SYNTHESIS OF RACEMIC α-AMINO ACIDS OF THE SERIES OF 4- AND 7-AZAINDOLES*

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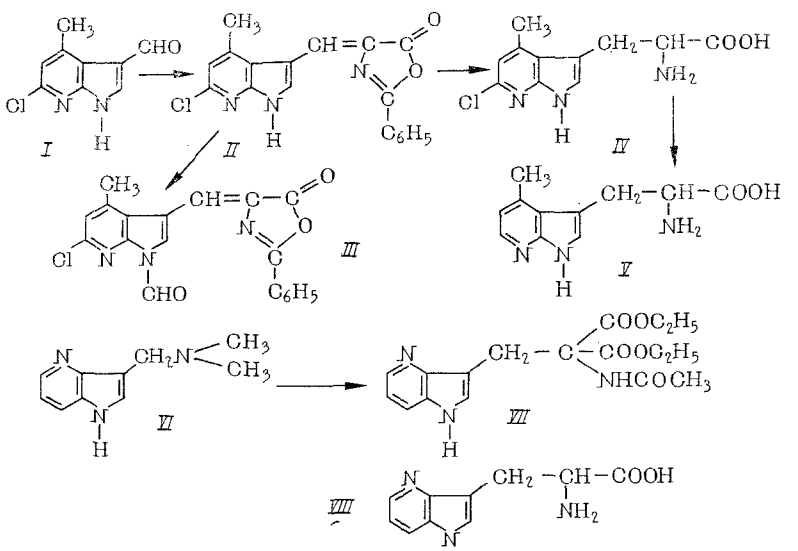
UDC 615.31:547.757].012.1

The natural α-amino acids participating in the composition of the proteins are of vital importance for the normal function of the human organism. The variation of the structure of these compounds opens the way for an active intervention into the metabolism of proteins, peptides, enzymes, hormones and other biologically important products the biosynthesis of which is realized based on amino acids. Among the different methods of modifying the structure of one of the irreplaceable amino acids, tryptophan, attention is attracted to the production of the azaanalogs of this compound which preserve the size and configuration of the natural product but differ in the distribution of the electron density inside the molecule. Before our studies, out of this type of compound only 7-azatryptophane has been described [1], which enters biological and biochemical tests on competitive terms with the natural amino acid: it inhibits the utilization of tryptophan by Tetrahymena pyriformis [2] and replaces tryptophan reaction of the latter with proteins of the E. coli and bacteriophage T-2 [3] blocking the formation of carbamyltransferase and D-serinedeaminase [4]. According to the private communication of Willett (USA), 5-methyl-7-azatryptophan has also interesting biological properties.

In the present paper the synthesis is described of the hitherto unknown 4-methyl-7-azatryptophan and the 6-chloroderivative thereof and of the first amino acid representative of the 4-azaindole series, 4-azatryptophan.



For the synthesis of racemic α-amino acids of the 7-azaindole series we used the general scheme, previously suggested by one of us together with M. V. Rubtsov [5], for obtaining substituted 7-azatryptophans from 3-formyl-7-azaindoles through derivatives of 2-phenyl-4-azaindolylmethylene-1,3-oxazolones-5.

*Communication XXXIII of the series "Azaindole Derivative."

S. Ordzhonikidze All-Union Scientific Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, No. 11, pp. 16-19, November, 1968. Original article submitted July 8, 1968.

3-Formyl-4-methyl-6-chloro-7-azaindole (I) [6], easily obtainable by the Vilsmeier reaction from the corresponding azaindole non-substituted in position 3, was brought into reaction with hippuric acid in acetic anhydride medium. The azalactone forming with yield of 56% dissolved with difficulty in water and the common organic solvents; it was only soluble in hot dimethylformamide, but after short heating already crystals soon separated from the hot dimethylformamide.the substance obtained had poorer solubility, gave a decrease of the melting point in the test of mixing with II, and according to the analytical data it proved to be the N-formyl derivative of II, 2-phenyl-4-(1'-formyl-4'-methyl-6'-chloro-7'azaindolyl-3'-methylene)-1,3-oxazone-5 (III).

To convert II into 4-methyl-6-chloro-7-azatryptophan (IV) the conventional method was used of reducing by hydriodic acid in the presence of red phosphorus with simultaneous splitting of the azalactone ring. The yield of substituted 7-azatryptophan (IV) was 55.5%. Unlike the analogous N-phenyl derivatives [5] non-substituted at the pyrrole nitrogen, II and IV form stable crystal hydrates. On conversion of II into the N-formyl derivative III the capability of the compound of retaining the water of crystallization decreases sharply.

The synthesis of 4-methyl-7-azatryptophane (V) was effected starting from the corresponding 6-chloroderivative (IV) by dehalogenation with sodium in liquid ammonia. Like in the case of other derivatives non-substituted at the pyrrole nitrogen V was separated as a stable crystal hydrate.

Unlike the 7-azaindole derivatives, where the 3-formyl substituted compounds are readily available, in the 4-azaindole series the introduction of the aldehyde function into position 3 proved a difficult task. Hence, for the synthesis of 4-azatryptophane (VIII) another scheme was applied which is based on the reaction of 4-azagramine (VI) with acetylaminomalonate and subsequent saponification and partial decarboxylation of the intermediate product 3-(β,β-dicarbethoxy-β-acetylaminoethyl)-4-azaindole (VII). Unlike analogous conversions of 7-azaindole compounds [1] the abovementioned reactions in the 4-azaindole series proceeded very smoothly and allowed to obtain 4-azatryptophan (VIII) with a total yield of 93.4% in 2 stages.

EXPERIMENTAL

2-Phenyl-4-(4'-methyl-6'-chloro-7'-azaindole-3'-methylene)-1,3-oxazolone-5 (II). A mixture of 0.5 g (2.5 in M) 3-formyl-4-methyl-6-chloro-7-azaindole (I) [6], 0.4 g (2.5 in M) hippuric acid and 0.2 g (2.5 in M) sodium acetate in boiled for 6 h with 5 ml freshly distilled acetic anhydride. During the boiling of the heterogeneous reaction mixture the gradual dissolution of the precipitate and the separation of crystals of II are observed. When the reaction is complete the mixture is cooled to 5° and placed during the night into the refrigerator. The crystals precipitated are filtered off and washed carefully first with ether and then with water. After drying 0.5 g (56%) II with mp 256° is obtained. The substance is poorly soluble in alcohols, acetone, chloroform, benzene, ethylacetate and ether and insoluble in water. Found, %: C 60.53; H 3.99; N 11.51; Cl 9.91. $C_{18}H_{12}N_3O_2Cl \cdot H_2O$. Calculated, %: C 60.76; H 3.94; N 11.81; Cl 10.00.

On boiling 0.1 g II with 3 ml. dimethylformamide for 3 min the precipitate dissolves completely, and then crystals of III with mp 272° which are insoluble in hot dimethylformamide precipitate. The substance is insoluble in water and the common organic solvents. IR spectrum: 1660 cm^{-1} (N–C=O), 1730 cm^{-1} (O–C=O). Found, %: C 62.02; H 3.77; N 11.35; Cl 9.33. $C_{19}H_{12}N_3O_3Cl$. Calculated, %: C 62.38; H 3.67; N 11.49; Cl 9.73.

4-Methyl-6-chloro-7-azatryptophane (IV). To a mixture of 5.9 g (16 mM) II, 1.47 g (47 mM) red phosphorus,and 35 ml acetic anhydride 50 ml freshly distilled hydriodic acid is added. Foaming and warming up of the reaction mixture are observed. Then, the reaction mixture is still boiled for 6 h, the red phosphorus is filtered off and the filtrate is evaporated in vacuo to dryness. The residue is dissolved in 30 ml water and carefully alkalized by sodium bicarbonate to pH 5.0. The reaction mixture is placed during the night into the refrigerator. The crystals of IV precipitated are filtered off, washed with water, then with acetone and dried in vacuo. Yield of IV 2.5 g (55.5%), mp 285°. The substance is poorly soluble in water and the common organic solvents, but readily soluble in hot water. Found, %: C 43.80; H 5.62; N 13.80; Cl 11.85. $C_{11}H_{12}N_3O_2Cl \cdot 2.5H_2O$. Calculated, %: C 44.22; H 5.69; N 14.07; Cl 11.89.

Hydrochloride, colorless crystals, mp 287° (from aqueous acetone). The substance is poorly soluble in chloroform, benzene and acetone; it is more soluble in alcohols and water. Found, %: C 45.17; H 6.40; N 14.76; Cl 24.25. $C_{11}H_{12}N_2O_2Cl \cdot HCl$. Calculated, %: C 45.52; H 4.48; N 14.48; Cl 24.48.

4-Methyl-7-azatryptophan (V). Over 0.6 g (2 mM) IV 50 ml liquid ammonia is poured, stirred for 10 min and then 0.23 g (10 mM) sodium metal is added gradually in small portions. After 2-h stirring 25 ml liquid ammonia is added and stirring is continued for 2 h. Then the ammonia is evaporated and after decomposition of the excess sodium by methanol the residue is dissolved in 5 ml water. The solution obtained is purified by activated carbon and carefully acidified with concentrated hydrochloric acid to pH 5.0. The precipitate of V separated after the reaction mixture has been kept during the night in the refrigerator is filtered off and dissolved again in 4 ml distilled water. The solution obtained is rid of insignificant admixtures by filtration and diluted with acetone. In the shape of crystals 0.25 g (52.5%) V precipitates as colorless crystals, mp 262° (from water). The substance is insoluble in ether, benzene and acetone, poorly soluble in alcohol and water in the cold. It is readily soluble in hot water. Found, %: C 55.93; H 6.06; N 17.54. $C_{11}H_{13}N_3O_2 \cdot H_2O$. Calculated %: C 55.70; H 6.33; N 17.72.

3-(β,β-Dicarbethoxy-β-acetylaminoethyl)-4-azaindole (VII). A mixture of 1 g (5.7 mM) 4-azagramine (VI), 1.24 g (5.7 mM) acetaminomalonate, 0.05 g ground caustic soda and 15 ml anhydrous xylene is boiled for 10 h. The hot xylene solution is filtered from the alkali. The alkali is washed with warm benzene. The united xylene-benzene solutions are cooled; at the same time crystals of VII precipitate. Yield 1.02 g, mp 142-143°. The substance is readily soluble in alcohols and chloroform, poorly soluble in ether, benzene, and water. Found, %: C 58.91; H 6.36; N 11.92. $C_{17}H_{22}N_3O_5$. Calculated, %: C 58.60; H 6.36; N 12.06.

According to the data of thin layer chromatography with silicagel (mobile phase: methanol–benzene, 1:3) the xylene solution contains VII (R_f 0.25, detection by irradiation with ultraviolet rays or treatment with iodine vapors) and traces of the initial VI (R_f 0.00). The xylene is distilled in vacuo to dryness. The residue is triturated with ether and 0.56 g VII is obtained additionally. Total yield of VII 1.58 g (79.4%).

The ethereal mother liquor equally contains considerable quantities of VII according to the data of thin layer chromatography with silicagel. To utilize them the ether is evaporated in vacuo and the residue (0.42 g) is subjected to saponification and partial decarboxylation using the method described below. Owing to a corresponding treatment 0.10 g (8.5%) 4-azatryptophane (VIII) is obtained; mp 269-272° (decomp.).

4-Azatryptophane (VIII). 1 g (2.9 mM) VII is boiled for 7 h with 10 ml concentrated hydrochloric acid. The reaction mixture is evaporated in vacuo to dryness. To the residue a dilute ammonia solution (about 5 ml) is added up to pH 8.0. The solution obtained is diluted by an equal volume of acetone and cooled in the refrigerator. A colorless precipitate of crystalline VIII separates. Yield 0.5 g (94.3%), mp. 272-274° (decomp.). The substance is poorly soluble in ether, benzene, acetone, chloroform, better in alcohol and water on heating. Found, %: C 58.45; H 5.63; N 20.57. $C_{10}H_{11}N_3O_2$. Calculated, %: C 58.52; H 5.40; N 20.48.

LITERATURE CITED

1. M. M. Robison and B. L. Robison, J. Am. Chem. Soc., 77, 457 (1955).
2. G. W. Kidder and V. C. Dewey, Biochim. Biophys. Acta, 17, 288 (1955).
3. A. A. Pardee, V. G. Shora, and L. S. Prestidge, Ibid., 21, 406 (1956).
4. A. A. Pardee and L. S. Prestidge, Ibid., 27, 330 (1958).
5. L. N. Yakhontov and M. V. Rubtsov, Chemistry of Heterocyclic Compounds [in Russian] (1967), p. 141.
6. L. N. Yakhontov, M. Ya. Uritskaya, and M. V. Rubtsov, Zh. Organ. Khim., No. 1, 2032 (1965).