SYNTHESIS AND PHARMACOLOGICAL EXAMINATION OF NOVEL PYRROLIDINE-2-THIONES AND 2-METHYLENEPYRROLIDINES

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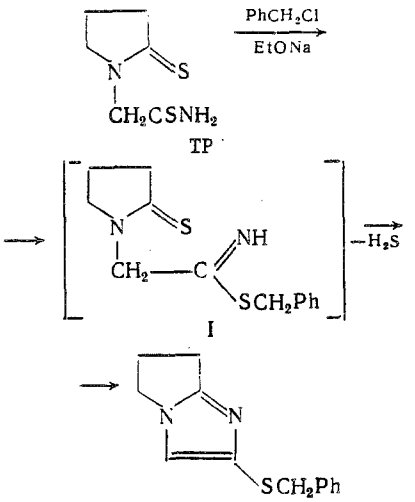
The authors have previously reported that the dithio-analog of pyracetam (1-thiocarbamoylmethylpyrrolidine-2-thione, TP) has high antihypoxic and nootropic activity [1, 2], and discussed possible modifications of this compound in order to obtain novel pharmacologically active compounds. We here report the modification of the functional group ($CSNH_2$) in TP in such a way that hydrolytic cleavage in the body would regenerate the original TP. We first attempted to S-alkylate the primary thioamide group to obtain the thioaminoether. However, benzylation of TP in the presence of NaOEt did not stop at the thioimidate stage (I), but resulted in cyclization with the formation of the pyrrolo[1,2-a]imidazole (II).



The structure of the bicyclic compound (II) was confirmed by its ^1H NMR spectrum in $CDCl_3$, which showed signals for the methylene groups of the pyrrolidine ring at 2.53 (quintet, 6-CH_2), 2.85 (t, 7-CH_2), 3.88 (t, 5-CH_2), 4.03 (s, SCH_2), 6.71 (s, 3-CH), and 7.28 ppm (m, Ph) respectively. Another way of obtaining depot drugs from TP is by preparation of thioacylamidines by reaction of TP (or 1-thiocarbamoylmethyl-2-pyrrolidone [6]) with amide and lactam acetals. We have recently shown [6] that TP reacts readily with DMF acetal (IVa) to give the dimethylaminomethylene derivative (Va). It is important to note that reaction of TP with amide acetals occurs much more readily than the reaction of pyracetam with the same reactants, i.e., condensation of the thiocarbamide group occurs at a greater rate than with the carbamide group. We have already reported [6] that this difference is so great that it is possible to separate compounds containing the thiocarbamide group from those containing the thioamide group by conversion of the former into the thioacylamidine. A measure of the reactivities of these compounds towards the acetal (IVa) is provided by the conditions for the reaction of (IVa) with pyracetam (xylene, 3-4 h, 110-140°C [7]) and with TP (20°C, 1 h [6]). This behavior is readily understandable when it is recalled that the rate-determining step in the condensation of amide acetals of the amide or thioamide group is cleavage of the N–H proton, and the transition state is similar in structure to the mesomeric anion (A). It is quite likely stabilization of A when X = S is considerably greater as a result of the energetic preference

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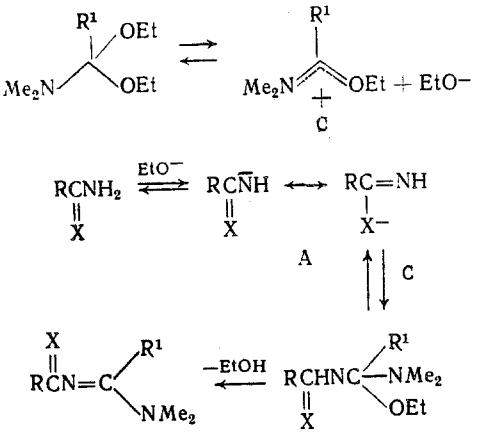
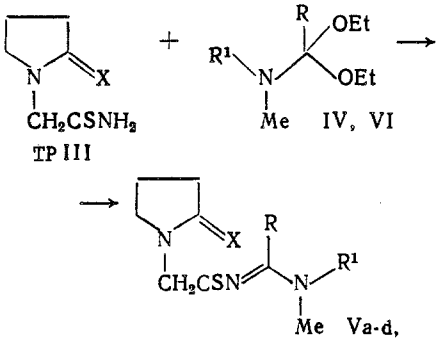
for the localization of the negative charge at the sulfur atom, rather than oxygen. In this connection, it is noteworthy that cleavage of a proton from the $CXNH_2$ group is due to the ability of amide acetals to exist in solution in equilibrium with the ambident cation (C) and the alkoxy-anion [8].

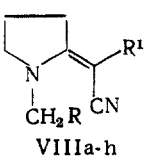


The reaction of TP with the diethyl acetals of dimethylacetamide (IVb), N-methylbutyrolactum (VIa), and caprolactam (VIb) proceeds just as readily as with DMF acetal (IVa). In all these cases, the thioacylamidines (Vb-d) were formed smoothly and in high yields. The presence of the thiolactam moiety in TP has no appreciable effect on the course of the reaction, since under the same conditions the lactam (VII) was obtained from 1-thiocarbamoylmethyl-2-pyrrolidone (III) and the acetal (VIa).



X = S (TP, V), O (III, VII);
R=H (IVa, Va), Me (IVb, Vb).
R^1 = Me (IVa, b, Va,b); $RR^1 = (CH_2)_3$ (Vc, VIa, VII), $(CH_2)_5$ (Vd, VIb)

Since there is some similarity between the amide (or lactam) and enamine groups (in both instances conjugation occurs with the formation of a partial negative charge on the exocyclic oxygen or carbon atom), it was desirable to examine the nootropic activity of some enamines, namely, the 1-substituted 2-methylenepyrrolidines (VIIIa-h), especially those in which the 1-substituent carried acylamino- (VIIIa) or thioacylamino- (VIIIb) fragments. The enamines (VIIIa-h) have been obtained previously [3-5]



VIIIa-h

R = CON=CHNMe$_2$ (a), CSN=CHNMe$_2$ (b), $CONH_2$ (c), $CSNH_2$ (d) CN (c-e); R^1 = COOEt (a-e), $CONH_2$ (f), $CSNH_2$ (g), CON=CHNMe$_2$ (h).

by the reaction between N-cyanomethyl-2-pyrrolidone and compounds containing a reactive methylene group, followed by transformation of the cyano-group in the 1-substituent.

TABLE 1. Physicochemical Properties of Compounds Obtained

Compound	Yield %	mp, °C (solvent)	Empirical formula
Va	62	96–99 (ether)	$C_9H_{15}N_3S_2$
Vb	62	109–110 (ethyl acetate)	$C_{10}H_{17}N_3S_2$
Vc	84	94–95 (ethanol)	$C_{11}H_{17}N_3S_2$
Vd	74	122–124 (ethyl acetate)	$C_{13}H_{21}N_3S_2$
VII	77	92–94 (ethyl acetate)	$C_{11}H_{17}N_3SO$

EXPERIMENTAL (CHEMISTRY)

The mass spectra of the compounds were obtained on an MAT-112 spectrometer, ionizing voltage 50 eV, ionization chamber temperature 140°C, and the ^1H NMR spectrum on an XL-200 spectrometer, internal standard TMS. Melting points were measured on a Boetius hot plate.

5,6-Dihydro-7H-2-benzylmercaptopyrrolo[1,2-a]imidazole (II). To a suspension of 5 g (28.7 mmole) of TP in 50 ml of absolute alcohol was added a solution of 1.15 g (28.7 mmole) of NaOH in 50 ml of absolute alcohol, and the mixture stirred for 1 h at 20°C, and boiled for 5 min. After cooling, 3.6 g (28.7 mmole) of benzyl chloride was added, and the mixture stirred for 2 h at 20°C, then boiled for 30 min, cooled, the solid filtered off, and the filtrate evaporated under reduced pressure. The residue was triturated with dry ether to give (II), $M^+\cdot$ 230.

1-[(N,N-Dimethylaminomethylene)thiocarbamidomethyl]pyrrolidine-2-thione (Va). To a suspension of 1.20 g (7 mmole) of TP in 25 ml of dry benzene was added 1.20 g (8 mmole) of the acetal (IVa), and the mixture stirred for 2 h at 20°C, then evaporated under reduced pressure. The residue was triturated with dry ether, filtered, and washed with a small amount of 2-propanol to give (Va), $M^+\cdot$ 229.

1-[(N,N-Dimethylamino-2-ethylidene)thiocarbamidomethyl]pyrrolidine-2-thione (Vb). To a suspension of 8.7 g (50 mmole) of TP in 100 ml of dry toluene was added 8.10 g (50 mmole) of the acetal (IVb), and the mixture heated at 65°C for 40 min. The mixture was then evaporated under reduced pressure, and the residue triturated with hexane and washed with 2-propanol to give (Vb), $M^+\cdot$ 243.

1-[N-(1-Methyl-2-pyrrolidene)thiocarbamidomethyl]pyrrolidine-2-thione (Vc). Obtained as for (Va), from TP and (VIa), $M^+\cdot$ 239.

1-[N-(1-Methylhexahydroazepinyl-2-ene)thiocarbamidomethyl]pyrrolidine-2-thione (Vd). Obtained as for (Va), from TP and (VIb), $M^+\cdot$ 283.

1-[N-(1-Methyl-2-pyrrolidine)thiocarbamidomethyl]-2-pyrrolidone (VII). Obtained as for (Va), from (III) and (VIa), $M^+\cdot$ 239.

The data for the compounds obtained are given in Table 1. The elemental analyses were in agreement with the calculated values.

EXPERIMENTAL (PHARMACOLOGY)

Tests were carried out using mongrel male white mice weighing 18-20 g, for nootropic, antihypoxic, and anticonvulsant activity.

Anticonvulsant activity was assessed by the effects on convulsions induced by bicucullin (1.25 mg/kg), corazole (125 mg/kg), strychnine (3 mg/kg), and thiosemicarbazide (TSC, 20 mg/kg).

Bicucullin and strychnine were dissolved in a drop of 0.1 N HCl, and distilled water added to the required volume. Bicucullin was introduced intravenously at a constant rate. Aqueous solutions of corazole, strychnine, and TSC were administered subcutaneously. Anticonvulsant activity was assessed by the capacity to extend the latent period for the onset of convulsions, and the time of death of the animals.

Antihypoxic activity was examined in model hypoxic hypoxia in mice. The animals were placed in a hermetically sealed vessel of capacity 250 ml. The lifespan of the animals was measured in parallel with the controls, in minutes.

Nootropic activity was examined in mice by the method of Bures and Buresova (1963). The times of residence in light and dark compartments were measured over 180 sec. Following exposure, the animals received a single electrical shock through the electrode floor of dark chamber. This gave rise to a passive flight conditioned reflex, which was repeated after 24 h.

Acute toxicities (LD_{50} values) were measured in mice, ten animals per group.

For the pharmacological tests, the compounds were administered intraperitoneally in doses of 1/10 of the LD_{50} values.

Anticorazole activity was shown by (VIIIb) and (VIIIg), the former also being active in model convulsions induced by bicucullin.

The most active compound against convulsions induced by TMS (which is a specific antagonist of GABA) was (VIIIa), which in an intraperitoneal dose of 30 mg/kg increased the latent period before onset of convulsions to 74.3 (70.3-78.3) min, as compared with 56.0 (50.4-61.6) min in the controls. None of the test compounds, however, showed any activity against strychine-induced convulsions.

Compounds (VIIIa-c) and (VIIIe) showed antihypoxic activity, increasing the lifespan of mice in sealed chambers. The most active compound was (VIIIc), which in an intraperitoneal dose of 200 mg/kg increased the lifespan of mice to 64.5 (63.1-65.9) min as compared with 27.3 (20.0-34.6) min in the controls.

Compounds (Vb, d) (VII), and (VIIIa, c, e) also had a favorable effect on learning and the consolidation of memory traces. The most active of these was (VIIIc), which in an intraperitoneal dose of 200 mg/kg increased the latent period of residence in the light chamber by 43% [170.5 (160.2-180.8) as compared with 119.2 (105.4-133.0) sec in the controls].

The LD_{50} values by the intraperitoneal route in mice were (mg/kg): (Vb) 950, (Vc) 800, (VII) 400, (VIIIa) 250, (VIIIe) 290, (VIIIf) 500, (VIIIg) 850, and (Vd), (VIIIb, c, d) > 1000.

Pyracetam is known to have no appreciable anticonvulsant activity, and has little protectant activity in hypoxia. TP, on the other hand, has been shown previously to possess high antihypoxic and anticonvulsant activity. 2-Pyrrolidone derivatives also increased the resistance of animals to hypoxia and showed anticonvulsant activity, but to a much lesser extent than the thio-analogs of pyracetam.

These results show that continued work on derivatives of pyracetam and its dithio-analog is desirable and holds promise.

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