SYNTHESIS OF THIOUREA DERIVATIVES. XI. SYNTHESIS AND TUBERCULOSTATIC ACTION OF 4,4'-DIBROMOBENZHYDRYL-, HETERYL-, AND ARYLTHIOUREAS

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With the objective of seeking substances with antitubercular activity in the substituted thiourea series, we have previously worked out the synthesis of a number of its symmetrically and unsymmetrically 1,3-disubstituted derivatives; thiocarbanilides [1, 2]; analogs of these containing heterocyclic residues (pyridine or pyrimidine [3], pyridazine [4], or 1,3-thiazane [5]); and various substituents in the benzene ring.

Investigation of the tuberculostatic activity of these compounds and elucidation of the dependence of antitubercular action of these substances on their structure showed that the presence of the thiocarbanilide group has great importance for manifestation of tuberculostatic activity [6]. Introduction of an N-methylpiperazine residue into the benzene ring led to obtaining a new preparation – butomelide [1, 7], N-[p-(1-methyl-4-piperazinyl)-phenyl]-N'-(p-butoxyphenyl)-thiourea, which is recommended by the Pharmacological Committee of the Ministry of Public Health of the USSR for medicinal use as an antitubercular preparation.

Among the 1,3-disubstituted thioureas containing the 2-methylmercapto-5-pyrimidine residue, which may be considered as heterocyclic analogs of thiocarbanilide [8], substances with a high tuberculostatic activity were also found; some of these proved active in experimental tuberculosis of white mice or guinea pigs.

Continuing studies in the direction of synthesizing analogs of thiocarbanilide and 1,3-disubstituted thioureas, we have synthesized and investigated the tuberculostatic action of previously unknown dibromobenzhydrylarylthioureas and also of a number of heterylarylthioureas. These studies showed that all of the compounds prepared (except XI) possess only weak bacteriostatic activity with respect to strain H-37R_V tuberculosis mycobacterium. Compound XI, 2-(1-methyl-4-piperazinyl)-4'-isopropoxythiocarbanilide, inhibits the growth of tuberculosis bacilli in a concentration of 8 μg/ml. This compound is an analog of butomelide, differing from it only in the alkoxy group. The bacteriostatic concentration of butomelide is 1 μg/ml in a medium containing no serum, or 8 μg/ml in a medium containing 10% normal horse blood serum. Thus, replacement of the butoxy group by an isopropoxy group led to a reduction in activity of the compound.

The 4,4'-dibromobenzhydryl- and heterylarylthioureas (I-IX and X-XV) were prepared by the condensation of equimolecular amounts of 4,4'-dibromobenzhydryl or isopropoxyphenyl isothiocyanate with aryl- or heterylamines (see Table 1).

4,4'-Dibromobenzhydryl isothiocyanate (m.p. 109°) was prepared by the reaction of 4,4'-dibromobenzhydrylamine hydrochloride with thiophosgene in chloroform or dichloroethane medium [9] under the conditions worked out for the synthesis of 3-methyl- and 4-methoxybenzhydryl isothiocyanates [10]. p-Isopropoxyphenyl isothiocyanate was prepared by heating 4,4'-diisopropoxythiocarbanilide with acetic anhydride [2].

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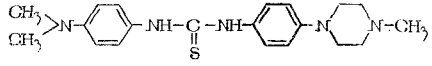
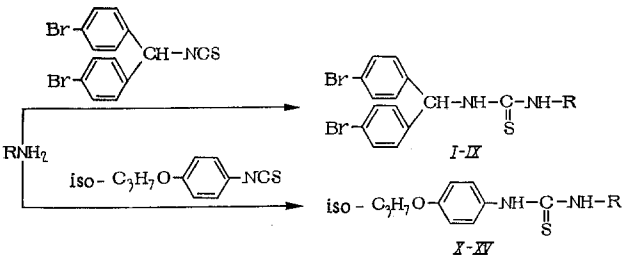
TABLE 1. Thiourea Derivatives.

Compound	R	Yield (%)	m.p., deg*	Found (%)					Empirical formula	Calculated (%)					Minimum tuberculostatic concn. (in μg/ml, strain H-37 Rv)	
				C	H	Br	N	S		C	H	Br	N	S	soton medium without serum	soton medium with serum
I	p-$CH_3C_6H_4$	80	199	51,53	3,87	32,39	5,94	6,61	$C_{21}H_{18}Br_2N_2S$	51,44	3,70	32,60	5,71	6,34	Inactive	
II	p-$C_7H_5OC_6H_4$	92	157,5—158	50,92	4,47	30,02	5,24	5,60	$C_{22}H_{20}Br_2N_2OS$	50,78	3,87	30,72	5,38	6,16	»	
III	p-$C_4H_9OC_6H_4$	42	156,5—157,5	52,45	4,27	28,24	5,22	6,12	$C_{24}H_{24}Br_2N_2OS$	52,56	4,41	29,14	5,10	5,84	>125	>125
IV	p-CH_3-N(C$_4$H$_8$)N-C_6H_4	82	181,5—182	51,96	4,37	27,72	9,34	5,63	$C_{25}H_{26}Br_2N_4S$	52,27	4,56	27,82	9,75	5,58	1000	>500
V	CH_3-N(C$_4$H$_8$)N-	90	193,5—195,5	16,20	4,41	31,81	10,99	6,54	$C_{19}H_{22}Br_2N_4S$	45,79	4,45	32,07	11,24	6,43	Inactive	
VI	CH_3O-(N=N)-	52	204,5	45,00	3,07	31,32	11,77	6,54	$C_{19}H_{16}Br_2N_4OS$	44,89	3,17	31,44	11,02	6,30	500	—
VII	C_4H_9O-(N=N)-	60	203—204,5	47,68	3,91	29,00	9,90	5,84	$C_{22}H_{22}Br_2N_4OS$	48,01	4,02	29,04	10,18	5,82	>125	—
VIII	CH_3S-(N=C-N=CH)-	46	160—161,5	43,13	2,89	30,79	10,28	12,27	$C_{19}H_{16}Br_2N_4S_2$	43,52	3,07	30,48	10,68	12,23	>125	>125
IX	(C$_5$H$_4$N)-	53	192—192,5	48,10	3,21	33,79	8,60	6,45	$C_{19}H_{15}Br_2N_3S$	47,81	3,16	33,49	8,80	6,71	>30	
X	CH_3-N(C$_4$H$_8$)N-	45	161,5—162,5	58,00	7,75		18,28	10,65	$C_{15}H_{24}N_4OS$	58,40	7,84		18,17	10,39	250	500
XI	n-CH_3-N(C$_4$H$_8$)N-C_6H_4	52	162—163	65,09	7,32		14,41	8,46	$C_{21}H_{28}N_4OS$	65,58	7,33		14,57	8,33	8	30
XII	CH_3O-(N=N)-	46	180—181	56,28	5,35		17,54	10,39	$C_{15}H_{18}N_4O_2S$	56,57	5,69		17,59	10,07	>125	>125
XIII	C_4H_9O-(N=N)-	58	160,5—161	60,25	6,39		15,47	9,24	$C_{18}H_{24}N_4O_2S$	59,97	6,71		15,54	8,89	60	>60
XIV	CH_3S-(N=C-N=CH)-	46	154—155	53,91	5,72		17,30	19,04	$C_{15}H_{18}N_4OS_2$	53,86	5,42		16,57	19,17	30	>30
XV†		69	134—136	64,50	7,32		19,03	8,70	$C_{20}H_{27}N_5S$	65,00	7,36		18,95	8,67	—	—

*Compounds I-VI and VII-XV were recrystallized from alcohol; VII was worked up with methylene chloride.

† The compound has the formula 



As the amino components we used p-toluidine, p-phenetidine, p-butoxyaniline, 2-aminopyridine, 3-methoxy-6-aminopyridazine [4] and 3-butoxy-6-aminopyridazine [11], 1-methyl-4-(p-aminophenyl)-piperazine [1], 1-methyl-4-aminopiperazine [6], and 2-methylmercapto-5-aminopyrimidine [12]. 4-(Dimethylamino)-4'-(1-methyl-4-piperazinyl)thiocarbanilide (XV) was prepared starting from p-dimethylaminoaniline and p-(1-methyl-4-piperazinyl)-phenyl isothiocyanate [8].

The synthesized compounds (I-XV) are crystalline substances with sharp melting points, soluble in the usual organic solvents, more difficultly so in alcohol, difficultly soluble in ether, and practically insoluble in water.

EXPERIMENTAL

1-(4,4'-Dibromobenzhydryl)-3-(p-ethoxyphenyl)-thiourea (II). To a solution of 0.29 g of p-phenetidine in 3 ml of dry benzene was gradually added, with stirring, 0.8 g of 4.4'-dibromobenzhydryl isothiocyanate in 8 ml of dry benzene. The reaction mixture was stirred at the b.p. for 1.5 h. The crystals which separated were filtered off and washed with a small amount of ether; compound II (1 g) was obtained. If no solid separated, the solvent was removed under vacuum, and the residue was worked up.

Compounds I, III-VI, VIII, and IX were prepared similarly.

1-(4,4'-Dibromobenzhydryl)-3-(2-methylmercapto-5-pyrimidyl)-thiourea (VII). To a solution of 0.37 g of 2-methylmercapto-5-aminopyrimidine in 13 ml of dry benzene, with stirring, was added a solution of 1 g of 4,4'-dibromobenzhydryl isothiocyanate in 9 ml of dry benzene; the stirring was continued for 2 h at room temperature and 30 min at 60°. The reaction mixture was cooled to 0°; the solid which fell was filtered off and washed with ether. There was obtained 0.63 g of VII. For analysis, compound VII was dissolved at room temperature in methylene chloride, the solution was treated with activated charcoal, it was evaporated under vacuum, and the residue was washed with ether.

1-(p-Isopropoxyphenyl)-3-(1-methyl-4-piperazinyl)-thiourea (X). To a solution of 0.58 g of 1-methyl-4-aminopiperazine in 2.5 ml of dry benzene was gradually added, with stirring, a solution of 0.97 g of p-isopropoxyphenyl isothiocyanate in 3.5 ml of dry benzene. Stirring was continued at the b.p. for 40 min. Upon cooling, the solid which separated was filtered off and it was washed with a small amount of ether; 0.8 g of X was obtained. If no precipitate fell, the solvent was removed under vacuum and the residue was worked up.

Compounds XI-XIV were prepared similarly.

4-Dimethylamino-4-(1-methyl-4-piperazinyl)-thiocarbanilide (XV). To a solution of 0.88 g of p-dimethylaminoaniline in 10 ml of dry benzene was gradually added, with stirring, a solution of 1.5 g of p-(1-methyl-4-piperazinyl)-phenyl isothiocyanate in 100 ml of dry benzene. The reaction mixture was stirred for 3 h at 50°. The solvent was removed under vacuum, a small amount of ether was added to the residue, and the solid was filtered off. Compound XV (1.1 g) was obtained.

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