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

II. 3, 4-Dimethyl- and 1, 3, 4-Trimethylimidazo[5, 1-b]benzimidazoles*

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By the cyclization of the formyl and acetyl derivatives of 2-(α-aminoethyl)-1-methylbenzimidazole under the action of phosphorus oxychloride we have synthesized, respectively, 3, 4-dimethyl- and 1, 3, 4-trimethylimidazo[5, 1-b]benzimidazoles. 2-(α-Aminoethyl)-1-methylbenzimidazole was obtained by reducing the oxime of 2-acetyl-1-methylbenzimidazole. The latter was synthesized from 1-methylbenzimidazole by an organolithium synthesis.

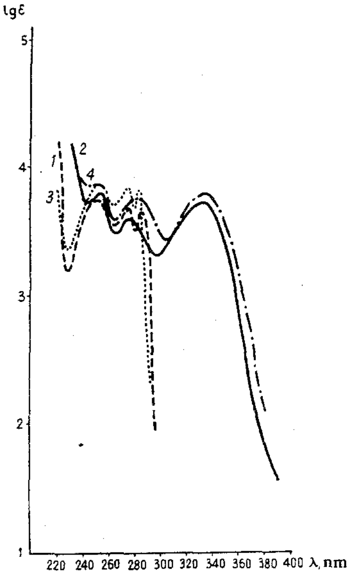
In a preceding paper [1] we have reported that acyl derivatives of 2-aminomethyl-1-methylbenzimidazole having a pyridine or phenyl residue on the C atom of the aminomethyl group undergo ring closure on being heated with phosphorous oxychloride to give a tricyclic system with the formation of the corresponding derivatives of imidazo[5, 1-b]benzimidazole.

In the present paper we report the synthesis of 3, 4-dimethyl- (V) and 1, 3, 4-trimethyl- (VII) -imidazo-[5, 1-b]benzimidazoles, which was effected by a scheme analogous to that given in the preceding communication [1]. By an organolithium synthesis, from 1-methylbenzimidazole [2] and ethyl acetate we obtained 2-acetyl-1-methylbenzamidazole (I), which has been synthesized previously in a different manner [3]. The oxime (II) of compound I was reduced with zinc in aqueous ammonia to the amine (III). Like the acyl derivatives of other substituted 2-aminomethyl-1-methylbenzimidazoles [1], the formyl and acetyl derivatives of III underwent ring closure under the action of phosphorus oxychloride with the formation of 3, 4-dimethyl- and 1, 3, 4-trimethylimidazo[5, 1-b]benzimidazoles, V and VII, respectively. The structure of the latter was confirmed by their IR and UV spectra. The IR spectra of V and VII (the IR spectra of V were taken in a tablet of KBr) lack the absorption band of the NH group that is characteristic for the starting materials IV and VI and have strong absorption bands at 1635 and 1645 cm^{-1}, respectively, and absorption bands at 1504 and 1505 cm^{-1}, respectively, due to the stretching vibrations of the C=C and C=N bonds of a ring.

The UV spectra of V and VII, like the spectra of other imidazo[5, 1-b]benzimidazole derivatives differ markedly from the spectra of the corresponding starting materials (IV and VI) (see figure).

EXPERIMENTAL

2-Acetyl-1-methylbenzimidazole (I). With stirring, at -60° C, a solution of 13.22 g (0.1 mole) of 1-methylbenzimidazole in 400 ml of absolute ether was gradually added to a solution of butyllithium prepared from 21.6 g (0.312 mole) of lithium in 50 ml of absolute ether and 11.6 g (0.125 mole) of butyl chloride in 26 ml of absolute ether [4]. The reaction mixture was kept at -60° C with stirring for 3 hr, and a solution of 8.81 g (0.1 mole) of freshly-distilled anhydrous ethyl acetate in 40 ml of absolute ether was added slowly in drops. The reaction mixture was stirred at a temperature not higher than -53° C for 3 hr and was then carefully poured into dilute (1 : 1) hydrochloric acid. The aqueous layer was separated off, treated with carbon, and, with cooling, made alkaline with aqueous ammonia. The precipitate that deposited was filtered off, washed with water, and dried. This gave 12.27 g (70.5%) of I, a white crystalline substance, mp 74°-74.5° C (from 25% aqueous ethanol); according to the literature [3], mp 64°-65° C. Found, %: N 16.29. Calculated for $C_{10}H_{10}N_2O$, %: N 16.08.



UV spectra: 1) 2-(α-formylaminomethyl)-1-methylbenzimidazole (IV); 2) 3, 4-dimethylimidazo[5, 1-b]benzimidazole (V); 3) 2-(α-acetylaminoethyl)-1-methylbenzimidazole (VI); 4) 1, 3, 4-trimethylimidazo[5, 1-b]-benzimidazole (VII).

Oxime of 2-acetyl-1-methylbenzimidazole (II). A solution of 11 g (0.0631 mole) of I and 11 g (0.1581 mole) of hydroxylamine hydrochloride in 55 ml of absolute ethanol and 55 ml of anhydrous pyridine was heated in the boiling water bath for 3 hr. Then the solvent was distilled off in vacuum and the residue was triturated with 55 ml of water. This gave 10.02 g (84%) of II, mp 218.5°-220° C (from absolute ethanol). Found, %: C 63.49; H 6.00; N 22.11. Calculated for $C_{10}H_{11}N_3O$, %: C 63.47; H 5.86; N 22.21.

2-(α-Aminoethyl)-1-methylbenzimidazole (III). A suspension of 8 g (0.0423 mole) of II in 100 ml of ethanol was boiled with 8 g of zinc dust, 8 g of ammonium acetate, and 300 ml of aqueous ammonia with stirring for 1 hr. Then in two equal portions at 2-hour intervals, another 8 g of zinc dust and 400 ml of aqueous ammonia

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*For part I, see [1].

were added. The hot solution was filtered, and the filtrate was treated with NaOH solution (44.5 g of NaOH in 68 ml of water) and extracted with benzene. After the solvent had been distilled off, 7.18 g (97%) of III was obtained in the form of an oily substance which was characterized in the form of the dihydrochloride. An ethereal solution of HCl was added to an ethereal solution of 0.97 g of III. This gave 1.29 g (94%) of the dihydrochloride of III in the form of colorless crystals, mp 275.5°-276° C (from absolute methanol). Found, %: C 48.38; H 6.28; N 16.91; Cl 28.77. Calculated for $C_{10}H_{13}N_3 \cdot 2HCl$, %: C 48.40; H 6.08; N 16.93; Cl 28.58.

2-(α-Formylaminoethyl)-1-methylbenzimidazole (IV). A solution of 4.9 g 0.028 mole) of III in 18 ml of 88% formic acid was boiled for 3 hr and was then made alkaline to give 5.38 g (94.7%) of IV which was a white crystalline substance with mp 168°-169.5° C (from methanol). Found, %: C 65.17; H 6.45; N 20.35. Calculated for $C_{11}H_{13}N_3O$. Calculated for C 65.00; H 6.45; N 20.68. IR spectrum: ν_{NH} 3230 cm^{-1}; ν_{CO} 1650 cm^{-1}.

3,4-Dimethylimidazo[5,1-b]benzimidazole (V). In drops, with stirring, 8.4 ml of phosphrous oxychloride was added to a suspension of 3 g (0.0148 mole) of IV in 36 ml of anhydrous benzene, whereupon the IV dissolved almost completely and a new precipitate deposited. The reaction mixture was slowly brought to the boil, boiled until the evolution of hydrogen chloride ceased, and then cooled. The precipitate (4.21 g) was filtered off, washed with anhydrous benzene, and treated with 5% sodium bicarbonate solution. The oily substance that separated out was extracted with ether. The ethereal solution was washed, dried, and evaporated in vacuum. The residue (1.52 g, 55%) was dissolved with heating in 5-7 ml of absolute methanol, and the solution was cooled and separated from a small amount of oily matter that had not dissolved. The methanolic solution was evaporated in vacuum and the residue was distilled. This gave V in the form of a light yellow viscous oil, bp 149° C (0.3 mm), which rapidly crystallized. Mp 99°-101.5° C. Found, %: C 71.25; H 6.18; N 22.34. Calculated for $C_{11}H_{11}N_3$, %: C 71.33; H 5.99; N 22.69. Readily soluble in chloroform, ethyl acetate, and ethanol, and sparingly soluble in ether. On standing in the air it deliquesces and becomes dark green. An ethereal solution is stable but a chloroform solution rapidly becomes dark green. It dissolves readily in dilute hydrochloric acid. **Picrate**, yellow crystals, mp 197.5°-199.5° C (from acetone). Found, %: C 49.01; H 3.43. Calculated for $C_{11}H_{11}N_3 \cdot C_6H_3N_3O_7$, %: C 49.28; H 3.41.

2-(α-Acetylaminoethyl)-1-methylbenzimidazole (VI). A solution of 1.31 g (0.00746 mole) of III in 6.5 ml of acetic acid and 3.5 ml of acetic anhydride were heated in the boiling water bath for 2 hr and then it was evaporated in vacuum and the residue was triturated with 2 ml of water. This gave 1.22 g (75.4%) of a white crystalline substance with mp 176.5°-177° C (from benzene). Readily soluble on heating in ethanol and water. Found, %; C 66.49; H 6.71; N 19.37. Calculated for $C_{12}H_{15}N_3O$, %: C 66.33; H 6.96; N 19.34. IR spectrum: ν_{NH} 3300 cm^{-1}; ν_{CO} 1642 cm^{-1}.

1,3,4-Trimethylimidazo[5,1-b]benzimidazole (VII). The reaction was carried out with 1 g (0.0046 mole) of VI, 12 ml of anhydrous benzene, and 2.8 ml of phosphorus oxychloride as in the case of V. The precipitate (1.43 g) was filtered off, washed with anhydrous benzene, and treated with 5% sodium bicarbonate solution. The residue (0.79 g) was filtered off, washed with water, and dried. For purification, the substance was dissolved in a small amount of ethanol, and the ethanolic solution was filtered and evaporated several times. This gave 0.61 g (74.6%) of a cream-colored crystalline substance with mp 119°-121.5° C (from a 1 : 1 mixture of benzene and hexane). Found, %: C 72.34; H 6.40; N 20.98. Calculated for $C_{12}H_{13}N_3$, %: C 72.33; H 6.57; N 21.09. Readily soluble in chloroform, ethanol, and benzene, more sparingly in ether. Stable on storage. Readily soluble in dilute hydrochloric acid. **Picrate**, yellow crystals with an orange tinge, mp 213.5°-214.5° C (from acetone). Found, %: C 50.84; H 3.56; N 19.83. Calculated for $C_{12}H_{13}N_3 \cdot C_6H_3N_3O_7$, %: C 50.47; H 3.77; N 19.62.

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