SYNTHESES IN THE PHENOTHIAZINE SERIES

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

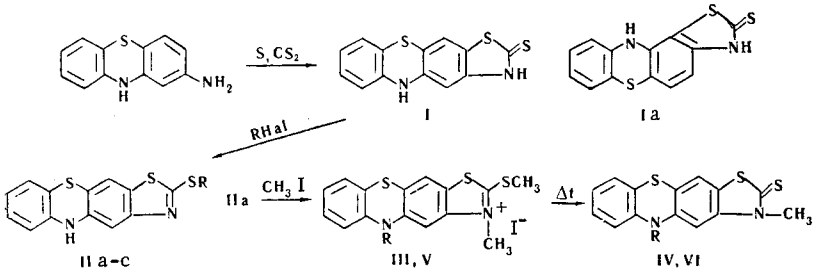
V. V. Shavyrina and S. V. Zhuravlev

UDC 547.86'789.1

2,3-Dihydrothiazolo[4,5-b]phenothiazine-2-thione was obtained by the reaction of 2-aminophenothiazine with sulfur and carbon disulfide, and the action of alkyl halides on it was studied.

A heterocyclic polynuclear condensed system including phenothiazine and thiazole rings may be of interest since both of its fragments are partially responsible for the manifestation of physiological activity. This sort of system is also of interest from a chemical point of view since it contains a number of reaction centers.

We have synthesized 2,3-dihydrothiazolo[4,5-b]phenothiazine-2-thione (I) from 2-aminophenothiazine, obtained according to the method in [2, 3]. One of the methods for including the thiazole ring in an aromatic series, viz., the action of sulfur and carbon disulfide on aromatic amines [4, 5], was used. In this reaction the formation of the isomeric thiazolophenothiazine (Ia) is possible, but only one substance was isolated from the reaction mixture. We gave preference to structure I since it is well known that substitution reactions in the phenothiazine series most often proceed at the 3 position and only in very rare cases at the 1 position. This was confirmed by reproduction of the indicated 4-ring system with Dreiding models: structure I is completely freely constructed; closing of the structure corresponding to formula Ia entails great strain. We subsequently proposed to confirm structure I by alternative synthesis.



II a R=CH_3, b R=C_2H_5, c R=$CH_2CH_2CH_2Cl$; III, IV R=H; V, VI R=CH_3

The thiazole ring in I turned out to be more stable to alkaline cleavage than that in benzothiazole. We could not cleave I to the corresponding aminothiol, as occurs in the case of 2-mercaptobenzothiazole [6], by the action of concentrated alkali at high temperatures.

Like 2-mercaptobenzothiazole, I can exist in two tautomeric forms, viz., the thione and thiol. According to the IR spectra (suspensions in mineral oil), in the solid state I has the thione structure since the spectrum does not contain an absorption band for the SH group (2550-2600 cm^{-1}) but does contain an absorption band for the C=S group (1050 cm^{-1}).

S-Alkyl derivatives of I (IIa-c) were obtained by alkylation of I in aqueous alkali with equimolecular amounts of alkyl halides. The UV spectrum (in alcohol) of 2-methylmercaptothiazolo[4,5-b]phenothiazine (IIa) has absorption maxima at 222 nm (log ε 4.30), 259 nm (log ε 4.57), and 358 nm (log ε 4.85), while the

*See [1] for communication XXVII.

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 42-44, January, 1971. Original article submitted April 28, 1969.

absorption maxima in the UV spectra of I are found at 262 nm (log ε 4.60), 293 nm (log ε 4.30), and 371 nm (log ε 4.30). This confirms the S-alkyl structure of II.

The water-insoluble methiodide of IIa (III), which on crystallization from toluene or dimethylformamide was readily cleaved with isomerization to 3-methyl-2,3-dihydrothiazolo[4,5-b]phenothiazine-2-thione (IV), was obtained by the action of methyl iodide on IIa. The UV spectrum of IV has absorption maxima at 262 nm (log ε 4.27) and 375 nm (log ε 3.90). The curves of the UV spectra of I and IV are similar, which confirms the thione structure of IV. Methylation of the nitrogen of the phenothiazine ring to form 2-methylmercapto-5-methylthiazolo[4,5-b]phenothiazine (V) occurs simultaneously during the action of methyl iodide on IIa at 145-160°; on heating, V is converted to 3,5-dimethyl-2,3-dihydrothiazolo[4,5-b]phenothiazine-2-thione (VI).

EXPERIMENTAL

2,3-Dihydrothiazolo[4,5-b]phenothiazine-2-thione (I). A mixture of 4.3 g (0.02 mole) of 2-aminophenothiazine, 0.7 g (0.022 g-atom) of pulverized stick sulfur, and 3 ml of carbon disulfide in a hermetically sealed, steel cylinder was heated on an oil bath to 200° for 1 h and held at this temperature for 2 h. The reaction mass was treated, with heating, with 5% NaOH, filtered, and the filtrate was acidified with dilute hydrochloric acid. The resulting precipitate was filtered and washed with water to give 4 g (70%) of yellow crystals with mp 278-283° (from aniline) which were insoluble in most organic solvents and had R_f 0.53 (Al_2O_3, alcohol). Found %: N 9.9; S 33.4. $C_{13}H_8N_2S_3$. Calc. %: N 9.7; S 33.4.

Methiodide of I. A solution of 1 g of I in 10 ml of tetrahydrofuran was allowed to stand for 2 days with 5 ml of methyl iodide. The resulting reddish-orange precipitate was filtered and washed with tetrahydrofuran and alcohol to give 0.3 g (20%) of a product with mp 187-192° (dec.). Found %: I 29.4; N 6.6; S 22.1. $C_{14}H_{11}IN_2S_3$. Calc. %: I 29.5; N 6.5; S 22.4.

2-Methylmercaptothiazolo[4,5-b]phenothiazine (IIa). A solution of 3.5 g (0.025 mole) of methyl iodide in 20 ml of alcohol was added in the course of 1 h with stirring at 45-50° to a solution of 5.7 g (0.02 mole) of I in 150 ml of 0.7% sodium hydroxide. The mixture was stirred for another 15-20 min, and the resulting precipitate was filtered and washed with water to give 3.6 g (60%) of a product with mp 228-230° (from toluene) and R_f 0.5 [Al_2O_3, benzene-chloroform (1:1)]. Found %: N 9.5; S 32.2. $C_{14}H_{10}N_2S_3$. Calc. %: N 9.3; S 31.8. IR spectrum: 1320 cm^{-1} (S–CH_3).

2-Ethylmercaptothiazolo[4,5-b]phenothiazine (IIb). Like IIa, this was obtained in 63% yield by the reaction of I with ethyl bromide and had mp 216-221° (from chloroform). Found %: N 9.1; S 30.6. $C_{15}H_{12}N_2S_3$. Calc. %: N 8.8; S 30.4.

2-(3-Chloropropyl)mercaptothiazolo[4,5-b]phenothiazine (IIc). Like IIa, this was obtained in 72% yield by the reaction of I with 1-chloro-3-bromopropane and had mp 145-146° (from benzene). Found %: Cl 9.4; N 7.8. $C_{16}H_{13}ClN_2S_3$. Calc. %: Cl 9.7; N 7.7.

2-Methylmercaptothiazolo[4,5-b]phenothiazine Methiodide (III). A solution of 1 g of IIa in 40 ml of dioxane was allowed to stand for 3 days with 10 ml of methyl iodide. The bright-orange precipitate was filtered and washed thoroughly with dioxane and alcohol to give 0.8 g (57%) of a product with mp 183-188° (dec.). Found %: I 28.3; N 6.3; S 21.6. $C_{15}H_{13}IN_2S_3$. Calc. %: I 28.5; N 6.3; S 21.6.

3-Methyl-2,3-dihydrothiazolo[4,5-b]phenothiazine-2-thione (IV). III (0.5 g) was dissolved with heating in 10 ml of dimethylformamide, and the solution was refluxed for 10 min, cooled, and poured into water. The resulting precipitate was filtered to give 0.4 g (80%) of a product with mp 245-253° (not sharp, from toluene) and R_f 0.28 (Al_2O_3, benzene-chloroform). Found %: N 9.3; S 31.8. $C_{14}H_{10}N_2S_3$. Calc. %: N 9.3; S 31.8.

2-Methylmercapto-5-methylthiazolo[4,5-b]phenothiazine (V). A mixture of 1 g of IIa, 8 ml of methyl iodide, and 10 ml of isopropyl alcohol was heated for 6 h in a sealed ampule at 145-160°. The red-orange substance was filtered to give 1.3 g (86%) of a product with mp 189-193° (from dimethylformamide, rapid heating). Found %: N 6.4; S 21.1. $C_{16}H_{15}IN_2S_3$. Calc. %: N 6.1; S 21.0.

3,5-Dimethyl-2,3-dihydrothiazolo[4,5-b]phenothiazine-2-thione (VI). Like IV, this was obtained in 78% yield from V and had mp 259-264° (from toluene). Found %: N 9.2; S 30.3. $C_{16}H_{15}N_2S_3$. Calc. %: N 8.8; S 30.4.

LITERATURE CITED

1. A. N. Gritsenko, Z. I. Ermakova, and S. V. Zhuravlev, Khim. Geterotsikl. Soedin., 1337 (1970).
2. S. V. Zhuravlev and V. A. Skorodumov, Zh. Obshch. Khim., 31, 3129 (1961).
3. A. N. Gritsenko and S. V. Zhuravlev, Zh. Obshch. Khim., 33, 3697 (1963).
4. T. Kimijima and S. Miyama, J. Soc. Chem. Ind. Japan, 45, 957 (1942); Chem. Abstr., 43, 2021 (1949).
5. M. Vodenicharov, T. Dyakovska, and N. Marinkov, Khim. Ind. (Sofia), 29, 24 (1957); Chem. Abstr., 53, 339 (1959).
6. A. I. Kiprianov, I. K. Ushenko, and A. L. Gershun, Zh. Obshch. Khim., 14, 865 (1944).