SYNTHESIS OF SUBSTITUTED 4H-IMIDAZO[5,1-b]BENZIMIDAZOLE

VII. DERIVATIVES OF 3-PHENYL-4-METHYLIMIDAZO[5,1-b]BENZIMIDAZOLE AND 3,4-DIMETHYLIMIDAZO[5,1-b]BENZIMIDAZOLE

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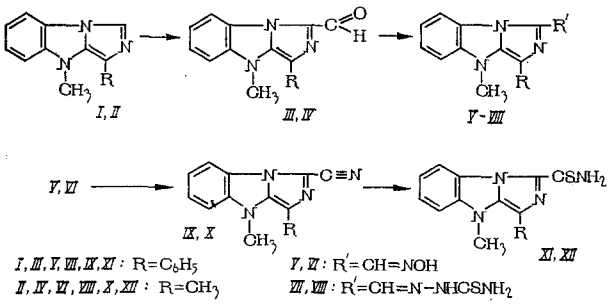
In previous papers [1, 3] the synthesis of a new heterocyclic system, i. e., 4H-imidazo[5,1-b]benzimidazole is described. In order to obtain compounds having potential antitubercular activity, we synthesized certain derivatives of 4-methylimidazo[5,1-b]benzimidazole, containing groupings which promote tubercularstatic activity, i. e., thiosemicarbazone, thioamide, and so on.

Under the conditions described for producing 3-phenyl-4-methylimidazo[5,1-b]benzimidazole-1-aldehyde [4] from 3,4-dimethylimidazo[5,1-b]benzimidazole (II), application of the Wilsmeir reaction gives 3,4-dimethylimidazo[5,1-b]benzimidazole-1-aldehyde (IV). On heating with hydroxylamine hydrochloride in pyridine, III and IV are changed into the corresponding oximes (V and VI). On boiling III and IV with thiosemicarbazone in ethanol in the presence of acetic acid, these compounds give the corresponding thiosemicarbazones (VII and VIII), respectively. On heating V and VI with acetic anhydride in the presence of dry sodium acetate, the nitriles of 3-phenyl-4-methyl-(IX) and 3,4-dimethylimidazo[5,1-b]benzimidazole-1-carboxylic acid (X) are formed. The spectra of IX and X clearly reveal adsorption bands which are characteristic for the CN group (at $\nu = 2215$ and 2210 cm^{-1} respectively). No success was achieved in obtaining the nitrile IX from aldehyde III by treating the latter with hydroxylamine hydrochloride and 98% formic acid in the presence of dry sodium acetate. Under these conditions only the oxime V is formed. The nitriles IX and X are converted into the corresponding thioamides in the usual way, i. e.,



Compounds I-V, VII, VIII, IX, and XII were tested for bacteriostatic activity in relation to tuberculosis mycobacteria of the human type (strain $H_{37}R_V$* the compound showing the greatest tuberculostatic activity was compound IV (the minimum tuberculostatic activity without serum was 15 mg/ml). However, in the presence of serum the activity fell rapidly. The remaining compounds had scarcely any activity.

EXPERIMENTAL

3,4-Dimethylimidazo[5,1-b]benzimidazole-1-aldehyde (IV). To 28.6 ml of purified and freshly distilled dimethylformamide, we added 4.9 ml of $POCl_3$, cooled in ice and stirred at a temperature not exceeding 5°.

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The solution was stirred for 15 min at 20°, cooled to 0°, and a solution of 3.68 grams of II [2] in 28.6 ml of dimethylformamide was added, which immediately precipitated a brick-red residue. We left the reaction mixture for a few days, filtered off the residue (5.53 g) formed, washed it with a small quantity of dimethylformamide followed by ether, treated it with a saturated solution of sodium acetate, dissolved it by heating in water, and extracted the aqueous solution with chloroform. Evaporation of the solvent gave 2.56 g of IV. Chloroform extraction of a further 0.48 g of IV from the mother liquor gave a total of 3.04 g (72%) of IV, in the form of light, cinnamon needles, of mp 178-179° (from benzene). Found %: C 67.65; H 5.48; N 19.87. Empirical formula $C_{12}H_{11}N_3O$. Calculated %: C 67.59; H 5.20; N 19.71.

Oxime of 3-Phenyl-4-methylimidazo[5,1-b]benzimidazole-1-aldehyde (V). A. We heated a mixture of 0.5 g of III [4], 0.5 g of hydroxylamine hydrochloride, 5 ml of absolute ethanol, and 5 ml of dry pyridine for 2 h at ~100°, evaporated off the solvent in vacuo, washed the residue with water, and filtered it off, to give 0.53 g of V, a light-yellow crystalline substance, melting point 214-214.5° (decomp., from ethanol). The yield is quantitative. Found %: C 69.87; H 4.72; N 18.97. Empirical formula $C_{17}H_{14}N_4O$. Calculated %: C 70.33; H 4.86; N 19.30.

B. We stirred a solution of 0.63 g of III, 0.21 g of hydroxylamine hydrochloride, 0.33 g of dry sodium acetate, and 5.25 ml of 98% formic acid for 4 h, left it for 12 h, whereupon yellow crystals were deposited. We filtered off the crystals, washed with water and dried to give 0.52 g (78%) of a substance which failed to give a melting point depression after a mixed melting point test with V, as prepared by method A.

Oxime of 3,4-Dimethylimidazo[5,1-b]benzimidazole-1-aldehyde (VI). Compound VI can be obtained from IV in a manner similar to that used for obtaining V by method A. The yield is 90%, and the mp 260-261.5° (decomp., from ethanol). Found %: C 63.30; H 5.35. Empirical formula $C_{12}H_{12}N_3O$. Calculated %: C 63.14; H 5.30.

Thiosemicarbazone of 3-Phenyl-4-methylimidazo[5,1-b]benzimidazole-1-aldehyde (VII). We boiled a mixture of 0.5 g of III [4], 0.2 g of thiosemicarbazide, 2 ml of acetic acid, and 14 ml of absolute ethanol for 3 h. Compound III gradually dissolved, and after 1 h a residue appeared. When heating was finished, we cooled the reaction mixture, filtered off the residue, and washed the residue first with ethanol, and then with ether, to give 0.61 g (96.5%) of VII, which is a yellow crystalline substance of mp 215-216° (decomp., from acetic acid), which is insoluble in water and ethanol. Found %: C 62.31; H 4.50; S 9.13. Empirical formula $C_{18}H_{16}N_6S$. Calculated %: C 62.05; H 4.63; S 9.20.

Thiosemicarbazone of 3,4-Dimethylimidazo[5,1-b]benzimidazole-1-aldehyde (VIII). Compound VIII is obtained from IV similarly to compound VII. The yield is 89.3%, mp 225.5-226° (decomp., from methanol), and is a yellow crystalline substance, soluble in hot acetic acid. Found %: C 54.23; H 5.09; N 29.07; S 10.90. $C_{13}H_{14}N_6S$. Calculated %: C 54.52; H 4.93; N 29.35; S 11.20.

Nitrile of 3-Phenyl-4-methylimidazo[5,1-b]benzimidazole-1-carboxylic Acid (IX). We boiled a mixture of 1.27 g of V, 0.6 g of dry sodium acetate, and 15 ml of acetic anhydride for 2.5 h, evaporated off the excess acetic anhydride in vacuo, triturated the residue with cold water, filtered it off, washed it, and dried it, to give 1.05 g (88.2%) of IX, mp 192-194° (from acetone). The substance dissolved on heating in ethanol, and gave an IR spectrum (in Vaseline oil) with $\nu C \equiv N$ 2215 cm^{-1}. Found %: C 74.87; H 4.68; N 20.45. Empirical formula $C_{17}H_{12}N_4$. Calculated %: C 74.98; H 4.44; and N 20.58.

Nitrile of 3,4-Dimethylimidazo[5,1-b]benzimidazole-1-carboxylic Acid (X). Compound X is obtained from VI similarly to IX. The yield is 96.7%, mp 179-179.5° (from benzene and then from ethanol). The IR spectrum (in vaseline oil) gives $\nu C \equiv N$ 2210 cm^{-1}. Found %: C 68.90; H 4.98; N 26.41. Empirical formula $C_{12}H_{10}N_4$. Calculated %: C 68.55; H 4.80; N 26.65.

Thioamide of 3-Phenyl-4-methylimidazo[5,1-b]benzimidazole-1-carboxylic Acid (XI). We passed H_2S through a suspension of 0.5 g of IX in 23 ml of absolute ethanol and 0.32 ml of dry triethylamine for 8 h at 20-22°, the H_2S having been previously dried over $CaCl_2$. Compound IX gradually changed, and a yellow residue appeared. After cooling, we filtered off this residue and washed it with absolute ethanol, to give 0.56 g of XI, in the form of light-orange needles, mp 249.5-250.5° (decomp., from acetic acid). The yield is quantitative. Found %: C 66.42; H 4.64; N 18.20; S 10.18. Empirical formula $C_{17}H_{14}N_4S$. Calculated %: C 66.64; H 4.61; N 18.29; S 10.47.

Thioamide of 3-4-Dimethylimidazo[5,1-b]benzimidazole-1-carboxylic Acid (XII). Compound XII is obtained from X similarly to IX. We passed the H_2S for 4 h: yield 99%, dark-orange needles, mp 242-244°

(decomp. from acetic acid). Found %: C 59.01; H 5.26; N 23.23; S 13.23. Empirical formula $C_{12}H_{12}N_4S$. Calculated %: C 58.99; H 4.95; N 22.93; and S 13.13.

LITERATURE CITED

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2. Ibid., p. 506.
3. Ibid., p. 509.
4. Ibid., p. 1108.