SYNTHESIS AND PHARMACOLOGICAL EXAMINATION OF NOVEL PYRACETAM-RELATED 2-PYRROLIDONES

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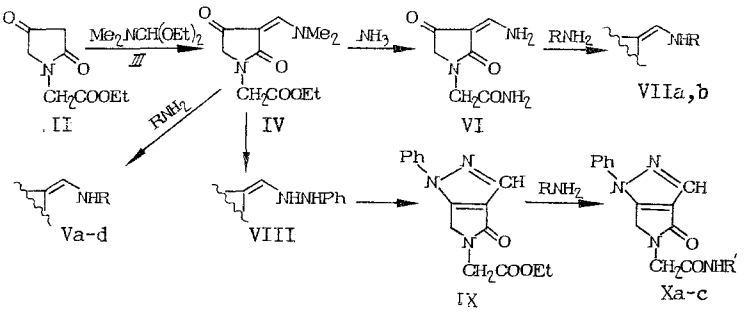
UDC 615.31:547.745].012.1.07

The usual approach to the synthesis of novel biologically active compounds is by structurally modifying known drugs. For example, relatively minor changes in the structure of one of the earliest nootropic drugs, pyracetam (I), have given rise to a whole series of nootropic drugs such as anipyracetam [13], oxypyracetam [12], and pramiracetam [11], in addition to a number of compounds with antihypoxic, nootropic, and other types of pharmacological activity [3, 4, 6-8] including thiopyracetam (1-thiocarbamoyl-methyl-2-pyrrolidinethione [2]) and compounds with pronounced antihypoxic and nootropic activity. One means of obtaining drugs with this type of pharmacological activity is by modifying the molecule (I) in such a way as to vary the partial positive and negative charges on the carbamide nitrogen of the N-carbamoylmethyl group and the lactam oxygen in (I), respectively. The latter aim can be achieved by introducing an electron-donor group conjugated with the lactam group in (I).

Adopting this strategy, the starting material selected was 1-ethoxy-carbonylmethyl-2,4-pyrrolidinedione (II), obtained as reported in [14]. Reaction of the ester (II) with dimethylformamide diethyl acetal (III) proceeded smoothly to give 1-ethoxycarbonylmethyl-3-dimethylaminomethylene-2,4-pyrrolidinedione (IV), in which the partial negative charge on the lactam carbonyl oxygen is increased by conjugation with the enamine fragment. On heating (IV) with amines in methanol, selective transamination occurs, the ethoxy-carbonyl group being unaffected, to give benzylamino- and β-phenylisopropylaminomethylene derivatives (Va) and (Vb). The analogous transamination with γ-aminobutyric acid required boiling in acetic acid, while transamination with glycine only occurred when the sodium salt of the latter was used. Using these methods, there were obtained compounds in which the enamine grouping contained aminoacid residues (Vc, d). In contrast to the reaction with



R=CH_2Ph(Va, VIIa), $CH(Me)CH_2Ph$(Vb, VIIb), $(CH_2)_3COOH$(Vc), CH_2COOH(Vd);
R'=H(Xa), CH_2Ph(Xb), $CH_2CH_2NEt_2$(Xc)

amines, passage of ammonia through a solution of (IV) in methanol resulted in both transamination and amidation of this compound to give 1-carbamoylmethyl-3-aminomethylenepyrrolidine-2,4-dione (VI). Transamination of this compound with benzylamine and β-phenylisopropylamine gave amides (VIIa, b).

The next step was to obtain bicyclic derivatives containing the 1-carbamoylmethyl-2-pyrrolidone grouping. To this end, the ester (IV) was subjected to transamination with phenylhydrazine to give the enehydrazine (VIII). On heating in a mixture of methanol and toluene in the presence of toluene-p-sulfonic acid, this cyclized to 2-ethoxycarbonylmethyl-3-oxo-6-phenyl-1,2-dihydro-3H-pyrrolo[3,4-c]pyrazole (IX), which on treatment with ammonia

Central Drug Laboratory, S. Ordzhonikidze All-Union Research Institute for Pharmaceutical Chemistry, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 26, No. 1, pp. 41-44, January, 1992. Original article submitted February 7, 1991.

0091-150X/92/2601-0053$12.50

TABLE 1. Physicochemical Properties of Compounds Obtained

Compound	Yield	Mp, °C	M+	Empirical formula	IR spectrum, ν_{max}, cm^{-1}
IV	70	58—9	240	$C_{11}H_{16}N_2O_4$	
Va	83	137—8 (MeOH)	302	$C_{16}H_{18}N_2O_4$	3280 (NH), 1730, 1690 (C=O)
Vb	37	70—2	330	$C_{18}H_{22}N_2O_4$	3230 (NH), 1760, 1690 (C=O)
Vc	67	172—3 (MeOH)	298	$C_{13}H_{18}N_2O_6$	3240 (NH), 1740, 1680 (C=O)
Vd	11	182—3 (alcohol)	270	$C_{11}H_{14}N_2O_6$	3250 (NH), 1720, 1685 (C=O)
VI	60	234—5 decomp. (H_2O)	183	$C_7H_8N_3O_3 \cdot H_2O$	3180, 3240, 3360 (NH_2), 1640, 1670, 1690 (C=O)
VIII	65	132—3	303	$C_{15}H_{17}N_3O_4$	3170 (NH), 1730, 1690 (C=O)
VIIa	73	234—6 (MeOH)	273	$C_{14}H_{15}N_3O_3$	3360, 3240, 3180 (NH, NH_2), 1690, 1680 (C=O)
VIIb	44	125—6	301	$C_{16}H_{19}N_3O_3$	3390, 3260, 3190 (NH, NH_2), 1690, 1660 (C=O)
IX	60	174—5	285	$C_{15}H_{15}N_3O_3$	1730, 1665 (C=O)
Xa	67	245—7 (MeOH)	256	$C_{13}H_{12}N_4O_2$	3290, 3140 (NH_2), 1670 (C=O)
Xb	95	218—9 (MeOH — DMF 4:1)	346	$C_{20}H_{18}N_4O_2$	3300 (NH), 1650 (C=O)
Xc	91	185—6 (*i*-PrOH)	355	$C_{19}H_{25}N_5O_2$	3295 (NH), 1680, 1640 (C=O)

or amines gave the bicyclic pyracetam analogs (Xa-c). The structures of these compounds were confirmed by their IR and mass spectra (Table 1).

EXPERIMENTAL (CHEMICAL)

IR spectra were obtained on a Perkin-Elmer 457 spectrophotometer as suspensions in vaseline grease. Mass spectra were obtained on a Varian MAT-112 instrument, ionizing electron energy 70 eV.

The properties of (IX-X) are shown in Table 1. The elemental analyses were in agreement with the calculated values.

1-Ethoxycarbonyl-3-dimethylaminomethylenepyrrolidine-2,4-dione (IV). To a solution of 1.85 g (10 mmole) of 1-ethoxycarbonylmethylpyrrolidine-2,4-dione (II) in 50 ml of methanol was added at room temperature 1.91 g (13 mmole) of dimethylformamide diethyl acetal (III). The mixture was kept for one hour, then the methanol was removed under reduced pressure. The residual yellowish-brown oil was dissolved in the minimum amount of chloroform, chromatographed on a column of silica gel (2 × 10 cm), eluent chloroform, and the solvent removed under reduced pressure. In all the following syntheses, the (IV) obtained following chromatography was used as an oil. For identification, this oil was recrystallized from light petroleum.

1-Carbamoylmethyl-3-aminomethylenepyrrolidine-2,4-dione (VI). Ammonia was passed through a solution of 2.4 g of (IV) in 30 ml of methanol for 3-4 h. The mixture was kept overnight, and the solid which crystallized out was filtered off and washed with methanol.

1-Carbamoylmethyl-3-benzylaminomethylenepyrrolidine-2,4-dione (VIIa). The amide (VI) (1.83 g) was dissolved with heating in 35 ml of water, and 1.8 ml of benzylamine added. The mixture was kept at room temperature for 30 min, and the solid filtered off and washed with methanol.

1-Carbamoylmethyl-3-(β-phenylisopropyl)aminomethylenepyrrolidine-2,4-dione (VIIb). A mixture of 1.83 g (10 mmole) of (VI), 1.48 g (11 mmole) of phenylisopropylamine, and 70 ml of methanol ws boiled for one h, and the solvent removed. The residue was dissolved in the minimum amount of chloroform, activated carbon added, and chromatographed in a column of silica gel (2 × 16 cm). Elution was carried out with chloroform, and the solvent evaporated under reduced pressure. The residue was triturated with light petroleum, and the crystalline solid which separated was filtered off.

1-Ethoxycarbonylmethyl-3-benzylaminomethylenepyrrolidine-2,4-dione (Va). Ester (IV) (2.4 g) was dissolved in 20 ml of methanol, 2.4 ml of benzylamine added, and the mixture boiled for 0.5 h. The methanol was evaporated, and the residue treated with 10 ml of propan-2-ol. The solid was filtered off and washed with propan-2-ol.

1-Ethoxycarbonylmethyl-3-(β-phenylisopropyl)aminomethylenepyrrolidine-2,4-dione (Vb). Obtained as for (Va). After removal of the methanol, the residue was dissolved in the minimum amount of chloroform, chromatographed on a column of silica gel (2 × 8 cm), eluted with chloroform, and the solvent removed under reduced pressure. The residue was triturated with ether, and the solid filtered off.

1-Ethoxycarbonylmethyl-3-(γ-carboxypropyl)aminomethylenepyrrolidine-2,4-dione (Vc). A mixture of 2.4 g (10 mmole) of (IV), 1.03 g (10 mmole) of γ-aminobutyric acid, and 30 ml of acetic acid was boiled for 2 h, then kept overnight and the solvent evaporated. The residue was treated with 10 ml of water, and the solid filtered off and washed with water and 2-propanol.

1-Ethoxycarbonylmethyl-3-carboxymethylaminomethylenepyrrolidine-2,4-dione (Vd). To a solution of 0.46 g (10 mmole) of NaOH in 50 ml of ethanol was added 0.46 g (10 mmole) of glycine, and the mixture boiled for 10-15 min. To the resulting solution was added 2.4 g (10 mmole) of (IV), and the mixture boiled for 0.5 h. The solvent was removed, and the residue treated with 5 ml of water and 2 ml of hydrochloric acid. After cooling, the solid was filtered off, and washed with water and acetone.

1-Ethoxycarbonylmethyl-3-phenylhydrazinomethylenepyrrolidine-2,4-dione (VIII). To a solution of 2 g of (IV) in 50 ml of methanol and 0.7 ml of acetic acid was added with stirring at 5°C 1 ml of phenylhydrazine, and the mixture stirred for 1 h. The solid was then filtered off, and washed with a 1:1 mixture of ether and methanol.

2-Ethoxycarbonylmethyl-3-oxo-6-phenyl-1,2-dihydro-3H-pyrrolo[3,4]c]-pyrazole (IX). A mixture of 3 g of the enehydrazine (VIII), 40 ml of methanol, 40 ml of toluene, and a catalytic amount of toluene-p-sulfonic acid was boiled for 7-10 h. The solvent was removed, and the residue dissolved in the minimum amount of chloroform and chromatographed on a column of silica gel (2 × 10 cm), eluting with a 1:1 mixture of benzene and chloroform, followed by removal of the solvent under reduced pressure.

2-Carbamoylmethyl-3-oxo-6-phenyl-1,2-dihydro-3H-pyrrolo[3,4-c]pyrazole (Xa). Ammonia was passed for 5-6 h through a suspension of 2.85 g of the pyrrolopyrazole (IX) in 100 ml of methanol at room temperature. The solid was filtered off and washed with methanol.

2-Benzylcarbamoylmethyl-3-oxo-6-phenyl-1,2-dihydro-3H-pyrrolo[3,4-c]-pyrazole (Xb). A mixture of 2.85 g of (IX) and 15 ml of benzylamine was boiled for 2 h. The mixture was then cooled, 15 ml of light petroleum added, and the solid filtered off and washed with light petroleum.

2-(Diethylaminoethylcarbamoyl)methyl-3-oxo-6-phenyl-1,2-dihydro-3H-pyrrolo[3,4-c]pyrazole (Xc). A mixture of 2.85 g (10 mmole) of (IX), 2.32 g (20 mmole) of diethylaminoethylamine, and 80 ml of methanol was boiled for 10-12 h. The solvent was then removed, and the residue treated with light petroleum. The crystalline solid which separated was filtered off and washed with light petroleum.

TABLE 2. Effects of Pyrrolidineacetic Acids on Hypoxia, Corazole-induced Convulsions, and Retention of the CPAR in Mice

Compound	Dose, mg/kg (internal)	Lifespan, min		Convulsant effects of corazole (135 mg/kg)		Effect on CPAR, time to entry into darkened chamber	Acute toxicity, LD_{50}, mg/kg
		hypoxic	hemic	latent period			
				convulsions	death		
Control (0.2 ml of CMC)	—	22,4±1,1	22±1,4	4±0,5	12,6±1,1	69,5±12	—
Va	200	26±1,4	20±1,6	3,7±0,6	11,2±1,1		1500
	400					67,5±14,5	
Vb	200	22,7±0,9	15,9±1,2	3±0,1	10,7±1,1		1300
	400					67,0±14,2	
Vc	200	26±0,6	25,7±0,8	5,1±0,7	16,7±2,3		1500
	400					70,3±13	—
VI	200	27,1±0,9	22,8±1,4	4,7±0,6	13,2±1,4		>2000
	400					70,7±13,9	—
VIII	200	20±1,0	21±1,2	3±0,1	12,0±2,0		>2000
	400					97,0±8,2	—
VIIa	200	24,8±0,9	21,6±2,5	3±0,4	12,0±2,0		1200
	400					70,0±12,8	—
IX	200	23±1,5	20±1,5	2±0,2	10,5±1,0		700
	400					60,0±12	—
Pyracetam	300	—	—	—	—	110,0±8,0	>5000
	500	35,2±2,0	—	—	—	136±6,4	

EXPERIMENTAL (BIOLOGICAL)

The compounds (V-IX) were examined for overall effects (spontaneous locomotion and group behavior), antihypoxic and nootropic activity, and anticonvulsant effects. The tests were carried out with male mice weighing 18-20 g, with 10-12 animals in each group.

Antihypoxic activity was measured in model hypoxic hypoxia with hypercapnia in an enclosed space [5], and in histotoxic hypoxia induced by administration of sodium nitrite (300 m/g, s/c). The lifespans of the animals were measured in both types of hypoxia.

Nootropic activity was assessed by the effects on CPAR memory and learning in mice, using the two-chamber avoidance method [9]. The latent period for entry into the darkened chamber, in which the animal had previously received an electric shock to the paws, and the residence time in the lightened chamber, were measured. The compounds were given internally in doses of 200-400 mg/kg.

Anticonvulsant activity was examined in model convulsions [15] induced by corazole (135 mg/kg, s/c) and maximum electric shock (MES, 50 mA, 60 Hz, 0.2 msec). The compounds were given internally in a dose of 200 mg/kg.

The effects on the general state and behavior of the animals were assessed by visual observation, and spontaneous motor activity was measured in an Ortho-Barimex apparatus (USA). Acute toxicities (LD_{50}) were determined in mice by the internal route (I).

Test Results. Nootropic compounds display cerebroprotectant properties, while being virtually inactive in classical neurophyschopharmacological tests and now showing typical psychopharmacotherapeutic properties [10].

In the present tests, pyracetam in doses of 300 and 1000 mg/kg did not affect levels of orientational and investigative activity, locomotion, or group behavior. The drug did, however, greatly facilitate retention of the CPAR, extending the latent period for entry into the darkened chamber one day after establishment of the conditioned avoidance reflex (Table 2). Pyracetam shows antihypoxic activity in a dose of 1000 mg/kg, the lifespan under conditions of hypoxic hypoxia being increased by 64%. In histotoxic hypoxia, the drug was inactive, as it was also in antagonizing the convulsant effects of corazole. The test compounds were used in doses of 1/4 to 1/6 of the LD_{50} values (200 and 400 mg/kg, by mouth). It was found that they had no effect on the lifespan of the mice in either of the two types of experimental hypoxia. In the same doses, they were without effect on the general behavior of the animals, or on the convulsant effects of MES or corazole. Of the compounds tested, only (VIIa) facilitated memory processes. In a dose of 400 mg/kg, the compound extended the latent period for entry into the darkened chamber by 39% (Table 2). The test results failed to reveal this type of activity in any of the other compounds. It is therefore apparent that the introduction of cyclic enaminoketone groupings into pyracetam and its analogs results in either a reduction, or total loss of nootropic and antihypoxic activity.

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BIOLOGICAL ACTIVITY OF FLUORINATED 3,4-DIHYDROISOQUINOLINES

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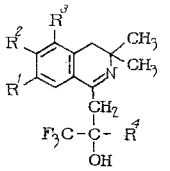
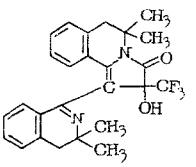
UDC 615.22:547.833.1].038

Cardiovascular diseases are commonly treated with isoquinoline derivatives (papaverine, 'no-shpa') [4]. In the past decade, fluororganic compounds have been progressively introduced into pharmacological practice, since they comprise compounds with a wide spectrum of activity.

We have now examined the biological activity of some fluorinated 3,3-dimethyl-3,4-dihydroisoquinolines (Ia-c, IIa-e, and III).



I, II



III

R^1=H (Ia, c, IIa, b, e), OCH_3 (Ib, IIc, d); R_2=H (Ia, IIb), OCH_3 (Ib, IIc, d); R^3=H (Ia, b, IIa-d); $R^2 + R^3$ = –CH=CH–CH=CH– (Ic, IIe); R^4=CF_3 (Ia-c), COOMe (IIa, c), COOEt (IIb, d, e).

EXPERIMENTAL (CHEMICAL)

Compounds (Ia-c), (IIa-e), and (III) were obtained by hydroxyalkylation of 1,3,3-trimethyl-3,4-dihydroisoquinolines with hexafluoroacetone or trifluoropyruvate esters, as reported in [6]. These compounds were obtained in a preparative form as their water-soluble hydrochlorides, prepared by passing HCl through a solution of the appropriate base in dry ether (Ia, c, IIa, b, d) or acetone (Ib, IIc, III), followed by isolation of the solid by filtration and crystallization from ethanol or methanol for (IIa, c). The elemental analyses for the hydrochlorides of (Ia-c), (IIa-e), and (III) were in agreement with the calculated values. Neutralization of aqueous solutions of the hydrochlorides with sodium bicarbonate resulted in precipitation of the original bases.

EXPERIMENTAL (PHARMACOLOGICAL)

The biological activity of the compounds was assessed in terms of their acute toxicity, antiarrhythmic activity, antiaggregational activity with respect to thrombocytes, and hypotensive activity.

Acute toxicities were determined in white mice of both sexes weighing 16-20 g by the oral route [1]. Antiarrhythmic activity was assessed in a model arrhythmia induced by intravenous administration of calcium chloride to mice in a dose of 280 mg/kg [3].

Antiaggregational activity was examined using the photometric method of Born [5] with dog plasma thrombocytes, expressed as a percentage reduction in optical density. Thrombocyte aggregation was induced by means of ADP in a dose of 0.05 mg/kg of plasma. All compounds were tested at the same dose, 0.2 mg/ml of plasma.

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