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SYNTHESIS OF NICOTINIC ACID AND HYDROXYMETHYLAMIDE BY THE HYDROFORMYLATION OF 3-CYANOPYRIDINE

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Nikodin, or nicotonic acid hydroxymethylamide (I), shows cholagogic action, and possesses bacteriostatic and bactericidal properties; it is effective in infections caused by Escherichia coli [1].

A known method for the isolation of nikodin is the formylation of nicotinamide (II) [2]; the latter, in turn, in obtained by the amination of nicotinic acid (III). The synthesis of (II) from 3-cyanopyridine (IV) in the presence of the anion exchanger AB-17-8 in the OH-form is hampered by the fact that the catalyst is rapidly deactivated, adsorbing the final products [3-5]. The hydrolysis of (IV) in the presence of aqueous ammonia affords (III); the ammonium nicotinate, which is thereby formed, is thermally decomposed to (III) and ammonia [6].

Therefore, in order to isolate (I), it is necessary to hydrolyze (IV) to (III) (a) or (II) (b). In the case of (a), the (III) is aminated to (II), and (II) is finally formylated to (I). Both the methods (a) and (b) for the isolation of (I) are multistage.

We developed a continuous single-stage method for the isolation of (I) based on the direct interaction of (IV) with an aqueous solution of formaldehyde (V) in the presence of the anion exchange resin AB-17-8 in the OH-form and ammonia, which serves as the reactivation agent for the catalyst.

EXPERIMENTAL

The synthesis of (I) was performed in a thermostatted reactor of the flow type with the internal diameter of 12 mm and the height of 300 mm. The solution containing (IV) (9.58%) and (V) (5.11%) in water was passed continuously in a descending stream through a

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stationary layer of the anion exchanger AB-17-8 (30 ml) at the temperature of 60-90°C; 0.5-1.5 mole of ammonia were added. The duration of the reaction was 1 h. The working life of the catalyst in the continuous process was 40 h.

The yield of 16.6 g (0.109 mole) of (I) was obtained; this corresponds with 75.7% of the theoretical value on the basis of (IV). The yield of 4.25 g (0.0319 mole) of (II) was also obtained; this comprises 23.2% on the basis of (IV). The liquid part of the reaction mixture was distilled off at atmospheric pressure or reduced pressure, and it was again returned into the reaction. The dry residue was recrystallized from alcohol. The (I) obtained is in the form of white crystals with the mp 147-149°C; $C_7H_8N_2O_2$. The data of the elemental analysis satisfy the calculated values. The alcoholic extract was distilled additionally for the isolation of (II) with the mp 130-131°C; $C_6H_5N_2O$.

The IR spectra were taken on the UR-20 spectrometer using tablets with KBr in the proportion of 1:200 in the region of 400-4000 cm^{-1}. The strongest characteristic absorption bands in the IR spectrum of (I) (ν, cm^{-1}) are as follows: 1030 (C–O), 1320 (C–N), 1610 (skeletal vibrations of the ring), 1690 and 1705 (doublet, C=O), 2840 and 2940 (CH_2), 3070 (C–H), 3000-3100 (OH), and 3340 (N–H).

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