**, 699 (1914).

(22) (a) R. Kitamura and S. Suzuki, *J. Pharm. Soc. Jap.*, **58**, 818 (1938); (b) E. W. Tillitson, U. S. Patent 2,493,471 (1950) [*Chem. Abstr.*, **45**, 659*b* (1951)]; J. Böeseken, *Recl. Trav. Chim. Pays-Bas*, **67**, 603 (1948).

(23) J. Böeseken, *Recl. Trav. Chim. Pays-Bas*, **55**, 1040 (1936); E. Havas, *Chem. Abstr.*, **33**, 4603 (1939); E. Ballard and T. B. Johnson, *J. Amer. Chem. Soc.*, **64**, 795 (1942); G. L. Wakefield, *Chem. Abstr.*, **53**, P 3959*b* (1959); L. P. Roosens and P. A. Faelens, *ibid.*, **54**, P 17128*d* (1960); Gevaert Photo-Production N.V., *ibid.*, **54**, P 22119*f* (1960); K. V. Rao, *ibid.*, **57**, P 15257*d* (1963); H. R. Kricheldorf, *Justus Liebigs Ann Chem.*, **745**, 81 (1971); O. A. Kunze, O. G. Malan, P. A. Bueger, and W. Fink, *Z. Naturforsch. B*, **26**, 8 (1971); *cf.*, however, ref 22a; E. O. Fischer and W. Hieber, *Z. Anorg. Allgem. Chem.*, **271**, 229 (1953); P. Kerber and J. Starnik, *Chem. Ber.*, **104**, 2035 (1971); K. Nakagawa and K. Minami, *Tetrahedron Lett.*, 343 (1972).

(24) R. A. L. Sullivan and A. Hargreaves, *Acta. Crystallogr.*, **15**, 675 (1962).

(25) The X-ray analysis[24] reveals the $SO_2$ plane to subtend a 68° angle with the NNC plane. Our calculations are in accord with this result predicting the nonplanar geometry to be lower in energy than the planar form.

(26) Y. Y. Kharitonov and I. V. Prokof'eva, *Dokl. Akad. Nauk SSSR*, **162**, 829 (1965); *Chem. Abstr.*, **63**, 9240*f* (1965).

(27) Rearrangement from the dioxide to the aminoiminosulfinic acid in aqueous solution has been claimed: N. I. Prorokov, Y. Schmukler, P. V. Moryganov, B. N. Melnikov, and A. N. Gruzdeva, *Tekst. Prom. (Moscow)*, **29**, 60 (1969); *Chem. Abstr.*, **72**, 13699*w* (1970).

(28) (a) W. Walter and G. Randau, *Justus Liebigs Ann. Chem.*, **722**, 80 (1969); (b) W. Walter and K. Ruess, *Chem. Ber.*, **102**, 2640 (1969).

hydrogen bonds. To our knowledge no case of a tetrasubstituted diaminosulfene is known with the exception of an unusual sulfene-like salt.[29] It remains to be seen whether the stability of aminosulfenes and similarly substituted cases is largely a consequence of hydrogen bonding or can be supported by the electronic factors outlined in Table I.

**Acknowledgments.**—We are grateful to the NATO Research Grants Program for partial funding of the work and to Professor David N. Harpp (McGill University) for hospitality and stimulation. Professor Martin Ettlinger (Copenhagen University) kindly drew our attention to the thiourea dioxide literature.

(29) E. Lindner and H. Weber, *Justus Liebigs Ann. Chem.*, **101**, 2832 (1968).

(30) Camille and Henry Dreyfus Teacher–Scholar Grant Recipient, 1971–1976.

DEPARTMENT OF GENERAL AND ORGANIC CHEMISTRY
UNIVERSITY OF COPENHAGEN
2100V COPENHAGEN, DENMARK

JAMES P. SNYDER[30]

RECEIVED JULY 27, 1973

## Photochemistry of Epoxy Olefins. II.[1] The Photosensitized Geometric Isomerization and Rearrangement of the Isomeric 4,5-Epoxy-2-hexenes

*Summary:* The isomeric monoepoxides of 2,4-hexadiene undergo geometrical isomerization of both the epoxy and olefinic moieties as well as rearrangement to *cis*- and *trans*-4-hexen-2-one when irradiated in acetone solution at 3000 Å.

*Sir:* In a continuation of our studies of the photochemistry of 3,4-epoxy olefins,[1] we have investigated the acetone-sensitized photolysis of the stereoisomers of 4,5-epoxy-2-hexene. The major results are outlined in Scheme I while representative data are shown in Table I. Photolysis of either **5** or **6** in acetone gives an equilibrium mixture of 55% **5** and 45% **6**. The same equilibrium values are obtained upon prolonged irradiation of **1**, **2**, **3**, or **4**.

SCHEME I
PHOTOCHEMICAL INTERCONVERSIONS

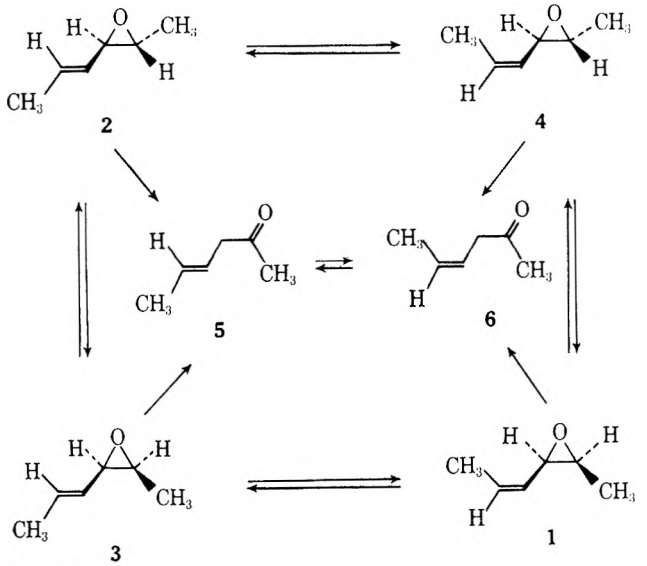


TABLE I

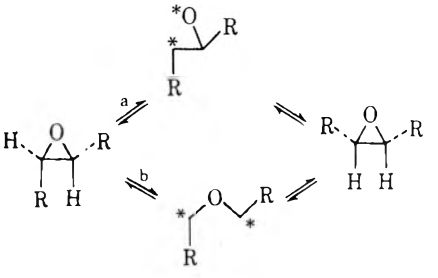
| Substrate | Photolysis products,[a] % | | | | | |
|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **6** |
| **1** | 12 | 13 | 6 | 17 | 25 | 27 |
| **2** | 3 | 12 | 2 | 12 | 37 | 34 |

[a] Photolyses were carried out in acetone solutions using a 450-W Hanovia medium-pressure mercury lamp equipped with a Pyrex filter. Values given are per cent of volatile product after irradiation of 0.6 g in 125 ml of acetone for 2.5 hr. The analyses were carried out by gas chromatography on a Carbowax 20M column. The products were identified by direct comparison with authentic samples.

The most striking feature of this work is the very facile geometric isomerization of the epoxide moieties. In their photochemical studies of phenyl-substituted oxiranes, Griffin and Trozzolo[2] did not observe any isomerization of epoxide isomers. Geometric isomerization of epoxides has been observed photochemically only in the case of the $\alpha,\beta$-epoxy ketone system.[3]

In Scheme II are shown two possible modes of epoxide

SCHEME II



geometrical isomerization with the asterisk indicating either ionic or radical centers. Thermal and Lewis acid catalysis of the epoxides was investigated to determine if ground electronic state ionic or radical intermediates would also produce geometrical isomerization of the epoxides. Both thermolysis and Lewis acid catalysis (Table II) gave the same ketones which are ob-

TABLE II
LEWIS ACID AND THERMAL CATALYZED REARRANGEMENTS

| Substrate | Temp, °C | Products (%) | | |
|---|---|---|---|---|
| 1[a] | 25 | 1 (0) | 5 (98) | 6 (2) |
| 2[a] | 25 | 2 (0) | 5 (40) | 6 (60) |
| 1[b] | 200 | 1 (89) | 5 (trace) | 6 (5) |
| 1[b] | 250 | 1 (68) | 5 (2) | 6 (26) |
| 1[b] | 300[c] | 1 (9) | 5 (20) | 6 (64) |
| 2[b] | 200 | 2 (88) | 5 (9) | 6 (0) |
| 2[b] | 250 | 2 (64) | 5 (32) | 6 (0) |
| 2[b] | 300[c] | 2 (4) | 5 (47) | 6 (21) |

[a] Rearrangement induced by treating substrate with $MgI_2$ in ether as described by N. Heap, G. E. Green, and G. H. Whitham, *J. Chem. Soc. C*, 1525 (1969). [b] The pyrolyses were carried out (15 min) in sealed Pyrex ampoules using 20 mg of substrate. Less than 1% of the epoxide isomers could have been detected if present. [c] At 300° and above several unidentified products were obtained.

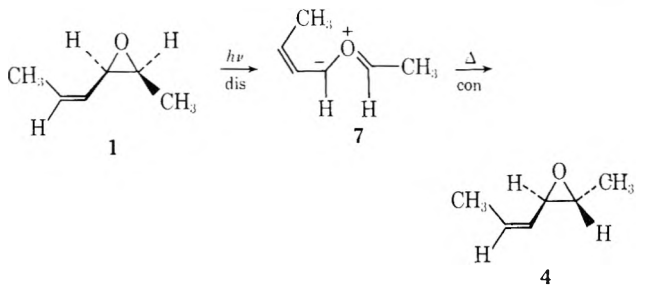
(1) For the previous paper in this series, see D. R. Paulson, G. Korngold, and G. Jones, *Tetrahedron Lett.*, 1723 (1972).

(2) T. Do-Minh, A. M. Trozzolo, and G. W. Griffin, *J. Amer. Chem. Soc.*, **92**, 1402 (1970), and references contained therein.

(3) C. K. Johnson, B. Dominy, and W. Reusch, *J. Amer. Chem. Soc.*, **85**, 3894 (1963).

tained photochemically. However, we failed to observe any geometrical isomerization of the epoxides under either conditions. The thermal rearrangements could be occuring by a radical path or by an ionic catalyzed wall reaction. In the photolysis these ketones are generated by a 1,2-hydrogen atom shift. Radical 1,2 shifts occur rarely, if at all, and they are symmetry forbidden.[4] However, 1,2-radical migrations might indeed be quite favorable starting from a 1,3 diradical since the energy gained from concurrent formation of the carbonyl group may overcome the orbital symmetry considerations.

In view of the failure of C–O bond opening by both ionic or thermal (Table II) conditions to produce any epoxide isomerization and the demonstrated formation of carbonyl ylides in the photochemistry of aryl-substituted epoxides,[5] it is tempting to assign the intermediate in pathway "b" (Scheme II) to a carbonyl ylide. Similar carbonyl ylides have also been generated thermally.[6] In the present case isomerization could be explained by a photochemically allowed disrotatory ring opening followed by a thermally allowed conrotatory ring closure as shown below for the conversion of **1** to **4**. However, a carbonyl ylide intermediate (*i.e.*, **7**) seems unlikely for several reasons. Photolysis of **1** in acetone solutions containing various amounts of dimethyl acetylenedicarboxylate (an efficient carbonyl ylide trapping agent[6]) at 25 or at −78° failed to produce any adduct of a carbonyl ylide. The only effect of the trapping agent was to slightly decrease the rate of product formation. Secondly, if **7** were generated in the photolysis of **1**, it seems highly likely that ring closure to a 4,5-dihydrofuran would occur. We could find no evidence for any dihydrofuran formation at 25 or at −78°. The only effect of low temperature was to slow the rate of reaction. For example, the formation of **5** and **6** was ~1.5 times as slow at −78° as at 25°. However, the overall results were identical. Thermolysis of epoxide **1** in the presence of dimethyl acetylenedicarboxylate also failed to trap any carbonyl ylide intermediate.




1 7 4

The photochemical reactions described here are most likely triplet sensitized processes resulting from energy transfer from triplet state acetone. Supporting evidence for this is found in that the reactions are efficiently quenched by piperylene. The cis–trans isomerization of the olefinic functionality of the epoxides and the β,γ-unsaturated ketones are most likely analogous to the well-studied triplet sensitized isomerizations of alkenes. A very inefficient photoisomerization of **5** and **6** by direct irradiation has been observed.[7] More recently Engel has reported an example of acetone sensitized cis–trans isomerization of a β,γ-unsaturated ketone.[8] Thus the formation of **5** in the photolysis of **1** and **4** and the formation of **6** in the photolysis of **2** and **3** are due in part to photoisomerization of the enones.

From the results presented here it is clear that, whether the epoxide isomerization occurs *via* a carbonyl ylide which is too short lived to be trapped or *via* an initial C–O bond cleavage, the intermediate is able to undergo reversible ring closure. We currently favor pathway "a" in Scheme II with homolytic bond cleavage, but any of several ionic pathways can not be ruled out at this time. The mode of formation of the β,γ-unsaturated ketones was discussed in a previous paper.[1]

We are currently investigating the nature of the intermediate responsible for the epoxide isomerization as well as extending our studies to nonconjugated epoxy olefins.

**Acknowledgment** is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(4) M. J. Perkins in "Organic Reaction Mechanisms, 1968," B. Capon and C. W. Rees, Ed, Interscience Publishers, London, 1969, p 293.
(5) D. R. Arnold and L. A. Karnischky, *J. Amer. Chem. Soc.*, 1404 (1970); see also ref 2.
(6) H. Hamberger and R. Huisgen, *Chem Commun.*, 1190 (1971); A. Dakmen, H. Hamberger, R. Huisgen, and V. Markowski, *ibid.*, 1192 (1971).
(7) H. Morrison, *Tetrahedron Lett.*, 3653 (1964).
(8) P. S. Engel and M. A. Schnexnayder, *J. Amer. Chem. Soc.*, **94**, 9252 (1972).

DEPARTMENT OF CHEMISTRY
CALIFORNIA STATE UNIVERSITY
LOS ANGLES, CALIFORNIA 90032

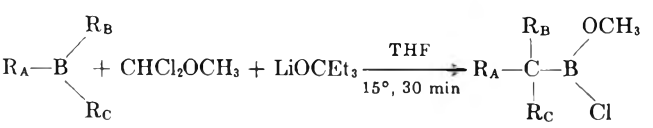
DONALD R. PAULSON*
FRANKLIN Y. N. TANG
RICHARD B. SLOAN

RECEIVED JULY 31, 1973

## The Facile Transfer of Tertiary Alkyl Groups from Boron to Carbon in the Base-Induced Reaction of α,α-Dichloromethyl Methyl Ether with Organoboranes Containing Tertiary Alkyl Groups. A Novel Route to Highly Hindered Trialkylcarbinols Involving Exceptionally Mild Conditions

*Summary:* Trialkylboranes containing tertiary alkyl groups, such as *tert*-butyl and thexyl (2,3-dimethyl-2-butyl), undergo rapid reaction with α,α-dichloromethyl methyl ether and lithium triethylcarboxide at 25° to give the corresponding highly branched trialkylcarbinols after oxidation. B–C migration of the tertiary group occurs under exceedingly mild conditions without isomerization.

*Sir:* Treatment of relatively hindered trialkylboranes containing a tertiary alkyl group with α,α-dichloromethyl methyl ether (DCME) and lithium triethylcarboxide under mild conditions (25°) results in the transfer of all three groups from boron to carbon without rearrangement (eq 1). The product can then be



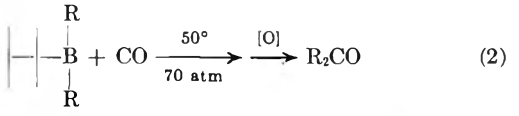

(1)

$R_A$ = *tert*-butyl, thexyl (2,3-dimethyl-2-butyl)

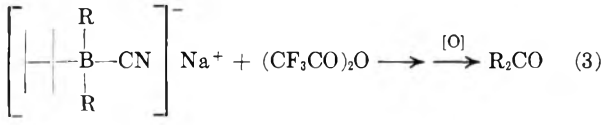
oxidized to the corresponding highly branched tertiary alcohol. This facile transfer of a tertiary alkyl group from boron to carbon in the present reaction is in marked contrast to the behavior of such groups in the related reactions with carbon monoxide[1] and sodium cyanide with trifluoroacetic anhydride.[2]

The reaction of carbon monoxide with trialkylboranes and the corresponding reaction of sodium cyanide with trialkylboranes induced by trifluoroacetic anhydride provides important procedures for replacing boron by carbon. This makes possible the "stitching" of relatively open structures with boron and the "riveting" of these structures by replacing the boron with carbon.[1]

One serious limitation has been the difficulty of extending these reactions to organoboranes containing tertiary alkyl groups. Such groups fail to migrate from boron to carbon under conditions suitable for primary and secondary. Advantage has been taken of this feature by using the thexyldialkylboranes for the synthesis of ketones[3,4] (eq 2 and 3).



(2)

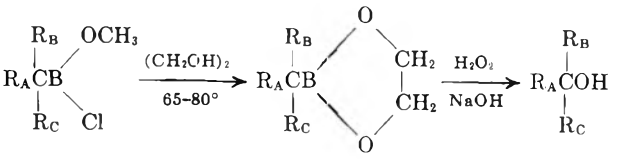


(3)

It proved possible to extend the carbonylation reaction to organoboranes containing a tertiary alkyl group by using higher temperatures, 3 hr at 150° under 70-atm pressure.[5] However, many highly hindered organoboranes are relatively labile. They are best prepared at relatively low temperatures[6] and it appeared undesirable to subject them to such comparatively high temperatures. Accordingly, we examined the applicability of the new reaction of organoboranes with DCME induced by lithium triethylcarboxide.[7]

We discovered that a wide variety of trialkylboranes containing a tertiary alkyl group (*tert*-butyl or thexyl) readily reacts with the reagent at 25° with transfer of all three alkyl groups from boron to carbon (eq 1). In the case of some of the more hindered derivatives use of an excess of the reagent improves the yield.

We did encounter a difficulty in the oxidation of the intermediate with alkaline hydrogen peroxide. With increasing steric bulk of the three alkyl substituents the rate of oxidation of the intermediate decreased[8] and required larger excesses of hydrogen peroxide. In the most hindered derivatives, such as thexyldiisobutylborane, thexyl-*sec*-butyl-*n*-pentylborane, and thexylcyclopentyl-*n*-pentylborane, it proved desirable to treat the initially formed intermediate with ethylene glycol to form the corresponding 2-(trialkylcarbinyl)-2-bora-1,3-dioxolane (eq 4). This cyclic ester proved to be more readily oxidized to the tertiary carbinol.



(4)

For example, when the intermediate from thexyldiisobutylborane was oxidized for 2 hr with a sixfold excess of sodium hydroxide and a tenfold excess of 30% hydrogen peroxide using ethanol as cosolvent at 50°, only 62% thexyldiisobutylcarbinol was obtained, with 20% residual boronic acid. Longer reaction times with double the amounts of sodium hydroxide raised the yield to 70%. However, prior conversion of the intermediate into the 2-bora-1,3-dioxolane by *in situ* treatment with ethylene glycol at 65–80° gave a faster oxidation, producing an 80% yield of the desired carbinol in 3 hr at 50°.

The results are summarized in Table I.

TABLE I

SYNTHESES OF TERTIARY CARBINOLS CONTAINING A TERTIARY ALKYL GROUP *via* REACTION OF TRIALKYLBORANES WITH DCME AND LITHIUM TRIETHYLCARBOXIDE

| Trialkylborane | Procedure[a] | Trialkylcarbinol[b] obtained on oxidn | Yield,[c] % (by isoln) |
|---|---|---|---|
| Thexyldi-*n*-butyl | I | 2,3,3-Trimethyl-4-(*n*-butyl)-4-octanol | 84 |
| Thexyldi-*n*-pentyl | I | 2,3,3,-Trimethyl-4-(*n*-pentyl)-4-nonanol | 85 (80)[d] |
| Thexyldiisobutyl | II | 2,3,3,6-Tetramethyl-4-isobutyl-4-heptanol | 80 |
| Thexyl-*sec*-butyl-*n*-pentyl | II | 2,3,3-Trimethyl-4-(*sec*-butyl)-4-nonanol | 78.5 |
| Thexylcyclopentyl-*n*-pentyl | II | 2,3,3-Trimethyl-4-cyclopentyl-4-nonanol | 75 |
| *tert*-Butyldicyclohexyl | I | 1,1-Dicyclohexyl-2,2-dimethyl-1-propanol | 77 |
| | I[e] | 1,1-Dicyclohexyl-2,2-dimethyl-1-propanol | 94 (90)[f] |
| *B*-(*tert*-butyl)-9-borabicyclo[3.3.1]nonane | I | 9-(*tert*-Butyl)bicyclo[3.3.1]-nonan-9-ol | 68 |
| | I[e] | 9-(*tert*-Butyl)bicyclo[3.3.1]-nonan-9-ol | 83[g] |

[a] I, stoichiometric quantities of DCME and lithium triethylcarboxide, oxidation with excess sodium hydroxide and hydrogen peroxide with ethanol as cosolvent as in the described procedure; II, 100% excess of DCME and lithium triethylcarboxide used, transformation of the intermediate borane into the ethylene trialkylcarbinylboronate and oxidation as in the described procedure. [b] Satisfactory nmr, ir, mass spectra, and elemental analyses data were obtained for all of the new compounds. [c] By glpc. [d] Bp 114° (0.2 mm), $n^{20}$D 1.4621. [e] 100% excess of DCME and lithium triethylcarboxide used. [f] Bp 136–138° (0.7 mm), mp 46–49°. [g] Mp 67.8–69°.

The following procedure for the preparation of 2,3,3-trimethyl-4-(*n*-pentyl)-4-nonanol is representative. In an oven-dried 100-ml flask maintained under a nitrogen atmosphere and fitted with a septum inlet, magnetic stirrer, and reflux condenser was placed 50 mmol (25.2 ml of a 1.98 *M* solution) of thexylborane in

(1) H. C. Brown, *Accounts Chem. Res.*, **2**, 65 (1969).
(2) A. Pelter, *Chem. Ind. (London)*, 206 (1973).
(3) H. C. Brown and E. Negishi, *J. Amer. Chem. Soc.*, **89**, 5285, 5477 (1967).
(4) A. Pelter, M. G. Hutchings, and K. Smith, *Chem. Commun.*, 1529 (1970).
(5) E. Negishi and H. C. Brown, *Synthesis*, 196 (1972).
(6) Research in progress with J.-J. Katz and E. Negishi.
(7) H. C. Brown and B. A. Carlson, *J. Org. Chem.*, **38**, 2422 (1973).
(8) The problem was encountered previously in the oxidation of derivatives, such as *sec*-$Bu_2BF(OCEt_3)$: H. C. Brown and B. A. Carlson, *J. Organometal. Chem.*, **54**, 61 (1973).

THF.[9] The solution was cooled to 0° and 100 mmol of 1-pentene (11 ml) was added dropwise. The mixture was stirred for an additional hour at 0° to ensure completion of the hydroboration. The reagent, DCME (5.0 ml, 55 mmol), was then added, followed by the addition of 50 mmol of lithium triethylcarboxide (27 ml of a 1.84 *M* solution in hexane) over 10 min. The reaction was allowed to come to room temperature over 30 min. The formation of a heavy white precipitate, presumably lithium chloride, was observed. Then 50 ml of 95% ethanol was added, followed by 12 g of sodium hydroxide. Oxidation was accomplished by the slow addition of 40 ml of 30% hydrogen peroxide at 0° followed by warming to 50–60° for 1 hr. The aqueous phase was salted out with sodium chloride and the organic phase separated. Solvents were removed with a rotary evaporator and the product, 2,3,3-trimethyl-4-(*n*-pentyl)-4-nonanol, was recovered by distillation under reduced pressure: 10.4 g, 80% yield, bp 114° (0.2 mm), $n^{20}$D 1.4621.

For the more hindered derivatives, such as thexylcyclopentyl-*n*-pentylborane, a slightly modified procedure proved advantageous. To 5.0 mmol of thexylborane at −25° was added 5 mmol (0.44 ml) of cyclopentene. After 1 hr at this temperature, 5 mmol (0.55 ml) of 1-pentene was added and the solution was brought to 25° to complete the hydroboration. The addition of DCME and lithium triethylcarboxide in 100% excess was carried out as described in the procedure above. To the reaction mixture was added 10 mmol (0.60 ml) of ethylene glycol and the solvents (THF and hexane) were removed by distillation. The reaction mixture was cooled to 0°; 10 ml of ethanol was added, followed by 2.4 g of sodium hydroxide and 10 ml of 30% hydrogen peroxide. The reaction mixture was then brought to 50–55° and maintained there for 3 hr. The organic products were extracted into 10 ml of THF after salting out the aqueous phase. Glpc examination of the organic phase using tridecane as internal standard revealed 3.80 mmol, a yield of 75%, of 2,3,3-trimethyl-4-cyclopentyl-4-nonanol.

It is evident from the results presented in Table I that the present procedure is broadly applicable for the conversion of highly branched organoboranes into the corresponding carbinols. The cyanoborate reaction at present cannot handle such derivatives. Carbonylation can be used, but requires much more drastic conditions. In view of the lability of organoborane structures which contain tertiary alkyl groups, the mild conditions of the present procedure greatly extends the range of applicability of "stitching" and "riveting."

(9) H. C. Brown, Y. Yamamoto, and C. F. Lane, *Synthesis*, 304 (1972).

(10) Graduate research assistant on Grant No. GM 10937 supported by the National Institutes of Health.

(11) Graduate research assistant on Grant No. GP 6942X supported by the National Science Foundation.

RICHARD B. WETHERILL LABORATORY
PURDUE UNIVERSITY
WEST LAFAYETTE, INDIANA 47907

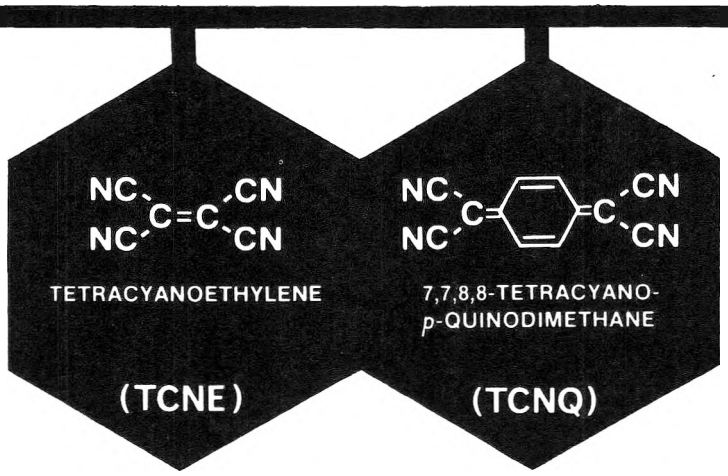
HERBERT C. BROWN*
JEAN-JACQUES KATZ[10]
BRUCE A. CARLSON[11]

JULY 5, 1973

# THE ELECTRON-THIRSTY ONES

### CHARGE-TRANSFER COMPLEXES --- SEMICONDUCTORS

Having a high electron affinity, both **TCNE** and **TCNQ** form charge-transfer complexes with suitable electron donors, such as aromatic $\pi$-systems. Some of the solid complexes exhibit semiconducting properties.[1] The most exciting one to date is the 1:1 complex of **TCNQ** and tetrathiofulvalene, which not only behaves like a metal over a large temperature range but has by far the largest maximum electrical conductivity of any known organic compound.[2]




### CYCLOADDITION REACTIONS

**TCNE** is a reactive dienophile and undergoes Diels-Alder type reactions with conjugated dienes with unusual ease and at relatively low temperatures. It even reacts spontaneously with sluggish dienes such as 2-vinylnaphthalene without added catalyst or application of external heat.[1] With a diene incapable of forming a Diels-Alder product it reacts to yield a cyclobutane derivative.[1] **TCNE** undergoes 1,6-cycloaddition to 1H-azepines.[3]

### DEHYDROGENATIONS

**TCNE** has been used successfully to aromatize 1,4-dihydrobenzenes[4] and to induce dehydrogenation of steroidal dienes.[5]

### FOR OZONOLYSIS

Being stable to ozone, **TCNE** provides a new method for the cleavage of ozonides to produce aldehydes and ketones directly in good yields.[6]

### SYNTHESIS OF HETEROCYCLIC COMPOUNDS

**TCNE** is a useful starting material for the synthesis of 5- and 6-membered heterocycles with one or two heteroatoms, such as thiophenes, pyrroles, isoxazoles, pyrazoles, pyridines pyrimidines, and other fused polynuclear heterocycles.[1]

### ANALYTICAL APPLICATIONS

Its ability to form $\pi$-complexes with a variety of organic compounds instantly under mild conditions makes **TCNE** useful for determining and/or detecting many organic compounds, *e.g.*, aromatic hydrocarbons, phenols, aryl ethers.[1] Other complexometric or photometric methods for the determination of organic compounds are essentially based on the chemical reactivity of **TCNE**, such as the diene reaction and aromatic substitution reaction.[1] **TCNQ** is a useful reagent for the colorimetric determination of free radical precursors, such as cysteine, proline, hydroxyproline, phenoxazines and mercaptans.[8] It is also useful in locating the above amino acids, some amino acid derivatives, acridines, polynuclear aromatic hydrocarbons, mercaptans, thioamides, thiohydantoins and thiosemicarbazones on paper or thin layer chromatograms.[8] These techniques can be applied to air pollution studies.[8] A fluorimetric method using **TCNQ** to locate and detect 1-20 $\gamma$ of some fifty organic compounds (amines, amino acids, proteins, enzymes) on paper and silica gel chromatograms has also been described.[9] Furthermore, **TCNQ** is a color reagent for the thin layer chromatographic identification of the alkali, alkaline earth, and some post-transition metal ions. It is particularly sensitive for the detection of the univalent cation.[10]

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| **15,763-5** | **7,7,8,8-Tetracyanoquinodimethane (TCNQ)**, 98% | **5g $14.50; 10g $27.50; 100g $160.00** |

† Designates one-tenth molar unit.

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