

BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 42 1454—1456 (1969)

Synthesis of 4,8-Diaminopyrimido[5,4-*d*]pyrimidine from Hydrogen Cyanide in Liquid Ammonia¹⁾

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(Received September 25, 1968)

In a previous paper,²⁾ the present authors have reported that adenine and 4,5-dicyanoimidazole are formed by heating anhydrous hydrogen cyanide in excess liquid ammonia. Furthermore, a precise investigation revealed that another product, 4,8-diaminopyrimido[5,4-*d*]pyrimidine (III) is also present in the reaction mixture.

In the present paper, the identification of the compound (III) and some discussions of the course

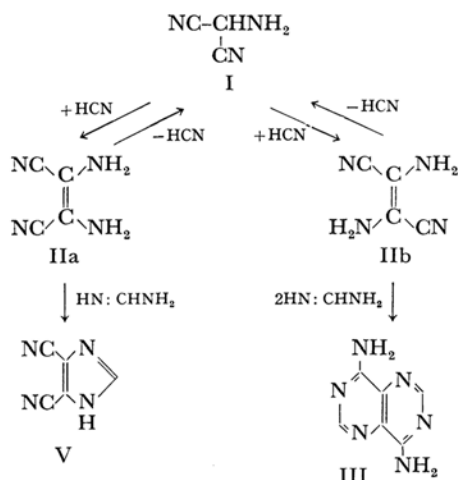
of its formation are presented. The compound (III) was not at all soluble, or only a little so, in dilute hydrochloric acid, aqueous ammonia, and most usual organic solvents. Although III was not extracted directly from the reaction mixture of hydrogen cyanide with liquid ammonia, the *N*⁴,*N*⁸-diacetyl derivative (IV) of III was found to dissolve in hot acetic anhydride. IV was easily deacetylated by aqueous ammonia to give the free base. The structure of III was determined by elementary analysis, by a study of its ultraviolet and infrared absorption spectra, and by means of the molecular ion peak of the mass spectrum, while it was identified by comparing it with an authentic sample

1) Presented at the 21st Annual Meeting of Chemical Society of Japan, Osaka, 1968.

2) H. Wakamatsu, Y. Yamada, T. Saito, I. Kumashiro and T. Takenishi, *J. Org. Chem.*, **31**, 2035 (1966).

of 4,8-diaminopyrimido[5,4-*d*]pyrimidine.³⁾ By acetylation with acetic anhydride, followed by deacetylation with aqueous ammonia, III was isolated in an 11% yield (based on the hydrogen cyanide used).

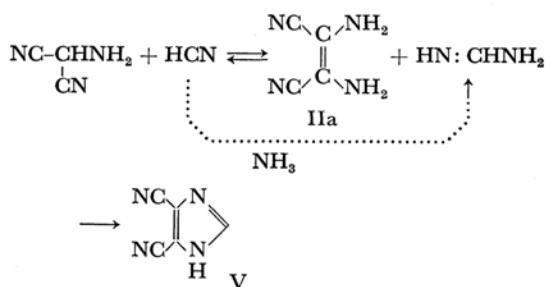
In a previous paper⁴⁾ the authors presumed that III would be derived from the postulated trans-isomer of the hydrogen cyanide tetramer, diamino-fumaronitrile (IIb).⁵⁾ However, when diamino-maleonitrile (IIa) and formamidine acetate were heated in liquid ammonia at 120°C, III was obtained in a 10% yield (based on the IIa). As an interpretation of the formation of III from the cis-tetramer (IIa) in the liquid ammonia system, an equilibrium between aminomalononitrile (I) and both tetramers of hydrogen cyanide, IIa and IIb, may be assumed



In order to demonstrate the existence of an equilibrium between I and the two tetramers, IIa and IIb, the following experiment was carried out.

When a solution of IIa in a large amount of liquid ammonia was heated in a sealed vessel, 4,5-dicyanoimidazole (V) was obtained, together with azulmic acids, but III was not isolated, probably because of its low yield. Therefore, the formation of V from IIa may be attributed to the conversion of IIa into I by dehydrocyanation prior to the cyclization to V. The hydrogen cyanide thus formed would react with ammonia to give formamidine, which may serve as a ring-closing agent.

IIa is usually obtained by the base-catalyzed oligomerization⁶⁾ of hydrogen cyanide, or as an



addition product⁷⁾ of I with hydrogen cyanide. However, IIb has not been found in these reaction mixtures because of its extreme lability in the presence of an acid or a base, although it has been prepared by the photochemical rearrangement of IIa.⁵⁾ Therefore, the effect of an added acid or a base on the formation of III in liquid ammonia was investigated.

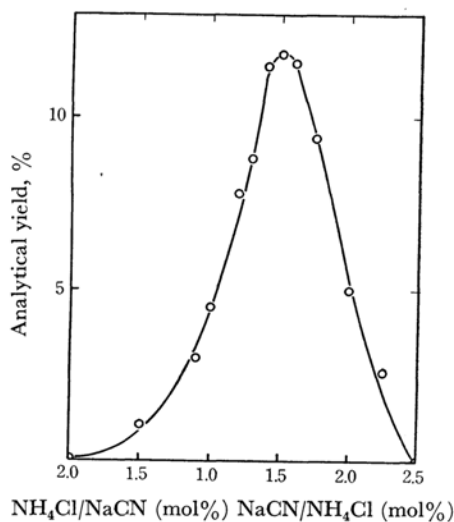


Fig. 1. The formation of III from mixtures of 20 ml of liquid ammonia and different amounts of sodium cyanide and ammonium chloride (120°C, 3 hr).

Although IIb is found to be most stable in a neutral medium,⁵⁾ a weakly basic region has apparently been observed to be most suitable for the formation of III.

Experimental⁸⁾

4,8-Diacetylaminopyrimido [5,4-*d*] pyrimidine (IV). A solution of hydrogen cyanide (27 g, 1 mol) in 200

3) F. G. Fischer, *Ann.*, **631**, 147 (1960).

4) Y. Yamada, I. Kumashiro and T. Takenishi, *J. Org. Chem.*, **33**, 642 (1968).

5) Y. Yamada, N. Nagashima, Y. Iwashita, A. Nakamura and I. Kumashiro, *Tetrahedron Letters*, **1968**, 4529.

6) T. Völker, *Angew. Chem.*, **72**, 379 (1960).

7) J. P. Ferris and L. E. Orgel, *J. Am. Chem. Soc.*, **88**, 3829 (1966).

8) The melting point is uncorrected. The ultraviolet and infrared absorption spectra were measured with a Hitachi EPS-2 and a JASCO Model IR-S recording spectrophotometer respectively.

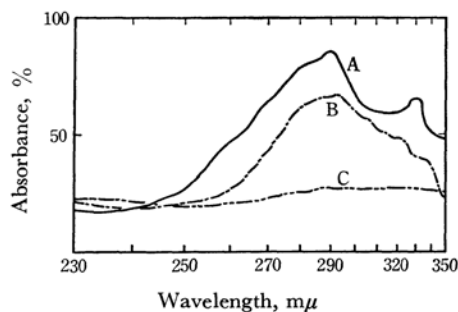


Fig. 2. UV absorption spectra of III. A, pH 1; B, pH 11; C, "hydrated" anionic molecule.

ml (at 20°C) of liquid ammonia was heated at 120°C for 8 hr in a 500-ml stainless-steel pressure vessel. After removing the ammonia and unchanged hydrogen cyanide, adenine and 4,5-dicyanoimidazole were extracted several times with hot dilute aqueous ammonia from the resulting residue. The dry extracted residue was heated under refluxing with acetic anhydride (250 g, 2.45 mol) and filtered while hot. The brown precipitate gradually formed when the filtrate stood.

The crude crystals were collected by filtration and recrystallized from acetic anhydride to give 4.55 g (11%) of IV, mp 277–278°C (dec.).

Found: C, 48.75; H, 4.58; N, 34.48%. Calcd for $C_{10}H_{10}N_6O_2$: C, 48.78; H, 4.09; N, 34.14%.

4,8-Diaminopyrimido[5,4-d]pyrimidine (III). When IV was, at room temperature, stirred into dilute aqueous ammonia, white crystals were immediately formed. The crystals were filtered and washed with water to give III quantitatively. $\nu_{\text{max}}^{\text{KBr}}$ 3380, 3200, 1665, 1555, 1540, 1440 and 1430 cm^{-1} .

Found: C, 44.25; H, 3.95; N, 51.66%. Calcd for $C_6H_6N_6$: C, 44.44; H, 3.73; N, 51.83%.

Although a detailed study was not made, a reversible hydration phenomenon,⁹ which has also been observed in some pteridines, was found from its ultraviolet absorption spectra to occur in III.

The authors wish to express their deep thanks to Dr. Toichi Yoshida, Director of these Laboratories, for his kind encouragement.

9) Y. Inoue and D. D. Perrin, *J. Chem. Soc.*, **1962**, 2600.