SYNTHESIS AND PHARMACOLOGICAL STUDY OF NEW PIRACETAM DERIVATIVES AND THEIR THIO ANALOGS

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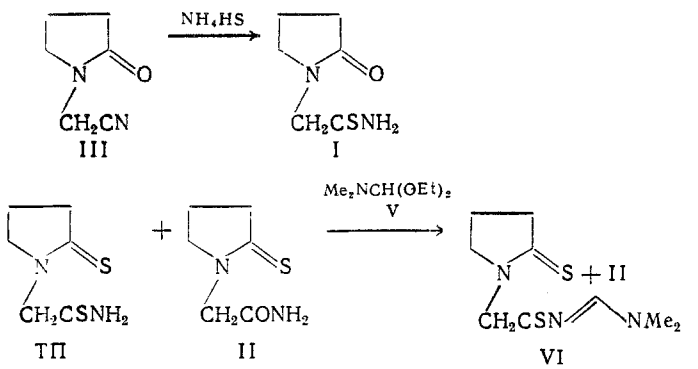
One of the traditional methods of searching for new biologically active compounds is to modify the structure of effective medicinal preparations. This method, and particularly the modification of one of the first representatives of the nootropic agents, piracetam, was employed to synthesize the drugs aniracetam [11], oxyracetam [13], and pramiracetam [12], as well as an entire series of substances that exhibit nootropic, antihypoxic, and antitremor action [3, 5, 7-9], including 1-thiocarbamoylmethylpyrrolidinethione (TP) which has a high degree of antihypoxic and nootropic activity [1, 2].

The purpose of the present work was to undertake a pharmacological study and synthesize piracetam derivatives substituted on the NH_2 of the carbamide group and their thio analogs. In the first phase of our work we thought it would be useful to investigate the biological activity of the monothio derivatives of piracetam, i.e., 1-thiocarbamoylmethylpyrrolidone-2 (I) and 1-carbamoylmethylpyrrolidinethione-2 (II), which are interesting not only because of their structural relationship to piracetam and TP, but also because there are metabolic products of TP.* The synthesis of compound I did not entail any complications and was accomplished by the transformation of the cyano group into 1-cyanomethylpyrrolidone-2 (III) [7] by reaction with NH_4HS. On the other hand, we ran into considerable difficulties in our synthesis of compound II. We were not able to synthesize this compound by thionization of the nitrile III followed by saponification of the CN-group since the reaction between III and P_2S_5 resulted in the formation of TP [1, 2] and when we used Lawesson's reagent, 2,4-bis(n-methoxyphenyl)dithiodiphosphetane-2,4-disulfide (IV), as the thiating agent [10, 14], we obtained a complex mixture of products from which we could not separate the target product of compound II.

In analyzing the reaction mixtures obtained by the reaction between piracetam and a certain deficiency of phosphorus pentasulfide, we found that the thione II was formed along with TP as the basic side product. We could not separate TP and II without the use of chemical reactions, although we found that the reaction of diemthylformamide diethylacetal V proceeded at considerably more moderate conditions and faster rate on the thiocarbamide group than on the carbamide. When acetal V was reacted with a mixture of TP and II at 20°C, only TP entered the reaction, in which case the resultant N,N-dimethylaminomethylene derivative of TP was considerably more soluble so that compound II could be separated without difficulty.



*Information about TP metabolism will be presented in one of our later reports.

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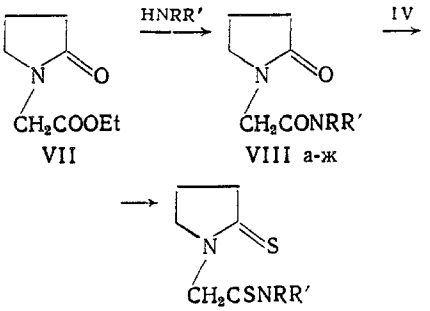
At the next stage of our work we used a semiproduct of piracetam synthesis, 1-ethoxycarbonylmethylpyrrolidone-2 (VII) [4], as the starting substance. The amidization of the ester VII by primary and secondary amines resulted in the piracetam analogs substituted on the nitrogen atom of the carbamide function (VIIIa-g). Some of these compounds were introduced into the reaction with Lawesson's reagent IV. The reaction does not proceed selectively. The replacement of the lactam and amide oxogroups by thiolactam and thiocarbamide groups, respectively, proceeds in parallel. Consequently, both carbonyl oxygen atoms in the resultant derivatives are replaced by a sulfur atom (IXa-d).



R = H, (a-c, f, g); R^1 = CH_2Ph (a), CH_2CH_2Ph (b) $CH(Me)CH_2Ph$ (c), $CH_2CH_2NEt_2$, adamantyl-1(g); NRR^1 = morpholino (d), 4-methylpiperazino (e)

EXPERIMENTAL (CHEMICAL)

IR spectra were recorded on a Perkin–Elmer-457 instrument in the form of a paste in petroleum jelly. Mass spectra of the compounds were obtained on a MAT-112 spectrometer, ionization voltage 50 eV, temperature of ionization chamber 140°C. Melting temperatures were measured on a Boetius-type heating stand. The characteristics of the synthesized compounds are given in Table 1. The found element analysis values corresponded to the calculated ones.

1-Thiocarbamoylmethylpyrrolidone-2 (I). A 1-ml portion of a 10% NH_4HS solution was added to a solution of 24.8 g (200 mmoles) of 1-cyanomethylpyrrolidone-2 in 50 ml of water. The mixture was kept at 20°C for 24 h and the resultant precipitate was filtered off and washed with water to yield compound I. $M^{+\cdot}$ 158. IR spectrum, ν_{max}, cm^{-1}: 3110, 3266 (NH_2), 1670 (CO).

Separation of 1-Carbamoylmethylpyrrolidine-2-thione (II) from a Mixture of TP and II. A quantity of DMPA diethylacetal five times in excess of TP was added to a suspension of a mixture of TP and II in dry benzene (any ratio of TP and II can be used in the mixture). The mass was stirred at 20°C for 2 h. The undissolved precipitate was filtered off and recrystallized from water with charcoal. $M^{+\cdot}$ 158. Physical constants of compound II coincided with the literature data [6].

1-Carboxymethylpyrrolidone-2 N-Benzylamide (VIIIa). A mixture of 15 g (87.7 mmoles) of 1-ethoxycarbonylmethylpyrrolidone-2 (VII) and 9.4 g (87.7 mmoles) of benzyl amide was kept for 3 h at 120-130°C. The reaction mixture was then cooled, hexane was added, and the precipitate was filtered off and recrystallized from ethyl acetate to yield VIIIa, M^+ 232. IR spectrum, ν_{max}, cm^{-1}: 3270 (NH), 1650, 1685 (CO).

1-Carboxymethylpyrrolidone-2 N-(β-Phenylethyl)amide (VIIIb). The same procedure was used to obtain VIIIa from a VII ester and β-phenylethylamine. $M^{+\cdot}$ 246. IR spectrum, ν_{max}, cm^{-1}: 3295 (NH), broad 1670 (CO).

1-Carboxymethylpyrrolidone-2 N-(β-phenyl-α-methylethyl)amide (VIIIc). The same procedure was used to obtain VIIIa from the VII ester and (β-phenyl-α-methyl)amine. $M^{+\cdot}$ 260. IR spectrum, ν_{max}, cm^{-1}: 3260 (NH); 1670, 1650 (CO).

1-Carboxymethylpyrrolidone-2 N-Morpholide (VIIId). Same procedure as for obtaining compound VIIIa from the VII salt and morpholine. Reaction conditions: temperature 150°C, time 3.5 h. $M^{+\cdot}$ 212. IR spectrum, ν_{max}, cm^{-1}: 1650, 1675 (CO).

1-Carboxymethylpyrrolidone-2 N-(4-Methylpiperazide) (VIIIe). Same procedure as for obtaining VIIId from the VII salt and N-methylpiperazide. After the reaction was completed

TABLE 1. Characteristics of Synthesized Compounds

Compound	Yield, %	mp, °C (solvent)	Empirical formula
I	50	156–9 (MeOH)	$C_6H_{10}N_2SO$
II	—	213–5 (water)	$C_6H_{10}N_2SO$
VIIIa	61	120–1 (ethylacetate)	$C_{12}H_{16}N_2O_2$
VIIIb	55	78–9 (butyl acetate)	$C_{14}H_{18}N_2O_2$
VIIIc	49	78–80 (butyl acetate)	$C_{15}H_{20}N_2O_2$
VIIId	64	130–3 (ethylacetate)	$C_{10}H_{16}N_2O_2$
VIIIe	54	91–3 (hexane)	$C_{11}H_{19}N_2O_2$
VIIIf	49	200–5/2 mm Hg	$C_{12}H_{22}N_2O_2$
VIIIg	42	134–6 (water)	$C_{16}H_{24}N_2O_2$
IXa	53	77–9 (50 % alcohol	$C_{13}H_{16}N_2S_2$
IXb	35	116–9 (50 % alcohol	$C_{14}H_{18}N_2S_2$
IXc	64	88–90 (50 % alcohol	$C_{15}H_{20}N_2S_2$
IXd	57	117–8 (i-PrOH)	$C_{10}H_{16}N_2S_2O$

the reaction mass was vacuum-distilled and the fraction at 183-185°C/2 mm Hg was collected, triturated with ether, and VIIIe was filtered off. $M^{+\cdot}$ 276. IR spectrum, ν_{max}, cm^{-1}: 1650 (CO).

1-Carboxymethylpyrrolidone-2 N-(2-Diethylaminoethyl)amide (VIIIf). Same procedure as for obtaining VIIId from the VII salt and 2-diethylaminoethylamine. The reaction mass was vacuum-distilled and the 200-205°C/2 mm Hg fraction was collected. $M^{+\cdot}$ 240. IR spectrum, ν_{max}, cm^{-1}: 3290 (NH), broad 1670 (CO).

1-Carboxymethylpyrrolidone-2 N-(2-Adamantyl)amide (VIIIg). Same procedure used as for obtaining VIIId from the VII salt and 2-aminoadamantane. $M^{+\cdot}$ 276. IR spectrum, ν_{max}, cm^{-1}: 3290 (NH), 1655, 1680 (CO).

1-Thiocarboxymethylpyrrolidine-2-thione (IXa). A 12.1 g portion (30 mmoles) of Lawesson's reagent (IV) was added to a solution of 6.96 g (30 mmoles) of the VIIIa amide in 100 ml of dry toluene. The reaction mixture was then boiled with stirring for 2 h after which the mixture was vacuum-evaporated. The residue was triturated with 100 ml of methanol, filtered, and the methanol mother liquor was evaporated. The residue was recrystallized from 50% aqueous alcohol to yield IXa. $M^{+\cdot}$ 264.

1-Thiocarboxymethylpyrrolidine-2-thione N-(β-Phenylethyl)amide (IXb) was obtained in the same way as IXa by the thiation of VIIIb by Lawesson's reagent. $M^{+\cdot}$ 278.

1-Thiocarboxymethylpyrrolidine-2-thione N-(β-phenyl-α-methyl)amide (IXc) was obtained in the same way as IXa by the thiation of VIIIc with Lawesson's reagent. $M^{+\cdot}$ 292.

1-Thiocarboxymethylpyrrolidine-2-thione N-morpholide (IXd) was obtained in the same manner as IXa by the thiation of VIIId by Lawesson's reagent. $M^{+\cdot}$ 244.

EXPERIMENTAL (PHARMACOLOGICAL)

Compounds I, II, VIIIa-g, and IXa-d were studied for certain properties characteristic of nootropic preparations such as effect on resistance to hypoxia, effect on the convulsive action of thiosemicarbazide (TSC), a GABA antagonist, and on the learning process in passive avoidance conditional reflex (PACR) tests.

Antihypoxic action was tested on nonpedigree white male mice weighing 20-22 g on an acute hypoxic hypoxia model with hypercapnea. Hypoxic hypoxia was created in hermetically sealed vessels 250 cm^3 in volume. In parallel control group tests animal longevity was measured in minutes after administration of the compounds intraperitoneally at doses of 100, 250, and 500 mg/kg. The compounds' effect on the threshold of TSC-induced convulsion reaction was tested by the intraperitoneal administration of the compounds at 100, 250, 500 mg/kg 20 min after the subcutaneous injection of TSC (20 mg/kg). The latent period of convulsion onset and mice death was recorded in minutes.

Acute toxicity was tested on the mice by measuring the LD_{50} of the compounds.

Our experiments showed that some of the compounds (I, VIIIb, IXa, and IXe) exhibit antihypoxic activity and prolong animal longevity in the hermetic chamber. The most active of the compounds was VIIIb which at doses of 250 and 500 mg/kg increased longevity up to 44.2 (34.7-53.7) and 66.8 (69.0-52.2) min [29.8 (23.2-33.4) min in the control].

Compounds VIIIb, I, IXa, e were also found to exhibit anticonvulsive activity and, once again, compound VIIIb was the most active. At a dose of 250 mg/kg it raised the latent period of tremor onset up to 81.7 (75.4-88.0) min [54.7 (51.4-63.4) min in the control].

The PACR tests showed that compounds VIIa, b, d and IXb had a positive effect on the learning process and consolidation of memory tracking. The most active of the compounds was IXb which, at an intraperitoneal dose of 200 mg/kg, increased the latent period for the animals' stay in the lighted chamber by 40% [166.4 (150.0-176.7) sec] in comparison to the control group for which the latent period was 117.5 (108.2-126.8) sec.

The LD_{50} for the mice upon intraperitoneal administration of the compounds was (in mg/kg) >2000 for compound I, >1000 for compounds II, VIIIa-e, and IXb, 850 for VIIIg, 500 for IXa, 557 for IXd, and 430 for compound IXe.

Thus, compounds I, VIIIb, IXa, e exhibited antihypoxic activity and antagonism to the convulsive effect of TSC. Compound VIIIb, which was active in these tests, also had a positive effect on learning.

Our experimental results indicate that substitution on the nitrogen of the carbamide or thiocarbamide group (both in the piracetam and piracetam thio analog series) has a significant influence on the compounds' activity, and that N-substitution, as a rule, reduces activity. It is possible that the presence of such a substituent increases the steric demand of the carbamide (thiocarbamide) function when it reacts with the receptor systems. Moreover, in this situation the substituent may contribute to lowered amide (thioamide) conjugation, thereby decreasing the partial positive charge on the nitrogen atom of the CONHR- or CSNHR-functions. Further pharmacological research on the N-substituted piracetam and TP might yield valuable information for a better understanding of the mechanism underlying the action of nootropic agents.

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