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INDOLE DERIVATIVES

XLV.* CYCLIZATION OF 2-(β-AMINOISOBUTYL)INDOLE WITH GLUTARIC ANHYDRIDE AND OPIANIC ACID

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UDC 547.759.3

New γ-carboline derivatives were synthesized on the basis of the reaction of 2-(β-aminoisobutyl)-indole with glutaric anhydride and opianic acid.

It is known [2] that indoles condensed with quinolizine or indolizine rings, derivatives of which have pronounced pharmacological activity, can be obtained by reaction of tryptamines with 1,4- and 1,5-dicarbonyl compounds. In connection with the fact that we have previously [3] developed the synthesis of compounds of the isotryptamine series, in particular, 2-(β-aminoisobutyl)indole (I), we undertook a study of the reactions of I with glutaric anhydride (II) and opianic acid (III). The reaction of I with II proceeds smoothly to give glutaric acid polyamide (IV), which was converted to ester (V) by the action of diazomethane. Under the influence of phosphorus oxychloride, ester V undergoes cyclization to a substituted 1,2-dihydro-γ-carboline, and, depending on the conditions used to work up the reaction mixture, the ester grouping is retained or undergoes partial hydrolysis to give, respectively, acids VIa and VIb. Ester VIb was converted to a substituted 1,2,3,4-tetrahydro-γ-carboline (VII) by hydrogenation over platinum. (See scheme on following page.)

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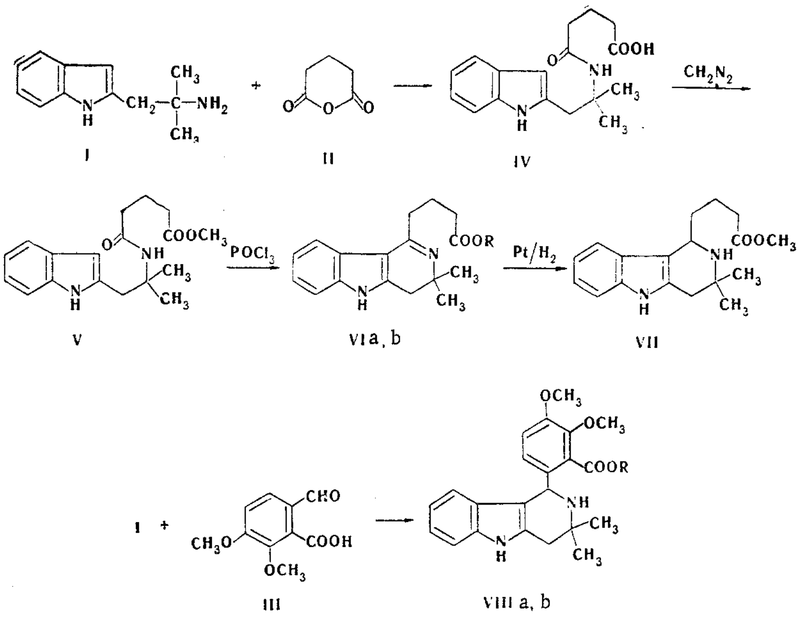
*See [1] for communication XLIV.

TABLE 1. Data on IV-VIII

Compound	mp, °C*	Empirical formula	Found, %				Calculated, %				Yield, %
			C	H	Cl	N	C	H	Cl	N	
IV	159,5—161	$C_{17}H_{22}N_2O_3$	67,3	7,3		9,2	67,5	7,3		9,3	60
V	82—83	$C_{18}H_{24}N_2O_3$	68,5	7,7		9,2	68,3	7,6		8,8	93
VIa	251—252	$C_{17}H_{20}N_2O_2$	71,9	7,3		10,1	71,8	7,1		9,8	50
VIb	143,5—145	$C_{18}H_{22}N_2O_2 \cdot HCl$	64,3	6,8	10,4	8,4	64,5	6,9	10,6	8,4	85
VII	191—192	$C_{18}H_{24}N_2O_2 \cdot HCl$	64,1	7,5	10,4	8,4	64,2	7,5	10,5	8,3	75
VIIIa	216—217	$C_{23}H_{26}N_2O_4 \cdot HCl$	63,7	6,2	8,0	6,7	64,1	6,3	8,2	6,5	83
VIIIb	204—205	$C_{24}H_{28}N_2O_4 \cdot HCl$	64,5	6,5	8,0	6,7	64,8	6,5	7,9	6,3	55

*Compounds V, VIIIa, and VIIIb were recrystallized from alcohol, V was recrystallized from benzene–petroleum ether, VIa and VII were recrystallized from isopropyl alcohol–ether, and VIb was recrystallized from methanol.

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1630-1632, December, 1976. Original article submitted November 17, 1975.



VI a R=H, b R=CH_3; VIII a R=CH_3, b R=C_2H_5

Tetrahydro-γ-carbolines with an aromatic ring in the 4 position (VIIIa, b) were synthesized as a result of cyclization of I with acid III in methanol or ethanol in the presence of acid.

Attempts to bring about the intramolecular cyclization of VII and VIII by refluxing in xylene were unsuccessful; this can be explained by the steric hindrance created by the gem-dimethyl groups.

EXPERIMENTAL

The PMR spectra of the compounds were recorded with a Varian T-60 spectrometer on the δ scale with hexamethyldisiloxane as the internal standard. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. Thin-layer chromatography (TLC) was carried out on plates with activity IV aluminum oxide (alkaline form).

2-{β-[N-(ω-Carboxybutyryl)]aminoisobutyl} Indole (IV). A solution of 10 g (0.053 mole) of I in 50 ml of absolute benzene was added to a solution of 6.6 g (0.052 mole) of anhydride II in 60 ml of absolute benzene, and the mixture was cooled to 15°. The liberated colorless oil was treated with aqueous sodium carbonate solution, and the alkaline solution was acidified with 2 N hydrochloric acid. The resulting precipitate was removed by filtration to give 9.7 g of IV. IR spectrum: 1716 (C=O) and 3380 cm^{-1} (NH).

2-{β-[N-(ω-Carbomethoxybutyryl)]aminoisobutyl} Indole (V). A 7.25-g (0.024 mole) sample of powdered indole IV was added in portions to a solution of diazomethane in ether, and the ether solution was partially evaporated on a water bath and allowed to stand overnight. The resulting oil was triturated to give 7.1 g of ester V with R_f 0.8 (ether). IR spectrum: 1715 (C=O) and 3355 cm^{-1} (NH).

2,2-Dimethyl-4-(γ-carboxypropyl)-1,2-dihydro-γ-carboline (VIa) and 2,2-Dimethyl-4-(γ-carbomethoxypropyl)-1,2-dihydro-γ-carboline (VIb) Hydrochloride. A mixture of 2 g (6.3 moles) of ester V in 20 ml of absolute benzene and 4 ml of freshly distilled phosphorus oxychloride was refluxed with distillation for 15 min, after which it was evaporated to dryness, 6 ml of water was added to the residue, and the solid material was removed by filtration to give 1.8 g of the hydrochloride of VIb.

When the phosphorus oxychloride was not removed completely by distillation, after treatment of the mixture with water, the ester underwent partial hydrolysis to give a mixture of 1 g of VIa and 1 g of VIb. The R_f value of VIb was 0.25 (ether). IR spectrum of VIb: 1729 (C=O) and 3360 cm^{-1} (NH).

2,2-Dimethyl-4-(γ-carbomethoxypropyl)-1,2,3,4-tetrahydro-γ-carboline (VII) Hydrochloride. A 2.4-g sample of VIb was hydrogenated in 30 ml of methanol over Pt (from 0.13 g of PtO_2) until hydrogen absorption ceased. The catalyst was separated, and the alcohol was removed by vacuum distillation. The residue was dissolved in absolute ether, and a solution of hydrogen chloride in ether was added to precipitate 2.1 g of the hydrochloride of VII with R_f 0.53 (ether). IR spectrum: 1730 (C=O) and 3492 cm^{-1} (NH). PMR spectrum (in CCl_4):

1.03 and 1.2 (two nonequivalent C$-$CH$_3$ groups), 1.3 (piperidine ring NH), 1.4-2.7 (unresolved CH$_2$ signals, 8 H), 3.6 (COOCH$_3$), 4.13 (unresolved 4-CH signal), and 8.47 (indole NH).

2,2-Dimethyl-4-(2-carbomethoxy-3,4-dimethoxyphenyl)-1,2,3,4-tetrahydro-γ-carboline (VIIIa) Hydrochloride. A solution of 1 g (5.3 mmole) of I and 1.3 g (5.6 mmole) of acid III in 15 ml of methanol and 1.5 ml of concentrated sulfuric acid was refluxed for 3 h, after which it was poured into water, and the aqueous mixture was made alkaline with aqueous potassium carbonate solution and extracted with ether. The ether solution was washed with potassium carbonate solution and water, dried with magnesium sulfate, and treated with a solution of hydrogen chloride in ether to give 1.5 g of the hydrochloride of VIIIa with R 0.68 (ether). IR spectrum: 1728 (C=O) and 3485 cm^{-1} (NH). PMR spectrum (in CHCl$_3$), ppm: 1.1, 1.23 [C(CH$_3$)$_2$], 1.93 (piperidine ring NH), 2.5 (center of two doublets of geminal CH$_2$ protons with J = 16 Hz), 3.66, 3.7 (6H, C$-$OCH$_3$), 3.8 (CO$-$OCH$_3$), 5.06 (4-H), and 8.4 (indole NH).

2,2-Dimethyl-4-(2-carbethoxy-3,4-dimethoxyphenyl)-1,2,3,4-tetrahydro-γ-carboline (VIIIb) Hydrochloride. A mixture of 1 g (5.3 mmole) of I, 1.3 g (5.6 mmole) of acid III, and 7 ml of a 16% solution of hydrogen chloride in alcohol was refluxed for 1 h, after which it was cooled, made alkaline with aqueous potassium carbonate solution, and extracted with ether. The ether extract was washed with potassium carbonate solution and water, dried with magnesium sulfate, and treated with a solution of hydrogen chloride in ether to give 1.3 g of the hydrochloride of VIIIb.

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