IMPROVEMENT OF THE SYNTHESIS OF ARECOLINE FROM NICOTINIC ACID

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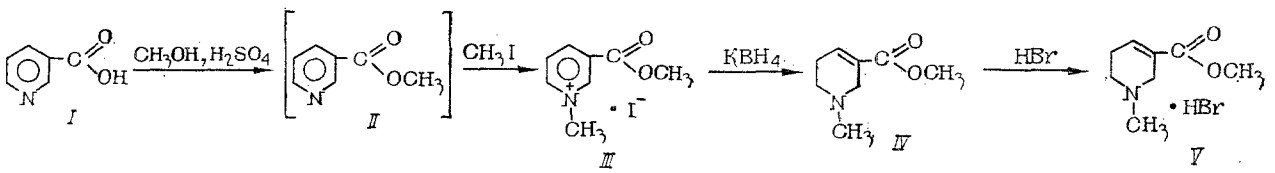
During the comparison of various methods of preparing arecoline, one of the active antihelminthic agents, we studied in detail its synthesis starting from nicotinic acid.

This method of synthesis was first published in 1951 [1]. This method is based on the selective ability of potassium borohydride to reduce partially the pyridine ring of methyl nicotinate methiodide. These data were confirmed in 1962 [2]. The yield of arecoline base reached 32-36% of the theoretical based on the methyl nicotinate methiodide taken for reduction.

In our experiments we also used potassium borohydride as the reducing agent, as did the preceding authors [1]; the synthesis was carried out in three stages:



Under laboratory conditions the preparation of methyl nicotinate methiodide (III), isolation of arecoline base (IV), and the preparation of its hydrobromide (V) were not associated with any difficulties. We did not carry out the reduction of methiodide (III) in methanol, as this was described by the preceding authors, but in water under a benzene layer, which made it possible to increase the yield of arecoline base to 42%.

EXPERIMENTAL

Methyl Nicotinate Methiodide (III). To a toluene solution of methyl nicotinate (II) obtained according to [3] from 24.6 g of nicotinic acid (I) (without separation of the pure material) was added with cooling 42.6 g of methyl iodide and the mixture was heated at 60-65° for 8 h, after which the reaction mass was cooled. The precipitated methiodide (III) was filtered, washed with dry benzene, and dried in air. We obtained 38.5 g of a crystalline product, mp 125-128°C. The yield was 69% of the theoretical calculated on nicotinic acid.

Arecoline Base (IV). We dissolved 38.5 g of methiodide (III) in 40 ml of water under a layer of 70 ml of benzene and, maintaining a temperature of 35-38° with intense stirring, poured in a freshly prepared solution of 9.2 g of 97.5% potassium borohydride in 80 ml of water. The addition of borohydride solution was carried out over 35 min, maintaining a pH 7.5-8.0 by addition of 7.5 ml of 50% potassium carbonate solution; the mixture was shaken and the benzene layer was separated quickly. The aqueous layer was extracted twice with 30-ml portions of benzene and they were combined with the main benzene solution.

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To purify the arecoline base, to the combined benzene extracts was added 25 ml of water and with mixing and maintaining a temperature of 20-22°C the mixture was acidified with 35 ml of dilute hydrochloric acid (1:1) to an acidic reaction to Congo, after which the contents of the flask were stirred for 2 h. The acidic aqueous layer was separated and the benzene layer was washed twice with small portions of water, which were combined with the main aqueous solution. Then with stirring and a temperature of 20-22° the aqueous arecoline hydrochloride solution under a fresh portion of 50 ml of benzene was made basic with solid potassium carbonate to phenolphthalein. The benzene extracts were evaporated at reduced pressure on a water bath. The residue was fractionated in vacuum, collecting the fraction with bp 80-82° (5 mm). The yield of IV was 42.2% calculated on III.

Arecoline Hydrobromide (V). An aqueous solution of arecoline base was acidified with 40% hydrobromic acid to pH 4.5-5.0 (pH meter reading) and at a temperature of 25-30°. The solution was evaporated to dryness on a water bath at 50°. The residue was recrystallized from absolute alcohol, mp 169-173°. Yield of V was 67.8% calculated on IV.

Found, %: N 5.59. $C_8H_{23}NO_2 \cdot HBr$. Calculated, %: N 5.93.

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HYDROLYSIS OF DIARYL N,N-BIS[2-(METHYLSULFONYLOXY)ETHYL]AMINOPHOSPHATES IN ACIDIC AND ALKALINE SOLUTION

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Since the diaryl N,N-bis[2-(methylsulfonyloxy)ethyl]aminophosphates whose synthesis we reported in [1] possess marked antiblastic properties, we decided to study their hydrolysis in acidic and alkaline solution. Our intentions were twofold: to confirm the chemical structure of these compounds and to ascertain the behavior of new and promising antiblastic preparations in acidic and alkaline solution.

According to published data, esters of methanesulfonic acid in aqueous solution and acidic and alkaline solution are easily hydrolyzed with loss of the methanesulfonate anion. Hydrolysis or reaction with nucleophilic reagents of esters of methanesulfonic acid that contain a heteroatom with a lone pair in a certain orientation to the reaction center initially gives a cyclic cation with loss of the methanesulfonate anion [2, 3].

On the other hand, hydrolysis of phosphorylated chloroethylamines such as diaryl N,N-bis(2-chloroethyl)aminophosphates in acidic or alkaline solution forms the diaryl phosphates and bis(2-chloroethyl)amine, i.e., they are cleaved at the P—N bond [4].

However attempted hydrolysis of the diaryl N,N-bis[2-(methylsulfonyloxy)ethyl]aminophosphates in 1 N aqueous solution with hydrochloric acid contrary to all expectations resulted in cleavage of the P—OAr bond, forming the phenols and N,N-bis[2-(methylsulfonyloxy)-ethyl]aminophosphoric acid.

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