# TAUTOMERISM OF DIHYDRO-1,2,4-TRIAZOLO[1,5-*a*]PYRIMIDINES CONTAINING 2-HYDROXY- AND 4-DIMETHYLAMINOARYL SUBSTITUENTS

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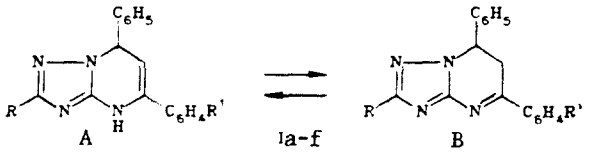
*We have studied the effect of structural factors and the nature of the solvent on the tautomeric composition of aromatic substituted dihydro-1,2,4-triazolo[1,5-a]pyrimidines. The kinetics of the tautomeric exchange of 5-(2-hydroxyphenyl)-7-phenyldihydro-1,2,4-triazolo[1,5-a]pyrimidines has also been investigated.*

We have shown [1] that the majority of aromatic substituted dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines exist in the enamine 4,7-dihydro form both in the solid state and in solution. However, in some solvents a mixture of the 4,7- and 6,7-dihydro tautomers has been observed with the introduction of a 4-methoxy- or 4-dimethylaminophenyl substituent at position 5 of triazolopyrimidines.

The aim of this work was to investigate the dependence of the tautomeric composition of 5,7-diaryl-4,7(6,7)-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines on a number of intra- and intermolecular factors (formation of intramolecular hydrogen bonds, conjugative effects, and the nature of the solvent). To this end we have investigated the triazolopyrimidines Ia-f.



A Ia-f B

I a—c R=H, d—f R=$NH_2$; a,d $R^1$=H, b,e $R^1$=*o*-OH, c,f $R^1$=*p*-$N(CH_3)_2$

Compounds Ia-d have been described before [1-3] and Ie, f were obtained by condensation of 3,5-diamine-1,2,4-triazole with 1-phenyl-3-($R_1$-phenyl)prop-1-en-3-ones (chalcones).

Unique information about the tautomeric composition of Ia-f comes from the PMR spectra measured in $CF_3COOH$, DMSO-$D_6$, DMF-$D_6$, and pyridine-$D_5$, and for the readily soluble materials Ib, c, e in $CDCl_3$. Aliphatic proton signals are seen in their spectra which are characteristic of the CH—CH tautomer A (two doublets) or of the CH—$CH_2$ protons of tautomer B (Table 1).

Unfortunately, the low solubility of Ia-f does not allow PMR spectroscopy to be used to determine the tautomer composition of these materials in many solvents. At the same time, it has previously been shown that the tautomeric forms of dihydroazolopyrimidines having different chromophoric systems differ significantly in their electronic absorption spectra [4]. In all investigated solvents the spectra of Ia, d are characterized (Table 2) by a longest-wavelength band at 282-295 nm, corresponding [1, 4] to the absorption of the dihydro form A. The intensity of these bands in various solvents varies within ±2% limits [$\varepsilon$ (in methanol): $4.5 \cdot 10^3$ for Ia and $3.1 \cdot 10^3$ for Id [1, 2]] but a long-wavelength absorption for dihydro form B is absent in this region. On this basis it was shown that Ia, d exist in the enamine form (A) in all of the studied solvents.

Thus, the electronic spectra of Ib, e in these solvents show a long-wavelength absorption at 355-390 nm (Table 2) and its intensity varies significantly with solvents. This band is in good agreement with quantum chemical calculations [3, 4] for the tautomeric form B of Ib, e, whereas tautomer form A, according to [3, 4], must be completely transparent in this region. Hence the electronic absorption spectra can be used to determine the tautomer composition of the dihydrotriazolopyrimidines Ib, e in a broad range of solvents via comparison of the intensities of the long-wavelength bands in $CHCl_3$ solutions (the PMR data for Ib, e in $CDCl_3$ show them to be virtually completely in the dihydro B form; see Table 1). In fact, we have ignored the dependence of the molar extinction coefficient of the given bands on the nature of the solvents. We have shown that the value of the concentration of tautomer forms B in Ib, e in DMSO and DMF, determined from the electronic spectra (Table 2)

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TABLE 1. PMR Spectra of Ib, c, e, f*[1]

| Compound | Solvent | δ, ppm, tautomer A | | | | δ, ppm, tautomer B | | | | Content of A, % |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 7-H, d*[2] | 6-H, d | NH, s | R', s | 7-H ($H_X$), t*[3] | $CH_2$ $H_A$, dd*[3] | $CH_2$ $H_B$, dd | R', s | |
| Ib | $CF_3COOH$ | — | — | — | — | 5.52 | 3.80 | 3.61 | — | 0 |
| | $CDCl_3$ | — | — | — | — | 5.63 | 3.67 | 3.63 | 13.40 | 0 |
| | DMF-$D_6$ | 6.16 | 5.00 | 9.51 | 10.32 | 5.91 | 3.98 | 3.88 | 13.70 | 60 |
| | $C_5D_5N$ | 6.23 | 5.11 | 10.35 | 11.00 | 5.80 | 3.75 | 3.65 | 13.91 | 75 |
| | DMSO-$D_6$ | 6.12 | 4.91 | 9.40 | 10.05 | 5.86 | 3.90 | 3.80 | 13.62 | 85 |
| Ic | $CF_3COOH$ | 5.96 | 5.23 | — | 3.10 | — | — | — | — | 100 |
| | $CDCl_3$ | 6.13 | 4.96 | 9.15 | 2.95 | 5.53 | 3.43 | | 3.03 | 35 |
| | DMF-$D_6$ | 6.29 | 5.05 | 9.60 | 2.93 | 5.76 | 3.65 | | 3.04 | 35 |
| | $C_5D_5N$ | 6.20 | 5.01 | 10.25 | 2.90 | 5.61 | 3.62 | | 3.00 | 40 |
| | DMSO-$D_6$ | 6.17 | 5.04 | 9.90 | 2.89 | 5.78 | 3.63 | | 2.99 | 45*[4] |
| Id | $CF_3COOH$ | — | — | — | — | 5.26 | 3.74 | 3.51 | — | 0 |
| | $CDCl_3$ | — | — | — | — | 5.40 | 3.63 | 3.43 | 13.62 | 0 |
| | DMF-$D_6$ | 5.86 | 4.92 | 9.15 | 10.20 | 5.59 | 3.86 | 3.72 | 13.86 | 30 |
| | $C_5D_5N$ | 6.00 | 5.02 | 10.45 | 11.20 | 5.51 | 3.62 | 3.46 | 13.90 | 40 |
| | DMSO-$D_6$ | 5.81 | 4.83 | 9.20 | 9.82 | 5.51 | 3.79 | 3.62 | 13.81 | 70 |
| Ie | $CF_3COOH$ | 5.63 | 5.10 | — | 3.00 | — | — | | — | 100 |
| | DMF-$D_6$ | 5.91 | 5.01 | 9.36 | 2.93 | 5.51 | 3.58 | | 3.00 | 25 |
| | $C_5D_5N$ | 5.85 | 5.05 | 10.15 | 2.89 | 5.55 | 3.62 | | 3.00 | 25 |
| | DMF-$D_6$ | 5.84 | 5.03 | 9.40 | 2.90 | 5.44 | 3.50 | | 3.02 | 30 |

*[1]The spectra of Ia, d in $CF_3COOH$ and DMSO-$D_6$ [1, 2] identify the single tautomer A.
*[2]J = 3.4-4.0 Hz.
*[3]$J_{AX} = J_{BX}$ = 6.0-8.0; $J_{AB}$ = −17.0 to −19.0 Hz.
*[4]According to [1], content of A = 50%. Aromatic signals found at 6.5-8.0 ppm.

TABLE 2. Values of $[D_{max}/(C \cdot l)] \cdot 10^{-3}$* for Compounds Ib, c, e, f

| Compound | $[D_{max}/(C \cdot l)] \times 10^3$ in solvents** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $CHCl_3$ | $C_6H_6$ | $CH_3CN$ | $(CH_3)_2CO$ | $CH_3OH$ | $C_2H_5OH$ | $(CH_3)_2CHOH$ | $(CH_3)_3COH$ | DMF | DMSO |
| Ib | 11.5 | 11.3 (98) | 11.2 (98) | 11.1 (97) | 7.3 (63) | 6.7 (58) | 6.3 (55) | 6.8 (59) | 5.6 (49) | 2.2 (19) |
| Ic | 29.7 | 30.0 (101) | 27.8 (94) | 28.0 (98) | 28.6 (96) | 29.4 (99) | 28.1 (95) | 27.8 (94) | 26.7 (90) | 26.5 (89) |
| Id | 11.0 | 11.0 (100) | 10.8 (98) | 10.9 (99) | 8.6 (78) | 8.5 (77) | 8.2 (75) | 8.3 (75) | 7.2 (65) | 3.6 (33) |
| Ie | 25.4 | —*** | 25.8 (102) | 25.0 (98) | 25.1 (99) | 25.0 (98) | 24.9 (98) | 24.5 (96) | 22.9 (90) | 21.0 (83) |

*Corresponds to ε for solutions of individual tautomers.
**The figure in brackets gives the % relative to the value in $CHCl_3$.
***Insoluble in benzene.

and from PMR spectroscopy (Table 1) are practically the same (within the ±5% accuracy of the PMR integrated intensity method) and this confirms the validity of the approach used.

Analysis of the data in Table 2 shows that, in acetonitrile, acetone, and benzene, the intensity of the long-wavelength band of the o-hydroxyaryl derivatives Ia, b differs little from the corresponding values in $CHCl_3$ and points to near 100% concentration of tautomer B in the listed solvents. Such a tautomeric equilibrium is not typical of the majority of 5,7-diaryldihydro-1,2,4-triazolo[1,5-*a*]pyrimidines [1] (including compounds Ia, c, d, f) and is undoubtedly due to stabilization of tautomer form B by intramolecular bond formation. The conditions for forming the latter in the imine tautomers is more favored than in the enamines. As is seen in Tables 1 and 2, a marked decrease in the content of this tautomer is observed only in proton donor (alcohol) and, particularly, in proton acceptor solvents (DMSO, DMF, pyridine). In our view this result is connected primarily with concurrent intermolecular H-bonding of the hydroxyl proton of tautomer A by solvent with intramolecular hydrogen bond

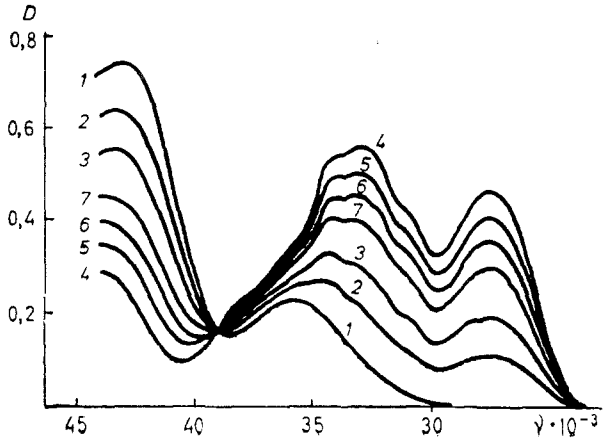


Fig. 1. UV spectra of Ib in methanol solution (c = $4 \cdot 10^{-5}$ M): 1-3) tautomer A; 4-6) tautomer B; 1, 4) directly after solution; 2, 5) 50 min after solution; 3, 6) 120 min after solution; 7) equilibrium mixture spectrum.

formation in tautomer B. It should be mentioned, however, that the lowering of the concentration of the imine tautomers (Tables 1 and 2) does not correspond to the change in proton-acceptor properties, i.e., there appears to be a marked effect of nonspecific solvation on the tautomer equilibrium.

According to PMR data (Table 1) in DMSO-$D_6$, DMF-$D_6$, pyridine-$D_5$, and $CDCl_3$ (Ic), the dimethylamino substituted Ic, f form a mixture of two tautomers with concentrations of A = 35-45 (Ic) and 25-30% (If). The effect of solvents on the tautomer composition for Ic, f is much less marked than in the case of the o-hydroxyaryl-substituted Ib, e, as shown by the comparative intensities of the long-wavelength absorptions for these compounds in different solvents (Table 2). The change of compounds Ic, f to the enamine form A in $CF_3COOH$ appears, at first sight, somewhat atypical. It should be pointed out that the PMR spectra of Ic, f, measured in $CF_3COOH$, show that the signal for the dimethylamino group has a J= 2.5 Hz splitting which indicates that the group is protonated and, hence, its electronic character is altered. Based on this result, the marked change observed from Ia, d to Ic, f in dihydro form B (excepting solutions in $CF_3COOH$) is primarily connected with the electron-donor effect of the dimethylamino group. The relative stability of tautomer B induced by this group is, in our opinion, connected with the ineffectiveness in tautomers A and B of conjugative effects for this substituent, such that only in form B does it achieve conjugation with the electron-acceptor azomethine group and the 2-triazolyl radical.

The shift in tautomer equilibrium on introduction of the amino groups into the triazole radical (from Ib, c to Ie, f) is significantly less marked (Tables 1 and 2). It must be linked to both the conjugative effects and the strengthening of the intramolecular hydrogen bonding in hydroxyaryls Ib, e induced by the increased basicity of the contributing nitrogen atom.

The marked dependence of the tautomer composition of Ib on solvent allowed us to separate both tautomers of this material into the individual forms, and this has been reported briefly before [3]. In this case we succeeded in obtaining crystalline Ib as the dihydro form A only in DMSO.* It crystallized as the imine form B from the rest of the solvents listed in Table 2. Attempts to separate both tautomers of the remaining compounds Ia, c-f by crystallization from various solvents were unsuccessful. In all cases Ia, d crystallized in dihydro form A and the dimethylamino-substituted Ic, f as B (as shown by the presence or absence of the $\nu_{C=C}$ band in the IR spectra of crystals in KBr tablets).

As shown by UV and PMR spectroscopy, dissolving crystals of tautomers A and B of Ib in alcohols, DMSO, DMF, and chloroform gave an equilibrium solution mixture after 1-5 h of the same composition. Using the marked difference in electronic absorption spectra for freshly prepared solutions of tautomers A and B (Fig. 1) we have studied the kinetics of the tautomer exchange of Ib in methanol and chloroform. The tautomer exchange constants were: in methanol, $k_{A \to B} = (9.3 \pm 0.1) \cdot 10^{-5}$, $k_{B \to A} = (5.4 \pm 0.1) \cdot 10^{-5}$ $sec^{-1}$, and in chloroform, $k_{A \to B} = (8.1 \pm 0.1) \cdot 10^{-4}$ $sec^{-1}$ ($k_{A \to B} >> k_{B \to A}$). Thus, the measured exchange proves to be significantly slower than is typical for amidine-type dihydropyrimidine tautomer exchange systems [5]. The tautomeric equilibrium constant for Ib in

*According to elemental analytical data and PMR spectroscopy, the crystals of tautomer A contain 1 mole of DMSO of crystallization per mole.

methanol is 1.71 and corresponds to 63% of tautomer B, which agrees well with data given in Table 2 for this substance.

## EXPERIMENTAL

Electronic absorption spectra were measured on a Specord M-40 spectrometer as $(2\text{-}5) \cdot 10^{-5}$ M solutions. IR spectra were measured on a Specord IR-75 for KBr tablets and PMR spectra on a Tesla BS-497 (100 MHz) instrument with TMS as internal standard. Kinetic measurements were made at 25°C. The reaction course and product purities were monitored by TLC on Silufol UV-254 plates with chloroform or acetone as eluants.

The nitrogen content of the compounds obtained agreed with those calculated.

Compounds Ia-d have been described before [1-3].

**2-Amino-5-(2-hydroxyphenyl)-7-phenyl-4,7(6,7)-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (Ie, $C_{17}H_{15}N_5O$).** A solution of 3,5-diamino-1,2,4-triazole (0.5 g, 5 mmoles) and 2'-hydroxychalcone (1.16 g, 5 mmoles) in DMF (1 ml) was refluxed for 15 min, filtered hot, and the precipitate washed with methanol and acetone to give Ie (1.2 g, 76%) with mp 233-235°C (from benzene—DMF, 1:1). IR spectrum, $\nu_{C=N}$ 1635 $cm^{-1}$. UV spectrum, $\lambda_{max}$ 388 nm (in ethanol).

**Compound If** was obtained similarly, mp 220-221°C. IR spectrum, $\nu_{C=N}$ 1628 $cm^{-1}$. UV spectrum, $\lambda_{max}$ 405 nm (in ethanol). Yield 65%.

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