A One-step Synthesis of 1,6-Naphthyridine

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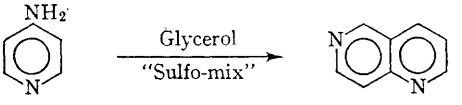
DURING the past ten years, several syntheses[1–3] of 1,6-naphthyridine (I) have been described. All of these preparations involve at least seven-step sequences yielding the 1,6-naphthyridine in overall yields of two per cent or less.

Our interest in naphthyridine chemistry[4–6] prompted us to investigate methods of syntheses which would afford the naphthyridines in higher yields and in fewer steps. The most reasonable approach would be the synthesis *via* a Skraup reaction.

All literature describing the syntheses of 1,6-naphthyridines (see ref. 7 and references therein) states that the Skraup synthesis is not applicable to 4-aminopyridine. The rationale for this assumption centres on the "low" basicity ($pK_a = 9{\cdot}2$) of the 4-aminopyridine (this statement was made prior to the availability of the pK_a data, which, of course, reveals 4-aminopyridine to be a fairly strong base). This conclusion is, however, not valid in view of the fact that 4-aminoquinoline ($pK_a = 9{\cdot}2$) undergoes reactions involving intermediates similar to those expected in the Skraup synthesis.[7a–c].

It became consequently of considerable interest to apply the Skraup reaction to 4-aminopyridine, utilizing the "sulfo-mix" described by Utermohlen.[8] When this reaction was attempted, the parent 1,6-naphthyridine (I) was obtained in forty per cent yield.



(I)

The reaction conditions employed in this preparation are the same as those described for the preparation of 1,5-naphthyridine by the Skraup method,[2] except for the use of "sulfo-mix" in place of the traditional oxidizing mixture. Anhydrous glycerol (25 g.) is added to 117 g. of cold (0—5°) "sulfo-mix" (a mixture of nitrobenzenesulphonic acids in sulphuric acid) and to this mixture is added 7·5 g. (0·08 mole) of 4-aminopyridine followed immediately by the addition of 40 ml. of water. This mixture is stirred until homogeneous (*ca.* 10 min.) and is finally heated in an oil bath with vigorous stirring at 130° for 5 hr. The resulting mixture is made basic (with cooling, ice–salt) to pH 10 with concentrated (50%) aqueous sodium hydroxide. The resulting mixture is subjected to stream distillation until the distillate no longer forms a precipitate with picric acid (approximately 3 l. of distillate is obtained). Extraction of the distillate with a total of 2 l. of chloroform, and drying of the chloroform extract with anhydrous $MgSO_4$, afforded, after removal of the solvent *in vacuo*, 4 g. of

pure 1,6-naphthyridine. The properties of the 1,6-naphthyridine thus obtained (m.p., n.m.r. spectrum, m.p. of the picrate) are identical to those reported[1-4] for 1,6-naphthyridine prepared by the classical multistep sequences.

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