A METHOD FOR THE PREPARATION OF NICOTINIC ACID AND ITS AMIDE FROM 2-METHYL-5-ETHYLPYRIDINE

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Potassium permanganate is a suitable agent for the preparative-scale synthesis of carbonic acids with a variety of structures. Such agents are also quite frequently used in technology, for example, for the preparation of nicotinic acid from β-picoline. We have shown that the permanganate method of oxidation can successfully be used for preparing nicotinic acid from such widely available raw materials as 2-methyl-5-ethylpyridine (MEP), although additional stages must be included, to extract and decarboxylate isocinchomeronic acid (ICA).

The first stage of the reaction is carried out using 6 moles of $KMnO_4$ for each mole of MEP. Addition of the correct quantity of oxidizing agent to the reaction vessel in a single aliquot or as 2-3 portions results in the reaction occurring too violently and with excessively low selectivity, and ICA is then formed with yields close to those described in the literature, i.e., not greater than 45% [1]. During experiments to identify the optimal reaction conditions it was found that the $KMnO_4$ dosing should be changed, reducing the amount of oxidizing agent to 0.5-1 moles per mole of pyridine base, and each portion should only be added after complete utilization of the preceding portion, which is easily detected because of the decolorization of the reaction solution.

MEP itself has an extensive tendency to oxidize: even at 80°C the first 2-3 portions of $KMnO_4$ are entirely utilized within 10-15 min. As shown in Table 1, the reaction product at this time point consists of three pyridinecarboxylic acids, namely, 6-methylnicotinic, 5-ethylpicolinic, and isocinchomeronic acids, though the first of these is predominant. As more oxidizing agent is added, the total rate of the process decreases, and the content of 6-methylnicotinic acid in the reaction mix decreases, and the proportion of isocinchomeronic acid increases. Side reactions occur simultaneously, accompanied by breakage of the pyrimidine ring, profound oxidation of the organic material, and correspondingly unexpected degradation of the oxidizing agent. Thus, both 6-methylnicotinic acid and the initial MEP are present in the decolorized oxidation reaction after addition of 6 moles of $KMnO_4$. Increasing the temperature of the reaction and addition of excess oxidizing agent promote ICA accumulation. At 90°C and at boiling temperature, addition of 7 moles of $KMnO_4$ results in completion of the oxidation process within 3-3.5 h. By this time, MEP and pyrimidine monocarboxylic acids are completely consumed, and the ICA yield is 68-72% of the theoretical maximum. Excess utilization of the oxidizing agent is no more than 15% of the amount required for the quantity of MEP used. Experiments with greater excess quantities of $KMnO_4$ did not give positive results: oxidation of the ICA product started, though all sources of ICA were exhausted before this started.

Experiments with increased quantities of oxidizable material and oxidizing agent present risks of overheating, especially in the initial phases of the reaction. In order to avoid complications, the first portions of $KMnO_4$ should be made smaller, the intervals between addition of $KMnO_4$ portions should be increased, the mixing of the reaction should be improved, removal of heat from the reaction area should be efficient, and the oxidizing agent should be added as an aqueous solution. It should also be noted that losses during extraction of ICA from the reaction are small, because its water solubility is low, i.e., 0.05-0.1 at pH 1.3-2.8 [2].

The stage producing nicotinic acid consists of decarboxylation of ICA, which is carried out by heating ICA in a steel autoclave at 230-250°C for 2 h in the presence of a minimal quantity of water: up to 15 mmoles per mole of initial substance [3]. In these conditions, the desired product is obtained with a yield of 98-99%.

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TABLE 1. Oxidation of the Dialkyl and Alkenyl Derivatives of Pyridine by Potassium Permanganate

Reaction temp., °C	$KMnO_4$, moles/mole of initial substance	Time, min	Conv. of initial substance, %	Yield of acids, %			
				5-methyl-picolinic	5-ethyl-picolinic	6-methyl-nicotinic	isocincho-meronic
2,5-Dimethylpyridine							
80	2	90	46,4	19,1	—	47,1	12,3
80	5	640	84,1	—	—	15,7	68,4
90	4	197	94,8	—	—	15,1	68,3
90	5	372	100,0	—	—	14,5	70,8
98	4	125	84,5	—	—	14,6	69,0
98	5	245	100	—	—	16,0	70,2
2-Methyl-5-ethylpyridine							
80	2	6	34,4	—	2,9	31,1	—
80	3	10	49,9	—	5,4	42,0	1,6
80	6	166	69,9	—	—	24,6	52,9
80	8	390	100,0	—	—	—	69,2
90	1	3	19,0	—	—	16,5	—
90	4	26	85,0	—	3,5	57,5	18,4
90	7	200	100,0	—	—	—	70,0
90	8	375	100,0	—	—	—	59,1
98	1	3	19,2	—	—	15,6	
98	4	20	84,5	—	4,4	57,5	13,8
98	7	180	100,0	—	—	—	71,2
98	8	260	100,0	—	—	—	63,7
2-Methyl-5-vinylpyridine							
80	3	3	100,0	—	—	84,2	—
90	3	9	100,0	—	—	74,7	—
90	6	370	100,0	—	—	—	49,6
98	6	189	100,0	—	—	—	72,4

The amide of nicotinic acid is obtained by the catalytic dehydration of ammonium nicotinate in an ammonia flow with constant removal of the resulting water [4], or by hydration of the nitrile [5, 6]. We have demonstrated [7] that dehydration of the ammonium salt of nicotinic acid can also be carried out in aqueous solution in the absence of a catalyst, by heating it with concentrated ammonia in an autoclave at 200-230°C. At a molar ratio of acid:ammonia:water of 1:1.8-4:25-30, the nicotinamide yield at 1 h is some 25-28% of the theoretical. Unreacted ammonium nicotinate is removed by filtration of the reaction mixture as a solution, and can be returned to the dehydration reaction along with the washing water. The process is characterized by the extremely high selectivity with which the desired product is formed, and is not complicated by any kind of side reactions.

Preparation of ICa by the permanganate method can also be carried out using other pyridine derivatives as raw material, when these have alkyl or alkenyl substituents in positions 2 and 5; examples include 2,5-lutidine and 2-methyl-5-vinylpyridine. Table 1 shows that in both cases ICA forms in the same conditions and with the same yields (~70%) as when MEP is used. When 2-methyl-5-vinylpyridine is used, the quantity of $KMnO_4$ is reduced and virtually the only product formed, with a yield of 84.2%, is 6-methylnicotinic acid, which is used for the synthesis of phytotoxic compounds and antibiotics [8].

METHODS

Oxidation of the initial pyridine bases with potassium permanganate was carried out in a three-necked flask fitted with reverse heat exchanger, stirrer, and thermometer. The mixture of oxidizable substance and water was heated to the required temperature and, with intensive stirring, portions of $KMnO_4$ powder were added. After decolorization of each portion of oxidizing agent, 1 ml samples were removed from the reaction vessel for analysis.

ICA was decarboxylated and subjected to ammoniolysis to produce nicotinamide in a model 1X18H9T steel autoclave.

Contents of 2,5-dimethylpyrimidine, 2-methyl-5-ethylpyrimidine, and 2-methyl-5-vinylpyrimidine were determined by GLC [9]. Pyridinecarboxylic acids were identified by a polarographic method [10].

Preparation of Nicotinic Acid

MEP (8 g, 0.071 mole) and water (150 ml) were heated to boiling, and 73.2 g (0.46 mole) of $KMnO_4$ was added in portions. After 3 h from the beginning of the reaction and after decolorization of the mixture, the manganese dioxide precipitate was removed by filtration and washed with hot water, and ICA was precipitated from the filtrate and washing water by acidification with hydrochloric acid to pH 2.3. The yield was 7.72 g (70.05). The melting temperature was 236°C. The neutralization equivalent was 83.6, compared with a theoretical value of 83.55. The molecular formula was $C_7H_5O_2N$.

ICA (2 g, 0.012 mole) was heated in a microautoclave with 10.1 g (0.561 mole) of water using an electric furnace to achieve a temperature of 230°C for 2 h. Polarographic studies showed that 1.47 g of nicotinic acid was obtained, i.e., the yield was 99.9%. After a single recrystallization, 1.20 g of extracted product was obtained, with a melting temperature of 235°C and a molecular formula of $C_6H_5NO_2$.

Preparation of Nicotinamide

A mixture of 2 g (0.016 mole) of nicotinic acid and 9.3 ml of 22% NH_4OH (0.120 mole of NH_3) was placed in a microautoclave, and an electric furnace was used to heat it to 230°C for 2 h. Polarographic measurements showed that 0.17 g of nicotinamide was obtained, i.e., the yield was 29.7%. After a single recrystallization from water, three parallel experiments gave 0.42 g of substance, with a melting temperature of 121-122°C and a molecular formula of $C_6H_6ON_2$.

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