SEARCH FOR NEW DRUGS

SYNTHESIS AND PSYCHOTROPIC ACTIVITY OF NEW 2-PYRROLIDONE DERIVATIVES

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As is known, many drugs used for the therapy of epilepsy have the disadvantage of lacking sedative and memory-enhancing properties [1]. For this reason, there is a continuing search for new anticonvulsive agents producing simultaneous tranquilizing action and / or antiamnestic effect [2].

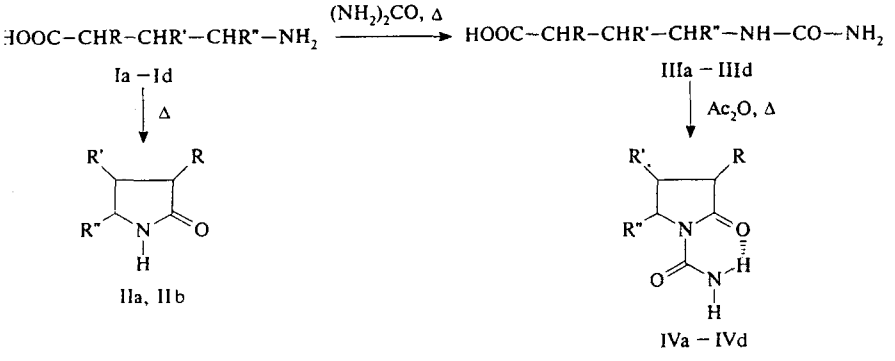
Anticonvulsive drugs exhibit a number of common structural elements, in particular, a nitrogen-containing heterocycle and at least one carbonyl group. Most of these preparations additionally contain two phenyl groups or a single phenyl group in combination with an alkyl substituent in the heterocycle [3]. The chemical structure of the antiamnestic drugs based on gamma-aminobutyric acid (GABA) also features these principal structural units, containing a nitrogen-containing heterocycle and carbonyl groups. This group of nootropic drugs includes 1-substituted 2-pyrrolidones, with a substituent at the nitrogen atom represented by aminocarbonylalkyl radical (pyracetam, oxiracetam, etiracetam, amacetam), arencarbonyl radical (aniracetam), or ureidomethyl radical (imuracetam) [4].

Recently we have suggested a simple method for the synthesis of 1-aminocarbonyl-2-pyrrolidone [5], which was originally isolated from the plant *Anona squamosa* [6]. Taking into account that the pharmacological properties of 2-pyrrolidones with carbamoyl substituents at the nitrogen atom in the heterocycle are almost unknown, while the given substituent frequently accounts for the anticonvulsive properties (e.g., of carbamazepine [7]), it was of interest to study the psychotropic properties of these GABA derivatives. Earlier we reported on the synthesis of a series of *p*-alkoxyphenylsuccinimides [8], among which the most pronounced anticonvulsive activity was observed for *p*-isopropoxyphenylsuccinimide later called pufemide. Therefore, in this study we have also selected the *p*-isopropoxyphenyl radical as a substituent at the carbon atoms.

Initial compounds for the synthesis were 2- and 4-isopropoxyphenyl-4-aminobutanoic acids (Ia and Ib, respectively), phenybut (Ic), and GABA (Id).

The isomeric pyrrolidones IIa and IIb were obtained by cyclization of the amino acids Ia and Ib, respectively. Ureidobutanoic acids IIIa – IIId, obtained by fusing aminoacids Ia – Id with urea, were cyclized through heating in acetic anhydride. Physicochemical characteristics of the synthesized compounds are presented in Table 1.

The formation of intramolecular hydrogen bonds in 1-carbamoyl-2-pyrrolidone structures explains the appearance of two distinct signals due to NH_2 protons in the ^1H NMR spectra of compounds IVa – IVd. We have confirmed



a: R = 4-*i*-PrOC$_6$H$_4$, R′ = R″ = H;
b: R″ = 4-*i*-PrOC$_6$H$_4$, R = R′ = H;
c: R′ = Ph, R = R″ = H;
d: R = R′ = R″ = H.

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the existence of these bonds, also reported in [9], by measuring the IR absorption spectra of compound IVb. For example, the IR spectrum measured in chloroform contains the absorption bands of free NH and C=O groups (ν_{max} = 3480 and 1730 cm^{-1}, respectively) and the same groups involved in the intermolecular [ν_{max} = 3380, 3325 cm^{-1} (NH) and 1705 cm^{-1} (C=O)] and intramolecular [ν_{max} = 3040 cm^{-1} (NH) and 1680 cm^{-1} (C=O)] association. In the spectra of dilute solutions, the bands characteristic of the intermolecular association vanish, in contrast to the bands due to the absorption of free groups and intramolecular associates. Unambiguous evidence that the cyclization of 4-ureidobutanoic acids in acetic anhydride leads to the formation of 2-pyrrolidones was provided by x-ray diffraction data [5].

EXPERIMENTAL CHEMICAL PART

The melting temperatures were determined using a PHMK 76 / 0904 instrument (Germany). The IR spectra were measured on an UR-20 spectrophotometer (Germany) using samples prepared as chloroform solutions or nujol mulls. The mass spectra were obtained with an MKh-1321A spectrometer (Russia) with a direct sample introduction in the electron-impact ionization source operated at an electron energy of 50 eV and a temperature 15 – 20°C below the melting point of the sample. The ^1H NMR spectra were recorded on a Varian T-60 spectrometer (USA) using TMS as the internal standard. TLC analysis was performed in supported silica gel (KSK grade) layers eluted with an upper phase of the butanol – NH_4OH (35 : 15) system (system A) or with an ether – chloroform (50 : 1) mixture (system B) and developed with a Bromocresol Purple (a) or molybdophosphoric acid (b). The data of elemental analyses agree with the empirical formulas proposed.

Compounds Ia and Ib were synthesized as described in [10]. The synthesis of ureido acid IIIc and pyrrolidones IVc and IVd was described in [5].

3-(4-Isopropoxyphenyl)-2-pyrrolidone (IIa). Amino acid Ia (1.185 g, 5 mmole) was kept in the molten state (210°C) for 15 – 20 min, cooled down to room temperature, and recrystallized from 50% ethanol with an activated charcoal additive. Yield of compound IIa, 0.89 g.

5-(4-Isopropoxyphenyl)-2-pyrrolidone (IIb). Compound IIb was obtained similarly from amino acid Ib (1.185 g, 5 mmole) melted at 190°C. Yield of compound IIb, 0.948 g.

2-(4-Isopropoxyphenyl)-4-ureidobutanoic acid (IIIa). A mixture of 1.706 g (7.2 mmole) of amino acid Ia and 4.32 g (72 mmole) of urea was fused together at 130°C for 1 h. Then the mixture was cooled down to room temperature and dissolved in 20 ml of water. The solution was discolorated with activated charcoal and acidified to pH 5 with 6 N HCl. The precipitated crystals were separated by filtration, washed with water, and dried to obtain 1.736 g of compound IIIa.

4-(4-Isopropoxyphenyl)-4-ureidobutanoic acid (IIIb). Compound IIIb was obtained similarly from amino acid Ib (1.185 g, 5 mmole) and 3 g (50 mmole) of urea. Yield of compound IIIb, 1.18 g.

1-Aminocarbonyl-3-(4-isopropoxyphenyl)-2-pyrrolidone (IVa) and **1-aminocarbonyl-5-(4-isopropoxyphenyl)-2-pyrrolidone (IVb).** Compounds IVa and IVb were synthesized by a procedure described for compound IVc [5] using acids IIIa and IIIb (2 g, 7.14 mmole) in 10 ml acetic anhydride.

EXPERIMENTAL BIOLOGICAL PART

The experiments were performed on white mongrel mice weighing 18 – 22 g and rats weighing 120 – 160 g.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Yield, %	M.p., °C	R_f (eluent, developer)	M^+	Empirical formula	IR spectrum (nujol mull) ν_{max}, cm^{-1}		1H NMR spectrum ($CDCl_3$) δ, ppm
						NH	C=O, C=C	
IIa	81.3	121 – 122	0.19 (B, b)	219	$C_{13}H_{17}NO_2$	3173, 3067	1710, 1690, 1680, 1667, 1647	1.28 (d, 6H, 2Me), 1.75 – 2.88 (m, 2H, CH_2CH), 3.23 – 3.70 (m, 3H, CH_2N, CHCO), 4.23 – 4.73 (m, 1H, $CHMe_2$), 6.70 – 7.40 (m, 5H, H_{arom}, NH)
IIb	86.6	124	0.28 (B, b)	219	$C_{13}H_{17}NO_2$	3333, 3173, 3067	1714, 1673, 1667, 1640	1.30 (d, 6H, 2Me), 1.62 – 2.77 (m, 4H,2 CH_2), 4.25 – 4.78 (m, 2H, 2CH), 6.63 – 7.32 (q, 5H, H_{arom}, NH)
IIIa	86.1	159 – 160	0.36 (A, a)	280	$C_{14}H_{20}N_2O_4$	...	...	
IIIb	84.3	188	0.36 (A, a)	280	$C_{14}H_{20}N_2O_4$	...	...	
IVa	80.2	123	0.56 (B, b)	262	$C_{14}H_{18}N_2O_3$	3393, 3272, 3234	1727, 1693, 1675, 1653, 1640	1.35 (d, 6H, 2Me), 1.90 – 2.66 (m, 2H, CH_2CH), 3.50 – 4.10 (m, 3H, CHCO, CH_2N), 4.30 – 4.80 (m, 1H, $CHMe_2$), 5.60 (bs, 1H, NH), 6.76 – 7.33 (m, 4H, H_{arom}), 8.25 (bs, 1H, NH)
IVb	83.4	183	0.58 (B, b)	262	$C_{14}H_{18}N_2O_3$	3340, 3167	1747, 1733, 1720, 1693, 1680, 1667, 1650	1.35 (d, 6H, 2Me), 1.50 – 2.85 (m, 4H, $2CH_2$), 4.20 – 4.65 (m, 1H, $CHMe_2$), 5.50 (m, 2H, $CHCH_2$), 6.60 – 7.25 (m, 4H, H_{arom}), 8.25 (bs, 1H, NH)

TABLE 2. Anticonvulsive and Neurotoxic Activity of the Synthesized Compounds

Compound	Antagonist test ED_{50}, mg/kg			TD_{99}, mg/kg
	corazole	maximum electroshock	thiosemicarbazide	
Ib	88 (46.8 – 167.2)	n/a	70 (48.1 – 103.6)	
IVa	120 (60 – 240)	155 (117.3 – 294.6)	50	>100
IVb	65 (36.1 – 117)	200 (175.4 – 228)	250 (226.8 – 290)	310 (172.2 – 558)
IVc	200	200	200	200
IVd	n/a	n/a	n/a	1000
Phenybut (Ic)	n/a	n/a	105 (80.1 – 132.3)	250 (131.5 – 475)
Piracetam	n/a	n/a	n/a	–

Note: n/a – no activity.

The tranquilizing action of the synthesized compounds was studied on a model of neurosis in rats (conflict situation test [11]). The antiamnestic properties were determined using a passive avoidance conditional reflex (PACR) test [12]. The anticonvulsive effect in mice was assessed using the antagonist tests with corazole (85 mg/kg, s.c.) and arecoline (15 mg/kg, s.c.) or thiosemicarbazide (24 mg/kg, i.p.) and nicotine (8 mg/kg, i.p.) and by the maximum electroshock (MES) test with corneal electrodes (50 mA, 0.2 sec).

The myorelaxant – neurotoxicity action, which is an undesired side effect for tranquilizers, was determined in mice by the rotating rod test.

The compounds tested were introduced 45 min prior to experiments by intraperitoneal injections with an aqueous suspension of carboxymethyl cellulose and Tween-80. Animals in the control groups were injected with the pure suspension. Reference drugs were represented by the tranquilizer phenybut [13] and the nootropic agent piracetam [14]. Each compound was tested in a group of 10 – 25 animals. The experimental results were statistically processed and expressed in the form of effective (ED) and neurotoxicity (TD) doses.

RESULTS AND DISCUSSION

Among the linear GABA derivatives studied (Ia – Ic), an anticonvulsive effect in the corazole antagonist test was observed only for compound Ib (Table 2), while amino acids Ia and Ic (phenybut) showed no evidence of activity (as well as lactams IIa and IIb). An antagonism with respect to corazole was also observed for compounds IVa – IVc, whereas compound IVd and piracetam were inactive.

The ability to prevent the convulsions induced by thiosemicarbazide was exhibited by amino acid Ib, its cyclic derivative IVb, and phenybut. Piracetam and compounds Ia, IIa, IIb, and IVd possessed no activity of this type.

None of the compounds studied showed activity in the tests for preventing the convulsive action of arecoline and nicotine. A weak protective effect in the MES test was observed for compounds IVa and IVb.

As for the conflict situation test, compounds IVb, IVd, and phenybut (but not piracetam) exhibited more or less pronounced tranquilizing effects (Table 3).

Pyrrolidones IVb and IVd also produced certain antiamnestic action (Table 3), the activity of IVb being close to that of piracetam.

As is known, the character and position of substituents in the pyrrolidone ring affect the manifestation of various types of the pharmacological activity. For example, 5-alkyl-2-pyrrolidones produce a sedative action in the absence of anticonvulsive effect [15], while 5-ethyl-5-phenyl-2-pyrrolidone exhibits simultaneous tranquilizing and anticonvulsive activity [16]. Nootropic activity was recently reported for N-acyl derivatives of 4-phenyl-2-pyrrolidone [17], in agreement with the earlier observation for a 4-phenyl analog of piracetam [18].

A comparative analysis of data on the anticonvulsive activity, as manifested in the corazole antagonist tests with lactams IIa and IIb, their N-carbamoyl analogs IVa and IVb, and 1-carbamoyl-2-pyrrolidone IVd (not substituted at the carbon atom), leads to a conclusion that simultaneous presence of an

TABLE 3. Tranquilizing and Antiamnestic Activity of the Synthesized Compounds

Compound, dose, mg/kg	Conflict situation test**	Electroshock amnesia test***
Control (n = 6)	1.6 (1.1 – 2.1)	7.4 (4.3 – 10.5)
IVb, 100 (n = 7),		149.0 (62.8 – 235.2)*
200	14.7 (4.9 – 24.5)*	
Control (n = 6)	3.3 (1.7 – 4.9)	7.4 (4.3 – 10.5)
IVd, 100 (n = 6)	7.8 (3.3 – 12.3)*	91.0 (25.6 – 156.4)*
Control (n = 6)	1.6 (1,1 – 2.1)	
Phenybut, 200 (n = 5)	10.2 (2.4 – 18.0)*	No data
Control (n = 6)	1.6 (1.1 – 2.1)	7.4 (4.3 – 10.5)
Piracetam,		
1000 (n = 13)		133.2 (86.2 – 180.2)*
1450	2.7 (2.0 – 3.4)	

* $p < 0.05$ relative to control.
** Number of water take trials [11].
*** Time of stay in the light compartment [12].

aryl substituent at the carbon atom in the pyrrolidone ring and a carbamoyl group at the heteroatom is a necessary condition for this type of activity. Indeed, no anticonvulsive effect was observed for the compounds missing aryl substituents at the carbon atom even in the presence of carbamoyl (IVd) or carbamidomethyl (piracetam) groups in position 1. Nor did we find this activity in $C_{(3)}$- and $C_{(5)}$-aryl-2-pyrrolidones with unsubstituted NH groups (compounds IIa and IIb, respectively). The carbamoyl group at a nitrogen atom of the C-substituted pyrrolidone ring also favored manifestation of the anticonvulsive effect in the thiosemicarbazide antagonist test (compounds IIb and IVb), although a linear form (compound Ib) is somewhat preferred in this respect.

Thus, the synthesis and characterization of a series of compounds containing structural elements of the known anticonvulsive drugs and nootropic agents led to compound IVb possessing simultaneously the tranquilizing, anticonvulsive, and antiamnestic properties.

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