CYCLIZATION OF N-HALOGENATED AMINES (The Hofmann–Löffler Reaction)

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I. INTRODUCTION

The chemist who sets out to synthesize, degrade or modify an organic structure customarily appraises the chemistry of that compound in terms of the properties of its functional groups. Such an approach is effective because of the inert nature of aliphatic and alicyclic chains. High temperature and catalytic methods for the isomerization of hydrocarbons are extensively employed industrial processes, but these procedures are too drastic or otherwise unsuitable for use with most polyfunctional compounds. Although conventional ionic organic reactions specifically occur at functional or otherwise activated positions in organic compounds, this is not the case in free radical reactions. Free radicals often attack inert methylene groups in preference to activated positions, but this very property gives rise to mixtures of polysubstituted products. It would appear that free radical reactions suitable for use in the modification of pre-selected, unactivated hydrocarbon groups would be of major utility in synthetic organic chemistry, and it is a remarkable fact that such a reaction, known for three quarters of a century, has received only minor exploitation.

The purpose of this review is to bring together the isolated applications of the Hofmann–Löffler reaction in the form of a general survey. A tabular summary of products obtained by the reaction is presented, and an effort has been made to review the literature through June, 1961.

A. GENERAL DEFINITION OF THE REACTION

The common over-all result of the Hofmann–Löffler reaction is the conversion of a suitable N-halogenated amine derivative I to a heterocyclic product II in which the nitrogen function is incorporated into the newly created pyrrolidine or piperidine ring.

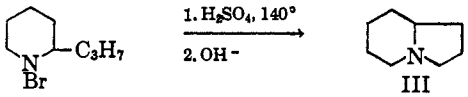
$$\underset{\text{I}}{RCH_2(CH_2)_{3-4}NXR'} \xrightarrow[\text{heat}]{H^+} RCHX(CH_2)_{3-4}N^+H_2R' \xrightarrow{OH^-} \underset{\text{II}}{RCH(CH_2)_{3-4}NR'}$$

The N-haloamine derivative, dissolved in a strong acid, is first heated, irradiated or subjected to other conditions which generate free radicals. This procedure affords a δ- or γ-haloamine derivative which can be isolated under special conditions. Usually, however, the intermediate alkyl halide is cyclized directly by treatment with alkali. The new carbon–nitrogen bond in-

volves a carbon atom which is "unactivated" in the usual sense, but is rendered reactive by virtue of a favorable spatial disposition relative to the nitrogen atom. Although acyclic secondary amines furnish pyrrolidines and piperidines, the use of cyclic secondary amines gives rise to more complex bridged and fused ring systems.

B. DISCOVERY OF THE REACTION

In 1878, the structure of piperidine was still unknown, and A. W. Hofmann (14) made attempts to add hydrogen chloride or bromine to it in the belief that the compound possessed unsaturation. These studies led to work (15) on the nature of N-haloamines and N-haloamides and, subsequently, to an examination of the action of acids and alkalies on such substances. In the course of this research, Hofmann (16, 17, 18) made the surprising discovery that by treatment of D-1-bromo-2-propylpiperidine with hot sulfuric acid, a tertiary amine was obtained, and this product was later shown (20, 21, 22, 25) to be D-octahydroindolizine III.



III

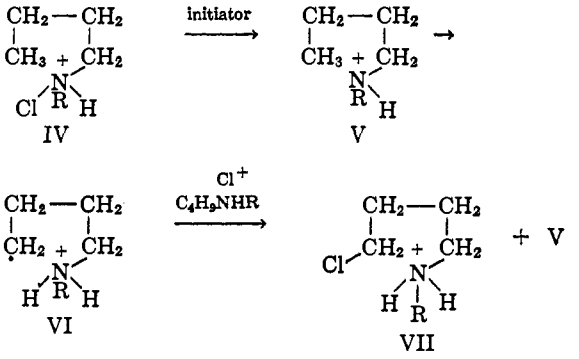
Hofmann's observations lay dormant for two decades until Löffler and Freytag (24) extended the application of his reaction to simple secondary amines and found it to be a general synthesis of pyrrolidines. Löffler (23) showed, later, that five-membered rings are invariably formed and attributed this to the proximity of the nitrogen atom to the δ-carbon atom, either constantly or during "swings." Hypotheses based on the Baeyer strain theory were advanced to account for the failure to obtain four- and six-membered rings. Developments made in the years since Löffler's work will be considered in later sections.

A number of names have been applied to the reaction including "Löffler's method" (1, 8), "Löffler–Freytag reaction" (28), "Hofmann–Löffler–Freytag reaction" (32), "Hofmann–Löffler reaction" (12), and descriptive names. Since the reaction was discovered by Hofmann and extended by Löffler and a number of co-workers, the name "Hofmann–Löffler reaction" appears to be the one of choice, particularly because it is difficult to formulate a truly descriptive name for the process.

II. MECHANISM OF THE REACTION

A. WAWZONEK MECHANISM

During work on the Hofmann-Löffler reaction of N-chloro-N-methylcyclooctylamine, Wawzonek and Thelan (39) obtained sufficient evidence to propose a mechanism for the reaction. They suggested that the N-chloroamine first forms a salt IV with the acid and then undergoes homolytic cleavage under the influence of heat, light or other initiators to afford amminium and chlorine free radicals. The amminium radical V intramolecularly abstracts a sterically favored hydrogen atom to afford an alkyl radical VI which, in a chain reaction, abstracts chlorine from another N-chloroammonium ion to form an alkyl chloride VII and a new amminium radical. The alkyl chloride VII is later chemically cyclized under the influence of alkali to afford the cyclic tertiary amine. Formulation



IV V VI VII

of the reaction as a free radical process is supported by the fact that it fails to proceed in darkness or the absence of chemical initiators.

B. INITIATION

In discussing the initiation step, the question of whether the N-haloamine reacts in the free base or the salt form must be considered (12). The K_b of N-chlorodiethylamine is 1.06×10^{-13} (40), and the N-haloamines exist largely as salts in strong sulfuric acid solution. Hence, in the case of chemical or thermal initiation, it is reasonable to assume that it is the N-haloammonium ion which affords the amminium free radical. Initiation by ferrous ion, for example, probably is an oxidation–reduction process (12) according to the equation

$$Fe^{+2} + R_2NH^+Cl \rightarrow Fe^{+3} + Cl^- + R_2\underset{H}{N}\cdot^+$$

A different situation arises, however, when radiation is utilized for initiation. In order for a photochemical reaction to occur, it is necessary that the radiation be absorbed and that the magnitude of the quantum of incident light be large enough to dissociate the bond in question (35). Because the conjugate acids of the N-chloroamines have no appreciable ultraviolet absorption above 225 mμ, whereas the free N-chloroamines absorb ultraviolet light of sufficient energy to cause dissociation (λ_{max} 263 mμ, ϵ_{max} 300) (30), it is considered (12) that the light acts on the small percentage of free N-chloroamine present in causing initiation. Presumably, the neutral nitrogen radical formed is immediately protonated. It is also possible, however, that the free N-haloamine is not dissociated into radicals by the light but simply functions as a photosensitizer, which

suggests the possibility of utilizing other photosensitizers in accelerating some of the more sluggish Hofmann-Löffler reactions.

In spite of the fact that acidic conditions retard the ultraviolet initiation process, there is no doubt that the reaction as a whole is acid catalyzed (Table I) (12). Since the N-haloamines exist as free bases in acetic acid, but as salts in 1 *M* sulfuric–acetic acid, presumably the salts do participate in the over-all process, and acid catalysis must involve acceleration of propagation, inhibition of chain termination or both.

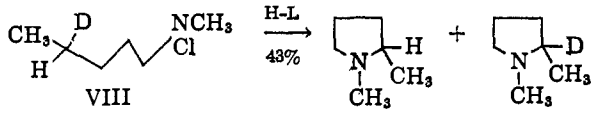
TABLE I

CONVERSION OF N-CHLORODIBUTYLAMINE TO 1-BUTYLPYRROLIDINE IN ACETIC ACID-SULFURIC ACID IN THE ABSENCE OF OXYGEN (ULTRAVIOLET INITIATION)

Concn. of H_2SO_4, *N*	Half-life, min.	Yield, %
0	2910	0
1	62	42
2	52	69
5	47	80

C. HYDROGEN ABSTRACTION

The best evidence for intramolecular hydrogen abstraction by the amminium radical to afford a carbon radical is furnished by the results of the cyclization of (−)N-methylpentylamine-4-*d* VIII (12). Although



an isotope effect (k_H/k_D) of 3.54 is observed in this conversion, the 1,2-dimethylpyrrolidine obtained is optically inactive, showing that a trigonal Cδ intermediate capable of inversion is formed.

Tedder (36) considers the factors governing the rate of intermolecular abstraction of hydrogen by a radical Z· from a molecule RH to be the following: (1) the

$$R—H + Z\cdot \rightarrow H—Z + R\cdot$$

strength of the bond Z–H which is formed; (2) the strength of the bond H–R which is broken; (3) the repulsion between the new radical R· and the new molecule ZH; and (4) the repulsion between the incoming radical Z· and the molecule RH.

Tedder's third and fourth parameters are of interest in considering the suggestion (12) that the amminium radical is more effective than a neutral nitrogen radical in abstracting hydrogen from carbon, and, in such a context, this would not seem to be the case. The coulombic forces generated by approach of the amminium radical to the positive end of the C–H dipole would be repulsive, whereas there would be attraction between the lone electron of the newly created carbon radical and the leaving ammonium ion. The fact (12) that N-chlorodiethylamine has an immeasurably long half-life

$$(C_2H_5)_2{}^+NHCl \rightleftarrows (C_2H_5)_2{}^+NH\cdot + Cl\cdot$$

under certain specific irradiation conditions wherein N-chlorodibutylamine has a half-life of 10 minutes clearly shows that the amminium radical is so *ineffective* that intermolecular hydrogen abstractions are not possible, and that simple radical recombination occurs. Conversely, the energy requirements of the intramolecular abstraction are necessarily lower, and hydrogen transfer occurs.

Corey and Hertler (12) have indicated that two factors control the tendency for 1,5-hydrogen abstraction. Hydrogen abstraction tends to proceed in a linear fashion (41), *i.e.*, the $^+$N–H–Cδ angle is 180°, and this factor is unfavorable with respect to 1,3 or 1,4-hydrogen shifting. In the case of 1,5 and 1,6 shifts, as well as in higher shifts, the angle is more nearly linear. A cyclic transition state is required for intramolecular hydrogen abstraction, and the formation of such a complex is subject to the usual factors controlling the ease of formation of such rings. In the case of 1,5 shifting, a six-membered quasi-ring is formed which may exist in a staggered, chair form conformation like that of cyclohexane, whereas the ring strain present in smaller cycles may preclude their formation. The absence of 1,7 and higher shifting may be explained by the relatively large free energy barrier to the formation of medium and large ring systems.

Other factors being equal, the ease of hydrogen abstraction by the amminium radical, in common with other radicals, follows the order tertiary > secondary > primary. Examples of the selectivity of hydrogen transfer are given in Section III.

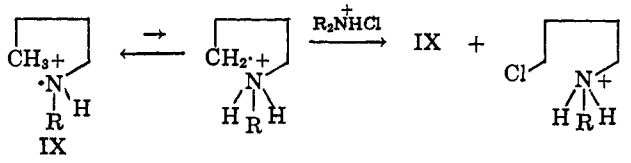
D. CHLORINE ABSTRACTION

The Wawzonek mechanism for the Hofmann–Löffler reaction embodies an intermolecular, radical propagating, chlorine abstraction following the hydrogen abstraction step.

$$R—CH_2\cdot + R_2N^+HCl \rightarrow RCH_2Cl + R_2N^+H\cdot$$

The initiation of the reaction with small amounts of chemical initiators (12, 39), as well as the inhibition of the reaction by radical trapping agents such as oxygen and N-chlorodiethylamine (12), provide good evidence for a chain mechanism. In the context of Tedder's factors, the activation energy of the chlorine abstraction will be relatively small because a weak N–Cl bond is broken, whereas a comparatively strong C–Cl bond is formed. Moreover, coulombic attraction, due to interaction of the N-chloroammonium ion with the alkyl radical, serves to facilitate approach of the two molecules and markedly lower the activation energy for the

process. At least a portion of the catalytic effect of acid on the entire reaction can be explained in this way.



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E. DIMERIZATION AND DISPROPORTIONATION

Dimerization and disproportionation of the intermediate radicals in the reaction lead to side products. Yields in the Hofmann–Löffler reaction range from 1 to 91% (Table II) and the importance of the side reactions depends largely on the starting materials. There are no data which permit an assessment of the importance of the individual side reactions, since the only identified by-products are the starting secondary amines, although high molecular weight materials are also obtained (37). Coupling of the amminium radicals is unlikely because of electrostatic repulsion from like charges (39). Dimerization of the intermediate carbon radicals, a possibility which seems to have been neglected, probably is slow in comparison with chlorine abstraction. Disproportionation reactions of the intermediate carbon and amminium radicals probably account for the by-products obtained in the reaction (37).

III. EXPERIMENTAL CONDITIONS

A. PREPARATION OF THE N-HALOAMINES

Both N-bromo- and N-chloroamines have been utilized as starting materials for the Hofmann-Löffler reaction, but N-chloroamines afford higher yields of simple pyrrolidines when heat is used as the initiator (8). By contrast, a comparison of yields of quinuclidines obtained by irradiation (39) showed, with one exception, that comparable yields are afforded by either N-bromo or N-chloro derivatives of the requisite piperidine. The greater thermal instability of the N-bromo compounds probably accounts for the differences in the two studies. Indeed, explosions of several particularly unstable free N-bromoamines have been reported (18, 24, 29) and there seems to be no reason to incur this risk.

The N-chloroamines have been prepared by several procedures. A number of workers have used the method described in "Organic Syntheses" (9), which involves saturating an iced mixture of dilute sodium hydroxide, the amine and ligroin with chlorine gas. In spite of the reliability of the source, this method is cumbersome and lengthy. The N-chloroamines are prepared readily by treatment of the amine in ether solution with N-chlorosuccinimide (31), or by stirring ether with a solution of sodium hypochlorite and the amine hydrochloride (3). A simplification of the last method involves treatment of a solution of the amine in methylene dichloride with household bleaching solution (5% NaOCl) (19).

Most workers who have used the ligroin–chlorine gas procedure have not isolated the chloroamine but have directly extracted it into sulfuric acid. The considerable heat of neutralization which is generated during this step creates practical problems in large-scale work. When ether or methylene dichloride are used as solvents for the N-chlorination, it is necessary to remove the solvent entirely from the N-chloroamine, which then is dissolved cautiously in the chilled acid. This method also must be used when trifluoroacetic acid is employed in the reaction.

B. THE ACID

For many years, only sulfuric acid was used in the Hofmann–Löffler reaction. Although concentrated acid was used in early work, higher yields are obtained when mixtures of sulfuric acid and water are employed (8) (Table II). The use of phosphoric acid or mixtures of sulfuric acid and phosphoric acid is claimed in a patent (1).

Among the disadvantages involved in the use of strong sulfuric acid are its poor solvent power for large, non-polar molecules, its destructive effect on complex organic structures, and its low volatility which obviates the possibility of direct evaporation of the solvent mixture. Some of these problems have been avoided by the use of sulfuric acid–acetic acid mixtures (12), such as a 5*N* solution of sulfuric acid in acetic acid. In some cases when sulfuric acid–acetic acid mixtures were utilized in the synthesis of conanines, however, rapid loss of chloroamine titer occurred even though no product and a high percentage of secondary amine was isolated (19). These data led to the conclusion that the acetic acid itself might be chlorinated in these instances and an alternate acid was sought. Trifluoroacetic acid, a non-dehydrating, strong, volatile acid which readily dissolves non-polar compounds, was investigated independently in two laboratories (38, 42). Although it has been reported to be inferior to sulfuric acid (38), more extensive studies show it to be the solvent of choice for the Hofmann–Löffler reaction (19, 42).

The effects of varying the concentration of N-haloamine in sulfuric acid have not been studied. Most workers have utilized 0.3 molal solutions, but it has been found recently (38) that 1.5 molal solutions afford superior yields. When trifluoroacetic acid is employed, 10% solutions are satisfactory (19, 42).

C. INITIATION

Heat was the original, and for many years the only, means for initiation of the reaction, and temperatures of 60–140° have been employed. The optimal temperature appears to depend on the nature of the starting

material and must be determined experimentally. In one carefully devised procedure (9), it was found that a deviation of more than 5° from the optimal temperature results in reduced yields. The exothermic character of the reaction makes close temperature control difficult.

The discovery that ultraviolet light can also serve as an initiator (37) markedly simplified the experimental procedure. Although it is possible to directly irradiate open beakers of the acid solution, it is more satisfactory to conduct the irradiation under nitrogen, since oxygen is known to be an inhibitor of the reaction (12). Containers for the acid solution must not be of Pyrex construction, since this glass is opaque to the activating wave length and the reaction will not proceed (19); fused quartz or Vycor (Corning No. 7910) is satisfactory. Even weak sources of ultraviolet light, such as chromatographic column scanners (12) are suitable for the irradiation; a convenient source (19, 42) is the 15-W General Electric Germicidal Lamp which fits a standard fluorescent fixture. When irradiation is used, the reaction frequently is conducted at room temperature or at 0° to minimize haloamine decomposition. A number of factors, including the steric strain attending the formation of the product (12), influence the duration of the reaction. Although some workers have irradiated for arbitrary time intervals, such as overnight, it is advantageous to terminate the procedure when the presence of N-haloamine no longer can be demonstrated with iodide solution (12, 19).

As is the case with other free radical reactions, the Hofmann–Löffler reaction can be initiated with chemical reagents. Hydrogen peroxide (39), potassium persulfate and ferrous ammonium sulfate or ferrous ammonium sulfate alone (12) can serve as initiating agents. There appears to be no advantage to the use of chemical initiators over ultraviolet light.

When chlorine or bromine is added during irradiation (37, 39) the yields are raised only slightly.

D. ISOLATION OF PRODUCTS

The majority of Hofmann–Löffler reactions have been conducted in sulfuric acid, and the intermediate alkyl halides have been cyclized without isolation. In these cases, the acid solution is made alkaline and heated to effect cyclization, and the resulting amines are separated by steam distillation. The desired tertiary amine frequently is contaminated with considerable amounts of secondary amine arising from disproportionation reactions of the intermediate radicals (37) and a Hinsberg separation with *p*-toluenesulfonyl chloride is normally carried out. Alternatively, acetic anhydride (19) is used for the same purpose. When trifluoroacetic acid is employed, the acid is recovered by distillation and the residual intermediate alkyl halide is cyclized in basic solution (19).

Cyclization under the influence of alkali is smooth and rapid, even when normally unreactive alkyl halides, such as the neopentyl chlorides intermediate in conanine formation (2, 11, 42), are involved. This behavior, which is due to the intramolecular nature of the reaction, necessitates special methods in the isolation of the uncyclized alkyl halide intermediates. By partial neutralization of a previously irradiated sulfuric acid solution of N-chloro-dibutylamine and subsequent treatment with barium chloride, the intermediate 4-chloro-N,N-dibutylamine hydrochloride X was isolated (38) in 37% yield.

$$(C_4H_9)_2NCl \xrightarrow[2.\ NaHCO_3,\ BaCl_2]{1.\ H_2SO_4,\ \text{ultraviolet}} ClCH_2CH_2CH_2CH_2{-}NHC_4H_9\cdot HCl$$

X

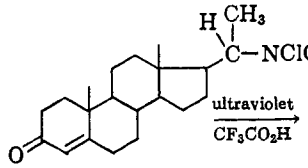
These intermediates also can be obtained by blocking the amino group using methods other than salt formation. N-Nitroso-4-chloro-N,N-dibutylamine XI was produced in 60% yield by treatment of a partially neutralized irradiated solution with sodium nitrite (38). N-Nitroso-N-methyl-4-chlorobutylamine (10%) was prepared similarly. The use of the N-nitroso inter-

$$(C_4H_9)_2NCl \xrightarrow[2.\ KHCO_3,\ NaNO_2]{1.\ H_2SO_4,\ \text{ultraviolet}} ClCH_2CH_2CH_2CH_2{-}\underset{\displaystyle NO}{\underset{|}{N}}C_4H_9$$

XI

mediates in a piperidazine synthesis is described in another section.

When trifluoroacetic acid is used as the reaction solvent, amides of the intermediate alkyl halides are obtained on evaporation of the solution. Irradiation of 20α-N-chloromethylaminopregn-4-en-3-one XII affords



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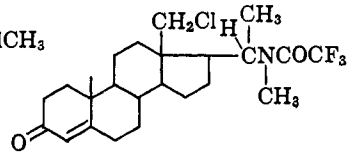


XIII

18-chloro-20α-N-methyltrifluoroacetamidopregn-4-en-3-one XIII in a yield of 87% (19). In analogous fashion, 3β-trifluoroacetoxy-18-chloro-20α-N-methyltrifluoroacetamido-5α-pregnane (68%) and 3β-trifluoroacetoxy-18-chloro-20α-N-methyl-trifluoroacetamido-5α-pregnan-11-one are obtained. In the last two cases, high yields result only when the irradiation is conducted in the presence of one equivalent of trifluoroacetic anhydride, which esterifies the hydroxyl group.

IV. SCOPE OF THE REACTION

Notwithstanding the fact that comparatively little use has been made of the Hofmann–Löffler reaction,

TABLE II

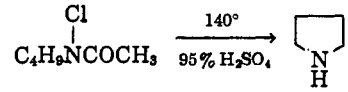
Starting material	N-Halogen	Product	Yield, %	Time,[a] hr.	Acid Spec. Grav.	Initiator[a] and/or T°C.	Ref.[b]
Acyclic Amines							
N-Methylbutylamine	Br	1-Methylpyrrolidine	..	3, 0.5	Concd. H_2SO_4	100, 125	24 (9)
N-Ethylbutylamine	Cl	1-Ethylpyrrolidine	..	..	H_2SO_4 (1.70)	110–115	9
N-Propylbutylamine	Cl	1-Propylpyrrolidine	..	..	H_2SO_4 (1.70)	80–85	9
Dibutylamine	Cl	1-Butylpyrrolidine	70	0.5	H_2SO_4 (1.70)	95	9, (1, 8)
Dibutylamine	Br	1-Butylpyrrolidine	43	24	CF_3CO_2H	Ultraviolet, 25	38
Dibutylamine	Cl	1-Butylpyrrolidine	79	20	85% H_2SO_4	Ultraviolet, 20	38 (12)
Dibutylamine	Cl	1-Butylpyrrolidine	69	0.5	85% H_2SO_4	$Fe(NH_4)_2(SO_4)_2$	12
N-Methyl-2-(3′-pyridyl)-butylamine	Br	Nicotine	..	12, 3	Concd. H_2SO_4	20, 100	26
N-Methyl-1-methylbutylamine	Br	1,2-Dimethylpyrrolidine	..	3, 0.5	Concd. H_2SO_4	100, 125	23
N-Methyl-2-methylbutylamine	Br	1,3-Dimethylpyrrolidine	..	3, 0.5	Concd. H_2SO_4	100, 125	23
N-Methyl-1-ethylbutylamine	Br	1-Methyl-2-ethylpyrrolidine	..	3, 0.5	Concd. H_2SO_4	100, 125	23
N-Methyl-1-propylbutylamine	Br	1-Methyl-2-propylpyrrolidine	..	3, 0.5	Concd. H_2SO_4	100, 125	23
1-Propylbutylamine	Br	Hexahydro-1*H*-pyrrolizine	29	1.5	Concd. H_2SO_4	Ultraviolet, 25	33
N-Methylpentylamine	Cl	1,2-Dimethylpyrrolidine	73	0.5	H_2SO_4 (1.70)	90	9 (8, 12)
N-Ethylpentylamine	Cl	1-Ethyl-2-methylpyrrolidine	..	..	H_2SO_4 (1.70)	80–90	9
N-Butylpentylamine	Cl	1-Butyl-2-methylpyrrolidine	35	..	H_2SO_4 (1.70)	95	12
N-Methylhexylamine	Cl	1-Methyl-2-ethylpyrrolidine 1,2-Dimethylpiperidine	17 2	0.7	Concd. H_2SO_4	Ultraviolet, 0	12
N-Methyloctylamine	Cl	1-Methyl-2-butylpyrrolidine	..	..	H_2SO_4 (1.70)	60–70	9
N-Methylcyclohexylamine	Cl	7-Methyl-7-azabicyclo-[2.2.1]heptane	11	30	90% H_2SO_4	Ultraviolet, 0	12
N-Methylcycloheptylamine	Cl	Tropane	40	..	84% H_2SO_4	65	7
N-Methylcyclooctylamine	Cl	9-Methyl-9-azabicyclo-[3.3.1]nonane	23	0.5	84% H_2SO_4	65	39
N-Methylcyclooctylamine	Cl	9-Methyl-9-azabicyclo-[3.3.1]nonane	12	8	84% H_2SO_4	H_2O_2, 5	39
N-Methylcyclooctylamine	Cl	9-Methyl-9 azabicyclo-[3.3.1]nonane	23	18	84% H_2SO_4	Ultraviolet, 0	39
20α-Methylamino-5α-pregnane	Cl	Conanine	..	..	H_2SO_4-HOAc	....	2
3β-Hydroxy 20α-methylamino-5α-pregnane	Cl	3β-Hydroxyconanine	84	0.5	CF_3CO_2H	Ultraviolet, 20	19
3β-Acetoxy-20α-methylamino-5α-pregnane	Cl	3β-Acetoxyconanine	..	..	H_2SO_4-HOAc	$FeSO_4$	32
20α-Methylamino-5α-pregnan-3-one	Cl	3-Oxoconanine	..	..	H_2SO_4-HOAc	$FeSO_4$	32
3β-Hydroxy-20α-methylamino-5α-pregnan-11-one	Cl	3β-Hydroxy-11-oxoconanine	70	0.3	CF_3CO_2H	Ultraviolet, 20	42, 19
20α-Methylaminopregn-4-en-3-one	Cl	3-Oxo-Δ^4-conanine	66	0.25	CF_3CO_2H	Ultraviolet, 20	19
3β-Dimethylamino-20α-methylamino-5α-pregnane	Cl	Dihydroconessine	80	..	90% H_2SO_4	Ultraviolet	11
Cyclic amines							
2-Propylpyrrolidine	Br	Hexahydro-1-*H*-pyrrolizine	..	3, 0.5	Concd. H_2SO_4	100, 135	34
2-Isobutylpyrrolidine	Br	2-Methylhexahydro-1-*H*-pyrrolizine	34	3, 0.8	Concd. H_2SO_4	100, 140	29
D-2-Propylpiperidine	Br	D-(−)-Octahydroindolizine	40	1	Concd. H_2SO_4	140	18, (20)
DL-2-Propylpiperidine	Br	DL-Octahydroindolizine	..	1	Concd. H_2SO_4	140	25
4-Ethylpiperidine	Cl	Quinuclidine	19	20	85% H_2SO_4	Ultraviolet, 0	37
4-Ethylpiperidine	Cl	Quinuclidine	7	0.5	85% H_2SO_4	120	37
4-Ethylpiperidine	Br	Quinuclidine	20	20	85% H_2SO_4	Ultraviolet, 0	37
4-Ethylpiperidine	Cl	7-Methyl-1-azabicyclo-[2.2.1]heptane	10	10	85% H_2SO_4	Ultraviolet, 47	28
4-Ethyl-4-methylpiperidine	Cl	4,7-Dimethyl-1-azabicyclo[2.2.1]-heptane	5	5, 7	85% H_2SO_4	Ultraviolet, then 120	28
2-Methyl-4-ethylpiperidine	Cl	2-Methylquinuclidine	1	20	85% H_2SO_4	Ultraviolet, 0	37
2-Methyl-4-ethylpiperidine	Br	2-Methylquinuclidine	2	20	85% H_2SO_4	Ultraviolet, 23	37
3-Methyl-4-ethylpiperidine	Cl	3-Methylquinuclidine	23	20	85% H_2SO_4	Ultraviolet, 23	37
3-Methyl-4-ethylpiperidine	Br	3-Methylquinuclidine	27	20	85% H_2SO_4	Ultraviolet, 23	37
2,6-Dimethyl-4-ethylpiperidine	Cl	2,6-Dimethylquinuclidine	Trace	20	85% H_2SO_4	Ultraviolet, 0	37
4-Propylpiperidine	Cl	2-Methylquinuclidine	8	20	85% H_2SO_4	Ultraviolet, 23	37
4-Propylpiperidine	Br	2-Methylquinuclidine	20	20	85% H_2SO_4	Ultraviolet, 23	37
4-Propylpiperidine	Br	2-Methylquinuclidine	1	20	85% H_2SO_4	Ultraviolet, 50	37
4-Butylpiperidine	Cl	2-Ethylquinuclidine	2	20	85% H_2SO_4	Ultraviolet, 23	37
4-Butylpiperidine	Br	2-Ethylquinuclidine	1	20	85% H_2SO_4	Ultraviolet, 23	37
Camphidine	Cl	1,8-Dimethyl-3,8-endomethylene-3-azabicyclo[3.2.1]octane	67	16	90% H_2SO_4	Ultraviolet, 0	13
Amides							
N-Butylacetamide	Cl	Pyrrolidine	50	0.5	95% H_2SO_4	140	10 (5)
N-Butylpropionamide	Cl	Pyrrolidine	..	..	H_2SO_4	Heat	6
1,3-Dibutylurea	Cl	Pyrrolidine	50	1	95% H_2SO_4	120–130	6
1-Butyl-3,3-dimethylurea	Cl	Pyrrolidine	5	1	95% H_2SO_4	120–130	6
N-Butyl-*p*-toluenesulfonamide	Cl	Pyrrolidine	50	0.5	95% H_2SO_4	140	4 (5, 10)

[a] Where two temperatures and times are given, the temperature was altered during the course of the reaction. [b] References in parentheses indicate other work in which essentially the same procedure was employed.

a variety of compounds have been prepared with this process. An effort has been made to include all starting materials, conditions and products which have been employed in connection with the procedure in Table II and significant aspects of these studies will be treated in subsequent sections.

A. THE USE OF N-HALOAMIDES

Although the majority of applications of the reaction utilize N-haloamines as starting materials, N-haloamides have been used occasionally. Pyrrolidine is



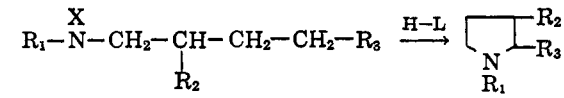
formed in 50% yield when N-chloro-N-butylacetamide is heated for one hour in sulfuric acid and subsequently treated with alkali (10). Similar yields are obtained when 1,3-dichloro-1,3-dibutylurea is allowed to react under the same conditions (6), but yields of pyrrolidine are much lower when the unsymmetrical 1-butyl-1-chloro-3,3-dimethylurea is used. N-Butyl-N-chloro-*p*-toluenesulfonamide affords a 50% yield of pyrrolidine together with 35% of N-butyl-*p*-toluenesulfonamide when subjected to similar conditions (4) and the use of N-butyl-N-chlorobenzenesulfonamide is claimed in a patent (5).

It is noteworthy that the use of amides provides a route for the preparation of cyclic secondary amines, in contrast to the usual tertiary amines, and that the free amines rather than the corresponding amides are isolated from the reaction mixture. Whether or not the N-haloamides are hydrolyzed to N-haloamines prior to the free radical step is not apparent from the work cited. The only initiator which has been utilized for amides is heat and the N-chloro-amides might be rapidly hydrolyzed under these conditions. The reported (4) recovery of N-butyl-*p*-toluenesulfonamide from the reaction utilizing the corresponding N-chloro derivative indicates that N-alkylsulfonamides themselves are not hydrolyzed readily under the conditions of the reaction and argues against the possibility of hydrolysis of the sulfonamides of the cyclized product, since these disubstituted sulfonamides should be even more stable. This is strong evidence for an initial hydrolysis of the N-haloamide. The question might best be answered by carrying out the reaction under non-hydrolytic conditions such as in anhydrous trifluoroacetic acid medium. If a preliminary hydrolysis step is required, it is likely that mono-N-haloalkylamines, which may be obtained by treatment of primary amines with N-chlorosuccinimide (31), could be used in the reaction for the direct preparation of cyclic secondary amines.

B. PREPARATION OF HETEROCYCLIC COMPOUNDS FROM N-HALOAMINES

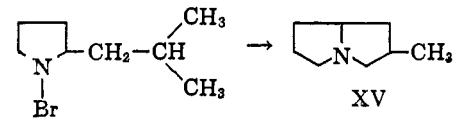
1. Pyrrolidines and Piperidines

Pyrrolidines substituted in the 1,2 and 3 positions (Table II) have been prepared by the reaction. When more than one course of the reaction is possible, the the following tendencies (12) exist in these simple cases. Secondary hydrogen atoms are more readily abstracted than those on methyl groups under thermal initiation, as illustrated by the observation that N-chloro-N-butylpentylamine affords only 1-butyl-2-methylpyrrolidine (35% yield). In comparing hydrogen abstractions from a δ and a γ methylene group, it was shown that, under irradiation, N-chloro-N-methylhexylamine affords both 1-methyl-2-ethylpyrrolidine (17%) and 1,2-dimethylpiperidine (2%). The fact that only the expected pyrrolidine was obtained (9) from N-chloro-N-methyloctylamine may be due to less careful separation of the reaction products.



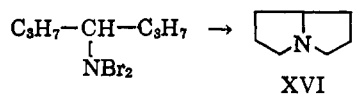
Tertiary hydrogen atoms apparently are abstracted exclusively in preference to primary and secondary hydrogens (12), but the resulting tertiary chlorides are solvolyzed readily under the conditions of the reaction and none of the expected 2,2-dialkylpyrrolidines or piperidines is obtained.

2. Hexahydro-1-H-pyrrolizines and Octahydroindolizine



N-Bromo-2-isobutylpyrrolidine furnishes 2-methylhexahydro-1-*H*-pyrrolizine XV on heating in sulfuric acid (29) and subsequent treatment with alkali. The large steric forces which operate against γ hydrogen abstraction are well illustrated in this example, since δ primary hydrogens are abstracted even in the presence of tertiary hydrogens in the γ position. Curiously, no product is said to be obtained when 1-bromo-2-butylpyrrolidine is treated in the same way, even though in this case the abstraction of a secondary hydrogen is sought. On the other hand, hot sulfuric acid does convert 1-bromo-2-propylpyrrolidine to hexahydro-1-*H*-pyrrolizine (34).

An alternative synthesis (33) of this ring system involves the only recorded example of the use of a N,N-dihalo primary amine. Heating N,N-dibromo-1-propylbutylamine in sulfuric acid affords only 2% of XVI, but a 29% yield is realized using irradiation.



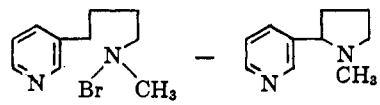
The low yield in the first instance probably is due to thermal instability of the dibromide.

The synthesis of D-octahydroindolizine is described in section IB.

3. Nicotine

Nicotine XVII has been synthesized by thermal de-

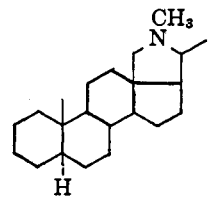
composition of N-bromo-N-methyl-2-(3′-pyridyl)-butylamine (26).



XVII

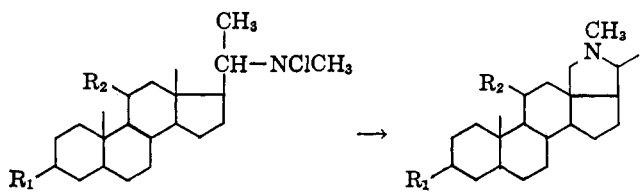
4. Conanines

The synthesis of derivatives of conanine XVIII from steroid intermediates is of interest for two reasons.



XVIII

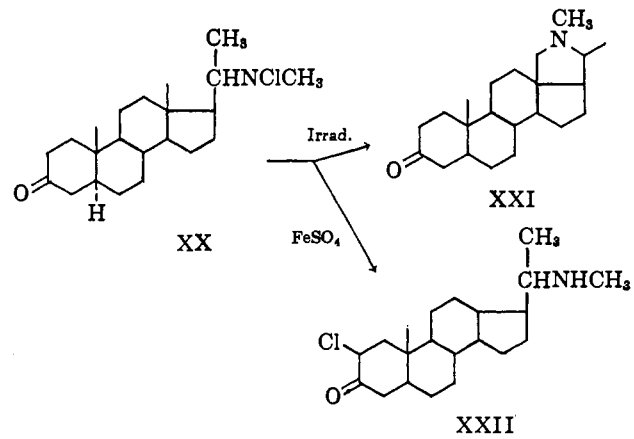
The conanine skeleton is found in many of the *Holarrhena* alkaloids and, in addition, represents a key intermediate between ordinary steroids and C(18) oxygenated steroids like aldosterone. By cyclization of a 20α-methylamino steroid XIX, the corresponding conanine is obtained, frequently in high yield (2, 11, 19, 42). Although cyclization to the 12, 14 and 15 positions of the steroid nucleus would also result in pyrrolidines,



XIX

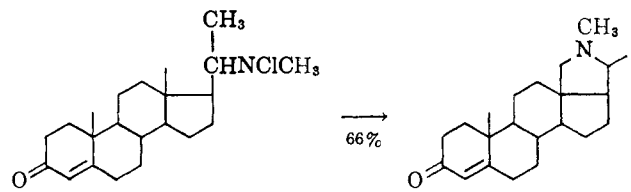
these transformations are prohibited on steric grounds and the primary hydrogens are, therefore, preferentially abstracted. The conanine syntheses represent the only examples of the reaction in which extraneous functional groups are present in the molecule. Tertiary amino (11), acetoxy (32), and keto functions (32) are stable in either strong sulfuric acid or sulfuric–acetic acid mixtures, whereas even hydroxy groups (19) and α,β-unsaturated ketones are stable when trifluoroacetic acid is used as solvent. Irradiation or chemical initiation rather than heat must, of course, be used for compounds having sensitive functional groups.

The presence of additional reactive groups in the molecule may lead to side reactions which do not involve the main reaction center. Irradiation of N-chloro-20α-methylamino-5α-pregnan-3-one XX in H_2SO_4–HOAc affords small yields of the expected conanine XXI, but when $FeSO_4$ is used as initiator, only 2-chloro-20α-methylamino-5α-pregnan-3-one XXII is isolated (32).



XX XXI XXII

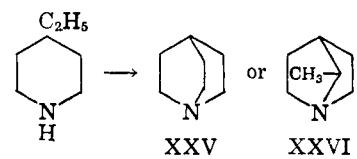
The question of whether or not irradiation leads to a more selective reaction than chemical initiation deserves further study, and it is noteworthy in this connection that, under irradiation, allylic chlorination does not occur appreciably in the cyclization of N-chloro-20α-methylamino-4-pregnen-3-one XXIII to the corresponding conanine derivative XXIV (19).



XXIII XXIV

5. Quinuclidines, 1-Azabicyclo[2.2.1]heptanes and 3,8-Endomethylene-3-azabicyclo[3.2.1]octane

The Hofmann–Löffler reaction on 4-ethylpiperidine derivatives presents a confusing picture with respect to the products. Either quinuclidines XXV or 7-methyl-1-azabicyclo[2.2.1]heptanes XXVI could be formed in this transformation. Lukes and Ferles (27)



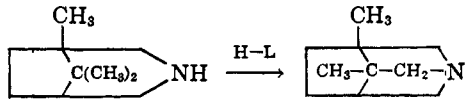
XXV XXVI

heated 1-chloro-4-ethylpiperidine in sulfuric acid and identified the product as quinuclidine on the basis of an undepressed mixture melting point of the picrate. Independently, Wawzonek, Nelson and Thelan (37) investigated the same reaction using either heat or irradiation as the initiator and obtained quinuclidine, identified as the free base, picrate and hydrochloride. Subsequently, Lukes and Ferles (28) published a complete account of their work correcting their earlier findings and indicating their product to be 7-methyl-1-azabicyclo[2.2.1]heptane, rather than quinuclidine, on the basis of a C-methyl determination and prepara-

tion of the picrate, hydrochloride and picrolonate salts. Although the melting points of quinuclidine picrate and 7-methyl-1-azabicyclo[2.2.1]heptane picrate are similar, this is not true for the other salts.

Two important opposing forces are involved in the Hofmann–Löffler reaction on 4-ethylpiperidine. There is much greater ring strain attending the formation of the azabicycloheptane relative to quinuclidine production. Conversely, abstraction of a secondary hydrogen atom is favored over primary hydrogen abstraction and to that extent quinuclidine formation is less facile. It is noteworthy that 4-ethyl-4-methylpiperidine affords only 4,7-dimethyl-1-azabicyclo[2.2.1]heptane, the product derived from abstraction of the secondary hydrogen. A difference in reaction conditions has been given (28) as a possible reason for the conflicting reports from the two laboratories, but it seems more likely that both compounds are products of the conversion and only one was isolated by each group.

Although formation of the 1-azabicyclo[2.2.1]heptane system occurs in poor yield from simple piperidines, where only material in the unstable boat conformation can lead to a cyclized product, this is not the case in the analogous ring in camphidine XXVII.



XXVII XXVIII

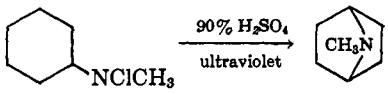
In this compound only interconvertible rigid boat and chair conformations are present, and only one Hofmann–Löffler product is possible. The synthesis of 1,8-dimethyl-3,8-endomethylene-3-azabicyclo[3.2.1]octane XXVIII has been carried out in 67% yield (13) and it is considered to be one of the most readily available bridged ring amines.

The cyclization of ring substituted 4-ethylpiperidines has afforded only the corresponding quinuclidines (37), and poor yields are obtained from starting materials having substituents in the α-positions, possibly because of F-strain in the transition state. Yields of the quinuclidine from 3-methyl-4-ethylpiperidine are normal. 4-Propylpiperidine furnishes a normal yield of 2-methylquinuclidine, but only small amounts of 2-ethylquinuclidine are obtained from 4-butylpiperidine.

6. Other Bridged Ring Systems

The Hofmann–Löffler cyclization of cycloalkylamines gives rise to a variety of bridged ring systems, but the ease and yield of these conversions depend largely on the geometry of the respective transition states.

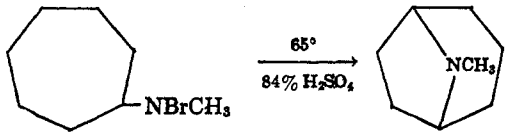
The half life of N-chloro-N-methylcyclohexylamine under irradiation in sulfuric acid is exceptionally long (15 hours) and even after a thirty-hour reaction period only 11% of the product, 7-methyl-7-azabicyclo[2.2.1]-heptane XXIX is obtained (12). The molecule is required to be in the thermodynamically unstable boat



XXIX

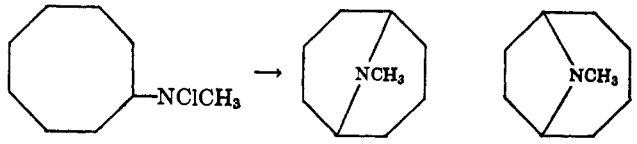
conformation for a fruitful hydrogen abstraction to occur, and the long half-life and low yield reflect this situation. The fact that the transition state in this reaction does not permit linear intramolecular hydrogen transfer may also be responsible in part for a slow and inefficient process.

By contrast, when N-methylcycloheptylamine is employed, a 40% yield of tropane XXX is realized under thermal initiation (7). In this case, the transition complex is destabilized by far fewer repulsive interactions, and hydrogen abstraction proceeds in a more nearly linear fashion as well.



XXX

Cyclization of N-chloro-N-methylcycloöctylamine could give rise to 9-methyl-9-azabicyclo[3.3.1]nonane (N-methylgranatanine) XXXI or 9-azabicyclo[4.2.1]-

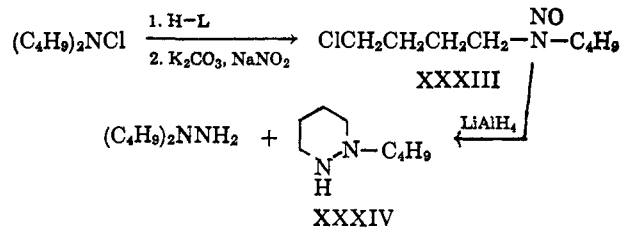


XXXI XXXII

nonane XXXII. Although the formation of XXXI involves closure to a bridged piperidine structure, it has been shown (39) that only this product is isolated. The failure to obtain XXXII has been explained on the basis of an examination of Fisher–Hirschfelder models, but these models show only slightly greater ring strain in XXXII as compared to XXXI and indicate that the steric barriers against the formation of XXXII are not much greater than those which are overcome readily in the cyclization of dibutylamine. The forces favoring the production of XXXI are evidently subtle and difficult to define. Yields as high as 23% are obtained by only a 30-minute reaction period.

7. Piperidazine

The piperidazine ring system is obtained (38) through the use of an uncyclized Hofmann–Löffler intermediate. N-Nitroso-4-chloro-N,N-dibutylamine XXXIII, obtained by the action of sodium nitrite on a partially neutralized solution from the irradiation of N-chloro-



dibutylamine, is reduced with lithium aluminum hydride to afford a mixture of N-butylpiperidazine XXXIV (8% yield) and 1,1-dibutylhydrazine (13% yield). The yield of the ring compound is low because of reduction of the alkyl halide, and would be higher if a selective reducing agent were found.

It is a pleasure to thank Professor L. Dallas Tuck for helpful discussions.

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