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3-*H*-Isoxazolin-5-ones

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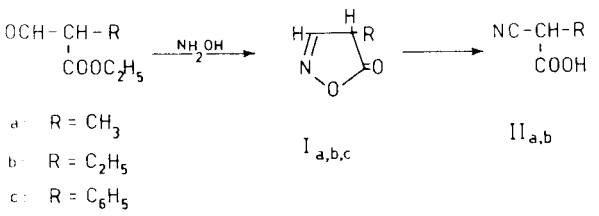
4-Alkyl and 4-phenyl isoxazolin-5-ones were prepared. The 4-alkyl compounds were found to isomerize easily to α-cyano carboxylic acids. The acidity and the tautomeric composition of the compounds prepared are surveyed and compared to the results of the previous literature.

Although a large number of 3- and 3,4-substituted isoxazolin-5-ones are known, among the 3-*H* derivatives only the 4-ethoxycarbonylisoxazolin-5-one has been described (2,3). The preparation of the 3-*H*, 4-methyl- and of the 3-*H*, 4-phenyl- isoxazolin-5-ones appears to be of considerable interest in order to extend the previous research (5,6,7) on tautomeric equilibria of isoxazolin-5-ones, and in order to study the stability of these compounds considering the ease of ring opening of the 3-*H*-isoxazoles (8,9) and of the 2-methyl-3-*H*-isoxazolin-5-ones (10,11) under alkaline conditions. Thus we have synthesized the 4-methyl- and the 4-phenylisoxazolin-5-ones and reinvestigated the synthesis of the 4-ethyl derivative, and have studied their tautomeric equilibria and stabilities.

Hydroxylamine reacted with ethyl α-formylpropionate in acidic solution at 15-20°, to yield 4-methylisoxazolin-5-one (Ia):



a R = CH_3
b R = C_2H_5
c R = C_6H_5

$I_{a,b,c}$ $II_{a,b}$

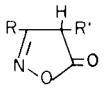
It was necessary to avoid heat during the preparation and purification of Ia, because it easily isomerizes into α-cyanopropionic acid (IIa). The crude solid could be sublimed, m.p. 58-60°. At room temperature the melting point gradually decreases, however under 0°, Ia was quite stable. The transformation from Ia to IIa can be easily observed by physical means. In the infrared spectrum, a band at 2245 cm^{-1}, characteristic of nitrile stretching vibration appears and becomes gradually stronger. The intensity of this band in THF solution can be used to determine the concentration of IIa. The UV spectra of Ia and IIa are very different, because IIa has no absorbance in the range near 260 mμ, whereas Ia shows a very strong absorption band at 260 mμ (methanol as solvent), which can be used for the determination of the concentration of Ia. By methylation of pure Ia with diazomethane in ethereal solution, the *O*-methyl and the *N*-methyl derivatives were isolated; while by methylation of Ia, after heating at 80° for 13 hours, a liquid was obtained, which was identified as methyl α-cyanopropionate by IR and gas-chromatographic comparison of an authentic sample.

Likewise 4-ethylisoxazolin-5-one (Ib), when heated, undergoes isomerization similar to Ia and because of this thermal instability, the product from the reaction between ethyl α-formylbutyrate and hydroxylamine, described as Ib (4), was in fact shown mainly to be the isomer IIb. This was established both by the nitrile stretching vibration (2245 cm^{-1}) in the infrared and by the weakness of the ultraviolet absorption band at 262 mμ (Log ε = 2.19, methanol as solvent). The compound Ib has not been isolated in the pure state, however its existence is established by carrying out the reaction at room temperature and methylation of the acidic products with diazomethane. Appreciable amounts (20-25%) of the *N*- and *O*-methyl derivatives of Ib were isolated by distillation.

The 4-phenylisoxazolin-5-one (Ic) was prepared by the reaction between hydroxylamine and ethyl formylphenylacetate. This compound was stable, in contrast to the alkyl derivatives Ia and Ib. However Ic was sensitive to light. It dissolved in aqueous sodium hydroxide solution and was precipitated again upon acidification. Compound Ic reacted with alcoholic sodium ethoxide to give the sodium salt, which was very stable and retained the

TABLE I

Acidic Properties of Isoxazolin-5-ones

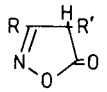


R	R′	*p*Ka at 25° In Methylcellosolve-Water 80/20	In Water	α For C = 10^{-4} *M* in Water
CH_3	H		6.3 (a)	0.07
H	CH_3		4.50	0.43
CH_3	CH_3		5.27 (b)	0.21
C_6H_5	H		4.2 (c)	0.54
H	C_6H_5	4.6	3.50	0.80
CH_3	C_6H_5	5.9		
C_6H_5	CH_3	6.4	4.08 (d)	0.59
C_6H_5	C_6H_5	5.2		
C_6H_5	Br		3.24 (e)	0.87

(a) Reported (6): 5.56. (b) Ref. (7). (c) Reported (5): 4.01. (d) Reported (5): 4.73. (e) Reported (5): 2.3.

TABLE II

Tautomeric Composition of Different Solutions of Isoxazolin-5-ones



R	R′	Cyclohexane	Hydroxylic (d) Solvents	Chloroform	Dioxan
CH_3	H	CH (a)	70 CH + 30 NH (a)	CH (a)	
H	CH_3	75 CH + 25 NH	NH	NH + CH	
CH_3	CH_3	95 CH + 5 NH (b)	NH (b)	NH + CH	OH + CH + NH (c)
H	C_6H_5	insoluble	NH	NH	NH + OH (c)
C_6H_5	H	CH (a)	70 CH + 30 NH (a)	CH (a)	CH (c)
CH_3	C_6H_5	insoluble	NH	NH + a little CH	NH + OH (c)
C_6H_5	CH_3	CH (a)	NH (a)	75 CH + 25 NH (a)	CH + NH + OH (c)
C_6H_5	C_6H_5			NH + CH	

(a) Ref. (6). (b) Ref. (7). (c) Ref. (13). (d) *M*/100 or *N*/100 aqueous sulfuric acid, but for R = R′ = CH_3, methanol.

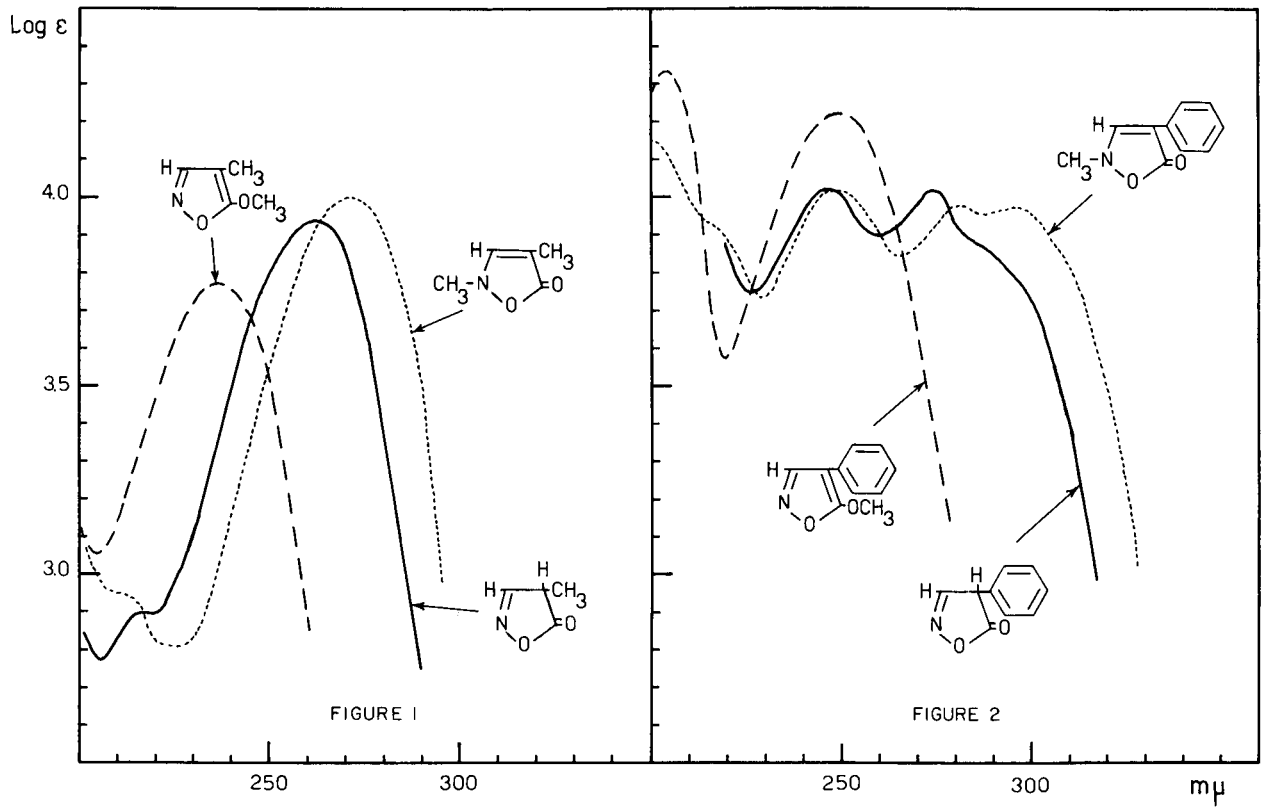
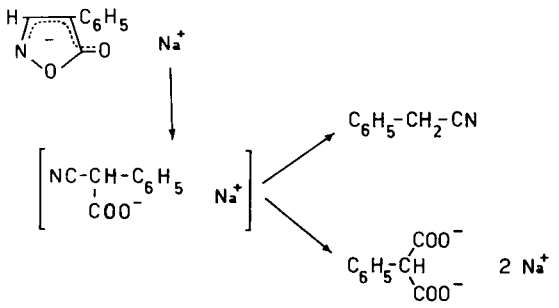


Fig. 1. UV spectra of 4-methylisoxazolin-5-one (Ia) and of its *N*- and *O*-methyl derivatives in *N*/100 aqueous sulfuric acid.

Fig. 2. UV spectra of 4-phenylisoxazolin-5-one (Ic) and of its *N*- and *O*-methyl derivatives in *N*/100 aqueous sulfuric acid.

ring structure, as proven by the absence of a nitrile absorption band in the IR spectrum. By warming Ic with bases, however, ring-opening slowly occurred to give mainly phenylmalonic acid in aqueous sodium hydroxide and benzyl cyanide in alcoholic sodium ethoxide. It is



possible that phenylcyanoacetate is an intermediate since, starting with this compound, the same final products were obtained.

Compound Ia also only formed salts with the bases at room temperature. We may conclude therefore that, in contrast to the 2-methyl derivatives (11), isoxazolin-5-ones are quite stable towards bases at room temperature, even if the position 3 is unsubstituted. This fact clearly depends upon salt formation.

Like Ia, Ic also afforded a mixture of the *N*-methyl and *O*-methyl derivatives, upon methylation with diazomethane in ethereal solution. The *N*-methyl derivatives of Ia, Ib and Ic were identified by comparison with samples prepared by other means (12).

Isoxazolin-5-ones are stronger acids than the carboxylic acids. The *p*Ka values measured potentiometrically are listed in Table I. It was necessary to use methylcellosolve-water solutions for the water insoluble compounds. The α values, calculated for C = 10^{-4} *M*, show that most compounds are highly ionized in aqueous solutions. This fact accounts for the great difference between the UV spectra of the most acidic compounds and those of their methyl-derivatives, not only in water, but also in methanol. On the other hand, the UV spectra of 4-phenylisoxazolin-5-one [216 (3.89), shoulder, 262 (4.15), shoulder, 276 (4.18)] (14) and of 3-phenyl-4-bromoisoxazolin-5-one [230 (4.07), 275 (3.52)] (14) in water are very similar to those of their sodium salts [217 (3.91), shoulder, 261 (4.21), shoulder, 274 (4.25) and 229 (4.13), 279 (3.58)

respectively] (14). The aryl derivatives of the series are more acidic than the methyl substituted compounds. In each group the strongest acid is the 3-*H* compound (except for the bromo derivative).

The proportion of the three possible tautomeric forms CH, NH, OH of Ia and Ic, as in the case of other isoxazolin-5-ones previously studied, depends greatly on the solvent. In neutral aqueous solution, Ia (in part) and Ic (mainly) are ionized (Table I); in very weak acidic solution, both Ia and Ic exist mainly in the NH form. In Figures 1 and 2 their UV spectra are compared with those of the respective *N*-methyl and *O*-methyl derivatives. No salt-formation occurs in diluted acids, since isoxazolin-5-ones are too weakly basic.

In non-polar solvents both Ia and Ic are fairly insoluble, however, even the low degree of solubility of Ia in cyclohexane allows the UV spectrum to be observed. In this solvent Ia behaves as the 3,4-dimethylisoxazolin-5-one (7): while the *O*-methyl and the *N*-methyl derivatives show strong absorption bands at 232 mμ (Log ε: 3.74) and 268 mμ (Log ε: 3.72) respectively, the weak absorption of Ia at 250 mμ (Log ε: 3.11) suggests that the CH form is predominant, besides a considerable proportion of the NH form (*ca.* 25%). This value is approximate for in this calculation we assumed the ε max of the NH form to be the same as that of the *N*-methyl compound.

In addition to the results of the preceding research (6,7), the data concerning Ia and Ic is collected in Table II, as well as that concerning the already known 3-methyl-4-phenyl- and 3,4-diphenylisoxazolin-5-ones. On this basis we may conclude that 3- and/or 4-methyl- and phenyl-substituted isoxazolin-5-ones exist mainly in the NH form in (acidified) *hydroxylic solvents* (only the 4-*H* compounds have a high percentage of CH form); on the other hand they are almost exclusively in the CH form in *aprotic solvents.* A general conclusion is impossible for *chloroform solutions,* because the different compounds are in CH or NH form or both: even in this solvent, OH forms are excluded. The tautomeric equilibrium of several isoxazolin-5-ones in *dioxan* has been recently investigated through dipole moment measurements: there are also stable OH forms in this solvent, owing to its associating power.

EXPERIMENTAL

Melting points and boiling points are uncorrected. UV spectra were measured with a Cary spectrometer Model 14, and potentiometric titrations with a Metrohm potentiograph Model E 336.

4-Methylisoxazolin-5-one (Ia).

A mixture of ethyl α-formylpropionate (0.1 mole) and aqueous hydroxylamine hydrochloride (0.2 mole in 50 ml. of water) was stirred overnight (the ferric chloride test gave a red colour while the ester was present, green at the end), then extracted with ether. The ethereal solution, after removal of the solvent, gave propionic acid (*ca.* 48%), ethyl propionate (*ca.*22 %) and Ia (*ca.* 11%), b.p. 64-65°/0.1 mm. The product solidified on standing. It was more convenient to have the product solidified, by removing the more volatile substances by mild warming (up to 50° at 0.1 mm), yield 25%. The product sublimed, m.p. 58-60°.

Anal. Calcd. for $C_4H_5NO_2$: C, 48.49; H, 5.09; N, 14.14; M.W., 99.1. Found: C, 48.75; H, 5.10; N, 14.07; M.W., 105 (cryoscopic in benzene).

The isomerization of Ia to IIa was 90% complete in 12 hours by warming pure Ia at 60°. Additional heating and methylation with diazomethane afforded a product boiling at 71°/15 mm, identified as methyl α-cyanopropionate by comparison of the infrared spectrum. The *sodium salt* of Ia, m.p. 205-210°, was obtained by adding an ethanolic solution of sodium ethoxide to a solution of Ia until the red-colour of phenolphthalein appeared, followed by concentration of the mixture.

Methylation of Ia.

From 3 g. of Ia, methylated with diazomethane in ethereal solution and fractionation of the mixture there was obtained 1.45 g. (yield 42.4%) of 4-methyl-5-methoxyisoxazole (15), b.p. 26-29°/0.5 mm or 61°/20 mm.

Anal. Calcd. for $C_5H_7NO_2$: C, 53.09; H, 6.24; N, 12.38; OCH_3, 27.41. Found: C, 52.85; H, 6.40; N, 12.38; OCH_3, 26.79.

2,4-Dimethylisoxazolin-5-one, 0.85 g. (yield 24.9%), b.p. 67°/0.2 mm, a known compound (12), was also obtained and identified by a comparison of the infrared spectrum.

Methyl Derivatives of 4-Ethylisoxazolin-5-one (Ib).

By the same procedure as for Ia, an ethereal solution was prepared, from ethyl α-formylbutyrate and hydroxylamine hydrochloride which was methylated with diazomethane, dried and fractionated. The 4-ethyl-5-methoxyisoxazole (yield 6-7%) had b.p. 28-30°/0.2 mm or 60°/20 mm.

Anal. Calcd. for $C_6H_9NO_2$: C, 56.68; H, 7.13; N, 11.02; OCH_3, 24.41. Found: C, 56.90; H, 7.05; N, 10.96; OCH_3, 25.08.

The 2-methyl-4-ethylisoxazolin-5-one (yield 14-15%) had b.p. 69-70°/0.2 mm. The latter compound was also synthesized by prolonged heating of ethyl α-formylbutyrate and *N*-methylhydroxylamine in anhydrous pyridine.

Anal. Calcd. for $C_6H_9NO_2$: N, 11.02. Found: N, 11.03.

4-Phenylisoxazolin-5-one (Ic).

Ethyl formylphenylacetate (26.5 g.) and hydroxylamine hydrochloride (10.6 g.) were refluxed for 8 hours in ethanol (200 ml.). Concentration of the solution gave 20.35 g. of crude Ic, m.p. 135-137° dec., from ethanol.

Anal. Calcd. for $C_9H_7NO_2$: C, 67.07; H, 4.38; N, 8.70; M.W., 161.14. Found: C, 66.85; H, 4.26; N, 8.80; M.W., (cryoscopic in benzene) 166.

The product was soluble in dilute sodium hydroxide from which it separated again upon acidification; it was soluble in methanol and in ethanol, insoluble in water and in non-polar organic solvents.

With sodium ethoxide, Ic gave the sodium salt, m.p. 215-217° dec., from ethanol.

Anal. Calcd. for $C_9H_6NO_2Na$: C, 58.97; H, 3.27; N, 7.64. Found: C, 59.26; H, 3.44; N, 7.80.

Alkaline Hydrolysis of Ic.

Ammonia vapour was evolved by warming Ic in excess 2 *N* sodium hydroxide at 50° for 6 hours. From this solution phenylmalonic acid (46.5%) separated. Phenylcyanoacetic acid gave, under the same conditions, 11.5% of benzyl cyanide and 74.5%

phenylmalonic acid.

An alcoholic solution of sodium and Ic (2 gram atoms per 1 mole) was heated at 50° for 12 hours, then concentrated. Benzyl cyanide (43.5%) was collected by distillation. Phenylcyanoacetic acid gave, under the same conditions, 76% of benzyl cyanide.

Methylation of Ic.

Compound Ic was methylated with diazomethane in ethereal solution. By standing, the known (12) 2-methyl-4-phenylisoxazolin-5-one separated. Upon concentration, further precipitation occurred, in yields up to 15%. Complete evaporation afforded 66% of 4-phenyl-5-methoxyisoxazole (15), m.p. 43-45°, from methanol.

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00; OCH_3, 17.7. Found: C, 68.87; H, 5.37; N, 8.18; OCH_3, 17.31.

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REFERENCES

(1) Present address: Department of Chemistry, University College, London.

(2) L. Claisen, *Ber.*, 30, 1481 (1897); S. Ruhemann, *ibid.*, 30, 1085, 2031 (1897).

(3) The 4-ethylisoxazolin-5-one was recorded also (4), but this is incorrect.

(4) Yuoh-Fong Chi and M. Chun-Hwa Yang, *J. Am. Chem. Soc.*, 58, 1152 (1936).

(5) A. J. Boulton and A. R. Katritzky, *Tetrahedron*, 12, 41 (1961).

(6) A. R. Katritzky, S. Øksne and A. J. Boulton, *ibid.*, 18, 777 (1962).

(7) F. De Sarlo, *ibid.*, 23, 831 (1967).

(8) See A. Quilico, in A. Weissberger, Ed., "The Chemistry of Heterocyclic Compounds," Vol. 17, p. 44, John Wiley and Sons, New York, N. Y. (1962).

(9) V. Bertini, A. De Munno and P. Pino, *Chim. Ind. (Milan)*, 48, 491 (1966).

(10) H. Ulrich, J. N. Tilley and A. A. Sayigh, *J. Org. Chem.*, 27, 2160 (1962).

(11) F. De Sarlo and G. Renzi, *Tetrahedron*, 22, 2995 (1966).

(12) F. De Sarlo, L. Fabbrini and G. Renzi, *ibid.*, 22, 2989 (1966).

(13) R. Cencioni, P. F. Franchini and M. Orienti, *ibid.*, in press.

(14) λ max in mμ and (Log ε) given.

(15) No C=O stretching band is present in the IR spectrum.

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