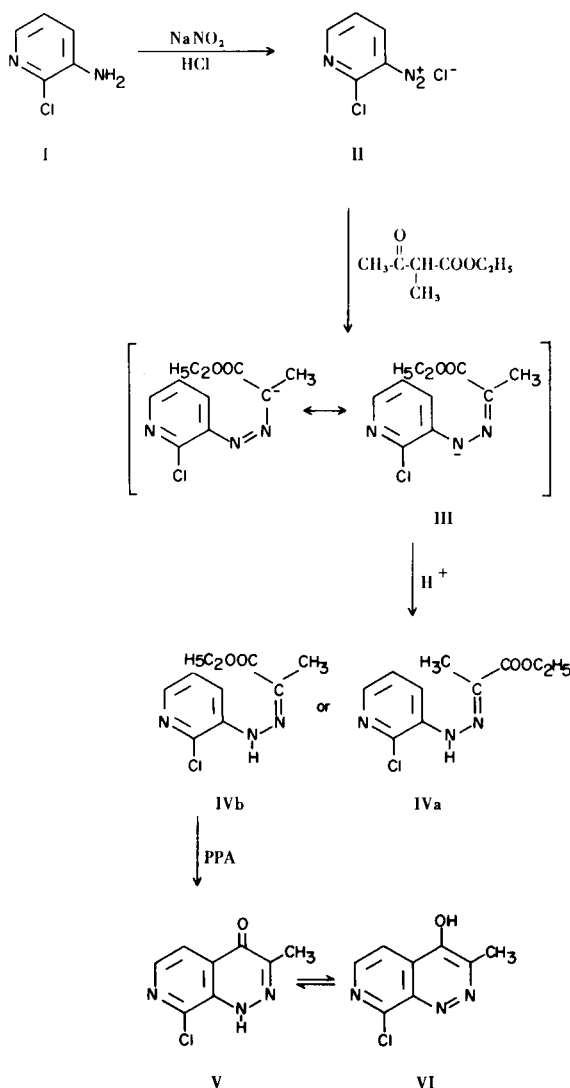


## 8-Chloro-4-hydroxy-3-methyl-pyrido[3,4-c]pyridazine

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Cinnolines have been recommended as chemotherapeutic agents in antitumor screening (1), in trypanosomiasis (2) and as bactericides and antiparasites (3). The antiviral and bacterial properties of cinnolines prompted us to synthesize pyrido[3,4-c]pyridazine (azacinnolines). Cinnolines have been synthesized by many workers but little attempt has been made toward the synthesis of azacinnolines. Syn- or anti isomers of substituted hydrazone (IVb) can be cyclized to a pyrido[3,4-c]pyridazine. The cyclization of arylhydrazones is well documented in the literature (4-8).



2-Chloro-3-aminopyridine (I) was converted to 2-chloro-3-pyridine diazonium chloride (II) using sodium nitrite and hydrochloric acid. Ethyl pyruvate 2-chloro-3-pyridylhydrazone (IVa and IVb) was obtained by reacting II with ethyl 2-methylacetoacetate in alkaline solution by the Japp-Klingmann reaction (9). No attempt has been made to isolate the isomers IVa and IVb. The low yields of the pyrido[3,4-c]pyridazine (VI) explains very clearly the existence of compound IVa. The cyclization of IVa with polyphosphoric acid should give rise to an azaindole whereas IVb should give rise to a pyrido[3,4-c]pyridazine. The failure of compound IVa to undergo cyclization to the pyrazolo[3,4-c]pyridine ring system can be attributed to the partial positive charge present at the 4 position in a pyridine ring which is in accord with the observed difficulty in substituting this position by an electrophilic reagent. The pyrido[3,4-c]pyridazine (VI) might exist in keto-enol tautomeric form. The infra-red spectra showed a strong hydroxyl band but no carbonyl function. This indicates that the pyrido[3,4-c]pyridazine exists mainly in the enol form.

## EXPERIMENTAL

## Ethyl Pyruvate 2-Chloro-3-pyridylhydrazone (IVb).

An ice cold solution of 50% potassium hydroxide (13 ml.) was added to a stirred solution of ethyl 2-methylacetoacetate (5.1 g., 0.035 mole) in absolute ethanol (37 ml.) at 0°. Ice water (150 ml.) was added followed by 2-chloro-3-pyridine diazonium chloride. The 2-chloro-3-pyridine diazonium chloride was prepared by adding small quantities of sodium nitrite (2.7 g., 0.038 mole) to a cooled mixture of 2-chloro-3-aminopyridine (3.2 g., 0.025 mole) in concentrated hydrochloric acid (15 ml.) and water (15 ml.) in such a way that the temperature of the mixture did not rise above 10°. The mixture was stirred for 10 minutes. A brick red solid separated which on recrystallization from ethanol gave an analytical sample melting at 105-107°, yield 3.7 g. (65%).

*Anal.* Calcd. for C<sub>10</sub>H<sub>12</sub>ClN<sub>3</sub>O<sub>2</sub>: C, 49.68; H, 4.96; N, 17.39. Found: C, 49.86; H, 4.86; N, 17.50.

## 8-Chloro-4-hydroxy-3-methyl-7-pyrido[3,4-c]pyridazine (VI).

Ethyl pyruvate 2-chloro-3-pyridylhydrazone (1.15 g., 0.005 mole) was added to polyphosphoric acid (10 g.) preheated to 60°. The mixture was stirred until the temperature reached 180°. Heating was continued for 5 minutes at this temperature. The reaction mixture was allowed to cool and diluted with water (180 ml.). The aqueous solution was extracted with ether ten times (50 ml. portions). The ether layers were combined, washed with 5% sodium bicarbonate solution, water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a

pale yellow solid, which on recrystallization from ethanol, afforded a pure sample melting at 198-200°, yield 150 mg. (20%).

*Anal.* Calcd. for C<sub>8</sub>H<sub>6</sub>ClN<sub>3</sub>O: C, 49.09; H, 3.06; N, 21.45. Found: C, 49.23; H, 3.21; N, 21.53.

#### REFERENCES

- (1) R. N. Castle, H. Ward, N. White and K. Adachi, *J. Org. Chem.*, **25**, 570 (1960).
- (2) J. R. Keneford, E. M. Lonrie, J. S. Morley, J. C. E. Simpson, R. Williamson, and P. H. Write, *J. Chem. Soc.*, 2595 (1952).
- (3) E. P. Taylor, M. D. Potter, H. O. J. Collier and W. C. Austin, British Patent 812,994 (May 6, 1959), *Chem. Abstr.*, **53**, 18971 (1959).
- (4) B. Robinson, *Tetrahedron Letters*, 5085 (1967).
- (5) E. Enders in Houben-Weyl, "Methoden der Organischen Chemie," 4th Ed., Thieme Verlag, Stuttgart, 1967, Vol. X2, p. 171.
- (6) M. H. Palmer, "The Structure and Reactions of Heterocyclic Compounds," St. Martin Press, New York, 1967, p. 182.
- (7) B. Robinson, *Chem. Rev.*, **63**, 373 (1963).
- (8) B. Robinson, *ibid.*, **69**, 227 (1969).
- (9) R. R. Phillips, "Organic Reactions," R. Adams, Ed. John Wiley and Sons, Inc., New York, Vol. X, 1959, p. 143.
- (10) Reported melting points are uncorrected. A Thomas Hoover Uni-Melt apparatus was used for melting point determinations. Galbraith Laboratories Inc., P. O. Box 4187, Knoxville, Tennessee, conducted the elemental analysis. Infra-red spectra were taken on Perkin Elmer Model 137-B Infra-cord spectrophotometer.

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