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STUDIES ON HETEROCYCLICS

Part 2. Bromination of some Benzimidazole Derivatives

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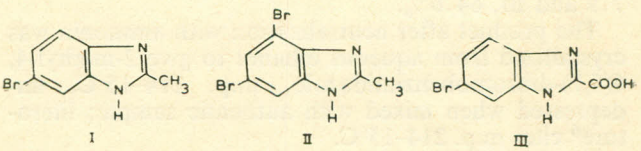
Abstract. Bromination of 2-methylbenzimidazole with bromine in chloroform gave 2-methyl-5(6)-bromobenzimidazole and 2-methyl-4,6(5,7)-dibromobenzimidazole. Bromination with *N*-bromosuccinimide gave only 2-methyl-5(6)-bromobenzimidazole. Bromination of 2-carboxybenzimidazole gave 2-carboxy-5(6)-bromobenzimidazole.

The halogenation reactions of benzimidazole and its derivatives have not been investigated extensively, although it is reported that bromination of heteroaromatic compounds proceeds by different paths depending on the nature of the brominating agent and the substrate.[1] Thus most of the known halogenobenzimidazoles have been synthesized by ring closure reactions of compounds containing the desired halogen substituent in the starting material itself. The present work is directed towards a study of bromination of 2-methyl- and 2-carboxybenzimidazole with bromine in chloroform and acetic acid respectively. The bromination of 2-methylbenzimidazole with *N*-bromosuccinimide has also been investigated.

In the existing relevant literature the following results have been reported. Treatment of 2-methylbenzimidazole with bromine in glacial acetic acid gives 2-methyl-4(7)-bromobenzimidazole.[2] With hypochlorites the imino hydrogen is replaced[3] and when 2,6-dimethyl-1-chlorobenzimidazole is refluxed in benzene solution the chlorine atom changes its place with a hydrogen atom on the benzene portion of the molecule; in this manner it is possible, through repetitions of this process, to replace all the hydrogen atoms of the benzene part of the molecule by chlorine atoms. Treatment of benzimidazole with iodine in presence of alkali gives a monoiodo derivative; the compound has been assumed to be 2-iodobenzimidazole.[4]

Discussion

The bromination of 2-methylbenzimidazole was carried out with one mole of bromine in chloroform solution and two products, a mono- and a dibromo-derivative, were obtained as hydrobromide salts. Treatment with ammonia yielded 2-methyl-5(6)-bromobenzimidazole (I) in the case of the monobromo derivative, and 2-methyl-4,6(5,7)-dibromobenzimidazole(II) in the case of the dibromo derivative. The identity of the compounds was established by synthesizing both the mono and the dibromo derivative through known synthetic procedures. Thus, 2-methyl-5(6)-bromobenzimidazole was prepared[5] by reducing *p*-bromo-*o*-nitroaniline with iron and hydrochloric acid to *p*-bromo-*o*-phenylenediamine and subsequent condensation with acetic anhydride. The 2-methyl-4,6(5,7)-dibromobenzimidazole was obtained by bromination of 2-methyl-5(6)-bromobenzimidazole in acetic acid.[6]



It is reported in the literature that *N*-bromosuccinimide brominates in the side chain specifically, e.g. bromination of 3-methylthiophene affords 3-bromoalkylthiophene rather than the nucleur-substituted products. In order to investigate the *N*-bromosuccinimide bromination of 2-methylbenzimidazole, this latter compound was treated with one mole of *N*-bromosuccinimide in carbon tetrachloride solution. An oily product was obtained which, when crystallized from aqueous ethanol, yielded an impure sample of 2-methyl-5(6)-bromobenzimidazole. The identity of this product was established by comparing the IR spectrum with that of an authentic sample and by determining the mixed melting point of the two, which remained undepressed. The R_f values on TLC of this product and that of the authentic sample were identical.

The bromination of 2-carboxybenzimidazole was carried out with one mole of bromine in acetic acid, yielding a monobromo derivative only. This bromocarboxylic acid was characterized as 2-carboxy-5(6)-bromobenzimidazole (III) by comparison with an authentic sample. Furthermore, this product was also afforded by the oxidation of 2-methyl-5(6)-bromobenzimidazole with potassium permanganate. The authentic sample of 2-carboxy-5(6)-bromobenzimidazole was prepared by condensation of *p*-bromo-*o*-phenylenediamine with glycolic acid, the 2-hydroxymethylbenzimidazole obtained in this manner was oxidized with potassium permanganate to form the desired product.

Experimental

Bromination of 2-Methylbenzimidazole. 2-Methylbenzimidazole (1.32 g) in chloroform (15 ml)

was treated with bromine (1.6 g) in chloroform (10 ml). The solution was left overnight at room temperature when a pale yellow solid (2.1 g) was obtained. Crystallization from chloroform–ethanol afforded white needles, m.p. 221–22°C of 2-methyl-5(6)-bromobenzimidazole hydrobromide. Found: C,33.6; H, 2.8; N, 9.9 and Br, 53.5%. $C_8H_8N_2Br_2$ requires: C, 32.8; H, 2.7; N, 9.5 and Br, 54.2%.

The hydrobromide (0.2 g) was neutralized with ammonia, giving 2-methyl-5(6)-bromobenzimidazole from aqueous ethanol, m.p. 214–15°C. The product was identical with an authentic sample from the point of the mixture melting point and IR spectrum.

After the separation of 2-methyl-5(6)-bromobenzimidazole, the filtrate was concentrated when another solid separated out. Repeated crystallization from chloroform–ethanol gave 2-methyl-4,6(5,7)-dibromobenzimidazole hydrobromide (0.3 g), m.p. 270°C (dec.). Found: C, 25.7; H, 1.8; N, 7.4 and Br, 62.0%. $C_8H_7N_2Br_3$ requires: C, 25.8; H, 1.9; N, 7.9 and Br, 64.6%.

The product after neutralization with ammonia was crystallized from aqueous ethanol to give 2-methyl-4, 6(5,7)-dibromobenzimidazole, m.p. 214–15°C, undepressed when mixed with authentic sample; literature[6] cites m.p. 214–15°C.

Bromination of 2-methylbenzimidazole with N-bromosuccinimide. 2-Methylbenzimidazole (1.32 g), *N*-bromosuccinimide (1.78 g) and benzoyl peroxide (few crystals) were taken in carbon tetrachloride (50 ml) and the solution was refluxed for 30 min. An oil (1.8 g) was obtained which on crystallization from aqueous ethanol gave white needles, m.p. 205°C. The product was identical with an authentic sample of 2-methyl-5(6)-bromobenzimidazole from the point of mixture melting point, IR spectra and R_f values for TLC on alumina using 8% benzene–petroleum mixture.

Bromination of 2-Carboxybenzimidazole. 2-Carboxy benzimidazole (0.56 g) in 6N acetic acid was treated with bromine (0.56 g) in acetic acid (10 ml). The solution was left overnight when a white product, 2-carboxy-5(6)-bromobenzimidazole, separated out and was washed with ether (3×10 ml); m.p. 158°C (dec.), undepressed when mixed with an authentic sample. Found: C, 39.9; H, 2.2; N, 12.4 and Br, 34.3%. $C_8H_5N_2O_2$ Br requires: C, 39.8; H, 2.0; N, 11.6 and Br. 33.1%.

The IR spectrum of the product is identical to that of an authentic sample.

2-Carboxy-5(6)-bromobenzimidazole. To *p*-bromo-*o*-nitroaniline (2.5 g) in water (25 ml) was added HCl(concd) (0.3 ml) and iron metal (5 g). The mixture was heated till all the nitro compound had reacted, when sodium carbonate (1 g) was added. The solution was filtered and the residue washed with hot water. The combined filtrate and washings on extraction with chloroform and subsequent drying and evaporation of the solvent (chloroform) gave *p*-bromo-*o*-phenylenediamine (0.5 g), m.p. 54–61°C.

p-Bromo-*o*-phenylenediamine (0.5 g) and glycolic acid (0.3 g) were refluxed together for 2 hr in 15% HCl. The solution was cooled and neutralized with ammonia to give 2-hydroxy-methyl-5(6)-bromobenzimidazole (0.5 g), m.p. 208°C. This compound on oxidation with a solution of potassium permanganate (1.4 g) in water (28 ml) containing sodium carbonate gave 2-carboxy-5(6)-bromobenzimidazole (0.3 g), m.p. 158°C (dec).

2-Methyl-5(6)-bromobenzimidazole. p-Bromo-*o*-nitro aniline (4.0 g) was reduced with iron powder (11.9 g) and HCl (concd) (0.5 ml) in water (20 ml) in presence of sodium carbonate (10 g) to give *p*-bromo-*o*-phenylenediamine (1.5 g), m.p. 59–60°C from benzene-petroleum ether mixture. The diamine (1.1 g) and acetic anhydride (1 ml) were refluxed in 4N HCl for 20 min. The mixture was neutralized with NaOH(dil) when a white precipitate was obtained. This was filtered out, washed with water, and crystallized from aqueous ethanol to give 2-methyl-5(6)-bromobenzimidazole, m.p. 214–15°C. Literature[5] cites m.p. 214–15°C.

2-Methyl-4,6(5,7)-dibromobenzimidazole. 2-Methyl -5(6)-bromobenzimidazole (0.5 g) in glacial acetic acid was treated with bromine (0.4 g) in glacial acetic acid (2 ml). The solution was left overnight, and then diluted with water and neutralized with sodium carbonate, when a solid was precipitated. This was filtered out, washed with water, and crystallized from aqueous ethanol to give 2-methyl-4, 6(5,7)-dibromobenzimidazole (0.51 g), m.p. 214–15°C. Literature cites m.p. 214–15°C.

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