Improvements in the Synthesis of 2,7- and 2,6-Naphthyridines

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In a recent publication¹, Paudler and Cornrich proposed for 2,7-naphthyridine (3) an elegant synthesis which represents an improvement with respect to the methods previously reported². We wish to report the following facile alternative procedure for the preparation of 3.

The synthesis of 4-formyl-2,7-naphthyridine (1) was performed following the method described by W. Müller et al.³. Compound 1 was then oxidized with potassium permanganate in acetone to give the corresponding carboxylic acid (2) in 90% yield. Decarboxylation of 2 with powdered copper (reaction time: 15 min) afforded a 78% yield of 2,7-naphthyridine (3) of high purity.
Another improved procedure, which simplifies the synthetic route originally proposed by Tan and Taurins, was also developed for the synthesis of 2,6-naphthyridine (8). Thus, 4-cyano-3-pyridylacetanilide (6) can be prepared by a shorter route and with an improved yield, from the commercially available 3-pyridylacetanilide.

Oxidation of 3-pyridylacetanilide gave 1-oxido-3-pyridylacetanilide (4) which was then converted into the quaternary salt 5 by treatment with dimethyl sulfate.

Reaction of the salt 5 with potassium cyanide gave 4-cyano-3-pyridylacetanilide (6) together with 2-cyano-3-pyridylacetanilide (7) which can be used as an intermediate in the synthesis of 1,7-naphthyridine.

4-Carboxy-2,7-naphthyridine (2):
Finely powdered potassium permanganate (5 g) was added to a solution of 4-formyl-2,7-naphthyridine (1; 5 g) in acetone (40 ml) and the mixture stirred overnight at room temperature. The solvent was then removed in vacuo and the residue washed with boiling water (~150 ml). The aqueous extracts were concentrated to 30 ml and cautiously acidified with 30% hydrochloric acid. The precipitated product was isolated by filtration and recrystallized from water; yield: 4.8 g (88%); m.p. 298.

C₉H₇N₂O₂ calc. C 62.07 H 3.47 N 16.09 (174.16) found 61.95 3.40 16.15

2,7-Naphthyridine (3):
In a flask equipped with a short condenser, a mixture of 4-carboxy-2,7-naphthyridine (2; 2 g) and copper powder (8 g) was cautiously heated with an open flame for 5–10 min. The reaction mixture was then cooled and extracted several times with chloroform. Evaporation of the solvent and sublimation of the solid residue under high vacuum afforded a pure product; yield: 1.1 g (78%); m.p. 96° (from light petroleum).

2-Cyano- and 4-Cyano-3-pyridylacetanilide (6 and 7):
Freshly distilled dimethyl sulfate (52 g) was added dropwise, with stirring, to the solid N-oxide 4 (55 g). When the initial exothermic reaction subsided, the material was warmed on a steam bath for 2 hr. The crude product 5 was dissolved in water (120 ml) and added with vigorous stirring over a period of 30 min to an ice-cooled solution of potassium cyanide (86 g) in water (180 ml). The reaction mixture was allowed to stand for 4 hr and was then extracted with chloroform. The organic layer was dried with sodium sulfate. The chloroform was evaporated and the residual oil distilled under high vacuum. The fraction boiling between 140 and 165°/0.5 torr was collected (27 g). Chromatography on neutral alumina (activity II–III) with benzene and chloroform afforded the two isomers. First product: 2-Cyano-3-pyridylacetanilide (7); yield: 11 g (20%); m.p. 66°.
Second product: 4-Cyano-3-pyridylacetanilide (6); yield: 13.3 g (25%); m.p. 79°.

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4 R. Tan, A. Taurins, Tetrahedron 36, 2737.