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IMINE—ENAMINE TAUTOMERIZATION OF DIHYDROAZOLOPYRIMIDINES

4.* SYNTHESIS AND TAUTOMERIZATION OF 5-(2-HYDROXYPHENYL)-DIHYDRO-1,2,4-TRIAZOLO[1,5-*a*]PYRIMIDINES

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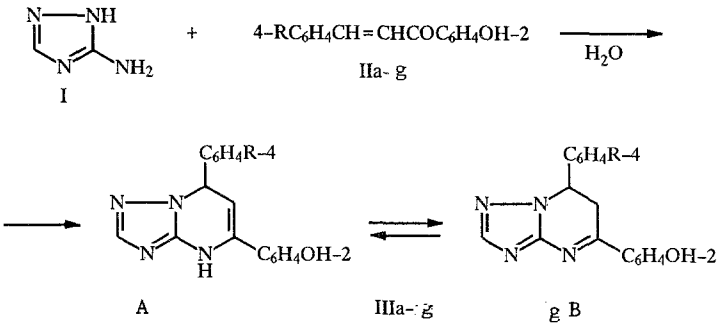
The condensation of 3-amino-1,2,4-triazole with 2'-hydroxychalcones gives 7-aryl-5-(2-hydroxyphenyl)-4,7(6,7)-dihydro-1,2,4-triazolo[1,5-a]pyrimidines. Both tautomeric forms were isolated for a number of these compounds. PMR spectroscopy was used to show that the enamine form is predominant in DMSO in contrast to the case in $CHCl_3$.

In a continuation of a study of the imine—enamine tautomerism of dihydroazolopyrimidines containing an angular nitrogen atom, we studied 5-(2-hydroxyphenyl)-4,7(6,7)-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines, which differ in the substituent at $C_{(7)}$. Products IIIb-IIIg were obtained by the condensation of 3-amino-1,2,4-triazole (I) with 2'-hydroxychalcones IIb-IIg.



II, III a R = H, b R = CH_3, c R = CH_3O, d R = $(CH_3)_2N$, e R = F, e R = Cl, f R = Br

In previous work [2], we have shown that IIIa crystallizes from alcohols and chloroform as imine B, while it crystallizes from DMSO in enamine form A. Using this method, we obtained both tautomeric forms A and B for IIIc and IIIe-IIIg. Products IIIb and IIId crystallized from all these solvents only as 6,7-dihydro form B.

The IR spectra of tautomeric forms A of IIIc, IIIe-IIIf contain a $\nu_{C=C}$ band at 1657-1672 cm^{-1} (Table 1). Bands at this frequency are typical for 1,4-dihydropyrimidine structures [1, 3]. There is no $\nu_{C=C}$ band in the spectra of tautomers B but a ν_{C-N} band is seen (Table 1).

The electronic absorption spectra of freshly prepared solutions of dihydro forms A and B of III also differ markedly. The imine tautomers B have stronger absorption at longer wavelength (λ_{max} 305-308 and 365 nm) due to the more extensive chromophore system than in form A (Table 1). Maintenance of solutions of form A leads to the appearance of these bands, while maintenance of solutions of form B leads to a reduction in the intensities of these bands (the isosbestic point is λ 255-258

*For Communication 3, see [1].

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TABLE 1. Characteristics of IIIb-IIIg*1

Compound	Chemical formula	Tautomer	Mp, °C	IR spectrum,*2 cm^{-1}	UV spectrum (i-PrOH)		Yield, %
					λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)	Tautomer content, %*3	
IIIb	$C_{18}H_{16}N_4O$	B	192...194	1614	306(11,1), 365(9,6)	70	56
IIIc	$C_{18}H_{16}N_4O_2$	A	174...176	1657	283(7,2)	26	52
		B	178...180	1615	305(11,2), 365(9,7)	74	
IIId	$C_{19}H_{19}N_5O$	B	219...222	1613	306(15,2), 365(11,4)	75	73
IIIe	$C_{17}H_{13}FN_4O$	A	184...186	1660	285(5,9)	40	57
		B	188...190	1615	305(10,8), 365(9,2)	60	
IIIf	$C_{17}H_{13}ClN_4O$	A	158...160	1672	285(5,2)	35	50
		B	192	1616	306(9,9), 365(8,1)	65	
IIIg	$C_{17}H_{13}BrN_4O$	A	194...196	1659	286(7,0)	37	55
		B	176...178	1612	308(12,0), 365(9,8)	63	
		A					

*1IIIa was characterized in our previous work [2]; the equilibrium tautomeric composition in 2-propanol A/B = 32:68.

*2$\nu_{C=C}$, cm^{-1}, ν_{C-N} for tautomers B.

*3In the equilibrium mixture.

nm for IIIa-IIIc and IIIe-IIIg and 269 nm for IIId). Equilibrium is established at 25°C over 3-5 h and this process is much faster upon heating. This behavior should undoubtedly be related to tautomeric transformations, leading to equilibrium mixtures of III. Comparison of the intensities of the long-wavelength absorption band of solutions of the equilibrium mixtures (in the region known to be transparent for enamine tautomers A) with the optical density of solutions of pure tautomers B at the same wavelengths was used to determine the equilibrium tautomeric composition of III in 2-propanol (Table 1).

PMR spectroscopy also provides information on the equilibrium tautomeric composition of III in $CDCl_3$ and DMSO-d_6 (Table 2).

Thus, in contrast to most dihydro-1,2,4-triazolo-[1,5-*a*]pyrimidines [1], IIIa-IIIg exist in chloroform in the imine tautomeric form. This finding is attributed to the stabilization of this form by intramolecular hydrogen bonding. The conditions for such hydrogen bonding are more favorable in the imine tautomer than in the enamine tautomer. Competition between intramolecular hydrogen bonding and hydrogen bonding with a solvent molecule is observed in solvents such as 2-propanol and DMSO. This diminishes the effect of intramolecular hydrogen bonding for stabilization of tautomer B, which is seen in the formation of mixtures of tautomeric forms A and B in comparable concentrations in these solvents (Tables 1 and 2).

Analysis of the variation in the tautomeric equilibrium in the series IIIa-IIIg also indicates a shift toward tautomer forms B with increasing electron-donor capacity of substituent R (Tables 1 and 2). However, the dependence of the tautomer concentration on the electronic properties of these substituents is much less pronounced than observed for 5-(R-phenyl)dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines [1]. This finding indicates that the saturated carbon atom in the dihydroazolopyrimidines significantly isolates the molecular fragment participating in the tautomeric transformation from the electronic effect of the substituent at $C_{(7)}$ in the bicyclic system.

EXPERIMENTAL

The IR spectra were taken on a Specord IR-75 spectrometer for KBr pellets. The electronic absorption spectra were taken on a Specord M-40 spectrophotometer in 2-propanol at from $2 \cdot 10^{-5}$ to $4 \cdot 10^{-5}$ mole/liter. The PMR spectra were taken on a Bruker WP-300 spectrometer in DMSO-d_6 and $CDCl_3$ with TMS as the internal standard. The reaction course and purity of the compounds formed were checked by thin-layer chromatography on Silufol UV-254 plates with chloroform and ethyl acetate as the eluents.

The nitrogen content in the compounds obtained corresponded to the calculated values. The synthesis of IIIa was described in our previous work [2].

TABLE 2. Chemical Shifts, δ, ppm of the Protons of Tautomers A and B in IIIa-IIIg*

Compound	Solvent	Tautomer	2-H (1H,S)	6-H**	7-H	NH (1H,S)	OH (1H,S)	CH_3 (3H,S)	Yield, %
IIIa	$CDCl_3$	B	7,70	H_A: 3,61 (dd) H_B: 3,80 (dd)	5,52	—	13,6	—	100
	DMSO-D_6	A	7,58	4,93 (d)	6,17	9,8	9,6	—	75
		B	8,05	H_A: 3,80 H_B: 3,90 (dd)	5,89	—	13,6	—	25
IIIb	$CDCl_3$	A	7,80	H_A: 3,55 (dd) H_B: 3,68 (dd)	5,56	—	13,5	2,25	100
		B							
	DMSO-D_6	A	7,55	4,91 (d)	6,11	9,8	9,6	2,28	75
		B	8,07	H_A: 3,82 (dd) H_B: 3,89 (dd)	5,84	—	13,6	2,26	25
IIIc	$CDCl_3$	B	7,84	H_A: 3,53 (dd) H_B: 3,64 (dd)	5,54	—	13,5	3,76	100
	DMSO-D_6	A	7,55	4,90 (d)	6,11	9,8	9,6	3,73	70
		B	8,02	H_A: 3,85 (dd) H_B: 3,91 (dd)	5,82	—	13,5	3,71	30
IIId	$CDCl_3$	B	7,86	H_A: 3,55 (dd) H_B: 3,62 (dd)	5,51	—	13,5	2,87 (6H)	100
	DMSO-D_6	A	7,51	4,87 (d)	6,01	9,8	9,4	2,86 (6H)	65
			8,00	3,83 (d)	5,74	—	13,6	2,83 (6H)	35
IIIe	$CDCl_3$	B	7,85	H_A: 3,60 (dd) H_B: 3,74 (dd)	5,84	—	13,4	—	100
	DMSO-D_6	A	7,60	4,91 (d)	6,20	9,9	9,7	—	75
		B	8,04	H_A: 3,78 (dd) H_B: 3,96 (dd)	5,87	—	13,5	—	25
IIIf	$CDCl_3$	B	7,91	H_A: 3,52 (dd) H_B: 3,68 (dd)	5,63	—	13,4	—	100
	DMSO-D_6	A	7,59	4,91 (d)	6,20	9,8	9,6	—	80
		B	8,04	H_A: 3,78 (dd) H_B: 3,95 (dd)	5,90	—	13,6	—	20
IIIg	$CDCl_3$	B	7,88	H_A: 3,50 (dd) H_B: 3,65 (dd)	5,67	—	13,6	—	100
	DMSO-D_6	A	7,60	4,91 (d)	6,19	9,9	9,7	—	80
		B	8,05	H_A: 3,79 (dd) H_B: 3,93 (dd)	5,88	—	13,5	—	20

*The aromatic proton signals for IIIa-IIIf are found at 7.0-8.2 ppm.

**Coupling constants: for tautomer A, J_{67} = 3.4-3.6 ppm; for tautomer B, J_{AB} = from −17.5 to −18.0 Hz, $J_{7A} = J_{7B}$ = 6.9-7.3 Hz.

7-(4-Methoxyphenyl)-5-(2-hydroxyphenyl)-4,7(6,7)-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (IIIc). A solution of 1.2 g (4.7 mmoles) 4-methyl-2′-hydroxychalcone and 0.4 g (4.7 mmoles) 3-amino-1,2,4-triazole in 0.5 ml DMF was heated at reflux for 1 h, cooled, mixed with 20 ml benzene, and filtered to give 0.8 g (52%) IIIc, mp 178-180°C (from 2-propanol, 6,7-dihydro form). Recrystallization from DMSO gave the 4,7-dihydro form, mp 174-175°C.

The 6,7-dihydro forms of IIIb and IIId-IIIg and the 4,7-dihydro forms of IIId-IIIg were analogously obtained.

REFERENCES

1. S. M. Desenko, V. D. Orlov, V. V. Lipson, O. V. Shishkin, S. V. Lindeman, and Yu. T. Struchkov, Khim. Geterotsikl. Soedin., No. 11, 1539 (1991).
2. S. M. Desenko and V. D. Orlov, Khim. Geterotsikl. Soedin., No. 7, 1000 (1989).
3. A. L. Weis, Tetrahedron Lett., No. 4, 449 (1982).