Biological tests of compounds III and V in the form of dihydrochlorides showed that they have pronounced antioxidant properties [3]. The action of compound V on a peroxidation system of lipids (POL) was evaluated according to the intermediate product, malonic dialdehyde, forming colored complexes with thiobarbituric acid (TBA). The operation was carried out with a liver homogenate of rats. The liver was first soaked with a 0.9% solution of NaCl. The homogenate was prepared on a Thirode solution (pH 7.4) and it was placed into penicillin vials containing the Thirode solution and compound V at different concentrations. It was incubated for 20 min in a vibrothermostat at 36°C. The probe was placed into centrifugal test tubes containing 1 ml of 15% trichloroacetic acid and 1 ml of 0.8% TBA. The mixture was centrifuged for 10 min at 70,000 rpm. The supernatant liquid was heated for 10 min on a boiling water bath. The MDA concentration was determined spectrophotometrically on an SF-18 apparatus at λ 525 nm.

It was shown that compound V is a strong POL inhibitor (Table 1), while compound III (Table 2) exhibits these properties more weakly.

The two compounds belong to a class of preparations with moderate toxicity. The LD_{50} is equal to 350 and 300 mg/kg for compounds V and III, respectively. They have more pronounced antioxidant properties than the known pharmacological preparation amidopyrine: Amidopyrine causes a 50% inhibition of POL at a concentration of $4 \cdot 10^{-3}$ M, while compounds V and III do so at concentrations of $5 \cdot 10^{-3}$ and $1 \cdot 10^{-4}$ M, respectively. Thus, the two compounds are strong antioxidants of POL.

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SYNTHESIS AND PHARMACOLOGICAL EXAMINATION OF SOME (6-DIALKYLAMINOPYRIMIDIN-4-YLTHIO)ACETIC ACIDS

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UDC 615.214.22+615.272.4]: 547.292'26].012.1

It has previously been shown [2, 3, 5] that substituted (pyrimidin-2-ylthio)acetic acids display considerable hypolipidemic activity. It was found that the type of substituents and their positions in the pyrimidine ring have a considerable influence on this activity. However, there is no information in the literature on the influence on the activity of the position of the thioglycollic acid residue. The object of the present study was therefore to synthesize the methyl esters, hydrazides, and isopropylidenehydrazides of some (6-dialkylaminopyrimidin-4-ylthio)acetic acids (IV-VI), these being structural analogs of compounds previously obtained by us [2, 3], and to examine their pharmacological properties.

Compounds (IV-VI) were obtained from 4,6-dichloropyrimidine (I) (see illustration on following page).

Reaction of (I) with ethyl thioglycollate, even in equimolar amounts, gave two compounds: ethyl (6-chloro-4-pyrimidinylthio)acetate (II) and 4,6-bis(ethoxycarbonylmethylthio)pyrimidine (III). It was found that the proportions of (II) and (III) were highly dependent on the order of mixing of the reactants and the temperature of the reaction mixture. When (I) was added to ethyl thioglycollate at room temperature (method A), (II) and (III) were formed in a molar ratio of 4:3. The inverse method of mixing the reactants (method B), when (I) was present in

V. Kapsukas Vilnius University. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 18, No. 11, pp. 1335-1339, November, 1984. Original article submitted April 3, 1984.

0091-150X/84/1811-0775$08.50

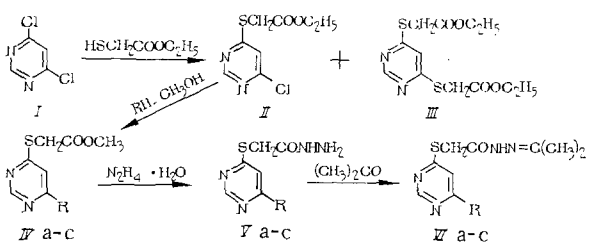
TABLE 1. Constants and Elemental Analyses for (II)-(VI)

Compound	Yield, %	mp, °C or bp, °C (mm)	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
II	30 (A) 88 (B)	146–8 (1)	41,11	3,95	12,25	$C_8H_9ClN_2O_2S$	41,29	3,90	12,04
III	49 (A) 3 (B)	220–5 (1) 51–1,5	45,63	5,20	9,05	$C_{12}H_{18}N_2O_4S_2$	45,55	5,10	8,85
IVa	73	164–5 (1) 40–1	47,71	5,71	18,63	$C_9H_{11}N_3O_2S$	47,56	5,77	81,49
IVb	74	95–96	49,15	5,69	15,48	$C_{11}H_{15}N_3O_3S$	49,06	5,61	15,60
IVc	72	45,5–7	53,76	6,49	15,91	$C_{12}H_{17}N_3O_2S$	53,59	6,41	15,72
Va	77	140–1,5	42,35	5,64	30,90	$C_8H_{13}N_3OS$	42,28	5,77	30,81
Vb	89	152–4	44,82	5,71	25,83	$C_{10}H_{15}N_3O_2S$	44,60	5,61	26,00
Vc	63	109,5–11	49,15	6,32	26,45	$C_{11}H_{17}N_3OS$	49,42	6,5	26,20
VIa	83	158,5–60	49,31	6,49	26,43	$C_{11}H_{17}N_3OS$	49,42	6,41	26,20
VIb	78	162,5–3,5	50,58	6,04	22,81	$C_{13}H_{19}N_3O_2S$	50,47	6,19	22,64
VIc	74	136 5–8	54,85	6,72	23,01	$C_{11}H_{21}N_3OS$	54,70	6,89	22,78

Note. Compound (III) crystallized from hexane; (IVa) and (IVc) from pentane; (IVb), (Va), and (Vb) from methanol; (Vc) from ethanol; and (VIa-c) from acetone.

TABLE 2. ^{1}H NMR Spectral Data for (II)-(IV)

Compound	^{1}H NMR spectrum, δ, ppm
II	1,20 (t, J-8Hz, 3H, CH_3), 3,87 (s, 2H, CH_2S), 4,11 (q, J-8 Hz, 2H, CH_2O), 7,22 (s, 1H, CH), 8,60 (s, 1H, CH)
III	1,20 (t, J-8Hz 6H, $2CH_3$), 3,83 (s, 4H, $2CH_2S$), 4,10 (q, J-8Hz, 4H, $2CH_2O$), 7,08 (s, 1H, CH), 8,56 (s, 1H, CH)
IVa	2,93 (s, 6H, $2CH_3N$), 3,63 (s, 3H, CH_3O), 3,85 (s, 2H, CH_2S), 6,18 (s, 1H, CH), 8,20 (s, 1H, CH)
IVb	3,50–3,88 (s, 11H, CH_3O + $2CH_2$ + $2CH_2N$), 3,96 (s, 2H, CH_2S), 6,41 (s, 1H, CH), 8,38 (s, 1H, CH)
IVc	1,67–1,95 (m, 6H, $3CH_2$), 3,80–4,10 (m, 9H, $2CH_2N$, CH_2S + CH_3O), 6,82 (s, 1H, CH), 8,45 (s, 1H, CH)
Va	3,10 (s, 6H, $2CH_3N$), 3,78 (s, 4H, CH_2S + NH_2), 6,35 (s, 1H, CH), 8,44 (s, 1H, CH), 8,81 (s, 1H, NH)
Vb	3,88–4,25 (m, 8H, $2CH_2N$ + $2CH_2O$), 3,42 (s, 2H, CH_2S), 6,90 (s, 1H, CH), 8,90 (s, 1H, CH)
Vc	1,68–2,00 (m, 6H, $3CH_2$), 3,60–4,00 (m 4H, $2CH_2N$), 4,23 (s, 2H, CH_2S), 6,75 (s, 1H, CH), 8,77 (s, 1H, CH)
VIa	1,83 (s, 3H, CH_3), 2,01 (s, 3H, CH_3), 3,01 (s, 6H, $2CH_3N$), 3,74 (s, 2H, CH_2S), 6,33 (s, 1H, CH), 8,39 (s, 1H, CH), 10,80, (s, 1H, NH)
VIb	2,66 (s, 3H, CH_3), 2,77 (s, 3H, CH_3), 3,93–4,25 (m, 10H, $2CH_2N$ + + $2CH_2$ + CH_2S), 7,01 (s, 1H, CH), 8,35 (s, 1H, CH)
VIc	1,73–1,93 (m 6H, $3CH_2$), 2,65 (s, 3H, CH_3), 2,78 (s, 3H, CH_3), 3,75–4,00 (m 4H, $2CH_2N$), 4,15 (s, 2H, CH_2S), 6,95 (s, 1H, CH) 8,44 (s, 1H, CH)



excess in the reaction mixture, and reducing the reaction temperature favored the formation of (II). Thus, at 0°C we were able to obtain (II) almost exclusively. The structures of (II) and (III) were confirmed by their elemental analyses (Table 1) and ^{1}H NMR spectra (Table 2), which showed that both compounds contained protons of the same type. The intensities of the signals for the methylenethio- and ethoxy-groups in the spectrum of (III) in comparison with the intensities of the protons in the 2- and 5-positions of the pyrimidine ring were however twice as great as in (II).

Reaction of (II) with secondary amines (dimethylamine, morpholine, and piperidine) in methanol afforded the corresponding 6-dialkylaminoderivatives (IV). Anhydrous sodium carbonate was employed to take up the hydrogen chloride liberated during the reaction.

It was found that replacement of the chlorine atom by the dialkylamine was accompanied by transesterification.

The reaction of (IV) with an excess of hydrazine hydrate gave the hydrazides (V), which on boiling in acetone were converted into the isopropylidenehydrazides (VI).

The structures of (II-VI) were confirmed by their elemental analyses (Table 1) and ^{1}H NMR spectra (Table 2).

EXPERIMENTAL CHEMISTRY

The course of the reactions was followed and the purity of the products checked by TLC on Silufol plates. The ^{1}H NMR spectra were obtained on a Tesla BS487C spectrometer (8 MHz) at 33°C. The internal standard for (II) and (III) was hexamethyldisiloxane, and for (IV)-(VI), tetramethylsilane. The solvent for (II), (III), and (IVa) was CCl_4, for (IVb), (Va), and (VIa), $CDCl_3$, and for (IVc), (Vb), (Vc), and (VIc), CF_3COOH.

4,6-Dichloropyrimidine (I). This was obtained from 4,6-dihydroxypyrimidine [6] as described in [7].

Ethyl (6-Chloropyrimidin-4-ylthio)acetate (II) and 4,6-Bis(ethoxycarbonylmethylthio)pyrimidine (III). A. To a solution of sodium ethoxide, obtained from 1.5 g (0.065 mole) of metallic sodium and 30 ml of absolute ethanol, was added dropwise at room temperature 7.8 g (0.065 mole) of ethyl thioglycollate, and the mixture was stirred at this temperature for 0.5 h. A solution of 9.6 g (0.065 mole) of (I) in 50 ml of absolute ethanol was then added dropwise, and the mixture stirred at room temperature until it was neutral (3 h). The inorganic salt was filtered off and washed with ethanol. The filtrate was evaporated under reduced pressure, and the residue fractionated *in vacuo*.

B. To a solution of 9.6 g (0.065 mole) of (I) in 80 ml of absolute ethanol was added dropwise with stirring at −5–0°C a mixture prepared as described above, from 1.5 g (0.065 mole) of metallic sodium, 30 ml of absolute ethanol, and 7.8 g (0.065 mole) of ethyl thioglycollate. The mixture was stirred at 0°C for 3 h and worked up as in method A. Data for (II) and (III) are given in Tables 1 and 2.

Methyl (6-Dimethylaminopyrimidin-4-ylthio)acetate (IVa). To a mixture of 2 g (0.0086 mole) of (II), 8 ml of absolute methanol, and 2.8 g (0.026 mole) of anhydrous Na_2CO_3 was added dropwise with vigorous stirring a solution of 1.9 g (0.042 mole) of dimethylamine in 5 ml of absolute methanol at such a rate that the temperature did not rise above 30°C. The mixture was stirred for a further 2 h at room temperature, filtered, and the filtrate evaporated to dryness under reduced pressure. The residue was treated with 40 ml of absolute ethanol, filtered, the ether evaporated, and the residue fractionated *in vacuo*.

Methyl (6-Morpholinopyrimidin-4-ylthio)acetate (IVb). To a mixture of 9.3 g (0.04 mole) of (II), 60 ml of absolute methanol, and 12.7 g (0.12 mole) of anhydrous Na_2CO_3 was added dropwise with stirring 3.5 g (0.04 mole) of morpholine. The mixture was boiled for 2 h, filtered hot, the filtrate cooled, and the solid which separated was filtered off and recrystallized.

Methyl (7-Piperidinopyrimidin-4-ylthio)acetate (IVc). Obtained as described for (IVb). Isolation: when the reaction was complete, the mixture was filtered, the filtrate evaporated under reduced pressure, the residue dissolved in methanol, saturated with gaseous hydrogen chloride, and basified with cooling with sodium carbonate solution. The solid which separated was filtered off and recrystallized.

(6-Dialkylaminopyrimidin-4-ylthio)acetohydrazides (Va-c). To a solution of 0.5 g (0.022 mole) of (IVa) in 1 ml of methanol was added 0.17 g (0.0033 mole) of 99% hydrazine hydrate, and the mixture was boiled for 2 h, cooled, and the solid filtered off and recrystallized.

Similarly obtained were (Vb) and (Vc), except that a fourfold excess of hydrazine hydrate was used, and the mixture was stirred for 4 h at room temperature.

(6-Dialkylaminopyrimidin-4-ylthio)acetoisopropylidenehydrazides (VIa-c). A mixture of 0.022 mole of the hydrazide (Va-c) and 80 ml of acetone was boiled for 0.5 h, cooled, the solid which separated from the residue filtered off, and the filtrate evaporated to dryness to give a further quantity of the compound which was added to the main crop and recrystallized.

Data for (II), (III), (IVa-c), (Va-c), and (VIa-c) are given in Tables 1 and 2.

EXPERIMENTAL PHARMACOLOGY

The hypolipidemic activity of the compounds was examined in white rats, which had been treated for seven days with the test compounds *per os*. On the eighth day, the rats were decapitated, and the total cholesterol, lipids, and triglycerides in the blood serum determined [4]. Acute toxicities and the effects of the test compounds on the CNS were studied in mongrel white mice by the oral route of administration. The LD_{50} values were calculated by the method of Litchfield and Wilcoxon [1]. The effects of the compounds on the CNS were studied using the method developed in [8]. The compounds were administered as suspensions in 1% starch mucilage (0.1 ml/10 g).

Studies with (IVb), (Vb), (Vc), (VIb), and (VIc) showed them [especially (Vb) and (VIc)] to cause, in the initial period of observation, a rapid decrease in spontaneous motor activity in mice, with the onset of ptosis, weakening of body position reflex, and considerable slowing of respiration. The LD_{50} of (IVa) and (IVb) were greater than 2000 mg/kg, of (IVc) 1350 mg/kg, and of (Va-c) and (VIa-c), between 285 and 460 mg/kg.

It was found that (IV) was devoid of hypolipidemic activity in rats, whereas (II) and (Vb) in a dose of 100 mg/kg reduced the triglyceride levels by 45.8% ($P < 0.05$) and 17.5%, respectively. In a dose of 100 mg/kg, (VIb) reduced total cholesterol by 21.2% ($P < 0.01$), total lipids by 14.4%, and triglycerides by 9.9% in the blood serum of the experimental animals.

In a dose of 50 mg/kg, (Vb, c) and (VIb, c) reduced the number of apertures in a plate figured out by mice by a factor of 1.9-13.1, 30 minutes after administration ($P < 0.05$). Chlorpromazine, in a dose of 5 mg/kg, reduced this index by a factor of 5.1, and in a dose of 10 mg/kg, by a factor of 74.2 ($P < 0.05$). Three hours after administration of the test compounds, the number of apertures figured out was reduced by a factor of 1.19-7.35 in comparison with the controls (chlorpromazine in a dose of 5 mg/kg reduced it by a factor of 8.4, and in a dose of 10 mg/kg it totally suppressed movement of the mice). After 3 h, (Vc) statistically significantly (in doses of 20, 30, and 40 mg/kg) shortened the time spent by mice in the suspended state. This compound in a dose of 40 mg/kg, like chlorpromazine in a dose of 2.5 mg/kg, significantly reduced the rectal temperature of the experimental animals one hour after administration.

In a dose of 50 mg/kg, (Vb, c) and (VIb, c), like seduxen (2.5 mg/kg) and chlorpromazine (2.5 mg/kg), had no effect on the lethal outcome of strychnine convulsions (2.5 mg/kg of strychnine nitrate intraperitoneally), and only slightly extended the time to death. In corazole convulsions (150 mg/kg intraperitoneally), seduxen completely prevented the deaths of mice (in a dose of 7 mg/kg; ED_{50} = 2.5 mg/kg), whereas (Vb) (50 mg/kg), (VIb) (30-50 mg/kg), and (VIc) (50-60 mg/kg) protected one third of the animals against death, but there was no increase in effectiveness when the dose was increased. Chlorpromazine (2.5 mg/kg orally) completely eliminated the rectal temperature rise in mice thirty mintues after the administration of amphetamine (10 mg/kg) intraperitoneally, and (Vc) in doses of 10-40 mg/kg substantially reduced this effect of amphetamine. In a dose of 50 mg/kg, all the test compounds extended hexobarbital sleep (80 mg/kg) in mice. The effects of (Vc) and (VIc) were statistically significant.

This series of (6-dialkylaminopyrimidin-4-ylthio)acetic acids thus contains compounds which display hypolipidemic activity and a suppressant effect on the CNS in mice. It is therefore concluded that the search for biologically active compounds amongst novel (pyrimidin-4-ylthio)acetic acid derivatives and their analogs is justified.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF COMPLEXES OF THE TRANSITION METALS WITH NITROFURAZONE DERIVATIVES OF 1-AMINO-1,3,4-TRIAZOLE

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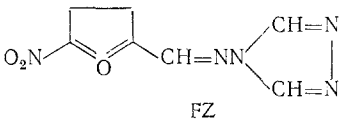
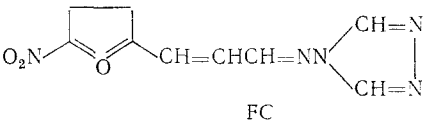
UDC 615.281:547.793.2].012.1

The preparation and extensive study of complexes of the transition metals with biologically active ligands has assumed increased importance in recent times. Such complexes frequently display high biological activity, together with toxicities which are lower than those of the original ligands, thus opening up the possibility of extensive applications in medicine, veterinary practice, and biochemistry [12].

In this connection, nitrofurazone derivatives of 1-amino-1,3,4-triazole, especially 1-(5-nitrofurfuryliideneamino)-1,3,4-triazole (furazonal, FZ) and 1-(5-nitrofurylacrylideneamino)-1,3,4-triazole (furacrylin, FC), which display high antibacterial activity against a variety of pathogenic microorganisms [7, 11], are worthy of attention as the ligands (L) for complexation with transition metals:



FZ



FC

The presence in the molecules of FZ and FC of various reaction centers (the nitro-group, furan ring, and triazole moiety) also makes them of interest from the point of view of competitive coordination.

We here describe the use of FZ and FC for the synthesis of complexes of Co(2+), Cu(2+), Pd(2+), and Pt(2+), some questions related to the structures of the products are discussed, and the results of studies of their biological properties are presented.

The FZ complexes were obtained by reacting a solution of the ligand in acetone with acetone [for Co(2+) and Cu(2+)] or aqueous [for Pd(2+) and Pt(2+)] solutions of salts of the appropriate metals (M), in the ratio M:L = 1:2. The complexes of Co(2+) and Cu(2+) with FC were obtained similarly, but to obtain the complexes of Pd(2+) and Pt(2+) the FC was dissolved in concentrated acetic acid.

All the products were nonelectrolytes, as shown by the values of the molar electrical conductivity of their solutions in DMF (λ = 1.6–48.0 $cm^{-1} \cdot cm^2 \cdot mole^{-1}$) [sic – Translator]. The compositions and structures of the complexes were established from their elemental analyses (Tables 1 and 2), thermographic analyses (Table 3) and IR spectra (Table 4).

The IR spectra of (I), (II), and (V) contained $\nu_{C=O}$ absorption (at 1710-1725 cm^{-1}) due to the presence of acetone in their composition [6]. The presence of water of crystallization in the Co(2+), Cu(2+), and Pt(2+) complexes was shown by their IR spectra (ν_{O-H} = 3200-3700 cm^{-1}) and thermographic analyses. The DTA plots of these compounds showed endo-effects corresponding to the removal of a molecule of water of crystallization. The weight loss in TG was in agreement with theoretical calculations (Table 3).

The thermal effects following the endo-effects due to removal of water of crystallization were due to decomposition of the complexes. It was, however, not possible to separate clearly the stages of cleavage and decomposition of the organic and inorganic parts of the molecule as a result of their superimposition. Noteworthy is the beginning of the rapid decomposition of

N. G. Chernyshevskii Saratov University. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 18, No. 11, pp. 1339-1344, November, 1984. Original article submitted May 4, 1984.

0091-150X/84/1811-0779$08.50