1,3-DIMERCAPTOPROPYL-2-THIOPYRIMIDINES

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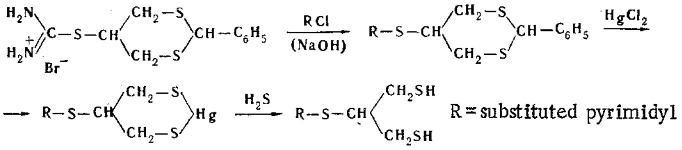
Reaction of 2-phenyl-1,3-dithiane-5-isothiuronium bromide with halopyrimidines gives 5-pyrimidylthio-1,3-dithianes and 1,3-dimercaptopropyl-2-thiopyrimidines. Some derivatives have been isolated and characterized. The complexing ability of the 1,3-dimercapto-2-thiopyrimidines has been examined by the metallic indicator method.

1,3-Dimercaptopropyl-2-thio derivatives of both aliphatic and aromatic compounds have been reported in the literature [1-3], but no derivatives of heterocyclic compounds have been described.

The object of this work was the synthesis of 1,3-dimercaptopropyl-2-thiopyrimidines.

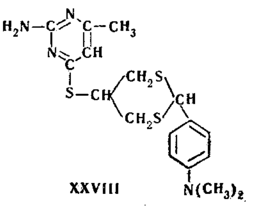


2-Phenyl-5-(thiopyrimidyl)-1,3-dithianes (I-X, Table 1) were synthesized first as intermediates in the synthesis of 1,3-dimercaptopropyl-2-thiopyrimidines.

Replacement of the chlorine atoms in di- and trihalopyrimidines occurs stepwise. This enabled us to synthesize (2-phenyl-1,3-dithianyl-5-thio)chloropyrimidines and 2,4-bis(2-phenyl-1,3-dithianyl-5-thio)pyrimidines (XI and XII). We suggest that the 4-chloro atom is the first one to be replaced [4]. Similar conclusions were reached in [5, 6].

1,3-Dimercaptopropyl-2-thiopyrimidines (XIII-XXII, Table 2) and 2,4-bis(1,3-dimercaptopropyl-2-thio)pyrimidines (XXIII and XXIV) were obtained from the corresponding dithianes.

The 1,3-dimercaptopropyl-2-thiopyrimidines were viscous oils with a strong mercaptan odor. They were fairly soluble in alcohol and propylene glycol, readily soluble in dimethylformamide and ether, but insoluble in water. They were identified and purified as their mercury and lead salts. The UV spectra of alcoholic solutions of 1,3-dimercaptopropyl-2-thiopyrimidines had absorption maxima at 223-227 nm. The absorption maxima of the 1,3-dimercaptopropyl-2-thiopyrimidines (XVII, XVIII, and XXI) which have a chlorine atom in the pyrimidine ring were shifted somewhat toward longer wavelengths, being found at 250-255 nm.



XXVIII

Oxidation of XV, XX, and XXI with 0.1-N iodine solution gave the corresponding bisdisulfides (Table 3).

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TABLE 1. 2-Phenyl-(5-pyrimidylthio)-1,3-dithianes

Compound	R	UV spectrum		Molecular formula	Found, %		Calculated, %		Yield, %
		λ_{max}, nm	$\varepsilon_{max} \cdot 10^{-4}$		S	N	S	N	
I	4-Amino-6-methyl-2-pyrimidyl	220 275	1.0 0.40	$C_{15}H_{17}N_3S_3$	28.66 28.50	12.86 12.72	28.65	12,53	80
II	4-Amino-5-methyl-2-pyrimidyl	225 283	1.96 0.66	$C_{15}H_{17}N_3S_3$	28.14 28.40	—	28.65	—	72
III	4-Amino-2-pyrimidyl	223 285	1.6 0.36	$C_{14}H_{15}N_3S_3$	29.05 29.14	—	29.90	—	95
IV	2-Amino-4-pyrimidyl	227 283	1.4 0.5	$C_{14}H_{15}N_3S_3$	28.70 28.93	—	29.90	—	78
V	2-Amino-6-methyl-4-pyrimidyl	220 290	1.5 0.58	$C_{15}H_{17}N_3S_3$	28.30 28.47	—	28.65	—	82
VI	2-Chloro-5-methyl-4-pyrimidyl	250 280	1.0 0.4	$C_{15}H_{15}N_2S_3Cl$	—	6.99 7.13	—	7.92	75
VII	2-Amino-6-chloro-4-pyrimidyl*	250 280	0.8 0.4	$C_{14}H_{14}N_3S_3Cl$	—	—	—	—	65
VIII	2-Hydroxy-4-pyrimidyl	221 278	1.1 0.35	$C_{14}H_{14}N_2OS_3$	30.34 30.17	8.07 8.13	29.80	8.69	73
IX	2-Chloro-6-hydroxy-4-pyrimidyl†	253	1.3	$C_{14}H_{13}N_2OS_3Cl$	—	—	—	—	78
X	2-Hydroxy-4-amino-6-pyrimidyl	220 275	1.2 0.54	$C_{14}H_{15}N_3OS_3$	—	11.75 11.50	—	12.46	75

*Found, %: Cl 9.01, 9.35. Calculated, %: Cl 9.99.
†Found, %: Cl 9.40, 9.17. Calculated, %: Cl 9.46.

Reaction of 4-(1,3-dimercaptopropyl-2-thio)-2-amino-6-methylpyrimidine (XVII) with p-dimethylaminobenzaldehyde gave a condensation product (XXVIII).

2-Phenyl-5-pyrimidylthio-1,3-dithianes were oxidized by hydrogen peroxide to the corresponding sulfones (Table 4).

EXPERIMENTAL

The intermediates were prepared by literature methods: 2-phenyl-1,3-dithiane-5-isothiuronium bromide [1, 2]; 2,4-dichloropyrimidine, 2-chloro-4-aminopyrimidine, and 2-amino-4-chloropyrimidine [7]; 2,4,6-trichloropyrimidine [8]; 2,6-dichloro-4-aminopyrimidine [9]; 2-chloro-4-amino-5-methylpyrimidine [10]; 2,4-dichloro-5-methylpyrimidine [11]; 2-chloro-4-amino-6-methylpyrimidine and 2-amino-4-chloro-6-methylpyrimidine [12]; and 2-amino-4-chloro-5-methylpyrimidine [13].

2-Phenyl-(5-pyrimidylthio)-1,3-dithianes (I-X). To a solution of 35.2 g (0.1 mole) of 2-phenyl-1,3-dithiane-5-isothiuronium bromide [2] in 400 ml of alcohol was added 0.1 mole of the halopyrimidine and 16 g (0.4 mole) of NaOH in 48 ml of water. The reaction mixture was heated on a boiling water bath for 6 hr, then extracted with ether. The ether extract was dried over Na_2SO_4, and the ether was removed, giving a viscous, undistillable oil which was readily soluble in nonpolar solvents, sparingly soluble in alcohol, and insoluble in water. It was analyzed without further purification, since the compounds were obtained in a sufficiently pure state (Table 1).

2,4-Bis(2-phenyl-1,3-dithianyl-5-thio)pyrimidine (XI). 3.2 g (0.021 mole) of 2,4-di-chloropyrimidine and 3.2 g (0.08 mole) of sodium hydroxide in 12 ml of water were added to a solution of 14.3 g (0.04 mole) of 2-phenyl-1,3-dithianyl-5-isothiouronium bromide in 50 ml of ethanol. The reaction mixture was heated on a boiling-water bath for 12 h and worked up as in the previous experiment.

Compound XI was a yellowish, viscous oil. Yield 7.4 g (70%). Found, %: N 5.76, 5.86. Calculated, for $C_{24}H_{24}N_2S_6$, %: N 5.26.

5-Methyl-2,4-bis(2-phenyl-1,3-dithianyl-5-thio)pyrimidine (XII). This compound was obtained in a similar manner from 7 g (0.02 mole) of 2-phenyl-1,3-dithiane-5-isothiuronium bromide, 1.8 g (0.012 mole) of 2,4-dichloro-5-methylpyrimidine, and 1.6 g (0.04 mole) of NaOH in 6 ml of water. Viscous, yellowish oil, yield 3 g (55%). Found, %: 5.23, 5.14. Calculated for $C_{25}H_{26}N_2S_6$, %: N 5.14.

TABLE 2. 1,3-Dimercaptopropyl-2-thiopyrimidines

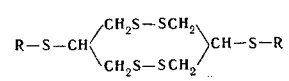
Compound	R	UV spectrum		Molecular formula	S, %		Lead salt of thiol				Yield, %
		λ_{max}, nm	$\varepsilon_{max} \cdot 10^{-4}$		Found	Calculated	Decomp. temp., °C	Molecular formula	Pb, %		
									Found	Calculated	
XIII	4-Amino-6-methyl-2-pyrimidyl	220	1,75	$C_8H_{13}N_3S_3$	38.57 38,40	38.86	125	$C_8H_{11}N_3S_3Pb$	45.55	45.79	20
XIV	4-Amino-5-methyl-2-pyrimidyl	225	1,70	$C_8H_{13}N_3S_3$	39.17 38.91	38.86	127	$C_8H_{11}N_3S_3Pb$	45,55	45.79	25
XV	4-Amino-2-pyrimidyl	223	1,75	$C_7H_{11}N_3S_3$	41.46 41.26	41.20	125	$C_7H_9N_3S_3Pb$	47.04	47.26	20
XVI	2-Amino-4-pyrimidyl	227	1,58	$C_7H_{11}N_3S_3$	40,65 40,80	41.20	128	$C_7H_9N_3S_3Pb$	46.50	47.26	20
XVII	2-Amino-6-methyl-4-pyrimidyl*	226	1,65	$C_8H_{13}N_3S_3$	38,97 40.00	38.86	125	$C_8H_{11}N_3S_3Pb$	45.90	45.79	23
XVIII	2-Chloro-5-methyl-4-pyrimidyl†	250	1,4	$C_8H_{11}N_2S_3Cl$	34,02 34.00	34.22	155	$C_8H_9N_2S_3ClPb$	44.50	43.94	25
XIX	2-Amino-6-chloro-4-pyrimidyl	250	1,5	$C_7H_{10}N_3S_3Cl$	35,95 35.70	35,95	155	$C_7H_8N_3S_3ClPb$	43.50	43.80	23
XX	2-Hydroxy-4-pyrimidyl	219	1,6	$C_7H_{10}N_2OS_3$	40.81 40.78	41.02	124	$C_7H_8N_2OS_3Pb$	45,82	46,93	26
XXI	2-Chloro-6-hydroxy-4-pyrimidyl‡	255	1,63	$C_7H_9N_2OS_3Cl$	36.02 36.26	35,82	147	$C_7H_7N_2OS_3ClPb$	43.00	43,63	25
XXII	2-Hydroxy-4-amino-6-pyrimidyl	225	1,55	$C_7H_{11}N_3OS_3$	39.05 38,90	38,55	127	$C_7H_9N_3OS_3Pb$	46,07	45,59	18

*Found, %: N 16.80. Calculated, %: N 17.00.

†Found, %: C 35.00; H 4.12. Calculated, %: C 36.02; H 3.92.

‡Found, %: Cl 12.88, 13.00; C 31.42, 31.61; H 4.00, 4.09. Calculated, %: Cl 13.29; C 31.34; H 3.34.

TABLE 3. 1,3-Dimercaptopropyl-2-thiopyrimidine Bisdisulfides

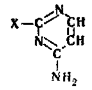
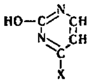
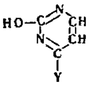
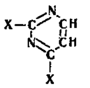
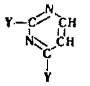


Compound	R	mp, °C	Molecular formula	S, %	
				Found	Calc.
XV	4-Amino-2-pyrimidyl	150—152	$C_{14}H_{18}N_6S_6$	40.50; 40.42	41.55
XVI	2-Hydroxy-4-pyrimidyl	160	$C_{14}H_{16}N_4O_2S_6$	41.13; 41.32	41.37
XXVII	2-Chloro-6-hydroxy-4-pyrimidyl	122	$C_{14}H_{14}N_4O_2S_6Cl_2$	35.78; 36.00	36.02

1,3-Dimercaptopropyl-2-thiopyrimidines (XIII-XXII). To a solution of 0.1 mole of the pyrimidylthio-1,3-dithiane in 100 ml of benzene was added 0.15 mole of mercuric chloride in 125 ml of alcohol. The mixture was heated on a water bath for 1 hr at 60-65°C. Sodium bicarbonate (0.3 mole) was then added, and the mixture was heated for 30 min. The mercury salt, obtained as a cream-colored crystalline solid, was filtered off, washed with water, alcohol, and ether, and decomposed with hydrogen sulfide under ether. The mercuric sulfide was filtered off, and the filtrates were combined and dried with Na_2SO_4. Removal of the ether in vacuo gave the 1,3-dimercaptopropyl-2-thiopyrimidines as yellowish oils. They decolorized 0.1-N iodine quantitatively.

Lead Salts of 1,3-Dimercaptoisopropylthiopyrimidines (Table 2). The 1,3-dimercaptopropyl-2-thiopyrimidine (0.001 mole) was dissolved in 50 ml of dimethylformamide, and the solution was added to a 25% aqueous solution of 0.0012 mole of lead acetate. The lead salt was filtered off and washed with water, alcohol, and ether.

TABLE 4. Sulphones Derived from 2-Phenyl-5-pyrimidyl-1,3-dithiane

Compound	Formula *	Molecular formula	Found, %		Calculated, %		Yield, %
			N	S	N	S	
XXIX		$C_{14}H_{15}N_3O_4S_3$	—	25.05; 25.16	—	24.93	75
XXX		$C_{14}H_{14}N_2O_5S_3$	7.55; 7.51	24.26; 24.42	7.26	24.86	80
XXXI		$C_{14}H_{14}N_2O_7S_3$	6.18; 5.96	22.45; 22.42	6.69	22.96	72
XXXII		$C_{24}H_{24}N_2O_8S_6$	3.76; 3.99	28.85; 28.98	4.24	29.09	76
XXXIII		$C_{24}H_{24}N_2O_{12}S_6$	3.62; 3.55	—	3.86	—	72

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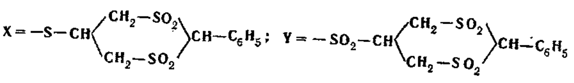

TABLE 5. Complex-Forming Ability of Mercapto Compounds

Name of compound	Molecular formula	Combined cations, %							
		Bi^{3+}	Cd^{2+}	Zn^{2+}	Pb^{2+}	Hg^{2+}	Cu^{2+}	Sn^{2+}	Co^{2+}
2,4-Bis-(1,3-dimercapto-2-propylthio)-5-methylpyrimidine	$C_{11}H_{18}N_2S_6$	60	100	35	100	100	85	95	100
2-Amino-4-(1,3-dimercaptopropyl-2-thio)pyrimidine	$C_7H_{11}N_3S_3$	30	100	38	—	—	40	10	40
2-(1,3-Dimercaptopropyl-2-thio)-4-aminopyrimidine	$C_7H_{11}N_3S_3$	10	—	40	30	0	0	10	65
4-(1,3-Dimercaptopropyl-2-thio)-2-hydroxypyrimidine	$C_7H_{11}N_2OS_3$	10	—	0	10	0	10	—	—
2,3-Dimercaptopropanesulfonic acid, sodium salt (Unithiol)	$C_3H_7O_3SNa$	80	27	60	70	68	70	63	67

2,4-Bis(1,3-dimercaptopropyl-2-thio)pyrimidine (XXXIII). A 5.32-g (0.01 mole) quantity of 2,4-bis-(2-phenyl-1,3-dithianyl-5-thio)pyrimidine in 40 ml of benzene was mixed with a solution of 8.13 g (0.03 mole) of mercuric chloride in 40 ml of ethanol. The mixture was heated on a water bath at 65° C for 1 hr, 6 g of sodium bicarbonate was added, and the mixture was worked up as above.

Viscous yellowish oil, yield 0.81 g (23%). Found, %: S 53.27, 53.45. Calculated for $C_{10}H_{16}N_2S_6$, %: S 53.93. Lead salt of XXXII, a lemon-yellow amorphous solid, decomp. 145° C. Found, %: Pb 53.50. Calculated for $C_{10}H_{12}N_2S_6Pb_2$, %: Pb 54.04.

2,4-Bis(1,3-dimercaptopropyl-2-thio)-5-methylpyrimidine (XXXIV). This was obtained in a similar manner. Viscous, yellowish oil. Yield 20%. Found, %: S 49.72, 49.48. Calculated for $C_{11}H_{18}N_2S_6$, %: S 52.30. Lead salt, lemon-yellow amorphous solid, decomp 155° C. Found, %: Pb 52.30. Calculated for $C_{11}H_{14}N_2S_6Pb_2$, %: Pb 52.92.

1,3-Dimercaptopropyl-2-thiopyrimidine bisdisulfides. 1,3-Dimercaptopropyl-2-thiopyrimidine (0.001 mole) was dissolved in 5 ml of dimethylformamide, and an excess of 0.1-N iodine solution was added. The mixture was kept at room temperature for 24 hr and the precipitate was filtered off, washed with alcohol and ether, and dried in the vacuum desiccator.

Oxidation of Pyrimidylthio-1,3-dithianes. Pyrimidylthio-1,3-dithiane (0.003 mole) was dissolved in 10 ml of glacial acetic acid, and to the solution was added 0.020 mole of perhydrol (to prepare the trisulfides XXVII and XXIX, 0.075 mole of perhydrol was used). The mixture was kept at room temperature for 24 hr, then it was transferred to a porcelain dish and evaporated on a water bath. The resulting disulfones were washed repeatedly with water, alcohol, and ether (Table 4).

2-p-Dimethylaminophenyl-5-(2-amino-6-methylpyrimidyl)thio-1,3-dithiane (XXVIII). A 1-g (0.004 mole) quantity of XVII was suspended in 5 ml of water, and mixed with 0.6 g (0.004 mole) of p-dimethylaminobenzaldehyde in 10 ml of conc HCl. The mixture was kept overnight, then evaporated on a water bath. The colorless, crystalline product had mp 90° C (from alcohol). Yield 0.95 g (62%). Found, %: S 25.61, 25.91. Calculated for $C_{17}H_{22}N_4S_3$, %: S 25.34.

The 1,3-dithiols are active complexing agents. With metal cations, they form water-insoluble complexes of the mercaptide type. The mercaptides of divalent copper were black in color, nickel mercaptide was muddy brown; lead, bismuth, and silver mercaptide were yellow; sodium, calcium, barium, zinc, cadmium, and aluminum mercaptide were colorless.

The complex-forming ability of the mercapto compounds with the cations of cadmium, zinc, lead, mercury, copper, tin, and cobalt have been examined by the metallic indicator method [14-16].

Results are given in Table 5, which also gives the comparative figures for the stability of the previously investigated complexes of the metal cations with Unithiol, which have found application in medicine and analysis. The most stable complexes with metal cations are those formed by tetrathiols.

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