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

VI.* SOME REACTIONS OF 3-PHENYL-4-METHYLIMIDAZO[5,1-b]BENZIMIDAZOLE

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Several substitution reactions (the Mannich reaction, azo coupling, and bromination) of 3-phenyl-4-methylimidazo[5,1-b]benzimidazole were carried out. The corresponding 1-nitro derivative was obtained from 1-bromo-3-phenyl-4-methylimidazo[5,1-b]benzimidazole.

In one of our previous studies [2], we reported several electrophilic substitution reactions of 3-phenyl-4-methylimidazo[5,1-b]benzimidazole (I). It was shown that I readily undergoes the Mannich reaction with formalin and aqueous dimethylamine. In a continuation of this research and also in a search for new pharmacologically active compounds among substituted 4H-imidazo[5,1-b]benzimidazoles, we carried out the reaction of I with formalin and N-methylpiperazine and isolated 1-(4-methylpiperazinyl)methyl-3-phenyl-4-methylimidazo[5,1-b]benzimidazole dihydrochloride (II) in high yields. However, II and its aqueous solutions proved to be unstable in light and in the presence of air oxygen, in connection with which it was impossible to study its pharmacological properties.

The reaction of I with p-bromo- and p-methoxybenzenediazonium borofluorides under the conditions described for the preparation of azo derivatives in the pyrrolo[1,2-a]imidazole series [3] gave, respectively, 1-(p-bromophenylazo)- (III) and 1-(p-methoxyphenylazo)-3-phenyl-4-methylimidazo[5,1-b]benzimidazole (IV).

The bromination of I with molecular bromine in chloroform gives a dark-brown substance, insoluble in water and organic solvents, which could not be purified by recrystallization. Considerably better results were obtained on heating I with N-bromosuccinimide in carbon tetrachloride under the conditions that we described for the preparation of 1-phenyl-3-bromo-4-methylimidazo[5,1-b]benzimidazole [4]. In this case, 1-bromo-3-phenyl-4-methylimidazo[5,1-b]benzimidazole (V) was obtained in high yields. This compound is quite stable in the solid state but decomposes on recrystallization from ethanol; solutions of it in chloroform darken rapidly.

Attempts were made to replace bromine by other groups in order to prove the structure of V and also to study the capacity of bromine in this compound for nucleophilic substitution reactions. Compound V did not undergo any change when it was heated in alcoholic alkali and was quantitatively recovered. Attempts to carry out the substitution of bromine by ethoxy or butoxy groups by refluxing in alcohol solutions of V with the corresponding sodium alkoxides were also unsuccessful. The starting material was isolated in both cases.

*See [1] for communication V.

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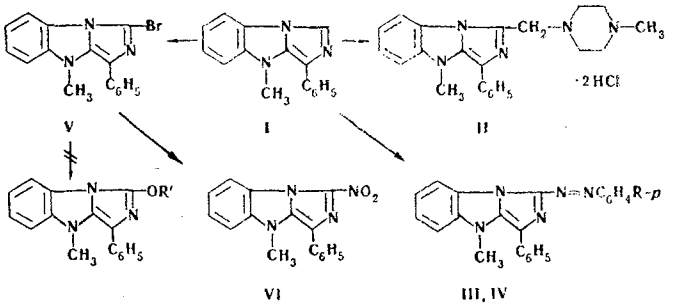

III R=Br; IV R=OCH$_3$; R′=H, C$_2$H$_5$, n-C$_4$H$_9$

Attempts to replace the bromine by a nitro group proved to be more successful. Heating of V with sodium nitrite in dimethyl sulfoxide [5] gave mononitro derivative VI, the PMR spectrum of which did not contain a signal from the 1-H proton. On the basis of this, it was concluded that the nitro group in VI and, consequently, the bromine in V are in the 1 position.

EXPERIMENTAL

1-(4-Methylpiperazinyl)methyl-3-phenyl-4-methylimidazo[5,1-b]benzimidazole Dihydrochloride (II). A total of 2 ml of 30% formalin and 2.02 g (20.2 mmole) of N-methylpiperazine were added with stirring to a suspension of 5 g (20 mmole) of I in 3 ml of absolute ethanol. Compound I gradually dissolved, and a viscous light-brown oil appeared. The reaction mass was stirred for 5 h, and an ether solution of hydrogen chloride was then added until a precipitate no longer formed. The solution was decanted, and the precipitate was triturated with a small amount of absolute ethanol. The solid was removed by filtration and washed initially with absolute alcohol and then with absolute ether to give 8.32 g (96%) of II with mp 220-223° (after reprecipitation from absolute ethanol by the addition of absolute ether). The colorless crystalline substance was quite soluble in absolute alcohol. Found: C 61.4; H 6.6; N 15.8; Cl 16.5%. $C_{22}H_{25}N_4 \cdot 2HCl$. Calculated: C 61.1; H 6.3; N 16.2; Cl 16.4%. The substance was unstable and became blue in light and on exposure to air. Aqueous solutions of it were also unstable.

1-(p-Bromophenylazo)-3-phenyl-4-methylimidazo[5,1-b]benzimidazole (III). A suspension of 0.67 g (2.5 mmole) of p-bromobenzenediazonium borofluoride in 5 ml of methanol was added to a solution of 0.62 g (2.5 mmole) of I in 13 ml of acetic acid. During the addition, the solution became crimson-colored, and a precipitate formed. The reaction mass was allowed to stand at 20° for 12 h, and the solid (0.94 g) was removed by filtration, washed with ether, and dissolved in the minimum amount of refluxing dimethylformamide (DMF)–methanol (1 : 1). Water was added to the solution until an amorphous orange precipitate appeared and the mixture was again boiled until the precipitate dissolved as drops of DMF were added. The solution was filtered and cooled to give 0.59 g (50%) of red needles of III with mp 200-201°. Found: C 61.5; H 3.6; Br 18.7; N 16.2%. $C_{22}H_{16}BrN_5$. Calculated: C 61.4; H 3.7; Br 18.6; N 16.3%.

1-(p-Methoxyphenylazo)-3-phenyl-4-methylimidazo[5,1-b]benzimidazole (IV). A 0.62-g (2.5 mmole) sample of I was added to a suspension of 0.5 g of anhydrous sodium acetate in 2.5 ml of acetic anhydride and 11 ml of acetic acid. A suspension of 0.56 g (2.54 mmole) of p-methoxybenzenediazonium borofluoride in 11 ml of methanol and 1.1 ml of acetic anhydride was then added to the resulting solution. The reaction mass was allowed to stand at 20° for 12 h, and the precipitate (0.87 g) was removed by filtration and extracted with hot benzene. Removal of the benzene by distillation gave 0.41 g (43%) of IV as a bright-red crystalline substance with mp 186-187° (needles from ethanol). Found: C 72.6; H 5.3; N 18.3%. $C_{23}H_{19}N_5O$. Calculated: C 72.4; H 5.0; N 18.4%.

1-Bromo-3-phenyl-4-methylimidazo[5,1-b]benzimidazole (V). A 0.9-g (5 mmole) sample of N-bromosuccinimide was added to a solution of 1 g (4 mmole) of I in 25 ml of anhydrous carbon tetrachloride, and the mixture was refluxed for 2 h. The hot mass was filtered, the filtrate was cooled, and the precipitated succinimide was removed by filtration. The filtrate was vacuum-evaporated to give 0.94 g (72%) of V as a light-yellow crystalline substance that was insoluble in water and had mp 191-194° (from methanol) and R_f 0.65 [on a plate with activity II Al_2O_3 in a hexane–chloroform system (1 : 2); an orange spot was developed in iodine vapors]. Found: C 58.8; H 3.6; Br 24.5; N 12.8%. $C_{16}H_{12}BrN_3$. Calculated: C 58.9; H 3.7; Br 24.5; N 12.9%.

1-Nitro-3-phenyl-4-methylimidazo[5,1-b]benzimidazole (VI). A mixture of 1 g (3 mmole) of V, 0.51 g (7.4 mmole) of sodium nitrite, and 10.2 ml of dimethyl sulfoxide was heated at 110° for 2 h, during which the

reaction mass became bright-orange. The mixture was cooled, and the precipitate was removed by filtration and washed with ether to give 0.82 g (92%) of VI as an orange crystalline substance that was insoluble in water, benzene, and lower aliphatic alcohols and had mp 233-234.5° (needles from butanol) and R_f 0.49 [on a plate with activity II Al_2O_3 in a petroleum ether–dichloroethane system (17:4); the yellow spot was developed in iodine vapors]. UV spectrum (in alcohol), λ_{max}, nm (log ε): 218 (4.44), 269 (4.34), 304 (4.11), and 452 (4.32). Found: C 65.6; H 4.0; N 19.4%. $C_{16}H_{12}N_4O_2$. Calculated: C 65.7; H 4.1; N 19.2%.

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