SYNTHESIS AND PSYCHOTROPIC ACTIVTY OF DIAMINES FROM THE ADAMANTANE SERIES

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Various amino derivatives of adamantane and other polycyclic hydrocarbons exhibit, besides a pronounced antiviral action [1, 2], a number of valuable psychopharmacological properties. For example, these compounds act as antidepressants and are also used in clinical practice as antiparkinsonic drugs [3]. The spectrum of psychotropic activity of these compounds is determined by the nature of amino substituents, their position in the polycyclic nucleus, and the basicity of the amino group [4]. In order to increase the assortment of potential psychotropic preparations with polyhedral structures, we have studied the psychopharmacological properties of diamines differing in the character of bonding of the primary amino group to adamantane nucleus in comparison with 1,3-diaminoadamantane (I) [5].

The previously described 1,3-di(aminoalkyl)adamantanes (II, III) were synthesized by deduction of the corresponding diamides of adamantanecarboxylic acids as described in [6]. The phenyl-containing diamines (IV, V) were obtained by condensation of N-acetylaminoalkyladamantanes with acetanilide in a medium of concentrated sulfuric acid in the presence of 65% nitric acid as oxidizer, followed by hydrolysis:

$$NH_2(CH_2)_n\text{–Ad–}(CH_2)_mNH_2$$

I – III

$$AcNH(CH_2)_n\text{–Ad–H} \xrightarrow[HNO_3/H_2SO_4]{PhNHAc} AcNH(CH_2)_n\text{–Ad–}C_6H_4NHAc \xrightarrow{HCl} NH_2(CH_2)_n\text{–Ad–}C_6H_4NH_2$$

IV, V

where Ad = 1,3-disubstituted adamantane; $n = 0$ (I), 1 (II, IV), 2 (III, VI); $m = 0$ (I), 1 (II), 2 (III); and Ia – Va denote the corresponding dihydrochlorides.

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The tertiary adamantyl cation, formed in the sulfuric acid medium in the presence of oxidizer, selectively replaces hydrogen in the *para* position of the aromatic nucleus of acetanilide, as evidenced by symmetric signals due to aromatic protons in the ^{1}H NMR spectra, which are typical of the *para* substituted benzene derivatives.

Because the free adamantane-containing diamines are poorly soluble in water, the biological tests were performed with the corresponding hydrochlorides (Ia – Va) obtained by saturating ethyl ether solutions of I – V with gaseous hydrogen chloride.

EXPERIMENTAL CHEMICAL PART

The ^{1}H NMR spectra were measured on a Tesla BS-567A spectrometer (Czechia) operated at 100 MHz (DMSO-d_6 solutions, HMDS standard). The IR spectra were measured on a Specord IR-80 spectrophotometer (Germany) using samples

TABLE 1. Physicochemical and Spectroscopic Characteristics of Aromatic Adamantane-Containing Diamines.

Compound	Yield, %	M.p., °C	Empirical formula	^{1}H NMR spectrum (δ, ppm); IR spectrum (ν_{max}, cm^{-1})
IV	63	121 – 122	$C_{17}H_{24}N_2$	1.20 – 1.72 (m, 12H, CH_2-adamantane), 2.08 (s, 2H, CH-adamantane), 2.28 (s, 4H, NH_2), 2.64 (s, 2H, CH_2N), 6.76 (m, 4H, *para*-phenylene)
V	40	98 – 99	$C_{18}H_{26}N_2$	1.13 – 1.68 (m, 14H, CH_2-adamantane), 2.11 (s, 2H, CH-adamantane), 2.39 (s, 4H, NH_2), 2.74 (s, 2H, CH_2N), 6.74 (m, 4H, *para*-phenylene)
IVa	85	258 – 260	$C_{17}H_{26}Cl_2N_2$	540, 720, 810, 860, 920, 1290, 13806, 1460, 1520, 1610, 1630, 2850, 3160, 3300, 3450
Va	96	220 – 223	$C_{18}H_{28}Cl_2N_2$	540, 720, 800, 830, 890, 970, 1050, 1190, 1290, 1340, 1380, 1460, 1520, 1630, 1700, 2860, 3180, 3290, 3450

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prepared as vaseline oil suspensions. The data of elemental analyses agreed with the results of analytical calculations.

1-Aminomethyl-3-(4-aminophenyl)adamantane (IV). To a mixture of 2.7 ml (32.2 mmole) of 65% nitric acid and 215 ml of 96% sulfuric acid at a temperature not higher than 30°C was added 24.0 g (109.0 mmole) of 1-N-acetylaminomethyl)adamantane and the mixture was stirred for 30 min. Then 11.5 g (85.2 mmole) of acetanilide was added and the stirring was continued for another 4 h at 35 – 40°C. The reaction mixture was cooled and poured onto ice. The precipitate of 1-(N-acetylaminomethyl)-3-[4-(N'-acetylamino)phenyl]adamantane was filtered and hydrolyzed by boiling for 10 h in a mixture of 80 ml 35% hydrochloric acid and 565 ml water. Then the solution is cooled, filtered, and neutralized with alkali. The precipitate of 1-aminomethyl-3-(4-aminophenyl)adamantane is filtered, dried, purified by sublimation in a vacuum at 150 – 160°C and a residual pressure of 4 Torr. Yield: 12.5 g (63%) of compound IV. The product was dissolved in 250 ml diethyl ether, the solution was saturated with gaseous hydrogen chloride, and the hydrochloride formed was separated by filtering to yield 13.6 g (85%) of IVa.

TABLE 2. Effect of Adamantane-Containing Diamine Hydrochlorides on the "Open Field" Test Behavior of Rats

Compound	Dose, mg/kg	Number of crossed squares	Number of get-ups onto hind legs	Number of looks into holes	Number of defecations	Grooming
Ia	0	49.5 ± 5.7	10.3 ± 0.9	11.1 ± 2.1	1.0 ± 0.5	4.3 ± 0.9
	30	37.1 ± 3.4*	5.5 ± 0.7*	9.1 ± 1.7	0.4 ± 0.2*	3.7 ± 1.2
IIa	0	62.3 ± 5.3	9.3 ± 0.9	18.7 ± 1.8	1.6 ± 0.6	2.1 ± 0.6
	4	59.0 ± 4.4	10.7 ± 1.4	14.8 ± 1.6*	1.9 ± 1.0	0.6 ± 0.4*
	40	40.1 ± 8.1*	7.0 ± 1.7	10.0 ± 2.1	1.6 ± 0.6	1.6 ± 0.7
IIIa	0	62.3 ± 5.3	9.3 ± 0.9	18.7 ± 1.8	1.6 ± 0.6	2.1 ± 0.6
	0.8	77.2 ± 8.4	4.4 ± 1.2*	15.5 ± 1.4*	2.4 ± 1.2	0.1 ± 0.1*
	8	48.3 ± 7.2	6.3 ± 1.6*	10.1 ± 1.7	0.3 ± 0.5*	1.0 ± 0.5*
IVa	0	49.5 ± 5.7	10.3 ± 0.9	11.1 ± 2.1	1.0 ± 0.5	4.3 ± 0.9
	5	45.0 ± 3.6	9.8 ± 1.3	8.4 ± 1.3	0.7 ± 0.2	4.1 ± 1.1
Va	0	49.5 ± 5.7	10.3 ± 0.9	11.1 ± 2.1	1.0 ± 0.5	4.3 ± 0.9
	5	31.8 ± 7.4*	5.0 ± 1.2*	10.5 ± 2.5	0.2 ± 0.1*	0.8 ± 0.4*

* Statistically reliable difference against the control ($p < 0.05$).

EXPERIMENTAL PHARMACOLOGICAL PART

The psychotropic activity and acute 24-h toxicity of hydrochlorides of diamino adamantane derivatives Ia – Va were studied on white mongrel rats weighing 150 – 200 g and on female mice weighing 18 – 22 g.

The effect of preparations on the rat behavior in the "open field" test was studied in a setup representing a round area with a diameter of 1 m, divided by marks into squares with holes. The observations were performed for 3 min under illumination of 90 – 100 Lux. The behavioral activity was characterized by the following parameters: the number of crossed squares (motor activity), the number of get-ups onto hind legs and looks into holes (research activity), and the number of defecations (emotionality).

The antidepressant activity of compounds was evaluated in the forced swimming test, in which a reduction in the immobilization time was considered a manifestation of the antidepressant activity of the test compounds [7].

The ataractic properties of the synthesized compounds were studied on a plus-labyrinth model, representing a cross-shaped plate raised 70 cm above the floor, with two arms open and two others having 40-cm-high semitransparent side walls.

The nootropic properties of the preparations were assessed on a model of violation of the conditioned passive escape (CPE) reaction. The antiamnesic effect was assessed by variation of the two main CPE characteristics: the latent period of stopping at the dark part and the visit time. The setup for the CPE reaction development comprised a light (20 × 30 cm) and a dark (15 × 18 cm) chambers where the rats were trained by unavoidable a.c. electric stimulation with the parameters individually selected by the vocalization threshold. During the first seconds after the training, the animals were subjected to a transcorneal electroshock (110 V) accompanied by a tonoclonic convulsive attack. The CPE reaction was reproduced in 24 h after the training.

The analgetic activity of substances was evaluated by changes in the detection and vocalization thresholds during gradual increase of the a.c. voltage, as manifested by pain reaction and vocalization.

The anticonvulsive properties were studied on a model of generalized convulsive attack induced by maximum electroshock.

The acute 24-h toxicity was determined by intraperitoneal injection of the preparations to white male mice. The results were statistically processed by the Wilcoxon – Whitney – Mann method and the LD_{50} values were calculated for the compounds studied.

The psychotropic properties of diamine hydrochlorides of the adamantane series were studied 1 h after intraperitoneal injections in the dose range of 1/10 – 1/100 LD_{50}.

Compounds Ia – Va produced various changes in the behavior of rats in the "open field" test, depending on the type (structure) and dose of the preparation. Compounds Ia, IIa, and Va (at a dose of 40, 30, and 5 mg/kg, respectively) decreased the spontaneous motor activity of rats. Compounds Ia and Va also reduced the research activity, as manifested by decreasing number of get-ups. Compounds Ia (30 mg/kg), IIIa (0.8 and 8 mg/kg), and Va (5 mg/kg) were found to stimulate emotionality, as manifested by the increasing number of defecations and grooming. The other compounds did not affect the behavior of animals within the framework of the given experimental model (Table 2).

As for the induced swimming test and the plus-labyrinth model, no antidepressant and ataractic action of compounds

TABLE 3. Antiamnesic Activity of Adamantane-Containing Diamine Hydrochlorides From Data of Electroshock (ES)-Induced Disruption of the CPE Reaction in Rats

Compound	Dose, mg/kg	Latent period of stop in the dark, sec	Dark visit time, sec
Control without ES		160.5 ± 12.3	19.5 ± 12.3
Control + ES	0	54.5 ± 14.2	117.7 ± 24.3
Ia	30	85.4 ± 33.6	94.5 ± 33.6
Control + ES	0	35.7 ± 2.6	160.6 ± 11.8
IIa	4	12.5 ± 6.4	171.5 ± 6.4
	40	27.0 ± 14.4	153.0 ± 13.9
Control + ES	0	105.5 ± 34.7	74.5 ± 33.9
IIIa	0.8	94.5 ± 30.1	85.5 ± 30.0
	8	86.9 ± 33.2	93.1 ± 32.9
Control + ES	0	54.4 ± 14.3	117.7 ± 14.3
IVa	5	94.5 ± 12.6*	85.4 ± 12.6*
Control + ES	0	54.4 ± 14.3	117.7 ± 24.3
Va	5	88.4 ± 32.9**	52.7 ± 27.8**

* Statistically reliable difference against the control ($p < 0.05$);
** Indications of nootropic activity ($0.05 < p < 0.1$).

Ia – Va was observed in the dose range studied (0.8 – 40 mg/kg).

The results of the antiamnesic activity investigation showed that compounds Ia – IIIa in the dose range studied did not affect the conservation of CPE reaction as compared to the control group of animals. Compound IVa injected at 5 mg/kg reliably increased the period of acquired CPE reaction, which is evidence of the amnesic activity of this preparation, and the same dose of compound Va exhibited indications of the nootropic action (Table 3).

Compounds IIa (40 mg/kg) and IVa (5 mg/kg) decreased the duration of generalized convulsive attack, predominantly at the expense of the clonic phase of convulsion.

The analgetic activity tests showed an increase in the threshold of electric-induced pain detection for compounds IIa (4 mg/kg), and IIIa (0.8 and 8 mg/kg) and IVa (5 mg/kg).

TABLE 4. Acute Toxicity of Adamantane-Containing Diamine Hydrochlorides Intraperitoneally Injected to White Mice

Compound	LD_{50}, mg/kg,
Ia	785 (534 – 894)
IIa	385 (311 – 459)
IIIa	76 (44 – 106)
IVa	141 (74 – 270)
Va	147 (58 – 371)

Data on the acute toxicity of synthesized compounds are given in Table 4, from which it follows that the toxicity of diamine hydrochlorides of the adamantane series markedly increases with the distance (the length of the aliphatic chain) between the adamantane nucleus and amino group.

Thus, the results of our experiments showed that 1-aminomethyl-3-(4-aminophenyl)adamantane hydrochloride (IVa) is worthy of further investigation, because this compound combines a pronounced antiamnesic and anticonvulsive activity with analgetic properties.

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