IMPROVEMENT OF THE LIPOIC ACID AMIDE SYNTHESIS

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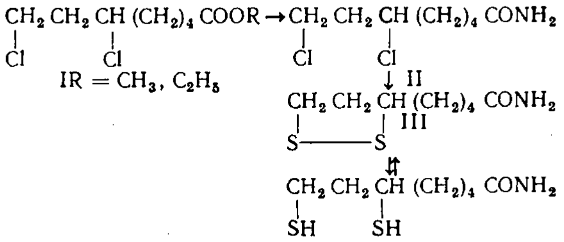
Lipoic (6,8-dithiooctanoic) acid and its amide participate in oxidative decarboxylation of pyruvic acid and other α-keto acids [1]. It and its derivatives enter into the composition of certain enzymatic systems. They fulfill an important role in many biochemical processes and find use as medicinal preparations [2].

In this connection we studied various ways of synthesizing them [3]. A description of a modified method of obtaining lipoic acid amide, based on using the ester of 6,8-dichlorooctanoic acid (I) [4], is given in this paper. The ester is transformed by reaction with an aqueous methanol solution of ammonia to the amide of 6,8-dichlorooctanoic acid (II) and the amide of lipoic acid (III) is obtained from the latter and sodium disulfide.

We introduced a series of simplifications and changes in the mentioned synthesis of (III). Conditions of obtaining (III) from (II) and from the amide of dihydrolipoic acid (IV) were studied.



$$\underset{Cl}{CH_2}CH_2\underset{Cl}{CH}(CH_2)_4COOR \rightarrow \underset{Cl}{CH_2}CH_2\underset{Cl}{CH}(CH_2)_4CONH_2 \;\text{II} \rightarrow \underset{S\text{———}S}{CH_2CH_2CH}(CH_2)_4CONH_2 \;\text{III} \rightleftarrows \underset{SH}{CH_2}CH_2\underset{SH}{CH}(CH_2)_4CONH_2$$

$$\text{I}\quad R = CH_3,\ C_2H_5$$

Compound (II) was thionated earlier with an alcoholic solution of sodium disulfide, obtained from sodium sulfide and sulfur. At the end of the thionation reaction the alcohol was distilled in vacuum and (III) was extracted from the residue with chloroform. The chloroform extracts were combined, the solvent was removed in vacuum, and from the residue was obtained (III), which was purified by recrystallization from toluene.

Conditions were found for thionating compound (II) with an aqueous sodium disulfide solution and the alcohol consumption was decreased significantly in this way. We established that after removal of alcohol from the reaction mass, (III) could be extracted from the aqueous residue with toluene at 85-90° and crystallized at 0-5°. This made it possible to exclude the use of chloroform, to shorten significantly the length of the technological process of obtaining (III), and to increase the quality of the product.

In addition, (III) was obtained by oxidation of (IV) with air oxygen in the presence of a catalytic amount of iron chloride in an aqueous alcohol medium at pH 8.0. Amide (III) was reduced with sodium borohydride in an alkaline water–alcohol medium to (IV).

The compounds obtained by us were characterized by elemental analysis, mp, and IR spectra.

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IR spectra of (II), (III), (IV), taken on a UR-10 spectrophotometer in mineral oil, showed the presence in all of these compounds of absorption bands in the region of 1650 cm^{-1}, characteristic for the amide carbonyl.

EXPERIMENTAL METHOD

Lipamide (III).

A. From 6,8-Dichlorooctanoic Acid Amide (II). In a stream of nitrogen 3.6 g of sodium sulfide (nonahydrate) was dissolved in 8 ml of water, 0.5 g of sulfur was added as a fine powder, and the mixture was stirred at 25-30° until complete disappearance of free sulfur (~40 min). To the obtained sodium disulfide solution was added a solution of 2.3 g of (II) (mp 82°, 92% from nitrogen content) in 20 ml of alcohol and the mixture was stirred for 2 h at 75-82° in a stream of nitrogen. At the end of thionation the alcohol was distilled from the reaction mixture under vacuum. To the residue was added 40 ml of toluene and the mixture was heated with stirring to 85-90°. During this the formed (III) passed into the toluene. Extraction was repeated two to three times with 20-ml quantities of toluene. The alcohol residue was removed from the toluene solution as an azeotropic mixture; it was filtered, poured into a crystallizer, and left for 4-5 h at 2-5° for crystallization of (III). Crystalline (III) was filtered, washed with 5 ml of toluene, and dried in vacuum at 50-60°. Yield of (III) was 1.3-1.4 g (63.4-68.3%), mp 123°. Found, %: C 46.00, 46.25; H 7.15, 7.26; N 7.37,7.34; S 31.88, 32.06. $C_8H_{15}NS_2O$. Calc., %: C 46.79; H 7.36; N 6.82; S 31.23. IR spectrum: ν_{CO} 1650, ν_{NH_2} 2900 cm^{-1}.

B. From 6,8-Dimercaptooctanoic Acid Amide (IV). We dissolved 1.6 g of (IV) (mp 65°, content 98%) in 20 ml of alcohol, added 2 ml of 1 N sodium hydroxide or sodium bicarbonate solution to pH 8.0 and 1 ml of 5% iron chloride solution, and passed it in air with good stirring of the reaction mass until decolorization. The oxidation process was continued for 1-1.5 h at 25-30°. At the end of oxidation the alcohol was removed from the reaction mass in vacuum at 40-50° and (III) was extracted from the residue with toluene (2 × 40 ml) at 85-90°. The toluene solution was filtered if necessary and left at 2-5° for crystallization of (III). Yield was 1-1.1 g (65-70%), mp 125-126°, 97% from nitrogen content.

Amide of Dihydrolipoic Acid (IV). We dissolved 2 g of (III) in 20 ml of alcohol in a stream of nitrogen, added 2 ml of 1 N sodium hydroxide solution, added, in portions, a solution of 0.5 g of sodium borohydride in 5 ml of water, and stirred the mixture for 2 h at 25-30°. Dilute hydrochloric acid (1:2) was added to the reaction mass to pH 3.0-4.0 and the alcohol was distilled in vacuum at a temperature not above 60°. To the residue was poured 40 ml of chloroform, the mixture was stirred, and the aqueous layer was separated and extracted again with chloroform (20 ml). The chloroform extracts were combined, the solvent was distilled in vacuum at a temperature not above 50°, and (IV) was in the residue. Yield 1.6-1.7 g (80-85%), mp 63-64°. Found, %: C 46.16, 46.23; H 8.16; N 6.70, 6.80. $C_8H_{17}NS_2O$. Calc., %: C 46.79; H 7.36; N 6.82. IR spectrum: ν_{SH} 2550, ν_{CO} 1650, ν_{NH_2} 2870 cm^{-1}.

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