

## SYNTHESIS OF SUBSTITUTED IMIDAZO[5,1-b]BENZIMIDAZOLES

## IV. Some Reactions of 3-Phenyl-4-methylimidazo[5,1-b]benzimidazole\*

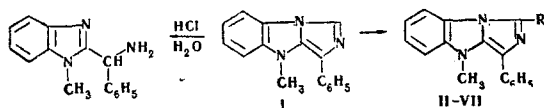
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Some chemical characteristics and reactions of 3-phenyl-4-methylimidazo[5,1-b]benzimidazole (I) have been examined. It has been shown that I undergoes electrophilic substitution (hydroxymethylation, acetylation, nitrosation, and the Mannich and Vilsmeier reactions), the substituent entering at the 1-position. Cyanoethylation of I gives 1-cyanoethyl-3-phenyl-4-methylimidazo[5,1-b]benzimidazole.

We have described in earlier papers [1-3] the synthesis of derivatives of the new tricyclic system imidazo[5,1-b]benzimidazole. We have used the 3-phenyl-4-methyl derivative (I) as an example for the study of the chemical behavior and reactions of imidazo[5,1-b]benzimidazoles unsubstituted in the 1-position, in view of its comparative stability and ease of access [1]. The behavior of I toward alkalis and acids has been examined; boiling with 20% NaOH is without effect; heating with 20% HCl results in fission of the ring and hydrolysis of the formyl group to give 1-methyl-2-( $\alpha$ -aminobenzyl)benzimidazole. The ionization constant of I in 50% aqueous ethanol was determined ( $pK_a$  4.75) (the physical chemistry and spectral examinations were carried out in the physical chemistry laboratory of the All-Union Chemical and Pharmaceutical Scientific-Research Institute), and the hydrochloride and picrate were prepared.



II, R=CHO; III, R=CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>; IV, R=CH<sub>2</sub>OH; V, R=NO;  
VI, R=COCH<sub>3</sub>; VII, R=CH<sub>2</sub>CH<sub>2</sub>CN.

Compound I readily undergoes the Vilsmeier and Mannich reactions. The Vilsmeier reaction proceeds without heating to give 1-formyl-3-phenyl-4-methylimidazo[5,1-b]benzimidazole (II). The entry of the formyl group into the 1-position was shown by NMR (a discussion of the NMR spectra of derivatives of imidazo[5,1-b]benzimidazoles will be published later). The Mannich reaction was also carried out under very mild conditions. Reaction of I with an aqueous solution of dimethylamine and formalin at room temperature gave a good yield of 1-dimethylaminomethyl-3-phenyl-4-methylimidazo[5,1-b]benzimidazole (III). By carrying out this reaction in isoamyl alcohol with dimethylamine hydrochloride and paraformaldehyde with heating, resinification occurred (apparently as a result of ring fission by HCl), no Mannich base being obtained.

Hydroxymethylation of I occurs with comparative ease. Heating with formalin in water resulted in the formation in 98% yield of a compound which, by its analysis and spectral data, was 1-hydroxymethyl-3-phenyl-4-methylimidazo[5,1-b]benzimidazole (IV).

Compound I was nitrosated and acetylated. Nitrosation was carried out under the conditions described for 3,5-diphenylimidazo[5,1-b]thiazole [4]. Nitrosation with sodium nitrite in acetic acid gave 1-nitroso-3-phenyl-4-methylimidazo[5,1-b]benzimidazole (V). No reaction occurred with isoamyl nitrite. Acetylation was effected under the conditions described for 3-methyl-6-phenylpyrrolo[5,1-b]thiazoles [5]. Acetylation of I with acetic anhydride and anhydrous sodium acetate gave 1-acetyl-3-phenyl-4-methylimidazo[5,1-b]benzimidazole (VI).

We have also cyanoethylated compound I. By boiling with an excess of acrylonitrile in the presence of Rodionov's reagent, there was obtained a poor yield of 1-cyanoethyl-3-phenyl-4-methylimidazo[5,1-b]benzimidazole (VII), together with the picrate of I.

The 1-substituted 3-phenyl-4-methylimidazo[5,1-b]benzimidazoles were characterized by their UV, IR, and NMR spectra.

## EXPERIMENTAL

## 3-Phenyl-4-methylimidazo[5,1-b]benzimidazole hydrochloride.

An alcoholic solution of I was treated with ethereal HCl. The resulting white crystalline solid, mp 242-244° C (from absolute ethanol), was rather sparingly soluble in water. Found, %: C 67.35; H 5.00; N 14.97; Cl 12.66. Calculated for C<sub>16</sub>H<sub>13</sub>N<sub>3</sub> · HCl, %: C 67.72; H 4.97; N 14.81; Cl 12.50. Picrate of I, yellow crystals with mp 187-188° C (from acetone), soluble in hot alcohol. Found, %: C 55.10; H 3.52; N 17.75. Calculated for C<sub>16</sub>H<sub>13</sub>N<sub>3</sub> · C<sub>6</sub>H<sub>3</sub>N<sub>3</sub>O<sub>7</sub>, %: C 55.46; H 3.39; N 17.64.

**The action of alkali on I.** A suspension of 0.5 g (0.00202 mole) of I in 10 ml of a 20% solution of NaOH was boiled for 3 hr. The mixture was cooled, the solid filtered off, washed with water, and dried. There was obtained 0.48 g of material which on admixture with I gave no depression of the melting point.

**The action of hydrochloric acid on I.** A solution of 0.4 g (0.00162 mole) of I in 15 ml of 20% HCl was boiled for 6 hr, cooled, treated with aqueous K<sub>2</sub>CO<sub>3</sub>, and the base extracted with benzene. Removal of the solvent gave 0.37 g (96.5%) of a white crystalline solid, mp 113.5-114° C, undepressed on mixing with 1-methyl-2-( $\alpha$ -aminobenzyl)benzimidazole [1].

**1-Formyl-4-methylimidazo[5,1-b]benzimidazole (II).** To 3.5 ml of freshly-distilled dimethylformamide was added, dropwise with cooling in a freezing mixture and stirring, 0.6 ml (0.0065 mole) of phosphoryl chloride, the temperature not rising above +5° C. The solution was stirred at room temperature for 15 min, then cooled to 0° C and a solution of 0.6 g (0.00243 mole) of I in 3.5 ml of dimethylformamide was added. There was an immediate precipitate of a yellowish-green color. On continued stirring at room temperature, this precipitate gradually redissolved and a new precipitate began to form. The reaction mixture was stirred for 4 hr at 25° C, cooled, the

\*For part III, see [3].

precipitate filtered off, washed with a small amount of dimethylformamide and absolute ether, and triturated with a saturated solution of sodium acetate. The solid was filtered off, washed with water, and dried to give 0.47 g of II. The dimethylformamide mother liquors were poured onto ice, and the solid filtered off and triturated with sodium acetate solution, giving a further 0.14 g of II. Total yield 0.61 g (91.5%) of II as a bright yellow crystalline solid, mp 199.5–200.5 °C (from ethanol), readily soluble in chloroform but insoluble in water and ether. Compound II gives a silver mirror on standing for several hours after heating with an ammoniacal solution of silver nitrate. The UV spectrum in ethanol shows  $\lambda_{\max}$ , nm (log  $\epsilon$ ): 261 (4.28); 298 (4.32); 386 (4.36). The IR spectrum (in vaseline oil):  $\nu_{\text{CO}}$  1640  $\text{cm}^{-1}$ . Found, %: C 74.12; H 5.00; N 15.24. Calculated for  $\text{C}_{17}\text{H}_{13}\text{N}_3\text{O}$ , C 74.16; H 4.76; N 15.26.

**1-Dimethylaminomethyl-3-phenyl-4-methylimidazo[5,1-b]-benzimidazole (III).** To a suspension of 1.2 g (0.00486 mole) of I in 0.6 ml of absolute alcohol was added 0.72 ml of 40% aqueous dimethylamine and 0.9 ml of 30% formalin solution. Addition of the latter caused evolution of heat, the I dissolving and an oil separating which gradually crystallized on standing. The reaction mixture was kept for two days at room temperature, and the precipitate filtered off, washed with water, and dried to give 1.45 g (98.5%) of III as a white crystalline solid with a yellowish cast, mp 114.5–116.5 °C (after recrystallization from ether or precipitation from alcohol with water). The compound turned yellow on standing in air. Found, %: C 74.73; H 6.54; N 17.84. Calculated for  $\text{C}_{19}\text{H}_{20}\text{N}_4$ , %: C 74.97; H 6.62; N 18.41.

**1-Hydroxymethyl-3-phenyl-4-methylimidazo[5,1-b]benzimidazole (IV).** A suspension of 1.2 g (0.00486 mole) of I in 40 ml of water and 1 ml of formalin was boiled for 4 hr, during which time a precipitate formed. The mixture was cooled, the precipitate filtered off, washed with water, and dried, giving 1.31 g (98%) of IV as a white crystalline solid with a cream tint, decomposition temperature 159–160 °C (from ethyl acetate). The compound is readily soluble in alcohol and chloroform, but insoluble in water. The UV spectrum in ethanol shows  $\lambda_{\max}$ , nm (log  $\epsilon$ ): 232 (4.41); 255 (3.90); 300 (4.32). The IR spectrum (in vaseline oil):  $\nu_{\text{OH}}$  3120  $\text{cm}^{-1}$ . Found, %: C 73.54; H 5.30; N 15.14. Calculated for  $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}$ , %: C 73.62; H 5.45; N 15.15.

**1-Nitroso-3-phenyl-4-methylimidazo[5,1-b]benzimidazole (V).** To a solution of 1.89 g (0.00765 mole) of I in 15 ml of acetic acid was added, with cooling and stirring, 0.75 g (0.011 mole) of sodium nitrite. A vigorous reaction set in at 5 °C, with foaming, the mixture turning brown. After stirring for 15 min, the mixture was poured into ice water, the yellow precipitate filtered off, washed with water, and dried to give 1.75 g (83%) of V as thin, dark green needles, decomposition temp. 222–222.5 °C (from ethanol), insoluble in water, and sparingly soluble in hot alcohol. The UV spectrum in ethanol shows  $\lambda_{\max}$ , nm (log  $\epsilon$ ): 265 (4.22); 286 (4.06); 322 (3.90); 427 (4.27).

Found, %: C 69.16; H 4.40; N 20.40. Calculated for  $\text{C}_{16}\text{H}_{12}\text{N}_4\text{O}$ , C 69.55; H 4.38; N 20.28.

**1-Acetyl-3-phenyl-4-methylimidazo[5,1-b]benzimidazole (VI).** A mixture of 0.58 g (0.0024 mole) of I, 0.5 g of anhydrous sodium acetate, and 5 ml of acetic anhydride was boiled for 2 hr, the I dissolving and the solution turning green. The excess of acetic anhydride was removed in vacuo, and the residue treated with water. The solid was filtered off, washed with water, and dried. There was obtained 0.64 g (94.2%) of VI as bright yellow needles, mp 209–210.5 °C (from absolute ethanol), readily soluble in chloroform, but sparingly so in alcohol, and insoluble in water. The UV spectrum in ethanol shows:  $\lambda_{\max}$ , nm (log  $\epsilon$ ): 257 (4.22); 300 (4.29); 382 (3.35). The IR spectrum (in vaseline oil):  $\nu_{\text{CO}}$  1645  $\text{cm}^{-1}$ . Found, %: C 74.44; H 5.42; N 14.46. Calculated for  $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}$ , %: C 74.72; H 5.23; N 14.52.

**1-Cyanoethyl-3-phenyl-4-methylimidazo[5,1-b]benzimidazole (VII).** To 10 ml of freshly-distilled acrylonitrile was added, with stirring, 1 g (0.0041 mole) of I. To the solution was added dropwise 1 ml of Rodionov's reagent, heat evolved, and the mixture darkened in color. The mixture was boiled for 8 hr, the excess of acrylonitrile removed in vacuo and the brown residue treated with boiling alcohol. The alcoholic extract was filtered, evaporated in vacuo, the residue triturated with a small amount of alcohol and the solid filtered off to yield VII, bright yellow needles mp 184–186 °C (from absolute ethanol). Found, %: C 76.00; H 5.44. Calculated for  $\text{C}_{19}\text{H}_{16}\text{N}_4$ , %: C 75.97; H 5.37. Treatment of the alcoholic filtrate with alcoholic picric acid gave 0.6 g (31.5%) of the picrate of I, mp 187–188 °C, undepressed on admixture with the picrate prepared from a pure sample of I.

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