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THE TAUTOMERISM OF HETEROAROMATIC COMPOUNDS WITH FIVE-MEMBERED RINGS—IX[1]

N-UNSUBSTITUTED PYRAZOLIN-3(5)-ONES

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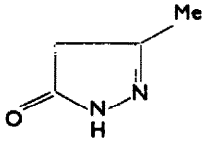
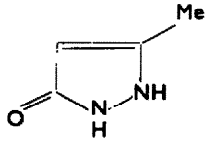
Abstract—The complex tautomerism of N-unsubstituted pyrazolin-3(5)-ones has been elucidated by UV spectroscopy and basicity measurements. For aqueous solution (polar medium) the stability of the forms is II > IV ⩾ III, I whereas for cyclohexane solution (nonpolar medium) the order is IV > I ⩾ II, III.

PREVIOUS papers have considered the tautomerism of 1-substituted pyrazolin-3-ones[2] and 1-substituted pyrazolin-5-ones.[3] The tautomeric possibilities in the corresponding N-unsubstituted derivatives are more complicated: in particular the distinction between the 3- and 5- one series disappears. The best discussion so far of this tautomerism has been given by Refn;[4] however, her limited data did not allow her to reach firm conclusions, e.g. the relative importance of hydroxy forms of types III and IV was not distinguished. The principal tautomeric forms are illustrated by formulae (I–IV), but other possibilities occur, such as V and VI.



I



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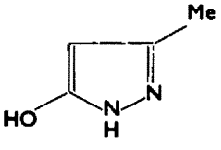

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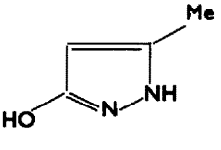
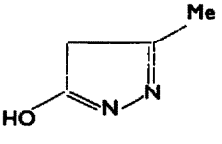
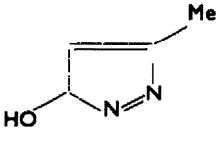


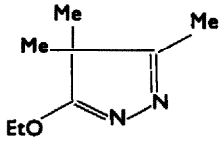
IV



V



VI

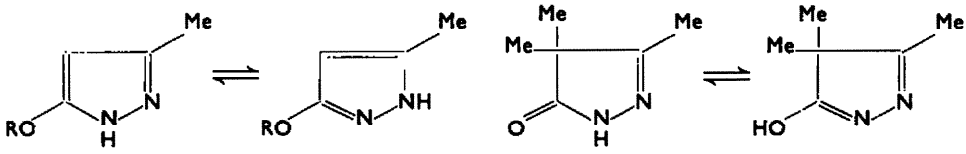


VII

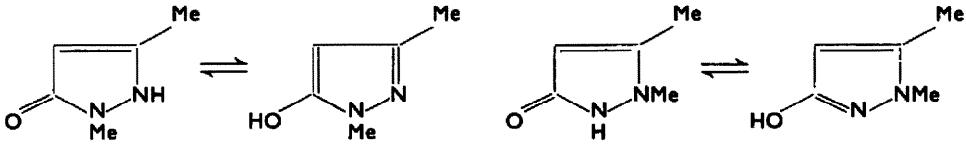
However, the fixed analogue (VII) of form V is quite unstable and rapidly oxidized in air, and VI is a type of carbinol–amine. As the tautomeric derivatives are reasonably stable in air, and do not show carbinolamine properties, it is concluded that forms other than those of type I-IV inclusive play no important part in the tautomeric equilibrium. Further evidence for this conclusion is considered later.

[1] Part VI A. R. Katritzky and B. Wallis, *Tetrahedron* in press.
[2] A. R. Katritzky and F. W. Maine, *Tetrahedron* **20**, 315 (1964).
[3] A. R. Katritzky and F. W. Maine, *Tetrahedron* **20**, 299 (1964).
[4] S. Refn, *Spectrochim. Acta* **17**, 40 (1961).

As previously, this series has been investigated by comparison of basicities and spectra of the potentially tautomeric compounds with methylated derivatives of fixed structure. Partially alkylated compounds (VIII, R = Me, Et; IX) in which limited tautomeric possibilities occur were also studied. The results previously obtained for the equilibria Xa ⇌ Xb[3] and XIa ⇌ XIb[2] are also relevant.



VIIIa VIIIb IXa IXb



Xa Xb XIa XIb

Preparation of compounds was by literature methods except for 5-ethoxy-3,4,4-trimethyl-(4H)-pyrazole (VII) which was obtained from the 3,4,4-trimethylpyrazolin-5-one and triethyloxonium fluoroborate; it was too unstable for analysis, but was characterized by the NMR spectrum.

3,4,4-*Trimethylpyrazolin-5-one* (IX). The IR spectrum of this compound shows that it exists in the lactam form (IXa). This conclusion was previously reached for the solid state spectrum by Refn.[4] A strong carbonyl peak is shown in chloroform at 1715 cm^{-1}, which occurs as a doublet at 1734 and 1718 cm^{-1} in carbon tetrachloride. The 0·2 M solution in chloroform shows free [3426 cm^{-1} (ε = 40)] and bonded NH bands [3235 cm^{-1} (30)]. The spectrum as a whole shows a strong resemblance to that of 1,3,4,4-tetramethylpyrazolin-5-one.[3] The NMR spectrum (in chloroform) shows the 4-position methyls at τ8·77, the 3-methyl at τ7·99 and a broad band at τ0·2 for the NH.

3-*Methyl-5-ethoxypyrazole* (VIII, R = Et) and the 5-methoxy analogue are shown by the spectral evidence to exist in the 2H-forms (VIIIb). The IR spectra of these compounds and those of the two fixed derivatives are given in Table 1. Although the differences are not large, there is definitely a greater resemblance of VIII to its 2-methyl derivative than to the 1-methyl analogue.

The UV spectrum of 3-methyl-5-ethoxypyrazole in cyclohexane shows a maximum at 217 mμ (ε = 4800). The 1- and 2-methyl derivatives show their maxima at <210 mμ and 225 mμ (ε = 5500) respectively. Since N–methylation is likely to cause a bathochromic shift, this provides further evidence for the predominance of the 2H-form (VIIIb). The UV spectra of all these compounds in aqueous solution are too similar for conclusions, but comparison of the basicity of 1,3-dimethyl-(+3·51)[3] and 2,3-dimethyl-5-ethoxypyrazole (+2·05)[2] indicates that the 2H-form (VIIIb) of the tautomer should be preferred in aqueous solution by a factor of ca. 30.

In the NMR spectra (of chloroform solutions) of the 3-methyl-5-alkoxypyrazoles, the 3-methyl group (at τ7·80–7·83) is coupled with the proton at the 4-position (τ4·56–4·64) by ca. 1 c/s; this is further evidence for a 3,4-double bond and thus for the

TABLE 1. INFRA-RED SPECTRA OF ALKOXYPYRAZOLES

Substits.					Conc.	Ring		Ring		OEt		Ring		?		OEt		?	
1	2	3	5	Phase	M	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A
Me	—	Me	OEt	$CHCl_3$	0·2	1562	340	1527	120	1486	75	1453	65	1425	75	1398	175	1369	45
—	Me	Me	OEt	CCl_4	0·2	1564	200	1501	260	1479	185	1447	100	—		1386	140	1359	135
—	—	Me	OEt	$CHCl_3$	0·2	1583	145	1500	150	1474	130	1448	80	—		1390	90	1360	75
—	—	Me	OMe	$CHCl_3$	0·2	1584	160	1508	150	1465	70	1444	70	1417	110	—		—	

OEt		?		?		?		OEt		OEt		?		?		OEt		?	
cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A
1277	65	1198	100	1165	45	1111	30	1092	25	1048	95	1010	55	—		915	25	898	10
1288	30	1188	45	1154	75	1117	20	1092	25	1058	85	1038	55	972	10	—		897	25
1277	65	1171	55	1150	50	1111	20	1092	30	—		1042	90	996	30	911	25	892	30
1280	50	1195	30	1155	45	1117	15	1088	20	1056	35	1034	90	985	30	—		—	

TABLE 2. ULTRA-VIOLET SPECTRA OF PYRAZOLINONES

Compound no.	3-Methylpyrazolin-5-one substituents at position[a]				Possible structure types		Ultra-violet spectral maxima (mμ) in aqueous buffer			in cyclohexane		p*Ka*
	1	2	4	5				λ	(ε)	λ	(ε)	
1	Me		Me_2		I			248	(3700)	250	(4300)	−3·8
2	Me	Me	H		II			247	(9600)	257	(9300)	2·22
3	Me		H	OEt	III			219	(5870)	219	(4800)	3·5
4		Me	H	OEt	IV			221	(6300)	225	(5500)	2·05
5	Me		H		I, II, III	II	I	241	(8000)	251	(4040)	2·35
6		Me	H		II, IV	II + IV	IV	245	(6700)	227	(5500)	2·57
7			Me_2		I (or V)	I	I	238	(4800)	241	(5100)	—
8			H	OEt	III, IV	IV	IV		[b]	217	(4800)	—
9			H		I, II, III, IV			238	(7600)	220	(3700)	2·80
10			Me		I, II, III, IV			246	(9350)	227	(3100)	2·68
11			$—(CH_2)_3$-3		I, II, III, IV			245·5	(9000)	250	(1000)	2·76
12			$—(CH_2)_4$-3		I, II, III, IV			246	(9250)	229 250	(3300) (2100)	2·61

[a] All compounds except Nos. 11 and 12 have a methyl group in the 3-position.

[b] End adsorption only.

occurrence of form VIIIb. The NH absorption occurs as a broad band at low field ($\tau -1{\cdot}2$ to $-1{\cdot}4$) reflecting strong hydrogen bonding and indicating that these compounds are largely dimerized in solution.

3-Methylpyrazolin-5-one. Previous work would lead us to expect the following order of stability between the possible forms (I–IV):-

for polar media (H_2O, solid state)	*for nonpolar media* (cyclohexane chloroform)
II $\gg$ III > I	I $\gg$ II > III (Ref. 3)
II > IV	IV $\gg$ II (Ref. 2)
IV $\gg$ III	IV $\gg$ III (preceding paragraph)

Hence, for the compounds under discussion, for which all forms are possible, we should expect to find:-

II > IV $\gg$ III > I for polar media.
IV $\approx$ I $\gg$ II > III for nonpolar media.

The spectral and basicity data obtained (Table 2) for these compounds can indeed most reasonably be explained on this basis.

The UV spectrum of 3-methylpyrazolin-5-one in cyclohexane is compared in Fig. 1 with those of the four fixed compounds. It may be seen that the spectra can be interpreted on the basis of forms IV:I in a ratio of approximately 5:1.

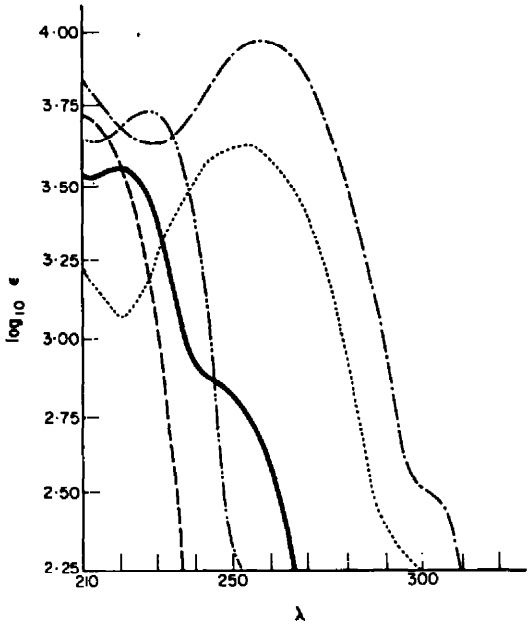


FIG. 1. Ultra-violet spectra in cyclohexane:

3-Methylpyrazolin-5-one	———
1,3-Dimethyl-5-ethoxypyrazole	– – – – –
1,5-Dimethyl-3-ethoxypyrazole	– · · – · · –
1,2,3-Trimethylpyrazolin-5-one	– · – · – · –
1,3,4,4-Tetramethylpyrazolin-5-one	· · · · · · · · ·

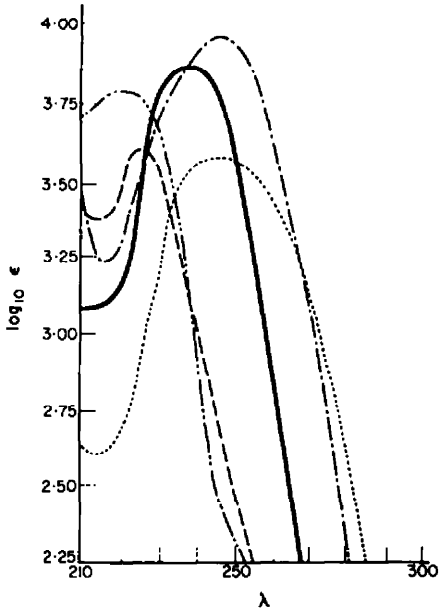
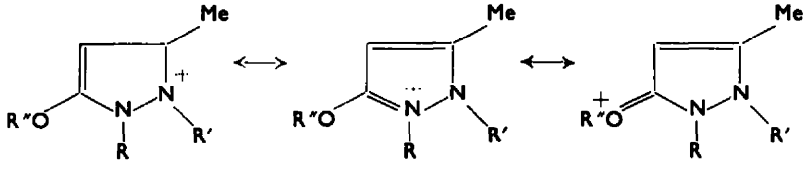


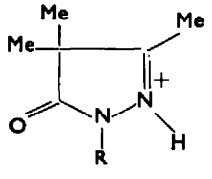
FIG. 2. Ultra-violet spectra in aqueous buffers:

3-Methylpyrazolin-5-one	(pH 5·2)	———
1,3-Dimethyl-5-ethoxypyrazole	(pH 4·4)	– – – – –
1,5-Dimethyl-3-ethoxypyrazole	(pH 7)	– · · – · · –
1,2,3-Trimethylpyrazolin-5-one	(pH 5)	– · – · – · –
1,3,4,4-Tetramethylpyrazolin-5-one	(pH 5)	· · · · · · · ·

Spectra for aqueous solutions are given in Fig. 2. It is obvious that form II predominates under these conditions, and it probably is present to the extent of about 80% from the extinction coefficients. From the UV spectra, the minor component present could be any of the other forms. The basicity measurements may now be used to elucidate further the tautomeric composition. Spectra of cationic forms in sulphuric acid (Table 2) show that all three compounds form cationic species of type XII, except for the 4,4-dimethyl derivative, which perforce forms cations of another type (probably XIII).

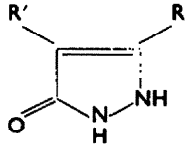


XII



XIII

The measured pK compound XI is 2·57 and in aqueous solution it exists ca. 70:30 in forms XIa and XIb.[2] These data allow calculation of the intrinsic pK value of XIa and XIb as 2·71 and 3·09 respectively. Compound X exists very predominantly as Xa and the measured[3] pK of 2·35 is therefore a good approximation for that of Xa. These results, and the measured value of 2·22 for 3-methyl-1,2-dimethylpyrazolin-5-one, indicate that in the 3-methylpyrazolin-5-one series methylation at the 1- and 2-position causes base weakening of 0·13 and 0·49 pK units, respectively. Assuming that such effects are additive, the intrinsic pK of form II of 3-methylpyrazolin-5-one would be 2·84. The measured value is 2·80, indicating that the compound does indeed exist largely in form II. Similar reasoning indicates that the proportions of forms IV and III will be ca. 15% and <5%, respectively.



XIV

The remaining tautomeric compounds. We have also examined 3,4-dimethyl- (XIV; R = R' = Me) 3,4-trimethylene- [XIV; R, R' = $(CH_2)_3$] and 3,4-tetramethylene-pyrazolin-5-one [XIV; R, R' = $(CH_2)_4$]. In aqueous buffers, the UV spectra closely resemble those of the 3-methyl analogue, and this and the pK values (Table 2) indicate that in aqueous solution their tautomeric composition also resembles the 3-methyl derivative. In cyclohexane solution there is also qualitative agreement, although the proportions of form of type I and IV present vary.

Due to poor solubility, IR spectra could be obtained only in the solid state, and thus served only to indicate that the compounds did not exist in the CH-form (I). NMR spectra were not obtainable.

EXPERIMENTAL

Compounds were prepared by literature methods, recrystallized before measurement, and had m.ps in agreement with quoted values.

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