EXPERIMENTAL (BIOLOGICAL)

The antimicrobial activity of the synthesized isothiocyanates was studied using the method of double serial dilution in liquid nutrient medium against Gram-positive (S. aureus), Gram-negative (E. coli, P. aeruginosa) and spore forming (B. subtilis) bacteria.

The test compounds exhibited antibacterial activity primarily against spore-forming Gram-positive bacteria. E. coli were found to be stable to the compounds at the concentrations used in the tests.

For the compounds tested, the minimum suppressing concentration was determined by the method of double serial dilution in Saboraud's medium against the yeast fungi C. albicans, dermatophite T. rubrum, and T. mentagrophytes, and also an example of the fungus A. niger.

Compounds I-VI possessed antifungal activity, including activity against fungal microflora. Some pathogenic strains of fungus were more stable to the test compounds.

The data obtained indicate that 2-isothiocyanato-1-aryl-3-butene (Table 2) exhibits both antibacterial and antifungal activity. The introduction of a methyl or methoxy group did not bring about any substantial change in biological properties, confirming that these properties are determined by the overall structure.

LITERATURE CITED

1. D. Barton and I. Hollis, General Organic Chemistry [Russian translation], Vol. 5, Moscow (1983), p. 675.
2. L. Bellamy, New Data on IR Spectra of Complex Molecules [Russian translation], Moscow (1971), pp. 65, 66-68.
3. B. D. Grishchuk, P. M. Gorbovoi, and N. I. Ganushchak, Thesis, in: Fifth All-Union Symposium on Organic Synthesis, Moscow (1988), p. 30.
4. S. Pataj, The Chemistry of the Cyanates and Their Thio Derivatives, Jerusalem, Vol. 2 (1977).

SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF AMINE ANALOGS OF PIRACETAM

T. A. Voronina, O. M. Glozman, É. K. Orlova, L. M. Meshcheryakova, V. Zauer, R. Ékkard, T. L. Garibova, I. Kh. Rakhmankulova, A. Rostok, and Kh. Zigemund

UDC 615.214.3:547.298.5].012.1

In order to explain the effect of structural factors on nootropic activity, we have synthesized analogs of piracetam (Ia-g) with an amidine group in the side chain in place of the amide group [3, 6].

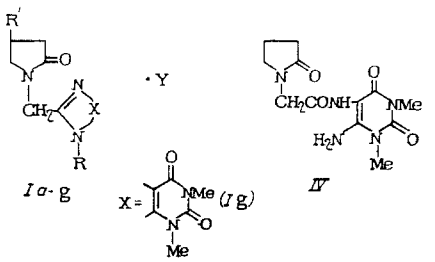
Compounds Ia, c were obtained by the thermal cyclization of the nitrile of 2-oxopyrrolidine-1-acetic acid (II) with o-phenylenediamine or 3,4-diaminopyridine in the presence of polyphosphoric acid.

Compound Ib was synthesized by the reaction between 4-phenylpyrrolidone-2 and the methyl ester of chloroacetic acid in toluene in the presence of MeONa, followed by fusion of the ethyl 2-oxo-4-phenylpyrrolidine-1-acetate (III) with o-phenylenediamine. Condensation of methyl 2-oxopyrrolidine-1-acetate with 4,5-diamino-1,3-dimethyluracil monohydrate in the presence of a catalytic amount of NH_4Cl gave 4-amino-5-[(2-oxopyrrolidinyl-1)acetamido]-1,3-dimethyluracil monohydrate (IV), which when heated with a dilute solution of NaOH was converted to Ig.

Scientific-Research Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. National Enterprise Pharmaceutical Combine Germed, Chief Production Arzneimittel'-verk, Dresden, German Democratic Republic.

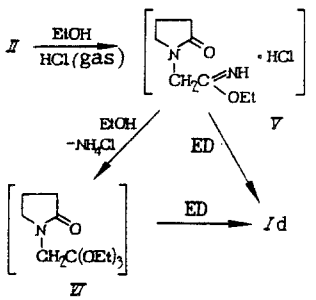
Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 24, No. 11, pp. 26-29, November, 1990. Original article submitted November 22, 1989.

0091-150X/90/2411-0798$12.50



R=H(Ia-d,g), $CH_2C_6H_5$ (Ie), $COCH_3$ (If); R'=H(Ia, c-g) Ph (Ib); X= o-phenylene (Ia, b), pyridinediyl-3,4(Ic), $-CH_2CH_2-$ (Id-f); Y=$C_2H_2O_4$(Ia, d), 0.5 $C_2H_2O_4$ (Ic), $C_4H_4O_4$ (Ie), $0.3H_2O$ (If).

Heating compound II with ethylenediamine did not result in cyclization; compound Id was synthesized from nitrile II by a reaction involving the intermediate iminoether (V). Compound Ie was obtained by the same method. The cyclization of V with ethylenediamine gave, in addition to Id, a by-product which could only be removed by column chromatography on Al_2O_3. Another method of obtaining the imidazoline ring Id was attempted: starting from the nitrile II through the iminoester V and orthoester VI, as shown in the following scheme:



The acylation of Id with Ac_2O gave the acetyl derivative If. The starting nitrile II, for the synthesis of compounds Ia, c-f, was obtained by one of three methods: direct alkylation of pyrrolidone-2-chloroacetonitrile in the presence of NaH, by dehydration of the amide 2-oxopyrrolidine-1-acetic acid by P_2O_5, or by the alkylation of O-methylbutyrolactim chloroacetonitrile.

EXPERIMENTAL (CHEMICAL)

IR spectra were obtained on a Perkin–Elmer 457 instrument (Sweden), PMR spectra were taken on a Varian T-60 (USA). Mass spectra were recorded on a variant MAT-112 chromatomass spectrometer (USA) with direct introduction of the sample into the ion source at 100°C and an ionization potential of 75 eV. TLC was carried out on Al_2O_3 (alkaline form, activity IV, eluant – a 10:1 mixture of $CHCl_3$ and absolute alcohol).

2-(2-Oxopyrrolidinomethyl)benzimidazole, Oxalate (Ia). A mixture of the nitrile II (2.2 g, 0.018 mole), o-phenylenediamine (1.62 g, 0.015 mole), and polyphosphoric acid (25 g) was heated for 7.5 h at 150-160°C. The reaction mixture was treated with water and made alkaline (pH 8-9) with sodium carbonate. The precipitate was filtered off, washed with $CHCl_3$, the chloroform solution dried, and evaporated to dryness. A solution of oxalic acid (0.72 g) in absolute alcohol was added to the residue to give the oxalate Ia (1.7 g). PMR spectrum (D_2O), δ, ppm: 2.05 dd (2H, 4-CH_2), 2.52 t (2H, 3-CH_2), 3.62 t (2H, 5-CH_2), 4.94 s (2H, CH_2N), 7.45 m (4H, arom.). Mass spectrum (base): 215 (M^+), 214 $(M-H)^+$.

Methyl Ester of 2-Oxo-4-phenylpyrrolidine-1-acetic Acid (III). To a solution of 4-phenylpyrrolidone-2 (16.1 g, 0.1 mole) in toluene (160 ml) was added 65% sodium methoxide (8 g, 0.1 mole). After stirring for 15 min, the mixture was heated at 150-160°C with evaporation of the toluene, cooled somewhat, and further toluene (15 ml) added. Methyl chloroacetate (12 g, 0.11 mole) was then added over a period of 10 min at 60°C and the reaction mixture heated for 2 h at 60-70°C, then cooled to 20°C, and water (50 ml) added. After mixing for 5 min, the organic layer was dried with Na_2SO_4 and evaporated in vacuum to give the ester III (20 g, 88.8%) with bp 160-163°C (0.3 mm Hg).

2-(2-Oxo-4-phenylpyrrolidinomethyl)benzimidazole (Ib). A mixture of the ester III (22 g, 0.094 mole), o-phenylenediamine (10.1 g, 0.094 mole), and NH_4Cl (0.5 g) was heated in a

TABLE 1. Cyclic Amidine Analogs of Piracetam

Compound	Yield, %	Bp, °C (solvent)	Empirical formula
Ia	37,0	164—5 (MeOH)	$C_{12}H_{13}N_3O \cdot C_2H_2O_4$
Ib	42,0	243—5.5 (DMFA)	$C_{18}H_{17}N_3O$
Ic	48,0	235 (alcohol)	$C_{11}H_{12}N_4O \cdot 0{,}5C_2H_2O_4$
Id	21,0	161—1 (absolute alcohol)	$C_8H_{13}N_3O \cdot C_2H_2O_4$
Ie	42,2	121—2 (absolute alcohol)	$C_{15}H_{19}N_3O \cdot C_4H_4O_4$
If	24,2	88—90 (ether-benzene)	$C_{10}H_{15}N_3O_2 \cdot 0{,}3H_2O$
Ig	63,9	263—7	$C_{12}H_{15}N_5O_3$

TABLE 2. Pharmacological Properties of Amidine Analogs of Piracetam

Compound	Dose, mg/kg	Antihypoxic activity (life-span in % of control)	Antiamnestic activity (time of stay in lighted cell in seconds)	Motor activity in open field (total observations)	Myorelaxant effect by test %		Sedative effect from position on screen test, %
					rotating rod	pulling up on cross-beam	
Control	—	100	24,6±6,12	61,0±6,9	—	—	—
Ia	50	132	18,4±9,6	44,8±5,5	—	—	50,0
	100	157	27,7±8,3	54,7±7.3	33,0	33,0	50,0
Control	—	—	39,2±8,3	Not used	No effect		0
Ib	100	—	40,6±6,6	» »	»		0
Control	—	100	41,0±12,5	—			
Ic	50	131	84,7±19,4*	Not used	»		0
	100	154	65,7±19,4	»	»		0
Control	—	100	65,6±15,3	—			
Id	50	—	—	—	»		0
	100	97	39,0±13,3	Not used	»		0
Control	—	100	33,8±9,9				
Ig	50	114	43,5±7,9	36,0±24,5	16,6	16,6	50,0
	100	109	72,5±13,3*	21,0±15,1	—	—	—
Control	—	100	43,8±11,8	Not used	No effect		0
Piracetam	300	120	81,8±20,8	» »	»		0

*$p < 0.05$.

metal bath to 150°C, then cooled to ~120°C, and the water and MeOH formed driven off at reduced pressure. The residue was heated for 1.25 h at 150°C, cooled to ~90°C and acetone (50 ml) added. Compound Ib (14.1 g, 51.5%) was filtered off.

2-(2-Oxopyrrolidinomethyl)imidazolo[4,5-c]pyridine, Hemioxalate (Ic). A mixture of the nitrile II (2.5 g, 0.02 mole), 3,4-diaminopyridine (2 g, 0.02 mole), and polyphosphoric acid (30 g) was heated for 2 h at 130°C and 1 h at 150°C, in the presence of $CHCl_3$. The melt (90°C) was decomposed with water (100 ml), made alkaline with K_2CO_3, and extracted with $CHCl_3$. The extract was dried, evaporated under vacuum, and the residue dissolved in absolute alcohol. This solution was poured into a solution of oxalic acid (1.8 g, 0.02 mole) in a mixture of absolute alcohol and ether (1:1), cooled to 0°C, and the precipitated material filtered to give 2.5 g of the hemioxalate Ic. IR spectrum (KBr), λ_{max}, cm^{-1}: 3415 (NH and OH), 1678 (C=O), 1640 (C=N).

2-(2-Oxopyrrolidinomethyl)-Δ^2-imidazoline, Oxalate (Id). Hydrogen chloride was passed for 1.5 h through a solution of the nitrile II (15.5 g, 0.125 mole) and absolute alcohol (8 ml) in anhydrous $CHCl_3$ (40 ml) and absolute ether (150 ml). The precipitated material was filtered off, washed with $CHCl_3$ and absolute ether, and dried over P_2O_5 and KOH. To the iminoester hydrochloride V obtained was added absolute alcohol (23.5 ml, 0.4 mole), the mixture shaken for 20 min, and the precipitate filtered off and washed with absolute alcohol. Ethylenediamine (7.5 g, 0.125 mole) was added to the alcoholic solution of the orthoester VI, the mixture stirred for 2 h at room temperature, and allowed to stand overnight. The alcohol was distilled off, the residue dissolved in $CHCl_3$, filtered, and dried over K_2ClO_3. The $CHCl_3$ was evaporated to give the base (10.9 g) which was dissolved in absolute

alcohol (15 ml). Addition of a solution of oxalic acid (5.85 g, 0.065 mole) in absolute alcohol (20 ml) gave the oxalate Id (6.8 g, 21%). IR spectrum, λ_{max}, cm^{-1}: 3415 (NH), 1675 (C=O), 1618 (C=N). PMR spectrum (D_2O), δ, ppm: 2.40 dd (2H, pyrrolidone 4-CH_2), 2.65 t (2H, 3-CH_2), 3.75 t (2H, pyrrolidone 5-CH_2), 4.22 s (4H, imidazoline 4- and 5-CH_2), 4.68 s (2H, NCH_2). Mass spectrum (base): 167 (M^+), 166 $(M-H)^+$.

1-Benzyl-2-(oxopyrrolidinomethyl)-Δ^2-imidazoline, Maleate (Ie). To a suspension of crude iminoester hydrochloride V (7.9 g, 0.038 mole) in absolute alcohol (20 ml) was added Et_3N (3.84 g, 0.038 mole), followed by the dropwise addition of N-benzylethylenediamine (6.2 g, 0.04 mole), and the mixture refluxed for 4 h. The reaction mixture was filtered, the filtrate evaporated, and the residue passed through Al_2O_3 (activity II). Elution with $CHCl_3$, and evaporation of the eluate gave the imidazoline Ie (4.1 g, 42.2%). The base Ie (1.3 g) was treated with maleic acid (0.58 g) to give the maleate of Ie. IR spectrum of the base Ie (liquid between plates), λ_{max}, cm^{-1}: 1680 (C=O); 1615 (C=N). PMR spectrum ($CDCl_3$), δ, ppm: 1.73-2.23 m (4H, pyrrolidione 3-CH_2 and 4-CH_2), 3.10-3.75 m (6H, pyrrolidone 5-CH_2, imidazoline 4- and 5-CH_2), 4.18 s (2H, N-CH_2), 4.35 s (2H, CH_2Ph), 7.26 s (5H, arom.).

N-Acetyl-2-(2-oxopyrrolidinomethyl)-Δ^2-imidazoline (If). To a solution of imidazoline Id (2.8 g, 0.016 mole) in anhydrous dioxane (40 ml) was added Ac_2O (1.63 g, 0.016 mole). After mixing for 2 h at 20°C, the reaction mixture was left overnight, then diluted with a mixture of heptane and petroleum ether to give the acetyl derivative If (0.8 g). IR spectrum (KBr), λ_{max}, cm^{-1}: 1683 (C=O), 1643 (C=O). PMR spectrum ($CDCl_3$ + d_6-DMSO), δ, ppm: 1.95 s (3H, CH_3-CO), 2.1-2.8 m (4H, pyrrolidone 3-CH_2, 4-CH_2), 3.2-3.62 (6H, pyrrolidone 5-CH_2, iomidazoline 4-CH_2 and 5-CH_2), 3.95 s (2H, CH_2N).

4-Amino-5-[(2-oxopyrrolidinyl-1)acetamido]-1,3-dimethyluracil (IV) Monohydrate. A mixture of 75.2 g (0.4 mole) of 4,5-diamino-1,3-dimethyluracilmonohydrate, 125.6 g (0.8 mole) of methyl ether 2-oxopyrrolidin-1-acetate, and 2.12 g of NH_4Cl was heated for 5 h at 150°C with evaporation forming MeOH, cooled, 200 ml of alcohol was added, and the residue was washed with 60 ml of alcohol to give the uracil of IV (47.5 g, 37.9%), mp 264-267°C (water). $C_{12}H_{19}N_5O_5 \cdot H_2O$.

8-[2]Oxopyrrolidinyl-1-methyl)theophylline (Ig). To a mixture of IV (15.6 g, 0.05 mole) and water (80 ml) was added dropwise at 70°C a solution of NaOH (2.6 g, 0.06 mole) in water (10 ml). The mixture was heated for 15 min at 80°C, cooled to 30°C, and acidified (pH 5-6) with dilute HCl (10 ml) to give Ig (8.8 g). IR spectrum (in KBr), λ_{max}, cm^{-1}: 2950, 2925, 2875 (alkyl groups), 1695, 1650 (amide CO), 1560 (C=N).

EXPERIMENTAL (PHARMACEUTICAL)

The pharmacological study of new amidine analogs of piracetam was carried out by tests on nonpedigree white male mice weighing 18-25 g, initially contained in a vivarium with free access to food, water, and natural light. The test compounds were administered intraperitoneally in physiological solution 30-40 min before the beginning of an experiment, in doses of 50 and 100 mg/kg. The data were treated statistically by the method given in [1, 4]. The known nootropic preparation piracetam was used for comparison.

For the evaluation of antiamnestic activity, a modification of the method described in [5], used to test for the suppression of a conditioned response, the passive avoidance of an electric shock, was employed. Electroshock was used as the amnestic agent. For this, the animal was placed in a lighted compartment and the time was recorded for the mouse to exit into a dark compartment, where it was given a single electric shock by means of an electric field (training). Immediately after the training an electroshock treatment was applied. A repetition of the reflex was performed within 24 h after training.

To evaluate the antihypoxic action of the substances, the method of hypobaric, hypopsychic, and hemic hypoxia was used. The acute hypobaric hypoxia was created in a circulating pressure chamber which simulated lifting the animals to a height of 11,000 m at a speed of 50 m/sec [7]. The effect of the compound on the orienting behavior and motor activity was determined by an open field test, recording the horizontal and vertical movements and the number of inspections of openings, and from the test positions on the screen. The myorelaxant properties were determined by the ability of the animal to maintain itself on a rotating rod and to pull itself up on a horizontal crossbeam [2].

A study of the pharmacological properties of amidine analogs of piracetam showed that in mice compounds Ic and Ie, in doses of 50 and 100 mg/kg, prevented the development of retro-

grade amnesia caused by maximum electroshock, and significantly increased, compared with the control, the residence time in the light chamber on repetition of the conditioned passive avoidance response. The remaining compounds in doses of 50 and 100 mg/kg did not exhibit any antiamnestic properties.

A study of antihypoxic activity showed that at the dosage used, compounds Ic and Ia increased the lifespan of mice with hypobaric hypoxia by 1.3-1.5 times; however, these changes were statistically uncertain.

It was also shown that compounds Ia and Ig had a depressing effect on the animals, 50% of which exhibited a decrease in orienting behavior and, in addition, these substances possessed weak myorelaxant properties. Among the amidine analogs of piracetam that we studied were some which exhibited antiamnestic activity, antihypoxic action, or depressing and myorelaxant effects. The pharmacological profile of the activity of the amidine analogs of piracetam — the nature of antiamnestic and antihypoxic action — is similar to that of the nootropic preparation piracetam.

LITERATURE CITED

1. M. L. Belen'kii, Elements of the Quantitative Evaluation of Pharmacological Effects [in Russian], Riga (1959), pp. 36-47.
2. T. A. Voronina, Yu. I. Vikhlyaev, L. N. Nerobkova, et al., Phenazepam [in Russian], Kiev (1962), pp. 145-151.
3. O. M. Glozman, T. A. Voronina, E. K. Orlova, et al., Khim.-farm. Zh., No. 9, 1142-1152 (1989).
4. E. V. Gubler, Computing Methods of Analysis and Diagnosis of Pathological Processes, Leningrad (1978), pp. 72-75.
5. I. Kh. Rakhmankulova, T. L. Garibova, K. E. Voronin, et al., Farmakol. Toksikol., 48, No. 4, 42-48 (1985).
6. T. V. Stezhko, V. G. Granik, R. G. Glushkov, et al., Khim.-farm. Zh., No. 7, 823-827 (1984).
7. U. M. Tileneeva, T. A. Voronina, V. I. Kuz'min, et al., Farmakol. Toksikol., 50, No. 1, 71-74 (1987).

SYNTHESIS OF AMINOMETHYL DERIVATIVES OF NAPHTHO[1,2-b]FURAN

T. I. Mukhanova, R. A. Zinov'eva, V. S. Velezheva, and G. A. Bogdanova

UDC 615.281.8:547.725]012.1

Aminomethyl derivatives of naphtho[1,2-b]furan have been unknown until now, although they are of interest from the biological aspect. The isoelectronic analogs of naphtho[1,2-b]-furan derivatives — the aminomethyl derivatives of benzo[g]indole and naphtho[1,2-b]thiophene exhibit antiviral [4] and antimicrobial activity [5], respectively.

To examine the antibacterial and antiviral activity, we synthesized 2- and 4-aminomethylnaphthofurans (II, III, VI, VII, X-XII, XV-XVII) with various substituents at the 2-, 4-, and 5-positions.

The 4-aminomethylnaphthofurans II and III were obtained by aminomethylation of naphthofuran I [1] by means of bis(dialkylamino) methanes.

2-Aminomethylnaphthofurans VI, VII were synthesized from naphthofuran I by consecutive acylation, bromination, and amination with secondary amines. The acylation step is necessary to prevent the readily occurring bromination of naphthofuran I at the 4-position [2]. It was carried out by treating naphthofuran I with Ac_2O in the presence of sulfuric acid, which is more convenient than the previously described acylation with Ac_2O in the presence of pyridine [6].

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow.

Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 24, No. 11, pp. 29-31, November, 1990. Original article submitted December 12, 1989.

0091-150X/90/2411-0802$12.50