PRODUCTION OF ESTERS OF PELVIRINIC ACID

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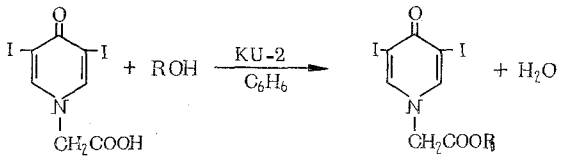
The further successes of x-ray diagnosis are involved with the development of new methods of synthesizing organoiodine x-ray constrast substances and the improvement of the existing methods. It is known that derivatives of 3,5-diiodo-4-pyridone-N-acetic (pelvirinic) acid, in particular, its n-propyl ester, are widely used in bronchography. However, the existing methods for the production of pelvirinic acid, based on its esterification by alcohols in the presence of mineral acids, are not without shortcomings, especially in use in industry, and also are protected by patents [1-4]. The intensive development of ion exchange catalysis in the last decade shows that in many catalytic reactions, ion exchange resins, which possess definite advantages, can successfully replace acid catalysts [5-6].

In this work we studied the esterification of 3,5-diiodo-4-pyridone-N-acetic acid by certain aliphatic alcohols in the presence of the cation exchange resin KU-2 as the catalyst:



R=n $-C_3H_7$, iso- C_3H_7 and n $-C_4H_9$

Our investigations indicated that the cation exchange resin KU-2 is a convenient and effective catalyst of the reaction studied (see Table 1). At a 2:1 ratio of the initial acid to KU-2, esterification ends in 40 min, and the yields of n-propyl-3,5-diiodo-4-pyridone-N-acetic reach 95% of the theoretical. When the amount of the catalyst is reduced (5:1 ratio of the acid to KU-2), the reaction time is somewhat increased, but in this case also a practically complete conversion of pelvirinic acid to the corresponding ester is observed. It is interesting that the cation exchange resin KU-2 is used repeatedly without any appreciable loss of activity; the reaction proceeds selectively, without the formation of side products. It should be mentioned that the n-propyl ester of 3,5-diiodo-4-pyridone-N-acetic acid is obtained in extremely pure form in the presence of the cation exchange resin KU-2: the crude product possesses mp 185-186°, and after only one recrystallization it reaches 188-189°. At the same time, the crude product obtained using, for example, phosphorous oxychloride, possesses mp 177-178°, and its purification requires repeated recrystallizations.

Thus, the esterification of 3,5-diiodo-4-pyridone-N-acetic acid by aliphatic alcohols in the presence of the cation exchange resin KU-2 as a catalyst proceeds readily and smoothly with high (90-95%) yields and leads to pure alkyl-3,5-diiodo-4-pyridone-N-acetic (alkyl = n-C_3H_7, iso-C_3H_7, and n-C_4H_9).

On the basis of the n-propyl ester of pelvirinic acid, synthesized by this method [7], we developed experimentally and clinically tested two drug forms of a suspension of bronchodiagnostin-1 and bronchodiagnostin-2 [8]. The synthetic blood replacers polyvinylpyrrolidone and polyglucin were used as the viscous base of the aqueous suspensions of n-propyldiiodopyridone acetate. A detailed description of the procedure for the preparation of these suspensions and their use for bronchography is cited in [9]. In one case, the base of the n-propyldiiodopyridone acetate suspension was a 30-35% aqueous solution of polyvinylpyrrolidone, and in the other a 16-25% aqueous solution of polyglucin; the iodine content in these 50% suspensions was about 30%. Densitometric measurements of the x-ray diffraction pictures of test tubes of the same diameter with a 50% "Propyliodone — Cilag" suspension (Switzerland) and our 50% suspensions of bronchodiagnostin-1

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TABLE 1. Conditions of the Esterification of Pelvirinic Acid

Experiment No.	Amount of pelvirinic acid (in g)	ROH		KU-2 (in g)	Multiplicity of work of KU-2	Reaction time (in h)	Reaction temperature (in degrees)	Yield (in %)
		R	Amount (in ml)					
1	10	n-C_3H_7	50	5	1	0,7	78—80	94,8
2	20	n-C_3H_7	50	5	1	3,0	78—80	93,5
3	10	n-C_3H_7	50	2	1	1,2	78—80	91,2
4	10	n-C_3H_7	50	2	2	1,5	78—80	94,8
5	10	n-C_3H_7	50	2	3	1,5	78—80	87,6
6	10	n-C_3H_7	50	2	4	1,5	78—80	93,1
7	10	n-C_3H_7	50	2	5	1,2	78—80	86,8
8	10	iso-C_3H_7	50	2	1	1,5	78—80	91,2
9	10	n-C_4H_9	100	2	1	2,0	110—120	87,0

and bronchodiagnostin-2, taken under identical technical conditions, gave almost analogous results (0.97 and 0.98, respectively), which is evidence of the high x-ray contrast properties of the preparations that we developed.

EXPERIMENTAL SECTION

The Initial 3,5-Diiodo-4-pyridone-4-acetic Acid was synthesized for the reaction of 3,5-diiodo-4-pyridone with monochloroacetic acid according to the method of [10] and possessed mp 242-243°, according to the literature data, mp 240° [10], 241-243° [11]. The cation exchange resin KU-2 that we used (6% divinylbenzene) had a static exchange capacity (SEC) of 4.65 mequiv/g and a moisture content of 0.5%.

Esterification of Pelvirinic Acid by alcohols was conducted according to the following procedure. In a round-bottomed flask, equipped with a mixer, thermometer, and water removing trap with reflux condenser, we placed 0.025 mole of the acid, the alcohol (see Table 1), 50 ml of benzene, the cation exchange KU-2, and boiled the reaction mixture with vigorous mixing until the evolution of water in the trap ceased. The hot solution was filtered to remove the catalyst (which was used in subsequent reactions without any additional treatment), and crystals of the ester precipitated immediately from the filtrate (an additional amount of the ester can be isolated from the mother liquor).

In this way we obtained the following esters of pelvirinic acid: n-propyl-3,5-diiodo-4-pyridone-N-acetate, mp 188-189° (from a 2:1 alcohol-heptane mixture), according to the literature data, mp 188-189° [1]; isopropyl-3,5-diiodo-4-pyridone-N-acetate, mp 214-215° (from a 2:1 alcohol-heptane mixture), according to the literature data, mp 215° [4]; and n-butyl-3,4-diiodo-4-pyridone-N-acetate mp 194° (from methanol), according to the literature data, mp 194° [4].

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