SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF 1-THIOCARBAMOYLMETHYLPYRROLIDINE-2-THIONE

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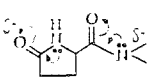
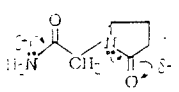
In the course of seeking new types of psychotropic preparations considerable interest has been shown in compounds that specifically affect cerebral integrative functions as well as in compounds that are grouped under the name of nootropic agents [6]. The principal representative of this new class of pharmacologically active substances is the compound piracetum – 2-oxo-1-pyrrolidine acetamide (I) which accelerates learning processes, elevates the brain's resistance to various types of harmful factors, particularly hypoxia, and enhances the transmission of intrahemispheric information.

Currently there is no single viewpoint about the mechanism underlying the pharmacological action of piracetam [7]. Nevertheless, from the available data in the literature one can assume that piracetam interacts in the body with receptors or closely related structures that are responsible for the binding of gamma aminobutyric acid (GABA) (II). On the one hand, this is indicated by the piracetamlike metabolic effects exhibited by GABA-ergic substances, and on the other hand by the ability of piracetam to potentiate the GABA-ergic inhibitory processes in the cerebral cortex [7]. It is in fact this viewpoint that is the basis for the current study in which we analyzed the structural characteristics of piracetam and which enabled us to substantiate our approach to the synthesis of compounds that are more active than piracetam.

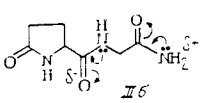
Previously, in examining piracetam as a preparation with a GABA-ergic mechanism of activity, researchers started from the hypothesis that it was chemically related to the cyclic form of GABA-pyrrolidone-2 which is one of the basic structural fragments of I [7]. However, that was not a sufficiently substantiated view inasmuch as the rupture of the pyrrolidine ring in piracetam is highly improbable under physiological conditions. Under such conditions GABA constitutes a charged zwitterion system which is impossible for pyrrolidone derivatives. Consequently, the very type of reaction with possible receptor structures in amino acids and their corresponding lactam derivatives, must be different. Proceeding from these assumptions, we examined other structural characteristics that approximate I and GABA and that are presented below.



IIa



I



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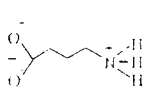

II

As can be seen from the drawn structures, the zwitterion form of II has integral positive and negative charges that belong to the N^+H_3 ammonium group and the COO^- carboxyl. A similar, although somewhat less pronounced distribution of charges can be observed for the structure

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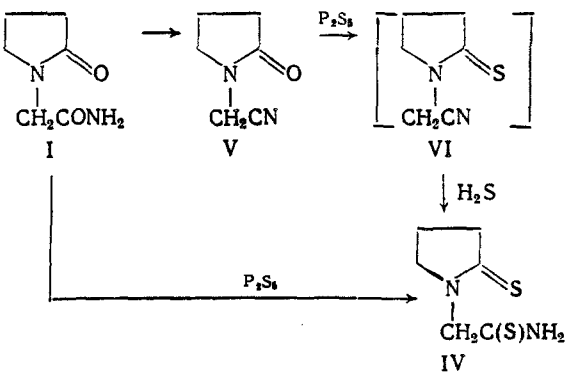
of compound I was well. Actually, the amide conjugation on the nitrogen of the carbamoyl residue of compound I results in a concentrated partial positive charge and a partial negative charge is concentrated on the lactam carbonyl (due to the same reason).

One can thus presume that the structural modifications that could lead to a greater localization of such charges (at least at the time of receptor reaction) must have brought the new structure close to that of II from the viewpoint of electron localizations. By the same token such modifications would have enhanced certain aspects of biological activity in compound I. Such conditions correspond, for example, to the structure of pyroglutamic acid derivatives (e.g., IIIa, b) that were recently described in the literature and whose nootropic activity exceeds that of compound I. In the present work we took another path and synthesized IV with consideration given to the fact that a sulfur atom retains a negative charge significantly better than an oxygen atom (one can compare, for example, the acidity of alcohols and mercaptans).

The present work is concerned with the synthesis of compound IV and an investigation of its pharmacological activity.

We synthesized compound IV by two methods. In the first method, compound I is treated with an excess of phosphorus pentasulfide in dry xylene, in which case the oxo groups of I are replaced by thiones. The yield of the target product IV, however, was small (≈30%). In examining possible alternative methods to synthesize IV we found that we could obtain a more satisfactory yield (~65%) of compound IV by reacting the previously synthesized 1-cyanomethylpyrrolidone-2 (V) [9] with P_2S_5 under the same conditions and followed by treating the resultant precipitate with boiling water. Apparently, the reaction between V and P_2S_5 results in a mixture of the monothioderivative (VI) and P_2S_5 which, when boiled with water, is accompanied by the release of hydrogen sulfide which when added to the cyano group converts it to a thiocarbamoyl group.



The structure of IV was confirmed by element analysis and spectral data. The IR spectrum exhibited absorption bands at 1630, 3110, and 3260 cm^{-1} (NH_2) and 1120 cm^{-1} (C=S). The mass spectrum had a molecular ion peak $M^{+\cdot}$ 174 and ion peaks 141 $[M - SH]^+$, 114 $[M - CSNH_2]^+$, 100 $[M - CH_2CSNH_2]^+$, 85 $[M - C_3H_7NS]^+$. The PMR spectrum had (DMPA-d_7) signals at 2.08 (2H, quint., 4-CH_2); 2.53 (2H, t, 3-CH_2); 3.92 (2H, t, 5-CH_2); 4.80 (2H, s, N-CH_2); 9.24 and 9.74 ppm (2H, broad s, NH_2).

EXPERIMENTAL (CHEMICAL)

The IR spectrum was recorded on a Perkin-Elmer-457 spectrophotometer (Sweden) in the form of a paste in petroleum jelly. PMR spectrum was obtained on a IMH-4H-100 spectrometer, internal standard tetramethylsilane. Solvent was DMPA-d_7. The mass spectrum was recorded on a MAT-112 instrument (ionizing voltage 50 eV, ionization chamber temperature 140°C). Purity was controlled chromatographically on Silufol UV-254 plates (Czechoslovakia). Melting temperature was measured on a Boetius-type heating stand.

1-Thiocarbamoylmethylpyrrolidine-2-thione (IV) was synthesized from 1-cyanomethyl-2-oxypyrrolidine. A mixture of 21.6 g (0.175 mole) of 1-cyanomethyl-2-oxypyrrolidine and 37.9 g (0.175 mole) of phosphorus pentasulfide was boiled in 850 ml of dry xylene for 4 h. The mixture was cooled to room temperature and the precipitate was filtered off and boiled in 2500 ml of water for 30 min. The reaction mixture was filtered. The mother liquor was cooled and the resultant precipitate IV was filtered off. An additional quantity of compound IV was

obtained by evaporating the mother liquor. Yield of IV was 65%. $C_6H_{10}N_2S_2$. Compound was crystallized from isopropanol for analysis; mp 156-158°C.

Compounds IV were also similarly obtained through the use of toluene, mesitylene, and benzene instead of xylene as the inert nonpolar solvent (yields of IV were 49%, 41%, and 62%, respectively).

1-Thiocarbamoylmethylpyrrolidine-2-thione (IV) was synthesized from 1-carbamoylmethylpyrrolidone-2 (piracetam). A mixture of 2.8 g (0.02 mole) of 1-carbamoylmethylpyrrolidone-2 and 8.8 g (0.04 mole) of phosphorus pentasulfide in 50 ml of dry xylene was boiled for 4 h. The mixture was cooled to room temperature, the precipitate was filtered off and boiled in 150 ml of water for 30 min. The reaction mixture was filtered. The mother liquor was cooled and the resultant precipitate IV was filtered off (yield 32%).

In deciding which approach to use in the pharmacological study of compound IV it seemed natural first to study the nootropic properties of this compound in comparison to compound I in a parallel series of experiments. In that connection we examined the effect of compound IV on the learning and memory processes and examined its reaction with thiosemicarbazide (TSC) which is a specific GABA antagonist.

Although there is much in the mechanism of nootropic substances that remains unclear, as indicated above, in the course of studying compound IV we felt that the effects of compound I are due to the compound's influence on nucleic and protein synthesis and the changes in the ratio of polysomes/ribosomes and the subsequent increase in the formation of ATP and other macroergs that are essential to the normal function of energy-dependent enzyme systems [11]. The ability to affect the formation and retention of macroergs allows us to presume that nootropes have antihypoxic properties, which has been experimentally and clinically proven [2-4, 8, 10, 12, 13]. With that in mind, considerable attention in our study was given to the investigation of the antihypoxic properties of compound IV.

PHARMACOLOGICAL ACTIVITY OF IV

Acute Toxicity and Examination of Nootropic Properties. The acute toxicity of compound IV was tested on mice weighing 18-20 g by intraperitoneal administration. We found that the preparation caused suppression of the animals' general condition beginning at a dose of 250 mg/kg. The LD_{50} upon intraperitoneal administration was 1200 mg/kg, and for compound I it was more than 10,000 mg/kg, i.e., compound IV is more toxic than piracetam. However, since the LD_{50} of compound IV exceeds 1000 mg/kg, it can be considered to be a compound of low toxicity.

Effect on Learning and Memory Processes. We studied the effect that compound IV has on the speed of learning, i.e., the performance of a conditional reflex in rats, and on the processes of memory consolidation in mice.

On 40 nonpedigree (4 groups of 10 each) male rats weighing 150-170 g we tested their reflexes to the sounding of a bell as a conditional stimulant, reinforced by an absolute stimulant which was an electric current (40-50 V) delivered to an electrified floor. The conditional reflex was considered performed if the rat jumped onto the stand in response to the sounding of the bell during the first 10 sec.

The first group of rats in a background of conditional reflex performance for 3 weeks (5 times per week) was given compound IV intraperitoneally at a dose of 250 mg/kg 24 h before the experiment. The animals of the second and third groups were given piracetam at doses of 500 and 1000 mg/kg, and the rats of the fourth group (the control) were given an isotonic NaCl solution.

We found that compound IV accelerates (by approximately two times) the performance and reinforcement of the conditional reflex (in the control animals the reflex was reinforced after 95-127 combinations of the conditional and absolute stimulants, and after 49-65 combinations in a background of IV administration). Piracetam exhibited a similar effect only at a dose of 1000 mg/kg.

In addition, we found that compound IV has a positive effect on the performance of the conditional avoidance reflex. At the dose employed, compound IV reduced the conditional reflex latent period by more than two times in comparison to the control (from 2.14 ± 0.71 to 0.87 ± 0.32 sec). Piracetam had a similar effect (0.98 ± 0.29 sec) only at a dose of 1000 mg/kg.

TABLE 1. Anticonvulsive Activity of IV and Piracetam

Preparation	Dose of TSC, mg/kg	Latent period of tremor onset, min	Lifetime, min
Control (0.9% NaCl solution)	—	63,5 (57,1—69,9)	69,5 (65,8—73,2)
IV	50	59 (51,5—66,5)	76 (64—88)
	250	82,6 (76,1—89,1)	100,8 (93,5—108,1)
	500	80 (75,6—86,4)	105 (95—115)
Piracetam	1000	66,6 (61,0—72,2)	79,9 (64—95,8)
	2000	70,6 (65,6—75,6)	82 (73,6—90,4)

Note. Here and in Table 2 limits of fluctuations are in parentheses.

TABLE 2. Effect of Compound IV on Mice Longevity (in min) in Acute Hypoxic Hypoxia

Preparation	Dose, mg/kg						
	0	100	250	500	750	1000	2000
Control	28,1 (22.5—33,7)	—	—	—	—	—	—
IV	—	56,3 (43,7—68,9)	60,3 (50,0—70,6)	95,2 (87,1—103,3)	119,2 (115,7—122,7)	Not tested	Not tested
Piracetam	—	27,4 (21,4—33,4)	33,5 (29,1—37,9)	39,6 (35,5—43,7)	34,4 (29,8—38,0)	41,4 (40,2—42,6)	45,0 (39,1—50,9)

Thus, compound IV is significantly more active in its ability to enhance the learning process in rats and to improve the performance of the conditional avoidance response in comparison to piracetam.

The effect on memory consolidation was tested on 400 nonpedigree male mice weighing 18-20 g by the conditional passive avoidance reflex method (CPAR) in a dual chamber apparatus in which one of the chambers darkened and whose bottom was affixed to an electrode floor to which an electric current (50-60 V) was delivered.

The mice usually preferred to be in the dark chamber. At the end of the exposure, which lasted 180 sec, an electric current which as a rule forced the animals in the darkened chamber to abandon their refuge. Thus, the mice learned the conditional passive avoidance reflex after a single training session. Reproduction of the effect, which was measured by the latent period (in sec) for running into the darkened chamber (or the time spent in the light chamber), was undertaken after 24 h.

Compound IV was administered at doses of 200-500 mg/kg, and pracetam was administered at doses of 200, 500, and 1000 mg/kg intraperitoneally, immediately after the performance of a conditional reflex. We found that compound IV at a dose of 200 mg/kg increases the latent period up to 136.2 ± 6.6 sec as opposed to 102.0 ± 6.9 sec in the control. A similar increase in the latent period of the reflex (up to 136.2 ± 6.4 sec) was observed when piracetam was employed only at a dose of 1000 mg/kg. Piracetam was inactive at smaller doses. The efficacy of the compound IVIES positive effect did not get any greater when the dose was raised to 500 mg/kg.

Thus, the experiments showed that compound IV has a positive effect on the speed of learning, the performance of a learned conditional reflex, and memory consolidation processes at doses that 4-5 times less than piracetam.

Reactions between IV and TSC. In connection with the fact that GABA plays an important role in learning and memory processes, we examined the possibility of a GABA-ergic component in the mechanism underlying the action of compound IV. To do this we investigated its ability to prevent tremors induced by TSC which inhibits the enzyme that synthesizes GABA.

The experiments were performed on 140 white mice weighing 18-20 g. TSC was administered subcutaneously at a dose of 20 mg/kg. Compound IV was administered intraperitoneally at doses of 50, 250, and 500 mg/kg 20 min after the administration of TSC.

TABLE 3. Effect of Compound IV on Mice Longevity (in min) at an Altitude of 11,000 Meters (M ± m)

Compound	Dose, mg/kg			
	0 (control)	100	250	500
Piracetam	6,1±2,75 (100,0±45,1%)	Inactive	6,16±0.72 (101,0±11,8%) $P>0,5$	8,13±2,43 (133,3±39,9%) $P>0,5$
IV	6,1±2,75 (100,0±45,1%)	12,58±3,64 (206,2±59,7%) $0,1<P<0,2$	19,97±4,93 (327,4±80,8%) $P<0,05$	30,0±0 (491,8±0%) $P<0,001$

TABLE 4. Effect of Compound IV on the "Altitude Ceiling" of Mice (in thousands of meters); M ± m

Compound	Dose, mg/kg		
	0 (control)	250	500
Piracetam	11,21±0,441	10,96±0,91 $P>0,5$	11,55±0,62 $P>0,5$
IV	11,21±0,441	14,0±0,707 $P<0,005$	15,57±0,85 $P<0,001$

Each dose was given to 20 mice. The presence of antitremor activity was determined by the change in the latent period of tremor onset and the prolonged onset of the animal's death. The experiments were done in comparison to piracetam. The resultant data are presented in Table 1.

As can be seen from Table 1, compound IV, when administered intraperitoneally at doses of 250 and 500 mg/kg, prolonged the latent period of tremor onset in rats by 25-30% and increases the period to the onset of animal death by 45-50% in comparison to the control.

When piracetam was administered at dose which exceeded the dose of IV by four times it increased the latent period of the tremor onset by only 10% in comparison to the control, and the period up to onset of animal death by 17%.

The resultant data indicate that GABA-ergic structures of the brain may participate in the mechanism underlying the action of compound IV. The same effect was poorly exhibited at higher doses.

Antihypoxic Action. Antihypoxic activity was tested on experimental models of hypoxic states in mice and rats. Compound IV was administered intraperitoneally in the form of an aqueous suspension prepared with Tween-80.

Acute Hypoxic Hypoxia Model with Hypercapnea. Tests were made on 540 nonpedigree white male mice weighing 20-22 g. Each animal was isolated in a hermetically sealed chamber (250 ml capacity) 60 min after the administration of compound IV at doses of 50, 100, 250, 500, and 750 mg/kg. The control animals were given an isotonic NaCl solution. Antihypoxic activity was measured by the number of minutes the animals lived in the hermetically sealed chamber.

As can be seen from the data shown in Table 2, in comparison to the control, compound IV approximately doubled the mice's longevity (by 103.9%) in acute hypoxic hypoxia even at a dose of 100 mg/kg, and at a dose of 750 mg/kg the longevity was quadrupled (by 324.5%), which is indicative of the compound's high level of antihypoxic activity.

Piracetam at a dose of 2000 mg/kg exhibited a comparable effect to that of compound IV at a dose of 100 mg/kg. Thus, compound IV exceeds the antihypoxic action of piracetam.

Acute Hypobaric Hypoxia Model. Acute hypobaric hypoxia was simulated in a flow barometric chamber at an air temperature of 17-22°C with absorption of CO_2 and water. Animals (male mice, tetrahybrids) weighing 15-22 g of a single generation "were raised" at an average velocity of 50 m/sec to an "altitude" of 11,000 m, at which longevity was measured in minutes in a single series of experiments. In addition, the mice were discretely "raised" at the same rate to an "altitude" of 10,000 m, where they remained for 1 min, after that, at 11,000 m

TABLE 5. Effect of Compound IV on Animal Longevity (in min) in Acute Normal Barometric Hypoxia (M ± m)

Compound	Animals	Dose, mg/kg		
		0 (control)	250	500
Piracetam	Mice	4,95±0,54 (100,0±12,6%)	3,73±0,254 (87,7±5,97%) $P>0,5$	6,08±0,74 (143,1±17,5%) $0,05<P<0,1$
IV		4,73±0,367 (100,0±7,75%)	22,21±3,23 (469,5±68,3%) $P<0,001$	—*
Piracetam	Rats	18,6±3,61 (100,0±19,4%)	— Inactive	17,3±5,25 (93,0±28,2%) $P>0,5$
IV		18,6±3,61 (100,0±19,4%)	27,38±7,07 (147,2±38,0) $0,1<P<0,2$	—*

*Test deemed inadvisable because effect obtained at small doses.

TABLE 6. Effect of Compound IV on Mice Resistance to Acute Histotoxic Hypoxia

Compound	Longevity, min (M ± m) dose, mg/kg			
	0 (control)	250	500	1000
Piracetam	19,5±6,55 (100,0±33,6%)	— Inactive	17,98±1,49 (92,2±7,62%) $P>0,5$	20,97±1,31 (107,6±6,7%) $P>0,5$
IV	19,5±6,55 (100,0±33,6%)	24,2±2,46 (124,1±12,6%) $P<0,5$	32,29±4,95 (165,6±25,4%) $0,1<P<0,2$	—

where they remained far 1 min, etc., until death in order to measure the "altitude ceiling." The animals' death was established upon the onset of agony respiration in a background of convolutions. A total of 200 mice were used in the experiments.

Compound IV and piracetam were administered 1 h before "ascent." The experimental results were statistically processed by the Student t-criterion and correlated with the control data which were taken as 100.

Similar experiments with nonpedigree male rats weighing 180-230 g were performed in the same barometric chambers with an "ascent" of up to an "altitude" of 12,000 m.

The experimental results for the acute hypobaric hypoxia model are given in Tables 3 and 4

As can be seen from the cited data, compound IV significantly exceeds (by three or four times) the effect of piracetam both with respect to survival time at an "elevation" of 11,000 m and with respect to the increase in the "elevation ceiling" (IV increases the "elevation ceiling" by 4,000 m in comparison to the control and piracetam at a dose of 500 mg/kg).

Acute Normal Barometric Hypoxia Model. Acute normal barometric hypoxia (ANBH) was simulated in a flow barometric chamber at an air temperature of 17-22°C with absorption of CO_2 and water. A gas mixture was delivered to the chamber (97% N_2 and 3% O_2) at a velocity of 10 liters/min. The animals' longevity was measured from the time the mixture was delivered into the chamber to the time of death, which was defined as agony respiration in a background of convulsions. The patterns of preparation administration and analysis of results are the same as those described above for acute hypobaric hypoxic hypoxia. The experiments were performed on 50 mice and 20 rats.

The results are given in Table 5.

The experimental results indicate that compound IV at a dose of 250 mg/kg reliably increases mice resistance to acute normal barometric hypoxia by 4.5 times and that of rats by 1.5 times in comparison to the control and exceeds the efficacy of piracetam by five times in this type of hypoxia.

Acute Histotoxic Hypoxia Model. Acute histotoxic hypoxia was effected by the subcutaneous injection of sodium nitroprusside at a dose of 20 mg/kg, which causes 100% animal death

TABLE 7. Effect of Compound IV on the Resistance of Rat Cerebral Cortex to Asphyxic Hypoxia

Compound	Number of animals with retained electrocorticogram after initial anoxia, %	Number of animals with restored electrocorticogram after fourth anoxia, %
Control	8,3	15,0
Piracetam, 1000 mg/kg	12,5	14,3
IV, 250 mg/kg	44,0	100,0

TABLE 8. Effect of Compound IV on Recorded Parameters of Electric Brain Activity after Repeated Anoxia of Variable Duration

Compound	Duration of successive anoxias, s (M ± m)											
	90			120			150			180		
	parameter*											
	I'	II'	III'	I'	II'	III'	I'	II'	III'	I'	II'	III'
Control	45,4±3,8	22,4±2,5	66,6±6,0	48,6±3,3	45,3±3,5	110,5±7,0	60,1±3,6	57,3±12,6	147,9±15,6	76,4±6,9	—	—
Piracetam (1000 mg/kg)	76,6±4,8	5,3±0,2***	17,8±4,9***	85,8±7,3***	21,8±6,9**	53,3±12,0***	95,0±16,3*	67,6±42,1	131,2±53,8	79,4±23,8	—	—
IV, 250 mg/kg	84,3±1,8***	3,7±1,5***	8,9±3,5***	89,0±6,2***	18,3±2,6***	52,4±5,6***	73,9±7,5	64,6±22,2	121,0±25,0	94,4±9,4	160,6±83,8	216,9±72,8

Note. Decoding of parameters given in the text. Asterisk denotes reliability of differences in comparison to the control: *) $P < 0.05$; **) $P < 0.05$; ***) $P < 0.001$.

within 15-25 min after injection. Animal longevity was determined following the injection of sodium nitroprusside in a background of the test compounds, and was defined as the cessation of respiration and heartbeat. A total of 40 animals was used in this series of experiments.

The experimental results are given in Table 6.

Thus, compound IV, at a dose of 500 mg/kg, exceeds the efficacy of piracetam (at doses of 500 and 1000 mg/kg) by 1.5 times in this type of hypoxia.

Acute Repeated Anoxia Model. Tests were conducted on nonpedigree male rats weighing 180-200 g in which Nichrome electrodes were preliminarily implanted into the cerebral sensomotor cortex. The animals were immobilized by an injection of ditilin (10 mg/kg intraperitoneally) and were connected to an artificial respirator following a tracheotomy. Anoxia was induced by repeated disengagement of respiration for 90, 120, 150, and 180 sec with 10-min intervals. The electrocorticogram (ECG) was recorded to evaluate the antihypoxic activity of the compounds by the following parameters (in sec): I') time up to the disappearance of cortical electrical activity after cutoff of respiration; II') time up to the appearance of the ECG after restoration of respiration; III') total cortical electrical silence for each of the successive anoxias. Experimental results are given in Tables 7 and 8.

The experimental results indicate that compound IV at a dose of 250 mg/kg exhibits distinct antihypoxic activity in asphyxic hypoxia. The time up to the disappearance of the ECG is almost doubled by the preparation, particularly during the first and second anoxias, and the time required for the restoration of brain function was significantly reduced.

Compound IV exhibited its most pronounced antihypoxic effect during the analysis of the number of animals with restored brain function after the fourth anoxia. Whereas not more than 15% of the animals exhibited restored function in the control and with the administration of piracetam, 100% of the animals showed restored electrical brain activity upon the administration of compound IV. This exceeded the effect of piracetam by seven times. At the same time, compound IV exhibited pronounced antihypoxic activity in the evaluation of the number of animals with retained ECG after the first 90-sec anoxia in which case compound IV tripled the efficacy of piracetam at a dose of 1000 mg/kg.

Thus, an analysis of our experimental data has shown that the complete thiomodification (replacement of oxygen by sulfur) of piracetam does not fundamentally alter the spectrum of its pharmacological activity, but significantly potentiates the nootropic and antihypoxic effects. Compound IV is effective in significantly smaller doses than piracetam and exhibits a pronounced systemic antihypoxic action. This allows us to view compound IV as a potential nootropic agent with particularly pronounced antihypoxic activity.

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