# SYNTHESIS IN THE 2-MERCAPTOBENZOTHIAZOLE SERIES

## V.* Thiazolidino[2, 3-b]-Benzothiazolines

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Reaction of 2-mercaptobenzothiazoles substituted at position 6 by chlorine, dimethylsulfamido, benzamido, and nitro groups, with chlorobromoalkanes, is used to synthesize the corresponding 6-substituted 2-(β-chloroalkylmercapto)benzothiazoles. Oxidation of these compounds with hydrogen peroxide in acetic acid converts them to sulfoxides and sulfones, while heating in nitrobenzene cyclizes them to 6 substituted 2,3-dihydrothiazolo[2,3-b]benzothiazolium chlorides. The latter and previously obtained quaternary salts are converted by sodium borohydride into derivatives of a new tricyclic system, thiazolidino[2,3-b]benzothiazoline.

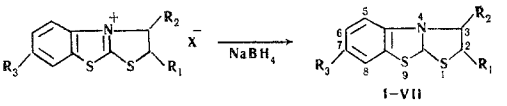
Developing previous research aimed at studying transformations of 2-(β-chloroethylmercapto)benzothiazole, we have synthesized derivatives of this substituted at position 6 in the ring, and studied their properties and reactivities. Cyclizations of substituted 2-(β-chloroethylmercapto)-benzothiazoles to quaternary salts, oxidation of these salts to sulfoxide and sulfones, and conversion of the latter to unsaturated compounds, were effected by methods described in our previous paper [1]. Replacement of a hydrogen atom at position 6 in 2-(β-chloroethylmercapto)-benzothiazole by chlorine, dimethylsulfamido, benzoylamino, and a nitro group, did not have any real effect on the cyclization of the compounds to benzothiazolium salts, and this might have been predicted from the electronic structure of benzothiazole.

Oxidation of 6 substituted 2-(β-chloroethylmercapto)benzothiazoles to sulfones was effected in the usual way with hydrogen peroxide in acetic acid [1]. Only in one case, when there was chlorine at position 6, was the corresponding sulfoxide isolated from the reaction products. With a number of sulfoxides and sulfones satisfactory analytical data for chlorine could not be obtained, due to their tendency to split off hydrogen chloride.

The sulfoxides and sulfones are readily dehydrochlorinated by treatment with aluminum oxide. Thus after passing benzene or chloroform solutions of 2-(β-chloroethyl)-6-chloro-, 6-dimethylsulfamido- and 6-benzamidobenzothiazolylsulfones through an alumina column, the substances did not give the Beilstein test for chlorine, and their IR spectra lacked the band characteristic of the $-HC=CH_2$ bond. This indicates that splitting off of hydrogen chloride from sulfoxides and sulfones is evidently accompanied by side reactions, complicating isolation of the unsaturated compounds. Only in one case was 2-(6-chlorobenzothiazolyl)-vinylsulfoxide isolated.

*For Part IV see [1].

Due to the large positive charge at the nitrogen atom, and the consequent decreased electron density at the carbon atom in position 2, quaternary benzothiazolium salts are interesting models for investigating nucleophilic substitution. In addition it was of interest to investigate reduction, and by this reaction to arrive at a new heterocyclic system. Actually, by reducing benzothiazolium salts with sodium borohydride in aqueous medium at room temperature high yields of the thiazolidino[2,3-b] benzothiazolines I-VII were obtained.




I-VII

I $R_1=R_2=R_3=H$; II $R_1=CH_3$; $R_2=R_3=H$;
III $R_1=R_3=H$; $R_2=CH_3$; IV $R_1=R_2=H$; $R_3=Cl$;
V $R_1=R_2=H$; $R_3=NO_2$;
VI $R_1=R_2=H$; $R_3=SO_2N(CH_3)_2$;
VII $R_1=R_2=H$; $R_3=NHCOC_6H_5$; X=Cl, B.

There is no information in the literature about either of these heterocyclic systems or their derivatives, so that independent interest attaches to the preparation and investigation of the properties of these compounds. The structure of compounds I–VII was confirmed by the elementary analytical data and IR spectra, which latter lacked absorption bands characteristic of SH and NH groups. Such a tricyclic system is stable at room temperature to dilute and concentrated acids. Treatment with cold dilute alkali decomposes them to give scission products. In some cases reduction of benzothiazolium salts preceded ambiguously, for along with the expected compounds products of deeper reduction were found; the latter will form the subject of a separate communication.

## EXPERIMENTAL

**2-Mercapto-6-dimethylsulfamidobenzothiazole (VIII).** 20 g (0.12 mole) 2-mercaptobenzothiazole was added in small portions to 200 ml chlorosulfonic acid cooled to 0°, the mixture then stirred for 15 min at 0–5°, and over a period of 1 hr 30 min the mixture carefully poured onto ice. The precipitate was filtered off, washed with ice water, carefully pressed, and dissolved with heating in excess 20% aqueous $Me_2NH$. The whole was boiled for 2 hr, diluted with water, acidified with AcOH, and the precipitate filtered off. Yield 25 g (76%) VIII mp 233–234.5° (ex dimethylformamide). Found: N 10.09; 10.28; S

## Thiazolidino[2,3-b]benzthiazolines

| Compound | $R_1$ | $R_2$ | $R_3$ | Method | Solvent for crystallizing | Mp, °C | Formula | Found, % | | | | Calculated, % | | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | C | H | N | S | C | H | N | S | |
| I | H | H | H | a | EtOH | 88—89 | $C_9H_9NS_2$ | 55.29<br>55.67 | 4.51<br>4.73 | 7.43<br>7.26 | 33.13<br>32.85 | 55.35 | 4.64 | 7.17 | 32.83 | 42 |
| II | $CH_3$ | H | H | a | EtOH | 71.5—72.5 | $C_{10}H_{11}NS_2$ | 57.59<br>57.41 | 5.21<br>4.97 | — | 30.91<br>30.79 | 57.41 | 5.26 | — | 30.62 | 40 |
| III | H | $CH_3$ | H | b | EtOH | 107—108 | $C_{10}H_{11}NS_2$ | 57.27<br>57.24 | 5.13<br>5.26 | — | 30.58<br>30.88 | 57.41 | 5.26 | — | 30.62 | 90 |
| IV | H | H | Cl | b | Aqueous EtOH | 106—106.5 | $C_9H_8ClNS_2$ | 47.02<br>47.26 | 3.41<br>3.48 | Cl 15.79<br>15.55 | 27.72<br>27.68 | 47.05 | 3.41 | Cl 15.46 | 27.89 | 85 |
| V | H | H | $NO_2$ | b | Dry EtOH | 114—115 | $C_9H_8N_2O_2S_2$ | 45.00<br>45.19 | 3.27<br>3.27 | — | 26.66<br>26.83 | 45.00 | 3.33 | — | 26.67 | 84.5 |
| VI | H | H | $SO_2N(CH_3)_2$ | b | Benzene-$CHCl_3$ | 190—191 | $C_{11}H_{14}N_2O_2S_3$ | 43.15<br>43.22 | 4.59<br>4.53 | 8.91<br>9.16 | 31.55<br>31.85 | 43.69 | 4.67 | 9.26 | 31.80 | 91 |
| VII | H | H | $NHCOC_6H_5$ | b | Aqueous EtOH | 171—173 | $C_{16}H_{14}N_2O_2S_2$ | — | — | 8.93<br>9.15 | 20.78<br>20.72 | — | — | 8.92 | 20.38 | 66 |

34.77; 34.97%. Calculated for $C_9H_{10}N_2O_2S_3$: N 10.21; S 35.00%.

**2-Mercapto-6-benzamidobenzothiazole (IX).** A solution of 12 ml benzoyl chloride in 200 ml dioxane was added dropwise to a mixture of 18.2 g (0.1 mole) 2-mercapto-6-aminobenzothiazole [2] in 400 ml dry dioxane and 12 ml dry pyridine, the whole refluxed for 4 hr, cooled, the precipitate filtered off, washed with water, and the filtrate plus washings poured into 8% HCl; the precipitates were bulked. Yield 10.6 g (72%) IX, mp 147–248° (ex n-PrOH). The literature gives [2] mp 231–234°. Found: N 9.54; 9.76; S 22.40; 22.33%. Calculated for $C_{14}H_{10}N_2OS_2$: N 9.80; S 22.38%.

**2-(β-Chloroethylmercapto)-6-nitrobenzothiazole (X).** A solution of 15.4 g (0.11 mole) chlorobromomethane in 100 ml EtOH was added, with stirring, to a solution of 21.2 g (0.1 mole) 2-mercapto-6-nitrobenzothiazole [3] in 260 ml 1.6% NaOH at 60°, after 5–6 hr the products cooled, 200 ml water added, and the precipitate filtered off. Yield 19.8 g (72%) sulfide X mp 97–98° (ex EtOH). The literature gives [4] mp 84°. Found: Cl 12.84; 13.02; S 23.50; 23.62%. Calculated for $C_9H_7ClN_2O_2S_2$: Cl 12.93; S 23.31%.

**2-(β-Chloroethylmercapto)-6-dimethylsulfamidobenzothiazole (XI).** 5.5 g (0.02 mole) mercaptan VIII in 50 ml 2% was mixed with 3.6 g (0.025 mole) chlorobromomethane in 25 ml EtOH, the precipitate separated and ground with ether; yield of XI 3.6 g (55%), mp 132–133° (ex EtOH). Found: Cl 10.22; 10.23; S 28.62; 28.66%. Calculated for $C_{11}H_{13}ClN_2O_2S_3$: Cl 10.54; S 28.55%.

**2-(β-Chloroethylmercapto)-6-benzamidobenzothiazole (XII).** 22.4 g (0.08 mole) mercaptan IX in 300 ml 1.5% NaOH and 14.6 g (0.1 mole) chlorobromethane in 100 ml gave 26.6 g (93%) sulfide XII, mp ~130° (ex n-PrOH, shrinks, solidifies and melts again at 267–268°). Found: Cl 9.91; 10.03; N 7.93; 8.04; S 18.39; 18.22%. Calculated for $C_{16}H_{13}ClN_2OS_2$: Cl 10.19; N 8.03; S 18.36%.

**2-(β-Chloroethylmercapto)-6-chlorobenzothiazole (XIII).** 6.5 g (0.032 mole) 2-mercapto-6-chlorobenzothiazole [5] in 150 ml 1.3% NaOH and 5.4 g (0.037 mole) chlorobromoethane in 50 ml EtOH were mixed and then diluted with water (about 100 ml), when an oil formed which was extracted with ether. The ether solution was washed with water and dried over anhydrous $MgSO_4$. After removing the ether there remained 6 g (71%) of the oil, which was used for subsequent reactions without further purification.

**2-(β-Chloroethyl)-6-chlorobenzothiazolysulfoxide (XIV).** A solution of 7 g (0.026 mole) sulfide XIII in 60 ml glacial AcOH and 39 ml (0.3 mole) 26% $H_2O_2$ were stirred together for 1 hr 30 min at 50°, cooled, poured into water, the precipitate filtered off, washed with water, and dried. Yield 3.7 g (50%) sulfoxide XIV, mp 113–114° (ex aqueous n-PrOH). In the IR spectrum $\nu_{SO}$ 1060 (1050) $cm^{-1}$. Found: S 22.42; 22.55% Calculated for $C_9H_7Cl_2NOS$: S 22.86%.

**2-(6-Chlorobenzothiazolyl)vinylsulfoxide.** 1 g sulfoxide XIV was dissolved in $CHCl_3$, and run onto an $Al_2O_3$ (activity IV–V) column, eluted with $CHCl_3$, the $CHCl_3$ solution then evaporated. Yield 0.5 g (57%), mp 107–108° (ex EtOH). In the IR spectrum $\nu_{SO}$ 1065, 965, 990 $cm^{-1}$ (-CH=$CH_2$). Found: Cl 14.62; 14.62; S 25.83, 26.05%. Calculated for Cl 14.62; 14.62; S 25.83, 26.05%: Cl 14.58, S 26.28%.

**2-(β-Chloroethyl)-6-chlorobenzothiazolysulfone.** A solution of 7 g (0.026 mole) sulfide XIII in 56 ml glacial AcOH and 39 ml (0.32 mole) 28% $H_2O_2$ were stirred together for 3 hr at 70°, the products cooled, poured into water, the precipitate filtered off, washed with water, and dried, yield 3 g (38%) sulfone, mp 114–115° (ex aqueous PrOH). In the IR spectrum $\nu_{SO_2}$ sym 1340 $cm^{-1}$, $\nu_{SO_2}$ asym 1156 $cm^{-1}$. Found: Cl 21.88; 21.85; S 23.63; S 23.63; 23.51%. Calculated for $C_9H_7Cl_2NO_2S_2$: Cl 21.62, S 23.97%.

**2-(β-Chloroethyl)-6-dimethylsulfamidobenzthiazolylsulfone.** A solution of 1.6 g (0.005 mole) sulfide XI in 80 ml glacial AcOH was stirred for 2 hr with 6.6 ml (0.054 mole) 28% $H_2O_2$ 55–65°, the products cooled and poured into about 250 ml water. The precipitate was filtered off, washed with water, and dried, yield 1.33 g (70%) sulfone, mp 149–150° (ex n-PrOH). In the IR spectrum: $\nu_{SO_2}$ sym 1340 $cm^{-1}$, $\nu_{SO_2}$ asym 1160 $cm^{-1}$. Found: Cl 9.35; 9.22; S 26.56; 26.48%. Calculated for $C_{11}H_{13}ClN_2O_4S_3$: Cl 9.61; S 26.07%.

**2-(β-Chloroethyl)-6-benzamidobenzothiazolysulfone.** A solution of 2.4 g (0.0007 mole) sulfide XII in 75 ml glacial AcOH and 9.4 ml (0.077 mole) 28% $H_2O_2$ were stirred together for 1 hr 30 min at 60–65°, the products cooled, the precipitate filtered off, washed with water, and dried. Yield 1.6 g material; the filtrate was poured into water, to give an additional 0.9 g material. Total yield 2.5 g (92%), mp 188–189° (ex n-PrOH). In the IR spectrum: $\nu_{SO_2}$ sym 1340 $cm^{-1}$, $\nu_{SO_2}$ asym 1140 (1153) $cm^{-1}$. Found: N 7.23; 7.49; S 16.76; 16.83%. Calculated for $C_{16}H_{13}ClN_2O_3S_2$: N 7.35; S 16.82%.

**2,3-Dihydrothiazolo[2,3-b]-7-chlorobenzothiazolium chloride.** 13.6 g (0.05 mole) sulfide, XIII was dissolved in 15 ml nitrobenzene, heated at 140° for 3–4 hr, cooled, the solid filtered off, washed with acetone, and dried. Yield 8.6 g (63.3%) chloride, mp 262–262.5° (ex dry EtOH). Found: Cl ion 13.16; 13.19; Cl total 26.45; 26.57; S 24.23; 24.55%. Calculated for $C_9H_7Cl_2NS_2$: Cl ion 13.44; Cl total 26.89, S 24.24%.

**2,3-Dihydrothiazolo[2,3-b-7-nitrobenzothiazolium chloride.** 14.5 g (0.05 mole) sulfide X was heated in 50 ml nitrobenzene for 8–10 hr at 120–140°, the products cooled, the solid filtered off, washed with acetone, and dried. Yield of chloride 80%; it decomposed when an attempt was made to recrystallize it, and for reduction the crude material was used.

**2,3-Dihydrothiazolo[2,3-b]-7-dimethylsulfamidobenzothiazolium chloride.** 4 g (0.012 mole) sulfide XI was heated in 8 ml nitrobenzene for 2–3 hr at 110–130°, the products cooled, the solid filtered off, washed with acetone, and dried. Yield 2 g (50%) chloride mp 165–167° (ex MeOH + ether). Found: Cl 10.45; 10.63%. Calculated for $C_{11}H_{13}ClN_2O_2S_3$: Cl 10.54%.

**2,3-Dihydrothiazolo[2,3-b]-7-benzamidothiazolium chloride.** 3 g sulfide XII was warmed with 30 ml nitrobenzene to dissolve it, and the whole then heated for 10 hr at 120–140°, the products cooled, the solid filtered off, washed with acetone, and dried. Yield 2.3 g (76%) chloride, mp 277–278° (ex EtOH). Found: Cl 10.23; 10.14; N 7.94; 7.93; S 18.40; 18.56%. Calculated for $C_{16}H_{13}ClN_2OS_2$: Cl 10.19; N 8.03; S 18.36%.

**Thiazolidino [2,3-b]benzothiazoline (I).** 2.85 g $NaBH_4$ (0.073 mole) in 50 ml water was added dropwise to a solution of 13.8 g (0.06 mole) 2,3-dihydrothiazolo[2,3-b]benzothiazolium chloride [1] in 150 ml water, and the whole stirred for 1 hr. Then the reaction mixture was heated at 40° for 30 min, cooled, and the solution decanted from an oil. The oil was dissolved in a minimum amount of concentrated HCl, the HCl solution diluted with about 500 ml water. The oil which separated was extracted with $CHCl_3$, the aqueous solution made alkaline with $NaHCO_3$, the precipitate filtered off, and carefully washed with water, when I was obtained (method a).

**3-Methylthiazolidino[2,3-b]benzothiazoline (III).** 1.9 g $NaBH_4$ (0.048 mole) in 50 ml water was added dropwise to a solution of 3-methyl-2,3-dihydrothiazolo[2,3-b)benzthiazolium bromide [1] in 100 ml water, the whole stirred for 1 hr, heated at 40° for 30 min, cooled, the precipitate filtered off, washed with water, and dried, when III was obtained (method b). The other benzothiazolines whose properties are given in the Table, were prepared similarly.

The IR spectra were determined by V. G. Vinokurov, V. S. Trotiskaya, and N. D. Solokhina, with a UR-10 IR spectrophotometer: mulls with vaseline or KBr discs were used.

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