

ing.¹³ Figure 7 shows the fraction of starting material in the form of the cyclic ethylene-immonium intermediate B as a function of time for the three sets of experimental conditions for which the calculations were made. The effect of added chloride ion is (1) to lower the steady-state concentration of the intermediate B; (2) to make (B) reach a stable concentration earlier in the run; (3) to retard the decline of its concentration. All these effects would be intuitively predicted from the chemical equations. Figure 7 also shows how a lower initial concentration of amine results in a larger fraction being converted into the cyclic intermediate, this fraction reaching about 30% in the run with $\alpha = 0.044$.

Acknowledgment.—We received indispensable aid in the application of the differential analyzer to our problem from Mr. John Löff of the Massachusetts Institute of Technology.

Summary

Methyl-bis- β -chloroethylamine, stable in non-polar solvents, is converted rapidly into a cyclic dimer in aqueous and part-aqueous solution. In 2:1 acetone-water solution the reaction proceeds at a convenient rate for measurement and is attended by a small amount (less than 10%) of hydrolysis. The dimerization involves successive reactions at comparable rates and corresponds to no simple kinetic order. It is markedly retarded by sodium chloride.

(13) Later Columbic, Fruton and Bergmann⁴ showed that the concentration of B could be determined by titration with thiosulfate.

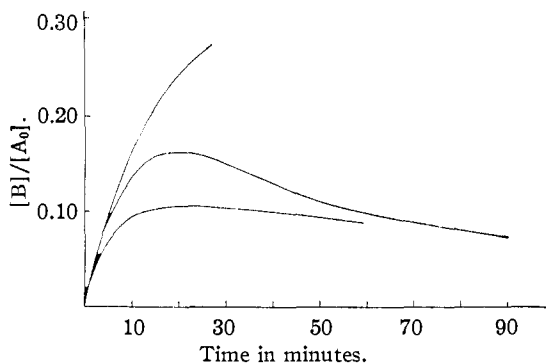


Fig. 7.—Concentration of cyclic intermediate B during reaction of methyl-bis- β -chloroethylamine in 2:1 acetone-water at 25° according to the differential analyzer: upper curve, $[A]_0 = 0.04407$; middle curve, $[A]_0 = 0.1180$; lower curve, $[A]_0 = 0.0460$, $[Cl^-]_0 = 0.0987$.

In the presence of sodium hydroxide, sodium thiosulfate or triethylamine displacement of the chlorine supersedes dimerization and the reactions all proceed at the same rate, first order with respect to the amine. These and other facts are interpreted as indicating that a cyclic ethylene-immonium ion is intermediate in both dimerization and displacement. Final proof of the mechanism is obtained by evaluating the separate rate constants involved in the dimerization by trial from the differential equations, and calculating the course of the reaction under different conditions.

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[CONTRIBUTION FROM THE WOLCOTT GIBBS LABORATORY OF HARVARD UNIVERSITY]

Kinetics and Mechanism of Reactions of Tertiary β -Chloroethylamines in Solution. II. Ethyl-bis- β -chloroethylamine¹

BY PAUL D. BARTLETT, JAMES W. DAVIS, SIDNEY D. ROSS AND C. GARDNER SWAIN

In Part I of this series² it was shown that methyl-bis- β -chloroethylamine, dissolved in 2:1 acetone-water, undergoes dimerization to a quaternary piperazinium dichloride with only a small amount of hydrolysis as a side reaction. It was also shown that dimerization, as well as hydrolysis and other displacements of the chlorine atoms, proceeds through a cyclic ethylene-immonium ion which is formed unimolecularly and reversibly from the β -chloroethylamine. The same types of product are found when the next homolog, ethyl-bis- β -chloroethylamine, is dissolved in 2:1 or 1:3 acetone-water. In this case, however, hydrolysis is the principal reaction and dimerization constitutes less than 50%, and under some conditions

practically none, of the reaction. The present study was undertaken to account for this quantitative difference between the homologs. It has been found that because of the special relations existing in this case between the magnitudes of the rate constants of the several reactions occurring, it is again possible, this time by a graphical method, to evaluate these rate constants separately and to confirm the correctness of the general mechanism already put forward.

Experimental

Material.—Ethyl-bis- β -chloroethylamine hydrochloride was most advantageously prepared by the reaction of ethyldiethanolamine (Carbide and Carbon) with thionyl chloride. The free base was prepared, like its lower homolog, by making an aqueous solution of the hydrochloride alkaline in the presence of benzene or ether, extracting rapidly, drying and evaporating the solvent. Solutions of the free base so prepared in dry acetone or ether could be kept for days without developing appreciable amounts of ionic chlorine.

(1) The work presented in this paper was performed under Contract NDCrc-136 between Harvard University and the National Defense Research Committee of the Office of Scientific Research and Development in 1943.

(2) Bartlett, Ross and Swain, *THIS JOURNAL*, **69**, 2971 (1947).

Basic Strengths of β -Chloroethylamines and Ethanolamines.—It was necessary to establish, before any kinetic analysis could be undertaken, that the final solutions after kinetic experiments contained only unhydrolyzed dimer and chlorohydrin hydrochloride, *i. e.*, no significant amounts of ethyl-bis- β -chloroethylamine hydrochloride and glycol hydrochloride. In this connection the basic dissociation constants in both 1:3 and 2:1 acetone-water were measured for ethyl-bis- β -chloroethylamine, ethyldiethanolamine, and ethyl- β -chloroethylethanolamine. In each case a half-neutralized solution of the amine was compared with a half-neutralized solution of triethylamine in the same solvent using two glass electrodes in vessels connected with a liquid junction. The exact K_B for ethyl- β -chloroethylethanolamine in 1:3 acetone-water could not be obtained with accuracy since this compound reacted rapidly. The figure chosen in this case was obtained by extrapolation to zero time. The results are expressed in Table I as the difference, ΔpK_A , between the logarithm of the acid dissociation constant of the ammonium ion being measured and that of triethylammonium ion as a standard. These differences are all negative, which means that the amines measured are all weaker bases than the standard.

TABLE I
BASIC STRENGTHS RELATIVE TO TRIETHYLAMINE

| Amine | ΔpK_A | ΔpK_A |
|---|--------------------------|--------------------------|
| | 1:3 Acetone- water | 2:1 Acetone- water |
| Ethyldiethanolamine | -1.76 | -1.17 |
| Ethyl- β -chloroethylethanolamine | -3.36 | -3.26 |
| Ethyl-bis- β -chloroethylamine | -4.55 | -4.87 |

From the difference in pK (1.61) between ethyl-bis- β -chloroethylamine and the related chlorohydrin in 2:1 acetone-water solution, it is evident that in any solution the ratio of ammonium ion to amine concentration will be forty times as great in the case of the chlorohydrin as in the case of the unhydrolyzed bis-chloroamine. In 1:3 acetone-water this ratio will be about 16.

Hydrolysis of Ethyl-bis- β -chloroethylamine Hydrochloride.—Ethyl-bis- β -chloroethylamine hydrochloride is very stable. A 0.0524 *M* solution required eighty-five days to reach 25% reaction (Table II). The average first-order rate constant for this run calculated between 16.6 and 21.8% reaction (twenty-eight and forty-nine days) is 2.12×10^{-4} min.⁻¹. Since the ammonium ions derived from the β -chloroethylamines have been found to be uniformly unreactive toward hydrolysis, displacement, and dimerization, it follows that the hydrolysis will come to a stop after the liberation of one inole of hydrochloric acid. The question remains whether the product at that point is substantially all chlorohydrin or a mixture containing important amounts of glycol and unhydrolyzed bis-chloroamine.

TABLE II
ETHYL-BIS- β -CHLOROETHYLAMINE HYDROCHLORIDE

| 0.0524 <i>M</i> Amine 2:1 Acetone-water | | | | 0.0306 <i>M</i> Amine 0.08 <i>M</i> NaOH 1:3 Acetone-water | | | |
|--|--------------------------------|---------------|--------------------------------|--|--------------------------------|---------------|--------------------------------|
| Time, min. | Re- act., ^a % | Time, days | Re- act., ^a % | Time, min. | Re- act., ^b % | Time, min. | Re- act., ^b % |
| 1.50 | 0 | 12 | 12.0 | 1.78 | 26.8 | 5.98 | 67.0 |
| 30.0 | 0.6 | 28 | 16.6 | 2.43 | 37.1 | 10.4 | 84.9 |
| 252 | 1.8 | 49 | 21.8 | 3.03 | 42.0 | 21.7 | 95.7 |
| 25.5 hrs. | 5.4 | 85 | 24.8 | 3.65 | 48.9 | 19.3 hrs. | 98.8 |
| 143 hrs. | 7.7 | | | | | | |

^a By titration with 0.100 *N* silver nitrate. ^b By titration with 0.1000 *N* silver nitrate.

Rate of Reaction of Ethyl- β -chloroethylethanolamine.—The fact that the hydrogen ions add very largely to the chlorohydrin does not in itself mean that little glycol will be formed. If the small fraction of chlorohydrin that is in the free base form were 16–40 times as reactive as ethyl-bis- β -

chloroethylamine, the hydrolysis of the chlorohydrin would be as important as that of ethyl-bis- β -chloroethylamine and a mixture would result. To prove that this is not the case, we isolated the chlorohydrin as its picryl sulfonate and purified it by crystallization. Its rate of reaction was only 2–3 times greater than that of ethyl-bis- β -chloroethylamine in both 2:1 and 1:3 acetone-water solutions. This rate was practically the same as that exhibited by a 1% solution of ethyl-bis- β -chloroethylamine in 1:3 acetone-water kept at room temperature for two days, then just neutralized with equivalent sodium hydroxide and silver nitrate, affording additional evidence that such solutions contain only chlorohydrin hydrochloride.

Kinetic Measurements.—All kinetic measurements were made at $25 \pm 0.05^\circ$. The method used was the same as that previously reported. In those runs in which both Cl^- and H^+ were determined, separate aliquots were taken since near the end-point of the H^+ titration, chloride liberation was very rapid. To correct for temperature rise and contraction on mixing acetone and water, the water solution was precooled to 15° for 2:1 and 19° for 1:3 mixtures. The data of Naville³ were used to make a volume correction. Unless otherwise noted all runs herein reported are so corrected. The results of the kinetic experiments are shown in Tables III–VII.

The Cyclic Intermediate.—An attempt was made to isolate the cyclic intermediate as its picrylsulfonate following the procedure used successfully by M. Bergmann and co-workers in the case of methyl-bis- β -chloroethylamine⁴ and later in the case of the ethyl compound itself.⁵ Difficulty was experienced because of our attempts to recrystallize the product, a step which Fruton and Bergmann found to be unnecessary. The heavy precipitate was filtered off, dried in a vacuum desiccator, and crystallized seven times from dry acetone and petroleum ether. However, its thiosulfate titer remained fairly constant at about 87% of two equivalents and its melting point about 142° , without complete melting. In an attempt to follow the rate of thiosulfate consumption, the intermediate was found to have completely consumed half of the thiosulfate by the time the first aliquot was taken, at twenty-six seconds, while the displacement of the second chlorine (involving a new cyclization) was half complete in about three minutes.

It seemed a reasonable interpretation of the low (87%) total thiosulfate titer that the hot acetone solution was decomposing about the same amount of intermediate in each crystallization. That heat destroys the ethyleneammonium picrylsulfonate was shown by heating a sample *in vacuo* over phosphorus pentoxide at 100° in a Fischer pistol for twenty hours. This decreased the thiosulfate titer to 47% of two equivalents, while the ionic chlorine remained negligible and the chloride liberated by a thirty-minute treatment with a slight excess of sodium hydroxide at room temperature remained unchanged at 100%. The change brought about by heat might be considered to be dimerization if it could be shown that the dimer, which is quite inert to hydrolysis in neutral or acid solution, is yet attacked by alkali as easily as the last result, cited above, would require.

Reaction of the Cyclic Dimer with Hydroxyl Ion.—The N,N' -diethyl- N,N' -di- β -chloroethylpiperazinium dichloride ("dichlorodimer") was treated with excess sodium hydroxide in water solution at 25° . It was found that two chloride ions were liberated per mole of amine. The percentage reaction is therefore given on this basis. Table XIII gives the kinetic data for initial hydroxyl ion concentration 1.94 times that theoretically required for liberation of two chloride ions. Table XIV gives the data for a 6.17 ratio. Wegscheider⁶ has shown that if a plot of $\log(Q - z)/Q(1 - z)$ against time, where $Q = b/2a$ and $z =$

(3) Naville, *Helv. Chim. Acta*, **9**, 913 (1926).

(4) Columbic, Fruton and Bergmann, *J. Org. Chem.*, **11**, 530 (1946).

(5) Fruton and Bergmann, *ibid.*, **11**, 548 (1946).

(6) Wegscheider, *Monatsh.*, **36**, 471 (1915).

TABLE III
 ETHYL-BIS- β -CHLOROETHYLAMINE IN 2:1 ACETONE-WATER

| 0.05505 M Amine | | | | 0.0250 M Amine | | | |
|-----------------|-------------------------------|-----------|--------------------|----------------|-------------------------------|------------|--------------------|
| Time, hr. | % H ⁺ ^a | Time, hr. | % Cl ^{-b} | Time, min. | % H ⁺ ^a | Time, min. | % Cl ^{-b} |
| 0.185 | 3.2 | 0.053 | 19.4 | 7.00 | 3.0 | 2.17 | 14.4 |
| .663 | 9.2 | .105 | 27.0 | 24.5 | 8.8 | 5.0 | 27.2 |
| 2.1 | 22.4 | .235 | 42.0 | 74 | 22.2 | 11.8 | 43.6 |
| 4.5 | 35.9 | .540 | 46.8 | 135 | 33.2 | 18.5 | 50.9 |
| 10.6 | 57.2 | 2.15 | 59.8 | 157 | 32.4 | 37.0 | 57.6 |
| 11.0 | 57.6 | 4.50 | 72.8 | 278 | 46.1 | 76 | 59.5 |
| 21.1 | 71.2 | 4.68 | 72.9 | 508 | 61.8 | 83 | 60.7 |
| 27.0 | 75.0 | 10.6 | 85.6 | 18.9 hrs. | 85.3 | 164 | 68.4 |
| 46.5 | 81.6 | 21.2 | 94.5 | 26.8 hrs. | 86.8 | 510 | 85.2 |
| 76.8 | 84.5 | 27.0 | 97.2 | 27.0 hrs. | 87.5 | 19 hrs. | 94.0 |
| 96.6 | 84.8 | 46.5 | 99.1 | 72.8 hrs. | 93 | 26.9 hrs. | 96.5 |
| 172 | 84.7 | 76.8 | 99.9 | 45 days | 108 | 72.8 hrs. | 101.2 |
| 42 days | 89.0 | 96.6 | 101 | | | 45 days | 111.0 |
| | | 172 | 103 | | | | |
| | | 42 days | 102 | | | | |

^a By titration with 0.0207 *N* sodium hydroxide. ^b By titration with 0.1000 *N* silver nitrate.

 TABLE IV
 ETHYL-BIS- β -CHLOROETHYLAMINE

| 0.1501 M Amine 2:1 Acetone-water | | | | 0.0243 M Amine 1:3 Acetone-water ^e | | | |
|-------------------------------------|---------------------------------|------------|----------------------|--|--------------------|-----------|-------------------------------|
| Time, min. | % H ⁺ ^{a,c} | Time, min. | % Cl ^{-b,c} | Time, min. | % Cl ^{-b} | Time, hr. | % H ⁺ ^a |
| 8.0 | 1.0 | 3.58 | 16.8 | 1.67 | 69.6 | 0.097 | 4.4 |
| 20.3 | 2.9 | 5.83 | 23.1 | 3.42 | 90.2 | .18 | 5.9 |
| 81.3 | 10.1 | 10.2 | 25.7 | 7.28 | 95.9 | .367 | 8.1 |
| 187 | 18.8 | 17.8 | 32.9 | 13.7 | 97.1 | .625 | 10.8 |
| 355 | 27.6 | 34.4 | 36.4 | 22.5 | 96.8 | 1.58 | 16.5 |
| 695 | 38.4 | 84 | 46.8 | 49 hrs. | 100.1 | 2.87 | 25.6 |
| 22.9 hrs. | 48.8 | 179 | 58.8 | 144 hrs. | 106 | 5.68 | 42.7 |
| 29.8 hrs. | 51.4 | 357 | 72.8 | 218 hrs. | 109 | 9.70 | 58.4 |
| 52.3 hrs. | 55.3 | 698 | 89.5 | 20 days | 114 | 18.2 | 76.4 |
| 101 hrs. | 57.4 | 22.9 hrs. | 93.5 | 44 days | 115.5 | 25.0 | 83.7 |
| 265 hrs. | 58.0 | 29.6 hrs. | 96.3 | | | 49.0 | 95.0 |
| | | 52.5 hrs. | 98.8 | | | 144 | 106.0 |
| | | 101 hrs. | 99.9 | | | 218 | 107.8 ^d |
| | | 265 hrs. | 101.4 | | | 20 days | 116.0 |
| | | | | | | 44 days | 120.0 |

^a By titration with 0.207 *N* sodium hydroxide. ^b By titration with 0.1000 *N* silver nitrate. ^c 5-cc. aliquots. ^d By titration with 0.0463 *N* sodium hydroxide. Not corrected for temperature.

 TABLE V
 ETHYL- β -CHLOROETHYLETHANOLAMINE PICRYL SULFONATE

| 0.00713 M Amine 0.0180 M Sodium hydroxide 2:1 Acetone-water | | 0.00561 M Amine 0.0238 M Sodium hydroxide 1:3 Acetone-water | |
|---|--------------------|---|--------------------|
| Time, min. | % Cl ^{-a} | Time, min. | % Cl ^{-a} |
| 1.03 | 14.7 | 1.18 | 43.6 |
| 2.20 | 25.1 | 1.85 | 59.4 |
| 2.97 | 32.6 | 2.38 | 67.0 |
| 5.17 | 48.4 | 3.2 | 75.9 |
| 11.3 | 74.8 | 4.28 | 84.5 |
| 5.33 hr. | 98.6 | 5.72 | 90.9 |
| | | 60 | 100.0 |

^a By titration with 0.00500 *N* silver nitrate.

Cl⁻/2 α in this case, falls off with increasing α , the second of the two successive bimolecular reactions has a rate constant less than half the first, *i. e.*, less than the statistically predicted rate constant for an equivalent and completely independent process such as hydrolysis of the diester of a

 TABLE VI
 ETHYL-BIS- β -CHLOROETHYLAMINE

^a By titration with 0.0463 *N* sodium hydroxide. ^b By titration with 0.1000 *N* silver nitrate.

long dibasic acid. This proves to be the case, showing that loss of the second chloride is considerably affected by loss of the first. The reaction is clearly bimolecular between the dimer and hydroxyl ion. Since the halogen in the β -position to an ammonium nitrogen atom is completely inert to stronger ionic competitors than hydroxyl, this is evidently an elimination and not a displacement reaction.

TABLE VII

| 0.0545 M N,N'-Diethyl-N,N'-di- β -chloroethyl-piperazinium dichloride 0.2113 M sodium hydroxide | | | 0.0171 M N,N'-Diethyl-N,N'-di- β -chloroethyl-piperazinium chloride 0.2113 M sodium hydroxide | | | 0.01972 M N,N'-Diethyl-N,N'- β -hydroxyethyl-piperazinium dichloride 0.0657 M sodium hydroxide | | |
|--|------------|-------------------------------|--|------------|-------------------------------|---|------------|-------------------------------|
| Time, min. | Re-act., % | $\frac{\log Q - z}{Q(1 - z)}$ | Time, min. | Re-act., % | $\frac{\log Q - z}{Q(1 - z)}$ | Time, min. | Re-act., % | $\frac{\log Q - z}{Q(1 - z)}$ |
| 1.07 | 7.8 | 0.0170 | 1.52 | 17.2 | 0.0686 | 2.25 | 4.0 | |
| 2.07 | 17.5 | .0414 | 2.98 | 25.2 | .1079 | 6.72 | 5.1 | |
| 3.17 | 24.9 | .0645 | 4.33 | 37.2 | .1747 | 25.0 | 11.2 | |
| 6.62 | 43.0 | .1335 | 7.20 | 54.7 | .3021 | 86.6 | 16.2 | |
| 9.93 | 53.9 | .1931 | 12.1 | 69.6 | .4669 | 18.5 hrs. | 37.5 | |
| 17.1 | 68.8 | .3160 | 19.9 | 81.3 | .6675 | 14 days | 85.1 | |
| 25.9 | 77.5 | .4281 | 32.5 | 87.5 | .8337 | 25 days | 99.9 | |
| 41.3 | 84.9 | .5694 | 20.5 hrs. | 92.0 | | | | |
| 24 hrs. | 89.8 | | 22 days | 92.4 | | | | |

^a By titration with 0.1000 N silver nitrate. ^b By titration with 0.0940 N hydrochloric acid.

To test whether or not the "dihydroxydimer," N,N'-diethyl-N,N'-diethanolpiperazinium dichloride, reacted with alkali, it was prepared by way of the chlorohydrin as follows: Twenty ml. of ethyl-bis- β -chloroethylamine was dissolved in two liters of 25% acetone and allowed to stand for four days at room temperature. Twenty-five ml. of concentrated hydrochloric acid was added and the solution evaporated under reduced pressure until the residue was a glass. This was covered with ether and 10 g. of sodium hydroxide in 10 ml. of water was added and the mixture shaken immediately. The ether solution was then separated and dried over sodium sulfate. The dried ether was distilled off, replaced with methanol, and the solution refluxed while dimerization took place. The dimer crystallized and was filtered from the cooled solution and weighed 12.6 g. Recrystallization from water-methanol-acetone gave white crystals, m. p. 246-247° (dec.).

The dihydroxydimer consumed one hydroxyl ion, but at a very low rate. The time for half reaction was about a week under our conditions, whereas the time for liberation of one chloride ion was less than ten minutes for the dichlorodimer. The reaction was followed by backtitrating the excess base to a colorless thymolphthalein end-point. Table XV gives the kinetic results.

Interpretation of the Kinetics

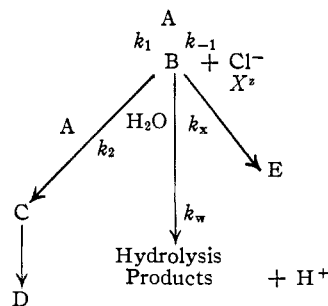
The Determination of k_1 .—The method of approaching the value of k_1 is to measure the rate of a displacement reaction of the amine which occurs under irreversible conditions, so that k_{-1} need not be taken into account. Such is the reaction with hydroxyl ion, since OH⁻ is a much stronger competitor for the cyclic intermediate B than is Cl⁻. However, this reaction has the disadvantage that two chlorines are replaced in succession without a detectable break, and the rate measured is therefore a composite of k_1 , for the dichloroamine, and k'_1 for the chlorohydrin. The full integration of the differential equations for two successive unimolecular reactions yields the expression

$$(\text{Cl}^-) = a \left[2 + \frac{k_1 - 2k'_1}{k'_1 - k_1} e^{-k_1 t} + \left(\frac{k_1}{k'_1 - k_1} \right) e^{-k'_1 t} \right]$$

It can be shown that $\log (2a - \text{Cl}^-)$ is a linear function of time for only two cases, namely, when $k'_1 \gg k_1$ and when $k'_1 = \frac{1}{2}k_1$, in which cases the determined unimolecular rate constant is k_1 and $k_1/2$, respectively. Although such a plot is

nearly linear for the reaction of ethyl-bis- β -chloroethylamine with hydroxyl ion, a comparison of the apparent k (0.06) with the k'_1 (0.13) determined in the same solvent (2:1 acetone-water) by starting with the chlorohydrin shows that the actual case does not correspond with one of these limits. Therefore the k_1 quoted in the tables was determined from the above equation, the experimental data and the experimental k'_1 ; a k_1 was found with which the experimental curve of (Cl⁻) against time could be calculated within the experimental error. It was found that the ratio of k'_1 to k_1 was 1.5 in 2:1 and 1.9 in 1:3 acetone-water.

Determination of the Separate Rate Constants.—The facts in the case of ethyl-bis- β -chloroethylamine are again consistent with the general reaction mechanism outlined in Part I and schematized as follows



Only k_1 is directly measurable in the displacement experiments. The fact that hydrolysis in 2:1 acetone-water constitutes 50-100% of the reaction instead of only 5-10% as in the case of methyl-bis- β -chloroethylamine makes possible here a complete analysis of the occurrences in solution, using only data on the rate of appearance of hydrogen ion and chloride ion, without the use of a mechanical differential analyzer. This can be done by a simple graphical method. When hydrogen ion concentration is plotted against time, the slopes are a measure of relative intermediate (B) concentrations, since the formation of hydrogen ion is a pseudo-unimolecular reaction of B. If the actual intermediate concentration at any time is known, then all the (B)'s can be assigned absolute values. As a first approximation, an early time is chosen at which chloride concentration has partly leveled off at a high value but hydrogen ion concentration is still small; the difference is assumed to equal (B). The slope of the (H⁺)-time curve divided by (B) at this point gives k_w .

Next dimerization is calculated as follows: The concentration of molecular amine (A) is measured by $(a - (\text{Cl}^-))$ at any time, where a = initial value of (A). The final concentration of dimer (which is measured as the difference $(\text{Cl}^-) - (\text{H}^+)$ for a very late aliquot, after all B has reacted) divided by $\int_0^\infty (\text{A})(\text{B})dt$ gives k_2 . The chloride ion concentration due to dimer at any

time is $k_2 \int_0^\infty (A)(B)dt = 2(D)$. The values of these integrals were determined within $\pm 0.5\%$ by plotting $(A)(B)$ against t and measuring the area under the curve by means of a polar planimeter.

Now much more accurate (B) values can be calculated $((Cl^-) - (H^+) - 2(D))$ for the early times, calculated from slopes as before for other times), and the process repeated until constant $\int_0^\infty (B)dt$ and $\int_0^\infty (A)(B)dt$ integrals (and hence constant k_w and k_2 values) are obtained. The most accurate k_w is the final amount of hydrolysis divided by $\int_0^\infty (B)dt$.

k_{-1} is obtained from the equation, true at the point where (B) is a maximum

$$k_1(A) = (k_w + k_2(A) + k_{-1}Cl^-)(B)$$

It is found that the first two terms on the right are relatively small, and in runs with added chloride the point of maximum (B) approximately coincides with the point of maximum curvature in the (Cl^-) versus t curve. The salt effect on k_{-1} is large.

The results from this analysis are as accurate as the slope measurements from the experimental data. Table VIII lists the rate constants, obtained by this method for four runs in 2:1 acetone-water, one with chloride added. The large negative dependence of k_{-1} on the ionic strength is strictly in accord with our previous observation in the case of methyl-bis- β -chloroethylamine. Figures 1 and 2 show the experimental curves of hydrogen and chloride ion concentrations and the calculated curves of (A) and (B) as functions of time, for two different initial concentrations of starting material.

TABLE VIII

| INDIVIDUAL RATE CONSTANTS IN 2:1 ACETONE-WATER | | | | |
|--|-------|----------|-------|--------|
| Initial amine concn. | k_1 | k_{-1} | k_2 | k_w |
| 0.0250 | 0.085 | 7.0 | 0.090 | 0.0061 |
| .05005 | .085 | 4.8 | .074 | .0053 |
| .0819 M amine | .085 | 2.4 | | .0063 |
| .1429 M Cl^- | | | | |
| .1501 | .085 | 1.5 | .086 | .0050 |

With 1:3 acetone-water, the method of analysis applied with 2:1 acetone-water is incapable of giving k_2 because (A) is immeasurably small. However, under these circumstances (Cl^-) approaches constancy early, and this makes (A) approximately proportional to (B) for the remainder of the run. Therefore a k_2f can be obtained, where f is the average $(A)(B)$ value, by plotting $\int_0^\infty (B)^2dt$ instead of $\int_0^\infty (A)(B)dt$. The k_{-1} term in the kinetic equation must be negligibly small because even a large excess of added chloride has no

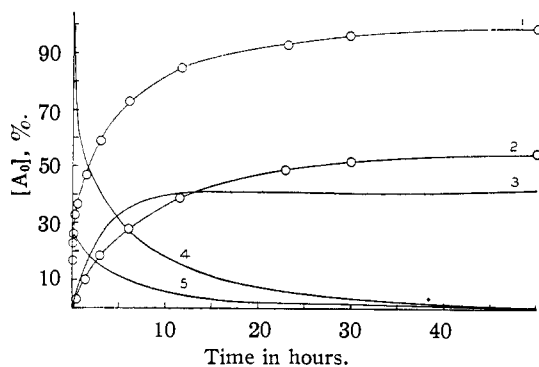


Fig. 1.—Ethyl-bis- β -chloroethylamine in 2:1 acetone-water at 25°, $[A]_0 = 0.1501$; curve 1, chloride ion liberated; curve 2, hydrogen ion liberated; curve 3, $(1) - (2) - [B] = 2 \times$ dimer formed; curve 4, $[A]$; curve 5, $[B]$.

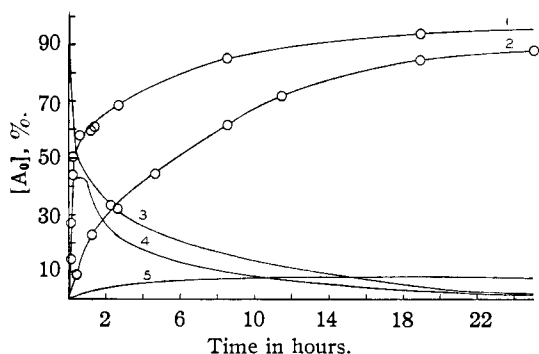


Fig. 2.—Ethyl-bis- β -chloroethylamine in 2:1 acetone-water at 25°, $[A]_0 = 0.0250$; curve 1, chloride ion liberated; curve 2, hydrogen ion liberated; curve 3, $[A]$; curve 4, $[B]$; curve 5, $(1) - (2) - [B] = 2 \times$ dimer produced.

effect in slowing the reaction until the maximum B concentration is attained.

Table IX lists the k 's determined by this method for three runs in 1:3 acetone-water. Figure 3 plots the experimental and calculated concentrations for a run with initial $(A) = 0.14$.

TABLE IX

| INDIVIDUAL RATE CONSTANTS IN 1:3 ACETONE-WATER | | | |
|--|-------|--------|--------|
| Initial amine concn. | k_1 | k_2f | k_w |
| 0.0243 | 0.24 | 0.0023 | 0.0017 |
| .0490 | .24 | .0023 | .0014 |
| .1401 | .24 | .0025 | .0013 |

The increased k_w in 2:1 acetone-water relative to 1:3 acetone-water, in spite of the decreased water concentration, is surprising. Since the transition state in the hydrolysis of B is an appreciably larger ion than is B itself, the formation of this transition state is attended by a decrease in electrostatic potential which is much more important, the lower the dielectric constant of the medium in which the hydrolysis is occurring. It might therefore be possible, though it certainly is

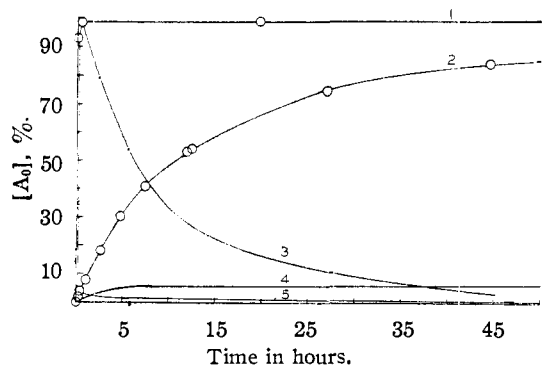


Fig. 3.—Ethyl-bis- β -chloroethylamine in 1:3 acetone-water at 25°, $[A]_0 = 0.1401$: curve 1, chloride ion liberated; curve 2, hydrogen ion liberated; curve 3, $[B]$; curve 4, $(1) - (3) - [B] = 2 \times$ polymer produced; curve 5, $[A]$.

not common, for the decreased dielectric constant of the less aqueous medium to overbalance the diminished concentration of the water, and result in an increased rate of hydrolysis of a positively charged molecular species.

Such a straightforward graphical determination of the separate rate constants could not be carried

out with our data on methyl-bis- β -chloroethylamine in 2:1 acetone-water (Part I of this series) because the amount of hydrolysis in that case was too small to permit reliable estimates of the slopes which served as the starting-point in the present case.

Summary

Ethyl-bis- β -chloroethylamine differs from its methyl homolog in undergoing a larger proportion of hydrolysis as compared to dimerization, in part-aqueous solution. Kinetic studies have been made of the reactions of this amine in 2:1 and 1:3 acetone-water solutions and the results are shown to be consistent with the general mechanism involving formation of an ethylene-immonium ion as an intermediate in dimerization, hydrolysis and displacement. The special quantitative relations among the separate rate constants make it possible to evaluate these constants by a graphical method.

The cyclic dimer of ethyl-bis- β -chloroethylamine, though inert to hydrolysis and displacement in neutral or acid solution, is readily subject to elimination of hydrochloric acid in the presence of sodium hydroxide.

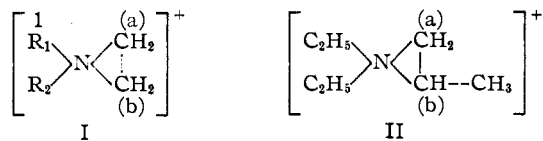
CAMBRIDGE, MASSACHUSETTS RECEIVED MARCH 27, 1947

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Role of Neighboring Nitrogen Atom in the Displacement Reaction; Rearrangement in the Hydrolysis of 1-Diethylamino-2-chloropropane

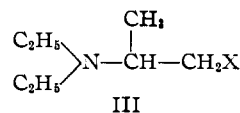
BY SIDNEY D. ROSS¹

There is a large body of evidence that a cyclic ethyleneimmonium ion of the type I, where (a) and (b) represent the points of attack, is an inter-



mediate in the dimerization, hydrolysis and displacement reactions of the tertiary β -chloroethylamines.^{1a} If an analogous intermediate were formed in the hydrolysis of 1-diethylamino-2-chloropropane it would have structure II. In the case of I (a) and (b) are methylene groups and attack by a reagent, X^- , at either position results in the same product. In the case of II (a) and (b) differ, and the attack of a reagent, X^- , at the two positions should result in two different prod-

ucts. Attack at (a) should give a product, III, having a rearranged carbon skeleton, whereas attack at (b) should restore the original carbon skeleton. Since the attack on II is of the SN_2



type, (a), being least substituted, would be the favored point of attack and the predominant product should be the one having the rearranged carbon skeleton. Moreover, the occurrence of such a rearrangement would constitute evidence for II as an intermediate in the reaction.

To test this hypothesis we prepared 1-diethylaminopropanol-2 by heating diethylamine with propylene oxide in a sealed tube. 1-Diethylaminopropanol-2, IV, has been previously prepared in this way,² and, also, by heating diethylamine with propylene chlorohydrin³ or propylene bromohydrin.⁴ The amino alcohol, IV, gave the

(2) (a) Cook and Rider, *THIS JOURNAL*, **58**, 1079 (1936); (b) Krasuskii and Pilyugin, *Urainskii Khim. Zhur.*, **5**, Sci. Pt. 135-138 (1930); *C. A.*, **25**, 2690 (1931).

(3) Ladenburg, *Ber.*, **14**, 2406 (1881).

(4) Fourneau and Fuval, *Bull. soc. chim.*, **81**, 429 (1922).

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(1a) Bartlett, Ross and Swain, *THIS JOURNAL*, **69**, 2971 (1947); Bergmann, Golumbic, Fruton, Stahmann and Stein, *J. Org. Chem.*, **11**, 518-585 (1946), and unpublished war research by Ogston and co-workers in England and Cohen and co-workers in this country. Since submission of this paper a communication by Brode and Hill (*THIS JOURNAL*, **69**, 724 (1947)) has reported similar results with dimethylaminopropyl chloride.