SYNTHESIS IN THE PHENOTHIAZINE SERIES

XXXVI.* QUATERNARY SALTS OF IMIDAZO[4,5,1-k,*l*]PHENOTHIAZINE AND THEIR TRANSFORMATIONS

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Quaternary salts of imidazo[4,5,1-k,*l*]phenothiazine were reduced with potassium borohydride to 1,2-dihydro-2-methylimidazo[4,5,1-k,*l*]phenothiazine, which was converted to 1,2-dihydro-2-methylimidazo[4,5,1-k,*l*]phenothiazine-1-thione and 1-methylamino-10-formylphenothiazine. The latter was hydrolyzed to 1-methylaminophenothiazine, which was also obtained by reduction of methyl phenothiazine-1-carbamate. The PMR and IR spectra of some of the derivatives are discussed.

A number of preparations with cardiovascular and psychotropic action have been found in the phenothiazine series. Imidazophenothiazine derivatives may also have physiological activity.

An attempt to reduce imidazo[4,5,1-k,*l*]phenothiazine (I) with potassium borohydride or lithium aluminum hydride [2] did not give the desired results. In this connection, the quaternary salts of I (IIa, b) with methyl iodide and dimethyl sulfate were obtained and reduced with potassium borohydride to 1,2-dihydro-2-methylimidazo[4,5,1-k,*l*]phenothiazine (III). The nature of the anion in the quaternary salt does not affect the course of the reduction. Singlets of the protons of the CH_2 group at 4.62 ppm and of the CH_3 group at 2.66 ppm were observed in the PMR spectrum of a chloroform solution of III. These data confirm the direction of the reduction. Just as in 1,2-dihydrobenzimidazole [3], the hydrogens of the methylene group in III have hydride lability. The reaction of III with sulfur gave 1,2-dihydro-2-methylimidazo[4,5,1-k,*l*]phenothiazine-1-thione (IV). Heating III with carbon tetrachloride, which is a proton acceptor in this reaction, gives chloride IIc, and the carbon tetrachloride is reduced to chloroform. The formation of the latter is confirmed by the PMR spectrum of the filtrate obtained after separation of chloride IIc (proton signal at 7.2 ppm). Like other quaternary salts, chloride IIc is reduced to III. When an attempt was made to convert III to imidazophenothiazone in analogy with [3], the imidazoline ring was cleaved to give 1,10-disubstituted phenothiazine (V).

The IR spectra of a mineral oil suspension of V and a 0.1 M solution of V in chloroform contain characteristic bands for the NH group at 3374 and 3325 cm^{-1} (less intense) and for the CO group at 1674 cm^{-1}; dilution of the chloroform solution to a concentration of $1 \cdot 10^{-3}$ M leads to the disappearance of the bands at 3374 and 3325 cm^{-1} and to the appearance of a band at 3430 cm^{-1}; this indicates the presence of intermolecular hydrogen bonds in the concentrated solutions. When V is deuterated ($CH_3OD + D_2O$), the band of the NH groups is shifted to 2453 cm^{-1}.

The PMR spectrum of a chloroform solution of V contains singlets of protons for the $N-CH_3$ group at 3.22 ppm, for the NH group at 6.5 ppm, and for the CHO group at 8.22 ppm. Compound V gives stable

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* See [1] for communication XXXV.

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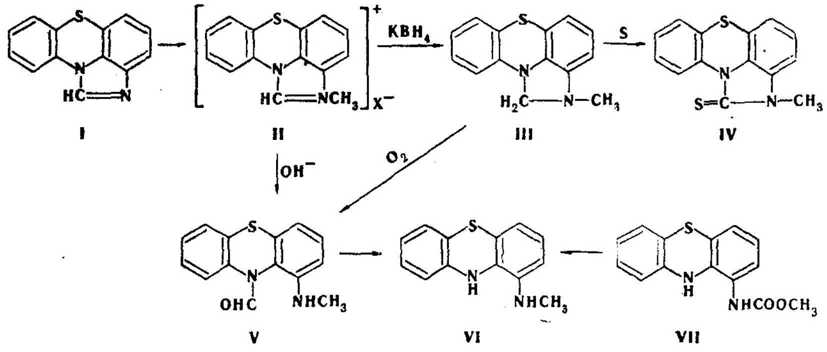

IIa X=I; b X=CH_3SO_4; c X=Cl

hydrochlorides. Thus the data obtained made it possible to assign the 1-methylamino-10-formylphenothiazine structure to V. Compound V was also obtained by alkaline hydrolysis of the quaternary salts of imidazophenothiazine at room temperature. Heating V in an alcohol solution of sodium hydroxide hydrolyzed it to 1-methylaminophenothiazine (VI); the latter was also obtained by alternative synthesis by reduction of methyl phenothiazine-1-carbamate (VII) with lithium aluminum hydride.

EXPERIMENTAL

The PMR spectra were recorded with a Varian T-60 spectrometer. The IR spectra were recorded with a UR-10 spectrometer.

2-Methylimidazolio[4,5,1-k,*l*]phenothiazine Iodide (IIa). A 2.24 g (0.01 mole) sample of imidazo[4,5,1-k,*l*]phenothiazine (I) was dissolved in a mixture of acetone and ether, 3 ml of methyl iodide was added, and the mixture was allowed to stand for 3 days. A crystalline precipitate formed from the solution; the yield was 3.1 g. The colorless needles were soluble in water and alcohol and had mp 248-250°. Found: I 34.2; N 7.4%. $C_{14}H_{11}IN_2S$. Calculated: I 34.7; N 7.6%.

2-Methylimidazolio[4,5,1-k,*l*]phenothiazine Methosulfonate (IIb). A 2.24 g (0.01 mole) sample of I was mixed with 5 ml of distilled dimethyl sulfate, and the mixture was heated at 100-110° for 1.5 h. It was then cooled, and the resulting precipitate was treated with ether to give 2.8 g (75%) of a substance with mp 247-248° (from anhydrous ethanol). Found: N 8.1; S 18.2%. $C_{15}H_{14}N_2O_4S_2$. Calculated: N 8.1; S 18.2%.

2-Methylimidazolio[4,5,1-k,*l*]phenothiazine Chloride (IIc). A 0.24 g (0.001 mole) sample of 1,2-dihydro-2-methylimidazolino[4,5,1-k,*l*]phenothiazine was refluxed in 5 ml of carbon tetrachloride, during which a colorless crystalline substance that was readily soluble in water precipitated. The yield of product with mp 243-244° (from anhydrous isopropyl alcohol) was 0.3 g. Found: Cl 12.5; N 9.9%. $C_{14}H_{11}ClN_2S$. Calculated: Cl 12.8; N 10.2%.

1,2-Dihydro-2-methylimidazo[4,5,1-k,*l*]phenothiazine (III). A 3.5 g (0.01 mole) sample of IIb was dissolved in 60 ml of 80% aqueous alcohol, and 1.5 g of potassium borohydride dissolved in water was added in portions. The reaction mixture was stirred at 50° for 1 h, after which it was cooled, and the resulting greenish precipitate was removed by filtration to give 1.8 g (75%) of III with mp 88-89° (from aqueous ethanol). The light-green needles were soluble in toluene and ethyl acetate but insoluble in water. Found: C 69.7; H 5.1; N 11.5; S 13.5%. $C_{14}H_{12}N_2S$. Calculated: C 70.0; H 5.0; N 11.6; S 13.3%. UV spectrum (in alcohol), λ_{max}, nm (log ε): 236 (4.40), 272-276 (4.20), 324-328 (3.67).

Compound III was similarly obtained by reduction of Ia and IIc.

1,2-Dihydro-2-methylimidazo[4,5,1-k,*l*]phenothiazine-1-thione (IV). A 0.48 g (0.002 mole) sample of III was fused with 0.1 g (0.003 mole) of sulfur at a bath temperature of 150° for 30 min. Hydrogen sulfide was evolved, and the mass solidified. Crystallization from toluene and then ethanol gave white needles with mp 162-163°. Found: N 10.4; S 24.0%. $C_{14}H_{10}N_2S_2$. Calculated: N 10.4; S 23.7%.

1-Methylamino-10-formylphenothiazine (V). A) A 0.70 g (0.002 mole) sample of IIb was dissolved in warm water, and a dilute solution of sodium hydroxide was added until the mixture was alkaline. A crystalline substance [0.43 g (70%)] with mp 169-170° (from ethanol) and R_f 0.63 [activity II Al_2O_3, alcohol–chloroform (1 : 10)] precipitated. Found: N 11.3; S 12.7%. $C_{14}H_{12}N_2OS$. Calculated: N 10.93; S 12.56%. The hydrochloride of V had mp 218° (dec., from aqueous ethanol). Found: Cl 11.9%. $C_{14}H_{12}N_2OS \cdot HCl$. Calculated: Cl 12.2%.

B) Oxygen was bubbled into a warm solution of 0.24 g (0.001 mole) of III in alcohol for 2 h, during which the mixture darkened. It was treated with charcoal and filtered, and 0.18 g (70%) of a colorless substance with mp 167-168° precipitated from the filtrate. No melting-point depression was observed for a mixture of this product with a sample of V obtained by method A.

1-Methylaminophenothiazine (VI). A) A solution of 0.54 g (0.002 mole) of methyl phenothiazine-1-carbamate [4] in 3 ml of anhydrous tetrahydrofuran (THF) was added to an ether solution of an excess of lithium aluminum hydride. The mixture was then stirred and refluxed for 5 h. The excess lithium aluminum hydride was decomposed with moist THF. The aluminum hydroxide was removed by filtration and washed with ether. The ether filtrate was evaporated, and the residue was dissolved in dilute hydrochloric acid. The acidic aqueous solution was treated with activated charcoal and filtered, and the base was isolated by treatment with aqueous sodium hydroxide solution. The precipitate was removed by filtration to give shiny plates with mp 84-85° (from aqueous alcohol) that darkened on exposure to air. The product had R_f 0.61 [activity II Al_2O_3, alcohol–chloroform (1:10)]. Found: N 12.3; S 13.9%. $C_{13}H_{12}N_2S$. Calculated: N 12.3; S 14.0%.

B) An aqueous solution of 0.1 g (2.5 mmole) of sodium hydroxide was added to a solution of 0.51 g (0.002 mole) of V in 5 ml of alcohol, and the mixture was refluxed for 2 h. It was then diluted with water and treated with activated charcoal. The mixture was filtered, and 0.25 g of VI with mp 83-84° precipitated from the filtrate.

C) Under the conditions of method B, 0.35 g (0.001 mole) of IIb gave 0.1 g of a substance with mp 83-84°, which was identical to the product obtained above.

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