

## THE SYNTHESIS OF COMPOUNDS WITH POTENTIAL ANTITUBERCULAR ACTIVITY

## XIII. N-(2-Benzoxazolyl)-N'-phenylthioureas\*

T. P. Sycheva, I. D. Kiseleva, and M. N. Shchukina

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A number of new N-(2-benzoxazolyl)-N'-phenylthioureas have been prepared by the reaction of 2-amino-benzoxazole and of its 6-substituted derivatives with phenyl and p-alkoxyphenyl isothiocyanates.

A number of thiourea derivatives are known to possess considerable tuberculostatic activity, some of them having been introduced into medical practice [1-3]. The subject of this paper is the synthesis of some N-(2-benzoxazolyl)-N'-phenylthioureas which have not previously been described in the literature, in order to assess their tuberculostatic activity.

These compounds were prepared by the reaction of 2-aminobenzoxazole and its 6-substituted derivatives with phenyl isothiocyanates. Since the presence of an alkoxy-group in the p-position of the benzene ring of the arylthioureas usually increases the tuberculostatic activity of these compounds, p-alkoxyphenyl isothiocyanates were employed. In order to examine the effect of groups in the 6-position of the benzoxazole nucleus; on the other hand, 6-alkoxy-2-aminobenzoxazoles were used, as well as other derivatives of 2-aminobenzoxazole.

Most of the 2-aminobenzoxazoles used as starting materials were prepared by the action of ammonia on the corresponding potassium benzoxazole-2-sulfonates [4, 5]. The preparation of 6-bromo-2-aminobenzoxazole was carried out by brominating 2-aminobenzoxazole with bromine in methanol [6].

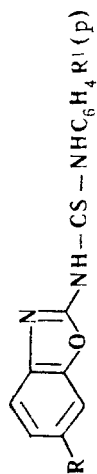
The reaction of amines with isothiocyanates is normally accomplished by boiling equimolecular amounts of the reactants in benzene for several hours [7, 8]. With 2-aminobenzoxazole, and in particular its 6-substituted derivatives, the rather low basicity of the amino group makes it necessary to use a twofold excess of the phenyl isothiocyanate, and to carry out the reaction in boiling toluene for 20-30 hr or more, if satisfactory yields of the benzoxazolylphenylthiourea are to be obtained. However, even under these conditions some of the starting amine remains unreacted. In the case of 6-nitro- and 6-acetamido-2-aminobenzoxazoles, the reaction was unsuccessful, the starting materials being recovered even after prolonged heating.

The tuberculostatic activity of the compounds was examined by T. N. Zykov in the chemotherapy section of this Institute. The most active compound was N-(2-benzoxazolyl)-N'-p-ethoxyphenyl thiourea. This compound inhibited the growth of Mycobacterium tuberculosis, strain H<sub>37</sub>Rv, at a concentration of 2 µg/ml in the absence of serum. In the presence of serum, however, its activity fell sharply to 15 µg/ml. Somewhat lower activity was shown by N-(2-benzoxazolyl)-N'-phenylthiourea (8 µg/ml in absence of serum and 250 µg/ml in presence of serum). The remaining compounds were of low activity. Introduction of an alkyl group into the 6-position of the benzoxazole nucleus did not result in an increase in tuberculostatic activity.

Experimental

N-(6-Ethoxy-2-benzoxazolyl)-N'-(p-butoxyphenyl) thiourea. 1.68 g of p-butoxyphenyl isothiocyanate was added to a suspension of 0.7 g of 6-ethoxy-2-aminobenzoxazole [5] in 15 ml of dry toluene and the mixture heated at 125°C (bath temp.) for 34 hr. The mixture was cooled and the precipitate filtered off, washed with toluene, and then with 5% hydrochloric acid. The insoluble material was filtered off; weight 0.64 g, colorless crystals mp 158°-162° (from ethanol) (see table). Neutralization of the hydrochloric acid solution with sodium acetate gave 0.16 g of material mp 182°-184°, a mixed mp with the starting material (6-ethoxy-2-aminobenzoxazole) giving no depression. The other N-(2-benzoxazolyl)-N'-phenylthioureas were prepared similarly (see table).

\* For part XII, see [5].



R	R'	Reaction time, hr	Mp, °C (from ethanol)	Formula	Found, %				Calculated, %				Yield, %
					C	H	N	S	C	H	N	S	
H	H	25	186—186.5	C <sub>14</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub> S	62.43	4.37	15.80	12.02	62.43	4.11	15.60	11.90	53.0
H	OCH <sub>3</sub>	22	188—189**	C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub> S	60.38	4.02	13.88	10.63	60.18	4.38	14.03	10.71	56.9
H	OC <sub>2</sub> H <sub>5</sub>	30	179—180	C <sub>16</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> S	61.91	4.93	13.60	10.20	61.32	4.82	13.41	10.23	33.0
H	OC <sub>4</sub> H <sub>9</sub>	20	179—180	C <sub>18</sub> H <sub>19</sub> N <sub>3</sub> O <sub>2</sub> S	63.65	6.03	—	9.48	63.32	5.60	—	9.39	16.0
Br	H	28	206—207***	C <sub>14</sub> H <sub>10</sub> BrN <sub>3</sub> O <sub>2</sub> S	48.45	3.17	12.03	9.15	48.28	2.89	12.07	9.21	34.0
Br	OC <sub>2</sub> H <sub>5</sub>	54	209—211	C <sub>16</sub> H <sub>14</sub> BrN <sub>3</sub> O <sub>2</sub> S	—	—	10.69	8.13	—	—	10.71	8.17	35.0
OC <sub>2</sub> H <sub>5</sub>	H	52	178.5—180	C <sub>16</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> S	—	—	—	10.43	—	—	—	10.23	38.0
OC <sub>2</sub> H <sub>5</sub>	OC <sub>4</sub> H <sub>9</sub>	34	158—162	C <sub>20</sub> H <sub>23</sub> N <sub>3</sub> O <sub>3</sub> S	62.26	6.22	10.93	8.26	62.32	6.01	10.90	8.32	41.0
OCH <sub>3</sub>	H	15	188.5—189.5	C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub> S	60.12	4.42	—	10.83	60.18	4.38	—	10.71	32.2

\* Yields calculated on amine reacted. In all experiments, part of the amine was recovered.

\*\* From ethyl acetate.

\*\*\* From isobutanol.

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Ordzhonikidze All-Union Scientific Research Chemical  
and Pharmaceutical Institute, Moscow