

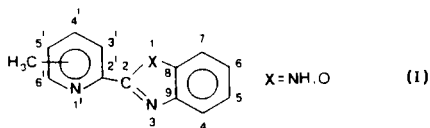
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The  $^{13}\text{C}$  nmr spectra of a series of pyridylbenzimidazoles and benzoxazoles and of their quaternary salts have been determined. The mutual effects of the two heterocyclic systems and the effect of the quaternization have been discussed. The results evidence the existence of some interactions between benzimidazole and pyridine moieties.

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In previous works [2-6] we studied the synthesis and the properties of heterocyclic systems of general formula **I** with particular attention to the relationships between structure and spectroscopic behavior.



In the present work the  $^{13}\text{C}$  nmr spectra of compounds **I** and of their quaternary salts are examined.

#### Results and Discussion.

In Table 1 the  $^{13}\text{C}$  chemical shifts of a series of 2-(2-pyridyl)benzimidazoles, as well as of some pyridines and benzimidazoles taken as reference compounds, are reported.

Spectral assignments have been made following three criteria: (i) comparison between  $^1\text{H}$ -decoupled and coupled  $^{13}\text{C}$  spectra in order to distinguish the signals of the C and CH groups; (ii) comparison of the various systems between themselves and with the parent structures, assuming the validity of the additivity of substituent effects; (iii) comparison of  $^1\text{J}(\text{CH})$ 's as indicated above for chemical shifts.

The spectra of benzimidazole **7** and its phenyl derivative **9** evidence only three signals for the benzo ring carbons. The fast tautomeric equilibrium of the H atom in the imidazole ring between the 1 and 3 positions makes equivalent the 8-9, 4-7 and 5-6 positions. A great difference is shown by compound **8** whose 1-methyl group blocks the tautomeric equilibrium [8-10]. In compound **7** chemical shift values for carbon atoms 8 and 9 (or 4 and 7) are about the average of the chemical shifts of the corresponding atoms in compound **8**. This is in agreement with the previously mentioned tautomerism. Data in Table 1 for compounds **1-3** show six different chemical shifts for the carbons of the benzo ring, indicating the disappearance of the tautomerism. Chemical shift assignments for carbons 8-9, 4-7 and 5-6 have been tentatively made in

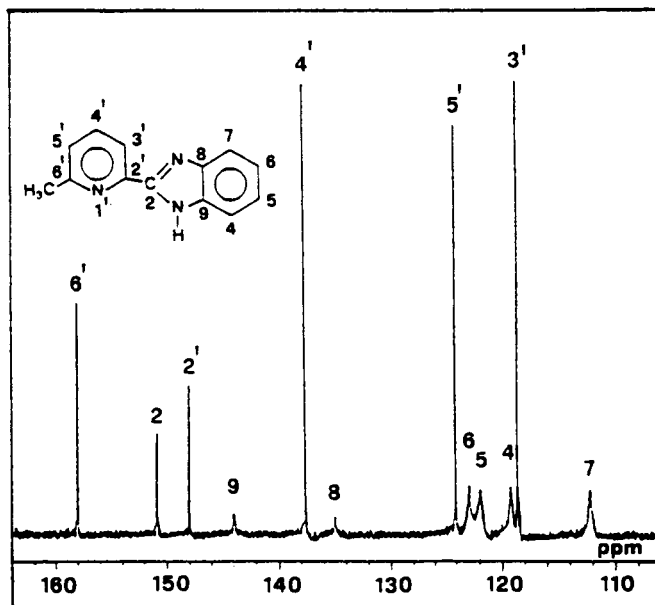


Figure 1. The  $^{13}\text{C}$  nmr spectrum of compound **3** at  $20^\circ$ .

agreement with those of literature data for compound **8**; possible inversion of the data cannot be excluded. Furthermore, carbons 8 and 9 (or 4 and 7) in compound **9** show chemical shifts that are about the average of the values of the corresponding atoms in compounds **1-3**, just as it has been noted for compound **7**.

In compounds **1** and **2** the intensities of the benzo carbon signals are comparable with those of the pyridine carbons. The spectrum of compound **3** (Figure 1) shows, on the contrary, more intense signals for the pyridine carbons than for the benzazole ones. This behaviour, at room temperature, could indicate the presence of a starting exchange phenomenon. Indeed, the spectrum, recorded at higher temperatures, exhibits, at  $70^\circ$ , a coalescence signal for carbons 4 and 7.

Using equation 1 [11], where  $\Delta G^\ddagger$  is the free energy of  $\Delta G^\ddagger = T_C \cdot 4.575 \cdot 10^{-3} \cdot (\log T_C/V_A \cdot V_B + 9.975)$  (1) activation, and  $T_C$  the coalescence temperature ( $^\circ\text{K}$ ) of the

Table 1  
Carbon Atom Chemical Shifts ( $\delta$ , ppm) of Benzimidazoles, Pyridines and Related Salts



Compound No.	CH <sub>3</sub> pos.	Structure		Carbon atom number																			
		X	Y	A	B	D	2'	3'	4'	5'	6'	4CH <sub>3</sub>	6'CH <sub>3</sub>	1'NCH <sub>3</sub>	3'NCH <sub>3</sub>	2	4	5	6	7	8	9	
1	-	N	NH	N	NH	N	148.62	121.48	137.58	124.75	149.42						150.81	119.37	121.95	123.18	112.14	135.00	143.97
2	4'	N	NH	N	NH	N	148.28	122.08	148.43	125.47	149.06	20.58					150.88	119.22	121.82	123.02	112.04	134.94	143.92
3	6'	N	NH	N	NH	N	147.99	118.64	137.63	124.14	158.04		24.15				150.89	119.25	121.95	122.98	112.25	135.03	143.98
4	4'	N	NCH <sub>3</sub>	NCH <sub>3</sub>	NCH <sub>3</sub>	NCH <sub>3</sub>	147.55	128.94	149.45	127.96	150.58	20.72					33.23	140.58	113.68	127.10	113.68	131.66	131.66
5	6'	N	NCH <sub>3</sub>	NCH <sub>3</sub>	NCH <sub>3</sub>	NCH <sub>3</sub>	147.47	125.60	138.31	126.99	159.93		24.10				33.26	140.00	113.69	127.09	113.69	131.64	131.64
6	4'	NCH <sub>3</sub>	NCH <sub>3</sub>	NCH <sub>3</sub>	NCH <sub>3</sub>	NCH <sub>3</sub>	139.02	133.91	160.30	131.72	149.77	21.92					46.56	132.84	114.28	128.04	128.04	114.28	132.40
7		X=H	NH	N	NH	N											142.04	115.43	121.84	121.84	115.43	136.00	136.00
7A [b]		X=H	NH	NH	NH	NH											139.27	114.81	127.53	127.53	114.81	130.44	130.44
7B		X=H	NCH <sub>3</sub>	NCH <sub>3</sub>	NCH <sub>3</sub>	NCH <sub>3</sub>											142.99	113.30	126.31	126.31	113.30	131.54	131.54
8 [c]		X=H	NCH <sub>3</sub>	N	NCH <sub>3</sub>	N											144.4	119.4	121.9	122.7	110.1	134.5	143.3
9 [d]	-	CH	NH	N	NH	N	130.67	130.00	127.71	131.10	127.71					130.00	152.12	116.07	123.48	123.48	116.07	139.85	139.85
10	4'	N	Y=H	Y=H	Y=H	Y=H	149.35	124.59	146.63	124.59	149.35	20.35											
11	2'	N	Y=H	Y=H	Y=H	Y=H	148.88	120.76	136.17	123.03	157.83		24.02										
12	4'	NCH <sub>3</sub>	Y=H	Y=H	Y=H	Y=H	144.49	127.96	158.21	127.96	144.49	21.37											
13	2'	NCH <sub>3</sub>	Y=H	Y=H	Y=H	Y=H	145.96	125.14	144.91	129.08	155.84		20.06										

[a] Assigned on the basis of signal intensity. [b] Data taken from reference [7]. [c] Data taken from reference [8]. [d] Data taken from reference [9].

[e] Signal of the atom of the phenyl ring.

Table 2  
Quaternization Effect in the Benzimidazole Series

Compound No.	Salt	Base	$\Delta\delta$ , ppm [a]															
			2'	3'	4'	5'	6'	4'CH <sub>3</sub>	6'CH <sub>3</sub>	1,3 NCH <sub>3</sub>	2	4	5	6	7	8	9	
<b>5</b>		<b>3</b>	-0.52	6.96	0.68	2.85	1.89			-0.05		-10.89	-5.56	5.14	4.10	1.44	-3.39	-12.31
<b>4</b>		<b>2</b>	-0.73	6.86	1.02	2.49	1.52	0.13				-10.30	-5.54	5.28	4.08	1.64	-3.28	-12.26
<b>6</b>		<b>4</b>	-8.53	4.97	10.85	3.76	-0.81	1.20			0.53	-7.74	0.60	0.94	0.94	0.60	0.74	0.74
<b>12</b>		<b>10</b>	-4.86	3.37	11.58	3.37	-4.86	1.02										
<b>13</b>		<b>11</b>	-2.92	4.38	8.74	6.05	-1.99											

[a]  $\Delta\delta = \delta_{\text{salt}} - \delta_{\text{base}}$ .

Table 3  
Mutual Effects of the Heterocyclic Systems

Compound No.	Pyridine carbons $\Delta\delta$ , ppm [a]								Benzimidazole carbons $\Delta\delta$ , ppm [b]								
	2'	3'	4'	5'	6'	4'CH <sub>3</sub>	6'CH <sub>3</sub>	1'NCH <sub>3</sub>	1,3 NCH <sub>3</sub>	2	4	5	6	7	8	9	
<b>1</b>	-0.98	-2.12	1.88	1.15	-0.18						8.77	3.94	0.11	1.34	-3.29	-3.00	5.97
<b>2</b>	-1.07	-2.51	1.80	0.88	-0.29	0.23					8.84	3.79	-0.02	1.18	-3.39	-3.06	5.92
<b>3</b>	-0.89	-2.12	1.46	1.11	0.21		0.13				8.85	3.82	0.11	1.14	-3.18	-2.97	5.98
<b>4</b> [c]	-1.80	4.35	2.82	3.37	1.23	0.37			-0.05	-2.41	0.38	0.79	0.79	0.38	0.12	0.12	
<b>5</b> [c]	-1.41	4.84	2.14	3.96	2.10		0.08		-0.02	-2.99	0.39	0.78	0.78	0.39	0.10	0.10	
<b>6</b> [c] [d]	-5.47	5.95	2.09	3.76	5.28	0.55			-0.65	-0.48	-10.15	0.98	1.73	1.73	0.98	0.86	0.86

[a]  $\Delta\delta = \delta_{\text{compound}} - \delta_{\text{corresponding picoline}}$ ; for compound **1** the corresponding chemical shifts of pyridine carbons are reported in reference [13]. [b]  $\Delta\delta = \delta_{\text{compound}} - \delta_{\text{benzimidazole}}$ . [c] For benzazolium ring carbons  $\Delta\delta = \delta_{\text{compound}} - \delta_{\text{benzimidazolium}}$ . [d] For pyridinium ring carbons  $\Delta\delta = \delta_{\text{compound 6}} - \delta_{\text{compound 12}}$ .

signals at the frequencies  $V_A$  and  $V_B$  (Hz) for carbons 4 and 7, a  $\Delta G^\ddagger$  of  $15.4 \pm 0.5$  Kcal mole<sup>-1</sup> has been calculated. This value is consistent with an exchange phenomenon involving a hydrogen bond. As compounds **1** and **2** in the same temperature range do not show any exchange phenomenon, the presence of the 6'-methyl seems to be responsible of the structural perturbation.

The hydrogen bond evidenced above for compound **1-3** is probably of intramolecular nature, as the mutual positions of the two heteroatomic rings allow the formation of a pentatomic system. Furthermore, data in our possession, not reported here, for the 2-(6-methyl-3-pyridyl)benzimidazole isomer show only three signals for the benzo ring carbons, indicating the presence of a tautomeric equilibrium not influenced by hydrogen bonds.

Data for compounds **4**, **5**, and **6** show equivalence of carbons 8 and 9, 4 and 7, and 5 and 6 respectively, in agreement with their structure of 1,3-dimethylbenzimidazolium salts. The chemical shifts of  $\geq\text{C-CH}_3$  methyl carbons and  $\geq\text{N-CH}_3$  are well distinguishable;  $\geq\text{N-CH}_3$   $\delta$  values allow for an easy distinction between azine and azole quaternization sites (45-47 and 33 ppm respectively).

Table 2 points out the effects of quaternization on compounds **2** and **3**. When quaternization involves only the

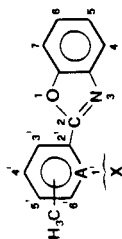
azole nitrogen (compounds **4** and **5**), carbons 2, 4, 8 and 9 are strongly shielded, whereas carbons 5, 6 and 7 are deshielded. This agrees with the data reported for protonation of the benzimidazole ring [7, 12] with the difference that in compounds **4** and **5**  $\Delta\delta$ 's for carbons 4 and 7 are obviously different. The positive charge on the azole nitrogen produces a deshielding of all pyridine carbons except for the 2' position. The deshielding effect is greatest for the 3' and 5' positions. The effect of the quaternization of pyridine nitrogen can be seen by comparing data of compounds **6** and **4**. Only for carbon 2 of the benzimidazole system is a strong shielding effect observed. Pyridine and  $\geq\text{C-CH}_3$  methyl carbons  $\Delta\delta$  values show the same pattern as the corresponding ones of 4-picoline (compound **12**).

The  $\Delta\delta$ 's between the chemical shifts of systems **1-6** and the corresponding heterocyclic reference rings, listed in

Table 3, illustrate the mutual effects of the rings. In compounds **1-3** the pyridine moiety deshields positions 2, 9, 4, 6 and 5 and shields the other ones. When the azole ring is positively charged (compounds **4-6**) only the 2-position is shielded. This, and the general weak deshielding effect shown by the quaternized compounds, can be due to proximity effects of the  $\geq\text{N-CH}_3$  groups. The electronic spec-

Table 4  
Carbon Atom Chemical Shifts ( $\delta$ , ppm) of Benzoxazole Derivatives and Related Salts

Compound No.	A	X	Chemical Shifts ( $\delta$ , ppm)													
			2'	3'	4'	5'	6'	4-CH <sub>3</sub>	6-CH <sub>3</sub>	1-N-CH <sub>3</sub>	2					
14	N	4'	145.15	125.06	148.53	126.93	149.90	20.51		161.48	120.28	126.16	124.23	111.29	150.49	141.24
15	N	6'	144.62	120.80	137.76	125.04	158.86		24.02	161.48	120.27	126.11	125.68	111.34	150.47	141.28
16	N-CH <sub>3</sub>	4'	139.05	129.29	150.39	130.07	148.18	21.44		48.67	121.38	126.26	128.47	111.70	149.79	140.63
17	N-CH <sub>3</sub>	6'	140.76	128.25	144.81	131.38	159.57		22.04	154.69	121.30	126.13	128.13	111.76	150.02	140.55
18 [a]	CH	-	130.6	127.0	128.8	131.4				162.1	119.6	125.1	124.4	110.5	150.1	141.5
19 [a]		X = CH <sub>3</sub>								163.5	119.0	124.1 [b]	123.8 [b]	110.0	150.5	141.4
20 [a]		X = H								153.7	120.1	124.3 [b]	125.3 [b]	110.8	149.6	140.0



[a] Data from reference [15]. [b] These data are reversed in reference [16].

tra of the compounds **1-6** have already demonstrated these effects [2-6,14]. The pyridinium substituent (compound **6**) produces higher  $\Delta\delta$  values for the benzazolium ring than does the pyridine ring.

The benzimidazole ring causes a deshielding of sites 4' and 5' and a shielding of the other pyridine positions (compounds **1-3**). The benzimidazolium moiety shifts downfield all the signals except for the 2' position (compounds **4-6**). The stronger electron withdrawing power of the benzimidazolium ring causes larger effects than benzimidazole. Higher  $\Delta\delta$  values for the 3' than 2' position can be attributed to anisotropic effect variation on the 2'-carbon produced by charge density variation on the azine nitrogen. The  $\Delta\delta$  values for carbons 2' and 6' are much higher in compound **6** than in **4** and **5**. This can be related to the structure of compound **6**, which is simultaneously a pyridinium and azolium salt. The binding of the lone pair electrons in the azine nitrogen quaternization gives rise to the disappearance of the anisotropic effects. Furthermore the repulsion between the positive charges and a reasonable distortion of the planes of the two rings must be taken into account.

The data relative to the benzoxazole derivatives are reported in Table 4. The chemical shifts of the benzo carbons do not show any appreciable change whether the 2-substituent is phenyl or pyridyl (compounds **14**, **15**, and **18**). With a pyridinium substituent significantly different chemical shifts are shown for carbons 2 and 6 (compounds **16** and **17**). Comparison of quaternary salts (**16** and **17**) with the corresponding bases (**14** and **15**) in Table 5 shows evidence of the effect of the positive charge, which is stronger on the pyridine than on the benzo carbons. A shielding effect is observed on carbons 2, 8 and 9 while the other carbons of the benzoxazole are deshielded. The higher  $\Delta\delta$  values for C-6 and C-4 compared to C-5 and C-7, suggest a preferential transmission of the positive charge through the nitrogen atom, as previously observed [17]. For pyridine and  $\geq$  C-CH<sub>3</sub> methyl carbons  $\Delta\delta$  values comparable to those reported for picolines are observed (compounds **12** and **13** in Table 2).

Table 6 shows the reciprocal effects of the pyridine and benzazole moieties. The pyridine substituent (compounds **14** and **15**) exerts a general deshielding effect, largest at the 2 position. The pyridinium group (compounds **16** and **17**) also deshields all the positions with a stronger effect at position 6. The benzoxazole group shields the 2' position and deshields all others. In compound **17** the appreciable positive effect on  $\geq$  C-CH<sub>3</sub> methyl and the negative one on  $\geq$  N-CH<sub>3</sub>  $\delta$ 's can be attributed to a distortion caused by the presence of the two adjacent methyl groups close to the azole ring.

Coupling Constants.

Table 7 lists the  $^1J(\text{CH})$  values for all compounds.

Table 5  
Quaternization Effect in the Benzoxazole Series

Compound No.		$\Delta\delta$ , ppm [a]													
Salt	Base	2'	3'	4'	5'	6'	4'CH <sub>3</sub>	6'CH <sub>3</sub>	2	4	5	6	7	8	9
16	14	-6.10	4.23	10.86	3.14	-1.72	0.93		-7.10	1.10	0.15	4.24	0.41	-0.70	-0.61
17	15	-3.86	7.45	7.05	6.34	0.71		-1.98	-6.79	1.03	0.02	2.45	0.42	-0.45	-0.73

[a]  $\Delta\delta = \delta_{\text{salt}} - \delta_{\text{base}}$ .

Table 6  
Mutual Effects of the Heterocyclic Systems

Compound No.	Pyridine carbon $\Delta\delta$ , ppm [a]							Benzoxazole carbon $\Delta\delta$ , ppm [b]							
	2'	3'	4'	5'	6'	4'CH <sub>3</sub>	6'CH <sub>3</sub>	1'NCH <sub>3</sub>	2	4	5	6	7	8	9
14	-4.20	0.47	1.90	2.39	0.55	0.16			7.8	0.2	1.9	-1.1	0.5	0.9	1.2
15	-4.26	0.04	1.59	2.01	1.03		0.00		7.8	0.2	1.8	0.4	0.5	0.9	1.3
16	-5.44	1.33	1.18	2.11	3.69	0.07		1.46	0.7	1.3	2.0	3.2	0.9	0.2	0.6
17	-5.20	3.11	-0.10	2.30	3.73		1.98	-1.97	1.0	1.2	1.8	2.8	1.0	0.4	0.5

[a]  $\Delta\delta = \delta_{\text{compound}} - \delta_{\text{corresponding picoline or picolinium salt}}$ . [b]  $\Delta\delta = \delta_{\text{compound}} - \delta_{\text{benzoxazole}}$ .

Table 7  
Coupling Constants  $^1J(\text{CH})$ , Hz

Compound No.	2'	3'	4'	5'	6'	4'CH <sub>3</sub>	6'CH <sub>3</sub>	1'NCH <sub>3</sub>	1,3 NCH <sub>3</sub>	2	4	5	6	7
1		166	164	165	179						160	160	158	166
2		164		165	178	128					160	158	159	166
3		169	161	162			127				161	159	158	166
4		169		164	182	127				144	167	164	164	167
5		170	167	164			127			144	166	164	164	166
6		184		171	190	130		146	145		174	165	165	174
7										205	155	159	159	155
7B									144	221	166	167	167	166
10	176	161		161	176	127								
11	176	164	161	162			127							
12	188	174		174	188	129		144						
13	195	179	170	175			130	145						
14		161		161	184	128					164	161	164	169
15		169	165	161			128				166	161	166	173
16		175		171	193	129		147			166	163	165	171
17		176	174	173			131	146			166	164	166	175
20 [a]										233	164	162	163	167

[a] Data from reference [15].

The following considerations can be made: (i) ring carbon J's show values consistent with data reported for heteroaromatic systems; (ii)  $>\text{C}-\text{CH}_3$  groups exhibit higher J values in pyridinium than in pyridine derivatives (129-131 vs 127-128 Hz); (iii)  $>\text{N}-\text{CH}_3$  J values are higher than  $>\text{C}-\text{CH}_3$  ones because of the stronger electron withdrawing power of the charged nitrogen and are about the same for azole and azine nitrogen; (iv) quaternization of azole and azine nitrogen produces a general increase of the J values of the quaternized ring. The high values of  $^1J(\text{C}-7, \text{H}-7)$  and  $^1J(\text{C}-4, \text{H}-4)$  in compound **6** show the ex-

istence of a perturbation between the rings, as previously observed for the chemical shifts.

### Conclusions.

The present study made it possible to highlight the formation of hydrogen bonds between benzimidazole and pyridine rings. Generally, the mutual effect of the two moieties shows the existence of perturbations, more evident at the positions nearest to the inter-ring bond. For benzoxazole systems the pyridine substituent effect on the benzo carbons appears to be mainly transmitted through

the nitrogen atom.

### EXPERIMENTAL

The nmr spectra were obtained with a Jeol GX 270 spectrometer in DMSO-d<sub>6</sub> solution (6% w/v), using the solvent signal (39.60 ppm) as the internal standard. The measurement conditions were as follows: number of data points 32 K, spectral width 18 KHz, cycle times 2-3 s, number of transients 1000-5000, flip angles 45°, line broadening factor 0.8, sample speed rotation 15 Hz.

Compound **1** was prepared by reacting picolinic acid with phenylenediamine in the presence of polyphosphoric acid following the general procedure reported in reference [2]. The product, crystallized from ethanol, is identical with that reported in reference [18]. Compounds **2**, **3**, **14** and **15** were prepared as indicated in reference [2], compounds **4** and **5** as indicated in reference [5], compounds **16** and **17** as indicated in reference [3] and compound **6** as indicated in reference [19].

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