NEW METHOD OF OBTAINING NICOTINIC ACID FROM 2-METHYL-5-ETHYLPYRIDINE

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At the present time nicotinic acid (I) is obtained from 2-methyl-5-ethylpyridine (II) by oxidizing it with nitric acid under pressure and decarboxylating the isocinchomeronic acid formed [1-3]. This method requires the use of an acid-resistant apparatus and laborious separation of the sought-after product from impurities composed of nitro compounds. A new method of obtaining I, which is free of these shortcomings and is based on the oxidative ammonolysis of II to 3-cyanopyridine (III) [4, 5] and the hydrolysis of the latter in an alkaline medium [6], has been devoloped at the Institute of Chemical Sciences of the Academy of Sciences of the Kazakh SSR and the All-Union Scientific-Research Vitamin Institute.

The oxidative ammonolysis of II was investigated in continuous-flow types of apparatus with a single reaction tube. The experiments were carried out on a catalyst consisting of 1 : 16 vanadium pentoxide and titanium dioxide using a molar ratio of II, oxygen, ammonia, and water of 1 : 20 - 150 : 5 - 35 : 300 - 330 and a temperature of 320-400°C. The principal reaction product usually was III over the range of conditions we invesgated. Besides III, unreacted II, 5-ethylpicolinonitrile (IV), 6-methylnicotinonitrile (V), 2,5-dicyanopyridine (VI), pyridine (VII), and also ammonium cyanide and carbon dioxide were present on the catalysts.

When 19.6 g of II, 2400 liter of air, 60.8 g of ammonia, and 898 g of water per hour were fed onto 1 liter of catalyst and the contact time was 0.45 to 0.5 sec, an increase in the yield of III from 45 to 64% resulted with an increase in the reaction temperature within 335-365°C (Fig. 1). The quantity of IV decreased; it practically had already disappeared completely from the reaction products at 320-325°C. The formation of VI was also observed in the greatest quantities in the experiments at the lowered temperatures. An increase in temperature led to some increase in the yield of VII. Ammonium cyanide and carbon dioxide were obtained in considerable quantities in the experiments at increased temperatures.

A change in the parameters of the process exerted a substantial effect on the yield of the sought-after product. The maximum yield of III (60-62%) was obtained at 360°C and with a contact time of 0.6 sec in experiments in which 14.4 g of III, 1770 liter of air, 51 g of ammonia, and 660 g of water were fed onto 1 liter of the catalyst per hour. The optimum molar ratio of II and oxygen usually fell in the 1 : 95-185 range. The effect of ammonia concentration in the reaction zone and temperature on the oxidative ammonolysis of II is reflected by the data given in Fig. 2. An increase in the ammonia feed from 6 to 35 mole per mole of II effected an increase in the overall conversion of II. Simultaneously the yield of V and VI decreased. The maximum amounts of III were obtained at a molar ratio of II and ammonia of 1 : 20-40 over the whole temperature range we investigated. With a further increase in the ammonia concentration the yield of III decreased and the relative intensity of the extended oxidation processes increased.

The hydrolysis of III goes well in both potassium and sodium hydroxide solutions. The dependences of the degree of conversion of III to I on the duration of the reaction, temperature, alkali concentration, and ratio between the alkali and nitrile were established. Figure 3 illustrates the accumulation of I in potassium hydroxide solutions of various concentrations at 95-97°C. It is highly evident that an increase in the alkali concentration from 0.05 to 0.25 g-eq./liter sharply accelerated the hydrolysis: All of the original amount of III

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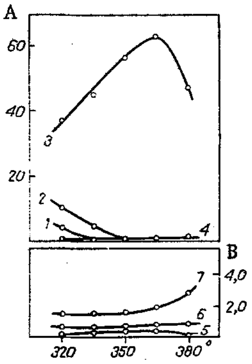

Fig. 1

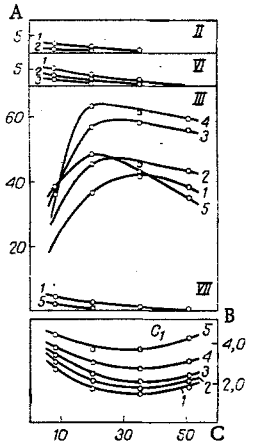

Fig. 2

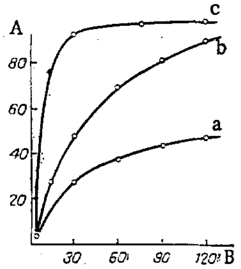

Fig. 3

Fig. 1. Effect of temperature on the oxidative ammonolysis of II. A) Yield (in %); B) yield (in mole/mole of II); 1) IV; 2) VI; 3) III; 4) VII; 5) NH_4CN; 6) CO; and 7) CO_2.

Fig. 2. Effect of the amount of ammonia on the oxidative ammonolysis of II. A) Yield (in %); B) yield (in mole/mole of II); C) amount of ammonia (in mole/mole of II). The feed rate of II was 19.6 g, air 2400 liter, and water 898 g per liter of catalyst per hour, contact time 0.48 to 0.51 sec; C_1) products of the composition. 1) 330°C; 2) 345°C; 3) 360°C; 4) 375°C; and 5) 390°C.

Fig. 3. Effect of the potassium hydroxide concentration and duration of the reaction on the hydrolysis of III to I at 97°C. A) Yield of I (in %); B) duration of reaction (in min). Alkali concentration: a) 0.05; b) 0.1; and c) 0.25 g-eq./liter.

was already entirely hydrolyzed to I within 1 h after the beginning of the process. Compound I can also be obtained in high yield (up to 97% of that theoretically possible) through the hydrolysis of the catalyzates obtained from the oxidative ammonolysis of II, which enables one to manage without the preliminary isolation of III in pure form from them.

The data from the laboratory investigations were reproduced in pilot-plant equipment used for the oxidative ammonolysis of II and the alkaline hydrolysis of III.

EXPERIMENTAL

Compound II, "ch." ["pure"] grade, b.p. 172-174°C (695 mm of Hg), d_4^{20} 0.9191, n_D^{20} 1.4972, was used as the starting substance.

The construction of the apparatus used for the oxidative ammonolysis of alkylpyridines was described in [7]. The reaction products were collected in water in air lift-type scrubbers.

In order to identify and accumulate III, the catalyzates obtained in the oxidative ammonolysis experiments involving II were extracted with organic solvents. After distilling the solvent off, III was fractionally distilled in vacuo. The isolated product had a m.p. of 49-50°C, b.p. 102°C (25 mm of Hg). Found, %: C 69.09; H 3.88; N 26.90. $C_6H_4N_2$. Calculated, %: C 69.21; H 3.87; N 26.98.

In order to obtain I in the pure form, the hydrolysis of III was carried out by boiling it in 0.25 N potassium hydroxide for 60 min. The solution of potassium nicotinate obtained was neutralized with hydrochloric acid until weakly acidic, boiled with activated carbon, and cooled to 12-15°C. After crystallization, filtration, washing with distilled water, and drying, I was obtained, m.p. 234-235°C, neutralization equivalent 123.5. Found, %: C 58.45; H 4.12; N 11.45. $C_6H_5NO_2$. Calculated, %: C 58.54; H 4.09; N 11.39.

Monitoring of the composition of the products from the oxidative ammonolysis of II and hydrolysis of III was accomplished through gas chromatography and polarography [8, 9].

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APPLICATION OF THE GTsN-907 HYDROPURIFIER IN THE MANUFACTURE OF SOLUTIONS FOR INJECTION

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The purity of liquids used for washing the glass packaging and those used in the actual solutions is of paramount importance in the manufacture of solutions for injection. The quality of the cleaning of the packaging intended for drugs depends in the main on the degree of purity of the washing water: tap, ion exchange, or distilled.

A variety of methods and apparatus containing different filter membranes are used at the present time for the filtration of liquids in the drug industry.

Experimental work has been carried out in the N. A. Semashko Pharmaceutical Chemical Works in collaboration with MTIMMP and VNIKhFI on the purification of washwater and of solutions by centrifugation and separation with the aim of increasing productive capacity and simplicity of maintenance.

It is known that separators are used for the purification of water in food manufacture [1]. Consequently the possibility was studied of applying a separator to the manufacture of solutions for injection. The work was carried out in an ASG-3M separator-clarifier. All liquids used in the manufacture of solutions for injection were subjected to clarification.

The results of trials of the ASG-3M separator showed that its productive capacity varied within the limits 300-380 liter/h with a very insignificant content of suspended matter in the clarified water.

Moscow Technological Institute for the Meat and Dairy Industry (MTIMMP). S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry (VNIKhFI). N. A. Semashko Pharmaceutical Chemical Works, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 10, No. 4, pp. 86-88, April, 1976. Original article submitted October 14, 1975.