IMINE—ENAMINE TAUTOMERISM OF DIHYDROAZOLOPYRIMIDINES

5.* STERIC EFFECTS AND THE TAUTOMERIC EQUILIBRIUM FOR DIHYDRO-1,2,4-TRIAZOLO[1,5-a]PYRIMIDINES


The reaction of 3-amino-1,2,4-triazole with β-dimethylaminopropiophenones or unsaturated ketones gives 5,7-disubstituted 4,7(6,7)-dihydro-1,2,4-triazolo[1,5-a]pyrimidines. An increase in the bulk of the substituent at C(7) in the bicyclic system leads to relative stabilization of the enamine tautomer of these compounds. An x-ray diffraction structural analysis of 7-tert-butyl-5-(4-methoxyphenyl)-4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidine showed that the introduction of a tert-butyl group into the dihydropyrimidine ring leads to significant loss of planarity of this system.

In a continuation of a study of the effect of structural factors on the imine—enamine tautomeric equilibrium in dihydro-1,2,4-triazolo[1,5-a]pyrimidines, we investigated derivatives containing substituents of various size at C(7). Products IVa-IVh were obtained by the reaction of 3-amino-1,2,4-triazole (I) with the hydrochloride salts of β-dimethylaminopropiophenones IIa and IIb or unsaturated ketones IIIc-IIIh according to a procedure described in our previous work [2].

---

*For Communication 4, see [1].
TABLE 1. Physical Indices of IVb, IVd-IVf, and IVh*1

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical formula</th>
<th>Mp, °C</th>
<th>IR spectrum, cm⁻¹ v C-C</th>
<th>UV spectrum, λmax, nm (ε·10⁻³)</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVb</td>
<td>C₃H₂N₄O</td>
<td>162...164</td>
<td>1652</td>
<td>279 (5,5)'², 325 (3,9)'²</td>
<td>70</td>
</tr>
<tr>
<td>IVc</td>
<td>C₃H₄N₄O</td>
<td>149</td>
<td>1658</td>
<td>278 (4,5)</td>
<td>65</td>
</tr>
<tr>
<td>IVd</td>
<td>C₃H₅N₄</td>
<td>176...177</td>
<td>1652</td>
<td>281 (2,7)</td>
<td>62</td>
</tr>
<tr>
<td>IVe</td>
<td>C₃H₆N₄</td>
<td>170...172</td>
<td>1666</td>
<td>284 (5,4)</td>
<td>68</td>
</tr>
<tr>
<td>IVf</td>
<td>C₄H₇N₄O</td>
<td>205</td>
<td>1668</td>
<td>282 (5,2)</td>
<td>70</td>
</tr>
</tbody>
</table>

*1IVa, IVc, IVg, and V were characterized in our previous work [2, 3].

*2The determination of ε is difficult in light of the unknown tautomeric composition.

Values of \[D_{\text{max}}/\sum(C_{A^*} + C_{B^*})\cdot10^{-3}\] are given.

Products IVb, IVd-f, and IVh were identified by spectral methods (Table 1), while IVa, IVc, and IVg were described in our previous work [2, 3]. The IR spectra of these products have strong νC=C bands at 1652-1668 cm⁻¹, indicating their 4,7-dihydro structure in the solid phase. The electronic absorption spectra of solutions of IVd-IVf and IVh are analogous to the spectra of other 4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidines, including IVa, IVc, and IVg [2, 3]. These spectra have weak bands at 279-284 nm. The lack of bands at longer wavelength indicates the absence of imine form B in solution [1, 4]. The spectrum of IVb differs from the spectra of the other products and has an additional band with \(\lambda_{\text{max}}\) 225 nm, probably related to the imine tautomer form.

PMR spectra gave unequivocal information on the tautomeric composition of IV in CDCl₃, DMSO-d₆, and CF₃CO₂D (Table 2). Dihydro form B has one hydrogen atom more at C(6) than tautomer A and, hence, the spectra of form B are significantly different in the aliphatic proton region. Comparison of the integral intensities of the corresponding groups of signals gave the tautomeric composition of these compounds (Table 3). The signals for 6-H in CF₃CO₂D solution do not appear due to their deuterexochange. In this case, the formation of a mixture of tautomeric forms is seen in a double set of signals for 2-H, 7-H, and the substituents (when R = CH₃, (CH₃)₃C or R₁ = CH₃O). The assignment of signals to specific protons was carried out using the position and integral intensity of the 7-H signal, which is found downfield in dihydro forms A relative to tautomers B by 0.04-0.6 ppm due to its allylic nature in forms A (Table 2).

Analysis of the data in Table 3 showed a steady increase in the equilibrium concentration of tautomers B upon introducing a methoxy group into the aryl substituent. A similar effect was observed in our previous work [2] and should be attributed to conjugation effects of the electron-donor R₁ substituent with the azomethine group and triazole system. The imine tautomer structure of dihydropyrimidines facilitates the manifestation of these conjugation effects.

A decrease in the concentration of tautomer A is observed in the series R = H, CH₃, (CH₃)₂C, and C₆H₅ in the case of identical R₁. In our previous work [1], we found in an analysis of the tautomeric composition of derivatives of IV with different R = Ar that there is only a slight shift in the equilibrium toward form B with increasing electron-donor capacity of R. Hence, the variation in the equilibrium composition for IVa-IVh cannot be attributed exclusively to the electronic effects of substituent R. In our view, steric factors play the predominant role in this effect (when R = CH₃, these effects may be partially compensated by electronic effects). The reason for the relative stabilization of dihydro forms A upon the introduction of bulky substituents R probably should be sought in the different conformational behavior of 4,7- and 6,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidines.

Using structural data for imine tautomers of dihydrazolopyrimidines, we have shown that the three-dimensional structure of their dihydropyrimidine fragment is hardly sensitive to the introduced substituents [5]. On the other hand, literature data on 1,4-dihydropyrimidines indicated that dihydro forms A might have high conformational lability, permitting bulky substituents to occupy a more favorable position than in form B. In order to check this hypothesis, we carried out an x-ray diffraction structural analysis of IVf and these results were compared with the our previous data for IVa and V [2].

The triazole ring in IVf is planar. The bond lengths (Fig. 1) and bond angles (Table 4) are similar to those observed in other such compounds: 5-phenyl-4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidine (IVa) [3] and 5-phenyl-7-(4-methyl-phenyl)-4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidine (V) [2].