[Contribution from the Metcalf Chemical Laboratories of Brown University]

# Reactions of Ethylenimines. IX. The Mechanisms of Ring Openings of Ethylenimines in Acidic Aqueous Solutions[1]

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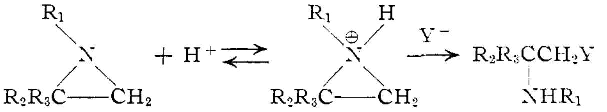
Received January 11, 1958

Kinetic measurements and product identifications have been carried out in order to elucidate the mechanisms of several more imine ring openings. Aziridines studied were 2,2-dimethylethylenimine, 2-ethylethylenimine, N-(*n*-butyl)-ethylenimine and ethylenimine; nucleophiles studied were acetate, bromide, chloride, iodide, thiocyanate and thiosulfate ions, thiourea and water. Hydrolysis rates were studied over a range of temperature and pressure so as to obtain activation parameters. All of the reactions studied have been found to correlate with known mechanistic patterns. The use of linear free energy equations for the evaluation of relative contributions of SN1 and SN2 behavior in solvolysis reactions is pointed out.

## Introduction

In a previous paper,[2] it was reported that two separate ring-opening reactions occur in solutions of 2,2-dimethylethylenimine in aqueous hydrochloric acid. One of these reactions, the attack of the chloride ion on the immonium ion to yield 1-chloro-2-amino-2-methylpropane was shown to be a second order (SN2) process. The other reaction, hydrolysis of the immonium ion to yield 1-amino-2-methyl-2-propanol was interpreted as being a unimolecular (SN1) process.

The present study, on eight nucleophiles and four ethylenimines (aziridines), was undertaken to find out more about the mechanisms of opening of these three-membered ring compounds. The imines studied and a generalized reaction scheme are presented in the equation



I, $R_1 = R_2 = R_3 = H$
II, $R_1 = n\text{-}C_4H_9$, $R_2 = R_3 = H$
III, $R_1 = R_2 = H$, $R_3 = C_2H_5$
IV, $R_1 = H$, $R_2 = R_3 = CH_3$

where $Y^-$ is the nucleophile. Another goal has been the working out of a method for estimation of the relative amounts of SN1 and SN2 character in solvolytic reactions.

## Experimental

Rate constants for reactions between the imines and four nucleophiles ($I^-$, $SCN^-$, $Br^-$ and thiourea) were measured by a method similar to that described earlier.[2] Perchloric acid customarily was used as the source of protons, although in some cases the conjugate acid of the nucleophile was employed. A three-to-one ratio of acid to imine was employed so that essentially all of the imine would exist in the form of the immonium ion.[3]

Rate constants for the reactions between the chloride ion and the imines were measured in a similar manner. Hydrochloric acid was used to provide both the nucleophilic ion and protons. As the hydrolysis reaction competes with the relatively slow attack of chloride ion, the second-order constants for these reactions were computed from the formula

$$k_2 = \frac{2.303}{(fa - b)} \frac{d}{dt} \left\{ \log \frac{(a - x)}{(b - fx)} \right\}$$

where $x$ is the amount of immonium ion which has been attacked by chloride ion by time $t$, $a$ the initial concentration of chloride ion and $b$ the initial concentration of immonium ion. The quantity $f$ is the ratio of the total amount of immonium ion which has undergone ring-opening (including that which has undergone hydrolysis) to the amount of immonium ion which has been attacked by chloride ion. The ratio, $f$, was evaluated by dividing the initial concentration of immonium ion by the amount of immonium ion which was shown to have reacted with chloride ion by titration of the reaction mixture after the reaction had been allowed to go to completion.

Because the hydrolysis of an immonium ion does not result in a decrease of hydrogen ion concentration of the solution, an alternative analytical method was needed. The rapid reaction between the thiosulfate and immonium ions has been suggested[4] as a method for the determination of ethylenimines. In order to use this rapid reaction to follow hydrolyses of immonium ions, the following procedure was employed. Solutions approximately 1 *F* in perchloric acid and 0.3 *F* in imine were prepared. At appropriate times, ten milliliter aliquots of these solutions were added to an equal volume of a solution 0.5 *F* in sodium thiosulfate and 1.2 *F* in sodium acetate. After the quenched aliquots had been set aside overnight, the unreacted thiosulfate was titrated with standard iodine solution to the starch end-point. The decrease in concentration of immonium ion in the perchloric acid solution was found to follow first-order kinetics.

Since the methyl orange end-point is masked in acetate buffers, the attack of acetate ion on various immonium ions was followed by a procedure similar to that used for the hydrolysis reactions. A large excess of acetate ion was used and a pseudo-first-order rate constant measured. This constant was corrected by subtraction of the first-order hydrolysis constant for the appropriate imine and then divided by the acetate ion concentration to give a second-order rate constant. The rate of the reactions between the immonium ions and the thiosulfate ion was measured by titrating aliquots of the reaction mixture with standard iodine solutions. Second-order rate constants were computed in the usual manner.

All of the experiments outlined above were carried out in a water-bath at 25.00 ± 0.05°. The reaction medium was cooled to about 20° and the imine added quickly, with vigorous swirling, from a weight buret or a pipet. The protonation of the imine released enough heat to raise the temperature of the reaction mixture to 25° and swirling in the bath brought about thermal equilibrium in a relatively short time.

Rate constants for the hydrolyses of three imines were also measured at elevated temperatures (40.15, 44.90, 65.19°) in an oil-bath held constant to within ±0.05°. Rates of hydrolysis were also measured at 21 ± 0.5° under 8000 p.s.i. This was done by enclosing the reaction mixtures in flexible polyethylene containers immersed in hydraulic fluid in a conventional high pressure bomb, fitted with an oil-pump and pressure gauge. This bomb was placed in a constant temperature room for a period of several weeks, during which aliquots were taken as usual.

**Identification of Reaction Products.**—The products of the reactions of 2,2-dimethylethylenimine with HCl, HBr, HI, HSCN and thiourea have been isolated, identified by conversion to derivatives and, in the cases of the first four, the

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[1] Taken from parts of the Ph.D. Theses of J. E. Earley and B. C. Lawes and the Sc.M. Thesis of C. E. O'Rourke. Presented in part at the Symposium on the Chemistry of Three-Membered Rings, 131st Meeting of the American Chemical Society, Miami, Florida, April 11, 1957.

[2] V. B. Schatz and L. B. Clapp, This Journal, **77**, 5113 (1953).

[3] C. E. O'Rourke, L. B. Clapp and J. O. Edwards, *ibid.*, **78**, 2159 (1956).

[4] E. Allen and W. Seaman, *Anal. Chem.*, **27**, 540 (1955).

structures related to one common derivative. From previous work the two chloroamines obtained from the reaction of IV with concentrated HCl, 1-chloro-2-amino-2-methylpropane hydrochloride and 2-chloro-1-amino-2-methylpropane hydrochloride, were proved to have the structures assigned by conversion to known benzamides.[2]

Products from the reaction of IV and HCl, HBr and HI were related to the corresponding product from HSCN. The oily reaction product from IV and HSCN, presumably 1-thiocyano-2-amino-2-methylpropane, was converted to 2-imino-4,4-dimethylthiazolidine by warming to 110° and was identified by conversion to a picrate. The iminothiazolidine structure was not proved by an independent synthesis since it was considered sufficient for present purposes to relate the four reaction products to the one compound. The reaction is one used by Gabriel[5] for the preparation of another iminothiazolidine. 1-Chloro-2-amino-2-methylpropane hydrochloride and the corresponding bromo and iodo compounds were each separately treated with potassium thiocyanate and then with an alcohol solution of picric acid to give the same 2-imino-4,4-dimethylthiazolidine picrate. With the same experimental conditions the isomeric 2-chloro-1-amino-2-methylpropane hydrochloride rearranges with loss of hydrogen chloride to β-methylallylamine, identified as the picrate.[6]

**1-Bromo-2-amino-2-methylpropane Hydrobromide.**—To an ice-cold solution of 27 ml. (0.23 mole) of 48% hydrobromic acid in 100 ml. of water, 5.56 g. (0.078 mole) of IV was added dropwise while the mixture was stirred vigorously. Stirring was continued for six hours at ice-bath temperature and then the mixture was allowed to come to room temperature. The solution was evaporated at room temperature in a stream of dry air until crystals started to appear. Removal of the crystals and repeated evaporations gave 14.8 g. (86%) of crude product, m.p. 182–185°. Three recrystallizations from acetone and sublimation gave an analytical sample, m.p. 184–186°.[7]

*Anal.* Calcd. for $C_4H_{11}NBr_2$: C, 20.60; H, 4.80; N, 6.00. Found: C, 20.67; H, 4.83; N, 6.32.

The bromo compound was converted into the picrate of 1-bromo-2-amino-2-methylpropane by treatment with aqueous sodium picrate solution. The picrate was recrystallized from water, m.p. 167–168°.

*Anal.* Calcd. for $C_{10}H_{13}N_4O_7Br$: C, 31.50; H, 3.41; N, 14.71. Found: C, 31.80; H, 3.66; N, 14.80.

**1-Iodo-2-amino-2-methylpropane Hydroiodide.**—The iodo compound was prepared in a manner similar to the bromo compound just described with a reaction time of 3 hours in 90% yield. Recrystallizations from an ethanol–ether mixture gave an analytical sample, m.p. 145–147°.

*Anal.* Calcd. for $C_4H_{11}NI_2$: C, 14.71; H, 3.39; N, 4.29. Found: C, 14.91; H, 3.62; N, 4.16.

A picrate was obtained by an analogous procedure, m.p. 168° dec.

*Anal.* Calcd. for $C_{10}H_{13}N_4O_7I$: C, 28.12; H, 3.07; N, 13.10. Found: C, 27.93; H, 3.29; N, 13.39.

**2-Imino-4,4-dimethylthiazolidine Picrate.**—To a solution of 6.84 g. (0.07 mole) of potassium thiocyanate and 5.0 g. (0.07 mole) of IV in 30 ml. of water, 9.85 g. (0.07 mole) of 72% perchloric acid diluted to 100 ml. was added over a 10-minute period with enough cooling to keep the solution at 40°. After standing one hour at 40°, the potassium perchlorate was removed by filtration and the solution was evaporated at 25° in a stream of dry air. The last traces of water were removed at reduced pressure and the product was heated to 110° for one hour. A quantitative yield, 9.8 g., of crude product was obtained but it could not be induced to crystallize. A sample of this was converted to the picrate in 95% ethanol and recrystallized twice from the same solvent, m.p. 200–203°.

Two grams (0.014 mole) of 1-chloro-2-amino-2-methylpropane hydrochloride was dissolved in 5 ml. of water and an equivalent amount of potassium thiocyanate (1.35 g.) was added. The solution was heated to 110° in an oil-bath and 3 ml. of water was added twice and evaporated over a 6-hour period. The product was treated with 3.48 g. (0.014 mole) of sodium picrate in 40 ml. of water. The picrate was recrystallized twice from 95% ethanol, yield 4.5 g., m.p. 204–206°. A mixed m.p. with the picrate described above gave a m.p. 203–206°. An analytical sample was prepared by three more recrystallizations from 95% ethanol m.p. 205.6–206.4°.

*Anal.* Calcd. for $C_{11}H_{13}N_5O_7S$: C, 36.77; H, 3.65; N, 19.49. Found: C, 37.08; H, 3.85; N, 19.63.

By a similar procedure, 1-bromo-2-amino-2-methylpropane hydrobromide and the corresponding iodo compound were converted to the same picrate.

**Hydrolysis Products. Potentiometric Analysis.**—Hydrolysis of imine III or IV gives two different products depending on the site of attack by water. Thus, data on the relative amounts of isomeric aminoalcohols for each case were needed. Because of the difference in basicity of the two aminoalcohols from IV, a direct potentiometric titration analysis could be applied to the reaction mixture.

If the equations corresponding to conservation of mass and charge are set up for a solution in which the acidity due to the presence of two weak acids has been exactly half-neutralized, one may derive the equation

$$\frac{G}{1 - G} = \left(\frac{[\mathrm{H}^+] + K_\mathrm{a}'}{[\mathrm{H}^+] - K_\mathrm{a}'}\right)\left(\frac{K_\mathrm{a}'' - [\mathrm{H}^+]}{K_\mathrm{a}'' + [\mathrm{H}^+]}\right)$$

where $G$ is the fraction of the original weak acid concentration accounted for by the acid A′ and $K'_\mathrm{a}$ is the dissociation constant of this acid. The second weak acid has a dissociation constant $K_\mathrm{a}''$. Solutions 0.15 $F$ in 2-hydroxy-2-methylpropylammonium perchlorate and 0.355 $F$ in perchloric acid were prepared and titrated potentiometrically with standard base at 25.0°. A small amount of formalin was added just before the second end-point to sharpen this end-point. Titrations of identical samples containing the perchlorate of 2-amino-2-methyl-1-propanol also were carried out. The $p$H at the half equivalence point of these titrations was taken as the $pK_\mathrm{a}$ of the aminoalcohol under the experimental conditions. The apparent $pK$ of the hydrolysate of IV was measured in an identical manner. The values obtained for these $pK$'s, 9.25 ± 0.01, 9.65 ± 0.02 and 9.32 ± 0.04, respectively, when inserted in the above equation, indicate that about 23% of the hydrolysate of IV is 2-amino-2-methyl-1-propanol. In previous work on the hydrolysis of imine IV in hydrochloric[2] or sulfuric acid[8] only the isomeric 1-amino-2-methyl-2-propanol was obtained.

**Distillation Analysis.**—Gas phase and "reversed phase" chromatography of the products of the imine hydrolysis were tried without success, but it was found possible to employ fractional distillation to the problem of separating the aminoalcohols since the boiling points are approximately 10° apart. The composition of the fractions obtained was checked by comparison of the refractive indices with those of the pure compounds.

From IV, the hydrolysis mixture was found to contain 85% of 1-amino-2-methyl-2-propanol and 15% of the 2-amino isomer. From III the ratio of 2-amino-1-butanol (61%) to 1-amino-2-butanol (22%) was close to three to one. However, a significant amount (~ 17%) of higher boiling material (polymer?) also was found.

## Results

**Kinetics.**—Before the study of various imines and nucleophiles was carried out, an intensive study of the reaction of four nucleophiles ($I^-$, $Br^-$, $SCN^-$, thiourea) with IV was made. The rate of the attack of such nucleophiles on the imine was found to be of the second order. The first-order dependence on nucleophile concentration was checked by variation of its initial concentration. The order in immonium ion was determined primarily by following its change in concentration with time over a considerable fraction of reaction in the presence of excess nucleophile; plots of log concentration against time were linear in such circumstances. Further, excellent straight lines were obtained when data for runs with comparable concentrations were plotted in accordance with second-order kinetic laws, and the second-order rate

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(5) S. Gabriel and J. Colman, *Ber.*, **47**, 1866 (1914).

(6) R. Adams and T. L. Cairns, THIS JOURNAL, **61**, 2464 (1939).

(7) Melting points are corrected; analyses by S. M. Nagy, Microchemical Laboratory, M.I.T., Cambridge, Mass.

(8) T. L. Cairns, THIS JOURNAL, **63**, 871 (1941).

constants from the different experiments were found to agree well. In Table I, the results for these experiments are presented.

TABLE I

REACTIONS OF 2,2-DIMETHYLETHYLENIMINE WITH SEVERAL NUCLEOPHILES

| Nucleophile | $\mu^a$ | Number of runs | $k_2{}^b$ | Av. % dev. | Reaction, % |
|---|---|---|---|---|---|
| $Br^-$ | 1.0 | 6 | $2.0 \times 10^{-3}$ | 2 | 83 |
| | 2.0 | 4 | $1.79 \times 10^{-3}$ | 0.5 | |
| $SCN^-$ | 1.0 | 3 | $1.6 \times 10^{-2}$ | 10 | 100 |
| | 2.0 | 6 | $1.46 \times 10^{-2}$ | 0.5 | |
| $I^-$ | 1.0 | 6 | $1.78 \times 10^{-2}$ | 3 | 93 |
| | 2.0 | 3 | $1.78 \times 10^{-2}$ | | |
| $SC(NH_2)_2$ | 1.0 | 6 | $4.1 \times 10^{-2}$ | 1 | 96 |

[a] Ionic strength. [b] Units are liter-mole$^{-1}$-sec.$^{-1}$, at 25° in aqueous solution.

As may be seen from the table, most of these experiments were carried out at ionic strength one. In the thiocyanate case some of the experiments were carried out at ionic strength two in order to get more reproducible results as at the lower ionic strength poor rate constants were obtained. In order to see how much difference this change in ionic strength caused, check runs at the higher ionic strength were made with iodide and bromide ions. In neither case was the rate seriously altered; in fact, with iodide ion the rate constant was the same at both ionic strengths.

In the fifth column of the table, the average percentage deviation of the rate constants from the mean is presented. In the final column are recorded the percentages of theoretical yields of product as calculated from the titration data. The divergences from 100% in the cases of bromide and iodide ions are felt to indicate that the primary product of the reaction is undergoing hydrolysis. Indeed, it was found that pure samples of this 2-iodo-amine were not easy to prepare, as a result of a marked instability of the compound.

**Rate Constants.**—In Table II, the rate constants for the reactions of four immonium ions and seven nucleophiles, other than water, are given. These rate constants can be correlated well by either of the equations[9,10] for relative rates in displacement reactions. Table III shows the values of the parameters which were found, by the method of least squares, to give the best fit of the rate data. For reasons discussed below, the values of $k_0$ which can be related to the rate of hydrolysis are treated as parameters at this point. The rate results are presented in the form of linear free energy plots in Fig. 1.

TABLE II

RATE CONSTANTS FOR RING OPENING REACTIONS

| | | $10^6 \times k$, l. mole$^{-1}$ sec.$^{-1}$, at 25°; $\mu = 1.0$ | | | |
|---|---|---|---|---|---|
| Nucleophile | $E_n$ | 2,2-Dimethylethylenimine | 2-Ethylethylenimine | Ethylenimine | N-Butylethylenimine |
| $H_2O^a$ | | 3.67 | 0.452 | 0.703 | 0.3 |
| $H_2O^b$ | 0.00 | 0.067 | 0.0083 | 0.0127 | 0.006 |
| $CH_3COO^-$ | 0.95 | 4.73 | 2.96 | 5.18 | 2.2 |
| $Cl^-$ | 1.24 | 7.56 | 3.56 | 5.48 | 1 |
| $Br^-$ | 1.51 | 33 | 17.8 | 28.5 | 8.3 |
| $SCN^-$ | 1.83 | 243 | 145 | 230 | 110 |
| $I^-$ | 2.06 | 297 | 163 | 436 | |
| $SC(NH_2)_2$ | 2.18 | 680 | | | |
| $S_2O_3^{=}$ | 2.57 | 4880 | 5920 | 5360 | 3500 |

[a] First-order rate constant $k_1$ calculated on the basis of the assumption that $k_1 = k_{exp}$. [b] Second-order rate constant $k_2$ calculated on the basis of the assumption that $k_2 = k_{exp}/[H_2O]$.

TABLE III

VALUES OF PARAMETERS FROM LINEAR FREE ENERGY EQUATIONS

| Imine | $k_0 \times 10^8$ (Edwards)[a] | $\alpha^a$ | $\beta^a$ | $k_0 \times 10^8$ (Swain and Scott)[b] | $s^b$ |
|---|---|---|---|---|---|
| Ethylen- | 2.73 | 2.12 | 0.026 | 1.54 | 0.87 |
| 2-Ethylethylen- | 1.39 | 2.21 | .043 | 0.658 | .91 |
| 2,2-Dimethylethylen- | 3.87 | 2.01 | .027 | 2.28 | .83 |

[a] Calculated from the equation $\log k - \log k_0 = \alpha E_n + \beta H$. [b] Calculated from the equation $\log k - \log k_0 = sn$.

It is worthy of mention that thiourea acts as a stronger nucleophile than iodide ion toward IV as predicted by the electrode potentials[10]; data on mustard cation displacements[11] had suggested that thiourea might have an abnormally low nucleophilic power.

There is firm evidence for the belief that in these reactions ring-opening occurs simultaneously with nucleophilic attack. The product isolated from the reaction of IV with thiocyanate has the thiocyanate group attached to the primary carbon; this situation certainly would not prevail if a carbonium ion intermediate were formed. The rings are opened by nucleophiles at relative rates which correspond to values of $\alpha$ and $s$ which are normal for displacements in rate-determining steps.[9,10] Again such a situation would not be expected to prevail if there were a carbonium ion intermediate. Finally, all four imines react at rates which reflect their nucleophilic character, suggesting that all proceed by a similar mechanism.

It seems rather likely that the mechanism of these reactions is one in which the nucleophile attacks the back side (to nitrogen) of the methylene carbon. Such a schematic equation is shown in the introduction.

Rates of hydrolyses for the four imines were measured at 25° using perchloric acid as the catalyst. The measured first-order rate constants are listed in Table II. For comparison with the second-order rate constants for reactions involving more active nucleophiles these hydrolysis constants divided by the concentration of solvent water are also shown in Table II and in Fig. 1. Rates of hydrolysis at temperatures other than 25° and at 8000 p.s.i. are shown in Table IV. The activation thermodynamic quantities are also shown in Table IV.

Although the reactions of active nucleophiles with the ionic form of IV are undoubtedly bimolecular, the hydrolysis of this ion has been reported to be unimolecular.[2] The tertiary carbonium ion which would be an intermediate for this hydrolysis would be expected to be more stable than the corresponding species which would be involved in

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(9) C. G. Swain and C. B. Scott, THIS JOURNAL, **75**, 141 (1953).

(10) J. O. Edwards, *ibid.*, **76**, 1540 (1954).

(11) A. G. Ogston, E. R. Holiday, J. St. L. Philpot and L. A. Stocken, *Trans. Faraday Soc.*, **44**, 45 (1948).

TABLE IV

RATE CONSTANTS AND ACTIVATION QUANTITIES FOR IMINE HYDROLYSES

| Imine | $T$, °C. | $k$, sec.$^{-1}$ | $\Delta H^*$, kcal./mole | $\Delta S^*$, e.u./mole | $\Delta V^*$, cc./mole |
|---|---|---|---|---|---|
| Ethylen- | 21 | $4.61 \times 10^{-7}$ | 23.0 ± 0.6 | − 9.4 ± 1.0 | 1.8 |
| | 21$^a$ | $4.43 \times 10^{-7}$ | | | |
| | 25 | $5.17 \times 10^{-7}$ | | | |
| | 45 | $9.76 \times 10^{-6}$ | | | |
| | 65 | $8.15 \times 10^{-6}$ | | | |
| 2-Ethyl-ethylen- | 21 | $2.64 \times 10^{-7}$ | 23.1 ± 0.1 | −10.0 ± 0.5 | −2.5 |
| | 21$^a$ | $2.79 \times 10^{-7}$ | | | |
| | 25 | $4.58 \times 10^{-7}$ | | | |
| | 45 | $5.83 \times 10^{-6}$ | | | |
| | 65 | $5.33 \times 10^{-6}$ | | | |
| 2,2-Di-methyl-ethylen- | 21 | $2.10 \times 10^{-6}$ | 24.3 ± 0.4 | −1.9 ± 1.0 | −4.4 |
| | 21$^a$ | $2.32 \times 10^{-6}$ | | | |
| | 25 | $3.63 \times 10^{-6}$ | | | |
| | 40 | $2.90 \times 10^{-5}$ | | | |
| | 45 | $5.23 \times 10^{-5}$ | | | |

$^a$ 8000 p.s.i.

mechanistically similar reactions of III or I. In the event that both unimolecular and bimolecular paths were important in these hydrolyses the experimental first-order rate constant would be composed of two terms

$$k_{\text{exp}} = k_1 + k_2[\text{H}_2\text{O}]$$

where $k_1$ is the first-order rate constant for SN1 ring-opening and $k_2[\text{H}_2\text{O}]$ pertains to the bimolecular, nucleophilic (SN2) attack of a water molecule on the imine ring.

It is not possible to evaluate $k_1$ and $k_2$ using only kinetic measurements on the hydrolysis reactions, since in the presence of excess solvent all these hydrolyses follow first-order kinetics. An indication that the mechanisms of the various hydrolyses are not all identical can be gained from the activation quantities listed in Table IV. The enthalpies of activation for the hydrolyses of III and I are almost identical, while that for the hydrolysis of IV is higher. The entropy of activation for the hydrolysis of IV is about 8 e.u. more positive than the corresponding entropies for the other hydrolyses. The influence of pressure on the hydrolysis of IV is about twice as great as on the hydrolyses of the other imines. Since the pressure effects are small, it does not seem appropriate to draw any conclusions from them; but the enthalpies and entropies of activation indicate that there is a significant difference between the hydrolysis of IV and the corresponding reactions of the other imines.

Analysis of the products of these hydrolyses supports this interpretation. Both potentiometric analysis and fractional distillation of the hydrolysate of IV show that approximately 20% of the product is 2-amino-2-methyl-1-propanol, the remainder being 1-amino-2-methyl-2-propanol. The former alcohol would be expected to be the predominant product of an SN2 mechanism, whereas the latter amino alcohol would be expected to predominate if an SN1 mechanism were operative. On the other hand, fractional distillation of the hydrolysis of III indicates that the aminoalcohol products of this reaction are approximately 22% 1-amino-2-butanol and 61% 2-amino-1-butanol. In this case the product corresponding to the SN2 reaction occurs in much greater yield than that corresponding to the SN1 mechanism.

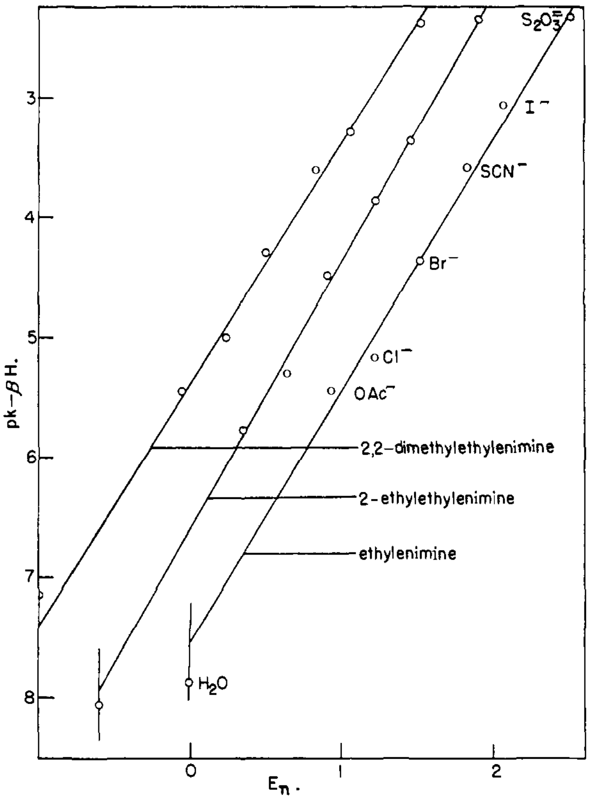

Fig. 1.—Linear free energy plots using equation of ref. 10 for three imines and six nucleophiles. Hydrolysis constants were not used to establish the best lines. Data for 25° were taken in aqueous solution.

Recent work has shown that the entropies of activation for SN1 and SN2 reactions in similar systems are distinctly different, with the $\Delta S^*$ for the SN1 reaction being as much as thirty units more positive than the $\Delta S^*$ for SN2.[12] Although quantitative comparison is not possible in view of the competing reactions, the more positive $\Delta S^*$ for the hydrolysis of IV is another indication of a significant SN1 contribution.

The parameter $k_0$ in the equation (either one) used to correlate the rate constants of the reactions of the more active nucleophiles corresponds to the value of the hydrolysis rate constant which is consistent with the second-order rate constants used to evaluate this parameter. Therefore, the computed value of $k_0$ should be close to the measured rate constant $k_{\text{exp}}$, when the concentration of solvent water is taken into account, if the hydrolysis involves the same mechanism (SN2) as do the reactions of the more active nucleophiles.

In Table V are listed the negative logarithms of $k_0$ and of $k_{\text{exp}}/[\text{H}_2\text{O}]$ for the various hydrolyses. It will be observed that the hydrolysis of IV proceeds at a faster rate than the rates of the reactions of the same imine with active nucleophiles would indicate. This is not surprising in view of the other evidence that there is a sizable SN1 contribution to this reaction. As a first approximation, we may

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(12) (a) R. W. Taft, Jr., E. L. Purlee, P. Riesz and G. A. DeFazio, THIS JOURNAL, **77**, 1584 (1955); (b) F. A. Long, J. G. Pritchard and F. E. Stafford, *ibid.*, **79**, 2362 (1957); (c) other references cited in a and b.

take the results of the product analyses as a measure of this contribution and compute an estimated second-order rate constant from the experimental rate constant. A similar though smaller correction may be applied to the hydrolysis of III, using the results of the fractional distillation as a measure of the SN1 contribution. In the case of the hydrolysis of III the amounts of the isomeric aminoalcohols would not be expected to be as good a measure of SN1 contribution since the steric effect of the single ethyl group would be less effective in blocking direct nucleophilic attack on the more substituted carbon than the steric effect of the two methyl groups in IV. On the other hand there seems to be a small amount of polymer formed during the hydrolysis reaction and this concurrent polymerization would require an additional correction, which would tend to offset the above-mentioned difficulty in the interpretation of the aminoalcohol analysis. The final corrected values of the second-order hydrolysis rate constants, computed from experimental data, are listed in Table V. It will be observed that these values, for all three hydrolyses, are below the corresponding values of $k_0$ from either correlation equation, computed from the rates of the faster reactions. The $k_0$ values using the equation of Swain and Scott[9] are closer to the experimental values than are those from the equation of Edwards.[10]

TABLE V

COMPARISON OF SECOND-ORDER HYDROLYSIS RATE CONSTANTS

| Imine | $pK$ ($H_2O$) | $pk_2$ (corr.) | $pk_0$ (E)[c] | $pk_0$ (SS)[c] |
|---|---|---|---|---|
| 2,2-Dimethylethylen- | 7.179 | 7.703[a] | 7.412 | 7.642 |
| 2-Ethylethylen- | 8.083 | 8.216[b] | 7.858 | 8.182 |
| Ethylen- | 7.898 | 7.898 | 7.560 | 7.812 |

[a] Corrected using product analysis by potentiometric method. [b] Corrected using product analysis by fraction distillation. [c] See data in Table III.

Several explanations might be advanced for this behavior, perhaps the most obvious being that the nucleophilic constant ($E_n$) for water is somewhat high (*i.e.*, water is not as strong a nucleophile as predicted). If the value of this constant were −0.14 for water, the estimated values would all agree within experimental error with the computed values of $k_0$. This small effect might be due to the fact that the species being attacked in these reactions are cations, while uncharged substrates were used in the evaluation of the nucleophilicity constants. Although the deviation certainly seems real, it is not large enough to invalidate the correlation equations.

The values of the activation thermodynamic quantities for these three hydrolyses, the product analyses and the relationship between the rates of imine hydrolysis and the rates of the faster reactions all point to the conclusion that the acid hydrolysis of 2,2-dimethylethylenimine is primarily an SN1 reaction although there is a small SN2 contribution. The acid hydrolysis of 2-ethylethylenimine is primarily SN2 with a possible small SN1 contribution. The comparable reaction of ethylenimine is probably exclusively SN2.[13]

Our results also indicate that the equations which have been presented[9,10] for the correlation of nucleophilic displacements, can be used to estimate amounts of SN1 and SN2 character in certain solvolysis reactions. When combined with data on activation entropies, etc.,[12] this method shows promise of giving satisfactory answers to solvolytic mechanism problems.

(13) Compare G. J. Buist and H. J. Lucas, THIS JOURNAL, **79**, 6157 (1957), a paper published while this one was in preparation.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TENNESSEE]

# Synthesis of 12-(Dialkylaminoalkyl)-benzo[a]phenothiazines

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RECEIVED JANUARY 16, 1958

A series of 12-(dialkylaminoalkyl)-benzo[a]phenothiazines has been synthesized for pharmacological evaluation. These compounds were obtained by thionation of various N-phenyl-α-naphthylamines and condensation of the resulting benzo[a]-phenothiazines with dialkylaminoalkyl chlorides using sodamide. Several N-acyl and sulfone derivatives of the benzo[a]-phenothiazines also were prepared.

The past decade has seen considerable work on phenothiazine chemistry which was initially stimulated by the observations of Halpern[3] and Charpentier[4] on the antihistaminic activity of 10-dialkylaminoalkylphenothiazines. More recently additional stimulus has been provided by the discovery of the effects of these phenothiazine types in treatment of mental illness.

In spite of the large amount of work on phenothiazine derivatives[5] little attention has been given to the benzophenothiazines. We have undertaken in this Laboratory a study of reactions and reaction products of the various benzophenothiazines. The present paper describes the synthesis of some new derivatives of benzo[a]phenothiazine with particular emphasis on the N-dialkylaminoalkyl types. Our initial objective has been the synthesis of compounds related to the therapeutically useful phenothiazine types.

Thionation of N-phenyl-α-naphthylamine in the presence of iodine catalyst leads to benzo[a]-

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(3) B. N. Halpern, *Compt. rend. soc. biol.*, **140**, 363 (1946).

(4) P. Charpentier, *Compt. rend.*, **225**, 306 (1947).

(5) S. P. Massie, *Chem. Revs.*, **54**, 797 (1954).