Studies on Heterocyclic Chemistry. Part XII.[1] Tautomerism of α-(5-Oxo-Δ³-isoxazolin-4-yl)benzylphosphonates

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α-(5-Oxo-Δ³-isoxazolin-4-yl)benzylphosphonates (2) mostly exist in the NH form in the solid state, and in the OH form in non-polar solvents, owing to chelation with the phosphonyl group. The tautomeric equilibrium in solution is influenced by the nature of the 3-substituent in the isoxazole ring; the 3-methyl compounds exist partially in the NH form. A modified synthesis of these compounds is described.

DURING our studies on thermal reactions of isoxazole derivatives,[2] we prepared a number of α-(5-oxo-Δ³-isoxazolin-4-yl)benzylphosphonates (2) and have studied their tautomeric equilibria. Katritzky *et al.*[3] have shown that 3-substituted Δ²-isoxazolin-5-ones exist predominantly in the C(4)H form in solvents with low dielectric constant and in the solid state, whereas in 3,4-disubstituted Δ²-isoxazolin-5-ones the NH form is considerably more favoured. Δ²-Isoxazolin-5-ones with a carbonyl function at C-4 are, however, exceptional in that they exist as the OH form, owing to chelation with the carbonyl group.[3,4] As a phosphonyl group

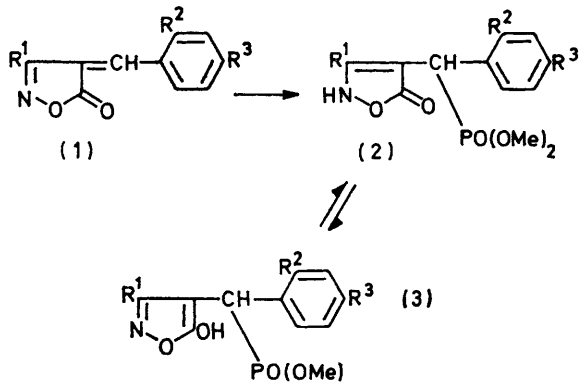
[1] Part XI, T. Nishiwaki and S. Onomura, *J. Chem. Soc.* (*C*), 1971, 3026.

[2] See Part X, T. Nishiwaki and T. Saito, *J. Chem. Soc.* (*C*), 1971, 3021, and references therein.

[3] A. J. Boulton and A. R. Katritzky, *Tetrahedron*, 1961, **12**, 41; A. R. Katritzky, S. Øksne, and A. J. Boulton, *ibid.*, 1962, **18**, 777.

[4] S. V. Sokolov and I. Ya. Postovskii, *Zhur. obshchei Khim.*, 1960, **30**, 600.

is a strong hydrogen acceptor,[5] this group, if present either directly attached to or separated by one carbon atom from the ring, could seriously influence the tautomeric equilibrium of Δ^2-isoxazolin-5-ones. Though our conclusions of the tautomerism of compounds (2) broadly parallel those of Katritzky[3] on alkyl 5-oxo-Δ^2-isoxazoline-4-carboxylates, an additional interesting feature has emerged.



By a modification (see Experimental section) of Arbuzov's procedure,[6] a number of dimethyl α-(5-oxo-Δ^3-isoxazolin-4-yl)benzylphosphonates (2) with 3-methyl, 3-aryl, or 3-(2-thienyl) substituents have been prepared in high yield (see Table). The structures assigned are based on microanalyses, evidence for the presence of a tautomerisable hydrogen atom (see later), and mass spectral observations. The abundance of the molecular ion was *ca.* 30%, and the $[M - PO(OMe)_2]^+$ ion was the base peak.* The preparative reaction is probably ionic in character, since it proceeds without the aid of a radical initiator. We also studied the reaction of the compound (1) with other dialkyl phosphites, but could not obtain any crystalline material, in contrast to the reactions of 5-benzylidene-2-thioxothiazolidin-4-one derivatives.[7]

The isoxazolinones (2) exist in the NH form in the solid state; their i.r. spectra (Nujol mulls) show an intense carbonyl absorption characteristic of Δ^3-isoxazolin-5-ones at 1725—1700 cm^{-1} for the 3-methyl compounds and at 1740—1720 cm^{-1} for the 3-aryl and 3-(2-thienyl) compounds (see Table). However, in chloroform, the 3-aryl and 3-(2-thienyl) compounds displayed two absorptions, at 1810—1800 ($\varepsilon < 20$) and 1735—1730 cm^{-1} ($\varepsilon < 30$). It is known that Δ^2- and Δ^3-isoxazolin-5-ones show intense carbonyl absorption at *ca.* 1800 and 1720 cm^{-1} respectively;[3] a decrease in these two absorptions for 3-aryl- or 3-(2-thienyl)-substituted isoxazolinones (2) indicates that they exist mostly as the 5-hydroxyisoxazole form (3) in chloroform, owing to chelation with the phosphonyl group. When ethanol was added to the chloroform solutions of compounds (2; R^1 = Ph, $R^2 = R^3$ = H) and (2; R^1 = 2-thienyl, $R^2 = R^3$ = H), an intense carbonyl absorption due to the Δ^3-isoxazolin-5-one system was observed at 1720 cm^{-1}. Intramolecular association of the phosphonyl group is destroyed, and consequently the compound (2) will have to exist either as the NH or CH form in polar solvents: spectral evidence rules out the presence of the CH form. However, formation of a hydrogen bond with the π-electrons of benzene ring could also be responsible for the stability of the 5-hydroxyisoxazole form. As such a bond is generally weak,[8] it ought to have little if any effect on the tautomeric equilibrium of compound (2). The i.r. spectra of the compounds (2) in chloroform also showed broad absorption at *ca.* 2500 cm^{-1}, indicative of the presence of a hydroxy-group strongly associated with an acceptor [the effect of intramolecular association upon the ν(P=O) band could not be ascertained because

Dimethyl α-(5-oxo-Δ^3-isoxazolin-4-yl)benzylphosphonates (2) [a]

						Analyses								
						Found (%)				Required (%)			$\nu_{max.}$/cm^{-1}	$\lambda_{max.}$(EtOH)$_4$
R^1	R^2	R^3	M.p. (°C)	Yield (%)	Crystal form	C	H	N	Formula	C	H	N	(C=O) [c]	nm (log ε)
Ph	H	H	156—158	95	Prisms	60·4	4·9	3·8	$C_{18}H_{18}NO_5P$	60·2	5·05	3·9	1725	278 (4·08)
Ph	H	Me	142—143	86	Needles	61·3	5·3	3·5	$C_{19}H_{20}NO_5P$	61·1	5·4	3·75	1740	279 (3·98)
Ph	Cl	H	140—141	66	Plates	54·9	4·5	3·5	$C_{18}H_{17}ClNO_5P$	54·9	4·35	3·6	1735	224 (4·27), 278 (3·89)
Ph	OMe	H	149—150	92	Rods	58·5	5·0	3·4	$C_{19}H_{20}NO_6P$	58·6	5·2	3·6	1730	220 (4·16), 275 (3·88), 281 (3·89)
2-Thienyl	H	H	156—157	57	Plates	52·8	4·5	3·6	$C_{16}H_{16}NO_5PS$	52·6	4·4	3·8	1720	265 (4·01)
p-MeO·C_6H_4	H	H	191—192	92	Prisms	58·4	5·4	3·4	$C_{19}H_{20}NO_6P$	58·6	5·2	3·6	1728	276 (4·16)
p-MeO·C_6H_4	H	Me	220—221 [b]	91	Plates	59·6	5·7	3·2	$C_{20}H_{22}NO_6P$	59·55	5·5	3·5	1725	273 (4·19)
Me	H	Me	144—145	70	Rods	53·9	5·85	4·4	$C_{14}H_{18}NO_5P$	54·0	5·8	4·5	1700	262 (4·01)
Me	H	OMe	149—151	67	Rods	51·4	5·6	4·1	$C_{14}H_{18}NO_6P$	51·4	5·5	4·3	1705	228 (4·04), 263 (3·96)

[a] Results of the reaction with 3 mol. equiv. of dimethyl phosphite. [b] Decomp. [c] Nujol mull.

* Major mass spectral fragmentation of the compounds (2) starts from the OH form. This will be dealt with elsewhere.

[5] E. Halpern, J. Bouck, H. Finegold, and J. Goldenson, *J. Amer. Chem. Soc.*, 1955, **77**, 4472; T. Gramstad and H. J. Storesund, *Spectrochim. Acta*, 1970, **26A**, 426.

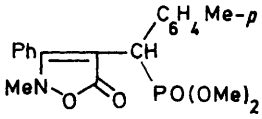
[6] B. A. Arbuzov, E. N. Dianova, V. S. Vinogradova, and Yu. Yu. Samitov, *Doklady Akad. Nauk S.S.S.R.*, 1967, **173**, 1321.

[7] B. A. Arbuzov, V. M. Zoroastrova, and N. D. Ibragimova, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1967, 1972.

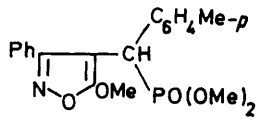
[8] M. Tichy, *Adv. Org. Chem.*, 1965, **5**, 115.

of possible overlap of a band due to associated P–O band with Me–O–P absorption [9].

These views are further supported by the u.v. spectra; the isoxazolinone (2; R^1 = Ph, R^2 = H, R^3 = Me) had $\lambda_{max.}$ (EtOH) 279 nm (log ε 3·98), but showed only end absorption in the region >250 nm in chloroform or dioxan. For comparison, the *N*-methyl derivative (4) and the *O*-methyl derivative (5) of compound (2; R^1 = Ph, R^2 = H, R^3 = Me) were prepared; the former was obtained in high yield by reaction of 3-phenyl-4-*p*-methylbenzylidene-Δ^2-isoxazolin-5-one (1; R^1 = Ph, R^2 = H, R^3 = Me) with trimethyl phosphite in ether. Its u.v. spectrum (in ethanol) resembled that of compound (4) [$\lambda_{max.}$ (EtOH) 281 nm (log ε 3·72)], but differed from that of compound (5) [$\lambda_{max.}$ (EtOH) 221 nm (log ε 4·35)]. Thus the isoxazolinones (2) exist mostly as the NH form in ethanol.



(4)



(5)

Arbuzov *et al.*[6] have shown that dimethyl α-(3-methyl-5-oxo-Δ^3-isoxazolin-4-yl)benzylphosphonate (2; R^1 = Me, R^2 = R^3 = H) in chloroform has a carbonyl absorption of medium intensity at 1708 cm^{-1}, indicating that it exists partially in the NH form. This view is further supported by the i.r. spectra of compounds (2; R^1 = Me, R^2 = R^3 = H), (2; R^1 = Me, R^2 = H, R^3 = Me), and (2; R^1 = Me, R^2 = H, R^3 = OMe), which showed medium-intensity absorption at 1713 cm^{-1} in chloroform (ε 80—100) but no band at 1800 cm^{-1} [*cf.* ε of dimethyl 2,3-dimethyl-5-oxo-Δ^3-isoxazolin-4-yl)benzylphosphonate, 490].

It is concluded that, in a non-polar solvent, α-(5-oxo-Δ^3-isoxazolin-4-yl)benzylphosphonates (2) with 3-aryl or a 3-(2-thienyl) substituent exist mostly in the OH form, whereas in a non-polar solvent compounds (2) with a 3-methyl group exist as a mixture of the NH and OH forms. The tautomeric equilibrium of Δ^2-isoxazolin-5-ones thus depends on the nature of the 3-substituent; an adequate explanation for this cannot be offered at present.

EXPERIMENTAL

Light petroleum refers to the fraction of b.p. 100—120° unless otherwise stated.

Reaction of 4-Arylidene-Δ^2-isoxazolin-5-ones (1) *with Dimethyl Phosphite.*—Typically the compound (1) (0·01 mol) and dimethyl phosphite (0·02 or 0·03 mol) were heated in toluene (10 ml) under reflux for 0·5—1 h. The mixture was cooled and light petroleum (10 ml) was added. The precipitates were filtered off, washed with ether, and recrystallised from benzene–light petroleum (see Table).

5-Amino-3-(2-thienyl)isoxazole.—This compound was prepared (63%) from *(2-thenoyl)acetonitrile* [prepared in 35% yield, as described for *p*-chlorobenzoylacetonitrile; [2] m.p. 134—135° (from benzene–hexane) (Found: C, 55·7; H, 3·4. C_7H_5NOS requires C, 55·6; H, 3·3%)] and hydroxylamine according to the method of Obrègia; [10] m.p. 96—97° (from carbon tetrachloride) (Found: C, 50·4; H, 3·75; N, 16·65. $C_7H_6N_2OS$ requires C, 50·6; H, 3·6; N, 16·9%).

3-(2-Thienyl)-Δ^2-isoxazolin-5-one.—5-Amino-3-(2-thienyl)-isoxazole (2·50 g), methanol (15 ml), and 6N-sulphuric acid (15 ml) were heated under reflux for 30 min. On concentration of the solution, a solid was obtained which afforded *needles* (1·29 g, 53%), m.p. 136—138° (decomp.) (from water) (Found: C, 50·4; H, 2·9. $C_7H_5NO_2S$ requires C, 50·3; H, 3·0%).

4-Arylidene-Δ^2-isoxazolin-5-ones (1).—The following Δ^2-isoxazolin-5-ones were prepared as described in ref. 11; *4-benzylidene-3-(2-thienyl)-* (1; R^1 = 2-thienyl, R^2 = R^3 = H), m.p. 132—133° (from methanol) (Found: C, 65·6; H, 3·8. $C_{14}H_9NO_2S$ requires C, 65·9; H, 3·55%); *4-benzylidene-3-p-methoxyphenyl* (1; R^1 = *p*-MeO·C_6H_4, R^2 = R^3 = H), m.p. 169—171° (from ethanol) (Found: C, 73·3; H, 4·65. $C_{17}H_{13}NO_3$ requires C, 73·1; H, 4·7%; 3-p-*methoxyphenyl-4-p-methylbenzylidene* (1; R^1 = *p*-MeO·C_6H_4, R^2 = H, R^3 = Me), m.p. 141—142° (from ethanol) (Found: C, 73·7; H, 5·4. $C_{18}H_{15}NO_3$ requires C, 73·7; H, 5·15%); and 4-(o-*methoxybenzylidene*)-3-*phenyl-* (1; R^1 = Ph, R^2 = OMe, R^3 = H), m.p. 166—167° (from ethanol) (Found: C, 72·8; H, 4·45. $C_{17}H_{13}NO_3$ requires C, 73·1; H, 4·7%).

Dimethyl α-(2-Methyl-5-oxo-3-phenyl-Δ^3-isoxazolin-4-yl)-p-methylbenzylphosphonate (4).—The compound (1; R^1 = Ph, R^2 = H, R^3 = Me) (2·6 g, 0·01 mol), trimethyl phosphite (1·5 g, 0·012 mol), and ether (20 ml) were heated under reflux for 1·5 h. The resulting solid (2·7 g; 71%) crystallised from ether–light petroleum (b.p. 30—70°) as *plates*, m.p. 105—107° (Found: C, 62·3; H, 5·8; N, 3·6. $C_{20}H_{22}NO_5P$ requires C, 62·0; H, 5·7; N, 3·6%), $\nu_{max.}$ ($CHCl_3$) 1735 cm^{-1} (C=O).

Dimethyl α-(5-methoxy-3-phenylisoxazol-4-yl)-p-methylbenzylphosphonate (5).—The compound (2; R^1 = Ph, R^2 = H, R^3 = Me) (1·72 g) was treated with diazomethane in ether and the product (1·49 g, 84%) crystallised from light petroleum as *plates*, m.p. 122° (Found: C, 62·0; H, 5·7; N, 3·5. $C_{20}H_{22}NO_5P$ requires C, 62·0; H, 5·7; N, 3·6%).

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[9] L. C. Thomas and R. A. Chittenden, *Spectrochim. Acta*, 1964, **20**, 489.

[10] A. Obrègia, *Annalen*, 1891, **266**, 324.

[11] T. Nishiwaki, *Tetrahedron*, 1969, **25**, 747.