INDOL DERIVATIVES. 48. SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF N-L-α'-GLUTAMYL-α-ETHYLTRYPTAMINE

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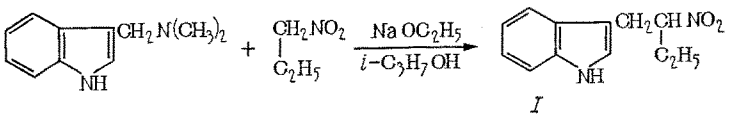
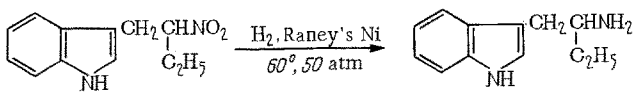
As the pharmacological study of amino acid derivatives of 5-methoxy-α-methyltryptamine [1] and α-methyltryptamine [2] has shown, on introduction of an amino acid radical into the side chain the pharmacological properties of these biogenous amines improve. Thus, the glutamyl derivative of α-methyltryptamine (N-L-α'-glutamyl-α-methyltryptamine), like α-methyltryptamine hydrochloride (indopane), an active stimulant of the central nervous system, has a less sudden and more prolonged action [2].

With the object of studying the pharmacological properties of the glutamyl derivative of α-ethyltryptamine, we synthetized this compound from α-ethyltryptamine [3, 4] obtained as follows:



I



II

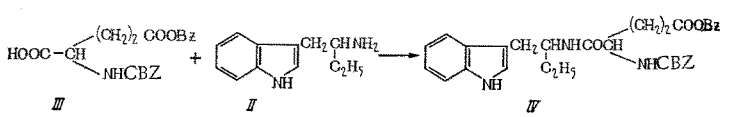
Carrying out the condensation reaction of gramine with 1-nitropropane in excess nitroalkane in the presence of solid NaOH according to the method of [5] the condensation product 3-(2'-nitrobutyl)indole (I) owing to a complex treatment of the reaction mixture was separated as a high-boiling oil which was indicative of the insufficient purity of the substance. Recently, however, Heath-Braun et al. [6] have carried out successfully the condensation of nitroalkanes with gramine in the presence of dimethyl sulfate (in this case gramine reacts as a quaternary ammonium salt) and sodium ethylate as a catalyst.

Applying this method to the production of 3-(2'-nitrobutyl) indole, we were able to show that under conditions of a marked dilution of the reaction mixture by isopropyl alcohol the reaction product is obtained at once in the crystalline state with a high yield, about 90% of the theoretical value.

By catalytic hydrogenation at a high pressure in the presence of Raney's nickel as a catalyst α-ethyltryptamine (II) was obtained with a yield of 95%. The amine was separated from the reaction mixture in the crystalline state so that it was not necessary to convert it into some derivative as in the production of α-ethyltryptamine by reduction of α-scatolydene nitropropane by lithium alumohydride [7].

α-Ethyltryptamine was defined by several derivatives: hydrochloride, adipinate, and picrate.

N-L-α'-Glutamyl-α-ethyltryptamine (V) was obtained analogously to the corresponding derivatives of α-methyltryptamine [2] by the method of mixed anhydrides from CBZ*-L-glutaminic acid γ-benzyl ester (III) and α-ethyltryptamine (II):



III II IV

*CBZ = carbobenzoxy.

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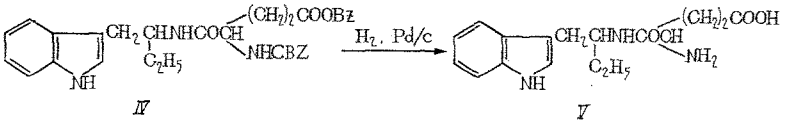
The separation of the free amino acid (V) from the protected product (IV) was effected by hydrogenation of the product (IV) above a Pd catalyst:



IV V

N-L-α'-Glutamyl-α-ethyltryptamine (V) was defined by the values R_f and $[\alpha]_D^{20}$.

The pharmacological study of N-L-α'-glutamyl-α-ethyltryptamine (V) was carried out in comparison with the structurally similar N-L-α'-glutamyl-α-methyltryptamine (VI), the glutamyl analog of indopane which is a stimulant of the central nervous system, but with a less marked exciting influence on the adrenoreactive systems of the organism [2]. Unlike N-L-α'-glutamyl-α-methyltryptamine, V is poorly soluble in water. On heating only a 0.5% solution can be obtained; hence, in comparative pharmacological studies usually 1 and 2% suspensions of the preparations in sizing are used.

The action of the preparations on the central nervous system was judged by the antagonism with the depressing effects of reserpine, the change of the general state of the animals and their motor activity (tests with white mice). The parameters of the influence on the adrenoreactive systems were the variations of the arterial pressure and the tonus of the musculus palpebralis tertius after intravenous injection to anesthetized cats and the changes of the lumen of blood vessels in the isolated ears of rabbits perfused with solutions of the preparations studied. The toxicity was compared by oral administration to white mice.

Like VI, V has a stimulating action on the central nervous system; it enhances the motor activity and the reflex excitability, in mice it causes stereotypy; the presence of the phenomenon of group toxicity was noted. But V is markedly inferior to VI in all parameters.

The lower stimulating activity of the preparation is confirmed in a special series of tests studying the individual and group toxicity. It was ascertained that V is less toxic than VI and at the same time the ratio of the individual to the group toxicity is somewhat lower than in VI: on oral administration of V the V LD_{50} for single mice is 460 mg/kg, for group mice 145 mg/kg, i.e., the index is 3.1; on administration of VI the LD_{50} is 202.5 mg/kg and 52.5 mg/kg, respectively, and the index is 3.85. The lower stimulating activity of V as compared to VI was also confirmed studying the motor activity of white mice by the actometric method. V inhibits less than VI the approach of ptosis and hypothermia after the use of reserpine. Unlike VI it has no stimulating effect on the peripheral adrenoreactive systems of the organism: it causes no rise of the arterial pressure, no peripheral vasoconstriction, and no contraction of the musculus palpebralis tertius.

EXPERIMENTAL

3-(2'-nitrobutyl)indole (I). To a solution of sodium ethylate composed of 1.46 g Na and 30 ml absolute ethanol 310 ml isopropyl alcohol is poured and 16.8 g nitropropane and 10.2 g gramine are added. Within 25 min 14.6 g dimethyl sulfate dissolved in 90 ml isopropyl alcohol is added at a temperature of the reaction mixture not exceeding 35°. It is allowed to stand during the night, then diluted by an equal volume of water and stirred thoroughly for 1-2 h. The pale yellow precipitate separated is filtered off, washed with water and dried in the air. Yield: 11.7 g (91%) of the substance with mp 90-92° (according to literature data, mp 90-91°).

The hydrogenation of 3-(2'-nitrobutyl)indole to α-ethyltryptamine is carried out in the autoclave in the presence of Raney's Ni in ethanol medium at 60° and an initial pressure of 50 atm. When the uptake of hydrogen is complete (after 3-4 h) the catalyst is filtered off and the filtrate is evaporated in the vacuum of a water-jet pump. The crystalline residue is treated with benzene and again the solvents are distilled off to dryness. From 11.5 g (I) one obtains 9.5 g α-ethyltryptamine (II) in the shape of a pinkish powder with mp 93-97°. After recrystallization from aqueous methanol, mp 104-105° (according to literature data mp 97-99° [8], 101-102° [6]). Found, %: C 76.74; H 8.77; N 14.83. $C_{12}H_{16}N_2$. Calculated, %: C 76.54; H 8.56; N 14.82.

α-Ethyltryptamine Hydrochloride. Mp 218-219° (according to literature data, mp 215.5-218° [7], 222-223° [8]). Found, %: N 12.73. $C_{12}H_{16}N_2 \cdot HCl$. Calculated, %: N 12.47

α-Ethyltryptamine Adipinate. Mp 212-213° (from ethanol). Found, %: N 10.49. $C_6H_{10}O_4 \cdot 2C_{12}H_{16}N_2$. Calculated, %: N 10.73.

α-Ethyltryptamine Picrate. Mp 202° (decomp.) (according to literature data [9], mp 198-204°). Found, %: N 16.59. $C_6H_{33}O_7 \cdot C_{12}H_{16}N_2$. Calculated, %: N 16.79.

CBZ-L-glutaminic Acid γ-Benzyl ester (III) was obtained according to the method of [10] with mp 73-75°.

CBZ-L-α'-glutamyl-α-ethyltryptamine γ-Benzyl Ester (IV). 13 g CBZ-L-glutaminic acid γ-benzyl ester is dissolved in 80 ml dry tetrahydrofuran (THF), 5.6 ml triethylamine is added at a temperature of -8 to -10°, the mixture is stirred from 10-15 min at the same temperature, 5.6 ml chlorocarbonic acid isobutyl ester is added, stirred again for 15 min at -10°, then 6.58 g α-ethyltryptamine dissolved in 150 ml (THF), is added and the mixture stirred again for 1 h at -10° and for 1.5 h at room temperature. The precipitate is filtered off and washed with (THF), the filtrate is evaporated in vacuo and the residue is dissolved in 300 ml ethyl acetate. The ethyl acetate solution is washed with 0.5 N HCL solution, 5% $NaHCO_3$ solution, and water. The organic layer is led into a flask, 200 ml benzene is added and the solvents are distilled. The almost completely crystallized residue is diluted with an equal volume of hexane, a white precipitate is filtered off and washed with a mixture of ethyl acetate and hexane. On further dilution of the filtrate an additional quantity of the reaction product is separated. Total yield 13.8 g (73% of the theoretical). Mp 155-157° (from a 10:1 benzene-hexane mixture). Found, %: C 71.01; H 6.49; N 7.73. $C_{32}H_{35}N_3O_2$. Calculated, %: C 70.98; H 6.47; N 7.76.

N-L-α'-Glutamyl-α-ethyltryptamine (V). 10.8 g (0.02 mole) IV is hydrogenated in the autoclave in 300 ml ethanol above 1 g 10% Pd/C at 50° and an initial pressure of 40 atm for 4-5 h. The catalyst is filtered off, the filtrate is evaporated in a nitrogen flow to a volume of 50 ml. The residue is transferred into a glass and placed into the refrigerator. The fine crystalline reaction product is filtered off and washed with methanol. Additionally, a substance is separated on dilution of the filtrate with dry ether. The total yield of the reaction product (pinkish powder) is 5.2 g (82.5% of the theoretical). Mp 175-176° (white powder after reprecipitation from methanol by dry ether). Found, %: C 64.40; H 7.38; N 13.11. $C_{17}H_{23}N_3O_3$. Calculated, %: C 64.35; H 7.25; N 13.21. R_f 0.82 (n-butanol-acetic acid-water, 4:1:5), $[\alpha]_D^{20}$ 29° (with 1.3%, methanol).

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