SYNTHESIS AND BIOLOGICAL ACTIVITY OF 3-R-1,2,3,4-TETRAHYDRO-β-CARBOLINE DERIVATIVES

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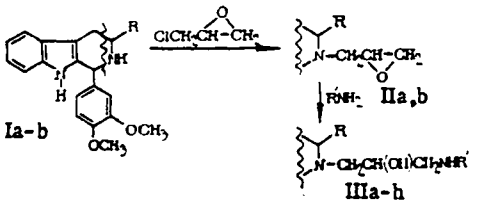
It is known from the literature that substituted tetrahydro-β-carbolines are compounds having a wide spectrum of biological activity, including hypotensive [4], analgesic [3], and psychotropic action [5, 6].

We have previously synthesized [7] new tetrahydro-β-carbolines containing an aminoalkyl group at the 2-position, which display psychotropic and antispasmodic activity.

In continuation of this research, and in order to study the influence of various substituents at the 2-position of the β-carboline ring on the pharmacological activity, we synthesized new tetrahydro-β-carbolines containing an aminopropanol substituent, which is a typical fragment of compounds acting on the adrenergic system [1].



R = H (Ia, IIa, IIIa-d); CH_3 (Ib, IIb, IIIe-h); R′ = CH_3 (IIIa, e); C_2H_5 (IIIb, f). $(CH_3)_2CH$ (IIIc, g); $(CH_3)_3C$ (IIId, h.

The starting compounds for the synthesis were 1-(3,4-dimethoxyphenyl)-3-R-1,2, 3,4-tetrahydro-β-carbolines (I) [7, 9], whose reaction with epichlotohydrin in the presence of sodium hydroxide gave 2,3-epoxypropyl-substituted β-carbolines (I).

The corresponding aminopropanol derivatives of the β-carboline series (IIIa-h) were obtained by the reaction of compounds II with aliphatic amines. Most of them are oily undistillable compounds; they were characterized in the form of dihydrochlorides.

EXPERIMENTAL CHEMICAL PART

The IR spectra were run in mineral oil on a UR-20 spectrophotometer (GDR). The TLC was carried out on aluminum oxide with grade II activity according to Brockman: II — in a chloroform–acetone (8:2) system of solvents, III — on UV-254 Silufol plates (CSSR) in a chloroform–alcohol (9:1) system. Iodine vapors were used as the developing agent.

1-(3,4-Dimethoxyphenyl)-2-(2,3-epoxypropyl)-1,2,3,4,-tetrahydro-β-carboline (IIa). A 1.8-g portion (0.02 mole) of epichlorohydrin is added in the course of 10 min, with stirring, to 6.16 g (0.02 mole) of tetrahydro-β-carboline Ia in 50 ml of benzene, maintaining the temperature of the reaction mixture in the range of 30-35°C. The mixture is stirred at this temperature for 30 min, and is then heated for 2.5 h at 70-75°C. It is then cooled and 2.2 g (0.022 mole) of a 40% aqueous solution of sodium hydroxide are added dropwise in the course of 20 min at 20-25°C. The mixture is stirred for 1 h at this temperature and for 2 h at 45-50°C. It is then cooled, the benzene solution is washed with water (3 × 15 ml), and the solvent is distilled off. The residue is dissolved in absolute ether, concentrated to a volume of 50 ml, passed through a column of aluminum oxide (200 g), and eluted with ether. The residue after the distillation of the solvent is an oily substance yield, 5.8 g (80%), R_f 0.57. Found, %: C 73.10; H 7.30; N 7.41. $C_{22}H_{24}N_2O_3$. Calculated, %: C 72.50; H 6.80) N 7.69.

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TABLE 1. 1-(3,4-Dimethoxyphenyl)-2-(hydroxy-3-alkylaminopropyl)-3-methyl-1,2,3,4-tetrahydro-β-carbolines IIIa-h

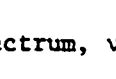
Compound	Yield, %	MP of hydrochlorides, °C	R_f	Found, %				Empirical formula	Calculated, %				IR spectrum ν_{max}, cm^{-1}
				C	H	N	Cl		C	H	N	Cl	
IIIa	64	242—3	0,78	70,32	8,0	10,6	—	$C_{23}H_{30}N_2O_3$	69,85	7,39	10,63	—	1600, 3200—3400
IIIa·2HCl	—		—	—	—	8,70	15,20	$C_{23}H_{32}Cl_2N_2O_3$	—	—	8,97	15,14	
IIIb	55	90—92*	0,48	71,00	7,60	10,50	—	$C_{24}H_{32}N_2O_3$	70,38	7,63	10,26	—	1600, 3200—3400
IIIb·2HCl	—		—	—	—	8,90	15,00	$C_{24}H_{34}Cl_2N_2O_3$	—	—	8,71	14,70	
IIIc	77	108—10	0,8	70,85	7,50	9,36	—	$C_{25}H_{34}N_2O_3$	70,89	7,85	9,92	—	1610
IIIc·2HCl	—		—	—	—	8,91	14,28	$C_{25}H_{36}Cl_2N_2O_3$	—	—	8,46	14,20	
IIId	88	180—82	0,65	72,07	8,80	9,40	—	$C_{26}H_{36}N_2O_3$	71,36	8,05	9,60	—	1600, 3200—3400
IIId·2HCl	—		0,65	—	—	8,39	14,00	$C_{26}H_{38}Cl_2N_2O_3$	—	—	8,23	13,89	
IIIe	62	85*	0,67	70,90	7,19	10,3	—	$C_{24}H_{32}N_2O_3$	70,38	7,63	10,26	—	1600, 3200—3400
IIIe·2HCl	—		—	—	—	8,50	14,90	$C_{24}H_{34}Cl_2N_2O_3$	—	—	8,71	14,70	
IIIf	87	190—92	0,61	70,65	8,00	9,70	—	$C_{25}H_{34}N_2O_3$	70,89	7,85	9,92	—	1600, 3200—3400
IIIf·2HCl	—		—	—	—	7,96	14,00	$C_{25}H_{36}Cl_2N_2O_3$	—	—	8,46	14,28	
IIIg	61	128*	0,66	71,90	8,84	9,70	—	$C_{26}H_{36}N_2O_3$	71,36	8,06	9,60	—	1600, 3200—3400
IIIg·2HCl	—		—	—	—	8,21	14,00	$C_{26}H_{38}Cl_2N_2O_3$	—	—	8,23	13,89	
IIIh	76	75*	0,69	71,47	7,80	8,93	—	$C_{27}H_{38}N_2O_3$	71,80	8,25	9,30	—	1610, 3200—3400
IIIh·2HCl	—		—	—	—	7,90	13,80	$C_{27}H_{40}Cl_2N_2O_3$	—	—	8,01	13,52	

*Melts with decomposition.

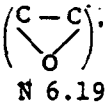
TABLE 2. Antispasmodic Activity and Toxicity Indexes of β-Carboline Derivatives and Puphemide

Compound	Antispasmodic activity towards electrical shock shock, ED_{50}, mg/kg	Toxicity, LD_{50}, mg/kg	Protective index, $PU = \frac{LD_{50}}{ED_{50}}$
IIb	126 (106,7—148,7)	220 (173—279)	1,75
IIIe	137 (128—147)	280 (244,5—320,6)	2,04
IIIa	170 (150—192)	235 (188—294)	1,38
Puphemide	77 (52,7—112,3)	2150 (1930—2390)	27,9

Note. Fluctuation limits are indicated in brackets.

IR spectrum, ν_{max}, cm^{-1}: 950, 1260  , 1620 (C-C atom.), 3360-3380 (NH ind.).

Hydrochloride of IIa, mp 125-126°C. Found, %: N 7.71; Cl 9.42. $C_{22}H_{25}N_2O_3Cl$. Calculated, %: C 6.99; Cl^- 8.86.

1-(3,4-Dimethoxyphenyl)-2-(2,3-epoxypropyl)-3-methyl-1,2,3,4-tetrahydro-β-carboline (IIb) was obtained in a similar way as IIa. Yield 73%, R_f 0.75. Found, %: C 73.20; H 7.28; N 7.38. $C_{23}H_{26}O_3N_2$. Calculated, %: C 73.03; H 6.87; N 7.40. IR spectrum, ν_{max}, cm^{-1}: 950, 1260  , 1620 (C=C arom.), 3360 (NH ind.). Hydrochloride of IIb, mp 115-117°C. Found, %: N 6.19; Cl^- 9.2. $C_{23}H_{27}ClN_2O_3$. Calculated, %: N 6.75, Cl^- 8.56.

1-(3,4-Dimethoxyphenyl)-2-(2-hydroxy-3-alkylaminopropyl)-3-substituted-1,2,3,4-tetrahydro-β-carbolines (IIIa-h). A 0.025-mole portion of the corresponding alkylamine in 50 ml of absolute alcohol is added dropwise to 0.01 mole of β-carboline II in 50 ml of absolute alcohol. The mixture is stirred for 6 h at room temperature and heated for 6 h at 40°C. The solvent is distilled off and precipitate is dissolved in ether. The ether solution is teated with a 10% solution of hydrochloric acid, the aqueous layer is made alkaline with sodium hydroxide, and extracted with ether. The ethereal layer is dried over sodium sulfate, concentrated to a volume of 50 ml, passed through a column of aluminum oxide (200 g), and eluted with ether.

The hydrochlorides are precipitated from the ethereal solution, and recrystallized from an ethanol—ether (1:1) mixture. The data for the compounds are given in Table 1.

In the mass spectra of the hydrochlorides there are several characteristic fragments. IIIf: m/z (I rel): 335 (15), 318 (16), 281 (9), 208 (16), 199 (22), 180 (44), 157 (57), 130 (100).

EXPERIMENTAL PHARMACOLOGICAL PART

The antispasmodic and β-adrenoblocking activities of 10 derivatives of 1,2,3-substituted β-carboline were examined.

The antispasmodic activity was studied on white mice each weighing 18-22 g. Electrical shock and spasms induced by the introduction of Corazole, nicotine, and arecoline served as spasmodic models. The compounds studied were administered intraperitoneally 30 min before the spasmodic agents or the application of electrical irritation.

A supramaximum current was used to induce the irritation. Prevention of tonic extension phase [12] served as an index of the antispasmodic activity. The method of minimal Corazole-induced paroxysm [11] was used for testing the compounds by the Corazole test.

The action on the spectral p^- and m-cholinergic system was evaluated from the ability of the compounds to prevent nicotine-induced spasms and arecoline tremor [2, 8].

The mean effective (RD_{50}) and toxic (LD_{50}) doses were determined by the Litchfield and Wilcoxon method [10]. The acute daily toxicity dosages of the compounds were determined in mice by intraperitoneal administration. Puphemide was used as the control preparation.

The β-adrenoblocking properties of the compounds were studied in experiments on nembutal narcoticized rats. The β-adrenoblocking activity was determined from the ED_{50} value according to the decrease in the positive chronotropic and depressant effect of isadrine (0.5 μg/kg). The compounds tested were introduced intravenously. The known β-adrenoblocking agent obzi-

dan (propranolol) was used as a control preparation.

The results of the investigations showed that all the derivatives of 1,2,3-substituted β-carbolines studied eliminate to a certain degree the tonic phase of the maximum electrical shock. The results of the evaluation of the most active among these compounds are given in Table 2.

Table 2 shows that among the compounds studied, compounds IIb, IIIe and IIIh, having 2,3-epoxypropyl, 2-methylaminopropyl- and 3-tert-butylaminopropyl groups, respectively, at the 2-position are the most interesting. In their activity and in the latitude of the pharmacological action, these compounds are much inferior to the anti-epileptic preparation puphemide of the succinimide group. The compound with an isopropyl radical at the 2-position (IIIg) cancels the tonic phase of the maximum electrical shock in a dose of 100/mg/kg in 60% of the animals. A further increase in the dose of this compound causes the death of the animals.

Compound having an ethylaminopropyl group at the 2-position (IIIb and IIIf) and also compounds IIa, IIIa, IIIc,d display weak anti-electrical shock activity.

All the compounds studied do not influence the Corazole-induced spasm in a dose of 200 mg/kg, and also do not prevent nicotine-induced spasms and arecoline tremor.

Compounds IIa and IIIc have weak β_2-adrenoblocking activity. Compounds IIb, IIIa,b,d-h do not act on β_1- and β_2-adreno-receptors.

Thus, in the 1,2,3-substituted derivatives of tetrahydro-β-carbolines, antispasmodic activity has been detected from the antagonism to the maximum electrical shock. It is of interest to note that the most active compounds (IIb, IIIe,g,h) contain a methyl group at the 3-position. Compounds having 2,3-epoxypropyl (IIa) and isopropylaminopropyl (IIIb) groups at the 2-position have weak β_2-adrenoblocking action.

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