SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF THIOPYRYLIUM SALTS

V. G. Kharchenko, S. N. Chalaya,
M. V. Noritsina, and L. K. Kulikova

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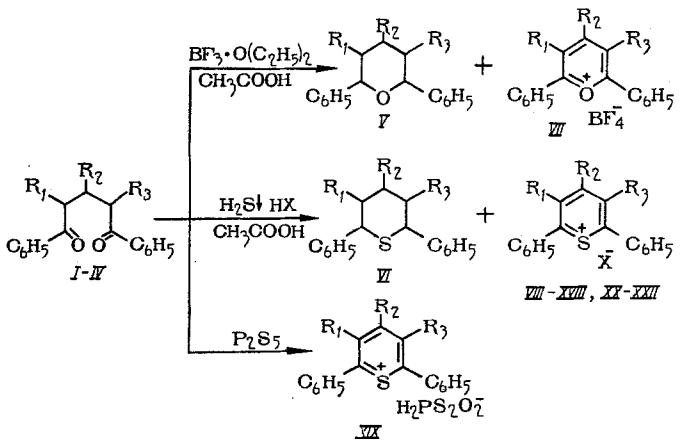
In a search for new biologically active substances, we synthesized compounds of the thiocyclohexane series, and thiopyrylium salts, since certain sulfur-containing compounds are known to possess fungistatic and antiviral activity [1, 2].

The sulfur-containing compounds were synthesized by the reaction of 1,5-diketones (I)-(IV) with hydrogen sulfide in the presence of proton acids (hydrogen chloride and perchloric acid) [3]. In this way, 2,6-diphenylthiocyclohexane (VI) and the thiopyrylium salts with anions Cl^- (XI), (XIV), and (XX) and ClO_4^- (VIII), (XII), (XV), and (XXI) (Table 1) are obtained.

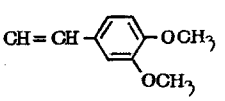


I, II, VIII-X: $R_1=R_2=R_3=H$; III, VII, XIV-XIX: $R_1=R_3=H$, $R_2=C_6H_5$
II, XI-XIII: $R_1=R_3=H$; $R_2=CH_3$; IV, V, XX-XXII: $R_1=R_3=CH_3$, $R_2=H$

The thiopyrylium salts with the anions $H_2PO_4^-$ (XVIII) and BF_4^- (IX), (XIII), (XVI) are obtained using the reaction between the diketones (I)-(IV) and hydrogen sulfide in the presence of polyphosphoric acid or boron trifluoride etherate.

The reaction between the diketone (III) and phosphorus pentasulfide in dioxane gives 2,4,6-triphenylthiopyrylium dihydrothiophosphate (XIX) containing the anion $H_2PS_2O_2^-$.

The condensation reaction between 2,6-diphenyl-4-methylthiopyrylium tetrafluoroborate (XIII) and veratraldehyde in acetic anhydride yields a salt of thiopyrylium (XXIII) having the large group



in the 4 position.

The thiopyrylium stannates (X), (XVII), and (XXII) are obtained from the reaction between thiopyrylium thiophosphate and tin tetrachloride.

N. G. Chernyshevskii Saratov University. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 10, No. 1, pp. 80-83, January, 1976. Original article submitted November 29, 1974.

TABLE 1. Characteristics of Thiopyrylium Salts

Compound	Yield (in %)	Melting point (deg)	Found (in %)			Empirical formula	Calculated (in %)		
			C	H	S		C	H	S
V	26	123—4	65,71	5,03	—	$C_{19}H_{20}O$	65,51	4,98	—
VII	50	232—7	69,65	4,38	—	$C_{23}H_{17}BF_4O$	69,52	4,29	—
IX	61	169—72	60,53	3,58	9,26	$C_{17}H_3BF_4S$	60,71	3,83	9,52
X	38	216—8	—	—	—	—	—	—	—
XIII	62	198—200	60,08	4,32	9,07	$C_{18}H_{15}BF_4S$	60,16	4,28	9,14
XVI	61	195—9	66,77	4,25	7,60	$C_{23}H_{17}BF_4S$	66,99	4,12	7,76
XVII*	30	250—2	—	—	6,11	$C_{46}H_{34}Cl_6S_2Sn$	—	—	6,53
XVIII	45	278—280	65,24	4,38	7,48	$C_{23}H_{19}O_4PS$	65,40	4,50	7,58
XIX	30	283—6	—	—	22,91	$C_{23}H_{19}O_2PS_3$	—	—	23,89
XX	45	105—7	73,02	5,61	10,38	$C_{19}H_{17}ClS$	72,96	5,44	10,24
XXI	24	155—6	60,8	4,5	8,58	$C_{19}H_{17}ClO_4S$	60,5	4,5	8,5
XXII†	35	272—4	—	—	6,94	$C_{38}H_{34}Cl_6S_2Sn$	—	—	7,23
XXIII	80	210—2	65,08	4,73	6,58	$C_{27}H_{23}BF_4O_2S$	64,93	4,61	6,41

*Found, %: Cl 22.50. Calculated, %: Cl 21.80.
†Found, %: Cl 24.29. Calculated, %: Cl 24.08.

TABLE 2. The Antimicrobial Activity of Thiopyrylium Salts (minimum bacteriostatic concentration; in μg/ml)

Compound	Microorganism				
	St. aureus	E. coli	Pr. vulgaris	Ps. pyoceaneum	Candida albicans
V	75	75	75	—	75
VI	75	75	75	37	75
VII	37	37	37	75	37
VIII	37	37	75	75	37
IX	17	37	37	37	25
X	17	37	37	37	37
XI	25	37	37	37	37
XII	37	37	37	37	50
XIII	17	37	37	37	37
XIV	45	37	37	37	37
XV	4,5	37	37	37	37
XVI	4,5	37	37	37	17
XVII	1,2	37	37	37	17
XVIII	2,25	37	37	75	4,5
XIX	1,2	37	50	—	4,5
XX	4,5	37	37	37	4,5
XXI	4,5	37	37	37	4,5
XXII	1,2	37	37	37	17
XXIII	37	75	75	37	37

The oxygen-containing compounds 2,6-diphenyl-3,5-dimethyl tetrahydropyran (V) and 2,4,6-triphenylpyrylium tetrafluoroborate (VII) are obtained from the reaction of the diketones (III) and (IV) with boron tetrafluoride etherate.

The structures of these compounds were confirmed by IR and UV spectroscopic measurements. The IR spectra of thiopyrylium salts have absorption bands in the region 1560-1580 cm^{-1} corresponding to the thiopyrylium cation. The spectra of the thiopyrylium tetrafluoroborates (IX), (XIII), (XVI), and (XXIII) show absorption at 1060-1070 cm^{-1}, characteristic of the BF_4^- anion; the spectrum of thiopyrylium thiophosphate contains the wide band of the $H_2PS_2O_2^-$ anion in the region 940-1050 cm^{-1}.

Two absorption maxima in the region 246-270 and 380-400 nm, characteristic for absorption of the thiopyrylium cation, are observed in the UV spectra of the thiopyrylium salts.

The absence of absorption corresponding to the oscillation of the C=C bond (1500-1600 cm^{-1}) in the IR spectra of compounds (V) and (VI) confirms the saturated structure of these compounds.

The antimicrobial activity of the synthesized compounds was determined by the double series culture method with the following test bacteria: *St. aureus* 209, *E. coli* M-17, *Pr. vulgaris* N35, *Ps. pyoceaneum* No. 7. The fungistatic action on the fungus *Candida albicans* was investigated using Sabouraud medium.

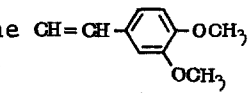
The substances were dissolved in dimethylformamide and diluted with sterile distilled water to a concentration which did not interfere with the growth of the bacteria.

The determination of the antimicrobial properties of the synthesized compounds enabled us to show that there is some relationship between the chemical structure and the activity of the substances. The data given in Table 2 indicate that the bacterial action of the compounds depends both on the character of the substituent in the thiopyrylium nucleus and on the presence of a given anion.

The diphenyl and methyldiphenyl substituted cations of thiopyrylium moderate the bacteriostatic activity, while for staphylococcus this activity increases somewhat with fluoroborates and stannates of thiopyrylium (IX), (X), and (XIII).

The dimethyldiphenyl substituted cations of thiopyrylium (XX), (XXI), (XXII) exhibit a highly selective activity toward staphylococcus and fungus candida. Triphenyl-substituted

thiopyryliums (XIV)-(XIX) exhibit even greater activity. The union of the triphenyl-substituted nucleus with the anions $H_2PO_4^-$, and $H_2PS_2O_2^-$ leads to compounds with highly selective activity towards the staphylococcus of yeast and the fungus *Candida* (XVIII) and (XIX).

The activity falls somewhat when the ring sulfur atom is replaced by oxygen (XVI) and (VII). The introduction of the  group into the 4 position of the thiopyrylium nucleus also weakens the antimicrobial effect.

Tetrahydropyran (V) and thiocyclohexane (VI) show an even weaker antimicrobial action.

Our data are mainly of theoretical interest and indicate that the search for new chemitherapeutic agents among the salts of thiopyrylium is promising.

EXPERIMENTAL METHOD

The thiopyrylium salts with the anions Cl^- (XI), (XIV), and (XX) and ClO_4^- (VIII), (XII), (XV), and (XXI) were obtained by the method described in [3].

Thiopyrylium Salts with the Anion BF_4^- (IX), (XIII), and (XVI) and $H_2PO_4^-$ (XVIII). A solution of the diketone I (4.28 g) in acetic acid (30 ml) is saturated for 2 h with hydrogen sulfide, and boron trifluoride etherate (10 ml) is then added. After 30 h the reaction mixture is poured into ether (150 ml). Filtration of the precipitate yields thiopyrylium tetrafluoroborate IX (3.6 g). The compounds (XIII), (XVI), and (XVIII) are obtained in the same way (using 10 ml polyphosphoric acid).

2,4,6-Triphenylthiopyrylium Dihydrothiophosphate (XIX). A mixture of the diketone III (3.28 g) and phosphorus pentoxide (1.2 g) in absolute dioxane (20 ml) is heated at 70-75° in an atmosphere of nitrogen for 6 h, then poured into ether (50 ml). Filtration of the precipitate yields XIX (2.08 g).

2,4,6-Triphenylthiopyrylium Hexachlorostannate (XVII). To the thiopyrylium hydrothiophosphate XIX (0.2 g) in acetic acid (10 ml) is added tin tetrachloride (1 ml) in concentrated hydrochloric acid (1 ml), and the mixture poured into ether. Filtration of the precipitate yields XVII (0.6 g). The compounds X and XXII are obtained in the same way.

2,6-Diphenyl-4-(3',4'-dimethoxystyryl)thiopyrylium Tetrafluoroborate (XXIII). To a solution of XIII (0.7 g) in acetic anhydride (20 ml) is added veratraldehyde (0.33 g). The reaction mixture is heated at 70-80° for 10 min, cooled, and poured into ether (50 ml). Filtration of the precipitate yields XXIII (0.8 g).

LITERATURE CITED

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3. V. G. Kharchenko, V. I. Kleimenova, and A. R. Yakoreva, The Chemistry of Heterocyclic Compounds [in Russian] (1970), pp. 900-907.