# 3-Cyanopyrrolidines

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**A series of 1-alkyl-3-cyanopyrrolidines was prepared by the reaction of 1-alkyl-3-chloropyrrolidines with sodium cyanide in dimethylsulfoxide. One of these compounds, 1-methyl-3-cyanopyrrolidine, was used as a model to study the chemical properties of this type of substance. It was converted into 1-methyl-3-aminomethylpyrrolidine by hydrogenation, hydrolyzed to 1-methyl-3-pyrrolidine carboxylic acid (ethyl ester and *N*-methylamide), reacted with phenyl magnesium bromide to give 1-methyl-3-pyrrolidinyl phenyl ketone, and alkylated to a series of 1-methyl-3-alkyl-3-cyanopyrrolidines with alkyl halides and sodium amide.**

CONSIDERABLE interest has been shown in 3-substituted pyrrolidines because of their biological activity. Compounds derived from 1-R-3-pyrrolidinol and 1-R-3-pyrrolidinylmethanol have been found to possess a wide range of physiological activity as antihistaminics (1), local anesthetics (2), cholinergic and parasympathetic depressants (3–5), ataractic agents (4), adrenergic blocking agents (6), muscle relaxants (7, 8), antispasmodics (9), antiallergenics (10, 11), anti-inflammatory agents (12), and central nervous system stimulants (13). 3-Cyanopyrrolidines, because of the reactivity of the CN group, may be the starting point for a large number of 3-pyrrolidine derivatives.

Up to now, no new 3-cyanopyrrolidines have been prepared by direct substitution on the ring. It has now been found that 1-alkyl-3-cyanopyrrolidines can be conveniently prepared from 1-alkyl-3-chloropyrrolidines by reaction with sodium cyanide in dimethylsulfoxide, a method recommended for the conversion of alkyl chlorides into the corresponding nitriles (14). The required 1-alkyl-3-chloropyrrolidines were prepared in 55–90% yield by reaction of the 1-alkyl-3-pyrrolidinols with thionyl chloride in benzene (3, 13, 15).

The chloro compounds were usually obtained as the free bases by addition of strong alkali to the reaction mixture. However, with the 1-benzyl derivative, a good yield of the hydrochloride was obtained directly from the reaction mixture. The bases were purified by vacuum distillation in order not to expose them to extreme temperatures. The lower members could, however, be isolated by distillation at ordinary pressures without much decomposition. The 1-alkyl-3-chloropyrrolidines were colorless liquids which slowly darkened on storage, depositing a solid formed by the self condensation of the chloro group with the tertiary amine. Storage at low temperature minimized this decomposition.

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## DISCUSSION

3-Chloropyrrolidine (V) was obtained as its hydrochloride by hydrogenolysis of 1-benzyl-3-chloropyrrolidine hydrochloride (IV, HCl) in isopropyl alcohol over palladium on charcoal. However, the free base, liberated by treatment with alkali, was found to be less stable than the 1-substituted 3-chloropyrrolidines. In one run, V decomposed suddenly while it was being isolated by distillation at a bath temperature of slightly higher than 100°.

In order to obtain a more reactive halide for use in the alkylation of 1-methyl-3-cyanopyrrolidine (see below), 1-methyl-3-bromopyrrolidine (VI) was prepared in 43% yield by the reaction of a large excess of phosphorus tribromide with 1-methyl-3-pyrrolidinol in benzene (11). Like the chloro derivatives, it could be isolated as the free base by vacuum distillation. Compound VI decomposed rather rapidly on storage at room temperature, forming a crystalline solid in a few hours. At zero or below, this decomposition, presumably a self quaternization, was considerably delayed. However, after several months at −10°, one sample had solidified completely. The corresponding chloro compounds stored at 5° remained liquid and undiscolored.

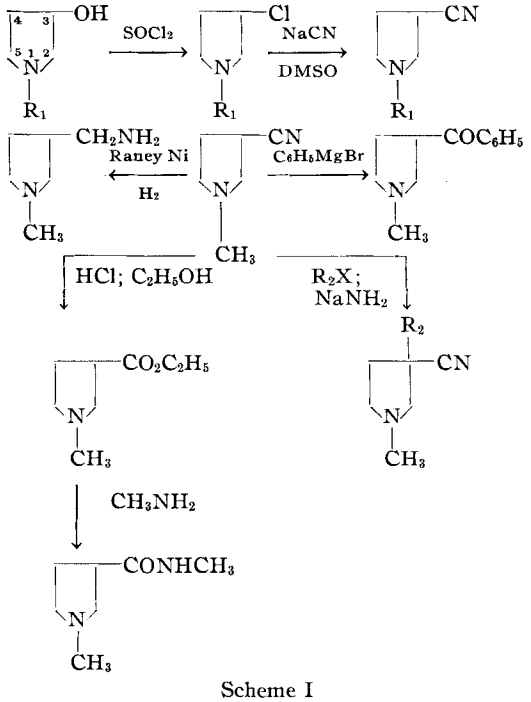
The 1-alkyl-3-chloropyrrolidines were converted to the corresponding 3-cyanopyrrolidines by reaction with sodium cyanide in dimethylsulfoxide (14). The reaction was effected by adding the 3-chloropyrrolidine to a slurry of sodium cyanide in dimethylsulfoxide at 90–100°. The reaction mixture was then heated at 155–170° for 30 min. The yields of the 1-alkyl-3-cyanopyrrolidines varied from 48–71%.

3-Chloropyrrolidine (V) failed to give pure 3-cyanopyrrolidine (XI) when it was treated in the same manner. A substance was obtained which appeared to contain about 72% of XI according to vapor–liquid chromatography analysis. An alternate approach to XI by hydrogenolysis of 1-benzyl-3-cyanopyrrolidine (X) failed.

A preliminary investigation of the chemical properties of these nitriles was made with 1-methyl-3-cyanopyrrolidine (VII) as a model (Scheme I, Table I).

Hydrogenation of VII over Raney nickel in acetic anhydride in the presence of sodium acetate (16) resulted in the formation of 1-methyl-3-acetylaminomethylpyrrolidine from which the free diamine, 1-methyl-3-aminomethylpyrrolidine (XII), was liberated by hydrolysis of the acetyl group (17).

Hydrolysis of VII with concentrated hydrochloric acid gave 1-methyl-3-pyrrolidine carboxylic




Scheme I

acid (18) which was esterified directly to ethyl-1-methyl-3-pyrrolidine carboxylate (XIII) (19). Compound XIII with methylamine gave the *N*-methylamide (XIV). Compound VII and phenyl magnesium bromide gave 1-methyl-3-pyrrolidinyl phenyl ketone (XV). A similar reaction with X gave 1-benzyl-3-pyrrolidinyl phenyl ketone (XVI). The intermediate ketimine magnesium halide of XVI was found to be resistant to the action of boiling concentrated hydrochloric acid. It was converted into the ketone by treatment with sodium hydroxide. The corresponding salt of XV was readily cleaved with ammonium chloride.

Compound VII was readily alkylated with alkyl halides and sodium amide. To effect the alkylation, VII was first added to a slurry of sodium amide in liquid ammonia followed by the alkyl halide. Toluene was then added to the mixture and the ammonia was allowed to evaporate. The toluene was then heated to reflux until the black color of the sodium amide disappeared. The 3-alkylated derivatives were isolated by distillation (20).

## EXPERIMENTAL[1]

### 3-Halopyrrolidines

The 1-alkyl-3-pyrrolidinols used in the preparation of the 1-alkyl-3-halopyrrolidines were prepared according to the method of Franko and Lunsford (3) from 1,4-dichloro-2-butanol (21, 22) and the appropriate monoalkylamine.

[1] All infrared spectra were made with a Perkin-Elmer Infracord spectrophotometer. All melting points are uncorrected. The microanalyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich., and by the S. B. Penick Quality Control Laboratories.

**1 - Methyl - 3 - chloropyrrolidine (I).**—The method given below for the preparation of I was also used for 1-ethyl and 1-isopropyl-3-chloropyrrolidines (II, III).

To a solution of 50.5 Gm. (0.5 mole) of 1-methyl-3-pyrrolidinol in 500 ml. of dry benzene was added 119 Gm. (1 mole) of thionyl chloride in 100 ml. of benzene at such a rate that the mixture warmed up to 75°. The mixture was refluxed for 1 hr., 300 ml. of benzene distilled off and replaced with 300 ml. of fresh benzene, cooled, and made strongly alkaline with 2 *N* sodium hydroxide solution. The benzene layer was separated, washed once with water, and distilled through a short Vigreaux column to yield 46.3 Gm. (79.5%) of I, b.p. 55–60° at 50 mm. [Lit. value (15) 55–58° at 50 mm.]

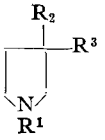
**1 - Ethyl - 3 - chloropyrrolidine (II).**—From 115.2 Gm. (1 mole) of 1-ethyl-3-pyrrolidinol and 180 Gm. (1.5 moles) of thionyl chloride, 105 Gm. (78.8%) of II was obtained; b.p. 157–159° at 760 mm. [Lit. value (13) 155° at 760 mm.]

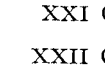
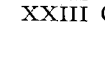
**1 - Isopropyl - 3 - chloropyrrolidine (III) (13).**—A yield of 99.5 Gm. (67.4%) of III was obtained from 129.2 Gm. (1 mole) of 1-isopropyl-3-pyrrolidinol and 180 Gm. (1.5 moles) of thionyl chloride; b.p. 93–94° at 47 mm.

*Anal.*—Calcd. for $C_7H_{14}ClN$: neutralization equivalent, 148. Found: 154.

**1 - Benzyl - 3 - chloropyrrolidine (IV) (13).**—Similarly, 177.4 Gm. (1 mole) of 1-benzyl-3-pyrrolidinol and 180 Gm. (1.5 moles) of thionyl chloride were reacted in 600 ml. of benzene. However, after the reaction was over, a solid crystallized on

TABLE I.—3-SUBSTITUTED PYRROLIDINES




| Compd. | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| I | $CH_3$ | H | Cl |
| II | $C_2H_5$ | H | Cl |
| III | *i*-$C_3H_7$ | H | Cl |
| IV | $C_6H_5CH_2$ | H | Cl |
| V | H | H | Cl |
| VI | $CH_3$ | H | Br |
| VII | $CH_3$ | H | CN |
| VIII | $C_2H_5$ | H | CN |
| IX | *i*-$C_3H_7$ | H | CN |
| X | $C_6H_5CH_2$ | H | CN |
| XI | H | H | CN |
| XII | $CH_3$ | H | $CH_2NH_2$ |
| XIII | $CH_3$ | H | $CO_2C_2H_5$ |
| XIV | $CH_3$ | H | $CONHCH_3$ |
| XV | $CH_3$ | H | $COC_6H_5$ |
| XVI | $C_6H_5CH_2$ | H | $COC_6H_5$ |
| XVII | $CH_3$ | $CH_3$ | CN |
| XVIII | $CH_3$ | *n*-$C_3H_7$ | CN |
| XIX | $CH_3$ | *i*-$C_3H_7$ | CN |
| XX | $CH_3$ | *n*-$C_4H_9$ | CN |
| XXI | $CH_3$ |  | CN |
| XXII | $CH_3$ | $C_6H_5CH_2$ | CN |
| XXIII | $CH_3$ |  | CN |
| XXIV | $CH_3$ | $(CH_3)_2NCH_2CH_2$ | CN |

cooling. This substance was filtered and washed free of color with benzene to yield 204.5 Gm. (86.0%) of IV hydrochloride, m.p. 140–142°. [Lit. value (13) 131–132°.]

*Anal.*—Calcd. for $C_{11}H_{15}Cl_2N$: neutralization equivalent, 232. Found: 236.

To liberate the free base, the hydrochloride was suspended in 1000 ml. of ether and treated with 400 ml. of 1.5 *N* sodium hydroxide. The ether phase was separated, dried over sodium sulfate, and distilled to give 166 Gm. (84.7%) of IV, b.p. 87–89° at 0.4–0.8 mm.

**3 - Chloropyrrolidine (V).**—A suspension of 38.0 Gm. (0.16 mole) of IV hydrochloride in 150 ml. of isopropyl alcohol was hydrogenated (Parr shaker) at 15–30 p.s.i. and 60–70° over 1.5 Gm. of 15% palladium on charcoal. The theoretical amount of hydrogen was absorbed in 5 hr. After filtration from the catalyst, the solution was concentrated and the product crystallized to yield 19.7 Gm. (83.4%) of crude V hydrochloride, m.p. 106–110°. The product was purified by recrystallization from isopropyl alcohol; yield, 15.4 Gm. (68.1%), m.p. 111–113°.

*Anal.*—Calcd. for $C_4H_9ClN^+ Cl^-$: $Cl^-$, 24.96. Found: 25.03.

The free base was liberated by treating a suspension of 15.0 Gm. (0.106 mole) of V hydrochloride in 100 ml. of ether with 20 ml. of 10 *N* sodium hydroxide. Distillation of the ether yielded 8.0 Gm. (72.1%) of V, b.p. 86–88° at 100 mm. 3-Chloropyrrolidine was a colorless liquid which rapidly darkened on storage. In another preparation, the substance suddenly decomposed upon distillation forming a solid black tar. Freshly prepared V was used in attempts to prepare 3-cyanopyrrolidine (XI).

**1 - Methyl - 3 - bromopyrrolidine (VI) (11).**—To a solution of 8.7 Gm. (0.087 mole) of 1-methyl-3-pyrrolidinol in 100 ml. of dry benzene cooled to below 10°, there was added 28.3 Gm. (0.105 mole) of phosphorus tribromide. The mixture was refluxed for 2 hr., cooled, and treated with 120 ml. of 25% potassium hydroxide. The benzene solution was separated and distilled to give 7.0 Gm. (49.1%) of VI, b.p. 78° at 40 mm. Compound VI was a colorless liquid which soon started to deposit a solid upon standing at room temperature. No attempt was made at analysis. It was used as rapidly as possible for the preparation of 1-methyl-3 - (1 - methyl - 3 - pyrrolidinyl) - 3 - cyanopyrrolidine (XXIII).

### 3-Cyanopyrrolidines

The following method, illustrated by the preparation of 1-methyl-3-cyanopyrrolidine (VII), was used to prepare all of the 3-cyanopyrrolidines.

**1-Methyl-3-cyanopyrrolidine (VII).**—To a suspension of 165 Gm. (3.2 moles) of sodium cyanide in 775 ml. of dimethylsulfoxide (dried over calcium hydride) heated to 90–100° was added, with stirring over a 25-min. period, 309 Gm. (2.58 moles) of I. The mixture was heated to 165–170° for 30 min., cooled to 25°, and diluted with 1300 ml. of chloroform. The mixture was poured into 4000 ml. of saturated salt solution. The chloroform phase was separated and the aqueous layer extracted with chloroform. The combined chloroform solution was washed several times with saturated salt to remove residual dimethylsulfoxide and distilled to yield 190 Gm. (67.1%) of VII, b.p. 92–93° at 23 mm. A picrate was prepared in alcohol, m.p. 204–205°.

*Anal.*—Calcd. for $C_{12}H_{13}N_5O_7$: N, 20.64. Found: 20.61, 20.58.

**1 - Ethyl - 3 - cyanopyrrolidine (VIII).**—From 26.7 Gm. (0.2 mole) of II and 12.0 Gm. (0.25 mole) of sodium cyanide, 12.0 Gm. (48.5%) of VIII, b.p. 102–104° at 23 mm., was obtained; picrate m.p. 140–141°.

*Anal.*—Calcd. for $C_{13}H_{15}N_5O_7$: N, 19.82. Found: 20.18.

**1 - Isopropyl - 3 - cyanopyrrolidine (IX).**—From 81.2 Gm. (0.55 mole) of III and 36.0 Gm. (0.7 mole) of sodium cyanide was obtained 40.0 Gm. (52.6%) of IX, b.p. 102–104° at 10 mm.

*Anal.*—Calcd. for $C_8H_{14}N_2$: neutralization equivalent, 138. Found: 140. A picrate, m.p. 136–137°, was prepared in alcohol.

*Anal.*—Calcd. for $C_{14}H_{17}N_5O_7$: N, 19.07. Found: 19.08.

**1 - Benzyl - 3 - cyanopyrrolidine (X).**—The same procedure was used except the reaction temperature was lowered to 155–160° from 165–170°. Thus, 265.0 Gm. (1.35 moles) of IV and 100.0 Gm. (2.05 moles) of sodium cyanide yielded 179.0 Gm. (71.3%) of X, b.p. 120–124° at 0.5–0.6 mm.

*Anal.*—Calcd. for $C_{12}H_{14}N_2$: neutralization equivalent, 186. Found: 188.

**3-Cyanopyrrolidine (XI).**—The procedure for X was used. From 10.6 Gm. (0.1 mole) of V and 6.4 Gm. (0.13 mole) of sodium cyanide, only 1.4 Gm. of a product, b.p. 82–84° at 5 mm., was isolated.

*Anal.*—Calcd. for $C_5H_8N_2$: neutralization equivalent, 96; C, 62.48; H, 8.38; N, 29.14. Found: neutralization equivalent, 107; C, 59.52; H, 8.20; N, 26.51.

Vapor phase chromatography[2] showed that one component comprised about 72.5% of the above product and three others the remainder. The infrared absorption spectrum of the product showed a distinct CN maximum at 4.48 $\mu$ and one for NH at 3.0 $\mu$. It was therefore concluded that XI was the major component of the mixture.

An attempt was made to prepare XI by hydrogenolysis of X hydrochloride. The latter, prepared by neutralizing a solution of X in isopropyl alcohol, was shaken with hydrogen over palladium on charcoal (Parr shaker). More than the theoretical amount of hydrogen was absorbed. Only a tarry product could be isolated. Compound X did not take up hydrogen under the same conditions.

### Products from 1-Methyl-3-cyanopyrrolidine

**1 - Methyl - 3 - aminomethylpyrrolidine (XII).**—A mixture of 11.0 Gm. (0.1 mole) of VII, 120 ml. of acetic anhydride, 12 Gm. of anhydrous sodium acetate, and 3 Gm. of Raney nickel (previously washed and suspended in acetic anhydride) was shaken at 50° at 15–25 p.s.i. of hydrogen (Parr shaker). Approximately 2 moles of hydrogen per mole of VII was absorbed in 1 hr. The reaction

[2] The authors thank Mr. F. A. E. Schilling of these laboratories for performing the analysis on a Perkin-Elmer 154 instrument. A 2-M. 1/4 in. i.d. stainless steel column filled with 20% Silicone SE 52 on Chromosorb W (45/60 mesh) and operated at 150° with 15 p.s.i. of helium at a rate of 33 ml./min. was used to effect the separation.

mixture was filtered from the catalyst and the acetic anhydride was removed by vacuum distillation. The semisolid residue was dissolved in benzene and filtered from the insoluble sodium acetate. A yield of 11.6 Gm. (75%) of what apparently was the acetyl derivative of XII was obtained by distillation of the filtrate, b.p. 104–106° at 0.3 mm. This substance discolored rapidly on standing. To liberate the free diamine, 7.3 Gm. (0.064 moles) of the above product was refluxed in 20 ml. of 7.5 *N* sodium hydroxide until all went into solution. The solution was cooled, neutralized with hydrochloric acid, and evaporated to dryness in vacuum. The residue was treated with excess 50% sodium hydroxide and extracted with ether. The ether extracts were dried over sodium hydroxide pellets and distilled to give 4.5 Gm. (87%) of XII, b.p. 72–76° at 30 mm. A dipicrate was prepared and recrystallized from alcohol, m.p. 206–207°. [Lit. value (17) 208–211°.]

**Ethyl - 1 - methyl - 3 - pyrrolidine Carboxylate (XIII) (19).**—A mixture of 11.0 Gm. (0.1 mole) of VII and 80 ml. of concentrated hydrochloric acid was refluxed overnight. The resulting orange solution was vacuum stripped to dryness and the residue dissolved in 150 ml. of anhydrous alcohol. The insoluble salt was filtered. Weight, 5.0 Gm. Calcd. for ammonium chloride: 5.2 Gm. The filtrate was saturated with hydrogen chloride and refluxed for 3 hr. The excess hydrogen chloride and alcohol were removed by vacuum distillation. The residue was dissolved in water and extracted with ether. The aqueous solution was made alkaline and extracted 7 times with ether. Distillation of the ether extracts gave 6.2 Gm. (39.3%) of XIII, b.p. 107–109° at 40 mm.

*Anal.*—Calcd. for $C_8H_{15}NO_2$: neutralization equivalent, 157. Found: 159.

**1 - Methyl - 3 - pyrrolidine - N - methylcarboxamide (XIV).**—A solution of 3.9 Gm. (0.025 mole) of XIII in 65 ml. of 40% aqueous methylamine was allowed to stand at room temperature for 1 week. The excess methylamine and water were removed and the residue distilled to give 2.4 Gm. of XIV, b.p. 90–94° at 0.2 mm. The liquid distillate soon solidified to give a waxy solid melting at about 35°.

*Anal.*—Calcd. for $C_7H_{14}N_2O$: N, 19.70. Found: 19.59.

**1 - Methyl - 3 - pyrrolidinyl Phenyl Ketone (XV).**—To a solution of phenyl magnesium bromide prepared from 62.8 Gm. (0.4 mole) of bromobenzene and 9.7 Gm. (0.4 atoms) of magnesium turnings in 100 ml. of ether, was added 11.0 Gm. (0.1 mole) of VII at such a rate that a gentle reflux was maintained. The reaction mixture was then stirred and refluxed for 5 hr. It was then cooled and treated with 50 ml. of saturated ammonium chloride solution. The ether layer was decanted from the semisolid aqueous phase. The latter was diluted with water to dissolve the solid and extracted with ether. The combined ether solutions were dried over sodium sulfate and distilled to give 7.8 Gm. (41.0%) of XV, b.p. 112–118° at 0.3 mm. A picrate was prepared and recrystallized from benzene, m.p. 146–147°.

*Anal.*—Calcd. for $C_{18}H_{18}N_3O_8$: N, 13.39. Found: 13.29.

The infrared spectrum of XIV showed a maximum at 5.9 $\mu$ corresponding to the C=O group and a doublet at 3.4 and 3.6 $\mu$ which characterized the spectra of most of the 1-alkyl-3-substituted pyrrolidines.

**1 - Benzyl - 3 - pyrrolidinyl Phenyl Ketone (XVI).**—In a manner similar to the procedure for XV, 18.6 Gm. (0.1 mole) of X was reacted with a solution of phenyl magnesium bromide prepared from 18.8 Gm. (0.12 mole) of bromobenzene and 2.7 Gm. (0.12 atoms) of magnesium turnings in 90 ml. of ether. The cold reaction mixture was decomposed with 70 ml. of 8 *N* hydrochloric acid to give, on filtration, 25 Gm. of a crystalline solid. This substance, apparently an acid resistant ketimine magnesium halide, gave an ash on fusion and was recovered unchanged after refluxing overnight with concentrated hydrochloric acid. Suspension in 300 ml. of toluene and agitation at 60° for 30 min. with 160 ml. of 4 *N* sodium hydroxide hydrolyzed it to the ketone. Filtration of the reaction mixture gave some solid magnesium hydroxide. The toluene layer was separated, dried over sodium sulfate, and distilled to yield 19.6 Gm. (74.0%) of XVI, b.p. 179–180° at 0.3 mm.

*Anal.*—Calcd. for $C_{18}H_{19}NO$: neutralization equivalent, 265. Found: 266.

A hydrochloride, m.p. 120–122°, was prepared by neutralizing a tetrahydrofuran solution of XVI with concentrated hydrochloric acid.

*Anal.*—Calcd. for $C_{18}H_{20}ClNO$: N, 4.64. Found: 4.25.

The infrared spectrum of XVI showed a maximum at 5.9 $\mu$ and a doublet at 3.35 and 3.58 $\mu$.

### Alkylation of 1-Methyl-3-cyanopyrrolidine

The following method illustrated in the preparation of XVIII was used for all of the 1-methyl-3-alkyl-3-cyanopyrrolidines.

**1,3-Dimethyl-3-cyanopyrrolidine (XVII).**—To a suspension of sodium amide prepared from 2.3 Gm. (0.1 atom) of sodium in 150 ml. of liquid ammonia (23) was added 11.0 Gm. (0.1 mole) of VII. The mixture was stirred in refluxing ammonia for several minutes and 17.0 Gm. (0.12 mole) of methyl iodide followed by 150 ml. of dry toluene were added. The ammonia was allowed to evaporate off, the mixture heated to reflux until the black color of the sodium amide disappeared (3–4 hr.), cooled, and mixed with 100 ml. of water. The aqueous layer was separated and extracted with toluene. The combined toluene solution was dried over sodium sulfate and distilled to yield 7.8 Gm. (63.2%) of XVII, b.p. 88–89° at 24 mm. A picrate was prepared in alcohol, m.p. 211–213°.

*Anal.*—Calcd. for $C_{13}H_{15}N_5O_7$: N, 19.82. Found: 19.89, 19.81.

**1 - Methyl - 3 - n - propyl - 3 - cyanopyrrolidine (XVIII).**—Compound XVIII, 9.6 Gm. (63.3%), b.p. 112–113° at 23 mm., was obtained in a similar manner from 20.4 Gm. (0.12 mole) of *n*-propyl iodide and the same quantities of sodium amide and VII; picrate, m.p. 163–164°.

*Anal.*—Calcd. for $C_{15}H_{19}N_5O_7$: N, 18.36. Found: 18.49.

**1 - Methyl - 3 -i-propyl - 3 - cyanopyrrolidine (XIX).**—Similarly, 7.1 Gm. (46.7%) of XIX, b.p. 76–79° at 5 mm., was obtained from 20.4 Gm. (0.12 mole) of *i*-propyl iodide; picrate, m.p. 221–223°.

*Anal.*—Calcd. for $C_{15}H_{19}N_5O_7$: N, 18.36. Found: 18.32.

**1 - Methyl - 3 - n - butyl - 3 - cyanopyrrolidine (XX).**—Similarly, 8.1 Gm. (48.5%) of XX, b.p. 136° at 25 mm., was obtained from 18.4 Gm. (0.1 mole) of *n*-butyl iodide; picrate, m.p. 158–160°.

*Anal.*—Calcd. for $C_{16}H_{21}N_5O_7$: N, 17.71. Found: 17.78, 17.62.

**1 - Methyl - 3 - cyclopentyl - 3 - cyanopyrrolidine (XXI).**—Similarly, 17.9 Gm. (0.12 mole) of cyclopentyl bromide yielded 3.3 Gm. (18.7%) of XXI, b.p. 106–108° at 5 mm.; picrate, m.p. 204–206°.

*Anal.*—Calcd. for $C_{17}H_{21}N_5O_7$: N, 16.78. Found: 17.10, 17.21.

**1 - Methyl - 3 - benzyl - 3 - cyanopyrrolidine (XXII).**—Similarly, 11.5 Gm. (57.6%) of XXII, b.p. 134–136° at 2 mm., was obtained from 12.7 Gm. (0.1 mole) of benzyl chloride; picrate, m.p. 176–177°.

*Anal.*—Calcd. for $C_{19}H_{19}N_5O_7$: N, 16.31. Found: 16.12, 16.38.

**1 - Methyl - 3 - (1 - methyl - 3 - pyrrolidinyl)-3 - cyanopyrrolidine (XXIII).**—Similarly, 19.7 Gm. (0.12 mole) of freshly prepared VI yielded 2.7 Gm. (13.8%) of XXIII, b.p. 120–126° at 8 mm.; dipicrate, m.p. 232–233° dec.

*Anal.*—Calcd. for $C_{23}H_{25}N_9O_{14}$: N, 19.35. Found: 19.60, 19.52.

**1 - Methyl - 3 - (2 - dimethylaminoethyl) - 3-cyanopyrrolidine (XXIV).**—Similarly, with double the amount of sodium amide used for the preceding compounds, 28.0 Gm. (0.12 mole) of 2-dimethylaminoethylbromide hydrobromide yielded 2.9 Gm. (16.2%) of XXIV, b.p. 110–112° at 6 mm.; dipicrate, m.p. 148–150° (opaque liquid), clear at 155–160°.

*Anal.*—Calcd. for $C_{22}H_{25}N_9O_{14}$: N, 19.71. Found: 19.60.

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# Separation and Quantitative Determination of Adrenaline Using Thin-Layer Chromatography

By N. H. CHOULIS

**The separation of adrenaline from noradrenaline and dopamine and its quantitative determination using thin-layer chromatography have been studied. A complete spot separation of the above amines can be achieved by the use of cellulose thin layers and a phenol–water solvent system. For the quantitative determination of the separated adrenaline two methods were used, namely (*a*) a method studying the weight/area relationship of the spots and (*b*) a method employing elution of the spots and measurement of the ultraviolet absorption of the eluents.**

PAPER CHROMATOGRAPHIC methods for the separation of catecholamines and related compounds using various solvent systems have been reported (1, 2). These methods require 5–20 hr. for a satisfactory development of the chromatograms, and as a result of the prolonged exposure, oxidation of the catecholamines to the corresponding red aminochromes is usually observed on the paper.

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Thin-layer chromatographic methods have often been used for the separation of various components of a mixture. The importance of this method and the ease with which it is carried out have been generally recognized since Stahl (3–5) introduced it as an analytical tool.

A complication in the interpretation of chromatograms of catecholamines (on paper or thin-layer chromatography) may result from the presence of multiple spots which are sometimes produced during chromatography of pure substances