RELATIONSHIP BETWEEN THE CHEMICAL STRUCTURE AND PHARMACOLOGICAL ACTIVITY OF CARBOLINE DERIVATIVES

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There has long been interest in carboline derivatives [1-3]. Derivatives of this group have newly attracted the attention of researchers, chiefly in connection with their ability to inhibit the activity of monoamine oxidase (MAO) and to influence the effects of cystamine and serotonin [4-9]. Certain compounds have a psychotropic action [10, 11]. However, up to the present time only two preparations among the carboline derivatives – harmine and diazoline – have found use in medical practice.

A new group of compounds has been synthesized at the Institute of Pharmacology of the Academy of Medical Sciences of the USSR: derivatives of hexahydro-γ-carboline [12, 13]. We have studied a number of preparations with various substituents in the aromatic and piperidine rings (Table 1) according to certain pharmacological indices (motor activity, suppression of aggression, and analgesic action). The experiments were conducted on white mice and rats. The preparations were injected subcutaneously in a dose of 10 μg/kg, with the exception of experiments on the determination of antiaggressive action, where the average effective doses were calculated.

The motor activity was measured within a 10-minute interval (according to the method of determining changes in the electric resistance during movement of the animals). Of the 21 compounds investigated, 12 preparations caused an inhibition of motor activity (Table 2). The strongest effect was given by preparation No. 16 and its analog (No. 14). More than half of the active compounds are derivatives of tetrahydro-γ-carboline. Harmine derivatives are the least effective. The activity of the compounds depends on the nature of the substituents in the 6-position of the aromatic ring. The introduction of bromine, carbethoxy, hydrazide, and diethylamide groups leads to a decrease in the activity (see Table 2, Nos. 14, 15, 9, 10). The position of the substituents has a significant effect on the activity of the preparations. Thus, 3,8-dimethyl-1,2, 3, 4, 4a, 9a-hexahydro-γ-carboline dihydrochloride is considerably less active than the 3,6-dimethyl derivative.

The overwhelming majority of the compounds have an antiagressive effect, while five preparations actually surpass the activity of aminazine (see Table 2). Preparation No. 16 is especially effective.

Among the derivatives of hexahydrocarboline, the greatest effect is also given by compounds with a methyl residue (see Table 2, Nos. 14 and 16). The significance of a substituent in the 6-position is also evident for derivatives of tetrahydrocarboline. In comparison with derivatives of α-carboline derivatives of β-carboline are less active. In contrast to aminazine, carboline derivatives have an antiaggressive effect in doses in which they do not cause any changes in the motor activity of the animals. As can be seen from Table 2, all the effective compounds, with the exception of one preparation, have an antiaggressive effect at substantially lower doses than those in which they cause an inhibition of motor activity.

The analgesic action was determined according to the threshold of sensitivity to an electrical pain stimulus in rats. Analgesic properties were detected for 13 preparations (see Table 2). A reduction of the pain sensitivity was noted after the injection of preparations Nos. 4 and 5 even at a dose of 5 mg/kg. Most of the derivatives of tetrahydro-γ-carbocholine proved active. Four compounds, Nos. 18-21 (among them,

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TABLE 1. Carboline Derivatives

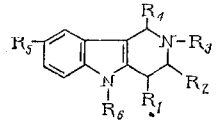
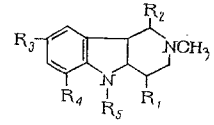
Preparation No.	R_1	R_2	R_3	R_4	R_5	R_6	Salt
							
1	H	H	CH_3	H	COOH	C_4H_9	HCl
2	H	H	CH_3	H	$COOC_2H_5$	C_4H_9	HCl
3	H	H	CH_3	H	COOH	H	HCl
4	H	H	CH_3	H	$COOC_2H_5$	H	HCl
5	H	H	CH_3	H	$COOC_2H_5$	H	CH_3
6	H	H	CH_3	H	$CONHNH_2$	H	HCl
7	H	H	CH_3	H	$CON(C_2H_5)_2$	H	HCl
8	H	H	CH_3	H	H	$(CH_2)_2N(CH_3)_2$	2HCl
9	H	$(CH_3)_2$	H	$(CH_3)_2$	H	$(CH_2)_2N(CH_3)_2$	2HCl
10	H	$(CH_3)_2$	H	$(CH_3)_2$	CF_3	$(CH_2)_2N(CH_3)_2$	2HCl
12	H	H	CH_3	H	$CH_2N(C_2H_5)_2$	C_4H_9	CH_3
13	H	H	CH_3	H	CH_3	H	HCl
							
14	H	H	H	H	H	—	2HCl
15	H	H	B_2	H	H	—	2HCl
16	H	H	CH_3	H	H	—	2HCl
17	H	H	CH_3	CH_3	H	—	2HCl

TABLE 1 (cont.)

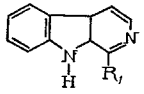
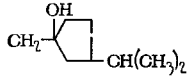
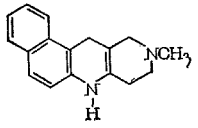
Preparation No.	R_1	R_2	R_3	R_4	R_5	R_6	Salt
							
18		—	—	—	—	—	CH_3I
19		—	—	—	—	—	CH_3I
20		—	—	—	—	—	HCl
21	$CH_2C(CH_3)_2OH$	—	—	—	—	—	HCl
11							HCl

TABLE 2. Pharmacological Activity of Carboline Derivatives

Preparation No.	Antiaggressive action, ED_{50} (in mg/kg)	Influence on motor activity (number of movements in 15 min)	Influence on pain sensitivity (threshold of sensitivity in V; number of observations in parentheses)		Toxicity, LD_{50} (in mg/kg)
Control	1,1 (0,8—1,7)	158 (129—252)	8,1±0,3	(560)	
1	2,4 (1,1—5,0)	167 (76—252)	13,4±2,1	(5)	45 (31—66)
2	3,9 (0,97—15,6)	116 (73—159)	12±3,6	(5)	55 (52—58)
3	Inactive	181 (104—258)	17,6±2,8	(5)	78 (54—112)
4	4,6 (2,8—7,7)	118 (84—152)	23±1,3	(10)	520 (423—640)
5	0,27 (0,04—1,0)	45 (23—67)	20±2,6	(10)	13 (8—21)
6	5,0 (1,5—16,5)	149 (95—203)	13±4,5	(4)	56 (43—73)
7	0,64 (0,38—1,1)	117±54	10±1	(6)	500 (383—640)
8	Inactive	65 (29—101)	25±2,7	(5)	72 (49—105)
9	14,0 (10—19,5)	95 (70—120)	8±1,9	(3)	88 (81—95)
10	2,8 (0,92—8,4)	136 (82—190)	Inactive		84 (64—109)
11	0,2 (0,13—0,3)	57 (30—87)	12±1	(7)	105 (103—107)
12	3,4 (1,1—10,9)	78 (53—103)	Inactive		35 (21—58)
13	Inactive	100 (64—136)	19±4	(5)	109 (101—113)
14	0,27 (0,11—0,65)	46 (28—68)	12±1,0	(8)	41 (26—63)
15	4,0 (1,1—14,8)	79 (25—133)	9±3,7	(8)	63 (52—76)
16	0,04 (0,03—0,08)	40 (28—52)	9±0,7	(10)	87 (80—95)
17	2,2 (1,8—2,7)	87 (24—150)	12±2,5	(3)	35 (30—41)
18	Inactive	115 (83—147)	20±1,1	(5)	42 (29—61)
19	0,56 (0,35—0,89)	117 (95—139)	18,7±3,7	(5)	43 (35—53)
20	3,6 (0,9—13,5)	198 (90—306)	12±1,5	(18)	58 (41—83)
21	6,5 (1,6—27,1)	98 (73—123)	11,0±1,4	(14)	53 (58—69)

No. 20 was named "carbidine"), are derivatives of β-carboline, and only No. 14 is a derivative of hexahydro-γ-carboline. The most effective preparations, Nos. 2 and 5, are the hydrochloride and methiodide of a 6-carbethoxy derivative of tetrahydro-γ-carboline, respectively.

Thus, as a result of our investigations we established the presence of pharmacological activity in a new group of carboline derivatives. These compounds have an inhibiting influence on the central nervous system, which is manifested in suppression of aggressive responses, inhibition of motor activity, and a reduction of the pain sensitivity. Certain compounds considerably surpass aminazine in individual types of action, which is primarily expressed in their influence on aggressive behavior and pain sensitivity.

From our experiments it follows that the introduction of substituents in the aromatic ring, and primarily into the 6-position of the ring, is of great significance for the pharmacological activity of the investigated compounds; it is reflected in all the investigated properties and is manifested most distinctly from the standpoint of the antiaggressive action. Among derivatives of hexahydro-γ-carboline the ability to reduce motor activity is most pronounced, whereas derivatives of β-carboline are considerably inferior to other preparations in this respect. Analgesic properties are characteristic of derivatives of tetrahydro-γ-carboline: most of these compounds have a moderate analgesic effect.

The relationship between the increase in the dose and the increase in analgesia even for the most active compounds is weakly expressed. They are considerably inferior to such analgesics as morphine or promedol, but at the same time surpass aminazine and analgesic agents of the pyrazoline in analgesic activity.

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