[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

The Reaction of 6-Methoxy-8-aminoquinoline with Alkylamino-alkyl Halides[1,2]

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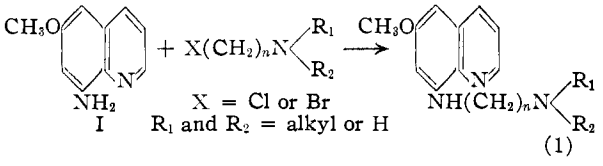
The reactions of four isopropylaminoalkyl halides with 6-methoxy-8-aminoquinoline at three separate temperatures over a *p*H range of 2.5–5.5 have been investigated. The optimum *p*H (about 4.7) for the maximum rate of alkylation of 6-methoxy-8-aminoquinoline by an isopropylaminoalkyl halide has been determined. Apparent energies and entropies of activation have been calculated for each reaction. Inconsistencies noted indicate that, under the conditions used, the observed effects cannot be explained solely on the basis of *p*H. The synthesis of 8-(5-isopropylamino-5-methylamylamino)-6-methoxyquinoline diphosphate (CN-1105) has been described. The acid dissociation constants for the quinoline nitrogen of 6-methoxy-8-aminoquinoline and the terminal aliphatic amino groups of pentaquine, isopentaquine and CN-1105 at 70.1° and at an ionic strength of 1.909 have been determined.

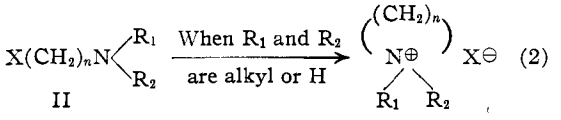
Of the methods for the synthesis of the class of antimalarial drugs comprised by the 8-alkylaminoalkylaminoquinolines, that embracing alkylation of an 8-aminoquinoline with an alkylaminoalkyl halide is by far the most important. This reaction is typified by the following equation in which the quinoline is 6-methoxy-8-aminoquinoline (I) a derivative of 8-aminoquinoline which, on the basis of present information, appears to represent the most desirable quinoline moiety of the final drugs insofar as optimum antimalarial action combined with favorable toxicity is concerned.



I (1)

In the above generalized formula, X may be chlorine or bromine, R_1 and R_2 may be either alkyl or hydrogen, and the alkyl residue between the halogen and the amino group may be either a straight chain, as illustrated in the type reaction, or a branched chain alkyl residue.

However, the above alkylation reaction is complicated by the simultaneous occurrence of a reaction involving intramolecular cyclization of the alkylaminoalkyl halide with resultant lowering of the yields of the desired drugs. This cyclization may be illustrated by the following generalized equation



II (2)

In the present work all such cyclizations resulted in the formation of either pyrrolidines or piperidines. That the ring systems formed are not intermediates in the formation of the alkylated quinoline drugs has been established by Freundlich and Krestovnikoff,[5] who showed that the ring closure of 5-chloroamylamine was non-reversible, and by Elderfield, *et al.*,[6] who were unable to alkylate I with 1,1-diethyl-2-methylpyrrolidinium chloride or bromide.

In order that reaction (1) may occur it is necessary that the *p*H of the reaction medium be sufficiently basic that the 8-amino group in I remain free, *i.e.*, not protonated. On the other hand, if the *p*H of the reaction medium be too basic, the cyclization reaction (2) predominates. In the past this critical adjustment of *p*H of the reaction medium has been made more or less on an empirical basis[6] and no quantitative data on the course of the two competing reactions are available. The purpose of the present study, therefore, is to provide such data for the reaction of I with certain representative alkylaminoalkyl halides.

Whereas no quantitative data on the alkylation of any quinoline or aminoquinoline are available, considerable data on the cyclization of various haloalkyl amines are at hand. The kinetics of the cyclization and the reactions of bis-chloroethyl amines have been studied thoroughly.[7–11] The linear polymerization and cyclization reactions of straight chain alkylaminoalkyl halides of the type of II in which n is 3, 4, 5 and 6 have been studied qualitatively.[12] Freundlich and co-workers[5,13] have carried out extensive studies of the cyclization of haloalkyl amines to cyclic imines, *e.g.*,

$$Br(CH_2)_nNH_2 \longrightarrow (CH_2)_nNH + HBr$$
$$n = 2 \text{ to } 6$$

The reaction was found to be first order in the presence of alkali in water or aqueous alcohols. Within wide limits it was independent of the hydroxide ion concentration in basic solution, irreversible, and unaffected by added salts. Further studies of linear polymerization and cyclization of haloalkyl amines and discussions of the relative

(1) The material reported in the present paper is taken from a dissertation submitted by Leon E. Rubin in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Columbia University.

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(5) H. Freundlich and A. Krestovnikoff, *Z. physik. Chem.*, **76**, 79 (1911).

(6) R. C. Elderfield, *et al.*, THIS JOURNAL, **68**, 1516 (1946).

(7) C. Golumbic, J. S. Fruton and M. Bergmann, *J. Org. Chem.*, **11**, 518 (1946).

(8) P. D. Bartlett and co-workers, THIS JOURNAL, **69**, 2971, 2977 (1947); **71**, 1415 (1949).

(9) R. Cohen, E. R. Van Artsdalen and J. Harris, *ibid.*, **70**, 281 (1948).

(10) A. L. Thompson, *et al.*, *Can. J. Research*, **26B**, 161, 170, 175, 192, 193 (1948).

(11) W. E. Hanby, *et al.*, *J. Chem. Soc.*, 519 (1947).

(12) C. S. Marvel and co-workers, THIS JOURNAL, **52**, 287 (1930); **55**, 753 (1933); **56**, 725 (1934); **57**, 1137 (1935).

(13) H. Freundlich and co-workers, *Z. physik. Chem.*, **79**, 681 (1912); **87**, 69 (1914); **101**, 177 (1922); **122**, 39 (1926); **146**, 321 (1930); **166**, 166 (1933).

ease of the two reactions have been reported.[14–16]

In order to limit the scope of the present investigation the terminal amino group of the haloalkyl amines used was held constant at isopropylamino. Further, the total number of carbon atoms between the halogen and the isopropylamino group was 5 or 6 with a straight chain of 4 or 5 atoms. On the basis of these restrictions the haloalkyl amines (as their hydrohalide salts) studied were III, IV, VI and VIII. The resulting drugs are then V (pentaquine), VII (isopentaquine) and IX (presently designated by CN-1105). Such a choice allows comparison of the reaction rates of I with alkylaminoalkyl halides containing (a) a primary chloride and a secondary amine with one of the alkyl groups attached to the nitrogen branched at the α carbon atom (III); (b) a primary bromide similar to (a) (IV); (c) a primary bromide and a secondary amine with both of the alkyl groups attached to the nitrogen branched at the α carbon atom (VIII); and (d) a secondary bromide and a secondary amine with one of the alkyl groups attached to the nitrogen branched at the α carbon atom.

TABLE I

$R\text{-}CH_2CH_2CH_2CH_2CH_2NHCH(CH_3)_2$

III R = Cl
IV R = Br
V R = 6-methoxy-8-quinolylamino

$R\text{-}CH(CH_3)CH_2CH_2CH_2NHCH(CH_3)_2$

VI R = Br
VII R = 6-methoxy-8-quinolylamino

$R\text{-}CH_2CH_2CH_2CH_2CH(CH_3)NHCH(CH_3)_2$

VIII R = Br
IX R = 6-methoxy-8-quinolylamino

Experimental[17,18]

6-Methoxy-8-aminoquinoline (I).—Commercial I (Winthrop–Stearns, Inc.) was purified by distillation under nitrogen at about 50 microns, and recrystallized from methanol (0.4 ml./g.), m.p. 41–42°. After several recrystallizations, the base remained colorless when exposed to air for months.

Hydrobromide of I.—Dry hydrogen bromide was passed into a stirred solution of 20 g. of I in 200 ml. of absolute ether until the solution was slightly acid to moist universal indicator paper. The precipitated hydrobromide was recrystallized five times from absolute alcohol, m.p. 230–231.5°.

Anal. Calcd. for $C_{10}H_{11}BrN_2O$: C, 47.0; H, 4.4; N, 11.1. Found: C, 47.1; H, 4.6; N, 10.9.

5-Chloro-1-isopropylaminopentane (III) **hydrochloride**, m.p. 124.5–126°, was prepared according to Drake, *et al.*[19]

Anal. Calcd. for $C_8H_{19}Cl_2N$: C, 48.0; H, 9.6; N, 7.0. Found: C, 47.9; H, 9.5; N, 7.0.

5-Bromo-1-isopropylaminopentane (IV) **hydrobromide**, m.p. 117.5–118°, was prepared according to Elderfield and Krueger.[20]

Anal. Calcd. for $C_8H_{19}Br_2N$: C, 33.2; H, 6.6; N, 4.8. Found: C, 33.5; H, 6.8; N, 4.8.

4-Bromo-1-isopropylaminopentane (VI) **hydrobromide** supplied through the courtesy of Eli Lilly and Co., was recrystallized twice from acetone–ether and melted at 167–167.5°.

5-Bromo-1-isopropylaminohexane (VIII) **hydrobromide**[21] was recrystallized first from acetone–ether and then from ethyl acetate, m.p. 96–97°.

Pentaquine (V) **monophosphate**, obtained through the courtesy of the Squibb Institute for Medical Research, was recrystallized twice from 95% alcohol, m.p. 189–190°.

Isopentaquine (VII) **oxalate** was prepared in these laboratories.[6]

8-(5-Isopropylamino-5-methylamylamino)-6-methoxyquinoline (IX) **Diphosphate** (CN-1105).—A mixture of 5.0 g. of VIII, 3.9 g. of I and 10 ml. of buffer solution, *p*H 4.7 (20.0 g. of disodium phosphate decahydrate, 5.0 g. of crystalline citric acid and 10 ml. of water) was stirred and heated under reflux for 4.5 hours at 65–75° and then at 90–100° for 18 hours. After cooling the mixture was diluted with 10 ml. of water, made strongly basic with 2.5 *N* sodium hydroxide solution, and extracted with ether. The ether extract was washed with a phosphate–citrate buffer, *p*H 6.48, and the buffer washes were then made strongly basic with 2.5 *N* sodium hydroxide and extracted with ether. After drying the ether extract over anhydrous potassium hydroxide, a solution of 2.6 g. of 85% phosphoric acid in 10 ml. of absolute alcohol was added. The supernatant liquid was decanted from the gummy precipitate to which a small amount of absolute alcohol was added. After several days in the refrigerator the phosphate crystallized. After several recrystallizations from absolute alcohol it melted at 140–142°. It was necessary to dry the salt for several days *in vacuo* to remove all traces of solvent.

Anal. Calcd. for $C_{18}H_{35}N_3O_9P_2$: C, 42.3; H, 6.9; P, 12.5. Found: C, 42.3; H, 7.1; P, 12.7.

Buffer Solutions.—The initial concentration of alkylaminoalkyl halide (hereafter referred to merely as amino halide) varied from 0.07 to 0.13 *M* and that of I from 0.005 to 0.14 *M*. Since both the alkylation and cyclization reactions release protons to the solution, a buffer was necessary to maintain a constant *p*H. Buffers of disodium phosphate, analytical reagent grade, and citric acid, analytical grade,[22] with the disodium phosphate being at least 0.55 *M* were employed.

The most basic of the buffer solutions (Table II) had an ionic strength of 1.909 as calculated from the dissociation constants of phosphoric and citric acids at 25°. The more acidic buffers were brought to ionic strength of 1.909 at 25° by addition of sodium sulfate. A 100% reaction with the most concentrated solution used would raise the ionic strength by 0.062 due to liberation of halide ion. However, any salt effect caused by such an increase in ionic strength would be small because of the high concentration of electrolytes present.[23] Table II lists the composition and observed *p*H's of the buffers used.

TABLE II

COMPOSITION, TEMPERATURE AND *p*H OF BUFFER SOLUTIONS

T, °C.					G. reagent per 100 ml. solution		
51.0	59.0	70.1	79.7	91.8	Disodium phosphate	Citric acid	Sodium sulfate
		*p*H					
2.70	2.65	2.61	2.56	2.51	25.0719	25.6299	3.7000
3.85	3.80	3.75	3.70	3.65	17.9085	7.4600	4.4520
4.82	4.73	4.64	4.54	4.45	19.6995	4.8034	1.1620
5.56	5.48	5.40	5.33	5.24	27.7244	4.5390	0.0000

Other Materials.—Sodium hydroxide solution was freed from carbonate by the addition of a trace of barium hydroxide and standardized against potassium acid phthalate.

Silver nitrate solution was standardized against C.P. potassium bromide.

(14) G. Salomon, *Trans. Faraday Soc.*, **32**, 153, 1627 (1936); **34**, 1311 (1938); G. M. Bennett, *ibid.*, **37**, 794 (1941).

(15) G. Salomon, *Helv. Chim. Acta*, **16**, 1361 (1933); **17**, 851 (1934); **19**, 743 (1936).

(16) L. Ruzicka, G. Salomon and K. E. Meyer, *ibid.*, **20**, 109 (1937).

(17) All m.p.'s are corrected for stem exposure.

(18) Microanalyses by the Clark Microanalytical Laboratories, Urbana, Ill., or the Schwarzkopf Microanalytical Laboratory, Middle Village, L. I., N. Y.

(19) N. L. Drake, *et al.*, THIS JOURNAL, **68**, 1524 (1946).

(20) R. C. Elderfield and G. L. Krueger, *J. Org. Chem.*, **17**, 358 (1952).

(21) R. C. Elderfield, B. M. Pitt and I. Wempen, THIS JOURNAL, **72**, 1334 (1950).

(22) W. M. Clark, "The Determination of Hydrogen Ions," 3rd Ed., The Williams and Wilkins Co., Baltimore, Md., 1928, p. 214.

(23) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 129.

Apparatus.—Only calibrated weights and volumetric apparatus were used. Temperatures were measured with a thermometer calibrated against a thermometer certified by the Bureau of Standards.

The apparatus used in all rate experiments is described as follows. The reaction vessel was a 200-ml. 3-necked, round bottom flask equipped with a gas inlet tube, a reflux condenser and a ground glass stoppered orifice through which solid alkylaminoalkyl hydrohalide was added and aliquots of the reaction mixture were pipetted out at convenient intervals. A stream of nitrogen gas entered through the gas inlet and served a dual function: (a) to keep the reaction free of oxygen, and (b) to stir the solution. The nitrogen entered the system through a wash bottle which contained 500 ml. of Fieser solution.[24] The nitrogen then passed through a second bottle containing lead acetate to remove hydrogen sulfide. It was finally preheated over 14 in. of rolled copper gauze, which also removed traces of oxygen, at a temperature just below the softening point of Pyrex glass and thence through a 200-ml. flask containing 100 ml. of sodium sulfate solution of ionic strength 1.909 to the reaction vessel. It was necessary to pass the gas through the sodium sulfate solution so that it would enter the reaction vessel saturated with water. Experiments showed that, if this were not done, the volume of the reaction solution decreased throughout the course of the reaction, and the internal temperature of the reaction solution was lowered from that of the thermostat. The temperature of the oil thermostat was controlled to ±0.1° for temperatures of 70.1° and higher, to ±0.15° at 59.1°, and to ±0.2° at 51.0°.

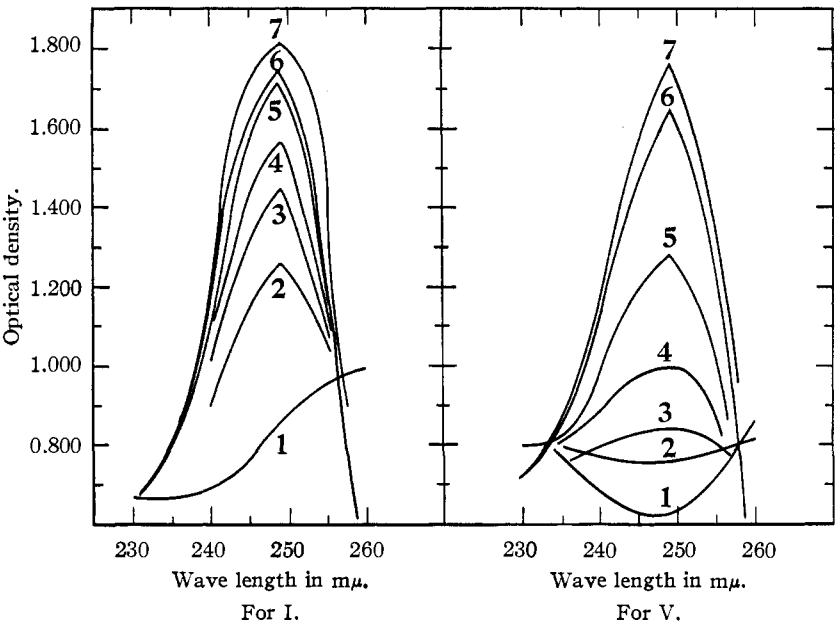

Fig. 1.—Ultraviolet absorption spectra: concn. 5.75 × 10^{-5} mole/liter in sulfuric acid of normality indicated: (1) 0.4 *N*; (2) 2.0 *N*; (3) 3.0 *N*; (4) 4.0 *N*; (5) 6.0 *N*; (6) 10.0 *N*; (7) 16.0 *N*.

All spectrophotometric measurements were made with a Beckman spectrophotometer, Model DU. The absorption cells were calibrated against a reference cell. In no case did the optical density of a standard solution in one of the calibrated cells differ by more than 0.003 density unit from the optical density of the same solution in the reference cell. As a blank in each measurement, a reference solution identical in composition to that of the measured solution except for the measured component was used in the reference cell.

The potentiometric titrations were made with a Beckman high temperature shielded glass electrode and a calomel electrode connected to a Model G Beckman *p*H meter. The glass electrode was standardized before each high temperature titration against a buffer composed of 21.008 g. of crystalline citric acid and 8.010 g. of sodium hydroxide per liter of solution. The characteristic variations of this buffer with temperature were determined.

In titrations at temperatures above 40° the temperature compensator of the *p*H meter was kept at 25° and suitable corrections based on the fact that a given change in *p*H of an isothermal solution affects the reading of the meter by an amount proportional to the absolute temperature of the solution.[25] In no case did the *p*H measurement of a standard buffer solution shift by more than 0.02 unit during the time required for titration.

The potentiometric titrations of halide ion were made with a silver–silver halide electrode[26] and a calomel electrode connected at times to a Model G Beckman *p*H meter and at times to a Fisher Titrimeter. The potential measured by two instruments at the end-point of the titration did not differ by more than 0.002 v.

Rate Measurements.—Measurements of the amount of alkylated I produced and of the increase in the concentration of halide ion in the solution provide the data necessary for the calculation of rate constants. Increase in the halide ion concentration is a measure of the total amount of amino halide that has reacted. The amount of alkylated I produced (equivalent to the amount of I reacted) subtracted from the total amount of amino halide reacted leaves the amount of amino halide cyclized.

It was found that variation of the optical density of equimolar solutions of alkylated I and I at 248–250 mμ could be obtained by controlling the acidity of such solutions (Fig. 1). This change of optical density with *p*H is believed to be due to the difference in basicities of the 8-amino groups in alkylated I and I. Irvin and Irvin[27] noted this with the drug, pamaquine, and the absorption curves published by them show the same type of variation of degree of absorption with *p*H. In very strongly acid solution, *e.g.*, 16 *N* sulfuric acid, both 8-amino groups are essentially protonated, and there is little difference between the optical densities at 248–250 mμ. In weakly acid solutions, *e.g.*, 0.4 *N* sulfuric acid or less, neither amino group is protonated to any extent, and again the optical densities at 248–250 mμ become more nearly equal as the acidity is reduced. However, in a solution of intermediate strength, 3 *N* acid, the 8-amino group of I is largely protonated, whereas that of alkylated I is not. The resulting optical densities differ by 0.6 unit.

Plots of the optical density *vs.* the mole per cent. alkylated I in mixtures of alkylated I and I are shown in Fig. 2 for pentaquine, isopentaquine and CN-1105. In all cases the optical densities were measured in 2.7 *N* sulfuric acid at 248–250 mμ and the total concentration of alkylated I and I was 5.75 × 10^{-5} mole per liter. In no case was there any deviation from the straight line relationship from zero to eighty mole per cent. of alkylated I.

All rate experiments were made in aqueous citrate–phosphate buffers of ionic strength 1.909. A solution of I in the desired buffer was placed in the reaction vessel and thermostated for from 2 to 3.5 hours. The alkylaminoalkyl halide was then added and the initial time taken. Samples for analysis (5 ml.) were pipetted out at convenient intervals. The reaction was quenched by pipetting the sample directly into cold dilute acid.

To determine the change in concentration of I, 5 ml. of the reaction solution was diluted with 0.1 *N* sulfuric acid so that the combined concentration of unreacted I and the product of the alkylation reaction was 5.75 × 10^{-4} mole

(24) L. F. Fieser, THIS JOURNAL, **46**, 2689 (1924).

(25) Details of the manner by which this correction was applied are given in ref. 1 and also in Bulletin 95-B, Beckman Instruments, Inc., South Pasadena, Cal.

(26) D. A. MacInnes and K. Parker, THIS JOURNAL, **37**, 1445 (1915); D. A. MacInnes and J. A. Beattie, *ibid.*, **42**, 1117 (1920).

(27) J. L. Irvin and E. M. Irvin, *J. Biol. Chem.*, **174**, 585 (1948).

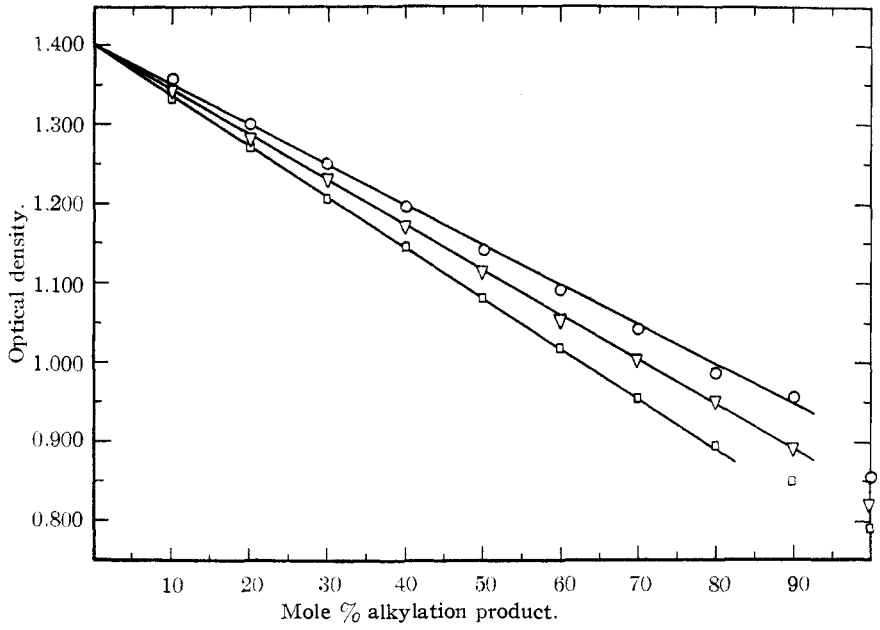

Fig. 2.—Optical density at 249 mμ *vs.* mole % of alkylation product and I; total concn. 5.75×10^{-5} moles/l.: O, I and pentaquine; ▽, I and isopentaquine; □, I and CN-1105.

per liter. A final tenfold dilution was made with 3.0 *N* sulfuric acid. From the optical density of this solution at 249 mμ the change in concentration of I was obtained from Fig. 2.

The change in concentration of the halide ion present in the solution was determined by potentiometric titration of a 5-ml. aliquot which had been pipetted directly into a solution of 5 ml. of 7.8 *N* nitric acid in 50 ml. of water. A 5-ml. aliquot of the reaction mixture was heated under reflux for one hour with excess sodium hydroxide solution and the halide ion concentration was then measured. Half of this value was taken as the halide ion concentration at zero time.

In no case did the *p*H of the buffered reaction mixture change by more than 0.03 *p*H unit during the course of a kinetic experiment.

Acid Dissociation Constants.—All measurements were made in an oil-bath at 70.1 ± 0.1°. Titrations were continuous and were done with aqueous solutions of the salts of the bases. In each 100 ml. of solution 10.0664 g. of potassium sulfate was present so that the ionic strength, exclusive of the amine salt, was 1.909. One of the bases was in the form of its hydrobromide; this was titrated directly. The others were phosphates or oxalates which could not be titrated directly.

An aqueous solution of the phosphate or oxalate (approximately 0.05 g.) was made strongly basic with sodium hydroxide and extracted with three 50-ml. portions of ethylene dichloride. The combined extracts were washed with two 25-ml. portions of water and the organic base was extracted into a known amount (excess) of standard hydrochloric acid.

The titrations were done in open beakers immersed in the thermostat and covered with an evaporating dish containing ice during the original thermostating (2.5 hours). Standard alkali was added from a 10-ml. micro-buret graduated in 0.01 ml.

In measurements up to 100% neutralization the acidity of the solution was great enough and titration rapid enough to avoid pick-up of sufficient atmospheric carbon dioxide to cause drifting of the *p*H. The concentration of sodium ions never became high enough to necessitate a correction for the glass electrode. Errors due to potassium ions are even smaller and may be neglected even at the highest *p*H readings.[28] It is believed that these titrations were performed under equilibrium conditions since no turbidity or precipitate was observed in any partially neutralized amine salt solutions.

The Effect of Atmospheric Oxygen on I.—Two samples (0.1250 g. each) of I were heated at 82.6° in 50 ml. of water and 0.5 ml. of 0.8 *N* sulfuric acid for 7.5 hours. One solution, under air, turned a deep red; the outer solution, under nitrogen, remained colorless.

Another solution of 0.2500 g. of I in 50 ml. of water and 0.15 ml. of 3 *N* sulfuric acid was heated under nitrogen as above. After dilution to a concentration of 5.75×10^{-5} mole per liter in 2.7 *N* sulfuric acid, the optical density at 249 mμ was 1.410 as compared with the theoretical value of 1.407.

Discussion[29]

In the subsequent discussion the following abbreviations will be used: [Q] is the concentration of I; [AH] is the concentration of the amino halide; *t* is time in seconds. All concentrations are in moles per liter.

From the generalized equations (1) and (2) the following relationships may be set up

$$-\mathrm{d[Q]}/\mathrm{d}t = k_1[\mathrm{Q}][\mathrm{AH}] \quad (3)$$

$$-\mathrm{d[AH]}/\mathrm{d}t = k_1[\mathrm{Q}][\mathrm{AH}] + k_2[\mathrm{AH}] \quad (4)$$

in which k_1 is the apparent bimolecular rate constant for the alkylation reaction (1), and k_2 is the apparent unimolecular rate constant for the cyclization reaction (2). Equation (4) may be written in the form

$$-\mathrm{d[AH]}/\mathrm{d}t = k'[\mathrm{AH}] \quad (5)$$

in which

$$k' = k_1[\mathrm{Q}] + k_2 \quad (6)$$

Equation (5) implies the assumption that $k_1[\mathrm{Q}]$ is much smaller than k_2 which is warranted by the curves. Values of k' were obtained from a plot of ln [AH] against time. A typical example is shown in Fig. 3. In all the experiments the plot of ln [AH] against time was a straight line at least for the major portion of the runs. In the few instances when a deviation from linearity appeared, it was always in the direction of decreasing slope.

The ratio k_1/k_2 was obtained by dividing equation (4) by equation (3) resulting in

$$\frac{\mathrm{d[AH]}/\mathrm{d}t}{\mathrm{d[Q]}/\mathrm{d}t} = 1 + \frac{k_2}{k_1[\mathrm{Q}]} \quad (7)$$

$$\mathrm{d[AH]} = \left(1 + \frac{k_2}{k_1[\mathrm{Q}]}\right)\mathrm{d[Q]} \quad (8)$$

(28) Bulletin 225, Beckman Instruments Inc., South Pasadena, Cal.

(29) In order to secure the desired information as to the optimum *p*H at which to secure maximum alkylation certain simplifying assumptions have been made in the treatment of the data. Chief of these is that the absolute rates of the two reactions are dependent on *p*H alone. As pointed out by one of the referees this is not strictly true. Neither do the data present a consistent picture where the calculations take into account possible roles played by H^+ in the systems. Apparently some presently unknown factor or factors enter into the determination of absolute rate constants. It has been suggested by the referee that possibly citrate ion may be entering into complexes with one or both of the reactants with resultant confusion in the determination of absolute rate constants. Whether this is indeed the case must await accumulation of more experimental data.

In the present treatment we shall use the term apparent rate constant, apparent energy of activation, etc., with the understanding that these values apply only to the systems under immediate investigation.

hence

$$[AH] = [Q] + (k_2/k_1) \ln [Q] + C \quad (9)$$

and

$$(k_1/k_2)([AH] - [Q]) = \ln [Q] + C' \quad (10)$$

where C and C' are constants of integration.

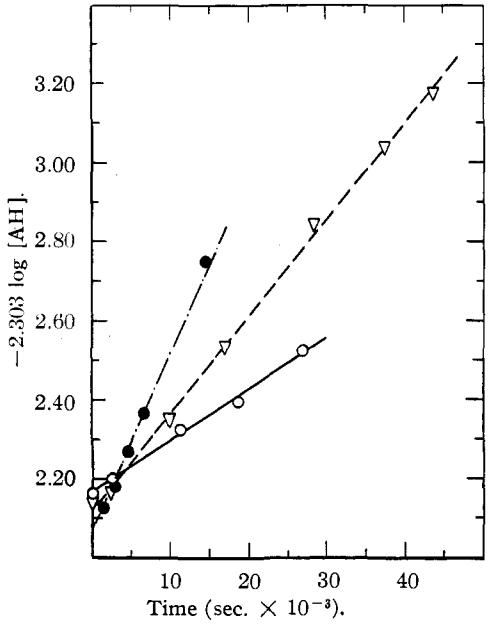

Fig. 3.—Plot of equation (5), reaction of III with I at (1) ●, 91.8° and *p*H 3.65; (2) ▽, 79.1° and *p*H 3.70; (3) ○, 70.1° and *p*H 3.75.

The value of k_1/k_2 was obtained from the slope of the plot of ln [Q] *vs.* ([AH] − [Q]). Figure 4 shows an example of these plots. Again in a few cases the slope of plots decreased after the major portion of the reaction had been completed. In every case the value of k_1/k_2 was determined from the initial straight line portion of the plots.

Finally, the values of k_1 and k_2 were calculated from k' and k_1/k_2. The value of [Q] substituted in the equation $k' = k_1[Q] + k_2$ was the initial concentration of I. The slopes of the plots of ln k_1 and ln k_2 *vs.* $1/T$ (Fig. 5) allowed evaluation of the apparent energies of activation of both the alkylation and cyclization reactions.

The apparent entropies of activation were calculated from equation (11)[30]

$$k = e\,(\mathbf{k}T/\mathbf{h})e^{-E^{exp}/RT}e^{\Delta S^*/R} \quad (11)$$

In this equation k is the experimentally found constant, **h** is Planck's constant, **k** is the Boltzmann constant, T is the absolute temperature, and R is the gas constant.

(30) S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 199.

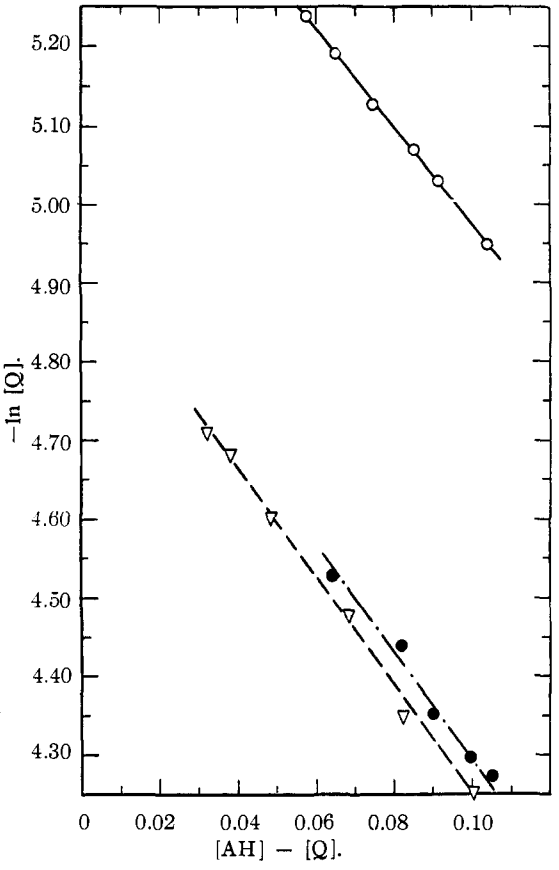

Fig. 4.—Plot of equation (10), reaction of I with III at (1) ●, 91.8° and *p*H 3.65; (2) ▽, 79.1° and *p*H 3.70; (3) ○, 70.1° and *p*H 3.75.

The cyclization of the amino halides to pyrrolidines or piperidines introduces complications in the application of any of the conventional methods for the determination of acid dissociation constants.

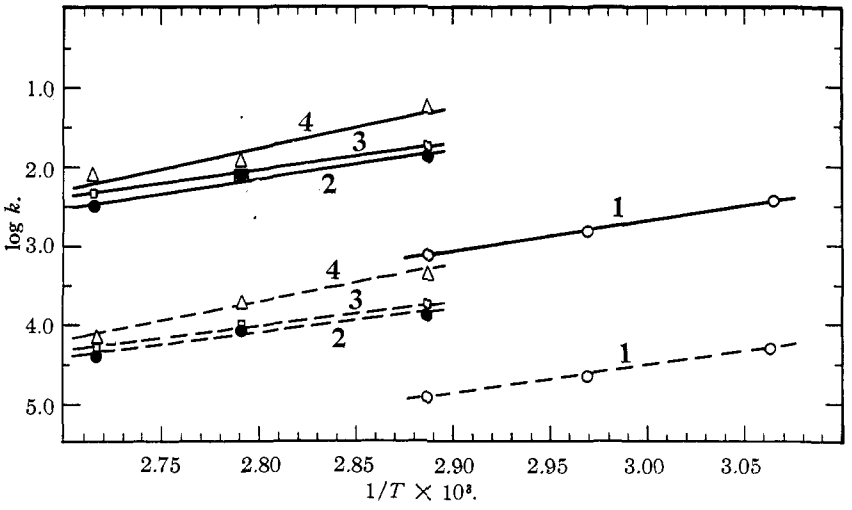

Fig. 5.—Reaction of I (solid lines) with (1) III; (2) IV; (3) VIII; and (4) VI. Cyclization reactions (dashed lines) of (1) III: (2) IV; (3) VIII; and (4) VI.

However, compounds which carry the terminal isopropylamino group on a 4 or 5 carbon atom aliphatic chain but which do not carry a halogen on the other end of the carbon chain should prob-

TABLE III

REACTION RATES FOR REACTIONS OF 5-CHLORO-1-ISOPROPYLAMINOPENTANE

Temp., °C.	pH	k_1/k_2	$k' \times 10^4$	$k_1 \times 10^4$	$k_2 \times 10^4$
70.1	2.61	2.40 ± 0.03	0.0928 ± 0.0003	0.220 ± 0	0.0911 ± 0.0001
70.1	3.75	6.11 ± .01	.131 ± .001	0.769 ± .001	.126 ± .001
70.1	4.64	8.69 ± .01	.171 ± .004	1.32 ± .003	.152 ± .004
70.1	5.40	2.78 ± .0	.170 ± .001	0.464 ± .001	.167 ± .002
79.1	2.56	2.69 ± .04	.154 ± .001	0.397 ± .009	.148 ± .001
79.1	3.70	6.94 ± .0	.238 ± .002	1.49 ± .01	.215 ± 0
79.1	4.54	8.97 ± .04	.285 ± .003	2.27 ± .04	.253 ± .003
79.1	5.33	2.79 ± .02	.307 ± .003	0.840 ± .002	.301 ± .001
91.8	2.51	2.74 ± .01	.341 ± .005	0.935 ± .018	.328 ± .005
91.8	3.65	6.94 ± 0	.528 ± 0	3.66 ± 0	.480 ± .002
91.8	4.45	8.97 ± .04	.629 ± .004	5.64 ± .01	.557 ± .004
91.8	5.24	2.82 ± .02	.674 ± .001	1.89 ± .01	.661 ± .001

TABLE IV

REACTION RATES FOR REACTIONS OF 5-BROMO-1-ISOPROPYLAMINOPENTANE

Temp., °C.	pH	k_1/k_2	$k' \times 10^4$	$k_1 \times 10^4$	$k_2 \times 10^4$
70.1	2.60	7.89 ± 0.02	1.12 ± 0.08	8.23 ± 0.03	1.06 ± 0.06
70.1	3.75	8.84 ± .04	1.63 ± .03	13.5 ± .1	1.53 ± .02
70.1	4.65	10.0 ± .03	1.92 ± .06	17.9 ± .2	1.79 ± .03
70.1	5.40	7.41 ± .03	2.20 ± .03	15.8 ± .2	2.09 ± .02
59.1	3.80	8.54 ± .03	0.765 ± .004	6.16 ± .03	0.721 ± .002
51.0	3.85	8.10 ± .04	0.418 ± .007	3.08 ± .02	0.381 ± .003

TABLE V

REACTION RATES FOR REACTIONS OF 4-BROMO-1-ISOPROPYLAMINOPENTANE

Temp., °C.	pH	k_1/k_2	$k' \times 10^4$	$k_1 \times 10^4$	$k_2 \times 10^4$
70.1	2.61	6.78 ± 0.04	2.70 ± 0.03	17.5 ± 0.3	2.57 ± 0.03
70.1	3.75	13.1 ± .2	4.76 ± .04	56.9 ± .2	4.34 ± .02
70.1	4.64	15.2 ± .3	6.06 ± .02	83.2 ± .2	5.60 ± .03
70.1	5.40	9.20 ± .05	7.38 ± .01	63.7 ± .3	6.92 ± .03
59.1	2.65	7.55 ± .04	1.30 ± .01	9.31 ± .03	1.23 ± .02
59.1	3.80	6.07 ± .03	1.98 ± .03	11.5 ± .3	1.89 ± .03
59.1	4.73	10.0 ± .5	2.61 ± .02	25.2 ± .4	2.42 ± .03
59.1	5.48	8.37 ± .02	3.30 ± .05	26.4 ± .3	3.16 ± .04
51.0	2.70	4.53 ± .02	0.484 ± .002	2.12 ± .02	0.468 ± .002
51.0	3.85	11.3 ± .6	0.704 ± .004	7.36 ± .05	0.651 ± .004
51.0	4.82	17.3 ± .4	0.980 ± .003	15.1 ± .3	0.872 ± .004
51.0	5.56	11.1 ± .1	1.09 ± .08	11.4 ± .5	1.03 ± .07

TABLE VI

REACTION RATES FOR REACTIONS OF 5-BROMO-1-ISOPROPYLAMINOHEXANE

Temp., °C.	pH	k_1/k_2	$k' \times 10^4$	$k_1 \times 10^4$	$k_2 \times 10^4$
70.1	2.60	4.07 ± 0	1.45 ± 0.02	5.74 ± 0.02	1.41 ± 0.02
70.1	3.75	9.13 ± .01	2.07 ± .05	17.8 ± .3	1.95 ± .04
70.1	4.65	10.8 ± .4	3.12 ± .01	31.3 ± .2	2.90 ± .01
70.1	5.40	4.15 ± .04	4.30 ± .02	17.6 ± .2	4.24 ± .01
59.1	3.80	8.58 ± .03	0.972 ± .006	7.68 ± .02	0.915 ± .004
51.0	3.85	8.53 ± .02	0.524 ± .001	4.19 ± .01	0.492 ± .001

ably have the same, or nearly the same, acid dissociation constants as the amino halides in question. Thus, Table I shows that the terminal aliphatic amino group of pentaquine (V) should have nearly the same basicity as the corresponding group in III and IV; that of isopentaquine (VII) should have nearly the same basicity as that of VIII. It also is apparent that the basicities of the terminal amino groups in V and VII should be approximately equal since there is no significant difference in structure about the amino groups. Also, the absolute values of the dissociation constants of the amino halides may differ to some extent from those values obtained from the drugs; however, the order of magnitude and the relative basicities should be the same.

These dissociation constants were determined from the titration curves at half neutralization in the usual manner. Activity coefficients were neglected.

Results

Curve (2) in Fig. 3 and curve (2) in Fig. 4 present typical data from which k' and the ratio k_1/k_2 were determined. From these values the values of the apparent rate constants for the alkylation of I with an amino halide and for the apparent unimolecular cyclization of the latter can be obtained.

In Tables III–VI are shown the average of two

TABLE VII

APPARENT ENERGIES AND ENTROPIES OF ACTIVATION

Alkylaminoalkyl halide	Alkylation reaction ΔE^* (kcal.)	Alkylation reaction ΔS^* (cal.)	Cyclization reaction ΔE^* (kcal.)	Cyclization reaction ΔS^* (cal.)
5-Chloro-1-isopropylaminopentane	18.5 ± 0.27	−25.6 ± 0.8	16.4 ± 0.30	−35.4 ± 0.9
5-Bromo-1-isopropylaminopentane	17.2 ± .40	−24.5 ± 1.2	14.6 ± .51	−35.7 ± 1.5
4-Bromo-1-isopropylaminopentane	22.8 ± .50	− 7.8 ± 1.5	20.2 ± .47	−17.2 ± 1.4
5-Bromo-1-isopropylaminohexane	16.7 ± .47	−24.7 ± 1.4	13.8 ± .54	−37.5 ± 1.6

reaction rate determinations under the conditions specified for the alkylation of I with the various alkylaminoalkyl halides (k_1), the average value of the cyclization of the same halides (k_2), the value of k', and the ratio k_1/k_2, which is of great use in the determination of the optimum pH condition for alkylation. Units for the rates of alkylation are liter/moles-sec., and those of cyclization are sec^{-1}.

Uncertainties.—Uncertainties in the apparent rate constants for both the alkylation (k_1) and cyclization (k_2) reactions due to uncertainties in temperature, pH, concentration of amino halide and concentration of I in all cases averaged about 4 to 5%. The extremes were 1.2 and 7.2%.

Table VII lists the values for the apparent energies of activation of the alkylation and cyclization reactions obtained from the values of the specific rate constants at pH of about 3.75 and the values of the apparent entropies of activation obtained from the apparent energies of activation and the specific rate constants at 70.1°.

The apparent first dissociation constants of 6-methoxy-8-aminoquinoline and several drugs derived from it at 70.1° and an ionic strength of 1.909 before titration are listed in Table VIII.

TABLE VIII

DISSOCIATION CONSTANTS

Amine	Concn., moles/l. × 10^3	pK_a
6-Methoxy-8-aminoquinoline	3.52	3.38 ± 0.01
Pentaquine	1.19	8.22 ± .02
Isopentaquine	1.27	8.29 ± .02
CN-1105	0.978	8.13 ± .02

The titration of pentaquine and isopentaquine measures the dissociation constant of the terminal aliphatic amino group $-CH_2NHCH(CH_3)_2$ (found in 5-chloro- and 5-bromo-1-isopropylaminopentane and 4-bromo-1-isopropylaminopentane), and that of CN-1105 measures the dissociation constant of the terminal aliphatic amino group $-CH(CH_3)-NHCH(CH_3)_2$ (found in 5-bromo-1-isopropylaminohexane).

One experimental run was made to determine if the presence of I had an effect upon the value of k_2, the apparent cyclization rate constant of an alkylaminoalkyl halide. The cyclization of III at 91.8°, pH 4.45 and ionic strength 1.909 at 25° was measured by following the increase in chloride ion in the solution. The rate of cyclization, determined from the slope of a plot of −ln concentration of III *vs.* time, was 0.555×10^{-4} $sec.^{-1}$. From Table VI, the value of the rate of cyclization of the same amino halide under the same conditions in the presence of I was shown to be $(0.557 \pm 0.004) \times 10^{-4}$ $sec.^{-1}$. Therefore, there is no obvious effect of the presence of I on the rate of cyclization.

Discussion

An important conclusion regarding the optimum conditions for the alkylation of I by an isopropylaminoalkyl halide may be deduced from the values of k_1 and the ratio k_1/k_2 given in Tables III–VI. At all temperatures k_1 is greater than k_2 and the ratio k_1/k_2 is the greatest in the pH range 4.5–4.8. Figure 6, a plot of the rates of alkylation of I with the various amino halides *vs.* pH of the reaction medium at 70.1° clearly emphasizes this fact. A similar conclusion was drawn by Elderfield, *et al.*,[6] from the values of the pK_a's of the various nitrogens in pamaquine. The most desirable pH range for this alkylation is stated to be 4.8–5.2. Although the data here presented indicate the optimum pH for the alkylation reaction, no explanation is available at present for the decrease in rates of alkylation above pH 5.

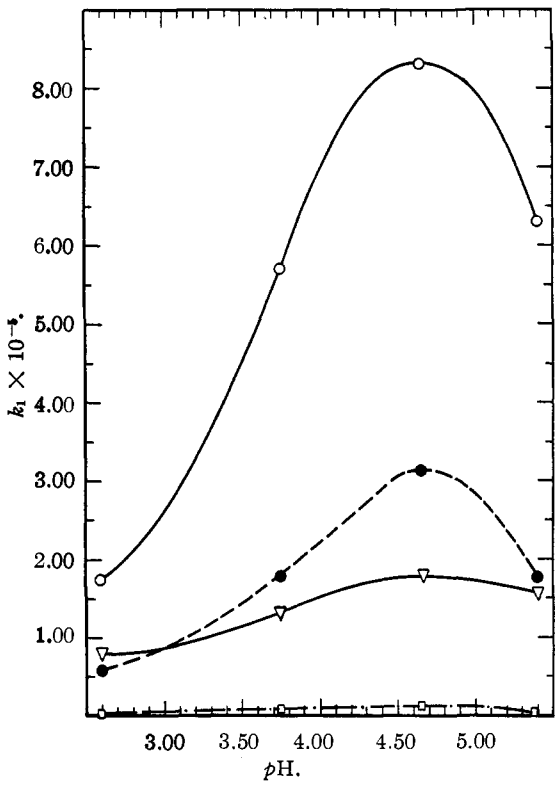

Fig. 6.—Reaction of I as a function of pH with: O, VI; ●, VIII; ▽, IV; □, III. Temp. 70.1°.

Another abnormality revealed by the present data is the apparent linear dependency of the rates of cyclization, k_2, on pH as shown in Fig. 7. A suitable explanation for this must also await accumulation of further information.

Only in the case of CN-1105 was the drug actually isolated from an alkylation reaction in this

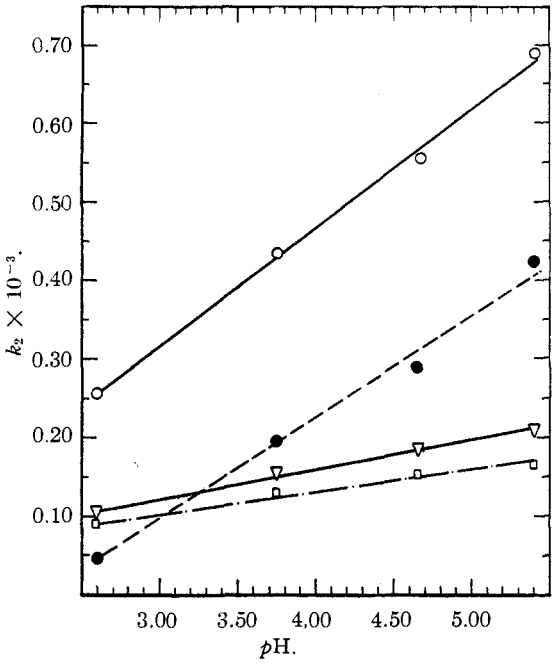

Fig. 7.—Rate of cyclization of alkylaminoalkyl halides *vs.* *p*H: ○, VI; ●, VIII; ▽, IV; □, III.

investigation. It was assumed that the other alkylations followed a similar course. An aliquot of an alkylation reaction using III was removed after 30 mole per cent. alkylation had occurred. The spectrum of this aliquot was identical with that of a known mixture of 30 mole per cent. of pentaquine and 70 mole per cent. of I. The combined concentrations of the mixture equalled that of the theoretical combined concentrations of the aliquot of the reaction solution.

The rates of alkylation by and the rates of cyclization of VI in Table V also show an inconsistency. This secondary bromide appears to react faster than any of the primary bromides studied. Ordinarily the rates of reaction of alkyl halides in bimolecular displacement reactions are MeBr > EtBr > iso-PrBr.[31] By analogy it would be expected that the amino halides with primary bromides should react faster than those carrying a secondary bromine. Table VII also shows that the apparent entropy of activation of the alkylation of I by VI is abnormally high as compared with the other apparent entropies of activation of alkylation measured under comparable conditions.

In Table IX are shown the log A terms of the Arrhenius equation computed by Freundlich and co-workers for the cyclization of chloro- and bromobutylamines and chloro- and bromoamylamines[11] together with the entropies of activation at 25° calculated from the log A terms by use of the equation $\Delta S^* = R \ln (A\mathbf{h}/\mathbf{k}t) - R$. The relative entropy changes involved in cyclization to a five- or six-membered ring accord well with similar relative changes in the apparent entropies given in Table VII.

TABLE IX

Haloamine	log A	ΔS^* (calcd.) (cal./degree)
$Cl(CH_2)_4NH_2$	12.2	−4.8
$Cl(CH_2)_5NH_2$	11.4	−8.4
$Br(CH_2)_4NH_2$	12	−5.6
$Br(CH_2)_5NH_2$	11	−10.1

One more point remains to be discussed. It has been assumed in the present investigation that the amino halides all cyclize to substituted pyrrolidine or piperidine structures and that no linear polymerization occurs. From inspection of the two reactions it is apparent that for the cyclization reaction first-order kinetics would be expected, whereas for the linear polymerization reaction the kinetics should be second order.[32] In one experiment a kinetic study of the cyclization of 5-chloro-1-isopropylaminopentane (III) in the absence of I showed that the reaction was first order through 63% reaction. Since there is no reason to assume that the reaction would not be first order if the measurements had been continued, the above assumption is clearly justified.

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(31) Work in this field has been well summarized by E. D. Hughes and C. K. Ingold, *Trans. Faraday Soc.*, **37**, 603 (1941).

(32) *Cf.* P. J. Flory, *Chem. Revs.*, **39**, 137 (1946).