SYNTHESIS IN THE PHENOTHIAZINE SERIES

XXXII.* 1,2-DIHYDROIMIDAZO[4,5,1-n,m]PHENOTHIAZINE-1-THIONE AND SOME OF ITS TRANSFORMATIONS

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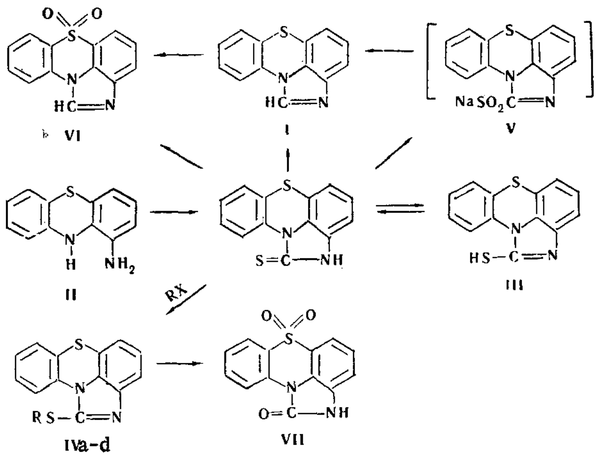
1,2-Dihydroimidazo[4,5,1-n,m]phenothiazine-1-thione (III) was synthesized by the reaction of 1-aminophenothiazine (II) with sulfur and carbon disulfide or potassium ethylxanthogenate. The oxidation of III with hydrogen peroxide in alkali and acid media leads to imidazo[4,5,1-n,m]phenothiazine (I) and imidazo[4,5,1-n,m]phenothiazine 6,6-dioxide (VI), respectively. Several S-alkyl and S-aralkyl derivatives of III (IVa-d) were obtained by the action of alkyl and aralkyl halides; the oxidation of IVa-d in acetic acid gave 1,2-dihydroimidazo[4,5,1-n,m]-1-phenothiazone 6,6-dioxide (VII).

In [2] we described the synthesis of imidazo[4,5,1-n,m]phenothiazine (I), a representative of a new heterocyclic system.

In this research we have synthesized 1,2-dihydroimidazo[4,5,1-n,m]phenothiazine-1-thione (III) and have studied some of its transformations.

It is known that many mercapto compounds have diverse physiological activities and low toxicities. This makes it possible to suppose that derivatives III may be used to obtain compounds with psychotropic activity and activity on the cardiovascular system. Mercaptoimidazophenothiazine is also of interest from a chemical point of view, since it has three reaction centers (the mercapto group and the cyclic nitrogen and sulfur atoms).



X = Cl, Br, I, IVa R = CH_3, IVb R = $(CH_2)_3N(CH_3)_2$, IVc R = CH_2COOH,
IVd R = $CH_2C_6H_5$

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*See [1] for communication XXXI.

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The reaction of 1-aminophenothiazine (II) with sulfur and carbon disulfide or potassium ethylxanthogenate yielded 1,2-dihydroimidazo[4,5,1-n,m]phenothiazine-1-thione (III), which was purified by treatment of its sodium salt with dilute hydrochloric acid.

The IR spectra of III in mineral oil and in KBr blocks contain an intense absorption band at 3150 cm^{-1}, which we assigned to the valence vibration of the NH group. The absorption band characteristic for the SH group (2500-2600 cm^{-1}) is absent. These results indicate that III exists in the thione form in the solid state, while, as expected, the band characteristic for the NH group vanishes in the alkylated products. Under the influence of alkalis, III readily forms salts, the aqueous solutions of which react with alkyl halides and aralkyl halides to form the corresponding S-alkyl and S-aralkyl derivatives (IVa-d). These derivatives were isolated as the hydrochlorides, which are readily hydrolyzed in polar solvents.

The oxidation of III with hydrogen peroxide proceeds in different ways as a function of the reaction medium. In alkaline media the sodium salt of the sulfinic acid (V) is formed and is decomposed on acidification with hydrochloric acid to give imidazo[4,5,1-n,m]phenothiazine (I). We obtained a similar compound via another route in [2]. The oxidation of III in acetic acid gives imidazo[4,5,1-n,m]phenothiazine 6,6-dioxide (VI), which is identical to the compound previously obtained by the oxidation of I [2]. Absorption bands of the SO_2 group were observed at 1320, 1118, 1134, and 1164 cm^{-1} in the IR spectrum of VI (in mineral oil).

The oxidation of IVa-d with hydrogen peroxide in acetic acid gives 1,2-dihydroimidazo[4,5,1-n,m]-1-phenothiazone 6,6-dioxide (VII), as confirmed by analytical data and the IR spectrum. An intense absorption band at 1733 cm^{-1}, which we assigned to the vibrations of the C=O group, is observed in the IR spectrum of VII [in mineral oil or in dioxane solution (c 10^{-2} M, l 0.25 mm)]. The broad absorption bands at 3055, 3115, and 3180-3250 cm^{-1} are characteristic for the NH group in amides. The absorption bands at 1142 and 1338 cm^{-1} characterize the presence of an SO_2 group.

Although benzimidazo-2-thione readily forms a Mannich base [3], we could not carry this reaction out for III.

The pharmacological data on III and IV indicate that they have sedative action.

EXPERIMENTAL

1,2-Dihydroimidazo[4,5,1-n,m]phenothiazine-1-thione (III). A. A mixture of 1.07 g (0.005 mole) of 1-aminophenothiazine, 0.18 g (0.0055 mole) of powdered sulfur, and 2 ml of carbon disulfide was heated for 4 h in a steel cylinder at a bath temperature of 180-190° C. The excess carbon disulfide was evaporated at the end of the reaction. The residue was dissolved in dilute sodium hydroxide, and the insoluble residue was filtered. The filtrate, containing the sodium salt of III, was treated with dilute hydrochloric acid. The resulting light-yellow precipitate was filtered to give 0.96 g (76%) of III with mp 280-281° (from aniline); the product was slightly soluble in most organic solvents. Found %: N 11.03; S 24.95. $C_{13}H_8N_2S_2$. Calculated %: N 10.92; S 25.02.

B. A 0.86 g (0.004 mole) sample of 1-aminophenothiazine was dissolved in 10 ml of alcohol, and 0.4 g (0.0042 mole) of carbon disulfide and 0.25 g (0.0044 mole) 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 resulting precipitate was filtered to give 0.8 g (80%) of a substance with mp 275-277°. It melted at 280-282° after recrystallization from aniline. Found %: N 11.01; S 25.05. $C_{13}H_8N_2S_2$. Calculated %: N 10.92; S 25.02. UV spectrum (dioxane, c 10^{-4} M), λ_{max}, nm (log ε): 244 (4.56), 300-302 (4.26).

1-Methylmercaptoimidazo[4,5,1-n,m]phenothiazine (IVa). Methyl iodide (1 ml) was added in the course of 1 h at room temperature with stirring to 1.2 g (0.004 mole) of III dissolved in dilute sodium hydroxide. The solution was cooled, and 0.85 g of a substance with mp 123-124° (from isopropyl alcohol) was isolated. The light-gray crystals were soluble in most organic solvents and insoluble in water. Found %: N 10.26; S 23.45. $C_{14}H_{10}N_2S_2$. Calculated %: N 10.39; S 23.30.

A hygroscopic hydrochloride that was hydrolyzed in aqueous solutions and had mp 136° (decomp.) was obtained from the ether solution of base IVa by the action of a saturated ether solution of hydrogen chloride. Found %: Cl 11.64. $C_{14}H_{10}N_2S_2 \cdot HCl$. Calculated %: Cl 11.60.

Products IVb, IVc, and IVd were similarly obtained.

(Imidazo[4,5,1-n,m]-1-phenothiazinyl)mercaptoacetic Acid (IVc). The sodium salt of IVc was isolated from 0.51 g (0.002 mole) of III and 0.45 g of bromoacetic acid and was converted in 85% yield (0.53 g) to IVc with mp 199-200° (from aqueous alcohol) by the action of an alcohol solution of hydrogen chloride. Found %: N 8.96; S 20.11. $C_{15}H_{10}N_2O_2S_2$. Calculated %: N 8.96; S 20.05.

1-Benzylimidazo[4,5,1-n,m]phenothiazine (IVd). A. A total of 0.55 g (80%) of base with mp 122-123° (from alcohol) was obtained from 0.51 g (0.002 mole) of III and 1 ml of benzyl chloride. The product was colorless needles that were soluble in hot alcohol and slightly soluble in cold alcohol. Found %: N 8.34; S 18.33. $C_{20}H_{13}N_2S_2$. Calculated %: N 8.08; S 18.51.

A hydrochloride with mp 237-238° that was readily hydrolyzed by water and alcohol was obtained from an ether solution of the base by the action of a saturated ether solution of hydrogen chloride. Found %: Cl 8.89; N 7.49. $C_{20}H_{14}N_2S_2 \cdot HCl$. Calculated %: Cl 9.30; N 7.27.

B. A mixture of 0.26 g (0.001 mole) of III and 1.5 ml of benzyl chloride was refluxed for 3 h in 3 ml of o-dichlorobenzene to give IVd with mp 121-122° (from alcohol). This product did not depress the melting point of the compound obtained by method A.

1-(β-Dimethylaminopropyl)mercaptoimidazo[4,5,1-n,m]phenothiazine (IVb). The oily precipitate obtained by the reaction of 1.02 g (0.004 mole) of III and 1.2 g (0.004 mole) of the hydrochloride of γ-dimethylaminopropyl chloride and aqueous alkali was extracted with toluene. The toluene extract was washed with water and dried with magnesium sulfate, and an ether solution of hydrogen chloride was added to give 1 g (72%) of IVb with mp 205-206° (from isopropyl alcohol). The white crystals were soluble in water and hot alcohols. Found %: Cl 9.75; S 17.40. $C_{18}H_{19}N_2S_2 \cdot HCl$. Calculated %: Cl 9.75; S 17.62.

Imidazo[4,5,1-n,m]phenothiazine (I). A. A 0.51 g (0.002 mole) sample of III was refluxed for 4 h with excess nickel catalyst in 30 ml of alcohol. The catalyst was filtered, and water was added to the filtrate to give a white precipitate with mp 162-164° (from aqueous alcohol). This product did not depress the melting point of the compound obtained by the method in [2]. Found %: S 14.25. $C_{13}H_8N_2S$. Calculated %: S 14.30.

B. A 0.51 g (0.002 mole) sample of III was dissolved in dilute sodium hydroxide, 3 ml of 30% hydrogen peroxide was added with stirring, and the mixture was stirred at room temperature for 30 min. The substance that precipitated from the acidified reaction mass dissolved on heating, and a solution of sodium hydroxide was added until the mixture gave an alkaline reaction. The resulting precipitate was filtered to give 65% of a product with mp 161-162° (from aqueous alcohol). This product did not depress the melting point of the compound obtained by method A. Found %: S 14.42. $C_{13}H_8N_2S$. Calculated %: S 14.30.

Imidazo[4,5,1-n,m]phenothiazine 6,6-Dioxide (VI). A 0.52 g (0.002 mole) sample of III was dissolved in 15 ml of glacial acetic acid, 3 ml of hydrogen peroxide was added, the mixture was stirred at 50-55° for 2 h, and water was added until the mixture became turbid. It was then treated with charcoal and filtered, and a light-yellow crystalline precipitate with mp 239-240° (from alcohol) formed from the filtrate. According to its melting point and chromatogram, it was identical to the compound obtained in [2] with mp 240-242° [2] and R_f 0.75 [alcohol–chloroform (1 : 4)]. Found %: N 10.90; S 12.38. $C_{13}H_8N_2O_2S$. Calculated %: N 10.94; S 12.25. UV spectrum (in dioxane, c 10^{-5} M), λ_{max}, nm (log ε): 260-262 (4.15), 304 (4.06), 312 (4.14).

1,2-Dihydroimidazo[4,5,1-n,m]-1-phenothiazone 6,6-Dioxide (VII). A 0.52 g (0.002 mole) sample of IVa was dissolved in 15 ml of glacial acetic acid, 3 ml of hydrogen peroxide was added, and the mixture was stirred at 50-55° for 2 h. The resulting precipitate was filtered and washed with water and alcohol to give a product with mp 320-322° (from alcohol). Found %: N 10.00; S 11.91. $C_{13}H_8N_2O_3S$. Calculated %: N 10.15; S 11.80. UV spectrum (in dioxane, c 10^{-4} M), λ_{max}, nm (log ε): 248 (4.17), 281 (3.98), 310 (3.98).

The IR spectra were recorded with a UR-10 spectrophotometer, while the UV spectra were recorded with an SF-4 spectrometer.

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