12. S.-E. Larsson and R. Lorentzon, Clin. Sci. Mol. Med., 53, 373-377 (1977).
13. H. E. Paaren, H. F. De Luca, and H. K. Schnoes, J. Org. Chem., 45, 3253-3258 (1980).
14. W. Rembock, H. Weisner, R. Haselbauer, and H. Zucker, Int. J. Vitam. Nutr. Res., 51, 353-358 (1981).
15. M. Sheves, Y. Mazur, D. Noff, and S. Edelstein, FEBS Lett., 96, 75-78 (1978).
16. H. H. Taussky and E. Shorr, J. Biol. Chem., 202, 675-678 (1953).
17. A. Wander, Chem. Abstr., 50, No. 5, 5783 (1956).

SYNTHESIS AND BIOLOGICAL ACTIVITY OF CHLORO-SUBSTITUTED 1.5-DIKETONES AND THEIR CYCLIZATION PRODUCTS

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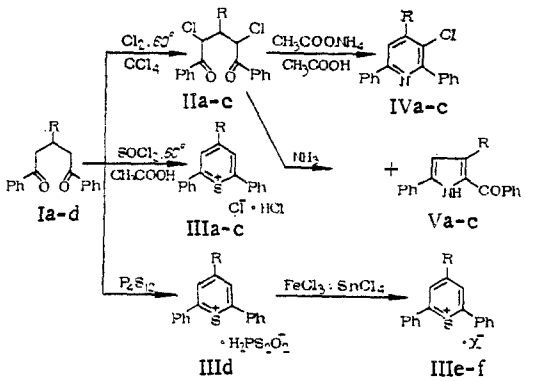
With the aim of preparing new biologically-active compounds, we synthesized chloro-substituted 1,5-diketones and their cyclization products, such as benzoylpyrroles, chloropyridines, and thiopyrilium salts, previously unknown, which serve as the bases for biologically-active preparations [2, 3].

The chlorination of the 1,5-diketones Ia-c was carried out with chlorine or thionyl chloride. The action of chlorine on 1,5-diketones leads to the electrophilic substitution of the hydrogen in the α-position to the carbonyl group to give the 2,4-dichlorosubstituted 1,5-diketones IIa-c [4]. Use of thionyl chloride instead of chlorine resulted in the cyclization of ketones Ia-c to give the corresponding thiopyrilium chlorides IIIa-c:



Ia—Va: R=H; Ib—Vb R=Me; Ic—Vc: R = Ph; Id, IIId-f: R = $C_6H_4NMe_2$-p.
IIIe: X = $FeCl_4$; IIIf: X=$SnCl_6$.

Structural features of these chloro-substituted 1,5-diketones IIa-c are shown specifically in their reactions with nucleophilic reagents [5]. Reaction of chlorodiketones IIa-c with ammonium acetate in acetic acid led to nucleophilic attack of the reagent on the carbonyl group and cyclization with formation of the 3-chloropyridines IVa-c. Reaction of IIa-c with ammonia also gave IVa-c as well as the 2-benzoylpyrroles Va-c produced as a result of nucleophilic attack of a chlorine atom and subsequent cyclization by reaction of the amino group with the carbonyl.

With the aim of introduction of dimethylamino groups, which strongly increase the biological activity of compounds, cyclization of diketone Id with phosphorus polysulfide resulted in the preparation of the thiopyrilium phosphate IIId. The thiopyrilium tetrachloroferrate (IIIe) and the hexachlorostannate (IIIf) were obtained by exchange reaction of salt IIId with ferric chloride and stannic chloride, respectively.

The structure of the compounds obtained was substantiated by data from elemental analysis and IR and NMR spectroscopy (Table 1).

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TABLE 1. Characteristics of the Chloro-Substituted 1,5-Diketones IIa-c, the Thiopyrilium Salts IIIa-f, the 3-Chloropyridines IVa-c, and the 2-Benzoylpyrroles Va-c

Compound	Yield, %	mp, °C	Found, %					Empirical formula	Calculated, %					IR-spectrum, cm^{-1}		
			C	H	Cl	N	S		C	H	Cl	N	S	ν_{CO}	ν_{NH}	ν thiopyrilium cation
IIa	55	88—9	63,6	4,2	22,2	—	—	$C_{17}H_{14}Cl_2O_2$	63,6	4,6	21,1	—	—	1677	—	—
IIb	65	56—7	64,7	4,4	21,0	—	—	$C_{18}H_{16}Cl_2O_2$	64,5	4,4	21,1	—	—	1683—1670	—	—
IIc	75	132—3	69,2	4,5	17,8	—	—	$C_{23}H_{18}Cl_2O_2$	69,2	4,6	17,9	—	—	1687—1677	—	—
IIIa	68	172—5	62,8	4,1	22,2	—	9,1	$C_{17}H_{14}Cl_2S$	63,5	4,4	22,8	—	9,9	—	—	1560
IIIb	65	180—4	63,1	4,9	20,6	—	8,7	$C_{18}H_{16}Cl_2S$	64,7	4,8	21,3	—	9,5	—	—	1565
IIIc	65	237—9	68,7	4,7	17,2	—	7,6	$C_{23}H_{18}Cl_2S$	69,5	4,5	17,8	—	8,1	—	—	1560
IIId	80	220—6	81,8	6,1	—	—	16,9	$C_{25}H_{24}NO_2PS_2$	82,1	6,5	—	—	17,5	—	—	1560
IIIe	50	181—5	53,0	3,9	—	—	6,0	$C_{25}H_{24}FeCl_4NS$	52,8	4,2	—	—	5,6	—	—	1565
IIIf	53	172—6	42,3	3,3	—	—	4,8	$C_{25}H_{24}Cl_6NSSn$	42,8	3,4	—	—	4,6	—	—	1560
IVa	80	136—8	77,6	4,5	13,2	5,1	—	$C_{17}H_{12}ClN$	77,8	4,5	13,4	5,3	—	—	1540	—
IVb	80	112—3	77,6	5,1	12,5	4,7	—	$C_{18}H_{14}ClN$	77,3	5,0	12,7	5,0	—	—	1545	—
IVc	92	153—4	81,0	4,5	10,6	4,0	—	$C_{23}H_{16}ClN$	81,0	4,6	10,3	4,1	—	—	1540	—
Va	43	164—5	82,5	5,5	—	5,6	—	$C_{17}H_{13}NO$	82,5	5,6	—	5,7	—	1640	3300	—
Vb	40	160—1	82,5	6,0	—	5,7	—	$C_{18}H_{15}NO$	82,7	5,7	—	5,3	—	1640	3320	—
Vc	44	160—2	84,0	5,3	—	4,2	—	$C_{23}H_{17}NO$	85,4	5,3	—	4,3	—	1640	3300	—

TABLE 2. Antimicrobial and Antiphagal Activity of the Chloro-Substituted 1,5-Diketones IIa-c, the Thiopyrilium Salts IIIa-f, the 3-Chloropyridines IVa-c, and the 2-Benzoylpyrroles Va-c

Compound	Minimum inhibitory concentration (in μg/ml) against					% inactivated phage at 100 μg/ml	
	St. aureus	E. coli	Pr. vulgaris	Ps. aeruginosa	C. albicans	T_4	MS-2
IIa	100	50	50	100	50	42	39
IIb	100	50	50	100	100	22	25
IIc	100	50	50	50	50	0	43
IIIa	100	50	50	100	50	44	66
IIIb	100	50	50	50	100	22	10
IIIc	12	50	50	100	25	0	0
IIId	50	50	50	50	25	5	9
IIIe	0,7	25	25	25	0,7	38	31
IIIf	0,7	25	25	25	0,7	37	31
IVa	100	50	50	100	50	49	39
IVb	100	50	50	50	100	39	8
IVc	100	50	50	50	50	23	6
Va	50	50	50	50	25	21	20
Vb	12	25	50	25	25	21	29
Vc	12	25	50	50	25	27	28

The results of studies of the biological activity of the compounds obtained are presented in Table 2, which indicates that the 2,4-dichlorosubstituted 1,5-diketones IIa-c, the thiopyrilium salts IIIa-c, the 3-chloropyridines IVa-c, and the 2-benzoylpyrroles Va-c show moderate antimicrobial activity, inhibiting the growth of the test microbes in concentrations of 12-100 μg/ml. Sharply increased activity, particularly against Staphlococcus and Candida yeasts, was obtained upon introduction of dimethylaminophenyl groups into the 4-position of the thiopyrilium ring (IIIe, f), but replacement of the anion (IIId) led to a decrease in the antimicrobial effect. With the thiopyrilium salts IIIe, f the antistaphlococcal activity was higher than that of many antibiotics.

The strongest antiviral activity, established against the intestinal phage, was shown by compounds IIa, IVa, IIIa, f. The antiphagal activity of these compounds was higher than that of the antitumor antibiotics rubomycin and bleomycin.

Thus this study shows that the search for new antiviral and antimicrobial materials in the chloro-substituted 1,5-diketones and their cyclization products has promise.

EXPERIMENTAL CHEMICAL

The 2,4-dichloropentadiones IIa-c, and 3-chloropyridines IVa-c, and the 2-benzoylpyrroles Va-c were prepared according to [4, 5].

2,6-Diphenylthiopyrilium Chloride IIIa. A mixture of 2.5 g of diketone Ia, 30 ml of acetic acid and 2 ml of thionyl chloride were heated at 60°C for 2 h. The reaction mixture was poured into 50 ml of ether, and the resulting precipitate was filtered off to give 2.2 g of thiopyrilium chloride IIIa. The salts IIIb and IIIc were prepared analogously.

2,6-Diphenyl-4-(4-dimethylaminophenyl)thiopyrilium Dihydrodithiophosphate IIId. A mixture of 2.5 g of diketone Id and 1.2 g of phosphorus polysulfide in 20 ml of absolute dioxane was heated for 6 h and poured into 100 ml of ether. The resulting precipitate was filtered off, washed with water and then with ether to give 2.7 g of thiopyrilium salt IIId.

2,6-Diphenyl-4-(4-dimethylaminophenyl)thiopyrilium Tetrachloroferriate IIIe. To 0.2 g of the dihydrodithiophosphate IIId in 10 ml of acetic acid was added 0.5 g of ferric chloride. The mixture was heated for 10 min at 50-60°C, then added to ether. The resulting precipitate was filtered off to give 0.2 g of the thiopyrilium tetrachloroferriate IIIe.

2,6-Diphenyl-4-(4-dimethylaminophenyl)thiopyrilium Hexachlorostannate IIIf. To 0.2 g of thiopyrilium dihydrodithiophosphate IIId in 10 ml of acetic acid was added 1 ml of stannic chloride in 1 ml of concentrated hydrochloric acid. The mixture was then added to ether, the resulting precipitate was filtered off to give 0.17 g of thiopyrilium salt IIIf.

EXPERIMENTAL BIOLOGICAL

The antimicrobial activity was determined by the method of double serial dilution in Khottinger bouillon at pH 7.2 against the test microbes St. aureus 209P, E. coli M-17, Pr. vulgaris 39, Ps. aeruginosa 165, and C. albicans 42.

The antiphagal activity of the materials was determined in the phage-bacteria systems against DNK (T_6)- and RNK(MS-2)-containing phages. The indicator cultures were E. coli B and E. coli Hfre, respectively. The antiphagal activity was studied by the agar gel method to determine the percent activation by the method of [1]. The materials were dissolved in DMSO and diluted with sterile distilled water to the desired concentration.

LITERATURE CITED

1. D. M. Gol'dfarb, Bacteriophages [in Russian], Moscow (1961), p. 125.
2. FRG Patent 3242519. Ref. Zh. Khim., No. 3-0-453P (1985).
3. Japanese Patent 59-31761. Ref. Zh. Khim., No. 7-0-466P (1985).
4. V. G. Kharchenko, S. N. Chalaya, O. V. Litvinov, et al., Zh. Org. Khim., No. 6, 1208-1211 (1984).
5. V. G. Kharchenko, S. N. Chalaya, and O. V. Litvinov, Khim. Geterotsikl. Soedin., No. 3, 352-354 (1985).

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF BIS[5-INDOLYL]METHANES AND BIS[5-INDOLYL] OXIDES

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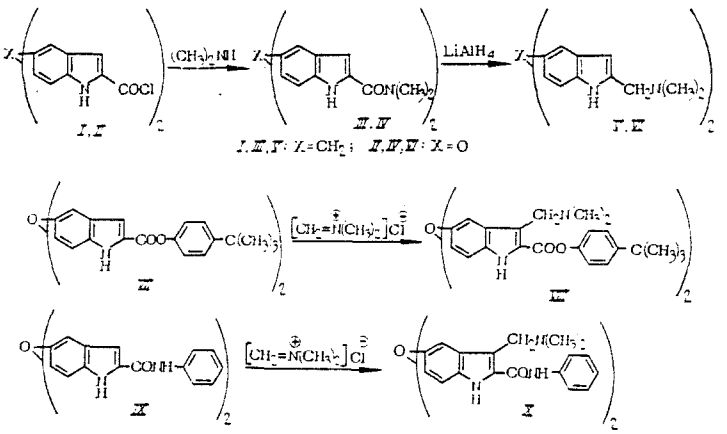
We have reported previously [3-5] the curariform activity of some bisindolyl quaternary ammonia compounds obtained by us.

Continuing this study, we examined the antimicrobial activity of some bis(5-indolyl)-methanes [1] and bis(5-indolyl) oxides [2].

For this purpose, we have synthesized the novel bisisogramine 2,2'-bis(dimethylamino-methyl)bis(5-indolyl) oxide (VI) and the bisisogramine (V) previously obtained by us [1], as follows:



Aminolysis of the diacid chlorides of 2,2'-dicarboxybis(5-indolyl)methane (I) and the corresponding oxide (II) was carried out in an aqueous dioxane solution of dimethylamine, subsequent reduction of the amides (III) and (IV) being carried out with lithium alumino-hydride [4]. Also synthesized were the biogramines (VIII) and (X), by reacting 2,2'-di(p-tert-butylphenoxycarbonyl)bis(5-indolyl) oxide (VII) and 2,2'-di(phenylaminocarbonyl)bis(5-

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