of those tested was 400 μg/ml. Sabouraud's agar (pH 6.0-6.8) was used to cultivate the fungi. The fungal load was 20 million fungal bodies. The maximum tested concentration was 500 μg/ml. The conducted tests demonstrated that basically the compounds either exhibited little or no antibacterial and antifungal activity (the minimum bacteriostatic concentration was 200 μg/ml and the minimum mycostatic concentration was 250 μg/ml). Compound VIII was found to have the highest level of activity. Its minimal mycostatic concentration against *Trichophyton mentagrophytes* was 50 ug/ml.

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SYNTHESIS AND BIOLOGICAL PROPERTIES OF DERIVATIVES OF (3-METHYL-7-ALKYLXANTHINYL-8) THIOACETIC ACIDS

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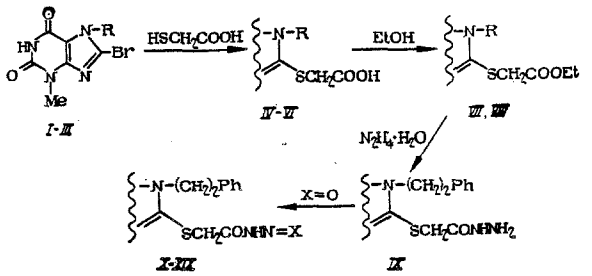
As a continuation of our search for biologically active compounds among the 3-methylxanthine series [1-3], we studied the reaction between 3-methyl-7-alkyl-8-bromoxanthines and thioglycolic acid, and investigated the antimicrobial properties of (3-methyl-7-alkylxanthinyl-8) thioacetic acid derivatives. The starting compounds 3-methyl-7-α-methylbenzyl- and 7-β-phenylethyl-8-bromxanthines (I, II) were obtained by the method described in [2]. 3-Methyl-7-β-cyanoethyl-8-bromxanthine (III) was synthesized by reacting 3-methyl-8-bromxanthine with an excess of acrylonitrile, similar to [4].

We found that when bromides I-III react with an excess of thioglycolic acid in boiling DMFA, they form (3-methyl-7-alkylxanthinyl-8)thioacetic acids (IV-VI). The structure of compounds IV-VI was confirmed by PMR spectra. The IR spectra of acids IV-VI are characterized by intense absorption bands in the region 1680-1770 cm^{-1} (νC=O) and 3300-3480 cm^{-1} (νOH).

Heating acids V and VI with ethyl alcohol in the presence of conc. H_2SO_4 resulted in the formation of corresponding ethyl esters of (3-methyl-7-alkylxanthinyl-8) thioacetic



I, VI, VII: R = CH(Me)Ph; II, V, VIII: R = $(CH_2)_2$Ph; III, IV: R = $(CH_2)_2$CN;
X: X = $CHC_6H_4NO_2$-*n*; XI: X = $CHC_6H_4NO_2$-*m*; XII: X = $CHC_6H_4NMe_2$-*n*;
XIII: X = CHC_6H_3OH-2-Br-5; XIV: X = $CHC_6H_3(OH)_2$-2,4; XV: X = $CHC_6H_3(OMe)_2$-2,4;
XVI: X = CHC_6H_4OH-*o*; XVII: X = CHC_6H_4OMe-*n*; XVIII: X = 5-nitrofurfurylidene;
XIX: X = 2,3-dihydroindolone-2-ilidene-3.

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TABLE 1. Characteristics of Synthesized Compounds (III-XIX)

Comp.	Yield, %	mp, °C	Found, %				Empirical formula	Calculated, %			
			C	H	N	S		C	H	N	S
III	70	291—2	36,4	2,9	23,2		$C_9H_8BrN_5O_2$	36,3	2,7	23,5	
IV	21	208—10	42,6	3,8	22,5	10,6	$C_{11}H_{11}N_5O_4S$	42,7	3,6	22,6	10,4
V	61	237—9	53,2	4,5	15,7	9,1	$C_{16}H_{16}N_4O_4S$	53,3	4,5	15,6	8,9
VI	31	252—4	53,4	4,2	15,6	8,7	$C_{16}H_{16}N_4O_4S$	53,3	4,5	15,6	8,9
VII	51	160—2	55,8	5,3	14,6	8,2	$C_{18}H_{20}N_4O_4S$	55,7	5,2	14,4	8,3
VIII	73	200—2	55,2	5,3	14,7	8,2	$C_{18}H_{20}N_4O_4S$	55,7	5,2	14,4	8,3
IX	69	204—6	51,5	5,1	22,7	8,3	$C_{16}H_{18}N_6O_3S$	51,3	4,9	22,5	8,6
X	80	255—7	54,7	4,1	19,4	6,2	$C_{23}H_{21}N_7O_5S$	54,4	4,2	19,3	6,3
XI	80	255—6	54,2	4,2	19,6	6,3	$C_{23}H_{21}N_7O_5S$	54,4	4,2	19,3	6,3
XII	80	263—5	59,6	5,3	19,5	6,1	$C_{25}H_{27}N_7O_3S$	59,4	5,4	19,4	6,3
XIII	89	250—2	49,4	3,7	15,4	6,0	$C_{23}H_{21}BrN_6O_4S$	49,6	3,8	15,1	5,8
XIV	90	260—2	56,0	4,3	16,7	6,2	$C_{23}H_{22}N_6O_5S$	55,9	4,5	17,0	6,5
XV	86	246—8	57,6	5,1	16,3	6,2	$C_{25}H_{26}N_6O_5S$	57,5	5,0	16,1	6,1
XVI	83	244—6	57,7	4,7	17,3	6,4	$C_{23}H_{22}N_6O_4S$	57,7	4,6	17,6	6,7
XVII	82	265—7	58,6	5,1	17,2	6,7	$C_{24}H_{24}N_6O_4S$	58,5	4,9	17,1	6,6
XVIII	70	255—7	50,6	3,9	19,8	6,4	$C_{21}H_{19}N_7O_6S$	50,7	3,9	19,7	6,5
XIX	100	240—2	57,1	4,5	19,7	6,4	$C_{24}H_{21}N_7O_4S$	57,2	4,2	19,5	6,4

acids (VII, VIII) whose structure was confirmed by the absence of carboxyl hydroxyl absorption in their IR spectra. The PMR spectrum of the ethyl ester of VI has proton signals of the ethoxy group at 1.07 (triplet, 3H, CH_3C) and 4.02 ppm (quartet, 2H, CH_2O), as well as 11.04 (singlet, 1H, $N_{(1)}H$), 7.27 (singlet, 5H, Ph), 6.03 (multiplet, 1H, $CHCH_3$), 3.27 (singlet, 2H, CH_2S), 3.20 (singlet, 3H, N_3CH_3), 1.87 ppm (doublet, 3H, CH_3CH).

Hydrazinolysis of the ester of VIII in an ethanol medium led to the formation of hydrazine (3-methyl-7-β-phenylethylxanthinyl-8) thioacetic acid (IX). The latter easily reacts with carbonyl-containing compounds in aqueous ethanol in the presence of glacial AcOH with the formation of the corresponding hydrazines (X-XIX).

EXPERIMENTAL — CHEMICAL

The IR spectra were recorded on a UR-20 instrument (GDR) in petroleum jelly. The PMR spectra were read on a Tesla BS 467 (60 MHz) instrument. The solvent was DMSO-d_6. Chemical shifts were given with reference to HMDS.

3-Methyl-7-β-cyanoethyl-8-broxanthine (III) was obtained in a manner similar to [4].

(3-Methyl-7-alkylxanthinyl-8) Thioacetic Acids (IV-VI). A solution of 0.01 mole of compounds I, II or III, 0.02 mole of thioglycolic acid in 15-20 ml of DMFA was boiled for 4 h, then cooled and filtered. The filtrate was diluted with water and the precipitate was filtered off and dissolved in a saturated soda solution. It was then filtered and the filtrate was acidified with glacial AcOH. The precipitate was filtered off, washed with cold water and crystallized from water (IV), from ethanol (V), and from dioxane (VI). The PMR spectrum of IV, ppm: 11.20 (singlet, 1H, N_1H), 4.42 (triplet, 2H, NCH_2), 4.07 (singlet, 2H, CH_2), 3.30 (singlet, 3H, NCH_3), 3.06 (triplet, 2H, CH_2CN). PMR spectrum of V, ppm: 11.08 (singlet, 1H, NH), 7.17 (singlet, 5H, Ph), 4.34 (triplet, 2H, NCH_2), 4.13 (singlet, 2H, CH_2), 3.27 (singlet, 3H, NCH_3), 3.0 (multiplet, 2H, CH_2Ph). PMR spectrum of VI, ppm: 10.72 (singlet, 1H, NH); 7.28 (singlet, 5H, Ph), 6.11 (quartet, 1H, $CHCH_3$), 4.11 (singlet 2H, CH_2), 3.27 (singlet, 3H, NCH_3); 1.89 (doublet, 3H, CH_3C).

Ethyl Esters of (3-Methyl-7-alkylxanthinyl-8) Thioacetic Acids (VII, VIII). A mixture of 7.2 g of V or VI, 150 ml of anhydrous ethanol, and 20 ml of conc. H_2SO_4 was heated on a boiling water bath for 1.5 h, then cooled and diluted with 100 ml of water. The precipitate was filtered off, washed with water and crystallized from ethanol.

(3-Methyl-7-β-phenylethylxanthinyl-8) Thioacetic Hydrazide (IX). A mixture of 1.94 g of VIII, 3 ml of hydrazine hydrate, and 70 ml of ethanol was boiled for 40 min. The mixture was filtered while boiling and cooled. The precipitate was filtered off, washed with ether, and crystallized from n-propanol.

Hydrazones of (3-Methyl-7-β-phenylethylxanthinyl-8) Thioacetic Hydrazide (X-XIX). A mixture of 0.37 g (1 mmole) of the hydrazide of IX, 1 mmole of the corresponding aldehyde or ketone, 10 ml of ethanol, 4 ml of water, and 1 ml of glacial AcOH was boiled for 10-30

min, cooled. The precipitate was filtered off, washed with water, and crystallized from aqueous DMFA.

Data on compounds III-XIX are given in the Table.

EXPERIMENTAL — BIOLOGICAL

The antimicrobial action of the synthesized compounds was tested by the double serial dilution method in a beef-peptone broth against *Staph. aureus* 209P, *E. coli* 675, *S. typhi* 1196, *Sh. flexneri* 2a 516, *Bac. anthracoides* 1312, *Ps. aeruginosa*, and *Proteus vulgaris* 261-III. The activity of the compounds was evaluated on the basis of their minimal bacteriostatic concentration (in μg/ml.) The maximum tested concentration was 200 μg/ml.

The results of our tests showed that the compounds do not exhibit antibacterial activity against the examined strains. The one exception was the hydrazide of XVIII which suppressed the growth of *Staph. aureus* at a concentration of 100 μg/ml, and the growth of *Bac. anthracoides* at a concentration of 12.5 μg/ml.

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ANTIMICROBIAL ACTIVITY OF O,O-DIETHYL N-ALKYLAMINOMETHYL-PHOSPHONATES AND O-ETHYL N-ALKYLAMINOMETHYLPHOSPHONIC ACIDS

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In order to establish the relationship between antimicrobial activity and structure, some O,O-diethyl N-alkylaminomethylphosphonates (Ia-f) and their derivatives the O-ethyl N-alkylaminomethylphosphonic acids (IIa-g) which have the betaine structure [1] have been synthesized.

$$\underset{\text{I a-f}}{RNHCH_2P(O)(OEt)_2} \qquad \underset{\text{II a-g}}{R\overset{+}{N}H_2CH_2P(O)(OEt)O^-}$$

$R = C_6H_{13}$-n (Ia, IIa); C_8H_{17}-n (Ib, IIb); C_9H_{19}-n (IIc); $C_{10}H_{21}$-n (Ic, IId); $C_{12}H_{25}$-n (Id, IIe); $C_{15}H_{31}$-n (Ie, IIf); $C_{16}H_{33}$-n (If, IIg)

Studies have been carried out on the relationship between the structure, surface activity, capacity to form micelles, and antimicrobial activity in these compounds. The fungistatic and bacteriological activity shown in Table 1 shows that antimicrobial activity increases as the length of the alkyl radical is increased, and is dependent on the structure and charge on the principal group in the compound.

The fungistatic activity of (I) is increased by an order of magnitude when a C_6 radical is replaced by C_8, but further increase in the length of this radical has little effect. The greatest fungistatic activity is shown by (Ie) and (If), which contain 15 and 16 carbon atoms, respectively. The bacteriostatic activity of the aminophosphonates (I) is increased when the C_6 radical is exchanged for C_{10}, but further increases in the size of the radical leave the activity unchanged.

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