The tautomeric properties of 6-(2-pyrrolyl)pyridazin-3-one and 6-(2-pyrrolyl)pyridazin-3-thione

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Abstract
The pyrrolyl substituent enhances the electron densities on the pyridazine ring and has the effect of shifting the positions of the tautomeric equilibria for **1c**,**d** ⇌ **2c**,**d**, which exist predominantly as the pyridazin-3-one and -3-thione forms, towards the hydroxyl (thiol) structures, compared with those of those for the parent unsubstituted systems.

Keywords: Tautomerism, pyridazin-3-ones, pyridazin-3-thiones, (2-pyrrolyl)pyridazines

Introduction

Protonation of the potentially tautomeric pyridazine systems **1** ⇌ **2** can lead to three monocationic species: a common N-protonated species **5**, which would be formed from both tautomers, and two other monocations **4** and **6**, which would be produced specifically from **1** and **2**, respectively. Thus, the observed pK_a values for the conjugated acids of the tautomeric systems **1** ⇌ **2** would be expected to reflect not only the tautomeric equilibrium constants but also the ratio-averaged values for the ionisation of the appropriate monoprotonated conjugate acid pairs **4** ⇌ **5** and **5** ⇌ **6**. A third tautomeric (zwitterionic) form **3**, which on protonation would give rise to **4** or **6**, is also possible, but is excluded from this study on the basis of AM1 MO calculations[1] for the three tautomeric forms, which indicate that **3** would contribute less than 0.1% to the tautomeric equilibria. Subsequent protonation of the each of the monocationic species, **4**, **5** and **6**, produces only the single dication **7**. Not unexpectedly, evidence has been provided indicating that the parent tautomeric systems **1a,b** ⇌ **2a,b** exist predominantly as the oxo/thione forms[2] and cursory studies indicating similar tautomeric equilibrium positions for substituted derivatives have also been reported.[3]

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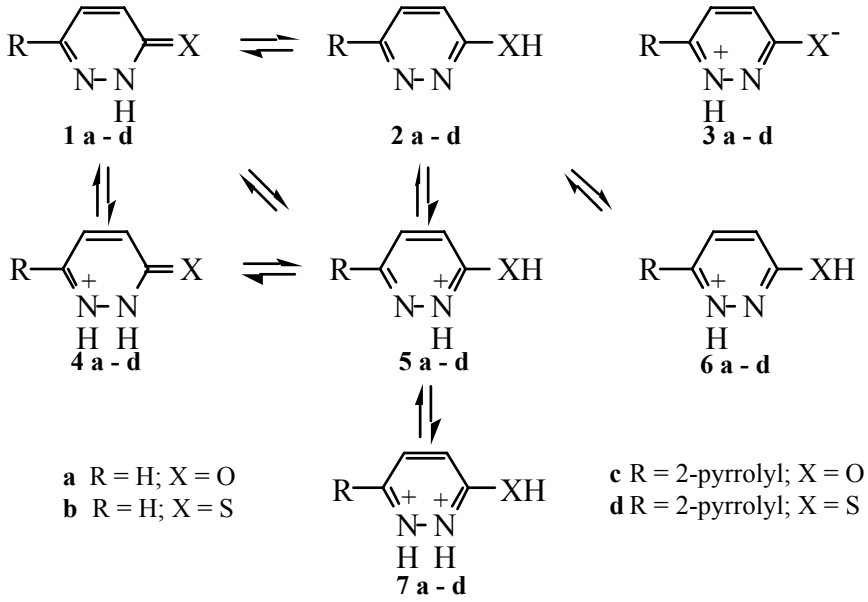
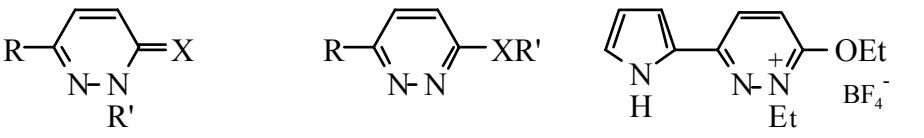
In the course of our studies on the effect of conjugation of π-electron excessive heteroaromatic systems with π-electron deficient hetero-aromatic systems[4] on their semi-conducting and non-linear optical properties.[5] we synthesised a series of 6-(2-pyrrolyl)pyridazines[6] and, in this communication, we report the effect of the 6-pyrrolyl group upon the equilibrium positions for the tautomeric system **1** ⇌ **2**.



Scheme 1

Results and Discussion

Electronic spectra of 6-(2-pyrrolyl)pyridazine derivatives. Examination of the electronic spectra (Table 1) for the oxygen derivatives shows a close correlation between spectral data for the fixed oxo-form **8c** (R' = Et) and the free base of the tautomeric system **1c** ⇌ **2c**, both of which differ significantly from that for the O-alkylated derivative **9c** (R' = Et). This evidence indicates strongly that the oxo-form **1c** is the predominant tautomeric species.



Scheme 2

The similarity between the electronic spectrum of the 3-ethoxy-2-ethyl-6-(2-pyrrolyl)-pyridazinium ion **10** and the spectra of the monoprotonated species derived from **1c** ⇌ **2c** and from **8c** (R' = Et) suggests that the monoprotonation leads preferentially to a single protonated species analogous to **5c** (*cf*. refs. 7, 8), although an equilibrium between **5c** and **6c** cannot be precluded completely. In contrast, the electronic spectrum of the monoprotonated derivative of the 3-ethoxy system **9c** (R' = Et) differs significantly from those for monocations of the tautomeric system **1c** ⇌ **2c** and of **8c** (R' = Et) and suggests that the protonated species analogous to **6c** makes an important contribution to the protonation of **9c** (R' = Et). These observations are compatible with AM1 MO calculations,[1] which indicate that the electron-donating mesomeric effect of the pyrrole ring enhances the electron density of the pyridazine ring generally and, in particular, at N(1). Not unexpectedly, the spectra for the diprotonated species derived from **1c** ⇌ **2c**, **8c** (R' = Et), **9c** (R' = Et) and **10** are similar with a bathochromic shift of 5 nm for N-alkylated derivative and hypsochromic shift of 5 nm for O-alkylated derivative, relative to the absorption maximum for the diprotonated species derived from tautomeric system **1c** ⇌ **2c**. These opposing effects are compensated in the spectrum of the dication of the O,N-diethylpyridazinium derivative **10**.

Table 1. Electronic spectra of the 6-(2-pyrrolyl)pyridazine derivatives and their mono- and di-cationic salts

Compound	Free Base[a]		Monocation		Dication[d]	
	λ_{max} (nm)	(ε)	λ_{max} (nm)	(ε)	λ_{max}(nm)	(ε)
1c ⇌ **2c**	275	(3.94)	290	(3.89)[b]	275	(4.00)
8c (R' = Et)	275	(4.00)	290	(4.00)[b]	280	(4.05)
9c (R' = Et)	290	(4.03)	280	(4.09)[c]	270	(4.18)
			365	(4.10)		
10			295	(4.00)[a]	275	(4.10)
1d ⇌ **2d**	310	(4.05)	321	(4.00)[b]	306	(4.10)
8d (R' = Et)	306	(4.09)	320	(4.02)[b]	310	(4.07)
9d (R' = Me)	295	(3.96)	320	(4.02)[c]	304	(4.10)

[a] measured at pH 7.00 [b] measured at H_o -2.10 [c] measured at H_o -1.36 [d] measured at H_o -8.77

Similarly, with the sulphur analogues, there is a closer correlation between the electronic spectra of the tautomeric system **1d** ⇌ **2d** and the thione **8d** (R' = Et) than there is with the methylthio derivative **9d** (R' = Me) indicating the greater contribution of the thione form **1d** to the equilibrium mixture. However, in contrast with the oxygen derivatives, the spectra for the monoprotonated species of the three systems **1d** ⇌ **2d**, **8d** (R' = Et) and **9d** (R' = Me) are virtually identical suggesting a predominant protonation of the free bases at N(2) leading to the same mono-cationic species analogous to **5d**. As with the oxygen derivatives, bathochromic and hypsochromic shifts respectively are observed in the spectra of the N- and S-alkylated

derivatives, **8d** (R' = Et) and **9d** (R' = Me), relative to the tautomeric system **1d** ⇌ **2d** upon formation of the diprotonated species.

Table 2. pK_a values for conjugate acids of 6-(2-pyrrolyl)pyridazin-3-one and -3-thione and related compounds

Compound	Monocation	Dication
Pyridazin-3-one (**1a** ⇌ **2a**)	-1.80 ± 0.30[a,b,c]	
2-Methylpyridazin-3-one (**8a**, R' = Me)	-2.10 ± 0.30[d]	
3-Methoxypyridazine (**9a**, R' = Me)	2.52 ± 0.01[a]	
Pyridazin-3-thione (**1b** ⇌ **2b**)	-2.68 ± 0.07[d]	
2-Methylpyridazin-3-thione (**8b**, R' = Me)	-2.95 ± 0.25[d]	
3-Methylthiopyridazine (**9b**, R' = Me)	2.26 ± 0.01[d]	
6-(2-Pyrrolyl)pyridazin-3-one (**1c** ⇌ **2c**)	-0.16 ± 0.02	-6.20 ± 0.02
2-Ethyl-6-(2-pyrrolyl)pyridazin-3-one (**8c**, R' = Et)	-0.71 ± 0.03	-6.29 ± 0.05
3-Ethoxy-6-(2-pyrrolyl)pyridazine (**9c**, R' = Et)	3.00 ± 0.02	-6.63 ± 0.05
6-(2-Pyrrolyl)pyridazin-3-thione (**1d** ⇌ **2d**)	-0.59 ± 0.02	-6.40 ± 0.03
2-Ethyl-6-(2-pyrrolyl)pyridazin-3-thione (**8d**, R' = Et)	-0.80 ± 0.02	-6.30 ± 0.02
3-Methylthio-6-(2-pyrrolyl)pyridazine (**9d**, R' = Me)	3.23 ± 0.05	-6.55 ± 0.04

[a] ref. 9. [b] ref. 4 gives -1.40 ± 0.1. [c] ref. 2 records two overlapping pKa values (-1.27 ± 0.07 and -2.42 ± 0.06) for protonation at N(1) and N(2). [d] ref. 10.

Basicity measurements of 6-(2-pyrrolyl)pyridazine derivatives. Previous examination[2] of the tautomeric parent pyridazin-3-one system **1a** ⇌ **2a** has indicated the probable simultaneous protonation at both the N(1) and N(2) positions to give the monocations **5a** and **6a**, but excludes formation of the cation analogous to **4a**. The reported pKa_1 measurements[9,10] for the conjugate acids of fixed forms of the parent compounds (Table 2) indicate that the tautomeric compound exists in the oxo form to the extent of *ca.*$10^{4.6}$:1, while it can be estimated that the pyridazinthione predominates over the thiol structure by a factor of *ca.*$10^{5.2}$:1.[3] In each case, there is no evidence for any contribution to the tautomeric equilibrium from zwitterionic structures analogous to **3**.

The increased basicities of the tautomeric systems **1c,d** ⇌ **2c**,**d** and their fixed forms **8c**,**d** and **9c**,**d**, relative to the parent systems, are consistent with the enhanced electron densities on the six-membered rings upon the introduction of the pyrrolyl group at the 6-position.[1] Significantly, the effect is greater for the protonation of the exocyclic O of **8c** than for the protonation of the annular N atoms of **9c**, compared with the corresponding sulphur compounds. As the electron-donating effect of the pyrrole group enhances the electron density on N(1) to a greater extent than on N(2), it is possible that the observed differences reflect small, but significantly different ratios in protonation at N(1) and N(2) for the pyrrolyl derivatives compared with the parent compounds, particularly with the pyridazinone systems. Consequently,

in contrast with studies of the tautomeric equilibria of systems having only two basic centres, the procedure for the calculation of the equilibrium constants is refined to allow for the possibility of protonation of the three basic centres of the tautomeric systems **1** ⇌ **2**.

Irrespective of the ratios of the monoprotonated species of the tautomeric systems, it can be shown that the tautomeric equilibrium constant, K_T, is related to the ionisation constants for mono- and diprotonation, K^1 and K^2, of the tautomers **1** and **2**:

$$K_T = \frac{K^1_{\mathbf{1}} \times K^2_{\mathbf{1}}}{K^1_{\mathbf{2}} \times K^2_{\mathbf{2}}}$$

As the values of ionisation constants for the individual tautomers can not be measured, they are replaced by the observed values for mono- and diprotonation of the fixed forms **8** and **9**. This close approximation is made on the assumptions that N- and O(S)-alkylation have minimal and equal effects on the ionisation constants of the tautomers and that the sites of protonation are same for the tautomers and their respective fixed forms. The wealth of data in the literature indicates that the first assumption is acceptable and the electronic spectra of the mono- and diprotonated species of **1c,d** and **8c,d** and of **2c,d** and **9c,d** (Table 1) indicate that the second assumption is also acceptable.

Thus, the value of K_T can be given as:

$$K_T = \frac{K^1_{\mathbf{8}} \times K^2_{\mathbf{8}}}{K^1_{\mathbf{9}} \times K^2_{\mathbf{9}}}$$

where K^1 and K^2 are the observed ionisation constants, respectively, for the mono- and diprotonated species of the fixed forms **8** and **9**.

Thus:

$$pK_T = (pK_a{}^1_{\mathbf{8}} + pK_a{}^2_{\mathbf{8}}) - (pK_a{}^1_{\mathbf{9}} + pK_a{}^2_{\mathbf{9}})$$

From the data given Table 2, the calculated value of K_T for the equilibrium **1c** ⇌ **2c** indicates that the oxo form **1c** is favoured to the extent of *ca*. 2350:1. Similarly, for the equilibrium **1d** ⇌ **2d**, the thione structure **1d** predominates by *ca*. 6250:1. The difference between the equilibrium positions for the pyridizin-3-one and -3-thione systems is analogous to that observed between those for pyrid-2-one[9] and pyrid-2-thione[x] and reflects the difference in electronegativities of the O and S atoms and, hence, basicities of the pyridazinone and –thione structures. Additionally, these results, compared with equilibrium constants estimated for **1a**,**b** ⇌ **2a**,**b** show significant shifts in the equilibrium positions towards the hydroxyl and thiol structures upon the introduction of the 2-pyrrolyl group at the 6-position. The differences in these shifts, which is more significant for the pyridazinone **1c**, can be rationalized in terms of the effect of the electron-

excessive pyrrole ring upon the electron density at C(3), which has a greater effect on increasing its basicity of the more electronegative exocyclic O atom of **1c**, compared with the S atom of **1d**, while effectively reducing the acidity of both **2c** and **2d**.

Experimental Section

General Procedures. Electronic spectra of the neutral species were measured for *ca*. 4 x 10^{-5} M buffered aqueous solutions at pH 7.0 using a Pye Unicam SP8-UV-VIS spectrometer and the spectra of the mono- and di-cationic species were measured in sulphuric acid at H_o values indicated in Table 1. The pKa values for the conjugate acids of the tautomeric pyridazinone and thione and their O(S)- and N-alkylated derivatives (Table 2) were determined spectrophotometrically using buffered aqueous phosphate solutions or aqueous sulphuric acid of known H_o using standard procedures.[12]

The syntheses and analytical characterization of the tautomeric systems, **1c,d** ⇌ **2c,d**, their fixed form systems **8c,d** (R' = Et) and **9c** (R' = Et),**d** (R' = Me), and 3-ethoxy-2-ethyl-6-(2-pyrrolyl)pyridazinium tetra-fluoroborate **10** have been described in an earlier publication.[6] The structure of **10** was established unequivocally by single crystal X-ray analysis.[13]

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