SYNTHESIS IN THE PHENOTHIAZINE SERIES

XXXV.* SOME TRANSFORMATIONS OF BROMOAMINOPHENOTHIAZINES

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UDC 547.869.2.07

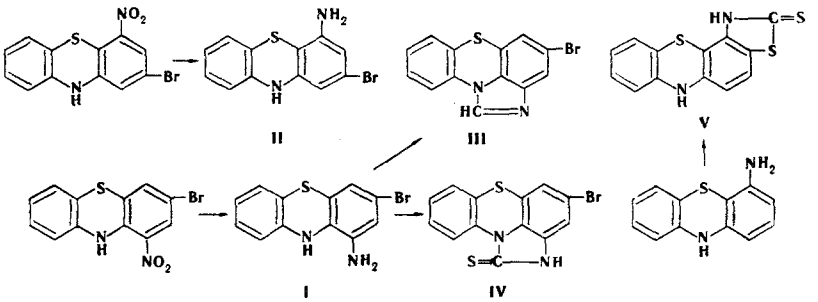
The corresponding amines were obtained by reduction of 1-nitro-3-bromophenothiazine and 2-bromo-4-nitrophenothiazine. 1-Amino-3-bromophenothiazine reacts with formic acid to give 4-bromoimidazo[4,5,1-k,*l*]phenothiazine and with carbon disulfide to give 4-bromo-1,2-dihydroimidazo[4,5,1-k,*l*]phenothiazine-1-thione. 4-Aminophenothiazine reacts with sulfur and carbon disulfide to give 2,3-dihydrothiazolo[5,4-c]phenothiazine-2-thione.

Within our plan to search for biologically active substances, 1-nitro-3-bromo- and 2-bromo-4-nitrophenothiazine [2] were reduced with hydrazine hydrate in the presence of a Raney nickel catalyst to 1-amino-3-bromophenothiazine (I) and 2-bromo-4-aminophenothiazine (II). In addition to I, 1-aminophenothiazine was also isolated from the reduction of 1-nitro-3-bromophenothiazine as a result of reductive dehalogenation.

Compound I, like 1-aminophenothiazine, undergoes reactions characteristic for o-arylenediamines. Heating of I with formic acid leads to 4-bromoimidazo[4,5,1-k,*l*]phenothiazine (III). Its IR and UV spectra differ little from those of unsubstituted imidazophenothiazine [3].

Compound I reacts with carbon disulfide in alcoholic potassium hydroxide solution to give 4-bromo-1,2-dihydroimidazo[4,5,1-k,*l*]phenothiazine-1-thione (IV).

The IR spectrum of IV in chloroform contains a band at 3425 cm^{-1}, which is characteristic for the N–H group, and a band at 1055 cm^{-1}, which is characteristic for the C=S group, while bands characteristic for the S–H group (2500-2600 cm^{-1}) are absent. This indicates thione form IV.



Reaction of II with sulfur and carbon disulfide did not give 4-bromo-1,2-dihydrothiazolo[5,4-c]phenothiazine-2-thione, while 4-aminophenothiazine under similar conditions forms 2,3-dihydrothiazolo[5,4-c]-phenothiazine-2-thione (V), which is identical to the compound previously obtained by a different method [4]. The IR spectrum of V in mineral oil does not contain absorption bands characteristic for the S–H group but does contain a band at 1050 cm^{-1} (C=S). The comparative data show that the introduction of bromine into the benzene ring hinders cyclization of the thiazole ring.

*See [1] for communication XXXIV.

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 202-203, February, 1974. Original article submitted September 28, 1972.

EXPERIMENTAL

The IR and UV spectra were recorded with UR-10 and SF-4 spectrometers, respectively.

1-Amino-3-bromophenothiazine (I). A solution of 0.5 g (10 mmole) of hydrazine hydrate in 2 ml of alcohol was added dropwise to a warm solution of 0.81 g (2.5 mmole) of 1-nitro-3-bromophenothiazine in 20 ml of ethanol and 5 ml of tetrahydrofuran containing 1 g of Raney nickel catalyst. The solution was decolorized during the reduction. After the addition of hydrazine hydrate, the reaction mixture was stirred at 50° for 1 h, and the catalyst was removed by filtration. Water was added to the filtrate until it became turbid, and the mixture was allowed to stand at 5-7° for 10 h. The precipitated amine was removed by filtration to give 0.45 g (62%) of a crystalline substance with mp 126-127° (from aqueous alcohol) that darkened in air. Found, %: Br 27.1; N 9.7. $C_{12}H_9BrN_2S$. Calculated, %: Br 27.2; N 9.6.

2-Bromo-4-aminophenothiazine (II). A similar reaction with 0.8 g (2.5 mmole) of 2-bromo-4-nitrophenothiazine gave 0.5 g (70%) of II with mp 169-170° (from aqueous alcohol); the colorless crystalline substance darkened in air and was soluble in most organic solvents but insoluble in water. Found, %: Br 27.6; N 9.4. $C_{12}H_9BrN_2S$. Calculated, %: Br 27.2; N 9.6.

4-Bromoimidazo[4,5,1-k,*l*]phenothiazine (III). A mixture of 0.8 g (3 mmole) of I and 3 ml of 85% formic acid was refluxed for 5 h. The mixture was then poured into 5% sodium hydroxide solution, and the resulting precipitate was removed by filtration and washed with water to give 0.64 g (80%) of III with mp 217-218° (from toluene); the colorless crystalline product was soluble in alcohol but insoluble in ether. Found, %: Br 26.10; S 10.75. $C_{13}H_7BrN_2S$. Calculated, %: Br 26.36; S 10.55. UV spectrum (in alcohol), λ_{max}, nm (log ε): 232 (4.52), 334-336 (3.90).

4-Bromo-1,2-dihydroimidazo[4,5,1-k,*l*]phenothiazine-1-thione (IV). A 0.6 g (2 mmole) sample of I was dissolved in 10 ml of alcohol, and 0.2 g (2.1 mmole) of carbon disulfide and 0.135 g (2.2 mmole) of potassium hydroxide in 2 ml of water were added with stirring. The mixture was refluxed for 5 h, cooled, and acidified with dilute hydrochloric acid. The light-yellow precipitate was removed by filtration to give 0.3 g (44%) of IV with mp > 360° (from aniline). Found, %: Br 23.6; S 19.3. $C_{13}H_7BrN_2S_2$. Calculated, %: Br 23.8; S 19.1.

2,3-Dihydrothiazolo[5,4-c]phenothiazine-2-thione (V). A 1.07 g (5 mmole) sample of 4-aminophenothiazine, 0.18 g (5.5 mmole) of powdered sulfur, and 1 ml of carbon disulfide were added to an ampule, and the ampule was sealed and placed in a hermetically sealed steel cylinder and heated at 180-190° for 3 h. At the end of the reaction, the excess carbon disulfide was evaporated, and the residue was dissolved in 20 ml of 15% sodium hydroxide solution (a portion of the residue was insoluble). The alkaline filtrate was acidified with hydrochloric acid, and the resulting precipitate was removed by filtration to give 0.36 g (25%) of V with mp 280-285° (from toluene) (mp 285-290° [4]). Found, %: N 9.3; S 33.1. $C_{13}H_8N_2S_3$. Calculated, %: N 9.7; S 33.5.

LITERATURE CITED

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