# COMPOUNDS WITH POTENTIAL ANTITUBERCULOSIS ACTIVITY

## XV. DERIVATIVES OF SOME S-HETERYLMERCAPTOACETIC ACIDS

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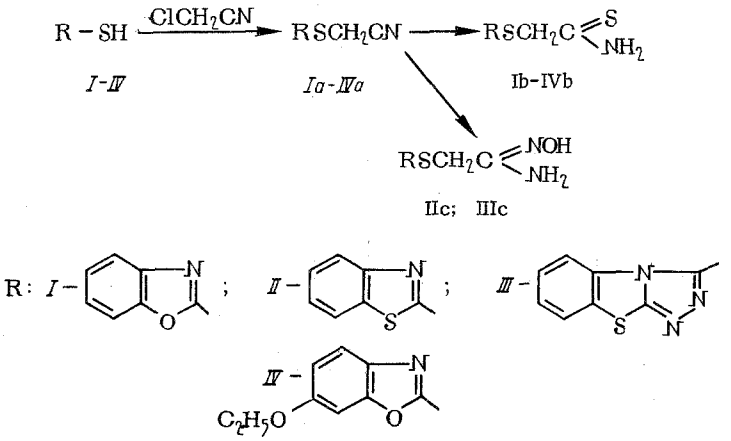
Since compounds possessing significant tuberculostatic activity have been found amongst thioamides [1, 2], and also amongst amidoximes [3], it was of interest to syntheisze a series of nitriles of mercaptoacetic acids containing a heterocyclic residue as a substituent on the mercapto group, with the aim of subsequently converting them into the corresponding thioamides and amidoximes.

TABLE 1. Results of the Examination of Compounds I-IV for Tuberculostatic Activity

| Compound | Minimum tuberculostatic concentration (in μg/ml) | | | |
|---|---|---|---|---|
| | Academia strain | | $H_{37}Rv$ strain | |
| | Soton medium | | | |
| | without serum | with serum | without serum | with serum |
| Ia | 64 | 125 | 32 | 64 |
| IIa | - | - | 64 | 1000 |
| IIIa | > 1000 | >1000 | 250 | 1000 |
| IVa | - | - | 16 | 250 |
| Ib | 2 | 64 | 1 | 32 |
| IIb | 2 | 125 | 2 | 125 |
| IIIb | > 1000 | >1000 | 8 | 1000 |
| IVb | 8 | 1000 | 2 | 500 |
| IIc | - | - | 32 | 250 |
| IIIc | - | - | >32 | >500 |

2-Mercaptobenzoxazole (I), 2-mercaptobenzthiazole (II), and 3-mercapto-symm.-triazole(3,4-c)benzthiazole (III) [4] were chosen as starting compounds. Since the presence of an alkoxy group in the molecule often promotes an increase in the tuberculostatic activity, analogous conversions were carried out with 6-ethoxy-2-mercaptobenzoxazole (IV) [5]. Compounds I-IV were reacted with chloracetonitrile; the reaction proceeded smoothly and the nitriles Ia-IVa were obtained in good yield. By reacting them with hydrogen sulfide in the presence of triethylamine, the nitriles were converted into the thioamides Ib-IVb; compound IIIb was obtained in the highest yield in this reaction.




The amidoximes IIc and IIIc were prepared from the compounds IIa and IIIa; the interaction of the nitrile Ia with hydroxylamine yielded a mixture of compounds difficult to separate.

All the compounds were examined for bacteriostatic activity in relation to two strains of bacteria of the human tuberculosis type (Academia – surface growth and $H_{37}Rv$ – deep growth). The greatest tuberculostatic activity was shown by the thioamide Ib (minimum tuberculostatic concentration without serum 1 μg/ml, with serum – 32 μg/ml) and by IIb (2 μg/ml without serum and 125 μg/ml with serum). However, for experimental tuberculosis of white mice, these compounds did not show medicinal properties.

The nitriles Ia-IVa and the amidoximes IIc and IIIc showed weak activity in vitro (Table 1).

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TABLE 2. Nitriles of S-(Heteryl)mercaptoacetic Acid, R–$SCH_2CN$

| Compound | Yield (in %) | mp (in °C) solvent for crystallization | Found (in %) | | | | Empirical formula | Calculated (in %) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | C | H | N | S | | C | H | N | S |
| Ia | 91,6 | 95—7, hexane | 56,86 | 3,20 | 14,79 | 17,00 | $C_9H_6N_2OS$ | 56,82 | 3,18 | 14,73 | 16,86 |
| IIa | 94,6 | 76—9. methanol | 52,17 | 3,07 | 13,48 | 31,31 | $C_9H_6N_2S_2$ | 52,40 | 2,93 | 13,58 | 31,09 |
| IIIa | 89 | 167—9, ethanol | 48,45 | 2,43 | 22,20 | 25,68 | $C_{10}H_6N_4S_2$ | 48,76 | 2,45 | 22,75 | 26,03 |
| IVa | 88,5 | 85—7, aqueous methanol | 56,73 | 4,29 | — | 13,84 | $C_{11}H_{10}N_2O_2S$ | 56,39 | 4,30 | — | 13,69 |

TABLE 3. Thioamides of S-(Heteryl)mercaptoacetic Acid, $RSCH_2C(S)NH_2$

| Compound | Yield (in %) | mp (in °C) solvent for crystallization | Found (in %) | | | | Empirical formula | Calculated (in %) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | C | H | N | S | | C | H | N | S |
| Ib | 49,1 | 131—3, aqueous methanol | 48,29 | 3,40 | 12,59 | 28,32 | $C_9H_8N_2O_2S$ | 48,19 | 3,59 | 12,49 | 28,59 |
| IIb | 64,1 | 137,5—138,5, methanol | 44,67 | 3,70 | 11,82 | 40,42 | $C_9H_8N_2S_3$ | 44,97 | 3,35 | 11,65 | 40,02 |
| IIIb | 91,9 | 166—8, butanol | 42,92 | 2,71 | 19,81 | 34,48 | $C_{10}H_8N_4S_3$ | 42,84 | 2,87 | 19,98 | 34,31 |
| IVb | 67,2 | 132—3, ethanol | 49,39 | 4,29 | 10,36 | 23,97 | $C_{11}H_{12}N_2O_2S_2$ | 49,23 | 4,50 | 10,44 | 23,90 |

## EXPERIMENTAL

Nitrile of S-(benzoxazolyl-2)-mercaptoacetic Acid (Ia). A solution of 6.8 g of 2-mercaptobenzoxazole (I) in 119 ml of 5% $Na_2CO_3$ solution was treated with charcoal, then 3.2 ml of chloracetonitrile was added continuously while cooling with iced water. The reaction mixture was agitated for several hours at room temperature and left overnight. The precipitate formed was filtered off and washed with water; yield of Ia was 7.88 g, mp 95–97°C (from hexane). Compounds IIa–IVa were prepared by an analogous method (Table 2).

Thioamide of S-(benzoxazolyl-2)-mercaptoacetic Acid (Ib). To a solution of 1.05 g of Ia in 15 ml of anhydrous ethanol was added two ml of triethylamine, and a stream of dry hydrogen sulfide was passed through the mixture for 2 h. The reaction mixture was cooled with an ice mixture, the precipitate was filtered off, and washed with chilled ethanol. Yield of Ib, as colorless crystals with mp 131–133°C (from aqueous methanol), was 0.61 g. The thioamides IIb–IVb were prepared by an analogous method (Table 3).

Amidoxime of S-(benzthiazolyl-2)-mercaptoacetic Acid (IIc). A solution of 0.32 g of hydroxylamine hydrochloride and 0.24 g of $Na_2CO_3$ in 5 ml of water was added to a warm solution of 0.72 g of IIa in 15 ml of ethanol. The yellow solution formed was boiled for 3 h, then evaporated to $^1/_3$ its volume, and water was added. The precipitate was filtered off. Yield of IIb, with mp 129.5–131.5°C (from water), was 0.75 g. Found, %: C 45.30; H 3.75; N 17.46; S 26.48. $C_9H_9N_3OS_2$. Calculated, %: C 45.17; H 3.79; N 17.56; S 26.80.

Amidoxime of S-symm.-triazolo(3,4-c)benzthiazolyl-3-mercaptoacetic Acid (IIIc) was prepared by an analogous method. Yield of IIIc from 0.5 g of IIIa was 0.52 g, decomp. temp. 199°C (from aqueous dimethylformamide). Found, %: C 43.18; H 2.94; N 24.83; S 22.56. $C_{10}H_9N_5OS_2$. Calculated %: C 43.00; H 3.25; N 25.07; S 22.96.

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