IMINE-ENAMINE TAUTOMERISM IN DIHYDROAZOLOPYRIMIDINES. 2.* SYNTHESIS AND TAUTOMERISM OF 1,4(3,4)-DIHYDROPYRIMIDO[1,2-*a*]BENZIMIDAZOLES

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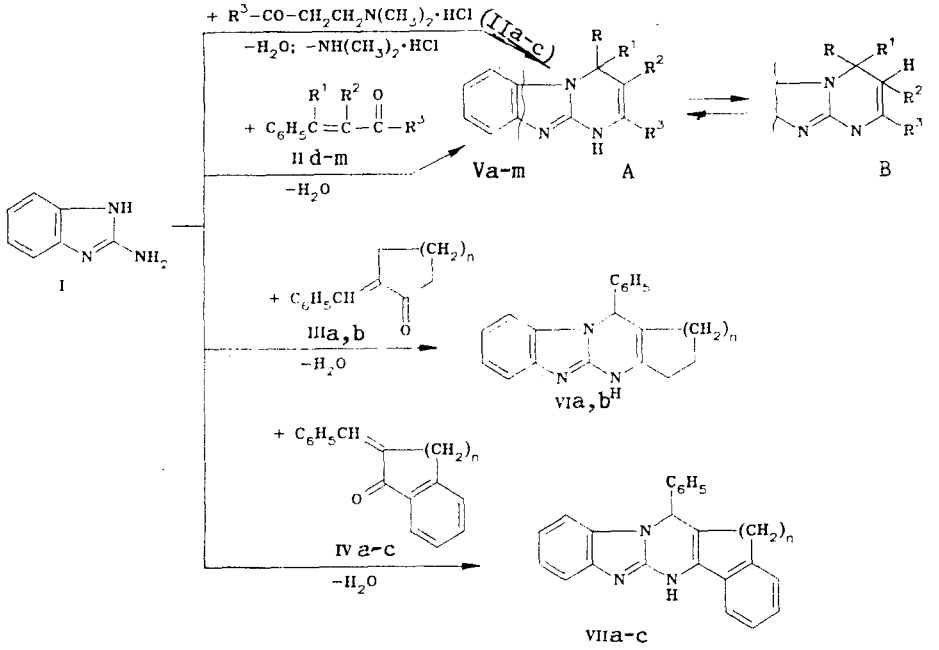
Cyclocondensation of 2-aminobenzimidazole with unsaturated ketones or the hydrochlorides of Mannich bases has yielded aromatic substituted 1,4(3,4)-dihydropyrimido[1,2-a]benzimidazoles. The dependence of the tautomer composition of the products on steric factors and on the electronic character of the substituents introduced has been studied.

It has been shown previously [2] that 2,4-diaryldihydropyrimido[1,2-*a*]benzimidazoles can form in solution a mixture of 1,4- and 3,4-dihydro forms but no detailed study of this tautomerism has been carried out; this is the subject of the present work.

Compounds Va-d, g, h, k-m, VIa, b, and VIIa-c were prepared by condensation of 2-aminobenzimidazole (I) with β-dimethylaminopropiophenones IIa-c or aromatic α, β-unsaturated ketones IId, g, h, k-m, IIIa, b, and IVa-c (compounds VIe, f, i, j were described in [2]).



II: Va-c, R = H; d-m, R = C_6H_5; a-k, m, R^1 = H; *l*, R^1 = CH_3; a-*l*, R^2 = H; m, R^2 = CH_3; a, e, *l*, m, R^3 = C_6H_5; b, g, R^3 = *p*-$CH_3OC_6H_4$; c, j, R^3 = *p*-$O_2NC_6H_4$; d, R^3 = CH_3; f, R^3 = *p*=$CH_3C_6H_4$; h, R^3 = p- $(CH_3)_2NC_6H_4$; i, R^3 = *p*-ClC_6H_4; k, R^3 = *p*-$C_6H_5C_6H_4$; VI, VII: a, n = 1; b, n = 2; c, n = 3.

*For Communication 1, see [1].

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TABLE 1. PMR Spectra of Tautomers A and B of Compounds V-VII

Compound	Tautomer	Solvent	Chemical shifts, δ, ppm (J, Hz)					Tautomer content, %
			H_{arom}	4-H	3-H	NH (1H, s)	protons of substituent*	
Va	A	DMSO-D_6	7,0 ... 7,9	4,87 (2H, d, J=3,4)	5,27 (1H, t)	9,7	—	100
	A	CF_3COOD	7,0 ... 8,3	5,11 (2H, s)	—	—	—	45
	B			4,71 (2H, s)	—	—	—	55
Vb	A	DMSO-D_6	7,0 ... 8,3	4,91 (2H, d, J=3,1)	5,37 (1H, t)	10,5	3,65 (3H, s)	80
	B			4,44 (2H, t, J=8,1)	3,81 (2H, t)	—	3,72 (3H, s)	20
	A	CF_3COOD	7,2 ... 8,4	5,17 (2H, s)	—	—	4,02 (3H, s)	5
	B			4,67 (2H, s)	—		4,08 (3H, s)	95
Vc	A	DMSO-D_6	7,6 ... 8,6	4,86 (2H, d, J=3,5)	5,45 (1H, t)	10,0	—	100
	A	CF_3COOD	7,8 ... 8,6	5,18 (2H, s)	—	—	—	90
	B			4,78 (2H, s)	—	—	—	10
Vd	A	DMSO-D_6	6,7 ... 7,4	6,09 (1H, d, J=2,8)	4,63 (1H, d)	9,8	1,65 (3H, s)	100
	A	CF_3COOD	7,0 ... 8,3	6,18 (1H, s)	—	—	—**	80
	B			5,92 (1H, s)	—	—	—**	20
Ve	A	DMSO-D_6	6,8 ... 7,8	6,34 (1H, d, J=4,0)	5,27 (1H, d)	10,1	—	100
	A	CF_3COOD	7,0 ... 8,3	6,38 (1H, s)	—	—	—	50
	B			6,00 (1H, s)	—	—	—	50
Vf	A	DMSO-D_6	7,0 ... 8,2	6,40 (1H, d, J=3,9)	5,25 (1H, d)	9,9	2,45 (3H, s)	100
	A	CF_3COOD	7,0 ... 8,2	6,35 (1H, s)	—	—	2,40 (3H, s)	30
	B			5,96 (1H, s)	—	—	2,51 (3H, s)	70
Vg	A	DMSO-D_6	7,0 ... 8,2	6,30 (1H, d, J=4,0)	5,17 (1H, d)	10,0	3,72 (3H, s)	100
	A	CF_3COOD	7,0 ... 8,3	6,40 (1H, s)	—	—	4,07 (3H, s)	10
	B			5,97 (1H, s)	—	—	4,13 (3H, s)	90
Vh	A	DMSO-D_6	6,7 ... 8,1	6,27 (1H, d, J=4,0);	5,09 (1H, d)	9,8	2,95 (6H, s)	40
	B			H_X: 5,96 (1H, d.d***)	H_B: 3,51 (1H, d.d);	—	3,04 (6H, s)	60
					H_A: 3,64 (1H, d.d)			
	A	CF_3COOD	6,9 ... 8,5	6,08 (1H, d, J=3,8)	5,38 (1H, d)		3,18 (6H, s)	100

TABLE 1. (Continued)

Compound	Tautomer	Solvent	Chemical shifts, δ, ppm (J, Hz)					Tautomer content, %
			^{11}arom	4-H	3-H	NH (1H, s)	protons of substituent*	
Vi	A	DMSO-D_6	6,7...7,8	6,36 (1H, d, J=4,0)	5,35 (1H, d)	10,0	—	100
	A	CF_3COOD	7,0...8,2	6,35 (1H, s)	—	—	—	55
	B			5,97 (1H, s)	—	—	—	45
Vk	A	DMSO-D_6	6,8...8,3	6,41 (1H, d, J=4,0)	5,55 (1H, d)	10,3	—	100
	A	CF_3COOD	7,1...8,6	6,44 (1H, d, J=3,8)	5,73 (1H, d)	—	—	100
Vl	A	DMSO-D_6	6,8...8,6	6,35 (1H, d, J=3,9)	5,35 (1H, d)	10,2	—	100
	A	CF_3COOD	7,0...8,4	6,37 (1H, s)	—	—	—	35
	B			5,99 (1H, s)	—	—	—	65
Vm	A	DMSO-D_6	6,9...8,3	—	5,30 (1H, s)	9,9	2,11 (3H, s)	100
	A	CF_3COOD	7,0...8,4	—	—	—	2,42 (3H, s)	50
	B			—	—	—	2,16 (3H, s)	50
Vn	A	DMSO-D_6	6,8...8,0	6,02 (1H, s)	—	9,8	1,45 (3H, s)	100
	A	CF_3COOD	6,8...7,9	5,83 (1H, s)	—	—	1,33 (3H, s)	100
VIa	A	DMSO-D_6	6,9...8,0	6,21 (1H, s)	—	9,6	2,0...2,8 (6H, m)	100
	A	CF_3COOD	6,8...8,1	6,18 (1H, s)	—	—	1,9...2,7 (6H, m)	100
VIb	A	DMSO-D_6	6,9...7,6	5,61 (1H, s)	—	9,5	1,4...2,0 (8H, m)	100
	A	CF_3COOD	6,7...7,6	5,54 (1H, s)	—	—	1,3...1,9 (8H, m)	100
VIIa	A	DMSO-D_6	6,8...8,0	6,53 (1H, s)	—	10,4	2,93 (1H, d, J=−22,5); 3,03 (1H, d)	100
	A	CF_3COOD	6,8...8,0	6,47 (1H, s)	—	—	2,83 (1H, d, J=−22,3); 3,01 (1H, d)	100
VIIb	A	DMSO-D_6	6,8...7,6	5,66 (1H, s)	—	10,2	1,4...3,5 (4H, m)	100
		CF_3COOD	6,7...7,5	5,60 (1H, s)	—	—	1,3...3,1 (4H, m)	100
VIIc		DMSO-D_6	6,6...7,5	5,92 (1H, s)	—	9,7	1,0...2,4 (6H, m)	100
		CF_3COOH	6,8...7,9	5,85 (1H, s)	—	—	1,1...2,5 (6H, m)	100

*$(CH_2)_n$ for compounds VI and VII.
**Lacking on account of deuteration.
***ABX system: J_{AB} = −18.3, J_{AX} = 8.4, J_{BX} = 2.7 Hz.

TABLE 2. Characteristics of Compounds Va-d, g, h, k-m, VI, and VII

Compound	Empirical formula	mp, °C	$\nu_{C=C}$, cm^{-1} (in KBr)	λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)		Yield, %
				tautomer A	tautomer B	
Va	$C_{16}H_{13}N_3$	213...214	1682	280 (9,5); 306 (9,5)	353 (3,3*)	77
Vb	$C_{17}H_{15}N_3O$	215...217	1662	278 (9,9); 297 (9,1)	357 (11,6*)	62
Vc	$C_{16}H_{12}N_4O_2$	290...292	1669	249 (6,3); 303 (11,8)	—	79
Vd	$C_{17}H_{15}N_3$	260...262	1695	254 (10,3); 306 (12,0)	—	90
Vg	$C_{23}H_{19}N_3O$	217...218	1675	279 (15,1); 310 (9,5)	360 (9,1*)	61
Vh	$C_{24}H_{22}N_4$	223...225	—	—	297 (12,2), 405 (23,9)	65
Vk	$C_{28}H_{22}N_3$	279...280	1663	288 (29,4); 315 sh	355 (5,5*)	60
Vl	$C_{23}H_{19}N_3$	190...192	1660	278 (10,7); 313 (6,8)	355 (2,0*)	70
Vm	$C_{23}H_{19}N_3$	254...255	1676	283 (9,2); 309 (8,4)	—	59
VIa	$C_{19}H_{17}N_3$	248...250	1672	255 (9,9); 306 (7,8)	—	55
VIb	$C_{20}H_{19}N_3$	245...246	1688	253 (9,7); 305 (11,6)	—	50
VIIa	$C_{23}H_{17}N_3$	232...234	1654	281 (16,1); 318 (6,6)	—	35
VIIb	$C_{24}H_{19}N_3$	275...277	1655	284 (18,9); 320 (5,6)	—	45
VIIc	$C_{25}H_{21}N_3$	239...241	1650	286 (9,9); 313 (7,5)	—	55

*Determination of ε was difficult on account of the unknown tautomer composition. Values of $D_{max}/l(C_A + C_B)$ for the equilibrium mixture are given in brackets.

The IR spectra of compounds Va-d, g, k-m, VIa, b, and VIIa-c (Table 2) show $\nu_{C=C}$ bands in the 1650-1695 cm^{-1} region which are typical of 1,4-dihydropyrimidine systems [3]. No absorptions in this frequency range are, however, observed for compound Vh, which points to the absence of the 1,4-dihydro structure **A** in the crystals of this compound. Electronic spectra of freshly-prepared solutions of compounds Va-d, g, k-m, VIa, b, and VIIa-c show bands in the 300-320 nm region which are characteristic for 2,4-diaryl-1,4-dihydropyrimido[1,2-*a*]benzimidazoles [2] and the position of which varies slightly with the effect of the substituent (Table 2). The spectrum of the dimethylamino-substituted Vh differs considerably, having an intense band with λ_{max} 405 nm. It was found also that on keeping alcohol solutions of compounds Vc, d, h, VIa, b, and VIIa-c for several days without access to oxygen their UV spectra remained unchanged, whereas in the spectra of compounds Va, b, g, k, *l* a band appeared in the 353-357 nm region and the intensity of the long-wave band of the original solution decreased. Equilibrium was established in 1-2 days at 20°C and the process was considerably speeded up by heating and by the addition of traces of acid. Bearing in mind that, from the results of [1, 2], imine tautomers of form **B** of dihydropyrimido[1,2-*a*]benzimidazoles and similar molecular systems absorb at markedly higher wavelengths than the dihydro forms **A**, the appearance of a long-wavelength band in the spectra of compounds Va, b, g, k, *l* could be connected with partial **A** → **B** transformation. The lack of any change in the spectra of the remaining compounds shows that their tautomeric structure (imine for compound Vh and enamine for Vc, d, VIa, b, and VIIa-c) is retained in solution in ethanol.

The dihydro-form **B** has one more hydrogen at the $C_{(3)}$ carbon than tautomer **A** and hence its PMR spectrum is considerably different. Thus one can monitor the tautomeric composition by comparing the integral intensities of the appropriate group of signals (Table 1). It should be noted that for several compounds (Va-g, i, k, *l*) in solution in CF_3COOD, signals from the proton on the $C_{(3)}$ atom of both tautomeric forms are not shown in their spectra because of rapid exchange for deuterium. In these cases the presence of a mixture of tautomers in the solutions was evident as a doubling of the signals of the $H_{(4)}$ protons and/or a substituent. In compounds Vh, j which under these conditions exist exclusively in the dihydro form **A** deuterium exchange of the $H_{(3)}$ proton takes place considerably more slowly (at 20°C $t_{1/2}$ = 15 and 60 min respectively) so that the signals from this proton can be recorded (Table 2).

From an examination of the data given in Table 2 one can, in the first instance, note the increase in the tautomer **B** content as the electron-donor character of the R^3 substituent increases (compounds Va-c, e-h). An exception is the solution of the dimethylamino-substituted Vh in CF_3COOD in which the transition to the enamine form **A** goes to completion. We have observed a similar phenomenon for the case of 5-(*p*-dimethylaminophenyl)-7-phenyldihydro-1,2,4-triazolo[1,5-*a*]pyrimidine [1]; it evidently arises from a change in the electronic character of the dimethylamino group as a result of its protonation. We note the considerable effect of protonation processes on the tautomer composition of the remaining compounds which we studied also (Table 2). The relative stabilization

of the dihydro form **B** by electron-donor substituents R^3 which is observed in both DMSO-D_6 and CF_3COOD results, in our opinion, from conjugation effects, since only in **B** tautomers is the substituent R^3 conjugated with the electron-acceptor azomethine group and the π system of the benzimidazole bi-cycle. This effect appears also in the shift of the tautomer equilibrium in the direction of the imine form **B** in the series of compounds Vd, e, k (R^3 = CH_3, C_6H_5, and 4-$C_6H_5C_6H_4$ respectively, Table 1).

On comparing the tautomer composition of compounds Va-c (R = H) and compounds Ve, g, j (R = C_6H_5) the marked effect of the substituent R on the tautomer composition will be noted (Table 2). Allowing for the fact that this electronic effect is not very significant, the increase in the equilibrium concentration of the 1,4-dihydro form **A** on introducing a phenyl substituent in the 4 position of dihydropyrimido[1,2-*a*]benzimidazole must be connected with steric factors. In our opinion, 1,4-dihydroaromatic systems are seen here to be more conformationally labile in comparison with their 1,2-dihydroanalogs [4] which enables bulky substituents to assume a more favorable spatial orientation. From this point of view, it would be natural for a complete displacement of the tautomeric shift in the direction of the dihydro **A** form to take place on introducing a second bulky substituent in the neighborhood of the R position (compound Vm, R = C_6H_5, R^2 = CH_3) and also on annelation of the dihydropyrimido[1,2-*a*]benzimidazole by carbocycles (compounds VI and VII, Table 2).

EXPERIMENTAL

IR spectra of compounds Ia-d, g, h, k-m, VIa, b, and VIIa were run on a Specord IR 75 as KBr disks and electronic absorption spectra on a Specord M 40 in ethanol [c = $(3\text{-}5)\cdot10^{-5}$ mole/liter]. PMR spectra of compounds V-VII were recorded on a Gemini 200 in CF_3COOD and DMSO-D_6 with HMDS as internal standard. Progress of the reactions and the purity of the products were monitored by TLC on Silufol UV 254 plates with chloroform and acetone eluents. The nitrogen content of the compounds prepared corresponded to the calculated value.

4-Phenyl-1,4(3,4)-dihydropyrimido[1,2-*a*]benzimidazole (Va). A solution of 0.66 g (5 mmoles) 2-aminobenzimidazole and 1.7 g (5 mmoles) β-dimethylaminopropiophenone hydrochloride in 10 ml isopropanol was heated at bp for 20 min, cooled, and the deposit which formed filtered off. Yield 1.25 g (90%) compound Va mp 213-214°C (from ethanol). **Compounds Vb, c** were prepared similarly.

2-Methyl-4-phenyl-1,4(3,4)-dihydropyrimido[1,2-*a*]benzimidazole (Vd). A solution of 1.33 g (10 mmoles) 2-aminobenzimidazole and 1.46 g (10 mmoles) benzalacetone in 1 ml DMF was heated at bp for 5 min, the deposit which formed filtered off and washed with methanol to yield 2.35 g (90%) compound Vd, mp 260-262°C (1:1 DMF-benzene).

Compounds Vg, h, k-m, VIa, b, and VIIa-c were prepared similarly.

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