

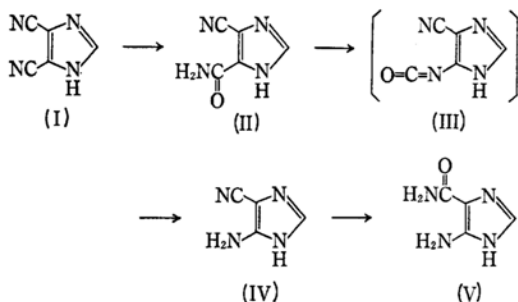
# Synthesis of 4-Amino-5-imidazolecarbonitrile and 4-Amino-5-imidazolecarboxamide from 4, 5-Dicyanoimidazole<sup>1)</sup>

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In a previous communication,<sup>2)</sup> we have reported that adenine and 4, 5-dicyanoimidazole were formed by heating anhydrous hydrogen cyanide, or an equivalent mixture of sodium cyanide and ammonium chloride, in excess liquid ammonia. In the present paper, the synthesis of 4-amino-5-imidazolecarbonitrile and 4-amino-5-imidazolecarboxamide (AICA) from 4, 5-dicyanoimidazole will be reported. AICA is a useful synthetic intermediate of purine derivatives. It has been prepared by various methods, from, for example, 4-nitro-5-imidazolecarboxylic acid<sup>3)</sup> or ethyl aminocyanacetate<sup>4)</sup>, however, these methods are complicated and the overall yields are unsatisfactory. It has now been found that 4-amino-5-imidazolecarbonitrile and AICA can be readily prepared from 4, 5-dicyanoimidazole by the use of Hofmann's rearrangement reaction:



Since 4, 5-dicyanoimidazole were found to be resistant to a boiling dilute aqueous solution of ammonia or hydrogen chloride, the partial hydrolysis of I to 4-cyano-5-imidazolecarboxamide (II) has been accomplished with a 1 N sodium hydroxide solution. II was treated with a 0.1 N solution containing 1.25 equivalents of sodium hypochlorite at 0°C for 30 min. A concentrated sodium hydroxide solution was then added so as to make 4 equivalents based on II, after which the reaction mixture was warmed at 80°C for 3 hr. The infrared absorption spectra of 4-amino-5-

imidazolecarbonitrile (IV), which was isolated by the ion-exchange resin treatment, agreed well with those of an authentic sample.<sup>5,6)</sup> By hydrolysis in a strongly basic medium at a higher temperature, IV was converted to AICA (V). When the intermediate (III), probably isocyanate, was hydrolyzed directly under drastic conditions, AICA could not be obtained successfully, but a tarry substance was found to be formed.

## Experimental<sup>7)</sup>

**4-Cyano-5-imidazolecarboxamide (II).** After a solution of 4, 5-dicyanoimidazole (30 g) in 600 ml of 1 N sodium hydroxide had been kept at 40°C for 6 hr, it was neutralized to pH 6 with concentrated hydrochloric acid. The solid precipitates, which were formed immediately, were filtered, washed with ice water, and recrystallized from hot water to give colorless needles. Yield: 31 g (90%); mp 272–273°C; infrared (CN) 2240, (amide CO) 1695 cm<sup>-1</sup>; ultraviolet  $\lambda_{max}^{pH 1}$  253 m $\mu$  ( $\epsilon$  8.32  $\times$  10<sup>3</sup>);  $\lambda_{max}^{pH 13}$  274 m $\mu$  ( $\epsilon$  10.10  $\times$  10<sup>3</sup>).

Found: C, 44.25; H, 3.05; N, 41.25%. Calcd for C<sub>5</sub>H<sub>4</sub>N<sub>4</sub>O: C, 44.12; H, 2.96; N, 41.17%.

**4-Amino-5-imidazolecarbonitrile (IV).** To a solution of 600 ml of 0.22 N sodium hydroxide, chlorine gas (1.28 l) was dissolved at 0°C. To this solution, II (6 g) was added at 0°C; the resulting solution was stirred at the same temperature for 30 min, and then 1.5 N sodium hydroxide (120 ml) was added to the reaction mixture. After being heated at 80–85°C for further 3 hr, the reaction mixture was passed through a column of Amberlite IR-120 (H<sup>+</sup> form). Then the column was washed with water and eluted with 3 N ammonium hydroxide. The eluate was decolorized and evaporated under reduced pressure to give the crude IV. This crude substance was recrystallized twice from hot water. Yield: 3.2 g (67%); mp 129–129.5°C; ultraviolet  $\lambda_{max}^{pH 1}$  237 m $\mu$  ( $\epsilon$  9.57  $\times$  10<sup>3</sup>) and 252 m $\mu$  ( $\epsilon$  8.27  $\times$  10<sup>3</sup>);  $\lambda_{max}^{pH 13}$  255 m $\mu$  ( $\epsilon$  1.08  $\times$  10<sup>4</sup>).

Found: C, 44.57; H, 3.98; N, 52.15%. Calcd for C<sub>4</sub>H<sub>4</sub>N<sub>4</sub>: C, 44.44; H, 3.73; N, 51.83%.

The ultraviolet and infrared absorption spectra were

1) Presented at the 19th Annual Meeting of the Chemical Society of Japan, Yokohama, April, 1966.  
2) H. Wakamatsu, Y. Yamada, T. Saito, I. Kumashiro and T. Takenishi, *J. Org. Chem.*, **31**, 2035 (1966).

3) A. Windaus and W. Langenbeck, *Ber.*, **56**, 683 (1923).

4) A. H. Cook, Sir. I. Heilbron and W. Smith, *J. Chem. Soc.*, **1949**, 1440.

5) K. Suzuki (of our Laboratories), private communication. He prepared the compound by the dehydration of AICA with phosphoryl chloride.

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

7) All the melting points are uncorrected. The ultraviolet and infrared absorption spectra were measured with Hitachi EPS-2 and JASCO model IR-S recording spectrophotometers.

identical with those of an authentic sample.

**4-Amino-5-imidazolecarboxamide (V).** An alkaline reaction mixture of IV was heated at 125–130°C for 6 hr in a sealed vessel and then passed through a column of Amberlite IR-120 (H<sup>+</sup> form). By treating the eluate as in the case of IV, 5.0 g (70%) of crude V were obtained. By recrystallization from dilute hydrochloric acid, the hydrochloride of V was obtained as colorless crystals, mp 254.5–255°C. Ultraviolet  $\lambda_{max}^{pH 1}$  242 m $\mu$  ( $\epsilon$   $6.30 \times 10^3$ ) and 269 m $\mu$  ( $\epsilon$   $8.66 \times 10^3$ );  $\lambda_{max}^{pH 13}$  278 m $\mu$  ( $\epsilon$   $1.06 \times 10^4$ ).

Found: C, 29.58; H, 4.42; N, 34.68%. Calcd for

C<sub>4</sub>H<sub>6</sub>N<sub>4</sub>O·HCl: C, 29.55; H, 4.34; N, 34.46%.

The product was identified with those of an authentic sample by a study of the spectral data, the paper chromatographic behavior, and the mixed melting point.

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