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

V. Some Substitution Reactions of 1,4-Dimethyl- and 4-Methyl-1-phenylimidazo[5,1-b]benzimidazoles*

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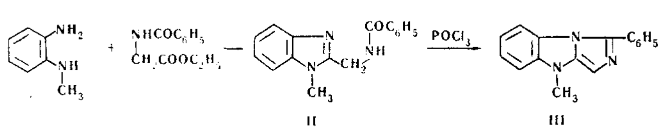
4-Methyl-1-phenylimidazo[5,1-b]benzimidazole (III) has been synthesized. It has been shown that 1,4-dimethylimidazo[5,1-b]benzimidazole (I) and III readily undergo acetylation and nitrosation at position 3. The reaction of I and III with formalin, like the Mannich reaction, leads to the formation of methylenebis derivatives. The bromination of III with N-bromosuccinimide forms the 3-bromo derivative of III (X).

As has been shown previously for the case of 4-methyl-3-phenylimidazo[5,1-b]benzimidazole, derivatives of 4H-imidazo[5,1-b]benzimidazole readily undergo electrophilic substitution reactions at position 1. It appeared of interest to study the reactivity of 1-alkyl and 1-aryl substituted 4H-imidazo[5,1-b]benzimidazoles having no substituent in position 3 – 1,4-dimethyl- (I) [2] and 4-methyl-1-phenyl-imidazo[5,1-b]benzimidazole (III). We synthesized the latter in the following way:



Just like I, compound III is fairly unstable and acquires a blue coloration on standing in the light in the presence of atmospheric oxygen. The structure of III was shown by its IR, UV, and PMR spectra. In the IR spectrum of III there is no absorption band of CO and NH groups, which are present in the IR spectrum of the initial compound (II), and there is a strong split absorption band at 1600-1620 cm^{-1} which is characteristic for such tricyclic compounds. In the UV spectrum of III (Fig. 1) there is a bathochromic shift of the long-wave absorption maximum by 28 nm as compared with the UV spectrum of I [2] and an increase in the intensity of absorption over the whole spectrum. In the PMR spectra of compounds I and III, there are signals of the proton at C_3 in the form of singlets at δ 5.96 and 6.51 ppm, respectively. The signals of the protons of the methyl group on the nitrogen atom in position 4 appear at 3.04 and 3.47 ppm, respectively.

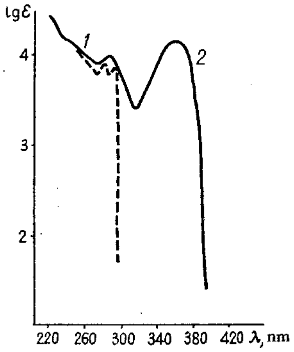


Fig. 1. UV spectra (in ethanol): 1) 2-benzoylaminomethyl-1-methylbenzimidazole (II); 2) 4-methyl-1-phenylimidazo[5,1-b]benzimidazole (III).

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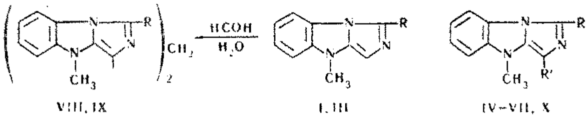
*For part IV, see [1].

The acetylation of I and III with acetic anhydride in the presence of anhydrous sodium acetate gave high yields of 3-acetyl-1,4-dimethyl- and 3-acetyl-4-methyl-1-phenylimidazo[5,1-b]benzimidazoles (IV and V, respectively).

The nitrosation of I and III with sodium nitrite in acetic acid led to the formation of 1,4-dimethyl-3-nitroso- and 4-methyl-3-nitroso-1-phenylimidazo[5,1-b]benzimidazoles (VI and VII, respectively).



R = CH_3 I, IV, VI, VIII; R = C_6H_5 III, V, VII, IX, X; R' = $COCH_3$ IV, V, R' = NO VI, VII; R' = Br X

We attempted to obtain the 3-hydroxymethyl derivative of compound I. However, when compound I was heated with formalin in water, a compound the analysis of which corresponded to bis(1,4-dimethylimidazo[5,1-b]benzimidazol-3-yl)-methane (VIII) was obtained. We isolated the same compound in an attempt to obtain a Mannich base by treating I with an aqueous solution of dimethylamine and formalin both at room temperature and with cooling. The attempted hydroxymethylation of III in an excess of formalin also took place with the formation of a methylenebis derivative (IX).

The bromination of III with N-bromosuccinimide under the conditions described for the preparation of 3-bromoimidazo[5,1-b]pyridine [3] led to the formation of 3-bromo-4-methyl-1-phenylimidazo[5,1-b]benzimidazole (X), which is extremely unstable in the air.

The structures of the 3-substituted compounds I and III obtained were confirmed by their PMR spectra (Fig. 2). The PMR spectra of compounds IV-VII, IX, and X lacked the signal of a proton at C_3. This shows that the substituent in these compounds is present in position 3. In the PMR spectra* of IV and V, signals of the protons of the acetyl group appeared (at δ 2.52 and 2.67 ppm, respectively), and the spectrum of IX showed the signal of the protons of a methylene group (at δ 4.66 ppm).

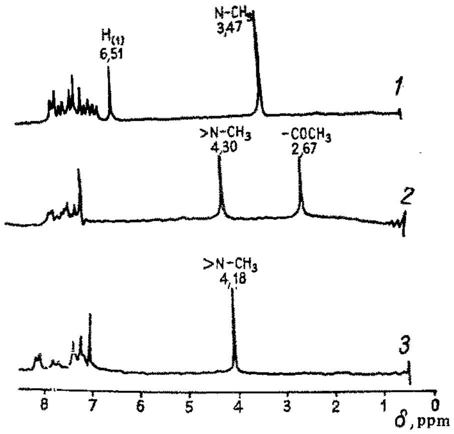


Fig. 2. PMR spectra (in $CDCl_3$): 1) 4-methyl-1-phenyl[5,1-b]benzimidazole (III); 2) 3-acetyl-4-methyl-1-phenylimidazo[5,1-b]benzimidazole (V); 3) 4-methyl-3-nitroso-1-phenylimidazo-[5,1-b]benzimidazole (VII) (internal standard; tetramethylsilane).

EXPERIMENTAL

2-Benzoylaminomethyl-1-methylbenzimidazole (II). A carefully stirred mixture of 10.98 g (0.09 mole) of freshly distilled N-methyl-o-phenylenediamine and 18.65 g (0.09 mole) of ethyl hippurate [4] was heated with stirring in a current

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*The PMR spectra were taken on a JNM-4-H-100 instrument at a working frequency of 100 MHz. The authors express their deep gratitude to G. N. Syrova of the Physical Chemistry Laboratory of VNIKhFI [Ordzhonikidze All-Union Chemical and Pharmaceutical Scientific-Research Institute] for taking the PMR spectra.

of nitrogen at 180-200°C for 3 hr. Then it was left to cool to room temperature (whereupon it gradually solidified) and was triturated with absolute ether or was treated with a small amount of hot ethanol. The precipitate after cooling was filtered off, giving 14.76 g (61.9%) of II, a white crystalline substance with mp 194.5-196°C (from methanol) readily soluble in hot ethanol, and insoluble in water. IR spectrum (in paraffin oil): ν_{NH} 3250; ν_{CO} 1655 cm^{-1}. UV spectrum (in ethanol), λ_{max}, nm (log ε): 225 (4.26)*, 270 (3.80), 278 (3.95), 284 (3.89). Found %: C 72.4; H 5.6; N 15.5. $C_{16}H_{15}N_3O$. Calculated %: C 72.4; H 5.7; N 15.8.

4-Methyl-1-phenylimidazo[5,1-b]benzimidazole (III). A suspension of 6.7 g (25.3 mM) of II in 80 ml of anhydrous toluene and 18.9 ml of phosphorus oxychloride was boiled until the evolution of hydrogen chloride ceased. The residue after the toluene and the excess of $POCl_3$ had been distilled off in vacuum was treated with sodium bicarbonate solution and extracted with chloroform. The extract was washed with saturated NaCl solution and dried with anhydrous K_2CO_3. The residue after the solvent had been evaporated off in vacuum (5.83 g) was distilled. Bp 219-221°C (0.25 mm). This gave 2.53 g (40.5%) of III in the form of a yellow viscous oily substance which immediately crystallized; mp 117-118.5°C. The substance is readily soluble in ethanol, chloroform, and ethyl acetate, somewhat less readily in benzene and ether, and insoluble in water. On standing in the air and in the light, it acquires a blue color. UV spectrum (in ethanol), λ_{max}, nm (log ε): 230 (4.17)*, 250 (4.02)*, 280 (4.00), 352 (4.16). PMR spectrum (in $CDCl_3$), δ, ppm: singlets 3.47 ($N-CH_3$), 6.51 (H_3). Found %: C 77.9; H 5.1; N 16.7. $C_{16}H_{13}N_3$. Calculated %: C 77.7; H 5.3; N 17.0. Picrate, light yellow crystals, decomp. p. 220-221.5°C (from ethanol). Found %: C 55.7; H 3.4; N 17.5. $C_{16}H_{13}N_3 \cdot C_6H_3N_3O$. Calculated %: C 55.5; H 3.4; N 17.6.

3-Acetyl-1,4-dimethylimidazo[5,1-b]benzimidazole (IV). A mixture of 0.7 g (3.78 mM) of 1,4-dimethylimidazo-[5,1-b]benzimidazole (I) [2], 0.81 ml (8.6 mM) of acetic anhydride, and 0.81 g (9.87 mM) of anhydrous sodium acetate was boiled for 3 hr. The excess of acetic anhydride was distilled off in vacuum and the residue was triturated with water. This gave 0.72 g (84%) of IV in the form of a light pink crystalline substance with mp 223.5-225.5°C (long needles from absolute ethanol). The substance is readily soluble in chloroform and is insoluble in water. IR spectrum (in paraffin oil), ν_{CO} 1634 cm^{-1}. UV spectrum (in ethanol), λ_{max}, nm (log ε); 214 (4.34), 224 (4.33), 242 (3.95)*, 303 (4.12), 332 (4.44). PMR spectrum (in $CDCl_3$), δ, ppm: singlets 2.52 ($COCH_3$), 2.71 (CH_3) and 4.19 ($N-CH_3$). Found%: C 68.9; H 5.7; N 18.3. $C_{13}H_{13}N_3O$. Calculated %: C 68.7; H 5.8; N 18.5.

3-Acetyl-4-methyl-1-phenylimidazo[5,1-b]benzimidazole (V). This was obtained in a similar manner to IV with a yield of 89% (1.26 g) from 1.21 g (4.9 mM) of III and 10 ml of acetic anhydride in the presence of 1 g of anhydrous sodium acetate. Cream-colored crystals with mp 247-249°C (from ethanol), readily soluble in chloroform. IR spectrum (in paraffin oil): ν_{CO} 1642 cm^{-1}. UV spectrum (in ethanol), λ_{max}, nm (log ε): 225 (4.28), 329 (4.54). PMR spectrum (in $CDCl_3$), δ, ppm: singlets 2.67 ($COCH_3$), 4.30 ($N-CH_3$). Found %: C 75.0; H 5.4; N 14.8. $C_{18}H_{15}N_3O$. Calculated %: C 74.7; H 5.2; N 14.5.

1,4-Dimethyl-3-nitrosoimidazo[5,1-b]benzimidazole (VI). With cooling and stirring, 0.5 g (7.25 mM) of sodium nitrite was added to a suspension of 0.94 g (5.06 mM) of I in 10 ml of acetic acid, and the mixture was stirred at room temperature for 15 min and poured into 15 ml of ice water. After 2-3 hr, lustrous crystals deposited, which were filtered off and washed with cold water. This gave 0.31 g (28.8%) of VI in the form of colorless needles with mp 125.5-126.5°C (from water), readily soluble in ethanol, chloroform, and hot water. UV spectrum (in ethanol), λ_{max}, nm, (log ε), 228 (4.04)*, 294 (4.21). PMR spectrum (in CD_3OD), δ, ppm: singlets 2.71 (CH_3), 4.14 ($N-CH_3$). Found %: C 61.6; H 4.8; N 25.9. $C_{11}H_{10}N_4O$. Calculated %: C 61.7; H 4.7; N 26.2.

4-Methyl-3-nitroso-1-phenylimidazo[5,1-b]benzimidazole (VII). This was obtained in a similar manner to VI. Yield 75.2%. Yellow crystals with mp 148-151°C (from ligroin), insoluble in water and ethanol, readily soluble in chloroform. UV spectrum (in ethanol), λ_{max}, nm (log ε): 238 (4.30), 259 (4.29), 283 (4.29). PMR spectrum (in $CDCl_3$), δ, ppm, 4.18 ($N-CH_3$, singlet). Found %: C 69.3; H 4.2; N 20.3. $C_{16}H_{12}N_4O$. Calculated %: C 69.5; H 4.4; N 20.3.

Bis(1,4-dimethylimidazo[5,1-b]benzimidazol-3-yl)methane (VIII). A) A suspension of 0.28 g (1.51 mM) of I in 12 ml of water was heated to the boil, and 0.3 ml (3mM) of 30% formalin was added. The oily substance gradually disappeared and a precipitate formed. The reaction mixture was heated for 30 min, and cooled, and the precipitate was filtered off. This gave 0.26 g (90%) of VIII, a cream-colored crystalline substance with mp 201-203°C (elongated needles from a 2 : 1 mixture of ethanol and water). The substance is soluble in ethanol, benzene, and ethyl acetate, and is insoluble in water. On standing in the air and in the light it acquires a pink color. Found %: C 72.3; H 5.9; N 21.8. $C_{23}H_{22}N_6$. Calculated %: C 72.2; H 5.8; N 21.9.

Inflection. Subsequently, inflections in the UV spectra will be denoted by.

B) With stirring and cooling, 0.32 ml (2.85 mM) of a 40% aqueous solution of dimethylamine and 0.38 ml (3.8 mM) of 30% formalin were added to a suspension of 0.46 g (2.48 mM) of I in 0.25 ml of absolute ethanol, whereupon the I dissolved completely and a precipitate deposited (when the formalin was added at room temperature, the reaction mixture became warm). The reaction mixture was left at room temperature for 24 hr. It was then cooled and the precipitate was filtered off. This gave 0.36 g (75.6%) of a substance identical with the material obtained by method (A).

Bis(4-methyl-1-phenylimidazo[5,1-b]benzimidazol-3-yl)methane (IX). With stirring at room temperature, a solution of 0.2 g (0.8 mM) of III in 4 ml of ethanol was added slowly, dropwise, to 6.4 ml (3.2 mM) of 15% formalin, and the mixture was stirred for 3 hr (whereupon a precipitate gradually deposited) and was left for 12 hr. The precipitate was filtered off, washed with water, and dried. This gave 0.18 g (87.7%) of IX in the form of yellowish crystals with mp 249.5-252°C (from butanol). The substance is soluble in hot chloroform and is insoluble in water and lower alcohols. In the light and in the presence of atmospheric oxygen, it becomes crimson. PMR spectrum (in $CDCl_3$), δ, ppm: singlets 3.82 ($N-CH_3$), 4.62 (CH_2). Found %: C 77.9; H 5.1; N 16.3. $C_{33}H_{26}N_6$. Calculated %: C 78.2; H 5.2; N 16.6.

3-Bromo-4-methyl-1-phenylimidazo[5,1-b]benzimidazole (X). With stirring, 0.22 g (1.2 mM) of N-bromosuccinimide was added to a solution of 0.27 g (1.1 mM) of III in 20 ml of anhydrous carbon tetrachloride. The mixture was boiled for 2 hr and filtered, the filtrate was evaporated in vacuum, and the residue (0.17 g) (46.2%) was crystallized from ether. This gave 0.09 g (24%) of X, a pink crystalline substance with mp 152-154°C (from absolute ether). The substance is readily soluble in ethanol, benzene, and chloroform. On standing in the air and in the light, it becomes green. Ethanolic and chloroform solutions also rapidly acquire a green coloration. Found %: C 58.9; H 3.7; N 12.6; Br 24.4. $C_{16}H_{12}N_3Br$. Calculated %: C 58.9; H 3.7; N 12.9; Br 24.5.

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