1,2-DIPHENYLIMIDAZO[1,2-a]BENZIMIDAZOLE IN ELECTROPHILIC SUBSTITUTION REACTIONS

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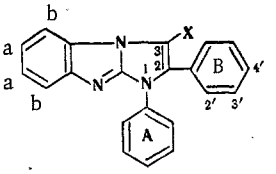
Vilsmeier formylation of 1,2-diphenylimidazo[1,2-a]benzimidazole leads to the 3-formyl derivative, while heating with acetic anhydride in sulfuric acid gives the 3-acetyl derivative. The nitration of this benzimidazole with potassium nitrate in sulfuric acid gives a mixture of mono-, di-, and trinitro derivatives. Bromination in chloroform leads to a mixture containing the mono- and dibromo derivatives. The structures of the compounds obtained were confirmed by their IR, PMR, and mass spectra.

In recent years imidazo[1,2-a]benzimidazole derivatives have attracted the attention of researchers owing to their pharmacological activity and interesting chemistry. However, primarily 2,9-disubstituted imidazo[1,2-a]benzimidazoles have been investigated [1-8]. The literature contains data [9] that indicate that 1-methyl-2-phenylimidazo[1,2-a]benzimidazole undergoes bromination and hydroxymethylation but does not undergo electrophilic substitution reactions such as nitrosation, diazo coupling, formylation, and acylation.

The aim of the present research was to investigate the formylation, acetylation, nitration, and bromination of 1,2-diphenylimidazo[1,2-a]benzimidazole (I). Since this compound has several reaction centers that are capable of undergoing electrophilic attack, chief attention was directed to the establishment of the structures of the expected reaction products II-V.



I X = H;
II X = COH;
III X = $COCH_3$;
IV X = NO_2;
V X = Br

Benzimidazole I readily undergoes the Vilsmeier reaction to give formyl derivative II, the IR spectrum of which contains a ν_{CO} absorption band at 1690 cm^{-1} and a ν_{CH} (aldehyde) band at 2840 cm^{-1}.

The acetylation of I with a mixture of acetic anhydride and sulfuric acid leads to derivative III, the IR spectrum of which contains a ν_{CO} band at 1660 cm^{-1} and a ν_{CH_3} band at 1360 cm^{-1}, which characterize the acetyl grouping.

The action of potassium nitrate in concentrated sulfuric acid on benzimidazole I leads to a compound with a PMR spectrum in which a series of signals in the form of complex multiplets centered at 8.35, 8.26, 8.17, and 7.44 ppm, as well as at 7.44 and 8.66 ppm, which we assigned to the signals of H_a and H_b protons, are recorded. Consequently, the phenylene part of benzimidazole I does not undergo nitration, and the reaction product is a mixture that contains several components [10].

The bromination of benzimidazole I in chloroform leads to a mixture of compounds, in the PMR spectrum of which the following signals are observed: two multiplets at 7.79 and 7.68 ppm in a ratio of 1:4 (H_a), two multiplets at 8.10 and 8.02 ppm in the same ratio (H_b), and a number of complex multiplets at 7.93, 7.68, 7.53, and 7.41 ppm, which we assigned to the signals of the protons of the A and B phenyl rings, respectively. These data show that two products are formed in the reaction.

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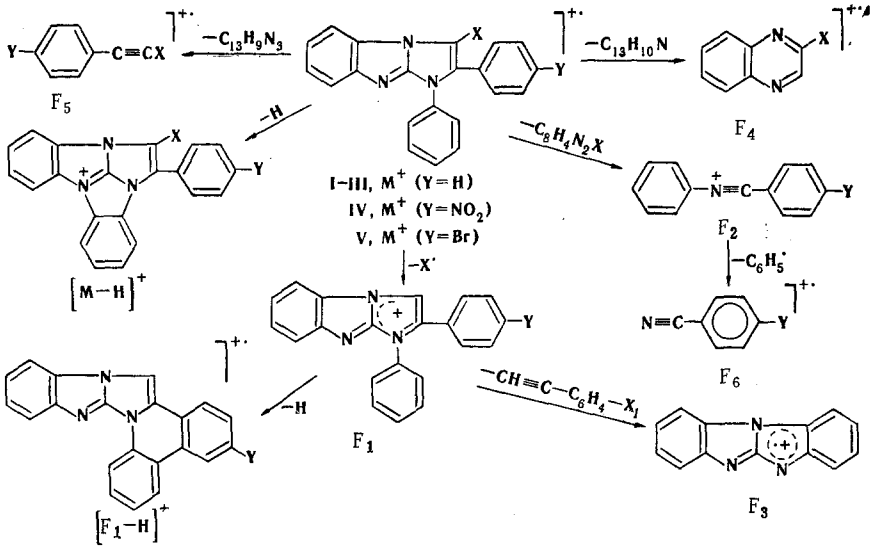
In a study of the mass spectra of the synthesized compounds we established that the m/z value of the molecular-ion (M^+) peak corresponds to the mass calculated for the empirical composition only in the case of I-III. In the mass spectra of the remaining reaction products we recorded, in addition to M^+ peaks, signals that indicate that the mixtures contain, in addition to monosubstituted derivatives, di- (IV and V) and trisubstituted benzimidazoles.

The fragmentation processes of substituted benzimidazoles I resemble the pattern of the fragmentation of the M^+ ion of 3-substituted thiazolo[3,2-a]benzimidazole [11]. The polycyclic structures of the $[M - H]^+$, F_1, $[F_1 - H]^+$, and F_3 fragment ions are confirmed by the peaks of doubly charged ions [12]. Thus there is no doubt that substitution takes place in the 3 position of the starting molecule in formylation and acetylation reactions.



An analysis of the mass spectra of mixtures IV and V provides evidence that nitration and bromination are realized in different positions of I. Peaks of ions with m/z 354, 399, and 444,* which we assigned to mono-, di-, and trinitro-substituted I, were observed in the mass spectrum of mixture IV. A similar situation was observed during a study of the mass spectrum of a mixture of V. We observed two groups of M^+ peaks, viz., peaks at 387 and 389 (with an isotope ratio of 1:1), which correspond to the monobromo-substituted derivative, and a group of peaks of 464, 465, 466, 467, 468, and 469 ions with an isotope distribution that corresponds to a compound containing two bromine atoms.

To investigate mixtures IV and V we used liquid chromatography with preparative isolation of the components and subsequent recording of the mass spectra of each component of the mixture (see Table 1).

Chromatographic peak 1 in the case of mixture IV corresponds to the monosubstituted product. The F_4 and F_5 ion peaks constitute evidence that the nitro group is in the 3 position of the outer imidazole ring [13]. The chromatographic data showed that a dinitro derivative is also formed (see Table 1). The successive splitting out of NO and NO_2 particles from the M^+ and F_1 ions constitutes evidence for the presence of two NO_2 groups in the compound (chromatographic peak 2). Their position in the molecule is confirmed by the elimination of an $HC{\equiv}CC_6H_4NO_2$ particle from the F_1 ion and by the appearance of F_2 (225), F_5 (192), and F_6 (148) ions. The mass spectrum of the next component (chromatographic peak 3) shows the presence of three nitro groups: peaks of F_1, $[F_1 - NO]^+$, $[F_1 - NO_2]^+$, and $[F_1 - 2NO_2]^+$ ions. The position of the nitro groups in this molecule is determined from the following ions: The F_3 (251) and F_5 (192) ions constitute evidence for the presence of NO_2 groups in the 3 and 4' positions in the phenyl substituent attached to the C_2 atom; the F_2 (270) and F_6 (148) ions, as well as the F_4 (174) ions, show that the N-phenyl substituent also underwent substitution (we were unable to establish the position of the NO_2 group in it from the PMR spectra because of the superimposition of the signals).

Product V is a mixture of mono- and dibromo-substituted derivatives of benzimidazole I. The first component (chromatographic peak 1) is the monobromo derivative with a bromine atom

*Here and subsequently, the numbers that characterize the ions are the mass-to-charge ratios.

TABLE 1. Mass Spectra of IV and V

Ions	m/z (relative intensity, %)				
	IV			V	
	peak 1	peak 2	peak 3	peak 1	peak 2
$[M+1]^+$	355 (17,3)	400 (25,2)	445 (25,6)	390 (23,8)	470 (10,1)
M^+	354 (80,6)	399 (100,0)	444 (96,3)	389 : 387 (98,0 : 100,0)	469 : 467 : 465 (22,6 : 44,6 : 22,6)
$[M-H]^+$	353 (76,5)	398 (40,4)	443 (15,2)	388 : 386 (75,8 : 53,7)	468 : 466 : 464 (20,1 : 27,4 : 10,4)
F_1	308 (100,0)	353 (22,4)	398 (100,0)	308 (10,5)	388 : 386 (98,6 : 100,0)
$[F_1-H]^+$	307 (25,8)	352 (32,7)	397 (26,1)	307 (18,8)	387 : 385 (16,6 : 12,7)
$[M-NO]^+$	324 (5,8)	369 (14,3)	414 (8,0)		
$[F_1-NO]^+$		323 (14,0)	368 (6,9)		
$[F_1-NO_2]^+$		307 (22,8)	352 (24,0)		
$[F_1-2NO_2]^+$			306 (25,2)		
F_2	180 (4,3)	225 (4,4)	270 (3,7)	180 (8,5)	258 : 260 (7,8 : 8,1)
F_3	206 (4,3)	206 (3,5)	251 (4,3)	206 (4,5)	206 (4,3)
F_4	174 (5,0)	174 (4,8)	174 (3,6)	209 : 207 (4,3 : 4,4)	209 : 207 (5,1 : 5,3)
F_5	147 (6,4)	192 (5,3)	192 (5,1)	182 : 180 (5,1 : 8,5)	262 : 260 : 258 (3,1 : 7,8 : 8,1)
F_6	103 (7,4)	148 (3,7)	148 (3,3)	103 (9,3)	183 : 181 (4,1 : 4,3)

in the 3 position. The other component (chromatographic peak 2) also contains a bromine atom in the 4' position of the phenyl substituent attached to the C_2 atoms. This is proved by the recording of the peaks of F_3 (206), F_5 or F_2 (258, 260, 262), and F_6 (181, 181, and 183; the ratio of the intensities of the ion peaks is 1:1) ions in the mass spectrum.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in $CDCl_3$ were recorded with a Brucker WH-90 MHz spectrometer with tetramethylsilane as the standard. The mass spectra were measured with a Varian MAT-311A spectrometer with direct introduction of the samples into the ion source at an ionizing voltage of 70 V, a cathode emission current of 300 μA, an accelerating voltage of 3 kV, and a source temperature of 190-280°C.

Mixtures IV and V were separated with a Waters Associates liquid chromatograph equipped with a 440 UV detector (λ = 254 nm); the stainless-steel column (l = 300 mm, d = 3.9 mm) was filled with Porasil. Mixtures of n-hexane and chloroform in ratios of 7:3 and 9:1, respectively, were used to elute mixtures IV and V. The eluent was fed at a rate of 1 cm^3/min in both cases. Samples (20 μl) of IV and V were introduced in the form of saturated solutions in the eluent.

1,2-Diphenylimidazo[1,2-a]benzimidazole (I). This compound was synthesized by the reaction of 1-phenacyl-2-chlorobenzimidazole with aniline in dimethylformamide (DMF). The constants of the product were in agreement with the data in [14].

3-Formyl-1,2-diphenylimidazo[1,2-a]benzimidazole (II). A 3-mmole sample of freshly distilled phosphorus oxychloride was added dropwise with stirring at 0-5°C to a solution of 20 ml of dry DMF, after which the mixture was stirred at 20°C for 30 min. It was then poured into a mixture of 3.09 g (1 mmole) of benzimidazole I in 30 ml of DMF, and the resulting mixture was heated on a boiling-water bath for 4 h. It was then cooled and poured over 100 g of ice. After 2 h, the resulting precipitate was removed by filtration and washed with water to give 3.0 g (88%) of a product with mp 188-189°C (from aqueous dioxane). PMR spectrum: 7.55 (2H, m, H_a), 8.17 (2H, m, H_b), 7.41 (5H, m, H_A), and 7.29 ppm (5H, m, H_B). Found: C 78.5; H 4.6; N 12.5%. $C_{22}H_{15}N_3O$. Calculated: C 78.3; H 4.5; N 12.5%.

3-Acetyl-1,2-diphenylimidazo[1,2-a]benzimidazole (III). A mixture of 3.09 g (1 mmole) of benzimidazole I, 20 ml of freshly distilled acetic anhydride, and 5 ml of H_2SO_4 (sp. gr. 1.83) was heated on a boiling-water bath for 2 h, after which it was cooled and poured over 50 g of ice. After 2 h, the resulting precipitate was removed by filtration and washed with water to give 3.2 g (90%) of a product with mp 254-255°C (from aqueous DMF). PMR spectrum: 7.71 (2H, m, H_a), 8.66 (2H, m, H_b), 7.44 (5H, m, H_A), 7.33 (5H, m, H_B), and 2.05 ppm (3H, s, $COCH_3$). Found: C 78.5; H 5.0; N 12.1%. $C_{23}H_{17}N_3O$. Calculated: C 78.6; H 4.9; N 12.0%.

The nitration of benzimidazole I led to the formation of a mixture of mono-, di-, and trinitro derivatives. A 1.54-g (0.5 mmole) sample of I was dissolved in 10 ml of concentrated H_2SO_4 (sp. gr. 1.83), and a solution of 0.5 g (0.5 mmole) of KNO_3 in 5 ml of concentrated H_2SO_4 was added dropwise with cooling and stirring. The mixture was then stirred at 20°C for 1.5 h, after which it was poured over 50 g of ice. After 2 h, the yellow precipitate was removed by filtration and washed with water. The overall yield was 1.3 g.

The bromination of benzimidazole led to the formation of a mixture of mono- and dibromo derivatives. A solution of 0.79 g (0.5 mmole) of bromine in 10 ml of chloroform was added with stirring to a solution of 1.54 g (0.5 mmole) of I in 20 ml of chloroform, and the mixture was stirred for 2 h. The chloroform was evaporated, and the residue was treated with 0.1 N NaOH solution. The solid material was removed by filtration and washed with water. The overall yield was 1.3 g.

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