Compounds III-XII were synthesized similarly; only the reflux times of the solutions were varied (Table 1).

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NUCLEOPHILIC ACYLATION OF BENZIMIDAZOLE

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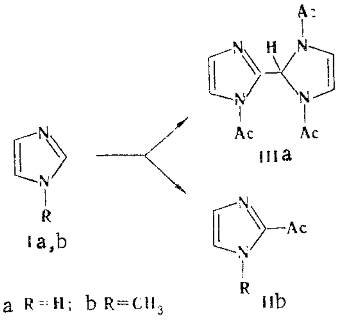
Conditions that make it possible to realize the direct $C_{(2)}$ acylation of benzimidazole and some of its derivatives were found. It is shown that bis products, which are converted to 2-acylbenzimidazoles upon heating to 140-200°C with acyl halides in the presence of triethylamine, are formed in attempts to carry out $C_{(2)}$ acylation.

The nucleophilic acylation of azoles was recently reported [1-4]. In particular, it was shown that an imidazole alkylated at the NH group (Ib) gives 2-acyl derivatives (IIb) smoothly and in good yields upon reaction with carboxylic acid halides in the presence of triethylamine in polar aprotic solvents.



This method was found to be sensitive to the structure of the starting heterocycle, and attempts to extend it to NH unsubstituted imidazole (Ia) and benzimidazole (IVa) lead to the formation of bis products IIIa and Va-e rather than to 2-acyl derivatives [4].

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TABLE 1. 2-Aroylbenzimidazoles VI

Compound	mp,* °C	Found, %	Empirical formula	Calc., %	Yield, %
VIa [7]	213—214	—	—	—	51
VIb [7]	71—72	—	—	—	83
VIc	92	N 10,5	$C_{16}H_{14}N_2O_2$	N 10,5	86
VId	129—130	N 9,6	$C_{17}H_{16}N_2O_3$	N 9,5	78
VIe	133	N 8,8	$C_{15}H_{11}BrN_2O$	N 8,9	78
VIf	129	N 10,5	$C_{15}H_{11}ClN_2O$	N 10,3	75
VIg	97—99	C 71,8; H 5,5; N 10,4	$C_{16}H_{14}N_2O_2$	C 72,2; H 5,3; N 10,5	67
VIh	176—177	C 68,6; H 5,4; N 9,8	$C_{17}H_{16}N_2O_3$	C 68,9; H 5,4; N 9,5	74
VIi	123—124	C 55,9; H 4,1; N 8,1	$C_{16}H_{13}BrN_2O_2$	C 55,7; H 3,8; N 8,1	68
VIj	99—100	N 9,5	$C_{16}H_{13}FN_2O_2$	N 9,9	62
VIk	191—193	N 14,2	$C_{15}H_{11}N_3O_3$	N 14,5	13

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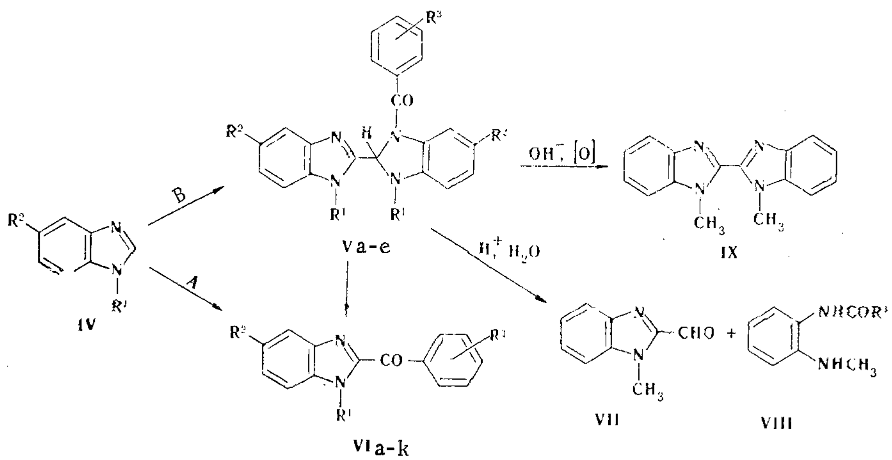
*From alcohol.



IV a $R^1=R^2=H$; b $R^1=CH_3$, $R^2=H$; c $R^1=CH_3$, $R^2=OCH_3$; d $R^1=CH_3$, $R^2=NO_2$; V a $R^1=C_6H_5CO$, $R^3=H$; VI a $R^1=R^2=R^3=H$; V, VI b $R^1=CH_3$, $R^2=R^3=H$; c $R^1=CH_3$, $R^2=H$, $R^3=4\text{-}OCH_3$; d $R^1=CH_3$, $R^2=H$, $R^3=3,4\text{-}(OCH_3)_2$; e $R^1=CH_3$, $R^2=NO_2$, $R^3=H$; f $R^1=CH_3$, $R^2=H$, $R^3=4\text{-}Cl$; g $R^1=CH_3$, $R^2=OCH_3$, $R^3=H$; h $R^1=CH_3$, $R^2=OCH_3$, $R^3=4\text{-}OCH_3$; i $R^1=CH_3$, $R^2=OCH_3$, $R^3=2\text{-}Br$; j $R^1=CH_3$, $R^2=OCH_3$, $R^3=3\text{-}F$; k $R^1=CH_3$, $R^2=NO_2$, $R^3=H$

We studied the behavior of methylated (at the NH group) benzimidazole under these conditions and found that it also does not give 2-acyl derivatives but forms bis products Vb-e.

The structure of Va-c is confirmed by their conversion to the previously described [6] 1-methyl-2-formylbenzimidazole (VII) [5] and 1,1'-dimethyl-2,2'-dibenzimidazoyl (IX), as well as by their IR and PMR spectra and the results of elementary analysis. In the IR spectrum the intensity of the CO group at 1660-1670 cm^{-1} was found to be somewhat decreased (approximately medium intensity), which is in agreement with its small mass in the molecule. The PMR spectra of Vb, c provide evidence for the presence of two N-methyl groups [3.7 ppm (3H, s) and 2.65 ppm (3H, s)], one methoxy group [3.73 ppm (3H, s)], and 14 and 13 "aromatic" protons, respectively, along with which signals of the proton of the benzimidazoline ring also appear.

In a study of the properties of V we observed their unexpected ability to undergo conversion to 2-acyl derivatives upon brief heating with acid halides in the presence of triethylamine over a wide range of temperatures. In conformity with these observations we attempted the direct acylation of IVa-d at elevated temperatures. We found that in this case, instead of bis products, 2-acyl derivatives are formed in 75-94% yields.

The simplicity of the process indicates the preparative convenience of the method. It should be noted that unsubstituted (at the NH group) benzimidazole and benzene ring-substituted benzimidazoles can be acylated under these conditions (see Table 1).

EXPERIMENTAL

The melting points are indicated without corrections. The IR spectra of solutions of the compounds in chloroform were recorded with a UR-20 spectrometer. The PMR spectra of solutions in $CDCl_3$ were obtained with a Tesla BS-467 spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard.

A. Preparation of the Bis Products (Vb-e). 1-Methyl-3-benzoyl-2-(1-methyl-2-benzimidazolyl)-4-benzimidazoline (Vb). A 3.3-g (33 mmole) sample of triethylamine was added to a solution of 5.04 g (38 mmole) of 1-methylbenzimidazole (IVb) in 20 ml of acetonitrile, after which 5.34 g (38 mmole) of benzoyl chloride was added with stirring in the course of 30 min, and the mixture was stirred at room temperature for 1 h. The precipitate was removed by filtration, washed with water, dried, and crystallized from alcohol to give 2.45 g (37%) of a product with mp 170-171°C. PMR spectrum: 2.65 (3H, s, CH_3), 3.7 (3H, s, CH_3), and 6.6-7.5 ppm (14H, m, aromatic). Found, %: C 75.2; H 5.4; N 15.0. $C_{23}H_{20}N_4O$. Calculated, %: C 75.0; H 5.5; N 15.2

1-Methyl-3-anisoyl-2-(1-methyl-2-benzimidazolyl)-4-benzimidazoline (Vc). Compound Va [4.57 g (42%)] was similarly obtained from 2.88 g (17 mmole) of p-methoxybenzoyl chloride. The slightly yellowish crystals had mp 168-169°C (from alcohol). PMR spectrum: 2.64 (3H, s, NCH_3), 3.65 (3H, s, NCH_3), 3.73 (3H, s, OCH_3), and 6.5-7.5 ppm (13H, m, aromatic). Found, %: C 72.5; H 5.6; N 14.5. $C_{24}H_{22}N_4O_2$. Calculated, %: C 72.3; H 5.6; N 14.1.

1-Methyl-3-veratroyl-2-(1-methyl-2-benzimidazolyl)-4-benzimidazoline (Vd). A 2.5-g (25 mmole) sample of triethylamine and a solution of 3.93 g (20 mmole) of 3,4-dimethoxybenzoyl chloride in 4 ml of dimethylformamide (DMF) were added to a solution of 3.4 g (26 mmole) of IVb in 2.5 ml of DMF, and the mixture was heated at 35°C for 2.5 h, after which it was poured into 150 ml of water with ice. The precipitate was crystallized from alcohol to give 3.23 g (29%) of a product with mp 179-180°C. Found, %: C 69.9; H 5.7; N 13.3. $C_{25}H_{24}N_4O_3$. Calculated, %: C 70.1; H 5.6; N 13.1.

1-Methyl-3-benzoyl-5-nitro-2-(1-methyl-5-nitro-2-benzimidazoyl)-2-benzimidazol-4-ine (Ve). A mixture of 0.9 g (5.1 mmole) of IVd, 1.0 g (10 mmole) of triethylamine, 0.92 g of benzoyl chloride, and 4 ml of acetonitrile was heated with a reflux condenser with stirring at 60°C for 1 h, after which the mixture was poured into 100 ml of petroleum ether, and the yellow precipitate was removed by filtration to give 0.96 g (84%) of a product with mp 225-226°C (from alcohol). Found, %: C 59.9; H 3.9; N 18.4. $C_{23}H_{18}N_6O_5$. Calculated, %: C 60.3; H 4.0; N 18.3.

B. Hydrolysis of the Bis Products in Acids and Alkalis. 1-Methyl-2-formylbenzimidazole (VII). This compound was obtained in 20% yield (0.12 g) from 1.44 g (4 mmole) of Vb by heating it in 20 ml of 10% HCl at 90°C for 20 min with subsequent neutralization of the solution with sodium bicarbonate and purification with a chromatographic column. The product had mp 118-119°C (from water) (mp 123.5°C [5]). The IR spectrum was identical to the spectrum of the compound obtained by alternative synthesis.

1,1'-Dimethyl-2,2'-dibenzimidazolyl (IX). A 2-ml sample of 10% NaOH solution was added to a solution of 0.7 mmole of bis product Vb-d in 3 ml of ethanol, and the mixture was refluxed for 20 min, after which 0.5 ml of 30% hydrogen peroxide was added dropwise, and the mixture was allowed to stand for 15 min. It was then cooled to room temperature, and the precipitate was removed by filtration to give ∿0.18 g of a product with mp 204-205°C (from alcohol) (mp 210-211°C [6]). The IR spectra of the product and an authentic sample were identical.

C. Conversion of the Bis Products to 2-Acylbenzimidazoles (VIb-d). A mixture of 1 mmole of bis product Vb-d, 2 mmole of absolute triethylamine, 1.3 mmole of aroyl halide, and 1.5 ml of acetonitrile was heated at 160°C for 2 h, after which the mixture was cooled to 50°C, 8 ml of acetone was added, and the solution was poured into 30 ml of 7% HCl. The acidic mixture was refluxed with carbon and filtered, and the 2-acyl derivative was isolated by alkalization with sodium hydroxide solution.

1-Methyl-2-benzoylbenzimidazole (VIb). This compound was obtained from 0.55 g (1.5 mmole) of Vb, 0.43 ml (3 mmole) of triethylamine, and 0.27 g (19 mmole) of benzoyl chloride at 150°C. The yield was 0.43 g (61%).

1-Methyl-2-(4'-Methoxybenzolyl)benzimidazole (VIc). A mixture of 0.5 g (1.3 mmole) of Vc, 0.26 g (2.6 mmole) of triethylamine, 0.27 g (1.6 mmole) of anisoyl chloride, and 1 ml of acetonitrile was heated at 150°C for 2 h. Workup gave 0.44 g (64%) of VIc. PMR spectrum: 3.8 (3H, s, OCH_3), 4.1 (3H, s, NCH_3), and 6.9-8.3 ppm (8H, m, aromatic).

1-Methyl-2-(3',4'-dimethoxybenzolyl)benzimidazole (VId). A mixture of 0.67 g (1.6 mmole) of Vd, 0.32 g (3.2 mmole) of triethylamine, 0.43 g (2.1 mmole) of veratroyl chloride, and 1.5 ml of acetonitrile was heated at 160°C, after which it was worked up to give 0.67 g (72%) of VId. PMR spectrum: 3.9 (6H, s), 4.0 (3H, s, NCH_3), and 6.8-8.1 ppm (7H, m, aromatic).

D. One-Step $C_{(2)}$ Alkylation of Benzimidazole. 2-Benzoylbenzimidazole (VIa). A 2.6-g (26 mmole) sample of triethylamine, 2 ml of absolute acetonitrile, and 3.66 (26 mmole) of benzoyl chloride were added to 1.06 g (9 mmole) of benzimidazole IVa, and the mixture was heated in an ampul at 145°C for 2 h. It was then dissolved in 20 ml of acetone, and the solution was poured into 100 ml of 7% HCl. The mixture was refluxed with charcoal for 30 min, after which it was filtered, and the filtrate was made alkaline with concentrated ammonium hydroxide. The yield was 1.05 g.

1-Methyl-2-benzoylbenzimidazole (VIb). A mixture of 1.85 g (14 mmole) of 1-methylbenzimidazole (IVb), 2 ml of acetonitrile, 2.1 g (21 mmole) of triethylamine, and 2.94 g (21 mmole) of benzoyl chloride was heated at 165°C for 1 h, after which 25 ml of acetone was added to it, and the oslution was poured with stirring into 120 ml of 7% HCl. The mixture was stirred and refluxed with charcoal for no less than 30 min. The 2-benzoyl derivative (IVb) was isolated by alkalization of the filtrate with 20% NaOH. Workup gave 2.5 g (75%) of a product with mp 71°C [7] (from aqueous alcohol).

Acylation in an Ampul. A 1.9-g (19 mmole) sample of triethylamine and 2.5 g (18 mmole) of benzoyl chloride were added to a solution of 1.77 g (13 mmole) of 1-methylbenzimidazole in 7 ml of acetonitrile, and the mixture was heated in an ampul at 140°C for 1 h. The contents of the ampul were transferred to 150 ml of dilute HCl, and the mixture was then worked up as in the preceding experiment to give 1.63 g (12 mmole) of product.

1-Methyl-2-(2'-bromobenzoyl)benzimidazole (IVe). A 1.63-g (12 mmole) sample of 1-methylbenzimidazole was added to 1.8 g (18 mmole) of trimethylamine and 3.97 g (18 mmole) of o-bromobenzoyl chloride, and the mixture was heated to 80°C. After the benzimidazole had melted, the temperature was raised to 140°C, and the mixture was maintained at that temperature for 1 h with periodic stirring. The mixture was then cooled to 60°C and worked up as in the preparation of VIb to give 2.94 g (78%) of VIe. PMR spectrum: 4.1 (3H, s, CH_3) and 7.4-7.6 ppm (8H, m).

1-Methyl-2-(4'-chlorobenzoyl)benzimidazole (VIf). A 1.6-g (16 mmole) sample of triethylamine and 2.8 g (16 mmole) of p-chlorobenzoyl chloride were added to a solution of 1.4 g (11 mmole) of IVb in 6 ml of dimethylformamide (DMF), and the mixture was heated at 120°C for 1.75 h. The precipitated triethylamine hydrochloride was removed by filtration and washed with 2 ml of DMF. The solutions were combined and poured into acid as in the preparation of VIb. Workup gave 2.1 g (73%) of VIf. PMR spectrum: 4.1 (3H, s, CH_3) and 7.3-8.2 ppm (8H, m, aromatic).

1-Methyl-2-benzoyl-5-nitrobenzimidazole (VIk). A mixture of 0.9 g (5.1 mmole) of IVd, 1.22 g (9 mmole) of benzoyl chloride, 1.08 g (10 mmole) of triethylamine, and 1 ml of acetonitrile was heated with stirring at 195°C for 2 h, after which it was worked up as in the preparation of VIb to give 0.19 g of VIk.

The remaining compounds were obtained in the same way as VIb in the presence of a solvent.

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