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SYNTHESIS AND PHARMACOLOGICAL INVESTIGATION OF A SERIES OF 1-SUBSTITUTED 2-PYRROLIDONES STRUCTURALLY CLOSE TO THE PREPARATION PYRACETAM

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It was established previously in [6] that 1-carbamidomethylpyrrolid-2-one (pyracetam) (I) reacted readily with the diethylacetal of dimethylformamide (II) with the formation of the N-dimethylaminomethylene derivative (III). Some properties of the acylamidine (III) and of a series of synthesized compounds based on it, which are structurally similar to pyracetam (I), have been investigated in the present work. The biological activity of the obtained compounds has been studied.

In the first stage of the work attempts were made to synthesize acylamidines of type (IV) by the transamination of (III) with primary amines. However, on interacting compound (III) with benzyl-, β-phenylethyl-, homoveratryl-, and β-diethylaminoethylamines, pyracetam was isolated in place of the expected amidines (IV), i.e., fission of the amidine fragment had taken place. In the example of the interaction of amidine (III) with homoveratrylamine it was shown (by chromato-mass spectrometry) that the second reaction product was N,N-dimethyl-N'-homoveratrylformamidine (V), i.e., on interacting acylamidine (III) with amines, stabilization of the intermediate acylaminal (VI) was effected by splitting off the appropriate formamidine and not dimethylamine as took place for amidines containing no N-acyl residue in [3].

It is known from [9] that acylamidines are hydrolyzed in AcOH to N-formyl derivatives and are able to react in this solvent with arylhydrazines with the formation of triazole derivatives. Treatment of amidine (III) with 70% AcOH like this led to N-formylpiracetam (VII) and on interaction of (III) with phenylhydrazine in AcOH at 20°C 1-(1-phenyl-1,2,4-triazolyl-5-methyl)pyrrolid-2-one (VIII) was formed.

In the reaction under consideration the formation of the other isomeric triazole (IX) is possible in principle. Attempts to isolate the intermediate compound (X) or (XI), the structure of which should give unambiguous proof of the structure of the final triazole, were not crowned with success. The triazole cyclization in the present case evidently proceeded more rapidly than transamination. In order to record the formation of the intermediate product, acylhydrazines of reduced basicity compared to phenylhydrazine, viz., p-nitrophenyl- and 2,4-dinitrophenylhydrazines, were put into a similar reaction. In these cases the intermediate acylamidrazones (IIa, b) were successfully isolated and their structures followed from data of elemental analysis and spectra (Table 1). By heating compound (XIIa) in AcOH the triazole derivative (XIII) was obtained. However, the basicity of the NH group in the dinitro derivative (XIIb) was reduced so much that intramolecular cyclization did not even take place, on heating (XIIb) in AcOH a fission of the side chain was observed and the N-acyl derivative (XIV) was successfully isolated. Compound (XIV) was also obtained by an alternative synthesis from 2,4-dinitrophenylhydrazine (XV) by the procedure of [7]. The 1,5 (and not the 1,3) di-

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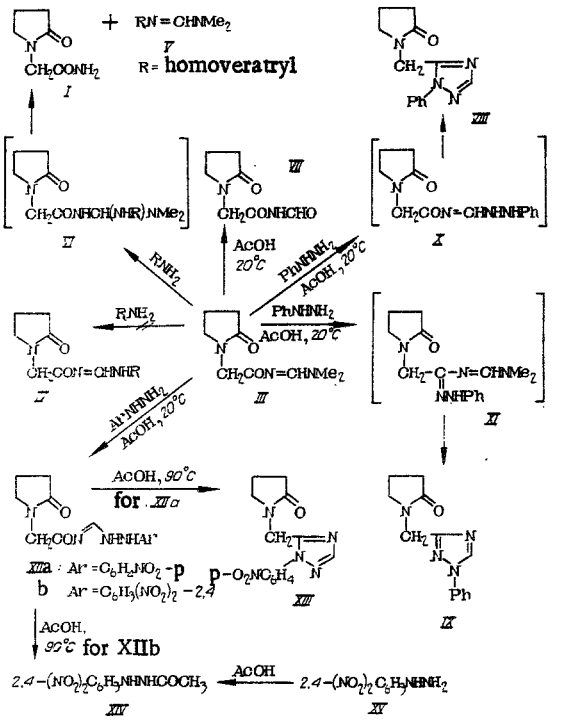
TABLE 1. Characteristics of Synthesized Compounds

Compound	Yield, %	mp, °C	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
VII	89	143—5	49,37	5,90	16,16	$C_7H_{10}N_2O_3$	49,41	5,92	16,46
VIII	86	78—80	64,89	6,14	23,40	$C_{13}H_{14}N_4O$	64,44	5,82	23,13
XIIb*	82	249—51	42,45	4,07	23,04	$C_{13}H_{14}N_6O_8 \cdot H_2O$	42,39	4,38	22,82
XIIa	55	215—6	51,46	4,82	23,24	$C_{13}H_{15}N_5O_4$	51,14	4,95	22,94
XIII	82	140—2	54,57	4,60	24,73	$C_{13}H_{13}N_5O_3$	54,35	4,56	24,38
XVII	49	129—33	50,47	6,87	22,77	$C_{13}H_{21}N_5O_4$	50,15	6,80	22,50
XIXa	87	162—4	63,29	6,80	17,17	$C_{13}H_{17}N_3O_2$	63,14	6,93	16,99
XIXb	89	125—7	51,83	8,46	22,92	$C_8H_{15}N_3O_2$	51,87	8,16	22,69
XIXc†	90	161—2	58,99	6,28	16,13	$C_{13}H_{17}N_3OS$	59,28	6,51	15,96

*Found, %: H_2O 5.24. Calculated, %: H_2O 4.89.
†Found, %: S 12.36. Calculated, %: S 12.17.

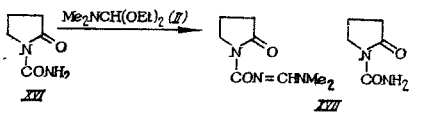
Note. Compounds (XVII) and (XIXb) were crystallized from ethyl acetate, (VII) and (XIII) from i-PrOH, (VIII) from hexane, (XIIb) from aqueous DMF, (XIIa) from a mixture of MeCN and DMF (3:1), and (XIXa, c) from EtOH.



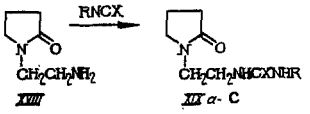
substituted 1,2,4-triazole was formed as a result of triazole cyclization which is in agreement with the data of [9] in which similar reactions were also investigated.

When studying the possibility of obtaining acylamidines homologous to compound (III) it was established that a complex of acylformamidine (XVII) with the initial urea derivative (XVI) was formed as a result of the reaction of 1-carbamidopyrrolid-2-one (XVI) with acetal (II). The structure of this complex followed from the data of elemental analysis and from its mass spectrum in which peaks for ions of m/z 183 and 128 were observed.

The formation of complexes of amidines with urea derivatives was recently recorded in [1].



Finally, concluding the present work, a series of pyrrolid-2-one derivatives was synthesized for pharmacological study. These were based on 1-(β-aminoethyl)pyrrolid-2-one (XVIII) obtained previously in [6] from piracetam (I).



XIX: a) R = Ph, X = O; b) R = Me, X = O; c) R = Ph, X = S.

In difference to [6] the N-carbamoyl(thiocarbamoyl) derivatives (XIXa-c) and not the N-acyl derivatives were obtained in the present work.

EXPERIMENTAL CHEMISTRY

IR spectra were taken on a Perkin-Elmer 457 instrument (Nujol mulls), UV spectra on an EPS-3 T (Hitachi) spectrometer in MeOH or ethanol. The mass spectra of compounds (V) and (XVII) were taken on an MAT-112 instrument (ionizing voltage 50 eV, temperature of ionization chamber 140°C). The purity of substances was checked chromatographically on Silufol-254 plates (Czechoslovakia). The results of analyses of the obtained compounds are shown in Table 1.

Reaction of N,N-Dimethyl-N'-(pyrrolid-2-on-1-ylacetyl)formamidine (III) with Homoveratrylamine. A mixture of compound (III) (1 g: 0.005 mole) and homoveratrylamine (0.9 g: 0.005 mole) in dry benzene (15 ml) was stirred at room temperature for 4 h. The reaction mixture was cooled and N-carbamidomethylpyrrolid-2-one (0.7 g: 100%) was filtered off. The mother liquor was evaporated and (V) was obtained.

The reaction of compound (III) with benzylamine, phenylethylamine, and dimethylaminoethylamine was carried out in a similar manner.

N-Formylcarbamidomethylpyrrolid-2-one (VII). Compound (III) (6.5 g: 0.033 mole) in 70% AcOH (43 ml) was stirred at 20°C for 15 h. The reaction mixture was evaporated in vacuum and the residue was rubbed under ether. Compound (VII) was obtained. IR spectrum, ν_{max}, cm^{-1}: 3160 (NH), 1740, 1710, 1650 (CO).

1-(1-Phenyl-1,2,4-triazol-5-ylmethyl)pyrrolid-2-one (VIII). Phenylhydrazine (3.2 ml: 0.033 mole) was added dropwise to a solution of (III) (5.9 g: 0.03 mole) in glacial AcOH (60 ml). The mixture was stirred at room temperature for 1.5 h, then heated at 70°C for 1.5 h. The reaction mixture was evaporated in vacuum, the residue was dissolved in $CHCl_3$, the chloroform solution was washed with 10% potassium carbonate solution, then with water, and dried over calcined Na_2SO_4. The chloroform was evaporated in vacuum and the residue was rubbed under hexane. Compound (VIII) was obtained. IR spectrum, ν_{max}, cm^{-1}: 1680 (CO), 1600 (C=N, C=C). UV spectrum, λ_{max}, nm (log ε): 207 (4.21), 227 (3.92).

N-(2,4-Dinitrophenylamino)-N'-(pyrrolid-2-on-1-yl)formamidine (XIIb). A mixture of (III) (5.9 g: 0.03 mole) and 2,4-dinitrophenylhydrazine (6.6 g: 0.033 mole) in glacial AcOH (150 ml) was stirred at 20°C for 1 h. The solid was filtered off. Compound (XIIb) was obtained. IR spectrum, γ_{max} cm^{-1}: 3500, 3400, 3250 (NH), 1690, 1640 (CO), 1610, 1585 (C=N, C=C), UV spectrum, λ_{max}, nm (log ε): 207 (4.27), 250 (4.16), 378 (4.37).

N-(p-Nitrophenylamino)-N'-(pyrrolid-2-on-1-ylacetyl)formamidine (XIIa). This was obtained in a similar manner to compound (XIIb) from (III) and p-nitrophenylhydrazine. IR spectrum, γ_{max}, cm^{-1}: 3260 (NH), 1690, 1650 (CO), 1600, 1590 (C=N, C=C). UV spectrum, λ_{max}, nm (log ε): 209 (4.33), 283 (3.99), 400 (4.40).

1-[1-(p-Nitrophenyl)-1,2,4-triazol-5-ylmethyl]pyrrolid-2-one (XIII). Compound (XIIa) (0.9 g) in glacial AcOH (20 ml) was heated at 90°C for 3 h. The reaction mixture was evaporated *in vacuo* and the residue rubbed with absolute ether. Compound (XIII) was obtained. IR spectrum, γ_{max}, cm^{-1}: 1675 (CO), 1615, 1600 (C=N, C=C). UV spectrum, λ_{max}, nm (log ε): 207 (4.20), 280 (4.05).

N-(2,4-Dinitrophenyl)-N'-acetylhydrazine (XIV). This was obtained in a similar manner to compound (XIII) from (XIIb) and by the known method from [7].

Adduct of N-(Dimethylaminomethylene)carbamidopyrrolid-2-one with N-Carbamidopyrrolid-2-one (XVII). A mixture of N-carbamidopyrrolid-2-one (XVI) [10] (14 g: 0.11 mole) and the diethylacetal of N,N-dimethylformamide (II) (20.8 g: 0.14 mole) in absolute alcohol (160 ml) was stirred at 20°C for 2 h. The reaction mixture was evaporated in vacuum and the residue rubbed under ether. Compound (XVII) was obtained.

N-Phenyl-N'-[β-(2-oxopyrrolidino)ethyl]urea (XIXa). Phenyl isocyanate (1.3 ml: 0.012 mole) was added dropwise to a solution of (XVIII) (1.3 g: 0.01 mole) in dry dichloroethane (20 ml). The mixture was stirred at room temperature for 1 h, cooled, and the solid filtered off. Compound (XIXa) was obtained.

N-Methyl-N'-[β-(2-oxopyrrolidino)ethyl]urea (XIXb). This was obtained in a similar manner to (XIXa) from (XVIII) and methyl isocyanate.

N-Phenyl-N'-[β-(2-oxopyrrolidino)ethyl]thiourea (XIXc). This was obtained in a similar manner to (XIXa) from (XVIII) and phenyl isothiocyanate.

EXPERIMENTAL PHARMACOLOGY

The synthesized compounds were investigated in a series of pharmacological tests including antihypoxic action, influence on the bioelectrical activity of the brain, on the convulsive action of the specific antagonist of GABA, viz., thiosemicarbazide, analgesic action, and also the influence on motor coordination (rotating rod method).

The use of different experimental models of the hypoxic state made it possible not only to establish the antihypoxic action of the synthesized compounds but also to predict the possibility of their potential nootropic activity since ability to increase the stability of the animal organism towards oxygen deficiency is one of the main characteristics of nootropic action.

Antihypoxic action was studied in the present work in experiments on white random bred male mice of weight 20-22 g using two experimental models of hypoxia.

Acute hypoxic hypoxia with hypercapnia was caused by putting each mouse into a hermetically sealed chamber of volume 250 ml [5]. For modeling hypoxia $NaNO_2$ (200 mg/kg s.c.) was used which caused methemoglobinemia [2]. Pyracetam derivatives were injected into the peritoneal cavity at doses of 250, 500, and 1000 mg/kg 50 min before placing mice in the sealed chamber or administering $NaNO_2$. The life span of animals (in min) was determined in the sealed chamber and after administration of $NaNO_2$ to controls (administration of isotonic NaCl solution) and on a background of administering the investigated compounds.

It was established that the synthesized compounds changed the sensitivity of animals to hypoxia in various ways. Compounds (XIIa, b), (XVII), and (XIXc) showed antihypoxic action, increasing the lifespan of mice in the sealed chamber. On the other hand compounds (XIXa, b) reduced the stability of the organism towards the deficiency of oxygen enabling more rapid death of animals under conditions of hypoxia. The obtained data are shown in Table 2.

As is seen from Table 2 compounds (XVII), (XIIa, b), and (XIXc) increases the life span of mice under conditions of acute hypoxic hypoxia by approximately 1.5-2 times in comparison with control. Compounds (XIXc) and (XVII) were the most active in this characteristic.

In difference to the compounds mentioned, compounds (XIXa, b) shortened the life of animals in the sealed chamber.

Compounds (VII), (IX), and (XVI) did not possess antihypoxic activity and did not influence the life span of mice under conditions of the sealed space.

The investigated compounds, except for compound (XIIb), did not possess protective properties against phenomena of hemic hypoxia lengthening the life of animals after administering $NaNO_2$ up to 49.0 (37.7-60.3) min. $NaNO_2$ caused death of mice after 32.0 (23.9-40.1) min.

The investigations conducted showed that four of the nine studied compounds (XIIa, b), (XVII), and (XIXc) possessed antihypoxic activity in the model of acute hypoxia. A small protective action was detected for compound (XIIb) against the occurrence of methemoglobinemia.

In the chronic experiments on rabbits with electrodes implanted in the sensomotor parietal and occipital region of the cerebral cortex it was established that compounds (XVII), (XIXc), (XIIa, b) , which possessed antihypoxic activity, did not influence brain bioelectric activity.

TABLE 2. Influence of the Synthesized Compounds on the Life Span of Mice in the Sealed Chamber

Compound	Dose, mg/kg	Life span, min
XVII	500	39,7 (32,4—47,0)
	1000	57,2 (47,5—66,9)
XIXa	250	23,7 (21,5—25,9)
	500	24,3 (22,1—27,5)
XIXb	250	24,8 (20,2—29,4)
	500	21,5 (17,9—25,1)
XIXc	250	45,7 (39,1—52,3)
	500	67,3 (56,8—77,8)
XIIa	250	35,5 (30,6—40,4)
	500	39,5 (33,6—45,4)
XIIb	250	45,3 (38,5—52,1)
	500	46,5 (39,7—53,3)
Control	0	28,1 (25,0—31,2)

Note. Limits of variation are given in brackets.

The indicated compounds did not change the spontaneous (background) EEG at doses of 100 and 200 mg/kg on intraperitoneal administration and also proved to have no influence on the application of photostimulation and acoustic stimulation, i.e., they did not change the functional mobility of cortical neurons and the state of the ascending activating system of the brain.

To judge the degree of expression of the GABA-ergic component in these compounds, a study was carried out of their ability to prevent convulsions caused by thiosemicarbazide (TSC) [4]. TSC is an inhibitor of glutamate decarboxylase which takes part in the synthesis of GABA.

The investigation was carried out in white mice of weight 18-20 g. The investigated substances were introduced into the peritoneal cavity 20 min after injection of TSC (20 mg/kg s.c.). The ability of compounds to extend the latent period of the onset of convulsions and the time of death of the animals indicated the presence of anticonvulsive activity.

Compounds (XIXa, b) proved to be the most active in relation to convulsions caused by TSC and at a dose of 500 mg/kg extended the latent period of convulsions from 47.2 (44.2-50.2) min to 81.8 (78.5-85.3) and 52.8 (51.8-53.8) min, respectively, and the time for the onset of death from 60.2 (53.2-67.2) min to 117.0 (112.7-122.7) and 114.7 (99.4-130) min, respectively (at $P = 0.05$). Compounds (XIIa, b) and (XVII) were less active. On injecting them at doses from 200 to 500 mg/kg they extended the latent period of convulsions by 20-50% and the time to death by 25-35%.

Compounds (VII), (IX), (XVI), and (XIXb) proved to have no appreciable influence on convulsions caused by TSC.

On studying analgesic activity it was established that a portion of the compounds extended the staying time of mice on a hot plate [11]. The most active in this respect were compounds (IX), (XIIb), and (XIXc). After injecting these compounds at doses of 100-250 mg/kg mice were on the hot plate for 13.9 (11.4-16.4), 13.0 (10.6-15.4), and 12.0 (9.9-16.9) sec and mice of the control group for 8.6 (7.0-9.8) sec. Compounds (XVI), (XVIII), and (XIXa) were less active and increased the staying time of mice on the hot plate by 25-40%. Compounds (VII), (XIIa), and (XIXb) were inactive in this respect.

On studying the influence of compounds on motor coordination (using the "rotating rod" method) [8] it was established that those compounds which increased the ability of mice to stay on the hot plate impaired motor coordination. Thirty minutes after the injection of compounds (IX), (XIIb), (XVI), and (XIXa) into the peritoneal cavity from 10 to 30% animals were not able to stay on the rotating rod. Motor coordination was restored 1 h after injection for the majority of compounds. It is possible that the ability of mice to stay on the hot plate for a more extended time compared to controls is linked with depression of the overall state of the animals.

The LD_{50} for white mice on intraperitoneal administration (in mg/kg) was 712.5 for (IX), 850 for (XIIa), and greater than 1000 for the rest of the compounds.

Among the studied compounds the most marked GABA-ergic component of the action (in the model of spasm using TCS) was displayed by compounds (XIXa, c) which contain urea or thiourea in the molecule. Other compounds were less active, (XIIa, b) and (XVIII), or did not possess activity in relation to convulsions caused by TCS, (VII), (IX), (XVI), and (XIXb).

The results of the experiments conducted indicate the expediency of further search for antihypoxic, potentially nootropic and neurotropic substances in the series of pyrrolid-2-one derivatives.

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SYNTHESIS OF DERIVATIVES OF PIPERIDINE AND DECAHYDROQUINOLINE, AND THEIR ANALGESIC AND PSYCHOTROPIC PROPERTIES.

XVI. NEW N-ANALOGS OF DESMETHYLPRODINE

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UDC 615.211+615.214/:547.823].012.1

We have shown earlier [1, 4] that some N-substituted analogs of desmethylprodine possess high analgesic activity. In the present work, as part of a search for effective substitutes for morphine, new derivatives of 4-phenyl-4-propionyloxypiperidine were synthesized from 4-phenylpiperidine-4-ol (I) [10], and their pharmacological activity was studied.

Aminomethylation of the corresponding alkyne (II, β, VI) with piperidine and $(CH_2O)_n$ in the presence of a catalytic amount of freshly-prepared Cu_2Cl_2 in dioxane under individually selected conditions gave the corresponding N-substituted 4-phenylpiperidin-4-ols III and VII in high yield.

Alkylation of I in acetone with propargyl bromide (IX) in the presence of anhydrous potassium carbonate at 70°C gave 1-propargyl-4-phenylpiperidin-4-ol (X). Interaction of the latter with bromophenylacetylene (XI) [3] under Khodkevich–Kado reaction conditions [6] formed the diacetylenic alcohol (XII) in 76.2% yield.

The piperidinols III, VII, and XII were heated with $(EtCO)_2O$ in EtCOOH to give esterification to the corresponding mono- and diesters which were obtained in the form of the crystalline, water-soluble hydrochlorides (IV, VIII, XIII). Selective hydrogenation of the triple bond in diester IV in the presence of Pd on $CaCO_3$ gave the dihydrochloride V.

The purity and structure of the synthesized compounds were established by TLC, elemental analysis, and IR spectra data (cf. Table 1).

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