Mechanism of formation of trimethylisoxazole and intermediates upon alkaline hydrolysis of nitroethane

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Nitroethane and higher homologous primary nitroalkanes undergo a base-catalyzed condensation yielding the corresponding 2,3,4-trialkyisoxazoles. Basic hydrolysis of nitroethane to acetaldehyde is the key initial step followed by a series of condensation and elimination reactions. Through the use of appropriately ^{14}C-labelled intermediates and acetaldehyde-d_4, a relatively simple mechanism is indicated which will satisfactorily account for all observed intermediates indicated in a summary of the reaction sequence.

1) nitroethane → acetaldehyde + nitrite

2) acetaldehyde + nitroethane → nitroalcohol → nitroolefin

3) nitroolefin + nitroethane → 2,4-dinitro-3-methylpentane → 3-methylpentan-2,4-dioxime → 3,4,5-trimethylisoxazole

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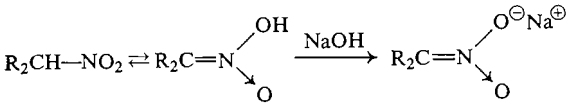
Discussion

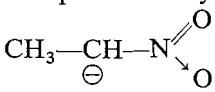
Primary and secondary nitroparaffins usually dissolve in aqueous or aqueous alcoholic solutions of strong alkali due to the formation of the corresponding salt of the aci-form, e.g.



Other reactions of such nitroparaffins with alkali and/or other reagents have been reported (1–6) and most have been considered to involve the aci-forms. One particularly common product of prolonged action of alkali on nitroethane is trimethylisoxazole. By treating nitroethane with a concentrated solution of potassium carbonate, Dunstan *et al.* (2, 3) identified acetonitrile, trimethylisoxazole, and nitrite ions. An aldehyde was also found in the reaction mixture of alcoholic KOH and nitroethane. Nitropropane gave under similar conditions propionitrile, triethylisoxazole, and nitrite ion (2).

In considerably more recent work, Lippincott (1) has shown that using an organic base such as propylamine in aqueous solution in conjunction with nitroethane, facilitates the isolation of crystalline 3-methyl-2,4-pentanedionedioxime, which upon subsequent heating in aqueous medium gives trimethylisoxazole. The 1,3-dioximes have long been known as suitable precursors in the preparation of isoxazoles (7). In the mechanism proposed by Lippincott (1), the aci-nitroethane was considered as the key starting compound.

It has been found that 2-methyl-2-nitro-1,3-propanediol decomposes in alkali to give nitrite in variable yields (8), with the reverse aldol reaction becoming increasingly important as the alkali concentration is increased. Even in the absence of a base, 2-methyl-2-nitro-1,3-propanediol and 2-ethyl-2-nitro-1,3-propanediol were found to generate formaldehyde when heated under reflux in water (ca. 30%). The resulting solution became acidic, whereupon no further formation of formaldehyde and only a trace of nitrite (0.5 %) could be detected in the decomposition mixture. In the absence of a base, the decomposition does not go to completion due to the acidity of the resulting solution, since the nitroparaffin may behave as a pseudo acid,



Treatment of nitroethane with saturated potassium carbonate resulted in the formation of a red-colored oil, which accumulated on the surface of the mixture on warming or upon storage at room temperature for several days. It was shown by gas chromatography to be composed of acetonitrile, acetaldoxime, and trimethylisoxazole (Fig. 1). The nitrite ion, up to 35% based on the nitroethane, could be detected in the aqueous solution. When a mixture of

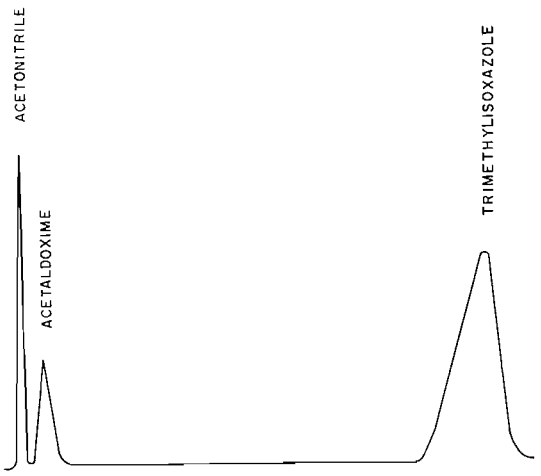
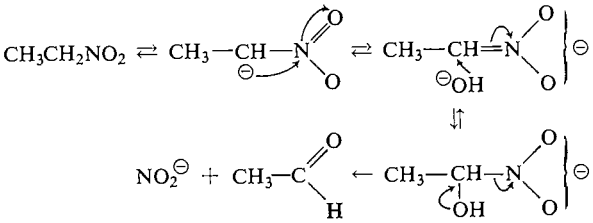


FIG. 1. Gas chromatography of product from nitroethane in potassium carbonate solution, silicone gum rubber column at 100 °C helium flow 30 ml/min.

nitroethane in carbonate solution was distilled prior to the appearance of the red oil, the distillate was shown to contain acetaldehyde which was identified as its 2,4-dinitrophenylhydrazone.

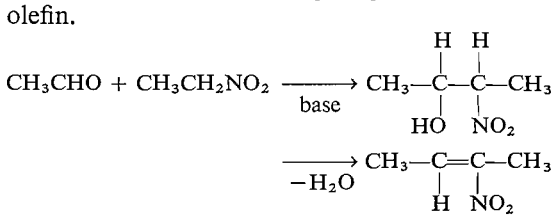
The conversion of primary and secondary nitroparaffins to aldehydes and ketones, respectively, by acidifying the aci-salts was discovered by Nef and has been extensively investigated (9). Oxidation of some nitroparaffins in basic media to the corresponding carbonyl compounds has also been reported (4, 10, 11). However, the isolation of acetaldehyde from a mixture of nitroethane in aqueous potassium carbonate solution has apparently not been reported before. To explain the formation of these reaction products, we formulate the reaction as follows (cf. 12).

(1) Conversion of nitroethane to acetaldehyde and nitrite ion in the following sequence



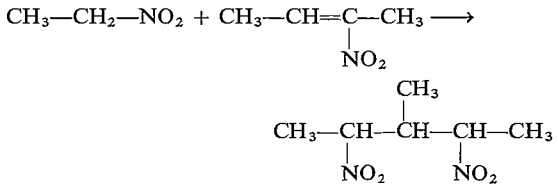
It has been suggested (4, 10) that an oxidative process involving free radical intermediates may be involved in this conversion. We have found little or no change in the rate of formation of the nitrite ion under nitrogen, and hence the hydrolytic mechanism involving the initial carbanion formation is favored.

(2) A condensation of acetaldehyde and nitroethane in the presence of a base, followed by facile elimination of water giving rise to a nitro-olefin.



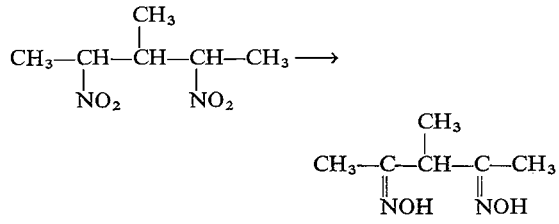
The formation of a nitro-olefin from the corresponding nitro-alcohol is not uncommon. For example, Reasenberg and Smith (13) have isolated 2-nitro-2-butene from a mixture of acetaldehyde and nitroethane in alcoholic solution with a trace of sodium hydroxide. With high base concentrations such as in our experiment, the elimination reaction would be very much enhanced.

(3) Condensation of nitroethane with 2-nitro-2-butene gives rise to 2,4-dinitro-3-methylpentane. Analogous reactions between primary or secondary aliphatic nitro compounds with



α-nitro-olefins have been described (14, 15) and this forms the basis of the preparation of 1,3-dinitroparaffins, although yields are reported to be variable.

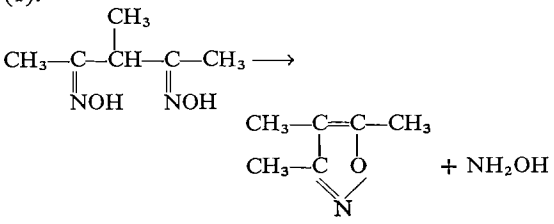
(4) The γ-dinitroparaffin is converted to the corresponding dioxime. Lippincott (1) has shown that the dioxime is an isolable intermediate in the reaction of nitroethane with an



organic base. The exact mechanism of the conversion of the dinitro compound to the

dioxime is as yet not clear. The possibility exists that acetaldehyde may serve as a reducing agent since some ^{14}C-labelled acetate was found when acetaldehyde-1-^{14}C was used. More likely, acetate is formed in the competitive alkaline oxidation of the corresponding aldehyde or via oxidation by the nitrite. Alternatively, the dinitroparaffin may be converted to the dioxime via a hydrolytic process either involving the carbanion or hydration of the nitro form. Detailed experimentation would be necessary to illucidate the exact mechanism involved in this particular step.

(5) The 2,4-dioxime, on hydrolysis with or without an acid or base, will give the expected trimethylisoxazole together with hydroxylamine (1).



(6) The formation of acetaldoxime and acetonitrile as by-products can be accounted for by the reaction between an aldehyde and hydroxylamine while acetonitrile results from

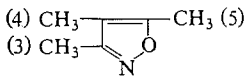
$$CH_3CHO + NH_2OH \longrightarrow$$

$$CH_3{-}CH{=}NOH \xrightarrow{-H_2O} CH_3CN$$

a dehydration of the oxime. In the preparation of heptaldoxime in the presence of a strong sodium carbonate solution, the corresponding nitrile has been identified (16).

The isolation of the intermediates indicated above has been accomplished either in our laboratory or reported by others and particularly, we have now isolated for the first time the intermediate 1,3-dioxime in the aqueous, basic reaction medium. The identity of the dioxime (3-methyl-acetylacetone-2,4-dioxime) was provided by nuclear magnetic resonance (n.m.r.) and by comparison of physical properties (melting point) with those of the corresponding dioxime provided by direct synthesis. Further proof of identity of the dioxime was its facile transformation in slightly basic aqueous media to form the expected 3,4,5-trimethylisoxazole.

We have obtained supporting evidence for the above mechanism by the reaction of nitroethane with formaldehyde, acetaldehyde-1-^{14}C, formaldehyde-^{14}C, and deuterated (d_4) acetaldehyde. When the reaction was carried out in the presence of formaldehyde, the products were 3,4,5-trimethylisoxazole and 3,5-dimethylisoxazole as predicted from the mechanism. Reactions carried out in the presence of acetaldehyde-1-^{14}C and formaldehyde-^{14}C resulted in radioactivity incorporation of a high percentage into the respective isoxazole. Decomposition of the labelled isoxazole and positive positioning of the radioactive carbon gave further proof for the suggested mechanism. Finally, deuterated (d_4) acetaldehyde was also incorporated in the predicted fashion as shown by n.m.r. The n.m.r. spectrum of 3,4,5-trimethylisoxazole consists of three singlet peaks with τ values of 8.2, 7.95, and 7.8. These peaks have been ascribed to the methyl groups on the 4, 3, and 5 positions, respectively.



The singlet at τ 7.95 has a maximum intensity while the other two have equivalent intensities but the intensity of each individually is about two-thirds of that at 7.95. Deuterated acetaldehyde was incorporated into trimethyl isoxazole with the D_3C-group appearing in the predicted 4 position since the intensity of the peak at τ 8.2 was reduced to about two-thirds its usual intensity, while the intensity ratio of the other peaks did not change.

Experimental

Analytical Methods

(1) Estimation of Nitrite Ions

The standard colorimetric method of determination of nitrite ion by diazotizing sulfanilic acid followed by coupling with α-naphthylamine was employed (17).

(2) Estimation of Formaldehyde

The colorimetric determination by complex formation with chromotropic acid was employed (18).

(3) Identification of Products by Gas Chromatography

Reaction products were separated by gas chromatography, on a column (5 ft long, 0.25 in. diameter) packed with 60–80 Chromosorb W containing 20% silicone gum rubber SE-30 as liquid phase. The helium flow rate was 30 ml/min. and the temperature adjusted to 100 °C. Each component in a mixture was identified by comparing its retention time with that of a known compound from other sources except for trimethylisoxazole. Trimethylisoxazole was separated from the rest of the product mixture by treating the mixture with a saturated aqueous solution of mercuric chloride. The grayish precipitate was collected,

washed with cold water, and dried between filter papers. This double salt of trimethylisoxazole was suspended in water and distilled. The distillate was extracted with petroleum ether (30–60°) and the extract dried with sodium sulfate. The residue of the extract, after evaporating off the solvent, was an oil of pyridine-like odor. This oil was shown to be the component having the longest retention time on gas chromatography and gave the expected n.m.r. spectrum with singlets of τ 8.2, 7.95, and 7.8.

Preparative Experiments

(1) Synthesis of 3,4,5-Trimethylisoxazole

To a saturated aqueous solution (100 ml) of potassium carbonate was added with thorough mixing, 3-methylpentane-2,4-dione (12 g) and hydroxylamine hydrochloride (16 g) and the mixture heated at 60–70° for 4 h. The reddish oil that formed was separated and excess saturated aqueous mercuric chloride added to yield the water insoluble mercury complex. The gray precipitate was suspended in water and the mixture distilled. The distillate was extracted with chloroform, the extract dried with sodium carbonate, and evaporation of the solvent left a pale yellow oil. Distillation under reduced pressure gave a clear oil the n.m.r. of which showed the three expected methyl singlets at τ 8.2 (C-4), 7.95 (C-5), and 7.8 (C-3).

Anal. Calcd. for C_6H_9NO: C, 64.86; H, 8.18; N, 12.61. Found: C, 64.86; H, 8.21; N, 12.75.

(2) Synthesis of 3,5-Dimethylisoxazole

This isoxazole was synthesized as described above from pentane-2,4-dione (11 g) and hydroxylamine hydrochloride (16 g) as described for 3,4,5-trimethylisoxazole. The n.m.r. spectrum showed the two expected methyl singlets with τ 7.82 (C-5) and 7.68 (C-3) with a vinylic proton singlet (C-4) at τ 4.15.

Anal. Calcd. for C_5H_7NO: C, 61.84; H, 7.21; N, 14.43. Found: C, 61.83; H, 7.29; N, 14.52.

(3) Synthesis of 3,4,5-Trimethylisoxazole from Nitroethane

Nitroethane (15 ml, 0.2 mole) was introduced to a saturated aqueous solution of potassium carbonate (138 g, 1 mole) and thoroughly mixed. The mixture was either heated gently to about 60–70 °C or left at room temperature for several days until a red oil (ca. 5 ml) separated at the surface. The oil was separated, followed by drying with potassium carbonate and by gas chromatography (Fig. 1). Alternatively, the cooled two phase mixture was extracted with chloroform and the chloroform extract was washed with water and evaporated under vacuum. Addition of an excess of a saturated aqueous solution of mercuric chloride to the residue gave a gray-brown precipitate which was filtered off and washed with cold water. The precipitate was suspended in water (300 ml) and the mixture distilled. The distillate was extracted with chloroform and the chloroform extract was evaporated to leave a pale yellow oil. Distillation of the oil under reduced pressure gave trimethylisoxazole with physical characteristics identical to trimethylisoxazole prepared from 3-methylpentane-2,4-dione.

(4) Isolation of 3-Methylpentane-2,4-dione Dioxime from Nitroethane – K_2CO_3 Reaction Mixtures

Reaction mixtures of nitroethane (15 ml) in saturated aqueous potassium carbonate solution (100 ml) were stored at room temperature for extended time periods (4–7 days). A white, crystalline solid that slowly collected at the interface of the reddish oil (trimethylisoxazole) and the aqueous phase, was collected, washed with ether, and recrystallized from acetone – ether, m.p. 130–131 °C, undepressed upon admixture with dioxime obtained from 3-methylpentane-2,4-dione. The n.m.r. spectrum was also identical to that of the dioxime synthesized from the dione (C-1 and C-5 methyl singlet, τ 8.25, C-3 proton quartet, τ 7.3, 3-methyl doublet, τ 8.9, and the N—O—H proton singlet downfield, τ −0.8 to −1.0).

Anal. Calcd. for $C_6H_{12}N_2O_2$: C, 50.00; H, 8.33; N, 19.44. Found: C, 50.09; H, 8.27; N, 19.32.

(5) Synthesis of Dioxime of 3-Methylpentane-2,4-dione

To an ethanolic solution (20 ml) of the dione (5.0 g) was added a neutral alcoholic solution (20 ml) containing a 2.2 molar equivalent of hydroxylamine. The mixture was gently heated (50–60°) for 30 min after which the volume of the solution was reduced and upon storage at 5 °C, a white, crystalline solid separated. Upon recrystallization from acetone – ether, it had m.p. 131–132 °C. The n.m.r. spectrum showed the expected singlet for the C-1 and C-5 methyl protons, τ 8.2, C-3 proton quartet, τ 7.3, 3-methyl doublet, τ 8.9, and the N—O—H proton singlet downfield, τ −0.7 to −1.0.

Anal. Calcd. for $C_6H_{12}N_2O_2$: C, 50.00; H, 8.33; N, 19.44. Found: C, 50.05; H, 8.30; N, 19.51.

(6) Incorporation of ^{14}C-Formaldehyde

To a solution (200 ml) of potassium carbonate (138 g) was added nitroethane (15 ml) and ^{14}C-formaldehyde (5 ml aqueous solution containing 5.25×10^6 d.p.m.) and the mixture refluxed for 4 h. Steam distillation followed by extraction of the distillate with chloroform, and evaporation, yielded a light yellow oil which upon gas chromatographic analysis showed the presence of trimethylisoxazole (main component) and 3,5-dimethylisoxazole. Collection of the components in the scintillator liquid showed no radioactivity in the trimethylisoxazole while 3,5-dimethylisoxazole was highly active (see Table I). Total activity (5.094×10^6 d.p.m.) in the mixture showed only a 3% loss of added ^{14}C-formaldehyde. Authentic 3,5-dimethylisoxazole was added to the reaction product and the mixture separated on a preparative vapor phase chromatographic (v.p.c.) column (XF-1150 liquid phase, 6 ft × 1/2 in., operating temperature 120 °C). The specific activity of 3,5-dimethylisoxazole was 73.6×10^6 d.p.m./mole.

(7) Degradation of Radioactive 3,5-Dimethylisoxazole

Label positioning was accomplished as follows: aliquots of dimethylisoxazole (DMI) in dry ethylacetate were subjected to ozone treatment. The ozonide was decomposed with water (10 ml) containing 6 *N* H_2SO_4 (3 ml). Nitrogen was passed through the reaction mixture for 20 min after which $KMnO_4$ solution (15 ml, 2 mmoles) was added. The CO_2 evolved was trapped in either barium hydroxide solution or ethanolamine (5 ml). Control experiments with pyruvic acid indicated about 80% decarboxylation under these conditions. Addition of acetate-1-^{14}C showed insignificant degradation (1–3%). The recoveries of $^{14}CO_2$ from C-1 of pyruvate (corresponding to the 4 position of 3,5-dimethylisoxazole) are summarized below in Table I.

TABLE I

Label positioning of radioactive 3,5-dimethylisoxazole

	d.p.m. of DMI	d.p.m. in CO_2	% recovery
1.	80 300	60 700	75
2.	4 620	3 690	80
3.	8 160	7 150	88
4.	6 010	5 520	91

(8) Incorporation of Acetaldehyde-1-^{14}C into 3,4,5-trimethylisoxazole

To a solution (200 ml) of potassium carbonate (45 g) and nitroethane (15 ml) was added aqueous (5 ml) acetaldehyde-1-^{14}C (11.1×10^6 d.p.m.) and the solution heated (70–80 °C) for 5 h, after which the reaction mixture was stored at room temperature overnight. A v.p.c. analysis of the red oil appearing at the surface indicated, as before, the presence of acetonitrile, acetaldoxime (both minor peaks appearing in that order), and trimethylisoxazole (major peak). Trapping of these components in the scintillator liquid showed minor radioactivity in acetonitrile and acetaldoxime while trimethylisoxazole was highly radioactive. Separate collections of acetonitrile and acetaldoxime were diluted with the cold compound followed by alkaline oxidation to acetate. The resulting acetate was degraded to CO_2 and the methylamine by the Schmidt procedure (19) (see Table II).

TABLE II

Label positioning of radioactive acetonitrile and acetaldoxime

d.p.m. in:	d.p.m. in CO_2	% recovery
Acetonitrile		
1. 75	73	97
2. 85	81	95
3. 105	101	97
Acetaldoxime		
1. 175	170	97
2. 140	135	96
3. 210	190	91

The alkaline reaction was exhaustively extracted with chloroform and the extract evaporated to yield a reddish oil, which upon v.p.c. analysis indicated almost pure 3,4,5-trimethylisoxazole (3.2 g, 9.1×10^6 d.p.m.). Total recovery of radioactivity in trimethylisoxazole was about 90%. The aqueous alkaline solution was acidified with sulfuric acid (8 *N*) and the acid solution extracted exhaustively with ether. Evaporation to a small volume (3 ml) and v.p.c. analysis indicated the presence of acetic acid containing some radioactivity. Glacial acetic acid (1.0 ml) was added and the solution neutralized with sodium carbonate followed by evaporation to dryness. The sodium salt was consequently degraded (in triplicate) to CO_2 and methylamine by the Schmidt procedure (19) (see Table III).

(9) Degradation of Radioactive Trimethylisoxazole

To aliquots of radioactive 3,4,5-trimethylisoxazole dissolved in water saturated ether was added metallic sodium. A typical run would involve about 100 mg of isoxazole (2845 d.p.m.) in 200 ml water saturated ether. Upon completion of refluxing (2 h), 2-butanone (5 ml) was added and the butanone fraction (4.5 ml) recovered by fractional distillation. The total radioactivity recovered was between 200 and 300 d.p.m. The butanone fraction was treated with alkaline hypoiodite, the iodoform which formed being collected and found to be inactive while the sodium propionate contained all the radioactivity. Propionate was decarboxylated to acetate via a Hoffman reaction (ethylamine being oxidized to acetate with permanganate) in the usual manner. All radioactivity remained in acetate. Acetate was degraded by the Schmidt procedure (see Table IV).

TABLE III

Label positioning in radioactive acetate

	d.p.m. in acetate	d.p.m. in CO_2	% recovery
1.	275	260	95
2.	350	340	97
3.	310	195	93

TABLE IV

Label positioning in methylethylketone from trimethylisoxazole

	d.p.m. in original MEK sample	d.p.m. in CO_2 from acetate	% recovery
1.	215	185	86
2.	275	255	93

(10) Incorporation of Acetaldehyde-d_4

To a solution (100 ml) of nitroethane (15 ml) and potassium carbonate (30 g) was added acetaldehyde-d_4 (5 ml) and the solution heated (80 °C) for 4 h followed by storage at room temperature for a further 16 h. The reaction mixture was worked up as described above and the 3,4,5-trimethylisoxazole formed analyzed by n.m.r. spectroscopy. A reduction (ca. 40%) in the intensity of the C-4 methyl singlet (τ, 8.2) was noted.

Acknowledgment

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