SYNTHESIS AND PSYCHOPHARMACOLOGICAL ACTIVITY OF N-(4-HYDROXY-4-METHYL-3-TETRAHYDROPYRANYL) DERIVATIVES OF AMINOACIDS

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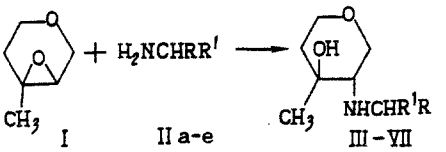
The introduction of aromatic and heterocyclic radicals into neuroactive mono- and dicarboxylic aminoacids leads to the appearance of different forms of psychotropic activity in these materials, as is demonstrated by gamma-aminobutyric acid (GABA) [6], glycine [2] and aspartic acids [5]. In particular, the addition to the aminoacid of oxygen-containing crown heterocycles gave compounds with antiamnestic and antispasmodic activity [1, 7]. Our work in this connection involves the synthesis and psychopharmacological study of the N-(4-hydroxy-4-methyl-3-tetrahydropyranyl) derivative of 5 essential neuroactive aminoacids.

Epoxides of the pyran series are convenient synthons for the introduction of the tetrahydropyranyl group into different organic structures by means of nucleophilic substitution reactions. In the plan of the search for new biologically active compounds we studied the reaction of 4-methyl-3,4-epoxytetrahydropyran (I), prepared earlier [4] with mono- and dicarboxylic aminoacids IIa-e. It was established that in basic solution the reaction involves the amino group with the formation of products of cleavage of the α-oxide ring, in correspondence with the Krasusski rule.



R=COOH (IIa, III), CH_2COON (IIb, d, IV, VI), CH_2CH_2COOH (IIc, e, V, VII); R'=H (IIa-c, III—V), COOH (IId,e, VI, VII).

EXPERIMENTAL (CHEMISTRY)

IR spectra were determined on an UR-20 instrument (as thin films or in Vaseline oil). The ^1H NMR spectra were determined with a Tesla BS-487 C instrument at 80 MHz in CF_3COOH and $CDCl_3$, and HMDS as the internal standard. Elemental analytical data corresponded with the calculated values.

4-Methyl-3,4-epoxytetrahydropyran (I) was prepared according to [4].

N-(4-Hydroxy-4-methyl-3-tetrahydropyranyl) Derivatives of Neuroactive Aminoacids (III-VII). Aminoacids IIa-e in 0.018 mole quantities were added to a solution of NaOH (0.02 mole) in 20 ml of water and to this salt solution was added dropwise 2 ml (0.018 mole) of epoxide I. The mixture was stirred 3-4 h at 80°C and neutralized with 4 N HCl to pH 7.0. The resulting precipitate was recrystallized from water.

The characteristics and yields of the compounds prepared are presented in Table 1.

EXPERIMENTAL (PHARMACOLOGY)

The experiments were carried out on 196 white rats weighing 180-280 g and on 120 white mice weighing 18-20 g.

The influence of the new materials on the spontaneous motor activity, exploratory reaction, and emotionality of rats was studied with the help of the "open field" test by record-

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TABLE 1. Characteristics of the Synthesized Compounds I and III-VII

Compound	Yield, %	mp, °C	Empirical formula	^{1}H NMR spectra, δ, ppm.				IR, spectra	
				4—CH_3 (3H) s	5—H (2H) t	2—H, 3—H, 6—H (5H) m	NH_2 s	CH_2OCH_2	COO^-
I	89	60*	$C_6H_{10}O_2$	1,40	1,90	3,45—3,92	—	1120	—
III	83	79	$C_8H_{15}NO_4$	1,32	1,75	3,35—3,60	7,05	1110	1610
IV	91	166	$C_9H_{17}NO_4$	1,35	1,75	3,45—4,0	7,65	1110	1620
V	96	181	$C_{10}H_{19}NO_4$	1,40	1,85	3,50—3,95	7,50	1120	1620
VI	81	80	$C_{10}H_{17}NO_6$	1,30	1,55	3,50—3,90	6,90	1120	1630
VII	88	116	$C_{11}H_{19}NO_6$	1,50	1,80	3,45—4,02	7,15	1120	1620

*bp (40 mm Hg).

TABLE 2. Psychotropic Activity of N-(4-Hydroxy-4-methyl-3-tetrahydropyranyl) Derivatives of Neuroactive Aminoacids III-VII in Experiments on Rats

Compound	Dose, mg/kg	"Open field" test		Duration of tonic convulsions, s	Duration of acute convulsions, s	Total duration of attack, s	Convulsion vocalization, v
		motor activity (number of quarters traversed)	emotionality (number of defecations)				
Control	—	25,4±4,0	2,8±0,7	14,4±1,2	15,8±5,0	30,2±5,5	33,8±1,6
I	10	40,6±2,0*	2,7±0,9	16,1±1,1	6,8±3,5	23,0±4,2	27,7±2,3
	50	17,3±4,0	1,7±0,6	17,8±0,6	9,2±3,8	27,0±4,1	32,0±1,8
Control	—	25,9±3,0	2,4±0,8	16,6±1,1	20,7±2,4	38,3±2,0	32,3±2,7
III	1	37,8±3,2*	1,4±0,9*	18,4±1,4	23,1±1,6	41,5±2,4	49,5±3,6*
	10	35,7±4,3*	4,9±1,4	15,9±1,4	21,9±1,9	37,8±2,7	33,0±2,0
Control	—	21,7±4,2	4,2±0,7	28,8±3,4	10,7±3,3	39,5±3,2	37,0±3,9
IV	1	24,9±4,0	2,5±0,7*	28,7±3,2	5,6±2,1	34,4±3,1	38,8±3,0
	10	32,3±5,3	3,7±0,6	31,6±3,8	8,1±4,0	39,7±3,1	37,7±2,0
Control	—	32,3±6,5	1,7±0,9	21,6±2,2	10,2±3,5	31,8±3,1	30,0±0,1
V	1	21,6±4,0	1,6±0,8	23,6±2,0	12,4±4,7	36,1±3,7	21,1±1,1
	10	34,8±4,9	3,0±1,3	21,4±1,9	4,1±2,2*	25,5±2,5	22,2±1,4
Control	—	44,0±4,3	1,4±0,9	17,2±1,7	19,1±3,5	36,3±4,0	31,0±2,6
VII	1	43,8±4,3	0,8±0,5	19,1±0,7	20,8±5,0	39,9±5,0	34,0±1,6
	10	48,4±5,4	1,5±0,6	23,0±3,3*	18,5±3,1	42,5±3,6	31,7±2,4

*Statistically significant compared to the control, $p < 0.05$. Criteria of Wilcoxon, Whitney, and Mann.

ing the following indicators of the behavior of the animals: the number of crossed-over quadrants (motor activity), the number of risings on the hind feet (exploratory activity), and the number of defecations (emotionality) [11]. The nootropic properties of the compounds were studied by the exterior conditional passive avoidance reaction (CPAR) after infliction of trans-corneal electroshock, which was accompanied by a tonic-clonic convulsive attack. The CPAR was produced 24 h after training [11].

The antispasmodic activity of the materials was measured by their influence on the duration of electroconvulsive generalized attacks in rats [3]. The influence of the materials on sensitivity to pain was studied by electrical stimulation of the rats, noting the individual thresholds of vocalization of the animals [3].

The samples were introduced intraperitoneally into the rats 1 h before psychopharmacological tests, and in experiments producing CPAR, 1 h after CPAR training.

The acute toxicity (LD_{50}) of the materials was determined by intraperitoneal injection into white mice.

The experimental data obtained were statistically worked up using the nonparametric criteria of Wilcoxon, Whitney and Mann.

The results of the study of the influence of N-(4-hydroxy-4-methyl-3-tetrahydropyranyl) derivatives of neuroactive aminoacids on the behavior of rats in the "open field", the electroshock convulsion, and the pain sensitivity tests are given in Table 2. Compounds I and III increased the spontaneous motor activity, but modified multifariously the exploratory reactions of the animals. Under the influence of compounds III and IV at a dose of 1 mg/kg, a decrease in the fear emotion upon single placement of the animals into an unknown open field situation was noted.

Compounds IV and V in doses of 1 and 10 mg/kg, respectively, showed antispasmodic action, selectively decreasing by one-half the length of the clonic phase of generalized spasmodic attack. In contrast to these, VI and VII potentiated the electroshock convulsions, while both of these compounds in doses of 10 mg/kg increased the length of the tonic phase, and compound VI in a dose of 1 mg/kg prolonged the clonic convulsions and total length of the convulsive attack. From both of the studied substances only two changed the pain sensitivity of the animals upon electrode stimulation; compounds III increased the vocalization threshold 1.5 times, showing analgetic action, and compound VI produced hyperalgesia.

Upon introduction 1 h after the CPAR training, none of the studied materials reduced the habit of passive avoidance, or the disruption of the electroshock amnestic effect. It was established that compounds III and IV at doses of 1 mg/kg potentiated retrograde electroshock amnesia; during regeneration of CPAR the latent period of turning into the dark compartment decreased respectively to 6.3 ± 3.3 and 9.2 ± 1.6 seconds by comparison with 22.9 ± 7.8 seconds for the control ($p < 0.05$).

A determination of the acute daily toxicity of the materials showed that they were of low toxicity: LD_{50} of compounds I, IV, V, and VII was above 4000 mg/kg, while that of III was above 3000 mg/kg.

It is known that the inhibitory monocarboxylic aminoacids (glycine, beta-alanine, GABA) poorly infiltrate through the hematoencephalic barrier, but show expressed antispasmodic action by intracerebroventrical introduction, decreasing the sensitivity to pain, and breaking conditioned reflex activity. The dicarboxylic excitatory aminoacids (glutamic and aspartic acids) are characterized by a wide spectrum of psychotropic activity, depending upon the dose and the route of introduction exerted multidirectional effects, but by central action unequivocally increase convulsive activity [8, 12]. Substitution of the amino group in the neuroactive aminoacid structures by the 4-hydroxy-4-methyl-3-tetrahydropyranyl radical leads to the appearance of new compounds with psychotropic properties not possessed by the same neuroactive aminoacids in small (less than 100 mg/kg) doses [5, 8]. In this case the pyranyl analogs of monocarboxylic aminoacids (compounds III, IV, and V) are capable of lowering the emotional fear reaction, of showing antispasmodic and analgetic activity, and of retarding the production of conditional reactions in situations with negative emotional reinforcement, i.e., to imitate the psychotropic effects of the inhibitory aminoacids in specific stages during their central activity. An increase in spontaneous motor activity under the influence of N-(4-hydroxy-4-methyl-3-tetrahydropyranyl) glycine, apparently proceeds by means of the psychostimulating action of the pyranyl fragment, which lessens with elongation of the carbon chain of the mono- and di-carboxylic aminoacids connected to the pyranyl ring. Potentiation of tonic and clonic convulsions under the influence of the pyranyl analogs of glutamic and aspartic acids (compounds VI and VII) indicates the possibility of the activation of the exciting aminoacid sinapses by the action of these compounds.

The data we obtained in determining the correspondence between psychotropic effects by inhibitory and stimulatory mediator aminoacids upon their central action and the N-(4-hydroxy-4-methyl-3-tetrahydropyranyl) derivatives of these aminoacids by systemic introduction indicates the possibility of increasing the properties of these aminoacids to penetrate into the brain by modification of their structure by the N-pyranyl radical. Taking into account the significant structural difference between N-pyranyl derivatives of the mediator aminoacids and the known agonists of aminoacid inhibitory and excitatory receptors [9, 10], it can be proposed that the pyranyl radical cleaves from the aminoacid structure upon entering the brain, with subsequent inclusion of the aminoacid in the sinaptic and metabolic processes.

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SYNTHESIS OF 2-METHYLQUINOLINE- AND 2-ARYLAMINO-5,6,7,8-TETRAHYDROQUINOLINE-3-CARBOXYLIC ACID β-DIALKALYLAMINOACETYLHYDRAZIDES AND THEIR BIOLOGICAL ACTIVITY

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Nicotinic acid hydrazides are widely used as medicinal preparations [4]. In recent years hydrazides of cinchoninic and 2,3-polymethylenequinoline-4-carboxylic acids have been obtained, which exhibited various types of physiological activity [3, 5]. In the search for biologically active compounds, previously unknown acylhydrazides of 2-methylquinoline- and 2-arylamino-5,6,7,8-tetrahydroquinoline-3-carboxylic acids were synthesized according to the following scheme:

$$\underset{\text{Ia-d}}{\text{XCONHNH}_2} \xrightarrow{\text{ClCH}_2\text{COCl}} \underset{\text{IIa-d}}{\text{XCONHNHCOCH}_2\text{Cl}} \xrightarrow{\text{HNR}'_2} \underset{\text{IIIa-m}}{\text{XCONHNHCOCH}_2\text{NR}'_2}$$

X=2-methylquinol-3-3 (Ia, IIa, IIIa-c), *n*-RC_6H_4NH-5,6,7,8-tetrahydroquinol-3-yl IIb-d, IIId-m);

R=H (IIId-f), CH_3 (IIb, g-j), CH_3O (IIc, IIIk, l), Br (IId, IIIm); R′=CH_3 (IIId, g, m), C_2H_5 (IIIe, h, k), n.-C_4H_9 (IIIc); NR'_2=piperidino (IIIa, f, i), morpholino (III b, j, l).

The synthesis of the starting hydrazides Ia-d was carried out by boiling the esters of the corresponding acids with hydrazine hydrate.

2-Methylquinoline- and 2-arylamino-5,6,7,8-tetrahydroquinoline-3-carboxylic acid β-chloroacetylhydrazides IIa-d (Table 1) were obtained in yields of 89-100% by the reaction of hydrazides Ia-d with chloroacetyl chloride in glacial acetic acid in the presence of anhydrous sodium acetate. Hydrazides IIa-d are yellow crystalline substances which are soluble in toluene, ethanol, and acetic acid. In their IR spectra there are bands at 1660-1700 (CO) and 3190-3400 cm^{-1} (NH). On heating compounds IIa-d with dialkyl amines in a benzene or dioxane medium, 2-methylquinoline- and 2-arylamino-5,6,7,8-tetrahydroquinoline-3-carboxylic acid β-dialkylaminoacetylhydrazides (IIIa-m) are formed. Peaks are observed in the IR spectra of these compounds at 1640-1650 and 1680-1700 (CO) and 3240-3400 cm^{-1} (NH).

EXPERIMENTAL (CHEMICAL)

The IR spectra were run on a UR-20 spectrophotometer in mineral oil. The data of the elemental analysis correspond to the calculated values.

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