SYNTHESIS AND TUBERCULOSTATIC ACTIVITY OF CERTAIN HETEROCYCLIC SUBSTITUTED ARYLTHIOUREAS

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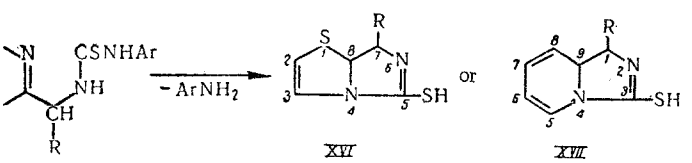
Substituted thioureas containing 2-thiazole, 2-pyridine, pyridylthiazolylmethane, and 6-aminopenicillanic acid residues, which exhibit tuberculostatic action, were produced. Among the compounds studied, five highly active ones were detected; however, their activity decreases substantially in the presence of blood serum.

In recent years, a number of compounds with pronounced tuberculostatic properties in experimental tuberculosis of white mice and guinea pigs have been detected among diaryl-substituted thioureas (thiocarbanilides). The most active (ethoxide, isoxyl, cyambutazine) are now used for the treatment of tuberculosis and leprosy [1-7]. When one aromatic nucleus is replaced by a heterocyclic nucleus or a residue of a different nature, the antitubercular activity is retained in a number of cases.

This work describes the production of certain new thiourea derivatives and a study of their bacteriostatic effects with respect to tuberculosis mycobacteria. In the compounds described, one or both benzene rings are replaced by heterocyclic radicals (pyridine, thiazole) or by 2- or 4-pyridylthiazolylmethane residues.

We produced compounds I-IV by the reaction of arylisothiocyanates with 2-aminopyridine and 2-aminothiazole. Compounds V and VI were produced by the same method, on the basis of the corresponding amine (2-pyridyl-2'-thiazolylmethylamine) and 4-carbethoxy- and 4-butoxyphenylisothiocyanates. Compounds VII-IX were produced analogously and were described in our earlier works. Substituted thioureas X-XIV were produced in the form of triethylammonium salts by condensation of 6-aminopenicillanic acid with arylisothiocyanates [8]. Among these compounds, only compound XII proved highly active. We also studied the tuberculostatic activity of derivatives of imidazo[5,1-b]thiazole XVIa, XVIb, and imidazo[1,5-a]pyridine XVII, which we had synthesized earlier.

Of the investigated substituted thioureas and their derivatives, five substances possess high tuberculostatic activity (II, III, VI, VII, and XII, Tables 1 and 2); however, their activity is sharply reduced in the presence of serum. (2,4'-Dipyridyl)methylisocyanate (XV, Table 3) proves to be weakly active in the presence of serum, just like cyclic derivatives of thiourea (XVI, XVII, Table 3), formed as a result of splitting out of the corresponding anilines from methylarylthioureas, substituted with the 2-thiazole or 2-pyridine residue:



A comparison shows that 7-(3'-pyridyl)-5-mercaptoimidazo[5,1-b]-thiazole (XVIb) is more active than the corresponding (4'-pyridyl)-substituted XVIa.

EXPERIMENTAL

N-2-Pyridyl-N'-carbethoxyphenylthiourea (I). A solution of 0.5 g p-carbethoxyphenylisothiocyanate in 5 ml dry benzene was boiled for 50 min with 0.23 g 2-aminopyridine and cooled; 0.63 g of a substance

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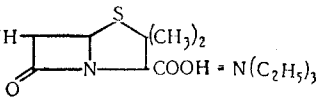
TABLE 1. $R_1NHCSNHR_2$

Compound number	R_1	R_2	Tuberculostatic activity in dilution			
			strain			
			without serum	with serum	without serum	with serum
I	2-Pyridyl	4-Carbethoxyphenyl	1:4,000	1:1,000	1:16,000	1:1,000
II	"	4-Butoxyphenyl	1:64,000	1:4,000	1:2 Million	1:16,000
III	2-Thiazolyl	4-Carbomethoxy-phenyl	1:1 Million	1:4,000	1:2 Million	1:16,000
IV	"	2-Pyridyl	1:32,000	1:1,000	1:128,000	1:2,000
V	(2-Pyridyl-2'-thiazolyl)methyl	4-Carbethoxyphenyl	1:1,000	1:1,000	1:8,000	1:1,000
VI	"	4-Butoxyphenyl	1:256,000	1:32,000	1:1 Million	1:32,000
VII	(2-Thiazolyl-4'-pyridyl)methyl	4-Ethoxyphenyl	1:8 Million	1:128,000	1:2 Million	1:128,000
VIII	(2,4'-Dipyridyl) methyl	"	1:1,000	1:1,000	–	1:1,000
IX	(4-Methoxyphenyl-2'-thiazolyl)methyl	4-Ethoxyphenyl	1:32,000	1:32,000	1:128,000	1:16,000

TABLE 2. $RC_6H_4NHCSNH$  $\cdot N(C_2H_5)_3$

Compound number	R	Tuberculostatic activity in dilution			
		strain Academia		strain N-37	
		without serum	with serum	without serum	with serum
X	4-Methoxy	1:4,000	1:1,000	1:8,000	1:2,000
XI	4-Ethoxy	1:64,000	1:64,000	1:128,000	1:32,000
XII	4-Butoxy	1:512,000	1:128,000		
XIII	4-Chloro	1:4,000	1:2,000	1:16-64,000	1:16,000
XIV	3-Chloro	1:8,000	1:2,000		

TABLE 3

Compound number	Substance	Tuberculostatic activity in dilution			
		strain Academia		strain N-37	
		without serum	with serum	without serum	with serum
XV	(2,4'-Dipyridyl)methyliso-thiocyanate	1:32,000	1:1,000	1:128,000	1:2,000
XVIa	7-(4'-Pyridyl)-5-mercapto-imidazo[5,1-b]thiazole	1:1,000	1:1,000	1:16,000	1:2,000
XVIb	7-(3'-Pyridyl)-5-mercapto-imidazo[5,1-b]thiazole	1:128,000	1:1,000	1:256,000	1:2,000
XVII	1-(4'-Pyridyl)-3-mercapto-imidazo[1,5-a]pyridine	1:1,000	1:1,000	1:64,000	1:2,000

with m.p. 171-172.5° (from absolute alcohol) was obtained. Found %: C 59.89; H 5.21; N 14.16. $C_{15}H_{15}N_3O_2S$. Calculated %: C 59.78; H 5.02; N 13.94.

N-2-Pyridyl-N'-p-butoxyphenylthiourea (II) was produced analogously from 2-aminopyridine and p-butoxyphenylisothiocyanate by boiling for 4 h. Colorless crystals, m.p. 143-144° (from absolute alcohol). Found %: N 13.71; S 10.60. $C_{16}H_{19}N_3OS$. Calculated %: N 13.94; S 10.62.

N-2-Thiazolyl-N'-p-carbomethoxyphenylthiourea (III) was produced analogously from 2-aminothiazole and p-carbethoxyphenylisothiocyanate. Transesterification occurred during recrystallization from methanol. Colorless crystals, m.p. 169-170° (from methanol). Found %: C 49.04; H 4.15; N 14.18; S 21.64. $C_{12}H_{11}N_3O_2S_2$. Calculated %: C 49.13; H 3.78; N 14.33; S 21.86.

N-2-Pyridyl-N-2-thiazolylthiourea (IV) was produced analogously from 2-pyridylisothiocyanate [9] and 2-aminothiazole. Colorless crystals, m.p. 193-194° (from methanol). Found %: C 46.20; H 3,49; N 23.80; S 26.31. $C_9H_8N_4S_2$. Calculated %: C 46.16; H 3.41; N 23.71; S 27.13.

N-(2-Pyridyl-2'-thiazolyl)methyl-N'-p-carbethoxyphenylthiourea (V) was produced analogously from (2-pyridyl-2'-thiazolyl)methylamine and p-carbethoxyphenylisothiocyanate. Colorless crystals, m.p. 147.5-149° (from absolute alcohol). Found %: N 14.03; S 16.21. $C_{19}H_{18}N_4O_2S_2$. Calculated %: N 14.06; S 16.09.

N-2(Pyridyl-2'-thiazolyl)methyl-N'-p-butoxyphenylthiourea (VI) was produced analogously from (2-pyridyl-2'-thiazolyl)methylamine and p-butoxyphenylisothiocyanate. Colorless crystals, m.p. 120-121° (from absolute alcohol). Found %: C 59.94; H 5.37; N 14.23; S 16.08. $C_{20}H_{22}N_4OS_2$. Calculated %: C 60.27; H 5.56; N 14.06; S 16.09.

Production of Thiocarbamoyl Derivatives of 6-Aminopenicillanic Acid (X-XIV). To a suspension of 1.62 g 6-aminopenicillanic acid in 5.7 ml dimethylformamide (DMFA), cooled to 0°, we added 3.75 g triethylamine, and then a solution of 1.35 g p-methoxyphenylisothiocyanate [10] in 5 ml DMFA. The mixture was mixed at 0° for 30 min and for 3 h at 20°. The yellowish-brown solution was freed of mechanical impurities through a dense filter and poured out into 300 ml of absolute ether, ground with ether, and 2.26 g of the triethylammonium salt of p-methoxyphenylthiocarbamoyl-6-aminopenicillanic acid filtered off in the form of an amorphous yellowish powder, sparingly soluble in water and alcohol. Other thiocarbamoyl derivatives were produced analogously. The percent content was determined by iodometric titration for 2-pyridyl-thiocarbamoyl-6-aminopenicillanic acid (83.2%).

(2,4'-Dipyridyl)methylisothiocyanate (XV). To a solution of 2 g (2,4'-dipyridyl)methylamine in 5 ml of dry benzene, cooled to 0°, we slowly added 0.66 ml carbon disulfide and 2 ml triethylamine. The reaction mixture was mixed for 3 h, and 3.7 g of the dithiocarbamic salt filtered off. The precipitate was dissolved in 7 ml of chloroform, cooled 0°, and 1.5 ml of chlorocarbonic ester gradually added. The reaction mixture became blue-black. Then it was mixed for 1 h at 0° and for 2 h at 18-20°. About 2 g of the substance was filtered off, m.p. 230-232° (from alcohol). Found %: S 14.05; N 18.18. $C_{12}H_9N_3S$. Calculated %: S 14.10; N 18.49.

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