ESTERIFICATION OF PYRIDINECARBOXYLIC ACIDS IN THE PRESENCE OF CATION-EXCHANGE RESINS

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Pyridinecarboxylic acids undergo esterification on refluxing with alcohols in the presence of cation-exchange resins. In the case of pyridine-2,6-dicarboxylic acid, in which the basicity of the nitrogen atom is reduced, esterification products are obtained in high yields. In the case of pyridinecarboxylic acids, in which the pyridine nitrogen atom displays considerable basicity, the cations of the acids are tied up by the cation-exchange resin, and the yields of preparatively isolable esters do not exceed 60%.

Cation-exchange resins are widely used as catalysts for the esterification of aliphatic, aromatic, and O-heteroaromatic acids, including compounds containing hydroxyl and mercapto groups, as well as multiple bonds [1]. In addition, the literature does not contain data on the application of cation-exchange resins in the esterification of nitrogen-nonacylated amino- or N-heterocyclic acids. The fear that substances containing a basic nitrogen atom would precipitate on the catalyst in the form of the cation evidently prevented carrying out studies of this type.

In development of the synthesis of the medicinal preparation parmidine (anginine) — 2,6-bis(hydroxymethyl)pyridine bis(N-methylcarbamate) — our task was to find a method for the esterification of pyridine-2,6-dicarboxylic acid (I) that would be suitable for industrial production. The known methods for the preparation of esters of this acid through the acid chloride [2, 3], potassium or silver salt [4, 5], and by reaction with alcohol and sulfuric acid [6] or with diazomethane [7] are characterized by the use of reagents that induce corrosion (thionyl chloride, hydrogen chloride, and sulfuric acid), that are expensive (silver salts), or dangerously explosive (diazomethane) or by the complexity of the isolation of the final products and relatively low yields.

An examination of the chemical peculiarities of pyridine-2,6-dicarboxylic acid and its esters provided us with a basis for the utilization, in this case, of esterification in the presence of cation-exchange resins. It is well known that pyridine-2,6-dicarboxylic acid and its esters, in contrast to other nitrogen-containing heterocyclic acids, are characterized by extremely low basicities of the nitrogen atom, which is associated with the strong electron-acceptor effect of two α,α'-carboxyl (alkoxyl) groups. Because of this, the indicated compounds do not form stable salts or quaternary derivatives at the nitrogen atom, and the isolation of free I from its potassium salt by means of hydrochloric acid at pH values from 0.2 to −0.2 is not accompanied by protonation of the nitrogen atom. All of this made it possible to assume that in the esterification of I in the presence of cation-exchange resins the latter would not tie up the starting materials and final products in the form of cations.

In fact, heating I in the presence of KU-2-8sch cation-exchange resin with lower aliphatic alcohols (methanol, ethanol, and butanol) leads in all cases to the formation of diesters in yields close to quantitative.

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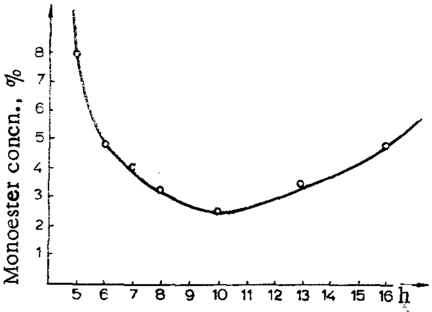

Fig. 1. Kinetics of the esterification of the monobutyl ester of I with butanol with KU-2-8sch cation-exchange resin.

In order to monitor the esterification process we used thin-layer chromatography (TLC) on Silufol. When this was done, it was shown that the reaction is realized in a stepwise manner through the formation of the corresponding monoesters of I. When the esterification was stopped at the first step, we were able to isolate and characterize the previously undescribed monoethyl and monobutyl esters, which were subsequently used as reference compounds in the study of the course of the reaction by TLC.

The optimum parameters for carrying out the process were worked out with the application of analytical monitoring. It was established that at loads up to 10 g, cation-exchange resin samples amounting to 40% of the weight of the starting acid are sufficient, and that it is expedient to increase the amount of cation-exchange resin to 100% of the weight of I for larger loads, and that the reaction mass needs to be stirred well. The cation-exchange resin in this reaction can be used repeatedly (10 or more times) without regeneration. In the case of dimethyl pyridine-2,6-dicarboxylate the esterification is practically complete after 7 h, as compared with 10 h for the diethyl and dibutyl esters; starting I is practically absent in the reaction mixture after 5 h, but it contains 5-10% of the monoester. The kinetics of the esterification of the second carboxyl group in the monobutyl ester in the final stage of the process is presented in Fig. 1 for dibutyl pyridine-2,6-dicarboxylate. As seen from the graph in Fig. 1, 10 h after the start of the reaction the amount of monobutyl ester reaches a minimum (2.5%), but its percentage in the reaction mixture gradually begins to increase on further refluxing and amounts to 4.8% after 16 h. The reverse reaction — saponification of the dibutyl ester of I to the monobutylester of I — is evidently associated with a side process — dehydration of butanol — inasmuch as cation-exchange resins of this type are simultaneously catalysts for the dehydration of alcohols [8], although the latter process is realized at a considerably lower rate.

The esterification of I in the presence of cation-exchange resins is accelerated by removal of the liberated water by azeotropic distillation. When the esterification is carried out with butanol, the water can be removed either by slow distillation from the reaction mass with butanol or by means of a Dean—Stark trap. In both cases butanol is used as a substance that forms an azeotrope with water. The addition of toluene or benzene, in which I is practically insoluble, markedly slows down the esterification.

For a number of processes, in particular, for the preparation of 2,6-bis(hydroxymethyl)-piperidine, the corresponding alcohol solutions, after esterification and separation of the cation-exchange resin, can be used without isolation of the esters in pure form [9].

The basicity of the pyridine nitrogen atom increases on passing from I to pyridinemonocarboxylic acids — picolinic, 6-methylpicolinic, nicotinic, and isonicotinic. In this connection, the tendency of the compounds to be tied up by the ion-exchange resin by means of the nitrogen atom of the pyridine ring increases during esterification of pyridinemonocarboxylic acids in the presence of cation-exchange resins. Monitoring of the esterification processes by means of TLC also in the case of monocarboxylic acids made it possible to establish the absence of the starting compounds in the reaction solutions. However, the yields of the corresponding esters during isolation of the reaction products were 27-31% for the methyl esters and 49-59% for the butyl esters. The indicated results were obtained by carrying out the reaction under optimum conditions with 1:1 ratios of the amounts of starting acids and ion-exchange resins.

As in the case of the esterification of I, a decrease in the amount of the cation-exchange resin substantially slowed down the process. However, the use of a 50% excess of the ion-exchange resin in this case lowered the yields of the corresponding monoesters by 15-20% due to more nearly complete tying up of the pyridine base by the cation-exchange resin.

The indicated interaction with the cation-exchange resin at the basic nitrogen atom is quite strong. No more than 10% of the substance in the form of a mixture of the ester and the acid can be additionally removed by refluxing the ion-exchange resin (removal by filtration) with three fresh portions of alcohol (for 16 h with each portion). The principal amounts of the products continue to remain on the ion-exchange resin.

In addition to KU-2-8sch cation-exchange resin, other KU-2 cation-exchange resins can also be used as catalysts for the esterification of pyridinecarboxylic acids. However, in these cases the possibility of repeated utilization of the catalyst without regeneration is reduced from 10 or more times to two or three times.

EXPERIMENTAL

The esterification was monitored by TLC on Silufol UV-254 plates in the following systems: A) 96% ethanol—25% ammonia—water (25:4:3); and B) butanol—25% ammonia—water (16:1:2) with development in UV light.

The following R_f values were observed in system A: pyridine-2,6-dicarboxylic acid (I) 0.36, diethyl ester of I 0.72, dibutyl ester of I 0.82, monoethyl ester of I 0.55, and monobutyl ester of I 0.70.

The following R_f values were observed in system B: picolinic acid 0.1, 6-methylpicolinic acid 0.1, nicotinic acid 0.21, isonicotinic acid 0.14, methyl picolinate 0.70, methyl 6-methylpicolinate 0.77, methyl nicotinate 0.74, methyl isonicotinate 0.80, butyl picolinate 0.72, butyl 6-methylpicolinate 0.70, butyl nicotinate 0.83, and butyl isonicotinate 0.70.

A method for the direct titration of a sample of the reaction mixtures with 0.1 N sodium hydroxide solution with Bromthymol Blue indicator in ethanol was also developed for determination of the end of the esterification. In the case of esters of I under selected conditions, the free carboxyl group of the monoesters is titrated without involvement of the ester groups of the mono- and diesters. The results of titrometric analysis and TLC were compared in all cases with the yields of esters obtained by preparative isolation.

Dimethyl Ester of I. A mixture of 10 g of I, 100 ml of methanol, and 4 g of KU-2-8sch cation-exchange resin was refluxed with stirring for 7 h, after which the mixture was cooled to room temperature, the catalyst was removed by filtration, and the filtrate was vacuum evaporated. The residue (11.6 g, mp 116-118°) was recrystallized from ethyl acetate to give 10.65 g (90%) of a product with mp 123-124° [10].

Diethyl Ester of I. This compound was similarly obtained from 10 g of I, 100 ml of anhydrous ethanol, and 4 g of KU-2-8sch cation-exchange resin. The reflux time was 10 h. The residue (12.6 g) remaining after separation of the catalyst and removal of the alcohol by distillation was vacuum fractionated to give 12.11 g (87%) of ester [10] with bp 143-145° (1 mm).

Dibutyl Ester of I. This ester was obtained by refluxing 10 g of I, 120 ml of butanol, and 4 g of KU-2-8sch cation-exchange resin with azeotropic removal of the water in a Dean—Stark adaptor for 10 h. According to the TLC data, the monobutyl ester of I (1%) and the dibutyl ester of I (99%) are present in the reaction mixture. The catalyst was separated and washed with hot butanol (three 20-ml portions), and the butanol was removed by distillation to give 16.4 g of residue, from which 15.7 g (94%) of the dibutyl ester, with mp 61-62°, and bp 168-170°, Found, %: C 64.5; H 7.7; N 5.2. $C_{15}H_{21}NO_4$. Calculated, %: C 64.5; H 7.6; N 5.0.

Monobutyl Ester of I. A mixture of 10 g of I, 120 ml of butanol, and 4 g of KU-2-8sch cation-exchange resin was refluxed with stirring for 1.5 h. According to the TLC data, the following compounds are present in the reaction mixture: I and its mono and dibutyl esters in a ratio of 3:4:3. The hot reaction solution was removed from the cation-exchange resin by filtration, and the filtrate was vacuum evaporated. The residue was treated with 20 ml of 50% aqueous potassium carbonate solution, and the dibutyl ester of I was extracted with benzene [removal of the benzene by distillation and recrystallization of the residue from heptane gave 3 g (18%) of a substance with mp 61-62°], after which the aqueous solution was acidified to pH 4 with hydrochloric acid, and the monobutyl ester of I was extracted with chloroform to give 4.25 g (32%) of colorless crystals with mp 118-119° (from ethyl acetate). Found, %: C 58.8; 5.7; 6.1. $C_{11}H_{13}NO_4$. Calculated, %: C 59.1; H 5.9; N 6.3.

Monoethyl Ester of I. This compound was similarly obtained from 10 g of I, 100 ml of anhydrous ethanol, and 2 g of KU-2-8sch cation-exchange resin. The yield of product with mp 116-117° (from ethyl acetate) was 3.5 g (30%). Found, %: C 55.4; H 4.7; N 7.2. $C_9H_9NO_4$. Calculated, %: C 55.4; H 4.7; N 7.2.

2,6-Bis(hydroxymethyl)pyridine. A 20.4-g sample of sodium borohydride was added in portions in the course of 2 h at 38-40° with stirring to a butanol solution of the dibutyl ester of I obtained from 30 g of I by the method described above. The reaction mixture was then allowed to stand at this temperature until the butyl 6-hydroxymethylpicolinate had vanished (about 2 h) according to TLC, after which 200 ml of water was added, and the mixture was stirred for 30 min. The butanol layer was separated, and the aqueous solution was extracted with butanol (three 120-ml portions) with the addition of water after each extraction in order to keep the volume of the water layer constant (200 ml). The combined butanol extracts were vacuum evaporated to dryness, and the residue was recrystallized from 360 ml of ethyl acetate to give 18.55 g (74% based on I) of 2,6-bis(hydroxymethyl)pyridine with mp 115-116° [11].

Butyl Picolinate. A mixture of 5 g of picolinic acid, 60 ml of butanol, and 5 g of KU-2-8sch cation-exchange resin was refluxed with stirring for 16 h and monitoring of the course of the reaction by TLC. The cation-exchange resin was removed by filtration and washed with hot butanol (three 50-ml portions). The combined butanol solutions were vacuum evaporated, and the residue was fractionated to give 4.3 g (59.1%) of a colorless mobile liquid with bp 141-142° (16 mm) and n_D^{20} 1.5013. Found, %: C 67.2; H 7.3; N 7.7. $C_{10}H_{13}NO_2$. Calculated, %: C 67.0; H 7.3; N 7.8.

Methyl Picolinate. In a similar experiment with methanol, 1.28 g (28.8%) of this ester, with bp 94-95° (9 mm) [12], was obtained after 20 h.

Butyl 6-Methylpicolinate. This ester was obtained from 5 g of 6-methylpicolinic acid by the method described above. Workup gave 4.1 g (49%) of a colorless mobile liquid with bp 145-147° (16 mm) and n_D^{20} 1.4949. Found, %: C 68.1; H 7.75; N 7.1. $C_{11}H_{13}NO_2$. Calculated, %: C 68.4; H 7.8; N 7.2.

Methyl 6-Methylpicolinate. This ester, with bp 96-97° (4 mm) [13], was similarly obtained in 28% yield.

Butyl Nicotinate. Reaction of 5 g of nicotinic acid with 150 ml of butanol and 5 g of KU-2-8sch cation-exchange resin by the method described above gave 3.75 g (51.6%) of a product with bp 119-120° (8 mm) [14].

Methyl Nicotinate. This ester, with mp 37-38° (from ethyl acetate) [12], was similarly obtained in 30.5% yield.

Butyl Isonicotinate. Similarly, reaction of 5 g of isonicotinic acid with 750 ml of butanol and 5 g of KU-2-8sch cation-exchange resin gave 4.1 g (56.3%) of a product with bp 126-127° (16 mm) and n_D^{20} 1.4922. Found, %: C 66.9; H 7.3; N 7.6. $C_{10}H_{13}NO_2$. Calculated, %: C 67.0; H 7.3; N 7.8.

Methyl Isonicotinate. When methanol was used, 2.7 g (48.5%) of this ester with bp 76-78° (5 mm) [12] was obtained after 20 h.

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