X-RAY CONTRAST MEDIA. SYNTHESIS OF ESTERS OF 3,5-DIIODOPYRID-4-ONE-N-ACETIC ACID IN THE PRESENCE OF KU-2 CATION-EXCHANGE RESIN

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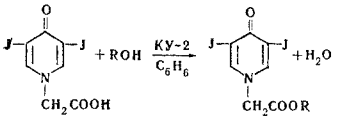
In a study of the esterification of 3,5-diiodopyrid-4-one-N-acetic acid with alipathic alcohols in the presence of KU-2 cation-exchange resin as catalyst, it was established that the reaction takes place readily and smoothly and gives the corresponding esters in high yields.

Recently, the development of new methods and the improvement of existing ones of synthesis of X-ray contrast media has acquired particular importance. Among the latter, great interest is presented by derivatives of 3,5-diiodopyrid-4-one-N-acetic (pelvirinic) acid and, in particular, its esters [1–3]. The usual method for the preparation of esters of pelvirinic acid is its esterification with alcohols in the presence of mineral acids [3–5]. However, when homogeneous acid catalysts are used, particularly in industry, difficulties connected with the isolation of the reaction products, the occurrence of side reactions, the necessity for using acid-resistant apparatus, etc., arise.

The intensive development of ion-exchange catalysis in the last decade shows that in many catalytic reactions ion-exchange resins, which possess certain advantages [6,7], may successfully replace acid catalysts.

In view of this, we have studied the esterification of pelvirinic acid with a number of alipathic alcohols in the presence of the Russian KU-2 cation-exchange resin as catalyst.



R = *n*-C_3H_7, *i*-C_3H_7 и *n*-C_4H_9

The investigations that we have carried out have shown that KU-2 ion-exchanger is a suitable and effective catalyst of the reactions studied. At a ratio of the initial acid and KU-2 of 2 : 1, esterification is complete in 40 min, and the yield of n-propyl 3,5-diiodopyrid-4-one-N-acetate amounts to 95% of theoretical. Decreasing the amount of catalyst (ratio of acid and KU-2 of 5 : 1) somewhat increases the time of the reaction, but in this case the pelvirinic acid is almost completely converted into the corresponding ester. It is interesting that KU-2 ion exchangers can be used repeatedly without appreciable loss of activity, and the reaction takes place selectively without the formation of by-products (see table).

The medicinal form of one of the substances that we have synthesized—n-propyl 3,5-diiodopyrid-4-one-N-acetate, which we have named "bronchodiagnostin"—has been tested in our laboratory and, with clinical approval, has shown good X-ray contrast properties with an insignificant toxic effect.

EXPERIMENTAL

The initial 3,5-diiodopyrid-4-one-N-acetic acid was synthesized by the reaction of 3,5-diiodopyrid-4-one with monochloroacetic acid [8] and had mp 242–243° C; according to the literature, mp 240° C [8], 241–243° C [2].

The KU-2 cation-exchange resin that we used had a SEC of 4.65 mg-equiv/g and a moisture content of 0.5%.

Esterification of pelvirinic acid with alcohols. A round-bottomed flask fitted with a stirrer, thermometer, and water-separating trap with a reflux condenser was charged with 0.025 mole of the acid, the alcohol, 50 ml of benzene, and KU-2 ion-exchange resin, and the reaction mixture was stirred vigorously at a given temperature until the appearance of water in the water separator ceased. The hot solution was filtered from the catalyst (which was used in subsequent reactions without any additional treatment), and crystals of the ester deposited directly from the filtrate (an additional amount of the ester can be isolated from the mother liquor). The following esters of pelvirinic acid were obtained in this way: n-propyl, 3,5-diiodopyrid-4-one-N-acetate, mp 188–189° C (from a mixture of ethanol and heptane; 2:1); according to the literature [3], mp 188–189° C; isopropyl 3,5-diiodopyrid-4-one-N-acetate, mp 214–215° C (from a mixture of ethanol and heptane, 2 : 1); according to the literature [5], mp 215° C; and n-butyl 3,5-diiodopyrid-4-one-N-acetate, mp 194° C (from methanol); according to the literature [5], mp 194° C.

Conditions for the Esterification of Pelvirinic Acid

Experiment no.	Pelvirinic acid, g	ROH		KU-2, g	Number of times KU-2 used	Reaction time, hr	Reaction temperature °C	Yield, %
		R	amount, ml					
1	10	*n*-C_3H_7	50	5	1	0.7	78—80	94.8
2	20	" "	50	5	1	3.0	78—80	93.5
3	10	" "	50	2	1	1.2	78—80	91.2
4	10	" "	50	2	2	1.5	78—80	94.8
5	10	" "	50	2	3	1.5	78—80	87.6
6	10	" "	50	2	4	1.5	78—80	93.1
7	10	" "	50	2	5	1.2	78—80	86.8
8	10	*i*-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

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THE AUTOXIDATION OF Δ^{10}-DODECAHYDROACRIDINE

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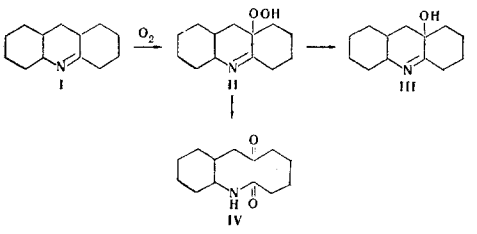
The autoxidation of Δ^{10}-dodecahydroacridine in heptane in an atmosphere of oxygen has given 12-hydroperoxy-Δ^{10}-dodecahydroacridine, which has been reduced to 12-hydroxy-Δ^{10}-dodecahydroacridine and has been converted into 5-azabicyclo[8, 4, 0]tetradecane-6, 11-dione. The two latter compounds were also isolated when Δ^{10}-dodecahydroacridine underwent autoxidation in air in the absence of a solvent.

Preparation of Δ^{10}-dodecahydroacridine has been reported previously [1]. Like its bicyclic analogs—$\Delta^{1,9}$-octahydroquinoline and $\Delta^{1,8}$-hexahydropyrindene [2]—the imine I proved to have an extremely high tendency to autoxidation both in a solvent and without a solvent.

When a solution of the imine I in heptane was stirred in an atmosphere of oxygen, about 1 mole of O_2 was absorbed; an unstable crystalline hydroperoxide—12-hydroperoxy-Δ^{10}-dodecahydroacridine (II)—deposited.

By a known method for the reduction of hydroperoxides [3], on treatment with sodium hydrosulfite the hydroperoxide II formed 12-hydroxy-Δ^{10}-dodecahydroacridine (III). In aqueous dioxane in the presence of a small amount of hydrochloric acid, the hydroperoxide II underwent rearrangement. Judging from the IR spectrum, the rearrangement product was a macrocyclic ketolactam—5-azabicyclo[8, 4, 0]tetradecane-6, 11-dione (IV). The formation of similar products by the rearrangement of hydroperoxides of cyclic imines has been mentioned in the literature [4, 5]. In the rearrangement of the hydroperoxide of $\Delta^{1,9}$-octahydroquinoline [2], the corresponding 10-membered ketolactam could not be isolated, since it underwent transannular cyclization (interaction of the keto and N—H groups across the ring). In our case, according to its IR spectrum, the product contained both a keto group and a —CONHR group—i.e., no cyclization took place.

The autoxidation of Δ^{10}-dodecahydroacridine on standing in the air without a solvent led to the formation of a mixture of oxidation products from which compounds III and IV were isolated. The formation of the first of them can be explained by the interaction of the hydroperoxide formed initially with the unoxidized imine. Similar reactions have been described in the literature [6]. Rearrangement of the hydroperoxide took place simultaneously, leading to the formation of compound IV.



I II III IV

EXPERIMENTAL

12-Hydroperoxy-Δ^{10}-dodecahydroacridine (II). A solution of 4 g of freshly distilled I in 80 ml of heptane was stirred in a flask connected with a burette filled with oxygen. In the first 7 min, 172 ml of O_2 was absorbed, and then the rate of absorption fell. Only after 1 hr 40 min had 392 ml of O_2 (84% by theory) been absorbed. The precipitate of hydroperoxide that had separated was filtered off with suction, washed with heptane, and kept at 0° C over paraffin wax until it had reached constant weight. Yield 3.9 g (83.5%). Mp 96° C (decomp.). The sub-