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THE TAUTOMERISM OF HETEROAROMATIC COMPOUNDS WITH FIVE-MEMBERED RINGS—VII[1,2]

ISOXAZOLIN-3-ONES*—3-HYDROXYISOXAZOLES

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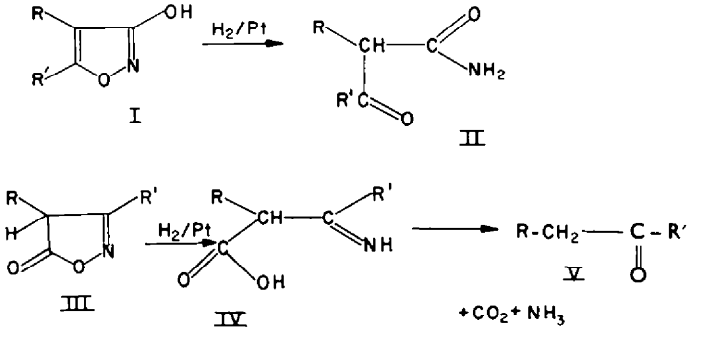
Abstract—The preparation of some 3-hydroxyisoxazoles from β-keto-esters and the proof of their structure is described. These compounds are shown to exist largely in the hydroxy form.

INVESTIGATION[1,3] of the tautomerism of isoxazolin-5-ones has shown that these compounds exist in the CH and/or the NH form depending on their structure and the dielectric constant of the medium: the OH form is not important unless stabilized by chelation. The product[4] from the reaction of methylacetoacetic ester and hydroxylamine is a hydroxy-compound.[3] If it were an isoxazolin-5-one derivative it would be an exception to the above generalizations; we therefore suspected that it might be an isoxazolin-3-one derivative, (I, R = R′ = Me) and proved this by reduction to α-methylacetoacetamide (II, R = R′ = Me). Reductions of isoxazolin-5-ones (III)



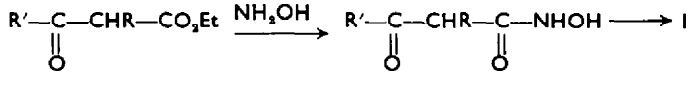
yield ketones (V).[1,5] Further, ethyl cycloheptanone-2-carboxylate and hydroxylamine yield 3-hydroxy-4,5-pentamethyleneisoxazole as shown by its hydrogenation to cycloheptanone-2-carboxamide. The product[4] from ethylacetoacetic ester is also a 3-hydroxyisoxazole on spectral evidence (see later). It follows that compounds

* *Chem. Abstr.* nomenclature. In previous papers of this series the oxo-compounds have been referred to as isoxazolones.

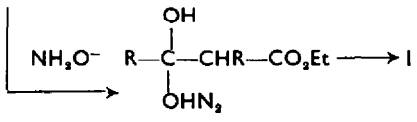
[1] Part V, A. R. Katritzky and F. W. Maine, *Tetrahedron* **20**, 315 (1964); Ref. 2 is considered as Pt. VI.
[2] A preliminary account of some of the present results has appeared in *Proc. Chem. Soc.* 387 (1961).
[3] A. J. Boulton and A. R. Katritzky, *Tetrahedron* **12**, 41 (1961).
[4] R. Uhlenhuth, *Liebigs Ann.* **296**, 33 (1897).
[5] L. Panizzi, *Gazzetta*, **76**, 44 (1946).

prepared by the action of diazoalkanes on 4, 5-dimethyl-3-hydroxyisoxazole, and previously[3,6] formulated as 5-alkoxy-3, 4-dimethyl derivatives are actually 3-alkoxy-4, 5-dimethylisoxazoles.

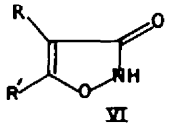
3-Hydroxyisoxazoles may be produced from β-keto-esters by routes which could involve initial attack on the ester (e.g. i) or the keto-group (e.g. ii). Keto- or enol-forms (or, less probably, enolate anions) of the β-keto-ester could react.



(i)



(ii)



VI

3-Hydroxyisoxazoles are tautomeric with isoxazolin-3-ones (VI). The first 3-hydroxyisoxazole to be recognised as such, the 5-phenyl derivative, was prepared by Quilico *et al.* by another route.[7] It was considered to exist in the hydroxy-form because of the similarity of its IR and UV spectra to those of the corresponding methoxy-derivative. Subsequently, the same group prepared derivatives fixed in the isoxazolin-3-one form.[8] Isoxazolin-3-ones have also been prepared by Stachel.[9]

Preparation of compounds. 3-Methoxy- and 3-ethoxy-5-phenylisoxazole, 2-methyl- and 2-ethyl-5-phenylisoxazolin-3-one, and 2, 4, 5-trimethylisoxazolin-3-one were made following the Italian workers.[7,8] 3-Hydroxy-4, 5-pentamethylene-isoxazole was made analogously to the 4,5-dimethyl derivative, and the preparation of the other compounds described in this paper has been given earlier.[2–4]

Ultraviolet spectra (Table 1). In water, the 4, 5-dialkyl-3-hydroxyisoxazoles, and the compounds of fixed structure of both types, have very similar spectra, and no definite conclusions regarding tautomeric composition can be drawn from them. Cyclohexane solutions show a distinct hypsochromic shift (-9 to -13 mμ) in the methoxy- and the tautomeric compounds, but a bathochromic shift ($+11$ mμ) in the N-methyl compound, as compared to the spectra in water. These spectra indicate the predominant occurrence of the 4, 5-dialkyl-3-hydroxyisoxazoles as such in cyclohexane. The unusual hypsochromic shift in cyclohexane solution found on O-methylation is possibly connected with the fact that the hydroxy-compounds probably exist largely as dimers in solution.

The similarity of the UV spectra of the N- and O-substituted derivatives (Table 1,

[6] A. R. Katritzky and A. J. Boulton, *Spectrochim. Acta* **17**, 238 (1961).
[7] P. Bravo, G. Gaudiano, A. Quilico and A. Ricca, *Gazzetta*, **91**, 47 (1961).
[8] S. Cabbidu, G. Gaudiano and A. Quilico, *Gazzetta* **92**, 501 (1962).
[9] H. D. Stachel, *Chem. Ber.* **96**, 1088 (1963).

TABLE 1. ULTRAVIOLET SPECTRA

	Cyclohexane		Water		20 N H_2SO_4	
	$\lambda(m\mu)$	$\varepsilon \times 10^{-3}$	$\lambda(m\mu)$	$\varepsilon \times 10^{-3}$	$\lambda(m\mu)$	$\varepsilon \times 10^{-3}$
3-Hydroxy-4,5-dimethylisoxazole[a]	213	6·58	224	6·25[b]	236	8·64
3-Hydroxy-4-ethyl-5-methylisoxazole	214	6·60	224	6·25[c]		—
3-Hydroxy-4,5-pentamethyleneisoxazole	213	6·60	226	6·30[c]		—
3-Methoxy-4,5-dimethylisoxazole[a]	209	5·63	218	6·2	229	9·27
2,4,5-Trimethylisoxazolin-3-one	241	4·34	230[d]	7·61	227[d]	7·45
3-Hydroxy-5-phenylisoxazole[f]	262[e]	19·5	261[e,d]	19·9	277[d,g]	20·1
3-Methoxy-5-phenylisoxazole	260[d]	17·1	260[d]	21·1	279[d,g]	21·2
2-Methyl-5-phenylisoxazolin-3-one	261	14·5	264[d]	21·7	278[d]	19·8

[a] cf. Ref. 3; [b] phosphate buffer pH 2; [c] ·01 N H_2SO_4; [d] containing 5% ethanol; [e] peak with substructure (5–6 inflections); [f] in ·01 N NaOH λ_{max} 261 mμ (ε 20,000); [g] ca. 5 min after preparing solution.

TABLE 2. INFRARED SPECTRA OF ISOXAZOLES

Substituents			Phase[a]	Ring stretching modes								Ring def	
3	4	5		cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A
OMe	Me	Me[b]	$CHCl_3$	1666	125	1528	410	1480	220	1451	85	914	60
OH	Me	Me[b]	$CHCl_3$	1665	170	1537	350	(–)		1440	40	932	30
OH	Et	Me	nujol/HB	1660	s	1538	vs	1464	s	(–)		936	m
			CCl_4	1659	135	1537	230	1465	55	(–)		935	45
			$CHCl_3$	1658	135	1537	240	1465	50	(–)		937	40
OH	$-(CH_2)_5-$		nujol/HB	1657	s	1536	vs	(–)		(–)		945	m
			$CHCl_3$	1658	140	1535	320	(–)		( )		948	30
OMe	H	Ph	$CHCl_3$	1625	200	1520	250	1491	50	1454	240	935	100
OEt	H	Ph	$CHCl_3$	1625	165	1515	315	1492	45	1454	210	935	95
OH	H	Ph	$CHCl_3$	1627	220	1531	370	1484	65	1450	60	935	45

TABLE 3. INFRARED SPECTRA OF ISOXAZOLIN-3-ONES[d]

Substituent			Phase[a]	νC—O[c]		νC—C		Other ring modes					
2	4	5		cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A	cm^{-1}	ε_A
Me	Me	Me	$CHCl_3$	1657	1200	(–)		1136	30	1045	30	928	40
Me	H	Ph	$CHCl_3$	1667	1100	1629	230	1112	25	1048	40	910	100
Et	H	Ph	$CHCl_3$	1662	1000	1627	235	1120	30	1050	40	910	125

Footnotes to Tables 2 and 3:
[a] 0·2 M solution except as otherwise indicated; [b] Taken from Ref. 6; in this reference the compounds were erroneously considered to be 5-hydroxyisoxazole derivatives; [c] 0·04 M solutions.

and also Ref. 8) in the 5-phenyl series makes it impossible to estimate proportions of tautomers in this series, as was pointed out by Stachel.[9]

Infrared spectra. Bands characteristic of the ring[6] for the isoxazole compounds are recorded in Table 2; the detailed spectra of these compounds will be submitted to the D.M.S. scheme. The hydroxy-compounds all show strong broad absorption in the 3200–2400 cm^{-1} region, with ten or twelve peaks, indicating very strong hydrogen bonding for nujol mulls and for solutions in chloroform and carbon tetrachloride. 4,5-Dimethyl-3-hydroxyisoxazole was examined in dilute chloroform solution: at 0·02 M (1 mm cell) a weak band ($\varepsilon_A = 10$) appeared at 3550 cm^{-1} which became

TABLE 4. PROTON RESONANCE SPECTRA

Solvent	Substituents and Peak Positions (τ)			
	2	3	4	5
CCl_4	—	OH −2·03	Me 8·17	Me 7·78
Me_2SO	—	OH −0·90[c]	Me —	Me —
CCl_4	—	OH −1·80	Et CH_2 7·67[a], CH_3 8·85[b]	Me 7·75
Me_2SO	—	OH − [c]	Et —	Me —
Me_2SO	—	OH −1·40[c]	H 3·42	Ph 2·0–2·9
CCl_4	—	OMe 6·08	Me 8·26	Me 7·80
CCl_4	—	OMe 6·03	H 3·94	Ph 2·1–2·8
CCl_4	—	OEt CH_2 5·70[a], CH_3 8·61[b]	H 3·97	Ph 2·1–2·8
CCl_4	Me 6·67	:O	Me 8·29[d]	Me 7·87[d]
CCl_4	Me 6·51	:O	H 4·07	Ph 2·50
CCl_4	Et CH_2 6·09[a], CH_3 8·69[b]	:O	H 3·97	Ph 2·50

[a] quartet, [b] triplet, J = 7·0 c/s. [c] in dimethyl sulphoxide the 3-hydroxyl protons were broadened or, in the case of the 4-ethyl-5-methyl compounds absent. Clearly this solvent is not suitable for the investigation of protons more active than alcohol hydroxyl (for which it has recently been recommended[10]); [d] Peaks broadened and reduced in intensity, in comparison with the N-methyl peak, doubtless due to long-range coupling between the two groups.

considerably stronger ($\varepsilon_A = 40$) in 0·004 M solution (5 mm cell). This peak is assigned to the free OH group. It cannot be detected in similarly dilute tetrachloroethylene solutions—the chloroform evidently forms a weak hydrogen bond to the isoxazole nitrogen atom which helps to stabilize the monomer.

The most prominent feature of the isoxazolin-3-one spectra (Table 3) is the very strong band (ε_A 1000–1200) at 1667–1657 cm^{-1}. Absorption occurs in this region also in the 5-alkyl-3-hydroxy- and -3-alkoxy-isoxazoles, but at much lower intensity (ε_A 125–170). In the 5-phenyl-3-hydroxy- and -3-alkoxy- series this band is at somewhat lower frequency (1627–1625 cm^{-1}) and higher intensity (165–220), in the three compounds studied (see Table 2).

Basicity measurements. pK_a determinations, so far as they went, confirmed the predominance of the hydroxy-form of the isoxazolin-3-ones. The spectrophotometric method, in aqueous sulphuric acid, when applied to 3-methoxy-4,5-dimethylisoxazole and 2,4,5-trimethylisoxazolin-3-one, gave pK_a values of $-2{\cdot}08 \pm {\cdot}05$ and $-1{\cdot}36 \pm {\cdot}05$, respectively. These values imply a pK_t of $-0{\cdot}72 \pm {\cdot}07$, or a K_t of $5{\cdot}2 \pm {\cdot}9$, in favour of the hydroxy-form. As in no case has the NH-tautomer been detected, it seems likely that this is an underestimate of the true K_t value. The 2,4,5-trimethylisoxazolin-3-one was not very suitable for pK_a determination by the spectrophotometric method because there was only a small difference in ultraviolet spectrum between the protonated and neutral forms (Table 1).

In the 5-phenyl series, pK_a values were not obtained because the spectra of the acid and neutral forms of the N-alkylated compounds differed little. In addition, the alkoxy-forms decomposed in concentrated acid: the spectrum of a solution made up

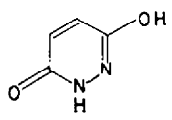
[10] O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.* **86**, 1256 (1964).

in 20 N H_2SO_4 and diluted to 5 N after standing for 20 min differed in peak position and intensity from one freshly made up in 5 N acid.

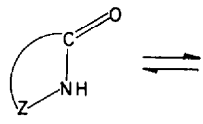
Proton magnetic resonance spectra. Data are collated in Table 4. The spectra showed no unexpected features, and served only to confirm the structures assigned. The sharpness of the peaks at about -2τ in carbon tetrachloride is good evidence for the OH structures in the tautomeric compounds. Their broadness or absence in dimethyl sulphoxide is not good evidence to the contrary, however; a more likely explanation is that the protons are exchanging more rapidly in this solvent.

CONCLUSIONS

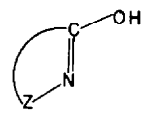
The foregoing results show that 3-hydroxyisoxazoles exist principally in the hydroxy-form. The majority of hetero-aromatic compounds with a potential hydroxy-group α or γ to a ring nitrogen atom occur predominantly in the oxo-form.[11] However, maleic hydrazide[12] (VII) and the 3-hydroxy-pyrazoles[1] are amongst other exceptions.



VII



VIII



IX

Compounds containing the system VIII $\rightleftharpoons$ IX (Z = O or NR) in a five- or six-membered monocyclic aromatic molecule may quite generally exist predominantly as IX: investigation of further such systems is in progress.

EXPERIMENTAL

Catalytic hydrogenation of 4,5-*dimethyl*-3-*hydroxyisoxazole*

The 3-hydroxyisoxazole (0·6 g) was shaken under H_2 in ethanol (20 ml) over PtO_2 (50 mg) at 20°/760 mm. During 30 min, 230 cc (ca. 0·95 mole) H_2 were absorbed, and the rate dropped off. The catalyst was filtered off, the solvent evaporated, and the residue crystallized from ether to give methylacetoacetamide (0·48 g, 53%), m.p. 77–78° and mixed m.p. 77–78° with an authentic specimen[13] m.p. 76–77° (lit.[13] m.p. 73°). IR spectra of the two samples also proved their identity.

4-*Ethyl*-3-*hydroxy*-5-*methylisoxazole*, colourless prisms, m.p. 49–50° (lit.[4] m.p. 50°), was prepared from ethyl ethylacetoacetate by the lit. method,[4] and sublimed at 65°/0·002 mm (Found: C, 56·6; H, 7·5; N, 11·3. $C_6H_9NO_2$ requires: C, 56·7; H, 7·1; N, 11·0%).

4,5-*Pentamethylene*-3-*hydroxyisoxazole*

Ethyl cycloheptanone-2-carboxylate[14] (1·84 g, b.p. 129–130°/14 mm, lit.[14] b.p. 122–126°/11 mm) was added below 0° to hydroxylamine hydrochloride (0·695 g) and NaOH (0·80 g) in water (5 ml). The whole was shaken until homogeneous and left at 0° for 12 hr. Water (3 ml) was then added, the mixture warmed to 25° and 12 N HCl added to pH 2. An oil separated which crystallized when stirred and cooled. After 4 hr the 3-*hydroxyisoxazole* (0·63 g) needles, m.p. 118°, was collected; it sublimed at 100°/002 mm to form prisms, m.p 119–120° (Found: C, 62·7; H, 7·3; N, 9·5. $C_8H_{11}NO_2$ requires: C, 62·7; H, 7·2; N, 9·1%).

[11] A. R. Katritzky and J. M. Lagowski, *Adv. Heterocyclic Chem.* **1**, 339 (1963); **2**, 27 (1963).
[12] A. R. Katritzky and A. J. Waring, *J. Chem. Soc.* 1523 (1964).
[13] T. Peters, *Liebig's Ann.* **257**, 339 (1890).
[14] V. Prelog and W. Hinden, *Helv. Chim. Acta* **27**, 1854 (1944).

Hydrogenation of 4,5-pentamethylene-3-hydroxyisoxazole

The 3-hydroxyisoxazole (0·32 g) was hydrogenated as for the 4,5-dimethyl analogue to give *cycloheptanone-2-carboxamide* (0·2 g, 62%), which formed colourless needles from ether, m.p. 118° (Found: C, 61·9; H, 8·1; N, 9·1. $C_8H_{13}NO_2$ requires: C, 61·9; H, 8·4; N, 9·0%).

3-Ethoxy-5-phenylisoxazole, plates m.p. 35°, from aqueous ethanol (Found: C, 69·9; H, 5·7. $C_{11}H_{11}NO_2$ requires: C, 69·8; H, 5·9%), and *2-ethyl-5-phenylisoxazolin-3-one*, plates, m.p. 74–75°, from benzene–light petroleum. (Found: C, 69·8; H, 5·8%), were prepared as described[7,8] for the analogous methyl derivatives.

IR spectra were measured on a Perkin-Elmer model 21 spectrophotometer, with NaCl prism. For further details see Tables 2 and 3, and Ref. 15. NMR spectra were taken at 40 Mc, using a Varian Associates 4300B or a Perkin-Elmer instrument, with sample spinning, and using tetramethylsilane as internal standard.

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We thank Lederle Laboratories, American Cyanamid Co., for financial assistance.

[15] A. R. Katritzky, A. M. Monro, J. A. T. Beard, D. P. Dearnaley and N. J. Earl, *J. Chem. Soc.* 2182 (1958).