

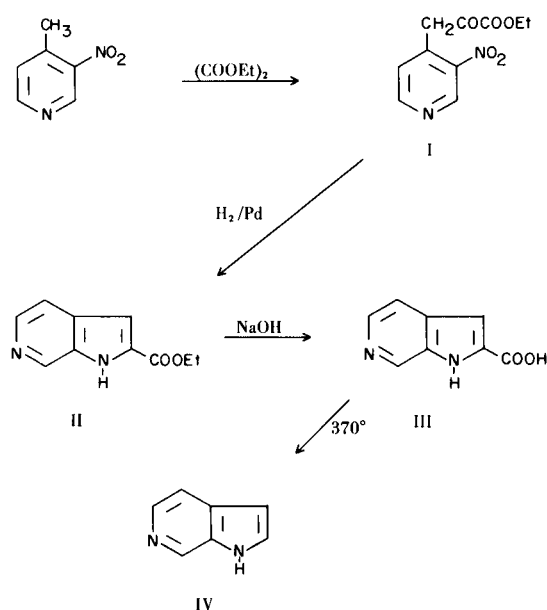
A Convenient Synthesis of 6-Azaindole

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It was recently necessary for us to prepare relatively large amounts of 6-azaindole, a compound not readily accessible by published routes. A convenient preparation has been developed *via* a modification of the Reissert indole synthesis, which has been used for azaindoles by Frydman, Despuy and Rapoport (1) and in these laboratories.

The scheme, shown below, proceeded smoothly as far as 6-azaindole-2-carboxylic acid (III) which required heating to a much higher temperature than was anticipated for decarboxylation. Presumably inner salt formation accounts for its high melting point and unusual stability.



EXPERIMENTAL (4)

Ethyl 3-(3-Nitro-4-pyridyl)pyruvate (I).

A solution of 125 ml. of dry ethanol in 125 ml. of dry ether

was added dropwise to a stirred suspension of 16.6 g. of potassium metal pieces in 300 ml. of dry ether. When the reaction was complete, a solution of 62.5 g. of diethyl oxalate in 100 ml. of dry ether was added and the solution was allowed to stir for 15 minutes. A solution of 3-nitro-4-picoline (2) in ether (from 73.8 g. of hydrochloride salt dissolved in water, basified with sodium hydroxide, extracted with 500 ml. of ether and dried with magnesium sulfate) was added dropwise to the stirred solution and stirring was continued for 20 hours at room temperature. The precipitated potassium salt was collected and washed with ether to give 96.1 g. (82%) of I. A small sample acidified with acetic acid gave an orange product, m.p. 129-130°, which crystallized from a mixture of dimethylformamide and water.

Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_5$: C, 50.42; H, 4.23; N, 11.76. Found: C, 50.52; H, 4.21; N, 12.01.

Ethyl 6-azaindole-2-carboxylate (II).

A solution of 96.1 g. of the potassium salt of ethyl 3-(3-nitro-4-pyridyl)pyruvate (I) in 500 ml. of acetic acid was reduced with hydrogen and 7.5 g. of 5% palladium on carbon catalyst at room temperature and 40 p.s.i. pressure. The catalyst was removed by filtration, washed with acetic acid and the total filtrate was concentrated to a small volume. The residue was dissolved in water, basified with sodium bicarbonate and allowed to stand in a refrigerator for 20 hours. The precipitate which formed was collected, dried and extracted with boiling ethyl acetate. After concentration to a small volume, the product crystallized to give 28.8 g. (44%) of II, m.p. 212-214°.

Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.07; H, 5.39; N, 15.04.

6-Azaindole-2-carboxylic Acid (III).

A solution of 6.5 g. of sodium hydroxide in 225 ml. of water was added to a solution of 20 g. of ethyl 6-azaindole-2-carboxylate in 385 ml. of ethanol and the mixture was refluxed for 30 minutes. The solution was concentrated to a small volume, diluted with water and acidified with acetic acid. The product which crystallized was collected by filtration and washed with water, 17.4 g. (99%), m.p. $> 360^\circ$.

Anal. Calcd. for $\text{C}_8\text{H}_6\text{N}_2\text{O}_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.17; H, 3.67; N, 17.28.

6-Azaindole (IV).

6-Azaindole-2-carboxylic acid (17.4 g.) was heated at 370° in a Woods metal bath. After obvious decarboxylation was complete the residual liquid was cooled and crystallized from a mixture of benzene and cyclohexane, 7.4 g. (58%), m.p. 133-135° (3).

Anal. Calcd. for $\text{C}_7\text{H}_6\text{N}_2$: C, 71.16; H, 5.12; N, 23.72. Found: C, 70.81; H, 5.28; N, 23.68.

REFERENCES

(1) B. Frydman, M. E. Despuy and H. Rapoport, *J. Am. Chem. Soc.*, **87**, 3530 (1965).

(2) O. Bremer, *Ann.*, **529**, 290 (1937).

(3) O. Süs and K. Möller, *ibid.*, **599**, 233 (1956).

(4) Melting points were taken on a Thomas-Hoover 'Unimelt' apparatus and are uncorrected.

Received June 23, 1969

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