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Tautomerism of 2-(pyridine-2-yl)-1,3-diazaspiro[4.4]non-1-en-4-one

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ABSTRACT

The work deals with both solution state (using ^{1}H, ^{13}C and ^{15}N NMR) and solid state (using X-ray) structure of 2-(pyridine-2-yl)-1,3-diazaspiro[4.4]non-1-en-4-one. The compound exists in the solution predominantly as 5-oxo tautomer where the amount of 4-oxo form depends on the solvent used. Mutual interconversion between the tautomers is slow on the NMR time scale and is studied by means of both EXSY and variable temperature NMR. In the solid state, the compound is solely as 5-oxo tautomer.

1. Introduction

Prototropic tautomerism is an important factor affecting many aspects of heterocyclic chemistry. Comprehension of tautomerism is vital for correct understanding of both the reactivity and biological activity of heterocycles [1,2]. For correct interpretation of experimental data it is therefore necessary to have at least an idea about the composition of a tautomeric mixture as even a minor tautomer can play a crucial role in the studied process. During the years many methods for establishing the composition of a tautomeric mixture has been developed [1–3]. The methodologies comprise chemical, physical and theoretical approaches.

Imidazolinones belong among practically important heterocycles. A number of them have been found to possess either biological activity such as pesticides [4] and drugs [5–8] (e.g. imidazolinone-based Irbesartan [9] has been marketed for the treatment of hypertension) or fluorescent properties [10,11]. An application of imidazolinone complexes with selected metal ions as catalysts of some reactions can be also found in the literature [12–18].

N-Unsubstituted imidazolin-4-ones can, in principle, exist in seven prototropic tautomeric forms (upon neglecting two mesoionic compounds) (Scheme 1).

The number of tautomers is greatly reduced for 4,4-disubstituted imidazolin-5-ones (Scheme 2).

These imidazolinones can, in principle, exist as the mixture of all the mentioned forms. Generally, tautomer **A** is stated as the energetically favourable form, both in a solution and in the gas phase [19]. The structure in the solid state does not necessarily reflect the thermodynamic stability but rather the specificity of the crystal packing (hydrogen bonding, π,π-stacking etc.) IR Measurements showed that imidazolinones **I** (R = H, R_1,R_2 = Ph; R = H, R_1,R_2 = Me, Fig. 1) exist in the solid phase as sole 5-oxo tautomer **IA** [20,21].

Spirocyclic imidazolinone **II** (R = H) appeared to be in its 4-oxo form **IIB** [20] but when R = pyridine-2-yl the compound was determined as 5-oxo tautomer **IIA** [22]. Imidazolinones **I** (R = Me, Ph, SMe; R_1,R_2 = Ph) appeared as the mixture of 4/5-oxo tautomers **B,A** [23–25] that can be either partially separated by vacuum sublimation (R = Me) [24] or obtained as individual tautomers in the dependence on the crystallization solvent (R = Ph, SMe) [24,25]. Compound **III** was proved (by means of X-ray) to be the 5-oxo tautomer in the crystalline state [26]. Tropane-3-spiro-4′-imidazol-5′-one **IV** exists in the solid state (on the basis of IR, Raman and X-ray studies) predominantly as 5-oxo tautomer **IVA** [27].

The situation in solution can be quite different. It can be clearly demonstrated by the fact, that dissolving both **IB** and **IA** (R = SMe,

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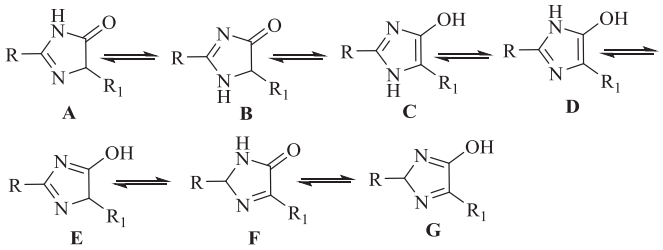
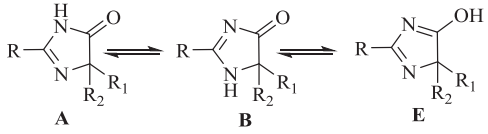


Scheme 1. Prototopic tautomerism of *N*-unsubstituted imidazolin-5-ones.



Scheme 2. Prototropic tautomerism of *N*-unsubstituted 4,4-disubstutited imidazolin-5-ones.

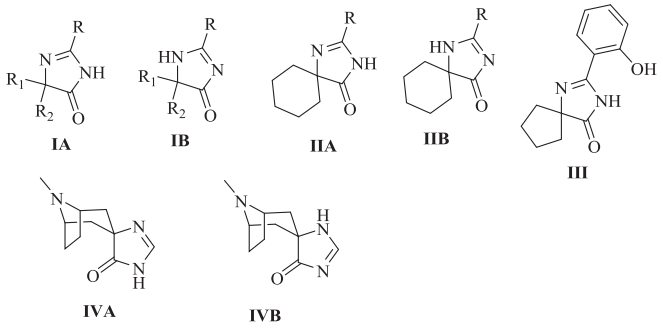


Fig. 1. *N*-Unsubstituted 4,4-disubstutited imidazolin-5-ones studied in the literature.

R_1,R_2 = Ph) afforded the same structure [23]. Generally, 5-oxo tautomers predominate, the exact composition depends on the polarity of the solvent and substitution of the imidazolinone ring [21–23,27]. Increasing the polarity of the solvent causes increasing the amount of 4-oxo form [23,27]. Edward and Lantos [23] even observed predominance of 4-oxo tautomer **IB** (R = SMe, R_1,R_2 = Ph) in water. Electron-donating substituents in 2-position also increased the amount of 4-oxo tautomer [23]. For the structures of the mentioned compounds see Fig. 1.

Most of the results mentioned above are relatively old, some of them were obtained using the derivatization methodology. An application of new instruments and methodology can thus bring novel insights into the issue. In this work we bring more detailed study of the tautomerism of 2-(pyridin-2-yl) substituted spirocyclic imidazolinone using modern NMR techniques.

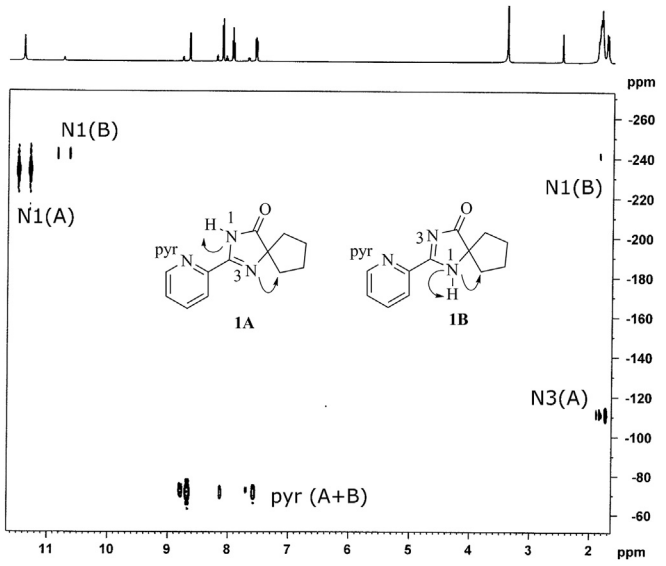


Fig. 3. 500 MHz ^{1}H–^{15}N HMBC spectrum of **1** in DMSO-d_6.

2. Experimental

NMR spectra were measured using either Bruker AVANCE III spectrometer operating at 400.13 MHz (^{1}H) and 100.62 MHz (^{13}C) equipped with *z*-gradient broadband probe or Bruker Ascend™ operating at 500.20 MHz (^{1}H), 125.79 MHz (^{13}C) and 50.70 MHz (^{15}N) equipped with CryoProbe™ Prodigy. All the pulse sequences were taken from the Bruker software library. Calibration of the ^{1}H spectra was done either on an internal TMS (δ = 0.00 in $CDCl_3$) or the middle of the solvent multiplet (δ = 2.50 in DMSO-d_6, δ = 2.05 in acetone-d6, δ = 1.94 in acetonitrile-d3, δ = 2.75 in DMF-d7, δ = 3.31 in methanol-d4, δ = 8.74 in pyridine-d5, δ = 2.09 in toluene-d8). ^{13}C spectra were measured using broadband proton decoupling either in an ordinary way or by means of APT pulse sequence. The calibration of the ^{13}C spectra was done on the middle of the solvent multiplet (δ = 29.92 (acetone-d6), δ = 1.39 (acetonitrile-d3), δ = 77.23 ($CDCl_3$), 39.51 (DMSO-d_6), 150.35 (pyridine-d5), 20.4 (toluene-d8)). ^{15}N NMR spectra were calibrated on an

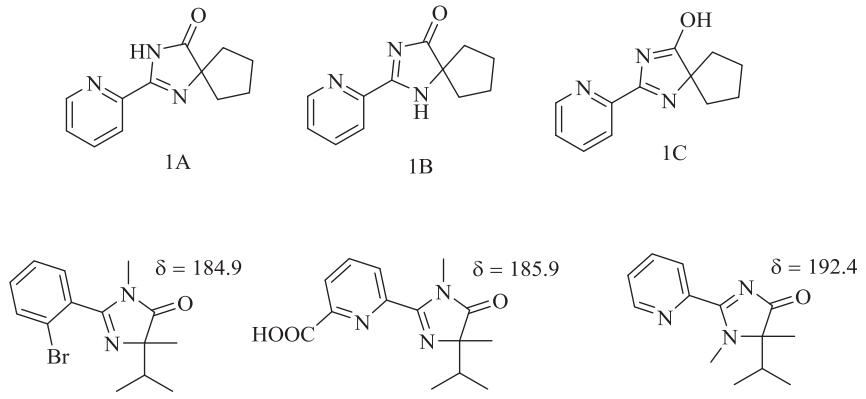


Fig. 2. Possible tautomeric forms of compound **1** and diagnostic ^{13}C chemical shifts of the standard compounds.