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

III. 1,4-Dimethyl- and 4-Benzylimidazo[5,1-b]benzimidazoles*

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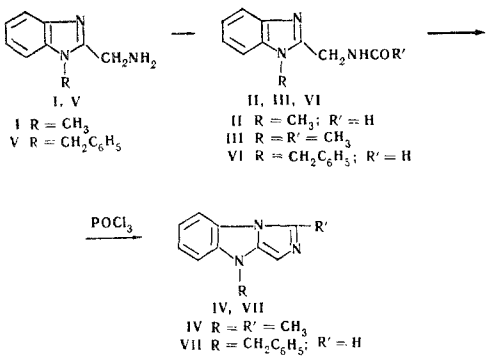
By heating 2-acetylamino-1-methyl- and 1-benzyl-2-formylaminomethylbenzimidazoles with phosphorus oxychloride in toluene, 1,4-dimethyl- and 4-benzylimidazo[5,1-b]benzimidazoles have been obtained.

In preceding communications [1,2] we have shown that when 2-acylaminomethyl-1-methylbenzimidazoles substituted at the C atom of the aminomethyl group are heated with phosphorus oxychloride in benzene, the corresponding 3-substituted imidazo[5,1-b]benzimidazoles are formed. It appeared of interest to obtain imidazo[5,1-b]benzimidazole derivatives not containing substituents in position 3. For this purpose we performed the synthesis of 1-methyl- [3] and 1-benzyl-2-aminomethylbenzimidazoles (I, V), acyl derivatives of which were then treated with phosphorus oxychloride.



The starting material for the synthesis of I and V was o-chloronitrobenzene. By heating this with an ethanolic solution of methylamine and with benzylamine, we obtained N-methyl- [4,5] and N-benzyl-o-nitroanilines [6], which were then reduced with stannous chloride in concentrated hydrochloric acid to N-methyl- [7] and N-benzyl-o-phenylenediamine [8], respectively. The latter is also formed in high yield by the hydrogenation of N-benzyl-o-nitroaniline in the presence of a nickel catalyst. Attempts to obtain N-methyl-o-phenylenediamine by the methylation of o-phenylenediamine with methyl iodide [9,3] led to the formation of a mixture apparently consisting of polymethylated compounds, and it was impossible to isolate pure N-methyl-o-phenylenediamine in adequate yield. The reaction of N-methyl-o-phenylenediamine with glycine ethyl ester hydrochloride gave I in the form of the dihydrochloride [3], from which the base I was isolated. Compound V was synthesized from N-benzyl-o-phenylenediamine analogously. Heating I and V with formic acid gave

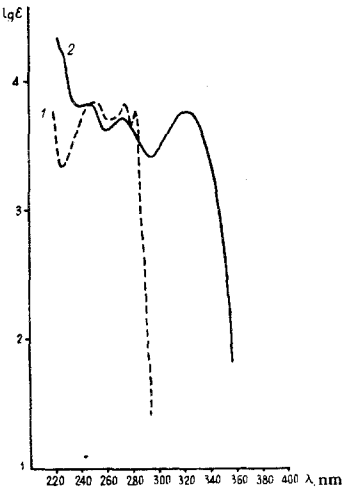


Fig. 1. UV spectra: 1) 2-acetylaminomethyl-1-methylbenzimidazole (III); 2) 1,4-dimethylimidazo[5,1-b]benzimidazole (IV).

the formyl derivatives II and VI. However, when II reacted with phosphorus oxychloride in boiling benzene pronounced resinification took place and only in some experiments was it possible to isolate a small yield of a compound with the composition $C_{10}H_9N_3$, with mp 187.5°-189° C, the structure of which was not established. The cyclization of the acetyl derivative of I (III) took place considerably better. In this case, 1,4-dimethylimidazo[5,1-b]benzimidazole (IV) was obtained as a very unstable compound which rapidly changed on contact with the air, acquiring a violet coloration. Compound VI, in contrast to II, also readily cyclized but the reaction product, 4-benzylimidazo[5,1-b]benzimidazole (VII) proved to be a stable compound.

The IR spectra of compounds IV and VII had strong absorption bands at 1628 and 1497 cm^{-1} and at 1610 and 1500 cm^{-1}, respectively, due to the stretching vibrations of the C=C and C=N bonds of the ring. The absorption bands of the NH and CO groups characteristic for the initial compounds (III and VI) were absent from the spectra of IV and VII. The UV spectra of the imidazo[5,1-b]benzimidazole derivatives IV and VII and of the corresponding starting materials are given in the figures. The UV spectra of compounds IV and VII are similar to those of 3,4-dimethylimidazo-[5,1-b]benzimidazole [2].

*For part II, see [2].

EXPERIMENTAL

2-Aminomethyl-1-methylbenzimidazole (I). A solution of 20 g of the dihydrochloride of I [3] in 50 ml of water was treated with aqueous potassium carbonate solution. The base was extracted with

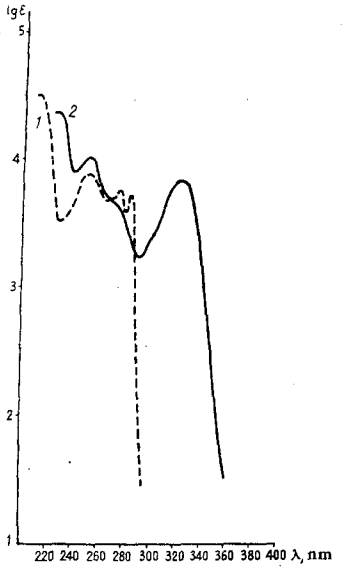


Fig. 2 UV spectra 1) 1-benzyl-2-formyl-aminomethylbenzimidazole (VI); 2) 4-benzylimidazo[5,1-b]benzimidazole (VII).

methylene chloride. After the solvent had been distilled off, 13.32 g (97%) of I was obtained. Colorless elongated needles, mp 72.3°-73.5° C (from water). Found, %: N 24.56. Calculated for $C_9H_{11}N_3 \cdot {}^1/_2H_2O$, %: N 24.69.

2-Formylaminomethyl-1-methylbenzimidazole (II). A mixture of 10 g (0.0426 mole) of the dihydrochloride of I, 10 g of sodium acetate in 50 ml of water, and 100 ml of formic acid was heated in the boiling water bath for 3 hr and evaporated in vacuum, and the residue was made alkaline. This yielded 7.29 g (90.5%) of II as a colorless crystalline substance with mp 143.5°-145° C (from water). Found, %: C 63.63; H 5.86; N 22.26. Calculated for $C_{10}H_{11}N_3O$, %: C 63.47; H 5.86; N 22.21.

2-Acetylaminomethyl-1-methylbenzimidazole (III). A mixture of 3.5 g (0.0217 mole) of I, 17.5 ml of acetic acid, and 8 ml of acetic anhydride was heated in the boiling water bath for 2 hr and was then evaporated in vacuum, and the residue was triturated with 7 ml of water. This gave 3.68 g (83.5%) of III, mp 159°-160° C (from absolute ethanol). Found, %: C 64.81; H 6.57; N 20.65. Calculated for $C_{11}H_{13}N_3O$, %: C 65.00; H 6.45; N 20.68. IR spectrum: ν_{NH} 3245 cm^{-1}; ν_{CO} 1665 cm^{-1}.

1,4-Dimethylimidazo[5,1-b]benzimidazole (IV). In drops, with stirring, 15 ml of phosphorus oxychloride was added to a suspension of 5 g (0.0246 mole) of III in 70 ml of anhydrous toluene, and the reaction mixture was heated at 96°-103° C until no more hydrogen chloride was evolved. After cooling, the solid matter (7.35 g) was filtered off, washed with anhydrous toluene, and, with cooling and stirring, treated with a solution of sodium bicarbonate. The oily substance liberated was extracted with ether or benzene. After the solvent had been distilled off in vacuum, 2.82 g (62%) of a substance was obtained which was dissolved in 5 ml of methanol with heating. The solution was cooled, a small amount of insoluble oily matter was separated off, and the filtrate was evaporated in vacuum and the residue was distilled. This gave IV in the form of a light yellow viscous oily substance which rapidly crystallized, bp 135°-136° C (0.25 mm), mp 92°-94° C. Found, %: C 71.01; H 5.99; N 22.78. Calculated for $C_{11}H_{11}N_3$, %: C 71.33; H 5.99; N 22.69; The substance is readily soluble in ethanol, ethyl acetate, and chloroform, and more sparingly in ether and benzene. It is stable on storage without the access of air and light. On standing in the air, it rapidly darkens and acquires a violet coloration. A solution of IV in ether is stable while a chloroform solution rapidly becomes dark violet. The substance dissolves in dilute hydrochloric acid. **Picrate**, yellow crystalline substance, mp 214° C (decomp., from acetone). Found, %: C 49.23; H 3.53; N 20.48. Calculated for $C_{11}H_{11}N_3 \cdot C_6H_3N_3O_7$, %: C 49.28; H 3.41; N 20.28.

2-Aminomethyl-1-benzylbenzimidazole (V). A carefully stirred mixture of 48.24 g (0.244 mole) of N-benzyl-o-phenylenediamine and 34.1 g (0.244 mole) of glycine ester hydrochloride was heated with stirring in a current of nitrogen at 180°-200° c for 3 hr. The reaction mixture was cooled at 40°-50° C and dissolved with heating in 100 ml of concentrated hydrochloric acid, and the hot solution was treated with carbon and filtered. The filtrate was evaporated in vacuum and the residue was dissolved in water; the insoluble viscous mass was filtered off. The filtrate was made alkaline with aqueous ammonia solution, with cooling, and was extracted with benzene. The residue after the benzene had been distilled off (30 g) was treated with an ethanolic solution of picric acid. This gave 34.34 g (30%) of the picrate of V, decomp. p. 189°-190° C (from ethanol). Found, %: C 54.37; H 4.08; N 18.30. Calculated for $C_{15}H_{15}N_3 \cdot C_6H_3N_3O_7$, %: C 54.08; H 3.89; N 18.02. The treatment of 1.65 g of the picrate of V with concentrated HCl gave a quantitative yield of the dihydrochloride of V in the form of colorless elongated needles, mp 170°-171.5° C (from concentrated HCl), readily soluble in water and ethanol. Found, %: Cl 22.51; N 13.50. Calculated for $C_{15}H_{15}N_3 \cdot 2HCl$, %: Cl 22.86; N 13.55. When the dihydrochloride of V was treated with potassium carbonate solution, the base V was obtained as a crystalline substance with mp 53°-53.5° C (from aqueous ethanol, 1:1), readily soluble in ethanol and ether. Found, %: C 75.46; H 6.13; N 17.79. Calculated for $C_{15}H_{15}N_3$, %: C 75.92; H 6.37; N 17.71.

1-Benzyl-2-formylaminomethylbenzimidazole (VI). This compound was obtained in a similar manner to II, yield 86%, mp 153°-154° C (from water). Found, %: C 72.75; H 5.78; N 15.89, Calculated for $C_{16}H_1N_3O$, %: C 72.43; H 5.70; N 15.84. IR spectrum: ν_{NH} 3235 cm^{-1}; ν_{CO} 1695 cm^{-1}.

4-Benzylimidazo[5,1-b]benzimidazole (VII). To 9.8 ml of phosphorus oxychloride was added to 3.5 g (0.0132 mole) of VI in 42 ml of anhydrous toluene and the mixture was worked up as for the production of IV. The oily substance formed after the treatment of the residue with sodium bicarbonate solution was extracted with benzene. The solvent was distilled off and the oily residue was triturated with ether. The solid produced (1.42 g, 42%) was filtered off, treated in the same way as IV, and distilled. This gave VII in the form of a yellowish oil which rapidly crystallized, bp 207°-208° C (0.3 mm). Mp 107-108° C. Found, %: C 77.75; H 5.45; N 16.73. Calculated for $C_{16}H_{13}N_3$, %: C 77.71; H 5.30; N 16.99. The substance dissolves readily in ethanol, chloroform, and ethyl acetate, and more sparingly in ether and benzene. It dissolves in dilute hydrochloric acid. **Picrate**, light yellow crystals, mp 189°-190.5° C (from ethanol). Found, %: C 55.62; H 3.47; N 17.54. Calculated for $C_{16}H_{13}N_3 \cdot C_6H_3N_3O$, %: C 55.46; H 3.39; N 17.64.

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