SYNTHESIS OF β--PYRIDYL CARBINOL TARTRATE

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(Received 21 Oct 1967)

A process for the synthesis of β-pyridine carboxylic acid ethyl ester starting from quinoline has been developed. β-pyridine carboxylic acid ethyl ester on reduction with lithium aluminium hydride gave β-pyridyl carbinol which on treatment with tartaric acid yielded β-pyridyl carbinol tartrate, a vaso dilator known in trade as "Ronicol. **tartrate**".

Ronicol tartrate, the β-pyridyl carbinol tartrate has a marked vasodilating action[1] and is therefore indicated for the treatment of peripheral circulating disturbances and all types of vascular spasm. It causes action of longer duration and is accompanied by less flushing than that of β-pyridine carboxylic acid[2]. It is also reported to be useful in the treatment of diseases of cerebral vessels, coronary vessels, opthalmology and otology. Although Ronicol tartrate in some cases is less effective than sulphapyridine for the treatment of dermatitis herpatiformis, but it possess wider applications in being less toxic and not depressing the hematopoietic system[3].

A review of the literature reveals that the synthesis of β-pyridyl carbinol has drawn attention of several workers[4–13]. In this communication synthesis of β-pyridyl carbinol has been achieved by starting from quinoline. Quinoline is subjected to oxidation[4–10] using selenium and concentrated sulphuric acid, followed by subsequent decarboxylation yielding β -pyridine carboxylic acid, which on esterification[8] with ethyl alcohol yield β-pyridine carboxylic acid ethyl ester. Alternately β-pyridine carboxylic acid on reacting with thionyl chloride yield acid chloride hydrochloride[13] which on esterification with ethyl alcohol yield β-pyridine carboxylic acid ethyl ester. This procedure[13], however, resulted in obtaining 70 per cent yield of β-pyridine carboxylic acid ethyl ester while oxidation of quinoline [6-10] followed by subsequent decarboxylation and esterification yield 35 per cent β-pyridine carboxylic acid ethyl ester. Esters of β-pyridine carboxylic acid had been prepared previously by the action of β-pyridine carboxylic acid,[10],[11] alcohol and hydrogen chloride; or β-pyridine carboxylic acid[12] alcohol and sulphuric acid. β-pyridine carboxylic acid ethyl ester on reduction [9] with lithium aluminum hydride yield β-pyridyl carbinol. Alcoholic solution of β-pyridyl carbinol[14] on treatment with alcoholic solution of tartaric acid gave β-pyridyl carbinol tartrate as a crystalline solid. β-pyridyl carbinol tartrate synthesised by these procedures was found to be identical in all respects with an authentic sample *viz* melting point, mixed melting point, infra-red and ultraviolet spectra.

EXPERIMENTAL PROCEDURE

β-Pyridine carboxylic acid ethyl ester

A mixture of 95 per cent concentrated AR sulphuric acid (650 ml) selenium metal powder (75 gm) and freshly distilled quinoline (129 gm) was heated in a flask provided with a distillation assembly for 4 to 5 hours. During this period 340 ml of water was distilled, temperature of the reaction mixture was not allowed to exceed 300°C. The mixture was then allowed to cool to room temperature. Absolute ethyl alcohol (300 ml) was added to it and the mixture was refluxed for 6 hours over a steam bath. The mixture was cooled and diluted with crushed ice. The mixture was made alkaline with liquor ammonia and repeatedly extracted with ether.

Ether extracts were combined, washed with water, dried over anhydrous potassium carbonate, and freed of the solvent. β-pyridine carboxylic acid ethyl ester thus obtained was distilled at 103-106°C (5 mm Hg pressure). Yield 54 gm; 36 per cent (Based upon the quantity of quinoline taken).

(*Alternative route*)

A mixture of nicotinic acid (β-pyridine carboxylic acid) (50 gm), thionyl chloride (200 gm) was refluxed over steam bath for 4 hours until complete solution of the reactants took place. The excess thionyl chloride was removed by distillation and the last traces removed under vacuum.

The crystalline mass was allowed to cool to room temperature. Absolute ethyl alcohol (100 ml) was added and the mixture was refluxed for 4 hours. The excess of alcohol was removed under vacuum.

The residual mass was covered with benzene (150 ml). Twenty per cent sodium carbonate solution (180 ml) was added in small lots with constant shaking of the flask until the aqueous layer was faintly alkaline. The benzene layer was separated, washed with water, dried over anhydrous sodium sulphate, and the solvent removed under vacuum. β-pyridine carboxylic acid ethyl ester was distilled at 103-106°C (5 mm, Hg pressure). Yield 42 gm; 70 per cent (Based upon the quantity of β-pyridine carboxylic acid taken).

β-Pyridyl carbinol

Lithium aluminum hydride (11·2 gm) was placed in a three necked flask provided with a dropping funnel, a reflux condenser, and a mechanical stirrer. The flask was kept in ice bath and anhydrous ether (240 ml) was slowly added during 20–30 minutes with constant stirring. β-pyridine carboxylic acid ethyl ester (23 gm) dissolved in anhydrous ether (155 ml) was placed in the dropping funnel and added dropwise during two hours into flask with constant stirring. After the completion of reaction, water (50 ml) was cautiously added dropwise with constant stirring to destroy unreacted lithium aluminum hydride.

The reaction mixture was filtered, and the filtrate was collected. The solid cake was suspended in hot methanol (30 ml) and the suspension was saturated with carbon dioxide, heated to boiling, filtered, and the filtrate was collected. The solid was repeatedly extracted with hot methanol. The ether and methanol fractions were combined and freed of the solvent.

The viscous liquid was distilled under vacuum. β-pyridyl carbinol was distilled at 142–145°C (20 mm, Hg pressure). Yield 12 gm; 70 per cent (Based upon the quantity of β-pyridine carboxylic acid ethyl ester taken).

β-Pyridyl carbinol tartrate

Tartaric acid (7·5 gm) dissolved in minimum quantity of ethyl alcohol (60 ml) was added dropwise to β-pyridyl carbinol (12 gm.) in ethyl alcohol (10 ml). During addition the mixture was constantly scratched and cooled.

β-pyridyl carbinol tartrate separated out after 15–30 minutes. It was filtered, crystallised and recrystallised twice from methanol when shining crystals were obtained mp 148°C. Yield 14 gm; 73 per cent (Based upon the quantity of β-pyridyl carbinol taken).

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M/S192—350—10-4 68—GIPS