Kurnakov Reaction. To a suspension of the complex (I) or (IV) in water was added an aqueous solution of thiourea in sixfold excess, whereupon the solid dissolved. Addition of conc. HCl to the solution precipitated colorless crystals of the complexes $[PtL_2(Thio)_2]Cl_2$, which were filtered off, washed with water and ether, and dried at 50°C. Yield 70%, mp 300°C, L=L'. Found, %: S 12.00. $PtC_{22}H_{38}N_6O_2S_2Cl_2$. Calculated, %: S 12.17. L=L" Found, %: S 9.27. $PtC_{24}H_{42}N_6O_2S_2Cl_2$. Calculated, %: S 9.78.

EXPERIMENTAL — BIOLOGICAL

Antibacterial and antifungal activity was determined by double serial dilution in Hottinger's bouillon of pH 7.2, using the standard test microorganisms *Staph. aureus* 209, *E. coli* 675, *Pr. vulgaris* 28, *Ps. aeruginosa* 165, and *Candida albicans* 45. Antiphage activity of the complexes was examined in the phage–bacteria system using the following pairs: DNA-containing phage T_6 and *E. coli* B, and the RNA-phage MS-2 and *E. coli* "Hfre." The compounds were dissolved in DMF at the rate of 1000 μg/ml, and diluted with distilled water to 100 μg/ml. The numbers of surviving phage particles were determined by Grazia's agar slope method. The antiphage activity of the compounds was determined from the percentage inactivation [1].

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SYNTHESIS AND BIOLOGICAL PROPERTIES OF DERIVATIVES OF (3-METHYL-8-BROMXANTHINYL-7) ACETIC ACID

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Substances possessing antiviral [5], antifungal [4], and antiprotozoan [3] activity have been found among substituted purine and xanthine compounds. Condensation derivatives of xanthine have also been reported to exhibit antimicrobial activity [1].

In the present work we examined reactions of ethyl (3-methyl-8-bromxanthinyl-7) acetate (I) and studied the antimicrobial properties of the resultant derivatives.

The ester I was obtained by reacting potassium 8-brom-3-methylxathinate [2] with ethyl chloroacetate in boiling DMFA. The IR-spectrum of I has stretching vibration bands of amide carbonyls at 1695 and 1720 cm^{-1}, and absorption of the complex ester CO group was observed at 1750 cm^{-1}. There are also characteristic absorption bands at 1615 (C=C), 1680 (C=N), and 3180 cm^{-1} ($N^1{}_2H$). (3-methyl-8-bromxanthinyl-7) acetic acid (II) was synthesized by the alkaline hydrolysis of ester I whose IR-spectrum indicates the presence of a broad absorption band of the carboxyl hydroxyl in the region of 3480 cm^{-1}. Two singlets at δ 3.03 (3H, NCH_3) and 4.40 ppm (2H, NCH_2) were recorded in the PMR spectrum of acid II. Amino amides (III-VI) were formed by heating ester I with primary and secondary amines in DMFA. The IR spectra of III-VI confirmed their structure by the absence of the stretching vibration bands that are characteristic of complex ester carbonyls as well as by the absorption

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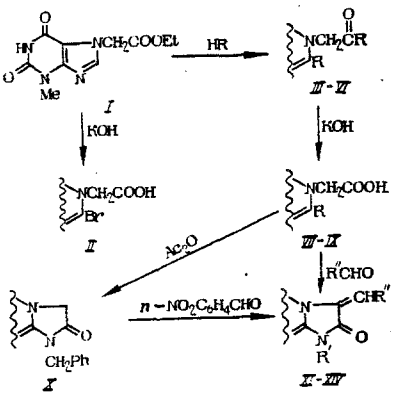
TABLE 1. Characteristics of Synthesized Compounds I-XIV

Comp.	Yield (%)	mp, °C	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
I	51	237—9	36,5	3,6	17,0	$C_{10}H_{11}BrN_4O_4$	36,3	3,4	16,9
II	58	>300	31,9	2,4	18,6	$C_8H_7BrN_4O_4$	31,7	2,3	18,5
III	58	130—2	57,6	6,9	22,3	$C_{18}H_{26}N_6O_3$	57,7	7,0	22,4
IV	21	274—5	61,4	4,7	21,3	$C_{20}H_{18}N_6O_3$	61,5	4,6	21,5
V	60	298—9	63,3	5,7	20,0	$C_{23}H_{22}N_6O_3$	63,1	5,3	20,1
VI	51	278—81	44,2	5,7	25,7	$C_{12}H_{18}N_6O_5$	44,2	5,6	25,8
VII	44	>240 (decomp.)	53,5	4,3	22,4	$C_{14}H_{13}N_5O_4$	53,3	4,2	22,2
VIII	63	255—7 (decomp.)	54,8	4,6	21,5	$C_{15}H_{15}N_5O_4$	54,7	4,6	21,3
IX	94	>220 (decomp.)	42,5	4,7	25,0	$C_{10}H_{13}N_5O_5$	42,4	4,6	24,7
X	71	306—8	58,0	4,4	22,8	$C_{15}H_{13}N_5O_3$	57,9	4,2	22,5
XI	79	331—3	59,1	3,3	19,4	$C_{22}H_{16}N_6O_5$	59,5	3,6	18,9
XII	84	290—2	63,3	4,5	15,2	$C_{24}H_{19}N_5O_5$	63,0	4,2	15,3
XIII	70	248—50	60,3	4,1	13,6	$C_{26}H_{21}N_5O_7$	60,6	4,1	13,6
XIV	50	310—2	51,4	3,4	20,8	$C_{17}H_{14}N_6O_6$	51,3	3,5	21,1

of associated NH groups in the 3320-3330 cm^{-1} region.



III:R = N-piperidino IV, VII: R = NHPh; V, VIII:R = $NHCH_2Ph$;
VI, IX:R = $NH(CH_2)_2OH$; XI:R′ = CH_2Ph, R″ = $C_6H_4NO_2$-*n*; XII:R′ = CH_2Ph,
R″ = C_6H_4OAc-*o*; XIII:R′ = CH_2Ph, R″ = $C_6H_3(OAc)_2$-*o*, *n*; XIV:R′ = $(CH_2)_2OH$;
R″ = $C_6H_4NO_2$-*n*.

The 8-substituted compounds of (3-methylxanthinyl-7) acetic acid (VII-IX) were obtained by heating the amino amides IV-VI in an aqueous alkaline solution. The signal position of the NCH_3 proton groups was practically unchanged in the PMR-spectra of amino acids VII-IX in comparison to the spectrum for acid II, and was recorded in the region of 3.05-3.06 ppm. The signals of the CH_2COO proton group shifted to a weaker field, i.e., δ = 4.73-4.83 ppm (singlet, 2H). The protons of the CH_2Ph group of acid VIII were recorded in the form of a singlet at δ 4.33 ppm (2H). The aromatic proton signals of acids VII and VIII were in the region δ 7.00 and 7.26 ppm (broadened singlet, 5H), respectively. The methylene, protons of the oxyethyl group of acid IX were recorded in the form of multiplets with centers at 3.75 (2H) and 3.43 ppm (2H).

Heating acid VIII in Ac_2O led to the cyclization of the latter and the formation of 1-methyl-8-benzyl-1,2,3,4,6,7-hexahydroimidazo[1,2-f]purinetrione-2,4,7 (X) whose structure was confirmed by PMR and mass spectra data. The PMR-spectrum of (CF_3COOH) had the following signals: 6.90 (singlet, 5H)-CH_{arom}, 4.60 (doublet 4H)-NCH_2, 3.23 ppm (singlet, 3H)-NCH_3. The peak M^+ in the mass spectrum of the tricycle X was recorded with m/z 311, which corresponded to the molecular weight. The presence of a N-benzyl radical was confirmed by the its direct elimination from M^+ (m/z 220) as well as by the fission ion of the tropyl structure (m/z 91). Subsequent $(M-CH_2C_6H_5)^+$ ion decay was characterized by the splitting off of HNCO and CO particles with m/z 192 and 177 respectively. The presence of an imidazolone fragment was characterized by an ion with m/z 178 which was due to the elimination of the $PhCH_2$-N=C=O particle from M^+.

When acdis VIII and IX were heated for a short period with aromatic aldehydes in an AcOH-Ac_2O mixture in the presence of AcONa, 6-ilidene derivatives of purinetrione-2,4,7 (XI-XIV) were formed. The n-nitrobenzylidene derivative of XI was also obtained by heating the tricycle X with n-nitrobenzaldehyde under the aforementioned conditions. One should note that O-acyl derivatives of XII and XIII were formed when compound X was reacted with

salicyl aldehyde or 2,4-dioxybenzaldehyde. Acetylation of the phenol hydroxyls was confirmed by PMR spectra and IR spectra data (the absence of OH group absorption). Proton signals of the acetyl groups were seen in the PMR spectra of the ilidene derivatives of XII and XIII at 2.33 (singlet, 3H) and 2.33 (singlet, 6H) ppm, respectively.

EXPERIMENTAL — CHEMICAL

IR spectra were recorded on a UR-20 (GDR) instrument in petroleum jelly. PMR spectra were read on a Tesla BS-467 (60 MHz) spectrometer. The solvent was CF_3COOH. Chemical shifts were given in a δ scale with reference to HMDS.

Ethyl (3-Methyl-8-bromxanthinyl-7)acetate (I). A mixture of 5.7 g (0.02 mole) of potassium 8-brom-3-methylxanthine, 2.1 ml (0.021 mole) of $ClCH_2COOEt$, and 50 ml of DMFA was boiled for 3.5 h. The mixture was filtered while still boiling. The filtrate was cooled, diluted with water, and the precipitate was filtered off. The residue was washed with water, dried, and crystallized from aqueous DMFA.

(3-Methyl-8-bromxanthinyl-7)acetic Acid (II). A solution of 9.93 g (0.03 mole) of ester I and 3.36 g (0.06 mole) of KOH in 100 ml of water was boiled for 8 h, then cooled and filtered. The filtrate was acidified with conc. HCl. The precipitate was filtered off and crystallized from water.

(3-Methyl-8-N-piperidinoxyxanthinyl-7)acetic N-Piperidinoamide (III). A mixture of 1.65 g (5 mmoles) of I, 1.5 ml (15 mmoles) of piperidine, and 15 ml of DMFA was boiled for 6 h, then cooled. The precipitate was filtered off, washed with water, and crystallized from aqueous DMFA.

(3-Methyl-8-N-phenylaminoxanthinyl-7)acetic anilide (IV) and (3-methyl-8-N-β-oxyethyl-aminoxanthinyl-7) acetic β-oxyethylamide (VI) were obtained in a similar fashion.

(3-Methyl-8-N-benzylaminoxanthinyl-7) Acetic N-Benzylamide (V). A mixture of 6.6 g (0.02 mole) of I, 8.8 ml (0.08 mole) of benzylamine, and 50 ml of dioxane was boiled for 8 h, then cooled, and diluted with water. The precipitate was filtered off, washed with water, and crystallized from DMFA.

8-Substituted (3-Methylxanthinyl-7) Esters of Acetic Acid (VII-IX). A mixture of 0.01 mole of the appropriate amide of IV, V, or VI, 0.03 mole of KOH, and 100-120 ml of water was boiled for 5 h (for obtaining VII), 15 h (for VIII), and 7 h (for IX). The mixture was then cooled, filtered, and the filtrate was acidified with conc. HCl. The precipitate was filtered off, washed with water, and crystallized from a mixture of H_2O and DMFA (for compounds VII and VIII) and from aqueous isopropanol (for IX).

1-Methyl-8-benzyl-1,2,3,4,6,7-hexahydroimidazo[1,2-f]purinetrione-2,4,7 (X). A 1.5 g portion of VIII in 15 ml of AC_2O was boiled for 2 h, cooled, and decanted into water. The precipitate was filtered off, washed with water, and crystallized from a H_2O-DMFA mixture.

6-Arylidene Derivatives of 1-Methyl-8-alkyl-1,2,3,4,6,7-hexahydroimidazo[1,2-f]purinetrione-2,4,7 (XI-XIV). A mixture of 2 mmoles of acid VIII or IX, 2 mmoles of the corresponding aldehyde, 1 g of AcONa, 5 ml of Ac_2O, and 10 ml of AcOH was boiled for 1.5-2 h, then cooled, and diluted with water. The precipitates were filtered off, washed with water, and crystallized from DMFA.

1-Methyl-6-n-nitrobenzylidene-8-benzyl-1,2,3,4,6,7-hexahydroimidazo[1,2-f]purinetrione-2,4,7 (XI) was obtained in the same manner as in the reactions between compound X and n-nitrobenzaldehyde. A blend test of XI samples obtained from various starting compounds did not result in mp depression.

Data on compounds I-XIV are given in the Table.

EXPERIMENTAL — BIOLOGICAL

The antimicrobial activity of the synthesized compounds was studied by double serial dilutions on a liquid nutrient medium for a range of microorganisms that included *Staphylococcus aureus* 209P, *E. coli* 675, *S. typhi* 1196, *Sh. flexneri* 2a 516, *Bac. anthracoides* 1312, *Ps. aeruginosa*, *Prot. vulgaris* 5(28-III), *Aspergillus niger* B KMF-1119, *Candida albicans* 624, *Microsporum lanosum* 257, and *Trichophyton mentagrophytes* IMI-124768. Hottinger's broth (pH 7.2-7.4) was used to cultivate the bacteria. The microbial load for the bacteria was 500,000 cells of an agar 18-hour culture. The maximum concentration

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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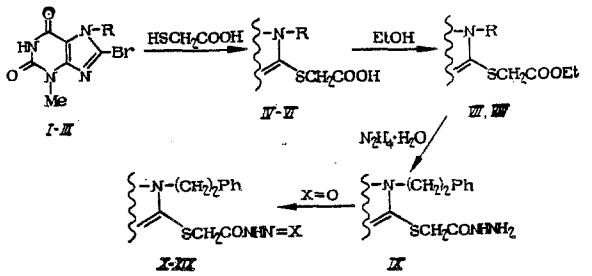
As a continuation of our search for biologically active compounds among the 3-methylxanthine series [1-3], we studied the reaction between 3-methyl-7-alkyl-8-bromoxanthines and thioglycolic acid, and investigated the antimicrobial properties of (3-methyl-7-alkylxanthinyl-8) thioacetic acid derivatives. 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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