Preferable Tautomer of Dihydropyrazolo[5,1-*c*][1,2,4]triazines in Solution

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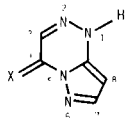
Received November 14, 1988

Dihydropyrazolo[5,1-*c*][1,2,4]triazines **6**, **7** and **8** were found to predominate as the 4,6-dihydro tautomeric form in solution by the measurement of 1D NOE different spectra.

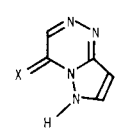
J. Heterocyclic Chem., **26**, 869 (1989).

Several studies have been reported concerning the synthesis of dihydropyrazolo[5,1-*c*][1,2,4]triazine derivatives, which possibly exist as either 1,4-dihydro or 4,6-dihydro tautomer (Chart 1), but direct spectral evidences to assign the above two tautomers have seldom been reported. Namely, the structural assignment of **1** as the 4,6-dihydro tautomer (Chart 2) depended on the results for the acylation of **1** and **2** and reduction of **2** and **3** [2], while no description was provided for the structural assignment of **4** and **5** as 1,4-dihydro tautomer [3,4]. We also reported the synthesis of the dihydropyrazolo[5,1-*c*][1,2,4]triazines **6** [5] and **7** [6], but we could not obtain the obvious spectral data to support the 1,4-dihydro structure of **6** and **7**. Thus, the tautomeric forms of the dihydropyrazolo[5,1-*c*][1,2,4]-triazines are ambiguously described in some papers, and it is necessary to specify the tautomeric form of the dihydropyrazolo[5,1-*c*][1,2,4]triazines in solution or solid state. Fortunately, our compounds **6** and **7** possessed the ester group at the C_8-position of the pyrazolo[5,1-*c*][1,2,4]triazine ring, which was expected to furnish a promising information in the nuclear Overhauser effect (NOE) measurements. Accordingly, we measured the NOE spectra of **6** and **7** to specify their preferable tautomeric form in solution. This paper describes the specification of the preferable tautomeric form of the dihydropyrazolo[5,1-*c*]-[1,2,4]triazines **6**, **7** and **8** in the dimethyl sulfoxide (DMSO) solution.

Chart 1



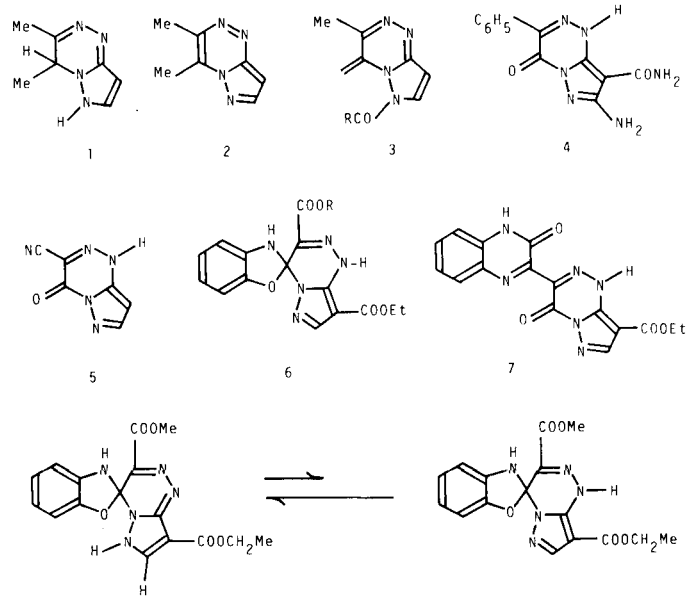
1,4-Dihydro Form



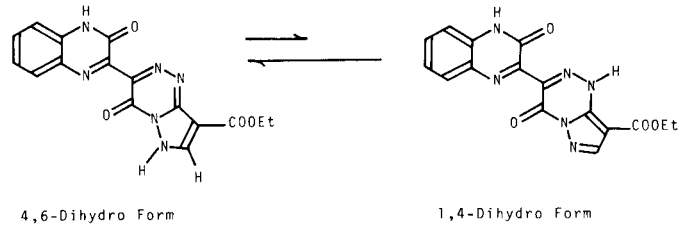
4,6-Dihydro Form

X=O, CH_2

Chart 2



Scheme 1. Preferable Tautomer of 6.

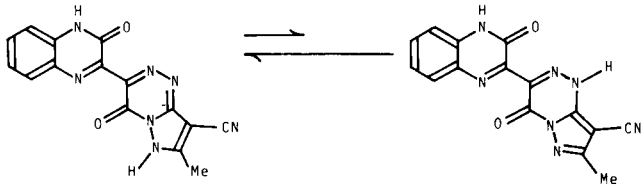


Scheme 2. Preferable Tautomer of 7.

One dimensional (1D) NOE different spectra of **6** and **7** were measured in the DMSO-d_6 solution. In compound **6**, radiation at the C_8-ester methyl proton signal (δ 1.43 ppm)

showed 4% NOE to the C_7-H proton signal (δ 8.57 ppm), but no NOE was exhibited to NH proton signal (δ 10.28 ppm) in the pyrazolotriazine ring, suggesting the presence of NH proton at the N_6-position, but not at the N_1-position. The location of the NH proton was ascertained by the radiation at the N_6-H proton signal (δ 10.28 ppm), which showed -5% NOE to the C_7-H proton signal. Thus, compound **6** was clarified to predominate as the 4,6-dihydro form in solution, at least in the DMSO-d_6 solution (Scheme 1). In compound **7**, the radiation at the NH proton signal (δ 12.84 ppm) in the pyrazolotriazine ring showed -18% NOE to the C_7-H proton signal (δ 8.44 ppm), while no NOE was observed on radiation at the C_8-ester methyl proton signal (δ 1.34 ppm). These data indicate that compound **7** also exists as the 4,6-dihydro form (Scheme 2).

In order to apply the above tautomer clarification to other dihydropyrazolotriazine, a similar NOE to the above was inspected in compound **8** synthesized in our previous paper [7] (Scheme 3). The radiation at the N_6-H proton signal (δ 12.82 ppm) showed -2% NOE to the C_7-methyl proton signal (δ 2.47 ppm), while no NOE was observed by the radiation at the C_7-methyl proton signal.



Scheme 3. Preferable Tautomer of 8.

In conclusion, we obtained the 1D NOE different spectral data to support the 4,6-dihydro tautomeric form of dihydropyrazolo[5,1-*c*][1,2,4]triazines **6**, **7** and **8** in solution. The study on the other examples is now in progress.

EXPERIMENTAL

The synthesis of compounds **6**, **7** and **8** was reported in previous papers [5,6,7]. All nmr spectra were measured in deuteriodimethyl sulfoxide with an EM 390 spectrometer at 300 MHz.

REFERENCES AND NOTES

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