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A STUDY OF PYRAZOLIN-5-ONE TAUTOMERISM—II
THE EFFECT OF 3-SUBSTITUENTS[1]

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Abstract—The IR and NMR spectra are reported for 4 potentially tautomeric 3-substituted-1-aryl-2-pyrazolin-5-ones. With three of the compounds the CH tautomer is predominant in the solid state, and also in solvents of widely different polarities such as CCl_4 or $CHCl_3$ and DMSO. With an ethoxycarbonyl substituent the CH form is not obtained in any of these media. Reasons for this behaviour are discussed.

INTRODUCTION

IN a previous paper[1] we reported a study of the tautomerism of some 1-aryl-2-pyrazolin-5-ones, two of which contained a 4-ethoxycarbonyl substituent. Generally, 2-pyrazolin-5-ones exist predominantly as the CH tautomer‡ in non-polar or low-polarity solvents, such as CCl_4 and $CHCl_3$. As the polarity of the solvent is increased, frequently a different tautomer or mixtures of tautomers are obtained. In the solid state, additional tautomeric forms are likely, owing to the possibility of strong H-bonding and these compounds are not usually present in the CH form. In the case of 1-aryl-4-ethoxycarbonyl-2-pyrazolin-5-ones in $CHCl_3$, we found previously that the NH form was present, but not the OH form which had been expected because in this case conjugate chelation could then be obtained between the OH of the pyrazolone ring and the ester CO group.

We now report results for some compounds having the same tautomeric form despite changes in their environment.

RESULTS

NMR spectra

The method whereby NMR spectroscopy may be used to distinguish the CH tautomer from the other possible tautomers has already been described.[1] In the case of 3-substituted pyrazolinones however there is no 3-H present, so that the multiplicity of the signal due to the interaction of this proton with the 4-H cannot be used to reinforce the conclusions reached by measurement of the chemical shift of the 4-proton(s). The results obtained for a number of 3-substituted pyrazolinones in deuterochloroform solution are shown in Table 1. It will be seen that, with the exception of compound **1** which has a 3-ester substituent and exists mainly in the OH or NH form, the CH form is generally favoured in this solvent. These observations are in agreement with those reported for 1-aryl-2-pyrazolin-5-ones without further substituents.[1]

The results obtained in DMSO-d_6 for the same compounds are shown in Table 2, and here the behaviour observed contrasts strongly with that previously found for pyrazolinones without 3- or 4- substituents. In the earlier work[1] it was found that in

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‡ For the nomenclature of the tautomers see Ref. 1.

TABLE 1. NMR SPECTRA OF 3-SUBSTITUTED 1-ARYL-2-PYRAZOLIN-5-ONES IN $CDCl_3$

Compound	Ar	R	Chemical Shift of H_4^a	Comments
1	C_6H_5	CO_2Et	3·73	CH (~30%)
			6·03	NH or OH
2	C_6H_5	NH_2	3·48	CH
3	2,4,6,-$Cl_3C_6H_2$	NH_2	3·45	CH
4	2,4,6,-$Cl_3C_6H_2$	OEt	3·44	CH

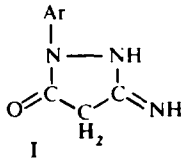
[a] Expressed in ppm downfield from internal TMS.

TABLE 2. NMR SPECTRA OF 3-SUBSTITUTED 1-ARYL-2-PYRAZOLIN-5-ONES IN DMSO-d_6

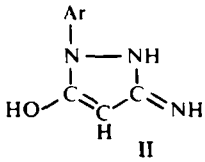
Compound	Ar	R	Chemical Shift of H_4^a	Comments
1	C_6H_5	CO_2Et	6·01	OH or NH
2	C_6H_5	NH_2	3·61	CH
3	2,4,6-$Cl_3C_6H_2$	NH_2	3·57	CH
4	2,4,6-$Cl_3C_6H_2$	OEt	3·90	CH (+ small amount OH or NH)

[a] Expressed in ppm downfield from external TMS.

this solvent the OH form existed almost exclusively but with these compounds, with the sole exception of compound 1 (having the 3-ester substituent), the CH form is obtained.



I



II

In the case of compounds 2 and 3 which both have 3-amino substituents two additional tautomeric forms (I and II) can be written. The observed spectra would eliminate the possibility that either compound exists in form II in $CDCl_3$ or DMSO-d_6, since the chemical shifts of the protons in the 4-position are in each case inconsistent with them being vinylic in nature. Form I cannot be completely excluded on NMR evidence alone, because although in all cases a single NH signal (intensity 2H) is observed, in $CDCl_3$ this could result from exchange averaging between the two sites in form I. The IR spectroscopic evidence (next section), however, clearly indicates that forms I or II are not predominant in the tautomeric equilibrium.

IR spectra

As reported previously[1] the two regions of principal interest are 3500–2000 cm^{-1} and 2000–1500 cm^{-1}. The IR spectra obtained from compound 1 examined in $CHCl_3$, in the solid state, and in DMSO are shown in Fig. 1. The results are almost identical.

A strong CO absorption is observed near 1720 cm^{-1} together with sharp phenyl ring "breathing" modes at 1600 cm^{-1} and 1500 cm^{-1}; The band at 1565 cm^{-1} is the ν C=C and/or ν C=N of the pyrazolone ring. The presence of some OH or NH form is indicated by the broad absorption with a max near 3000 cm^{-1}. In the CH form the two CO frequencies i.e. ring CO and $\alpha\beta$ unsaturated ester would be expected to occur with approximately coincidental or overlapping values of about 1720 cm^{-1} in $CHCl_3$. In the NH form, the absorption due to the $\alpha\beta$ unsaturated ring CO would be expected near 1670 cm^{-1}, but there is no strong evidence of this as is shown in Fig. 1. In DMSO

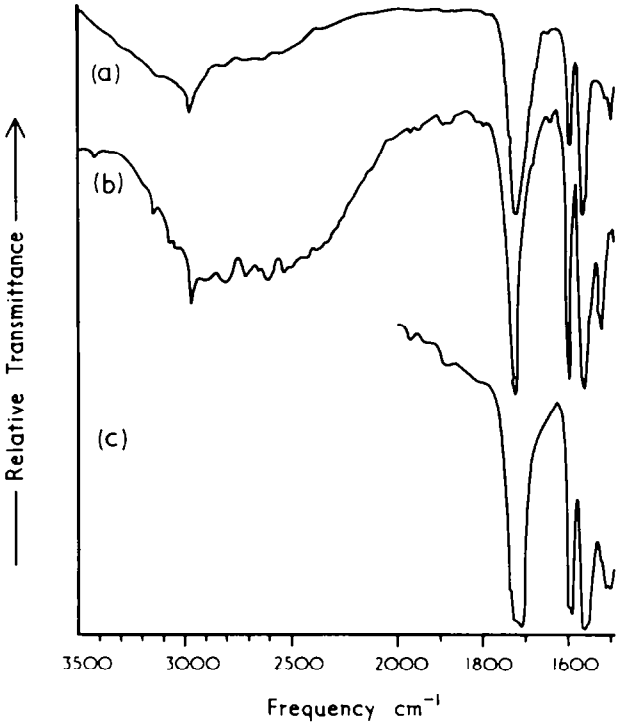


FIG. 1 IR spectra of 3-ethoxycarbonyl-1-phenyl-2-pyrazolin-5-one: (a) in $CHCl_3$; (b) solid state; (c) in DMSO.

the CO absorption frequency is strong and broad and there may be some intermolecular H-bonding between this group and the ring OH. Both in $CHCl_3$ and DMSO solvents the OH form is found but the presence of some CH form is not excluded.

Protonation must occur at the ring CO group because it is not possible to write a satisfactory structure with the ester CO protonated. In the solid state very strong intermolecular H-bonding is indicated by the multiplicity of broad bands with a max at the low frequency of ca. 2600 cm^{-1}. The CO band is extremely sharp and is found at a rather high frequency for the solid state. Its value is in good agreement with that obtained in $CHCl_3$ and it suggests that the CO group is relatively unperturbed. The CO absorption is thus assigned to ν C=O ester and its sharpness further indicates that there is no CH form present. The strong H-bonding is thus of the type —OH.... N

or alternatively proton transfer may occur. Furthermore the spectrum of the solid in the 1800–1400 cm^{-1} region differs from that observed in 4-ethoxycarbonyl-1-phenyl-2-pyrazolin-5-one in which an intramolecular chelate H-bonded tautomeric equilibrium was proposed.[1]

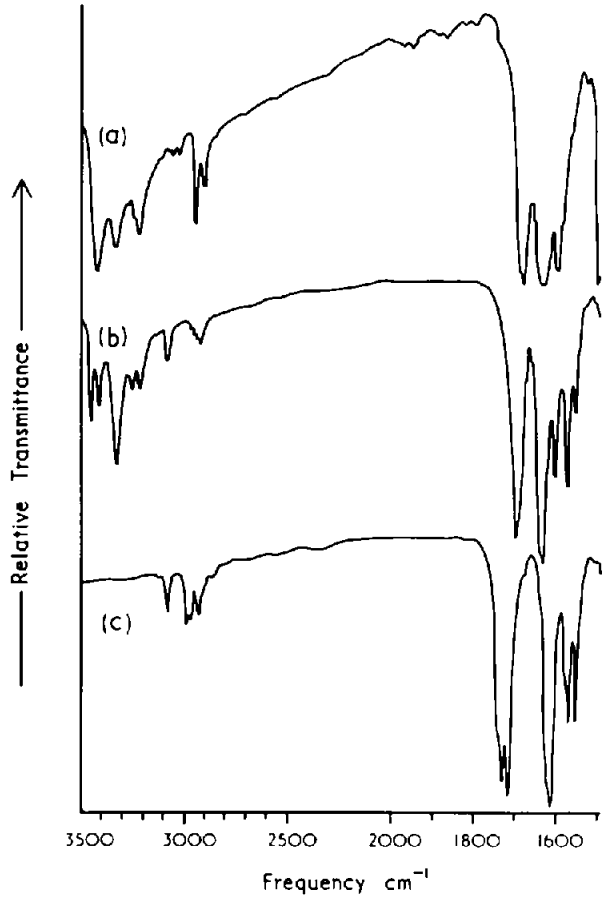
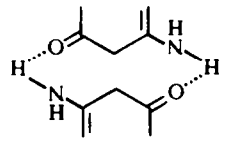


FIG. 2 Solid state IR spectra of (a) 3-amino-1-phenyl-2-pyrazolin-5-one; (b) 3-amino-1-(2',4',6', trichlorophenyl)-2-pyrazolin-5-one; (c) 3-ethoxy 1-(2',4',6', trichlorophenyl)-2-pyrazolin-5-one.

Individually, compounds **2**, **3** and **4** have very similar spectra when examined in $CHCl_3$, DMSO, and the solid state. The results of the solid state examination are shown in Fig. 2. The spectrum of compound **2** is remarkably simple in the 1600–1500 cm^{-1} region, comprising two phenyl ring vibrations. The δ NH_2 scissors vibration absorbs at 1635 cm^{-1} and was assigned on the basis of deuteration studies. The position of the CO band (1685 cm^{-1}) indicates that it is H-bonded in the solid. Above 3200 cm^{-1} the three distinct peaks are assigned in order of decreasing frequency to the asymmetric, symmetric, and H-bonded NH_2 stretching vibrations. Primary amines should only produce two peaks but the presence of three absorptions, particularly in the solid state, is well known,[2, 3] The two highest frequencies obey the Bellamy-Williams rule,[4] and the assignment of these frequencies was established by means of deuteration.

In compound **3** a ring CO absorption is always observed and the spectrum is consistent with that expected from the CH tautomer. Some H-bonding from the amino groups to the CO groups is evidenced by the shifts in ν C=O frequencies in the solid compared with those obtained from chloroform solution. The symmetrical nature of the NH_2 stretching vibration bands is remarkable. The shape is consistent with polymeric association through strong intermolecular H-bonding and is markedly different when compared with that normally observed for pyrazolin-5-ones in the solid state. Formation of a dimer (III) is quite likely.

III 

With compounds **2** and **3** the imino structures (I and II) are eliminated because of the position, intensity and number of bands observed for the NH_2 stretching and NH_2 scissors vibrations.[5] Furthermore, in chloroform solution only two NH_2 stretching vibrations are observed (3500 and 3407 cm^{-1}) and these obey the Bellamy-Williams equation.[4]

TABLE 3

Compound	νOH	νC = O	Other frequencies 1625–1500 cm^{-1}	Media
1	~3000 (m, b)	1720 (s)	1596 (m) 1565 (s) {1510 (w), 1500 (mw)}	$CHCl_3$
	~2500 (mb)	1723 (s)	1597 (s) 1562 (s) 1520 (m)	Solid
	N.I.	1720 (s, b)	1595 (s) 1562 (s) {1520, 1510} (m,d)	DMSO
	νNH_2^a		δNH_2^a	
2	3400 (vs, b)		1694 (m) 1640 (s) 1596 (m) 1499 (m)	$CHCl_3$
	3421 (m) 3330 (m) 3213 (m)		1681 (s) 1630 (s) 1595 (s) 1522 (vw) 1497 (s)	Solid
	N.I.		1695 (s) 1646 (s) {1612 (m), 1594 (s)} 1495 (s)	DMSO
3	3500 (m) 3407 (m)		1713 (s) 1635 (s) 1600 (w) 1572 (m) 1550 (m)	$CHCl_3$
	3450 (m) 3407 (m) 3325 (ms) 3248 (m) 3210 (m)		1698 (s) 1632 (s) 1600 (m) 1571 (m) 1550 (m)	Solid
	N.I.		1710 (s) 1640 (s) 1600 (ms) 1570 (ms) 1549 (m)	DMSO
4			1746 (vs) 1622 (vs) 1577 (m) 1556 (m)	CCl_4
			{1740 (sh), 1725 (vs)} 1617 (vs) 1575 (m) 1554 (m)	$CHCl_3$
			{1728, 1714} (vs, d) 1612 (vs) 1569 (m) 1550 (m)	Solid
			1723 (vs) 1610 (vs) 1570 (s) 1550 (m)	DMSO

Intensities—s, strong; m, medium; w, weak; v, very; b, broad; sh, shoulder; d, doublet.
N.I.—region not investigated.
[a] Assignment established by means of deuteration.

When compound **4** is examined in CCl_4 and $CHCl_3$ the flat background in the 3600–1750 cm^{-1} (except for absorptions due to CH vibrations) indicates the presence of the CH form.

The IR absorption frequencies of these compounds, examined in the region 3600–1500 cm^{-1}, are shown in Table 3.

DISCUSSION

We have found in this and in previous work that the presence of an ester substituent in the 3- or 4- position of a pyrazolin-5-one ring produces unexpected results. With a 4-ethoxycarbonyl substituent the OH form was expected to be favoured because an intramolecular chelate structure could be formed. In $CHCl_3$ the evidence indicated the presence of the NH form. With a 3-ethoxycarbonyl substituent chelation would be expected in the NH form but in fact the OH form appears to be present in $CHCl_3$. However, in this case, models seem to indicate that an intramolecularly H-bonded NH form would not be very stable. Although this would be a 5-membered ring and therefore usually favoured, considerable steric strain is introduced because it is fused to another 5-membered ring. With a 4-ester substituent in the OH form a far less strained 6-membered chelate ring could be formed.

The only other evidence we have found in the literature of an ester substituent in a pyrazolinone ring is the special case of 3-ethoxycarbonyl-1-phenyl-4-phenylazo-2-pyrazolin 5-one.[6,7] Here, a type of CH form (the phenylhydrazone form) was found in which chelation could still occur.

We believe that the presence of substituents in the 3-position of the pyrazolinone ring can influence the ease with which tautomeric changes occur. When one considers the electronic influence of substituents on the tautomeric equilibrium, the results reported here, and elsewhere[1,8–10] form a fairly clear pattern (Table 4). Strongly electron-attracting or electron-releasing groups in the 3- or 4- position of the pyrazolinone ring tend to lead to the preference of one tautomeric form which is more or less insensitive to influences exerted by the media. In the case of electron-attracting groups the preferred tautomer is the OH form, whilst for electron-releasing groups it is the CH form. In the absence of a 3- or 4- substituent, or when one is present which has only weak electronic effects, the preferred tautomer depends largely upon the medium.

The observed behaviour may be accounted for either by assuming that the most thermodynamically stable tautomer always predominates and that relative stability is determined mainly by the electronic effects of substituents, or by assuming that under certain circumstances a relatively less stable tautomer can persist in solution because equilibration is either very slow or effectively prevented. In the case of keto-enol tautomerism it is well known[11,12] that electron-attracting substituents can greatly enhance the rate of ionization by stabilizing the resulting anion, thus the rate of ionization of acetyl acetone is faster than that of acetone itself by a factor of more than 10.[8] A similar effect in the pyrazolinone series could result in the rate at which the tautomeric equilibrium is established being suppressed to such an extent that the form which is preferred in the solid state would persist in solution for a considerable time. Katritzky and Maine[13] demonstrated that equilibration can be slow in the pyrazolinone series because solutions of 3,4 dimethyl-1-phenyl-2-pyrazolin-5-one required approximately one week to come to equilibrium. However, this compound

which contains two weak electron-releasing groups gave the CH form on standing, which is in agreement with the results reported here for electron-releasing groups, and suggests that the preference for the CH form is due to its high relative stability rather than to slow equilibration. This is supported by the fact that the IR spectra of

TABLE 4. THE EFFECT OF 3-SUBSTITUENTS ON THE TAUTOMERIC FORM OF 1-ARYL-2-PYRAZOLIN-5-ONES.

(a) Electron-Attracting Substituents.

Substituent 1	Substituent 3	Medium	Tautomer	Reference
C_6H_5	CO_2Et	DMSO, Solid	OH	This work
		$CDCl_3$	OH + some CH	

(b) No Substituent.

Substituent 1	Substituent 3	Medium	Tautomer	Reference
C_6H_5	H	$CHCl_3$	CH	
		DMSO	OH	
		Solid	OH/NH	Newman and
O-$NO_2C_6H_4$	H	$CHCl_3$	CH	Pauwels[1]
		DMSO	OH	
		Solid	OH/NH	

(c) Electron-Releasing Substituents.

Substituent 1	Substituent 3	Medium	Tautomer	Reference
2,4,6-$Cl_3C_6H_2$	OEt	CCl_4, $CHCl_3$DMSO, solid	CH	This work
2,4,6-$Cl_3C_6H_2$	NH_2	$CHCl_3$, DMSO, solid	CH	This work
C_6H_5	NH_2	$CHCl_3$, DMSO, solid	CH	This work
C_6H_5	NHC_6H_5	$CHCl_3$, DMSO, pyridine	CH	Lestina *et al.*[9]
C_6H_5	CH_3	$CHCl_3$, CCl_4, C_6H_{12}	CH	
		DMSO	OH + CH	Newman and
		Solid	OH + NH	Pauwels,[1]
		Dioxan	90% CH	Elguero *et al.*[10]
		CH_3CN	CH + OH	
CH_3	CH_3	CCl_4, $CHCl_3$, C_6H_{12}	CH	
		Pyridine	OH + trace CH	
		Solid	OH/NH	
H	CH_3	$CHCl_3$	CH	
		C_6H_{12}	85% CH	Elguero *et al.*[10]
			15% OH	
		Pyridine, CH_3CN	OH	
		Solid	OH/NH	

compound 2 in $CHCl_3$, and DMSO solutions remained unchanged for a period of more than a week. It thus seems probable that substituents influence the tautomeric equilibrium by affecting the relative stabilities of the three possible tautomers. Hence it seems likely that the presence of strongly electron-attracting 3- or 4- substituents

reduces the electron density on the heterocyclic ring thus favouring ionization (cf keto-enol tautomerism). Conversely, strongly electron-releasing substituents stabilize the CH form because of the increasing electron density in the ring. These electronic effects are sufficiently strong for the effect of the medium to be relatively insensitive.

In the case of pyrazolinones (Table 4) with no 3- or 4- substituent, or with only a single methyl substituent, it is readily understood why medium effects should predominate. Such compounds are clearly intermediate between the cases discussed above and, as such, would be expected to show a less marked preference for a given tautomeric form. It is interesting to note that the OH form tends to be preferred in polar solvents; this is the reverse of what is normally observed in keto-enol tautomerism, where the enol form is usually favoured in non-polar solvents. This behaviour indicates that in pyrazolinones the OH form is more polar than the CH form, which is a reflection of the inability of the former to form intramolecular hydrogen bonds.

EXPERIMENTAL

NMR spectra were determined for 2–5% solns at 100 MHz with a Varian HA-100 spectrometer, and IR spectra were recorded on Perkin–Elmer 257 and 225 instruments. The solid-state spectra were determined from dispersions in mineral oil, and in hexachlorobutadiene. Similar results were obtained from samples pressed in KBr.

Preparation of compounds

Compounds **1**, **3** and **4** were kindly supplied by our colleagues Mr. J. Bailey and Dr. D. Stanway. Compound **2** was a commercial sample (K and K Laboratories) which was recrystallized from hot water.

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