SYNTHESIS IN THE PHENOTHIAZINE SERIES

XXIX.* IMIDAZO[4,5,1-k,*l*]PHENOTHIAZINE AND ITS DERIVATIVES

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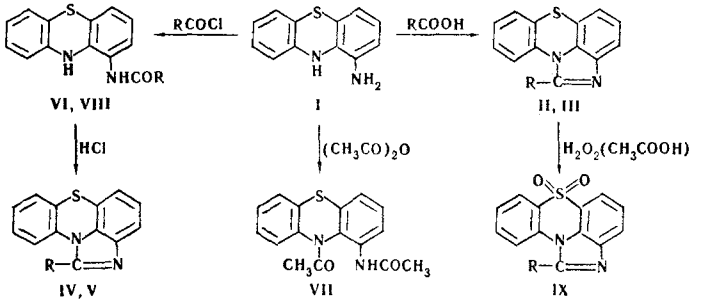
A new condensed system – imidazo[4,5,1-k,*l*]phenothiazine – was synthesized by the reaction of 1-aminophenothiazine with formic acid. The reaction of 1-aminophenothiazine with trifluoroacetic acid resulted in the formation of 1-trifluoromethylimidazo[4,5,1-k,*l*]phenothiazine. The cyclization of 1-acetamido- and 1-benzamidophenothiazines in the presence of hydrochloric acid gave 1-methyl- and 1-phenylimidazo[4,5,1-k,*l*]phenothiazines.

Continuing our search for pharmacologically active compounds in the substituted phenothiazine series, we have synthesized a four-membered heterocyclic system that includes an imidazole ring.

We used 1-aminophenothiazine (I) as the starting compound for the synthesis of imidazo[4,5,1-k,*l*]-phenothiazine (II) and its derivatives. It was, of course, expected that the same reactions that are peculiar to o-arylenediamines [2] would also be characteristic for I. Acids were used as the second component in the synthesis of II.

The reactions of I with organic acids proceed at different rates. The acidity constant of the reacting acid apparently has a decisive effect on the reaction rate. Thus, for example, heating of I with formic or trifluoroacetic acid leads, respectively, to imidazo[4,5,1-k,*l*]phenothiazine (II) and 1-trifluoromethylimidazo[4,5,1-k,*l*]phenothiazine (III). Attempts to obtain 1-methylimidazo[4,5,1-k,*l*]phenothiazine (IV) and 1-phenylimidazo[4,5,1-k,*l*]phenothiazine (V) by the reaction of I with acetic acid, acetic anhydride, and benzoic acid were unsuccessful: 1-acetamidophenothiazine (VI) and 1-acetamido-10-acetylphenothiazine (VII), respectively, were obtained. Compounds VI and 1-benzoylaminophenothiazine (VIII) were obtained via the Schotten–Baumann reaction of I with acetic anhydride or benzoyl chloride. We were able to obtain IV by heating VI in 10% hydrochloric acid. Compound VIII could be cyclized to V in low yield by prolonged heating in 25% hydrochloric acid; the low yield is apparently due to the deactivating effect of the phenyl group on the carbonyl group. An attempt to obtain V in analogy with 2-phenylbenzimidazole [3] by heating I with benzoic acid in the presence of 25% hydrochloric acid did not give the expected results.



IV, VI R=CH_3; V, VIII R=C_6H_5; II, IX R=H; III R=CF_3

*See [1] for communication XXVIII.

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The new heterocyclic system – imidazo[4,5,1-k,*l*]phenothiazine – is resistant to prolonged heating and to the action of alkalis and acids. Heating this compound under severe conditions over a nickel catalyst did not give 1-phenylbenzimidazole – the product of the reductive desulfurization of II. However, II is readily oxidized, and, depending on the oxidation conditions, forms an oxide or dioxide.

As compared with phenothiazine, a bathochromic shift of the long-wave maximum and a hypsochromic shift of the more intense short-wave maximum are observed in the UV spectrum of II. In addition, six fine structure bands arise at 240-320 nm; these characterized the entire system as one with more pronounced aromatic properties. When the UV spectra of II in neutral and acid media are compared, in the latter case one observes a shift of 10 nm in the band of the benzene absorption of the phenothiazine ring to shorter wavelengths. A shift of the long-wave maximum is also observed in the UV spectrum of IV in acid media.

Bands that could be assigned to the valence vibrations of the NH bond are absent in the IR spectrum of II from 3100-3500 cm^{-1}. In addition to the bands at 1600 and 1573 cm^{-1} due to the benzene ring of the phenothiazine ring, there is a band at 1630 cm^{-1} that is apparently associated with the vibration of the C=N bond in the imidazole ring. In comparing the IR spectrum of II with the spectrum of phenothiazine, it should be noted that the bands at 1502 and 1492 cm^{-1} are shifted to 1480 and 1465 cm^{-1} while retaining the same relative intensities, while the 1438 cm^{-1} band of II is shifted to 1385 cm^{-1} in phenothiazine. In addition, there are intense bands at 1287 and 1270 cm^{-1} in the spectrum of II that to some degree may also characterize the formation of a new condensed system.

The introduction of a CF_3 group into the imidazole ring led to a shift in the C=N band to 1625 cm^{-1}; the band at 1573 cm^{-1} overlaps the band at 1600 cm^{-1} and, in place of the intense band at approximately 1500 cm^{-1} in II, a doublet appears at 1520 and 1480 cm^{-1}. An intense band, apparently related to the asymmetrical deformation vibration of the CF_3 group [4], can be isolated in the spectrum of III.

EXPERIMENTAL

Imidazo[4,5,1-k,*l*]phenothiazine (II). A mixture of 2.14 g (0.01 mole) of I and 5 ml of 85% formic acid was refluxed for 4 h. The reaction mass was poured into a dilute solution of sodium hydroxide, and the resulting precipitate was recrystallized from aqueous alcohol to give 1.8 g (72%) of a colorless substance with mp 164-165° that was soluble in alcohol, toluene, and ether. UV spectrum (in alcohol): λ_{max} 225, 248, 262, 288, 300, 320, 326-336 nm; log ε 4.40, 4.10, 3.98, 3.88, 3.66, 3.80, 3.80. Found %: C 69.2; H 3.6; N 12.4; 12.7; S 14.2, 14.3. $C_{13}H_8N_2S$. Calculated %: C 69.6; H 3.6; N 12.5; S 14.3. The hydrochloride, obtained by dissolving the base in hydrochloric acid, was isolated after cooling the solution and drying the precipitate and melted at 248-250°. Found %: Cl 13.6, 13.6; N 10.7, 10.9. $C_{13}H_8N_2S \cdot HCl$. Calculated %: Cl 13.6; S 10.7. UV spectrum (in alcohol): λ_{max} 224, 318-322 nm; log ε 4.64, 3.79.

1-Trifluoromethylimidazo[4,5,1-k,*l*]phenothiazine (III). A mixture of 1.07 g (0.005 mole) of I and 3 ml of trifluoroacetic acid was refluxed for 17 h. The reaction mass was then poured into dilute sodium hydroxide, and the precipitate was filtered and washed with water. Two crystallizations from aqueous alcohol gave 0.75 g (52%) of a substance with mp 100-101°. (Starting amine I was isolated by dilution of the filtrate with water.) Found %: N 9.6, 9.6; S 11.3, 11.2. $C_{14}H_7F_3N_2S$. Calculated %: N 9.6; S 11.0.

1-Acetamidophenothiazine (VI). Acetic anhydride (3 ml) was added to a solution of 0.84 g (0.004 mole) of I in 5 ml of pyridine, and the mixture was stirred at 30-35° for 40 min and diluted with water. The resulting precipitate was filtered to give 0.85 g (85%) of a substance which melted at 178-179° after recrystallization from toluene. Found %: N 11.1, 11.1; S 12.5, 12.4. $C_{14}H_{12}N_2OS$. Calculated %: N 11.0; S 12.5.

1-Benzamidophenothiazine (VIII). Under the conditions of the Schotten–Baumann reaction, 0.71 g (75%) of a substance with mp 209-210° (from alcohol) was obtained from 0.63 g (0.003 mole) of I, 0.5 g (0.0033 mole) of benzoyl chloride, and 0.35 g of sodium bicarbonate in 10 ml of ethanol. The light-yellow crystalline product was quite soluble in most organic solvents. Found %: N 8.9, 9.1; S 10.1, 10.1. $C_{19}H_{14}N_2OS$. Calculated %: N 8.8; S 10.1.

1-Acetamido-10-acetylphenothiazine (VII). A total of 0.43 g (0.002 mole) of I was refluxed in 5 ml of acetic anhydride for 1 h. The reaction mass was then poured into water, and the precipitate was recrystallized first from aqueous alcohol and then from toluene to give a colorless, crystalline substance with mp 204-205°. Found %: N 9.1, 9.2; S 10.1, 9.8. $C_{16}H_{14}N_2O_2S$. Calculated %: N 9.1; S 10.1.

1-Methylimidazo[4,5,1-k,*l*]phenothiazine (IV). A total of 0.76 g (0.003 mole) of VI was refluxed with stirring for 2 h in 50 ml of 10% hydrochloric acid; VI gradually dissolved. Heating was stopped, and dilute sodium hydroxide was added to the reaction mass until it was alkaline. The resulting precipitate was filtered and washed with water to give 0.5 g (70%) of a substance with mp 130-135° that melted at 135-136° after recrystallization from aqueous alcohol. Found %: N 11.9, 11.7; S 13.8, 13.7. $C_{14}H_{10}N_2S$. Calculated %: N 11.8; S 13.5. The base, which dissolved on heating in dilute hydrochloric acid, formed a hydrochloride with mp 222-224°. Found %: Cl 12.9, 13.0. $C_{14}H_{10}N_2S \cdot HCl$. Calculated %: Cl 12.9. UV spectrum of the base in alcohol with 0.1 N HCl: λ_{max} 230, 292, 312-314 nm; log ε 4.54, 3.84, 3.87.

1-Phenylimidazo[4,5,1-k,*l*]phenothiazine (V). Product VIII [0.4 g (0.0012 mole)] was refluxed with stirring in 30 ml of 25% hydrochloric acid for 20 h; VIII dissolved partially. The addition of sodium hydroxide to the acid filtrate gave 0.15 g of a substance with mp 115-116° (from aqueous alcohol). Found %: N 9.3, 9.1; S 10.8, 10.7. $C_{19}H_{12}N_2S$. Calculated %: N 9.2; S 10.8.

Imidazo[4,5,1-k,*l*]phenothiazine S,S-Dioxide (IX). Hydrogen peroxide (1.5 ml of a 30% solution) was added to a solution of 0.66 g (0.003 mole) of II in 5 ml of glacial acetic acid, and the mixture was refluxed for 3 h. The reaction mass was then poured into a dilute sodium hydroxide, and the resulting precipitate was recrystallized from alcohol to give 0.6 g (78%) of a substance with mp 240-242°. Found %: N 11.0, 11.1; S 12.3, 12.4. $C_{13}H_8N_2O_2S$. Calculated %: N 10.9; S 12.5.

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