SYNTHESIS AND PROPERTIES OF DERIVATIVES OF 2-MERCAPTOBENZOTHIAZOLE

VIII. (Perhydro-1,3-thiazino)[2,3-b]benzothiazolines*

E. A. Kuznetsova, S. V. Zhuravlev, and T. N. Stepanova

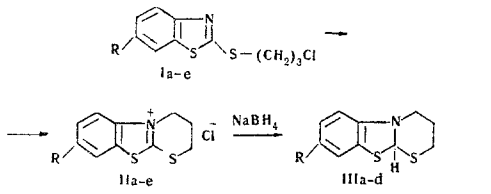
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 4, pp. 630–633, 1969

UDC 547.789.6.07'869.1

2,3-Dihydro-4H-[1,3]-thiazino[2,3-b]benzothiazolium chlorides have been synthesized and their reduction with sodium borohydride has given previously-unknown derivatives of (perhydro-1,3-thiazino)[2,3-b]benzothiazoline. The stability of the compounds in acid and alkaline media has been studied.

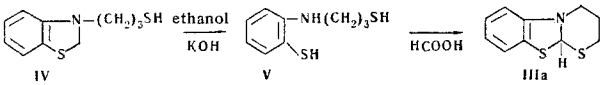
We have previously reported the synthesis of cyclic benzothiazolium salts including a thiazoline ring in their structure [2, 3]. Continuing work directed to the preparation of cyclic benzothiazolium salts and the study of their reactivities, by cyclizing the corresponding 2-(γ-chloropropylmercapto)benzothiazoles (Ia–Id) we have synthesized substituted 2,3-dihydro-4H-[1,3]-thiazino[2,3-b]benzothiazolium chlorides (IIa–IIe).

The salts II consist of high-melting substances with an ionic structure. Their structure was shown by reactions described below. On comparing the cylization of the various ω-chloroalkyl sulfides we found that the tendency to cyclization to form quaternary salts decreased with an increase in the length of the carbon chain. The γ-chloropropyl sulfides I cyclized with poorer yields than the β-chloroethyl sulfides [2], and 2-(δ-chlorobutylmercapto)benzothiazole did not cyclize at all but underwent decomposition on prolonged heating in nitrobenzene or in vacuum without a solvent.



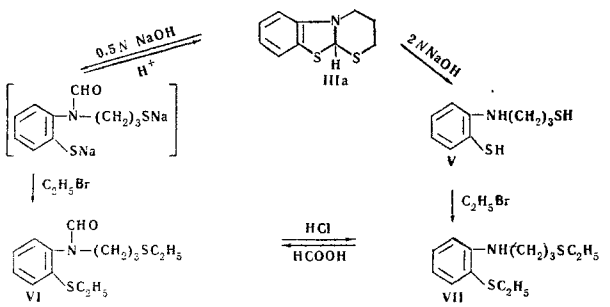
a R=H; b R=Cl; c R=NHCOC$_6$H$_5$; d R=NO$_2$; e R=NHCOCH$_3$

The reduction of II with sodium borohydride gave representatives of a previously-unreported condensed system—(perhydro-1,3-thiazino)[2,3-b]benzothiazoline (III). The reduction of IIa took place with the partial cleavage of the C—S bond and two substances were isolated from the reaction mixture: IIIa and the benzothiazoline IV. The structure of IIIa was confirmed by independent synthesis—by the condensation of the o-aminothiophenol V [4, 5] with formic acid. The structure of IV is proposed on the basis of its IR spectrum and its conversion under the action of ethanolic caustic potash into V.



The action of sodium borohydride on the salt IIe ga gave an oil apparently consisting of several substances which could not be separated. The other salts IIb–IId were reduced to III in high yields.

We also studied the hydrolytic stability of IIIa in acid and alkaline media. It was found that IIIa underwent no change on being heated in dilute or concentrated hydrochloric acid but in an alkaline medium it underwent the conversions illustrated by the following scheme:



*For part VII, see [1].

8-R-2,3-Dihydro-4H[1,3]-thiazino[2,3-b]benzothiazolium Chlorides

Compound	Mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
			Cl	N	S	Cl	N	S	
IIb	290—291	$C_{10}H_9Cl_2NS_2 \cdot H_2O$	23.54	4.74 4.79	21.86 21.94	23.98	4.73	21.62	44
IIc	284—285	$C_{17}H_{15}ClN_2OS_2 \cdot 1/2C_2H_5OH$	—	7.08 7.22	16.52 16.28	—	7.26	16.60	66
Nitrate* of IIc	211—212	$C_{17}H_{15}N_3O_4S_2$	—	10.53 10.77	16.30 16.51	—	10.79	16.45	80
IId	256—257	$C_{10}H_9ClN_2O_2S_2 \cdot C_2H_5OH$	—	8.49 8.36	18.98 19.01	—	8.37	19.13	46
IIe	304—305	$C_{12}H_{13}ClN_2OS_2 \cdot 1/2C_2H_5OH$	10.76 10.65	8.61 8.52	19.61 19.43	10.87	8.96	19.79	33

*Obtained by mixing an aqueous solution of IIc with a small excess of dilute HNO_3.

When **IIIa** was heated with 0.5 N caustic soda solution, it dissolved through the opening of the ring. On acidification, cyclization took place again. To elucidate the nature of the intermediate substances formed, after the compound had dissolved in the reaction mixture, ethyl bromide was added. On the basis of its analysis and IR spectrum we ascribed to the substance isolated the structure **VI**. The formyl group of this compound is readily eliminated by concentrated HCl and the substance obtained was identified by its melting point, refractive index, and IR spectrum as compound **VII**, which is formed by the alkylation of V. In addition, the treatment of **VII** with formic acid reformed **VI**.

EXPERIMENTAL

We have described the synthesis of **Ia**, **IIa**, and 2-(δ-chlorobutylmercapto)-benzothiazole (bp 178° C, 0.5 mm), (n_D^{20} 1.6507) previously [2].

2-(γ-Chloropropylmercapto)-6-benzamidobenzothiazole (Ic). At 60° C, a solution of 5.6 g (0.035 mole) of 1-bromo-3-chloropropane in 25 ml of ethanol was added dropwise to a solution of 9.2 g (0.03 mole) of benzamido-2-mercapto-benzothiazole in 100 ml of 2% caustic soda solution. After 4–5 hr at 60° C, the mixture was cooled, and the precipitate was washed with water and dried. Yield 14.3 g (95%). Mp 122–124° C (n-propanol). Found, %: N 8.01, 7.82; Cl 9.80, 9.67; S 18.05. Calculated for $C_{17}H_{15}ClN_2OS_2$, %: N 7.72; Cl 9.79; S 17.62.

2-(γ-Chloropropylmercapto)-6-nitrobenzothiazole (Id). Similarly, 21.2 g (0.10 mole) of 2-mercapto-6-nitrobenzothiazole in 200 ml of 2.5% caustic soda and 17 g (0.11 mole) of bromochloropropane in 50 ml of ethanol yielded 23.7 g (82%) of **Id**. Mp 83.5–84.5° C (ethanol). Found, %: Cl 12.29, 12.35; S 22.16, 22.08. Calculated for $C_{10}H_9ClN_2O_2S_2$, %: Cl 12.31; S 22.32. The sulfides **Ib** and **Ie** were obtained similarly in the form of undistillable oils and were used for the subsequent reactions without purification.

8-Substituted 2,3-dihydro-4H-[1,3]-thiazino[2,3-b]benzothiazolium chlorides. A solution of 0.01 mole of the γ-chloropropyl sulfide I in 10–15 ml of nitrobenzene was heated at 110–140° C for 2–10 hr and, after cooling, the precipitate that had deposited was filtered off with suction, washed with acetone, dried, and recrystallized from ethanol (see table).

(Perhydro-1,3-thiazino)[2,3-b]benzothiazoline (IIIa) and N-(γ-mercaptopropyl)-benzothiazoline (IV). A solution of 48.6 g (0.2 mole) of the chloride **IIa** in 500 ml of water was treated dropwise with 15.2 g (0.4 mole) of sodium borohydride in 100 ml of water. After 30 min at 40° C and 2–3 hr at ~20° C, the liquid was decanted off and the oil was dissolved in the minimum amount of conc HCl; this solution was diluted with water and the oil that separated out was extracted with chloroform. After treatment with solid sodium bicarbonate, the aqueous solution yielded 20.8 g (50%) of **IIIa** [2]. The chloroform solution was washed with water, dried, and evaporated. Yield 12.6 g (30%) of **IV**. Bp 140–141° C (1.5 mm), n_D^{21} 1.6510. Found, %: C 56.66, 56.85; H 6.12, 6.14; S 29.99, 30.16. Calculated for $C_{10}H_{13}NS2$, %: C 56.83; H 6.15; S 30.29. IR spectrum (thin layer), ν, cm^{-1}: 2552 (SH).

8-Chloro(perhydro-1,3-thiazino)[2,3-b]benzothiazoline (IIIb). 2.7 g (0.0100 mole) of the chloride **IIb** in 100 ml of water was reduced with 0.47 g (0.0125 mole) of sodium borohydride in 10 ml of water. After the reaction mixture had stood at 40° C for 1 hr and at room temperature for 2 hr, the precipitate was filtered off, giving 1.68 g (70%) of a product with mp 115–116° C (aqueous ethanol). Found, %: C 49.43, 49.61; H 3.96, 4.02; Cl 14.55, 14.58; S 26.40, 26.33. Calculated for $C_{10}H_{10}ClNS_2$, %: C 49.28; H 4.10; Cl 14.57; S 26.28.

8-Benzamido(perhydro-1,3-thiazino)[2,3-b]benzothiazoline (IIIc). In a similar manner to the preceding experiment, the reduction of 2 g (0.005 mole) of the chloride **IIc** in 250 ml of water with 0.27 g (0.007 mole) of sodium borohydride gave 1.3 g (70%) of a product with mp 203–204° C (aqueous ethanol). Found, %: C 61.99, 62.19; H 5.05, 4.98; N 8.70, 8.78; S 19.61, 19.74. Calculated for $C_{17}H_{16}N_2OS_2$, %: C 62.19; H 4.86; N 8.53; S 19.51.

8-Nitro(perhydro-1,3-thiazino)[2,3-b]benzothiazoline (IIId). This was obtained in a similar manner to the preceding compound from 1.3 g (0.005 mole) of the chloride **IId** in 150 ml of water and 0.27 g (0.007 mole) of sodium borohydride in 10 ml of water. Yield 1 g (91%). Mp 180–181° C (ethanol). Found, %: C 47.73; H 3.95; N 11.18, 10.94; S 24.91, 25.15. Calculated for $C_{10}H_{10}N_2O_2S_2$, %: C 47.24; H 3.93; N 11.02; S 25.19.

N-(γ-Mercaptopropyl)-o-aminothiophenol (V). A) A mixture of 10.5 g (0.05 mole) of **IIIa** and 500 ml of 2 N caustic soda was boiled for 5 hr, and after cooling it was acidified with hydrochloric acid and the oil that separated out was extracted with chloroform. The chloroform was evaporated off, giving 8.7 g of oil which was dissolved in 15 ml of concentrated HCl. This solution was poured into water and the oil that separated out was extracted with chloroform. From the aqueous layer 0.7 g (7%) of the initial **IIIa** was isolated. The chloroform layer yielded 5 g (50%) of a product with mp 142–143° C (2 mm), n_D^{20} 1.6285. Found, %: N 7.27, 7.16. Calculated for $C_9H_{13}NS_2$, %: N 7.06. IR spectrum (thin layer), ν, cm^{-1}, 2565 (SH), 3385 (NH).

B) A mixture of 31 g (0.55 mole) of caustic potash in 90 ml of ethanol and 25 g (0.11 mole) of **IV** in 80 ml of ethanol was boiled for 3 hr. Then it was filtered and the filtrate was concentrated to small volume, diluted with water, and extracted with ether. The aqueous layer was acidified with dilute acetic acid and the oil that separated out was extracted with ether. The extract yielded 11.1 g (43%) of **V**. Bp 136–137° C (1 mm), n_D^{22} 1.6290.

(Perhydro-1,3-thiazino)[2,3-b]benzothiazoline (IIIa). A mixture of 11.1 g (0.055 mole) of **V** and 90 ml of 98% formic acid was boiled for 4 hr. After cooling, it was poured into ~200 ml of water and the mixture was made alkaline with sodium bicarbonate. This gave 11 g (93%) of a product with mp 89–90° C (ethanol). A mixture with a sample obtained by a different method gave no depression of the melting point.

o-Ethylmercapto-N-(γ-ethylmercaptopropyl)formanilide (VI). A) A suspension of 10.5 g (0.05 mole) of **IIIa** in 500 ml of 0.5 N caustic soda was boiled until the solid matter had dissolved (~1 hr). At 50° C, the filtrate was treated dropwise with 16 g (0.15 mole) of ethyl bromide in 50 ml of ethanol. After 2 hr at 50–60° C, the reaction mixture was cooled and the oil that separated out was extracted with ether. After drying, the extract yielded 6.5 g (46%) of a product with bp 180–182° C (1 mm), n_D^{20} 1.5782. Found, %: N 4.97, 5.14; S 22.59, 22.70. Calculated for $C_{14}H_{21}NOS_2$, %: N 4.95; S 22.62. IR spectrum (thin layer), ν, cm^{-1}: 1682 (CO in an amide).

B) A mixture of 3 g (0.002 mole) of **VII** and 30 ml of 98% formic acid was boiled for 2 hr. The solution was left overnight and was then poured into water and the oil was extracted with ether. After the ethereal solution had been washed with sodium bicarbonate and with water and had been dried, it yielded 1.3 g (40%) of **VI**. Bp 180–182° C (1 mm), n_D^{20} 1.5782.

o-Ethylmercapto-N-(γ-ethylmercaptopropyl)aniline (VII). A) A solution of 5.7 g (0.03 mole) of **V** in 50 ml of 5.6% caustic soda solution (0.07 mole) was extracted with ether and the aqueous layer was treated dropwise at 50° C, with 11 g (0.11 mole) of ethyl bromide in 20 ml of ethanol. The reaction mixture was kept at 50–60° C for 3 hr and was cooled, diluted with water, and extracted with ether, giving 6.8 g (89%) of **VII**. Bp 146–147° C (1 mm), n_D^{20} 1.5820. Found, %: N 5.55, 5.28; S 25.04, 24.94. Calculated for $C_{13}H_{21}NS_2$, %: N 5.49; S 25.09.

B) A mixture of 4.5 g (0.016 mole) of **VI** and 30 ml of conc HCl was boiled for 5 hr and was then poured into water. Chloroform extraction of the aqueous solution yielded 3 g (74%) of **VII**. Bp 148–150° C (1.5 mm), n_D^{20} 1.5828.

REFERENCES

1. E. A. Kuznetsova, S. V. Zhuravlev, and T. N. Stepanova, KhGS [Chemistry of Heterocyclic Compounds], 4, 245, 1968.

2. E. A. Kuznetsova, S. V. Zhuravlev, and T. N. Stepanova, ZhOrKh, **1**, 767, 1965.

3. E. A. Kuznetsova, S. V. Zhuravlev, and T. N. Stepanova, KhGS [Chemistry of Heterocyclic Compounds], **3**, 261, 1967.

4. V. A. Bogolyubskii and L. T. Bogolyubskaya, USSR patent no. 183203; Byull. izobr., 13, 19, 1966.

5. E. A. Kuznetsova, V. A. Bogolyubskii, L. T. Bogolyubskaya, T. N. Stepanova, and S. V. Zhuravlev, KhGS [Chemistry of Heterocyclic Compounds], **3**, 834, 1967.

18 February 1967

Institute of Pharmacology and Chemotherapy AMS USSR, Moscow