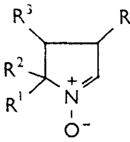
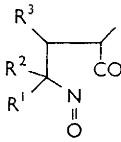
The Periodate Oxidation of Nitrones

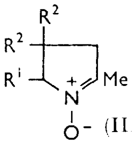
By A. K. Qureshi and B. Sklarz

The periodate oxidation of some Δ^1-pyrroline 1-oxides with two substituents at C-5 but unsubstituted at C-2 leads to a series of 4-nitrosopentanoic acids. Evidence is adduced for the course of the reaction. An *N*-alkylhydroxyamino-compound is oxidised in chloroform to the nitroso-compound by tetraethylammonium periodate, a potentially useful reagent soluble in various organic solvents.

An earlier study[1] of the dimers of 5,5-dimethyl-Δ^1-pyrroline 1-oxide (Ia) had shown that these could be distinguished from each other by oxidation with sodium periodate. It was found at that time that the nitrone (Ia) itself was rapidly attacked by the reagent giving 4-methyl-4-nitrosopentanoic acid (IIa) as a colourless dimer which crystallised from the blue reaction mixture. Total periodate uptake was 1·7 mol. in 24 hours, at a rate increasing slightly with pH. The nitrones (Ib–d)[2] were similarly oxidised to the nitrosopentanoic acid (IIb–d) dimers. The infrared spectra of their blue-green melts all showed a band at 1555—1565 cm.$^{-1}$ characteristic of the nitroso-group.[3] The ultraviolet absorption at 293—298 mμ, which was observed for three of the dimers, indicated the more stable *trans*-configuration, but the spectra of the compounds before recrystallisation were not recorded. The solids were rather unstable, particularly to light.


(I)


(II)


(III)

a: $R^1 = R^2 = Me, R^3 = R^4 = H$
b: $R^1 = R^2 = R^3 = Me, R^4 = H$
c: $R^1 = R^2 = R^4 = Me, R^3 = H$
d: $R^1 = Me, R^2 = CO_2Et, R^3 = R^4 = H$
e: $R^1 = Me, R^2 = CO_2H, R^3 = R^4 = H$

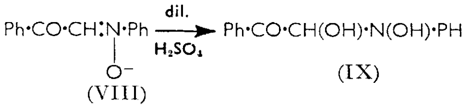
a: $R^1 = Me, R^2 = H$
b: $R^1 = H, R^2 = Me_3$

By contrast, 5-carboxy-5-methyl-Δ^1-pyrroline 1-oxide (Ie) instantly afforded iodine in an exothermic reaction, from which lævulinaldehyde was isolated as its bis-2,4-dinitrophenylhydrazone.

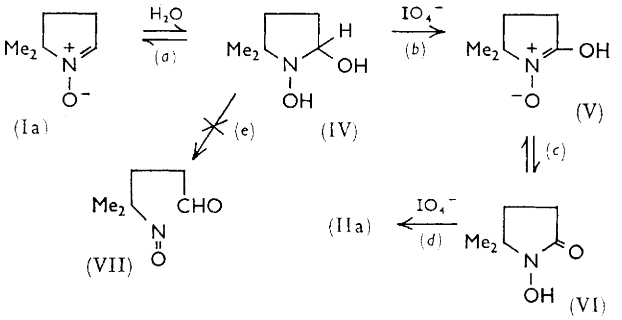
The nitrones[2] (IIIa and b) and (XI) were attacked very slowly by periodate.

The oxidation is thought to take the following course shown in Scheme 1, for which some experimental evidence is presented below.

The Δ^1-pyrroline 1-oxides are rather hygroscopic substances, (Ia) being obtained on occasion as a low-melting solid hydrate, but there is no evidence[4] for the formation of the adduct (IV) in bulk. The intensity of ultraviolet absorption of (Ia) was not decreased in water, weak hydrochloric acid, or 2N-alkali. Likewise, there was no significant difference in the appearance of the n.m.r. spectrum in deuterochloroform, water, or very dilute hydrochloric acid. Nevertheless, nucleophilic additions to the aldonitrone double bond are well known,[2] and a small amount of (IV) probably exists in equilibrium with (I) (step *a*). This addition of water is exemplified by the colourless crystalline hydrate (IX)[5]


$$\underset{\substack{| \\ O^-}}{Ph{\cdot}CO{\cdot}CH{:}N{\cdot}Ph} \xrightarrow[H_2SO_4]{dil.} Ph{\cdot}CO{\cdot}CH(OH){\cdot}N(OH){\cdot}PH$$
(VIII) (IX)

obtained from the yellow nitrone (VIII)[5] with dilute acid. These compounds were prepared and their relationship confirmed by their infrared spectra.



Scheme 1

The adduct (IX) was oxidised by periodate almost instantaneously, irrespective of pH. In contrast, the oxidation of the nitrone (VIII) was considerably slower at pH 4·5 and 6·5, although at pH 2·9 and 9·2 the rate increased owing to the presumed catalysis of the hydration step (see Table 2). Nitrosobenzene and benzoic acid were isolated as reaction products. It is, however, surprising that the total uptake of periodate by the two compounds was not the same. The hydrate was not oxidised by tetraethylammonium periodate (see below) in dimethylformamide. Retardation or failure of the hydration step (*a*) may be the bar to the oxidation of nitrones (IIIa and b) and (XI), for these compounds are less susceptible to nucleophilic addition.[2]

A fast periodate oxidation of the type


$$H{-}\overset{|}{\underset{|}{C}}{-}N(OH)R \longrightarrow \overset{|}{\underset{|}{C}}{=}N^+(R){-}O^-$$

is involved in the oxidations described previously.[1] Similarly, the *N*-hydroxypyrrolidine (X) was oxidised instantly to the nitrone (XI), characterised as its picrate. The alternative to this very fast oxidation (step *b*) would be a cleavage step (*e*) of the glycolysis type, which

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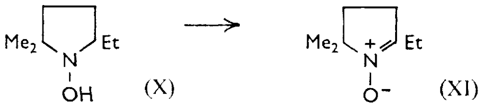
[1] V. M. Clark, B. Sklarz, and Sir A. Todd, *J. Chem. Soc.*, 1959, 2123.

[2] R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland, and Sir A. Todd, *J. Chem. Soc.*, 1959, 2094.

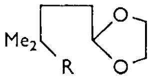
[3] B. G. Gowenlock and W. Lüttke, *Quart. Rev.*, 1958, **12**, 321.

[4] J. Thesing and W. Sirrenberg, *Chem. Ber.*, 1959, **92**, 1748.

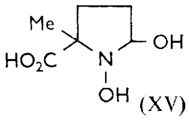
[5] F. Kröhnke and E. Börner, *Ber.*, 1936, **69**, 2006.



would give the nitroso-aldehyde (VII). However, as is well known, aldehydes are only oxidised very slowly by periodate, so that an accumulation of (VII) might be expected. In experiments with limited amounts of periodate in the presence of chloroform, no aldehyde could be detected (negative 2,4-dinitrophenylhydrazine test). It is considered unlikely that the γ-nitroso-aldehyde (VII) can cyclise sufficiently quickly to the hydroxamic acid (VI), since, in an analogous case[6] in the bornyl series, this reaction was shown to be photochemical rather than thermal.



(XII: R = NO_2)
(XIII: R = NH·OH)
(XIV: R = NO)



(XV)

Rapid tautomerisation (step *c*) gives the hydroxamic acid structure (VI), established for the known compound by the infrared band[7] at 1690 cm.$^{-1}$.

The rapid oxidation of hydroxamic acid (VI) by periodate has already been described,[1] and the reaction has since been shown to be general.[8]

In an attempt to prepare the aldehyde (VII), the nitro-dioxolan (XII) was reduced with zinc dust and ammonium chloride to the hydroxyamino-compound (XIII), a colourless liquid giving a strong tetrazolium test.[9] It was oxidised instantly by excess of aqueous sodium periodate,[10] when the colourless crystalline dimer of the nitroso-compound (XIV) was precipitated from the blue solution. All attempts to hydrolyse the dioxolan ring in (XIV) failed. 0·1N-Acid at 50° destroyed the compound, while other mild conditions such as toluene-*p*-sulphonic acid in acetone[11] or ethanol[12] had no effect.

It is of interest that the oxidation of the hydroxylamine (XIII) even proceeded instantly in chloroform solution with tetraethylammonium periodate, which is very soluble in that solvent. The reagent is a white crystalline solid prepared by neutralising tetraethylammonium hydroxide with the calculated amount of paraperiodic acid. It is recrystallised from t-butyl alcohol, and we found that in contrast to the experience of other workers,[13] it is stable in the desiccator for periods of weeks and can be comfortably handled in the air. Its great solubility in water makes it useful in oxidations where the relative insolubility of the sodium and potassium salts is troublesome. Being soluble in various common organic solvents, it may also find use as co-oxidant in homogeneous organic phases.[14]

The anomalous oxidation of the nitrone acid (Ie) can be rationalised as follows. Preliminary hydration as before gives an α-hydroxylamino-acid (XV). Simple α-hydroxylamino-acids have been shown[9,15] to undergo rapid oxidative decarboxylation with periodate:

$$R{\cdot}CH{\cdot}(NHOH){\cdot}CO_2H \longrightarrow R{\cdot}CHO + CO_2 + [HNO] \longrightarrow \tfrac{1}{2}H_2N_2O_2 \longrightarrow N_2O$$

The oxidation of (XV) to lævulinaldehyde is closely analogous.

EXPERIMENTAL

Preparations.—*Tetraethylammonium periodate.* Paraperiodic acid (7·72 g., 0·034 mol.) in water (20 ml.) was added in portions to cold 25% tetraethylammonium hydroxide (20 ml., 0·034 mol.). Evaporation under reduced pressure left a crude solid which was extracted with hot t-butyl alcohol. The *compound* was precipitated with di-isopropyl ether and recrystallised from t-butyl alcohol, (8·5 g., 82%), m. p. 176—177°; n.m.r. signals ($CDCl_3$), τ 8·62 (triplet, *J* = 7 c./sec.), 6·67 p.p.m. (quadruplet, *J* = 7 c./sec.) (Found: C, 30·05; H, 6·25; N, 4·05; IO_4^-, 61·1. $C_8H_{20}INO_4$ requires C, 29·9; H, 6·3; N, 4·35; IO_4^-, 59·5%). Approximate minimum solubility at room temperature in the following common solvents (g./100 ml. of solvent): water (130), acetic acid (100), acetone (80), pyridine (70), dimethylformamide (60), nitromethane (50), methanol (30), ethanol (10), ethyl acetate, ether, benzene (insoluble). In chloroform two clear layers are obtained with 22 g./100 ml. Complete miscibility is not attained at 2·3 g./100 ml. but the dense lower layer is very small and the main layer contains much periodate.

5,5-*Dimethyl*-Δ^1-*pyrroline* 1-*oxide* (Ia). The nitrone was prepared as described earlier;[2] $\lambda_{max.}$ (EtOH) 234 mμ (ε 7500); (in water, N/1000-hydrochloric acid, and 2N-sodium hydroxide) 226 mμ (ε 7500); n.m.r. signals ($CDCl_3$), 8·55(s), 7·78(d), 7·48(d), 3·17(t); areas 6 : 2 : 2 : 1. The last peak appears at 2·8 in D_2O, 2·5 (H_2O), 2·8 (N/1000-HCl) without changes in area or appearance of new peaks.

Phenylglyoxal N-*phenyloxime* (VIII).[5] The nitrone was prepared as a yellow solid, m. p. 109—110°, $\lambda_{max.}$ (mull) 1580, 1600, 1645 cm.$^{-1}$.

Phenylglyoxal N-*phenyloxime hydrate* (XI). In a slight modification of Kröhnke's procedure,[5] the oxime (VIII), (1·8 g.) in ice-cold ethanol (25 ml.) was stirred with 0·1N-sulphuric acid (40 ml.) for 1 hr. Extraction with ether gave a yellow-white residue which on recrystallisation from chloroform–light petroleum gave the colourless hydrate, m. p. 88°, which became yellow on standing in the air (Found: C, 70·05; H, 5·2; N, 6·15. Calc. for $C_{14}H_{13}NO_3$: C, 69·15; H, 5·4; N, 5·75%).

2-(3-*Hydroxyamino*-3-*methylbutyl*)-1,3-*dioxolan* (XIII). The nitro-dioxolan[2] (XII) (10 g.), suspended in 5% aqueous ammonia chloride (60 ml.) at 10° was reduced by the addition of zinc dust (14 g.) during 20 min., with

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[6] P. Kabasakalian and E. R. Townley, *J. Org. Chem.*, 1962, **27**, 3562.

[7] R. Bonnett, V. M. Clark, and Sir A. Todd, *J. Chem. Soc.*, 1959, 2102.

[8] T. E. Emery and J. B. Neilands, *J. Amer. Chem. Soc.*, 1960, **82**, 4903; *J. Org. Chem.*, 1962, **27**, 1075; B. Sklarz and A. F. Al-Sayyab, *J. Chem. Soc.*, 1964, 1318.

[9] G. A. Snow, *J. Chem. Soc.*, 1954, 2588.

[10] Cf. H. Tanabe, *J. Pharm. Soc. Japan*, 1956, **76**, 1023 (*Chem. Abs.*, 1957, **51**, 2598); T. E. Emery and J. B. Neilands, *J. Amer. Chem. Soc.*, 1960, **82**, 3658.

[11] R. E. Beyler, F. Hoffman, L. H. Sarett, and M. Tishler, *J. Org. Chem.*, 1961, **26**, 2426.

[12] F. Sondheimer and Y. Klibansky, *Tetrahedron*, 1959, **5**, 15.

[13] C. A. Bunton and V. J. Shiner, *J. Chem. Soc.*, 1960, 1593.

[14] H. Nakata, *Tetrahedron*, 1963, **19**, 1959.

[15] J. B. Neilands and P. Azari, *Acta Chem. Scand.*, 1963, **17**, S 190.

vigorous stirring. Ice was added to keep the temperature below 15°. After filtration and repeated washing of the inorganic solids with hot water, the aqueous filtrates were concentrated under reduced pressure. Extraction with chloroform gave an oil which, on fractional distillation under nitrogen (air condenser), gave as the main fraction the *dioxolan* (XIII) (6 g., 65%), b. p. 100—110°/0·5 mm., freezing in the refrigerator to a colourless solid (Found: C, 54·65; H, 9·65; N, 7·95. $C_8H_{17}NO_3$ requires C, 54·85; H, 9·8; N, 8·0%); n.m.r. signals ($CDCl_3$) (8·9(s), 8·38(s), 6·05(d), 5·09(t), 4·4(s); areas, 6 : 4 : 4 : 1 : 2.

The Nitroso-dioxolan (XIV).—(*a*) *Aqueous method*. The hydroxylamino-compound (XIII) (1·6 g.) in ethanol (10 ml.) was added dropwise to a stirred solution of sodium periodate (3 g., 1·5 mol.) in water (10 ml.). After 1 hr. the precipitate was filtered and the blue filtrate extracted with chloroform. The residue from this, combined with the solid, was recrystallised from acetone–hexane to give colourless *dimeric* 2-(3-*nitroso*-3-*methylbutyl*)-1,3-*dioxolan* (XIV) (1·4 g., 93%), m. p. 60—62° (blue melt) (Found: C, 55·25; H, 8·5; N, 8·2. $C_8H_{15}NO_3$ requires C, 55·5; H, 8·75; N, 8·1%).

(*b*) *Non-aqueous method*. The hydroxyamino-compound (1·0 g.) in chloroform (10 ml.) was added dropwise to tetraethylammonium periodate (2·8 g., 1·5 mol) in chloroform with magnetic stirring. A blue colour appeared immediately, but iodine was also slowly formed. After 1 hr., the mixture was washed with sodium thiosulphate solution, and water, dried and evaporated to give a blue-green semisolid residue, which, on recrystallisation from acetone–hexane again gave the nitroso-dioxolan (XIV), m. p. 60—62°.

Periodate Estimations.—Samples (*ca*. $1·25 \times 10^{-3}$ mol.) were weighed and dissolved in water (50 ml.), and aliquot portions (10 ml.) of this stock solution diluted to 100 ml. with water (50 ml.), 0·25M-sodium periodate (10 ml.), and buffer solution (30 ml.) of the composition given below. Aliquot portions (10 ml.) of the reaction mixture were added at intervals to saturated borax (10 ml.) containing solid boric acid and 15% potassium iodide. The iodine was titrated after 2 min. with standard 0·01N-sodium arsenite. The pH's were pre-determined on blank solutions made up as above with the following buffer solutions (30 ml.):

pH of total blank	2·9	4·5	6·5	9·2
0·2M-Sodium acetate (ml.) ...	0·0	13·5	30	—
0·2M-Acetic acid (ml.)	30	16·5	0·0	—
2N-Sodium hydroxide (ml.) ...	—	—	—	1·1

The rate and extent of periodate oxidation are shown in Tables 1 and 2. For the aromatic oxime (VIII) and its hydrate (Table 2), the estimations were carried out as above but with half the quantity of oxime and of periodate solution. At full strength, the oxidation of even (VIII) was too fast to be followed.

Preparative Oxidations.—5,5-*Dimethyl*-Δ'-*pyrroline* 1-*oxide* (Ia). The nitrone hydrate (0·4 g.) in water (2 ml.) was mixed with sodium metaperiodate (1·5 g., 2·8 mol.) in water (12 ml.). The solution soon turned blue and crystallisation of a white compound commenced. This was filtered after being left overnight, and combined with the resiude obtained from chloroform extraction of the blue filtrate and evaporation of the extract. Recrystallisation from water containing a little ethanol gave 4-methyl-4-nitrosopentanoic acid (IIa), (0·3 g., 58%), m. p. 109—110°, identical with the compound already described;[1] $\lambda_{\text{max.}}$ (EtOH) 295 mμ (ε 4640); $\nu_{\text{max.}}$ (mull) 1720 cm.$^{-1}$.

4,5,5-*Trimethyl*-Δ^1-*pyrroline* 1-*oxide* (Ib). The freshly distilled nitrone[2] (0·4 g.) was oxidised as above with sodium metaperiodate (1·4 g., 2·8 mol.). The white solid was collected after 18 hr., washed and recrystallised with difficulty from water–ethanol, to give the *dimer* of 3,4-*dimethyl*-4-*nitrosopentanoic acid* (IIb), m. p. 116—118° (Found: C, 53·0; H, 8·5; N, 8·8. $C_7H_{13}NO_3$ requires C, 52·8; H, 8·2; N, 8·8%); $\nu_{\text{max.}}$ (mull) 1699 cm.$^{-1}$; (melt in chloroform), 1708, 1565; no u.v. maxima.

TABLE 1

Uptake of periodate (mols./mol. substrate)

Time (hr.)	(Ia)		(IIIa)	(IIIb)	(X)		(XI †)	(XIII)
pH	4·5	9·2	*	*	4·5	9·2	4·5	4·5
0·067						0·53		0·77
0·1		0·17			0·86			
0·2	0·12							
0·5					0·91	0·55		0·85
1·0	0·24	0·33			0·93	0·57		0·88
2·0	0·36	0·51			0·93	0·59		0·90
4·0	0·56	0·87						
24·0	1·70		0·17	0·29	0·93	0·61	0·16	0·90

* Unbuffered. † Crude material.

TABLE 2

Uptake of periodate (mols./mol. substrate)

Time (hr.)	Nitrone (VIII)				Hydrate (IX)			
pH	2·9	4·5	6·5	9·2	2·9	4·5	6·5	9·2
0·05	1·78	0·36	—	—	2·56	—	3·10	2·04
0·1	1·84	0·6	0·40	1·92	—	2·56	—	—
0·2	1·88	0·91	0·68	—	2·78	—	—	—
0·5	1·90	1·58	—	2·27	2·78	2·88	3·10	
1·0	1·96	2·16	1·54	2·58	—	3·00	—	4·68
1·25	—	2·3	—	—	—	—	—	—
1·5	2·02	2·35	1·66	—	—	—	3·10	6·20
24	2·02	2·42	2·18	*	2·78	3·00	3·10	*

* Precipitation.

3,3,5,5-*Tetramethyl*-Δ^1-*pyrroline* 1-*oxide* (Ic). Oxidation as above and recrystallisation from water gave 2,2,4-*trimethyl*-4-*nitrosopentanoic acid* (IIc) *dimer*, m. p. 105—106° (Found: C, 55·4; H, 9·0; N, 8·1. $C_8H_{15}NO_3$ requires C, 55·5; H, 8·7; N, 8·1%); $\lambda_{\text{max.}}$ (EtOH), 298 mμ, decreasing with time; $\nu_{\text{max.}}$ (mull) 1715 cm.$^{-1}$; (melt in chloroform), 1696, 1560 cm.$^{-1}$.

5-*Ethoxycarbonyl*-5-*methyl*-Δ^1-*pyrroline* 1-*oxide* (Id). The nitrone (1·8 g.) was treated with aqueous sodium periodate (4 g., 1·8 mol.) at 0° and kept at this temperature for 3 days. The organic crystals were separated from a deposit of oil and inorganic material and recrystallised from aqueous ethanol to give the *dimer* of 4-*ethoxycarbonyl*-4-*nitrosopentanoic acid* (IId), m. p. 113—114° (Found: C, 47·5; H, 6·5; N, 6·6. $C_8H_{13}NO_5$ requires C, 47·3; H, 6·5; N, 6·9%); $\lambda_{\text{max.}}$ (EtOH) 293 mμ (ε 6400); $\nu_{\text{max.}}$ (mull) 1743, 1700 cm.$^{-1}$; (melt in chloroform) 1725, 1640, 1550 cm.$^{-1}$.

5-*Carboxy*-5-*Methyl*-Δ'-*pyrroline* 1-*oxide* (Ie). The acid (0·1 g.) in water (4 ml.) was mixed with sodium periodate (0·6 g., 4 mol.) in water (4 ml.) with external cooling, when iodine was liberated. After being left overnight the (now colourless) solution was extracted with ether to give an oil (0·11 g.). Treatment with 2,4-dinitrophenylhydrazine in methanolic sulphuric acid gave lævulinaldehyde bis-2,4-dinitrophenylhydrazone which was recrystallised from dimethylformamide, m. p. 230°[16] (Found: C, 44·8; H, 4·0; N, 24·3. Calc. for $C_{17}H_{16}N_8O_8$: C, 44·4; H, 3·5; N, 24·2%).

Phenylglyoxal N-*phenyloxime* (VIII). The oxime (0·75 g.), in ethanol (25 ml.), was added dropwise during 2 hr. to sodium periodate (2·1 g., 3 mol.) in water (25 ml.), with constant stirring. Free iodine was destroyed with sodium thiosulphate, the solution made mildly alkaline ($NaHCO_3$), and extracted with chloroform. Drying and evaporation gave crude nitrosobenzene m. p. 66—67°. The aqueous layer was acidified, iodine again removed, and the solution extracted with ether to give benzoic acid, recrystallised from hot water, m. p. and mixed m. p. 121°.

The oxime hydrate (IX) was oxidised in a similar manner, giving the same products.

5-*Ethyl*-1-*hydroxy*-2,2-*dimethylpyrrolidine* (X). The *N*-hydroxypyrrolidine (1 g.) in water (10 ml.), was treated dropwise with aqueous sodium periodate (1·5 g., 1 mol.) neutralised with a little potassium carbonate. The mixture was stirred for 1 hr., and extracted continuously with chloroform, the extracts giving crude 2-ethyl-5,5-dimethyl-Δ^1-pyrroline 1-oxide (XI)[2] (0·75 g., 75%), $\lambda_{max.}$ (EtOH) 234 mμ (ε 8100). The picrate[2] was prepared in ether and recrystallised from ethanol, m. p. 71—72° (Found: C, 45·45; H, 4·6; N, 15·4. Calc. for $C_{14}H_{18}N_4O_8$: C, 45·4; H, 4·9; N, 15·1%).

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