**B. Separation of Aromatic Hydrocarbons from Reaction Product.**—The separation was accomplished using an F & M Model 300 programmed temperature gas chromatograph[12] with an 11 mm. × 2.4 m. preparative v.p.c. column filled with 5% 7,8-benzoquinoline on 30–60-mesh Chromosorb. The column temperature used was 75° with a helium flow rate of 105–114 ml./min. The sample recovery was the same as described previously.[1]

**C. Oxidation of the Xylenes.**—The xylenes which were separated and collected from the preparative v.p.c. column were diluted from five–fifty times with their inactive xylenes and oxidized to the corresponding phthalic acids with hot alkaline potassium permanganate as described previously.[1]

**D. Separation of the Phthalic Acids.**—The separation and purification of the phthalic acids produced before was accomplished as described earlier.[11]

**E. Radiochemical Assay.**—The radiochemical assay of the resulting phthalic acids and their decarboxylation products was the same as previously described.[13]

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[12] F & M Scientific Corp., Avondale, Pa.

[13] H. Pines and G. Benoy, *J. Am. Chem. Soc.*, **82**, 2483 (1960).

# Kinetics of the Reaction of 2-Nitropropane with Methylenebisamines. A Study of the Mannich Reaction

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The Mannich reactions of 2-nitropropane with methylenebispiperidine and with methylenebismorpholine exhibit second-order kinetics, first order in each component. The 2-nitropropane reacts through the *aci* form. The rate increases with increasing dielectric constant, and decreases in basic media. Methylenebispiperidine exhibits a faster rate than methylenebismorpholine. The greater reactivity of the piperidine derivative is attributed to its greater base strength. Mechanisms are presented for media of low and high dielectric constant.

The Mannich reaction has been reviewed by Blicke[2] and Hellman,[3] and two excellent kinetic studies have been reported.[4,5] Alexander and Underhill studied the reaction of ethylmalonic acid as active hydrogen compound and dimethylamine as amine component. Cummings and Shelton used cyclohexanone and dimethylamine. Both of these studies employed aqueous solvents and both involved the over-all Mannich reaction of active hydrogen compound, formaldehyde, and amine.

$$Z-\overset{|}{\underset{|}{C}}-H + HCHO + HNR_2 \longrightarrow Z-\overset{|}{\underset{|}{C}}-CH_2NR_2 + H_2O \quad (1)$$

The present kinetic study was undertaken to investigate (1) the effect of amine basicity and (2) the effect of solvent dielectric constant.

Attempts to follow the rate of reaction of the mixture of reactants shown in eq. 1 necessarily leads to complex results because of the known initial reaction of amine and formaldehyde to form any of several intermediate species, *e.g.*, aminomethylol, methylenebisamine, and methyleneimmonium ion. The complexities of this reaction have been reviewed by Wagner.[6] The above mechanisms[4,5] are thus complicated by this initial reaction and further by the participation of water in the amine–formaldehyde equilibrium.[6]

$$R_2NH + HCHO \rightleftharpoons R_2NCH_2OH \xrightleftharpoons{R_2NH} R_2NCH_2NR_2 + H_2O$$

For these reasons, deductions about the intermediates (aminomethylol *vs.* methylenebisamine) and deductions based on activation parameters were prevented.

In the present work we studied the reaction of 2-nitropropane with two methylenebisamines. It is well-known that nitro alkanes react to form Mannich bases. Senkus[7] and Johnson[8] reported that the Mannich reaction of nitro alkanes proceeds through an intermediate formed by the condensation of the amine with formaldehyde. Butler[9] found that methylenebisamines react with 2-methyl-2-nitro-1-propanol (formed by the reaction of 2-nitropropane with formaldehyde) to form the usual Mannich bases. Another interesting feature of 2-nitropropane is its acidity which is intermediate between those of the active hydrogen compounds used in the kinetics studies discussed.[4,5]

The use of methylenebisamines in the present study can be explained on the following basis. Aminomethylols are not generally isolable,[6] thus they are difficult to study. It is known that methylenebisamines react with active hydrogen compounds to produce normal Mannich bases.[9–11] Fernandez and Butler[12] have demonstrated recently that the reaction of formaldehyde with secondary aliphatic amines produces primarily the methylenebisamine and only small proportions, if any, of the aminomethylol. While aminomethylols are not excluded as intermediates, evidence offered for their reactivity as intermediates is indirect and only recently was inferred[11] through a study of the reaction of α-amino ethers with β-naphthol to produce normal Mannich bases.

We have thus attempted to simplify the system at the risk of narrowing the scope of the results. Anhydrous solvents were employed in all runs to avoid formation of aminomethylol by hydrolysis of the methylenebisamines. We employed the methylenebisamines of piperidine and morpholine because of the rather large

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[1] Student participant sponsored by National Science Foundation Undergraduate Science Education Grants No. G-21888 and GE-1210.

[2] F. F. Blicke, *Org. Reactions*, **1**, 303 (1942).

[3] H. Hellman, *Angew. Chem.*, **65**, 473 (1953).

[4] E. R. Alexander and E. J. Underhill, *J. Am. Chem. Soc.*, **71**, 4014 (1949).

[5] T. F. Cummings and J. R. Shelton, *J. Org. Chem.*, **25**, 419 (1960).

[6] E. C. Wagner, *ibid.*, **19**, 1862 (1954).

[7] M. Senkus, *J. Am. Chem. Soc.*, **68**, 10 (1946).

[8] H. G. Johnson, *ibid.*, **68**, 12, 14 (1946).

[9] G. B. Butler, *ibid.*, **78**, 482 (1956).

[10] S. V. Liebermann and E. C. Wagner, *J. Org. Chem.*, **14**, 1001 (1949).

[11] J. E. Fernandez, C. Powell, and J. S. Fowler, *J. Chem. Eng. Data*, **8**, 600 (1963).

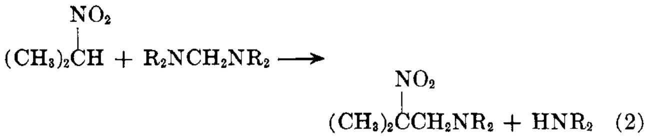
[12] J. E. Fernandez and G. B. Butler, *J. Org. Chem.*, **28**, 3258 (1963).

TABLE I

INITIAL RATES OF REACTION OF 2-NITROPROPANE WITH METHYLENEBISPIPERIDINE AT 78.6°

| Run no. | Concn. of 2-nitropropane, $M$ | Concn. of methylenebispiperidine, $M$ | Initial rate, mole/l./hr. | $k_1$, hr.$^{-1}$ | $k_2$, l./mole/hr. |
|---|---|---|---|---|---|
| 1 | 2.50 | 0.125 | 0.205 | 0.714 | 0.295 |
| 2 | 2.50 | 0.250 | 0.393 | 0.747 | 0.286 |
| | | | | | Av. = 0.290 ± 0.005 |
| 3 | 2.50 | 0.375 | 0.620 | 0.438 | 0.187 |
| 4 | 2.50 | 0.375 | | 0.397 | 0.159 |
| 5 | 0.125 | 2.50 | 0.0175 | | |
| 6 | 0.125 | 2.50 | 0.020 | 0.0614 | 0.0246 |
| 7 | 0.250 | 2.50 | 0.0425 | 0.0832 | 0.0361 |
| 8 | 0.375 | 2.50 | 0.062 | 0.0692 | 0.0286 |
| | | | | | Av. = 0.0298 ± 0.0042 |

difference in basicity (p$K_b$ 2.78 and 5.64 for piperidine and morpholine, respectively) and their nearly identical steric properties. The solvents used were dioxane, dimethylformamide, nitrobenzene, and triethylamine. Reaction rates were followed by the spectrophotometric analysis of the N–H overtone band[13] at 1.53 $\mu$ of the secondary amine produced.



$$\mathrm{(CH_3)_2\overset{NO_2}{C}H + R_2NCH_2NR_2 \longrightarrow (CH_3)_2\overset{NO_2}{C}CH_2NR_2 + HNR_2} \qquad (2)$$

## Experimental

**Kinetics.**—Kinetic runs were carried out using 2-nitropropane with methylenebispiperidine and with methylenebismorpholine. Eastman practical grade 2-nitropropane was redistilled through a Vigreux column and the fraction boiling at 119–120° retained. Methylenebispiperidine[14] and methylenebismorpholine[15] were prepared from the corresponding secondary amines and formaldehyde, b.p. 100–105° (3.5–4.0 mm.) and 107–109° (4.5 mm.), respectively. The near infrared spectra of these methylenebisamines showed no secondary N–H amine absorbance at 1.53 $\mu$.[13]

Kinetic runs were carried out in dioxane, nitrobenzene, and dimethylformamide, and various mixtures of these solvents to determine the effect of dielectric constant on the reaction rate. Eastman practical grade *p*-dioxane was refluxed over sodium for 3 days, then distilled through a 25-plate sieve tray column. Eastman practical grade nitrobenzene was redistilled through a Vigreux column (b.p. 209°). Eastman Spectro Grade dimethylformamide was used as received.

Runs were made in constant temperature oil baths maintained at 78.60 ± 0.03°, 82.76 ± 0.03°, and 87.94 ± 0.04°. The reactants were mixed in a 50-ml. volumetric flask and quickly brought to temperature before immersing in the bath. The warm-up period normally took less than 1 min. Samples were withdrawn at recorded time intervals and the reaction quenched in a chilled glass tube. The progress of the reaction was followed by measuring spectrophotometrically the concentration of secondary amine produced (eq. 2). The 1.53-$\mu$ band due to the N–H overtone was convenient for this purpose since other bands did not interfere in this region.

All analyses were performed using a Perkin-Elmer Infracord Model 137-G spectrophotometer and 1-cm. silica cells. Beer's law for piperidine and morpholine was confirmed in all the solvents and solvent combinations used.

The order of the reaction of 2-nitropropane with methylenebispiperidine was determined by measuring the initial rate graphically when each component was in large excess. The linear variation of initial rate with concentration (Table I) shows that the reaction is first order with respect to each component. The second-order rate constants were determined by using low concentrations of each reactant and plotting the second-order function $C_t/C_0(C_0 - C_t)$ against time where $C_0$ = initial concentration of reactants, $C_t$ = amount of reactants consumed at time $t$. The slope (rate constant) was obtained by the method of least squares. Most runs were carried out to more than 50% completion (Table II).

The second-order rate constants for the reaction of methylenebismorpholine with 2-nitropropane were also determined at three temperatures (Table III).

**Kinetic Runs in Basic Media.**—An effect due to excess basicity was suspected from the low values of $k_2$ obtained in runs 3–8. Reactions were, therefore, run in mixtures of dioxane and triethylamine (Table II). The triethylamine was redistilled through a Vigreux column after refluxing for 2 days over solid potassium hydroxide (b.p. 89°). This material showed no absorption at 1.53 $\mu$. These runs were carried out only to *ca.* 35% completion because evaporation of triethylamine during analysis became increasingly important during the later stages of each run.

**Runs in the Absence of 2-Nitropropane.**—These runs were carried out to determine the extent of hydrolysis of methylene bisamine during the course of a kinetic run. A mixture of equal volumes of dimethylformamide and methylenebispiperidine was allowed to stand in the 78.60° bath for 71 hr. At the end of this time the mixture was analyzed for piperidine. The concentration was 0.06 $M$ corresponding to a loss of 1% of the methylenebisamine. Runs carried out under similar conditions using 2-nitropropane were virtually complete (80%) in 1 hr. A similar run of methylenebispiperidine in dioxane yielded no measurable amount of secondary amine after 50 hr.

## Interpretation

From the previous data the following deductions can be made. (1) The reaction is first order in 2-nitropropane and first order in methylenebisamine. (2) The rate is decreased when an excess of methylenebisamine is used or when triethylamine is added. (3) Reactions of methylenebispiperidine exhibit a faster rate than those of methylenebismorpholine. (4) The reaction rate increases with an increase in the dielectric constant of the medium. (5) Reactions employing excess 2-nitropropane exhibit faster rates than can be explained on the basis of dielectric effects alone.

The order of the reaction was confirmed by the linear variation of initial rate with concentration of each reactant. In addition to this, all second-order plots were linear.

The effect of a basic medium on the reaction can be shown by the rates of reaction determined in triethylamine (runs 19–22, 27, 28), and in excess methylenebispiperidine (runs 5–8). The 2-nitropropane anion is the predominant species in these basic media,[16] and the

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(13) W. Kaye, *Spectrochim. Acta*, **6**, 257 (1954).

(14) Schmidt and Kohler, *Arch. Pharm.*, **240**, 232 (1902).

(15) U. S. Patent 2,388,058 (October 30, 1945).

(16) The equilibrium constant for the neutralization $(CH_3)_2CHNO_2 + ET_3N \rightleftharpoons [(CH_3)_2CNO_2]^-[ET_3NH]^+$ is given by the relation $K = K_aK_0/K_w \cong 10^6$.

TABLE II

KINETIC DATA FOR THE REACTION OF 2-NITROPROPANE WITH METHYLENEBISPIPERIDINE

| Run no. | Concn. of 2-nitropropane, *M* | Concn. of methylenebispiperidine, *M* | $k_1$, l./mole/hr. | Solvent[a] | Dielectric[b] constant |
|---|---|---|---|---|---|
| | | | Temp. = 78.60 ± 0.03° | | |
| 9 | 0.500 | 0.125 | 0.0897 | Dioxane | 2.12[c] |
| 10 | 0.250 | 0.250 | 0.0848 | | 2.12 |
| 11 | 0.250 | 0.250 | 0.0797 | | 2.12 |
| 12 | 0.125 | 0.125 | 0.0909 | | 2.12 |
| | | | Av. = 0.0863 ± 0.0047 | | |
| 13 | 0.250 | 0.250 | 0.354 | 28.95% DMF in dioxane | 11.77 |
| 14 | 0.250 | 0.250 | 0.354 | | 11.77 |
| | | | Av. = 0.354 ± 0.0 | | |
| 15 | 0.250 | 0.250 | 0.820 | 62.0% DMF in dioxane | 19.47 |
| 16 | 0.250 | 0.250 | 0.700 | | 19.47 |
| | | | Av. = 0.760 ± 0.060 | | |
| 17 | 0.250 | 0.250 | 1.64 | 100% DMF | 27.5 |
| 18 | 0.250 | 0.250 | 1.48 | | 27.5 |
| | | | Av. = 1.56 ± 0.08 | | |
| 19 | 0.250 | 0.250 | 0.0177 | 56.4% TEA in dioxane | 1.82[d] |
| 20 | 0.250 | 0.250 | 0.0182 | | 1.82 |
| 21 | 0.250 | 0.250 | 0.0196 | | 1.82 |
| 22 | 0.250 | 0.250 | 0.0257 | | 1.82 |
| | | | Av. = 0.0204 ± 0.0027 | | |
| 23 | 0.250 | 0.250 | 0.167 | 21.3% $PhNO_2$ in dioxane | 6.45[e] |
| 24 | 0.250 | 0.250 | 0.194 | | 6.45 |
| | | | Av. = 0.181 ± 0.014 | | |
| 25 | 5.57 | 0.250 | 0.505 | 49.7% 2-NP in dioxane | 11.1 |
| 26 | 5.57 | 0.250 | 0.417 | | 11.1 |
| | | | Av. = 0.461 ± 0.044 | | |
| 27 | 0.250 | 0.250 | 0.220 | 50% TEA in DMF | |
| 28 | 0.250 | 0.250 | 0.225 | | |
| | | | Av. = 0.223 ± 0.003 | | |
| | | | Temp. = 82.76 ± 0.03° | | |
| 29 | 0.250 | 0.250 | 0.113 | Dioxane | |
| 30 | 0.250 | 0.250 | 0.114 | | |
| | | | Av. = 0.1135 ± 0.0005 | | |
| 31 | 0.250 | 0.250 | 2.13 | DMF | |
| 32 | 0.250 | 0.250 | 2.00 | DMF | |
| | | | Av. = 2.065 ± 0.065 | | |
| | | | Temp. = 87.94 ± 0.04° | | |
| 33 | 0.250 | 0.250 | 0.160 | Dioxane | |
| 34 | 0.250 | 0.250 | 0.155 | | |
| | | | Av. = 0.158 ± 0.003 | | |
| 35 | 0.250 | 0.250 | 3.30 | DMF | |
| 36 | 0.250 | 0.250 | 3.06 | DMF | |
| | | | Av. = 3.18 ± 0.12 | | |

[a] Concentrations are in mole %; DMF = dimethylformamide, TEA = triethylamine, 2-NP = 2-nitropropane, $PhNO_2$ = nitrobenzene. [b] The dielectric constant of DMF at this temperature was obtained by a linear extrapolation of the data of G. R. Leader and J. F. Gormley [*J. Am. Chem. Soc.*, **73,** 5731 (1951)]. The dielectric constants for the mixtures were calculated from the equation

$$\epsilon_{\text{solution}} = \text{mole fraction } A(\epsilon_A) + \text{mole fraction } B(\epsilon_B)$$

The dielectric constant of 2-nitropropane was obtained from "Lange's Handbook of Chemistry," 9th Ed., Handbook Publishers, Inc., Sandusky, Ohio, p. 1224 [$\epsilon$ (30°) = 25.5, $\alpha$ = 0.109]. [c] "Handbook of Physics and Chemistry," Chemical Rubber Publishing Co., 41st Ed., Cleveland, Ohio, 1960. [d] "International Critical Tables," Vol. VI, McGraw-Hill Book Co., Inc., New York, N. Y., 1939, p. 82.

low rates observed can be explained by the reaction of this anion to produce the very reactive amide ion $R_2N^-$. (See p. 405, col. 2.)

Methylenebismorpholine, which has a basic dissociation constant *ca.* 1/800th as great as that of methylenebispiperidine,[17] is considerably less reactive toward 2-nitropropane (Table III). Since these amines are nearly identical sterically, difference in reactivity can be attributed only to difference in basic strength.

A plausible mechanism in media of low dielectric constant involves the union of one molecule of 2-nitropro-

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(17) H. K. Hall, *J. Am. Chem. Soc.*, **79,** 5441 (1957).

TABLE III

KINETIC DATA FOR THE REACTION OF 2-NITROPROPANE WITH METHYLENEBISMORPHOLINE

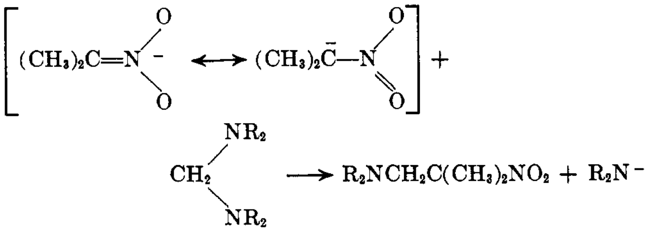
| Run no. | Concn. of 2-nitropropane, $M$ | Concn. of methylenebismorpholine, $M$ | $k_2$, l./mole/hr. | Solvent |
|---|---|---|---|---|
| | | Temp. = 78.60 ± 0.03° | | |
| 37 | 0.250 | 0.250 | 0.0097 | Dioxane |
| 38 | 0.250 | 0.250 | 0.0067 | |
| 39 | 0.250 | 0.250 | 0.00979 | |
| 40 | 0.250 | 0.250 | 0.00784 | |
| | | | Av. = 0.0085 ± 0.0013 | |
| 41 | 0.250 | 2.50 | 0.00222 | |
| 42 | 0.250 | 2.50 | 0.00167 | |
| | | | Av. = 0.00195 ± 0.00027 | |
| 43 | 0.250 | 0.250 | 0.0525 | DMF |
| 44 | 0.250 | 0.250 | 0.0457 | DMF |
| | | | Av. = 0.0491 ± 0.0034 | |
| | | Temp. = 82.76 ± 0.03° | | |
| 45 | 0.250 | 0.250 | 0.00785 | Dioxane |
| 46 | 0.250 | 0.250 | 0.00945 | |
| | | | Av. = 0.00865 ± 0.0008 | |
| 47 | 0.250 | 0.250 | 0.0532 | DMF |
| 48 | 0.250 | 0.250 | 0.0703 | DMF |
| | | | Av. = 0.0617 ± 0.0086 | |
| | | Temp. = 87.94 ± 0.04° | | |
| 49 | 0.250 | 0.250 | 0.0127 | Dioxane |
| 50 | 0.250 | 0.250 | 0.0120 | |
| | | | Av. = 0.0124 ± 0.0004 | |
| 51 | 0.250 | 0.250 | 0.0773 | DMF |
| 52 | 0.250 | 0.250 | 0.0865 | DMF |
| | | | Av. = 0.0819 ± 0.0046 | |

TABLE IV

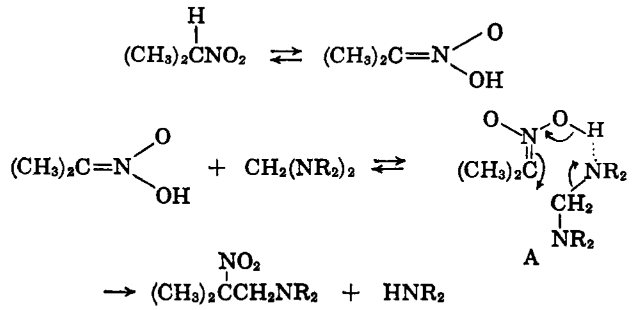
ACTIVATION PARAMETERS[a]

| Amine | Solvent | $E^{*b}$ | $\Delta H^{*b}$ | $\Delta F^{*b}$ | $\Delta S^{*b}$ |
|---|---|---|---|---|---|
| Methylenebispiperidine | Dioxane | 16.32 | 15.63 | 21.81 | −17.35 |
| Methylenebispiperidine | DMF | 20.30 | 19.61 | 19.73 | −0.33 |
| Methylenebismorpholine | Dioxane | 11.40 | 10.71 | 23.52 | −35.98 |
| Methylenebismorpholine | DMF | 14.53 | 13.84 | 22.26 | −23.61 |

[a] The values of $E^*$ were determined from plots of log $k_2$ *vs.* $1/T$ (Fig. 3); $\Delta H^* = E^* - RT$; $\Delta F^* = \Delta H^* - T\Delta S^*$; and $\Delta S^*$ was determined from $k_2 = \kappa(k_BT/h)\exp(\Delta S^*/R - E^*/RT)$, $\kappa$ assumed to be unity (S. Glasstone, K. J. Laidler, and H. Eyring, "Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 21). [b] The values for $E$, $H$, and $F$ are in kcal./mole; values for $S$ are in cal./mole/deg.



pane in the *aci* form with one molecule of methylenebisamine to form a hydrogen-bonded complex which can rearrange to form the Mannich base and a molecule of secondary amine.



Such a complex avoids formation of the amide ion $R_2N^-$ and is consistent with the entropy of activation observed for this reaction (Table IV).

The enhanced reactivity of the piperidine derivative compared with that of the morpholine derivative can be attributed to its greater basicity which results in a greater electron shift to the α carbon atom in the transition state. The higher values of $\Delta S^*$ for the morpholine reaction can be explained best by assuming that the morpholine transition state A is associated with more solvent molecules than the piperidine species.

The results of reactions carried out in solvent mixtures of varying dielectric constant are pictured in Fig. 1. In all the solvent combinations except excess 2-nitropropane and excess amine, the dependence of rate constant on dielectric constant follows a smooth curve. It is of interest that the logarithm of the rate constant is a nearly linear function of dielectric constant (Fig. 2). This implies a nearly linear dependence of $\Delta F^*$ on dielectric constant. A consideration of the activation parameters listed in Table IV leads one to the conclusion that in a medium of high dielectric constant the mechanism changes to one which involves a slightly higher enthalpy of activation and a lower entropy of

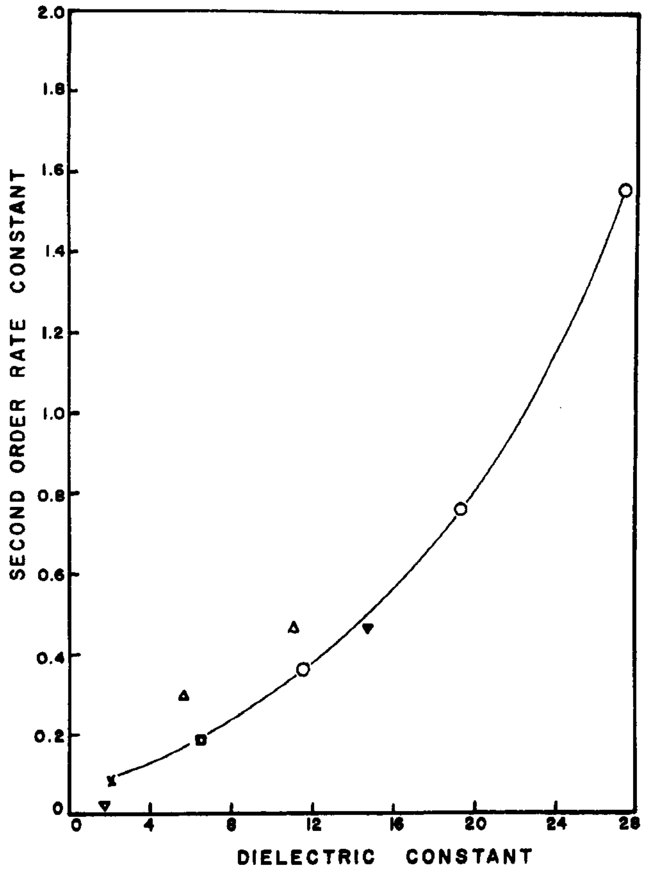


Fig. 1.—Effect of dielectric constant on rate constant: O, DMF–dioxane mixtures; □, nitrobenzene–dioxane; ▽, triethylamine–dioxane; Δ, excess 2-nitropropane; X, dioxane.

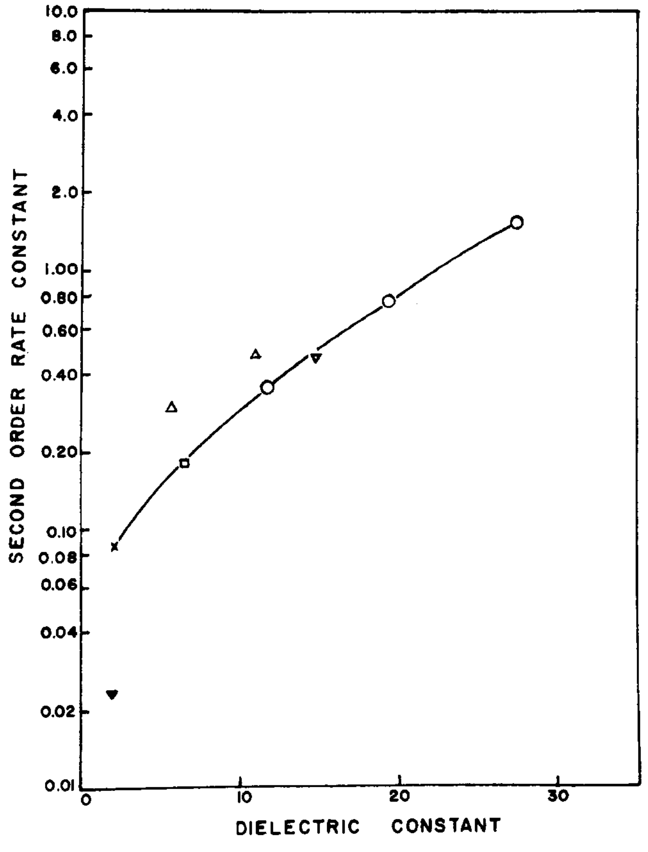


Fig. 2.—Effect of dielectric constant on log $k_2$ (the points are the same as in Fig. 1).

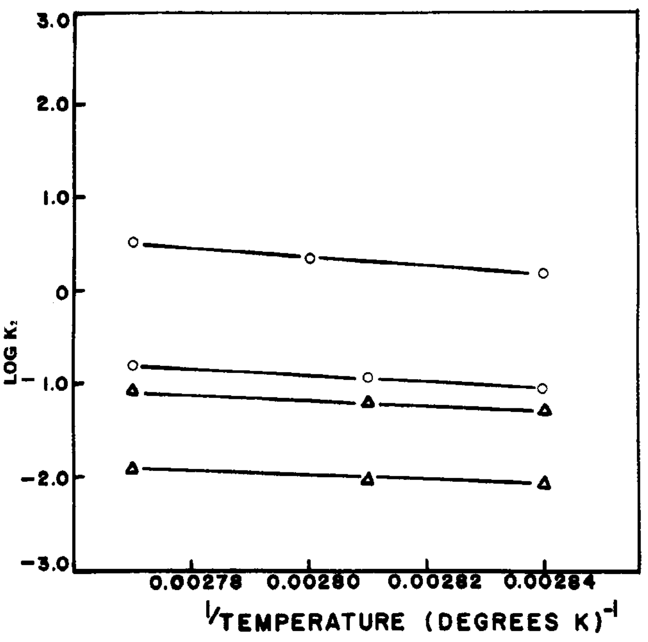
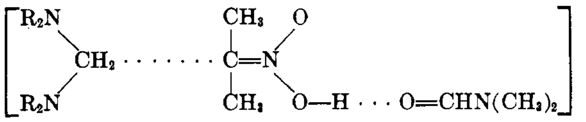


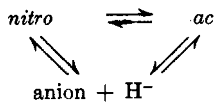
Fig. 3.—Arrhenius plots of the reaction of 2-nitropropane with methylene bispiperidine (O) and with methylenebismorpholine (Δ). In each case the upper curve represents the reaction in DMF; the lower one represents the reaction in dioxane.

activation (see Fig. 3). This effect is readily explained if one considers that the above transition state A involves replacing at least one solvent molecule in the "solvent shell" of the nitro alkane by a molecule of methylenebisamine before the transition state is formed. In the more polar solvent the transition state can be represented by B. This species does not require so great a $\Delta S^*$ as does A, although it requires a greater $E^*$ because of the transitory formation of $R_2N^-$. The more polar solvent in this case reduces the energy of this ion.



B

The accelerating effect of excess 2-nitropropane on the rate constant (runs 1–4) could be due to the following two factors. (1) At high concentrations of 2-nitropropane there is a larger amount of *aci* form and



(2) nitropropane has a rather large dielectric constant. Runs in which 2-nitropropane was in excess exhibited larger rate constants than can be explained on the basis of dielectric effects alone. This is demonstrated in Fig. 1 and 2 in which the points corresponding to runs using excess 2-nitropropane are considerably above the curve. Hence the accelerating effect of excess 2-nitropropane must be in part due to the larger

concentration of *aci* form present in these mixtures and the rate equation should be expressed in the form

$$\text{rate} = k_2[aci]\,[\text{methylenebisamine}]$$

or

$$\text{rate} = k_2K_e[\text{nitro}]\,[\text{methylenebisamine}]$$

where $K_e$ is the equilibrium constant for the nitro-*aci* interconversion. That the inhibiting effect of base is not due entirely to dielectric effects is shown by the runs in excess triethylamine which fell below the curve in Fig. 1 and 2.

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# Synthesis and Study of Mannich Bases from 2-Naphthol and Primary Amines[1]

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*Received August 16, 1962*

Several 1-alkylaminomethyl-2-naphthols (III) were prepared from the corresponding naphthoxazines (I). These new Mannich bases (III) were found to undergo self-condensation with great ease in warm ethanol to form mainly either *N,N*-bis(2-hydroxy-1-naphthylmethyl)alkylamines (II) or the original naphthoxazine along with bis(2-hydroxy-1-naphthyl)methane. The course of the reaction depended largely on the structure of the primary amine used in the synthesis of I.

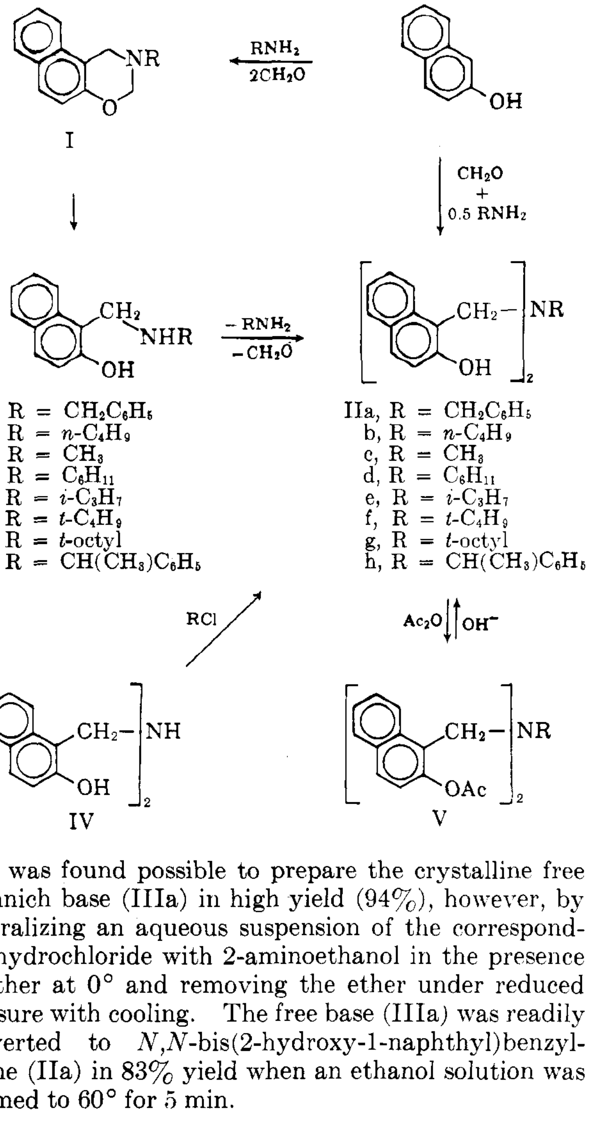
Mannich bases have been used widely as synthetic intermediates.[4,5] Work in this laboratory[6,7] on phenolic Mannich bases derived from primary amines has shown the importance of several reaction variables on the course of the condensation. These included the nature and position of substituents on the phenol, reactant ratios, temperature, and the basicity of the amine.

Marked differences in behavior also were found between phenols and naphthols. For example, phenols having a free *ortho* or *para* position reacted readily with equimolar quantities of formaldehyde and primary amines to form Mannich bases. However, use of 2-naphthol in place of the phenol led to a 2-substituted 2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazine (I) or the corresponding *N,N*-bis(2-hydroxy-1-naphthylmethyl)-amine (II) depending on the particular amine and temperature employed.[6]

Hydrochlorides of Mannich bases (III) from 2-naphthols and primary amines were obtained indirectly, however, by the acidic hydrolysis of naphth[1,3]oxazines.[6] In the present study, neutralization of the Mannich base (IIIa) hydrochloride from benzylamine resulted in a solid product which upon recrystallization from warm ethanol did not give the corresponding free base but rather a good yield of *N,N*-bis(2-hydroxy-1-naphthylmethyl)benzylamine. This result was of particular interest since earlier attempts[6] to prepare the latter compound (IIa) by direct condensation of 2-naphthol with formaldehyde and benzylamine in the calculated 2:2:1 molar ratio led to an 86% yield of the corresponding naphthoxazine (Ia).

The structure of IIa was confirmed by an independent synthesis involving the condensation of benzyl chloride with *N,N*-bis(2-hydroxy-1-naphthylmethyl)amine (IV) and also by the synthesis of a diacetate (V). The latter was reconverted to IIa upon saponification.

The ease with which the self-condensation of IIIa occurs is rather surprising in view of the comparative stability of naphtholic Mannich bases from secondary amines although the structure of the latter would, of course, preclude an analogous reaction.



I

IIIa, R = $CH_2C_6H_5$
b, R = $n$-$C_4H_9$
c, R = $CH_3$
d, R = $C_6H_{11}$
e, R = $i$-$C_3H_7$
f, R = $t$-$C_4H_9$
g, R = $t$-octyl
h, R = $CH(CH_3)C_6H_5$

IIa, R = $CH_2C_6H_5$
b, R = $n$-$C_4H_9$
c, R = $CH_3$
d, R = $C_6H_{11}$
e, R = $i$-$C_3H_7$
f, R = $t$-$C_4H_9$
g, R = $t$-octyl
h, R = $CH(CH_3)C_6H_5$

IV

V

It was found possible to prepare the crystalline free Mannich base (IIIa) in high yield (94%), however, by neutralizing an aqueous suspension of the corresponding hydrochloride with 2-aminoethanol in the presence of ether at 0° and removing the ether under reduced pressure with cooling. The free base (IIIa) was readily converted to *N,N*-bis(2-hydroxy-1-naphthyl)benzylamine (IIa) in 83% yield when an ethanol solution was warmed to 60° for 5 min.

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[4] F. F. Blicke, *Org. Reactions*, **1**, 303 (1942).

[5] J. H. Brewster and E. L. Eliel, *ibid.*, **7**, 99 (1953).

[6] W. J. Burke, M. J. Kolbezen, and C. W. Stephens, *J. Am. Chem. Soc.*, **74**, 3601 (1952).

[7] W. J. Burke, R. P. Smith, and C. Weatherbee, *ibid.*, **74**, 602 (1952); W. J. Burke, K. C. Murdock, and Grace Ek, *ibid.*, **76**, 1677 (1954); W. J. Burke, C. R. Hammer, and C. Weatherbee, *J. Org. Chem.*, **26**, 4403 (1961).