# Effect of Ion Pairing on the Rate and Site of Alkylation of Oxime Salts[1]

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Abstract: The kinetics of the reaction of sodium 9-fluorenone oximate with methyl iodide in 33.5% acetonitrile–66.5% t-butyl alcohol solvent ($D$ 19.5) at 25.0° have been studied as a function of oximate concentration. Increasing oximate concentration from $1 \times 10^{-3}$ to $88 \times 10^{-3}$ $M$ causes the second-order rate constant to decrease from $19.6 \times 10^{-3}$ l./mol sec to $2.5 \times 10^{-2}$ l./mol sec and the product composition to change from 65 to 46% oxygen methylation. The data may be correlated with a dissociated 9-fluorenone oximate which is more reactive than the sodium oximate ion pair by a factor of 60 by using a measured dissociation constant of $1.2 \times 10^{-4} M$. The analysis indicates that the dissociated ion gives 65% oxygen methylation and 35% nitrogen methylation while the ion pair reacts with methyl iodide to produce 30% oxygen methylation.

The predictive control of the site of alkylation of ambident systems, e.g., eq 1, is of mechanistic importance and synthetic utility. Factors[3] affecting the course of such reactions for the case of ambident

$$RX + A\!=\!\!=\!Z\!=\!\!=\!B^- M^+ \longrightarrow RAZ\!=\!\!=\!B + A\!=\!\!=\!ZBR + M^+ X^- \quad (1)$$

anions include the extent of association,[4-6] cation,[5,6] solvent,[5-7] and alkylating agent.[8,9] These factors do not necessarily act independently. Although concentration, cation, and solvent effects are often noted[3] a complete analysis in terms of the relative reactivities of the various possible ionic species at each potential reaction site is usually not possible. Forsblad,[4c] however, has determined the rate constants for oxygen and carbon alkylation of the ion-paired and dissociated forms of salts of the ethyl esters of β-hydroxycoumarilic acid with methyl iodide in methanol and demonstrated a substantial cation effect on the reactivity and site of methylation of associated ions.

The dependence of the oxygen to carbon alkylation product ratio on cation and solvent for various phenoxides studied by Curtin[5a,b] and the change of the nitrogen to carbon pyrrole alkylation product ratios noted by Van der Werf[6] suggest that ion association is important in determining the course of reactions of the type depicted in eq 1.

Oxime salts may be alkylated either on oxygen or nitrogen.[10] Brady and coworkers[12] have suggested that the site of oxime alkylation depends on the degree of dissociation of the oxime salt. More recently Smith and Robertson[11] investigated the effects of changes in oxime anion structure, cation, alkylating agent, and solvent on the nitrogen to oxygen alkylation product radio. Under the conditions employed by Smith,[11] association did not contribute significantly to the product specificity.

This work is concerned with dissociation effects on the alkylation of the sodium salt of 9-fluorenone oxime (I)

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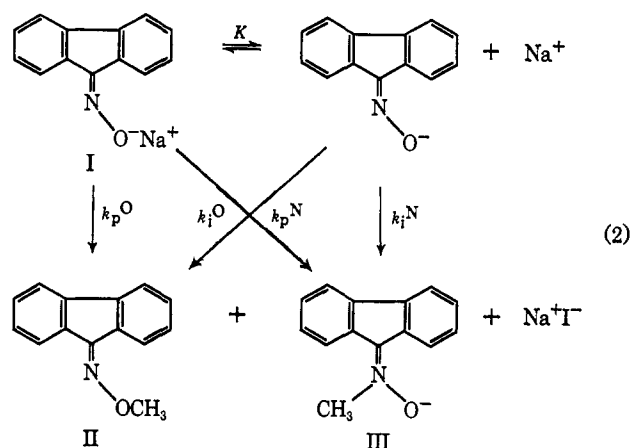
with methyl iodide. This system has properties which allow convenient analysis. The effects of concentration on the rate of methylation and product selectivity are correlated with conductance studies which allow estimates of the free-ion and ion-pair reactivities and alkylation product ratios.

## Results

The methylation of sodium 9-fluorenone oximate with methyl iodide was studied at 25.0° using a 33.5% acetonitrile–66.5% t-butyl alcohol mixture as solvent. This solvent mixture has an experimentally useful

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(2) (a) Alfred P. Sloan Fellow. (b) National Science Foundation Predoctoral Fellow, 1966–1967; National Aeronautics and Space Administration Fellow, 1963–1966.

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(4) (a) S. F. Acree, Am. Chem. J., 48, 353 (1912); (b) A. Brandström, Arkiv Kemi, 11, 567 (1957); (c) I. Forsblad, ibid., 15, 403 (1960); C. K. Ingold, Ann. Rept., 23, 142 (1926).

(5) D. Y. Curtin, R. J. Crawford, and M. Wilhelm, J. Am. Chem. Soc., 80, 1394 (1958); (b) D. Y. Curtin and D. H. Dybvig, ibid., 84, 225 (1962); (c) H. E. Zaugg, ibid., 83, 837 (1961).

(6) C. F. Hobbs, C. K. McMillin, E. P. Papadopoulos, and C. A. Van der Werf, ibid., 84, 43 (1962).

(7) (a) N. Kornblum, P. J. Berrigan, and W. J. leNoble, ibid., 85, 1141 (1963); (b) N. Kornblum, R. Seltzer, and P. Haberfield, ibid., 85, 1148 (1963); (c) H. D. Zook, ibid., 82, 1259 (1960).

(8) E.g. (a) G. Brieger and W. M. Pelletier, Tetrahedron Letters, 40, 3555 (1965); (b) S. T. Yoffe, K. V. Vatsuro, F. E. Kagatchev, and M. I. Kabachnik, ibid., 10, 593 (1965); (c) W. J. leNoble and J. E. Puerta, ibid., 10, 1087 (1966).

(9) (a) R. G. Pearson and J. Songstad, J. Am. Chem. Soc., 89, 1827 (1967); (b) R. F. Hudson and G. Klopman, Tetrahedron Letters, 1103 (1967).

(10) Alkylation on carbon to form a nitroso compound has not been observed.[11]

(11) P. A. S. Smith and J. E. Robertson, J. Am. Chem. Soc., 84, 1197 (1962).

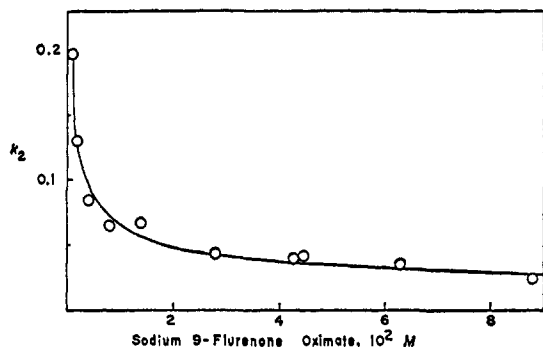(12) O. L. Brady and N. M. Chokshi, J. Chem. Soc., 2271 (1929).

Figure 1. Plot of $k_2$ vs. concentration for the reaction of methyl iodide with sodium 9-fluorenone oximate in 33.5% acetonitrile–66.5% t-butyl alcohol at 25.0°. The line is calculated for $k_i$ = 0.55 l./mol sec and $k_p$ = 9.0 × 10⁻³ l./mol sec.
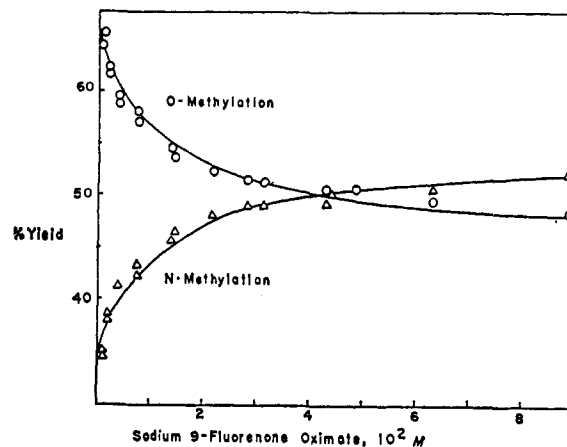


Figure 2. Plot of yield of methyl ether II and nitrone III from the reaction of methyl iodide with sodium 9-fluorenone oximate vs. oximate concentration in 33.5% acetonitrile–66.5% t-butyl alcohol at 25.0°.

dissociating power ($D$ 19.5) and specific solvation properties which allow a substantial product spread from the various ionic species. Solutions of the oxime salts were prepared by adding 9-fluorenone oxime to the solvent lyate salt.

**Kinetics.** The disappearance of oximate was followed by titration of aliquots with acid using an automatic photometric titrator[13] developed for this purpose. The titrator provided sufficient accuracy that reactions could be followed at relatively low concentration. Reaction was initiated by introduction of neat methyl iodide into thermostated (25.00 ± 0.02°) solutions of the oximate salt with a syringe. The initial reactant concentration ratio, (methyl iodide)/(oximate), was varied from 100:1 to 1:2 to enable a wide range of second-order rate constants to be measured. The observed integrated second-order rate constants decrease during a run (Table I) since the iodide salt formed depresses the dissociation of the oximate salt. The addition of excess sodium iodide results in data which yield linear second-order rate plots (Table II). Because of the depression of reaction rates during a run, the initial rate constants were obtained by extrapolating integrated second-order rate constants to zero reaction.

Table I. Relative Titration Volume and Integrated Rate Constan as a Function of Time for the Reaction of 0.0433 $M$ Sodium 9-Fluorenone Oximate with 0.0253 $M$ Methyl Iodide in 33.5% Acetonitrile at 25.0°

| Time, sec | Relative titration vol | $10^2 k$ (integrated), l./mol sec |
|---|---|---|
| 0 | 6.036 | |
| 39 | 5.800 | 4.18 |
| 135 | 5.380 | 3.73 |
| 229 | 5.040 | 3.68 |
| 401 | 4.626 | 3.38 |
| 506 | 4.424 | 3.29 |
| 587 | 4.264 | 3.31 |
| 671 | 4.182 | 3.13 |
| 832 | 3.940 | 3.17 |
| 944 | 3.851 | 3.04 |
| 1036 | 3.758 | 3.02 |
| 1160 | 3.656 | 2.98 |
| | 2.505 | 2.98 |
| | Weighted least squares | 3.01 ± 0.06[a] |
| | Initial rate constant | 4.08 |

[a] Error given is one standard deviation from the weighted least-squares fit to the second-order rate law.

(13) R. Anderson and C. Hawley, unpublished work.

These rate constants are summarized in Table II. The observed second-order rate constants change markedly with oximate concentration (Table II and Figure 1). For example, the initial second-order rate constant increases from 2.5 × 10⁻² l./mol sec to 19.6 × 10⁻² l./mol sec for a change in concentration from 88 × 10⁻³ to 1 × 10⁻³ $M$.

**Product Analysis.** The concentrations of methyl nitrone III and methyl ether II resulting from the reaction of methyl iodide with sodium 9-fluorenone oximate (I) were determined by quantitative uv absorption spectroscopy. Calibration spectra for the two products were obtained from purified authentic materials prepared from the reaction of N-methylhydroxylamine and methoxylamine with 9-fluorenone. Absorbance values at two wavelengths, 346 and 308 mμ, which are the respective maxima for the N- and O-methylated products were employed after demonstrating adherence to Beer's law. Both products were found to be stable to the reaction conditions. The product yields summarized in Table II were obtained by dividing the product concentration as determined by uv analysis by the initial concentration of oximate as measured by base titration. The total product yield varied from ca. 90 to 100% and was normalized to 100% for graphical presentation in Figure 2 and subsequent calculations. The data indicate that at low concentrations the oxygen-methylated products approach 65% yield while at 9 × 10⁻² $M$ ca. 50% of the product results from methylation on nitrogen.

**Conductivity.** The conductivity of solutions containing various concentrations of sodium oximate (I) was determined at 25.0°. The measured conductance and equivalent conductance for various concentrations of this salt are tabulated in Table III. From the plot of equivalent conductance vs. sodium oximate concentration given in Figure 3 and the plot of observed second-order rate constants vs. concentration given in Figure 1, it is apparent that both conductance and rate constants increase with decreasing oximate concentration in a similar manner. A plot of log Λ vs. log concentration is linear with a slope of −0.43 suggesting that conductive aggregates are not important at these concentrations. The values of the ion-pair

**Table II.** Summary of Rate Constants and Product Yields as a Function of Oximate Concentration for the Reaction of Sodium 9-Fluorenone Oximate with Methyl Iodide in 33.5% Acetonitrile at 25.0°

| $10^3$[oximate], $M$ | $10^3$[MeI], $M$ | $10^3$[NaI], $M$ | $10^2 k,^a$ l./mol sec | O-prod (II), % yield$^d$ | N-prod (III), % yield$^d$ | % O/% N |
|---|---|---|---|---|---|---|
| 1.03 | 5.23 | 0.00 | 19.6 | 59.8 | 30.9 | 1.94 |
| 1.05 | 5.22 | | 19.6 | 59.8 | 32.5 | 1.84 |
| 2.07 | 8.33 | | 13.0 | 57.2 | 34.9 | 1.64 |
| 2.07 | 38.2 | | ... | 57.5 | 36.1 | 1.59 |
| 3.96 | 72.9 | | ... | 55.4 | 37.9 | 1.46 |
| 4.07 | 8.29 | | 8.24 | 54.0 | 37.8 | 1.43 |
| 7.27 | 134 | | ... | 54.9 | 39.9 | 1.38 |
| 7.72 | 15.1 | | 6.58 | 53.2 | 40.3 | 1.32 |
| 14.0 | 8.8 | | 6.96 | 50.4 | 42.3 | 1.19 |
| 14.7 | 53.7 | | ... | 49.9 | 43.2 | 1.16 |
| 22.0 | 80.5 | | ... | 48.9 | 44.7 | 1.09 |
| 28.3 | 16.6 | | 4.21 | 48.2 | 45.2 | 1.04 |
| 31.6 | 115 | | ... | 48.8 | 46.3 | 1.05 |
| 43.3 | 25.3 | | 4.08 | 46.8 | 45.2 | 1.04 |
| 44.0$^c$ | 21.7 | | 4.18 | ... | ... | ... |
| 44.2 | 161 | | ... | 47.2 | 47.8 | 0.99 |
| 63.4 | 52.3 | | 3.36 | 45.8 | 46.7 | 0.98 |
| 88.2 | 80.2 | | 2.51 | 46.6 | 50.2 | 0.93 |
| 1.05 | 10.4 | 4.59 | $4.33 \pm 0.03^b$ | 55.2 | 38.8 | 1.42 |
| 1.05 | 20.5 | 17.9 | $2.93 \pm 0.02^b$ | 51.8 | 42.8 | 1.21 |
| 1.05 | 20.5 | 46.2 | $2.44 \pm 0.02^b$ | 49.9 | 44.8 | 1.11 |
| 1.07 | 40.5 | 45.7 | ... | 49.1 | 45.6 | 1.08 |
| 2.09 | 9.7 | 45.8 | $2.36 \pm 0.01^b$ | 47.9 | 48.0 | 1.00 |
| 2.49 | 9.7 | 45.7 | ... | 44.7 | 47.2 | 0.97 |
| 3.57 | 38.6 | 44.7 | ... | 45.2 | 48.6 | 0.93 |
| 4.05 | 9.7 | 44.8 | $2.27 \pm 0.02^b$ | 49.8 | 48.3 | 0.93 |

$^a$ Initial rate constant except where noted. $^b$ Integrated rate constant. Error given is one standard deviation from the weighted least-squares fit to the second-order rate law within a run. $^c$ Methyl iodide was added to the solvent at 25.0° 6 hr before the addition of the sodium 9-fluorenone oximate. $^d$ From a uv analysis of the reaction mixture.
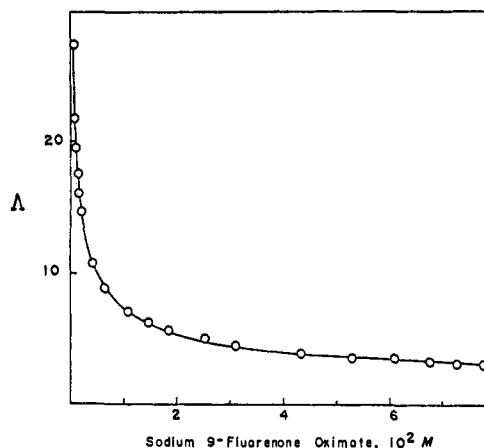
**Table III.** Summary of the Measured Conductance and Equivalent Conductance for Various Concentrations of Sodium 9-Fluorenone Oximate in 33.5% Acetonitrile–66.5% $t$-Butyl Alcohol with 19.1% Excess 9-Fluorenone Oxime Added at 25.0°

| $10^3$[sodium oximate], $M$ | Measd conductance, $\mu$mhos | Equiv conductance, mhos l./mol cc |
|---|---|---|
| 0.375 | 66.82 | 27.30 |
| 0.717 | 102.0 | 21.80 |
| 1.030 | 128.0 | 19.146 |
| 1.319 | 150.5 | 17.486 |
| 1.585 | 168.6 | 16.296 |
| 2.055 | 197.2 | 14.700 |
| 4.494 | 311.3 | 10.612 |
| 6.843 | 394.4 | 8.830 |
| 11.02 | 517.7 | 7.194 |
| 14.93 | 614.7 | 6.306 |
| 19.60 | 695.9 | 5.732 |
| 25.22 | 826.6 | 5.022 |
| 31.11 | 932.5 | 4.592 |
| 43.55 | 1128 | 3.968 |
| 53.25 | 1260 | 3.626 |
| 61.03 | 1385 | 3.478 |
| 67.41 | 1429 | 3.246 |
| 72.73 | 1584 | 3.128 |
| 77.22 | 1531 | 3.036 |

dissociation constant and equivalent conductance at infinite dilution were calculated from the data by the Shedkovsky[14] method for oximate I concentrations up to $8 \times 10^{-3}$ $M$. Over this concentration range the Shedkovsky plot is linear; however, at higher concentrations this plot tends to display upward curvature. In the conductivity measurements it was necessary to have excess 9-fluorenone oxime present to minimize solvent decomposition which results in decreased solu-

(14) T. Shedlovsky, *J. Franklin Inst.*, **225**, 739 (1938).

tion conductivity. The data summarized in Table IV indicate that approximately doubling the excess oxime



Figure 3. Plot of equivalent conductance *vs.* concentration for sodium 9-fluorenone oximate in 33.5% acetonitrile–66.5% $t$-butyl alcohol at 25.0°.

does not change the results within the experimental error of these data.

**Table IV.** Summary of Ion-Pair Dissociation Constants for Salts in 33.5% Acetonitrile–66.5% $t$-Butyl Alcohol at 25.0°

| Salt | Excess oxime, % | $10^4 K_d$, $M$ | $\Lambda_0$, mhos l./mol cc |
|---|---|---|---|
| Sodium 9-fluorenone oximate | 19.1 | 1.28 | 31.4 |
| | 37.5 | 1.10 | 34.0 |
| | Av | 1.19 | 32.7 |
| Sodium iodide | ... | 19.6 | 73.2 |

**Table V.** Summary of the Specific Conductance and Equivalent Conductance for Various Concentrations of Sodium Iodide in 33.5% Acetonitrile –66.5% Solvent at 25.0°

| $10^3$[NaI], $M$ | Measd conductance, $\mu$mhos | Equiv conductance, mhos l./mol cc |
|---|---|---|
| 0.340 | 274.4 | 123.60 |
| 0.650 | 482.6 | 113.66 |
| 0.935 | 657.3 | 107.74 |
| 1.196 | 808.9 | 103.60 |
| 1.437 | 936.7 | 99.84 |
| 1.864 | 1167 | 95.88 |
| 4.169 | 2203 | 80.96 |
| 6.388 | 3049 | 73.12 |
| 8.257 | 3784 | 64.00 |
| 10.59 | 4448 | 64.34 |
| 12.58 | 5040 | 61.78 |
| 14.50 | 5609 | 59.20 |
| 16.36 | 6119 | 47.30 |
| 18.16 | 6591 | 55.62 |
| 19.89 | 7037 | 54.18 |
| 23.01 | 7806 | 54.98 |
| 25.94 | 8517 | 50.32 |

The conductance of sodium iodide was also studied (Table V), and the results of the Shedkovsky treatment, summarized in Table IV, indicate that sodium iodide is more dissociated than sodium 9-fluorenone oximate by a factor of 16.

## Discussion

For the alkylation of sodium 9-fluorenone oximate in 33.5% acetonitrile–66.5% $t$-butyl alcohol solvent with methyl iodide it has been found that (a) the second-order rate constants increase with decreasing oximate concentration (Figure 1); (b) the fraction of the reaction which results in methylation on oxygen increases with decreasing oximate concentration (Figure 2); and (c) the change in equivalent conductance with concentration parallels the change in both $k_2$ and the fraction of O-methylation. Although the actual chemical reaction may differ in detail, the scheme in eq 2 which involves an equilibrium between ion pairs and dissociated ions with each reacting with a characteristic rate constant at oxygen and nitrogen is able to account for the observations.[4,15] In this scheme, higher aggregates may contribute to the actual description of the system at the highest concentration. The observed rate constant, $k_{obsd}$, is related to the rate constants for the reaction at oxygen and nitrogen of the ion pair, $k_p{}^O$ and $k_p{}^N$, and the corresponding constants for the dissociated ion, $k_i{}^O$ and $k_i{}^N$, by eq 3[4a] where $\alpha$ is the degree of dissociation for a given oximate concentration.

$$k_{obsd} = (k_i{}^O + k_i{}^N)\alpha + (k_p{}^O + k_p{}^N)(1 - \alpha) \quad (3)$$

The application of eq 3 to the data for the sodium oximate I is complicated by the fact that during a run the conversion of oximate salt to the more highly dissociated sodium iodide causes the degree of dissociation, $\alpha$, of eq 3 to decrease with the result that the fraction of the reaction going through ion pairs increases during a run. This causes the calculated second-order rate constant to decrease during a kinetic run, as observed, and results in a product mixture integrated over a reac-

(15) In principle, all reactions could proceed by way of a dissociated ion with ionic strength or salt effects changing the activity coefficient of the transition state for reaction on nitrogn relative to reaction on oxygen.

tion in which the contribution from the various ionic species is changing. To facilitate treatment of the equilibrium relationship between the two ion-pair dissociation constants, four rate constants, and initial concentrations, the reaction was simulated on an EAI TR 20 analog computer programmed to produce integrated % O-methyl ether, % N-methyl nitrone yields and concentration $vs.$ time plots for various values of the rate constants and the ion-pair dissociation constants determined by conductivity. Because of the difficulty of assessing activity coefficients in this solvent and the likelihood that the concentration range exceeds the applicability of the Debey–Hückel limiting law,[16] activity coefficients were ignored in these calculations. The use of appropriate activity coefficients will, of course, change the quantitative results but not the general conclusions. The results of calculations, based on $k_i = 5.5 \times 10^{-1}$ l./mol sec, $k_p = 1.0 \times 10^{-3}$ l./mol sec, $k_i{}^O = 0.65k_i$, $k_i{}^N = 0.35k_i$, $k_p{}^O = 0.3k_p$, and $k_p{}^N = 0.7k_p$, reproduce the observed variation in rate and products within experimental error, the curves in Figures 1 and 2 being calculated from these parameters. These rate constants correspond to the dissociated ion, being more reactive than the ion pair by a factor of 60. Similar reactive ratios have been observed in other systems.[16] A large product specificity is also apparent with the dissociated ion giving 65% oxygen methylation while the data are consistent with the ion pair alkylating 70% on nitrogen. The control of the product composition made possible by this specificity has substantial utility. However, the inversion of the O/N alkylation ratio with oximate concentration indicates that theoretical treatments[9,17] of ambient reactivity which do not take ion association into account are significantly oversimplified.

The absolute values of the derived rate constants, $k_i{}^O$, $k_i{}^N$, $k_p{}^O$, and $k_p{}^N$, depend upon the values of the ion-pair dissociations constants used, the choice of activity coefficients[16] for the dissociated ions, and the assumption that salt effects are negligible. Since it is likely that the fraction of ionic species counted as paired by conductance is larger than the fraction evidenced by these reaction rate constants and product yields, the values of the kinetic parameters may have to be refined as better estimates of the appropriate degree of association become available.

Heterogeneity has been reported[18] to be a factor in the control of the position of alkylation of ambient ions. The low $(2.2 \times 10^{-3}\ M)$ solubility of the lithium salt of 9-fluorenone oxime in 33.5% acetonitrile–66.5% $t$-butyl alcohol at 25.0° provides an interesting test of this hypothesis. Treatment of a homogeneous solution of $1.5 \times 10^{-3}\ M$ lithium oximate with methyl iodide gives 50% methylation on oxygen. In contrast an initially heterogeneous mixture containing $40 \times 10^{-3}\ M$ lithium oximate forms only 30% of the O-methylated product. However, as noted above for the sodium salt, as the reaction proceeds lithium iodide, which depresses the dissociation of the oximate salt, is formed causing the integrated product yield from the homogeneous reaction to approach that derived from an ion pair.

(16) (a) N. N. Lichtin and K. N. Ra, *J. Am. Chem. Soc.*, **83**, 2417 (1961); (b) W. M. Weaver and J. D. Hutchison, *ibid.*, **86**, 261 (1964).

(17) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *ibid.*, **77**, 6269 (1955).

(18) N. Kornblum and A. P. Lurie, *ibid.*, **81**, 2705 (1959).

Accordingly, methylation of the homogeneous solution of $1.6 \times 10^{-3}$ M lithium oximate in the presence of $29 \times 10^{-3}$ lithium iodide yields only 29% O product. Thus the heterogeneous reaction can most simply be envisioned as a solution reaction in which lithium oximate is replenished by the solid oximate salt with the concomitant buildup of lithium iodide continually decreasing the lithium oximate's degree of dissociation. It is not necessary to invoke reaction at the solid surface[5b] to account for the observed product composition of the heterogeneous reactions.

## Experimental Section

**9-Fluorenone Oxime.** Treatment[19] of 9-fluorenone with hydroxylamine hydrochloride in 30% aqueous ethanol containing sodium carbonate gave the desired oxime in 62% yield, mp 194–195° (lit.[19] mp 195–196°) after recrystallization from ethanolic benzene.

**9-Fluorenone O-Methyloxime.** 9-Fluorenone O-methyloxime was prepared from 8.3 g of methoxylamine hydrochloride and 9 g of 9-fluorenone using the reported[19] procedure for preparation of the oxime except that the reaction mixture was refluxed 22 hr. The light yellow solid recovered by filtration of the water-treated reaction mixture was extracted with petroleum ether (bp 30–60°). Purification was effected by chromatography on silica gel using petroleum ether as the eluent. After removal of the solvent and vacuum sublimation, a pale yellow solid, 0.7 g (7% yield), mp 39.5–40.5°, was obtained. The uv spectrum ($\lambda_{max}$ 225 m$\mu$), infrared spectrum (strong characteristic[12] absorption at 1050 cm$^{-1}$), and nmr spectrum are consistent with the O-methyl structure.

*Anal.* Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.64; H, 5.58; N, 6.43.

**9-Fluorenyl N-Methyl Nitrone.** Reaction of 5.0 g of N-methylhydroxylamine hydrochloride with 5.4 g of 9-fluorenone in 250 ml of t-butyl alcohol containing 6 g of sodium carbonate at reflux for 17 hr followed by precipitation with water and recrystallization from ethanol gave 2.0 g (37%) of a yellow solid, mp 147–148°. The infrared spectrum exhibits a characteristic[12] strong absorbance at 1280 cm$^{-1}$. The uv spectrum has $\lambda_{max}$ 346 m$\mu$ ($\epsilon$ 23,500).

*Anal.* Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.32; H, 5.57; N, 6.81.

**t-Butoxide Solutions.** Alkali metal t-butoxide solutions were prepared by allowing sodium metal or lithium hydride (8–35 mesh, Foot Mineral) to react with dry t-butyl alcohol.

**Solvent.** t-Butyl alcohol and acetonitrile were dried before use by percolation through a column of Linde 4-A Molecular Sieve followed by distillation through a 3-ft packed column into a solvent storage bottle. Karl Fischer titration indicated the solvent contained less than 0.005% water. Subsequent transfers of solvents were made with the exclusion of moisture. The mixed solvent was prepared by mixing measured volumes of solvent.

**Sodium Iodide.** Baker AR grade sodium iodide was recrystallized from freshly distilled, deionized water under a nitrogen atmosphere. Prior to preparation of solutions, the salt was dried for 18 hr at 110° (0.1 mm). All solutions used for kinetic, product, and conductance studies were prepared under a nitrogen atmosphere.

**Lithium Iodide.** Lithium iodide was prepared in t-butyl alcohol by allowing excess methyl iodide to react with lithium t-butoxide. Subsequently sufficient acetonitrile, 9-fluorenone oxime, and additional lithium t-butoxide were added to yield $1.65 \times 10^{-3}$ M lithium oximate and $2.9 \times 10^{-2}$ M lithium iodide.

**Viscosity Measurements.** The viscosity of 33.5% acetonitrile–66.5% t-butyl alcohol solvent was found to be $7.74 \pm 0.01 \times 10^{-3}$ P at 25.00° at using a Cannon flow viscometer of the Ostwald type.

**Dielectric Constant Determinations.** Using a standard heterodyne-beat method[20] the dielectric constant was found to be 19.47 D at 25.0°.

**Conductance Measurements.** Conductance measurements were made using a silicon rubber serum-capped Pyrex conductance cell having bright platinum electrodes and a cell constant of 0.0766 ± 0.0002 (one standard deviation) determined using aqueous potassium chloride solutions at six concentrations in the range $0.387$–$2.23 \times 10^{-3}$ M. All solution resistance measurements were made using an Industrial Instruments conductivity bridge and auxiliary compensating capacitance when necessary. For all conductance measurements the temperature of the solution-containing bath was maintained by a proportional temperature controller at 25.00 ± 0.02° as determined by comparison with an NBS-certified thermometer. The total cell volume was *ca.* 220 ml; however, the addition of *ca.* 15 ml of liquid more than sufficiently covered the electrodes. The dependence of conductance upon the concentration of a given alkali metal 9-fluorenone oximate was determined in the following manner. The cell was first filled with a known volume of solvent in the 15–20-ml range and the resistance of this solvent at 25.0° determined. Then known-volume aliquots of concentrated oximate salt stock solutions at 25.0° were added to the cell using Chaney adapter equipped syringes, the contents of the cell were mixed, and the resistances of the solutions were determined. The solvent correction was at most 0.6% of the measured conductance. At low concentrations of oximate I (IV) and especially when the percentage excess of 9-fluorenone oxime was small, the resistance of the solution was observed to increase significantly over time. This effect is apparently due to the decomposition of acetonitrile in the presence of alkali t-butoxide. The addition of a larger excess of this oxime (III) enabled meaningful conductance data to be obtained. The calculation of the ion-pair dissociation constants, degrees of dissociation, and equivalent conductances at infinite dilution was accomplished by means of an IBM 7094 computer program written in FORTRAN II. This program is based on the Shedlovsky method[14] of calculation.

**Solution Preparation.** Stock solutions of the desired 9-fluorenone oximate were prepared by adding the appropriate t-butoxide solution to a slight excess of 9-fluorenone oxime in the desired solvent. Acetonitrile was then added when necessary to bring its percentage back to that of the solvent prior to the addition of the solution of t-butoxide in t-butyl alcohol. All solvent transfers were made so as to minimize exposure to atmospheric moisture and carbon dioxide usually through the use of syringes equipped with Chaney adapters enabling known-volume aliquots to be added. Solutions for rate and product determinations were then made by quantitatively diluting aliquots of the stock solution with the approprirate solvent in Pyrex bottles equipped with silicon rubber serum caps.

**Kinetics by Titration.** Once prepared in the above manner, the sample-containing bottles were transferred to a constant-temperature bath maintained at 25.00 ± 0.02° by means of proportional temperature control. The temperature of the bath was calibrated by comparison with an NBS-certified thermometer. After at least 0.5-hr equilibration time, an aliquot was withdrawn and titrated to determine the initial base concentration. The reaction was subsequently initiated by injecting neat methyl iodide (at *ca.* 25°) into the solution using a Chaney adapter equipped microsyringe. The initial solution volume and the weight of methyl iodide injected were known within 1%. After initiation aliquots of the reacting sample were withdrawn using calibrated Chaney adapter equipped syringes which were not cleaned between points but rather were kept at 25.0°. These aliquots were then quenched upon injection into the solvent-containing cell of an automatic photometric titrator. The time of injection was recorded and the base concentration determined. Infinity points were taken at least ten half-reaction times after initiation.

The spectrophotometric titrator employed[13] consisted of a regulated tungsten source and a band-pass filter, $\lambda_{max}$ 600 m$\mu$, focused on a CdS photocell through an enclosed, 30-ml beaker containing the solution to be titrated. The photocell was part of a servo system consisting of a chopper amplifier and servo-motor which operated a syringe buret containing standard hydrochloric acid. When a slightly alkaline solution of brom phenol blue in 20% aqueous acetone was placed in the titration cell, the servo system would add acid to the stirred solution until a blue-green end point was obtained. An aliquot of the reaction mixture was then added and automatically titrated to the same end point. Titration reproducibility was better than 1% for the lowest sample concentration titrated ($5 \times 10^{-4}$ M base).

**Product Concentration Determinations.** Product concentrations were determined through the use of a two-wavelength uv spectral method. Reagent grade methanol was employed for all dilutions, and absorbances were obtained by using either a Perkin-Elmer 202 or a Beckman DU spectrophotometer. When ob-

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tained, the recorded spectra were consistent in appearance with their being due only to a summation of the spectra of the two products. The uv spectral values used in the calculations are as follows:

for the nitrone III, $\epsilon_{308}$ 8100 and $\epsilon_{346}$ 23,500; for the O-methyl ether II, $\epsilon_{308}$ 11,260 and $\epsilon_{346}$ 450. These values were obtained from the slopes of the Beer's law plots for the nitrone and O-methyl ether.

# Ceanothus Alkaloids. Americine

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Abstract: Americine, a tryptophan-containing monobasic peptide alkaloid, has been isolated from dried, ground Ceanothus americanus root bark. Evidence from chemical degradation and high-resolution nmr and mass spectrometry established for americine a structure incorporating a p-alkoxystyrylamino residue in a 14-membered ring.

Peptide alkaloids[2] have thus far been isolated from several species of plants in five different botanical orders of the Dicotyledonae.[3-8] Stimulus for the pharmacognosic examination of these plants has largely been their utilization as folk medicines in North and South America, Africa, and Asia. Much attention has been devoted to plants of the Rhamnaceae (order Rhamnales), from three genera of which peptide alkaloids have been isolated and structurally characterized.[4,6,7] One of these genera, Ceanothus, is endemic to North America and consists of approximately 55 species, about 45 of which occur abundantly in California.

Ceanothus americanus Linn. ("New Jersey Tea") is native to the United States east of the Mississippi River. The Cherokee Indians made medicinal use of the plant as early as 1700, and infusions of various parts of this plant were used as panaceas for a wide variety of afflictions. Its proprietary use continued well into the 20th century, and root bark alkaloid mixtures were shown to have hypotensive effects.[9] A series of fruitless chemical investigations of C. americanus alkaloids spanning 76 years has been reviewed.[6]

Recently,[6a] five alkaloids have been isolated from dried, ground Ceanothus americanus root bark, and a

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(2) Peptide alkaloids may represent a new class of photochemicals more widely distributed in the plant kingdom than might be suspected from the limited scope of existing investigations. On the basis of preliminary observations on other fractions and other species, we anticipate the discovery of considerably greater structural variety than has thus far been encountered.

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structure was proposed for one of them, ceanothine-B[66]. All alkaloidal materials reported in that investigation displayed uv spectra characteristically devoid of any absorption maxima or minima. Our studies dealing with alkaloids isolated from ostensibly identical plant material revealed that perhaps 40% of our total alkaloid was composed of materials displaying uv spectra with maxima strongly suggestive of an indole chromophore. This paper deals with one of these intriguing alkaloids.
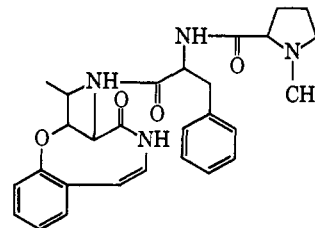


We herein report the isolation and structure elucidation of americine, an optically active alkaloid constituting 0.02% of dried, ground C. americanus root bark. Ethanolic extracts obtained by exhaustive continuous percolation of solvent through the plant material, after removal of neutral and acidic material, yielded crude alkaloid subsequently purified by alumina chromatography and multiple recrystallizations. Accompanying this alkaloid and extremely difficult to remove by preparative thin layer chromatography was 4% of a second alkaloid, homoamericine, as estimated by thin layer chromatography and mass spectroscopy. Once the close, homologous relationship between these two substances was established early in the investigation, all structural work was conducted on this americine–homoamericine (4%) mixture. Elemental ultramicroanalysis of americine fitted the empirical formula $C_{31}H_{39}N_5O_4$, corroborated by observation in the mass spectra of $M^+$ and $M^{2+}$ peaks at $m/e$ 545 and 272.5, respectively. Homoamericine would therefore be $C_{32}H_{41}N_5O_4$, corresponding to the less abundant peak found at $m/e$ 559. Although a high degree of unsaturation was implied in the empirical formula, americine reacted quantitatively (followed by tlc) with only 1 equiv of hydrogen under catalytic conditions to yield dihydroamericine ($m/e$ 547; $m/e$ 545 ion absent).

Extremely intense amide absorption in the infrared spectrum of americine ($\nu_{max}$ 3260 cm$^{-1}$, NH stretch;