NEW METHOD OF SYNTHESIS OF *D,L*-5-OXOPROLINE

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A new method was proposed for synthesis of D,L-*5-oxoproline from N-acetyl-*L-*glutamic acid in weakly acid medium in the presence of water, and hydrolysis of an acetyl group and cyclization and total racemization of the acid simultaneously take place. The advantage of the method is the possibility of obtaining two individual amino acids with high yields in one chemical process using* L-*glutamic acid.*

The interest in 5-oxoproline (II) and its derivatives in the form of optical isomers and racemates is not decreasing and is due to expansion of the area of application of these compounds both as drugs and in cosmetics [1, 2]. Data have recently appeared on the use of *D*-II and *D,L*-II derivatives as biologically active substances. Of the amides of II having nootropic activity, the *D*-amides and *D,L*-amides of II had higher activity than one of the most effective existing analogs of piracetam, aniracetam [3].

There are several methods of preparation of racemate (II): from *D*-glutamic acid via its α-ethyl ester hydrochloride, formation of ammonium salt II, and separation of the free acid with hydrogen sulfide [4]; cyclization of *L*-glutamic acid at high (approximately 200°C) temperature [5]; by a microbiological method from *L*-glutamic acid in nutrient medium with pH 6.8 containing 0.5% glucose, 0.5% yeast extract, 2% casein hydrolysate, and inorganic salts in the presence of *Pseudomonas cruciv* under the effect of glutamate dehydrase in aerobic conditions [6].

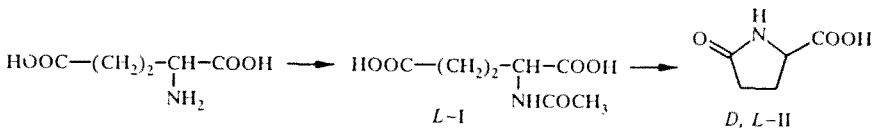
We conducted systematic studies on synthesis of 5-oxoproline and *L*-glutamic acid derivatives. In particular, N-acetyl-*L*-glutamic acid (I), a component of a drug with a nootropic action, demanol aceglumate (DEMANOL), is one of these compounds.

The method of acylation of *L*-glutamic acid with acetic anhydride in the presence of water was selected as the basis in developing the method of synthesis of compound I [7]. Reproduction of the US patent [7] in laboratory conditions showed that the direct yield of compound I does not exceed 60%, and a significant part of the target product remains in the mother liquor, which also contains acid I, impurities of amide II and the starting acid, other unidentified compounds, acetic acid, and water.

We developed conditions in which an additional amount of optically pure acid I can be obtained from the mother liquor. The mother liquors were treated by removing the solvent in different conditions with subsequent crystallization of the residue at 5-10°C. In the optimum version, 20-22% of technical acid I was additionally extracted from the mother liquor, and after recrystallization from water, it was an optically pure enantiomer.

It was found during the study that acid I is almost quantitatively converted into compound II at atmospheric pressure and 100-120°C. After recrystallization from 90% acetone, a product with a melting point of 181-183°C and specific rotation equal to zero was obtained; according to the published data, it corresponds to compound II [8, 9]. The individuality and structure of the substance were confirmed by thin-layer chromatography and spectral analysis.

Cyclization of compound I with simultaneous racemization is of interest because it is accompanied by splitting of the acetyl group in dilute (50%) acetic acid medium.



L-I *D, L*-II

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Racemization of optically active acid I (in the *D* or *L* form) takes place in glacial acetic acid medium under the effect of acetic anhydride in the amount of 0.1-0.5 M per 1 M of *D*- or *L*-glutamic acid. In formation of compound II, cyclization of the acid and racemization and hydrolysis of the acetyl group take place in weakly acid medium in the presence of water.

A new method of obtaining *D,L*-oxoproline not described in the literature is thus proposed. In addition, the method has the advantage that two individual amino acids I and II are obtained with high yields in one chemical process.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-75 in suspension in petrolatum.

The data from elemental analysis of compounds I and II obtained on a Carlo Erba CHNS 1108 automatic analyzer corresponded to the calculations. The course of the reactions and the individuality of the compounds obtained were analytically controlled by TLC on Silufol UV-254 plates in the solvent — *n*-butanol—glacial acetic acid—water system, 40:15:10, development with chlorotolidine reagent. The melting point of the compounds obtained was determined on a PTP instrument. The angle of optical rotation was measured on a Polomat A polarimeter.

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N-Acetyl-*L*-glutamic Acid (I, $C_7H_{11}NO_5$). It was synthesized from 20 g of *L*-glutamic acid with the modified method in [7] and purified by recrystallization from water (1:4) with preliminary purification of the aqueous solution with active carbon. After recrystallization, 14.6 g (0.077 mole) of pure acid I was obtained (58% yield). Mp = 195-197°C; $[\alpha]_D^{20} = -15.7$ (3%, water); IR spectrum: 3720, 3120, 1940, 1705, 1575 cm^{-1}. The filtrate obtained in the stage of acetylation of *L*-glutamic acid was used for preparation of acid II.

***D,L*-5-Oxoproline (II, $C_5H_7NO_3$).** Here 96.2 ml of mother liquor containing 4% acid I was heated in an oil bath to a temperature of 100-120°C for 1 h. The solution was then concentrated to 1/8 of the initial volume at atmospheric pressure and 110-120°C, yielding 2.0 g of technical acid II, purified by recrystallization from 90% acetone (1:5). A water—acetone solution of the acid was heated to 50°C, 0.2 g of active carbon was added and stirred for 15 min, and the carbon was filtered off. The filtrate was cooled to 5-10°C and crystallized for 5 h, yielding 1.6 g (0.012 mole) of compound II. Mp = 181-183°C; $[\alpha]_D^{20} = 0$ (3%, water); IR spectrum: 3305, 2720, 1950, 1710, 1620 cm^{-1}.

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