[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

THE VON BRAUN CYANOGEN BROMIDE REACTION. II. APPLICATION TO N-ARYLPYRROLIDINES[1, 2]

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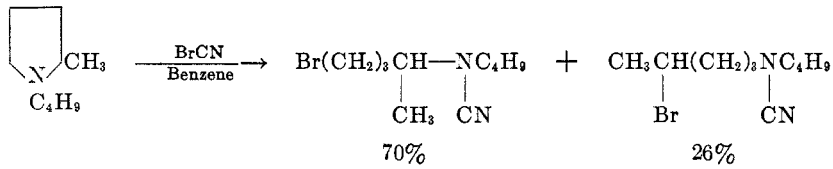
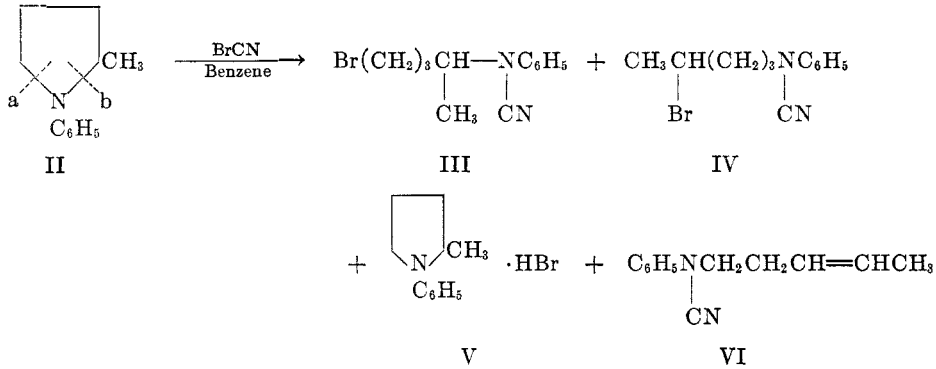
In a preceding communication (1) a study of the direction of ring cleavage of a number of unsymmetrically substituted saturated N-alkyl heterocycles under the influence of cyanogen bromide was reported. As a typical example the cleavage of 1-(*n*-butyl)-2-methylpyrrolidine may be given.



We now wish to report the results of a similar investigation with a series of 2-methylpyrrolidines which carry a phenyl or substituted phenyl group on the nitrogen.

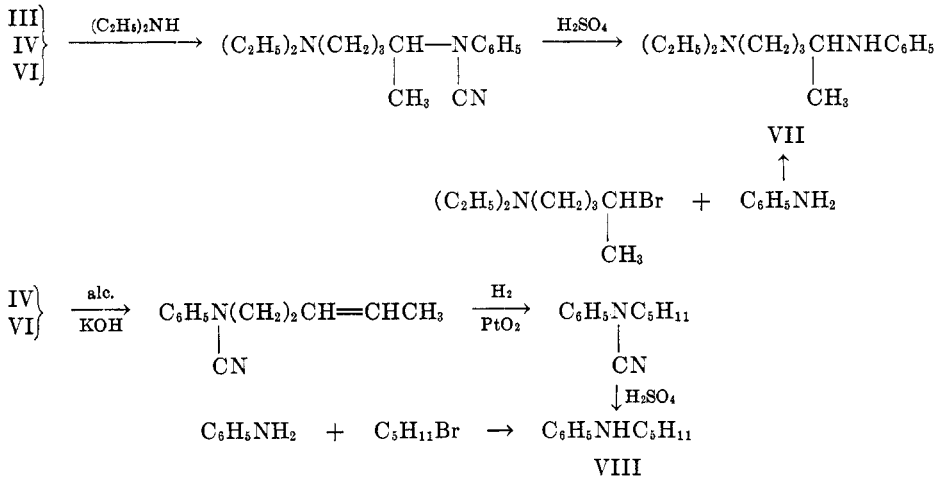
Substitution of a phenyl group for the *n*-butyl group of I decreases the basicity of the nitrogen with the result that the phenylpyrrolidine was much less reactive to cyanogen bromide. When 1-phenyl-2-methylpyrrolidine (II) was treated with cyanogen bromide in benzene in the manner described previously, it was immaterial whether the pyrrolidine was added to the cyanogen bromide or *vice versa* as far as the nature or relative amounts of the products was concerned. 20% of unreacted II was recovered as the hydrobromide, an additional 20% of II was recovered as the free base, and 56% of the starting material appeared as isomeric products of ring cleavage, including dehydrohalogenated compounds,—a total recovery of 96%. The course of the cleavage may then be represented as follows.



[1] The material here presented is taken from a dissertation submitted by Milton Green in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Columbia University.

[2] We wish to acknowledge a generous grant from Eli Lilly and Co., Indianapolis, Ind., for the support of this work.

Separation and identification of the products was accomplished by the following scheme (1). The pyrrolidine hydrobromide, V, was soluble in benzene and was obtained in crystalline form when anhydrous ether was added to the residue after removal of the benzene.



VII was identified as the citrate by comparison with a known sample prepared from aniline and 1-diethylamino-4-bromopentane. Bergmann (2) reports the preparation of VII by reductive alkylation of aniline with 1-diethylamino-pentanone-4, but we have been unsuccessful in repeating this.

The mixture of IV and VI could not be distilled. It was characterized by dehydrobromination, reduction of the resulting double bond, and hydrolysis to VIII which was identified by comparison of the oxalate and *p*-toluenesulfonyl derivative with known samples. In most of the reactions the amount of VI formed was considered equivalent to the amount of V isolated. As a check, in two runs and in those experiments in which the hydrobromide was not isolated, the mixture of IV and VI remaining after removal of III by reaction with diethylamine was dehydrobrominated with alkali and the bromide ion formed was determined, thus giving the amount of IV in the mixture. VI was then determined by difference. The two methods gave results in close agreement.

When the ring opening was carried out in ether, no V was found indicating that the elimination reaction had not occurred to any appreciable extent.

The proportions of the products of ring cleavage from the reaction of II with cyanogen bromide, about 20% of primary halide and 80% of secondary halide, is almost exactly the reverse of the proportions of the two halides obtained from I (1). In order to ascertain the effect of changing the basicity of the nitrogen in II on the relative amounts of the two bromides, 1-(*p*-chlorophenyl)- and 1-(*p*-methoxyphenyl)-2-methylpyrrolidine were prepared and treated with cyanogen bromide. The presence of the methoxyl group increased the amount of ring cleavage at *a*, whereas the presence of a chlorine resulted in somewhat more cleavage at *b*. When the reaction was carried out in a more polar solvent cleavage at *b* was favored. These results are summarized in Table I.

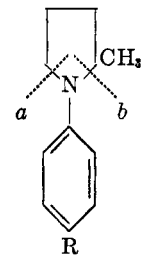
The data presented in Table I, taken in conjunction with those previously presented (1), are consistent with the formulation of the reaction as occurring by simultaneous SN_1 and SN_2 mechanisms. Thus in I, in which the presence of an alkyl group on the nitrogen atom of the pyrrolidine would be expected to increase the basicity of the nitrogen, the mechanism originally suggested by Von Braun (3) involving an SN_2 displacement by bromide ion would be expected to predominate:

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

On the other hand, with a phenyl group attached to the nitrogen atom, the basicity of the nitrogen would be decreased to the extent that the SN_1 reaction,

TABLE I

REACTION OF 1-PHENYL-2-METHYLPYRROLIDINES WITH CYANOGEN BROMIDE

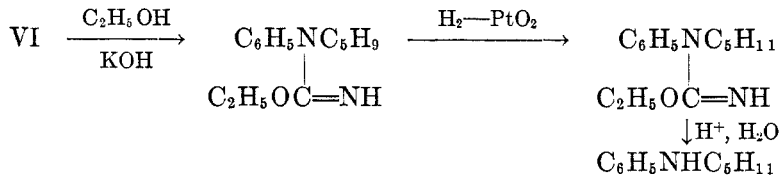


R	SOLVENT	CLEAVAGE AT *a* 1° HALIDE, %	CLEAVAGE AT *b*		RATIO OF CLEAVAGE AT *b* TO CLEAVAGE AT *a*
			2° HALIDE, %	OLEFIN, %	
H	Ether	18.8	81.2	0	4.3
H	Benzene	19.7	58.5	21.8	4.1
H	Benzene	21.3	56.9	21.8	3.7
H	Benzene	20.1	58.5	22.4	4.0
H	Acetonitrile	15.7	58.7	25.6	5.4
H	Acetic acid	10	—	—	—
CH_3O	Ether	26.5	73.5	0	2.8
CH_3O	Benzene	22.5	53.6	23.9	3.4
Cl	Benzene	16.7	49.9	33.4	5.0

involving an intermediate carbonium ion would be expected to predominate. In view of the known stability of secondary carbonium ions with respect to primary carbonium ions, the results of these experiments become readily explainable.

In connection with the above experiments, mention should be made of one run with II in which the mixture of IV and VI in which IV was undergoing dehydrobromination was allowed to remain in contact with alcoholic potassium hydroxide overnight. The sole product of the subsequent reduction, obtained in excellent yield was a basic, oxygen-containing substance, the formation of which indicated that the solvent had participated in the reaction. This substance was shown to be N-(*n*-amyl)-N-phenylethylisourea which was undoubtedly formed

by the addition of alcohol to the initial product of the reaction (VI) by the following reactions:



The addition of alcohols to cyanamides to give isoureas is a general one, usually proceeding under the influence of acids (4) and requiring several days for completion. It has also been reported as taking place when the cyanamide is heated with equimolar amounts of sodium ethoxide or potassium hydroxide in alcohol, but the yields, especially in the latter instance are poor (5). There is no indication from preceding reports that the reaction may occur under very mild conditions, or that the effect of alkali is a catalytic one. It has been shown in the present work that ethylphenylcyanamide is converted to N-ethyl-N-phenylethylisothiourea in 85% yield under the influence of an alcoholic solution containing 0.1 equivalent of potassium hydroxide at room temperature in 12 hours. This reaction is discussed at greater length in the following paper.

The reaction of 1-(*p*-chlorophenyl)-2-methylpyrrolidine with cyanogen bromide was very slow. Since the initial attack of cyanogen bromide is assumed to occur through the CN^+ ion, it seemed reasonable that a catalyst such as ferric chloride should facilitate the reaction by forming the complex $(FeCl_3Br)^- CN^+$. This was found to be so and about three times as much product was obtained when the pyrrolidine was refluxed with cyanogen bromide in benzene-ether with ferric chloride for 3 hours, or with stannic chloride in benzene for 2 hours as was obtained in the absence of a catalyst under comparable reaction conditions. Less than 10% of the products of ring cleavage consisted of primary halide when these catalysts were used. Although the reaction is facilitated, the loss of material as a result of tar formation and the difficulty in separating the products of the reaction militate against the use of such catalysts.

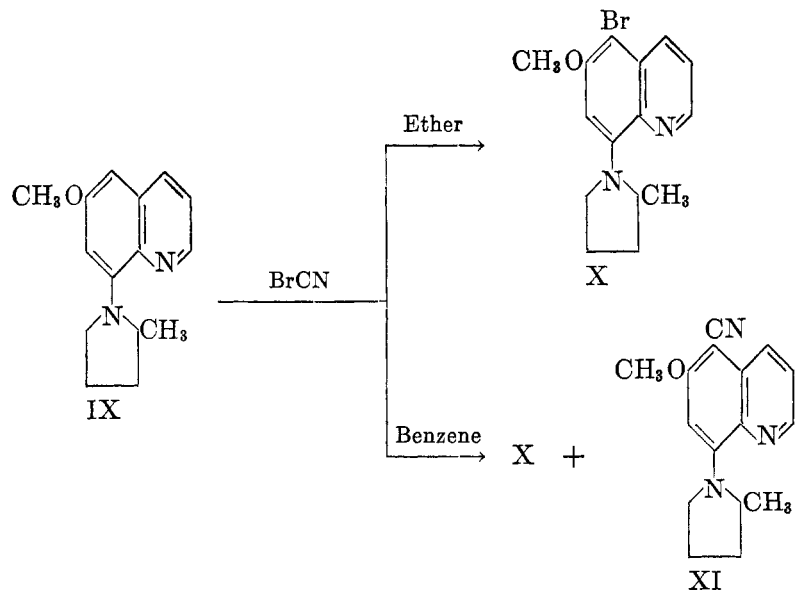
Although the reaction of cyanogen bromide with 1-phenyl-2-methylpyrrolidine to give a preponderance of secondary bromide is consistent with the probable mechanism of the reaction, the amount of primary halide formed was disappointing. Reaction of the primary bromoalkyl cyanamide with diethylamine followed by removal of the cyano group by hydrolysis leads to the familiar 1-methyl-4-diethylaminobutyl configuration present in pamaquine. It therefore appeared that an exploration of the preparation of this antimalarial by this route might be fruitful.

6-Methoxy-8-(2′-methylpyrrolidinyl)quinoline (IX) was prepared by condensation of 6-methoxy-8-aminoquinoline with 1,4-dibromopentane. The reaction of IX with cyanogen bromide is complicated by the presence of the quinoline nitrogen (6) which can be expected to react preferentially. For example the reaction of cyanogen bromide with quinine in chloroform at 0° followed by

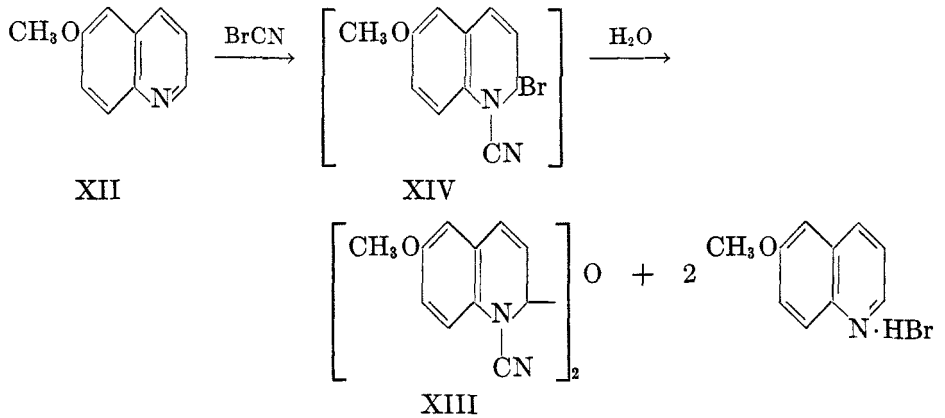
hydrolysis with ammonia gives 2-hydroxyquinine hydrocyanide (7). Since it is known (8) that the first proton adds to the quinoline nitrogen in aminoquinolines, it was hoped that in the monohydrochloride of IX the quinoline nitrogen would be tied up. In ether-chloroform solution no reaction occurred under the usual conditions. When the hydrochloride of IX was heated with cyanogen bromide in a sealed tube in the steam-bath for 4 hours large amounts of carbonaceous material were formed along with a small amount of a substance which apparently was identical with that described below.

The free base (IX), on the other hand, reacted with cyanogen bromide in ether solution, but instead of the expected product, a 27% yield of a crude monobromo compound, m.p. 95–98° after recrystallization from hexane, was obtained. This was identical with the substance formed when IX was brominated in acetic acid. Although the position of the bromine was not proved definitely the structure X appears reasonable in view of the known bromination of 6-methoxyquinoline and 6-methoxy-8-acetaminoquinoline in the 5-position.

When the reaction of IX with cyanogen bromide was carried out in boiling benzene the total yield of product was somewhat lower than when the reaction was done in ether. Further, the product consisted of approximately equal amounts of X and a cyano compound which contained no bromine. The structure of the latter compound was not determined although quinolinic acid was obtained from it on permanganate oxidation which showed that the cyano group had not entered the pyridine ring. In all probability the structure of the cyano compound is represented by XI since in every known instance in which cyanogen bromide acts to introduce either bromine or a cyano group into the same molecule, both groups enter the same position. These reactions are summarized in the following formulas.



Steric hindrance by the bulky 2-methylpyrrolidyl group in IX was probably responsible for the failure of the expected attack of cyanogen bromide on the quinoline nitrogen which is ordinarily very reactive toward this reagent. In order to confirm this, 6-methoxyquinoline (XII) was treated with cyanogen bromide in commercial anhydrous ether. Formation of a precipitate began almost immediately. This consisted of a mixture of the hydrobromide of XII and an ether (XIII) formed by the expected reaction of the initial product of the reaction (XIV) with moisture in the solvent (6, 7) which was not dried specially. XIII was not soluble in cold dilute sodium hydroxide or hydrochloric acid but was rapidly hydrolyzed to XII in warm hydrochloric acid.



EXPERIMENTAL[3, 4]

The *cyanogen bromide* used was either prepared according to Hartman and Dreger (9) or purchased from the Eastman Kodak Co. Contrary to Hartman and Dreger, we have found that the substance is stable, one batch having been stored in the refrigerator for more than one year with no sign of decomposition.

1-Phenyl-2-methylpyrrolidine (II). A mixture of 161.6 g. of aniline and 200 g. of *1,4*-dibromopentane was warmed on the steam-bath with shaking in a flask fitted with an air-condenser. Crystals formed gradually. After 15 min. when about half the mixture was a mass of crystals, the reaction, until now only mildly exothermic, suddenly became vigorous. The flask was cooled under the tap, but boiling continued, and in a few minutes the mixture set to a solid mass. After addition of 500 ml. of a 20% sodium hydroxide solution to the cooled mixture, the upper layer was separated, and the aqueous part was extracted with two 100-ml. portions of ether. The original upper layer was combined with the ether extracts and dried over potassium carbonate. After removal of the ether, fractionation gave 86 g. of aniline, and 121.5 g. (87%) of II, b.p. 133° (25 mm.). The *picrate* melted at 109–110° after crystallization from alcohol. Reported b.p. for the base is 134° (25 mm.) (10) and reported m.p. of the picrate is 109–110° (10) and 110° (11).

1-(p-Methoxyphenyl)-2-methylpyrrolidine. This was prepared from *p*-anisidine in the same manner as II. The substance (79% yield) boiled at 110–112° (0.2 mm.). It was analyzed as the *hydrochloride*, m.p. 176–178°, which was precipitated from an ethereal solution with hydrogen chloride and recrystallized from alcohol-ether.

[3] All melting points are corrected and boiling points are uncorrected.

[4] Microanalyses by Clark Microanalytical Laboratories, Urbana, Ill., Microtech Laboratories, Skokie, Ill., or Dr. Francine Schwarzkopf, Elmhurst, N. Y.

Anal. Calc'd for $C_{17}H_{18}ClNO$: N, 6.2. Found: N, 6.1.

1-(p-Chlorophenyl)-2-methylpyrrolidine. A solution of 35 g. of 1,4-dibromopentane, 40 g. of *p*-chloroaniline, and 2 g. of sodium iodide in 200 ml. of absolute alcohol was refluxed for 48 hours. After removal of the solvent, the viscous syrup was worked up as was II yielding 19.95 g. (68%) of product, b.p., 116–120° (1 mm.). It gradually solidified on standing.

Anal. Calc'd for $C_{11}H_{14}ClN$: C, 67.5; H, 7.2.; N, 7.2.
Found: C, 67.1; H, 7.0; N, 7.1.

6-Methoxy-8-(2'-methylpyrrolidyl)quinoline (IX). A solution of 78 g. of 6-methoxy-8-aminoquinoline, m.p. 42–44°, and 52 g. of 1,4-dibromopentane in 150 ml. of Butyl Cellosolve was refluxed gently for 45 min. The almost solid mass was filtered and the crystals were well washed with 200 ml. of 2-propanol. Recovery of the hydrobromide of 6-methoxy-8-aminoquinoline was 55.5 g. (theory 58.6 g.). The filtrate and washings were treated with a solution of 13.6 g. of sodium methoxide in 100 ml. of methanol, the precipitated sodium bromide was filtered off, and the filtrate was concentrated as far as possible. The residue was taken up in 300 ml. of anhydrous ether, filtered from some inorganic salts and tar, and, after removal of the ether, was distilled. The product, obtained in 49% yield, is a viscous, straw-colored oil which darkens rapidly on exposure to air. It boiled at 165–170° (0.3–0.8 mm.). n_D^{25} 1.6326.

Anal. Calc'd for $C_{15}H_{18}N_2O$: C, 74.4; H, 7.4; N, 11.6.
Found: C, 74.2; H, 7.2; N, 11.8.

The *picrate* formed orange needles, m.p. 167–168.5°, from 95% ethanol.

Anal. Calc'd for $C_{21}H_{21}N_5O_8$: C, 53.5; H, 4.5; N, 14.9.
Found: C, 53.6; H, 4.5; N, 15.0.

Reactions with cyanogen bromide. (*a*) *1-Phenyl-2-methylpyrrolidine* (II). A solution of 15.9 g. of II in 35 ml. of benzene was added during an hour to a refluxing solution of 13 g. (25% excess) of cyanogen bromide in 60 ml. of benzene. The solution gradually turned green. After boiling for an additional one-half hour, the mixture was allowed to stand overnight. The solvent was removed at the water pump and the residual green oil was taken up in 300 ml. of anhydrous ether leaving 3.10 g. of insoluble hydrobromide of II. After recrystallization from alcohol-dioxane this formed pale green tetrahedra, m.p. 120–121°.

Anal. Calc'd for $C_{11}H_{16}BrN$: N, 5.8. Found: N, 5.8.

The ether solution was extracted with two 40-ml. portions of 5% hydrochloric acid. The acid extracts gave an additional 4.41 g. of II on being made alkaline.

When the ring cleavage was done in ether no hydrobromide of II separated.

After removal of the solvent from the above ether solution, the mixture was refluxed for 4 hours with 20 g. of diethylamine. After removal of excess diethylamine at the water pump, the residue was acidified with dilute hydrochloric acid and extracted with ether for separation of the secondary bromocyanamide and olefin. The aqueous acid solution was made alkaline and extracted with ether. After drying over magnesium sulfate and removal of the solvent, 3.31 g. of phenyl-(4-diethylamino-1-methylbutyl)cyanamide, equivalent to 3.40 g. of III, was obtained. From the neutral fraction, 11.48 g. of secondary bromide and olefin was obtained. On the assumptions that the olefin formed is equivalent to the amount of hydrobromide of II isolated and that the secondary bromide was the source of all of the hydrobromide, the amount of secondary bromide formed in the ring opening then is 12.53 g. The yield of primary bromide then is 21.3% of the products of ring cleavage.

1-(p-Methoxyphenyl)-2-methylpyrrolidine. The reaction of this compound with cyanogen bromide was carried out in a manner exactly analogous to that described above.

1-(p-Chlorophenyl)-2-methylpyrrolidine. A solution of 15.1 g. of the pyrrolidine in 25 ml. of benzene was added to 14 g. of cyanogen bromide in 60 ml. of benzene and the resulting solution was refluxed for 15 hours. Treatment as described above gave 5.6 g. of a resinous ether-insoluble residue, probably a polymer of cyanogen bromide, in addition to the hydrobromide of the starting material. The recovered unreacted pyrrolidine amounted to 4.53 g., and from reaction with diethylamine, 2.10 g. of diethylaminocyanamide, equivalent to 2.15 g. of primary halide, was obtained. The per cent of secondary halide in the 9.58-g.

mixture of secondary halide and olefin was estimated by titration of an aliquot after conversion of the halide to the ionic form by treatment with alcoholic potassium hydroxide. The yield of primary bromide was calculated to be 16.7% of the products of ring cleavage.

With stannic chloride as catalyst. To a solution of 16.6 g. of 1-(*p*-chlorophenyl)-2-methylpyrrolidine and 12 g. of cyanogen bromide in 60 ml. of benzene was added 20 g. of stannic chloride in 35 ml. of benzene. The solution, which turned dark brown immediately, was refluxed for 2 hours and allowed to stand overnight. The solvent was removed, 150 ml. of ether was added to the residue, and the mixture was shaken with small portions of 10% hydrochloric acid until no more starting material was removed. From the acid extracts 3.45 g. of starting material was recovered. The ether extract, after treatment with diethylamine in the usual manner, gave 7.71 g. of acid-insoluble residue, and only 0.44 g. of the primary halide (a yield of 6%). The large amount of black tar formed in the reaction was not investigated further.

Proof of structure of III. Fractionation of the acid-soluble product obtained after treatment of the products of ring cleavage of II with diethylamine gave 1-methyl-4-diethylaminobutylphenylcyanamide (III), b.p. 153° (1.5–2 mm.), n_D^{25} 1.5139. The oxalate was precipitated from an ether solution of the cyanamide and recrystallized from dioxane. It softened at 95° and melted at 98–100°.

Anal. Calc'd for $C_{18}H_{27}N_3O_4$: C, 61.9; H, 7.7; N, 12.0.
Found: C, 61.4; H, 7.8; N, 12.1.

The cyano group was removed by refluxing 11 g. of the cyanamide for 3 hours with 14 g. of sulfuric acid and 30 ml. of water. The resulting solution was made alkaline, extracted with two 50-ml. portions of ether, and the combined extracts were dried over potassium hydroxide. Distillation gave 5 g. of a pale yellow liquid (VII), b.p. 164–168° (8 mm.), n_D^{25} 1.5200. The *citrate*, precipitated from ether and recrystallized from dioxane-ether, formed fine white crystals, m.p. 108–110° after softening at 104°.

Anal. Calc'd for $C_{21}H_{34}N_2O_7$: C, 59.1; H, 8.0; N, 6.6.
Found: C, 58.7; H, 7.9; N, 6.8.

1-Methyl-4-diethylaminobutylaniline. A mixture of 10 g. of 1-diethylamino-4-bromopentane and 25 g. of aniline was refluxed for 48 hours. The mixture was made alkaline with 10% sodium hydroxide solution and extracted with ether. After drying over magnesium sulfate and removal of the solvent, the residue from the ether extract was fractionated yielding 2.7 g. of product, b.p. 160° (10 mm.). Shiho (12) reports b.p. 174–176° (14 mm.). The *citrate* melted at 108–110° and gave no depression in m.p. when mixed with the citrate obtained above.

Identification of IV. A 15-g. portion of the acid-insoluble mixture of IV and VI remaining after removal of III was dissolved in 100 ml. of absolute ethanol to which 3.5 g. of potassium hydroxide had been added. The solution was refluxed for 1.5 hours. After cooling, the precipitated potassium bromide was removed and the filtrate was concentrated to dryness. After addition of 50 ml. of water the oil was extracted with two 25-ml. portions of ether. After drying over magnesium sulfate, removal of the solvent left 12.5 g. of an orange-brown oil. This was dissolved in 150 ml. of absolute alcohol, 0.2 g. of Adams platinum oxide was added, and the substance was reduced at 30 lb. hydrogen pressure at room temperature. Reduction was complete in 45 min. After filtering from the catalyst and removal of the solvent, the residual oil was refluxed for 18 hours with 25 g. of sulfuric acid and 60 ml. of water. After making the solution alkaline, and extraction with ether, distillation gave 7 g. of a colorless liquid, b.p. 137–139° (20 mm.); n_D^{25} 1.5256. This was *n*-amylaniline.

The *p-toluenesulfonyl derivative* formed fine white needles from 95% alcohol, m.p. 70–72°.

Anal. Calc'd for $C_{18}H_{23}NO_2S$: C, 68.2; H, 7.3; N, 4.3.
Found: C, 68.1; H, 7.1; N, 4.6.

The *oxalate*, precipitated from ether and recrystallized from dioxane, formed clumps of fine white needles, m.p. 142–143°.

Anal. Calc'd for $C_{13}H_{17}NO_4$: C, 61.7; H, 7.5; N, 5.5.
Found: C, 61.5; H, 7.2; N, 5.6.

An authentic sample of *n*-amylaniline was prepared by alkylating aniline with *n*-amyl bromide (13). It boiled at 260–261°. Mixture m.p's. of the *p*-toluenesulfonyl derivative and the oxalate with those of the above substance showed no depression.

To be certain that the same type of reaction occurred when stannic chloride was used as catalyst, the product remaining after treatment of 1-(*p*-chlorophenyl)-2-methylpyrrolidine with cyanogen bromide in the presence of stannic chloride was worked up as described above. After reaction with diethylamine and separation of the resulting acid-soluble fraction, the residue was dehydrohalogenated, reduced, and hydrolyzed. From the small amount of yellow-orange oil thus obtained, an oxalate was prepared in ether and recrystallized from dioxane-ether. It formed microscopic white needles, m.p. 148–150.5°.

For comparison N-(*n*-amyl)-*p*-chloroaniline, b.p. 152°(12 mm.), n_D^{25} 1.5444, was prepared by refluxing 25 g. of *p*-chloroaniline and 15 g. of *n*-amyl bromide in 75 ml. of Butyl Cellosolve for 24 hours. After removal of the solvent *in vacuo*, the residue was made alkaline and the product was extracted with ether.

Anal. Calc'd for $C_{11}H_{16}ClN$: C, 66.8; H, 8.1; N, 7.1.
Found: C, 67.0; H, 8.1; N, 7.1.

The *oxalate* melted at 149–151° and the m.p. of mixtures of it with the oxalate obtained as above was not depressed.

Isourea formation. In one run with 1-phenyl-2-methylpyrrolidine, the dehydrohalogenation reaction mixture was not worked up for several hours. Instead of the expected neutral cyanamide, the product was completely basic. It boiled at 152° (12 mm.), n_D^{25} 1.5214 and was a colorless mobile liquid.

Hydrogenation of 6.5 g. in 150 ml. of absolute ethanol over 0.2 g. of platinum oxide was complete in 10 min. The product, N-(*n*-amyl)-N-phenylethylisourea, boiled at 148–150° (11 mm.), n_D^{25} 1.5088.

Anal. Calc'd for $C_{14}H_{22}N_2O$: C, 71.8; H, 9.4; N, 11.9.
Found: C, 72.2; H, 9.1; N, 12.0.

Acid hydrolysis gave *n*-amylaniline, identified as the *p*-toluenesulfonyl derivative.

To show more clearly what was taking place in this reaction, it was investigated further using the more readily available ethylphenylcyanamide. This was prepared by adding 0.5 mole of ethylaniline to a solution of 0.25 mole of cyanogen bromide in 250 ml. of ether. After 30 min. the ethylaniline hydrobromide was filtered off, the ether solution was washed with 5% hydrochloric acid, and the solvent was removed.

When this cyanamide was allowed to stand at room temperature for 2 weeks in alcoholic solution, no reaction occurred. However when 0.1 equiv. of potassium hydroxide was added to the solution, the entire substance was converted overnight into an acid-soluble product. Solvent was removed and the residue was taken up in ether leaving a small insoluble residue. Passage of hydrogen chloride into the ether solution precipitated clusters of white needles, m.p. 111–112° (dec.), after recrystallization from 1:1 ethanol-dioxane. The analytical data agreed with those for the hydrochloride of N-phenyl-N-ethylethylisourea.

Anal. Calc'd for $C_{11}H_{17}ClN_2O$: C, 57.9; H, 7.5; N, 12.3.
Found: C, 57.9; H, 7.4; N, 12.2.

Reaction of 6-methoxy-8-(2-methylpyrrolidyl)quinoline (IX) *with cyanogen bromide.* (*a*) *In ether.* A solution of 10 g. of IX and 9 g. of cyanogen bromide (100% excess) in 100 ml. of ether was refluxed for 3 hours and then allowed to stand overnight. After decanting the solution from a dark brown gummy residue, the solvent and excess cyanogen bromide were removed at the water pump. The residue was taken up in 100 ml. of boiling hexane and treated with decolorizing carbon. After 3 days in the refrigerator 3.52 g. of crystals had separated. After several recrystallizations from hexane, this substance formed short yellow prisms, m.p. 95–98°. Analytical data agreed with those demanded by a bromo derivative of IX (X).

Anal. Calc'd for $C_{15}H_{17}BrN_2O$: C, 56.1; H, 5.3; N, 8.7; Br, 24.9.
Found: C, 56.3; H, 5.3; N, 8.8; Br, 24.6.

Concentration of the original hexane mother liquor from the above substance gave 3.4 g. of unreacted IX which was identified by m.p. and mixture m.p.'s of the picrate.

(*b*) *In benzene.* A solution of 7.5 g. of IX and 7 g. of cyanogen bromide (100% excess) in 75 ml. of benzene was refluxed for 2 hours and the solvent was removed at the water pump. The residue was extracted with 125 ml. of hexane and then with six 50-ml. portions of ether. The combined extracts were concentrated to 25 ml. and 2.6 g. of product separated on cooling. This was collected and taken up in 40 ml. of ether. Hexane was added to the ether solution until the solution became cloudy. On refrigeration two types of crystals separated: fluffy, yellow-brown needles, the first to precipitate, which did not adhere to the side of the flask when the solution was swirled and short prisms, similar in appearance to (X) obtained from the reaction in ether, which adhered to the flask. These substances were separated fairly satisfactorily mechanically. X was identified as the picrate. The less-soluble substance was recrystallized from 1:9 benzene-hexane and formed short, slim, yellow prisms, m.p. 140–142° (dec.). Another batch, recrystallized from absolute ethanol-hexane, formed yellow platelets, m.p. 138.5–141° (dec.). Analytical data agreed with those demanded by XI.

Anal. Calc'd for $C_{16}H_{17}N_3O$: C, 72.0; H, 6.4; N, 15.7.
Found: C, 71.7; H, 6.1; N, 15.5.

Oxidation of XI *to quinolinic acid.* To a stirred refluxing mixture of 0.6 g. of XI, 3 g. of potassium carbonate, and 150 ml. of water, 10 g. of potassium permanganate was added in small portions during 8 hours. After cooling, excess permanganate was destroyed with sodium bisulfite. The precipitated manganese dioxide was filtered and washed with 100 ml. of hot water. The combined filtrates were acidified with hydrochloric acid to *p*H 3 and concentrated to 50 ml. After addition of 50 ml. of a 12% solution of copper acetate, the solution was warmed on the steam-bath for 2 hours and cooled. The light blue-green copper salt which separated was suspended in 200 ml. of water and decomposed with hydrogen sulfide. The filtrate from the copper sulfide was evaporated to dryness. The residual quinolinic acid was suspended in 100 ml. of absolute methanol and refluxed for 2 hours during which dry hydrogen chloride was passed in. After refluxing for an additional 2 hours, the solvent was removed, and 25 ml. of water was added to the residue. After making the solution basic with potassium carbonate, it was extracted with ether. From the ether extract white crystals of the dimethyl ester of quinolinic acid, m.p. 52–53.5° after recrystallization from a small amount of pentane, were obtained. Engler (14) reports m.p. 53–54°.

Bromination of IX. To a solution of 0.3 g. of IX in 10 ml. of glacial acetic acid was added 0.2 g. of bromine in 15 ml. of glacial acetic acid. After standing for 15 min., the mixture was poured into 150 ml. of water. The yellow oil which separated slowly solidified. After extraction with three 30-ml. portions of ether, 0.11 g. of yellow crystals, m.p. 94.5–97° (dec.) and mixture m.p. with X, 94.0–97.5° (dec.), after recrystallization from hexane with decolorizing carbon, was obtained.

SUMMARY

1. The reaction of cyanogen bromide with a series of N-aryl-2-methylpyrrolidines has been studied and the direction of ring opening has been shown to vary with the substituent on the nitrogen.

2. Another example of the action of cyanogen bromide primarily as a brominating agent has been noted.

3. Isourea formation has been shown to be catalyzed by alkali.

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