[Contribution from the Department of Chemistry, University of Buffalo]

THE REACTION OF CYANOGEN WITH ORGANIC COMPOUNDS. II. PRIMARY ALIPHATIC AMINES[1, 2]

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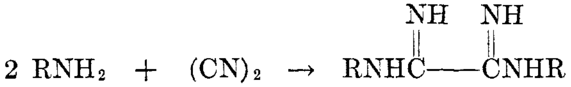
In the first paper of this series (1) the production of cyanoformamidines from cyanogen and secondary amines was described.

$$R_2NH + (CN)_2 \rightarrow R_2NC(=NH)CN$$

The reaction was most satisfactory when *anhydrous* solvents such as ethyl acetate, benzene or toluene were employed, and no compounds were isolated in which both CN groups of cyanogen had undergone amine addition.

It was interesting to discover, therefore, in extending the reaction to primary aliphatic amines, that in this case both CN groups reacted simultaneously with the production of symmetrically substituted oxamidines.



$$2\ RNH_2 + (CN)_2 \rightarrow RNH\overset{\overset{NH}{\|}}{C}-\overset{\overset{NH}{\|}}{C}NHR$$

A similar reaction for aniline was described by Hoffmann (2) in 1848 and for benzylamine by Strakosch (3) in 1873, but no reaction of cyanogen with purely aliphatic amines has hitherto been reported.

Depending on the amine, the oxamidines were obtained by us in one of two ways, either directly by saturation of an *aqueous* solution of the amine with purified cyanogen, or indirectly by neutralizing the hydrochloride salt. The latter was produced by saturating an alcoholic solution of the amine first with cyanogen, then with anhydrous hydrogen chloride. The substituted oxamidine hydrochlorides are less soluble in alcohol than the hydrochlorides of the amines from which they are made. There is no difficulty, therefore, in separating the oxamidine salts from amine impurities. Whether or not the direct method gives good results depends on the water-solubility and the melting point of the product, those having both high solubility and low melting point being best obtained through their hydrochlorides.

The reaction has been investigated for all the primary amines up to and including normal amyl. In the case of *tert*-butyl amine no product could be obtained in spite of many attempts which were made with varying reaction conditions. A Hirschfelder model of the desired substance indicated that it would be sterically very difficult for such a molecule to form.

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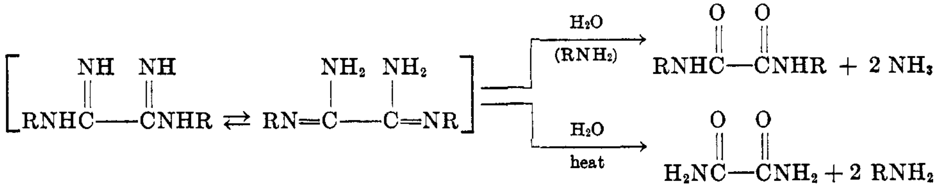
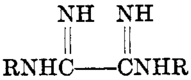
The eight oxamidines described in this paper are white crystalline solids or colorless liquids. Their solubility in water decreases with increasing molecular weight and becomes very small at C_4. In organic solvents the lower members are less soluble than the higher ones. The hydrochloric or nitric acid salts are often more suitable for storage than the free bases since the latter hydrolyze slowly on standing. Cold aqueous solutions, especially if small amounts of alkylamine are present, hydrolyze to disubstituted oxamides. Refluxing, with or without amine, causes complete breakdown to unsubstituted oxamide.



$$\left[\mathrm{RNH\overset{NH}{\overset{\|}{C}}—\overset{NH}{\overset{\|}{C}}NHR} \rightleftarrows \mathrm{RN{=}\overset{NH_2}{\overset{|}{C}}—\overset{NH_2}{\overset{|}{C}}{=}NR}\right] \begin{cases} \xrightarrow[(RNH_2)]{H_2O} \mathrm{RNH\overset{O}{\overset{\|}{C}}—\overset{O}{\overset{\|}{C}}NHR} + 2\,NH_3 \\ \xrightarrow[heat]{H_2O} \mathrm{H_2N\overset{O}{\overset{\|}{C}}—\overset{O}{\overset{\|}{C}}NH_2} + 2\,RNH_2 \end{cases}$$

TABLE I

Properties of



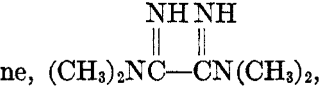
$$\mathrm{RNH\overset{NH}{\overset{\|}{C}}—\overset{NH}{\overset{\|}{C}}NHR}$$

R	M.P., °C.	B.P., °C.	M.P., °C., HCl SALT	M.P.°C., HNO_3 SALT
CH_3	103–104		289–290 dec.	215–216 dec.
C_2H_5	53		274–276 dec.	226–228 dec.
n-C_3H_7		95 dec.	272–274 dec.	207–210 dec.
iso-C_3H_7		80	285–287 dec.	222–224 dec.
n-C_4H_9	63		270–272 dec.	206–208 dec.
iso-C_4H_9	79		300–302 dec.	220–223 dec.
sec-C_4H_9		140 dec.	295–297 dec.	220–224 dec.
n-C_5H_{11}	dec. above 100		278–279 dec.	208–209 dec.

The comparison by mixed melting point of the oxamides resulting from hydrolysis, with the same compounds made by an alternative procedure (4), together with analyses of the original compounds, constitute the chief arguments for the oxamidine structure used in this paper, since we have not yet been able to synthesize the compounds by other methods. The action of ammonia on symmetrically substituted oxamides or on oximidic chlorides has failed, but other investigations reported in the succeeding paper (5) leave no reason to doubt the accuracy of the formulas.

The isolation of cyanoformamidines as the reaction product of secondary amines (1), while oxamidines resulted from primary amines suggested that the course of the cyanogen-amine reaction might be through initial formation of cyanoformamidine with further addition sterically hindered in the secondary amines.

$$\mathrm{RNH_2} + \mathrm{(CN)_2} \rightarrow \left[\mathrm{RNH\overset{NH}{\overset{\|}{C}}CN}\right] \xrightarrow{\mathrm{RNH_2}} \mathrm{RNH\overset{NH}{\overset{\|}{C}}—\overset{NH}{\overset{\|}{C}}NHR}$$

Experiments were, therefore, run with secondary amines which involved changes in the original procedures (1) as to solvent, cyanogen-amine ratio, and mode of recovery, with the result that a di-addition compound of cyanogen and dimethylamine,  $(CH_3)_2N\overset{\overset{NH}{\|}}{C}—\overset{\overset{NH}{\|}}{C}N(CH_3)_2$, was finally isolated in the form of its hydrochloride, together with the expected cyanoformamidine. No other secondary amine has as yet yielded such a product.

Attempts were also made to isolate a cyanoformadine precursor from the primary amine reaction mixture. Results have thus far been completely negative.

EXPERIMENTAL

Analyses were carried out as described in the first paper of this series (1). Melting and boiling points are uncorrected. An improvement in the method of purifying the cyanogen was made by replacing the calcium chloride tower by one filled with activated alumina. Under these circumstances water was so completely removed that no noticeable heat developed in the succeeding sodium hydroxide tower and the tendency for cyanogen to polymerize and contaminate the reaction mixture with tar was greatly decreased.

sym-Dimethyloxamidine. (*a*) A 25% aqueous solution of methylamine containing 31 g. of amine (1.0 mole) was treated with purified cyanogen gas (0.5 mole) at 0°. The resulting light yellow liquid was kept in an ice-chest for 24 hours and then frozen solid in Dry Ice; (when the reaction mixture was not allowed to stand, but frozen solid immediately the yield of desired product was much lower). It was then placed in an ice-salt bath until enough had melted to form a slush, which consisted of a mixture of ice and crystalline product. Filtration gave an 8.5% yield of white crystlas. It was essential to have rapid and efficient filtration of the melting ice as the product was extremely soluble in water. Recrystallization from ether gave white crystals melting at 103–104°. The substance was unstable and changed upon standing to dimethyloxamide (m.p. 212°).

The *hydrochloric acid salt* was prepared by saturating an alcoholic solution of *sym*-dimethyloxamidine with dry hydrogen chloride. Recrystallization from ethyl alcohol yielded white crystals, m.p. 289–290° with decomposition.

Anal. Calc'd for $C_4H_{10}N_4 \cdot 2\ HCl$: C, 25.7; H, 6.4; N, 29.9; Molecular weight, 187.
Found: C, 25.8; H, 6.6; N, 29.9; Molecular weight, 187.

The *nitric acid salt* was prepared by neutralizing an ether solution of the free base with concentrated nitric acid. Recrystallization from an alcohol-ether solution gave white crystals, m.p. 215–216° with decomposition.

(*b*) A solution of 12.4 g. (0.4 mole) of anhydrous methylamine in 200 ml. of 95% ethyl alcohol was reacted with purified cyanogen gas (0.2 mole) at 0°. The reaction mixture was saturated immediately with dry hydrogen chloride forming a solid product. Recrystallization from ethyl alcohol gave a 27% yield of white crystals, m.p. 289–290° with decomposition.

sym-Diethyloxamidine. A 33% aqueous solution of ethylamine containing 45 g. of amine (1.0 mole) was treated as in (*a*) above. Recrystallization of the product from ether gave a 35% yield of white solid, m.p. 53°.

The *hydrochloric acid salt* prepared as above melted at 274–276° with decomposition.

Anal. Calc'd for $C_6H_{14}N_4 \cdot 2\ HCl$: C, 33.5; H, 7.4; N, 26.1; Molecular weight, 215.
Found: C, 33.8; H, 7.8; N, 26.1; Molecular weight, 215.

The *nitric acid salt* prepared as above melted at 226–228° with decomposition.

sym-Di-n-propyloxamidine. (*a*) A 33% aqueous solution of *n*-propylamine containing 29.6 g. (0.5 mole) of amine was reacted with purified cyanogen gas (0.25 mole) at 0°. Since freezing with Dry Ice did not lead to the isolation of a product, the reaction mixture was extracted with ether. Addition of an equal volume of ethyl alcohol followed by saturation with dry hydrogen chloride produced white crystals of the *hydrochloride* which after recrystallization from ethyl alcohol melted at 272–274° with decomposition. The yield was 22%.

Anal. Calc'd for $C_8H_{18}N_4 \cdot 2\ HCl$: C, 39.5; H, 8.2, N, 23.1; Molecular weight, 243.
Found: C, 39.7; H, 8.5; N, 23.3; Molecular weight, 247.

(*b*) A 50% alcoholic solution of *n*-propylamine containing 29 g. (0.5 mole) of amine was treated with purified cyanogen gas (0.25 mole) at 0°. Saturation of the reaction mixture with dry hydrogen chloride formed white crystals which on recrystallization from ethyl alcohol melted at 272–274° with decomposition. The percentage yield of *hydrochloride* was slightly larger than that obtained by the previous method.

The *free base* was formed by neutralizing an aqueous solution of the hydrochloride with a solution of sodium hydroxide. Extraction with ether yielded a colorless liquid, b.p. 95° with decomposition.

The *nitric acid salt* prepared from the free base melted at 207–210° with decomposition.

sym-Diisopropylamine. A 50% alcoholic solution of isopropylamine containing 59.1 g. (1 mole) of amine was treated with purified cyanogen gas (0.5 mole) at 0°. The reaction mixture was saturated with dry hydrogen chloride forming a solid product. Recrystallization from ethyl alcohol gave a 22% yield of *the hydrochloride,* white crystals melting at 285–287° with decomposition.

Anal. Calc'd for $C_8H_{18}N_4 \cdot 2\ HCl$: C, 39.5; H, 8.2; N, 23.1; Molecular weight, 243.
Found: C, 39.5; H, 8.9; N, 23.3; Molecular weight, 241.

The *free base* was formed by neutralizing an aqueous solution of the hydrochloride with a solution of sodium hydroxide. Extraction with ether gave a colorless liquid boiling at 80°.

The *nitric acid salt* prepared from the free base melted at 222–224° with decomposition.

sym-Di-n-butyloxamidine. A 33% aqueous solution of *n*-butylamine containing 73.1 g. (1.0 mole) of amine was treated with purified cyanogen gas *until the solution started to turn milky* (slightly less than 0.5 mole). If the reaction was not stopped at this point the mixture separated into two layers and isolation of a pure product was difficult. After the reaction mixture was cooled in an ice-chest for 24 hours, a crystalline solid formed. Recrystallization from ether gave a 30% yield of white crystals, m.p. 63°.

The *hydrochloride* was formed by saturating an ether solution of the oxamidine with dry hydrogen chloride. Recrystallization from ethyl alcohol yielded white crystals, m.p. 270–272° with decomposition.

Anal. Calc'd for $C_{10}H_{22}N_4 \cdot 2\ HCl$: C, 44.3; H, 8.9; N, 20.7; Molecular weight, 271.
Found: C, 44.3; H, 9.0; N, 20.2; Molecular weight, 276.

The *nitric acid salt* prepared as above melted at 206–208° with decomposition.

sym-Diisobutyloxamidine. A 33% aqueous solution of isobutylamine containing 18.5 g. (0.25 mole) of amine was treated as above with 0.12 mole of cyanogen. Recrystallization from ether gave an 11% yield of white crystals, m.p. 79°.

The *hydrochloric acid salt* prepared by saturating the ether filtrate with anhydrous hydrogen chloride gave 11 g. of the hydrochloride, m.p. 300–302° with decomposition, corresponding to an additional 32% yield of free base.

Anal. Calc'd for $C_{10}H_{22}N_4 \cdot 2\ HCl$: C, 44.3; H, 8.9; N, 20.7; Molecular weight, 271.
Found: C, 44.4; H, 8.9; N, 20.6; Molecular weight, 277.

The *nitric acid salt* melted at 220–223° with decomposition.

sym-Di-sec-butyloxamidine. A 33% aqueous solution of *sec*-butylamine containing 18.5 g. (0.25 mole) of amine was treated with purified cyanogen gas (0.12 mole) at 0°. After standing in an ice-chest for 24 hours an oil separated.

The *hydrochloride* was formed by saturating an alcoholic solution of the oil with dry hydrogen chloride. Recrystallization from ethyl alcohol gave a 13% yield of white crystals, m.p. 295–297° with decomposition.

Anal. Calc'd for $C_{10}H_{22}N_4 \cdot 2$ HCl: C, 44.3; H, 8.9; N, 20.7; Molecular weight, 271.
Found: C, 43.8; H, 8.8; N, 20.7; Molecular weight, 272.

The *free base* was obtained by neutralizing an aqueous solution of the hydrochloride with a solution of sodium hydroxide. Extraction with ether gave a colorless liquid boiling at 140° with decomposition.

The *nitric acid salt* melted at 220–224° with decomposition.

sym-Diamyloxamidine. A solution of 30 g. (0.35 mole) of *n*-amylamine in 20 ml. of 95% ethyl alcohol and 60 ml. of water was treated with 0.5 mole of purified cyanogen at 0°. Increase in weight indicated that only about 0.25 mole of cyanogen was absorbed. Cooling in Dry Ice caused a separation of two layers but no crystals had formed after two days.

The organic layer was, therefore, separated, washed with water, and extracted with ether. Addition of an equal volume of ethyl alcohol followed by saturation with dry hydrogen chloride produced white crystals of the *hydrochloride salt.* After recrystallization from ethyl alcohol the crystals melted at 278–279° with decomposition; yield, 27%.

Anal. Calc'd for $C_{12}H_{26}N_4 \cdot 2$ HCl: C, 48.2; H, 9.4; N, 18.7; Molecular weight, 299.
Found: C, 48.5; H, 9.4; N, 18.5; Molecular weight, 300.

The *free base* was obtained by neutralizing an aqueous solution of the hydrochloride with a solution of sodium hydroxide. Extraction with ether gave a colorless, oily liquid of high viscosity. It decomposed quickly even though stored in the ice-chest.

The *nitric acid salt* was prepared by neutralizing an ether solution of the free base with concentrated nitric acid. It was a fine, white powder, m.p. 208–209° with decomposition.

Hydrolysis of sym-disubstituted oxamidines. (*a*) *sym*-Dimethyloxamidine (10 g.) was dissolved in 25% aqueous methylamine and allowed to stand in the ice-chest for two days Needle-like crystals separated which, after recrystallization from ethanol, melted at 212°. No depression of melting point resulted from admixture with *dimethyloxamide.* The yield of hydrolyzed product was 3 g.

(*b*) *sym*-Diethyloxamidine dissolved in 33% aqueous ethylamine was allowed to stand in the ice-chest for one week. The solid product, recrystallized from ethanol, melted at 179° and gave no melting point depression with *sym-diethyloxamide.*

(*c*) A water solution containing 6 g. of *sym*-Diethyloxamidine was heated to boiling in an open beaker. A strong ammoniacal odor was noted. After one-half hour the mixture was cooled in ice. A white powder separated which was insoluble in organic solvents and only slightly soluble in water. It did not melt but sublimed above 360°. The compound was evidently *oxamide.* Two grams was recovered.

The same material resulted when *sym*-dibutyloxamidine was boiled with water, with a water-alcohol mixture or with a water-butylamine mixture.

N,N-Tetramethyloxamidine. A 25% aqueous solution of dimethylamine containing 27.5 g. (0.5 mole) of amine was treated with purified cyanogen gas (0.25 mole) at 0°. The reaction mixture was then allowed to stand at room temperature for 24 hours after which it was extracted with ether to remove any cyanoformamidine that had formed or amine that had not reacted. To the water layer was added an excess of conc'd hydrochloric acid and the solution was evaporated carefully on a steam-bath until a thick slush remained. Ethyl alcohol was then introduced to throw out additional solid and after filtration the crystals were purified by recrystallization from hot alcohol. The yield of *hydrochloride* was 11%; white crystals melting at 280° with decomposition.

Anal. Calc'd for $C_6H_{14}N_4 \cdot 2$ HCl: C, 33.5; H, 7.4; N, 26.1; Molecular weight, 215.
Found: C, 33.3; H, 7.7; N, 26.0; Molecular weight, 219.

The free *base* liberated from the hydrochloride by neutralization with sodium hydroxide was extracted from the aqueous solution with ether and without isolation was converted to the *nitric acid salt* by the addition of conc'd nitric acid. White crystals melting at 170° with decomposition resulted.

The ether extract from the original cyanogenation mixture, saturated with dry hydrogen chloride gas, gave a 4% yield of white crystals of *dimethylcyanoformamidine hydrochloride,* m.p. 197–198°.

SUMMARY

The reaction of cyanogen with the aliphatic primary amines from C_1 through n-C_5 to produce symmetrically disubstituted oxamidines is described.

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