SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF 4-PIPERAZINYL-9-OXO-6,7,8,9-TETRAHYDRO-PYRIMIDO[4,5-b](1,4)BENZOTHIAZINES

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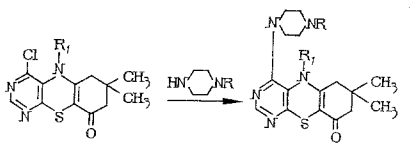
A study of the biological properties of the 9-oxo-6,7,8,9-tetrahydropyrimido[4,5-b](1,4)benzothiazines shows that some of them possess antifolic, cytostatic, and cytotoxic activity [1].

Molecules of this class of material belong to the tricyclic derivatives of 6,7-polymethylenepyrimido[4,5-b]-(1,4)thiazines with polar regions side-by-side (the nitrogen atoms of the pyrimidine ring and the eneamine ketonic group), possessing hydrophobic properties. This information encouraged the examination of the 9-oxo-6,7,8,9-tetrahydropyrimido[4,5-b](1,4)benzothiazine structure as a possible biologically active structural combination.

In this connection, compounds of this type show elements of similarity with other tricyclic compounds possessing psychotropic activity. In further consideration of the similarity of these compounds with earlier-described derivatives of dihydropyrimidobenzothiazines [2] was an investigation of a series of recently-synthesized, pharmacologically significant 9-oxo-6,7,8,9-tetrahydropyrimido[4,5-b](1,4)benzothiazines containing dialkylaminoalkyl residues. The substituents were predominantly monosubstituted piperazines. Among these polymethylenepyrimidobenzothiazines, the most accessible were the 9-oxo-6,7,8,9-tetrahydropyrimidobenzothiazines containing the N-alkyl- or N-aralkylpiperazine residue in position 4 of the molecule, inasmuch as it is known that the corresponding chlorine derivative is easily substituted by different nucleophilic agents [3].

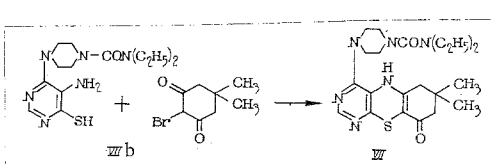
In practice, treatment of 4-chloro-7,7-dimethyl-9-oxo-6,7,8,9-tetrahydropyrimido- (Xa) and 4-chloro-5,7,7-trimethyl-9-oxo-6,7,8,9-tetrahydropyrimido[4,5-b](1,4)benzothiazine (Xb) with N-substituted piperazines gave the desired compounds (I-VI); it was established that the substitution reaction proceeds most easily in boiling triethylamine [4].



Xa,b I-VI

I: R = CH_3, R′ = H; II: R = CH_2CH_2OH, R′ = H;
III: R = R′ = CH_3; IV: R = CH_2Ph, R′ = H.
V: R = CH_2CH = $CHPh$, R′ = H; VI: R = CH_2CH_2Ph, R′ = H.

The synthesis of compound VII carrying a piperazine substituted with the diethylcarbamoyl radical in position 4 was brought about by direct cyclization of the corresponding 5-amino-6-mercaptopyrimidine with 2-bromodimedone by the method of [1].



VIIb VII

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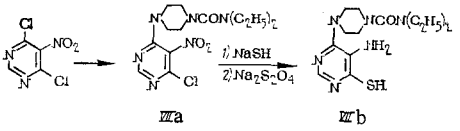
The starting 5-amino-6-mercaptopyrimidine was prepared according to the following scheme:



IIIa IIIb

We conducted an analogous substitution reaction for the case of monoalkyl or monoaralkylpiperazines, and did not obtain elimination, apparently as a result of the high basicity of both nitrogen atoms in the piperazine derivative.

In order to clarify the influence of the dialkylaminoalkyl fragment on the biological properties of the compounds prepared, a comparative study to check 9-oxotetrahydropyrimidobenzothiazines containing groups such as OCH_3, $N(CH_3)_2$, and Cl in position 4 (compounds VIII-X) showed that the latter, as distinguished from compounds I-VII, did not show any elements of neurotropic activity.

EXPERIMENTAL CHEMISTRY

General Method for Obtaining Substituted 4-Piperazinyl-7,7-dimethyl-9-oxo-6,7,8,9-tetrahydropyrimidobenzothiazines (III-VI) and their Hydrochlorides (I-II, IIIa-VIa). To a suspension of 1 g (3.56 mmoles) of 4-chloro-7,7-dimethyl-9-oxo-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b](1,4)benzothiazine in 50 ml of triethylamine was added about 4 mmoles of the corresponding monosubstituted piperazine. The reaction mixture was boiled with stirring for at least 12 h, cooled, and the precipitate was filtered to give III-VI (cf. Table 1).

Hydrochlorides IIIa, IVa, VIa were prepared by treating a benzene solution of the corresponding base with ethereal HCl. The constants for these hydrochlorides are given in Table 1.

4-(N-Diethylcarbamoylpiperazino)-7,7-dimethyl-9-oxo-6,7,8,9-tetrahydropyrimido[4,5-b](1,4)benzothiazine (VII). A. 4-(N-Diethylcarbamoylpiperazine)-5-nitro-6-chloropyrimidine (VIIa). To a suspension of 5 g of 4,6-dichloro-5-nitropyrimidine in 30 ml of dioxane at 5°C was added a solution of 7 g of N-diethylcarbamoylpiperazine in 30 ml of water, neutralized with acetic acid. The reaction mixture was stirred at less than 15°C for 3.5 h, poured into 500 ml of water, and the resulting oil was extracted with ethyl acetate. The extract was concentrated, the residue was triturated with cyclohexane to give 4 g (45%) of yellow crystals, mp 95-97°C (from cyclohexane). Found, %: C 46.02; H 5.72; N 24.31; Cl 10.33. $C_{13}H_{19}ClN_6O_3$. Calculated, %: C 45.55; H 5.58; N 24.52; Cl 10.34.

B. 4-(N-Diethylcarbamoylpiperazinyl)-5-amino-6-mercaptopyrimidine (VIIb). The preceeding compound (9 g) was added in small portions to a methanolic solution of KSH prepared by saturating a methanolic solution of 2.7 g of KOH with H_2S. The reaction mixture was stirred for 1 h and evaporated to dryness. To the residue was added 120 ml of 2 N NaOH and to this mixture was added 18 g of $Na_2S_2O_4$ (solid) in small portions. After completion of the reduction, the reaction mixture was filtered and acidified with acetic acid to give 7 g (85%) of fine, light-yellow crystals, mp 197-199°C (from ethanol). Found, %: C 50.39; H 7.14; N 27.28; S 10.30. $C_{13}H_{20}N_6OS$. Calculated, %: C 50.3; H 7.14; N 27.1; S 10.33.

4-(N-Diethylcarbamoylpiperazino)-7,7-dimethyl-9-oxo-6,7,8,9-tetrahydropyrimido[4,5-b](1,4)benzothiazine (VII). To a solution of 1 g of 4-(N-diethylcarbamoylpiperazinyl)-5-amino-6-mercaptopyrimidine in 30 ml of methanol containing 0.8 g of KOH was added a solution of 0.71 g of bromodimedone in 20 ml of methanol and the mixture was stirred for 12 h. The solution was concentrated, and the residue was treated successively with dilute HCl and ethyl acetate. The precipitate was filtered and recrystallized from methanol to give 0.7 g (50%) of orange solid, mp 211-213°C (from alcohol). Found, %: C 58.57; H 7.02; N 19.52. C 58.58; H 7.10; N 19.68. $C_{21}H_{30}N_6O_2S$. Calculated, %: C 58.57; H 7.02; N 19.52.

EXPERIMENTAL PHARMACOLOGY

The study of compounds I-X was conducted in a series of tests to show neurotropic (psychotropic) activity on the following systems: influence on the central adrenergic and dopaminergic [interaction with phenamin (phenocoll), tetrabenazin, L-DOPA, apomorphine], serotoninergic (interaction with 5-hydroxytryptophan), and cholinergic (interaction with arecholine and nicotine).

In addition, the influence of the compounds on the catalepsy produced by triftazin (trifluoperazine), on the sedative action of hexenal (hexobarbital), on the bioelectrical activity of the brain, and on the conditioned re-

TABLE 1. Derivatives of 4-Piperazinyl-7,7-dimethyl-9-oxo-6,7,8,9-tetrahydropyrimido[4,5-b](1,4)benzothiazines (III-VI) and Their Hydrochlorides (I, II, IIIa, V, VIa)

Compound	Yield, %	mp, °C*	Found, %				Empirical formula	Calculated, %			
			C	H	N	Cl		C	H	N	Cl
I	66	276—8	53,4	6,5	18,5	9,7	$C_{17}H_{23}N_5SO \cdot HCl$	53,5	6,3	18,3	9,3
II	87	245—7	52,0	6,5	16,9	8,8	$C_{16}H_{25}N_5SO_2 \cdot HCl$	52,5	6,7	17,0	8,6
III†	80	162—4	60,4	7,3	19,8	—	$C_{16}H_{25}N_5SO$	60,2	7,0	19,5	—
IIIa	83	>300	50,2	6,7	16	8,3	$C_{16}H_{25}NSO_2 \cdot HCl \cdot 2H_2O$	50,2	7,0	16,2	8,2
IV	63	194—5	63,1	6,9	15,7	—	$C_{23}H_{27}N_5SO \cdot H_2O$	62,9	6,6	15,9	—
IVa	78	270—1	—	—	—	7,8	$C_{23}H_{27}N_5SO \cdot H_2O \cdot HCl$	—	—	—	7,4
V	75	170—2	66,7	6,5	15,6	—	$C_{25}H_{29}N_5SO$	67,1	6,5	15,7	—
Va	81	255—7	—	—	—	7,9	$C_{25}H_{29}N_5SO \cdot HCl$	—	—	—	7,34
VI	87	157—9	65,9	6,5	16,2	—	$C_{24}H_{29}N_5SO$	66,2	6,7	16,2	—
VIa	85	272—4	—	—	—	7,3	$C_{24}H_{29}N_5SO \cdot HCl$	—	—	—	7,5

*Compounds I, II, IV, and VI were purified by recrystallization from alcohol; compound III from ether.
†Compound III was prepared by conducting the substitution reaction in isopropanol.

flexes was studied. The acute toxicity of the compounds also was studied. Experiments were carried out on white mice of both sexes (weight 16-17 g), Wistar rats weighing 100-120 g, and cats and rabbits weighing 2.5-3 kg.

It was determined that the compounds containing OCH_3, $N(CH_3)_2$, or Cl (VIII, IX, X) in position 4 were all of low toxicity.

Compounds I-VII containing the piperazinyl group in the 4-position showed some degree of central neuropharmacological activity.

The most activity was shown by all compounds on the symptomatology stimulated by apomorphine on white rats. However, the compounds differed from each other in the force and direction of their action.

Compounds I and V, introduced orally in a dose of 25 mg/kg lengthened the symptomatology by 20-30%, but II, VII, VII, and particularly III and IV weakened it. Also, by oral introduction in rats of a dose of 25-50 mg/kg, compounds III and IV shortened the symptomatology elicited by apomorphine by 45-50%.

Compounds I (10 mg/kg, subcutaneously) and VII (50 mg/kg, orally) diminished the hyperthermic action of phenamine in mice. Compound V (25 mg/kg, orally), on the contrary, strengthened the phenamine action, and also weakened the hypothermia and blepharoptosis elicited by tetrabenazine in mice.

Compounds V and VI (25-50 mg/kg, orally) increased the number of "shaking" heads in mice elicited by 5-hydroxytryptophan by 100-125%; i.e., showed central serotonin-opposition activity, while compounds I and VII (100 mg/kg, orally) showed central antiserotonin action, which was expressed by diminishing the number of head "shakes" by 45%.

Compounds I and III (5-10 mg/kg, intravenously) produced convulsive activity in the EEG of cats and rabbits, and facilitated the production of conditioned reflex activity in rats. Compounds V, VI, VIII showed a synchronizing effect of the EEG. In the remaining tests, the compounds were shown to be only slightly active.

Thus, we studied derivatives of 9-oxo-6,7,8,9-tetrahydropyrimido[4,5-b](1,4)benzothiazines containing a piperazinyl group in position 4 which showed psychotropic activity which is most significant for compound V (experiments in mice showed that it strengthened the hyperthermic activity and weakened the hypothermia and ptosis caused by tetrabenazine, lessened the number of head "shakes" in mice caused by 5-hydroxytryptophan, and extended the symptomology in rats elicited by apomorphine). The activity spectrum of V resembles that of the tricyclic antidepressants, but it is more active than the "classical" antidepressants (imipramine, amitrypzyline, etc.).

The LD_{50} in white mice was determined: for I, 235 mg/kg (subcutaneously), 290 mg/kg (orally); for II, 410 mg/kg (subcutaneously), 480 mg/kg (orally); the absence of significant difference in the toxicity by subcutaneous and oral introduction indicates the good absorption of the compounds. The remaining compounds were introduced orally and the LD_{50} were: for III, 142.5; IV, 435; V, 575; VI, 750; VII, 780; and for VIII, IX, and X, greater than 1000 mg/kg.

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ADAMANTANE DERIVATIVES.

V. SYNTHESIS AND RADIOPROTECTIVE PROPERTIES OF N-ADAMANTYL DERIVATIVES OF AMINOTHIOLS

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The synthesis of new compounds containing the structure of mercaptoethylamine is a promising direction in the search for new synthetic radioprotective agents. It is known that the introduction at the nitrogen atom of mercaptoethylamine of aminoalkyl [1] and adamantyl [2] substituents contributes a strengthening of the antiradiation action.

The synthesis has been carried out and the radioprotective properties have been studied for the adamantyl substituted compounds of general formula (1).

$$\underset{\text{I}}{\text{Ad}X(CH_2)_nX'NH(CH_2)_mSR}$$

Ad = adamantyl-1; X = NH, CH_2; X′ = CH_2, CO;
R = H, PO_3H_2, C(=NH)NH_2·HBr; $n = 0,1$; $m = 2,3$

The initial N-(adamantyl-1-)chloroacetamide (IIa), N-(adamantyl-1-methyl)chloroacetamide (IIb), and N-(adamantyl-1)-3-chloropropionamide (IIc) were obtained by the known method of [3]. The aminoalkyl chlorides (IIa, b) were converted by reaction with aminoethanol (IIIa) and 3-aminopropanol (IIIb) into N-(adamantyl-1)-2-(2-hydroxyethylamino)acetamide (IVa), N-(adamantyl-1)-2-(3-hydroxypropylamino)acetamide (IVb), N-(adamantyl-1-methyl)-2-(2-hydroxyethylamino)acetamide (IVc), and N-(adamantyl-1-methyl)-2-(3-hydroxypropylamino)acetamide (IVd) isolated as the hydrochlorides. It was shown with the aid of PMR spectra that dialkylation took place at a small excess of alcohol (III) [for example, at III/II = (1-2.5):1] which was detected by the increase in the number of protons of the adamantane nucleus in relation to the number of protons of the alkylene groups. At a 3-5-fold quantity of hydroxyalkylamine (III) practically pure monoalkylation products (IV) were obtained. Reaction was carried out in boiling isopropyl alcohol for 4-8 h.

On interacting (IIc) with hydroxyamine (IIIa) no alkylation product was obtained but the N-(adamantyl-1)-acrylamide (V), i.e., under these conditions in the presence of base (IIIa) dehydrohalogenation occurred as is characteristic of β-halogen derivatives. The IR and PMR spectra of the isolated product (V) were identical with the literature data of [4].

The hydrochloride of N-(adamantyl-1)-3-(2-hydroxyethylamino)propionamide (IVe) was synthesized by the Ritter reaction from adamantan-1-ol and 3-(2-hydroxyethylamino)propionitrile in the presence of trifluoroacetic acid [5].

There were absorption bands in the IR spectra of amides (IVa-e) in the region of 3360-3460 cm^{-1} characteristic of hydroxyl groups, at 3280-3100 cm^{-1} characteristic of NH groups, and at 1655-1680 and 1555-1580 cm^{-1} assigned to amide I and amide II.

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