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Prevention of Pyrrole Polymerization In Acidic Reaction Media

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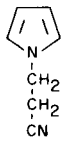
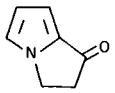
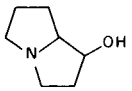
As part of a program on the synthesis and pharmacology of glycolate esters of aminoalcohols (1), a large scale preparation of 1-hydroxypyrrolizidine (III) was undertaken. The synthesis of this aminoalcohol via the reduction of 1-oxo-3*H*-1,2-dihydropyrrolo[1,2-*a*]pyrrole (II) has been well described by Adams, *et al.* (2). However, the preparation of II given by Clemo and Melrose (3) proved to give erratic results. Whenever any product was isolable, the yields were very small and most of the starting material appeared to be converted to a reddish-brown polymer.



I



II



III

The conditions employed by Clemo and Melrose (3) called for the addition of anhydrous hydrogen chloride to a cold solution of 1-β-cyanoethylpyrrole (I) containing a small amount of zinc chloride. Since the conversion of the starting material to the reddish-brown polymer was probably initiated by the addition of a proton to a pyrrole ring, a method was sought to inhibit this initiation step. It was recognized that if the formation of the initial π-complex between the proton and the pyrrole ring could be repressed, addition polymerization of the pyrrole rings would be impeded. With this end in mind, the ethyl ether complex of boron trifluoride was substituted for the ether solvent in the reaction. Boron trifluoride apparently forms a metastable π-complex with the pyrrole ring and does not hinder the formation of the imino chloride from the nitrile group when the anhydrous hydrogen chloride is passed into the mixture. When this procedure was used the desired compound was obtained in consistently high yields without contamination by polymeric tars. Purification of the product should be carried out in an efficient fume hood because it appears to have a fairly high vapor pressure and it was found to induce analgesia.

EXPERIMENTAL

A mixture of 36 g. (0.3 mole) of 1-β-cyanoethylpyrrole (4), 3 grams of zinc chloride, and 300 ml. of boron fluoride-ethyl ether (Eastman practical grade) was placed in a 1000 ml. Erlenmeyer flask which was then cooled in an ice bath. Anhydrous hydrogen chloride was passed in slowly for 45 minutes. The ketimine hydrochloride began precipitating from solution during the addition of the hydrogen chloride. The flask was stoppered and allowed to remain in the ice bath for an additional hour. The entire contents of the flask was poured into 1000 ml. of ice water and was neutralized by the addition of sodium hydroxide pellets. The ether layer was separated from the aqueous phase which was then extracted five times with 100 ml. portions of methylene dichloride. The combined organic material was dried over sodium sulfate and evaporated under reduced pressure. The crude product was recrystallized from petroleum ether as pale yellow needles, m.p. 54°; reported (3) m.p. 54°. The yields ranged from 60-80%.

REFERENCES

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