# Quinazolinone Derivatives. Kinetics of the Reaction of 2-Chloromethyl-3-hydroxy-4-(3H)quinazolinone with Nucleophiles

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Reaction of 2-Chloromethyl-3-hydroxy-4(3H)quinazolinone (1) with aliphatic amines and hydroxide follows two different routes affording substituted methyl quinazolinones and a dimer 2 derived from 1. The former were formed by $S_N^2$ reactions while the latter was formed by an intermolecular nucleophilic displacement. Second-order and third-order rate constants, respectively, were determined, and the kinetic factors influencing both parallel reactions were analysed.

The object of this work is to enlarge the study on a subject outlined in a previous paper (1): the reaction of the cyclic hydroxamic acid 2-chloromethyl-3-hydroxy-4(3H)-quinazolinone (1) with several nucleophiles, in order to clarify the effect of basicity, quantitatively.

It was observed that 1 with methylamine or ethylamine did not undergo the Sternbach and Reeder's expansion reported for quinazoline N-oxides (2), which we hoped could occur due to the tautomeric contribution of the N-oxide forms that compound 1 exhibits (Scheme I: B,C).

Scheme I
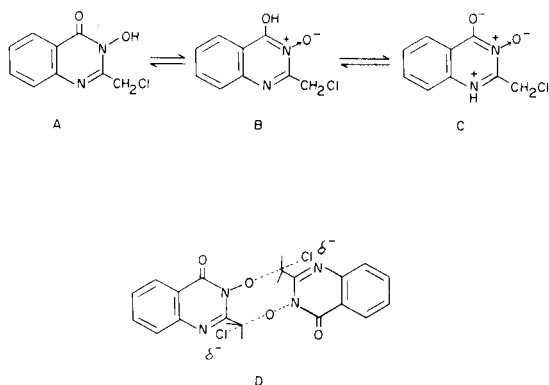


However, expansion did not occur and instead 1 afforded substituted aminomethylquinazolinones and a dimer 2 by a novel and unexpected reaction (Scheme II). The former were obviously formed by $S_N^2$ reactions while the latter was formed by a double intermolecular nucleophilic displacement. Both competitive reactions depended on the nature of the basic reactant and its free base concentration; two matters attracted our attention: the low yields obtained on treatment of 1 with secondary amines and the failure in the attainment of the alcohol 3 (Scheme II) under the standard experimental conditions used for compounds of type 4 (i.e., large excess of the base at room temperature).

Kinetic studies and the application of some known

Scheme II
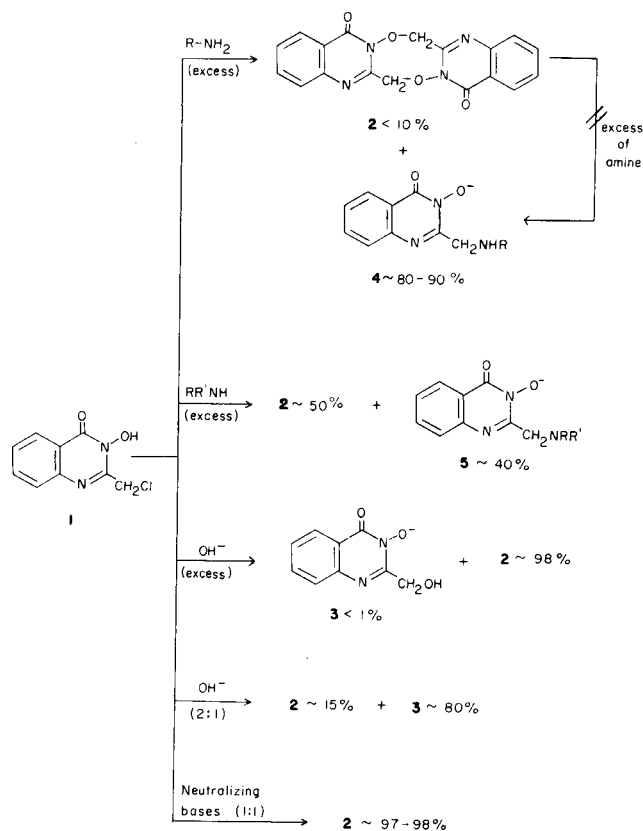


linear relationships allowed us to gain further insight into the nature of these reactions.

## $S_N^2$ Reactions.

At 25°, the reaction of 1 with primary and secondary aliphatic amines afforded N-substituted aminomethyl-3-hydroxy-4(3H)quinazolinones 4 and 5 and variable amounts of dimer 2 (Scheme II). In the presence of high concentrations of primary amines, high yields of 4 and low yields of 2 were obtained, while with secondary amines the

Table I

Observed Rate Constants of the Reaction of 2-Chloromethyl-3-hydroxy-4-
(3H)quinazolinone (1) in Methylamine Buffers

| [Methylamine] (M) | % Free base | [Base]free (M) | $k_{obs}$ (min⁻¹) |
|---|---|---|---|
| 1.5 | 80 | 1.2 | $4.22 \times 10^{-2}$ |
| 1.5 | 60 | 0.9 | $3.16 \times 10^{-2}$ |
| 1.5 | 40 | 0.6 | $2.10 \times 10^{-2}$ |
| 1.5 | 20 | 0.3 | $1.06 \times 10^{-2}$ |
| 1.0 | 80 | 0.8 | $2.80 \times 10^{-2}$ |
| 1.0 | 60 | 0.6 | $2.12 \times 10^{-2}$ |
| 1.0 | 40 | 0.4 | $1.39 \times 10^{-2}$ |
| 1.0 | 20 | 0.2 | $0.70 \times 10^{-2}$ |
| 0.5 | 80 | 0.4 | $1.41 \times 10^{-2}$ |
| 0.5 | 60 | 0.3 | $1.05 \times 10^{-2}$ |
| 0.5 | 40 | 0.2 | $0.72 \times 10^{-2}$ |
| 0.5 | 20 | 0.1 | $0.35 \times 10^{-2}$ |

yields of **2** were greatly increased. On the other hand, the reaction of **1** with hydroxide gave 2-hydroxymethyl-3-hydroxy-4(3H)quinazolinone (**3**) and variable amounts of **2** depending on the concentration of base used (Scheme II).
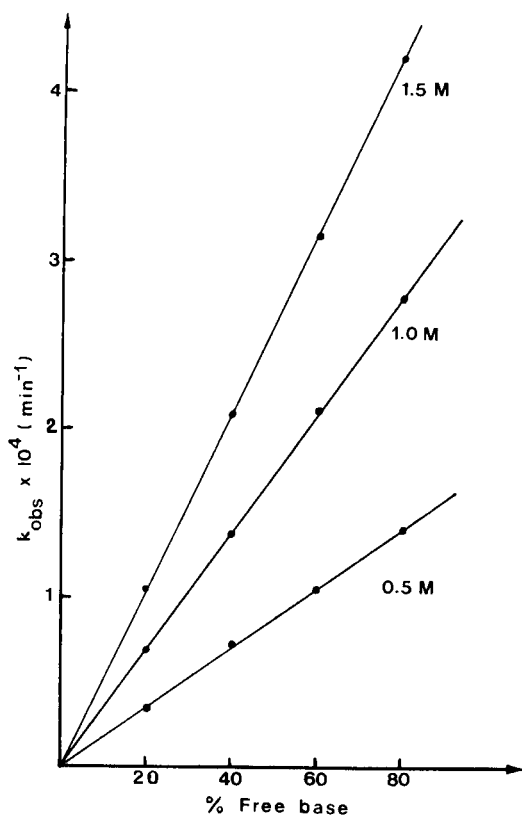


Figure 1. Dependence of Observed Rate Constants for the Reaction of 2-Chloromethyl-3-hydroxy-4(3H)quinazolinone (**1**) with Methylamine on Free Base Concentration. Reactions were Performed at 25° with Ionic Strength 1.5M.

Kinetics.

Kinetic studies were performed in buffered media. Disappearance of **1** was followed by uv spectrophotometry at 288 nm. General results are illustrated with the reaction of **1** in methylamine buffers (Table I, Figure 1). The amine concentration was varied, thus showing reactions with a first-order dependence on the free base concentration. Further, second-order rate constants ($k_1 = k_{obs}/[B]$) were found to be independent of $aOH^-$. Thus, these reactions follow the rate law $v = [1][B]$, where B is the basic form of the buffer or hydroxide ion. Second-order rate constants are listed in Table II.

Kinetic Factors Influencing the $S_N^2$ Reactions.

a) Basicity of the Amines.

The $k_1$ values (Table II) appear to show an unusual insensitivity to the reactivity of the amine base. In fact, the logarithmic rate constants (log $k_1$) are not linear with the basicities (pka). This suggests that another factor must be considered.

b) Steric Factor.

To a certain extent, the amine substituents must have a steric effect, since the Taft equation (3) [log ($k_1/k_o$) = $\varrho^* \sigma^*$ + Es] showed linearity (Figure 2) $\varrho^* = 1.60$, r = 0.998, s = 0.027). The Taft equation demonstrates the role played by the steric factor (Es, Table II), which affects the transition state of the $S_N^2$ reactions, and explains the low yields obtained on treatment of **1** with bulky secondary amines.

c) Base Nucleophilicity.

The low rate constant of the reaction of **1** with an excess of sodium hydroxide must be attributed to the latter's low nucleophilicity. It is well known that despite its high basicity (pka = 15.6), the hydroxide ion has a low nucleophilic constant (n = 4.20) (4), which is comparable

Table II

Rate Constants of the $S_N^2$ Reaction Between 2-Chloromethyl-3-hydroxy-4-(3$H$)quinazolinone (**1**)
and Several Nucleophiles in Water at 25° (Ionic Strength 1.5$M$)

| Base | p$ka$ | $k_1$ ($M^{-1}$ min$^{-1}$) (a) | $-\log k_1$ | $\log (k_1/k_o)$ (b) | Base Substituent | $\sigma^*$ (c) | Es (d) |
|---|---|---|---|---|---|---|---|
| Methylamine | 10.64 | $3.52 \times 10^{-2}$ | 1.45 | 0.00 | $CH_3$ | 0.00 | 0.00 |
| Ethylamine | 10.67 | $2.09 \times 10^{-2}$ | 1.68 | $-0.23$ | $C_2H_5$ | $-0.10$ | $-0.07$ |
| Propylamine | 10.58 | $1.05 \times 10^{-2}$ | 1.98 | $-0.53$ | $n$-$C_3H_7$ | $-0.115$ | $-0.36$ |
| *iso*-Propylamine | 10.63 | $5.62 \times 10^{-3}$ | 2.25 | $-0.80$ | $i$-$C_3H_7$ | $-0.20$ | $-0.47$ |
| $n$-Butylamine | 10.60 | $8.71 \times 10^{-3}$ | 2.06 | $-0.61$ | $n$-$C_4H_9$ | $-0.13$ | $-0.39$ |
| Ethanolamine | 9.45 | $1.12 \times 10^{-2}$ | 1.95 | | | | |
| Cyclohexylamine | 10.65 | $2.00 \times 10^{-3}$ | 2.70 | $-1.25$ | Cyclohexyl | $-0.29$ (e) | $-0.79$ |
| Dimethylamine | 10.70 | $7.08 \times 10^{-3}$ | 2.15 | | | | |
| Diethylamine | 11.00 | $2.24 \times 10^{-3}$ | 2.65 | $-1.20$ | $(C_2H_5)_2$ | $-0.20$ (f) | $-0.88$ (e) |
| Piperidine | 11.12 | $1.58 \times 10^{-3}$ | 2.80 | | | | |
| Sodium hydroxide | 15.7 | $1.53 \times 10^{-4}$ | 3.82 | | | | |

(a) Calculated from $k_1 = k_{obs}$/[B] in reactions with primary amines. (b) Methylamine was taken as a reference compound. (c) Reference 11. (d) Reference 3. (e) Calculated by the Taft equation (3). (f) Calculated taking into account that $\sigma^*$ values for aliphatic groups are shown to be additive (11).
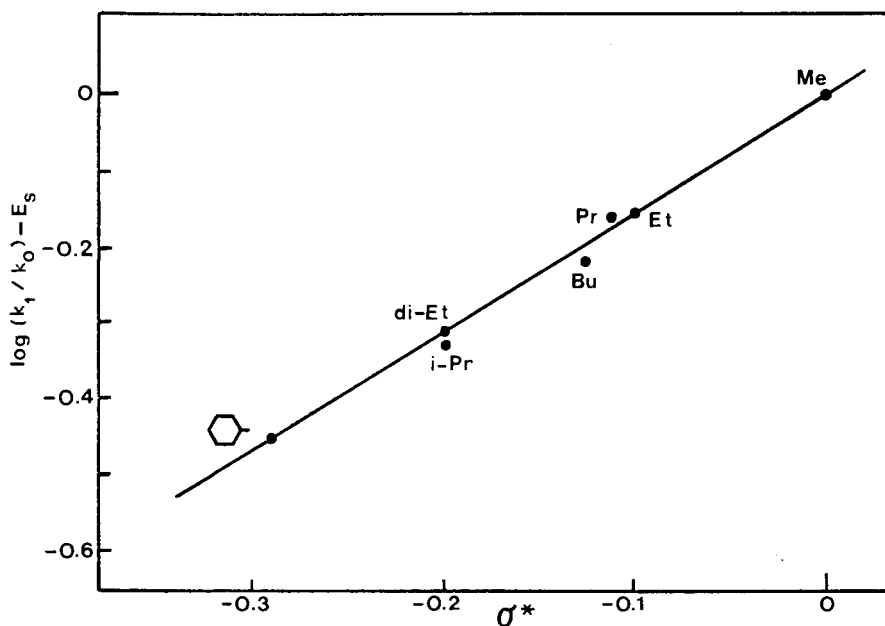


Figure 2. Application of Taft's Equation to the Attainment of Substituted-Aminomethyl Quinazolinone Derivatives

to that of aniline (n = 4.49) (4), although the latter has a much lower p$ka$ (4.58). This can well account for the failure in the attainment of the alcohol **3** using an excess of alkali. As it will be shown later, a medium of high $p$H favors the reaction *via* the substrate anion to give the dimer **2**.

d) Base Concentration.

When **1** was treated with large excess of sodium hydroxide, the $S_N^2$ reaction was negligible and only the dimer was obtained (Scheme II). However, when molar ratios of [OH]/[**1**] = 2:1 were used, the $S_N^2$ reaction was more favored and the alcohol **3** was obtained in good yield. This same principle was observed for derivatives of type **5**.

Dimer Formation.

In basic media, given by any neutralizing base, the two anionic species of **1**, (A⁻), react to give the dimer **2**. It was observed experimentally that this is a base-catalysed reaction (Table III), though the occcurrance of base catalysis in this reaction is unexpected, since it is difficult to envisage a function for the base in a reaction of two anionic species.

Kinetics.

Kinetic studies were performed by spectrophotometry in the visible region. The disappearance of **1** in different buffered media (Table IV) was monitored by measuring the decrease at 540 nm of the red color of the complex of **1** with ferrous chloride. When **4** or **5** were also formed in the reaction, they gave the same absorption at 540 nm in the presence of ferrous chloride. Since all the complexes had similar extinction coefficients at 540 nm ($\epsilon$ = 6900), the formation of **2** was accurately measured by the absorption decrease at this wavelength. The plots of $1/(A - A_\infty) - 1/(A_o - A_\infty)$ were linear in all the reactions in which only **2** was formed (treatment of **1** with carbonate, tertiary amines or a great excess of alkali), whereas when **2** was formed together with **4, 5** or **3**, linearity held up for 70-80% of the reactions. In all the buffers (Table IV), the observed rate constants had a second-order dependence on the substrate and a first-order dependence on the basic forms of the buffers. Zero slopes were obtained when third-order rate constants, $k_2 = (k''_{obs} - k_o)/[B]$, were plotted against $aOH^-$ (*i.e.*, the rate law did not contain a term in hydroxide ion).
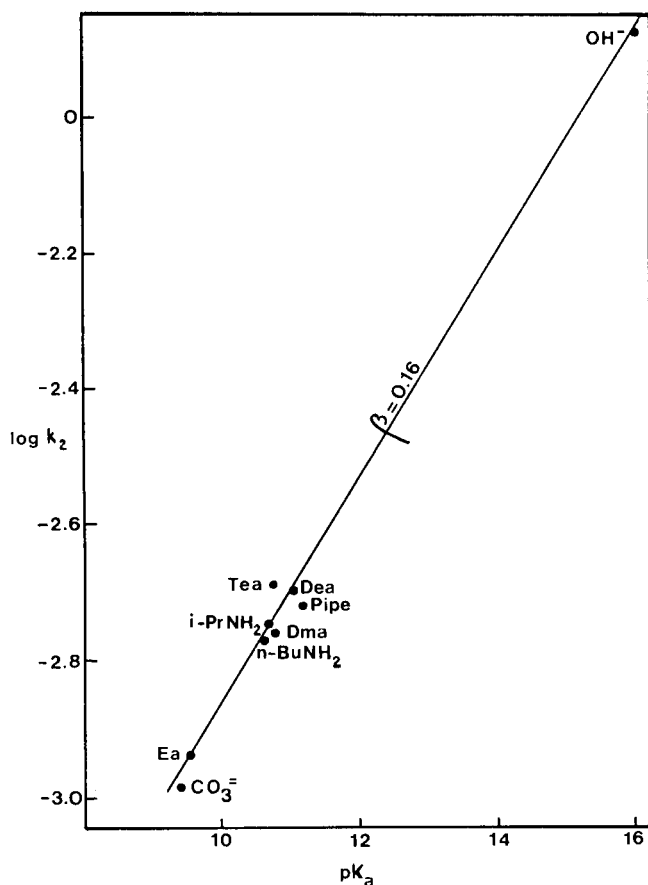
Therefore, the reaction follows the rate law:

$$v = k''_{obs}[A]^2 = k_o[A^-]^2 + k_2[A^-]^2[B] \quad \text{(Equation 1)}$$

where $k''_{obs} = k_o + k_2[B]$, and $k_o = 7.40 \times 10^{-4} \, M^{-1}min^{-1}$ is the rate constant of the non-catalysed reaction. The insolubility of **1** in water at 25° excludes the term $(k_w[AH]^2[H_2O])$ from Equation 1, *i.e.*, eliminates water as a possible nucleophile.

Kinetic Factors Influencing the Dimer Formation.

a) General Base Catalysis.

In a reaction such as that involved in the dimerization of **1**, which is the subject to general base catalysis (Table IV), a relation should exist between the strength of the base, as measured by its ionization constant, and its efficiency as a catalyst, as determined by the observed rate constants. If we define a catalytic rate constant $k_2$, the relation can be expressed by the Brönsted catalysis law (5) $\log k_2 = \beta \, pka + C$. Figure 3 shows the plot of this equation. The straight line in the figure indicates a good fit for the points for both simple primary and secondary amines. Triethylamine is above the line and this is consistent with the known greater reactivity of tertiary amines as base catalysts over that of primary amines of comparable basicity (6). Piperidine falls below this line and this may be attributed to the greater steric requirements of this compound.

The values for hydroxide and carbonate were corrected according to Brönsted's modified equation (7), thus giving a better fit to the regression.

The value of the slope near zero ($\beta$ = 0.16) indicates that in the reaction of **1** with catalysts (AH + B $\rightleftharpoons$ A$^-$ + BH$^+$) where A$^-$ is less basic than B, the rate changes are smaller than the differences in the equilibrium constants for proton removal of AH. Therefore, it is conceivable to propose the occurrance of a prior ionization of **1** followed by a slow-self condensation of the resulting anion:
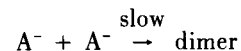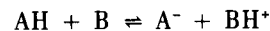
$$AH + B \rightleftharpoons A^- + BH^+$$

$$A^- + A^- \xrightarrow{\text{slow}} \text{dimer}$$



Figure 3. Brönsted Plot for the Base-Catalysed Formation of the Dimer **2**.

Table III

Catalytic Formation of the Dimer **2** in Sodium Hydroxide at 25°
(Ionic Strength 1.5$M$, Rate Constant of the Non-Catalysed
Reaction $k_o = 7.40 \times 10^{-4} \, M^{-1}min^{-1}$)

| [OH]($M$) | $k''_{obs}(M^{-1}min^{-1})$ | $k_2 = (k''_{obs} - k_o)/[B]$ ($M^{-2}min^{-1}$) |
|---|---|---|
| $2.8 \times 10^{-2}$ | $1.11 \times 10^{-3}$ | $13.21 \times 10^{-3}$ |
| $5.0 \times 10^{-2}$ | $1.40 \times 10^{-3}$ | $13.20 \times 10^{-3}$ |
| $8.9 \times 10^{-2}$ | $1.92 \times 10^{-3}$ | $13.26 \times 10^{-3}$ |
| $3.2 \times 10^{-1}$ | $4.95 \times 10^{-3}$ | $13.16 \times 10^{-3}$ |
| $7.1 \times 10^{-1}$ | $1.01 \times 10^{-2}$ | $13.18 \times 10^{-3}$ |

Table IV

Third-Order Rate Constants for the Base-Catalysed Formation of the Dimer **2** at 25° (Ionic Strength 1.5$M$)

| Base | p$ka$ | $k_2$ ($M^{-2}$min$^{-1}$) | $-\log k_2$ |
|---|---|---|---|
| Hydroxide | 15.7 | $1.32 \times 10^{-2}$ | 1.88 |
| Carbonate | 9.78 | $3.09 \times 10^{-3}$ | 2.51 |
| Triethylamine (Tea) | 10.72 | $2.04 \times 10^{-3}$ | 2.69 |
| Diethylamine (Dea) | 11.00 | $1.99 \times 10^{-3}$ | 2.70 |
| Dimethylamine (Dma) | 10.70 | $1.74 \times 10^{-3}$ | 2.76 |
| Piperidine | 11.12 | $1.90 \times 10^{-3}$ | 2.72 |
| Cyclohexylamine | 10.65 | $1.78 \times 10^{-3}$ | 2.75 |
| *iso*-Propylamine | 10.63 | $1.82 \times 10^{-3}$ | 2.74 |
| *n*-Butylamine | 10.60 | $1.70 \times 10^{-3}$ | 2.77 |
| Ethanolamine | 9.45 | $1.15 \times 10^{-3}$ | 2.94 |

Thus, **1** being a weak acid (p$ka$ = 5.89), the excess of B displaces the equilibrium towards the right and accelerates the dimer formation.

b) Temperature. Determination of Activation Parameters.

The non-catalysed reaction **1** → **2** was followed in a phosphate buffer at $p$H = 7.50. The reaction was performed at three different temperatures (25°, 38° and 50°). The values of the enthalpy ($\Delta H^*$) and entropy ($\Delta S^*$) of activation were obtained according to the procedure described by Cagle and Eyring (8):

$$\Delta H^* = 15.00 \text{ Kcal. mole}^{-1}$$
$$\Delta S^* = -22.50 \text{ cal. mole}^{-1} {}^\circ K^{-1}$$

The relatively low value of $\Delta H^*$ found for this reaction is similar to others obtained in normal nucleophilic substitutions (9) but the negative value of the entropy ($\Delta S^*$) is markedly increased. This suggests that the formation of the transition state is rather limited. In fact, molecular models of the dimer show that its most stable conformation could be the one having the greater separation between both methylene groups. This conformation can be achieved if the attacking nucleophilic residues ($N - O^-$) combine with the carbon atoms at the opposite side of the displaced chlorines. This decreased freedom of configuration may account for the high negative value of $\Delta S^*$. Thus, on this basis and since experimental evidence showed that this reaction occurs in one step, it may be assumed that formation of the dimer **2** proceeds by a double intermolecular nucleophilic displacement, where D is the possible transition state of the reaction.

c) Base Concentration.

When the reaction **1** → **2** was peformed in 1$M$ sodium hydroxide at 25°, 38° and 50° a much lower value of enthalpy of activation ($\Delta H^*$ = 11.70) was obtained, which demonstrates the important role played by basic catalysis in the dimer formation. In this case, the reaction is kinetically controlled and **2** predominates. However, if **1** was treated with two equivalents of sodium hydroxide at 25°, the S$_N^2$ reaction predominated and the alcohol **3** was formed in good yield (Scheme II). A rate constant $k' = 1.70 \times 10^{-4} M^{-1}$min$^{-1}$ was calculated for the dimer formation under these experimental conditions. This value is a little higher than that for the alcohol **3** formation ($k_1 = 1.53 \times 10^{-4} M^{-1}$min$^{-1}$); however, the latter predominates. This indicates that when the reaction at 25° is adjusted to a molar ratio [OH$^-$]/[**1**] = 2:1, and the reacting system reaches thermodynamic equilibrium, the proportions of dimer and alcohol are determined by their relative free energies. In this situation, the dimer **2** is the kinetically controlled product and the alcohol **3** is the thermodynamically controlled product, and it predominates.

Conclusion.

The kinetic results discussed above indicate that in the reaction of **1** with primary and secondary amines, the steric requirements of the transition states are of paramount importance in determining the rates of the S$_N^2$ reactions. Thus, lower reaction rates (Table II) were obtained with bulky primary amines (isopropylamine, cyclohexylamine) than with some secondary amines (dimethylamine).

The S$_N^2$ reaction of **1** with excess of hydroxide is negligible, a fact that must be attributed to the latter's low nucleophilicity.

When the molar ratios [B]/[**1**] = 2:1 were used at 25°, the S$_N^2$ reactions predominated and **3** or **5** were formed in good yields. When the energy requirements for both reactions are similar, the adjustment of the reaction conditions allows a thermodynamic control and the alcohol formation dominates. Thus, at the same concentration of **1**, the yields of **3** are increased from 1% to 80% when the molar ratio [NaOH]/[**1**] is decreased from 10 to 2. Similar results were obtained with the derivatives of type **5**.

EXPERIMENTAL

Kinetic Measurements.

Reactions were followed spectrophotometrically in a Beckman DB-G Grating Spectrophotometer. Reaction mixtures were incubated in a water bath at 25° ± 0.1 and at 38° ± 0.1 and 50° ± 0.1 for the determination of activation parameters. The ionic strength was maintained at 1.5$M$ by the addition of potassium chloride. Measurements of $pH$ were carried out with a Beckman Zeromatic II $pH$ meter using a standardized glass electrode.

$S_N^2$ Reactions.

The reactions of **1** with primary amines were carried out under *pseudo*-first-order conditions in buffered media with an excess concentration of the amine (100:1) over the concentration of **1** (0.005$M$). The $pH$ values were carefully controlled at the beginning and at the end of the reactions and were observed to remain constant. Disappearance of **1** was followed at 288 nm ($\epsilon_{max}$ = 3600). Plots of 2.303 log (A$_o$ - A$_\infty$ /A - A$_\infty$) against time were linear for at least 80% of the reaction for all primary amines, except for isopropylamine and cyclohexylamine for which linearity held up for 60% of the reactions. *Pseudo*-first-order rate constants were calculated from $k_{obs}$ = ln 2/$t_{1/2}$. Values of the second-order rate constants were obtained from the relationship $k_1 = k_{obs}/[B]$.

Reactions of **1** with sodium hydroxide and with secondary amines were also followed at 288 nm in solutions of molar ratios [B]/[1] = 2:1 since the competitive reaction **1** → **2** did not interfere under these conditions. Solutions (0.1$M$) of **1** were potentimetrically neutralized; an exactly measured equal amount of base was then added to give a molar ratio [B]/[conjugate base of **1**] = 1:1. A dilution was then made to give 0.005$M$ solutions. Plots of [(A$_o$ · A$_\infty$) - (A - A$_\infty$)]/(A$_o$ - A$_\infty$)(A - A$_\infty$) *versus* time were linear for at least 90% of the reactions. If larger molar ratios were used, early deviations from second-order kinetics were observed due to the parallel transformation of **1** into **2**, which precipitated as a white solid insoluble in all the reaction media. Second-order rate constants were determined from the slopes of the plots mentioned above.

The reactions were always stopped by adding 1$N$ hydrochloric acid (2 ml.) to aliquots of the reaction mixtures (1 ml.) before they were diluted to the proper volume with distilled water (100 ml.). Absorbances at time zero were estimated by extrapolation.

The products of the reactions were identified by the uv spectra of the reaction mixtures at the end of the kinetic runs, and their concentrations calculated from their absorbances at the corresponding nm.

Dimer Formation.

Reaction **1** → **2** in different basic media (Table IV) was followed in the visible region. Buffer solutions of the bases were used. Disappearance of **1** (0.005$M$) was followed by addition of aliquots of the reaction mixture (0.5 ml.) to 4 ml. of 5% anhydrous ferrous chloride in 0.5$M$ hydrochloric acid. The extinction was measured at 540 nm ($\epsilon_{max}$ = 6900) after 4

minutes against a blank. *Pseudo*-second-order rate constants were calculated from plots of 1/(A-A$_\infty$) - 1/(A$_o$ - A$_\infty$) *versus* time. The reactions followed the rate law of Equation 1, and the values of the catalytic rate constants ($k_2$) and that of the non-catalysed reaction ($k_o$) were determined from the slopes and intercept, respectively, of the plots of log $k''_{obs}$ vs. the free base concentration.

The final concentrations of dimer were gravimetrically determined. Statistical corrections from the Brönsted plot were used according to equation $k/q = Gb(p/qKa)^\beta$ where p is the number of equivalent protons in the acid and q is the number of equivalent basic sites in the base (7).

p$Ka$ Determinations.

The p$Ka$ value of compound **1** was determined by a potentiometric titration, following the procedure described in the literature (10).

The p$Ka$ of the buffers listed in Tables II and IV were obtained from the measured $pH$ values and the stoichiometric composition of the solutions.

Acknowledgement.

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