[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF BUFFALO]

THE REACTION OF CYANOGEN WITH ORGANIC COMPOUNDS. IV. AMINOPYRIDINES[1, 2]

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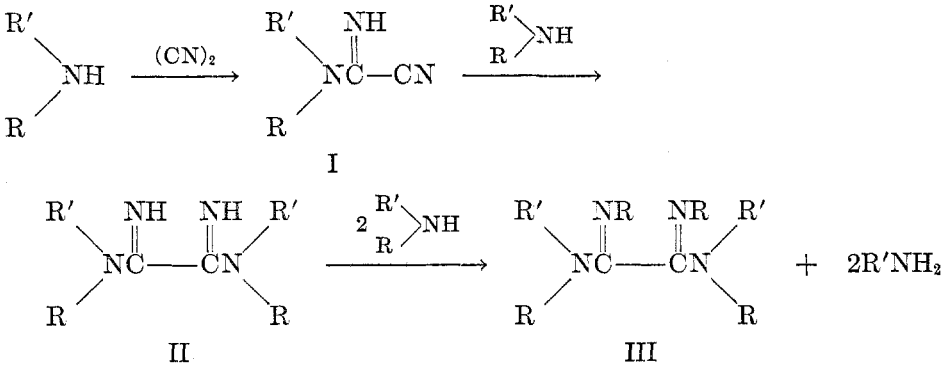
Previous studies of the reactions of cyanogen with amines (1–5) have indicated that the products are formed by a stepwise mechanism as follows:



When R and R′ are alkyl groups, the reaction stops at the cyanoformamidine (I).

When R is alkyl and R′ is hydrogen, the reaction proceeds to the oxamidine (II); however, the intermediate cyanoformamidine has not been isolated. Neither have attempts to cause known cyanoformamidines to react with an alkylamine been successful. Further reaction of an oxamidine with an alkylamine may give the tetraalkyloxamidine (III).

When R is aryl and R′ is hydrogen, the product is an oxamidine. The intermediate cyanoformamidine has not been isolated.

This paper reports a study of the reactions of certain amines in which R is heterocyclic (*i.e.*, pyridyl) and R′ is hydrogen. It is shown that, with these amines, conditions can be arranged (a) to stop the reaction at the first stage, (b) to cause it to proceed to the second stage without separation of the intermediate cyanoformamidine, or (c) to allow isolation of the intermediate which then by reaction with more amine gives the oxamidine (II).

The selection of suitable conditions was based on the following observations. Cyanoformamidines of the pyridine series are insoluble in water and can be obtained by cyanogenation of cold, dilute, neutral aqueous solutions of the amine. Failure to neutralize the solution allows the formation of tarry materials to

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proceed at a rate comparable to or faster than the rate of formation of the cyanoformamidine.

Use of a water-alcohol solution of the amine in which the proportion of alcohol is such that the cyanoformamidine is soluble but the oxamidine insoluble allows the preparation of the latter compounds. Here also the solution must be essentially neutral to inhibit tar formation.

Finally, addition of a neutral aqueous solution of an aminopyridine to an alcoholic solution of a pyridyl cyanoformamidine gives, on standing, a dipyridyloxamidine.

These results represent the first isolation of a cyanoformamidine from a *primary* amine and the first demonstrated preparation of an oxamidine from a cyanoformamidine.

The pyridyloxamidines are white, stable compounds with melting points near 200°. They show very low solubilities in water and ether and may be obtained as long, white needles from benzene or dilute alcohol if the rate of cooling is slow. They are much more susceptible to acidic than to basic hydrolysis. Ammonia, the aminopyridine, and oxalate ion may be detected in the hydrolysis mixture.

The cyanoformamidines are white, low-melting compounds which decompose on melting. They are sparingly soluble in water, cold petroleum ether (b.p. 30–60°) and cold ligroin (b.p. 60–90°) but very soluble in acetone, methanol, ethanol, ethyl acetate, and ether. Ligroin and benzene-ligroin are useful recrystallization solvents.

When crystals of cyanoformamidines were exposed to air that contained even a trace of acid vapors, they changed from white to deep red. Further investigation uncovered the following information.

Addition of hydrochloric acid to a slurry of cyanoformamidine in water produced the red color. This faded rapidly, leaving a clear, colorless solution which deposited a voluminous white precipitate when made basic with ammonia. The product, insoluble in all common organic reagents, hot or cold, was recrystallized from hot water. Analysis, complete hydrolysis, and solubility tests characterized it as a carbamylformamidine. The identity of the red material was not established; however, its source, color, and ease of hydrolysis point to a nitrilium chloride (6).

$$\mathrm{RNHC(=NH)CN} \xrightarrow{\mathrm{HCl}} \mathrm{(RNHC(=NH)CNH)^{+}Cl^{-}} \xrightarrow{\mathrm{H_2O}} \mathrm{RNHC(=NH)CONH_2} + \mathrm{HCl}.$$

All of the cyanoformamidines showed this acid-catalyzed hydration. N-(4-methylpyridyl-2)cyanoformamidine, however, gave a product which could not be purified sufficiently to establish its physical constants accurately.

Both the cyanoformamidines and the carbamylformamidines were hydrolyzed completely by hot 20% sodium hydroxide to give ammonia, aminopyridine and oxalate. Table I lists the compounds prepared with their melting points.

A plausible mechanism for the reaction of amines and cyanogen may be based

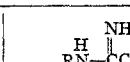
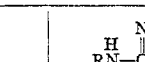
on the Lewis theory of acids and bases. Amines are Lewis bases and cyanogen, due to the relative electronegativities of carbon and nitrogen, may be considered as a Lewis acid with that activity centered on the carbon atoms. Attraction of the electron-deficient carbon of cyanogen to the electron pair of the amine would produce a weak complex of the dipole type. Now if the amine also contains an active hydrogen, that atom could shift to produce a stable molecule.

In line with this theory, any factor that would make the electron pair on the amine more easily available should increase the rate of cyanogen addition. Certain results of this investigation, although not quantitative in nature, bear out this contention.

The methyl group is electron-releasing and a methyl group *ortho* or *para* (but not *meta*) to an amino group on an aromatic ring should make the unshared electron pair of the amino group more easily available to the electrophilic cyanogen. We have noted that, under comparable conditions, the order of precipitation, and presumably, therefore, the rate of formation of the cyanoformamidine is— 5-methyl-2-aminopyridine > 3-methyl-2-aminopyridine > 2-aminopyridine >

TABLE I

MELTING POINTS OF COMPOUNDS DERIVED FROM 2-AMINOPYRIDINES

R			
Pyridyl-2	125–126° dec.	148–149°	215–216°
3-Methylpyridyl-2	95.5–96° dec.	127–127.5°	
4-Methylpyridyl-2	116.5–117° dec.	149–151° approx.	
5-Methylpyridyl-2	143–144° dec.	196–197°	
6-Methylpyridyl-2			189–190°

4-methyl-2-aminopyridine > 6-methyl-2-aminopyridine (no cyanoformamidine isolated).

EXPERIMENTAL

Analyses were carried out as previously described (3). Melting points are uncorrected. In the preparation and purification of cyanogen (3, 4) the precaution should be taken to "condition" fresh charges of the alumina drying agent by first passing the gas through rather slowly until the entire tube is barely warm to the touch. Otherwise rapid preliminary absorption generates sufficient heat to cause tar formation in the tube. A properly conditioned tube will dry the gas effectively for a long period of time.

Amounts of cyanogen given in the experiments below are approximate and are based on the sodium cyanide used. No correction is made for hydrogen cyanide and carbon dioxide removed by the purifying train.

The 2-aminopyridines were obtained from the Reilly Tar and Chemical Company. They were of sufficiently high purity (95–98%) to be used without further treatment.

PREPARATION OF CYANOFORMAMIDINES

Unless otherwise noted all cyanoformamidines were made in the same way. Details of the preparation, therefore, are given in only one case.

N-(Pyridyl-2)cyanoformamidine. A neutral solution containing 9.4 g. (0.1 mole) of 2-

aminopyridine and 2 ml. of glacial acetic acid in 150 ml. of water was placed in a 250-ml. gas absorption bottle and treated with 0.6 mole of cyanogen at 0°. The rate of cyanogenation was controlled so that the full charge of cyanogen was passed into the solution in 20 to 30 minutes.

During the cyanogenation, the solution went through a gradual color change. A yellow-orange color developed slowly and then deepened to red. Shortly after the formation of the red color, precipitation of the cyanoformamidine began. The amount of precipitate increased as cyanogenation continued.

The precipitate was washed with water and air-dried. The yield of crude product was 2 g. (13%). Recrystallization from benzene-ligroin gave white plates melting at 125–125.5° with decomposition.

Anal. Calc'd for $C_7H_6N_4$: C, 57.5; H, 4.1; N, 38.3.

Found: C, 57.6; H, 4.6; N, 38.0.

N-(3-Methylpyridyl-2)cyanoformamidine. A cold, neutral solution containing 10.8 g. (0.1 mole) of 3-methyl-2-aminopyridine and 1.5 ml. of glacial acetic acid in 150 ml. of water was treated with 0.6 mole of cyanogen. The characteristic color change was followed by precipitation of the cyanoformamidine. The yield of crude, dry product was 4 g. (25%). Recrystallization from ligroin gave white needles melting at 95.5–96° with decomposition.

Anal. Calc'd for $C_8H_8N_4$: C, 60.0; H, 5.0; N, 35.0; Mol. wt., 160.

Found: C, 60.3; H, 5.2; N, 34.7; Mol. wt. (crysoscopic, in benzene), 164.

N-(4-Methylpyridyl-2)cyanoformamidine. A cold, neutral solution containing 5.4 g. (0.05 mole) of 4-methyl-2-aminopyridine and 1 ml. of glacial acetic acid in 200 ml. of water was treated with 0.6 mole of cyanogen. The reaction between this amine and cyanogen was comparatively slow. Nearly the full charge of cyanogen was passed into the solution before precipitation began. The yield of crude, dry product was 1.4 g. (17.5%). Recrystallization from ligroin gave white needles melting at 116.5–117° with decomposition.

Anal. Calc'd for $C_8H_8N_4$: C, 60.0; H, 5.0; N, 35.0.

Found: C, 60.1; H, 5.1; N, 34.8.

N-(5-Methylpyridyl-2)cyanoformamidine. A cold, neutral solution containing 10.8 g. (0.1 mole) of 5-methyl-2-aminopyridine and 1 ml. of glacial acetic acid in 150 ml. of water was treated with 0.6 mole of cyanogen. The characteristic color change and precipitation of the cyanoformamidine took place within a few minutes. This was the most rapid reaction observed in this work. The yield of crude, dry product was 2.6 g. (16%). Recrystallization from benzene-ligroin gave white plates melting at 143–144° with decomposition.

Anal. Calc'd for $C_8H_8N_4$: C, 60.0; H, 5.0; N, 35.0.

Found: C, 60.2; H, 5.4; N, 34.7.

Unsuccessful reactions. (a) *With 2,6-diaminopyridine.* A cold, neutral solution containing 10.9 g. (0.1 mole) of 2,6 diaminopyridine and 1.5 ml. of glacial acetic acid in 150 ml. of water was treated with 0.6 mole of cyanogen. No precipitate was formed during the cyanogenation or after the solution had been allowed to stand in the ice-chest for 24 hours.

(b) *With 2-amino-6-methylpyridine.* A cold neutral solution containing 10.8 g. (0.1 mole) of 2-amino-6-methylpyridine and 1.5 ml. of glacial acetic acid in 150 ml. of water was treated with 0.6 mole of cyanogen. No precipitate was formed during the cyanogenation or on standing.

PREPARATION OF DIPYRIDYLOXAMIDINES

N,N'-Di-(pyridyl-2)oxamidine. (a) *By direct cyanogenation.* A cold solution of 18.8 g. (0.2 mole) of 2-aminopyridine in 36 ml. of water and 24 ml. of alcohol was treated with 0.4 mole of cyanogen. Dilution and neutralization were effected with 50 ml. of water and 4 ml. of glacial acetic acid. The solution was allowed to stand in an ice-chest for 48 hours after which filtration gave 3.9 g. (16%) of crude, black product. Recrystallization from benzene or dilute alcohol (with Norit) gave white needles, m.p. 215–216°.

Anal. Calc'd for $C_{12}H_{12}N_6$: C, 60.0; H, 5.0; N, 35.0.

Found: C, 60.1; H, 5.0; N, 34.9.

(b) *By amination of N-(pyridyl-2)cyanoformamidine.* A neutral solution containing 18.8 g. (0.2 mole) of 2-aminopyridine and 4 ml. of glacial acetic acid in 100 ml. of water was mixed with a solution of 5.0 g. (0.03 mole) of N-(pyridyl-2)cyanoformamidine in 50 ml. of 95% ethanol. The mixture was allowed to stand in an ice-chest. The characteristic red color associated with direct cyanogenation developed. After 72 hours filtration yielded 0.8 g. (10%) of crude product. Recrystallization gave dipyridyloxamidine melting at 213–214° and giving no depression in melting point when mixed with a sample prepared by direct cyanogenation.

N,N'-Di-(6-methylpyridyl-2)oxamidine. A cold solution of 43.3 (0.4 mole) of 2-amino-6-methylpyridine in 72 ml. of water and 48 ml. of alcohol was treated with 0.75 mole of cyanogen. Dilution and neutralization were effected with 100 ml. of water and 14 ml. of glacial acetic acid. The solution was allowed to stand in an ice-chest. Filtration, after 72 hours, gave 8.7 g. (16%) of crude product. Recrystallization from dilute alcohol (with Norit) gave white needles, m.p. 189–190°.

Anal. Calc'd for $C_{14}H_{16}N_6$: C, 62.7; H, 6.0; N, 31.3.
Found: C, 62.8; H, 6.2; N, 31.2.

Unsuccessful reactions. (a) *With 3-methyl-2-aminopyridine.* A cold solution of 21.6 g. (0.2 mole) of 3-methyl-2-aminopyridine in 36 ml. of water and 24 ml. of alcohol was treated with 0.4 mole of cyanogen. Dilution and neutralization were effected with 50 ml. of water and 3 ml. of glacial acetic acid. The solution after standing 72 hours in an ice-chest gave only a small amount of tar.

(b) *With 4-methyl-2-aminopyridine.* A cold solution of 10.8 g. (0.1 mole) of 4-methyl-2-aminopyridine in 36 ml. of alcohol was treated with 0.4 mole of cyanogen. The solution was then diluted and neutralized with 50 ml. of water and 1 ml. of glacial acetic acid. After standing for 5 days in an ice-chest, the solution yielded only a small amount of tar.

(c) *With 5-methyl-2-aminopyridine.* A cold solution of 21.6 g. (0.2 mole) of 5-methyl-2-aminopyridine in 36 ml. of water and 24 ml. of alcohol was treated with 0.4 mole of cyanogen. Dilution and neutralization were effected with 50 ml. of water and 2 ml. of glacial acetic acid. The solution was allowed to stand in an ice-chest for 72 hours. Filtration gave a black, amorphous material. Extraction of this solid with hot benzene, hot alcohol, and a water-alcohol mixture failed to recover any crystalline material.

HYDRATION OF CYANOFORMAMIDINES TO CARBAMYLFORMAMIDINES

The following method of preparing a carbamylformamidine was found to be applicable to any N-(pyridyl-2)cyanoformamidine.

Three to four drops of 20% hydrochloric acid (representing 35–40 mole-% of the cyanoformamidine used) was added to a slurry consisting of approximately 0.5 g. of the N-(pyridyl-2)cyanoformamidine in 25 ml. of water. A red color developed immediately and the cyanoformamidine dissolved. After a few minutes, the color faded completely. The colorless solution was filtered and cooled in an ice-bath. Concentrated ammonium hydroxide was added, with stirring, until the solution was basic. At that point a voluminous precipitate formed. The material was purified by recrystallization from water.

Physical data and analyses of the compounds prepared are summarized below.

N-(5-methylpyridyl-2)-C-carbamylformamidine. White crystals melting at 196–197°.

Anal. Calc'd for $C_8H_{10}N_4O$: C, 53.9; H, 5.7; N, 31.4.
Found: C, 54.0; H, 5.4; N, 31.0.

N-(Pyridyl-2)-C-carbamylformamidine. White crystals melting at 148–149°.

Anal. Calc'd for $C_7H_8N_4O$: N, 34.1. Found: N, 33.7.

N-(3-Methylpyridyl-2)-C-carbamylformamidine. White crystals melting at 127–127.5°.

Anal. Calc'd for $C_8H_{10}N_4O$: N, 31.4. Found: N, 31.1.

N-(4-Methylpyridyl-2)-C-carbamylformamidine. N-(4-methylpyridyl-2)cyanoformamidine showed the typical color change when treated with hydrochloric acid. Addition of ammonia caused the precipitation of a pale yellow solid (m.p. 149–151°). However, attempts to obtain this material in a pure state were unsuccessful. The carbamylformamidine was

probably partially hydrolyzed during recrystallization from water and the aminopyridine resulting, due to its relatively low water solubility, contaminated the material. No solvent more suitable than water for recrystallization could be found.

SUMMARY

1. Cyanogen reacts with neutral aqueous solutions of certain 2-aminopyridines to give N-(pyridyl-2)cyanoformamidines.

2. Under proper conditions cyanogen reacts with certain 2-aminopyridines to give N,N′-di-(pyridyl-2)oxamidines.

3. N-(pyridyl-2)cyanoformamidine has been made to react with 2-aminopyridine to give N,N′-di-(pyridyl-2)oxamidine.

4. N-(pyridyl-2)cyanoformamidines hydrate rapidly in acid solution to give C-carbamylformamidines.

5. The isolation of the cyanoformamidines and the conversion of a cyanoformamidine to an oxamidine is the first direct evidence for the existence of cyanoformamidines as intermediates in the reaction of cyanogen with primary amines.

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