2-Substituted 3,4-Unsubstituted Isoxazolin-5-ones: Synthesis and Comparison with the Natural Compounds

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Various ways to substitute the nitrogen atom of isoxazolin-5-one are described. The properties of synthetic 2-substituted 3,4-unsubstituted isoxazolin-5-ones are compared with the natural compounds. The structure of the natural 2-(2-cyanoethyl)-3-isoxazolin-5-one has been proven by establishing its identity with the synthetic compound.

A NUMBER of 2-substituted 3,4-unsubstituted isoxazolin-5-ones have been isolated from *Pisum sativum* and *Lathyrus odoratus* seedlings.[1-5] They are the only known natural compounds with an isoxalin-5-one ring. The confirmation of their chemical structure by synthesis was therefore desirable. Isoxazolin-5-one was first mentioned as a reaction product arising from nucleic acids by treatment with hydroxylamine.[6,7] Its synthesis and properties were described by De Sarlo,[8] and on alkylation with diazomethane it gave 2-methyl-3-isoxazolin-5-one. This paper reports other ways to alkylate the nitrogen atom of isoxazolin-5-one.[9]

RESULTS AND DISCUSSION

The isoxazolin-5-one anion (1) was alkylated by allyl bromides, dialkyl sulphates and toluene-*p*-sulphonates. Cyanoethylation of isoxazolin-5-one (1) was achieved with acrylonitrile. Only strong alkylating agents could substitute the isoxazolin-5-one anion (1). Dialkyl sulphates react readily, while toluene-*p*-sulphonates react rather slowly. Alkyl iodides, ethyl chloroacetate, and ethyl bromoacetate failed to substitute the heterocyclic ring. Attempts to substitute isoxazolin-5-one with toluene-*p*-sulphonates in dimethylformamide or dimethyl sulphoxide instead of dry methanol, were unsuccessful.

Allyl bromides gave 2- and 4-substitution. No other alkylating agent gave carbon substitution, dialkyl sulphates and toluene-*p*-sulphonates giving rise to carbonyl oxygen and 2-substitution. The reactions can be followed by n.m.r. spectrometry. In case of 2-substitution, the ring protons of isoxazolin-5-one show two doublets, δ *ca.* 5 and 8 (J 3·4—3·6 Hz). The resulting 2-substituted isoxazolin-5-ones were isolated by g.l.c. or t.l.c. The most characteristic parameters (n.m.r. and u.v.) of synthetic and of natural 2-substituted 3,4-unsubstituted isoxazolin-5-ones are compared in the Table. The 5-alkoxyisoxazoles isomerised in the gas chromatograph to the corresponding cyanoacetic esters.[10] This is similar to the rearrangements of isoxazolin-5-one [8] and 4-methyl-2-isoxazolin-5-one.[11] The isomerisation of 5-alkoxyisoxazoles can be avoided by using t.l.c. instead of g.l.c. to purify the compounds.

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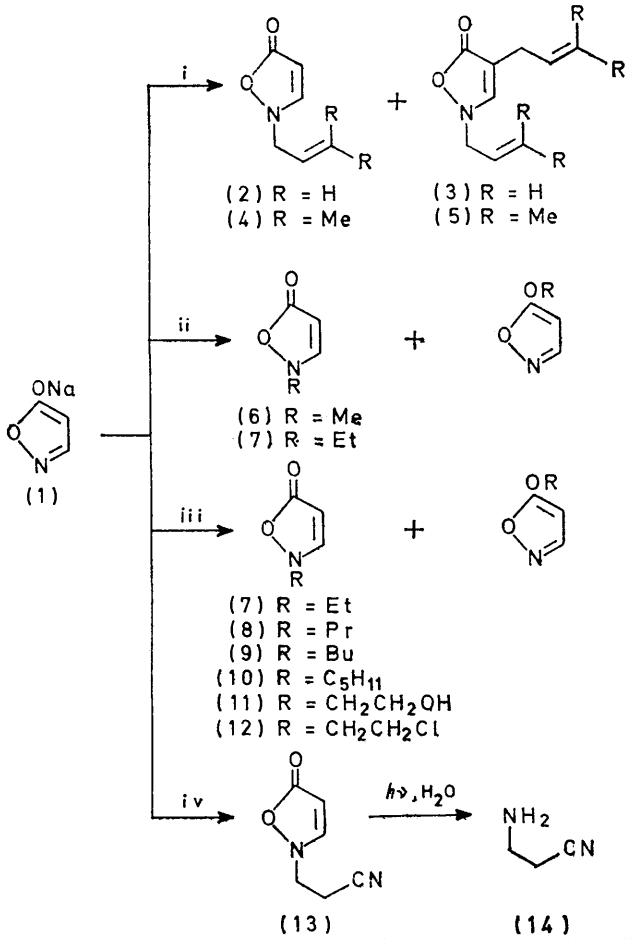
We tried without success to introduce naturally occurring substituents on the nitrogen atom of isoxazolin-5-one by means of the following toluene-*p*-sulphonates: diphenylmethyl *O*-*p*-tolylsulphonyl-*N*-benzoyloxyserinate, ethyl *O*-*p*-tolylsulphonylycolate and 2-cyanoethyl



Reagents: i, allyl bromide or 3,3-dimethylallyl bromide; ii, R_2SO_4; iii, ROTs; iv, acrylonitrile.

toluene-*p*-sulphonate. Their lack of reactivity may be due to the presence of electron-withdrawing groups near the reaction centre. This view is supported by comparing the yields of nitrogen substitution from propyl (25%), 2-chloroethyl (13%), and 2-cyanoethyl toluene-*p*-sulphonate (0%). The yield of the propyl-substituted product was not increased if other leaving groups were introduced such as *p*-bromobenzene-, *p*-fluorobenzene-, or methane-sulphonate. The same alterations in the leaving group of the 2-cyanoethyl sulphonates did not induce substitution of isoxazolin-5-one.

On the other hand, 2-hydroxyethyltoluene-*p*-sulphonate gave the expected 2-(2-hydroxyethyl)-3-isoxazolin-5-one (11). This compound was not identical with any natural product from *Lathyrus odoratus* seedlings.

2-(2-Cyanoethyl)-3-isoxazolin-5-one (13) obtained by addition of isoxazolin-5-one to acrylonitrile, was compared with the natural compound to which this structure has been assigned.[5] Their identity was proven by u.v., i.r., n.m.r. and mass spectra, and by t.l.c. and paper chromatography. Moreover, the synthetic and the natural compound both liberate β-aminopropionitrile (14), upon u.v. irradiation.[12] We tried to obtain 2-(2-cyanoethyl)-3-isoxazolin-5-one (13) from the chloro-analogue (12) by treatment with sodium cyanide or silver cyanide, but the heterocyclic ring was destroyed.

Comparison of n.m.r. and u.v. data from 3,4-unsubstituted 2-R-isoxazolin-5-ones

R	δ Values [a]		
Synthetic compounds	3-H	4-H	$\lambda_{max.}$/nm [b]
Me (6)	7·7	5·1	264
Et (7)	7·8	5·1	265
Pr (8)	7·7	5·0	265
Bu (9)	8·0	5·0	265
C_5H_{11} (10)	7·9	5·0	265
$CH_2CH{=}CH_2$ (2)	7·9	5·1	265
$CH_2CH{=}CMe_2$ (4) [c]	7·9	5·07	266
CH_2CH_2OH (11)	8·0	5·0	265
CH_2CH_2Cl (12)	8·0	5·1	265
CH_2CH_2CN (13)	8·0	5·3	265
Natural compounds			
$CH_2CH(NH_2)(CO_2H)$ [d]	8·1	5·2	265
$CH_2CH_2CH(NH_2)(CO_2H)$ [d]	8·2	5·2	265
CO_2Me [d]	8·7	5·7	266
CH_2CH_2CN (13)	8·0	5·3	265

[a] N.m.r. spectra were recorded in deuteriochloroform with tetramethylsilane as internal standard, unless specified. [b] Measured in water. [c] N.m.r. spectrum measured in CCl_4. [d] N.m.r. spectrum measured in D_2O.

The mass spectra of the 2-alkyl-substituted isoxazolin-5-ones (7)—(10) were compared. Besides the molecular ions, the spectra show a fragment of *m/e* 99 when the substituent has four or five carbon atoms. The propyl compounds shows a fragment of *m/e* 98 instead and 2-methyl-3-isoxazolin-5-one a fragment of *m/e* 99 which is the molecular ion.

The i.r. spectra of synthetic and of natural 2-substituted 3,4-unsubstituted isoxazolin-5-ones show bands at *ca.* 1550 (C=C), 1730 (C=O), 3060—3080 (3-H), and 3120—3150 cm^{-1} (4-H).[10] The agreement of the properties of synthetic and of natural 3-isoxazolin-5-ones confirms the structure of the heterocyclic ring in the natural compounds.

EXPERIMENTAL

N.m.r. spectra were recorded on a Varian T-60 60 MHz spectrometer, u.v. spectra on Cary 14 or Gilford 2400 spectrophotometers, mass spectra on A.E.I. MS902, MS30 or C.E.C. 21—104 spectrometers, and i.r. spectra on a Perkin-Elmer 257 spectrophotometer. Ethyl and 2-chloroethyl-toluene-*p*-sulphonates were purchased from Aldrich. Propyl, butyl, and pentyl toluene-*p*-sulphonates were prepared according to standard procedures.[13]

2-Allyl- (2) *and 2,4-Diallyl-3-isoxazolin-5-one* (3).—Ethyl 3-hydroxyiminopropionate [14] (20 g, 0·152 mol) was treated with 2·5N-sodium methoxide (61·5 ml) in dry methanol.

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Allyl bromide (20·5 g, 0·17 mol) was added with cooling. The mixture was stirred magnetically at room temperature for 8 h, the solvent was removed under vacuum, and the remaining slurry was extracted four times with dry ether. The ether was evaporated and the remaining oil was distilled under vacuum. The fraction distilling at 86 °C and 0·01 mmHg was 2-*allyl*-3-*isoxazolin*-5-*one* (2) (7·15 g, 37·5%), δ ($CDCl_3$) 4·1 (2H, d, *J* 6·0 Hz, CH_2N), 5·1 (1H, d, *J* 3·5 Hz, 4-H), 5·2—6·2 (3H, m, CH_2=CH), 7·7 (1H, d, *J* 3·5 Hz, 3-H), *m/e* 125 (M^+, 12%), 85 (2·5), 54 (12), 44 (48), and 41 (100), $\nu_{max.}$ (NaCl) 3120—3150 (C-4–H), 3080 (C-3–H), 1730 (C=O), and 1550 cm^{-1} (C=C) [Found: M^+ (mass spectrum), 125·0489. $C_6H_7NO_2$ requires M^+, 125·0476]. The fraction distilling at 105 °C and 0·01 mmHg was 2,4-*diallyl*-3-*isoxazolin*-5-*one* 3) (3·15 g, 12·5%), δ ($CDCl_3$) 2·9 (2H, dd, *J* 6·0, 1·0 Hz, 4-CH_2), 4·0 (2H, d, *J* 6·0 Hz, CH_2N), 4·8—6·2 (6H, m, CH_2=CH), and 7·4 (1H, t, *J* 1·0 Hz, 3-H), *m/e* 165 (M^+, 8%), 120 (4), 93 (42), 80 (6), 53 (10), and 41 (100), $\nu_{max.}$ (NaCl) 3080 (C-3–H), 1730 (C=O), and 1615 cm^{-1} (C=C) (Found: M^+, 165·0809. $C_9H_{11}NO_2$ requires M^+ 165·0789).

2-(3,3-*Dimethylallyl*)- (4) *and* 2,4-*Bis*-(3,3-*dimethylallyl*)-3-*isoxazolin*-5-*one* (5).—In an analogous experiment, addition of 3,3-dimethylallyl bromide (1·3 g, 0·0086 mol) to ethyl 3-hydroxyiminopropionate [14] (1 g, 0·0076 mol) gave a mixture which was analysed by t.l.c. [Merck silica gel PF 254; toluene–chloroform–acetone (40 : 25 : 35)]. Extraction of the separated bands with acetone, yielded, after evaporation, 2-(3,3-*dimethylallyl*)- (4) (405 mg, 34%) and 2,4-*bis*-(3,3-*dimethylallyl*)-3-*isoxazolin*-5-*one* (5) (290 mg, 17%). Compound (4) had δ (CCl_4) 1·7 (6H, d, *J* 3·2 Hz, Me_2C=), 4·2 (2H, d, *J* 7·5 Hz, CH_2N), 5·1 (1H, d, *J* 3·4 Hz, 4-H), 5·3 (1H, m, =C*H*CH_2), and 8·0 (1H, d, *J* 3·4 Hz, 3-H), *m/e* 153 (M^+, 10%), 69 (100), 59 (30), and 41 (38), $\nu_{max.}$ (NaCl) 3120—3160 (C-4–H), 3060 (C-3–H), 1735 (C=O), and 1557 cm^{-1} (C=C) (Found: M^+, 153·0790. $C_8H_{11}NO_2$ requires M^+, 153·0789). Compound (5) had δ (CCl_4) 1·7 (6H, d *, *J* 3·2 Hz, Me_2C=C·C·C), 1·7 (6H, d *, *J* 3·2 Hz (Me_2C=C–C–N), 2·8 (2H, dd, *J* 7·5, 1·0 Hz, 4-CH_2), 3·9 (2H, d, *J* 7·0 Hz, CH_2N), 4·9—5·4 (2H, m, =C*H*CH_2N and =C*H*CH_2C), 7·4 (1H, t, *J* 1·0 Hz, 3-H), *m/e* 221 (M^+, 2%), 137 (3), 108 (6), 69 (100), and 41 (69), $\nu_{max.}$ (NaCl) 3090 (C-3–H), 1740 (C=O), and 1620 cm^{-1} (C=C) (Found: M^+, 221·1405. $C_{13}H_{19}NO_2$ requires M^+, 221·1416).

2-*Methyl*- (6) *and* 2-*Ethyl*-3-*isoxazolin*-5-*one* (7).—2·5N-Sodium methoxide (15·3 ml) in dry methanol was added to ethyl 3-hydroxyiminopropionate [14] (5 g, 0·038 mol). Dimethyl sulphate (5 g, 0·039 mol) or diethyl sulphate (6 g, 0·039 mol) was added with cooling. At −20 °C 2-*methyl*-3-*isoxazolin*-5-*one* (6) precipitated as crystals (1·15 g, 30%), δ ($CDCl_3$) 3·4 (3H, s, CH_3) and 5·1 (1H, d, *J* 3·5 Hz, 3-H), *m/e* 99 (M^+, 100%), 98 (7), 71 (12), 54 (17), 44 (87), and 42 (50), $\nu_{max.}$ (NaCl) 3120—3150 (C-4–H), 3060 (C-3–H), 1725 (C=O), and 1560 cm^{-1} (C=C) (Found: M^+, 99·0322. $C_5H_5NO_2$ requires M^+, 99·0320). The ethylation mixture was extracted with dry ether. The ether was evaporated and the residual oil was analysed by n.m.r. spectrometry. The presence of 2-ethyl-3-isoxazolin-5-one (7) was proven by doublets of δ 7·8 and 5·1 (*J* 3·5 Hz). The purification is described below.

2-*Hydroxyethyl Toluene*-p-*sulphonate*.—Freshly distilled toluene-*p*-sulphonyl chloride (20 g, 0·105 mol), dissolved in dry pyridine (25 ml) was added dropwise to ethylene glycol (100 g) with cooling. The mixture was left overnight in the refrigerator, and poured in ice–water. 2-Hydroxyethyl toluene-*p*-sulphonate separated as an oil, and was used without further purification, δ ($CDCl_3$) 2·4 (3H, s, CH_3), 3·8 (2H, t, *J* 4·6 Hz, CH_2OH), 3·9 (1H, s, OH), 4·1 (2H, t, *J* 4·6 Hz, CH_2OTs), 7·2 (2H, d, *J* 7·0 Hz, 2 × C*H*=CMe), 7·8 (2H, d, *J* 7·0 Hz, 2 × CH=CS). When equimolar quantities of toluene-*p*-sulphonyl chloride and ethylene glycol were used, the major reaction product was the bistoluene-*p*-sulphonate.

General Preparation of 2-R-3-*isoxazolin*-5-*ones* (7)—(12).—2·5N-Sodium methoxide (6·15 ml) in dry methanol was added to ethyl 3-hydroxyiminopropionate [14] (2 g, 0·015 mol). The appropriate toluene-*p*-sulphonate (0·015 mol) was added and the mixture, protected against moisture with a $CaCl_2$ tube, was magnetically stirred during 5 days at room temperature. The remaining slurry was extracted three times with dry ether and the ether (250 ml) was evaporated. The residual oil was analysed by g.l.c. or t.l.c. G.l.c.: SE 30 15%; Chromosorb G; 60—80 DMCS; 140° isothermal. T.l.c.: Merck silica gel PF 254; toluene–chloroform–acetone (40 : 25 : 35). Short-wave u.v. light revealed two spots, one for the toluene-*p*-sulphonate (R_F 0·73) and the other for the slower migrating 2-R-3-isoxazolin-5-one (R_F varied with the chain length of R). After elution with acetone, n.m.r., i.r., and mass spectra were recorded.

2-*Ethyl*-3-*isoxazolin*-5-*one* (7). This (40% yield) had δ ($CDCl_3$) 1·3 (3H, t, *J* 7·0, CH_3), 3·7 (2H, q, *J* 7·0 Hz, CH_2), 5·1 (1H, d, *J* 3·5 Hz, 4-H), and 7·8 (1H, d, *J* 3·5 Hz, 3-H), *m/e* 113 (M^+, 43%), 98 (20), 85 (29), 44 (20), and 28 (100), $\nu_{max.}$ (NaCl) 3120—3150 (C-4–H), 3060 (C-3–H), 1725 (C=O), and 1560 cm^{-1} (C=C) (Found: M^+, 113·0471. $C_5H_7O_2N$ requires M^+, 113·0476).

2-*n*-*Propyl*-3-*isoxazolin*-5-*one* (8). This (25%) had δ ($CDCl_3$) 0·9 (3H, t, *J* 7·0 Hz, CH_3) and 1·4—2·1 (2H, m, CH_2Me), *m/e* 127 (M^+, 40%), 98 (40), 85 (52), 71 (12), and 43 (100) (Found: M^+, 127·0617. $C_6H_9O_2N$ requires M^+, 127·0620).

2-*n*-*Butyl*-3-*isoxazolin*-5-*one* (9). This (50%) had δ ($CDCl_3$) 0·9 (3H, t, *J* 7·0 Hz, CH_3) and 1·1—2·0 (4H, m, CH_2CH_2Me), *m/e* 141 (M^+, 55%), 99 (28), 98 (55), 85 (41), 71 (11), 57 (100), and 48 (87) (Found: M^+, 141·0772. $C_7H_{11}O_2N$ requires M^+, 141·0789).

2-*n*-*Pentyl*-3-*isoxazolin*-5-*one* (10). This (20%) had δ ($CDCl_3$) 0·8—2·0 (9H, m, $[CH_2]_3CH_3$), *m/e* 155 (M^+, 22%), 99 (31), 85 (11), 71 (14), 56 (19), and 44 (100) (Found: M^+, 155·0948. $C_8H_{13}O_2N$ requires M^+, 155·0945).

2-(2-*Hydroxyethyl*)-3-*isoxazolin*-5-*one* (11). This (50%) could not be purified by g.l.c., and t.l.c. was used, δ ($CDCl_3$): 3·9 (4H, s, CH_2CH_2), 4·3 (1H, s, OH), *m/e* 129 (M^+, 89%), 98 (100), 85 (24), 71 (50), and 43 (78) (Found: M^+, 129·0431. $C_5H_7NO_3$ requires M^+, 129·0426).

2-(2-*Chloroethyl*)-3-*isoxazolin*-5-*one* (12).—This (13%) was purified on a silica gel (0·05—0·2 mm; Merck) column, eluting with benzene–acetone (90 : 10). The separation was monitored by t.l.c. on silica gel (PF 254 Merck) in the same solvent, for which the R_F value is 0·34, δ ($CDCl_3$) 3·8—4·1 (4H, m, AA'BB', CH_2CH_2Cl), *m/e* 147 (M^+, 24%), 98 (100), 85 (7), and 71 (9) (Found: M^+, 147·0092. $C_5H_6NO_2Cl$ requires M^+, 147·0087).

2-(2-*Cyanoethyl*)-3-*isoxazolin*-5-*one* (13).—The sodium salt of isoxazolin-5-one, obtained as before (10 g, 0·096 mol), was dissolved in 0·1M-sodium acetate buffer (20 ml), pH 4·25. Acrylonitrile (4 ml) was added and the solution was stirred overnight at room temperature. The mixture was extracted

* Both doublets were not well resolved owing to overlapping.

twice with ether. The ether was evaporated, and the remaining oil was analysed on a Dowex 50 W (H^+) column. Some coloured material was eluted with water, and 2-(2-*cyanoethyl*)-3-*isoxazolin*-5-*one* (13) (1%) was eluted with 0·5N-HCl. The acid was removed by repeated evaporation to dryness from methanol, δ ($CDCl_3$) 2·8 (2H, t, J 6·4 Hz, CH_2CN), 4·0 (2H, t, J 6·4 Hz, CH_2N), 5·3 (1H, d, J 3·5 Hz, 4-H), 8·0 (1H, d, J 3·5 Hz, 3-H), *m/e* 138 (M^+, 26%), 98 (100), 71 (25), 54 (30), and 43 (30), $\nu_{max.}$ 2260 (C≡N), 1730 (C=O), and 1550 cm^{-1} (C=C) (Found: M^+, 138·0434. $C_6H_6O_2N_2$ requires M^+, 138·0429). The natural product had identical properties.

Compound (13), both natural and synthetic, liberated β-aminopropionitrile, identified by comparison with an authentic sample, upon u.v. irradiation in aqueous solution.

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