[CONTRIBUTION OF THE CHEMISTRY DEPARTMENT COLUMBIA UNIVERSITY]

THE VON BRAUN CYANOGEN BROMIDE REACTION I. APPLICATION TO PYRROLIDINES AND ETHYLENIMINES (1)

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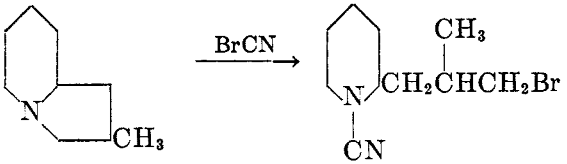
Received February 23, 1949

The search for synthetic hypoglycemic agents presents an attractive field for the efforts of the organic chemist. Several synthetic substances have already been explored in this connection, the most noteworthy of which have been Synthalin and Neo-synthalin. However, these two substances are far from satisfactory drugs since their protracted use is accompanied by severe impairment of the glycogenic functions of the liver. Notwithstanding, a further exploration of various synthetic guanidine derivatives presents at present the most hopeful line of approach to the problem of the production of synthetic hypoglycemic agents. In the light of the literature on this subject, further work in the guanidine series demands the synthesis of radically new types of guanidines.

Accordingly, the preparation of various bromoalkylcyanamides as intermediates for the preparation of guanidines appeared to be worthy of study. The classical von Braun ring opening of nitrogen heterocycles under the influence of cyanogen bromide provides a convenient source of such substances. Therefore a systematic study of this reaction has been undertaken, during the course of which several problems presenting distinct chemical interest aside from the major end in view have arisen.

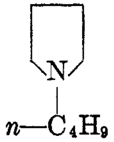
Emphasis has been placed on the manner in which substituted pyrrolidines and ethylenimines undergo ring cleavage with cyanogen bromide to yield the desired cyanamides. No reports of the reaction of cyanogen bromide with any ethylenimine are to be found in the literature. A few examples (2, 3, 4) of the reaction of various pyrrolidines with cyanogen bromide are recorded. Such examples concern the ring opening under the influence of cyanogen bromide of N-alkylpyrrolidines in which no alkyl substituents are carried in the 2- or 5-positions of the pyrrolidine ring. Only one similar ring opening which involves the opening of an indolizidine (in which rupture of the pyrrolidine ring is effected in the following manner) is recorded (3).



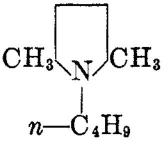
However, in this case, which can be considered analogous to that of an N-alkyl-2-alkylpyrrolidine, rupture of the pyrrolidine ring in the opposite direction would hardly be expected.

Although very extensive studies on the extent of ring opening versus dealkylation under the influence of cyanogen bromide have been made by von Braun, there appear to be no data on the relative amounts of the two possible products resulting from the cleavage of unsymmetrically substituted pyrrolidines.

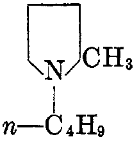
The following compounds have been prepared in order to study their behavior when subjected to the action of cyanogen bromide:



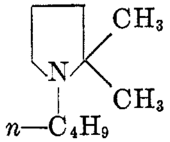
I



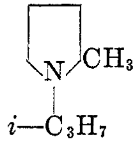
II



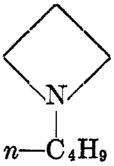
III



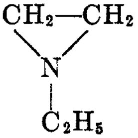
IV



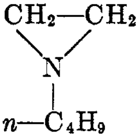
V



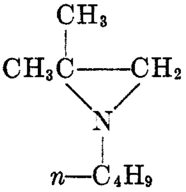
VI



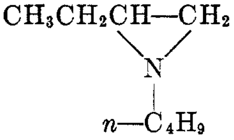
VII



VIII



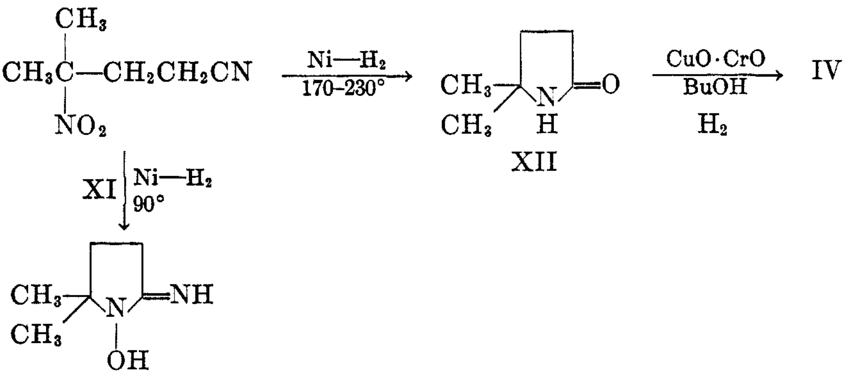
IX



X

The preparation of the pyrrolidines, with the exception of IV, afforded no difficulty. The recent availability of 1,4-dichlorobutane and 1,4-dichloropentane (5) opened up an easy route to the pyrrolidines I, III, and V by heating the dihalide with the appropriate amine. This procedure possesses distinct advantages from the point of view of simplicity over that of Coleman, Nichols, and Martens (6) which involves treating an *N*-chlorosecondary amine with sulfuric acid. Pyrrolidine II was readily prepared by catalytic reduction of *n*-butyl-2,5-dimethylpyrrole which was in turn prepared from acetonylacetone and *n*-butylamine.

At the time the present work was begun, no satisfactory method for the preparation of pyrrolidines of the type of IV was available. Lukeš (7) describes what appears to be a rather unsatisfactory preparation of 1,2,2-trimethylpyrrolidine from 1-methyl-2-pyrrolidone and methylmagnesium bromide. A more convenient synthesis for IV has been developed according to formulas XI–XIII.



XIII

Yields of XII in the order of 60% were obtained and XII was converted to IV in 45% yield. When XI was reduced under milder conditions a moderate yield of 1-hydroxy-2,2-dimethyl-5-iminopyrrolidine (XIII) was obtained. After this synthesis had been worked out, the excellent study of the reduction of γ-nitronitriles by Buckley and Elliot (8) appeared. Very recently Leonard and Beck (9) have described the preparation of 1,2-diethylpyrrolidine by reduction and hydrogenolysis of ethyl γ-nitrocaproate.

Although Gabriel and Hirsch (10) have prepared ethylenimines by the action of alkali on β-haloamines, the most satisfactory method for the synthesis of these substances is that of Wenker (11) involving treatment of the inner salt of the sulfate ester of a β-aminoalcohol with strong alkali. Since considerable quantities of N-alkylethylenimines were required in the present work a more convenient laboratory procedure which has given consistent yields of N-alkylethylenimines of the order of 70–80% was developed by modification of Wenker's general method. The solid hydrochloride of the amino alcohol is treated with a slight excess of chlorosulfonic acid and the ethylenimine is then steam-distilled from an aqueous alkaline solution of the sulfuric acid ester of the amino alcohol.

When applied to the preparation of N-*n*-butylazetidine, this method gave only a 30% yield. Due to the difficulty of obtaining the requisite azetidines, the present investigation was not extended to this group.

The manner by which tertiary amines react with cyanogen bromide has been well formulated by von Braun (12) as involving formation of an initial intermediate complex:

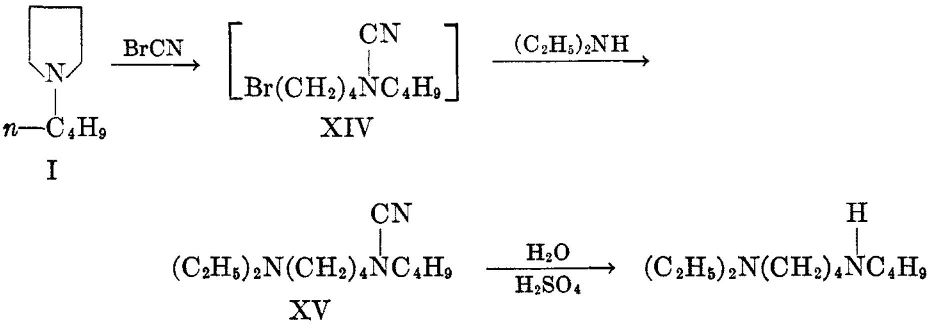
$$R_3N\!: + BrCN \rightarrow [R_3NCN]^+ Br^- \rightarrow R_2NCN + RBr$$

This is in agreement with the mode of cleavage of the cyanogen bromide or chloride molecule to yield a negative bromide or chloride ion under the influence of alkali (13).

In the cleavage of an unsymmetrical tertiary amine the bond broken is determined by the nature of the radicals of the amine. In the more special case of an N-alkyl heterocycle, one mode of cleavage can involve merely elimination of the substituting N-alkyl group without cleavage of the ring. Since von Braun (2) has observed that N-methylpyrrolidine undergoes partial demethylation whereas N-*n*-propylpyrrolidine does not but rather reacts with cyanogen bromide in a manner resulting exclusively in ring cleavage, the experiments here described were carried out with N-*n*-butylpyrrolidines in order to avoid side reactions caused by elimination of the N-substituting group.

In several cases in which the tertiary amines and cyanogen bromide were mixed all at once with or without a solvent, the formation of considerable amounts of quarternary salt arising from alkylation of the original tertiary amine by the bromide formed on cleavage was noted (14). In order to avoid this side reaction and thus increase the yield of the bromocyanamide all reactions were carried out by slowly adding a solution of the amine to a stirred solution of cyanogen bromide. By taking the above two factors into account the ring openings have been carried out with no detectable formation of quarternary salt and with no detectable debutylation with formation of the N-cyanopyrrolidines. Except in the case of the pyrrolidine IV crude yields of 90–100% of bromoalkylcyanamides resulted from the ring-opening reactions.

Before proceeding to the study of the direction of ring opening of the unsymmetrically substituted heterocycles, development of a method suitable for determining the relative amounts of products formed became necessary. Isolation of the bromocyanamides formed as primary products of the ring cleavage reaction is not suitable since they are somewhat unstable and difficultly separable. For this purpose the action of cyanogen bromide on two symmetrically substituted pyrrolidines I and II was investigated. These substances were chosen because I can lead only to a bromocyanamide containing primary halogen and II to a similar compound containing secondary halogen. The reaction of I with cyanogen bromide has previously been studied by Ochai, Tsuda, and Yokoyama (3) who obtained a 70% yield of *n*-butyl-δ-bromobutylcyanamide (XIV). By the methods now used this yield has been raised to 94% of crude XIV. The crude bromocyanamide (XIV) reacted readily with diethylamine on refluxing for three hours to yield 82% of distillable *n*-butyl-δ-diethylaminobutylcyanamide (XV) which on acid hydrolysis yielded δ-diethylamino-di-*n*-butylamine. Thus a method was provided for demonstrating the structure of similar products.



I

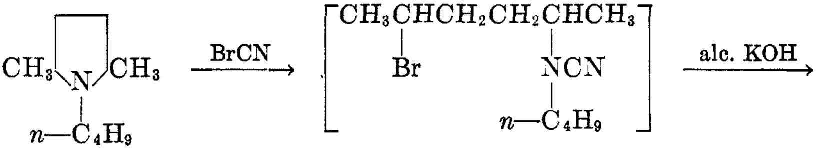
$\left[Br(CH_2)_4\overset{\displaystyle CN}{\overset{|}{N}}C_4H_9\right]$

XIV

$(C_2H_5)_2N(CH_2)_4\overset{\displaystyle CN}{\overset{|}{N}}C_4H_9 \xrightarrow[H_2SO_4]{H_2O} (C_2H_5)_2N(CH_2)_4\overset{\displaystyle H}{\overset{|}{N}}C_4H_9$

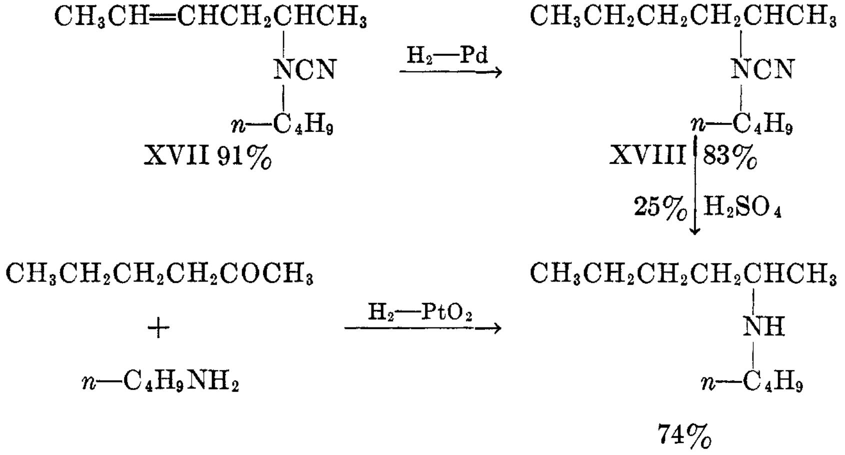
XV

In contrast to the behavior of the bromocyanamide, XIV, on reaction with diethylamine, the secondary bromocyanamide XVI reacted only very sluggishly if at all, 96.4% of unreacted XVI being recovered. Therefore, in order to characterize the bromocyanamide (XVI) and to demonstrate its structure it was dehydrobrominated to XVII



II

XVI 94%



$$\underset{\text{XVII } 91\%}{CH_3CH{=}CHCH_2\underset{\underset{n\text{—}C_4H_9}{|}}{\underset{|}{\overset{}{CH}}}CH_3 \;(\text{—}NCN\text{—})} \xrightarrow{H_2\text{—}Pd} \underset{\text{XVIII}}{CH_3CH_2CH_2CH_2CHCH_3 \;(\text{—}NCN\text{—}n\text{—}C_4H_9)}$$

$$\text{XVIII} \xrightarrow[25\%]{83\%\; H_2SO_4} CH_3CH_2CH_2CH_2CHCH_3\;(\text{—}NH\text{—}n\text{—}C_4H_9)$$

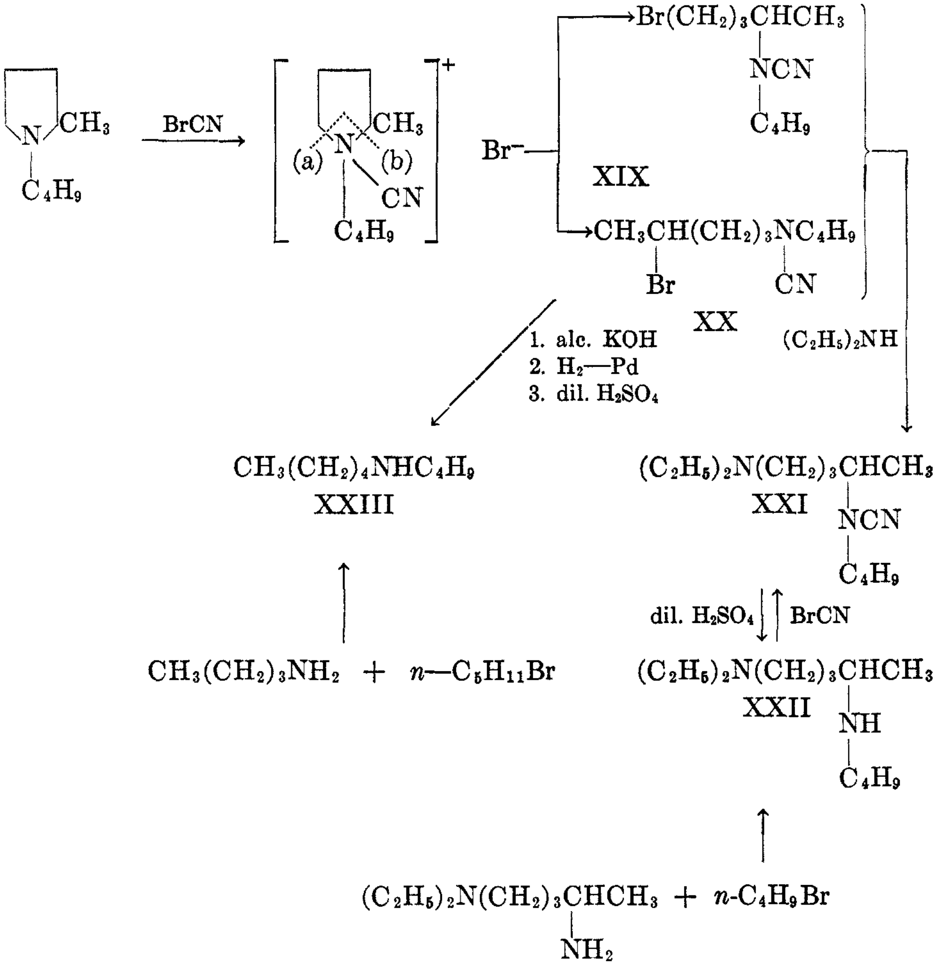
$$CH_3CH_2CH_2CH_2COCH_3 + n\text{—}C_4H_9NH_2 \xrightarrow{H_2\text{—}PtO_2} CH_3CH_2CH_2CH_2CHCH_3\;(\text{—}NH\text{—}n\text{—}C_4H_9)\quad 74\%$$

in which the position given the double bond is purely arbitrary. Hydrogenation of XVII to XVIII followed by hydrolysis of the latter gave 2-*n*-butylaminohexane which was also prepared by reductive amination of hexanone-2 with *n*-butylamine.

Finally, in order to establish the usefulness of the reaction with diethylamine as a means of differentiating bromocyanamides containing a primary halide from those containing a secondary halide, mixtures of XIV and XVI were subjected to the action of diethylamine under conditions identical to those used with the individual substances. Crude non-basic XVI was recovered to the extent of 95% of the XVI taken, and crude basic XV was found to the extent of 99% of the XIV taken. This difference in the observed reactivity of the two halides under these conditions is in accord with the observation of Morell (15) who reports substantially complete separation of 1-bromo-4-acetoxypentane from 1-acetoxy-4-bromopentane by treatment with diethylamine. The primary bromide reacts readily, while the secondary bromide reacts in negligible amounts. Data reported by Hass and Huffman (16) and by Conant and Hussey (17) also indicate a considerable difference in reactivity between primary and secondary halides in similar reactions.

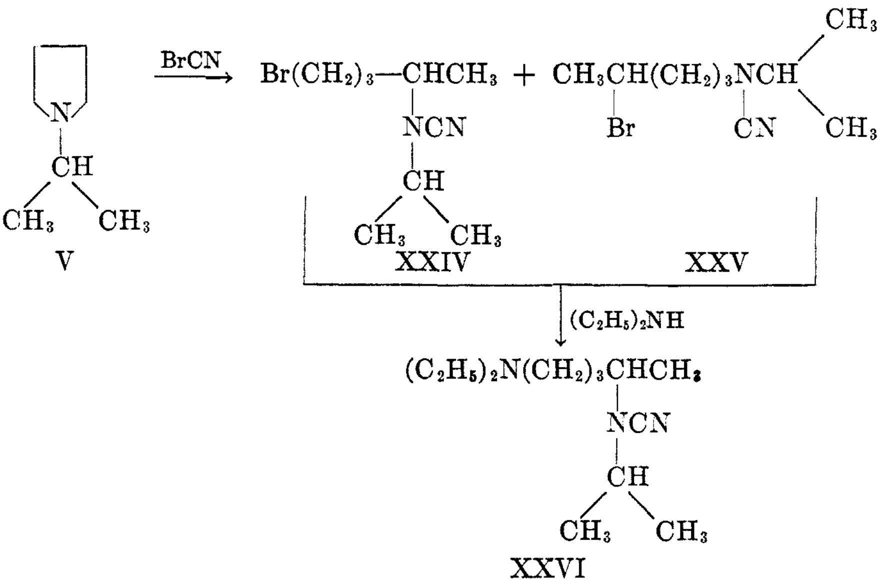
When a substance such as 1-*n*-butyl-2-methylpyrrolidine (III) undergoes ring opening with cyanogen bromide, two isomeric bromoalkylcyanamides (XIX and XX) are possible products. If the mechanism of the cleavage involves a nucleophilic displacement by bromide ion, then a higher proportion of cleavage at (a) than at (b) would be expected in accordance with the generally observed faster rate of displacement reactions involving primary alkyl linkages as compared to secondary linkages. On this basis XIX should be the major component of the product of the ring cleavage.

When a solution of 1-*n*-butyl-2-methyl pyrrolidine (III) in benzene was added slowly to a benzene solution of cyanogen bromide, a 98% yield of a crude mixture of isomeric bromoalkylcyanamides was obtained. Separation and identification of the isomers comprising this mixture were effected according to the following scheme:



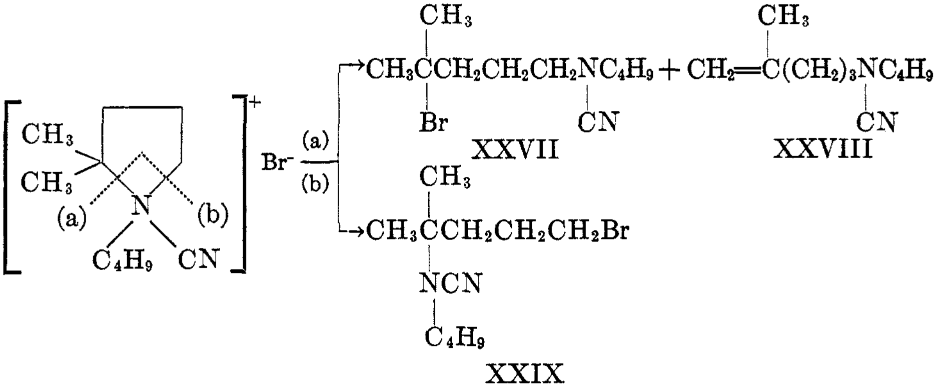
From two separate experiments identical crude yields of 70% of isomer XIX and 26% of isomer XX were obtained. The diethylaminocyanamide (XXI) prepared as indicated by the two methods was characterized as the oxalate and was hydrolyzed in 86% yield to the diamine (XXII). The hydrochloride of XXII was identical with the same substance prepared by butylation of 1-diethylamino-4-aminopentane. The bromocyanamide (XX) was converted by three steps to *n*-amyl-*n*-butylamine (XXIII) in 48% yield. The picrolonate of the amine thus obtained was identical with that resulting from amylation of *n*-butylamine.

In order to determine the effect of a secondary alkyl substituent on the nitrogen of the pyrrolidine, cleavage of 1-isopropyl-2-methylpyrrolidine (V) was investigated.



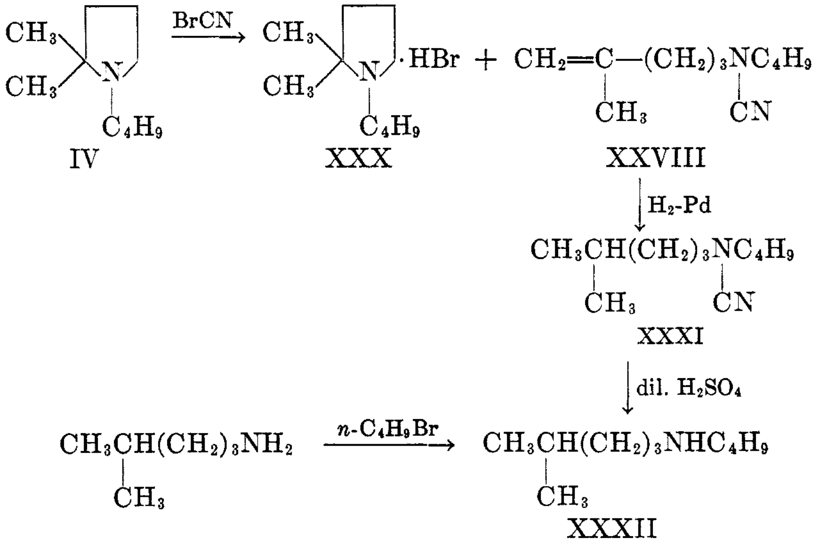
A crude yield of 94% of mixed cyanamides, XXIV and XXV, was obtained. Separation of the mixture as in the previous case showed it to consist of 32% of XXV and 65% of XXIV, the latter figure being calculated on the basis of crude XXVI isolated. Although XXVI was characterized as the oxalate, no work was done to establish definitely the structures of XXIV and XXV. The argument here rests solely on analogy with the preceding case.

When considering the products of the ring opening of a substance such as 1-*n*-butyl-2,2-dimethylpyrrolidine (IV) with cyanogen bromide, the possible formation of three products must be taken into account:



In a non-polar solvent such as benzene or ether, cleavage at (a) by means of a solvolytic reaction would not be expected and the formation of XXVII would seem unlikely. A more logical type of cleavage at (a) would involve an elimination reaction resulting in the formation of XXVIII. A second order nucleophilic displacement reaction appears to account most reasonably for cleavage at (b) with the formation of XXIX.

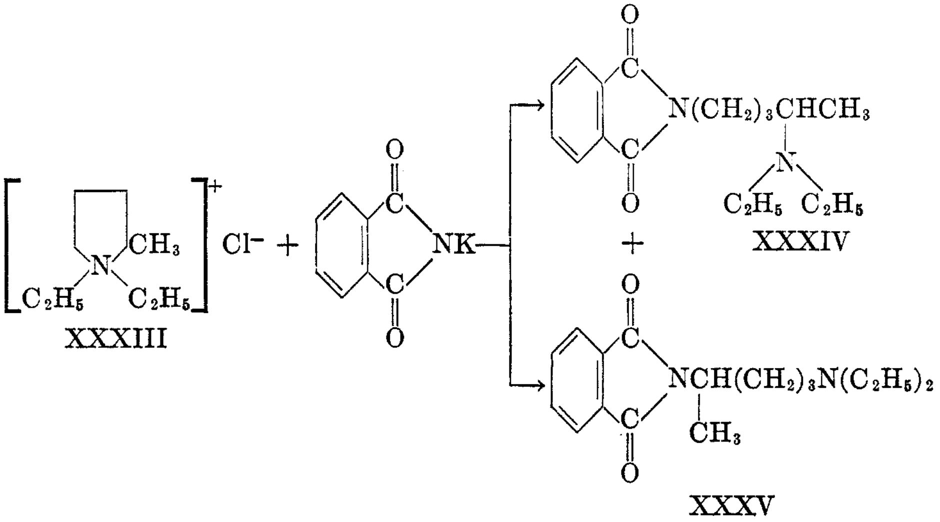
When cleavage of the pyrrolidine (IV) was carried out in ether or benzene substantially the same products were obtained in essentially the same yields in both cases. The mode of cleavage of IV and the identification of the products is shown in the following formulas:



When the reaction was carried out in anhydrous ether, a white solid (XXX) separated. This was characterized as the hydrobromide of the pyrrolidine IV. The only acid-insoluble, non-basic product isolated from the reaction mixture was XXVIII in which, as previously, the position of the double bond is assigned arbitrarily. In a typical experiment starting with 0.320 mole of IV, total recovery of IV both as such and as its hydrobromide (XXX) was 0.136 mole. Crude XXVIII was isolated in the amount of 0.135 mole which is consistent with the amount of IV recovered and excludes the formation of significant amounts of other possible products. The quantity of hydrogen bromide (0.136 mole) required for the formation of XXX could result from the formation of an equimolar amount of XXVIII.

Apparently the hydrobromide (XXX) is appreciably more soluble in benzene than in ether since the above reaction when carried out in benzene resulted in no precipitation of XXX. In this case all of the recovered starting material was isolated as the free base (IV). To determine if any XXIX had been formed, the neutral fraction from the reaction mixture was refluxed with excess diethylamine. From this 85% of non basic material was recovered and only 1.0 per cent of oily basic material was found. On the basis of this experiment, it may be concluded that ring opening proceeded to yield exclusively the unsaturated cyanamide (XXVIII).

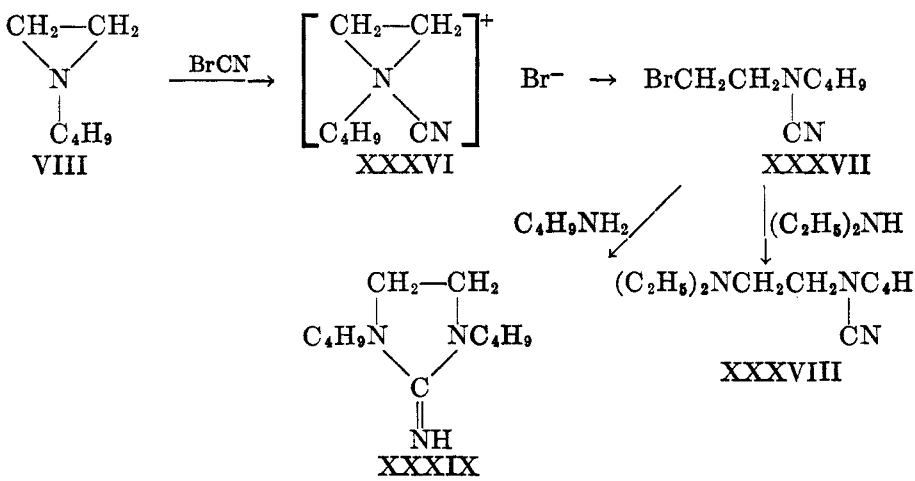
Closely related to the problem at hand is the work reported by Kharasch and Fuchs (18) in which the reaction of pyrrolidinium halides with potassium phthalimide at 150–160° is described. Rupture of the pyrrolidine ring in XXXIII as represented by the following equations is reported:



XXXIII XXXIV XXXV

Yields of crude mixtures of XXXIV and XXXV resulting from the ring opening of 80–85% are given. Fractionation through a 100-plate column of the products of the hydrolysis of the mixture of XXXIV and XXXV indicated that the mixture consisted of 90% of XXXIV and 10% of XXXV.

Ring cleavage of N-substituted ethylenimines by cyanogen bromide is unique in that it affords ring-opened products of far greater stability than the haloamines resulting from cleavage with hydrogen halides. When the reaction is properly carried out by the gradual addition of an ether solution of the imine to a stirred ether solution of cyanogen bromide, good yields of β-bromoethylcyanamides can be obtained from simple N-substituted ethylenimines. Thus N-*n*-butylethylenimine and N-ethylethylenimine give 94% and 88% respectively of the bromocyanamides. The preparation and some reactions in a typical case are as follows:



VIII XXXVI XXXVII XXXVIII XXXIX

In contrast to epoxy compounds, ethylenimines, in the absence of electrophilic reagents, are very stable toward ring opening. However when the nitrogen is converted to the quaternary state the ring is ruptured with extreme ease, *e.g.*, the ready formation of β-haloamines by treatment of ethylenimines with hydrogen halides (19, 20). The behavior of ethylenimines with cyanogen bromide parallels the reaction with halogen acids in so far as the easy rupture of the ring in the postulated quaternary intermediate is concerned.

The β-bromoalkylcyanamides are relatively stable and can be purified by vacuum distillation, although a freshly distilled sample gradually darkens after a few days at room temperature. They are unaffected by transient treatment with aqueous alkali or acid. This greater stability as compared to the haloamines can be attributed to the greatly lowered basicity of the nitrogen atom due to the presence of the cyano group. The fact that these cyanamides are insoluble in 25% sulfuric acid confirms the lack of any significant nucleophilic character in the cyanamide grouping. Therefore one would not expect step XXXVI–XXXVII to be reversible.

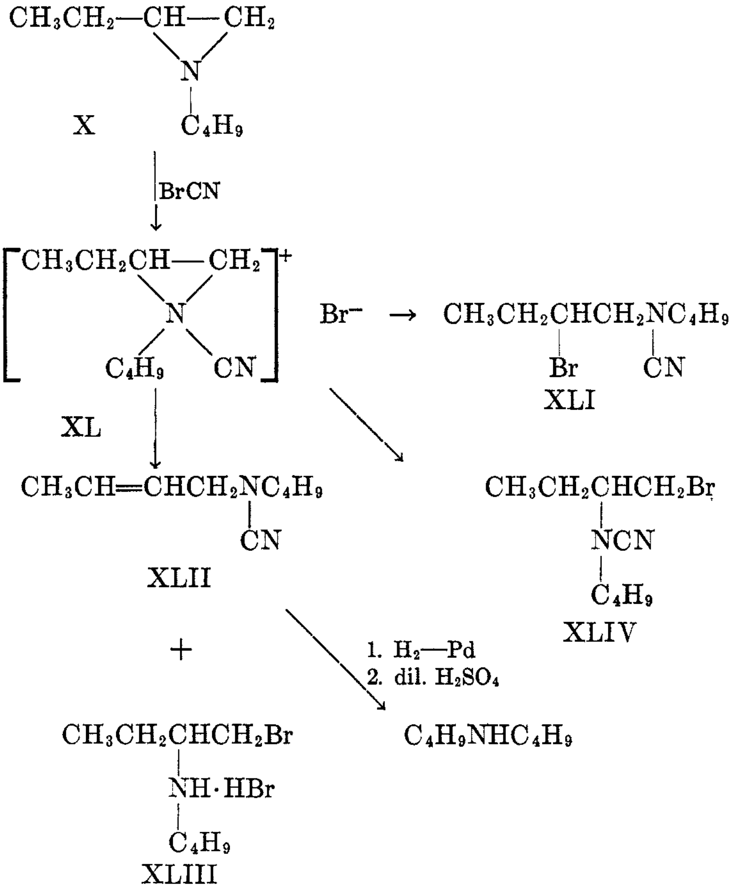
It has been established that when β-haloalkylamines act as alkylating agents, they may first undergo cyclization to an ethylenimmonium ion which is the actual alkylating agent (21). An analogous situation when the bromocyanamides are used as alkylating agents as in the formation of XXXVIII and XXXIX does not seem likely because of the properties of the cyanamides discussed above. Rather, a normal displacement of the bromine by the reagent involved would appear to be the process involved.

Reaction of the bromoalkylcyanamide (XXXVII) with a secondary amine proceeds at a moderate rate without use of a diluent. On the other hand the reaction with a primary amine proceeds with almost explosive violence. By use of a diluent, such as alcohol, cyclic guanidines of the type of XXXIX can be prepared smoothly and in good yield. The mechanism of the formation of these guanidines can be considered similar to that by which ethyleneguanidine results from the action of cyanogen bromide on ethylenediamine (22).

As representative of an N-substituted ethylenimine also carrying a single substituent on one of the carbon atoms, the action of cyanogen bromide on 1-*n*-butyl-2-ethylethylenimine (X) was investigated. The expected cleavage products may be formulated as in XL–XLIV.

When an ether solution of X was added very slowly to an ether solution of cyanogen bromide, a small amount of a white precipitate separated. This was identical with the hydrobromide of the bromoamine obtained by the action of hydrogen bromide on the ether solution of the ethylenimine X. Although the structure of this bromoamine has not been definitely settled, it is assigned the structure XLIII on the basis of the following earlier observations. Gabriel and Ohle (23) and Smith and Platon (24) have shown that propylenimine opens with hydrogen halides to yield the primary alkyl halide. Gensler (25) also reports the cleavage of 1-sulfonyl-2-bromomethylethylenimine to give the primary halide.

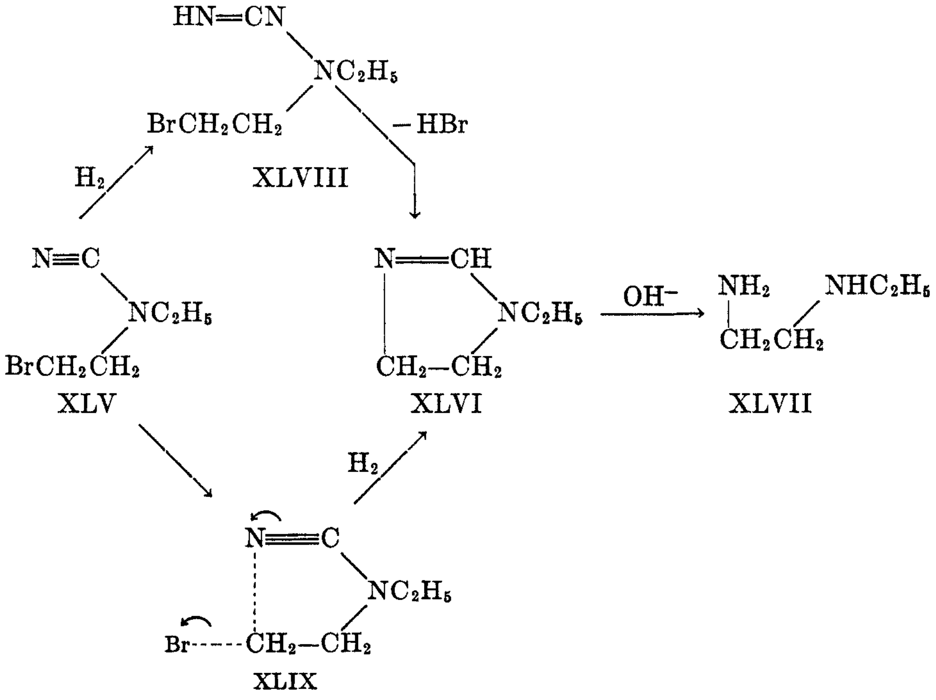
The non-basic water-insoluble material resulting from the reaction, on vacuum



distillation yielded a small forerun which was shown to consist mostly of the cyanamide XLII by its conversion to di-*n*-butylamine. The position of the double bond in XLII is assigned on arbitrary grounds. The main product, amounting to some 53% of distilled material furnished satisfactory analytical figures for either of the bromoalkylcyanamides XLI or XLIV or a mixture of the two. The problem of determining the relative amounts of the two substances in this product was not settled in such a clean-cut manner as with the bromoalkylcyanamides arising from the opening of the pyrrolidines.

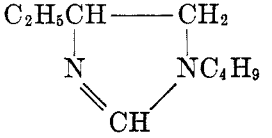
When the mixture of XLI and XLIV was treated with diethylamine, 90% of the material taken was recovered as a neutral fraction, which after purification, gave analytical figures for the bromoalkylcyanamide. However it cannot be concluded that the mixture consists predominantly of XLI. Such a conclusion would be based on the assumption that typical primary and secondary bromines occur in XLI and XLIV. The influence of the neighboring cyanamido and ethyl groups in the β-position to the bromine on the reactivity of the bromine in compounds of this type is not known and may be such as to lower the reactivity of the bromine considerably. The deactivating influence of such a β-cyanamido group appears to be relatively unimportant since when *n*-butyl-β-bromoethylcyanamide (XXXVII) was similarly treated with diethylamine a 71% yield of the diethylaminocyanamide (XXXVIII) resulted. Any significant effect of the cyanamido group should make itself apparent in both XXXVII and XLI. This evidence indicates that the major product of the reaction of the ethylenimine (X) with cyanogen bromide may be XLI. This interpretation is supported by the recovery of 80% of neutral starting material when the mixture under consideration was refluxed with benzylamine in alcohol in an attempt to prepare a cyclic guanidine of the type of XXXIX. Under similar conditions XXXIX is readily formed from the β-bromoethylcyanamide (XXXVII) on treatment with *n*-butylamine.

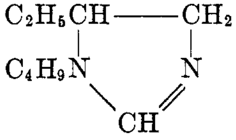
When catalytic removal of the bromine in the mixture of XLI and XLIV by reduction over Raney nickel was attempted, the reaction took an interesting and unexpected course. In methanol solution with a large amount of catalyst, one equivalent of hydrogen as required for removal of the bromine was taken up. However instead of the expected neutral cyanamide derivative, the product isolated from the reduction was a strongly basic substance sparingly soluble in water. Therefore, the similar reduction of the more available ethyl-β-bromoethylcyanamide (XLV) was investigated. Reduction was very rapid in this case and the product isolated after warming with alkali was identified as N-ethylethylenediamine (XLVII). Although the proposed intermediate, XLVI, was not isolated, the course of the reaction can be explained on the assumption of its formation as the initial product of the reduction of XLV by the following steps: (A) re-



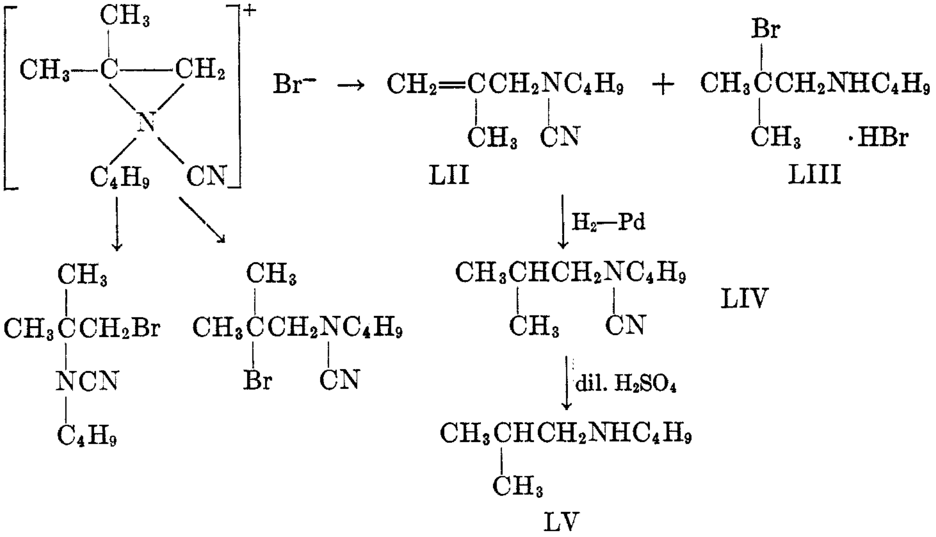
moval of the bromine from XLV via a transition state such as XLIX with reduction to the cyclic amidine (XLVI), (B) hydrolysis of XLVI to yield the diamine XLVII). The alternate route to XLVI via XLVIII does not appear likely since it involves reduction of the cyano group. It has been consistently observed throughout this work that cyanamides are not readily attacked under these conditions by catalytically activated hydrogen. The reaction XLV to XLVI is very rapid and is over in about five minutes.

The product from the reduction of the mixture of XLI and XLIV was isolated as the free base by treatment with alkali in the cold. Due to its extremely hygroscopic nature not entirely satisfactory analytical figures could be obtained. No satisfactory salt could be found. The neutralization equivalent was consistent with either structure L or LI. While no further work has been done at present on these substances, their formulation as imidazolines is consistent with the mechanism for the reduction discussed above. Further investigation of this point will be undertaken.


L


LI

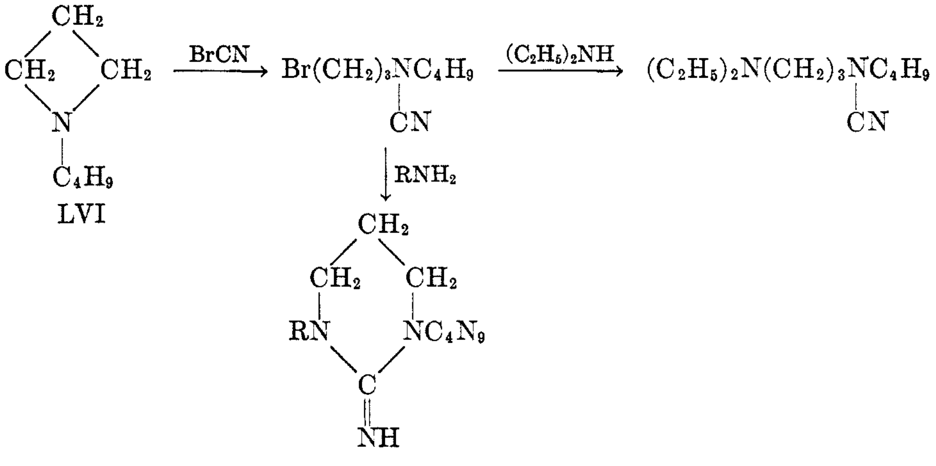
The reaction of 1-*n*-butyl-2,2-dimethylethylenimine with cyanogen bromide was not as clean cut as the ring openings discussed above. By postulating the same general type of intermediate complex, the possible modes of ring cleavage may be represented as follows:



When the reaction was carried out by the very gradual addition of an ether solution of the imine to a stirred ether solution of cyanogen bromide, precipitation of a white solid began shortly. This behavior is similar to that observed in the cleavage of 1-*n*-butyl-2,2-dimethylpyrrolidine which proceeds exclusively by an elimination reaction at the tertiary alkyl linkage. From 0.62 mole of the imine 0.10 mole of the solid amine hydrobromide (LIII) was isolated. This was identical with the bromoamine hydrobromide obtained by cleavage of 1-*n*-butyl-2,2-dimethylethylenimine with hydrogen bromide, and while its structure has not been proved unequivocally, the structure LIII appears to be most likely by analogy with other published work. Cairns (11) reports the cleavage of 2,2-dimethylethylenimine with dilute sulfuric acid as yielding amino-*tert*-butanol. Campbell and Campbell (26) likewise state that 2,2-dimethylethylenimine opens with hydrogen chloride to give the tertiary chloride.

From the ether-soluble neutral material obtained in the reaction, 0.18 mole of the unsaturated cyanamide (LII) was obtained. The structure of this, exclusive of the position of the double bond, was shown by conversion to *n*-butylisobutylamine (LV) as shown. The amount of LII isolated corresponded to about 30% of the crude ether-soluble neutral material and the total amount of LII and LIII isolated accounted for about 45% of the starting ethylenimine. The remainder of the ether-soluble material was a red-brown gum, possibly polymerized ethylenimine, from which no chemical individual was isolated. While no bromocyanamides were isolated, this does not preclude the possibility of their formation.

The reactions of N-*n*-butylazetidine (LVI) are similar to those of the corresponding ethylenimine:



LVI

LVII

The only difference lies in the formation of a six-membered cyclic guanidine (LVII). Although all of these reactions proceed in good yield thus opening up a wide variety of guanidines, the limiting factor in their usefulness is the lack of a suitable method for the synthesis of azetidines in good yield.

Though a sufficiently large number of cases has not yet been studied to justify any broad generalizations, the data presently at hand have led to some conclusions worth summarizing.

A pyrrolidine of the type of 1-*n*-butyl-2,5-dimethylpyrrolidine (II) undergoes ring opening with cyanogen bromide to yield a secondary alkyl bromide with no detectable amount of olefin formation and gives a yield of bromoalkylcyanamide comparable to that obtained from the ring opening of a pyrrolidine carrying no substituents in the α-positions.

An unsymmetrically substituted pyrrolidine such as 1-*n*-butyl-2-methylpyrrolidine (III) has been shown to undergo ring cleavage in both directions, yielding predominantly the primary alkyl bromide.

When competition between the cleavage of a nitrogen-primary alkyl linkage and a nitrogen-tertiary alkyl linkage is possible, the reaction proceeds essentially with rupture of the latter linkage with the formation of an olefin as exemplified by the ring opening of 1-*n*-butyl-2,2-dimethylpyrrolidine (IV).

Simple N-alkyl ethylenimines, bearing no alkyl substituents on either carbon atom, have been cleaved in excellent yields with cyanogen bromide to afford the new and chemically interesting β-bromoethylalkylcyanamides.

An ethylenimine such as 1-*n*-butyl-2-ethylethylenimine (X) which can cleave at either the primary alkyl-nitrogen linkage or the secondary alkyl-nitrogen linkage has been shown to cleave to a small extent at the latter linkage with olefin formation and to give as the main product, in moderate yield, a bromoalkylcyanamide. Sufficient work has not yet been done to conclude whether this product is predominantly a primary or secondary alkyl bromide.

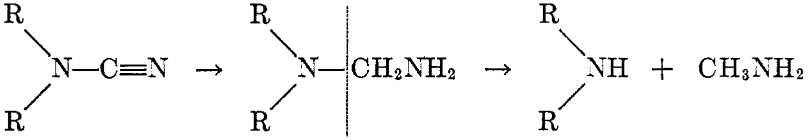
As in the pyrrolidine series, an ethylenimine such as 1-*n*-butyl-2,2-dimethylethylenimine (IX) which can cleave at either a primary or a tertiary alkylnitrogen linkage does so predominantly at the latter linkage with olefin formation. As yet, there has been isolated no bromoalkylcyanamide from this cleavage.

A simple N-alkyl azetidine has been shown to cleave to give in good yield a γ-bromopropylalkylcyanamide.

When various unsaturated cyanamides were subjected to catalytic hydrogenation, there was observed the formation of moderate amounts of basic reduction products which presumably resulted from a partial hydrogenation of the cyanamide group. This behavior has also been observed by Ochiai and Tsuda (4) and by Winterfeld and Holschneider (27) during the catalytic removal of bromine from bromoalkylcyanamides. As a basic side product, Winterfeld and Holschneider report the isolation of a compound in which they consider the basic group to be $>NCH_2NH_2$ on the basis of an analysis of the chloroplatinate.

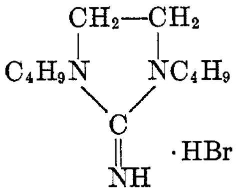
In order to find out how readily and in what manner the cyanamide grouping would undergo catalytic reduction, a sample of *n*-butyl-δ-diethylaminobutylcyanamide (XV) was submitted to catalytic hydrogenation. As shown in the experimental section, this reduction does not proceed very readily. Since the reduction of the dialkylcyanamide group yielded the secondary amine, N-*n*-butyl-

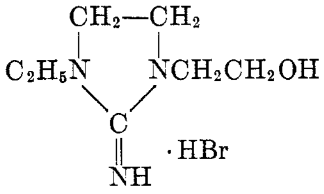
N′-diethylputrescine, the following seems to represent a reasonable course for this reduction:

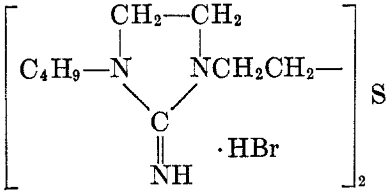


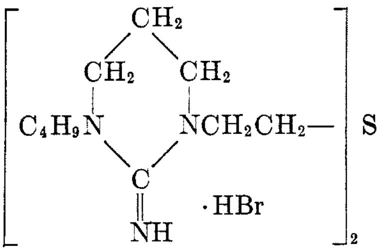
This type of catalytic removal of the cyano group may be of value in cases where a compound is sensitive to strongly acid or alkaline hydrolysis.

Although the different bromoalkylcyanamides prepared in this work can be employed for the synthesis of a great variety of guanidines, only a few of a rather unique type have been prepared. The simplicity of the preparation of cyclic guanidines from either a β-bromoethyl- or a γ-bromopropyl-cyanamide and a primary amine opens up a method for the future preparation of a wide variety of such compounds. The following have been prepared for orientation in testing as potential hypoglycemic agents:



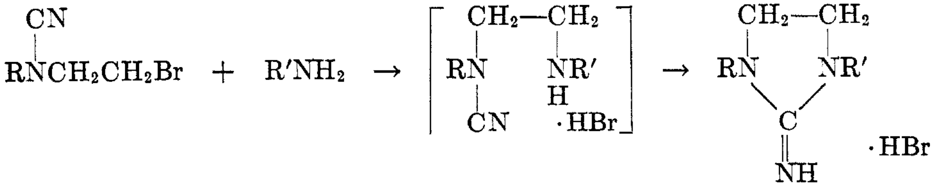






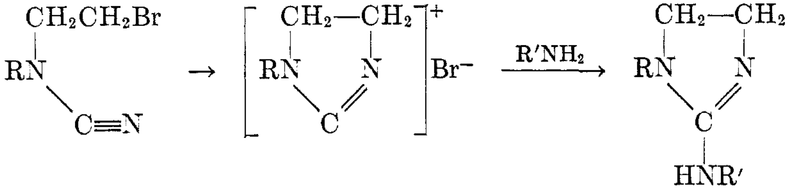
As mentioned previously, compounds of this type result from a rather vigorous reaction between the bromocyanamide and one equivalent of a primary amine.

The general Erlenmeyer method of preparing guanidines from a cyanamide and the salt of an amine apparently represents an intermediate step in this reaction which can be given for the general case as follows:



LVIII

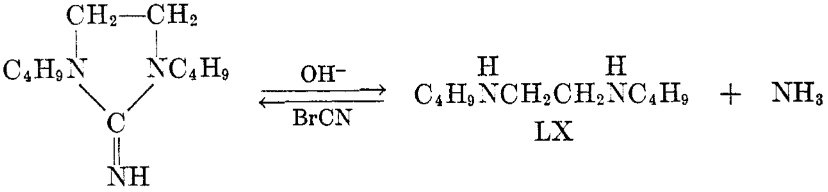
However, in view of the previously noted anomalous behavior of these β-bromoethylcyanamides upon catalytic reduction in which the nitrogen atom of the nitrile group has apparently displaced the bromine atom, a possible alternate mechanism for this reaction can be considered. Such a reaction course would lead to compounds of the type of LVIII, which would be isomeric with those of the type of LIX. One observation which



LIX

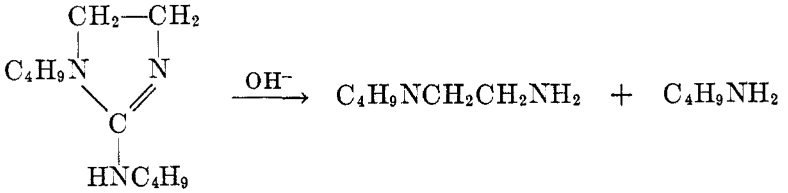
seems to favor the first mechanism in which the bromine is displaced directly by the amine was the vast difference in the vigor of reaction of the bromocyanamide with a primary amine versus a secondary amine. If the second mechanism were in operation, the reaction with both a primary and a secondary amine should yield guanidines in much the same manner.

For one case, that of XXXIX, the structure has been proved to be as indicated rather than the possible isomeric structure of the type of LXI and the remainder of the guanidines are assumed to have similar structures. The method of this simple proof can be readily understood from the following equations which consider both possible structures.



XXXIX

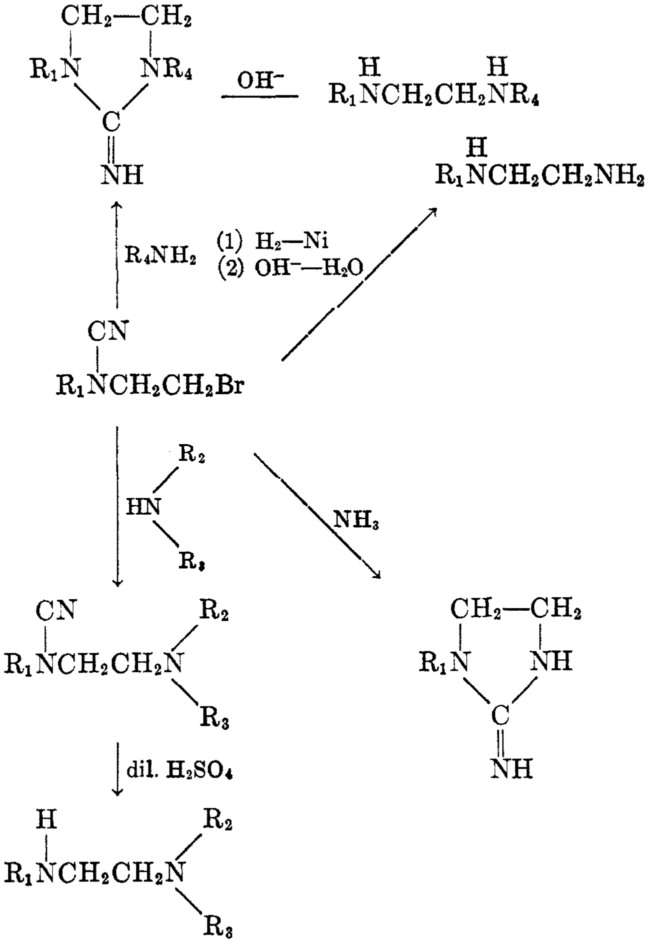
LX



LXI

Hydrolysis of a sample of the guanidine with aqueous alkali yielded a compound (LX) which, on treatment with cyanogen bromide, reformed the original guanidine hydrobromide. By considering the above equations, it is readily seen that the only one of the two possible structures consistent with these results in XXXIX.

As a result of the various reactions of β-bromoethylcyanamides noted in this work, one example of the potential synthetic value of these compounds may be brought out by considering their applicability to the preparation of various alkylated ethylenediamines otherwise difficultly obtainable.



Here the nature of the groups R_1, R_2, R_3, and R_4 can be varied practically at will and the products should be obtained in a relatively pure state.

EXPERIMENTAL (28, 29)

I. PREPARATION OF THE NITROGEN HETEROCYCLIC COMPOUNDS.

A. ETHYLENIMINES

N-(n-Butyl)-ethylenimine (VIII). The slightly hygroscopic hydrochloride of N-(*n*-butyl)ethanolamine (b.p. 102–103°/20 mm.) (30) was prepared by treating an absolute ether solution of the amino alcohol with dry hydrogen chloride. To 117 g. of the crude hydrochloride was added cautiously, under a good hood, 145 g. of freshly distilled chlorosulfonic acid in portions with shaking. After the initial vigorous reaction had subsided, the mixture, protected with a calcium chloride tube, was heated on the steam-bath for forty minutes and then heated in an oil-bath first at 80° under water pump vacuum and finally at 140–145° for one and one-half hours. The light-brown gummy residue, after cooling, was dissolved by long stirring in 200 ml. of cold water. This solution was added to a solution of 280 g. of potassium hydroxide in 300 ml. of water contained in a 2-liter 3-necked flask in portions with vigorous agitation. The flask was intermittently cooled under the water tap during the addition so that the temperature of the mixture did not exceed 60–70°. After adding 2 ml. of propylene glycol to reduce frothing, the mixture was steam-distilled, a few pellets of potassium hydroxide being placed in the receiver. A total of about 500 ml. of distillate was collected. After addition of 60 g. of potassium hydroxide, with cooling, the distillate was extracted with three 150-ml. portions of ether. After drying the combined extracts with potassium carbonate there was obtained 55 g. (74%) of material boiling at 104–108°. Redistillation over sodium gave 51 g., b.p. 106–108°; n_D^{25} 1.4118.

Anal. Calc'd for $C_6H_{13}N$: C, 72.6; H, 13.2; N, 14.1.
Found: C, 72.6; H, 13.6; N, 14.3.

N-Ethylethylenimine (VII). This substance has been prepared previously in low yield by Lasselle and Sundet (19). It can be prepared by substantially the method described above in about 70% yield. Difficulty was encountered in separating the imine from the ether used to extract it from the steam-distillate. Therefore, the distilled ether solution was used directly for the subsequent ring opening with cyanogen bromide. The yield was calculated on the basis of the product obtained in the latter reaction. For identification of the imine, the *hydrochloride* of *ethyl-β-chloroethylamine*, m.p. 221–222°, was prepared by treatment of a portion of the ether solution of the imine with hydrogen chloride. Lasselle and Sundet (19) report m.p. 223° for this substance.

1-(n-Butyl-2,2-dimethylethylenimine (IX). The requisite 2-methyl-2-*n*-butylaminopropanol, b.p. 121–126° (55 mm.), was prepared either by the method of Pierce, *et al.* (31), or by the method of Cope and Hancock (32).

By treating a portion of 150 g. of the hydrochloride of this amino alcohol with 182 g. of chlorosulfonic acid and following the procedure described above there was obtained 84 g. (80%) of 1-*n*-butyl-2,2-dimethylethylenimine, b.p. 135–136°; n_D^{25} 1.4162.

Anal. Calc'd for $C_8H_{17}N$: C, 75.6; H, 13.4; N, 11.0.
Found: C, 75.3; H, 13.5; N, 11.2.

For characterization, an ether solution of the imine was treated with hydrogen chloride and a *chloroamine hydrochloride*, m.p. 209–210°, giving analytical figures for either 1-*n*-butylamino-2-chloro-2-methylpropane hydrochloride or 1-chloro-2-*n*-butylamino-2-methylpropane hydrochloride was obtained. Which of the two isomers was at hand was not determined, since regardless of which isomer was obtained, the structure assigned to the imine is corroborated.

Anal. Calc'd for $C_8H_{19}Cl_2N$: C, 48.0; H, 9.6.
Found: C, 48.0; H, 9.8.

1-n-Butyl-2-ethylethylenimine (X). Employing the method of Cope and Hancock (32), 2-aminobutanol-1 was reductively alkylated to give a 46% yield of 2-*n*-butylaminobutanol-1, b.p. 105–108° (18 mm.). From 75 g. of the crude hydrochloride of this amino alcohol 36.5 g. (70%) of 1-*n*-butyl-2-ethylethylenimine, b.p. 63–65° (55 mm.) or 137–139°; n_D^{25} 1.4152, was obtained.

Anal. Calc'd for $C_8H_{17}N$: C, 75.5; H, 13.4; N, 11.0.
Found: C, 75.4; H, 13.2; N, 10.9.

Treatment of an ether solution of the above imine with hydrogen bromide gave a *bromoamine hydrobromide*, m.p. 197–198° (from dioxane).

Anal. Calc'd for $C_8H_{19}Br_2N$: C, 33.2; H, 6.6.
Found: C, 33.2; H, 6.5.

B. AZETIDINE

1-n-Butylazetidine (VI) *picrate.* By reacting trimethylene chlorohydrin (Eastman Kodak) with *n*-butylamine in a manner similar to that of Goldberg and Whitmore (33) a 60% yield of γ-butylaminopropanol, b.p. 110–113° (18 mm.), was obtained. One hundred twenty-eight grams of crude γ-butylaminopropanol hydrochloride was treated with 145 g. of chlorosulfonic acid. When carried through the procedure described above for the preparation of the ethylenimines, there was obtained 26 g. (30%) of a colorless liquid, b.p. 53–55° (55 mm.) or 127–128°. The *hydrobromide* of this base melted at 92–94° but was unstable on standing. The *picrate* recrystallized from benzene formed bright yellow rods m.p. 109–111° (softening 106–109°).

Anal. Calc'd for $C_{13}H_{18}N_4O_7$: C, 45.6; H, 5.3; N, 16.4.
Found: C, 45.9; H, 5.2; N, 16.4.

C. PYRROLIDINES

N-n-Butylpyrrolidine (I). A mixture of 254 g. of 1,4-dichlorobutane (5) (E.I. du Pont de Nemours & Co., Inc., material redistilled, b.p. 153–154°), 219 g. of *n*-butylamine, 138 g. of anhydrous potassium carbonate, and 200 ml. of absolute ethanol was heated on the steam-bath for sixty hours. Upon working up the reaction mixture there was obtained 133 g. (52%) of a colorless liquid b.p. 152–153° or 70–72° (45 mm.). Ochiai, Tsuda, and Yokoyama (3) report b.p. 88° (63 mm.).

1-n-Butyl-2,5-dimethylpyrrolidine (II) *hydrobromide.* When equimolar quantities of acetonylacetone and *n*-butylamine were mixed in absolute ethanol solution and allowed to stand for one hour a 90% yield of 1-*n*-butyl-2,5-dimethylpyrrole, b.p. 101–104° (22 mm.) was obtained. Bishop (34) reports b.p. 69° (4.0 mm.) for this compound prepared from the same starting materials in a slightly different manner.

Reduction of 135 g. of the above pyrrole in 200 ml. of absolute ethanol over 12 g. of Raney nickel and 2000 lbs. of hydrogen at 180–190° resulted in the absorption of the calculated amount of hydrogen during one-half hour. There was obtained 115 g. (82%) of a colorless, basic liquid, b.p. 72–74° (25 mm.). The *hydrobromide* once recrystallized from dioxane–ethanol formed white needles m.p. 173–174.5°.

Anal. Calc'd for $C_{10}H_{22}BrN$: C, 50.9; H, 9.4.
Found: C, 50.9; H, 9.6.

1-n-Butyl-2-methylpyrrolidine (III). A mixture of 141 g. of 1,4-dichloropentane (5), 73 g. of *n*-butylamine, and 138 g. of anhydrous potassium carbonate was heated on the steam-bath for fifty-five hours. After the addition of sufficient water to dissolve the solids present, the organic material was taken up in ether. The ether solution was extracted with excess dilute hydrochloric acid and then dried over calcium chloride. Eighty grams of unreacted 1,4-dichloropentane was recovered. From the acidic aqueous extracts 60 g. (43%) of a colorless liquid b.p. 74–75° (35 mm.) or 83–84° (50 mm.) was isolated. The *hydrochloride* recrystallized from acetone melted at 167–168°. Kyosuke and Tsuda (35) report b.p. 85–87° (57 mm.); hydrochloride m.p. 168° for 1-*n*-butyl-2-methylpyrrolidine.

1-n-Butyl-2,2-dimethylpyrrolidine (IV). Before the appearance of a paper by Buckley and Elliot (8) on the nature of the products obtained by the reduction of γ-methyl-γ-nitrovaleronitrile similar work was being carried out for the purpose of preparing the above pyrrolidine. Following the procedure of Bruson (36), 2-nitropropane was condensed with acrylonitrile to give a 72% yield of γ-methyl-γ-nitrovaleronitrile (XI), b.p. 105–108° (1.0 mm.). Attempts to reduce this nitronitrile using a platinum oxide catalyst either in glacial acetic acid or in absolute ethanol at 1 to 2 atmospheres of hydrogen resulted in the isolation of no definite products.

A solution of 71 g. (0.50 mol) of γ-methyl-γ-nitrovaleronitrile in 300 ml. of absolute ethanol after shaking for three hours with 6 g. of Raney nickel at 50° under 1250 lbs. of hydrogen, absorbed no hydrogen. Reduction set in at 90° and during one hour 1.1 moles of hydrogen was absorbed. No pressure drop was observed during an additional one hour of shaking. Removal of the catalyst and the ethanol (under reduced pressure) left a residue of 48 g. Addition of 150 ml. of ether to this residue followed by filtration yielded 13 g. of a white crystalline solid, m.p. 237–238°. Removal of the ether from the filtrate and distillation of the residual liquid gave 9.5 g. of a fraction of b.p. 115–120° (18 mm.). This material was not investigated.

A sample of the solid obtained, after two recrystallizations from dioxane–ethanol, gave white plates m.p. 238–239°.

Anal. Calc'd for $C_6H_{12}N_2O$: C, 56.3; H, 9.5.
Found: C, 56.2; H, 9.5.

Buckley and Elliot (8) report m.p. 238° for 1-hydroxy-5-imino-2, 2-dimethylpyrrolidine (XIII).

Treatment of a methanolic solution of the above material with hydrogen chloride gave a solid *hydrochloride*, which after two recrystallizations from dioxane–ethanol formed white needles m.p. 174–175°.

Anal. Calc'd for $C_6H_{13}ClN_2O$: C, 43.8; H, 8.0.
Found: C, 43.9; H, 8.1.

Buckley and Elliot (8) report m.p. 173° for this hydrochloride.

A reduction carried out identically to that above except for the substitution of 1 g. of platinum oxide for the 6 g. of Raney nickel gave 28 g. (44%) of *1-hydroxy-5-imino-2,2-dimethylpyrrolidine.*

A solution of 141 g. (1.0 mol) of γ-methyl-γ-nitrovaleronitrile in 250 ml. of absolute methanol was heated in a bomb to 170° without shaking, in the presence of 12 g. of Raney nickel under 2200 lbs. of hydrogen. Initiation of shaking caused a rapid rise in temperature to 230°. Shaking was stopped after one minute and resumed when the temperature had fallen to 200°. Hydrogen absorption stopped after ten minutes and further shaking at 240° and 2800 lb. pressure resulted in no additional hydrogen uptake.

After removal of the catalyst and the methanol, distillation of the residue yielded 69 g. (61%) of a colorless liquid b.p. 147–148° (32 mm.) or 140–142° (26 mm.) which solidified to a hygroscopic white crystalline solid. Buckley and Elliot (8) report b.p. 140° (20 mm.) for 2, 2-dimethyl-5-pyrrolidone (XII). A sample of this material when heated to 100° for three minutes with an equal weight of *p*-nitrobenzoyl chloride gave an alkali-insoluble solid which, after two recrystallizations from ethanol formed white needles m.p. 147–149°.

Anal. [For 1-(*p*-nitrobenzoyl)-2, 2-dimethyl-5-pyrrolidone]
Calc'd for $C_{13}H_{14}N_2O_4$: C, 59.5; H, 5.4.
Found: C, 59.5; H, 5.2.

A duplicate reduction gave a 58% yield of this pyrrolidone.

A mixture of 104 g. (0.92 mole) of 2, 2-dimethyl-5-pyrrolidone in 300 ml. of *n*-butanol and 13 g. of copper chromite catalyst was reduced under 2750 lbs. of hydrogen at 250°. In four hours 1 mole of hydrogen was absorbed. After filtration of the catalyst and removal of the solvent, distillation gave 45 g. of material, b.p. 175–185°. Distillation of the residue under vacuum gave a recovery of 41 g. of the starting pyrrolidone. Redistillation of the fraction b.p. 175–185° gave 39.4 g. of a colorless liquid, b.p. 176–178°; n_D^{25} 1.4380.

Anal. Calc'd for $C_{10}H_{21}N$: C, 77.3; H, 13.6.
Found: C, 76.9; H, 13.8.

The *hydrobromide* of the pyrrolidine was recrystallized from dioxane and formed long white needles, m.p. 148–149.5°.

Anal. Calc'd for $C_{10}H_{22}BrN$: C, 50.9; H, 9.4; N, 5.9.
Found: C, 50.9; H, 9.3; N, 5.9.

Calculated on the basis of recovered pyrrolidone the yield of 1-*n*-butyl-2, 2-dimethylpyrrolidine was 45%.

1-Isopropyl-2-methylpyrrolidine (V). This material, b.p. 140–142°, was prepared in 26% yield by refluxing, for two days, a mixture of 1 mole of 1, 4-dichloropentane (5) and 3 moles of isopropylamine. A sample of b.p. 140°; n_D^{25} 1.4350 was taken for analysis.

Anal. Calc'd for $C_8H_{17}N$: C, 75.7; H, 13.4.
Found: C, 75.3; H, 13.5.

The *hydrobromide*, m.p. 193–194°, was recrystallized from dioxane–ethanol mixture.

Anal. Calc'd for $C_8H_{18}BrN$: C, 46.2; H, 8.7.
Found: C, 46.4; H, 9.0.

II. REACTION OF THE NITROGEN HETEROCYCLES WITH CYANOGEN BROMIDE.

The *cyanogen bromide* used was prepared following the procedure of Hartman and Dreger (37).

With 1-n-butylpyrrolidine. To a solution of 59 g. (0.55 mole) of cyanogen bromide in 300 ml. of dry benzene a solution of 60 g. (0.47 mole) of 1-*n*-butylpyrrolidine in 300 ml. of dry benzene was added from a dropping-funnel with stirring during two and one-half hours. During the addition the solution remained clear and remained at a temperature of 35–40°. After standing overnight the mixture was extracted with 200 ml. of 5% hydrochloric acid and then with two 100-ml. portions of water. After drying the benzene solution over calcium chloride and removing the benzene (finally under water-pump vacuum at 90°), there remained 110 g. of a clear amber-colored liquid. The theoretical yield of *n*-butyl-δ-bromobutylcyanamide is 110 g.

A portion of 64 g. of this material was distilled through a 6-inch vacuum-jacketed Vigreux column yielding 36 g. of distillate b.p. 136–138° (1.0 mm.). Ochiai, Tsuda, and Yokoyama (3) report b.p. 120° (0.01 mm.) for this material. The residue in the distilling flask, which had been darkening slowly, turned to a thick, gummy mass and rapid decomposition set in. The possibility of securing satisfactory purification by distillation at a higher vacuum was not investigated.

The remainder (46 g.) of the crude reaction product was refluxed for three hours with 110 g. of diethylamine. Separation of a large amount of solid material began immediately. A solution of 20 g. of potassium hydroxide in 30 ml. of water was added and the excess diethylamine was removed under reduced pressure. Sufficient water was added to the residue to dissolve the potassium bromide and the brown oil was taken up in 250 ml. of ether and dried over potassium carbonate. Removal of the ether gave 41 g. (91%) of residue which, when distilled through a 6-inch vacuum-jacketed Vigreux column, gave 37 g. (82%) of *n*-butyl-δ-diethylaminobutylcyanamide, b.p. 125–126° (0.5 mm.). An *oxalate* recrystallized from dioxane formed white needles m.p. 93–96° (softening 88°).

Anal. Calc'd for $C_{15}H_{29}N_3O_4$: C, 57.1; H, 9.2.
Found: C, 56.8; H, 9.4.

A subsequent run using 138 g. (0.59 mole) of the crude bromocyanamide and 130 g. (2.06 moles) of diethylamine gave 120 g. (91%) of the distilled diethylamino derivative (XV), b.p. 128–130° (0.7 mm.). When a sample of 20 g. of this material was refluxed for fourteen hours with a solution of 40 g. of sulfuric acid in 120 ml. of water, there was isolated 14.2 g. (80%) of a liquid b.p. 135–137° (26 mm.); n_D^{25} 1.4418. A *dihydrobromide* melted at 168–170°. This material is *1-diethylamino-4-butylaminobutane*. Analytical data for the substance are listed under a later experiment.

With 1-n-butyl-2,5-dimethylpyrrolidine. In the manner described above, a solution of 62 g. (0.40 mole) of 1-*n*-butyl-2,5-dimethylpyrrolidine in 300 ml. of dry benzene was added, over two hours to a solution of 44.6 g. (0.44 mole) of cyanogen bromide in 300 ml. of dry benzene. A clear yellow solution resulted which was allowed to stand overnight. After washing the benzene solution with dilute acid and water, as previously described, the benzene solution was dried over calcium chloride. Removal of the benzene (finally under water-pump vacuum at steam-bath temperature) yielded 94 g. of a red-brown oil. The theoretical yield of *butyl-(1-methyl-4-bromoamyl)cyanamide* (XVI) is 100 g. This material was not purified.

When a solution of 50 g. (0.20 mole) of the above substance in 124 g. (1.70 moles) of diethylamine stood for sixty hours at room temperature, only a very slight amount of solid salts was formed. Refluxing for three hours caused no noticeable reaction. After standing for two weeks at room temperature a moderate amount of precipitated solid gradually formed. Removal of the excess diethylamine and treatment of the residue with excess 5% hydrochloric acid caused the separation of an acid-insoluble oil which was taken up in ether and dried over calcium chloride. Removal of the ether yielded 35 g. of a red-brown oil which was presumably recovered starting material. There was isolated 7.8 g. of a basic product b.p. 130–131° (0.6 mm.). This material was not characterized.

A sample of 25.0 g. (0.10 mole) of the crude reaction product was refluxed for three hours with 73 g. (1.0 mole) of diethylamine. The diethylamine was removed, finally under reduced pressure, the residue was treated with excess dilute hydrochloric acid, the insoluble oil was taken up in 200 ml. of ether, washed with 50 ml. of water and dried over calcium chloride. Removal of the ether and subjection of the residue to aspirator vacuum on the steam-bath for ten minutes, gave 24.1 g. (96.4% recovery) of a red-brown oil.

A mixture of 56 g. (0.21 mole) of crude bromocyanamide and 13 g. (0.23 mole) of potassium hydroxide in 200 ml. of absolute ethanol was refluxed for one and one-half hours and then cooled and filtered to remove the potassium bromide. Removal of the ethanol from the filtrate and treatment of the residue with 50 ml. of water yielded an oil which was taken up in ether and dried over magnesium sulfate. Removal of the ether and distillation of the residue gave 34.9 g. (91%) of a colorless liquid (XVII) b.p. 108–110° (1.9 mm.); n_D^{25} 1.4518.

Anal. Calc'd for $C_{11}H_{20}N_2$: C, 73.3; H, 11.2.
Found: C, 73.3; H, 11.4.

Reduction of 33.9 g. of this unsaturated cyanamide in 150 ml. of absolute ethanol using 0.5 g. of palladium black at 2 to 3 atmospheres of hydrogen resulted in the theoretical hydrogen uptake during forty-five minutes. Removal of the catalyst and the ethanol left a pale yellow liquid which was dissolved in 200 ml. of ether and extracted with 60 ml. of 5% hydrochloric acid, then with 60 ml. of water. Drying over calcium chloride, removal of the ether, and distillation of the residue gave 28.1 g. (83%) of a colorless liquid (XVIII) b.p. 103–105° (1.5 mm.); n_D^{25} 1.4390.

Anal. Calc'd for $C_{11}H_{22}N_2$: C, 72.5; H, 12.2.
Found: C, 72.5; H, 12.1.

A sample of 27.1 g. of this cyanamide was refluxed for twenty hours with a solution of 57 g. of sulfuric acid in 170 ml. of water. The cooled solution was made strongly alkaline with potassium hydroxide and extracted with three 100-ml. portions of ether. After drying over potassium carbonate, the ether was removed and the residue distilled. There was collected 21.2 g. (74%) of *2-n-butylaminohexane* b.p. 92–94° (30 mm.). The *hydrochloride* was recrystallized from acetone as fine, white rods m.p. 140–141.5°.

Anal. Calc'd for $C_{10}H_{24}ClN$: C, 62.0; H, 12.5.
Found: C, 62.3; H, 12.7.

An authentic sample of 2-*n*-butylaminohexane, prepared in 66% yield by the catalytic reduction of equimolar quantities of hexanone-2 and *n*-butylamine in ethanol solution using platinum oxide and three atmospheres of hydrogen boiled at 85–87° (24 mm.). The *hydrochloride* was recrystallized from acetone and formed fine white rods m.p. 139–140.5°. A mixed melting point of the two samples was 139.5–141°.

Separation of a mixture of n-butyl-δ-bromobutylcyanamide and n-butyl-(1-methyl-4-bromoamyl)cyanamide by reaction with diethylamine. The materials used were the crude products obtained from the ring opening of the respective pyrrolidines with cyanogen bromide.

A mixture of 50.3 g. (0.192 mole) of XVI and 40.2 g. (0.172 mole) of XIV in 266 g. (3.64 moles) of diethylamine (distilled over sodium) was refluxed for three hours. Removal of the excess diethylamine, under vacuum, using a large bore capillary, left a residue which was treated with sufficient 10% hydrochloric acid to yield a definitely acidic aqueous portion. The acid-insoluble oil was taken up in 300 ml. of ether, extracted with 50 ml. of water and dried over calcium chloride.

The acidic aqueous portion, to which had been added the 50 ml. of wash water, was made strongly alkaline with potassium hydroxide and extracted with two 200-ml. portions of ether and the combined ether extracts were dried over potassium carbonate.

Removal of the ether from the solution of the non-basic material (finally under water-pump vacuum at steam-bath temperature) left as residue 47.8 g. of an amber colored oil. This corresponds to a recovery of 95% of XVI.

Removal of the ether from the solution of the basic product (finally at 23 mm. and 80° for ten minutes) gave 38.3 g. (99%) of *butyl-δ-diethylaminobutylcyanamide.* Upon distillation this gave 34.8 g. of material; b.p. 128–130° (0.6 mm.).

With 1-n-butyl-2-methylpyrrolidine. Addition, over four hours, of a solution of 70.5 g. (0.50 mole) of 1-*n*-butyl-2-methylpyrrolidine in 200 ml. of benzene to a stirred solution of 58.2 g. (0.55 mole) of cyanogen bromide in 200 ml. of benzene gave a clear, pale yellow solution which was allowed to stand overnight. Extraction of this benzene solution with 100 ml. of 5% hydrochloric acid was followed by extraction with two 100-ml. portions of water. Drying over calcium chloride and removal of the benzene under reduced pressure left as residue 120 g. of a clear, red-brown liquid. The theoretical yield of ring-opened product is 123 g.

This crude product (120 g., 0.49 mole), suspected of being a mixture of isomers, was refluxed for three and one-half hours with 292 g. (4.0 mols) of diethylamine. After removal of the excess diethylamine the residue was treated with a solution of 50 ml. of concentrated hydrochloric acid in 200 ml. of water. The acid-insoluble oil was taken up in 350 ml. of ether and dried over calcium chloride. Removal of the ether left 31.9 g. of a yellow liquid. As shown below, this is the isomer (XX) containing the secondary alkyl bromide.

The above acidic aqueous solution was made strongly alkaline with potassium hydroxide. The oil which separated was taken up in 400 ml. of ether and dried over potassium carbonate. Removal of the ether and traces of diethylamine left, as residue, 81.0 g. of a clear, red-brown liquid.

In another experiment 60 g. of crude ring-opened product similarly treated with diethylamine gave 15.5 g. of non-basic material and 40.7 g. of the basic diethylamino derivative (XXI).

Distillation of 40.7 g. of this crude basic product gave 35.8 g. of a pale yellow oil b.p. 130–133° (0.7 mm.). The *oxalate*, on recrystallization from dioxane formed thin white needles m.p. 103–105° (shrinks 101–103°).

Anal. Calc'd for $C_{16}H_{31}N_3O_4$: C, 58.3; H, 9.5.
Found: C, 58.4; H, 9.6.

A sample of 15.0 g. of the above liquid, b.p. 130–133° (0.7 mm.) was refluxed five hours with a solution of 20 g. of sulfuric acid in 40 ml. of water. After making this solution alkaline, extracting with ether, drying over potassium carbonate, and removing the ether, distillation of the residue gave 11.5 g. (86%) of a colorless liquid (XXII) b.p. 125–126° (14 mm.). The *dihydrochloride* was recrystallized from acetone as white needles m.p. 201–203°.

Anal. Calc'd for $C_{13}H_{32}Cl_2N_2$: C, 54.3; H, 11.2; N, 9.7.
Found: C, 54.7; H, 11.2; N, 9.4.

Alkylation of a sample of Novol diamine (1-diethylamino-4-aminopentane), b.p. 85–86° (20 mm.) (purified *via* the dithiocarbamate) with *n*-butyl bromide gave a 47% yield of 1-diethylamino-4-*n*-butylaminopentane b.p. 136–138° (22 mm.). The *hydrochloride* formed white needles, m.p. 201–203°, from acetone. A mixed melting point with the above material gave m.p. 201–203°.

Treatment of a sample of the *n*-butyl-Novol diamine with cyanogen bromide gave in low (15%) yield a pale yellow liquid b.p. 128–130° (0.5 mm.). The *oxalate* after one recrystallization from acetone formed thin, white needles m.p. 103–105° (shrinks 100–103°). A mixed melting point of this material with the oxalate derived from the ring-opened product was 103–105° (shrinks 100–103°).

The isomer in the crude reaction mixture obtained from the ring-opening reaction, which did not react with diethylamine, was treated as follows:

A sample of 31.9 g. (0.13 mole) of this material was refluxed for one and one-half hours with a solution of 7.3 g. of potassium hydroxide in 125 ml. of absolute ethanol. After cooling in an ice-bath, the potassium bromide was removed by filtration. The ethanol was removed from the filtrate, the residue treated with 30 ml. of water, and the insoluble oil taken up in 100 ml. of ether and dried over magnesium sulfate. Removal of the ether and distillation of the residual brown liquid gave 19.2 g. (90%) of a colorless liquid b.p. 85–87° (0.5 mm.).

Reduction of 18.4 g. of this unsaturated material in 150 ml. of absolute ethanol using

0.4 g. of palladium black and 2 atmospheres of hydrogen resulted in the absorption of the theoretical amount of hydrogen at the end of one hour. Removal of the catalyst and ethanol and distillation of the residue gave 15.8 g. (85%) of a colorless liquid b.p. 90–92° (0.8 mm.).

Refluxing 14.6 g. of this material with a solution of 40 g. of sulfuric acid in 120 ml. of water for twenty hours and working up, as previously described, gave 11.4 g. of a brown liquid. Upon distillation over sodium there was collected 7.8 g. (63%) of colorless *butylamylamine* (XXIII) b.p. 80–81° (24 mm.); n_D^{20} 1.4220; n_D^{25} 1.4192. Henze and Humphreys (38) report b.p. 180–182° (743 mm.); n_D^{20} 1.4230 for butylamylamine.

The *picrolonate* formed pale yellow needles m.p. 215.5–216° from ethanol.

By the alkylation of *n*-butylamine with *n*-amyl bromide a sample of butylamylamine b.p. 81–82° (26 mm.); n_D^{25} 1.4190 was obtained.

The *picrolonate* formed pale yellow needles m.p. 215.5–216° from ethanol and showed no depression when mixed with the above picrolonate.

Anal. Calc'd for $C_{18}H_{29}N_5O_5$: N, 17.7. Found: N, 17.5.

With 1-isopropyl-2-methylpyrrolidine. The addition of 33.0 g. (0.26 mole) of this pyrrolidine in 150 ml. of benzene to a solution of 30.0 g. (0.28 mole) of cyanogen bromide in 200 ml. of benzene over four hours gave, after working up in the manner previously described, 57.0 g. (94%) of crude reaction product consisting of an amber-colored liquid. This was refluxed four hours with 146 g. of diethylamine. There was isolated 18.4 g. of an acid-insoluble amber-colored liquid assumed to be the ring-opened product containing the secondary alkyl bromide. No work was done to establish the structure of this material.

There was isolated 36.1 g. of basic material consisting of a brown liquid. When twice distilled, 30.7 g. of a pale yellow liquid b.p. 107–110° (0.4 mm.) was collected. An *oxalate* was recrystallized from dioxane–ethanol as fine white needles m.p. 132–134° (dec.).

Anal. Calc'd for $C_{15}H_{29}N_3O_4$: C, 57.1; H, 9.3.
Found: C, 57.3; H, 9.1.

Though no work was done to prove definitely the structure of this material, it is assumed to be *1-diethylamino-4-(isopropylcyanamido)pentane* (XXVI).

With 1-n-Butyl-2,2-dimethylpyrrolidine. There was added, over five hours with stirring, a solution of 49.3 g. (0.320 mole) of 1-*n*-butyl-2,2-dimethylpyrrolidine in 150 ml. of absolute ether to a solution of 33.9 g. (0.320 mole) of cyanogen bromide in 200 ml. of absolute ether. When the addition was approximately one-half complete, the clear solution became cloudy and a small quantity of a white crystalline solid began to separate. The amount of this steadily increased during the remainder of the addition. After standing overnight at room temperature, the mixture was filtered and the solid washed with ether yielding 21.0 g. of a white crystalline solid m.p. 145–147°. Recrystallization of a sample from dioxane gave white needles m.p. 148–149°. A mixed m.p. showed this to be the *hydrobromide* of *1-n-butyl-2,2-dimethylpyrrolidine.*

Extraction of the ether solution with two 60-ml. portions of water gave a neutral aqueous solution, which after making strongly basic, was extracted with ether. After drying these combined ether extracts over potassium hydroxide, removal of the ether left 3.8 g. of a colorless basic liquid.

After extracting the ether solution of the original reaction mixture with 100 ml. of 7% hydrochloric acid followed by extraction with two 100-ml. portions of water, it was dried over magnesium sulfate. By making these acidic aqueous extracts basic and extracting with ether there was obtained 6.1 g. more of a basic liquid. Distillation of the total of 9.9 g. of this base gave 7.2 g. of a colorless liquid b.p. 74–76° (22 mm.). Total recovery of the starting material in the form of the hydrobromide and the free base amounted to 0.136 mole.

Removal of the ether from the solution of the non-basic product left as residue 30.0 g. of an amber-colored liquid, which, upon distillation, gave 24.3 g. of a yellow liquid b.p. 108–111° (1.3 mm.). This, upon standing overnight, turned to a clear red-brown liquid.

This 24.3 g. (0.135 mole., assuming it to be an unsaturated cyanamide) in 150 ml. of absolute ethanol was hydrogenated at three atmospheres pressure, over 0.5 g. of palladium black. After shaking for three hours, the calculated amount of hydrogen was absorbed. When removed from the shaker, an ammoniacal odor was noticed. Removal of the catalyst and ethanol yielded 24.4 g. of a yellow liquid, which was dissolved in 150 ml. of ether and extracted with 100 ml. of 7% hydrochloric acid and then with 50 ml. of water. After drying over calcium chloride and removing the ether, 16.5 g. of an amber-colored liquid was obtained. Distillation of this gave 13.0 g. of a colorless liquid b.p. 101–103° (1.0 mm.). A cut of b.p. 102° (1.0 mm.); n_D^{25} 1.4450 was taken for analysis.

Anal. Calc'd for $C_{11}H_{22}N_2$: C, 72.5; H, 11.6.

Found: C, 72.4; H, 11.6.

This material is *n-butylisohexylcyanamide* (XXXI).

A sample of 11.9 g. of this cyanamide was hydrolyzed by refluxing for twenty hours with a solution of 25 g. of sulfuric acid in 75 ml. of water. Upon working up this mixture, there was obtained 7.1 g. of *n-butylisohexylamine* (XXXII) b.p. 94–96° (28 mm.). The *hydrochloride*, twice recrystallized from acetone, formed colorless plates m.p. 279–280° (darkens 276–278°).

Anal. Calc'd for $C_{10}H_{24}ClN$: C, 62.0; H, 12.5.

Found: C, 62.1; H, 12.5.

A sample of *n-butylisohexylamine*, prepared by the alkylation of isohexylamine (b.p. 122–125°) with *n*-butyl bromide, gave b.p. 87–88° (20 mm.). The *hydrochloride* formed colorless plates m.p. 276–277° (darkens 272–274°) from acetone. A mixed melting point of this material with that above was 276–278° (darkens 272–276°).

A *second* ring opening of 1-*n*-butyl-2,2-dimethylpyrrolidine with cyanogen bromide was carried out as follows:

A solution of 34.3 g. (0.22 mole) of 1-*n*-butyl-2,2-dimethylpyrrolidine in 150 ml. of dry benzene was added over three hours, with stirring to a solution of 27.0 g. (0.25 mole) of cyanogen bromide in 150 ml. of benzene. The resulting clear yellow benzene solution was refluxed for fifteen minutes and allowed to stand overnight at room temperature. After extracting with 100 ml. of 5% hydrochloric acid and two 100-ml. portions of water, the benzene solution was dried over calcium chloride.

From these acidic aqueous extracts there was recovered 15.2 g. (0.10 mole) of 1-butyl-2,2-dimethylpyrrolidine b.p. 63–65° (14 mm.).

Removal of the benzene from the above solution of non-basic products left 21.0 g. of a light amber-colored liquid which was refluxed for three hours with 58 g. of diethylamine and allowed to stand overnight. The formation of no solid salts was noticed. Removal of the diethylamine left a dark red-brown liquid which was treated with excess dilute hydrochloric acid. The acid-insoluble liquid was taken up in ether and dried over magnesium sulfate. Removal of the ether left 17.8 g. of a red-brown liquid which gave on distillation 14.2 g. of a clear yellow liquid b.p. 91–95° (0.45 mm.) which turned to a red-brown color on standing overnight. This 14.2 g. (0.08 mole) of unsaturated cyanamide together with the 15.2 g. (0.10 mole) of recovered starting material accounts for 0.18 mole of the 0.22 mole of starting material. By making the acidic extracts of the product resulting from the reaction with diethylamine basic and extracting with ether, there was isolated 0.2 g. of a dark oil which was discarded.

With 1-n-butylazetidine. Addition, over three hours with stirring, of a solution of 18.5 g. (0.16 mole) of 1-*n*-butylazetidine in 150 ml. of absolute ether to a solution of 17.4 g. (0.16 mole) of cyanogen bromide in 200 ml. of absolute ether gave a clear, pale yellow solution which was allowed to stand overnight at room temperature. After extracting with 100 ml. of 5% hydrochloric acid and two 50-ml. portions of water, the ether solution was dried over magnesium sulfate. Removal of the ether left 35.1 g. of a pale yellow liquid which gave, on distillation, 30.7 g. (85%) of a colorless liquid b.p. 110–112° (0.4 mm.); n_D^{25} 1.4778. A sample on redistillation gave b.p. 115–116° (0.7 mm.); n_D^{25} 1.4783.

Anal. Calc'd for $C_8H_{15}BrN_2$: C, 43.9; H, 6.9.

Found: C, 43.8; H, 6.6.

A solution of 10.8 g. of this material in 50 g. of diethylamine was allowed to stand for twenty hours at room temperature. A copious precipitate of solid salts formed. After removing the excess diethylamine under water-pump vacuum, the residue was treated with excess aqueous potassium hydroxide and extracted with three 50-ml. portions of ether. After drying the combined ether extracts over potassium carbonate, the ether and traces of diethylamine were removed under reduced pressure, leaving 11.0 g. of a straw-colored liquid. Distillation gave 8.7 g. (83%) of a pale yellow liquid b.p. 108–110° (0.4 mm.). This material is *n-butyl-γ-diethylaminopropylcyanamide*. An *oxalate* formed white needles m.p. 131–132.5° (dec.) from acetone.

Anal. Calc'd for $C_{14}H_{27}N_3O_4$: C, 55.8; H, 9.0.
Found: C, 55.9; H, 9.3.

With 1-n-butylethylenimine. When a solution of 65 g. (0.65 mole) of 1-*n*-butylethylenimine in 300 ml. of absolute ether was added over four hours, with stirring, to a solution of 75 g. (0.71 mole) of cyanogen bromide in 200 ml. of ether, the heat of reaction was sufficient to maintain gentle refluxing of the ether. After standing overnight, the clear pale yellow ether solution was extracted with 100 ml. of 5% hydrochloric acid and two 100-ml. portions of water and then dried over calcium chloride. Removal of the ether and distillation of the residue (131 g.) gave 126 g. (94%) of a colorless liquid b.p. 106–108° (0.6 mm.). A middle cut b.p. 106–107° (0.6 mm.); n_D^{25} 1.4804 was taken for analysis.

Anal. Calc'd for $C_7H_{13}BrN_2$: C, 41.0; H, 6.4; N, 13.7.
Found: C, 41.1; H, 6.2; N, 13.7.

A sample of 20.5 g. of this material was refluxed for three hours with 73 g. of diethylamine. The formation of a large amount of solid amine salts took place rapidly. After standing overnight at room temperature, the excess diethylamine was removed and excess aqueous potassium hydroxide was added. Extraction with ether, drying over potassium carbonate and removal of the ether and distillation of the residue gave 14.0 g. (71%) of a colorless liquid b.p. 98–110° (0.4 mm.). An *oxalate*, recrystallized from dioxane–isopropanol (3:1), formed clusters of short, white needles m.p. 95–96° (dec.).

Anal. Calc'd for $C_{13}H_{25}N_3O_4$: C, 54.3; H, 8.8.
Calc'd for $[C_{13}H_{25}N_3O_4]_2 \cdot C_3H_8O$: C, 54.9; H, 9.3.
Found: C, 54.8; H, 9.2.

With 1-ethylethylenimine. Addition over six hours of a solution of 71 g. (1.0 mole) of 1-ethylethylenimine in 300 ml. of ether to a solution of 106 g. (1.0 mole) of cyanogen bromide in 300 ml. of ether gave, after working up as above 156 g. (88%) of a colorless liquid b.p. 92–94° (0.6 mm.); $n_D^{25°}$ 1.4864. Redistillation of a sample gave b.p. 89–90° (0.4 mm.); n_D^{25} 1.4862.

Anal. Calc'd for $C_5H_9BrN_2$: C, 33.9; H, 5.1.
Found: C, 34.2; H, 5.3.

With 1-n-butyl-2,2-dimethylethylenimine. Over a period of seven hours there was added, with stirring, a solution of 80.0 g. (0.62 mole) of 1-*n*-butyl-2,2-dimethylethylenimine in 300 ml. of absolute ether to solution of 65 g. (0.62 mole) of cyanogen bromide in 300 ml. of ether. Approximately one hour after the addition was started a small amount of a white, crystalline solid began to precipitate. This slowly increased in quantity during the remainder of the addition. After standing overnight the reaction mixture consisted of a yellow solution and a precipitated tan solid. Addition of 250 ml. of absolute ether caused the precipitation of more solid. Filtration of the mixture and washing the collected solid with ether gave a slightly sticky light brown solid. Addition of 400 ml. of absolute ether to a solution of this in 40 ml. of absolute alcohol caused the precipitation of a white, crystalline solid. The collected solid was washed with ether yielding 28.0 g. (0.10 mole) of white plates m.p. 192.5–193.5°. A mixed melting point with the material of m.p. 192.5–193.5°, obtained by treating 1-*n*-butyl-2,2-dimethylethylenimine with hydrogen bromide, showed no depression. Recrystallization from dioxane of a sample of the material obtained from the reaction mixture gave white plates m.p. 193.5–194.5°.

Anal. Calc'd for $C_8H_{19}Br_2N$: C, 32.2; H, 6.6.
Found: C, 32.1; H, 6.7.

After extracting the ether filtrate from the above solid with 100 ml. of 5% hydrochloric acid and then with two 100-ml. portions of water, it was dried over calcium chloride. Removal of the ether left 84 g. of a clear amber-colored liquid which gave upon distillation 27 g. of a colorless liquid b.p. 81–83° (0.9 mm.). At this stage the material in the distilling flask darkened and resinified. The distillation was stopped at this point and the hardened residue (52 g.) was saved. The above colorless liquid turned yellow on standing overnight. Redistillation gave 19.9 g. of a colorless liquid b.p. 68–69° (0.4 mm.); n_D^{25} 1.4518.

Anal. Calc'd for $C_9H_{16}N_2$: C, 71.0; H, 10.6.
Found: C, 71.1; H, 11.0.

There remained in the distilling flask from the second distillation 6.1 g. of an amber-colored gum. This indicates that this unsaturated cyanamide has a tendency to polymerize on heating.

When 19.8 g. (0.13 mole) of the distilled unsaturated cyanamide in 200 ml. of absolute methanol was shaken under 33 lbs. of hydrogen with 0.4 g. of palladium black for one hour absorption of one-third of the calculated amount of hydrogen and apparent cessation of any further uptake occurred. Addition of 0.4 g. more of palladium black and shaking for forty-five minutes resulted in the absorption of the calculated amount of hydrogen. After removing the catalyst and the methanol, there was obtained 19.7 g. of a yellow liquid. After adding 60 ml. of 5% hydrochloric acid, the mixture was extracted with two 60-ml. portions of ether and these extracts were dried over calcium chloride. When the acidic aqueous portion was made alkaline, 2 to 3 g. of a basic liquid separated. This material was not investigated.

Removal of the ether from the solution of the non-basic material left 15.7 g. of a yellow liquid. Distillation gave 13.8 g. of a colorless liquid b.p. 74–75° (0.8 mm.); n_D^{25} 1.4382.

Anal. Calc'd for $C_9H_{18}N_2$: C, 70.1; H, 11.7.
Found: C, 70.3; H, 11.1.

A sample of 13.4 g. of this material, assumed to be *butylisobutylcyanamide*, was refluxed for twenty hours with a solution of 40 g. of sulfuric acid in 120 ml. of water. Upon working up, as in previous examples, 9.0 g. of a pale yellow liquid was obtained. Distillation over sodium gave 6.6 g. of a colorless liquid b.p. 147–148°; $n_D^{20°}$ 1.4125. Henze and Humphreys (38) report b.p. 150–151° (738 mm.); $n_D^{20°}$ 1.4120 for *butylisobutylamine*. The *phenylthiourea* prepared from this was recrystallized from ethanol-water giving colorless rhombohedra m.p. 83–84.5° (softens 82–83°). A mixture of this phenylthiourea with a sample prepared from a known sample of butylisobutylamine melted at 83–84.5° (softens 82–83°).

Anal. Calc'd for $C_{15}H_{24}N_2S$: C, 68.1; H, 9.1.
Found: C, 67.7; H, 8.8.

From the total of 84 g. of non-basic products there was isolated 27 g. of an unsaturated cyanamide and 52 g. of a non-distillable gum. Treatment of an ethanolic solution of this gum with ethanolic potassium hydroxide resulted in the precipitation of a considerable amount of potassium bromide but there was isolated only a viscous material which would not distill under a pressure of 0.8 mm. and a bath temperature of 230°. This material was discarded.

When a ring-opening reaction was carried out in benzene solution employing 40.0 g. of the 1-*n*-butyl-2,2-dimethylethylenimine and 37.0 g. of cyanogen bromide, there was isolated 17.0 g. of solid m.p. 192.5–193.5° and 44.5 g. of a non-basic liquid which, on distillation gave 17.3 g. of the unsaturated cyanamide b.p. 79–81° (0.7 mm.) and 23.0 g. of a residual gum.

With 1-n-butyl-2-ethylethylenimine. A solution of 35.0 g. (0.28 mole) of 1-*n*-butyl-2-ethylethylenimine in 250 ml. of absolute ether was added, with stirring, over eight hours to a solution of 33.0 g. (0.31 mole) of cyanogen bromide in 200 ml. of ether. Approximately one-half of the addition was complete when a small amount of a white solid began to precipitate. After standing overnight, the mixture was filtered from 4.2 g. of a white solid of m.p. 185–190°. A sample of the solid after one recrystallization from dioxane formed white plates m.p. 197–198°. No depression was observed on melting a mixture of this material and the *bromoamine hydrobromide* m.p. 197–198° obtained by treating 1-*n*-butyl-2-ethylethylenimine with hydrogen bromide in ether solution.

The ether filtrate from the above hydrobromide was extracted with three 50-ml. portions of water and then dried over magnesium sulfate. Evaporation of the combined aqueous extracts to dryness left 4.0 g. of an amber-colored semi-solid gum. This constitutes a total of 8.2 g. of water-soluble material obtained from the reaction mixture.

Removal of the ether from the above solution left 54.6 g. of an amber-colored liquid. Distillation of 14.0 g. of this material gave, after 2.1 g. of a forerun b.p. 73–107° (0.4 mm.), 9.5 g. of a colorless liquid of b.p. 107–109° (0.4 mm.). There remained 2.0 g. of a non-distillable, dark brown residue. On refluxing 40.6 g. of the crude product for seven hours with 73 g. of diethylamine and allowing the mixture to stand overnight, only traces of solid salts were formed. After removing the excess diethylamine and making the residue acidic with dilute hydrochloric acid, it was extracted with three 50-ml. portions of ether. After drying the ether extracts, containing the non-basic material, over magnesium sulfate, removal of the ether left 36.0 g. of an amber-colored liquid. Distillation gave 6.0 g. of a forerun b.p. 75–110° (0.4 mm.) and 24.5 g. (38%) of a colorless liquid b.p. 108–110° (0.5 mm.) which slowly darkened on standing. Redistillation of 15 g. of this material gave 8.8 g. of a colorless liquid of b.p. 106° (0.5 mm.); n_D^{25} 1.4792.

Anal. Calc'd for $C_9H_{17}BrN_2$: C, 46.4; H, 7.3; N, 12.0.
Found: C, 46.3; H, 7.4; N, 12.1.

This material is a *bromocyanamide* which did not react with diethylamine under the above conditions. The only basic product obtained from the treatment with diethylamine consisted of 2.0 g. of a dark brown liquid which was not investigated.

TABLE I

RING OPENING OF 1-*n*-BUTYL-2-ETHYLETHYLENIMINE

IMINE USED, G.	UNSATURATED CYANAMIDE, G.	SALT OF M.P. 197–198°, G.	CRUDE BROMOCYANAMIDE, G.
35.0	5.7	4.2	49
36.8	4.9	6.1	54
57.0	8.6	6.4	87
70.0	9.7	9.0	105

The combined foreruns (8.1 g.) of b.p. 73–107° (0.4 mm.) and 75–110° (0.4 mm.) were redistilled, and 5.7 g. of a colorless liquid b.p. 73–75° (0.6 mm.); $n_D^{25°}$ 1.4510, was collected.

Anal. Calc'd for $C_9H_{16}N_2$: C, 71.1; H, 10.5.
Found: C, 70.8; H, 10.3.

This material decolorized bromine water and dilute aqueous potassium permanganate. It must be an unsaturated cyanamide resulting from an elimination reaction which furnished the hydrogen bromide required for the formation of the bromoalkylamine hydrobromide which was isolated.

Table I shows the quantities of the various products obtained from four ring openings carried out in an identical manner.

The values given for the crude bromocyanamide are those calculated by subtracting the quantity of unsaturated cyanamide obtained from the crude yield of non-basic material.

The combined unsaturated cyanamide from three runs was redistilled, giving 16.6 g. of material b.p. 75–77° (0.7 mm.); n_D^{25} 1.4491. Hydrogenation of this material in 200 ml. of methanol, over 0.5 g. of palladium black under two to three atmospheres of hydrogen resulted in absorption of 90% of the calculated amount of hydrogen after shaking for two hours. Shaking for an additional hour caused no further absorption of hydrogen. After removing the catalyst and methanol, the residue was refluxed for twenty hours with a solution of 40 g. of sulfuric acid in 120 ml. of water. Working up this hydrolysis product as in the above cases gave, after two distillations over sodium, 4.8 g. (34%) of a colorless amine of b.p. 154–156°; n_D^{25} 1.4116. A *phenylthiourea* (from ethanol-water) melted at 83–84° and a mixed melting point with the phenylthiourea, m.p. 83–84°, of di-*n*-butylamine (b.p. 157–158°; n_D^{25} 1.4141) showed no depression. Suggitt and Wright (39) report m.p. 85.5–86° for the phenylthiourea of di-*n*-butylamine.

In an attempt to remove the bromine from the bromoalkyl cyanamide of b.p. 110–112° (0.5 mm.) for the purpose of structure identification, the following results were obtained: To a solution of 23.3 g. (0.10 mole) of the bromodibutylcyanamide in 200 ml. of absolute methanol was added 20 g. of Raney nickel (wet with ethanol). Shaking under 2 to 3 atmospheres of hydrogen resulted in the uptake of 0.10 mole of hydrogen over forty minutes. After filtering off the catalyst and distilling off the methanol at atmospheric pressure, the residue was treated with 60 ml. of 20% aqueous potassium hydroxide. The insoluble oil was taken up in 150 ml. of benzene. After distilling off the benzene (and traces of water) under atmospheric pressure, the residual brown liquid (15 g.) was distilled over sodium. After collecting 2.0 g. of a colorless liquid b.p. 55–110° (25 mm.) and 2.5 g. b.p. 110–123° (25 mm.), there was obtained 7.2 g. of a colorless distillate b.p. 123–125° (25 mm.). A residue in the distilling flask of approximately 5 g. of a light brown solid remained. Another reduction carried out similarly gave 6.8 g. of product b.p. 123–125° (25 mm.). This material was slightly water soluble, yielding a strongly basic solution. It was completely soluble in dilute acid. Redistillation of these combined products gave 11.2 g. of distillate b.p. 123–125° (25 mm.); n_D^{25} 1.4598. The substance was extremely hygroscopic and gained weight even during weighing of an analytical sample in a fine capillary. However, all available data support the structure assigned to it. If the found analytical data are corrected on the basis of the assumption that the failure of the carbon, hydrogen, and nitrogen found to add up to 100% is due to water acquired during weighing the sample, the figures obtained are consistent with calculated ones.

Anal. Calc'd for $C_9H_{18}N_2$: C, 70.1; H, 11.8; N, 18.2.
Found: C, 68.7; H, 12.0; N, 17.6.

If these figures are corrected to take into account 1.7% of water necessary to make them total 100%, the following are obtained:

Found (corr.): C, 70.0; H, 12.0; N, 17.9.

Neutral equiv.: Calc'd, 154. Found, 150.

The substance can hardly have a structure other than one of the two assigned to it (L or LI) since it obviously is a monoacidic base containing two nitrogens.

CATALYTIC HYDROGENATION OF CYANAMIDES

n-Butyl-(4-diethylaminobutyl)cyanamide. When 107 g. (0.48 mole) of butyl-(4-diethylaminobutyl)cyanamide [b.p. 122–123° (0.4 mm.)] was shaken with 15 g. of Raney nickel in 200 ml. of absolute ethanol under an initial pressure of 1800 lb. of hydrogen, reduction began at 170°. After two hours approximately one mole of hydrogen had been absorbed.

Removal of the catalyst and ethanol and distillation of the residue yielded 39.0 g. of a colorless liquid b.p. 140–144° (26 mm.). Redistillation of this fraction over sodium gave 36.5 g. of a colorless liquid b.p. 137–138° (28 mm.); n_D^{25} 1.4410.

Anal. Calc'd for $C_{12}H_{28}N_2$: C, 72.1; H, 14.1.
Found: C, 71.9; H, 14.2.

A *dihydrobromide* prepared in ether and twice recrystallized from dioxane–ethanol mixture formed clusters of long, white needles m.p. 168–170° (softens 163–168°).

Anal. Calc'd for $C_{12}H_{30}Br_2N_2$: C, 39.8; H, 8.3; N, 7.7.
Found: C, 39.8; H, 8.6; N, 7.8.

These analytical data check for *1-n-butylamino-4-diethylaminobutane* and its *dihydrobromide.* The residue from the first distillation was fractionated. There was collected 50.0 g. of a colorless liquid b.p. 135–137° (1.4 mm.) which constitutes a recovery of 47% of the starting material.

Ethyl-β-bromoethylcyanamide. To 20.0 g. (0.11 mole) of ethyl-β-bromethylcyanamide (b.p. 92–94°/0.4 mm.) in 200 ml. of absolute methanol was added 20 g. of Raney nickel wet with ethanol. When placed in an Adams' shaker under 35 lbs. of hydrogen there took place, during five minutes' shaking, a pressure drop of 110% of that calculated for removal of the bromine. Shaking for an additional ten minutes caused no further drop in pressure. After filtering off the catalyst, the methanol was removed by distillation at atmospheric pressure. Addition of 50 ml. of water to the residue caused the separation of no water-insoluble material. Extraction with ether (100 ml.) and removal of the ether from the extract left no residue. After making the aqueous solution strongly basic with potassium hydroxide, the mixture was warmed for twenty minutes on the steam-bath. After cooling, the oil was taken up in 100 ml. of ether and dried over potassium carbonate. Removal of the ether and distillation of the residue over sodium gave 7.2 g. (72%) of a colorless liquid of b.p. 126–129°. This material was readily soluble in water to give a strongly basic solution. Aspinall (40) reports b.p. 129–131° for N-ethylethylenediamine and gives the following derivatives: dipicrate m.p. 195°, dibenzamide m.p. 120°; di-(*p*-bromobenzenesulfonamide) m.p. 126°. When these derivatives were prepared from the above liquid, there were obtained the following: *dipicrate* m.p. 194–195°, *dibenzamide* 117–118°, *di-(p-bromobenzenesulfonamide)*, m.p. 124–125°. These data identify the above product as *N-ethylethylenediamine*. The residue from the distillation consisted of 2 to 3 g. of a brown, semi-solid material which was not investigated.

PREPARATION OF CYCLIC GUANIDINES

The *general procedure* for the preparation of these compounds was to mix equimolar quantities of the β-bromoethylcyanamide and the primary amine in absolute ethanol (50 ml. for 0.1 mole) and reflux three to four hours. The majority of the ethanol was removed by distillation and the solidified residue broken up and washed with ether and recrystallized.

1,3-Di-n-butyl-2-iminoimidazolidine hydrobromide was prepared in 86% yield from butyl-β-bromoethylcyanamide and *n*-butylamine. It formed white needles from dioxane-ethanol m.p. 177–179°.

Anal. Calc'd for $C_{11}H_{24}BrN_3$: C, 47.5; H, 8.7.
Found: C, 47.6; H, 8.7.

1-Ethyl-3-(2-hydroxyethyl)-2-iminoimidazolidine hydrobromide was prepared in 77% yield from ethyl-β-bromoethylcyanamide and ethanolamine. Colorless stout rods from butanol m.p. 122–123° were formed.

Anal. Calc'd for $C_7H_{16}BrN_3O$: C, 35.3; H, 6.8.
Found: C, 35.3; H, 7.0.

Bis-[2-(3-n-butyl-2-imino-1-imidazolidyl)ethyl]sulfide dihydrobromide was prepared in 95% yield from butyl-β-bromoethylcyanamide and β,β'-diaminodiethyl sulfide. It formed fine, white needles from isopropanol m.p. 204–206°.

Anal. Calc'd for $C_{18}H_{38}Br_2N_6S$: C, 40.8; H, 7.2.
Found: C, 40.5; H, 7.3.

Bis-[2-(3-n-butyl-2-imino-1-hexahydropyrimidyl)ethyl]sulfide dihydrobromide was prepared in 62% yield from butyl-γ-bromopropylcyanamide and β,β'-diaminodiethyl sulfide. It formed fine, white needles from isopropanol m.p. 198–199.5° (softens 196–198°).

Anal. Calc'd for $C_{20}H_{42}Br_2N_6S$: C, 43.0; H, 7.6.
Found: C, 42.7; H, 7.5.

Proof of structure of the guanidine (XXXIX). A solution of 48.0 g. of XXXIX (m.p. 177–179°) in 50 ml. of water was made alkaline. The resulting oily layer (slightly water soluble) was separated and refluxed eighteen hours with a solution of 40 g. of potassium hydroxide in 160 ml. of water. After cooling and dissolving the oil in ether, the ether solution was dried first with pellets of potassium hydroxide then over sodium. Removal of the ether and distillation of the residue over sodium gave 1.5 g. of a colorless forerun b.p. 80–123° (23 mm.), 4.9 g. (17%) of a colorless liquid (LX) b.p. 123–125° (23 mm.) and finally 19.2 g. of a colorless liquid b.p. 168–169° (23 mm.). A sample of this last fraction was converted to a *hydrobromide* in ether. After one recrystallization from dioxane-ethanol white needles of m.p. 177–179° were obtained. When mixed with a sample of XXXIX no depression in melting point was observed. This material b.p. 168–169° (23 mm.) is therefore the unhydrolyzed cyclic guanidine.

When a sample of the fraction b.p. 123–125° (23 mm.) in ether was treated with an ether solution of cyanogen bromide, there precipitated a white solid, which, after one recrystallization from dioxane–ethanol, formed white needles m.p. 177–179°. No melting point depression was observed when this was mixed with an original sample of XXXIX. The fraction 123–125° (23 mm.) must be *N,N′-di-n-butylethylenediamine*. King and McMillan (41) report b.p. 119–125° (23 mm.) for N,N′-di-*n*-butylethylenediamine. The formation of this hydrolysis product and its conversion back to XXXIX with cyanogen bromide furnish conclusive proof of the structure assigned to XXXIX.

SUMMARY

1. The reaction with cyanogen bromide of various N-alkylpyrrolidines and ethylenimines has been studied.

2. Two β-bromoethylalkylcyanamides have been prepared and shown to behave in an unpredicted manner upon catalytic reduction.

3. The reaction of a β-bromoethylalkylcyanamide with a primary amine has been shown to yield a cyclic guanidine.

New York 27, New York

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