[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

A Study of the Formation of Haloamines and Cyclic Amines by the Free Radical Chain Decomposition of N-Haloammonium Ions (Hofmann–Löffler Reaction)[1]

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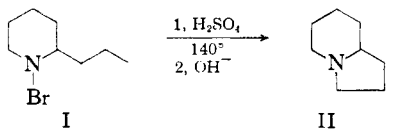
Several features of the Hofmann–Löffler reaction relevant to the mechanism have been examined, including stereochemistry, hydrogen isotope effect, initiation, inhibition, catalysis, intermediates and selectivity of hydrogen transfer. The results point conclusively to a free radical chain mechanism involving intramolecular hydrogen transfer as one of the propagation steps.

In 1883 Hofmann,[3] in the course of a study of the reactions of N-bromoamides and N-bromoamines, treated N-bromoconiine (I) with hot sulfuric acid and observed the formation of a tertiary amine which was later[4] shown to be δ-coneceine (II). Although this type of reaction was to become a general and expeditious process for the synthesis of pyrrolidines, it was not until some twenty-five years after Hofmann's work that further examples appeared in the literature in three papers by Löffler and co-workers[5–7] which include among other instances an elegant synthesis of nicotine (III).[6] Löffler[7] also found that N-bromo-N-methyl-2-butylamine failed to give any tertiary amine and concluded that four-membered rings cannot be formed from N-bromoamines. Later studies[8–17] have revealed that pyrrolidine formation is favored over six- and higher-membered rings (*e.g.*, methyloctylchloroamine is reported to cyclize to 1-methyl-2-butylpyrrolidine in good yield[12]), that secondary pyrrolidines are formed by heating N-chloro-N-alkylamides in sulfuric acid[13,15–17] and that bridged-ring structures can be synthesized as well as fused-ring and monocyclic ones (*e.g.*, Coleman's[14] cyclization of N-chloro-N-methylcycloheptylamine to tropane in about 40% yield). These contributions amply demonstrate that the N-haloamine reaction provides a tool of great power for succinct and efficient synthesis of many cyclic amines. However, the theoretical implications of these results are also extremely important since it is obvious that the formation of pyrrolidines from N-chloroamines is mechanistically a very unusual transformation.



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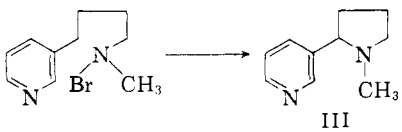

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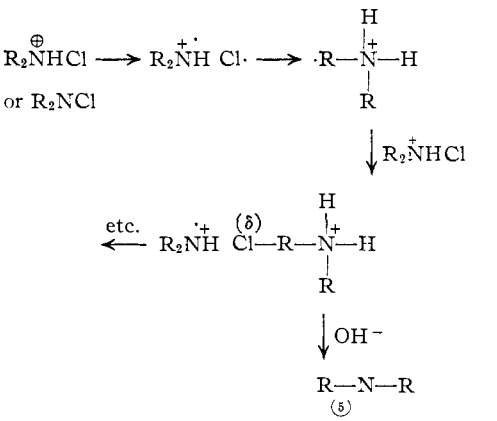
In connection with recent work on the application of the Hofmann–Löffler reaction[18] to various synthetic problems[19,20] we have sought to gain an understanding of the reaction mechanism and this paper describes the results of these experiments.

Wawzonek and co-workers[21,22] made the first study of the mechanism of the cyclization of N-haloamines. They found that a solution of N-chloro-N-methylcycloöctylamine (IV) in sulfuric acid when irradiated with ultraviolet light in the presence of chlorine or when treated with hydrogen peroxide in the dark gave up to 24% yield of N-methylgranatinine (V), much more than is formed in the absence of light and peroxide.[21] It was proposed from this evidence that the reaction proceeds by a free radical chain mechanism



(1) Taken from the Ph.D. dissertation of W. R. Hertler, University of Illinois, June, 1958.

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(3) A. W. Hofmann, *Ber.*, **16**, 558, 586 (1883).

(4) A. W. Hofmann, *ibid.*, **18**, 5, 109 (1885).

(5) K. Löffler and C. Freytag, *ibid.*, **42**, 3427 (1909).

(6) K. Löffler and S. Kober, *ibid.*, **42**, 3421 (1909).

(7) K. Löffler, *ibid.*, **43**, 2025 (1910).

(8) G. Menshikoff, *ibid.*, **69**, 1802 (1936).

(9) F. Sorm and J. Brandejs, *Coll. Czech. Chem. Comm.*, **12**, 333 (1947).

(10) E. C. Britton, U. S. Patent 1,607,605 (1926); *C. A.*, **21**, 249 (1927).

(11) G. H. Coleman and G. E. Goheen, THIS JOURNAL, **60**, 730 (1938).

(12) G. H. Coleman, G. Nichols and T. F. Martens in "Organic Syntheses, Coll. Vol. III, Jonn Wiley and Sons, Inc., New York, N. Y., 1955, p. 159.

(13) G. H. Coleman, *Proc. Iowa Acad. Sci.*, **46**, 217 (1939).

(14) G. H. Coleman and J. J. Carnes, *ibid.*, **49**, 288 (1942).

(15) G. H. Coleman, C. C. Schulze and H. A. Hoppens, *ibid.*, **47**, 264 (1940).

(16) G. H. Coleman and G. Allinger, *ibid.*, **48**, 246 (1941).

(17) G. H. Coleman, U. S. Patent 2,285,413 (1942).

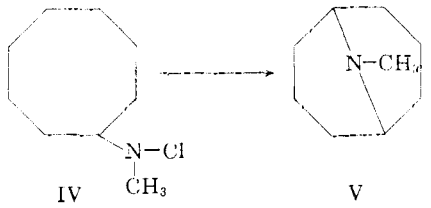
(18) Also known as the "Löffler–Freytag" reaction; see R. Lukes and M. Ferles, *Coll. Czech. Chem. Comm.*, **20**, 1227 (1955).

(19) E. J. Corey and W. R. Hertler, THIS JOURNAL, **80**, 2903 (1958).

(20) E. J. Corey and W. R. Hertler, *J. Org. Chem.*, **24**, 572 (1959).

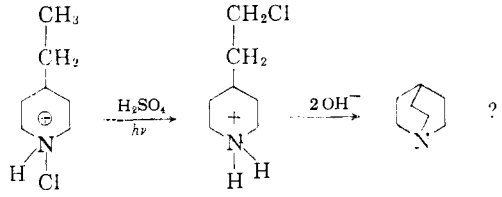
(21) S. Wawzonek and P. J. Thelen, THIS JOURNAL, **72**, 2118 (1950).

(22) S. Wawzonek, M. F. Nelson, Jr., and P. J. Thelen, *ibid.*, **73**, 2806 (1951).

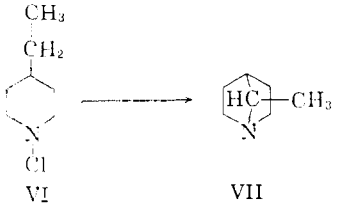


IV V

Wawzonek[22] also studied the cyclization of various N-chloro- and N-bromo-4-ethylpiperidines in sulfuric acid under the influence of ultraviolet light. The tertiary amine products were reported to be quinuclidines. It was found that when the irradiated sulfuric acid solutions were carefully neutralized and adjusted to *p*H 9 at room temperature, the *p*H slowly dropped to *ca.* 5, and this was interpreted in terms of an intermediate 4-(β-haloethyl)-piperidinium salt which cyclized under basic conditions *via* the corresponding amine to a quinuclidine.



Under conditions which are apparently similar to those employed by Wawzonek,[22] Lukes[18] obtained 7-methyl-1-azabicyclo(1,2,2)heptane (VII) as the sole tertiary amine from N-chloro-4-ethylpiperidine (VI).



VI VII

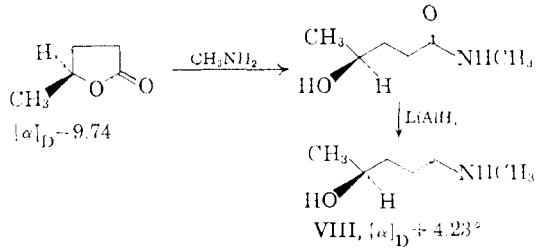
Evidence regarding the stereochemistry of the Hofmann–Löffler reaction is limited to the finding that the (−)-δ-coniceine (II) obtained from the cyclization of the N-bromo derivative of natural (+)-coniine (I) possesses an optical rotation[23] equal to that of fully resolved material.[24]

The above evidence, which was the only information pertinent to mechanism at the start of our work, was clearly not sufficient to establish the course of the Hofmann–Löffler reaction with regard to most of the important details. Consequently we undertook to characterize the reaction further in terms of: (1) stereochemistry; (2) isotope effect; (3) initiation, inhibition and acid catalysis; (4) intermediates; and (5) geometrical requirements.

Results

A. Stereochemistry.—In order to determine whether the replacement of hydrogen in the cyclization of N-haloamines proceeds with retention, inversion or equilibration of configuration, it was necessary to prepare a secondary amine with an asymmetric δ-carbon atom and since, as will be described later, cyclization to a tertiary carbon atom does not occur under normal conditions, the asymmetric center had to be a secondary carbon possessing a hydrogen and a deuterium substituent. The compound chosen for study was the N-chloro derivative of (−)-methylamylamine-4-*d*. The determination of the stereochemistry of cyclization of this substance requires data on the relative configurations of the starting amine and 1,2-dimethylpyrrolidine and on the amount of hydrogen isotope lost in the cyclization.

Valerolactone, the starting point for the synthesis of asymmetrically deuterated methylamylamine, was hydrolyzed with aqueous barium hydroxide to the barium salt of γ-hydroxyvaleric acid which was converted to the free acid and thence to the cinchonidine salt. The complete separation of the diastereomeric cinchonidine salts according to the procedure of Levene and Haller[25] proved to be a very laborious process and was not attempted. The valerolactone which was isolated after twenty-four recrystallizations of the salt from methanol–acetone consisted of 66.2% of L-(−)-isomer and 33.8% of D-(+)-isomer and this material was treated with methylamine under pressure to give N-methyl-γ-hydroxyvaleramide as a viscous liquid. Reduction of the amide with lithium aluminum hydride in tetrahydrofuran solution afforded (+)-N-methyl-4-hydroxyamylamine (VIII). At this point it was desirable to check on the optical purity of the alkanolamine VIII and at the same time to determine the magnitude of the optical rotation of the 1,2-dimethylpyrrolidine corresponding in optical purity to the alkanolamine and the valerolactone. This was done by conversion of the (+)-alkanolamine VIII to 1,2-dimethylpyrrolidine using the process



VIII, $[\alpha]_D$ +4.23°

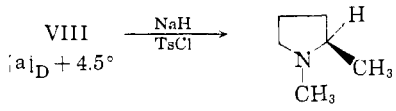
(1) treatment with sodium hydride to form the sodium alkoxide, (2) reaction of the alkoxide with *p*-toluenesulfonyl chloride to give N-methyl-4-*p*-toluenesulfonoxyamylamine and (3) cyclization of the latter with inversion of configuration at the asymmetric carbon atom to (−)-1,2-dimethylpyrrolidine which had a specific rotation of −14.5°. If it be assumed that the pyrrolidine has the same optical purity as the starting valerolactone, then the rotation for the pure L-1,2-dimethylpyrrolidine would be −44.6°. Since the rotation of L-1,2-dimethylpyrrolidine has not been reported, it was necessary to prepare a sample from the known L-2-methylpyrrolidine which was generously provided by Prof. P. Karrer. Methylation of a small amount of Karrer's L-2-methylpyrrolidine (derived from proline) gave with formic acid–formaldehyde L-1,2-dimethylpyrrolidine showing a rotation of −38.5°. This

(23) E. Lellmann, *Ber.*, **21**, 2141 (1890).

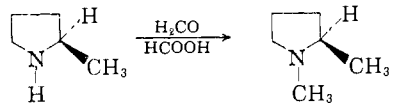
(24) N. J. Leonard and W. J. Middleton, THIS JOURNAL, **74**, 5776 (1952).

(25) P. A. Levene and H. L. Haller, *J. Biol. Chem.*, **69**, 165 (1926).

observed value is doubtless somewhat low since infrared analysis indicated the methylation product was contaminated with a small amount of extraction solvent (*n*-dodecane). Thus it can be con-

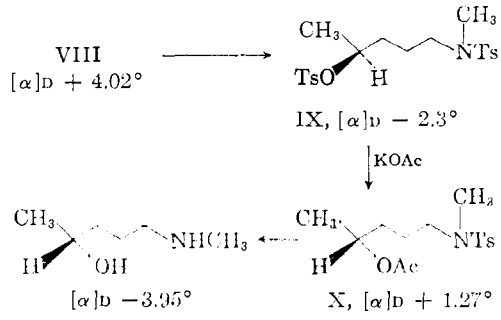


[α]D −14.5° (obsd.), [α]D −44.6° (extrap. to opt. purity based on compn. of starting valerolactone)
[α]D > |−38.5°|



cluded that there was probably no racemization in the conversion of (−)-valerolactone to (+)-N-methyl-4-hydroxyamylamine.[26]

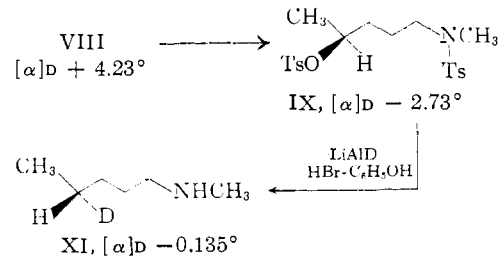
The next step in the synthesis of the deuterated amine was the conversion of (+)-N-methyl-4-hydroxyamylamine to (−)-N-methyl-N-(4-*p*-toluenesulfonoxyamyl)-*p*-toluenesulfonamide (IX) with *p*-toluenesulfonyl chloride and pyridine. The optical purity of IX was checked by reconversion to alkanolamine VIII using displacement by potassium acetate in ethanol solution to give (+)-N-methyl-N-(4-acetoxyamyl)-*p*-toluenesulfonamide (X) (with inversion of configuration at the asymmetric carbon atom), and reduction with lithium aluminum hydride in tetrahydrofuran solution. As expected, the (−)-N-methyl-4-hydroxyamylamine obtained had a specific rotation essentially equal in magnitude but opposite in direction to that of the original alkanolamine VIII.



The di-*p*-toluenesulfonyl compound IX was treated with lithium aluminum deuteride in tetrahydrofuran solution, and the resulting N-methyl-N-amyl-*p*-toluenesulfonamide-4-*d* was hydrolyzed directly with hydrobromic acid and phenol by the procedure of Snyder[27] to (−)-methylamylamine-4-*d* (XI), which had a small but observable rotation.

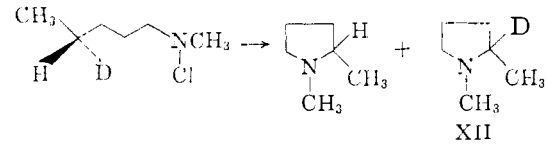
(26) (−)-Valerolactone has been correlated with (+)-β-hydroxybutyric acid[25] and (−)-β-hydroxybutyric acid has been correlated with D(−)-lactic acid [P. A. Levene and H. L. Haller, *ibid.*, **65**, 49 (1925); **67**, 329 (1926); P. Karrer and W. Klarer, *Helv. Chim. Acta*, **8**, 393 (1925)]. (−)-2-Methylpyrrolidine has been correlated with L(−)-proline [P. Karrer and K. Erhhardt, *ibid.*, **34**, 2202 (1951)]. Thus, the conversion of L-(−)-valerolactone to L-(−)-1,2-dimethylpyrrolidine, and the conversion of L-(−)-2-methylpyrrolidine to L-(−)-1,2-dimethylpyrrolidine confirm these correlations and the absolute configurational assignments which are based thereon.

(27) H. R. Snyder and R. E. Heckert, THIS JOURNAL, **74**, 2006 (1952).



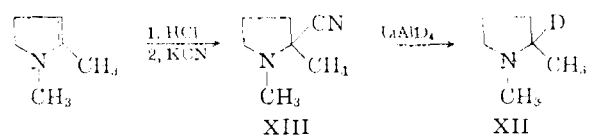
Chlorination of the deuterated amine XI followed by thermal decomposition of the N-chloro derivative in sulfuric acid at 95° by the procedure of Coleman[12] gave a 43% yield of pure 1,2-dimethylpyrrolidine which was *optically inactive* (in spite of the fact that an isotope effect was observed as described below). This is strong evidence that the decomposition of N-chloroamines in acid involves an intermediate in which Cδ is trigonal.

B. Isotope Effect.—The hydrogen isotope effect for the replacement of hydrogen attached to Cδ in the decomposition of the N-chloro derivative of methylamylamine-4-*d* XI could be determined readily by analyzing the resulting mixture of 1,2-dimethylpyrrolidine and 1,2-dimethylpyrrolidine-2-*d* (XII) for deuterium content. Combustion analysis of the mixture of deuterated and undeuterated 1,2-dimethylpyrrolidines showed the presence of 0.78 atom of deuterium per molecule which corresponds to an isotope effect (k_H/k_D) of 3.54.



Combustion analysis of the picrate of the 1,2-dimethylpyrrolidines gave exactly the same value for deuterium content—0.78 atom of deuterium per molecule.

It was desired to use an independent method of deuterium analysis as a check against the combustion analysis. For this purpose a sample of pure 1,2-dimethylpyrrolidine-2-*d* was synthesized and used as a standard for infrared analysis. Treatment of the hydrochloride of 1,2-dimethylpyrroline-2 with potassium cyanide gave 1,2-dimethyl-2-cyanopyrrolidine (XIII) which was then allowed to react with lithium aluminum deuteride to give 1,2-dimethylpyrrolidine-2-*d*.[28] The appearance of the C–D stretching absorptions in the infrared

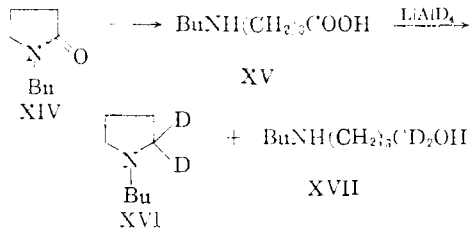


spectra of the mixed 1,2-dimethylpyrrolidines from cyclization of the deuterated amine XI and the pure 1,2-dimethylpyrrolidine-2-*d* was identical except that the intensity of the absorption in the mixture was 0.774 that of the pure monodeuterated compound. This corresponds to an isotope effect of 3.42 in good agreement with the value obtained

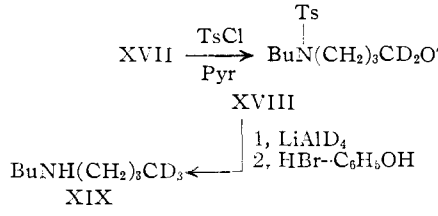
(28) See N. J. Leonard and A. S. Hay, *ibid.*, **78**, 1984 (1956); N. J. Leonard and R. R. Sauers, *ibid.*, **79**, 6210 (1957).

from combustion analysis. The maximum theoretical isotope effect at 95° is close to 4.7.[29] Thus, breaking of the C–H bond has proceeded to a rather considerable extent in the transition state.

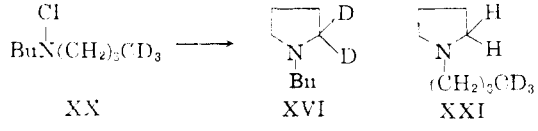
It was also desired to determine the isotope effect for cyclization to a primary carbon atom. For this purpose, the system dibutylamine-4-d_3 was chosen. The hydrogen isotope effect in cyclization of the N-chloro derivative could again be determined by deuterium analysis of the resulting N-butylpyrrolidine. The starting material for the synthesis, N-butylpyrrolidone-2 (XIV), was hydrolyzed with barium hydroxide to 4-butylaminobutyric acid (XV) which was reduced with lithium aluminum deuteride in tetrahydrofuran solution to a mixture of two products. The lower boiling product (20%) was N-butylpyrrolidine-2-d_2 (XVI) and the higher boiling product (36%) was the desired 4-butylamino-1-butanol-1-d_2 (XVII). Treatment of the alkanolamine XVII with *p*-toluenesulfonyl chloride and pyridine gave N-butyl-N-(4-*p*-toluenesulfonoxybutyl)-*p*-toluenesulfonamide-4-d_2



(XVIII) as an oil which was reduced directly with lithium aluminum deuteride. The crude reduction product was treated with hydrobromic acid and phenol[27] to give dibutylamine-4-d_3 (XIX). Chlorination of the deuterated dibutylamine and cyclization of the N-chloro derivative XX in sulfuric



acid at 90–100° gave 30% yield of a mixture of dideuterated (XVI) and trideuterated (XXI) N-butylpyrrolidine. Unfortunately, the combustion analysis of the product gave too high a value for the deuterium content—a value not significantly lower



than the value for the dibutylamine-4-d_3. The infrared spectrum of the product, however, showed C–D stretching bands corresponding to those observed in the spectra of pure XVI and XIX. Although the bands were not completely separated, it was possible, by comparing the absorption intensities with the intensities of the C–D bands of pure XVI and XIX, to arrive at an approximate isotope effect of 2.6.

(29) K. B. Wiberg, *Chem. Revs.*, **55**, 713 (1955).

C. Initiation, Inhibition and Catalysis.—Since both Wawzonek[21,22] and Lukes[18] have reported that N-haloamines can be cyclized by the action of ultraviolet light, we have carried out some rough rate studies on the reaction in order to document this effect more adequately. The disappearance of N-chloroamine was followed by adding aliquots of the sulfuric acid solution to excess iodide and titrating the liberated iodine with thiosulfate. Using this method it was ascertained that N-chlorodi-*n*-butylamine was stable in 85% sulfuric acid at 25° in the dark, but began to disappear soon after irradiation with ultraviolet light. N-Butylpyrrolidine was isolated as the sole tertiary amine product in *ca.* 63% yield. In a typical experiment in which a rather weak ultraviolet source (chromatographic column scanner: Ultra Violet Prod. Inc. quartz lamp, range 200–400 mμ) was used with a quartz reaction flask the following observations were made: no change in chloroamine titer after 43 minutes in the dark, an induction period of about 12 minutes after the start of irradiation, decomposition of one-half of the chloroamine after 32 minutes of irradiation, complete disappearance of chloroamine by 167 minutes after the start of irradiation. Sweeping the reaction mixture with nitrogen to remove oxygen eliminated the induction period almost completely. When N-chloroamine decomposition (under nitrogen) was interrupted by discontinuing irradiation, the reaction could be started immediately by irradiating again. Furthermore, we have observed generally that the light-catalyzed decomposition of N-chloroamines proceeds much more rapidly, once reaction starts, when oxygen is excluded. These observations provide a clear indication of inhibition by molecular oxygen.

It was further found that addition of catalytic amounts of potassium persulfate and ferrous ammonium sulfate or ferrous ammonium sulfate alone to a solution of dibutylchloroamine in sulfuric acid in the dark caused disappearance of the chloroamine. Workup of the reaction mixtures gave good yields of N-butylpyrrolidine. This is evidence that the decomposition of the chloroamine is a free radical chain process. Initiation by ferrous ion is probably an oxidation–reduction process according to the equation

$$Fe^{++} + R_2\overset{\oplus}{N}HCl \longrightarrow Fe^{+++} + Cl\ominus + R_2\overset{\oplus}{N}\cdot$$

It follows from this equation that for best results ferrous ion should be used only in small amounts because the chloride ion which is formed as a result of the oxidation of the ferrous ion can cause the decomposition of another chloroammonium ion according to the equation

$$Cl\ominus + R_2\overset{\oplus}{N}HCl \longrightarrow R_2NH + Cl_2$$

In contrast to the behavior of N-chlorodi-*n*-butylamine, N-chlorodiethylamine was decomposed far more slowly by irradiation in 85% sulfuric acid solution. Moreover, it was discovered that diethylchloroamine is a strong inhibitor of the decomposition of dibutylchloroamine. Irradiation of dibutylchloroamine together with an equimolar amount of diethylchloroamine in sulfuric acid increased the half-life of the former more than tenfold.

Wawzonek[21] has proposed that the reactive species in the Hofmann–Löffler reaction is a protonated chloroamine (a chloroammonium ion) and Coleman[13] has isolated a salt of this type from dibutylchloroamine–sulfuric acid. In order to ascertain the importance of chloroammonium ions in the reaction under normal conditions, the irradiation of dibutylchloroamine in media of varying acidity was investigated. Acetic acid was chosen as the solvent in order to minimize solvolysis of the chloroamine and the acidity was varied by adjusting the concentration of added sulfuric acid. It should be noted that dialkylchloroamines are weak bases ($K_B \cong 10^{-13}$ in water)[30] which, although preponderant in acetic acid solution, are almost completely converted to conjugate acid in 1.0 *M* sulfuric acid–acetic acid. The results of a brief study are presented in Table I which show the catalytic action of strong acid.

TABLE I

ULTRAVIOLET-CATALYZED DECOMPOSITION OF DIBUTYLCHLOROAMINE IN ACETIC ACID (OXYGEN EXCLUDED)–SULFURIC ACID

Concn. of dibutylchloroamine, *M*	Concn. of H_2SO_4, *N*	Half-life, min.	Yield of N-butypyrrolidine, %
0.255	0	2910	0
.260	1	62	42
.255	2	52	69
.245	5	47	80

In acetic acid alone decomposition was extremely slow; no N-butylpyrrolidine could be isolated, the only basic product being dibutylamine (23%). Wright[31] has reported that N-butylpyrrolidine is not formed when N-chlorodi-*n*-butylamine is subjected to decomposition at 90° in acetic acid solution, a similar result. The data in Table I show clearly that strong acid increases the rate of decomposition of chloroamine and also the yield of pyrrolidine. The catalytic influence of acid is probably not due to its effect on the initiation step since the free chloroamine absorbs ultraviolet light (λ_{max} 263 mμ, ϵ_{max} 300)[32] of sufficient energy to cause dissociation whereas the conjugate acid shows no appreciable ultraviolet absorption above 225 mμ. Indeed, it is likely that under the conditions used in our experiments with ultraviolet irradiation, the *free* chloroamine is responsible for most of the initiation and, hence, that the initiation rate has been decreased. Acid catalysis must therefore involve acceleration of the propagation process and/or retardation of chain termination.

D. Intermediates.—The evidence thus far presented points to a free radical chain mechanism for the decomposition of chloroamines in strongly acidic solution and to the possible intermediacy of a δ-chloroamine salt as postulated by Wawzonek.[21] In order to show conclusively that δ-chloroamines are the products of decomposition of N-chloroamines, a sulfuric acid solution of dibutylchloroamine was irradiated and then treated with silver sulfate. Practically no silver chloride precipitated. After the solution was made basic, however, an almost quantitative yield (99%) of silver chloride could be obtained. This proves that there is no chloride ion present in the acidic solution, but that it appears only after basification. This can be explained only by assuming that the chlorine is bound to carbon and, since a pyrrolidine ring is formed subsequently the chlorine must specifically be attached to the δ-carbon. When the acidic solution is made basic, the δ-chloroamine cyclizes to give cyclic amine and chloride ion. Similar but less quantitative results were obtained in the case of thermal decomposition of dibutylchloroamine in sulfuric acid (see Experimental).

δ-Hydroxyamine was eliminated from consideration as an intermediate by heating N-methyl-4-hydroxyamylamine in sulfuric acid, treating with base, and attempting to isolate 1,2-dimethylpyrrolidine. No 1,2-dimethylpyrrolidine could be isolated.

Finally, 4-chlorodibutylamine has recently been isolated from the decomposition of dibutylchloroamine in sulfuric acid.[33]

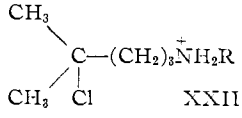
E. Selectivity of Hydrogen Transfer.—The formation of a δ-chloro secondary amine from an N-chloro secondary amine by a free radical route clearly must be interpreted in terms of intramolecular hydrogen transfer. Mechanisms involving intermolecular hydrogen transfer are unacceptable since they provide no basis for and are inconsistent with the predominance of δ-position attack, *e.g.*, in the reaction of N-chloromethyloctylamine.[12] In order to obtain some evidence regarding the structural and geometrical factors which affect the intramolecular rearrangement of hydrogen, a number of different N-chloroamines have been examined in the Hofmann–Löffler reaction. The systems were chosen specifically to obtain data on the following points: (1) relative migration tendencies of primary (methyl), secondary (methylene) and tertiary (methine) hydrogens; (2) relative rates of 1,5- and 1,6-hydrogen rearrangement (leading to pyrrolidine and piperidine, respectively); and (3) facility of hydrogen rearrangement in cyclic systems of restricted geometry.

Radicals which are able to abstract hydrogen atoms from carbon generally show a preference for hydrogen in the order tertiary > secondary > primary, although the magnitude of this preference varies considerably with the abstracting species.[34] Because of this fact, but even more importantly because $-\overset{|}{\underset{|}{N}}\cdot^{+}$ and $-\dot{\underset{\cdot\cdot}{N}}-$ are unusual radicals, it seemed imperative to study this point in the Hofmann–Löffler reaction. In order to study primary *vs.* secondary hydrogen migration in the simplest system the free radical decomposition of N-chlorobutylamylamine was investigated. Attack by the nitrogen radical on the δ-methyl group would lead subsequently to 1-*n*-amylpyrrolidine whereas attack on the δ-methylene group would result in formation of 1-*n*-butyl-2-methylpyrrolidine. Remarkably, only the latter compound appeared to be formed in the

(30) I. Weil and J. C. Morris, THIS JOURNAL, **71**, 3123 (1949).
(31) G. F. Wright, *ibid.*, **70**, 1958 (1948).
(32) W. S. Metcalf, *J. Chem. Soc.*, 148 (1942).
(33) S. Wawzonek and T. P. Culbertsou, THIS JOURNAL, **81**, 3367 (1959).
(34) See for example C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, Chapter 8.

Hofmann–Löffler cyclization since the reaction product was indistinguishable from authentic N-*n*-butyl-2-methylpyrrolidine (kindly provided by Prof. R. Adams) with respect to boiling point, index of refraction, quantitative infrared spectrum and melting point (and mixture melting point) of the picrate derivative. Thus, radical attack in this case is extremely selective in favor of secondary over primary hydrogen.

In order to determine the selectivity of radical attack in an instance where there is a choice of abstracting a tertiary or a primary δ-hydrogen and in a case involving competition between tertiary and secondary δ-hydrogen, the N-chloro derivatives of *n*-butylisohexylamine and *n*-amylisohexylamine were prepared and subjected to the usual Hofmann–Löffler conditions. No pyrrolidine could be isolated in either case and, at most, only traces of tertiary amine were produced. It was shown by gas chromatography of the crude amine fraction that no N-isohexylpyrrolidine was formed. The disappearance of N-chloroamine in these cases was, nonetheless, extremely rapid and was accompanied by evolution of hydrogen chloride. It appears that there is a high selectivity for the tertiary hydrogen in both of these cases, but that the intermediate tertiary chloro compound XXII is rapidly solvolyzed in strong sulfuric acid to give products which do not lead to tertiary amine on basification. Indeed, it was found that when *t*-butyl chloride was shaken with 85% sulfuric acid, hydrogen chloride was liberated.



XXII

Information regarding the relative ease of 1,5- and 1,6-hydrogen migration from methylene groups was obtained by a quantitative study of products from the Hofmann–Löffler reaction of N-chloromethyl-*n*-hexylamine. Ultraviolet-catalyzed decomposition of the chloroamine at 0° followed by basification led to a mixture consisting of 89.5 ± 1% of 1-methyl-2-ethylpyrrolidine and 10.5 ± 1% of 1,2-dimethylpiperidine as determined by gas chromatography. Thus, it appears that, although five-membered ring formation (1,5-hydrogen shift) is intrinsically favored, the extent of formation of six-membered rings can be appreciable. In cases such as the decomposition of N-chloromethyl-*n*-amylamine the production of pyrrolidine to the exclusion of piperidine is due to two large and reinforcing factors: the intrinsic preference for secondary over primary hydrogen abstraction and the intrinsic preference for 1,5-hydrogen migration.

Lastly, to evaluate further the geometrical requirements in the intramolecular rearrangement of hydrogen we have investigated the Hofmann–Löffler reaction in a few cases which appear to be extreme with respect to the restriction of the angle Cδ–H–N during hydrogen migration. Our data together with pertinent findings from previous studies are summarized in Table II. Under identical reaction conditions the light-catalyzed decomposition of methylcyclohexylchloroamine and N-chloroazacycloheptane proceeded far more slowly than that of dibutylchloroamine, as is apparent from the half-lives listed in the table. The slowness of reaction in these cases and also the low yields of tertiary amine indicate that the geometry which prevails is relatively unfavorable for rearrangement.

TABLE II

Compound	Tertiary amine product	$t_{1/2}$, min.	Yield, %
N-Chlorodi-*n*-butylamine	N-Butylpyrrolidine	10	*ca.* 90[a]
N-Chloro-N-methylcyclooctylamine	N-Methylgranatanine	..	24[21]
N-Chloro-N-methylcycloheptylamine	Tropane	..	42[14]
N-Chloro-4-ethylpiperidine	Quinuclidine	..	21[22]
N-Chloro-4-ethylpiperidine	7-Methyl-1-azabicyclo-(1,2,2)heptane	..	10[18]
N-Chloromethylcyclohexylamine	1,4-Methyliminocyclohexane	579	11[a]
N-Chloroazacycloheptane	?	2140	*ca.* 3[a]

[a] Present work.

Discussion

The experimental results cited above clearly support the Wawzonek mechanism[21] for the Hofmann–Löffler reaction, at least with regard to gross features. The free radical chain character of the reaction is indicated by the effectiveness of ultraviolet light, ferrous ion or ferrous ion–persulfate as initiators and of oxygen as an inhibitor. The stereochemical results point to the intermediacy of a carbon free radical and the identification of δ-chloroammonium ions as stable intermediates describes the fate of the carbon radical. Furthermore, as mentioned above, the course of the reaction as observed in the many cases studied argues strongly for intramolecular hydrogen transfer from carbon to nitrogen.

In addition to the gross mechanism there are three aspects of the conversion of N-chloroamines to pyrrolidines which deserve attention here: (1) the influence of acids, (2) selectivity of attack by the nitrogen radical on a δ-hydrogen, and (3) the influence of alkyl substituents on the δ-carbon on hydrogen abstraction. Our data on acid catalysis provide evidence that such catalysis results because acid decreases the rate of termination of the radical chain reaction and/or because of an acceleration of the propagation steps. Although further conclusions are not derivable from the available data and although the presence of strong acid may be beneficial with respect to *both* termination and propagation, it seems inescapable that strong acid should greatly inhibit chain termination. Interaction of two protonated, positively charged nitrogen radicals either by coupling or atom transfer would be far slower than for neutral species, especially since the cationic radicals are highly solvated. Electrostatic repulsions clearly would be of much less importance in the propagation part of the Wawzonek mechanism with the over-all result that termination should be relatively disfavored. It would also seem probable that even if unprotonated N-chloroamine participates in the propagation step by reaction with a carbon radical, the resulting divalent nitrogen radical would undergo rapid protonation in the presence of strong acid to produce an aminium radical (). Consequently, it seems reasonable to

assume that essentially all of the intramolecular hydrogen transfers take place from carbon to an aminium radical. Whether the aminium radical is especially effective in removing hydrogen from carbon (relative to a neutral nitrogen radical) also must remain unanswered for the present; however, this is not an unlikely possibility.

With regard to the apparent propensity of attack by an aminium radical on a δ-hydrogen, it would appear that there are two controlling factors, first the tendency of hydrogen transfer to be linear, *i.e.*, for the $-\overset{\oplus}{N}-H-C\delta$ angle to be *ca.* 180°, and secondly the minimization of angle strain and steric repulsions involving non-bonded atoms in the transition state for rearrangement. The linearity factor has long been recognized for the neutral H_3 complex[35] and doubtless also operates in radical displacement on hydrogen.[36] This factor apparently serves to prevent 1,3- and 1,4-hydrogen migration. In addition, the slowness and inefficiency of the Hofmann–Löffler reaction with cyclic chloroamines which do not permit a linear intramolecular hydrogen transfer, *e.g.*, N-chloromethylcyclohexylamine and N-chloroazacycloheptane (Table II), provides a further indication of this effect. The N–H–C angle for hydrogen shifts of higher order, *i.e.*, 1,5-, 1,6,1,7-, etc., can, however, assume a value close to 180° in acyclic systems. The absence of observable 1,7- 1,8- and higher order shifting is doubtless due to the unfavorable free-energy change associated with the formation of the corresponding eight- and higher-membered cyclic transition states. From the data cited in the previous section on the cyclization of N-chloromethyl-*n*-hexylamine, it would appear that the energetics for 1,5-shifting are considerably, but not overwhelmingly, more favorable than for 1,6- shifting: $\Delta F^{\ddagger}(1,6) - \Delta F^{\ddagger}(1,5) \cong 1.3$ kcal./mole. The greater facility of 1,5-shifting may be due to the fact that the transition state can adopt a cyclohexane-like, chair-formed conformation which is more favorable than the homologous seven-membered cyclic structure for 1,6-shifting. A study of the effect of temperature on the relative amounts of 1,5- and 1,6- shifting in the case of N-chloromethyl-*n*-hexylamine is planned and should provide interesting information regarding the importance of entropy and enthalpy factors.

One of the most striking results in the present work is the high degree of selectivity of aminium radicals in the transference of primary, secondary and tertiary hydrogen from carbon. As is clear from the discussion in section E above and the corresponding data in the Experimental section, the abstraction of a primary hydrogen from carbon was not measureably competitive with the abstraction of a secondary hydrogen, and similarly removal of tertiary hydrogen completely dominates removal of secondary hydrogen. This is another interesting feature of the Hofmann–Löffler reaction which warrants further investigation. It is not unreasonable that the observed selectivity, which is reminiscent of selectivity in carbonium ion formation, may be associated with the positive charge of the aminium radical since the activated complex for hydrogen transfer from carbon to nitrogen may involve the development of considerable positive charge on the former.

(35) (a) F. London, "Probleme der modernen Physik," Sommerfeld Festschrift, 1928; (b) see C. A. Coulson, "Valence," Oxford University Press, London, p. 176.

(36) See D. J. Wilson and H. S. Johnston, THIS JOURNAL, **79**, 29 (1957).

Experimental[37]

L(−)-Valerolactone.—Valerolactone was partially resolved through the cinchonidine salt of γ-hydroxyvaleric acid according to the method of Levene and Haller.[25] The valerolactone had $[\alpha]^{27}D$ −9.74° for the pure liquid and $[\alpha]^{27}D$ −9.2° (*c* 8) in chloroform. Comparison of these rotations with the best values obtained by Levene indicates that the valerolactone consists of 66.2% (−)-isomer and 33.8% (+)-isomer.

N-Methyl-4-hydroxyvaleramide.—(−)-Valerolactone ($[\alpha]D$ −9.74°, 26 g., 0.26 mole) was divided into two parts and sealed in two tubes with excess liquid methylamine under nitrogen. After standing 7 days at room temperature the tubes were opened, and the methylamine was evaporated. The residue was dissolved in chloroform and concentrated under reduced pressure to remove the last traces of methylamine. The viscous N-methyl-4-hydroxyvaleramide (34 g., 100%) failed to crystallize and was not purified further. The infrared spectrum of this oil showed an amide C=O stretching band at 1650 cm.$^{-1}$ and a broad OH and NH stretching band at 3280 cm.$^{-1}$ (smear).

(+)-N-Methyl-4-hydroxyamylamine (VIII).—The crude N-methyl-4-hydroxyvaleramide (34 g., 0.34 mole) was dissolved in a small amount of tetrahydrofuran and added dropwise to a stirred slurry of 13.5 g. (0.355 mole) of lithium aluminum hydride in 150 ml. of tetrahydrofuran. The mixture was stirred and heated at reflux for 9 hours and then stored for 12 hours. A slight excess of water was added with stirring, and the precipitate was removed by filtration. The combined filtrate and washings was dried first over potassium hydroxide pellets, then over magnesium sulfate. Distillation through a 25-cm. Holzmann column gave 15.4 g. (39%) of N-methyl-4-hydroxyamylamine, b.p. 97–98° (8 mm.), $n^{25}D$ 1.4460, $[\alpha]^{22}D$ +4.23° (*c* 10, ethanol).

Anal. Calcd. for $C_6H_{15}NO$: C, 61.49; H, 12.90; N, 11.95. Found: C, 61.31; H, 12.70; N, 11.73.

(−)-1,2-Dimethylpyrrolidine from (+)-N-Methyl-4-hydroxyamylamine.—(+)-N-Methyl-4-hydroxyamylamine ($[\alpha]D$ + 4.5°, 3.72 g., 0.0317 mole) was dissolved in 30 ml. of dry ether, and 1.36 g. (0.057 mole) of sodium hydride was added in one portion. The mixture was stored with occasional stirring for 20 hours, then after cooling in a Dry Ice–isopropyl alcohol-bath 6 g. (0.032 mole) of *p*-toluenesulfonyl chloride was added portionwise with stirring. After two hours the reaction was allowed to warm to room temperature, 0.76 g. (0.032 mole) of sodium hydride was added, and the mixture was stirred at room temperature for 12 hours. After addition of ethanol to destroy the excess sodium hydride, the mixture was steam distilled and the distillate was collected in dilute hydrochloric acid. The distillate was concentrated, basified with sodium hydroxide, and stirred with 0.5 ml. of benzene-sulfonyl chloride. This reaction mixture was steam distilled into dilute hydrochloric acid which was then concentrated, basified, and extracted with ether. After drying over barium oxide, distillation through a 25-cm. Holzmann column gave 0.335 g. (11%) of 1,2-dimethylpyrrolidine, $[\alpha]^{24}D$ −14.5° (*c* 6, 50% ethanol), $n^{29.5}D$ 1.4195.

(37) All melting points are corrected, and boiling points are uncorrected. Microanalyses were performed by Mr. Josef Nemeth and associates; infrared spectra by Mr. James Brader and Mr. Paul McMahon (in carbon tetrachloride solution unless specified otherwise); nuclear magnetic resonance spectra by Mr. Ben Shoulders; deuterium analyses by Mr. Josef Nemeth by the falling drop method. The mercury arc lamp that was used in the irradiation experiments was manufactured by the Hanovia Chem. and Mfg. Co., Newark, N. J. (type 7420, 500 watts). The weak ultraviolet source was manufactured by Ultra Violet Prod., Inc., Los Angeles, Calif. We are indebted to Dr. William Garrison for the gas chromatographic analysis of the product from N-chloromethyl-*n*-hexylamine.

L-(−)-1,2-Dimethylpyrrolidine from L-2-Methylpyrrolidine.—About 0.2 ml. of L-2-methylpyrrolidine, which was kindly supplied by Prof. P. Karrer, was heated at 100° for 16 hours with 0.7 ml. of formic acid and 0.7 ml. of 40% formaldehyde. The reaction mixture was treated with dilute hydrochloric acid and concentrated. The concentrate was made basic with sodium hydroxide and stirred with a few drops of benzenesulfonyl chloride. The product was then steam distilled into dilute hydrochloric acid, concentrated, basified, and extracted into *n*-dodecane. After drying over barium oxide, the product was distilled in a Craig column giving 0.0755 g. of L-1,2-dimethylpyrrolidine, $[\alpha]^{25}D$ −38.5° (*c* 2.5, 50% ethanol). The product was contaminated with a small amount of *n*-dodecane.

(−)-N-Methyl-N-(4-*p*-toluenesulfonoxyamyl)-*p*-toluenesulfonamide (IX).—N-Methyl-4-hydroxyamylamine ($[\alpha]D$ + 4.23°, 15 g., 0.128 mole) was added slowly to a stirred slurry of 97 g. of *p*-toluenesulfonyl chloride in 269 ml. of methylene chloride and 135 ml. of pyridine cooled below −50°. Stirring at this temperature was continued for 2.25 hours and then for 10.5 hours at +5°. A small excess of water was added with stirring to destroy excess *p*-toluenesulfonyl chloride, and the cold reaction mixture was then poured into a mixture of 400 ml. of 6 *N* hydrochloric acid and ice. The oily product was extracted with methylene chloride which was then washed with water and dried over magnesium sulfate at 5°. Removal of solvent left 47 g. of reddish oil. The oil was stored in a desiccator at 0.5 mm. for 10 hours leaving 44.8 g. (82%) of viscous N-methyl-N-(4-*p*-toluenesulfonoxyamyl)-*p*-toluenesulfonamide, $[\alpha]^{20}D$ −2.73° (*c* 10, chloroform). On one occasion crystals of the *dl*-compound precipitated from ether solution. After decolorization with charcoal and recrystallization from ether–tetrahydrofuran, the compound melted at 71–73°. The infrared spectra of the crystalline *dl*-material and the (−)-oily material were nearly identical.

Anal. Calcd. for $C_{20}H_{27}NS_2O_5$: C, 56.44; H, 6.39; N, 3.28. Found: C, 56.82; H, 6.68; N, 3.24.

(+)-N-Methyl-N-(4-acetoxyamyl)-*p*-toluenesulfonamide (X).—Potassium acetate (2.4 g.), 4.7 g. (0.011 mole) of N-methyl-N-(4-*p*-toluenesulfonoxyamyl)-*p*-toluenesulfonamide ($[\alpha]D$ −2.3°) and 20 ml. of absolute ethanol were refluxed for 17 hours. The mixture was poured into water and extracted with ether–methylene chloride. After drying over magnesium sulfate the solvent was removed leaving 1.7 g. of oily N-methyl-N-(4-acetoxyamyl)-*p*-toluenesulfonamide, $[\alpha]^{22}D$ +1.27° (*c* 5, chloroform). The infrared spectrum of this compound showed an acetate C=O stretching band at 1735 cm.$^{-1}$ and practically no OH stretching band (smear).

(−)-N-Methyl-4-hydroxyamylamine.—N-Methyl-N-(4-acetoxyamyl)-*p*-toluenesulfonamide ($[\alpha]D$ + 1.27°, 1.7 g.) was dissolved in 25 ml. of tetrahydrofuran, and 2.5 g. of lithium aluminum hydride was added. The mixture was refluxed for 6 days and then hydrolyzed with water. After removal of solids, the filtrate was dried over potassium hydroxide and then over magnesium sulfate. Removal of solvent and distillation at 22 mm. gave 0.172 g. (13.4% from the *p*-toluenesulfonoxy-*p*-toluene-sulfonamide) of N-methyl-4-hydroxyamylamine, $[\alpha]^{20}D$ −3.95° (*c* 1.5, ethanol), $n^{20}D$ 1.4393. The infrared spectrum of this compound is similar to that of known N-methyl-4-hydroxyamylamine.

(−)-Methylamylamine-4-*d* (XI).—N-Methyl-N-(4-*p*-toluenesulfonoxyamyl)-*p*-toluenesulfonamide ($[\alpha]D$ −2.73°, 44.8 g., 0.105 mole) was dissolved in 200 ml. of dry tetrahydrofuran and added to a slurry of 4.06 g. (0.097 mole) of lithium aluminum deuteride in 50 ml. of tetrahydrofuran. After 2.5 days an additional 161 mg. of deuteride was added, and the reaction mixture was heated to reflux. After 6 days an additional 2.1 g. of deuteride was added and the reactants were heated at reflux for 168 hours. After addition of a small excess of water the solids were filtered off, and dry hydrogen chloride was passed into the filtrate. Only a trace of amine hydrochloride formed. The solvent was removed under reduced pressure, and the residue was refluxed for 24 hours with 200 ml. of 48% hydrobromic acid and 30 g. of phenol. The reaction mixture was diluted, washed with ether, basified, and extracted with pentane. The pentane solution was extracted with 10% hydrochloric acid which was then concentrated, basified, and extracted with a small amount of pentane. After drying over potassium hydroxide, the solution was distilled from calcium hydride giving 7.79 g. (73%) of methylamylamine-4-*d*, $n^{25}D$ 1.4068, $\alpha^{20}D$ −0.135 ± 0.03° (1 dm.). The infrared spectrum of this compound shows a single C–D stretching band at 2160 cm.$^{-1}$ and is otherwise similar to that of known methylamylamine.

Anal. Calcd. for $C_6H_{14}DN$: C, 70.52; H, 14.77; N, 13.71; D, 6.66 at. %. Found: C, 70.16; H, 14.88; N, 13.51; D, 7.10, 7.32, 7.27 at. %.

Cyclization of (−)-Methylamylamine-4-*d*.—Methylamylamine-4-*d* ($[\alpha]D$ −0.135°, 7.1 g., 0.0695 mole) was chlorinated and cyclized by the procedure of Coleman.[12] The reaction temperature was maintained at about 95°. The final extraction of the product was carried out using pentane rather than ether since the latter solvent is difficult to separate completely from 1,2-dimethylpyrrolidine. Distillation of the product through a 25-cm. Holzmann column gave 2.97 g. (43%) of 1,2-dimethylpyrrolidine, b.p. 95–97°, $n^{28}D$ 1.4195, $[\alpha]^{26}D$ 0.00° (*c* 20, 50% ethanol).

Anal. Calcd. for $C_6H_{13}N$: C, 72.66; H, 13.21; N, 14.13. Calcd. for $C_{16}H_{12}DN$: C, 71.94; H, 13.08; N, 13.99; D, 7.69 at. %. Found: C, 72.01; H, 13.20; N, 13.78; D, 6.00, 5.98 at. % (0.78 at. D).

Picrate, m.p. 234–235° d., mixed m.p. with 1,2-dimethylpyrrolidine picrate 234–235° dec. (lit.[7] 233.5°).

Anal. Calcd. for $C_{12}H_{16}N_4O_7$: C, 43.90; H, 4.91; N, 17.07. Calcd. for $C_{12}H_{15}DN_4O_7$: C, 43.77; H, 5.20; N, 17.02; D, 6.25 at. %. Found: C, 44.00; H, 4.92; N, 16.88; D, 4.88 at. % (0.78 at. D).

The infrared spectrum of the amine showed a C–D stretching band with a maximum at 2040 cm.$^{-1}$ and shoulders at 2005, 2075 and 2140 cm.$^{-1}$ The C–D band was identical in appearance to the C–D band of 1,2-dimethylpyrrolidine-2-*d* (prepared below), and its peak height was 0.774 that of the latter. The isotope effect, k_H/k_D calculated from the microanalytical data of the 1,2-dimethylpyrrolidine and its picrate is equal to 0.78/1-0.78, or 3.54 ± 0.5. The isotope effect calculated from the peak height of the C–D stretching band of the infrared spectrum is equal to 0.774/1-0.774, or 3.42 ± 0.5

1,2-Dimethyl-2-cyanopyrrolidine (XIII).—1,2-Dimethylpyrroline-2 (30 g., 0.31 mole)[38] was dissolved in 150 ml. of water and exactly neutralized with 3 *N* hydrochloric acid (phenolphthalein). This solution was added to a solution of 20.8 g. (0.32 mole) of potassium cyanide in 100 ml. of water. The product was extracted into ether and dried over sodium sulfate. Distillation through a 30-cm. Vigreux column gave 30.3 g. (79%) of 1,2-dimethyl-2-cyanopyrrolidine, b.p. 83–84° (36 mm.), $n^{22.5}D$ 1.4447. The nitrile turned yellow on long exposure to air.

Anal. Calcd. for $C_7H_{12}N_2$: C, 67.69; H, 9.74; N, 22.56. Found: C, 68.00; H, 9.68; N, 22.33.

The picrate, m.p. 154.5–156.5° (yellow needles from benzene–ethanol), failed to give a good analysis due to elimination of some hydrogen cyanide.

1,2-Dimethylpyrrolidine-2-*d* (XII).—A solution of 5 g. (0.04 mole) of 1,2-dimethyl-2-cyanopyrrolidine in 20 ml. of dry ether was added dropwise with stirring to a slurry of 0.5032 g. (0.012 mole) of lithium aluminum deuteride in 150 ml. of dry ether.[28] The reaction mixture was stirred for 4 hours and then refluxed for 13 hours. A small amount of water was added, the solids removed, and the filtrate extracted with 200 ml. of 10% hydrochloric acid. The acid solution was concentrated, basified, and extracted with pentane. After drying over potassium hydroxide the product was distilled from calcium hydride through a 25-cm. Holzmann column. 1,2-Dimethylpyrrolidine-2-*d* (2.88 g., 72%) was obtained with b.p. 94–95°, $n^{25}D$ 1.4203. The infrared spectrum of this compound shows a C–D stretching band at 2040 cm.$^{-1}$ and shoulders at 2000, 2080 and 2145 cm.$^{-1}$.

Anal. Calcd. for $C_6H_{12}DN$: C, 71.94; H, 13.08; D, 7.80 at. %. Found: C, 72.02; H, 13.46; D, 7.91 at. % (1.03 at. D).

N-Butylpyrrolidone-2 (XIV).—Pyrrolidone (383 g., 4.5 moles) was added dropwise to a stirred refluxing mixture of 103.5 g. (4.5 moles) of molten sodium in 1.5 liters of toluene under an atmosphere of dry nitrogen. The reaction mixture was stirred and refluxed overnight and then cooled to room temperature. Butyl bromide (844.3 g., 6.15 moles) was added dropwise, and the resulting slurry was stirred for 24 hours. The solid material was filtered off, and the filtrate

(38) L. C. Craig, THIS JOURNAL, **55**, 295 (1933).

was distilled through a 30-cm. Vigreux column under reduced pressure to give 544 g. (85%) of N-butylpyrrolidone-2, b.p. 127–131° (17–21 mm.), $n^{25}D$ 1.4634 (lit.[39] b.p. 121° (16 mm.), $n^{20}D$ 1.4650).

4-Butylaminobutyric Acid (XV).—N-Butylpyrrolidone-2 (79 g., 0.56 mole) was refluxed with 315 g. (1 mole) of barium hydroxide hydrate in one liter of water for 24 hours. The barium was precipitated with carbon dioxide, the last traces being removed by addition of a few drops of 10% sulfuric acid. Filtration followed by concentration of the filtrate gave 46.7 g. (52%) of crude white amino acid. Repeated crystallization from methanol–ether gave 26 g. of 4-butylaminobutyric acid, m.p. 145–146°.

Anal. Calcd. for $C_8H_{17}O_2N$: C, 60.34; H, 10.76; N, 8.80. Found: C, 60.39; H, 10.81; N, 8.52.

4-Butylamino-1-butanol-1-d_2 (XVII) and N-Butylpyrrolidine-2-d_2 (XVI).—To a slurry of 6.7 g. of lithium aluminum deuteride in 70 ml. of dry tetrahydrofuran was added portionwise 15 g. (0.094 mole) of 4-butylaminobutyric acid with vigorous agitation by means of a Vibromixer. After 48 hours of mixing and refluxing water was added, and the precipitate was extracted thoroughly with moist ether. The combined extracts were dried over potassium hydroxide and then over magnesium sulfate. The products were distilled through a Holzmann column giving 2.39 g. (20%) of N-butylpyrrolidine-2-d_2, b.p. 53–54° (15 mm.), $n^{25}D$ 1.4368 (lit.[10] $n^{27}D$ 1.437), and 5.04 g. (36%) of 4-butyl-amino-1-butanol-1-d_2, b.p. 131–132° (16 mm.), $n^{24.5}D$ 1.4508. The N-butylpyrrolidine-2-d_2 was analyzed.

Anal. Calcd. for $C_8H_{15}D_2N$: C, 74.35; H, 13.26; N, 10.84; D, 11.76 at. %. Found: C, 74.43; H, 13.30; N, 11.17; D, 11.17 at. % (1.9 at. D). Picrate, m.p. 124.5°, mixed m.p. with N-butylpyrrolidine picrate, 123.5–124.5° (lit.[40] 124.5°).

The infrared spectrum of N-butylpyrrolidine-2-d_2 showed C–D stretching bands at 2040 and 2180 cm.$^{-1}$.

The 4-butylamino-1-butanol-1-d_2 was analyzed.

Anal. Calcd. for $C_8H_{17}D_2NO$: C, 65.25; H, 13.01; N, 9.58; D, 10.52 at. %. Found: C, 65.09; H, 12.45; N, 9.86; D, 10.80 at. % (2.05 at. D).

The infrared spectrum of 4-butylamino-1-butanol-1-d_2 showed C–D stretching bands at 2080 and 2180 cm.$^{-1}$. Reduction of 4-butylaminobutyric acid with lithium aluminum hydride under the same conditions gave N-butylpyrrolidine and 4-butylamino-1-butanol, b.p. 97° (4 mm.), $n^{25}D$ 1.4502 (lit.[41] b.p. 80–80.5° (0.2 mm.), $n^{25}D$ 1.4503).

Anal. Calcd. for $C_8H_{19}NO$: C, 66.15; H, 13.18; N, 9.65. Found: C, 66.18; H, 13.13; N, 9.41.

N-Butyl-N-(4-*p*-toluenesulfonoxybutyl)-*p*-toluenesulfonamide-4-d_2 (XVIII).—4-Butylamino-1-butanol-1-d_2 (4.641 g., 0.0315 mole) was dissolved in 10.5 ml. of dry pyridine and added dropwise with stirring to a solution of 18 g. (0.0845 mole) of *p*-toluenesulfonyl chloride in 52 ml. of pyridine with cooling below −50°. After standing 1.5 hours at this temperature the mixture was stored at +5° for 46 hours. Isolation of the product by the procedure described for N-methyl-N-(4-*p*-toluenesulfonoxyamyl)-*p*-toluenesulfonamide gave 7.7 g. (54%) of oily N-butyl-N-(4-*p*-toluenesulfonoxybutyl)-*p*-toluenesulfonamide-4-d_2. The infrared spectrum of this compound showed two weak C–D stretching bands at 2150 and 2230 cm.$^{-1}$. The remainder of the spectrum was nearly identical to that of N-butyl-N-(4-*p*-toluenesulfonoxybutyl)-*p*-toluenesulfonamide prepared from 4-butylamino-1-butanol.

Dibutylamine-4-d_3 (XIX).—Crude N-butyl-N-(4-*p*-toluenesulfonoxybutyl)-*p*-toluenesulfonamide (7.7 g., 0.0170 mole) was dissolved in 40 ml. of dry tetrahydrofuran and added to a stirred slurry of 2 g. (0.05 mole) of lithium aluminum deuteride in 40 ml. of tetrahydrofuran and 20 ml. of ether. The reaction was refluxed and occasionally stirred for 14 days. The product was hydrolyzed with hydrobromic acid and phenol and isolated by the procedure used with methylamylamine-4-*d*. Distillation over calcium hydride gave 1.49 g. (66%) of dibutylamine-4-d_3, b.p. 76–77° (46 mm.). The infrared spectrum showed C–D stretching bands at 2080, 2120 and 2205 cm.$^{-1}$, and was otherwise similar to that of known dibutylamine.

Anal. Calcd. for $C_8H_{16}D_3N$: C, 72.66; H, 14.41; N, 10.59; D, 15.79 at. %. Found: C, 72.50; H, 14.17; N, 10.83; D, 16.03 at. % (3.04 at. D).

Hydrochloride, m.p. 292–296° dec.; known dibutylamine hydrochloride, m.p. 292–296° dec. (lit.[42] 283–284°).

Cyclization of Dibutylamine-4-d_3.—Dibutylamine-4-d_3 (1.3 g., 0.01 mole) was chlorinated and cyclized by Coleman's procedure.[12] The temperature of the sulfuric acid treatment was maintained between 90 and 100°. The product was separated from pentane solvent by distillation over calcium hydride through a 25-cm. Holzmann column. The N-butylpyrrolidine (0.536 g., 39%) boiled at 75° (55 mm.). The infrared spectrum shows the presence of all five C–D stretching bands corresponding to N-CD_2– and C-CD_3: 2040, 2080, 2120, 2180 (shoulder) and 2220 cm.$^{-1}$ Comparison of C–D peak heights of the single-beam infrared spectra of the product of N-butylpyrrolidine-2-d_2 and of dibutylamine-4-d_3 indicates an approximate isotope effect of 2.6.

Anal. Calcd. for $C_8H_{15}D_2N$: C, 74.35; H, 13.26; D, 11.77 at. %. Calcd. for $C_8H_{14}D_3N$: C, 73.78; H, 13.16; D, 17.65 at. %. Found: C, 73.90; H, 13.01; D, 17.80, 17.77 at. % (3.02 at. D).

Irradiation of Dibutylchloroamine in Sulfuric Acid.—A solution (159 ml.) of 0.086 mole of dibutylchloroamine in 85% sulfuric acid was prepared in the manner to be described for the preparation of butylisohexylchloroamine. The chloroamine content was determined by titration as described in the Results section. The chloroamine titer of the solution remained essentially constant over a period of 43 minutes in the dark. Irradiation of the solution in a quartz flask with ultraviolet light was begun, and after an induction period of about 12 minutes, chloroamine began to disappear. One-half of the chloroamine had reacted 32 minutes after irradiation was begun, and essentially all of the chloroamine had reacted after 167 minutes. Workup of one-half of the solution gave 3.47 g. (55%, 63% based on chloroamine) of N-butylpyrrolidine, $n^{22}D$ 1.4381.

Cyclization of Dibutylchloroamine with Potassium Persulfate and Ferrous Ion.—A solution (81 ml.) of 0.045 mole of dibutylchloroamine in 85% sulfuric acid was kept in the dark, and treated with catalytic amounts of potassium persulfate and ferrous ammonium sulfate. One-half of the chloroamine had reacted after 13 minutes, and essentially all of the chloroamine had reacted after 34 minutes. N-Butylpyrrolidine (5.2 g., 91% based on titrated chloroamine) was isolated by the procedure described by Coleman.[12] A control solution of 0.034 mole of dibutylchloroamine in 78 ml. of 85% sulfuric acid showed no loss of chloroamine over a period of 285 minutes in the dark.

Cyclization of Dibutylchloroamine with Ferrous Ammonium Sulfate.—A 82-ml. solution of 0.053 mole of dibutylchloroamine in 85% sulfuric acid was treated with about 300 mg. of ferrous ammonium sulfate in the dark. Heat was generated, and 87% of the chloroamine had reacted after 13 minutes. No chloroamine remained after 28 minutes. N-Butylpyrrolidine (4.64 g., 69% based on chloroamine, $n^{20}D$ 1.4385) was isolated in the usual way[12]; picrate, m.p. 123–124°, mixed m.p. 123.5–124.5°. When a solution (82 ml.) of 0.056 mole of dibutylchloroamine in 85% sulfuric acid was treated with 300 mg. of potassium persulfate in the dark, the chloroamine titer decreased only 14% over a period of 657 minutes.

Irradiation of Diethylchloroamine.—Diethylamine hydrobromide (0.15 mole) was dissolved in 3 *N* sodium hydroxide solution and converted to the chloroamine.[12] A solution of the diethylchloroamine in 146 ml. of 85% sulfuric acid titrated for 0.12 mole of chloroamine. There was no loss of chloroamine on standing 20 minutes in the dark. The chloroamine solution was then placed in a quartz flask and irradiated with ultraviolet light. The chloroamine titer remained constant for 63 minutes after irradiation was begun. A solution of 0.1 mole of dibutylamine in 65 ml. of sulfuric acid was then added and irradiation continued. The chloroamine titer did not decrease over a period of 217 minutes.

Cyclization of Dibutylchloroamine in Presence of Iodine.—Dibutylamine (6 g.) was chlorinated and decomposed thermally in sulfuric acid by the procedure of Coleman[12] except that 0.7 g. of iodine was added to the reaction flask before thermal decomposition was begun. Additional iodine was added from time to time during the decomposition to

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replace that which continually sublimed from the reaction mixture. The mixture was diluted and extracted with methylene chloride to remove the excess iodine and was then basified and worked up.[12] N-Butylpyrrolidine (0.8685 g., 15%) was obtained, $n^{25}D$ 1.4348; picrate, m.p. 124–125°, mixed m.p. 124–125°.

Effect of Diethylchloroamine on Rate of Decomposition of Dibutylchloroamine.—A 100-ml. solution of 0.624 molar dibutylchloroamine in 90% sulfuric acid was divided in half. To one half was added 50 ml. of a solution of about 0.5 molar diethylchloroamine in 90% sulfuric acid. To the other half was added 50 ml. of 90% sulfuric acid. Both solutions were placed in quartz flasks and irradiated side-by-side with the same ultraviolet source. The solution of dibutylchloroamine alone required 30 minutes for decomposition of one-half of the chloroamine as determined by titration of aliquots in the usual way. The solution which contained diethylchloroamine required about 300 minutes for decomposition of one-half of the dibutylchloroamine.

Irradiation of Dibutylchloroamine in Acetic Acid Containing Varying Amounts of Sulfuric Acid.—A solution of dibutylchloroamine in pentane was concentrated *in vacuo*, and a 5-ml. aliquot of the residue was placed in a 100-ml. volumetric flask. To the dibutylchloroamine were added absolute acetic acid (containing about 0.3% acetic anhydride) and 10 *N* sulfuric acid (in absolute acetic acid) in the amounts necessary to obtain a 100-ml. solution of the desired sulfuric acid concentration. The resulting solution was placed in a 200-ml. Pyrex side-arm flask fitted with a gas dispersion tube for introduction of nitrogen gas, a gas outlet tube fitted with a stopcock and leading to a bubble-counter, and an outlet leading to a vacuum line. The sidearm was covered with a rubber cap through which one-ml. aliquots were withdrawn by means of a syringe and titrated with 0.10 *N* sodium thiosulfate solution. The flask was evacuated and flushed with nitrogen five times before irradiation with a weak source of ultraviolet light was begun. During irradiation a slow stream of nitrogen was bubbled through the solution in order to exclude oxygen.

A 0.255 *M* solution of dibutylchloroamine in acetic acid without any added sulfuric acid was found to have a half-life of about 2,909 minutes. After irradiation was completed, the solution was made basic and extracted with pentane. The pentane solution was dried over sodium sulfate and then treated with gaseous hydrogen chloride to precipitate all amine present. The amine hydrochloride was filtered, washed with ether, and dried *in vacuo* over phosphorus pentoxide to give 983.3 mg. (23.3%). The infrared spectrum of the crude hydrochloride in chloroform solution was identical to that of known dibutylamine hydrochloride. In other runs, attempts to isolate any N-butylpyrrolidine (through picrate formation) proved futile.

A 0.260 *M* solution of dibutylchloroamine in 1 *N* sulfuric acid (in absolute acetic acid) was irradiated in identical fashion. The half-life of the chloroamine was 62 minutes. The solution was made basic with a mixture of ice and sodium hydroxide and extracted with pentane. After drying over sodium sulfate the solvent was removed, and the residue was converted to a picrate, 3.474 g. (42%), m.p. 121.5–123°, mixed m.p. with N-butylpyrrolidine picrate, 121.8–123.2°.

A 0.255 *M* solution of dibutylchloroamine in 2 *N* sulfuric acid (in acetic acid) had a half-life of 52 minutes and gave 5.831 g. (69%) of N-butylpyrrolidine picrate, m.p. 121–123°, mixed m.p. 121–123°.

A 0.245 *M* solution of dibutylchloroamine in 5 *N* sulfuric acid (in acetic acid) had a half-life of 47 minutes and gave 5.9111 g. (80%) of N-butylpyrrolidine picrate, m.p. 123–124°, mixed m.p. 123–124°.

Cyclization of Dibutylchloroamine in D_2O – Sulfuric Acid.—Dibutylamine (0.05 mole) was converted to the chloroamine by the method of Coleman[12] and extracted into 85% sulfuric acid which was prepared from 55 ml. of sulfuric acid and 4.6 ml. of D_2O. The resulting solution was irradiated in a quartz flask, and catalytic amounts of potassium persulfate and ferrous ammonium sulfate were added. The reaction mixture became warm. After work up,[12] 4.42 g. (70%) of N-butylpyrrolidine was obtained. The infrared spectrum of this compound showed no absorption in the C–D stretching region.

Identification of Product of Irradiation of Dibutylchloroamine.—A solution of 0.086 mole of dibutylchloroamine in 159 ml. of 85% sulfuric acid was irradiated for 3 hours and then treated with 31 g. of silver sulfate. The precipitate was filtered and extracted with boiling water. Only 40 mg. of insoluble silver chloride was obtained. One-half of the solution of irradiated chloroamine was basified with sodium hydroxide, and the amines steam distilled. The residue was acidified with dilute nitric acid, additional silver nitrate was added, and the solution was filtered. The filter cake was extracted with concentrated ammonium hydroxide and acidified with dilute nitric acid to give 6.1 g. (99% based on chloroamine) of white silver chloride. N-Butylpyrrolidine (3.5 g., 63% based on chloroamine), $n^{22}D$ 1.4381, was isolated in the usual way.

Identification of Product of Thermal Decomposition of Dibutylchloroamine.—A 78-ml. solution of 0.035 mole of dibutylchloroamine in 85% sulfuric acid was placed in a wax-bath heated at 110°. As the temperature of the sulfuric acid solution rose, the chloroamine titer decreased. When the temperature had reached 80°, two-thirds of the chloroamine had disappeared. At 90° virtually all of the chloroamine had reacted. After 10 minutes at 95°, the reaction mixture was allowed to cool to room temperature. The sulfuric acid solution was treated with silver sulfate as described above. After basification of the reaction mixture, 3.27 g. (65% based on chloroamine) of silver chloride was isolated.

Attempted Cyclization of N-Methyl-4-hydroxyamylamine in Sulfuric Acid.—N-Methyl-4-hydroxyamylamine (1.76 g., 0.015 mole) was dissolved in a mixture of 10 ml. of sulfuric acid and 2.8 ml. of water with the formation of a dark red color. The resulting solution was added dropwise to a stirred solution of 6.31 ml. of water and 1.24 ml. of sulfuric acid heated to 120°. The temperature inside the reaction flask was kept below 110° during the addition. After addition was complete, the resulting mixture was cooled, basified and steam distilled. No 1,2-dimethylpyrrolidine was isolated or detected.

N-Butylvaleramide.—To a stirred solution of 50 g. (0.415 mole) of valeryl chloride in 250 ml. of dry toluene was added dropwise 66 g. (0.9 mole) of *n*-butylamine with cooling in a Dry Ice–isopropyl alcohol-bath. After addition was completed, the reaction was allowed to stand at room temperature for 2 hours. About 100 ml. of pentane was added to the toluene solution, and the reaction mixture was poured into a mixture of ice and excess 5% hydrochloric acid. The organic layer was separated and washed with water and 5% sodium bicarbonate solution. After drying over sodium sulfate, the solution was distilled through a Vigreux column giving 53 g. (81%) of N-butylvaleramide, b.p. 98° (0.1 mm.), m.p. 32°.

Anal. Calcd. for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.82; H, 12.19; N, 8.77.

Butylamylamine.—N-Butylvaleramide (35 g., 0.222 mole) was dissolved in 125 ml. of ether and added dropwise to a stirred slurry of 12.5 g. (0.333 mole) of lithium aluminum hydride in 150 ml. of ether. The reaction was refluxed for 10 hours and the product isolated by the same procedure used for N-methyl-4-hydroxyamylamine. Butylamylamine (27.9 g., 88%) was obtained with b.p. 70–75° (22 mm.), $n^{20}D$ 1.4230 (lit.[43] b.p. 180–182° (743 mm.), $n^{20}D$ 1.4230).

Cyclization of Butylamylamine.—Butylamylamine (5 g., 0.035 mole) was chlorinated and cyclized according to the procedure of Coleman.[12] The reaction temperature was maintained at 95°. Distillation of the product from calcium hydride gave 1.698 g. (35%) of N-butyl-2-methylpyrrolidine, b.p. 80.5–81° (43 mm.), $n^{21}D$ 1.4378 (lit.[44] b.p. 86–86.5° (57 mm.)). A sample of N-butyl-2-methylpyrrolidine kindly provided by Prof. R. Adams had b.p. 79° (42 mm.), $n^{20}D$ 1.4378. The picrate of the cyclized material had m.p. 121–122° and mixed m.p. with known N-butyl-2-methylpyrrolidine picrate 121.5–122.5° (lit.[44] m.p. 122°). Quantitative infrared spectra of the cyclized product and the known N-butyl-2-methylpyrrolidine were completely superimposable.

N-Amylisocaproamide.—Isocaproyl chloride (39 g.) and 54.3 g. of amylamine were allowed to react in the manner described for the preparation of N-butylvaleramide except that the reaction was carried out in pentane solution. Distillation of the product gave 42 g. (78%) of N-amylisocaproamide, b.p. 103–105° (0.35 mm.), $n^{22}D$ 1.4481.

Anal. Calcd. for $C_{11}H_{23}NO$: C, 71.30; H, 12.51; N, 7.56. Found: C, 71.17; H, 12.31; N, 7.77.

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Amylisohexylamine.—N-Amylisocaproamide (36 g.) was reduced with 11 g. of lithium aluminum hydride in ether solution in the manner described for the preparation of butylamylamine. Distillation of the product gave 26.8 g. (81%) of amylisohexylamine, b.p. 99–102° (16 mm.), $n^{22}D$ 1.4295.

Anal. Calcd. for $C_{11}H_{25}N$: C, 77.11; H, 14.71; N, 8.18. Found: C, 77.18; H, 14.72; N, 8.23.

Hydrobromide (plates from dioxane–ethanol), m.p. 291–292.5° dec.

Anal. Calcd. for $C_{11}H_{26}NBr$: C, 52.37; H, 10.39; N, 5.55. Found: C, 52.22; H, 10.32; N, 5.66.

Attempted Cyclization of Amylisohexylamine.—Amylisohexylamine (6 g.) was chlorinated and decomposed thermally in sulfuric acid according to the method of Coleman.[12] The reaction temperature was maintained at 73–77°. Much hydrogen chloride was evolved. Workup in the usual way[12] failed to give any tertiary amine products.

N-Butylisocaproamide.—Isocaproyl chloride (50 g.) and *n*-butylamine (60 g.) were allowed to react in the manner described for the preparation of N-butylvaleramide. The N-butylisocaproamide (51.3 g., 80%) had b.p. 109–111° (0.9 mm.), $n^{22}D$ 1.4465.

Anal. Calcd. for $C_{10}H_{21}NO$: C, 70.12; H, 12.36; N, 8.18. Found: C, 70.28; H, 12.21; N, 8.38.

Butylisohexylamine.—N-Butylisocaproamide (40 g.) was reduced with 13.3 g. of lithium aluminum hydride in ether solution in the manner described for the preparation of butylamylamine to give 20.6 g. (56%) of butylisohexylamine, b.p. 93–95° (22 mm.), $n^{22.5}D$ 1.4252 (lit.[45] b.p. 87–88° (20 mm.)).

Attempted Thermal Cyclization of Butylisohexylamine.—Butylisohexylamine (6 g.) was chlorinated and allowed to react with hot sulfuric acid according to the procedure of Coleman.[12] The reaction temperature was maintained at 95° (hydrogen chloride evolved). Only 0.147 g. of product was obtained, b.p. *ca.* 75° (14 mm.), $n^{21.8}D$ 1.4378. The amine gave a hydrobromide (plates from dioxane), m.p. 162–164°, mixed m.p. with butylisohexylamine hydrobromide, 150–230° dec. The melting point of the hydrobromide corresponds neither with that of N-butyl-2,2-dimethylpyrrolidine hydrobromide (149.5°,[45] 147°[46]) nor that of N-isohexylpyrrolidine hydrobromide (180°, prepared below).

N-Isocaproylpyrrolidine.—Isocaproyl chloride (50 g.) and 58 g. of pyrrolidine were allowed to react in toluene solution in the manner described for the preparation of N-butylvaleramide. The N-isocaproylpyrrolidine (42.2 g., 68%) had b.p. 75–77° (0.35 mm.), $n^{25}D$ 1.4706.

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.28. Found: C, 71.04; H, 11.06; N, 8.26.

N-Isohexylpyrrolidine.—N-Isocaproylpyrrolidine (20 g.) was reduced with 3.8 g. of lithium aluminum hydride in ether solution as in the preparation of butylamylamine. The N-isohexylpyrrolidine (13.6 g., 74%) had b.p. 79–82° (15 mm.), $n^{25}D$ 1.4428.

Anal. Calcd. for $C_{10}H_{21}N$: C, 77.34; H, 13.63; N, 9.02. Found: C, 77.51; H, 13.59; N, 8.77.

Hydrobromide (plates from dioxane), m.p. 179–180°

Anal. Calcd. for $C_{10}H_{22}NBr$: C, 50.85; H, 9.39; N, 5.93. Found: C, 51.09; H, 9.55; N, 6.05.

Picrate (yellow needles from 95% ethanol), m.p. 137.5–139°.

Anal. Calcd. for $C_{16}H_{24}N_4O_7$: C, 49.99; H, 6.29; N, 14.58. Found: C, 49.72; H, 6.19; N, 14.31.

Irradiation of Butylisohexylchloroamine.—Butylisohexylamine (7.9 g., 0.05 mole) was converted[12] to butylisohexylchloroamine. The chloroamine was extracted into 75 ml. of cold 85% sulfuric acid and placed in a quartz flask. An aliquot was analyzed for chloroamine content by adding to excess 10% potassium iodide solution and titrating the liberated iodine with standard sodium thiosulfate solution. The analysis showed 0.0506 mole of chloroamine to be present in the sulfuric acid solution. Irradiation with an ultraviolet lamp was begun, and an aliquot removed only seconds later contained almost no chloroamine. A great deal of hydrogen chloride was liberated from the reaction mixture. It was found that *t*-butyl chloride when shaken with 85% sulfuric acid also liberated hydrogen chloride. The sulfuric acid solution of irradiated chloroamine was basified and steam distilled into dilute hydrochloric acid which was then concentrated, basified, and extracted with pentane. The products were distilled over calcium hydride to give 4.3 g. of a mixture of amines boiling at 97–140° (23 mm.). The hydrobromide of an early cut (plates from dioxane) had m.p. 215–255° dec. Gas-phase chromatography of the mixture on a dinonyl phthalate column showed the absence of any isohexylpyrrolidine.

N-Methylhexylamine.—To a stirred slurry of 13.6 g. of lithium aluminum hydride in 200 ml. of ether was added dropwise a solution of 31.3 g. (0.243 mole) of N-hexylformamide in 125 ml. of ether. When the addition was complete, stirring at reflux was continued for 19 hours. The resulting slurry was cooled and treated with aqueous methanol and filtered. The filtrate was extracted with 10% hydrochloric acid solution and the extract made alkaline with sodium hydroxide. The amine which separated was taken up in pentane, dried over magnesium sulfate, and distilled, giving a forerun of 1.96 g. (b.p. 137–140°, $n^{25}D$ 1.4148) and a main fraction of 17.97 g. of N-methylhexylamine (b.p. 140–142°, $n^{25}D$ 1.4148; lit.[47] b.p. 140–142° (735 mm.)).

Cyclization of N-Chloromethyl-*n*-hexylamine.—A solution of 18 g. (0.156 mole) of N-methylhexylamine in 300 ml. of dry ether was swirled with 21.6 g. (0.162 mole) of N-chlorosucciniinide for 0.5 hour with occasional cooling in an ice-bath. The ethereal solution was washed with water, cold dilute sulfuric acid, and water. After drying over magnesium sulfate, the ether was removed in the dark *in vacuo*. The residual methylhexylchloroamine was added portionwise to 150 ml. of cold concentrated sulfuric acid in a quartz vessel immersed in an ice-bath. When the addition was complete, the cold solution was irradiated with a sun lamp while a stream of nitrogen gas was bubbled through the solution. After 40 min. a potassium iodide test showed that nearly all of the "positive chlorine" had disappeared, and the solution was diluted with ice and made strongly alkaline with sodium hydroxide. The mixture was allowed to become quite warm during the final stages of basification to ensure complete cyclization of the δ-chloroalkylamine intermediate. The amine which separated was taken up in pentane, dried over magnesium sulfate, and precipitated as the hydrochloride with dry hydrogen chloride gas. The pentane solution was also extracted with a small volume of 10% hydrochloric acid to ensure collection of all of the amine. The combined hydrochloride was stirred with 150 ml. of 10% sodium hydroxide solution and 6 ml. of benzenesulfonyl chloride in an ice-bath for 0.5 hour and then warmed to 45°. The mixture was acidified with hydrochloric acid and extracted with ether. The acid solution was made alkaline with sodium hydroxide, and the amine which separated was taken up in pentane. Distillation over calcium hydride gave 3.39 g. of colorless distillate, b.p. 126–129° (uncor.), $n^{25}D$ 1.4303, collected in one fraction.

Picrate, m.p. 168–176°, recrystallized from ethanol, m.p. 168–172°; lit.: picrate[48] of 1-methyl-2-ethylpyrrolidine, m.p. 171°; picrate[49] of 1,2-dimethylpiperidine, m.p. 240°.

Gas chromatography of the product on a column containing carbowax as the liquid showed the presence of a major component (7.86 min.) doubtless 1-methyl-2-ethylpyrrolidine and two minor components, one of which (10.5 min.) corresponded to 1,2-dimethylpiperidine (known sample, 10.4 min.). The second component, a very minor one, remains unidentified. The ratio of 1-methyl-2-ethylpyrrolidine to 1,2-dimethylpiperidine (as estimated from the ratio of integrated intensities) is 8.5:1.

1,4-Methyliminocyclohexane Methiodide.—Methylcyclohexylamine (10 ml.) was dissolved in 70 ml. of pentane and converted[12] to methylcyclohexylchloroamine. After removal of the pentane *in vacuo*, the residue was dissolved in 100 ml. of cold 90% sulfuric acid. Titration of a 1- ml. aliquot of the acid solution showed a chloroamine content of 58.7 mmoles (8.66 g.). The acid solution was placed in a quartz flask and irradiated with a mercury arc lamp. The disappearance of chloroamine was followed by titration of aliquots. The reaction had a half-life of about 900 minutes. After 30

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hours the dark solution was poured over ice, and the resulting acidic solution was washed with ether, made basic with sodium hydroxide, and heated on a steam-bath overnight. The basic solution was extracted with ether. The ethereal solution was dried over sodium sulfate, and dry hydrogen bromide was passed in. The precipitate was removed, dissolved in dilute sodium hydroxide solution, and stirred overnight with 20 ml. of benzenesulfonyl chloride. The solution was acidified to *p*H 1 and the sulfonamide extracted with ether. The acidic solution was then made basic with sodium hydroxide, and was extracted with ether. The ether solution was treated with excess methyl iodide, and the precipitated 1,4-methyliminocyclohexane methiodide (1.5932 g., 10.7%) had m.p. 279–284°. Crystallization from ethanol–methanol gave granular crystals, m.p. 295–295.5° (lit.[50] m.p. 299–300°).

Anal. Calcd. for $C_8H_{16}NI$: C, 37.96; H, 6.37; N, 5.54. Found: C, 37.87; H, 6.60; N, 5.36.

The nuclear magnetic resonance spectrum of the methiodide (D_2O solvent, methylene chloride standard) had three distinct peaks. The peak at +27 c.p.s. (at 40 megacycles) is assigned to the bridgehead hydrogens, the sharp peak at +60.6 c.p.s. is assigned to the N-methyl hydrogens, and the peak at +100 c.p.s. is assigned to the methylene hydrogens. The relative areas under these peaks were, respectively, 2.0, 6.0 and 8.14. Methyliminocyclohexane methiodide requires 2.0, 6.0 and 8.0.

(50) J. V. Braun and K. Schwarz, *Ann.*, **481**, 56 (1930).

In order to compare the rate of decomposition of methylcyclohexylchloroamine with that of dibutylchloroamine under the same conditions, a 0.327 *M* solution of the chloroamine in 90% sulfuric acid in a quartz flask was irradiated with a mercury arc lamp under a stream of nitrogen. The half-life of the chloroamine was about 570 minutes. Under these conditions a 0.28 *M* solution of dibutylchloroamine in 90% sulfuric acid had a half-life of 10 minutes.

Irradiation of N-Chloroazacycloheptane.—N-Chloroazacycloheptane was prepared from azacycloheptane by the same procedure described for methylcyclohexylchloroamine. Approximately 1.8 ml. of the chloroamine was dissolved in 40 ml. of cold 90% sulfuric acid. Titration of a 1-ml. aliquot showed the solution to be 0.38 *M* in chloroamine. The solution was irradiated as with methylcyclohexylchloroamine. The half-life was about 2140 minutes. The solution was diluted with ice-water, made alkaline with sodium hydroxide, and heated on the steam-bath for 6 hours. The alkaline solution was then stirred with 5 ml. of benzenesulfonyl chloride for four hours, and extracted with ether. Dry hydrogen bromide was passed into the ether solution, and the material which separated as an oily suspension was extracted with water. The aqueous solution was made alkaline and extracted with ether. Methyl iodide was added to the ether solution; the oil which separated out (72.6 mg., 3% corrected for aliquots removed) could not be induced to crystallize.

URBANA, ILL.

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, THE WEIZMANN INSTITUTE OF SCIENCE]

The Constituents of *Ecballium elaterium* L. XI. Proposed Structures for α-Elaterin and its Degradation Products[1,2]

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α-Elaterin has been identified as a tetracyclic triterpene. A full structure locating all the oxygenated functions is proposed. Structures are also proposed for ecballic acid and other degradation products. The different changes involving the alkaline treatment of α-elaterin are reviewed.

The oxygen functions of α-elaterin (cucurbitacin E), the crystalline compound readily obtained from the fruit juice of *Ecballium elaterium*, have been previously described.[3,4] More recently the side chain of this compound has been elucidated.[5–7] The present paper deals with the full structure of elaterin which is one member of a group of compounds called cucurbitacins[8] isolated from different species of the Cucurbitaceae. An interrelationship has been found among four members of this group through a common degradation product and interconversion.[9] Elaterin as well as elatericin A and B possess anti-tumor activity[10]; a biological investigation is now undertaken to study the different aspects of their action.[11] In view of these properties the full structure proposed for elaterin in this paper might be of interest in the evaluation of new drugs for cancer chemotherapy.

In previous papers[5,6] we have described the periodate oxidation of elaterin and the isolation of *trans*-4-hydroxy-4-methylpent-2-enoic acid. It was therefore proposed that elaterin should have a side chain similar to elatericin A (cucurbitacin D).[2,12] However the yields of this acid were very low when compared to those obtained during the oxidation of the side chain of elatericin A. Sublimation of the oily product, obtained from the mother liquors of the crystallization of the above acid, yielded a crystalline product which was identified as *trans*-4-acetoxy-4-methylpent-2-enoic acid (full details will be published by P. R. Enslin).[7]

(1) (a) This investigation was supported by a research grant C-2810 (C2) from the National Cancer Institute of the National Institutes of Health, Public Health Service; (b) abstracted in part from the doctoral dissertation submitted to The Hebrew University of Jerusalem by David Willner.

(2) Part X, D. Lavie and Y. Shvo, THIS JOURNAL, **82**, 966 (1960).

(3) D. Lavie and S. Szinai, *ibid.*, **80**, 707 (1958).

(4) J. N. T. Gilbert and D. W. Mathieson, *Tetrahedron*, **4**, 302 (1958).

(5) D. Lavie, Y. Shvo and D. Willner, *Chemistry & Industry*, 1361 (1958).

(6) D. Lavie, Y. Shvo and D. Willner, THIS JOURNAL, **81**, 3062 (1959).

(7) P. R. Enslin and K. B. Norton, *Chemistry & Industry*, 162 (1959).

(8) P. R. Enslin, S. Rehm and D. F. A. Rivett, *J. Sci. Food Agric.*, **8**, 673 (1957), and subsequent papers.

(9) D. Lavie, Y. Shvo and D. Willner; P. R. Enslin, J. M. Hugo and K. B. Norton, *Chemistry & Industry*, 951 (1959).

(10) D. Lavie, D. Willner, M. Belkin and W. G. Hardy, presented at the Symposium on the Chemotherapy of Cancer, Tokyo, October, 1957, Abstracts, p. 53; *ACTA, Unio Int. Contra Cancrum*, 15 bis, 177 (1959). Dr. E. Schwenk, The Worcester Foundation for Experimental Biology, Shrewsbury, Mass., kindly informed us that these compounds were found to delay the growth of implanted tumors in the cheek pouch of the hamster.

(11) We thank the National Cancer Institute of the National Institutes of Health, Public Health Service, for an additional research grant C-2810 (C3S) supporting the biological aspects of this investigation. A full report will be published elsewhere.

(12) D. Lavie and Y. Shvo, *Chemistry & Industry*, 429 (1959).