AN IMPROVED METHOD OF PREPARATION OF ARECOLINE, STARTING FROM ACETALDEHYDE (EXCHANGE OF EXPERIENCE)

I. A. Kozello, V. I. Khmelevskii,
A. Ya. Gasheva, and G. N. Birbaeva

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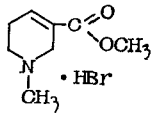
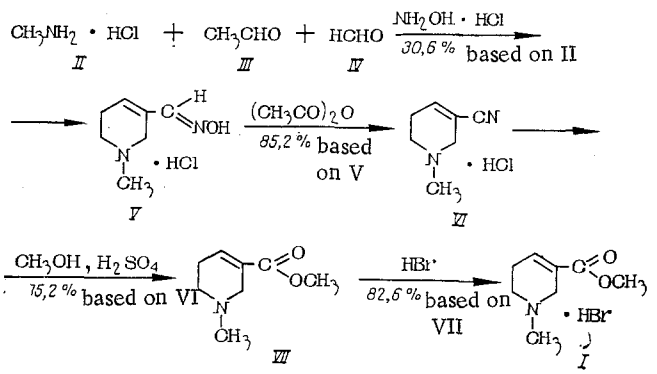
Arecoline — the hydrobromide of methyl N-methyl-1,2,5,6-tetrahydronicotinate (I) — is used in veterinary medicine as an antihelminthic and a laxative.



I

A number of methods of preparing this compound have been described, starting from compounds such as acetal β-chloropropionaldehyde, ethylene oxide, bromomethylmalonic ester, ethyl β-bromo-(or chloro)-propionate, methyl acrylate, acrylonitrile, citric or nicotinic acids [1-10]. The synthesis of arecoline starting from acetaldehyde was reported in 1942 [8]: acetaldehyde (III) is condensed with methylamine hydrochloride (II) and formaldehyde (IV) in aqueous medium to give arecaidine aldehyde as the hydrochloride of the oxime (V), in yields of up to 21%. Refluxing (V) with acetic anhydride gave the nitrile VI, which was converted to the methyl ester VII in 66% yield. According to [8], the overall yield of product, based on the starting material II, was 12.4%.

We have synthesized arecoline by a similar method:



The yield of I, based on II, was 16.2%.

The experimental conditions employed in the condensation of the starting compounds, II, III, and IV, and also in the preparation and isolation of the intermediate products V, VI, and VII have been modified.

For example, in the first stage of the process, sodium acetate was used as a catalyst in the condensation of acetaldehyde, methylamine, and formaldehyde, as a result of which the yield of V was increased to 30.6%. The preparation of V was also simplified: In place of the alcoholic solution of hydroxylamine hydrochloride, which with sodium methylate gave the free hydroxylamine, we used an aqueous solution of hydroxylamine hydrochloride and sodium acetate. In the preparation of the nitrile VI, the ether was replaced by benzene or toluene and the product was analyzed by conductometry to determine the percentage of VI. The conversion of the nitrile VI to arecaidine and its subsequent etherification were also modified. Formerly, these stages in the process were carried out using large amounts of methanol and dry hydrogen chloride [8], but in our scheme saponification and etherification were carried out in one

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step by heating the nitrile VI with concentrated sulfuric acid in a comparatively small (10 moles) quantity of methyl alcohol. With these changes, the synthesis of arecoline is much simplified and the yield increased from 12.4 to 16.2%.

EXPERIMENTAL CHEMISTRY

Arecaidine Aldomine Hydrochloride (V). Methylamine hydrochloride II (16.9 g; 0.25 mole) was dissolved in a mixture of acetaldehyde VI (44 g; 1 mole) and water (18 ml; 1 mole). The solution was transferred to a thick-walled tube and formalin (15 g; 0.5 mole or 39.5 ml; 35% solution) and crystalline sodium acetate (0.5 g) were added. The tube was sealed, placed in a rotating device in a thermostat, and heated at 70°C for 15 h. The tube was then opened and the reaction mixture evaporated at reduced pressure on the water bath until distillation ceased (distillation temperature 50-55°C). To the dark-cerise solution remaining was added hydroxylamine hydrochloride (17.4 g; 0.25 mole) dissolved in water (15 ml) and a solution of crystalline sodium acetate (34.0 g; 0.25 mole) in water (15 ml) (the solutions were added hot). After standing overnight, the precipitate of V was filtered off, washed on the filter with absolute alcohol, and dried at 60°C to give 13.6 g (30.6% based on II) of product with mp 240-242°C.

Arecaidine Nitrile Hydrochloride (VI). A suspension of V (13.6 g) in acetic anhydride (68 ml) was refluxed for 25 min, the reaction mixture evaporated to dryness on the water bath at reduced pressure, and benzene (50 ml) added to the dry residue. After heating to 70°C, the product was filtered off, and washed on the filter with benzene to give 10.4 g of VI (85.2% based on V).

Arecoline (VII). Concentrated sulfuric acid (23.6 g; 0.24 mole) was added to VI (10.4 g; 0.067 mole) in dry methanol (30 ml; 0.7 mole) at 50°C. After heating at 80-103°C for 6 h, the dark solution was poured into water (40 ml), benzene (70 ml) was added, and the solution made alkaline to phenolphthalein by the addition of 50% potash solution at 20-24°C. The precipitated sulfates were filtered off, the benzene-aqueous-alkaline filtrate transferred to a separating funnel, and the precipitate washed on the filter with benzene (80 ml), which then was used to extract (2 × 40 ml) the aqueous-alkaline layer after separation of the benzene. The benzene extracts were combined with the benzene layer and evaporated on the water bath at reduced pressure. The residue was evaporated under high vacuum, and the fraction with bp 103-105°C (12 mm) collected; 7.6 g of VII were obtained (75.2% based on VI).

Arecoline Hydrobromide (I). An aqueous solution of arecoline was acidified with 40% hydrobromic acid to pH 4.5-5.0 (measured on a pH-meter) at 25-30°C. The solution was evaporated to dryness on the water bath under vacuum at 50°C. The residue was recrystallized from absolute alcohol to give a yield of 16.2% of I (based on II), mp 170-172°C.

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