# INVESTIGATIONS IN THE IMIDAZOLE SERIES. SYNTHESIS OF THIAZOLINO-(3, 2- $\alpha$ ) BENZIMIDAZOLE AND SEVERAL OF ITS DERIVATIVES\*

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It is known that 2-(thiazolyl-4')benzimidazole (thiabendazole) has a high antihelminthic activity [1]. Changing the structure of this compound by coupling the imidazole and the thiazole rings into one heterocyclic system and introducing a phenyl group into position 5 of this bicyclic compound forms 6-phenylimidazolino (2,1-b)-thiazoline (tetramizole), a new anthelminthic compound having a broad spectrum of effect [2].



There is no data in the literature on the study in the direction indicated of derivatives of thiazolino- $(3,2-\alpha)$  benzimidazole, in which, in contrast to tetramizole, the benzene ring is condensed with the imidazo-thiazole group. It was of interest to us to prepare thiazolino- $(3,2-\alpha)$  benzimidazole (VIII) and several of its derivatives with the purpose of studying the anthelminthic activity.\*

Literature data on the synthesis of (VIII) are very sparse and contradictory [3-5]. In this connection, we studied more carefully the reactions of 2-mercapto- and 5,6-dimethyl-2-mercaptobenzimidazoles (I, II) with ethylene chloro(bromo)hydrins and 1,2-dichloro(dibromo)ethanes as the simplest way of synthesizing (VIII) and its derivatives.

 $2-(\beta-\text{Hydroxyethyl})$  mercaptobenzimidazoles (III, IV) were obtained upon reaction of (I) and (II) with ethylene chloro(bromo)-hydrins in ethanol. Treatment of (III) and (IV) with thionyl chloride and subsequent heating of the 2-( $\beta$ -chloromethyl)mercaptobenzimidazoles (V, VI) in aqueous methanol in the presence of KOH yielded (VIII) and its 6,7-dimethyl homologue (IX), characterized as the salts and methiodides. Compounds (VIII) and (IX) are also formed upon boiling (V) and (VI) in toluene. The structure of (VIII) was confirmed by counter synthesis from 1-( $\beta$ -hydroxyethyl)-2-mercaptobenzimidazole (VII) by its treatment with thionyl chloride and cyclization of the intermediate 1-( $\beta$ -chloroethyl)-2-mercaptobenzimidazole to (VIII).

Reaction of (I) with 1,2-dihaloethanes proceeds in different directions. Dichloroethane in isopropanol in the presence of sodium bicarbonate by the method of [3] yielded (VIII). Dibromoethane upon heating in toluene and ethanol in the presence of KOH yielded 1,2-di(2'-mercaptobenzimidazolyl)ethane (X), the structure of which was confirmed by its transformation to the diacetyl derivative (XI). Reaction of (I) with dibromoethane in dimethylformamide in the presence of potassium carbonate, in contrast to data of [4], leads to the formation of a mixture of (VIII) and (X).

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<sup>&</sup>lt;sup>†</sup>The results of biological investigations, carried out at VNIKhFI by A. N. Tareev, will be reported separately.

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## EXPERIMENTAL

# 2-Mercapto- and 5,6-Dimethyl-2-mercaptobenzimidazoles (I, II) were prepared earlier [6].

 $\frac{2-(\beta-\text{Hydroxyethyl}) \text{ mercaptobenzimidazole (III)}. A. To a solution of 4 g of NaOH in 100 nd of ethanol were added 15 g of (I) and 10.8 g of ethylene chlorohydrin. The mixture was heated for 1 h at 60-65°C and for 10 min at boiling (in the presence of carbon); the solution was filtered, poured into water (1 liter), and cooled to 4-5°; the separated precipitate was filtered and washed with water. Yield 11.54 g (60 %), mp 119-120°. Colorless plates having mp 125-126° (dec., in a sealed capillary, from a 15% solution of ethanol). Data of [7]: mp 126-127°; data of [8] (clearly incorrect): mp 220°. Found, %: C 55.30; H 5.19; N 14.66; S 16.63. C<sub>9</sub>H<sub>10</sub>N<sub>2</sub>OS. Calculated, %: C 55.64; H 5.19; N 14.42; S 16.51.$ 

B. To a warm  $(35-40^\circ)$  solution of 7.5 g of (I) in 75 ml of ethanol was added 6.2 g of ethylene bromohydrin. The mixture was boiled for 1 h (the last 5 min in the presence of activated carbon), filtered, poured into water, and neutralized with NaHCO<sub>3</sub>; the separated precipitate was filtered and washed with water. Yield 5.8 g (60.2%), mp 122-124°; after recrystallization from aqueous alcohol, mp 125-126°.

5,6-Dimethyl-2-( $\beta$ -hydroxyethyl)mercaptobenzimidazole (IV). The compound was obtained analogously to (III) (method B). Yield 94.9%. The colorless prisms have decomposition temperature 165-175° (from a 70% solution of ethanol). Found, %: C 59.11; H 6.04; N 12.80; S 14.65. C<sub>11</sub>H<sub>14</sub>N<sub>2</sub>OS. Calculated, %: C 59.43; H 6.35; N 12.60; S 14.42.

 $2-(\beta-\text{Chloroethyl})$  mercaptobenzimidazole (V). A mixture of 4 g of (III) and 10 ml of thionyl chloride was boiled for 30 min, the excess thionyl chloride was distilled in vacuum, to the residue was added an aqueous solution of sodium carbonate, and the precipitate was filtered and washed with water. Yield 3.5 g (82.9%), mp 110-112°. The colorless prisms have mp 113-114° (from 50% ethanol). Data of [8, 9]: yield 47%, mp 122-124°.

5,6-Dimethyl-2-( $\beta$ -chloroethyl)mercaptobenzimidazole (VI). The compound was obtained analogously to (V). Yield 96.2%. The colorless plates have mp 103-104° (dec., from 50% ethanol). Found, %: C 55.15; H 5.63; Cl 14.84; N 11.50; S 13.59. C<sub>11</sub>H<sub>13</sub>ClN<sub>2</sub>S. Calculated, %: C 54.87; H 5.44; Cl 14.73; N 11.64; S 13.32.

 $1-(\beta-Hydroxyethyl)-2$ -mercaptobenzimidazole (VII) was prepared by the method of [7].

<u>Thiazolino(3,2-a)benzimidazole (VIII)</u>. A. To a mixture of 100 ml of isopropanol, 13.6 g of NaHCO<sub>3</sub>, and 18.8 g of 1,2-dichloroethane heated to boiling was added over 1 h a solution composed of 5 g of (I), 15 ml of a 20% solution of KOH, and 85 ml of isopropanol. The mixture was boiled for 3 h, the solvent and excess dichloroethane were distilled in vacuum, to the residue was added 30 ml of a 15% solution of KOH, the mixture was extracted with chloroform, the extract was washed with a dilute solution of KOH, then water, and dried over MgSO<sub>4</sub> and the solvent was distilled. Yield 2.5 g (42.2%), mp 93-100°. The colorless plates have mp 108-109° (from aqueous methanol). From data of [3] (yield not indicated), mp 141-142°. Found, %: C 60.99; H 4.42; N 15.84; S 17.96.  $C_9H_8N_2S$ . Calculated, %: C 61.33; H 4.57; N 15.89; S 18.19. The hydrobromide has mp 219-220° (dec., from a 10% solution of HBr). Data of [4]: mp 220-222°. The picrate has mp 230-231° (dec., from CH<sub>3</sub>COOH). Found, %: C 44.30; H 2.66; N 17.15; S 7.77.  $C_9H_8N_2S \cdot C_6H_3N_3O_7$ . Calculated, %: C 44.44; H 2.73; N 17.28; S 7.91. The methiodide has mp 239-240° (dec., precipitated from ether with ethanol). From data of [4]: mp 185-187°. Found, %: C 37.92; H 3.29; J 40.10; N 8.55; S 10.20.  $C_{10}H_{11}IN_2S$ . Calculated, %: C 37.74; H 3.48; I 39.89; N 8.80; S 10.08. B. To a solution of 3.2 g of (V) in 40 ml of methanol was added a solution of 2 g of KOH in 10 ml of water, the mixture was boiled for 3 h, the solvent was distilled in vacuum, to the residue was added 10 ml of a 10% solution of KOH, and the base (VIII) was extracted with chloroform. Yield 1.86 g (70.4%), mp 108-109° (from aqueous methanol).

C. A solution of 2.12 g of (V) in 20 ml of toluene was boiled for 30 min, the solvent was distilled in vacuum, and to the residue was added 30 ml of ethanol; the solution was poured into water, neutralized with NaHCO<sub>3</sub>, and extracted with chloroform. The residue after distillation of the chloroform was dissolved in ethanol, a solution of picric acid was added, and the precipitate was filtered with water. We obtained 1.82 g (44.8%) of the picrate of base (VIII) having mp 230-231° (dec., from CH<sub>3</sub>COOH).

D. A mixture of 2.91 g of (VII) and 5 ml of thionyl chloride was heated for 7 min on a boiling water bath, the excess thionyl chloride was distilled in vacuum, and to the residue was added 10 ml of chloroform which was distilled in vacuum (this operation was repeated an additional two times). The residue was dissolved in 10 ml of ethanol and boiled for 2-3 min with carbon; the solution was filtered, poured into water, neutralized with NaHCO<sub>3</sub>, and extracted with chloroform. Yield 2.08 g (79%), mp 108-109° (from aqueous methanol). A mixed sample with (VIII) prepared by methods A-C did not give a melting point depression. The picrate has mp 230-231° (dec., from CH<sub>3</sub>COOH).

<u>6,7-Dimethylthiazolino(3,2-α)</u> benzimidazole (IX). A. A solution of 3.6 g of (VI) in 20 ml of toluene was boiled for 3 h, cooled, and 30 ml of ether was added; the residue was filtered, washed with ether, dissolved in 50 ml of ethanol, and neutralized with aqueous NaHCO<sub>3</sub>. The residue was filtered and washed with water. Yield 2.8 g (91.5%). The colorless prisms have mp 167-168° (from a 65% ethanol solution), and are soluble in organic solvents and insoluble in water. Found, %: C 64.54; H 5.93; N 13.30; S 15.93. C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>S. Calculated, %: C 64.67; H 5.92; N 13.71; S 15.69. 253-254° (dec., from CH<sub>3</sub>COOH). Found, %: C 16.09; C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>S. C<sub>6</sub>H<sub>3</sub>N<sub>3</sub>O<sub>7</sub>. Calculated, %: N 16.16. The methiodide, colorless plates, has mp 245-246° (dec., precipitation from ethanol with ether). Found, %: J 37.00; N 7.82; S 9.50. C<sub>12</sub>H<sub>15</sub>IN<sub>2</sub>S. Calculated, %: I 36.66; N 8.09; S 9.26.

B. To a solution of 3.6 g of (VI) in 40 ml of methanol was added a solution of 2 g of KOH in 10 ml of water. The mixture was boiled and treated as in the preparation of (VIII) (method B). Yield 2.48 g (81%), mp 166-168°. The picrate has mp 253-254° (dec.).

<u>1,2-Di-(2'-mercaptobenzimidazolyl)ethane (X).</u> A. A mixture of 7.5 g of (I), 32.7 g of 1,2-dibromoethane, and 50 g of toluene was boiled for 8 h, then cooled, and the precipitate was filtered, washed with ether, suspended in water, neutralized with aqueous ammonia; the precipitate was filtered, washed with a 10% solution of KOH, then water. Yield 2.3 g (28.2%), mp 190-195°. The colorless crystals have mp 228-230° (dec., from a mixture of ethanol-water, 1:1), and are soluble in methanol, ethanol, glacial CH<sub>3</sub>COOH, and insoluble in water. Found, %: C 58.60; H 4.33; N 17.14; S 19.60. C<sub>16</sub>H<sub>14</sub>N<sub>4</sub>S<sub>2</sub>. Calculated, %: C 58.87; H 4.32; N 17.16; S 19.65.

B. To a solution of 2.24 g of KOH in 30 ml of ethanol and 10 ml of water was added 6 g of (I) and 4.13 g of dibromoethane. The mixture was heated for 1 h at  $60-65^{\circ}$  and for 10 min at the boiling point, then cooled, and 20 ml of a 10% solution of KOH was added; the mixture was poured into water, and the precipitate was filtered and washed with a 10% solution of KOH, then water. Yield 3.82 g (58.6%), mp 204-206°, and after recrystallization from aqueous ethanol, the mp is 228-230°.

C. To a solution of 3 g of (I) in 30 ml of dimethylformamide was added 2.76 g of anhydrous, finely pulverized  $K_2CO_3$  and 3.74 g of dibromoethane. The mixture was left at 20-22° for 24 h with periodic stirring, then poured onto water; an aqueous solution of NaHCO<sub>3</sub> was added, and the precipitate was filtered and washed with water. We obtained 1.5 g of a mixture of (VIII) and (X). Fractional crystallization of the precipitate from a 50% solution of ethanol yielded pure (X) having mp 228-230°. To the mother aqueous-alcohol solutions was added a solution of picric acid, and the residue was filtered and crystallized from CH<sub>3</sub>COOH. The picrate of the base (VIII) having mp 230-231° (dec.) was separated. A mixed sample with the picrate of (VIII) prepared as described above did not give a melting point depression.

<u>1,2-Di(1'-acetyl-2'-mercaptobenzimidazolyl)</u>ethane (XI). A solution of 1.1 g of (X) in 10 ml of acetic anhydride was heated on a boiling water bath for 30 min, then cooled, and the precipitate was filtered and washed with ethanol. Yield 1.35 g (97.8%), mp 207-209°. The colorless plates have mp 214-215° (dec., from a mixture of dimethylformamide-acetic anhydride, 4:1), and are sparingly soluble in the majority of organic solvents.

#### CONCLUSIONS

The reaction of 2-mercapto- and 5,6-dimethyl-2-mercaptobenzimidazoles with ethylene chloro (bro o)hydrins and 1,2-dichloro(dibromo)ethanes was studied. With dihaloethanes, the process proceeds in two directions, formation of thiazolino(3,2-a)benzimidazoles and 1,2-di-(2'-mercaptobenzimidazolyl) ethanes. Thiazolino(3,2- $\alpha$ )benzimidazole and several of its derivatives were synthesized by cyclization of 2-( $\beta$ -chloroethyl)mercapto- and 1-( $\beta$ -chloromethyl)-2-mercaptobenzimidazoles.

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