

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

Reaction of Cyanogen with Organic Compounds. XIII. Some Nitrogen Heterocycles¹

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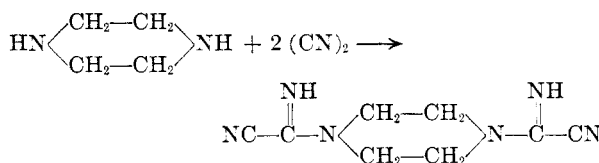
Solutions of pyrrolidine, piperidine, 2-methylpiperidine, 2,4-dimethylpiperidine, morpholine, piperazine, 2-methylpiperazine, (*cis*) 2,5-dimethylpiperazine, and (*trans*) 2,5-dimethylpiperazine react with cyanogen to yield cyanoforamidine derivatives. Where two amine functions are present in the ring both react. In the absence of a solvent pyrrolidine yields an oxamidine. Neither pyrrole nor Δ^3 -pyrroline could be made to react with cyanogen.

In this paper we report the behavior toward cyanogen of a series of nitrogen-containing heterocycles. Compounds chosen for study were pyrrole, Δ^3 -pyrroline, pyrrolidine, piperidine, 2-methylpiperidine, 2,4-dimethylpiperidine, morpholine, 2-methylpiperazine, (*cis*) 2,5-dimethylpiperazine and (*trans*) 2,5-dimethylpiperazine. Each compound contains ring-nitrogen in the reduced state, thus making imino hydrogen available for the reaction, but no other functional group. Simple secondary aliphatic amines have been found to react with cyanogen to produce cyanoforamidines³ but *N,N'*-dialkylethylenediamines and diethylenetriamine reacting through the secondary amino group, gave oxamidines.^{4,5} One cannot, therefore, predict with certainty the result of employing a heterocyclic reagent.

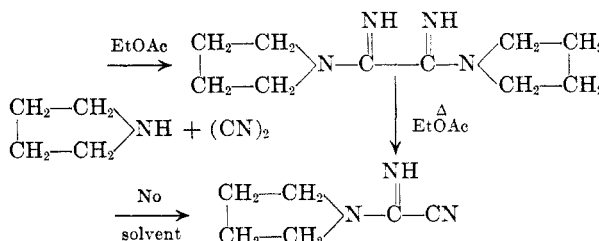
Of the compounds listed, only pyrrole and Δ^3 -pyrroline failed to react. In the case of pyrrole this is understandable, since the NH function is conjugated with two unsaturations and has some of the properties of an imide. Despite many attempts in this laboratory we have not been able to bring about a reaction between cyanogen and an imide (or amide).

On the other hand, Δ^3 -pyrroline has a structural relationship with allyl- and diallyl amine, which add to cyanogen with great ease,⁶ and might be expected to behave in a similar fashion. Nevertheless no product save paracyanogen could be isolated.

All other compounds produced cyanoforamidines, those with two ring-nitrogens reacting at both centers:



Under varying conditions pyrrolidine gave both a cyanoforamidine and an oxamidine, the former being quite unstable:



The key to a successful reaction was the discovery of a suitable solvent. Water, 95% ethanol, ether and ethyl acetate were effective in individual cases. Generally only one solvent system gave good results with a given heterocycle. An exception was morpholine which reacted equally well in water and in 95% ethanol. In those cases where the product separated as an oil it was advisable to terminate the admission of cyanogen soon after the oil appeared. Otherwise considerable tar was formed. Buffering with glacial acetic acid⁷ did not obviate this difficulty or improve the yields.

Liquid products were purified by vacuum distillation. Solids were recrystallized from a chloroform-carbon tetrachloride solvent pair. Best yields were obtained with morpholine and the derivatives of piperazine.

The cyanoforamidines derived from one-nitrogen heterocycles were liquids or low melting solids. When pure they were fairly stable but darkened in 3 to 4 weeks (or more rapidly when exposed to air), and developed the odor of cyanogen. Redistillation rendered them colorless and pure once more. In several cases stable salts of mineral acids could be formed. The cyanoforamidines from two-nitrogen heterocycles were stable solids.

(1) From a dissertation submitted by Winfield S. Zehring III in partial fulfillment of the requirements for the Ph.D. degree, June 1957.

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(3) H. M. Woodburn, B. A. Morehead, and W. H. Bonner, *J. Org. Chem.*, **14**, 555 (1949).

(4) H. M. Woodburn and R. C. O'Gee, *J. Org. Chem.*, **17**, 1235 (1952).

(5) H. M. Woodburn and J. R. Fisher, *J. Org. Chem.*, **22**, 895 (1957).

(6) H. M. Woodburn, M. C. Chen, and D. H. Thorpe, *J. Org. Chem.*, **22**, 846 (1957).

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EXPERIMENTAL

Reagents. Cyanogen was prepared by the action of an aqueous sodium cyanide solution on a boiling copper sulfate solution.³ Two silver nitrate bubblers were employed in the purifying train and the gas was dried by passing it first through a calcium chloride tower then through phosphorus pentoxide. Pyrrole, pyrrolidine, morpholine, piperidine, 2-methylpiperidine, 2,4-dimethylpiperidine, and piperazine hydrate were purchased from Distillation Products Industries. Pure samples of 2-methylpiperazine and the *cis*- and *trans*-isomers of 2,5-dimethylpiperazine were the gift of the Wyandotte Chemical Co. Δ^3 -Pyrroline was synthesized by the method of Andrews and McElvain,⁸ the reduction of pyrrole using zinc and hydrochloric acid.

Reactions of heterocyclic compounds with cyanogen. *bis(1-Pyrrolidyl)glyoxalimine from pyrrolidine.* A large excess of pyrrolidine was used in this preparation because preliminary experiments had shown that stoichiometric quantities or an excess of cyanogen caused the formation of a great deal of tar.

A cold (0°) solution of 63.6 g. (0.9 mole) of pyrrolidine in 75 ml. of dry ethyl acetate was treated with 14 g. (0.27 mole) of cyanogen. Placed in an ice chest, the reaction mixture slowly deposited crystals. After 48 hr. these were collected and dried in a vacuum desiccator over calcium chloride. The yield of crude material was 24.2 g. or 46% based on cyanogen.

Recrystallization from ethyl acetate gave white crystals melting at 120–122°. The compound decomposed slowly in moist air. Attempts to form salts from mineral acids gave only oils which would not crystallize.

Anal. Calcd. for $C_{10}H_{18}N_4$: C, 62.0; H, 9.3; N, 28.9. Found: C, 62.0; H, 9.3; N, 28.6.

During the process of recrystallization an oil separated from the ethyl acetate solution. This was collected and on cooling in a vacuum desiccator it crystallized to a white solid different from the one described above. Recrystallization from ether gave a material melting at 55–56°, very sensitive to moisture, decomposing to cyanogen and pyrrolidine on exposure. From the melting point of a mixture with the compound prepared below it is obvious that it was 1-(*cyanoformimino*)pyrrolidine.

1-(Cyanoformimino)pyrrolidine from pyrrolidine. Approximately 0.3 mole of cyanogen was passed into 63.6 g. (0.9 mole) of pyrrolidine which had been cooled to 0°. After 48 hr. in the ice chest a mass of crystals had formed in the reaction vessel. (If crystallization did not occur within 48 hr., the addition of a small amount of absolute ether followed by several more hours of cooling caused crystals to form.) These were rapidly collected on a sintered glass funnel, washed with cold anhydrous ether, and dried in a vacuum desiccator. The yield of crude product was 10 g. (9.1%). Recrystallized from anhydrous ether the compound melted at 55–56°.

Anal. Calcd. for $C_6H_8N_3$: C, 58.5; H, 7.3; N, 34.1. Found: C, 57.8; H, 7.2; N, 33.5.

The extreme sensitivity of the compound to moisture made it impossible to obtain an accurate analysis. All attempts to obtain the hydrochloric acid salt of the compound failed.

1-(Cyanoformimino)piperidine from piperidine. Cyanogen was passed through a cold solution of 14.7 g. (0.125 mole) of piperidine in 50 ml. of water until an oil separated. About 10 g. (0.19 mole) of cyanogen was required. The oil was extracted with ether, dried over anhydrous magnesium sulfate, and vacuum distilled, giving 10.0 g. (47.1%) of a colorless liquid; b.p. 79–80°/3 mm. The product was soluble in water, acids, and common organic solvents. It darkened in 3 to 4 weeks but could be purified by redistillation.

Anal. Calcd. for $C_7H_{11}N_3$: C, 61.2; H, 8.0; N, 30.6. Found: C, 60.8; H, 7.9; N, 30.6.

The *hydrochloride*, prepared by passing dry hydrogen chloride into an ether solution of the free base and recrystallizing the precipitate from absolute ethanol, was a white solid melting at 156° (dec.). It was stable if protected from moisture.

Anal. Calcd. for $C_7H_{12}N_3Cl$: C, 48.4; H, 6.9; N, 24.4; Cl, 20.4. Found: C, 48.2; H, 7.1; N, 24.6; Cl, 20.2.

1-(Cyanoformimino)-2-methylpiperidine from 2-methylpiperidine. A cold aqueous solution of 29.0 g. (0.293 mole) of 2-methylpiperidine was treated with cyanogen until an oil separated. This was recovered and purified in the manner described above; b.p. 88°/3 mm.; yield 14.0 g. (23.5%).

Anal. Calcd. for $C_8H_{13}N_3$: C, 63.6; H, 8.6; N, 27.8. Found: C, 63.2; H, 8.2; N, 28.0.

Preparation of the *hydrochloride* was attempted but a crystalline product failed to appear. The *nitrate* was prepared by the addition of a stoichiometric quantity of concentrated nitric acid to a dilute solution of the free base in ether. Recrystallized from absolute ethanol, the product melted at 134–135° (dec.).

Anal. Calcd. for $C_8H_{13}N_3 \cdot HNO_3$: C, 44.9; H, 6.5; equiv. wt., 214. Found: C, 44.9; H, 6.5; equiv. wt., 216.

1-(Cyanoformimino)-2,4-dimethylpiperidine from 2,4-dimethylpiperidine. A cold suspension of 10 g. (0.089 mole) of 2,4-dimethylpiperidine was treated with cyanogen until an oil separated. This was recovered and purified in the manner described above; b.p. 84°/1 mm.; yield 2.4 g. (16.5%).

Anal. Calcd. for $C_9H_{15}N_3$: C, 65.4; H, 9.1; N, 25.4. Found: C, 65.0; H, 8.9; N, 24.9.

Attempts to prepare the *hydrochloride* and *nitrate* produced oily materials not suitable for the determination of physical constants.

4-(Cyanoformimino)morpholine from morpholine. (a) In ethanol solution.⁹ A solution of 16 g. (0.184 mole) of morpholine in 40 ml. of 95% ethanol was cooled to 0° and treated with 8.0 g. (0.154 mole) of cyanogen. After about half of the cyanogen had been passed in a white solid began to form. The reaction mixture was kept cool for 0.5 hr. to allow complete precipitation after which the product was filtered, washed with cold ethanol, and dried in air. The yield of crude material was 19.0 g. (76%). Recrystallization from ethanol gave white crystals; m.p. 90–92°. (b) In water solution. A cold solution of 8.7 g. (0.10 mole) of morpholine in 30 ml. of water, treated with 6.0 g. (0.115 mole) of cyanogen, produced 9.2 g. (66.2%) of product, m.p. 90–92°.

Anal. Calcd. for $C_6H_9ON_3$: C, 51.7; H, 6.5; N, 30.2. Found: C, 51.5; H, 6.6; N, 30.2.

The free base was quite unstable. Overnight it turned brown and the melting point dropped appreciably. The *hydrochloride* prepared by saturating an ether solution of the free base with dry hydrogen chloride was a stable, white salt. Recrystallized from absolute ethanol it melted at 188–189° (dec.).

Anal. Calcd. for $C_6H_{10}ON_3Cl$: Cl, 20.4; equiv. wt., 175.5. Found: Cl, 20.4; equiv. wt., 175.2.

1,4-Bis(cyanoformimino)piperazine from piperazine. A cold solution of 11.6 g. (0.135 mole) of piperazine (26.2 g. of piperazine hydrate) in 100 ml. of water was treated with approximately 0.3 mole of cyanogen. Deposition of crystals began almost immediately and continued throughout the cyanogenation. The product, filtered and air-dried, weighed 17.9 g. (70%).

Recrystallization was accomplished by suspending the product in boiling carbon tetrachloride and adding hot chloroform until solution was complete. The white crystals which separated on cooling melted at 187.5–188° and were apparently very stable since no depression in melting point was noted after long standing.

(8) L. H. Andrews and S. M. McElvain, *J. Am. Chem. Soc.*, **51**, 887 (1929).

(9) The original work on morpholine was done in this laboratory by E. L. Graminski with the support of the Mallinckrodt Chemical Co.

Anal. Calcd. for $C_8H_{10}N_6$: C, 50.4; H, 5.3; N, 44.2; mol. wt., 190. Found: C, 50.2; H, 5.5; N, 44.2; mol. wt., (Rast) 185.

1,4-Bis(cyanoformimino)-2-methylpiperazine from 2-methylpiperazine. A cold solution of 10.0 g. (0.1 mole) of 2-methylpiperazine in 200 ml. of dry ether was treated with approximately 0.3 mole of cyanogen. Crystal deposition began almost immediately and continued throughout the cyanogenation. The crystals were collected, washed with ether and air-dried. The yield was 12.0 g. (58.8%).

Recrystallized from a chloroform-carbon tetrachloride solvent pair, the white solid melted at 113–113.5°. The pure product appeared to be stable.

Anal. Calcd. for $C_8H_{10}N_6$: C, 53.0; H, 5.9; N, 41.1; Found: C, 53.2; H, 5.3; N, 41.4.

Attempts to prepare the *hydrochloride* from an ether solution of the free base produced an oil which would not crystallize.

1,4-Bis(cyanoformimino)-cis-2,5-dimethylpiperazine from (cis) 2,5-dimethylpiperazine. A cold ether solution of 11.4 g. (0.1 mole) of (*cis*) 2,5-dimethylpiperazine was treated with cyanogen and worked up in the manner described above. The yield of tan crystals was 19.2 g. (88.1%). Recrystallized from a chloroform-carbon tetrachloride solvent pair, the white product melted at 124–125°. The purified material was quite stable.

Anal. Calcd. for $C_{10}H_{14}N_6$: C, 55.0; H, 6.4; N, 38.5. Found: C, 55.4; H, 6.1; N, 38.4.

The *hydrochloride* was prepared by saturating a very dilute ether solution of the free base with dry hydrogen chloride. The salt decomposed very rapidly in air and could not be analyzed.

1,4-Bis(cyanoformimino)-trans-2,5-dimethylpiperazine from (trans) 2,5-dimethylpiperazine. A cold solution of 9.0 g. (0.079 mole) of (*trans*) 2,5-dimethylpiperazine in 50 ml. of water was treated with about 0.3 mole of cyanogen. Crystallization began when about half of the cyanogen had been added. Seven g. (40.7%) of dark brown solid was recovered. Recrystallized from a chloroform-carbon tetrachloride solvent pair, the white crystals melted at 166–167°. The pure product was very stable.

Anal. Calcd. for $C_{10}H_{14}N_6$: C, 55.0; H, 6.4; N, 38.5. Found: C, 54.7; H, 6.7; N, 38.6.

The limited solubility of the free base prevented the preparation of the *hydrochloride* or other derivative.

Unsuccessful Reactions. Pyrrole. One-tenth mole (6.7 g.) of pyrrole in each of the following solvents was cyanogenated without success: water, ether, 50% ethanol, benzene, ethyl acetate. In some cases tars resulted; in others the unreacted pyrrole was recovered. A suspension of pyrrole in *N* NaOH was also unreactive, as was pure pyrrole. Δ^2 -Pyrroline. One-tenth mole (6.9 g.) of Δ^2 -pyrroline was treated with cyanogen (a) in the absence of a solvent, (b) in ether solution, (c) in ethyl acetate solution. Only paracyanogen was recovered.

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF THE AMERICAN OIL COMPANY]

Reaction of the Saturated Dimer of α -Methylstyrene with Aluminum Chloride. The Preparation of a Substituted Tetrahydroindenoindene

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When the saturated dimer of α -methylstyrene is heated in the presence of anhydrous aluminum chloride, attack on the five-membered ring occurs followed by condensation reactions. The products of the reaction are benzene, cumene, 1,1,3-trimethylindene, 1,1,3-trimethylindan, 4b,9,9,10,10-pentamethyl-4b,9,9a,10-tetrahydroindeno[1,2-*a*]indene, and polymer.

Most of the chemical reactions of the saturated dimer of α -methylstyrene (I) have been confined to the two aromatic rings, as the five-membered ring and its methyl groups appear to be very unreactive. The aromatic rings can be nitrated, sulfonated, and chlorinated without any effect on the five-membered ring. It is noteworthy that vigorous oxidation, with chromic acid, of the related saturated dimer of *p*, α -dimethylstyrene does not result in attack on the five-membered ring or its methyl groups; only the methyl groups on the aromatic ring are oxidized.¹

No reference to the effect of anhydrous aluminum chloride on the saturated dimer of α -methylstyrene has been found. In this study, the saturated dimer was treated with aluminum chloride, and condensations involving the five-membered ring occurred. The products were benzene, cumene,

1,1,3-trimethylindene, 1,1,3-trimethylindan, indene polymers, and a compound having a melting point of 132°. The latter compound has been shown to be 4b,9,9,10,10-pentamethyl-4b,9,9a,10-tetrahydroindeno[1,2-*a*]indene (VII). The yield of crude compound VII was 27 wt. % based on the saturated dimer charged when the reaction was carried out with 20% aluminum chloride at 80° for 24 hrs. or 100° for 6 hr. If the reaction time was increased to 72 hr. at 80°, the yield of compound VII decreased to 16 wt. %. It was demonstrated that this decrease in yield was due to further reaction of compound VII in the presence of aluminum chloride to produce lower and higher boiling compounds.

The addition of a solvent, such as benzene, to the reaction mixture had no effect on the course of the reaction. Saturation of the reaction mixture with anhydrous hydrogen chloride prevented the formation of compound VII and increased polymer yield, although it had only little effect on the amount of saturated dimer reacting. Water had a

(1) V. N. Ipatieff, H. Pines, and R. C. Olberg, *J. Am. Chem. Soc.*, **70**, 2123 (1948).