Dodecyl-bis-(β-hydroxyethyl)benzylammonium chloride (III). A mixture of 2.5 g of benzyl chloride and 5.46 g of dodecyl-bis-(β-hydroxyethyl)amine was heated at 100° for 2 h; the mixture was allowed to stand for 3 days at room temperature, and was then boiled with 20 ml of absolute ether and filtered. Compound (III) was obtained (7.3 g); $R_f = 0.71$.

(Undecyl-tridecyl)-bis-(β-hydroxyethyl)methallylammonium chloride (IV). A mixture of 2.8 g of methallyl chloride and 8.19 g of (undecyl-tridecyl)-bis-(β-hydroxyethyl)amine (mean equivalent weight 273) in 20 ml of isopropyl alcohol was heated at 100-130° in a sealed ampule for 10-15 h, and the mixture was then evaporated under vacuum. The residue was boiled with absolute ether (3 × 20 ml), decanting the ether layer each time; the residue was dissolved in a minimum amount of alcohol and was reprecipitated with absolute ether. There was obtained 9.8 g of IV; mean $R_f = 0.78$. Compounds (V)-(VIII) were prepared similarly.

Dodecyl-tris-(β-hydroxyethyl)ammonium chloride (IX). A mixture of 1.61 g of ethylene chlorohydrin and 5.46 g of dodecyl-bis-(β-hydroxyethyl)amine was heated at 100° for 20 h with stirring; 5.2 g of (IX) was obtained, $R_f = 0.73$.

Dodecyl-(β-hydroxyethyl)diethylammonium bromide (X). A mixture of 13.3 g of β-diethylaminoethanol and 29 g of dodecyl bromide was boiled in isopropyl alcohol for 35 h; the solution was evaporated under vacuum, and 31 g of (X) was obtained, $R_f = 0.78$.

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SYNTHESIS AND ANTIMICROBIC PROPERTIES OF SUBSTITUTED 2,3-TRIMETHYLENETHIAZOLIUM SALTS AND CERTAIN THIOCYANIN DYES

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A series of preparations possessing antimicrobic properties [1, 2] has been detected among derivatives of 2,3-polymethylenethiazolium salts; however, there are no data in the literature on the biological activity of the thiazolium salts themselves.

For the purpose of searching for new biologically active materials we synthesized a series of earlier unknown alkyl- and aryl-substituted 2,3-trimethylenethiazolium salts by the known method [3] of condensation of the 5-alkyl-2-thiopyrrolidones (I)-(V) obtained by us earlier [4] with chloroacetone (VI) and phenacyl bromide (VII). (See scheme on following page.)

We isolated some of the synthesized thiazolium salts (VIII)-(XVII) as the perchlorates (Table 1). The IR spectra of compounds (VIII)-(XVII) contain absorption bands in the region

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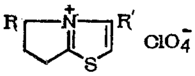
N. G. Chernyshevskii Saratov University. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 10, No. 1, pp. 66-70, January, 1976.

TABLE 1. Substituted 2,3-Trimethylenethiazolium Perchlorates



Compound*	R	Yield (%)	Mp (deg)	Found (%)		Emperical formula	Calculated (%)	
				N	S		N	S
VIII	C_3H_7	78	82—3	5,02	11,90	$C_{10}H_{16}ClNO_4S$	4,99	11,41
IX	C_4H_9	70	81—2	5,08	10,98	$C_{11}H_{18}ClNO_4S$	4,73	10,87
X	iso C_4H_9	80	131—2	5,04	11,08	$C_{11}H_{18}ClNO_4S$	4,73	10,87
XI	iso C_5H_{11}	84	84—5	4,81	10,04	$C_{12}H_{20}ClNO_4S$	4,53	10,38
XII	C_6H_{13}	82	88—9	4,48	10,41	$C_{13}H_{22}ClNO_4S$	4,34	9,93
XIII	C_3H_7	90	103—4	4,40	10,17	$C_{15}H_{18}ClNO_4S$	4,08	9,35
XIV	C_4H_9	85	128—9	3,79	9,30	$C_{16}H_{20}ClNO_4S$	3,92	8,98
XV	iso C_4H_9	82	148—50	3,93	9,27	$C_{16}H_{20}ClNO_4S$	3,92	8,98
XVI	iso C_5H_{11}	81	91—2	3,76	8,49	$C_{17}H_{22}ClNO_4S$	3,68	8,42
XVII	C_6H_{13}	89	98—9	3,87	9,01	$C_{18}H_{24}ClNO_4S$	3,64	8,33

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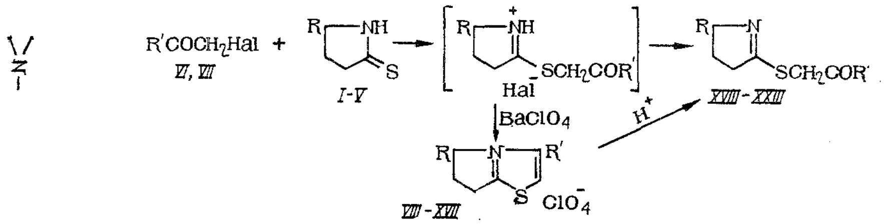
*For compounds (VIII)-(XII) R' = CH_3, (XIII)-(XVII) R' = C_6H_5.



of 1090-1100 cm^{-1} of the ClO_4^- ion and bands of the substituted thiazolium ring in the region of 1360, 1450, and 1575 cm^{-1}.

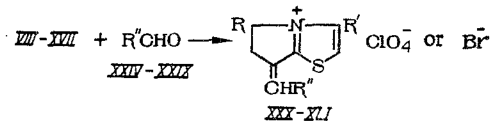
Upon carrying out the condensation of 5-alkyl-2-thiopyrrolidones (I)-(V) with (VI) or (VII) in the presence of metallic sodium we could separate for the first time the earlier unknown intermediate 5-alkyl-2-acetonylthiopyrrolines (XVIII)-(XXIII), which upon reaction with mineral acids are transformed easily into the corresponding 2,3-trimethylenethiazolium salts.

We also obtained compounds (XVIII)-(XXIII) upon treatment of alkyl- and aryl-substituted 2,3-trimethylenethiazolium salts with 1 N potassium hydroxide. Physical constants of products obtained by both methods coincide completely (Table 2).

Absorption bands appear in IR spectra of compounds (XVIII)-(XXIII) at 1700-1710 cm^{-1} of the C=O group and bands at 1640-1660 cm^{-1} of the C=N group. NMR spectra also confirm the presence of the ketosulfide group in compounds (XVIII)-(XXIII). Protons of the methylene group bonded with sulfur give a signal at 7.71 ppm and the signal of the protons of the methyl group bonded with the carbonyl are observed at 8.06 ppm. Pyrrolidine ring protons appear as a complex multiplet at 6.01 ppm.

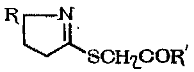
Our data confirm that splitting of the thiazolium ring upon reaction with base occurs at the C—N bond in position 3, 4.

Upon condensation of (VIII)-(XVII) with substituted benzaldehydes (XXIV)-(XXVIII) and with 5-nitrofurfural (XXIX) in acetic anhydride [5] we obtained a group of earlier unknown thiocyanin dyes (XXX)-(XLI) (Table 3).



Absorption bands appear in IR spectra of compounds (XXX)-(XLI) at 600-630 cm^{-1} of the C—S—S group and at 1530-1570 cm^{-1} of the C=C double bond conjugated with the mercaptan grouping.

TABLE 2. 5-Alkyl-2-acetonyl-, 5-Alkyl-2-phenacylthiopyrrolines-2



Compound*	R	Yield (%)	Mp (deg)	Found (%)				Empirical formula	Calculated (%)			
				C	H	N	S		C	H	N	S
XVIII	C_3H_7	43	112—14	60,51	8,63	7,41	16,63	$C_{10}H_{17}NOS$	60,30	8,54	7,03	16,5
XIX	C_4H_9	41	117—18	62,21	9,50	6,72	15,03	$C_{11}H_{19}NOS$	62,02	8,99	6,5	15,0
XX	iso C_5H_{11}	42	114—15	63,95	9,26	6,31	14,72	$C_{12}H_{21}NOS$	63,43	9,41	6,1	14,1
XXI	C_3H_7	55	60—2	—	—	5,03	14,42	$C_{15}H_{19}NOS$	—	—	5,37	12,29
XXII	iso C_5H_{11}	49	114—16	—	—	5,02	10,36	$C_{17}H_{22}NOS$	—	—	4,85	11,10
XXIII	C_6H_{13}	60	75—6	—	—	4,29	10,76	$C_{18}H_{25}NOS$	—	—	4,62	10,58

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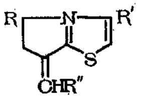
*In compounds XVIII-XX R' = CH_3, XXI-XXIII R' = C_6H_5.

TABLE 3. Thiocyanin Dyes Based on Substituted 2,3-Trimethylenethiazolium Salts



ClO^- or Br^-*

Compound*	R	R″	Yield (%)	Mp (deg)	Found (%)		Empirical formula	Calculated (%)	
					N	S		N	S
XXX	iso C_4H_9	$3\text{-}NO_2C_6H_4$	52	134—35	6,91	7,42	$C_{18}H_{21}ClN_2O_6S$	6,73	7,71
XXXI	C_6H_{13}	$3\text{-}NO_2C_6H_4$	54	74—5	5,38	7,22	$C_{20}H_{25}ClN_2O_6S$	6,35	7,69
XXXII	iso C_4H_9	$4\text{-}N(CH_3)_2C_6H_4$	56	122—23	6,72	8,11	$C_{20}H_{27}ClN_2O_4S$	6,58	7,53
XXXIII	C_6H_{13}	$4\text{-}N(CH_3)_2C_6H_4$	55	69—70	6,31	7,50	$C_{22}H_{31}ClN_2O_4S$	6,18	7,08
XXXIV	iso C_4H_9	$4\text{-}N(CH_3)_2C_6H_4$	70	185—6	5,98	6,33	$C_{25}H_{29}BrN_2S$	5,97	6,84
XXXV	C_5H_{11}	$4\text{-}N(CH_3)_2C_6H_4$	73	168—70	5,88	6,21	$C_{26}H_{31}BrN_2S$	5,80	6,64
XXXVI	iso C_4H_9	$3\text{-}NO_2C_6H_4$	50	89—90	5,78	6,69	$C_{23}H_{23}BrN_2O_2S$	5,95	6,81
XXXVII	C_5H_{11}	$3\text{-}NO_2C_6H_4$	51	89—9	6,00	7,01	$C_{24}H_{25}BrN_2O_2S$	5,78	6,61
XXXVIII	iso C_4H_9	$4\text{-}HOC_6H_4$	69	137—8	3,28	7,19	$C_{23}H_{24}ClNO_5S$	3,03	6,93
XXXIX	iso C_4H_9	$4\text{-}CH_3OC_6H_4$	70	114—15	3,22	6,58	$C_{24}H_{26}ClNO_5S$	2,94	6,73
XL	iso C_4H_9	$4\text{-}ClC_6H_4$	65	123—4	3,42	7,23	$C_{23}H_{23}Cl_2NO_4S$	2,96	6,66
XLI	iso C_4H_9	2-nitrofuryl-5	54	129—30	6,78	7,61	$C_{16}H_{19}ClN_2O_7S$	6,69	7,64

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*For compounds XXX-XXXIII R' = CH_3, XXIV-XLI R' = C_6H_5.

TABLE 4. Antimicrobic Activity of Substituted Thiazolium Salts and Thiocyanin Dyes

Compound	Minimum bacteriostatic concentrations (μg/ml)			
	St. aureus	E. coli	Pr. vulgaris	Candida albicans
VIII	37,5	37,5	37,5	37,5
IX	37,5	37,5	37,5	37,5
XIII	50,0	50,0	50,0	35,0
XXXIII	50,0	50,0	50,0	50,0
XXXII	50,0	37,5	37,5	17,5
XLI	17,5	25,0	75,0	17,5
XXXV	9,0	37,5	—*	17,5
XXXIX	75,0	37,0	—	75,0

*Antimicrobic effect is absent.

Antimicrobic activity of all synthesized preparations was studied by the method of two serial dilutions in Hottinger broth of pH 7.2 in relation to test bacteria *St. aureus* 209P, *E. coli* M-17, *Pr. vulgaris* No. 30; fungistatic effect was studied on a Sabouraud medium in relation to the fungi *Candida albicans*. Preparations (VIII)-(XVII), (XXX)-(XLI) were dissolved in alcohol with their subsequent dilution with sterile distilled water to the desired concentration.

Compounds (VIII)-(XVII) possess weak antimicrobic properties (Table 4). Highly active compounds were not found among the thiocyanin dyes. Compounds (XXXV) and (XLI) (see Table 4) show relatively high antimicrobic effect in relation to the bacteria *St. aureus* and the fungi genus *Candide albicans*. The length of the alkyl substituent in position 3 does not affect the antimicrobic activity.

EXPERIMENTAL METHOD

General Method of Preparing Substituted 2,3-Trimethylenethiazolium Salts (VIII)-(XVII). A benzene solution of equimolar amounts of 5-alkyl-2-thiopyrrolidones (I)-(V), with (VI) and (VII) was boiled for 30 min; an oily layer formed which was separated and treated with barium perchlorate. The crystalline residue was recrystallized from benzene (see Table 1).

5-Butyl-2-acetonylthiopyrroline-2 (XIX). Method A. We dissolved 3.14 g (0.02 mole) of (II) in 20 ml of sodium methoxide (0.02 mole of metallic sodium), cooled the mixture to —10°, and added a drop at a time 2 ml (0.02 mole) of chloroacetone in 5 ml of methanol. The mixture was stirred for 4 h and then left for 12 h at 0°; the precipitate was filtered, and the filtrate was evaporated and cooled. The residue was dissolved in acetone and treated with ice water; the crystals were separated and recyrstallized from water. Yield was 1.73 g (40.5%).

Method B. Into a flask was placed a solution of 1.4 g (0.005 mole) of (II) in 15 ml of a 1 N alcohol solution of potassium hydroxide. A precipitate separated out upon standing; this precipitate was separated from the mixture, dissolved in acetone, and treated with ice water; the precipitated crystals were filtered and recrystallized from water. Yield was 0.44 g (41%). A sample of products obtained by methods A and B did not give a melting point depression.

Compounds (XVIII) and (XX)-(XXIII) were obtained analogously (see Table 2).

General Method of Preparing Thiocyanin Dyes (XXX-XLI). Equimolar ratios of (VIII)-(XVII) and (XXIV)-(XXIX) were heated in a medium of acetic anhydride for 30 min at 100-120°. The reaction mixture was cooled and treated with ether; the precipitated crystals were filtered and washed with ether (see Table 3).

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