SYNTHESES IN THE PHENOTHIAZINE SERIES

XXXVII.* SOME PROPERTIES OF QUATERNARY SALTS OF 2-METHYLMERCAPTOTHIAZOLO[4,5-b]PHENOTHIAZINE

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Some nucleophilic substitution reactions of 2-methylmercapto-3-methylthiazolo[4,5-b]phenothiazinium methosulfate were studied. Cleavage of the latter with alcoholic alkali gives bis-(2-2-methylamino-3-phenothiazinyl) disulfide; cleavage and subsequent alkylation gives new disubstituted phenothiazines.

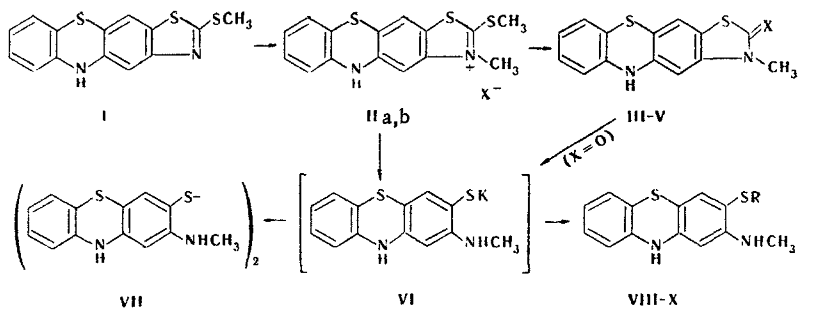
Continuing our investigation of the chemical properties of thiazolo[4,5-b]phenothiazine derivatives [2, 3], we have studied some reactions of quaternary salts of 2-methylmercaptothiazolo[4,5-b]phenothiazine (I).

It is known that quaternary salts of 2-alkylmercaptobenzothiazole have increased reactivity as compared with benzothiazole itself. Owing to the considerable positive charge on the carbon atom bonded to the alkylmercapto group, benzothiazolium salts readily undergo nucleophilic substitution reactions at this atom [4-6].

Inasmuch as the quaternary salts of I are similar in structure to the quaternary salts of 2-alkylmercaptobenzothiazole, it might have been expected that they would also prove to have similar chemical properties.

Heating of I with dimethyl sulfate in dioxane gave 2-methylmercapto-3-methylthiazolo[4,5-b]phenothiazinium methosulfate (IIb), which, in contrast to methiodide IIa [2], is more soluble in hot water and in hot alcohol. We therefore carried out our study of the reactions of the quaternary salts primarily with methosulfate IIb.

3-Methyl-2,3-dihydrothiazolo[4,5-b]phenothiazin-2-one (III) is formed by refluxing IIb with water or by the action of a concentrated alkali solution on an aqueous solution of IIa or IIb at room temperature. 3-Methyl-2,3-dihydrothiazolo[4,5-b]phenothiazin-2-one (IV), which was previously obtained by isomerization of IIa, was synthesized by the action of sodium sulfate solution on an aqueous solution of IIb. The



IIa X = I, b X = $CH_3SO_4^-$; III X = O; IV X = S; V X = NCH_3; VIII R = CH_3; IX R = C_2H_5; X R = C_4H_9

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*See [1] for communication XXXVI.

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reaction of an aqueous solution of IIb with methylamine gave 2-methylimino-3-methyl-2,3-dihydrothiazolo-[4,5]phenothiazine (V).

When IIb is refluxed with an alcohol solution of potassium hydroxide the thiazole ring is opened, but bis(2-methylamino-3-phenothiazinyl) disulfide (VII) was isolated from the reaction mixture instead of the expected 2-methylamino-3-mercaptophenothiazine (VI) after acidification. Similar results were obtained in the reaction of an alcohol solution of alkali with IIa and III. If the alkaline cleavage of these substances is carried out in a stream of nitrogen, the initially formed VI can be alkylated with alkyl halides without isolation from the reaction medium. This method was used to obtain 2-methylamino-3-alkylmercaptophenothiazines (VIII-X).

EXPERIMENTAL

2-Methylmercapto-3-methylthiazolo[4,5-b]phenothiazinium Methosulfate (IIb). A 5-ml (0.05 mole) sample of dimethylsulfate was added to a suspension of 9 g (0.03 mole) of I in 40 ml of dioxane, and the mixture was heated on a boiling-water bath for 3 h. It was then cooled, and the precipitate was removed by filtration and washed with alcohol and ether to give 10.6 g (83%) of IIb. The orange powder was insoluble in most organic solvents but soluble in hot water; it did not have a characteristic melting point after recrystallization from alcohol or water. Found %: N 7.0; S 30.1. $C_{16}H_{16}N_2O_4S_4$. Calculated %: N 6.5; S 29.9.

3-Methyl-2,3-dihydrothiazolo[4,5-b]phenothiazin-2-one (III). A) A total of 5 ml of a 30% solution of sodium hydroxide was added at room temperature to a solution of 6.3 g (0.015 mole) of IIb in 300 ml of water. After 15-20 min, the grayish precipitate was removed by filtration, washed with water, and dried to give 3.1 g (72%) of III with mp 266-269° (dec., from dichloroethane) and R_f 0.57 [Al_2O_3, benzene–methanol (10:2)]. IR spectrum: 1706 (CO), 3335 cm^{-1} (NH). Found %: N 9.9; S 22.3. $C_{14}H_{10}N_2OS_2$. Calculated %: N 9.8; S 22.4.

B) A solution of 0.4 g (0.001 mole) of IIb in 50 ml of water was refluxed for 6 h, and the resulting grayish precipitate was removed by filtration and dried to give 0.2 g (71%) of product.

The identical character of the compounds obtained by these methods was confirmed by the absence of a melting-point depression for a mixture of the two products, by thin-layer chromatography (TLC), and by IR spectroscopy.

3-Methyl-2,3-dihydrothiazolo[4,5-b]phenothiazin-2-thione (IV). A solution of 0.7 g (0.003 mole) of sodium sulfate in 2 ml of water was added with stirring at 50° to a solution of 1 g (0.0023 mole) of IIb in 50 ml of water, and the mixture was then stirred at 50° for 1 h. It was then cooled, and the precipitate was separated and washed with water to give 0.4 g (60%) of a product with mp 252-255° (dec., from toluene) and R_f 0.35 [Al_2O_3, chloroform–benzene (1:1)]. Found %: N 9.1; S 31.4. $C_{14}H_{10}N_2S_3$. Calculated %: N 9.3; S 31.8.

2-Methylimino-3-methyl-2,3-dihydrothiazolo[4,5-b]phenothiazine (V). A 2.5-ml (0.02 mole) sample of a 25% aqueous solution of methylamine was added dropwise with stirring to a solution of 1.5 g (0.0035 mole) of IIb in 100 ml of water, after which the mixture was stirred for 30 min. The precipitate was separated, dried, and chromatographed in chloroform with a column filled with aluminum oxide. Elution with chloroform gave 0.3 g (30%) of III (R_f 0.57, Al_2O_3, chloroform) and 0.4 g (40%) of V (R_f 0.52) with mp 225-229° (from benzene). IR spectrum: 1630 cm^{-1} (C=N). Found %: N 14.0; S 21.9. $C_{15}H_{13}N_3S_2$. Calculated %: N 14.0; S 21.4.

Bis(2-methylamino-3-phenothiazinyl) Disulfide (VII). A suspension of 2.1 g (0.005 mole) of IIb in a solution of 5 g (0.09 mole) of potassium hydroxide in 90 ml of alcohol was refluxed for 1 h. It was then cooled, and diluted with water. The aqueous mixture was acidified with dilute hydrochloric acid, and the precipitate was separated and washed with alcohol to give 1 g (77%) of VII with mp 228-230° (dec., from aniline). IR spectrum: 3405, 3340 cm^{-1} (NH). Found %: N 10.7; S 24.3; M 527 (by the Rast method). $C_{26}H_{22}N_4S_4$. Calculated %: N 10.8; S 24.7; M 519.

2-Methylamino-3-methylmercaptophenothiazine (VIII). A mixture of 1 g (0.0023 mole) of IIb and 2.5 g (0.045 mole) of potassium hydroxide in 25 ml of alcohol was refluxed for 2 h in a stream of nitrogen on an oil bath. The bath temperature was lowered to 35-40°, and 15 ml of hot water was added to the reaction mixture. A solution of 0.3 ml (0.005 mole) of methyl iodide in 2 ml of alcohol was added dropwise, and the mixture was stirred at 40-45° (bath temperature) for 1 h. It was then filtered, and the filtrate was diluted with water until it became turbid. The precipitate was separated and washed with water to give 0.5 g (78%) of VIII. After chromatography on aluminum oxide in a benzene–chloroform system (2:1) and recrystallization from methanol the product had mp 149-151°. IR spectrum: 3398, 3325 cm^{-1} (NH). Found %: N 10.3; S 23.1. $C_{14}H_{14}N_2S_2$. Calculated %: N 10.2; S 23.4.

2-Methylamino-3-ethylmercaptophenothiazine (IX). This compound, with mp 144-146° (from aqueous methanol), was obtained in 74% yield from IIb and ethyl bromide by the method used to prepare VIII. Found %: N 9.4; S 21.9. $C_{15}H_{16}N_2S_2$. Calculated %: N 9.7; S 22.2.

2-Methylamino-3-butylmercaptophenothiazine (X). A mixture of 1.2 g (0.04 mole) of III and 5 g (0.09 mole) of potassium hydroxide in 60 ml of alcohol was refluxed for 2 h in a stream of nitrogen, after which 30 ml of water and a solution of 0.6 ml (0.005 mole) of butyl iodide in 7 ml of alcohol were added successively, and the mixture was heated at 60-70° for 1.5 h. The hot solution was filtered, and a small amount of water was added to the filtrate. Cooling of the filtrate gave 1 g (83%) of X with mp 153-154° (from alcohol). Found %: N 9.0; S 20.6. $C_{17}H_{20}N_2S_2$. Calculated %: N 8.8; S 20.3.

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