RELATIVE REACTIVITIES OF THE PYRIDINE AND BENZIMIDAZOLE SYSTEMS IN THE CHICHIBABIN REACTION

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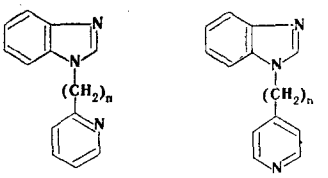
1-α (or γ)-Pyridyl- and 1-α (or γ)-pyridylethylbenzimidazoles were synthesized, and their behavior with respect to methyl iodide and sodium amide was studied. The results are discussed from the point of view of the basicities, magnitudes of the dipole moments, interaction of the heterorings, and the electron density distribution in them, calculated by the Hückel MO method or estimated on the basis of the relative position of the chemical shifts in the PMR spectra. It was established that the benzimidazole system undergoes the Chichibabin reaction considerably more readily than the pyridine system. On the basis of the PMR spectral data for the pyridine and benzimidazole bases and cations, it is assumed that this is due to the greater polarizability of the C=N bond of benzimidazole as compared with the C=N bond of pyridine during coordination with $NaNH_2$.

In our previous papers, we stated the assumption that sorption factors [1] are of great significance for the occurrence of the Chichibabin reaction under heterogeneous conditions. The process apparently commences with sorption of the N-heteroaromatic compound on the surface of sodium amide due to coordination of the pyridine N atom with the Na^+ ion. This explains the symbatic dependence of the ease of amination of heterocyclic compounds on the magnitude of their basicities [2]. When other centers capable of effective coordination with the Na^+ ion are present in the molecule, they compete in this respect with the pyridine N atom, which hinders the reaction or even entirely prevents it. The behavior of heterocyclic compounds that contain several nonequivalent N atoms of the pyridine type with respect to sodium amide is of particular interest. In the case of imidazole[4,5-*f*]quinoline derivatives, it has been shown that the C atom adjacent to the most basic N atom undergoes amination in these cases [3].



I a, b II a, b

a n=0; b n=2

Continuing our research in this direction, we turned to N-pyridylbenzimidazoles (I and II) – compounds that contain, in the same molecule, heterocyclic rings for which the Chichibabin reaction has been particularly thoroughly studied. It seemed of interest to ascertain which of the two rings, pyridine or benzimidazole, would be aminated more readily by sodium amide. To explain the behavior of I and II with respect to sodium amide, it was necessary to first solve two problems: 1) which of the two atoms of the pyridine type in them is more basic, and 2) what is the character of the interaction of the pyridine and imidazole rings.

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TABLE 1. Basicities of I and II and Direction of Their Reaction with Methyl Iodide

Compound	pK_a [water – alcohol (9:1), 25 ± 1°C]	Site of quaternization
Ia	3,78	Imidazole ring
Ib	5,39 (3,81)*	Imidazole ring
IIa	4,09	Pyridine ring
IIc	5,56 (4,28)*	Pyridine ring

*The values in parentheses are the second protonation constants.

Determination of the Site of Protonation of I and II. Because of the proximity of the basicities of benzimidazole (pK_a 5.53) and pyridine (pK_a 5.21)* and their distortion in Ia and IIa because of the interaction of the heterorings, the ionization constants of the compounds obtained (Table 1) per se cannot provide an answer to the question of the site of protonation of their molecules. We solved this problem by means of PMR spectroscopy in the case of the methiodides of I and II. For this, as is usually assumed in the chemistry of heterocyclic compounds, it was presumed that the sites of protonation and quaternization coincide.

Only one signal at 3.8-4.4 ppm corresponded to the protons of the CH_3 group in the PMR spectra of all of the methiodides, which attested to the absence of admixtures of the isomeric methiodide or the bismethiodide; i.e., the reaction proceeded at practically one center. In addition to the methiodides of I and II, the PMR spectra of the methiodides of a number of model compounds – pyridine and N-substituted benzimidazoles – were measured. Because of the low solubilities of the quaternary salts, measurements with aqueous solutions could be made only in a few cases.† Usually, however, dimethyl sulfoxide (DMSO) and trifluoroacetic acid were used as the solvents. The disadvantage of trifluoroacetic acid proved to be protonation by it of the second nonquaternized N atom, which reduced the difference in the chemical shifts of the protons of the imidazole and pyridine rings and sometimes hindered the interpretation of the spectra.

By and large, with rare exception (the 2-H proton in 1-methylbenzimidazole methiodide), the proton signals in the benzimidazolium and pyridinium salts are shifted successively to the high-field region on passing from water to DMSO and then to CF_3COOH. This undoubtedly reflects the degree of specific interaction between the heterocyclic cations and the negatively charged poles in the CF_3COO^-, $(CH_3)_2S^+-O^-$, and $D_2\overset{\delta+}{O}\overset{\delta-}{}$ particles. The degree of this sort of interaction and, consequently, the magnitude of shielding of the protons in the heterocyclic rings will apparently be a minimum for water and a maximum for CF_3COOH.

The establishment of the structures of the quaternary salts is most simply achieved by joint analysis of the magnitudes of the chemical shifts of the protons of the CH_3 group and the α protons of both heterocyclic rings. It was found that the position of the signal of the CH_3 group in methiodides of N-substituted benzimidazoles depends very little on the type of N-substituent and ranges from 3.78 to 3.91 ppm in CF_3COOH (Table 2). The CH_3 signal in the N-methylpyridinium cation is found at weaker field (4.13 ppm). Although this difference is small, it can be used to establish the structures of the methiodides of Ia and IIa. In the first of them, the δ_{CH_3} value in CF_3COOH (3.96 ppm) corresponds to the structure of the benzimidazolium salt, while in the second (4.28 ppm), it corresponds to the structure of the pyridinium salt. However, this criterion is not satisfied for the methiodides of 1-(β-pyridylethyl)benzimidazoles (Ib and IIb), since the shielding effect of the $-CH_2-CH_2$ bridge (it has a greater effect on the pyridine ring) equalizes the δ_{CH_3} values in the benzimidazolium and pyridinium cations.

In this case, the problem of the direction of quaternization is solved unambiguously from the characteristic difference in the chemical shifts of the α protons of the pyridine and benzimidazole rings. In the

*Here and elsewhere, the pK_a values presented in the text, except where otherwise stated, were determined in water at 25° and borrowed from [4]. The pK_a values determined in 10% alcohol (Table 1) are usually lower by 0.1-0.15 as compared with those in aqueous solutions, while those determined in 50% alcohol are usually lower by 0.4-0.5.

† The measurements were made with deuterium oxide solutions and were not complicated by possible deuteration of the investigated substances. Appreciable exchange of the 2-H proton by deuterium was observed only for 1-methylbenzimidazole methiodide in D_2O under the experimental conditions (50°). The spectrum of this salt was therefore measured in ordinary water.

TABLE 2. Parameters of the PMR Spectra of the Methiodides

Methiodide	Solvent	Chemical shift, δ, ppm				
		CH_3	2-H*	H_α†	H_β†	H_γ†
Pyridine	CF_3COOH	4,13	—	8,45	7,76	8,17
	$(CH_3)_2SO$	4,37	—	8,98	8,17	8,58
	D_2O	4,96	—	9,11	8,46	8,63
1-Methylbenzimidazole	CF_3COOH	3,78	8,65	—	—	—
	$(CH_3)_2SO$	4,10	9,61	—	—	—
	H_2O	4,19	9,23	—	—	—
1-Phenylbenzimidazole	CF_3COOH	3,91	8,90	—	—	—
1-(p-Methoxyphenyl)benzimidazole	CF_3COOH	3,85	8,76	—	—	—
1-(p-Nitrophenyl)benzimidazole	CF_3COOH	3,86	8,88	—	—	—
1-(2-Pyridyl)benzimidazole (Ia)	CF_3COOH	3,96	9,45	8,67	7,93	8,34
	$(CH_3)_2SO$	4,13	10,48	8,70	Complex multiplet	
1-(4-Pyridyl)benzimidazole (IIa)	CF_3COOH	4,28	9,53	8,97	8,31	—
	$(CH_3)_2SO$	4,38	9,08	9,15	8,33	—
1-β-(2-Pyridyl)ethylbenzimidazole (Ib)	CF_3COOH	3,81	9,08	8,36	7,88	8,26
	$(CH_3)_2SO$	4,13	9,93	8,50	Complex multiplet	
1-β-(4-Pyridyl)ethylbenzimidazole (IIb)	CF_3COOH	4,01	9,00	8,33	7,67	— ‡
	D_2O	4,40	7,88	8,40	7,47	—

*The 2-H signal is related to the benzimidazole ring, while the H_α, H_β, and H_γ signals are related to the pyridine ring.
† The center of a doublet.
‡ The $N-CH_2$ signal appears at 4.69 ppm, while that of $C-CH_2$ appears at 3.38 ppm.

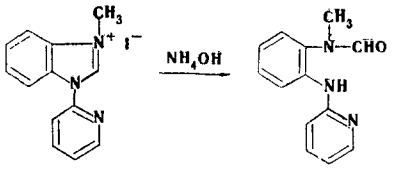
TABLE 3. Data Characterizing the π Interaction of the Imidazole and Pyridine Rings in N-Pyridylbenzimidazoles

Compound	$E^{\pi*}$	E^{π}_{int}	Δq_{Py}	μ_{exp}, D†	μ_{th}, D	μ_{int}, D
1-Phenylbenzimidazole	22,771	0,086	−0,019	3,37[11]		0,35—0,40[11]
1-(2-Pyridyl)benzimidazole (Ia)						
φ=0°	22,470	0,236	−0,060	4,29	5,14	0,85
φ=40°	23,367	0,134	−0,033		5,77	1,48
1-(4-Pyridyl)benzimidazole (IIa)	23,325	0,091	−0,023	1,13	1,94	0,81

*The E^{π} and E^{π}_{int} values are given in β° units.
† The dipole moments were determined in benzene at 25°C.

PMR spectra of pyridines, these protons appear as a well-resolved doublet (each peak of the doublet is split slightly due to meta combination), while these protons appear as a singlet in the PMR spectra of benzimidazoles. The signals of the α protons are shifted considerably to the weak-field region (because of the shielding effect of the pyridine N atom) as compared with the signals of the other protons and can be readily distinguished from them. It is curious that while the pyridine α protons in the bases are deshielded to a greater degree (δ 8.6 ppm, $CDCl_3$ [5]) than the benzimidazole protons (δ 7.8 ppm, $CDCl_3$ [6]), the pattern is reversed in the cations. Although transition from the bases to the cations for both classes of compounds is accompanied by an overall shift of the entire spectrum to weak field, in benzimidazolium salts this effect for the α proton is expressed more strongly in DMSO and D_2O than in pyridinium salts. Thus, if the singlet in the PMR spectra of methiodides measured in DMSO or water is found at weakest field, the salt has the imidazolium cation structure, while if the doublet is found at weakest field, the salt has the pyridinium cation structure. On the basis of this, we found that Ia and Ib are quaternized and, apparently, protonated at the imidazole ring, while IIa and IIb are quaternized at the pyridine ring.

An independent chemical proof of the structure of the methiodides of Ia and IIa was their behavior with respect to ammonium hydroxide. While the pyridinium salt (the methiodide of IIa) was resistant to the action of 22% ammonium hydroxide, the benzimidazolium salt (III) reacts with ammonium hydroxide to give a pseudo base that exists in acyclic form IV. This behavior relative to ammonium hydroxide is also typical for other N-arylbenzimidazolium salts [7]. Pyridinium salts do not form pseudo bases on reaction with ammonia [8].

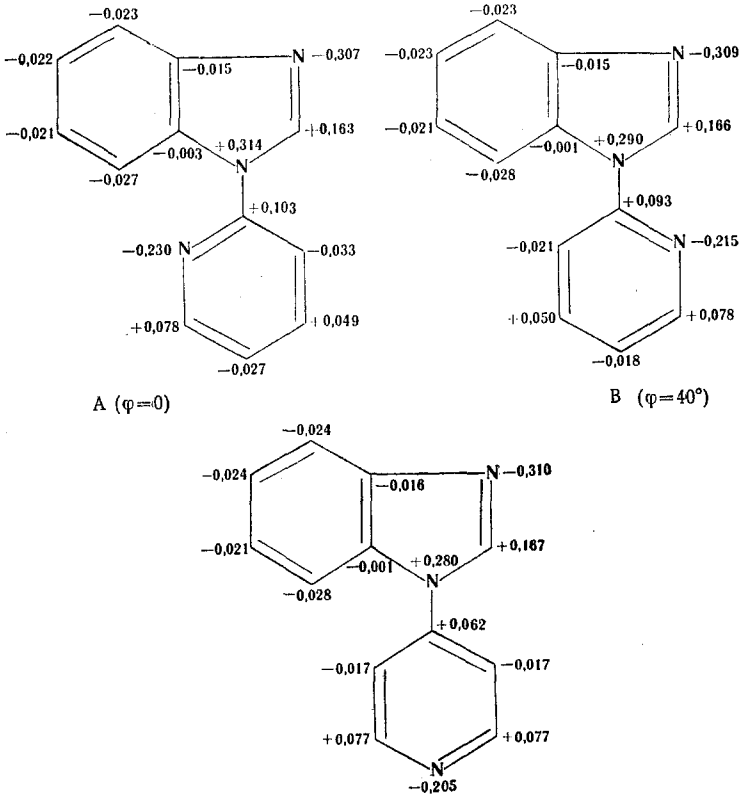


III IV

Character of the Interaction of the Imidazole and Pyridine Rings in N-Pyridylbenzimidazoles. In analogy with 1-phenylbenzimidazole [9], one might have expected that the π interaction of the imidazole ring and the N-substituent in Ia and IIa would have a substantial effect on their reactivities. To study this problem, we calculated the total π-electron energies of the ground states of N-pyridylbenzimidazoles (E^{π}) by the Hückel MO method, on the basis of which we computed the π-electron interaction energies of the pyridine and benzimidazole rings (E^{π}_{int}) from the formula

$$E_{int}^{\pi}=E^{\pi}-E_{Bzm}{}^{\pi}-E_{Py}{}^{\pi},$$

where E^{π}_{Bzm} and E^{π}_{Py} are the π-electron energies of the isolated benzimidazole and pyridine rings, which are equal, respectively, to $14.685\beta°$ and $8.549\beta°$. In the calculation of the E^{π} values for 1-phenylbenzimidazole and 1-pyridylbenzimidazole, allowance was made for the noncoplanarity of the molecules, and the angle of rotation (φ) of the N-substituent about the C—N bond relative to the plane of the benzimidazole portion was taken as 40° [10]. For Ia, planar conformation A (φ = 0°), for which calculations were also performed, is also possible in addition to nonplanar conformation B.



π-Electron charges of N-pyridylbenzimidazole molecules (ground state)

A comparison of the E^{π}_{int} and Δq (total negative π charge in the N-substituent) values demonstrates that the pyridine ring in Ia and IIa is a π acceptor that is somewhat stronger than the N-phenyl group.

The conjugation of the two heterorings in Ia and IIa is reflected in the sharp decrease in the basicity of the imidazole ring (it is considerably greater than in 1-phenylbenzimidazole, the pK_a of which is 4.32 in 5% alcohol) [12] and in the exaltation of the dipole moment values. From a comparison of experimental dipole moment values with the values calculated theoretically via the vector scheme, it follows that an additional π moment (μ^{π}_{int}), the vector of which (in a direction from the positive end of the dipole to the nega-

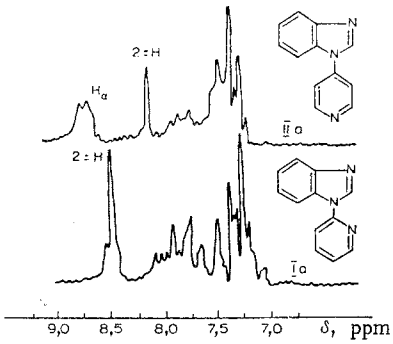
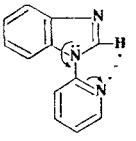


Fig. 1. PMR spectra of 1-(2-pyridyl)-benzimidazole (Ia) and 1-(4-pyridyl)-benzimidazole (IIa) in $CDCl_3$ (H_α are the pyridine ring protons, while 2-H are the imidazole ring protons).

tive end) is directed along the $N_{(1)}-C$ bond toward the N-substituent and is subtracted from the dipole moment of the benzimidazole ring (the latter is directed at an angle of about 13° to the bisector of the $C-N_{(1)}-C$ angle) [9], arises during π,π conjugation of the imidazole and pyridine rings in Ia and IIa. Thus the μ_{int}^{π} value was estimated approximately as the scalar difference between the μ_{exp} and μ_{th} values.*

In agreement with the results of quantum-mechanical calculations, the moment of interaction in Ia and IIa is considerably larger than in 1-phenylbenzimidazole. The μ_{int}^{π} value for 1-(2-pyridyl)benzimidazole is particularly large and can scarcely be ascribed only to the difference in the electron-acceptor character of the 2- and 4-pyridyl radicals. In our opinion, the major reason for this consists in the existence of Ia in the B form, which is stabilized during conjugation by the formation of a hydrogen bond between the ortho N-atom of the pyridine ring and the μ-hydrogen atom of the imidazole ring (V).



V

The formation of an intramolecular hydrogen bond leads to the appearance of a partial positive charge on the N atom of the pyridine ring and through it to an increase in the additional moment of interaction of the two heterocyclic rings. The stabilization of structure V through a hydrogen bond can fully compensate for the small (0.1β° or about −2 kcal/mole, if it is assumed that β° = −20 kcal/mole [13]) loss in energy on passing from planar conformation A to nonplanar conformation B. This also explains why Ia, in contrast to IIa, is methylated in the imidazole ring, despite the high electron-acceptor character of the 2-pyridyl group as compared with the 4-pyridyl group.

The participation of the hydrogen atom of the C−H bond in the formation of a hydrogen bond in this case is due to its considerable acidity [14], which increases even more on closing of the hydrogen bridge. This is also confirmed by the PMR spectra (Fig. 1).

The singlet from the hydrogen atom of the imidazole ring (δ 8.50 ppm) in the PMR spectrum of 1-(2-pyridyl)benzimidazole (Ia) is found at considerably weaker field as compared with IIa (δ 8.22 ppm) and 1-alkylbenzimidazole (δ 7.8 ppm) [6]. A particularly pronounced drift of this signal to weak field appears in the methiodide of Ia (Table 2), which is certainly caused by the further increase in the acidity of the μ-hydrogen atom as a result of quaternization of the imidazole ring and strengthening of the intramolecular hydrogen bond of the V type. The position of the α protons of the pyridine ring in the PMR spectrum of Ia is also anomalous in comparison with the spectrum of IIa. While the signals of the α protons (doublet, δ 8.76 ppm) in the latter are found at weaker field than the 2-H signal of the imidazole ring, the pattern is reversed in the PMR spectrum of Ia (Fig. 1). The shielding of the α protons of the pyridine ring in Ia is apparently a consequence of the greater (than in IIa) π,π conjugation of the two heterorings, which is accompanied by feeding of π electron density to the pyridine ring.

Behavior of N-Pyridylbenzimidazoles with Respect to Sodium Amide. If one takes into account the importance of prior coordination of the pyridine N atom with the Na^+ ion in sodium amide, in conformity with the relative basicities of the heterorings, Ia should have been aminated in the imidazole ring, while IIa should have been aminated in the pyridine ring. However, their absolute basicities lie below the limit necessary for successful occurrence of the Chichibabin reaction (for imidazoles, this limit was determined to be 4.2-4.3 pK_a units) [12]. In fact, 1-(4-pyridyl)benzimidazole (IIa) and (taken for comparison) 1-(p-nitrophenyl)benzimidazole (pK_a 3.64, 50% alcohol) do not react with sodium amide in dimethylaniline or

*The true μ_{int}^{π} values are apparently somewhat higher than those presented in Table 3, since vector addition of the μ_{exp} and μ_{th} values would be more accurate. In this case, this sort of addition is impossible because of the difficulty involved in estimating the angle (θ) between the two vectors.

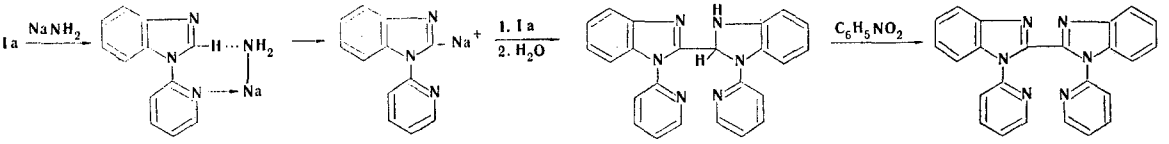
TABLE 4. Results of Amination of 1-Methylbenzimidazole and α-Picoline with Sodium Amide

Compound	Solvent	Amount of $NaNH_2$, mole	Bath temp., °C*	Reaction time, h	Yield of amine, %
1-Methylbenzimidazole	Dimethyl-aniline	1,2	115	1	79 [2]
α-Picoline	Dimethyl-aniline	4	160	4	42
1-Methylbenzimidazole	Xylene	4	110—115	1	82
α-Picoline	Xylene	2	145	3,5	56

*The reaction does not proceed below the indicated temperatures.

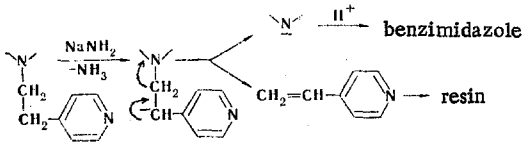
xylene at temperatures up to 170° and are recovered unchanged from the reaction mixture (only partial resinification is observed).

In this case, 1-(2-pyridyl)benzimidazole (Ia) also behaves anomalously: when it is heated with sodium amide in xylene it is converted (in 51% yield) to a compound, which, from the results of elementary analysis and the presence of an N–H band in the IR spectrum at 3360 cm^{-1}, we identified as 1,1'-di(2-pyridyl)-2,3-dihydro-2,2'-dibenzimidazole (VIII). When VIII is heated briefly in nitrobenzene, it is aromatized to a dimer (IX), the structure of which was confirmed by PMR spectroscopy (absence of 2-H signals of the imidazole ring and presence of a doublet at δ 8.25 ppm from the α protons of pyridine rings). The formation of a dimerization product in such a high yield during the action of sodium amide on a N-heteroaromatic compound is an extremely rare phenomenon [2]. The reason for this may be the above-noted elevated acidity of the C–H bond in the imidazole ring of Ia and the possibility of reaction through complex VI. Both factors should facilitate the formation of an organosodium derivative (VII), which, by reacting with Ia, gives a dimer. The low yield of VIII in dimethylaniline (10%) is apparently also associated with the fact that dimethylaniline, as a stronger base (pK_a 5.1) than Ia, solvates sodium amide, thereby hindering both coordination via the mechanism for VII and subsequent metallation.



VI VII VIII IX

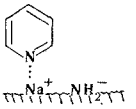
The interaction of the pyridine and imidazole rings in Ib and IIb is minimal, and the electronic factor should therefore have no effect on their behavior with respect to sodium amide. Their basicities are sufficiently high for successful amination. Nevertheless, an amino group cannot be introduced into Ib and IIb under the normal Chichibabin conditions (xylene or dimethylaniline, 110-150°, 2 h), and they are recovered unchanged from the reaction mixtures. Under more severe conditions (150-170°, 10 h), the molecules of Ib and IIb decompose to give benzimidazole and resins, probably as a result of the following reaction:



Since the experiments described above did not provide a direct answer to the problem of the relative ease of entry of the pyridine and benzimidazole systems into the Chichibabin reaction, we carried out the competitive amination of a mixture of pyridine and 1-methylbenzimidazole with sodium amide (present in insufficient amounts). We found that 1-methylbenzimidazole is primarily aminated in dimethylaniline (145°) and in xylene (135°), and we did not detect even traces of 2-aminopyridine by means of gas-liquid chromatography (GLC). This indicates that the benzimidazole system undergoes the Chichibabin reaction much more readily than the pyridine system. One can arrive at the same conclusion by comparing the conditions under which one usually carries out the amination of pyridines and benzimidazoles: the reaction proceeds at higher temperatures and considerably more slowly for pyridines [2].

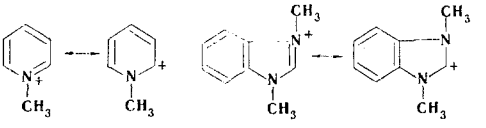
The relative reactivities of pyridines and benzimidazoles with respect to sodium amide are not in agreement with the effective positive charges on their C_α atoms. According to the PMR spectroscopic data, the α protons of the pyridine ring are deshielded to a greater degree than the 2-protons in 1-alkylbenzimidazoles, and the positive charge on the C_α atom of pyridine thus should also be higher [15]. At first glance, the somewhat elevated basicities (pK_a 5.5-5.6), as compared with pyridine (pK_a 5.21), favor the amination of 1-alkylbenzimidazoles. However, experiments involving competitive amination of 1-methylbenzimidazoles and α-picoline refuted this assumption. We found that the more basic α-picoline (pK_a 5.97) is aminated with greater difficulty in xylene and, particularly, in dimethylaniline (Table 4).

In our opinion, the electronic effects in the pyridinium and benzimidazolium cations formed during coordination of the bases with sodium amide* are of decisive significance in the relative reactivities of both heterosystems in the Chichibabin reaction. The PMR spectra demonstrate (Table 2) that, in contrast to the bases, in the pyridinium and benzimidazolium cations the α proton of the latter is even more deshielded:



X

The CH_3 group in the N-methylpyridinium cation is simultaneously associated with a more electropositive N atom, since the signal of this group is found at weaker field than the analogous signal in the 1,3-dimethylbenzimidazolium cations.



XI XIa XII XIIa

This is evidence that the positive charge in the pyridinium cation is localized to a considerable degree on the N atom, i.e., the contribution of carbonium structure XIa to the ground state of the molecule is less than the contribution of structure XIIa to the ground state of the benzimidazolium cation. In other words, the polarizability of the C=N bond in the benzimidazolium salts is higher than in the pyridinium cation, and coordination at the nitrogen in the benzimidazoles thus favors nucleophilic substitution at the 2 position more than in pyridine.

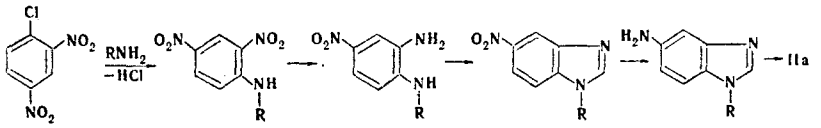
This reason apparently also determines the increased reactivity of benzimidazole as compared with pyridine in many other nucleophilic substitution reactions that proceed with the participation of quaternary salts or coordination of the bases with aprotic Lewis acids: reaction with organometallic reagents (benzimidazoles are metallated in the 2 position [16], while pyridines add the organometallic reagent at the C=N bond [17]), hydroxylation with alkalis [2], and formation of pseudo bases during the action of alkali on quaternary salts.

EXPERIMENTAL

1-(2-Pyridyl)benzimidazole (Ia). A mixture of 10.3 g (0.1 mole) of 2-chloropyridine, 9.44 g (0.08 mole) of benzimidazole, 13.8 g (0.1 mole) of anhydrous potassium carbonate, and 0.4 g of CuBr in 80 ml of nitrobenzene was refluxed with stirring for 20 h. The nitrobenzene was then removed by steam distillation, and the residue was extracted with chloroform. The chloroform extract was passed through a column filled with Al_2O_3 with collection of the fraction with R_f 0.5-0.6. This fraction was vacuum-distilled at 195-198° (5 mm) to give 12.5 g (74%) of colorless needles with mp 70° (from petroleum ether, bp 40-70°), which is in agreement with the data in [18].

*It is possible that this sort of coordination leads to the formation of a relatively weak donor–acceptor $N \rightarrow NaNH_2$ bond in adsorption complex X rather than to the formation of a pyridinium ion in the usual understanding of this term. However, this does not alter the proceedings in the sense of the appearance on the N atom of a partial positive charge and the resulting additional polarization of the C=N bond.

Compound IIa was obtained in relatively low yield by arylation of benzimidazole with 4-chloropyridine hydrochloride in analogy with Ia. It was therefore obtained in accordance with the following scheme:



XIII XIV XV XVI

R = 4-pyridyl

N-(4-Pyridyl)-2,4-dinitroaniline (XIII). A mixture of 7.52 g (0.08 mole) of 4-aminopyridine and 8.1 g (0.04 mole) of 2,4-dinitrochlorobenzene in 25 ml of xylene was refluxed for 2 h. The mixture was cooled, and the orange precipitate was separated from the resinous product that remained on the bottom of the flask and was washed with ether to give 2.9 g of product. Extraction of the resinous residue with hot xylene gave another 1.6 g of XIII. The overall yield of XIII was 4.5 g (50%). The orange needles had mp 197° (from alcohol). Found: C 50.6; H 3.3; N 21.7%. $C_{11}H_8N_4O_4$. Calculated: C 50.8; H 3.1; N 21.5%.

2-Amino-4-nitro-N-(4-pyridyl)aniline (XIV). A suspension of 2.6 g (0.01 mole) of XIII in 15 ml of alcohol was added carefully to a solution of 0.64 g (0.02 mole) of sulfur and 4.8 g (0.02 mole) of $Na_2S \cdot 9H_2O$ in 15 ml of water, and the mixture was refluxed with stirring on a water bath for 1.5 h. It was then cooled, and the red precipitate was separated and washed with hot water and alcohol to give 2 g (86%) of red prisms of XIV with mp 255° (dec., from aqueous alcohol). Found: C 57.1; H 3.7; N 24.2%. $C_{11}H_{10}N_4O_2$. Calculated: C 57.4; H 3.4; N 24.3%.

5-Nitro-1-(4-pyridyl)benzimidazole (XV). A solution of 1.4 g (6 mmole) of XIV in 10 ml (0.26 mole) of 85% formic acid and 0.5 ml of concentrated HCl was refluxed for 2.5 h. Water was then added, and the mixture was decolorized by boiling with activated charcoal. The hot solution was filtered and neutralized with 22% ammonium hydroxide. The orange precipitate was separated and washed with water to give 1.4 g (97%) of yellow crystals with mp 225° (from dimethylformamide). Found: C 59.8; H 3.7; N 23.1%. $C_{12}H_8N_4O_2$. Calculated: C 60.0; H 3.4; N 23.3%.

5-Amino-1-(4-pyridyl)benzimidazole (XVI). A 2.4-g (0.01 mole) sample of XV was added in portions to a warm solution of 6.77 g (0.03 mole) of $SnCl_2 \cdot 2H_2O$ in 30 ml of concentrated HCl (a precipitate formed), and the mixture was stirred on a boiling-water bath for 2 h. It was then cooled, and the precipitated tin complex was separated, washed with 50 ml of water, and decomposed with excess 40% sodium hydroxide solution. The amine was extracted with chloroform to give 1.8 g (87%) of rose-tinted needles with mp 205° (from water). Found: C 68.7; H 5.0; N 26.8%. $C_{12}H_{10}N_4$. Calculated: C 68.6; H 4.8; N 26.7%.

1-(4-Pyridyl)benzimidazole (IIa). A. A solution of 1.03 g (15 mmole) of sodium nitrite in 4 ml of water was added in portions to a cooled (to 0°) solution of 2.8 g (12.5 mmole) of XVI in 35 ml of 20% HCl, and 7 ml of concentrated HCl was added. A solution of 7.6 g (0.06 mole) of potassium hypophosphite in 10 ml of water was then added gradually. The mixture was cooled and stirred for 1 h and was then placed in a refrigerator for 20 h to complete the reaction. It was then made alkaline with 22% ammonium hydroxide and extracted with chloroform. The chloroform extract was passed through a column filled with Al_2O_3 to give 1.8 g (72%) of a fraction with R_f 0.6. Recrystallization from benzene–petroleum ether gave colorless prisms with mp 119-120°, which is in agreement with the melting point in [18].

B. A mixture of 2.4 g (0.02 mole) of benzimidazole, 3 g (22 mmole) of 4-chloropyridine hydrochloride, 5.5 g (0.04 mole) of anhydrous potassium carbonate, and 0.2 g of CuBr in 40 ml of nitrobenzene was refluxed for 10 h. The nitrobenzene was removed by steam distillation, and the residue was extracted with chloroform to give 1.6 g (41%) of a product with mp 120°.

1-β-(2-Pyridyl)ethylbenzimidazole (Ib). A mixture of 5.9 g (0.05 mole) of benzimidazole, 6 g (0.057 mole) of 2-vinylpyridine, and 0.3 g of glacial acetic acid was fused at 130° for 5 h. The unchanged vinylpyridine was removed by vacuum distillation at 100°, and the residue was dissolved in 30 ml of benzene and passed through a column filled with Al_2O_3 (R_f 0.8) to give 6.5 g (55%) of colorless needles with mp 68-69° (from ether), which is in agreement with the data in [19].

1-β-(4-Pyridyl)ethylbenzimidazole (IIb). A mixture of 2.36 g (0.02 mole) of benzimidazole, 2.3 g (21 mmole) of 4-vinylpyridine, and 0.3 g of glacial acetic acid was fused at 135° for 7 h. Isolation and purification as in the preparation of Ib gave 4 g (85%) of colorless prisms with mp 101° (from CCl_4), which is in agreement with the data in [19].

TABLE 5. Methiodides of N-Substituted Benzimidazoles

Methiodide*	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
			C	H	N	C	H	N	
1-Phenylbenzimidazole	192	$C_{14}H_{13}IN_2$	—	—	8,5	—	—	8,3	80
1-(p-Methoxyphenyl)benzimidazole	238—239	$C_{15}H_{15}IN_2O$	—	—	8,0	—	—	7,7	87
1-(p-Nitrophenyl)benzimidaz.	272	$C_{14}H_{12}IN_3O_2$	—	—	11,2	—	—	11,0	57
1-(2-Pyridyl)benzimidazole	202	$C_{13}H_{12}IN_3$	46,4	3,8	12,7	46,3	3,6	12,5	83
1-(4-Pyridyl)benzimidazole	252 (dec.)	$C_{13}H_{12}IN_3$	46,5	3,8	12,6	46,3	3,6	12,5	98
1-β-(2-Pyridyl)ethylbenzimidazole	105—106	$C_{15}H_{16}IN_3$	49,2	4,7	11,5	49,4	4,4	11,5	98
1-β-(4-Pyridyl)ethylbenzimidazole	208—209	$C_{15}H_{16}IN_3$	49,4	4,6	11,6	49,4	4,4	11,5	98

*The methiodides of 1-(p-nitrophenyl)- and 1-(4-pyridyl)benzimidazoles were yellow compounds, while the remaining methiodides were colorless. The 1-(β-pyridylethyl)benzimidazole methiodides were recrystallized from alcohol, while the remaining methiodides were recrystallized from water.

General Method for the Preparation of Methiodides (Table 5). A solution of 0.05 mole of the base and 0.05 mole of methyl iodide in 10 ml of acetone was refluxed for 3 h. The mixture was cooled, and the precipitate was separated, washed with acetone, and recrystallized.

N-(2-Pyridyl)-N'-methyl-N'-formyl-o-phenylenediamine. A solution of 0.5 g (15 mmole) of the methiodide of Ia in 15 ml of water was treated with 5 ml of 22% ammonium hydroxide, and the mixture was allowed to stand in a refrigerator for 48 h. The liberated oil began to crystallize in the course of 4 days at room temperature to give 0.3 g (88%) of rose-tinted prisms with mp 121-122° (from water). Found: C 68.9; H 5.7; N 18.4%. $C_{13}H_{13}N_3O$. Calculated: C 68.7; H 5.8; N 18.5%. IR spectrum, cm^{-1} (in chloroform): ν_{CO} 1685; ν_{NH} 3340, 3410, 3435 (d_{NaCl} 0.6 mm; c $5.1 \cdot 10^{-2}$ M).

Action of Base on the Methiodide of IIa. This experiment was carried out in analogy with the preceding experiment, but the precipitate obtained was the starting compound. The yield of product with mp 249-250° (dec.) was 90%. Pronounced resinification occurred during the action of 5% sodium hydroxide solution on the methiodides of Ib and IIb at 25°. No individual compound could be isolated from the resulting resinous mass (it was insoluble in chloroform).

1,1'-Di(2-pyridyl)-2,3-dihydro-2,2'-dibenzimidazole (VIII). A mixture of 1.95 g (0.01 mole) of Ia and 1.56 g (0.04 mole) of sodium amide in 10 ml of xylene was stirred at 145° for 1.5 h. It was then cooled, 10 ml of water was added, and the precipitate was separated and washed with water, benzene, and petroleum ether to give 1.5 g of product. The precipitate dissolved in hot alcohol and precipitated on cooling but was no longer soluble in it. This method was used to isolate 1 g (51%) of colorless prisms of VIII with mp 252-253° (from dimethylformamide). Found: C 73.7; H 4.9; N 21.5%. $C_{24}H_{18}N_6$. Calculated: C 73.8; H 4.6; N 21.5%. IR spectrum, cm^{-1}: δ_{NH} 1678; ν_{NH} 3360. The yield of VIII was 10% when the experiment was carried out in dimethylaniline at 140°.

1,1'-Di-(2-pyridyl)-2,2'-dibenzimidazole (IX). A solution of 0.19 g of VIII in 3 ml of nitrobenzene was refluxed for 1 h, the nitrobenzene was removed by steam distillation, and the residue was extracted with chloroform. The chloroform solution was passed through a column filled with Al_2O_3 to give 0.18 g (98%) of a fraction with R_f 0.7. The pale yellow prisms had mp 207-208° (from benzene–petroleum ether). Found: C 74.1; H 4.2; N 21.8%. $C_{24}H_{16}N_6$. Calculated: C 74.2; H 4.2; N 21.7%.

Action of Sodium Amide: a) On 1-(4-Pyridyl)benzimidazole (IIa). A mixture of 0.97 g (5 mmole) of IIa and 0.78 g (0.02 mole) of sodium amide in 10 ml of xylene was stirred at 145° for 2 h. No gas evolution was observed. The mixture was cooled, 10 ml of water was added, and the xylene solution was separated and evaporated to dryness. The residual brown oil was contaminated starting compound. The yield was 0.8 g (85%). Recrystallization from benzene–petroleum ether gave a material with mp 119° that did not depress the melting point of an authentic sample. A similar result was obtained when the experiment was carried out in dimethylaniline.

b) On 1-β-(2-Pyridyl)ethylbenzimidazole (Ib). The starting compound was recovered in 80-85% yield from the reaction of a fourfold excess of sodium amide with Ib in xylene at 135° or in dimethylaniline at 145° for 2 h. After prolonged heating (10 h) in xylene under nitrogen, benzimidazole (80%) precipitated from the aqueous layer during neutralization after decomposition of the mixture with water. A resinous product, which dissolved in alcohol but was insoluble in other organic solvents, was also formed.

c) On 1-β-(4-Pyridyl)ethylbenzimidazole (IIb). A mixture of 1.2 g (0.005 mole) of IIb and 0.78 g (0.02 mole) of sodium amide in 10 ml of xylene was stirred under nitrogen for 10 h. It was then cooled, 10 ml of water was added, and the resinous product was separated. The aqueous layer was separated and neutralized to pH 7-8 with concentrated HCl. The precipitated benzimidazole was removed by filtration and washed with water to give 0.5 g (83%) of colorless plates with mp 170-171° (from water). No melting-point depression was observed for a mixture of this product with an authentic sample. The starting compound (85%) was isolated from the reaction with sodium amide in xylene (140°) or dimethylaniline (145°) for 2 h.

Competitive Amination. a) 1-Methylbenzimidazole and Pyridine. A mixture of 1.32 g (0.01 mole) of 1-methylbenzimidazole, 0.78 g (0.01 mole) of pyridine, and 0.39 g (8 mmole) of 80% sodium amide in 7 ml of dimethylaniline was stirred at 140-145° for 2 h. The mixture was cooled, 4 ml of water was added, and the precipitated 1-methyl-2-aminobenzimidazole was removed by filtration and washed with water, benzene, and petroleum ether to give 0.8 g (68% based on sodium amide) of colorless needles with mp 200°, which is in agreement with the data in [20]. The dimethylaniline solution was treated with 50 ml of chloroform, and the mixture was dried with sodium sulfate and subjected to GLC analysis, on the basis of which it was established that about 100% of the pyridine and 30% of the 1-methylbenzimidazole remained in the reaction mixture.

In another experiment, the same quantities of starting compounds were stirred at 130-135° in 6 ml of xylene for 1.5 h. 1-Methyl-2-aminobenzimidazole was isolated as above. The yield was 0.22 g (19%). About 100% of the pyridine and 71% of the 1-methylbenzimidazole remained in the reaction mixture.

b) 1-Methylbenzimidazole and α-Picoline. A mixture of 1.32 g (0.01 mole) of 1-methylbenzimidazole, 0.93 g (0.01 mole) of α-picoline, and 0.46 g (0.01 mole) of 80% sodium amide in 7 ml of xylene was stirred at 100-115° for 1.5 h. The mixture was cooled, 10 ml of water was added, and the precipitated 1-methyl-2-aminobenzimidazole was removed by filtration and washed with water, benzene, and petroleum ether. The yield was 0.9 g (63%). About 100% of the α-picoline and 25-30% of the 1-methylbenzimidazole remained in the xylene solution.

Equimolecular amounts of α-picoline, 1-methylbenzimidazole, and sodium amide in 8 ml of dimethylaniline were stirred at 125-130° for 2 h. The reaction commenced very vigorously at 125°. The mixture was cooled, 5 ml of water was added, and the precipitated 1-methyl-2-aminobenzimidazole was separated and washed with water, benzene, and petroleum ether. The yield was 48%. The dimethylaniline was removed from the filtrate by steam distillation, during which the α-picoline also distilled. 1-Methyl- and 1-methyl-2-aminobenzimidazole remained in the residue (according to chromatography).

Ionization Constants. The ionization constants were measured by potentiometric titration at 25 ± 1° with an LPU-01 pH meter. The solvent was 10% (by volume) alcohol: a 0.001 M solution of the base was titrated with 0.01 N hydrochloric acid.

PMR Spectra. The PMR spectra at concentrations of 10-15% were recorded with a PE-2305 spectrophotometer with an operating frequency of 60 MHz at 50° with hexamethyldisiloxane as the internal standard. The chemical shifts are given on the δ scale and are converted with respect to the signal of tetramethylsilane.

Quantum-Mechanical Calculations. These calculations were carried out by the Hückel MO method and the method in [10]. In the calculation of nonplanar conformation B, the integral of the N–C bond between the pyridine and imidazole rings was taken as $\beta_{N-C} = 0.9\beta^\circ \cos^2 40^\circ = 0.7\beta^\circ$. The solution of the secular determinants was obtained with a Razdan computer.

Dipole Moments. The dipole moments were determined according to the method in [21] with an IDM-2 dipole meter in benzene at 25 ± 0.1° for concentrations of 0.001-0.01 mole fraction. The theoretical values of the dipole moments of N-pyridylbenzimidazoles were calculated from the formula

$$\mu_{th} = (\mu_1^2 + \mu_2^2 + 2\mu_1\mu_2 \cdot \cos\theta)^{1/2},$$

where μ_1 and μ_2 are the dipole moments of the benzimidazole (4.03 D) and pyridine (2.21 D) [22] molecules, and θ is the angle between the directions of the μ_1 and μ_2 vectors.

The IR spectra were measured with a UR-20 spectrophotometer.

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