SYNTHESIS AND HYPOLIPIDEMIC ACTIVITY OF (4-DIALKYLAMINO-6-METHYL-2-PYRIMIDINYLTHIO)ACETHYDRAZIDES

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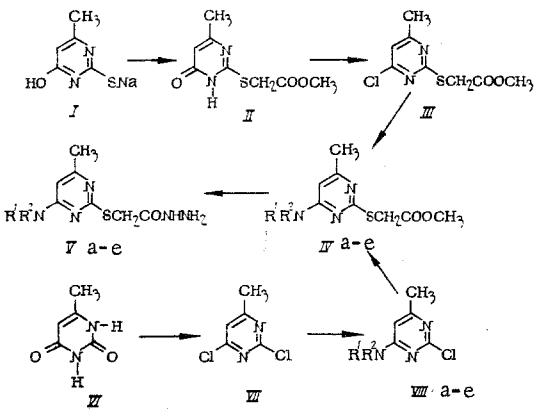
2-Pyrimidinylthioacethydrazides (V) with a 2,3-xylidine or p-chlorobenzylamine residue at the 4-position of the pyrimidine ring and a chlorine atom at the 6-position have hypolipidemic activity [1]. To clarify the need for the chlorine atom and the 2,3-xylidine or p-chlorobenzylamine residue for hypolipidemic activity to be present in the derivatives of (2-pyrimidinylthio)acetic acids, and to search for new hypolipidemic compounds in the pyrimidine series, we synthesized compounds V containing dialkylamino and methyl groups at the 4 and 6 positions of the pyrimidine ring, respectively:



a: $R^1R^2N = (CH_3)_2N$; b: $R^1R^2 = (C_2H_5)_2N$; c: $R^1R^2N = (C_4H_9)_2N$;
d: R^1R^2N = N-piperidino; e: R^1R^2N = N-morpholino

Hydrazides V were obtained by the action of hydrazine hydrate on esters IV at 15-20°C in ethanol. Esters IV are polyfunctional compounds containing three groups in their composition which are sensitive to nucleophilic agents (besides the ester, methylenethio- and dialkylamino groups). Therefore, with increase in the temperature, secondary compounds are formed, which leads to a loss in the yield of the desired products V. Esters V were obtained by two methods. The first was similar to that described in [1]. In this method, 4-methyl-2-thiouracil (I) was the starting material, and in the second, 4-methyluracil (VI). The second method, according to which esters IV are obtained smoothly and in high yields by boiling 2-chloropyrimidines VIII with methyl thioglycolate in the presence of triethylamine, is preferable over the first method, whose disadvantage is the formation of resinification products at the stage of the preparation of III, which leads to losses in the yield of the main compound.

The identity and structure of compounds IV and V were confirmed by elementary analysis (Table 1) and data of UV and ^{1}H NMR spectroscopy (Table 2). In the ^{1}H NMR spectra of compounds IV and V, together with signals of pyrimidine ring substituents, a methylene group singlet was observed in the 3.70-3.86 ppm region characteristic of derivatives of 2-pyrimidinylthioacetic acids. Also, in the ^{1}H NMR spectra of V, the ester methoxy group signals, characteristic of esters IV (3,55-3.75 ppm), were absent, while signals of the secondary amino group (8.5 ppm) were present. The signals of the primary amino group fall within the range of signals of the methylene group, and are superposed on them.

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TABLE 1. Parameters and Data of Elementary Analysis of IV and V

Compound	Yield, %	mp, °C (solvent)	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
IVa	68 (A) 91 (B)	83—84 (pentane)	50,06	6,39	17,28	$C_{10}H_{15}N_3O_2S$	49,77	6,29	17,41
IVb	67 (A) 89 (B)	42—43 (petroleum ether)	53,50	7,32	15,67	$C_{12}H_{15}N_3O_2S$	53,51	7,11	15,60
IVc	70 (A) 82 (B)	38—39 (petroleum ether)	59,21	8,43	12,93	$C_{16}H_{27}N_3O_2S$	59,05	8,36	12,91
IVd	65 (A) 86 (B)	87,5—88 (ethyl acetate)	55,48	6,71	14,88	$C_{13}H_{19}N_3O_2S$	55,49	6,81	14,93
IVe	63 (A) 89 (B)	120,5—121,5 (ethyl acetate)	50,24	6,00	14,54	$C_{12}H_{17}N_3O_3S$	50,87	6,05	14,82
Va	97	147—148 (ethanol)	45,14	6,30	29,41	$C_9H_{15}N_5OS$	44,80	6,27	29,02
Vb	85	95,5—96,5 water	49,33	6,92	26,12	$C_{11}H_{19}N_5OS$	49,05	7,11	26,00
Vc	80	62—63 (methanol—water)	55,99	8,06	21,23	$C_{15}H_{27}N_5OS$	55,35	8,36	21,25
Vd	91	139,5—140 (water)	46,50	5,91	24,34	$C_{11}H_{17}N_5O_2S$	46,63	6,05	24,72
Ve	87	107—108 (water)	51,64	6,80	24,73	$C_{13}H_{19}N_5OS$	51,22	6,81	24,89

TABLE 2. Data of UV and ^1H NMR Spectra of IV and V

Compound	UV spectrum, λ_{max}, nm (log ε)	^1H NMR spectrum, δ, ppm
IVa	237 (4,21), 255 (4,06), 285 (3,73)	2,13 (s, 3H, CH_3), 2,85 (s, 6H, $2CH_3$), 3,55 (s, 3H, CH_3O), 3,73 (s, 2H, SCH_2), 5,85 (s 1H, CH)
IVb	237 (4,20), 263 (4,13), 290 (3,84)	1,14 (t, 6H, $2CH_3$), 2,25 (s, 3H, CH_3), 3,5 (q, 4H, $2CH_2$), 3,7 (s 3H, CH_3O), 3,85 (s, 2H, SCH_2), 5,95 (s, 1H, CH)
IVc	240 (4,05), 256 (4,05), 285 (3,83)	1,0 (t, 6H, $2CH_3$), 1,5 (m, 8H, $2CH_2CH_2$), 2,25 (s, 3H, CH_3), 3,43 (d, 4H, $2CH_2N$), 3,68 (s, 3H, OCH_3), 3,86 (s 2H, SCH_2), 5,92 (s, 1H, CH)
IVd	240 (4,21), 263 (4,19), 294 (3,89)	1,65 (m, 6H, $3CH_2$), 2,25 (s, 3H, CH_3), 3,55 (d, 4H, $2CH_2N$), 3,7 (s, 3H, OCH_3), 3,82 (s 2H, SCH_2), 6,06 (s, 1H, CH)
IVe	238 (4,26), 255 (4,14), 285 (3,87)	2,32 (s, 3H, CH_3), 3,66 (q, 8H, $2CH_2O+2CH_2N$), 3,75 (s, 3H, OCH_3), 3,85 (s, 2H, SCH_2), 6,07 (s 1H, CH)
Va	237 (4,21), 253 (4,15), 282 (3,80)	2,14 (s, 3H, CH_3), 2,88 (s, 6H, $2CH_3N$), 3,73 (m, 4H, SCH_2+NH_2), 5,88 (s 1H, CH), 8,54 (s, 1H, NH)
Vb	237 (4,20), 263 (4,16), 290 (3,80)	1,15 (t, 6H, $2CH_3$), 2,28 (s, 3H, CH_3), 3,47 (m, 6H, $2CH_2N+NH_2$), 3,74 s, 2H, SCH_2), 5,99 (s, 1H, CH), 8,5 (s, 1H, NH)
Vc	237 (4,21), 263 (4,13), 290 (3,86)	1,0 (t, 6H, $2CH_3$), 1,5 (m, 8H, $2CH_2$, CH_2), 2,3 (s 3H, CH_3), 3,42 (m, 6H, $2CH_2N+NH_2$), 3,75 (s, 2H, SCH_2), 5,99 (s, 1H, CH), 8,55 (s. 1H, NH)
Vd	237 (4,02), 263 (3,94), 290 (3,66)	1,65 (m, 6H, $3CH_2$), 2,28 (s 3H, CH_3), 3,56 (m, 6H; $2CH_2N+NH_2$), 3,70 (s, 2H, SCH_2), 6,09 (s, 1H, CH), 8,5 (s, 1H, NH)
Ve	238 (4,22), 255 (4,13), 285 (3,87)	2,32 (s, 3H, CH_3), 3,65 (m, 1OH, $2OCH_2+2CH_2N+$ $+NH_2$), 3,72 (s, 2H, SCH_2), 6,11 (s, 1H, CH), 8,52 (s, 1H, NH)

EXPERIMENTAL PHARMACOLOGICAL SECTION

The acute toxicity of the compounds was studied on nonpedigree white mice with peroral or subcutaneous administration. The LD_{50} was calculated by the Litchfield—Wilcoxon method [2]. The hypolipidemic activity was studied on white rats, which for 7 days were put on a diet including 2% cholesterol and 1% cholic acid, as well as the compounds studied taken perorally with 1% starch paste in doses corresponding to 0.2 LD_{50}. On the 8-th day, the rats were decapitated, and the content of total cholesterol, the total lipids, phospholipids and β-lipoproteids was determined in the blood serum [3]. The same parameters, as well as the amount of triglycerids, were determined in the blood serum of the rats 18 h after intravenous administration of WR-1339 Triton (Serva, GDR) in a dose of 200 mg/kg, with simultaneous peroral introduction of the compounds studied in doses corresponding to 0.2 LD_{50} [4]. The results were compared with the data obtained in the study of blood serum of rats of the control groups. The results are listed in Table 3.

Table 3 shows that the compounds studied have a hypolipidemic activity. The Miscleron (from the firm Chinoin, Hungarian People's Republic), used as a standard under the same conditions (dose equal to 0.2 LD_{50}) decreased the amount of total cholesterol by 40.2%, phospholipids by 31.3%, β-lipoproteids by 63.2%, and total lipids by 33% ($P < 0.05$). Compounds Va and Vb had hypolipidemic activity on a model of Triton-induced hyperlipidemia in white rats, while Miscleron is inactive in this experimental model.

TABLE 3. Results of Study of Acute Toxicity and Hypolipidemic Activity of V

Compound	LD_{50}, mg/kg	Change in biochemical parameters of lipid metabolism under the influence of compounds studied, % compared with control							
		cholesterol diet				Triton-induced hyperlipidemia			
		cholesterol	phospholipids	β-lipoproteids	total lipids	cholesterol	phospholipids	β-lipoproteids	triglycerids
Va	420	—65,0†	—40,2†	—74,7†	—53,9†	—21,0†	—14,0	—24,0	—10,9
Vb	160*	—64,5†	—37,2†	—75,2†	—44,5†	—0,7	—12,0	—20,0	—14,5
Vc	290	—47,5†	—25,0†	—58,2†	—25,9	0	0	0	0
Vd	460	—47,3†	—22,8†	—59,0	—37,8	0	0	0	0
Ve	450*	—22,9	—28,1†	—44,0	—21,2	0	0	0	0

*At subcutaneous administration.
†Difference with control statistically reliable ($P < 0.05$).

Thus, our investigations show that the presence of chlorine and 2,3-xylidine or p-chlorobenzylamine residue is necessary for the appearance of hypolipidemic activity of 2-pyrimidinylthioacethydrazides, so that the search for new active hypolipidemic agents in the pyrimidine series is promising.

EXPERIMENTAL CHEMICAL SECTION

The course of the reaction was controlled by TLC on Silufol plates. The UV spectra were run on the "Specord UV-VIS" apparatus (GDR). Water was used as the solvent. The ^1H NMR spectra were recorded on the BS487C "Tesla" spectrometer with a working frequency of 80 MHz at 33°C in $CDCl_3$, using tetramethylsilane as the internal standard.

The following compounds were obtained by the above methods: methyl thioglycolate [5, 6], bp 142°C, methyl ester II [7], mp 155-156°C, chloropyrimidines VII [8], mp 47°C, VIIIa [9], mp 86-87°C; VIIIb [9], bp 138-140°C (18 mm); VIIIc [9], bp 198-200°C (5 mm); VIIId [9], mp 97-98°C; VIIIe [9], mp 57-58°C. Methyl ester III was synthesized in analogy to ethyl ester of (4,6-dichloro-2-pyrimidinylthio)acetic acid [1], mp 33-35°C.

Methyl (4-Dialkylamino-6-methyl-2-pyrimidinylthio)acetates.(IVa-e). A. A 12.7-g portion (0.12 mole) of anhydrous sodium carbonate was added to a solution of 9.3 g (0.04 mole) of (6-methyl-4-chloro-2-pyrimidinylthio)acetate (III) in 60 ml of methanol, and the 0.04 mole of the corresponding amine was added dropwise at a temperature below 10°C. For IVa, the reaction mixture is stirred for 2 h at 7-10°C, for IVc for 4 h at 40°C, for IVb the mixture is boiled for 7 h, and for IVd, e for 2 h. The methanol is then removed on a rotary evaporator. In the case of IVa-c, the residue is diluted with water (80 ml), and the product extracted by ether. After distillation of ether, the residue is recrystallized from a suitable solvent. In the case of IVd, e, after the distillation of methanol, the solid residue is recrystallized.

B. The reaction mixture consisting of 0.05 mole of VIII, 7.6 g (0.075 mole) of triethylamine and 5.3 g (0.05 mole) of methyl thioglycolate is boiled for 3 h. The mixture is then cooled, diluted with 50 ml of water, and extracted by ether. After distillation of ether, the residue is recrystallized from a suitable solvent. Data on compounds IVa-e are listed in Table 1 and 2.

(4-Dialkylamino-6-methyl-2-pyrimidinylthio)acethydrazides (Va-e). A reaction mixture consisting of 0.025 mole of IV, 5.0 g (0.1 mole) of hydrazine hydrate, and 15 ml of ethanol is left to stand for 3 h in a closed vessel at 15-20°C. The precipitate is filtered and recystallized from a suitable solvent. Data on compounds Va-e are listed in Tables 1 and 2.

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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 6-FLUORO-2,3-DIMETHYL- AND 2,3-BIS[HYDROXY(ACETOXY)METHYL]QUINOXALINE DI-N-OXIDES

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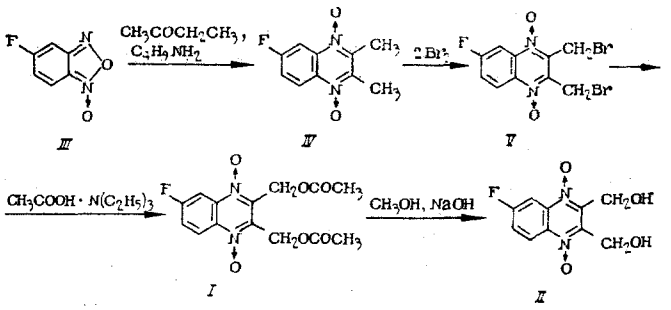
In continuation of work aimed at the discovery of new quinoxaline di-N-oxides with antibacterial activity, the synthesis has been undertaken of the di-N-oxides of 6-fluoro-2,3-bis(acetoxymethyl)- and 2,3-bis(hydroxymethyl)quinoxaline (I and II), which are analogs of quinoxidine and dioxidine [1, 2].

Compounds (I) and (II) were synthesized from 5-fluorobenzofuroxan (III), obtained as described in [3].

Compound (III) was reacted with methyl ethyl ketone butyleneamine, prepared directly in the reaction mixture from methyl ethyl ketone and butylamine. The resulting 6-fluoro-2,3-dimethylquinoxaline di-N-oxide (IV) was brominated, and the dibromo-derivative (V) reacted with triethyl-ammonium acetate, to give 6-fluoro-2,3-bis(acetoxymethyl)quinoxaline di-N-oxide (I). The latter compound (I) was converted into the dioxidine analog (II) by treatment with methanol in the presence of catalytic amounts of NaOH.



The antibacterial activity of (I), (II), (IV), and (V) was examined in comparison with that of dioxidine and quinoxidine.

In *in vitro* experiments, the bacteriostatic activity of the compounds was determined against *E. coli*, *Sh. flexneri*, *S. typhi*, *Pr. vulgaris*, *Kl. pneumoniae*, *Ps. aeruginosa*, and *Staph. aureus* by the twofold serial dilution method on a liquid nutrient medium, using an inoculation dose of $1 \cdot 10^6$ cells per ml. *In vivo* experiments were carried out with 100 mongrel white mice weighing 15-16 g. In experiments on healthy animals, tolerance to the compounds was examined following a single internal or subcutaneous administration of the compound in doses up to 500 mg/kg. Chemotherapeutic activity was studied in experiments using *S. typhi*, *Ps. aeruginosa*, and *Staph. aureus* in model generalized infections induced by intraperitoneal introduction of the infective agent. Infecting doses were employed which resulted in the deaths

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