SYNTHESES IN THE PHENOTHIAZINE SERIES

XXXIII.* NEW SYNTHESIS OF 2,3-DIHYDROTHIAZOLO[4,5-b]PHENOTHIAZINE-2-THIONE

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UDC 547.869.2.07'789.6:543.422.4

The structure of the previously obtained 2,3-dihydrothiazolo[4,5-b]phenothiazine-2-thione (I) was confirmed by a new synthesis of it by the action of sulfur on 5-phenylamino-2,3-dihydrobenzothiazole-2-thione.

We have previously obtained 2,3-dihydrothiazolo[4,5-b]phenothiazine-2-thione (I) by the action of sulfur and carbon disulfide on 2-aminophenothiazine [2]. The present communication is devoted to a new method for the synthesis of I, in which the thiazole ring of the molecule is obtained initially, and the phenothiazine ring is then closed by the action of sulfur. This method made it possible to confirm the linear structure of I.

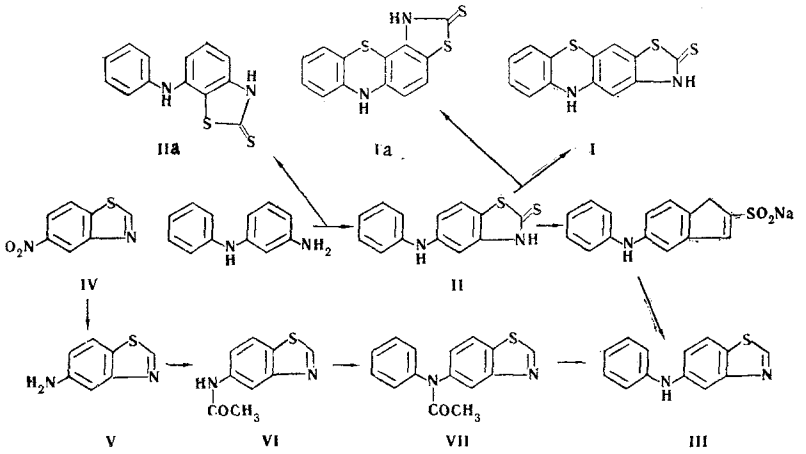
Two isomeric phenylaminobenzothiazoles – 5-phenylamino-2,3-dihydrobenzothiazole-2-thione (II) and 7-phenylamino-2,3-dihydrobenzothiazole-2-thione (IIa) – are obtained by the reaction of 3-aminodiphenylamine with sulfur and carbon disulfide.

The thione structure of the compounds was confirmed by IR spectroscopy. The IR spectra of II and IIa do not contain absorption bands of the SH group (2500-2600 cm^{-1}) but do contain absorption bands of the C=S group (1080 and 1087 cm^{-1}). The major reaction product is II; this is in agreement with the available literature data on the predominant formation of 5-substituted benzothiazoles during similar reactions in the aromatic series [3]. The structure of II was confirmed by alternative synthesis; for simplification of the latter, 5-phenylaminobenzothiazole (III), which does not contain a thione group, was obtained rather than II. The oxidation of II with hydrogen peroxide in alkali gives the sodium salt of the corresponding sulfinic acid, which, after acidification and heating, decomposes to form III [5]. The alternative synthesis of III was accomplished as follows. 5-Nitrobenzothiazole (IV) [4] was reduced to 5-aminobenzothiazole (V) with stannous chloride in hydrochloric acid; the acetyl derivative of V (VI) was converted to N-acetyl-5-phenlyaminobenzothiazole (VII) by reaction with bromobenzene in the presence of copper powder and potassium carbonate. The hydrolysis of VII gave III. According to the absence of a melting point depression, thin-layer chromatography, and IR spectroscopy, this compound was identical to III obtained from II. Compound II was converted to I by heating with sulfur in the presence of iodine in o-dichlorobenzene.

It is known that the formation of 4-substituted compounds is also possible in addition to the formation of 2-substituted compounds during the thionation of diphenylamine derivatives [6]. In the case of the thionation of II, this isomer may be 1,2-dihydrothiazolo[5,4-c]phenothiazine-2-thione (Ia). The major product in the thionation of II was I; according to the absence of a melting point depression with an authentic sample, IR spectroscopy, and thin-layer chromatography, it was identical to I that we previously obtained in [2].

*See [1] for communication XXXII.

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 38-40, January, 1972. Original article submitted December 22, 1970.



Compound Ia, which was isolated from the reaction mass in small amounts, has different physical properties.

EXPERIMENTAL

5-Phenylamino-2,3-dihydrobenzothiazole-2-thione (II). A mixture of 9.2 g (0.065 mole) of 3-aminodiphenylamine, 1.6 g (0.05 mole) of ground stick sulfur, and 8 ml of carbon disulfide in a hermetically sealed steel tank was heated to 170-180° for 1 h and held at this temperature for 3 h. The heated reaction mass was treated with 50 ml of ~5% sodium hydroxide solution and filtered. The addition of dilute hydrochloric acid to the filtrate produced a precipitate. This material was separated and refluxed with 550 ml of 0.5 N ammonium hydroxide. The solution was filtered, and the filtrate was acidified with dilute hydrochloric acid. The precipitate was separated and washed with water. The dry product was refluxed with 400 ml of dichloroethane, and the mixture was filtered hot. The filtrate was cooled to give 6.4 g (50%) of II with mp 193-197° (from dichloroethane). Found: N 11.0; S 24.8%. $C_{13}H_{10}N_2S_2$. Calculated: N 10.8; S 24.8%. IR spectrum (in mineral oil): 1080 cm^{-1} (C = S), 825, 822, 800 cm^{-1}.

7-Phenylamino-2,3-dihydrobenzothiazole-2-thione (IIa). The substance that remained in the filtrate during the crystallization of II in the previous experiment was crystallized from aqueous acetone to give 1.2 g (10%) of IIa with mp 254-256°. Found: N 11.0; S 25.0%. $C_{13}H_{10}N_2S_2$. Calculated: N 10.8; S 24.8%. IR spectrum: 1087 cm^{-1} (C = S), 760, 745, 715 cm^{-1}.

5-Nitrobenzothiazole (IV). A 16-g (0.066 mole) sample of crystalline sodium sulfide was added to a solution of 10 g (0.04 mole) of 1-formylamino-2-bromo-5-nitrobenzene in 100 ml of dimethylformamide (the mixture warmed up in the process), and the solution was heated at 60-65° for 1 h. It was then cooled and poured into water, and the precipitate was removed by filtration, dried, and chromatographed with a column filled with aluminum oxide. Chloroform eluted a substance with R_f 0.85 (Al_2O_3, chloroform) to give 5.2 g (72%) of IV with mp 164-164.5° (from alcohol) (mp 159-160° [4]). Found: N 15.6; S 17.7%. $C_7H_4N_2O_2S$. Calculated: N 15.6; S 17.8%.

5-Aminobenzothiazole (V). A 14.6-g (0.08 mole) sample of IV was added in portions to a solution of 60 g (0.27 mole) of stannous chloride in 80 ml of concentrated hydrochloric acid, a small amount of zinc powder was added, and after 30 min, the mixture was heated on a boiling-water bath for 30 min. The precipitated double salt was crystallized from alcohol. The salt was dissolved in warm water, and a solution of sodium hydroxide was added until the mixture was alkaline. It was the extracted with ether, and the extract was dried with magnesium sulfate. The ether was removed by distillation to give 8.5 g (70%) of V with mp 58-60° (from alcohol). The hydrochloride had mp 209-212° (dec., from isopropyl alcohol). Found: N 15.1; S 17.1%. $C_7H_5N_2S \cdot HCl$. Calculated: N 15.1; S 17.2%.

5-Acetamido (VI). A 7-ml (0.1 mole) sample of acetyl chloride was added carefully to a solution of 5 g (0.045 mole) of V in 60 ml of hot benzene, and the mixture was refluxed on a water bath for 3 h and cooled. The benzene was decanted, and the residue was triturated with cold water, filtered, and washed with cold water to give 4.1 g (64%) of VI with mp 196-196.5° (from 50% alcohol). Found: N 14.7; S 16.5%. $C_9H_8N_2OS$. Calculated: N 14.6; S 16.7%.

5-Phenylaminobenzothiazole (III). A total of 2.8 ml of 30% hydrogen peroxide was added with stirring at 35-40° to a solution of 5.2 g (0.02 mole) of II in 60 ml of 2% sodium hydroxide, and the mixture was heated at 35-40° for 1 h. The precipitate that formed on cooling was removed by filtration and dissolved in hot water. The solution was acidified with dilute hydrochloric acid, and the mixture was refluxed for 30 min and cooled to give 2.2 g (50%) of III with mp 142-144° (from alcohol) and R_f 0.78 (Al_2O_3, chloroform). Found: N 12.5; S 14.4%. $C_{13}H_{10}N_2S$. Calculated: N 12.4; S 14.1%. IR spectrum: 3320, 1600, 870 cm^{-1}.

B) A mixture of 2.9 g (0.015 mole) of VI, 5 ml (0.03 mole) of bromobenzene, 1.1 g (0.008 mole) of anhydrous potassium carbonate, and a small amount of copper powder was heated for 20 h at 180-190°. The bromobenzene was removed by steam distillation, and the residue was washed with water and dissolved in 10 ml of alcohol. The solution was treated with 8 ml of concentrated HCl, and the mixture was refluxed for 4h. A large portion of the alcohol was removed by distillation, and the residue was diluted with water. The compound was separated, washed with alcohol, dried, and chromatographed in chloroform on aluminum oxide to give 1.5 g (45%) of III with mp 141-143° (from alcohol) and R_f 0.78 (Al_2O_3, chloroform). Found: N 12.7; S 14.2%. $C_{13}H_{10}N_2S$. Calculated: N 12.4; S 14.1%. IR spectrum: 3320; 1600, 870 cm^{-1}.

2,3-Dihydrothiazolo[4,5-b]phenothiazine-2-thione (I). A mixture of 15.5 g (0.06 mole) of II, 5.1 g (0.16 mole) of ground stick sulfur, and 50 ml of o-dichlorobenzene was heated on an oil bath until all of the solids dissolved, and 0.6 g of iodine was added to the solution at 130-140°. The mixture was heated in such a way as to achieve moderate hydrogen sulfide evolution (for 2 h at 130-140°, for 2 h at 150-160°, and for 4 h at 180-190°). The mixture was cooled, and the precipitated compound was removed by filtration and refluxed with 200 ml of toluene. The mixture was filtered hot to give 11.5 g (60%) of I with mp 275-280° (from aniline) and R_f 0.53 (Al_2O_3, alcohol). Found: N 10.0; S 33.6%. $C_{13}H_8N_2S_3$. Calculated: N 9.7; S 33.6%. IR spectrum: 865 cm^{-1} (the para H atoms in a tetrasubstituted benzene ring).

1,2-Dihydrothiazolo[5,4-c]phenothiazine-2-thione (Ia). The aniline filtrate from the recrystallization of I was vacuum evaporated, and the residue was triturated with benzene and filtered to give 1.4 g (9%) of Ia with mp 285-290° (dec., from o-dichlorobenzene) and R_f 0.53 (Al_2O_3, alcohol). Found: N 9.4; S 33.5%. $C_{13}H_8N_2S_3$. Calculated: N 9.7; S 33.4%. IR spectrum: 802 cm^{-1} (the ortho H atoms in a tetrasubstituted benzene ring).

LITERATURE CITED

1. A. N. Gritsenko, Z. I. Ermakova, and S. V. Zhuravlev, Khim. Geterotsikl. Soedin., 770 (1971).
2. V. V. Shavyrina and S. V. Zhuravlev, Khim. Geterotsikl. Soedin., 42 (1971).
3. J. Teppema and Z. B. Sebrell, J. Am. Chem. Soc., 49, 1748 (1927).
4. I. Spieler and B. Prijs, Helv. Chim. Acta, 33, 1429 (1950).
5. W. F. Russell, US Patent No. 2,509,453 (1950); Chem. Abstr., 44, 7885 (1950).
6. J. P. Bourquin, G. Schwarb, G. Camboni, R. Fischer, Z. Ruesch, S. Guldimann, V. Theus, E. Schenker, and J. Renz, Helv. Chim. Acta, 41, 1061 (1958).