SYNTHESIS IN THE PHENOTHIAZINE SERIES

XXV*. 1-BROMOPHENOTHIAZINE AND 1,3-DIBROMOPHENOTHIAZINE

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1-Bromophenothiazine (I) and 1,3-dibromophenothiazine (II) have been synthesized by the intramolecular rearrangement of 2-acetylaminophenyl 2-bromo-6-nitrophenyl sulfide (III) and 2-acetylaminophenyl 2,4-dibromo-6-nitrophenyl sulfide (VIII) and the subsequent cyclization of resulting N-acetyl-2-bromo-2'-mercapto-6-nitrodiphenylamine (IV) and N-acetyl-2,4-dibromo-2'-mercapto-2-nitrodiphenylamine (IX), followed by saponification of the acetyl groups of the latter, respectively.

10-Aminoalkyl and 10-aminoacyl derivatives of 2-substituted phenothiazines and, especially, 2-chlorophenothiazine have found wide use in medicinal practice as psychotropic drugs [1]. Some representatives of this series of compounds have proved to be effective agents for the treatment of cardiovascular diseases [2].

In the search for new pharmacologically active preparations with the action mentioned above, we considered it desirable to synthesize derivatives of phenothiazine starting from 1-bromophenothiazine (I) and 1,3-dibromophenothiazine (II), since only 2-bromo- [3], 3-bromo- [4] and 2,4-dibromophenothiazines [5] have been described in the literature, the fact that I and II have not been described being apparently due to their poor accessibility.

In one of our papers [6] we have shown that when 2-acetylaminophenyl 2-bromo-6-nitrophenyl sulfide (III) is heated in nitrobenzene in the presence of copper bronze, a Smiles rearrangement takes place with cyclization, the III being converted into N-acetyl-2-bromo-2'-mercapto-6-nitrodiphenylamine (IV), as an intermediate, which splits out hydrobromic acid and forms 10-acetyl-1-nitrophenothiazine (V) with a yield of about 50%. A further study of this reaction has shown that the cyclization of IV takes place ambiguously. In addition to forming V, the substituted diphenylamine IV splits out a molecule of nitrous acid under the same conditions and forms 10-acetyl-1-bromophenothiazine (VI) in a yield of about 40%. The alkaline saponification of V gave the nitrophenothiazine (XII) and VI gave 1. The reaction products were separated on the basis of the different solubilities of the acetyl derivatives in ethanol (VI is considerably more soluble than V). The purity of the substances was checked by thin-layer chromatography on alumina.

A change in the temperature conditions of the reaction and the replacement of the nitrobenzene by other solvents did not lead to the predominant formation of either V or VI. However, when the reaction was carried out in ethanol—acetone and caustic soda was used instead of potassium carbonate, as is the case in the synthesis of 1-chlorophenothiazine [7], compound I was obtained with a yield of 87%.

By the reaction of o-aminothiophenol and 2,3,5-tribromonitrobenzene [8] with subsequent acetylation of the resulting 2-aminophenyl 2,4-dibromo-6-nitrophenyl sulfide (VIIb) was obtained 2-acetylaminophenyl 2,4-dibromo-6-nitrophenyl sulfide (VIII) which was converted in 65% yield by reactions similar to those for the case of III into 10-acetyl-1,3-dibromophenothiazine (X), the saponification of which gave 1,3-dibro-

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*For Communication XXIV see [6].

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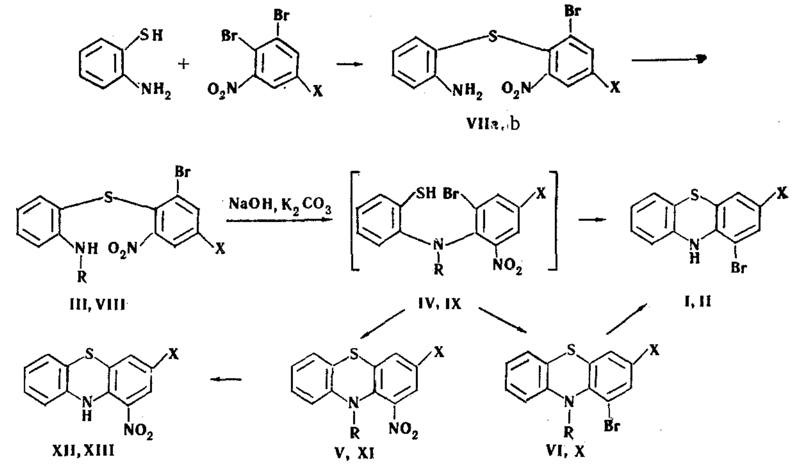
mophenothiazine (II). We explain the increased yield of X as compared with VI by the presence of two bromine atoms in the same aromatic nucleus (VIII) in the ortho and para positions with respect to the sulfur atom. This, in our opinion, weakens the C—S bond, which facilitates both the rearrangement and the cyclization.

By analogy with V [6], we proposed to isolate a substance which would correspond to the structure of 10-acetyl-3-bromo-1-nitrophenothiazine (XI), the saponification of which would lead to 3-bromo-1-nitrophenothiazine (XIII). However, our attempts have not yet been successful.



I X=H; II X=Br; III X=H, R=$COCH_3$; IV X=H, R=$COCH_3$; V X=H, R=$COCH_3$; VI X=H, R=$COCH_3$; VII a X=H, b X=Br; VIII X=Br, R=$COCH_3$; IX X=Br, R=$COCH_3$; X X=Br, R=$COCH_3$; XI R=$COCH_3$; XII X=H; XI, XIII X=Br not isolated.

The structures of 1-bromophenothiazine (I) and 1,3-dibromophenothiazine (II) were confirmed by their elementary analyses and infrared spectra. The IR spectrum of I had absorption bands in the 769 and 712 cm^{-1} regions characteristic for three adjacent hydrogen atoms in an aromatic ring [9] and an absorption band at 753 cm^{-1} characteristic for the four hydrogen atoms of the other aromatic ring. An absorption band is also observed in the 3345 cm^{-1} region which is characteristic for the N—H group. The IR spectrum of II did not have the absorption band 769 cm^{-1} characteristic for I and the absorption at 712 cm^{-1} was weaker than in I; furthermore, the absorption band at 3345 cm^{-1} was shifted to 3375 cm^{-1}, which is apparently due to the conjugation of the electron pair of the nitrogen of the N—H group with the bromine present in the para position*.

EXPERIMENTAL

10-Acetyl-1-nitrophenothiazine (V) and 10-Acetyl-1-bromophenothiazine (VI). A mixture of 14.68 g (0.04 mole) of 2-acetylaminophenyl 2-bromo-6-nitrophenyl sulfide (III) [6], 5.6 g (0.04 mole) of powdered calcined potassium carbonate, and 0.8 g of copper bronze in 140 ml of nitrobenzene was heated with stirring in an oil bath at 160-165°C for 5 hr and then the bath temperature was raised to 175-185°C and heating was continued for another 5 hr. The cooled reaction mixture was filtered from inorganic solids, the nitrobenzene was distilled off from the filtrate in the vacuum of a water pump, and the viscous oily residue was triturated in ethanol. After recrystallization from ethanol 5.0 g (45%) of substance V with mp 177-178°C was obtained. Found, %: N 9.54, 9.78; S 11.08, 10.95. Calculated for $C_{14}H_{10}N_2O_3S$, %: N 9.78; S 11.20.

The bulk of the ethanol was distilled off from the combined alcoholic filtrate obtained after the isolation and crystallization of V and the residue was diluted with water. This yielded 5.8 g (45%) of substance VI, which, after recrystallization from aqueous acetone (1 :1) and then from aqueous ethanol, had mp 111-112°C. Found, %: S 10.07, 9.91; Br 24.59, 24.66. Calculated for $C_{14}H_{10}BrNOS$, %: S 10.01; Br 24.96.

1-Bromophenothiazine (I). a. With stirring 0.44 g (0.11 mole) of caustic soda in 5 ml of anhydrous ethanol was added to a boiling solution of 3.2 g (0.01 mole) of 10-acetyl-1-bromophenothiazine (VI) in 30 ml

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*The IR spectra were taken by V. S. Troitskaya on a UR-10 spectrophotometer in paraffin oil.

of dry acetone. The inorganic precipitate was filtered off, and the acetone was distilled off from the filtrate. The precipitate that deposited on cooling [2.2 g (82%)] was filtered off and crystallized from ethanol. This gave a substance with mp 109-110°C. Found, %: Br 28.70, 28.65. Calculated for $C_{12}H_8BrNS$, %: Br 28.73.

b. With stirring, 0.4 g (0.01 mole) of caustic soda in 10 ml of anhydrous ethanol was added to a boiling solution of 3.76 g (0.01 mole) of 2-acetylaminophenyl 2-bromo-6-nitrophenyl sulfide (III) in 40 ml of dry acetone, and the reaction mixture was boiled for 30 min. Then the same amount of alcoholic alkali was added and boiling was continued for another 30 min. The reaction mixture was cooled, the inorganic precipitate was filtered off, and the acetone was distilled off from the filtrate. On cooling, the residual ethanolic solutions deposited 2.41 g (87%) of a substance with mp 106-107°C which, after crystallization from ethanol, melted at 109-110°C. A mixture with a sample of the substance obtained by variant (a) showed no depression of the melting point. White crystalline substance, becoming pink under the action of light. Found, %: N 5.45, 5.35; S 11.70, 11.75; Br 28.57, 28.59. Calculated for $C_{12}H_8BrNS$, %: N 5.04; S 11.53; Br 28.73.

2-Aminophenyl 2,4-dibromo-6-nitrophenyl Sulfide (VIIb). With stirring, a solution of 3.0 g (0.075 mole) of caustic soda in 15 ml of water was added to a boiling solution containing 18 g (0.05 mole) of 2,3,5-tribromonitrobenzene [8] and 7.0 g (0.056 mole) of o-aminothiophenol in 150 ml of ethanol, and the reaction mixture was boiled for 30 min. The ethanol was distilled off, and, after cooling, the crystalline precipitate with mp 84-85°C was recrystallized from aqueous ethanol. This gave a substance having mp 97-98°C. Found, %: S 7.92, 7.74; Br 39.80, 39.62. Calculated for $C_{12}H_8Br_2N_2O_2S$, %: S 7.91; Br 39.45.

2-Acetylaminophenyl-2,4-dibromo-6-nitrophenyl Sulfide (VIII). The ethanol was distilled off from a reaction mixture containing the same amounts of starting materials as given in the preceding experiment on the preparation of VIIb. The residue was dissolved in a mixture of 50 ml of ethyl acetate and 50 ml of toluene, and the inorganic precipitate was filtered off. To the filtrate at room temperature was added 30 ml of acetic anhydride, whereupon the temperature of the reaction mixture rose; it was then stirred for an hour. As it cooled, the reaction mixture deposited a precipitate, and on the following day this was filtered off and washed with toluene. The product consisted of VIII (13.66 g; 60.6%), and after recrystallization from ethanol it had mp 170-171°C. Found, %: Br 35.61, 35.56; N 6.40, 6.21. Calculated for $C_{14}H_{10}Br_2N_2O_2S$, %: Br 35.83; N 6.28.

10-Acetyl-1,3-dibromophenothiazine (X). This was synthesized similarly to VI from 4.4 g (0.01 mole) of VIII, 1.4 g (0.01 mole) of potassium acetate, and 0.2 g of copper bronze in 40 ml of nitrobenzene. This gave 2.9 g (64%) of a substance with mp 137-138°C forming, after recrystallization from ethanol, yellowish crystals darkening in the air with mp 144-145°C. Found, %: Br 39.69, 39.54; S 8.02, 8.04. Calculated for $C_{14}H_9Br_2NOS$, %: Br 40.04; S 8.02.

1,3-Dibromophenothiazine (II) (obtained similarly to I) a. A mixture of 1.19 g (0.003 mole) of 10-acetyl-1,3-dibromophenothiazine (X) in 20 ml of acetone and 0.16 g (0.004 mole) of an ethanolic solution of caustic soda gave 1.0 g (93%) of a substance which, after crystallization from ethanol, melted at 130-131°C. Found, %: Br 44.58, 44.65. Calculated for $C_{12}H_7Br_2NS$, %: Br 44.81.

b. A mixture of 4.4 g (0.01 mole) of 2-acetylaminophenyl 2,4-dibromo-6-nitrophenyl sulfide (VIII) in 80 ml of dry acetone and an ethanolic solution of 0.8 g (0.02 mole) of caustic soda gave 3.0 g (83%) of a substance with mp 128-129°C. After recrystallization from ethanol, yellow crystals darkening under the action of light and air with mp 130-131°C were obtained. A mixture with the sample obtained by variant (a) showed no depression of the melting point. Found, %: Br 44.95, 44.87; S 9.18, 9.04. Calculated for $C_{12}H_7Br_2NS$, %: Br 44.81; S 8.96.

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