INVESTIGATIONS IN THE FIELD OF BENZIMIDAZOLE DERIVATIVES

XXII*. BENZIMIDAZOLE DERIVATIVES WITH ELECTRON-DONATING SUBSTITUENTS IN THE CHICHIBABIN REACTION

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The influence of the electron-donating groups CH_3O, $N(CH_3)_2$, OH, NH_2, CH_3 in various positions of the benzimidazole molecule on the occurrence of the Chichibabin reaction in this series has been studied. While all monosubstituted 1-alkylbenzimidazoles undergo amination with sodium amide with greater or smaller readiness, 5,5-dimethoxy- and 5,6-methylenedioxybenzimidazoles do not take part in this reaction. The behavior of benzimidazole derivatives toward sodium amide is discussed from the point of view of the electron density at the pyridine nitrogen atom and at the C_2 atom of the imidazole ring, which was evaluated on the basis of molecular orbital calculations, ionization constants, and the chemical shifts of the protons attached to the C_2 atom in the PMR spectra.

Continuing a study of the Chichibabin reaction in the benzimidazole series [2], we have subjected benzimidazole derivatives containing electron-donating groups in various positions of the molecule to the action of sodium amide. It was found that all monosubstituted 1-alkylbenzimidazoles containing the above-mentioned substituents are readily aminated by $NaNH_2$ with the formation of 2-aminobenzimidazoles (Table 1). Exceptions are 5-hydroxy- and 5-aminobenzimidazoles, which can be caused to participate in the amination reaction only under special conditions (200°C, paraffin oil). This is due to the fact that the anions formed initially by the action of $NaNH_2$ on the OH and NH_2 groups naturally take part in the Chichibabin reaction with considerably greater difficulty. However, it must be mentioned that in the case of the 5-hydroxy derivative we were unable to isolate a 2-amino derivative (probably because of its ease of oxidation), and we judged that the Chichibabin reaction had taken place from the evolution of hydrogen (70%). The previous conclusions [2] on the passivity of 5-hydroxy- and 5-aminobenzimidazoles with respect to $NaNH_2$ relate to their behavior under the usual conditions (xylene, dimethylaniline, 110-140°C).

We found that the introduction of a second methoxy group into the ortho position to the first completely inhibits the amination reaction: unlike the 5,6-dimethylbenzimidazoles [3], 1-alkyl-5,6-dimethoxybenzimidazoles de not take part in the Chichibabin reaction. 1-Methyl-5,6-methylenedioxybenzimidazole behaves similarly with respect to $NaNH_2$.

In order to interpret the behavior of imidazole derivatives in the Chichibabin reaction, it is necessary to have information on the electron density both on the C_α atom and on the pyridine nitrogen atom [4]. The latter is easy to evaluate by measuring the ionization constant, pK_a, of the imidazolium ions. For all benzimidazole derivatives containing electron-donating substituents, the basicity of the N atom is above the critical region of pK_a (4.2-4.3) [4] and is therefore sufficient for its ready coordination with the sodium atom of the $NaNH_2$ molecule, which is essential for the occurrence of the first stage of the Chichibabin reaction – the addition of $NaNH_2$ to the C=N bond. Consequently, all the differences in the behavior of these compounds must be due to differences in the electron density at the C_α atom, or to some other factors. The

*For Communication XXI, see [1].

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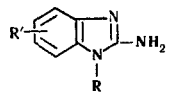
TABLE 1. 2-Amino Derivatives of Benzimidazole Obtained by Direct Amination



R	R′	mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
				C	H	N	C	H	N	
CH_3	4-CH_3O	171—172*	$C_9H_{11}N_3O$	61,03	6,45	23,90	61,59	6,25	23,71	57
$C_6H_5CH_2$	5-CH_3O	208—209†	$C_{15}H_{15}N_3O$	71,48	5,89	16,76	71,12	5,97	16,59	85
C_2H_5	6-CH_3O	197—198‡	$C_{10}H_{13}N_3O$	62,52	6,72	22,14	62,80	6,85	21,97	53
$C_6H_5CH_2$	7-CH_3O	211—212†	$C_{15}H_{15}N_3O$	71,15	5,79	16,61	71,12	5,97	16,59	64
CH_3	5-$N(CH_3)_2$	217—218*	$C_{10}H_{14}N_4$	63,42	7,09	29,60	63,13	7,41	29,45	83
C_2H_5	5-$N(CH_3)_2$	255—256*	$C_{11}H_{16}N_4 \cdot C_6H_3N_3O_6$	47,37	4,53	22,83	47,11	4,42	22,62	75
o-$CH_3OC_6H_4$	H	191—192†	$C_{14}H_{13}N_3O$	70,56	5,57	17,33	70,27	5,47	17,56	82
p-$CH_3OC_6H_4$	H	183—184†	$C_{14}H_{13}N_3O$	70,36	5,61	17,67	70,27	5,47	17,56	74
p-$(CH_3)_2NC_6H_4$	H	240—241‡	$C_{15}H_{16}N_4$	71,69	6,34	21,45	71,97	6,44	21,58	71

*From benzene.
† From ethanol.
‡ From aqueous ethanol.

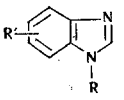
TABLE 2. π-Electronic Charges (q), Energies of Anionic Localization (L^-), and Chemical Shifts of the Protons (τ) in Position 2 of 1-Methylimidazole Derivatives.

Compound	q	L^-	τ	Capacity for amination
Benzimidazole	+0,170	1,931	2,18	+
4-methoxy	+0,156	1,956	—	+
5-methoxy	+0,162	1,932	2,20	+
6-methoxy	+0,158	1,949	2,23	+
7-methoxy	+0,168	1,939	—	+
5,6-dimethoxy	+0,155	1,952	2,24	−
5,6-methylenedioxy	+0,156	1,952	2,25	−
4,7-dimethoxy	+0,156	1,961	—	?
5-dimethylamino	+0,168	1,932	2,16	+
Imidazole	+0,094	3,290	2,57	−
3H-Naphtho[1,2]imidazole	+0,151	1,964	2,10	+

combined consideration of the results of molecular orbital calculations [5] and of the chemical shifts of the protons attached to this atom [6,7] must be regarded as a reliable method of evaluating the electron density at the C_α atom of the imidazole ring. In this connection we have performed quantum-mechanical calculations by the HMO method of a number of the benzimidazole derivatives studied and we have also measured their PMR spectra in deuterochloroform solution. The electron density values, the energies of anionic localization, and the chemical shifts τ of the protons on the C_α atom that were obtained (Table 2) show that the reactivities of the μ positions in all the compounds studied cannot differ substantially from one another, which generally speaking is not surprising in view of the remoteness of the substituents from the reaction center. For comparison, Table 2 gives the results of calculations by the HMO method for benzimidazole, imidazole, and naphthimidazole taken from [5].

Thus, the inhibiting effect of the two methoxy groups on the reactivity of the imidazole ring cannot be explained by their strong electron-donating action, with the decrease in the positive charge on the μ-carbon atom following from it. This is also shown by the fact that 5,6-dimethoxybenzimidazole, like other benz-

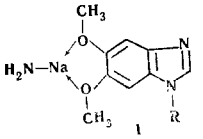
TABLE 3. Ionization Constants (pK_a) of Benzimidazolium Ions at 25 ± 1°C.



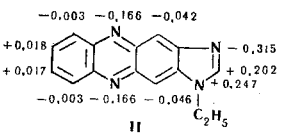
R	R′	pK_a (water : ethanol, 95 : 5)	Capacity for Amination
CH_3	4-CH_3O	5,25	+
CH_3	5-CH_3O	5,78	+
$C_6H_5CH_2$	5-CH_3O	5,38	+
CH_3	6-CH_3O	5,65	+
C_2H_5	6-CH_3O	5,47	+
$C_6H_5CH_2$	7-CH_3O	5,10*	+
C_2H_5	5,6-$(CH_3O)_2$	5,97	–
CH_3	5,6-OCH_2O	5,83	–
CH_3	5-OH	5,94	+
CH_3	5-NH_2	6,21	+
CH_3	5-$N(CH_3)_2$	6,10	+
C_2H_5	5-$N(CH_3)_2$	6,27	+
C_2H_5	6-CH_3	5,07†	+
CH_3	5,6-$(CH_3)_2$	5,43†	+
$C_6H_5CH_2$	5,6-$(CH_3)_2$	5,12	+
n-$CH_3OC_6H_4$	—	4,81	+
o-$CH_3OC_6H_4$	—	4,77	+
p-$(CH_3)_2NC_6H_4$	—	4,87	+

*In 10% aqueous ethanol;
† In 50% aqueous ethanol.

imidazole derivatives [8], does not take part in azo coupling reactions with diazonium salts in an alkaline medium, i.e., a fairly high positive charge is always retained in position 2. Finally, the values of pK_a (Table 3) show that the electron-donating effect of the substituents in 5,6-dimethyl- and, particularly, 5-dimethylaminobenzimidazoles is greater than in 5,6-dimethoxybenzimidazole and, nevertheless, these compounds aminate. It appears to us to be most likely that the inert behavior of 5,6-dimethoxy- and 5,6-methylenedioxybenzimidazoles to $NaNH_2$ is due to the formation, during the reaction, of a stable solvate complex of type I in which both oxygen atoms actually become electron-accepting centers and, like other electron-accepting substituents (F, Cl, NO_2 COOR, etc.) in the benzene ring of benzimidazole [2] lower the basicity of the nitrogen atom, interfering with its coordination with the sodium atom and thereby preventing the Chichibabin reaction itself. As has recently been established, such complexes are particularly stable just when two oxygen atoms are adjacent, as in the case of veratrole, 2-methoxytetrahydrofuran [9] and, apparently, in 5,6-dimethoxy- and 5,6-methylenedioxybenzimidazoles.



I



II

An alternative explanation, consisting in the blocking of the $NaNH_2$ molecules by coordination of type I is excluded by the fact that the reaction does not take place even in the presence of a large excess of $NaNH_2$. In addition to this, 1-methylbenzimidazole can be aminated in veratrole, dioxane, or anisole with yields of, respectively, 50, 69, and 55%, although the isolation of the amine in these cases is made difficult by pronounced resinification (the latter most probably the result of the destruction of the solvent molecules by the sodium amide).

A similar phenomenon may occur in 1-ethylimidazo [4,5-b]phenazine (II), which does not react with $NaNH_2$, either, and which may be considered to a certain extent as a structural analog of the difficultly accessible 5,6-bisdimethylaminobenzimidazole. Another possible reason for the inert behavior of compound II to $NaNH_2$ is its low basicity (pK_a 3.62 in 50% ethanol at 25°C) which, as already pointed out [4], may prevent amination even in spite of a considerable positive charge on the μ-carbon atom (see the results of the molecular orbital calculations of II).

As was to be expected, the presence of electron-donating substituents in the phenyl nucleus of N-phenylbenzimidazole facilitates the amination reaction as compared with the unsubstituted compound,

which is in harmony with the conclusions drawn previously on the influence of a phenyl substituent in position 1 on the reactivity of the imidazole nucleus [10].

EXPERIMENTAL

5-Nitro-4-p-toluenesulfonamidoveratrole (III). This was obtained by nitrating 4-p-toluenesulfonamidoveratrole by analogy with 3-nitro-4-p-toluenesulfonamidoanisole [11]. Yield 92%. Yellow plates with mp 203-204°C (from benzene). Found, %: C 51.09; H 4.41; N 7.96. Calculated for $C_{15}H_{16}N_2O_9$; %: C 51.13; H 4.57; N 7.95.

4-(N-Methyl-p-toluenesulfonamido)-5-nitroveratrole (IVa). This was obtained by methylating III [11]. Yield 80%. Colorless needles with mp 193-194°C (from benzene). Found, %: C 52.51; H 5.09; N 7.90. Calculated for $C_{16}H_{18}N_2O_6$, %: C 52.46; H 4.95; N 7.64.

4-(N-Ethyl-p-toluenesulfonamido)-5-nitroveratrole (IVb). Colorless needles with mp 151-152°C (from ethanol). Found, %: C 53.71; H 5.38; N 7.72. Calculated for $C_{17}H_{20}N_2O_6$, %: C 53.67; H 5.29; N 7.36.

4-Methylamino-5-nitroveratrole (Va). This was obtained from IVa as given in [11]. Yield 90%. Bright red needles with mp 149-150°C (from ethanol). Found, %: C 50.78; H 5.47; N 13.01. Calculated for $C_9H_{12}N_2O_4$, %: C 50.94; H 5.70; N 13.20.

4-Ethylamino-5-nitroveratrole (Vb). This was obtained from IVb as in [11]. Yield 92%. Bright orange needles with mp 169.5-170°C (from ethanol). Found, %: C 53.37; H 6.29; N 12.37. Calculated for $C_{10}H_{14}N_2O_4$, %: C 53.09; H 6.23; N 12.38.

5,6-Dimethoxy-1-methylbenzimidazole (VIa). With cooling and stirring, 7.2 g (0.06 g-at) of powdered tin was added to a solution of 4.24 g (0.02 mole) of Va in 20 ml of hydrochloric acid (d 1.18) and 25 ml of 80% formic acid. The mixture was heated at 100°C until it had lost its color, and then it was cooled and the double salt was filtered off. This was dissolved in 20 ml of water, treated with 50 ml of 40% alkali, and extracted with chloroform. The filtrate left after the separation of the double salt was made alkaline and extracted with chloroform, the extracts were combined and saturated with potassium carbonate, and the solvent was distilled off. Yield 2.8 g (74%). Colorless plates with mp 125-126°C (from benzene with the addition of petroleum ether). Found, %: C 62.71; H 6.03; N 14.70. Calculated for $C_{10}H_{12}N_2O_2$, %: C 62.45; H 6.28; N 14.46.

1-Ethyl-5,6-dimethoxybenzimidazole (VIb). This was obtained in a similar manner to VIa. Colorless needles with mp 110-111°C (from ethanol with the addition of ether). Found, %: C 63.90; H 6.74; N 13.68. Calculated for $C_{11}H_{14}N_2O_3$, %: C 64.05; H 6.84; N 13.58.

5,6-Methylenedioxybenzimidazole (VII). This was obtained in a similar manner to VIa by the reductive cyclization of 1,2-methylenedioxy-4,5-dinitrobenzene [12]. The double salt was decomposed with sodium sulfide. The filtrate was evaporated and the base was liberated from the 5,6-methylenedioxybenzimidazole hydrochloride formed (lustrous colorless needles with mp 275-276°C) by the action of alkali. Yield 77%. Colorless crystals with mp 209-210°C (from ethanol with the addition of ether). Found, %: C 59.47; H 3.92; N 17.39. Calculated for $C_8H_6N_2O_2$, %: C 59.27; H 3.73; N 17.27.

5,6-Methylenedioxy-1-methylbenzimidazole. This was obtained by the methylation of VII with methyl iodide (1.5 mole) in ethanolic alkali (1.5 mole) at room temperature. Yield 90%. Colorless crystals with mp 154-155°C (from aqueous ethanol). Found, %: C 61.26; H 4.41; N 15.91. Calculated for $C_9H_8N_2O_2$, %: C 61.35; H 4.57; N 15.89.

1-Benzyl-7-methoxybenzimidazole (VIII). This was obtained from 2-benzylamino-3-nitroanisole [13] in a similar manner to VIa. Colorless crystals with mp 118-119°C (from ethanol). Found, %: C 75.56; H 6.27; N 12.17. Calculated for $C_{15}H_{14}N_2O$, %: C 75.60; H 5.92; N 11.75.

Methiodide of VIII, mp 202-203°C (from ethanol with the addition of ether).

4-Methoxy-1-methylbenzimidazole. Obtained by the debenzylation of the methiodide of VIII with sodium (2 g-at) in liquid ammonia by a method described previously [14]. Yield 40%. Colorless crystals mp 140-141°C (from petroleum ether). Found, %: C 67.03; H 6.46; N 17.46. Calculated for $C_9H_{10}N_2O$, %: C 66.66; H 6.21; N 17.28.

1-Ethylimidazo[4,5-b]phenazine (II). This was obtained by the ethylation of imidazo[4,5-b]phenazine [15] with ethyl iodide (1.6 mole) in ethanolic alkali (1.6 mole) at the boil for 2 hr. Yield 48%. Dark yellow prisms with mp 237-238°C (from ethanol). Found, %: C 72.32; H 5.07; N 22.57. Calculated for $C_{15}H_{12}N_4$, %: C 72.56; H 4.87; N 22.56.

N-Anisyl- and N-p-Dimethylaminophenylbenzimidazoles. These were obtained by the direct arylation of benzimidazole with the corresponding aryl bromides [16]. Yields 40-60%. The constants of the compounds obtained agreed with those given in the literature [16,17].

Reaction of N-Substituted 5,6-Dimethoxy- and 5,6-Methylenedioxybenzimidazoles with Sodium Amide. When the compounds were heated with a threefold excess of $NaNH_2$ in absolute xylene or in dimethylaniline at 130-150°C for 6 hr, no evolution of hydrogen was observed. The compounds were recovered from the reaction mixture unchanged with yields of 60-80%. When the heating was carried out in paraffin oil at 200°C, resinification took place.

The amination of the other compounds in xylene or in dimethylaniline was carried out by a published method in a current of nitrogen [2,3]. As an example of amination in paraffin oil, the procedure for the preparation of 2,5-diamino-1-methylbenzimidazole is given below.

2,5-Diamino-1-methylbenzimidazole (hydrochloride). A suspension of 1.47 g (0.01 mole) of 5-amino-1-methylbenzimidazole and 1.2 g (0.03 mole) of $NaNH_2$ in 20 ml of absolute paraffin oil was heated at 200°C with stirring in a current of nitrogen for 2 hr. After cooling, 20 ml of 10% hydrochloric acid was added and the mixture was extracted with petroleum ether. The hydrochloric acid solution was evaporated and the residue was extracted with hot ethanol. After two recrystallizations from ethanol, the hydrochloride formed colorless crystals with mp 332-333°C. Yield 1.62 g (69%). Found, %: Cl 29.74; N 24.00. Calculated for $C_8H_{10}N_4 \cdot 2HCl$, %: Cl 30.16; N 23.83.

The HMO calculations were performed as described by Minkin et al. [18] with the parameters recommended by Streitwieser [19]: h_O 2; $h_{N'}$ 1,5; h_N 0,5; $k_{C-O}=k_{C-N}=0{,}8$; $k_{CN}=k_{CC}=1$. The solution of the secular determinant was obtained on a "Razdan" electronic digital computer.

The PMR spectra were measured on a Perkin-Elmer R-10 (60 MHz) spectrometer with 4-10% solutions of the substances in deuterochloroform. Tetramethylsilane was used as the internal standard.

The ionization constants were measured on the LPU-01 pH-meter at a temperature of 25±1°C by the method described previously [4].

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