

## 5-Vinylisoxazole

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Cycloaddition of fulminic acid to 1-butyne-3-ol gave a mixture of 5- $\alpha$ -hydroxyethylisoxazole (I) and 4- $\alpha$ -hydroxyethylisoxazole (II) in the ratio 9:1. By the dehydration of I, 5-vinylisoxazole (III) was obtained. Compound III has also been prepared by cyclization of 4-penten-2-ynal as well as its diethylacetal with hydroxylamine hydrochloride; in both instances no isomers have been obtained. Compound III spontaneously polymerizes even at room temperature yielding a polymer still containing isoxazole rings.

Among the numerous isoxazole derivatives known, vinyl derivatives have been studied only recently (1,2), and of the 3-unsubstituted vinylisoxazoles only the 4-vinyl-5-methylisoxazole was known (2). No other unsubstituted vinylisoxazoles have been prepared up to the present.

In order to find a suitable method to prepare 3-unsubstituted vinylisoxazoles, which might be useful in preparing vinylpolymers containing highly reactive groups, 1-butyne-3-ol has been allowed to react with fulminic acid (Scheme 1a) by slowly adding to 1-butyne-3-ol an aqueous solution of sodium fulminate and a dilute solution of sulfuric acid while maintaining the pH of the reaction mixture below 7.

In contrast to the expected course, based on data in the literature (3,4,5), of this reaction, a 9:1 mixture of 5- $\alpha$ -hydroxyethylisoxazole (I) and 4- $\alpha$ -hydroxyethylisoxazole (II) was obtained as shown by the N.M.R. spectra (6) on the two samples (see experimental part) separated by preparative gas chromatography. The structure of II was confirmed by the infrared spectrum (bands at 592, 849 and 1607  $\text{cm}^{-1}$  and absence of a band at about 800  $\text{cm}^{-1}$ ).

The 5-vinylisoxazole (III) was obtained from I by dehydration in the presence of 1:1 sulfuric acid in poor yield (30%).

In order to obtain better yields and to avoid the presence of isomers which are difficult to separate, a further attempt was made to synthesize III by allowing 4-penten-2-ynal diethyl acetal (7,8,9) (IV) to react with hydroxylamine hydrochloride by the method of Ch. Moureu, *et al.* (10).

Compound IV smoothly reacts with hydroxylamine hydrochloride giving practically pure III (yield 58%), as

shown by VPC and N.M.R. spectra, showing that path b is much more convenient for preparation of III than path a (Scheme 1).

Compound III, upon treatment with a 30% aqueous solution of cadmium chloride gave a white, slightly water-soluble crystalline precipitate which easily released the isoxazole compound by distillation of the aqueous suspension.

The formation of such a complex with III is a very effective purification method for this compound when obtained by path a, since I does not give, under the same conditions a precipitate. Compound III spontaneously polymerizes at room temperature yielding a polymer still containing isoxazole rings as shown by the infrared spectra.

Compound III is ring opened by bases just as all other isoxazole derivatives having unsubstituted 3-position.

Potassium methylate in ether solution immediately precipitates a white solid which was shown by infrared and ultraviolet spectra as well as elemental analysis to be the potassium enolate of cyanomethylvinyl ketone (V). In the presence of aqueous potassium hydroxide a similar reaction takes place as shown by ultraviolet spectra (Fig. 1), the rate depending upon the base concentration, in agreement with the kinetic order and the mechanism of the reaction, which already has been investigated for the unsubstituted isoxazole and some of its derivatives (11).

With potassium dichromate I or III quantitatively yields isoxazole-5-carboxylic acid (12); by stepwise oxidation, first with performic acid, then with periodic acid, III gave 5-isoxazolaldehyde which was characterized by the 2,4-dinitrophenylhydrazone (4). By exposure to the air, the aldehyde is spontaneously transformed into isoxazole-5-carboxylic acid.

## Scheme 1

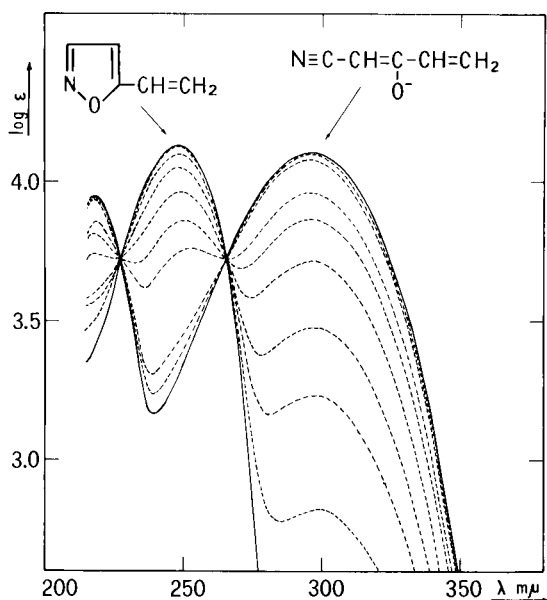
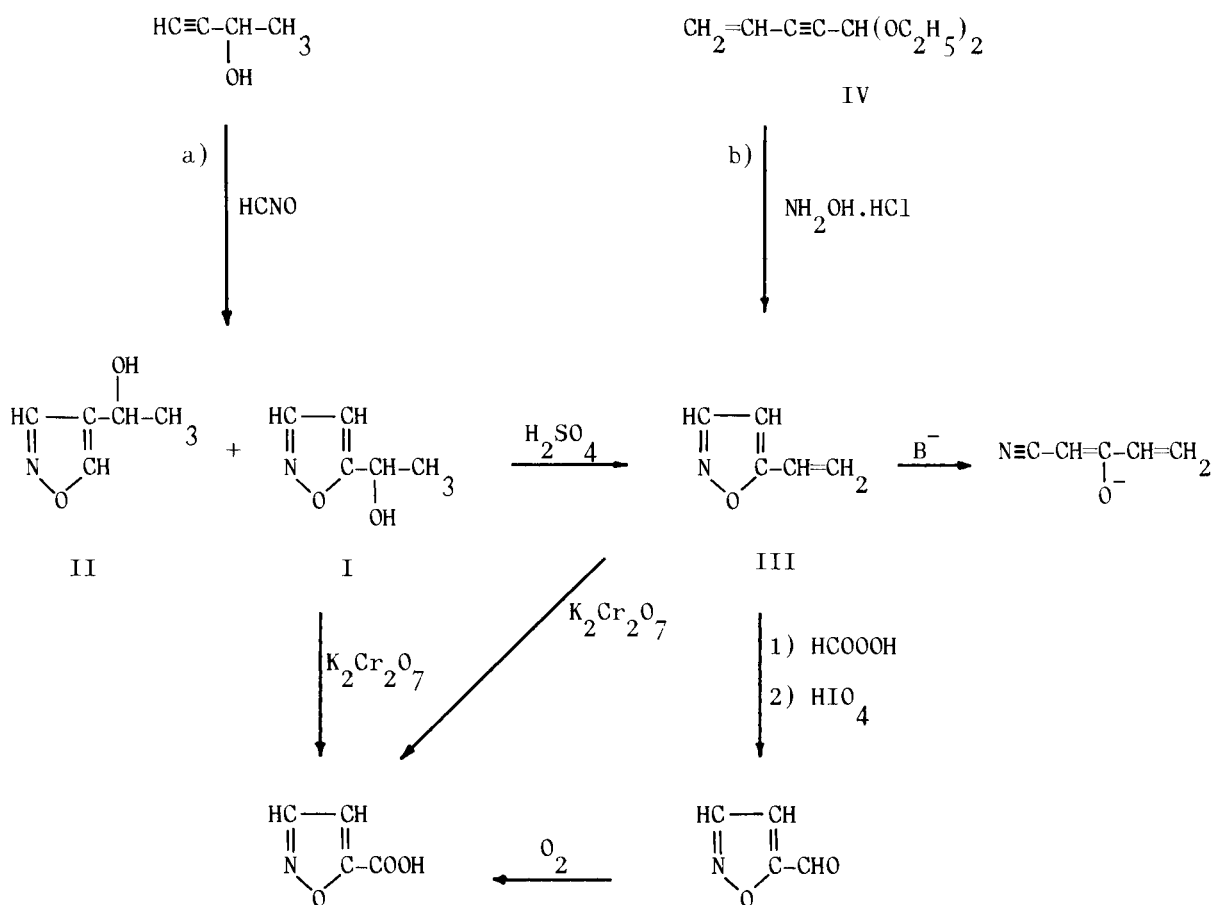


Figure 1. The change with time in the ultraviolet spectrum of 5-vinylisoxazole in 0.1 N potassium hydroxide solution.

## EXPERIMENTAL.

## Reaction of Fulminic Acid with 1-Butyn-3-ol.

To 80 ml. of a 55% aqueous solution of 1-butyn-3-ol in a vessel having two dropping funnels, a mechanical stirrer and a reflux condenser was added simultaneously, dropwise at such a rate that the reaction mixture was always slightly acidic, 50 ml. of 5.27 N aqueous sulfuric acid and 50 ml. of an aqueous solution of sodium fulminate, obtained from 30 g. of mercury fulminate and 300 g. of 2% sodium amalgam. Addition was complete in about 3 hours. The reaction mixture was saturated with ammonium sulfate and exhaustively extracted with ether. The ether extracts, dried over anhydrous sodium sulfate, after removal of the solvent and the unreacted 1-butyn-3-ol by fractional distillation, yielded 11.9 g. of distilled product. Gas chromatography on 2 m. polypropylene glycol columns shown two peaks with areas in the ratio 9:1. The product, by careful fractional distillation under reduced pressure, gave 5- $\alpha$ -hydroxyethylisoxazole (I) in the first fractions. It appeared to be practically pure by gas chromatographic analysis, b.p.  $109^\circ/7$  Torr;  $n_D^{25} = 1.4725$ ;  $\lambda_{\text{max}}$  (methanol), 216  $\text{m}\mu$ , ( $\log \epsilon = 3.76$ ). Infrared (neat)  $\text{cm}^{-1}$ , 3380(vs), 3140(w), 3110(w), 2980(s), 2935(m), 2900(w), 2875(w), 1592(s), 1476(s), 1453(m), 1408(m), 1372(m), 1317(s), 1290(m), 1232(m), 1203(s), 1182(s), 1105(vs), 1080(w), 1030(s), 1015(m), 978(s), 918(s), 900(s), 870(w), 804(vs), 740(w), 628(m); N.M.R. signals ( $\delta$  in p.p.m.; solvent, deuterium

oxide; TMS, external standard), 8.80 (doublet, ring proton 3 position), 6.80 (doublet with hyperfine structure, ring proton 4 position) 5.48 (quartet, ClI), 5.09 (singlet, OII in equilibrium with solvent), 1.99 (doublet, CH<sub>3</sub>).

*Anal.* Calcd. for C<sub>5</sub>H<sub>7</sub>NO<sub>2</sub>: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.30; H, 6.51; N, 12.48.

The last fraction of the fractional distillation, when analyzed by gas chromatography on 2 m. polypropylene glycol columns, showed two peaks with areas in the ratio 7:3 and by preparative gas chromatography on 2 m. "Carbowax" columns gave besides an additional quantity of I, a small sample of 4- $\alpha$ -hydroxyethylisoxazole (II); U. V.  $\lambda$  max (methanol), 214 m $\mu$ , (log  $\epsilon$  = 3.49); infrared (neat) cm<sup>-1</sup>, 3390(vs), 3125(m), 3030(w), 2980(s), 2930(w), 2900(w), 2880(w), 1607(m), 1438(s), 1374(s), 1296(m), 1180(s), 1114(s), 1093(vs), 1035(s), 1017(w), 986(s), 914(w), 887(vs), 849(s), 700(m), 655(w), 633(w), 592(m); N.M.R. signals ( $\delta$  in p.p.m.; solvent, deuterium oxide; TMS external standard), 8.95 (singlet with hyperfine structure, ring proton 5 position), 8.85 (singlet, ring proton 3 position), 5.29 (quartet, ClI), 5.09 (singlet, OII in equilibrium with solvent), 1.88 (doublet, CH<sub>3</sub>).

#### Oxidation of 5- $\alpha$ -Hydroxyethylisoxazole (I).

A mixture of I (0.095 g.), potassium dichromate (1.0 g.) and 5 M sulfuric acid (50 ml.) was refluxed for about 1 hour. The reaction mixture was extracted with ether and the solution was dried over anhydrous sodium sulfate. The 5-isoxazolecarboxylic acid (0.093 g.) obtained after removal of the solvent was sublimed at 90°/1 Torr., m.p. 146°. The infrared spectrum in potassium bromide was superimposable with one from an authentic sample (12).

#### 5-Vinylisoxazole (III).

##### (a) From 5- $\alpha$ -Hydroxyethylisoxazole (I).

A 4.6 g. sample of I was treated with 80 ml. of aqueous sulfuric acid (1:1) and distilled. Treatment of the distilled mixture with a 30% aqueous solution of cadmium chloride gave a white precipitate of III in the form of a complex salt from which III could be recovered by distillation of the aqueous suspension. Precipitation and distillation was repeated, and the product which separated, after drying over anhydrous sodium sulfate, was distilled under reduced pressure and collected in a dry-ice cooled container; b.p. 41°/21 Torr  $n_D^{25}$  = 1.4892;  $\lambda$  max (methanol) 247 m $\mu$  (log  $\epsilon$  = 4.14);  $\lambda$  max (isooctane) 246 m $\mu$  (log  $\epsilon$  = 4.11); infrared (neat) cm<sup>-1</sup>, 3145(s), 3105(m), 3025(w), 1867(w), 1648(m), 1624(w), 1587(s), 1556(s), 1470(vs), 1413(s), 1402(s), 1339(s), 1295(w), 1254(vs), 1204(s), 1183(s), 1027(s), 981(vs), 933(vs), 918(vs), 890(s), 800(vs), 657(w), 647(m), 621(s), 558(w), 476(w); N.M.R. signals ( $\delta$  in p.p.m.; solvent, deuteriochloroform; TMS internal standard) 8.15 (doublet, ring proton 3 position), 6.58 (quartet, vinyl ClI), 6.17 (doublet, ring proton 4 position), 6.02 (quartet, H (*trans*) of vinyl ClI<sub>2</sub>), 5.55 (quartet, H (*cis*) of vinyl ClI<sub>2</sub>).

*Anal.* Calcd. for C<sub>5</sub>H<sub>5</sub>NO: C, 63.14; H, 5.30; N, 14.73. Found: C, 62.88; H, 5.22; N, 14.61.

The addition complex of 5-vinylisoxazole with cadmium chloride obtained from the second precipitation was dried *in vacuo* over phosphorus pentoxide to constant weight (3.4 g.). The addition compound was found to contain 33% by weight of III.

##### (b) From the Diethylacetal of 4-Penten-2-ynal (IV).

A mixture of IV (8) (5.9 g.) dissolved in 60 ml. of ether and hydroxylamine hydrochloride (8.0 g.) dissolved in 10 ml. of water

was refluxed over 24 hours then distilled. The distilled mixture was treated with cadmium chloride as described above; 6.2 g. of the addition compound of III with cadmium chloride was obtained.

##### (c) From the 4-Penten-2-ynal.

A mixture of 4-penten-2-ynal (8,13), obtained by hydrolyzing IV with aqueous hydrochloric acid (3.5 g.), dissolved in 65 ml. of ether and hydroxylamine hydrochloride (9.1 g.) dissolved in 10 ml. of water was stirred until the aldehyde had disappeared (no reaction with 2,4-dinitrophenylhydrazine, about 36 hours), then the mixture was distilled. The distilled liquid was treated with cadmium chloride as described above. The addition compound of III with cadmium chloride was obtained (3.65 g.).

#### Oxidation of 5-Vinylisoxazole (III).

##### (a) With Potassium Dichromate.

A 0.11 g. sample of III was treated with potassium dichromate as described for the oxidation of I. Isoxazole-5-carboxylic acid (0.12 g.) was obtained, m.p. 146°.

##### (b) With Performic Acid.

A 1.1 g. sample of III was treated with 99% formic acid (12 g.) and 32% hydrogen peroxide (1.3 g.) and stirred at room temperature over a period of 24 hours. A solution of periodic acid dihydrate (3.0 g.) in 24 ml. of water was added. The mixture was stirred for 2 hours. By extracting with ether, after drying and removal of the solvent, a residue of crude 5-isoxazolaldehyde was obtained. The aldehyde was partly oxidized to isoxazole-5-carboxylic acid (m.p. 145-146°) by exposure to the air. The aldehyde portion was transformed into the corresponding 2,4-dinitrophenylhydrazone (4) (m.p. after crystallization from ethanol 220-221°).

#### Potassium Enolate of the Cyanomethylvinyl Ketone (V).

To a solution of potassium methylate prepared from 0.15 g. of potassium and 1.1 g. of methanol in 20 ml. of ether was added a solution of III (0.36 g.) in 20 ml. of ether. A white crystalline precipitate was formed immediately which, after standing overnight, was filtered under a nitrogen atmosphere, washed with anhydrous ether and recrystallized from anhydrous methanol; U. V.  $\lambda$  max (aqueous 0.1 N potassium hydroxide), 297 m $\mu$  (log  $\epsilon$  = 4.10); infrared (potassium bromide) cm<sup>-1</sup>, 3095(vw), 3045(vw), 3020(vw), 2160(vs), 1867(w), 1630(m), 1496(vs), 1445(s), 1280(w), 1238(w), 1152(m), 1050(m), 1020(vw), 983(m), 930(s), 921(s), 781(s), 667(w), 617(s).

*Anal.* Calcd. for C<sub>5</sub>H<sub>4</sub>NOK: C, 45.09; H, 3.03; N, 10.52; K, 29.35. Found: C, 44.90; H, 2.98; N, 10.32; K, 28.92.

The infrared spectra were determined with a Perkin-Elmer Model 225 spectrophotometer. The ultraviolet spectra were determined with a Hilgher Watts "Uvispek" H 700 apparatus. The N.M.R. spectra were determined with a DA 60 IL Varian instrument.

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