NITROGEN-CONTAINING BISHETEROCYCLIC SYSTEMS

II. The Nature of the Effect of the 2-Benzimidazolyl Radical*

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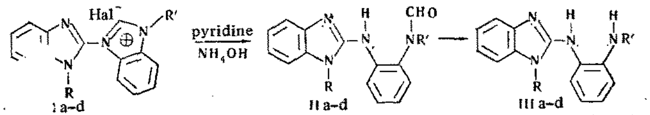
The ease of opening of the imidazole ring in quaternary salts of benzimidazole bearing a 2-benzimidazolyl radical on one of the N-atoms, and the basicity constants of N-(2-benzimidazolyl)- and N-(2-benzimidazolylmethylene)-azoles, indicate the considerable electron-acceptor effect of the 2-benzimidazolyl grouping. Examination of the UV absorption spectra permits the elucidation of the part played by mesomeric effects between the heterocyclic rings in these compounds.

The properties of 2-substituted benzimidazoles show that the 2-benzimidazolyl radical possesses considerable electrophilicity [2]. This explains the ease of opening of the imidazole ring in quaternary benzimidazolium salts [3] bearing a 2-benzimidazolyl radical on one of the nitrogen atoms (Ia) by weakly basic reagents. This reactions occurs with special ease in 1-aryl-3-(2-benzimidazolyl) benzimidazolium salts (Ib), which undergo ring-opening even during preparation. The resulting compounds undergo partial deformylation even on recrystallization.

The quaternary salts Ic and Id, which possess a free NH-group in the 2-benzimidazolyl radical, behave similarly with bases. The formation of ylides is not observed, as it is in the case of N-(2-benzimidazolyl)pyridinium salts [4]. Investigations of the UV and IR spectra of the ring-opening products IIc, IId and IIIc, IIId, and comparison of their spectral curves with those obtained for the quaternary salts Ia and Ib, and with those of the o-phenylene diamine derivatives with the structure shown (IIa and IIIa) [3], lead to the same conclusion.



I a R = CH_3, R' = CH_3, C_2H_5; b R = CH_3, R' = Ph; c R = H, R' = CH_3; d R = H, R' = Ph

The IR spectra of all the initial ring-opening products contain strong absorption bands at 1650–1680 cm^{-1} and 1555–1565 cm^{-1} due, respectively, to the valency vibrations of the C=O of the secondary amide group, and to the deformational vibrations of the secondary amino group [5]. The latter band is also present in the spectra of the deformylation products III.

The properties of the quaternary salts I as described are similar to those of benzimidazolium 2, 4-dinitrophenoxide [3], indicating the similarity of the electron-acceptor effect of the 2, 4-dinitrophenyl and the 2-benzimidazolyl radicals.

Table 1. Absorption Maxima in the Spectra of the Quaternary Salts and Their Ring-Opening Products

Compound	UV Spectra,* λ_{max}, nm (lg ε)	IR Spectra,** ν, cm^{-1}
Ia	278 (4.12); 290 (4.08)	1628, 1619, 1584, 1538
Id	278 (4.04); 292 (4.14)	1626, 1613, 1580, 1545
IIa	292 (4.46)	1650; 1616; 1558; 1497
IIc	260 (4.05); 292 (4.37)	1674; 1609; 1555; 1497
IId		1681; 1631; 1595; 1555; 1496
IIIa	242 (4.25); 290 (4.15)	1629, 1596; 1565, 1507
IIIc	244 (4.00); 288 (3.90)	1605, 1565, 1510
IIId		1596, 1566, 1499

*In methanol, on an SF-4A spectrophotometer.

**Absorption bands in the 1700–1470 cm^{-1} region are shown; IKS-14A spectrometer.

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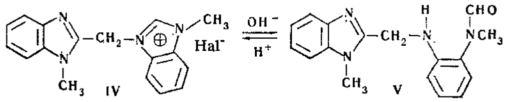
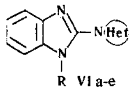
*For part I, see [1].

The insertion of a methylene group between the nitrogen atom of the benzimidazolium cation and the 2-benzimidazolyl radical results in considerable weakening of the effect of the latter, the quaternary salt IV being converted into the o-phenylenediamine derivative V only by strong alkalis. The reaction is also reversible; in acid solution, as in the case of NN'-dialkylbenzimidazolium compounds [6], the equilibrium is shifted in the direction of the formation of the starting material IV (the UV spectra of IV and V in 1 N HCl are coincident).

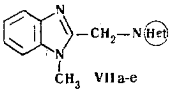


IV V

In order to examine more closely the effect of the 2-benzimidazolyl radical, the UV spectra and basicity constants of some N-(2-benzimidazolyl)azoles (VI) and their methylene analogs (VII) were examined.



VI a-e



VII a-e

VI a-d R = CH_3, e R = H;

VI, VII a-e N(Het) = a, N-imidazolyl; b, N-benzimidazoly; c, N-pyrazolyl; d, N-indazolyl; e, N-indazolyl.

In view of the low solubilities of VI and VII in water and in water-alcohol mixtures, their pK_a values were determined by the potentiometric titration method, in acetonitrile solution [6]. The wide range of the pH scale, and the large differentiating effect of acetonitrile, permitted the reliable determination of the constants for both the first and second stages of the protonation pK_{a1} and pK_{a2}, the numerical values of which were 7-7.5 pK units higher than when determined in aqueous solution (this follows from [8], and comparison of the ionization constants of N-alkylbenzimidazoles where alkyl = CH_3, p-C_3H_7, in acetonitrile (Table 2) with the corresponding values relative to aqueous solutions (5.62 and 5.46 respectively) [9]). The results obtained are given in Table 2.

The course of protonation in VI and VII has been established. In the N-(2-benzimidazolyl)-substituted imidazole VIa and the benzimidazole VIb, the first ionization constant apparently relates to the N-hetero-substituted ring. This conclusion is supported by the course of the quaternization of VIb [3], and agrees with the fact that the basicity of 2-hetero-substituted azoles is known to be reduced as a result of the shielding of the pyridine N-atom [10, 11]. The second basicity constant (pK_{a2}) of VIa and VIb relates to the 2-benzimidazolyl radical, and is substantially reduced as a result of the strong inductive effect of the imidazole cation.

The same sequence of protonation of the heterocyclic rings is suggested for VIIa and VIIb, by comparison of the pK_a values of the imidazole and benzimidazole derivatives.

On the other hand, in the cases of the N-(1-methyl-2-benzimidazolyl)-substituted pyrazole (VIIc) and indazole (VIId), the first proton apparently becomes attached to the pyridine nitrogen atom of the more basic 2-benzimidazolyl radical, since the steric accessibility of both basic centers is approximately equal. Unlike VIa and VIb, VIc and VId are monoacid bases. Comparison of the pK_{a1} values for VIIc and VIId with the probable basicity constants of pyrazole (2.47 + 7) and indazole (1.22 + 7) in acetonitrile suggests that the first stage of protonation, in the present case also, relates to the 2-benzimidazolyl radical. Comparison of the basicity of the imidazole and benzimidazole VIa, VIb, and VIIa and VIIb shows the powerful electrophilic effect of the 2-benzimidazolyl radical in VIa and VIb, which results in a marked reduction in the basicities of the imidazolyl and benzimidazolyl rings with which it is directly linked. This is in agreement with the high value of the Taft inductive constant (σ^* 2.0) of the 2-benzimidazolyl radical [12].

The part played by mesomeric effects in the interaction between the 2-benzimidazolyl radical and the N-

Table 2. Protonation Constants

Compound	pK_{a1}	pK_{a2}	Compound	pK_{a1}	pK_{a2}
VIa	11,46	5,34	VIIa	13,73	9,25
VIb	9,91	5,01	VIIb	12,58	9,21
VIc	9,59	—	VIIc	12,27	4,29
VId	8,80	—	VIId	12,03	4,72
N-Ethyl-benzimidazole	13,22	—	N-n-Propyl-benzimidazole	13,22	—

heterocycle in VI and VII is shown by the UV spectra (Table 3, Figs. 1 and 2). The N-(2-benzimidazolylmethylene)-azoles VII are taken as models of unconjugated compounds. The validity of this assumption is confirmed by the virtual identity of the spectral curves of the pyrazole (VIIc) and the imidazole derivative (VIIa), both with each other and also with the absorption spectra of the 1,2-dialkylbenzimidazoles [13]. This identity is explained by the fact that the isolated chromophores, i.e., the imidazole [14] and pyrazole [15] rings, absorb outside the limits of the spectral regions under consideration.

Table 3. Absorption Maxima in the UV spectra of N-(2-Benzimidazolyl)- and N-(2-Benzimidazolylmethylene)azoles

Compound	λ_{max}, nm (lg ε)			Compound	λ_{max}, nm (lg ε)			
VIa	255 (3.93)	278 (4.01)	285 (3.98)	VIIa	255 (3.89)	270 (3.64)	276 (3.92)	284 (3.84)
VIb	250 (4.35)	276 (4.28)	284 (4.25)	VIIb	252 (4.18)	268 (4.02)	275 (4.10)	282 (4.03)
VIc	238—238 (4.01)	256—258 (3.98)	288 (4.14)	VIIc	255 (3.93)	270 (3.82)	276 (3.91)	284 (3.85)
VId	268 (3.98)		306—308 (4.45)	VIId	246 (4.04)	257 (4.09)	277 (4.23)	284—286 (4.09)
VIe	268 (3.86)		304—310 (4.50)					

The increase in intensity of the absorption maxima in the cases of **VIIb** and **VIId** results from the superposition of the spectra of benzimidazole and indazole. In contrast to **VIIa** and **VIIb**, the absorption spectra of the imidazole derivative **VIa** and of the benzimidazole **VIb**, in which these rings are linked directly to the heterocycles, are characterized by a small increase in the intensity of the short wavelength band at 250–255 nm, and by the partial smoothing out of the fine structure of the B-band at 268–282 nm. A more marked change is seen in the spectrum of the benzimidazole **VIb**.

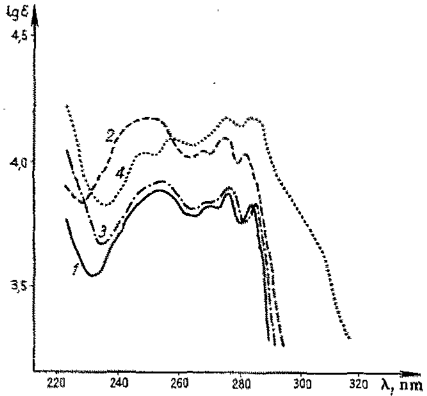


Fig. 1. UV absorption spectra in methanol: 1) N-(1-methyl-2-benzimidazolylmethylene)-imidazole (**VIIa**); 2) N-(1-methyl-2-benzimidazolylmethylene)benzimidazole (**VIIb**); 3) N-(1-methyl-2-benzimidazolyl benzimidazolylmethylene)pyrazole (**VIIc**); 4) N-(1-methyl-2-benzimidazolylmethylene)-indazole (**VIId**).

The results given here indicate without doubt the existence of conjugation between N- and C-heterocyclic nuclei of **VIa** and **VIb**, the extent of which is, however, small, perhaps as a result of the departure from planarity of the molecular structure. The increase in conjugation in the benzimidazole (VIb) is explicable by the increase in the length of the conjugated chain in comparison with that of the imidazole derivative.

The spectrum of N-(1-methyl-2-benzimidazolyl)pyrazole (VIc) has a band at 236–238 nm resulting from conjugation between the pyrazole and benzimidazole rings. This band is shifted bathochromically relative to the absorption band of unsubstituted pyrazole, but this shift is 26 nm smaller than in N-phenylpyrazole (40 nm) [16], the benzimidazole, in 74% yield, as snow-white needles, mp 91–92° C from light petroleum, readily soluble in most organic solvents. Found, %: C 66.8; H 5.0; N 28.1. Calculated for $C_{11}H_{10}N_4$, %: C 66.6; H 5.1; N 28.3.

Table 4. Benzimidazolium salts

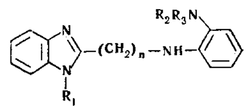
Compound	Mp, °C	Solvent for crystallization	Molecular formula	Found, %		Calculated, %		Yield, %
				N	Cl	N	Cl	
Ia*	257—258	Alcohol and ether	$C_{17}H_{17}ClN_4$	18,1	11,6	17,9	11.3	64
IV	259 (decomp.)	Alcohol	$C_{15}H_{13}ClN_4 \cdot H_2O$	18.4	11.6	18.5	11.7	44
Ic	226—227	Alcohol and ether	$C_{17}H_{17}ClN_4$	18.0	11.6	17.9	11,3	78

* $R' = C_2H_5$.

N-(2-Benzimidazolyl)indazole (VIe). Equimolar amounts of indazole and 2-chlorobenzimidazole were fused together at 110–120° C. The reaction mixture was treated with boiling alcohol, filtered, and the filtrate cooled. The precipitate which separated was crystallized repeatedly from alcohol to give a 57% yield of snow-white plates, mp 171–172° C. Found, %: N 23.9. Calculated for $C_{14}H_{10}N_4$, %: N 23.9.

N-(1-Methyl-2-benzimidazolylmethylene)azoles (VIIa-d). A solution of 2-chloromethyl-1-methylbenzimidazole (10 mM) and 15–20 mM of the appropriate azole in xylene (for VIIc and VIId) or toluene (for VIIa and VIIb) was boiled for 2–3 hr. The solvent was removed in vacuo, and the residue was worked up as described below.

Table 5



Compound	R_1	R_2	R_3	*n*	Mp, °C	Solvent for crystallization	Molecular formula	N, %		Yield, %
								Found	Calculated	
IIc	H	CHO	CH_3	0	207—208	Aqueous alcohol	$C_{15}H_{14}N_4O$	21.3	21.0	72
V	CH_3	CHO	CH_3	1	164—165	Methanol	$C_{17}H_{18}N_4O \cdot 0.5H_2O$	18.6	18.5	63
IIIa	CH_3	H	C_2H_5	0	222—223	Toluene	$C_{16}H_{18}N_4$	21.2	21.0	68*
IIIc	H	H	CH_3	0	226—227	Aqueous alcohol	$C_{14}H_{14}N_4$	23.6	23.5	80
IIIb	CH_3	H	Ph	0	183—184	Alcohol	$C_{20}H_{18}N_4$	18.1	17.8	34**
IIId	H	H	Ph	0	268—269	Alcohol	$C_{19}H_{16}N_4$	18.7	18.6	39**

*Calculated on starting quaternary salt.

**Calculated on 1-phenylbenzimidazole.

VIIa. The residue was triturated with 10% alkali, washed with cold water, and recrystallized from carbon tetrachloride, giving a 58% yield (calculated on 2-chloromethyl-1-methylbenzimidazole) of colorless needles, mp 150° C. Found, %: C 68.0; H 5.8; N 26.6. Calculated for $C_{12}H_{12}N_4$, %: C 67.9; H 5.7; N 26.4.

VIIb. After treatment of the residue with 10% alkali, it was dissolved in the minimum amount of alcohol, and the solution kept overnight. The alcoholic mixture was filtered and diluted with water. The precipitate which separated was recrystallized from carbon tetrachloride to give a 46% yield (calculated on 2-chloromethyl-1-methylbenzimidazole) of colorless prisms, mp 165–166° C, from aqueous alcohol. Found, %: C 73.5; H 5.5; N 21.5. Calculated for $C_{16}H_{14}N_4$, %: C 73.26; H 5.38; N 21.36.

VIIc. The residue was dissolved in water with warming, the solution basified, and the reaction product extracted with ether, to give a 71% yield of colorless prisms, mp 109.5–110° C (from hexane). Found, %: C 67.8; H 5.8; N 26.5. Calculated for $C_{12}H_{12}N_4$, %: C 67.9; H 5.7; N 26.4.

VIId. The solid residue was boiled in water containing a few drops of alkali, and the hot mixture was filtered and the residue washed with ether, giving a 75% yield of colorless prisms, mp 167–168° C (from benzene). Found, %: C 73.5; H 5.5; N 21.4. Calculated for $C_{16}H_{14}N_4$, %: C 73.3; H 5.4; N 21.4.

The basicity constants were determined on a LPU-01 potentiometer by the method described in [7].

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