CYCLIC NITRONES

OXIDATION STUDIES

AND

THE SYNTHESIS OF A HETEROCYCLIC NITRONE

by

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SUMMARY

Part 1.

The synthesis of the heterocyclic nitrone, Δ^3-dihydro-1,4-oxazine 4-oxide, by the oxidation of solutions of 4-hydroxymorpholine is described. The UV and IR spectra of the solutions were consistent with the structure proposed. Removal of the solvent gave linear polymers with the N-O-C repeating unit.

Typical nitrone-reducing agents have been shown to be effective towards the heterocyclic nitrone. Arylhydrazines oxidised the heterocyclic nitrone with cleavage of the ether bond, yielding glyoxal osazones. The same nitrone was very rapidly oxidised to 4-hydroxy-3-morpholone by ferric chloride. This cyclic hydroxamic acid underwent further oxidation at a slower rate, ultimately yielding diglycollic acid and nitrous oxide.

1,3-Cycloaddition products were formed when the heterocyclic nitrone was heated together with cyclohexene, with phenylisocyanate and with ethyl acrylate. All the products incorporated the fused bicyclic skeleton of morpholino-isoxazolidine and were each characterised by analysis, IR and p.m.r. spectra.

Part 2.

Cyclic aldonitrones and some related cyclic hydroxylamines have been shown to undergo oxidation by ferric chloride to cyclic hydroxamic acids. For example, the 2-unsubstituted 1-pyrroline 1-oxides gave 1-hydroxy-2-pyrrolidones , and 1-piperideine 1-oxide gave 1-hydroxy-2-piperidone. The reaction could be followed titrimetrically or

spectrophotometrically. The former involved the determination of the ferrous ion released, whereas the latter technique entailed observing the increase in the intensity of the colour of the solution.

Cyclic ketonitrones, the 2-methyl-1-pyrroline 1-oxides, were also observed to undergo oxidation by ferric chloride but at much slower rates than the cyclic aldonitrones. Moreover no characteristic colours resulted and the products were the result of oxidative cleavage of the nitrone group. Nitrous oxide and ketonic compounds were products. Preliminary gas-liquid chromatographic examination of the products would suggest that a radical mechanism resulting in some C-C fragmentation was operative. A mechanism for the oxidation of these cyclic ketonitrones has been tentatively advanced.

The oxidation of 4,5,5-trimethyl-1-pyrroline 1-oxide by ferric chloride has been examined in detail to ascertain the overall mechanism. Kinetic studies involved the determination spectrophotometrically of pseudo-first order rate constants in the presence of large excesses of ferric chloride. From the studies on the effects of ionic strength and of acid concentration, it was deduced that the active oxidant ion was $FeCl(OH)(OH_2)_4^+$. Spectral and kinetic studies showed that a cyclic 1 : 1 ferric-nitrone complex was formed in a two-step mechanism, the actual cyclization being the rate-determining step for the whole reaction. The nitrone within the complex, by rapidly losing two electrons *via* the N-O bond, gave a 1 : 1 ferric-hydroxamate complex absorbing near 540 mμ and having a stability constant, $K = 3.7 \times 10^9$ lit. mole^{-1}. The entropy of activation (- 6.6 e.u.)

and comparative studies on the pseudo-first order rate constants for related cyclic nitrones and cyclic hydroxylamines provide further evidence in support of the mechanism postulated.

TO

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CONTENTS

PART 1. HETEROCYCLIC NITRONES.

1. Introduction 1

2. Δ^3-Dihydro-1,4-Oxazine 4-Oxide: Synthesis and Reactions. 6

PART 2. OXIDATIONS OF CYCLIC NITRONES BY FERRIC CHLORIDE.

1. Introduction 43

2. Product Studies on Oxidations of Cyclic Aldonitrones 52

3. Product Studies on Oxidations of Cyclic Ketonitrones 60

4. Mechanism for Oxidation of Cyclic Aldonitrones 77

PART 3. EXPERIMENTAL.

Section.1. Δ^3-DIHYDRO-1,4-OXAZINE 4-OXIDE.

1.1. Preparation 106
1.13. Polymer 114
1.2. Reductions 116
1.3. Oxidations 120
1.4. Cycloadditions 126

Section 2. OXIDATIONS OF CYCLIC NITRONES BY FERRIC CHLORIDE.

2.1. Preparation of Compounds Required 131
2.2. Stoichiometric and Product Studies 146
2.3. Spectral and Kinetic Studies 163

APPENDIX 1. FIGURES.
APPENDIX 2.
INDEX.
ACKNOWLEDGEMENTS.
BIBLIOGRAPHY.

ABBREVIATIONS

The following abbreviations are used in the course of this thesis.

2,4-D.N.P.	2,4-dinitrophenylhydrazone
e.s.r.	electron spin resonance
G.L.C.	gas-liquid chromatography
IR	infrared
p.s.i.	pounds per sq. in.
T.L.C.	thin layer chromatography
UV	ultraviolet

PART 1.

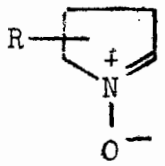
HETEROCYCLIC NITRONES.

PART I.

HETEROCYCLIC NITRONES.

1. Introduction.

Increasing attention has been accorded to the nitrones during the last decade. This may well be attributed in the main to the Cambridge research school under Sir Alexander (now Lord) Todd in 1957[1] which published a series of papers some two years later on the preparation and reactions of the 1-pyrroline 1-oxides (I).[2,3,4,5,6,7] These compounds, which were the first nitrones to be isolated in the monomeric state, were reported to undergo a wide range of interesting and potentially useful reactions. While new and novel methods for the preparation of nitrones have since been reported, it is the wide diversity of their chemical reactions that has attracted more interest. This field encompasses so broad a spectrum of reactions, such as additions and cycloadditions, oxidations, condensations and rearrangements (both thermal and photolytic) that two comprehensive reviews[8,9] have appeared in the last four years.

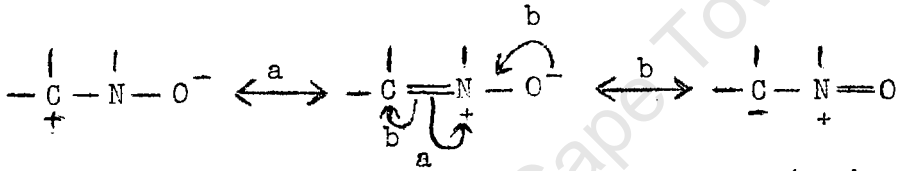


(I)

The author's interest has been directed towards those cyclic structures incorporating both a nitrone function and an electronegative atom other than nitrogen in the same ring in order to determine what influence, if any, an atom with one or more lone electron pairs may

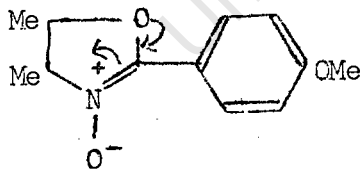
exert upon the reactivity of the nitrone group. The author proposes to adopt the term "heterocyclic nitrones" to describe such compounds. The term "cyclic nitrone" is accepted as the connotation for cyclic systems incorporating the nitrone group[8,9] e.g. (I). It would therefore follow logically that the term "heterocyclic nitrone" would accord with the author's definition given above.

It is important to distinguish between a true heterocyclic nitrone and other heterocyclic N-oxides. The term "nitrone" describes those azomethine N-oxides which react in one of the canonical forms (IIa, b or c) with no further delocalisation of the positive charge.[9]

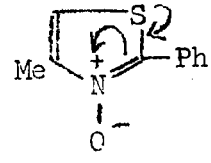


(IIb) (IIa) (IIc)

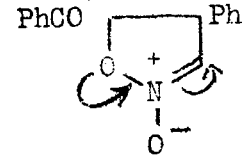
In both the oxazole N-oxide (III)[10] and the thiazole N-oxide (IV),[11] the positive charge can be delocalised as shown, and therefore these compounds are best described as heteroaromatic N-oxides.



(III)



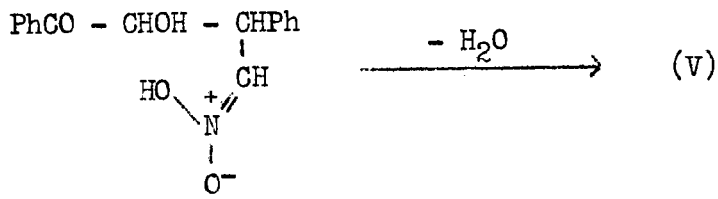
(IV)



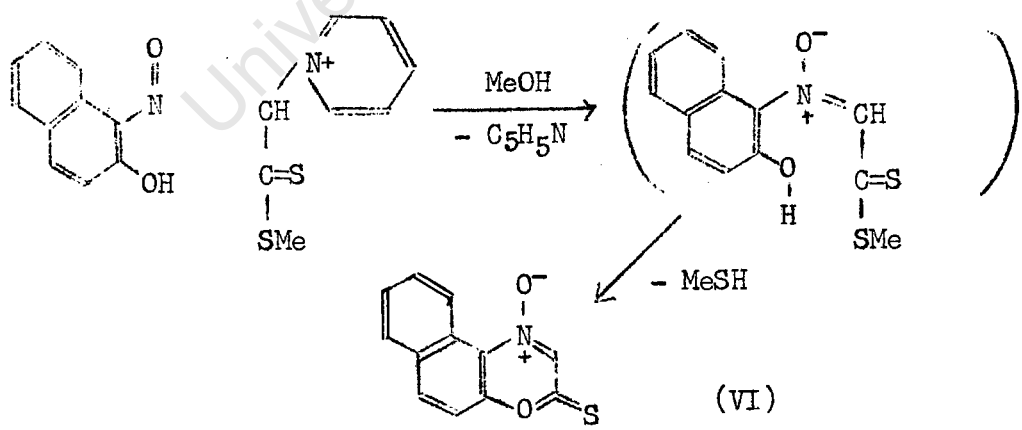
(V)

The 2-isoxazoline 2-oxides, e.g. (V), prepared and studied fully by Kohler and his collaborators over 40 years ago,[12] were regarded as cyclic nitrones by Smith in his review thirty years ago.[13] However, delocalisation of the positive charge can occur by the electronic shifts shown and

for this reason these compounds are not regarded as nitrones.[9] Moreover their reactions are not typical of nitrones[13] but rather confirm that structure (V) is equivalent to an internal ester of the aci-form of a δ-nitroalcohol:

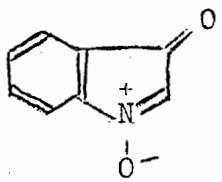


As far as the author is aware, the only heterocyclic nitrone which has been reported is the naphthoxazine-thia-N-oxide (VI).[14] It was prepared by the Krohnke method of synthesis of nitrones by base-catalysed condensation of aromatic nitroso compounds on pyridinium salts.[15,16] The preparation of this particular compound is of interest because the nitrone group was first formed by reacting α-nitroso-β-naphthol with the pyridinium betaine of dithioacetic esters. The subsequent elimination of methanthiol resulted in cyclization to the heterocyclic nitrone (VI).

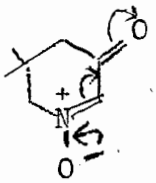


No reference is made, however, to its chemical behaviour in order to establish it as a typical nitrone.[14] The structure (VI) finds its analogues in the isatogens (VII)[17] and the β-oxo-nitrones (VIII).[4,18]

While the isatogens have been reported to undergo 1,3-cycloadditions typical of nitrones,[13,19] 1,3-cycloadditions to the β-oxo-nitrones (VIII) have not been recorded. It may be that delocalisation of the negative charge may occur as shown, with reduction in the activity of the nucleophilic site of the nitrone.



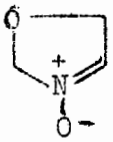
(VII)



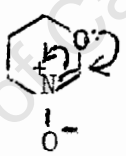
(VIII)

The author aimed to synthesise cyclic nitrones in which no double bonded system would be conjugated with the nitrone group. The structures (IX) - (XIII) represent potential heterocyclic nitrones incorporating oxygen in 5- and 6-membered rings.

(IX)



(X)

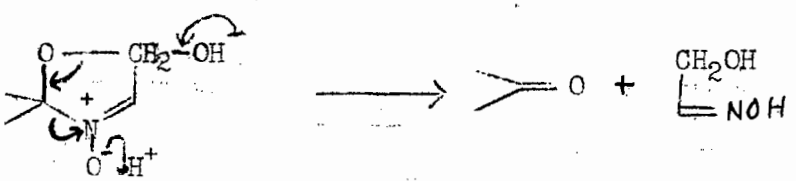


(XI)

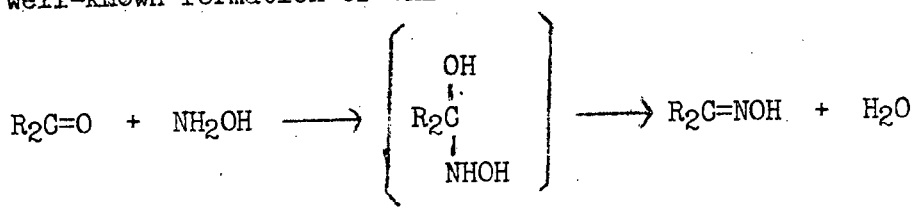
(XII)

(XIII)

Examination of the structures shows that the 2-oxazoline 3-oxide system (IX) as well as its ring homologue (XI) would be excluded from the definition of nitrones owing to delocalisation of the positive charge. It is highly questionable as to whether compounds represented by the ring-homologous structures (X) and (XII), if they could be prepared, would be stable as they incorporate an acetal-type function which could render them labile to hydrolytic agents:



The preparation, too, would present problems for the reason that a search of the literature for alcohols and ethers containing either a nitro- or hydroxylamino- group on the same carbon atom proved fruitless, except where a compound may be a transient intermediate, as, for example, in the well-known formation of oximes:



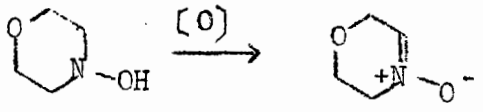
(XIV)

In this reaction the hydroxylamino-alcohol (XIV) has but a short-lived existence.

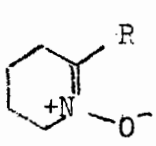
Structure (XIII) which has the oxygen atom in a position where its lone electron pairs cannot directly interact with the nitrone system, appeared most feasible. In Part I of this thesis, the preparation, characterisation and some reactions of the heterocyclic nitrone (XIII) are described.

2. Δ^3-Dihydro-1,4-Oxazine 4-Oxide: Synthesis and Reactions.

In this work, it was considered that the simplest route to the desired heterocyclic nitrone (XIII) would be by oxidation of the known 4-hydroxymorpholine. (XV).



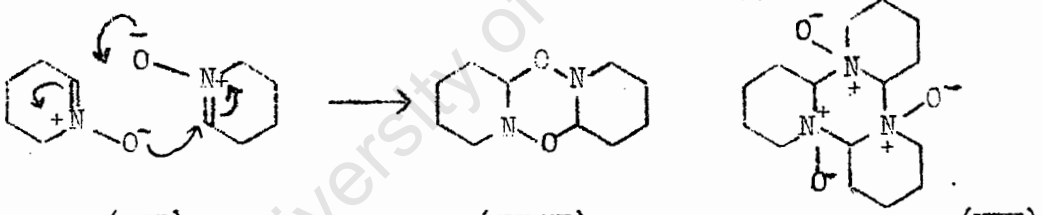
(XV) (XIII)



(XVI) R = H

(XVII) R = Ph

It was further considered that comparative studies between the heterocyclic nitrone (XIII) and the related cyclic nitrone (XVI) should reveal what influence the ring oxygen atom may exert upon the nitrone system. For example, the six-membered cyclic nitrones (XVI)[20] and (XVII)[11] were only isolable as dimers[20,21] (e.g. XVIII)[20] or a trimer (XIX).[11] The dimerisation of (XVI) has been suggested to occur as follows:[20]



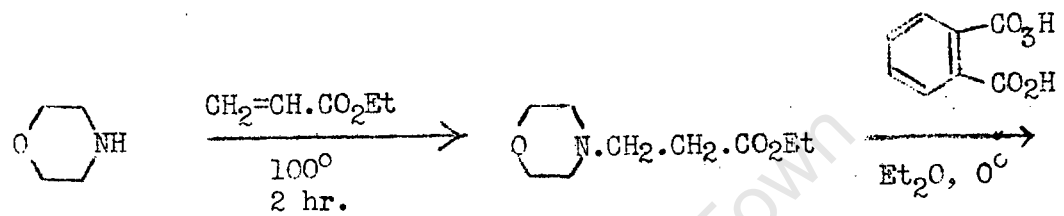
(XVI) (XVIII) (XIX)

If the repulsive field due to the lone pairs of electrons on the ring-oxygen atom in (XIII) were sufficient to prevent the nucleophilic attack by the exocyclic oxygen atom of a neighbouring nitrone molecule analogous to the process shown above, there would be a possibility that the heterocyclic nitrone (XIII) could be isolated in its monomeric state.

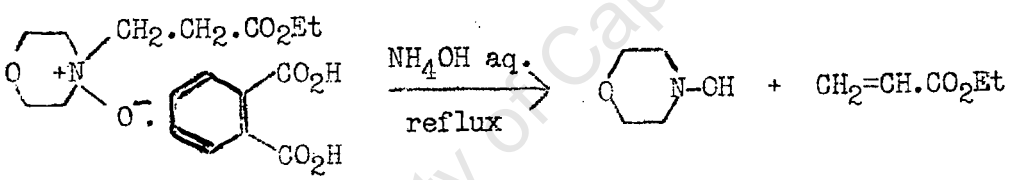
Synthesis. At the commencement, difficulties were initially experienced in obtaining pure 4-hydroxymorpholine. The simpler method involving the direct oxidation of morpholine with 30% hydrogen peroxide[22,23] resulted

in very low (<5%) yields of (XV). Moreover the product was never entirely free of morpholine, even after repeated refractionation. Very small amounts of morpholine in the 4-hydroxymorpholine gave misleading results in subsequent studies and this may be the reason why the further oxidation of this secondary hydroxylamine has not been reported before.

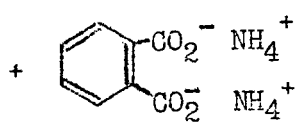
The pure hydroxylamine (XV) was obtainable in 35 - 40% yield from morpholine by the indirect method of Rogers[24] as outlined below.



(XX)



(XXI) (XV)

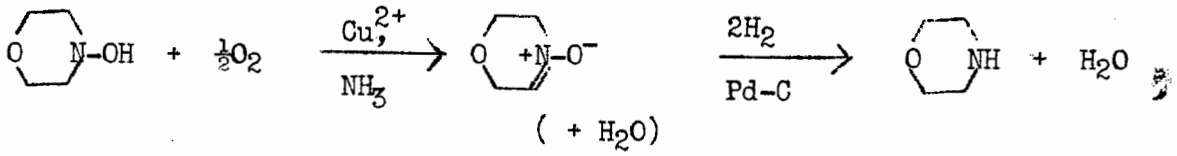


Ethyl 4-morpholinopropionate (XX), obtained in high yield by the Michael-type addition of ethyl acrylate to morpholine,[25] was oxidised quantitatively to the ether-insoluble crystalline salt, (XXI), an N-oxide phthalate, which, on refluxing with ammonium hydroxide underwent a reverse Michael-reaction. 4-Hydroxymorpholine could be recovered in 40 - 45% yield, and, on redistillation, the colourless oil crystallised in the refrigerator. After 2 years storage in such conditions, thin layer chromatography (T.L.C.)

showed but a trace of higher oxidation products. Morpholine was completely absent. The hydrogen-integrated proton magnetic resonance spectrum was complex (Fig. 2, App. 1). Since methylene protons adjacent to an oxygen atom are deshielded more than when adjacent to a nitrogen atom due to the greater electronegativity of the oxygen atom,[26a] it is reasonable to assign the lower field multiplet, centred at τ 6.2 to the protons in the $-CH_2-O-CH_2-$ moiety, and the higher field multiplet centred at about τ 7.0 to the protons in the $-CH_2-N-CH_2-$ moiety. The elucidation of later structures which incorporate this ring system is facilitated when the signals due to these ring protons can be recognised. For this reason the p.m.r. spectrum of 4-hydroxymorpholine has been introduced at this stage.

4-Hydroxymorpholine was observed to undergo facile oxidation in a variety of solvents under a variety of conditions. Thus after aeration of an aqueous solution containing ammonia and a catalytic amount of copper sulphate, the resulting solution on paper chromatography or T.L.C. showed, in addition to some starting compound (XV), a second elongated, slower moving spot. Both spots could be revealed either by iodine vapour or by spraying with 5% ferric chloride solution when, in the latter instance, the compounds gave wine-red colours. Similar colours have been reported previously for the action of ferric chloride on the nitrone dimer (XVIII)[20] and on the peroxidic material reported to be formed when N,N'-di-iso-propylhydroxylamine was catalytically oxidised.[27] [See also Part 2.] Under more controlled pH conditions, the oxalate of (XV) was found to absorb rapidly about $\frac{1}{2}$ mole of oxygen per mole of the hydroxylamine. On catalytic hydrogenation over 5% palladised charcoal under quantitative

conditions, the resulting solution after oxidation was observed to take up 2 moles of hydrogen per initial mole of (XV) and morpholine was recovered from the resulting solution. From these results it can be inferred that the following sequence occurred:-



(XV) (XIII)

and that the heterocyclic nitrone (XIII) was probably present in the solution of oxidised hydroxymorpholine. An attempt was made to isolate the nitrone (XIII) by continuous aeration on a preparative scale until no more hydroxylamine remained. After several hours, only about half of the hydroxylamine had undergone oxidation, as observed on T.L.C.

A thick, viscous gum, which on standing over phosphorus pentoxide under high vacuum slowly became a glass, was isolated. Because of the contamination with starting material, this route to the nitrone (XIII) was not pursued further.

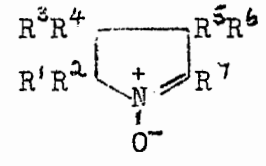
Yellow mercuric oxide has been used with much success in oxidising secondary hydroxylamines to nitrones[28,29,30] in a variety of solvents and it was natural to investigate its use in these studies. Both aqueous and chloroform solutions of 4-hydroxymorpholine were observed to reduce yellow mercury oxide rapidly to grey-black mercury exothermically. The reaction proceeded more slowly at temperatures between 5 - 10° and required a much longer period for the complete oxidation of the hydroxylamine, as revealed by T.L.C. studies. Aqueous solutions after shaking with

mercuric oxide for 15 minutes showed but a single spot (T.L.C.) which travelled more slowly than the parent hydroxylamine (XV).

Spectral studies.

The centrifuged aqueous solution on appropriate dilution with 95% ethanol in one instance and with water in a second instance, showed a single strong ultraviolet absorption band in each case, at 238 mμ (ε 6800) in ethanol and 232 mμ (ε 7900) in water. These values closely agree with those cited for the mononocyclic nitrones, the 1-pyrroline 1-oxides (I) which in 95% ethanol absorb near 234 mμ ($\varepsilon \sim 8000$)[2] but in water absorb near 227 mμ (ε 8000).[31] This evidence points to the presence in solution of a compound containing the nitrone chromophore, $-\overset{|}{C}=\overset{+}{N}(O^-)-$.

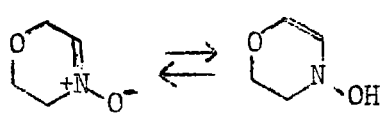
Further spectral evidence was adduced from the infrared spectrum of a freshly prepared dry chloroform solution of the compound, obtained by mercuric oxide oxidation of 4-hydroxymorpholine in A.R. chloroform, filtration and drying over anhydrous magnesium sulphate. The IR spectrum showed strong absorption bands at 3300, 1628 and 1100 $cm.^{-1}$ Since a six-membered cyclic system is less strained than a five-membered ring structure, and because a given chromophore will absorb in the IR at higher frequencies in less strained ring systems,[32a] it follows that a nitrone group in a six-membered ring would be expected to absorb at a frequency higher than 1570 - 1580 $cm.^{-1}$, the range reported for the five-membered cyclic nitrones (I, R^7 = H).[2] In addition, the strong band at 1100 $cm.^{-1}$ is attributed to the C-O-C deformation[32b] for the reason that both 4-hydroxymorpholine and morpholine showed similar strong absorptions



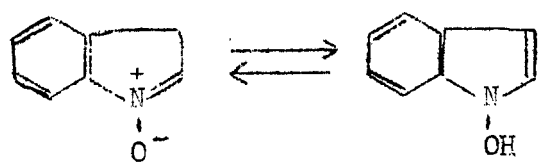
(I)

at 1100 $cm.^{-1}$ whereas a chloroform solution of the cyclic nitrone (XVI), prepared by the action of mercuric oxide on 1-hydroxypiperidine in chloroform (experimental section) showed only two strong bands at 3300 and 1625 $cm.^{-1}$ and no band at 1100 $cm.^{-1}$

The strong broad band at 3300 $cm.^{-1}$ (-OH) merits some discussion for it suggests the presence of some N-hydroxy-tautomer (XXII). The literature contains conflicting evidence as to whether the N-hydroxy-tautomeric form of nitrones has any existence. In support of this, it has been claimed on the basis of n.m.r. evidence that the tautomer (XXIIIb) is the predominant form of the indolene N-oxide (XXIIIa),[33] while, in contrast n.m.r. studies on some of the 1-pyrroline 1-oxides (I) point to the absence of the tautomeric species.[34] The author himself has examined IR spectra of chloroform solutions of the cyclic nitrones (Ia, $R^1 = R^2 = Me$, $R^3 = R^4 = R^5 = R^6 = R^7 = H$) and (Ib, $R^1 = R^7 = Me$, $R^2 = R^3 = R^4 = R^5 = R^6 = H$). These also showed strong absorption bands at 3300 $cm.^{-1}$ which would also support the existence of the N-hydroxy tautomeric species.

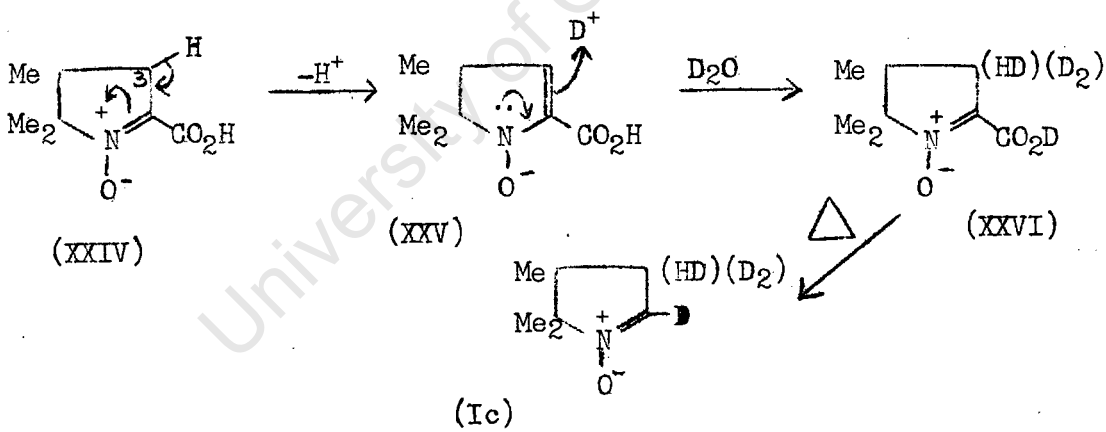


(XIII) (XXII)



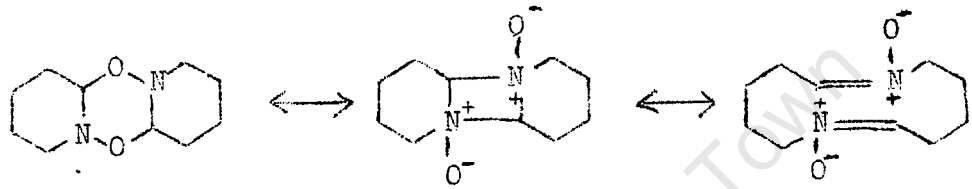
(XXIIIa) (XXIIIb)

The following observation on the effect of deuteration of the carboxynitrone (XXIV) in which the protons at C-3 appeared to be exchangeable, can only be explained by a mechanism invoking the anion (XXV) of the N-hydroxytautomer as an intermediate in the exchange process. The author, in repeating recent work of Lord Todd and his co-workers on the preparation of the deuterated nitrone (Ic, $R^1 = R^2 = R^3 = Me$, $R^4 = R^5 = R^6 = H$, $R^7 = D$),[35] obtained a product which, on mass spectral analysis contained significant proportions of di- and tri-deuterated nitrone (Ic) in addition to the desired mono-deuterated product [see Experimental section, 2.11(d)]. The following mechanism in which deuterium exchange could have occurred at C-3 via the anion (XXV) to yield, ultimately, the tri-deuterated carboxynitrone (XXVI), is consistent with the results.



The spectral evidence therefore would suggest that the solutions prepared above contain the heterocyclic nitrone (XIII) in its monomeric form. It is apposite and of interest to mention that the aqueous solution of the cyclic nitrone (XVI) also showed strong ultraviolet absorption at 229 mμ (ε 8400). This, coupled with the infrared spectrum of its chloroform solution mentioned above, is strong evidence for

believing that the nitrone (XVI) has monomeric existence in solution. Moreover it must be presumed to have transient existence when its dimer (XVIII) was observed to undergo 1,3-cycloadditions,[36] reactions which are typical of the monomeric cyclic nitrones (I). The author's observation conflicts with a recent report[37] that the dimer (XVIII) showed no ultraviolet absorption in aqueous solution. It was suggested that the structure was a hydrated di-N-oxide of (XVIII) with the three canonical forms (XVIIIa, b, c) contributing to a resonance hybrid.[37]



(XVIIIa) (XVIIIb) (XVIIIc)

Evidence has been accumulated[31] to show there is no marked lowering of the intensity of the UV absorbance of cyclic nitrones in aqueous solutions, thus demonstrating that "hydrated nitrones" if they exist cannot have the structure $-\overset{|}{C}(OH).N(OH)-$. The author believes that the deliquescent character of many cyclic nitrones originates in the highly polar character of the nitrone group tending to associate with the polar water molecules without addition to the nitrone group.

Attempts to isolate the heterocyclic nitrone (XIII):

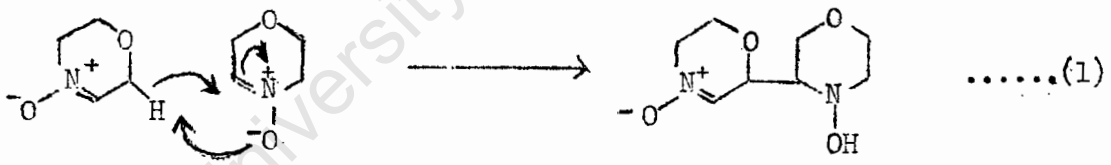
Polymers of Δ^3-dihydro-1,4-oxazine 4-oxide.

With strong evidence that the nitrone (XIII) was indeed present in solutions of 4-hydroxymorpholine treated with yellow mercuric oxide, the obvious course was to remove the solvent and recover the nitrone. Freeze-drying of aqueous solutions gave a white, sticky, extremely hygroscopic solid which showed a weak absorption band at 1630 cm^{-1}. It dissolved readily in polar solvents such as water, alcohol or acetone, the solutions showing UV absorption bands at 232 mμ (water) and 238 mμ (alcohol) due to the nitrone chromophore. When the alcoholic solutions were treated with ether, the same hygroscopic solid was precipitated out as a floc.

The evaporation of dry chloroform solutions yielded pale yellow, viscous liquids which, on drying under high vacuum over phosphorus pentoxide, became a glass. On removal of the unchanged 4-hydroxymorpholine by trituration with dry ether, a pale cream-coloured resinous solid was obtained. This non-hygroscopic solid was insoluble in all solvents, analysed satisfactorily for $(C_4H_7NO_2)_n$, melted over a wide temperature range, 156 - 165° with decomposition, and showed no significant bands in the IR spectrum above 1480 cm^{-1}. This polymer, while only sparingly soluble in water, dissolved readily in M-hydrochloric acid in which solution it rapidly absorbed 1 mole of hydrogen in the presence of Adam's catalyst to yield 4-hydroxymorpholine. The polymer, like the hygroscopic form, also dissolved readily in 5% ferric chloride to yield a deep wine-red solution.

As this insoluble polymer was observed to dissolve slowly in chloroform under prolonged reflux, an attempt was made to determine its molecular weight by an ebullioscopic method. The temperature rise was irregular(Fig.1 Append. 1/2). Two temperatures which remained steady for brief periods could be associated with a dimer and monomer of the nitrone (XIII) but the final temperature suggested that the polymer had undergone further changes and decomposition. Both T.L.C. and IR studies on the resulting solution indicated the presence of the monomeric nitrone together with other products containing C=O and C=N systems. Thus the IR spectrum showed absorption bands at 1735 and 1670 $cm.^{-1}$ as well as at 1630 $cm.^{-1}$

On the basis of the foregoing facts one can exclude the aldol-type of dimerisation (1) which is displayed by certain acyclic nitrones such as C,C-dimethyl-N-phenylnitrone.[38] This would result in the formation of an intramolecular C-C bond giving, for example, (XXVII). It would be difficult to explain the ease of dissociation of such a structure.

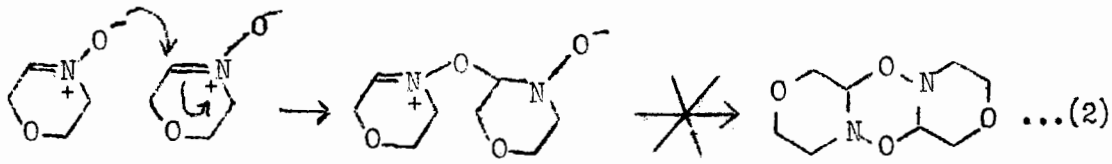


.....(1)

(XXVII)

The IR spectrum of the resinous polymer showed a strong absorption band at 1120 $cm.^{-1}$ (C-O-C of the morpholine ring) with shoulders at 1140, 1130, 1115 and 1100 $cm.^{-1}$ In accordance with Bergman's assignment of bands near 1160, 1120 and 1105 $cm.^{-1}$ to the O-C-N group,[39] this would suggest the same grouping to be present in the polymers. The hygroscopic solid, which also showed absorption near 1630 $cm.^{-1}$ (C=N ?)[32c] is thus tentatively assigned the open dimeric structure (XXVIII) rather than the

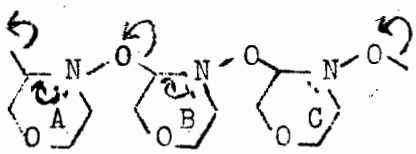
cyclised structure (XXIX) analogous to the dimer (XVIII) of the nitrone (XVI).



...(2)

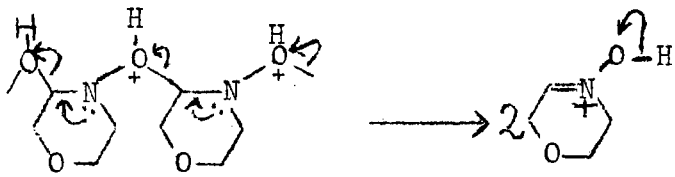
(XXVIII) (XXIX)

The insoluble resinous polymer is considered to have the chain-structure (XXX) arising by extension of the dimerisation process represented in (2).

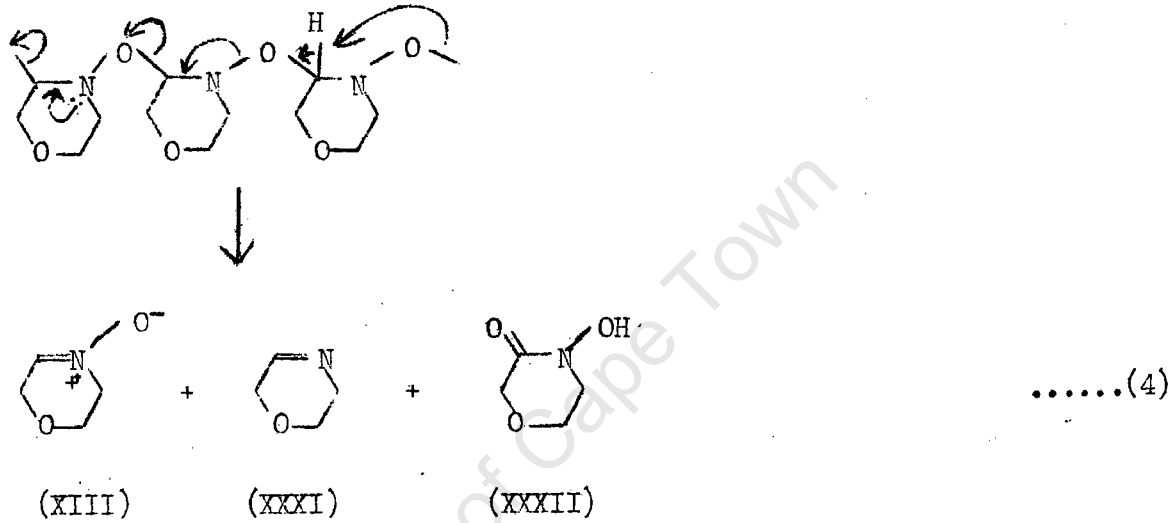


(XXX)

The skeletal -N-O-C- repeating unit in (XXX) has also been proposed for the white resins of high molecular weight and ill-defined melting points resulting from the polymerisation of fluoronitrones.[40] The chain-like structure (XXX) can now account for the insoluble nature of the resin. Moreover its slow dissociation into dimer and monomer on prolonged reflux is readily explained by the electron shifts shown in (XXX). Thus ring A would yield the monomer (XIII) while rings B and C would yield the open chain dimer (XXVIII). The dissociation would clearly be hastened if the linking oxygen atoms were to be protonated, and hence the solubility in acids is explained (3).



An interesting aspect of this mechanism of dissociation is that it becomes possible to account for the observed decomposition of the polymer on prolonged reflux conditions.



Here is depicted disproportionation to yield three products, the nitrone (XIII), the dihydro-oxazine (XXXI) and hydroxymorpholone (XXXII). However no attempt was made to separate and identify the products.

Picrate of Δ^3-dihydro-1,4-oxazine 4-oxide.

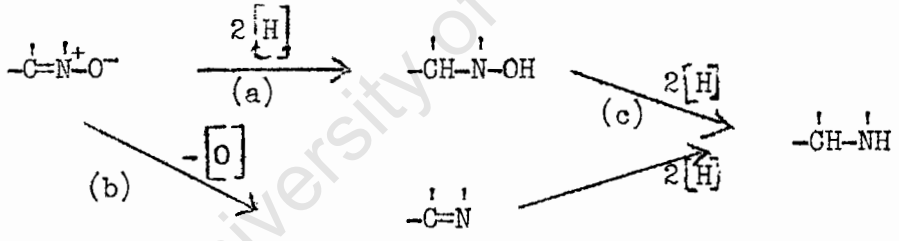
Because of their basic character, cyclic nitrones give rise to salts with acids and an attempt to isolate the picrate of the heterocyclic nitrone (XIII) was made. The picrate obtained by evaporation of an aqueous solution of picric acid and the nitrone (XIII) had a higher melting point (94°) than that obtained from chloroform solutions of the same mixture (89°). Their identity was confirmed by comparison of their

infrared spectra and X-ray scatter patterns of the powders. Both samples decomposed extensively on attempts to recrystallise for analysis. For this reason the preparation and isolation were performed under conditions preventing contamination with undesirable solids. Analysis and equivalent weight, as determined spectrophotometrically in ethanolic solutions,[41] were satisfactory for a 1 : 1 salt, viz., $C_4H_7NO_2.C_6H_3N_3O_7$. The picrates slowly decomposed, even on storage in a desiccator, to dark oils. The heterocyclic nitrone (XIII) could be recovered by passing an aqueous solution of the picrate over a short alumina column. Paper chromatograms of the eluate revealed the presence of the heterocyclic nitrone (XIII).

Reactions.

Reduction of Δ^3-dihydro-1,4-oxazine 4-oxide.

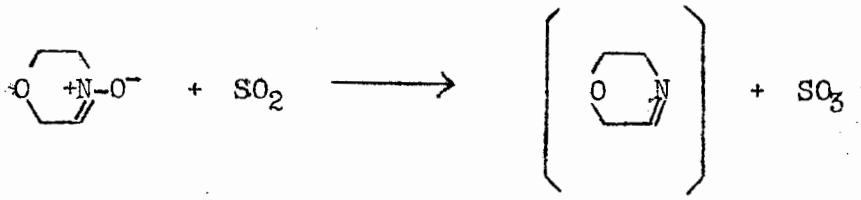
In general nitrones can be reduced in one or more steps as shown below:



Path (a) can be effected by hydride agents e.g. sodium borohydride, on solutions of a nitrone, and the production of a secondary hydroxylamine by these reductants has been suggested as being diagnostic for a nitrone.[42] The re-formation of 4-hydroxymorpholine by the action of sodium borohydride on aqueous solutions of 4-hydroxymorpholine previously treated with yellow mercuric oxide would therefore provide chemical corroboration for the spectral evidence that the heterocyclic nitrone (XIII) was indeed present in the above solutions.

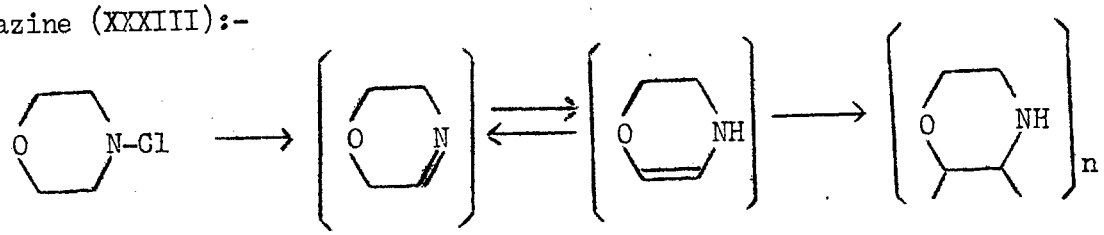
Nitrones are capable of being reduced further to secondary amines (path c) under more vigorous reducing conditions. Thus the 1-pyrroline 1-oxides (I) were reduced to pyrrolidines by zinc and dilute hydrochloric acid[2] whereas milder reagents such as zinc-acetic acid[2], sulphur dioxide[2] and triphenylphosphine[43] reduced the same cyclic nitrones (I) to the 1-pyrroline compounds, corresponding with pathway (b). The heterocyclic nitrone (XIII), however, was reduced to morpholine by the action of zinc on acetic acid. Catalytic reduction over 5% palladium-charcoal using hydrogen at pressures of the order of 35 p.s.i. to give morpholine has been referred to earlier. It is interesting to compare this result with the hydrogenation of the polymer in M-HCl over Adam's catalyst which yielded 4-hydroxymorpholine. In none of these cases was the dihydro-oxazine (XXXI) observed, i.e. corresponding with pathway (b) in the scheme above.

From a preliminary examination of the action of sulphur dioxide on dry chloroform solutions of the heterocyclic nitrone (XIII), the only conclusions that could be drawn were that reduction had indeed occurred as sulphate ion was present in the solid product isolated, and that in the mixture of products obtained by dissolving the above solid in aqueous ammonia and extracting into chloroform, neither morpholine nor 4-hydroxy-morpholine were observable on thin layer chromatograms. At this stage one can only tentatively suggest that reduction to the dihydrooxazine (XXXI) had occurred by de-oxygenation of the nitrone:-



(XXXI)

However, it has been reported that dehydrohalogenation of 4-chloro-morpholine under basic conditions gave not the compound (XXXI) but a polymeric solid (XXXIV), resulting by polymerisation of the tautomeric oxazine (XXXIII):-

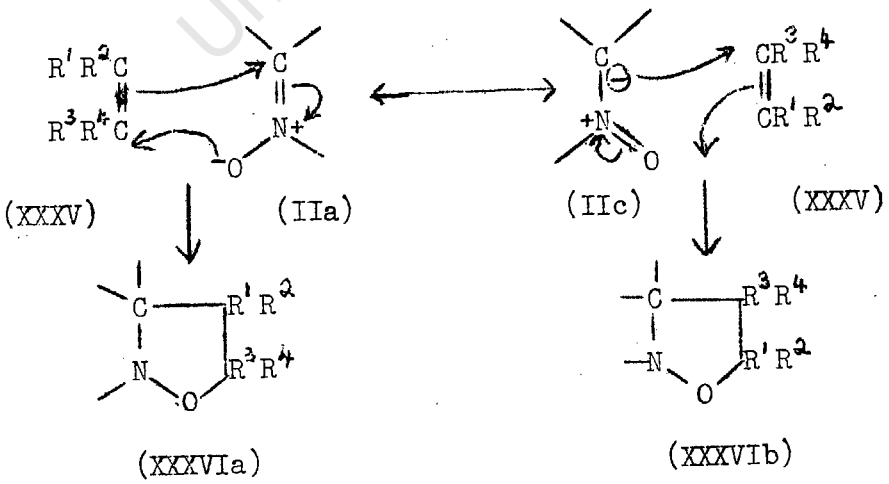


(XXXI) (XXXIII) (XXXIV)

It may well be, therefore, that the solid material in the mixture referred to above contained this polymer. Further detailed studies on the mixture are required, however, before drawing definite conclusions as to the course of the reduction.

Cycloadditions of olefins to Δ^3-dihydro-1,4-oxazine 4-oxide.

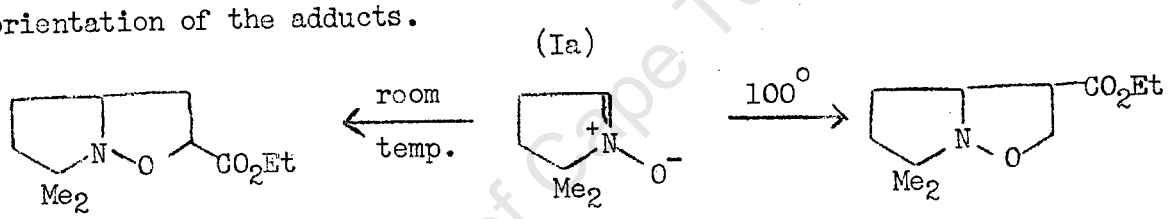
The rapidly growing interest in nitrones during the last decade stems essentially from the ease with which reactive olefins add to yield 1,3-cyclic adducts incorporating essentially the isoxazolidine ring (XXXVI).



(XXXV) (IIa) (IIc) (XXXV)

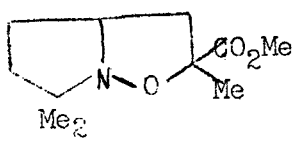
(XXXVIa) (XXXVIb)

Fused bicyclic systems incorporating a bridgehead nitrogen atom have been shown to form when cyclic nitrones, e.g. (I), add to olefins.[36] Fused tricyclic systems arise when the olefin itself forms part of a ring such as in cyclohexene.[36] It is obvious, however, that two structural adducts are possible when an unsymmetrical olefin (XXXV, $R^1R^2 \neq R^3R^4$) adds to a nitrone since the nitrone may react in the one polar form (IIa) to yield the adduct (XXXVIa), or it may react in its "back polar" state (IIc) to yield the isomeric isoxazolidine (XXXVIb). Delpierre and Lamchen,[44] who examined the products obtained by the addition of ethyl acrylate to 5,5-dimethyl-1-pyrroline 1-oxide (Ia), unquestionably established the orientation of the adducts.

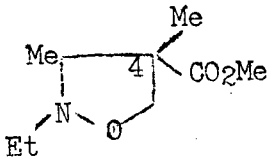


(XXXVIIa) (XXXVIIb)

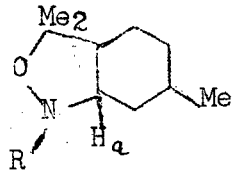
In this elegant classical work they were able to show that at ordinary temperatures the isoxazolidine (XXXVIIa) was formed whereas at elevated temperatures, the isomer (XXXVIIb) was the product. They were able to conclude that the nitrone reacted in its "back polar" canonical form at room temperature, but reacted in its "normal" polar state at 100°. The use of p.m.r. studies has assisted not only in confirming the orientation of these and other similar adducts but also, to a limited extent, the stereochemistry of the ring substituents. Thus methyl methacrylate was shown to add in the cold to the cyclic nitrone (Ia) to to yield the expected adduct (XXXVIII), as established by p.m.r.[45]



(XXXVIII)



(XXXIX)



(XL)

In contrast however, it has been reported that methyl methacrylate as a nitrone trapping agent yielded the adduct (XXXIX) with the nitrone formed *in situ* by the oxidation of N,N-diethylhydroxylamine by *t*-butyl hydroperoxide.[46] Moreover it is claimed that the C-4 epimers were separable.[46] The p.m.r. spectra of the adducts upon which the evidence was based were, however, not reported. P.m.r. has proved to be a valuable tool in conformational analysis in this field. Thus from the isoxazolidine (XL) four conformers were isolated by preparative gas-liquid chromatography (G.L.C.) and the configuration of the two rings and the geometrical relationship between the tertiary hydrogen H_a and the N- substituent R in each conformer were determined by p.m.r. studies.[47]

The heterocyclic nitrone (XIII) as prepared *in situ* in chloroform solutions was observed to behave as a typical nitrone towards reactive π-bond systems, what Huisgen has termed "dipolarophiles",[19,48] and the 1,3-cycloadducts were shown to be the expected fused N-bridged isoxazolidines. The adduct in each case was prepared by adding the dipolarophile to a dry chloroform solution of the freshly prepared nitrone (XIII) and evaporating off most of the solvent. In this way, cyclohexene, phenylisocyanate and ethyl acrylate were observed to add to the dihydrooxazine oxide (XIII).

Addition of cyclohexene

Cyclohexene was observed to give a colourless crystalline base having a penetrating mouse-like odour. The direct purification of this by distillation and recrystallisation failed to give an analytically pure product. However it readily formed a picrate whose analysis and equivalent weight, as determined spectrophotometrically,[41] were in satisfactory agreement with $C_{10}H_{17}NO_2.C_6H_3N_3O_7$. From the pure picrate the base was recovered as a low melting (29 - 30°) crystalline solid analysing for $C_{10}H_{17}NO_2$, and showing no absorption bands above 1480 cm^{-1}, thus establishing the absence of both C=N and C=C in the adduct. The fused tricyclic structure (XLI) assigned to the adduct was confirmed on the basis of the p.m.r. spectrum. The spectrum consisted of a series of

(XLI)

complex multiplets in which 5 distinct groups were recognisable (Fig. 2c, Appendix 1). The broad band centred near τ8.4 is assigned to the protons on 4 methylene groups at C-8 to C-11. The multiplet centered at τ7.4 (1H) is assigned to the tertiary hydrogen at C-12. The multiplets at τ7.0 (3H) and 6.2 (4H) are due to the 7 protons on the morpholine moiety of the adduct. Finally the remaining low field multiplet centered at τ5.6 (1H) is assigned to the tertiary proton at C-7 since a hydrogen in this position, adjacent to an oxygen atom which in turn is bonded to a nitrogen atom, should be least shielded and hence would be expected to give a signal at a field lower than any of the other protons. 26a

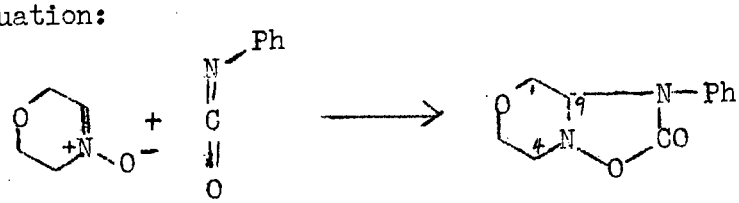
Reaction with phenylisocyanate.

The nitrone (XIII) with phenylisocyanate gave a colourless, crystalline solid, m. pt. 117 - 118°, which analysed for a 1 : 1 adduct. The fused bicyclic oxadiazolidinone structure (XLII) is assigned to this product on the following grounds:

(i) The addition of phenylisocyanate to nitrones to give oxadiazolidinones is well attested, having been reported initially by Beckmann[49] and investigated more fully by Staudinger.[50]

(ii) the IR spectrum of the above product showed strong absorption at 1770 $cm.^{-1}$ (γ-lactone)[32d] but no absorption due to C=C and C=N.

(iii) The signals in the p.m.r. spectrum were assigned without difficulty as follows: the multiplet at τ 6.58 to the methylene protons at C-4, the multiplet at τ 6.09 to the four methylene protons at C-1 and C-3, and the multiplet at τ 4.95 to the tertiary proton at C-9, the low resonance signal of this proton being expected owing to the de-shielding effect of the two adjacent nitrogen atoms.[26a] The splitting in this last signal is probably due to the non-equivalence of the C-1 protons in which case their coupling constants with the C-9 proton would be different. The five aromatic protons gave rise to a multiplet at τ 2.63. The reaction may therefore be represented by the equation:



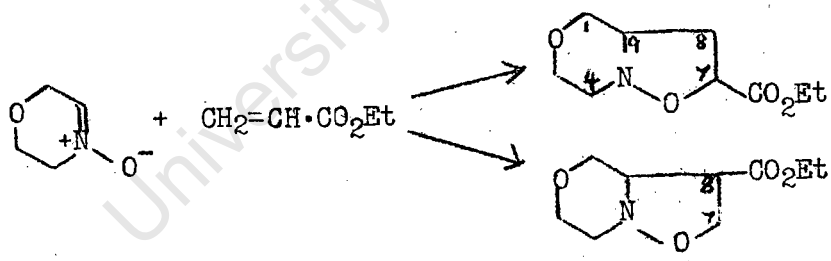
(XIII) (XLII)

Reaction with ethylacrylate.

An oily adduct, analysing for $C_9H_{15}NO_4$, was obtained when the dihydro-oxazine 4-oxide (XIII) was refluxed with ethyl acrylate for one day at 100°. It resembled related isoxazolidines in that it failed to yield a picrate but readily gave a picrolonate[44] whose analysis and molecular weight (determined spectrophotometrically[51]) were consistent for $C_{19}H_{23}N_5O_9$. The isoxazolidine structure (XLIII) together with the orientation of the ethoxycarbonyl group shown is assigned to the adduct on the following grounds:

(i) Ethyl acrylate has been shown beyond all reasonable doubt to add 1, 3 to the nitrone system.[44]

(ii) The IR spectrum showed significant absorption bands at 1745 (C=O ester) and 1128 $cm.^{-1}$ (C-O-C, morpholine moiety) but no bands due to C=C or C=N. The adduct can therefore be only one of the isoxazolidines, (XLIII) or (XLIV).



(XLIII)

(XLIV)

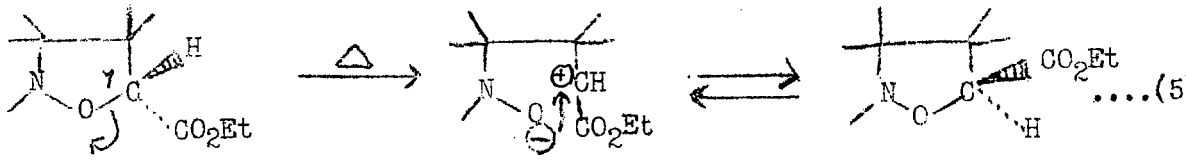
(iii) In the p.m.r. spectrum (Fig. 2b, App. 1) the triplet at τ ~~8.75~~ 8.69 and quartet at τ ~~8.69~~ 5.73 are characteristic for the ethyl ester while the multiplet bands ranging from τ 5.8 - 7.2 are assigned to the protons at C-1, C-3, C-4 and C-9. The two multiplet bands at τ 7.48 (2H) and 5.28 (1H) are assigned respectively to the methylene protons at C-8 and the methine proton at C-7 in (XLIII). The C-7 proton being

adjacent to both the ring oxygen and an ethoxycarbonyl group would be expected to give a low field signal.[26a] The multiplet appearance of the low field signal is due to spin-spin coupling with the non-equivalent methylene protons at C-8, the non-equivalence of these protons being the result of the 2 rings lying folded along the C-N junction, so that the axial and equatorial protons at C-8 would be endo- and exo-orientated respectively.

(iv) The isomeric structure (XLIV) is excluded for the reason that the protons giving rise to the multiplets at τ7.48 (2H) and τ5.28 (1H) in the p.m.r. spectrum cannot be assigned to this particular structure.

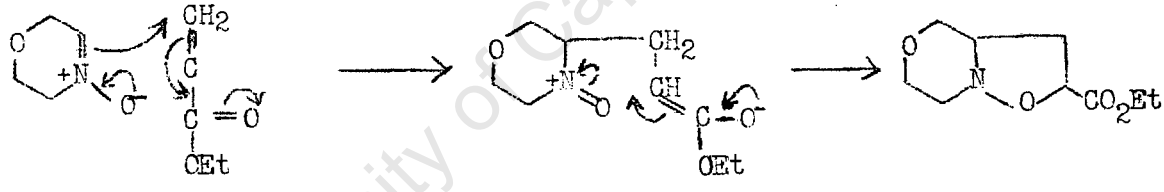
A careful examination of the p.m.r. spectrum of the isoxazolidine ester (Fig. 2 b, App. 1) reveals that each of the signals due to the ethyl ester protons is accompanied by a very weak, but nevertheless significant signal at a slightly higher field, i.e. a quartet at τ5.76 (J = 7 c.p.s.) and a triplet at τ8.72 (J = 7 c.p.s.). This suggested that two C-7 epimers were present, the mixture containing a greater preponderance of the one. This hypothesis appears to find support in the further observation that, after extending the reflux period of the reaction between the heterocyclic nitrone (XIII) and ethyl acrylate to 4 days at 100° in the hope of obtaining the isomer (XLIV) analogous with the ester (XXXVIIb), only the same isoxazolidine (XLIII) was recovered and the p.m.r. spectrum of this product was identical with that shown in Figure 2 b. However the relative intensity of the above-mentioned weak ester signals

had markedly increased. This can only be explained by assuming that the proportion of the less abundant epimer had increased. The epimerisation may well occur through the C-O cleavage in the isoxazolidine ring on heating, followed by reclosure with inversion at C-7.



....(5)

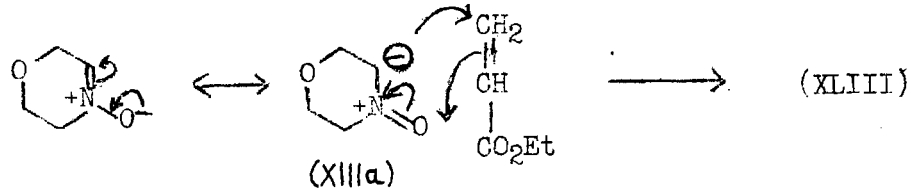
An examination of the structure of the isoxazolidine (XLIII) leads one to conclude that the nitrone (XIII) has reacted via a "back polarisation" mechanism, the addition possibly occurring by initial nucleophilic attack on the β-carbon of the acrylic ester, to form the intermediate zwitterion (XLV) which then cyclises in the manner shown (Mechanism 1.).



(XIII) (XLV) (XLIII)

Mechanism 1.

On the other hand the cyclisation may involve a concerted process with cis addition of the olefin to the nitrone reacting in its "back polar" form (XIIIa) (Mechanism 2.).



(XIIIa) (XLIII)

Mechanism 2.

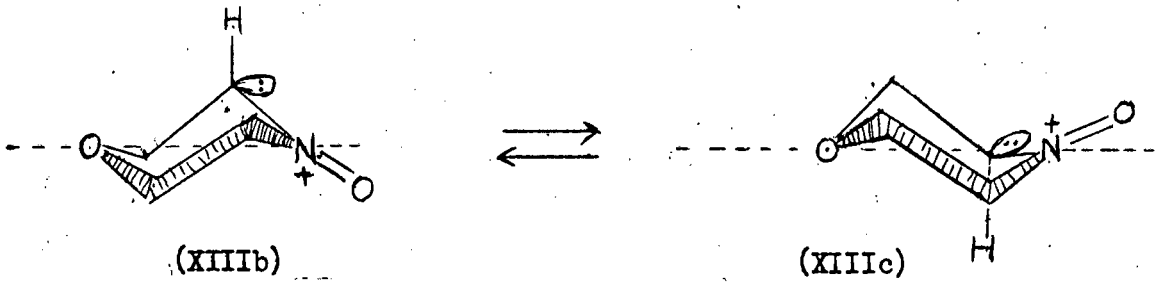
Huisgen, in a very comprehensive review on 1,3-cycloadditions,[48] favoured a single step concerted process as represented by Mechanism 2.

Stereochemical and Conformational Considerations.

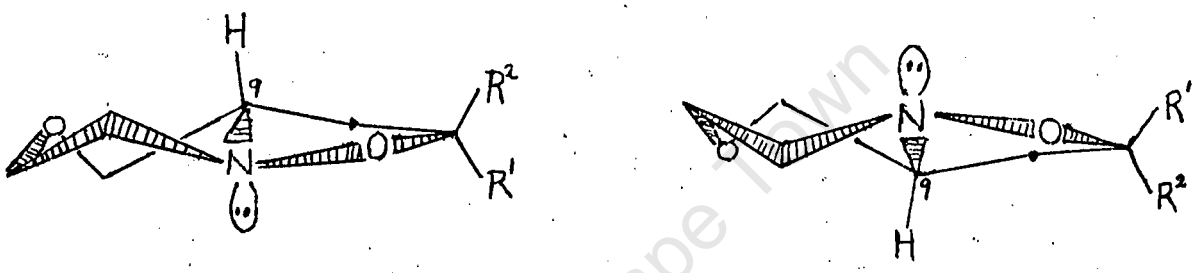
An attempt to determine the most probable stereochemistry and conformation of the morpholinoisoxazolidine ester (XLIII) by examining Drieding models of the intermediate and final structures and correlating these with the limited information from the p.m.r. spectra was not entirely fruitless. The following observations and deductions drawn therefrom are noted:

(i) Maximum charge separation between the lone electron pairs on the cyclic and exocyclic oxygen atoms of the heterocyclic nitrone would occur when the structure (XIIIa) adopted a chair conformation (XIIIb $\leftrightarrow$c). The exocyclic oxygen atom would be pseudo-equatorial due to sp^2-hybridisation of the nitrogen atom and therefore would not lie in the plane of the ring (Chart 1).

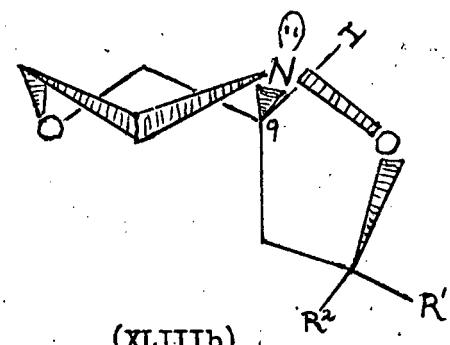
(ii) A thermodynamically more stable bicyclic structure would be expected to result when the two rings in (XLIII) are least inclined to one another. This is observed when the rings are trans-fused, as in (XLIIIa). The axial lone pair on the nitrogen is seen to be trans to the axial methine hydrogen at C-9. Cis-fusion would result in structure (XLIIIb) which, since it is folded, might be expected to be thermodynamically less favoured. While the complex character of the p.m.r. spectrum precludes a detailed analysis to ascertain the geometry of the ring fusion, the ester proton signals (next paragraph) tend to support the expectation that the rings should be trans-fused.



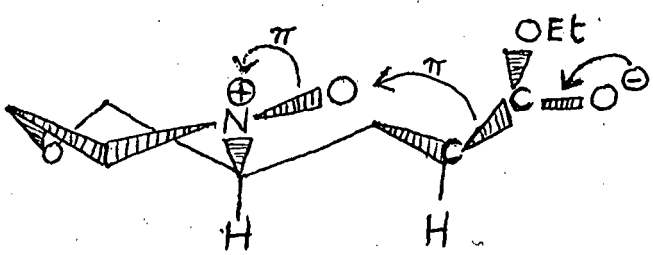
(XIIIb) (XIIIc)



(XLIIIa) (XLIIIc)



(XLIIIb)



(XLV)

CHART 1.

(iii) In the trans-fused structure (XLIIIa: $R^1 = CO_2Et$, $R^2 = H$) (Chart 1), the ester protons on the ethoxycarbonyl group can approach the lone-electron pair on the nitrogen atom more closely than the same protons in the epimer (XLIIIa: $R^1 = H$, $R^2 = CO_2Et$). Thus one would expect small magnetic resonance differences between the ester protons in the two epimers.[26a]

In contrast, an examination of the epimeric esters derived from the cis-fused structure showed that in one case (XLIIIb: $R^1 = H$, $R^2 = CO_2Et$) the ethoxycarbonyl group was orientated into the fold, i.e. endo- orientated, whereas in the epimer (XLIIIb: $R^1 = CO_2Et$, $R^2 = H$), the same ester group was exo-orientated with respect to the ring fold. One would therefore expect more marked differences in the magnetic properties of the ester protons of these two epimers.

In the absence of suitable data on comparable structures, clearly one cannot assign a definite value to $\delta\nu_a$, the chemical shift difference between the ester proton signals for the two trans-epimers, and $\delta\nu_b$, for the two cis-epimers. However since the actual observed value ($\delta\nu = 0.03$ p.p.m.) was very small, the author would tentatively suggest that this correlates more closely with a trans-fused structure (XLIIIa). Furthermore, in view of the closer proximity of the ethyl ester protons in (XLIIIa: $R^1 = CO_2Et$, $R^2 = H$) to the axial lone pair on the nitrogen atom, these protons would be expected to experience a slightly greater de-shielding effect and would therefore be expected to give resonance signals at slightly lower field than in the

case of the epimer (XLIIIa: $R^1 = H$, $R^2 = CO_2Et$).

If this assumption were correct, it would imply that since the downfield ester proton signals largely predominate in the p.m.r. spectrum, the isoxazolidine ester produced contained a high proportion of the conformer (XLIIIa: $R^1 = CO_2Et$, $R^2 = H$). Both Mechanism 1 and Mechanism 2 can account for this formation (paragraph vi below).

(iv) For <u>trans</u>-fusion of the rings to occur, the nucleophilic carbon atom generated in the back polar state in (XIIIa) must have the electron-pair located in an equatorial sp^3-orbital, while the hydrogen atom on the same carbon becomes axial (XIIIb).

(v) Since the two chair conformers (XIIIb) and (XIIIc) of the nitrone in its back polar form would be expected to be present in equal amounts, the absence of optical activity in the cyclo-addition product would indicate that the enantiomeric esters (XLIIIa: $R^2 = H$, $R^1 = CO_2Et$) and (XLIIIc: $R^2 = H$, $R^1 = CO_2Et$), of the more abundant adduct are present in equal amounts, i.e. a racemic mixture is formed. Similarly the less abundant adduct must also be present as a racemic mixture of its enant-iomers (XLIIIa: $R^1 = H$, $R^2 = CO_2Et$) and (XLIIIc: $R^1 = H$, $R^2 = CO_2Et$).

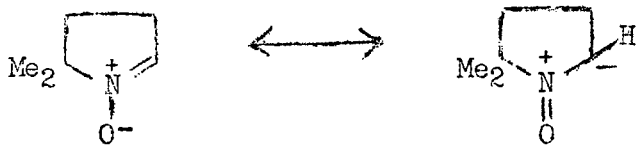
(vi) A consequence of the conclusions arrived at in paragraphs (iii) and (v) is that the nett result of the addition of ethyl acrylate cannot be random but stereospecific.

If the ester (XLIIIa: $R^1 = CO_2Et$, $R^2 = H$) were formed by a concerted cyclization (Mechanism 2), then the orientation of

the olefinic ester would be such that the ethoxycarbonyl group was directed to the same side of the plane of the nitrone ring as the exocyclic oxygen. Moreover, since the above epimeric ester, together with its enantiomer, was the most abundant stereoisomer, the implication follows that this orientation of the ethyl acrylate is preferred to the alternative where the ester group is directed away from the side of the ring plane on which the exocyclic oxygen lies.

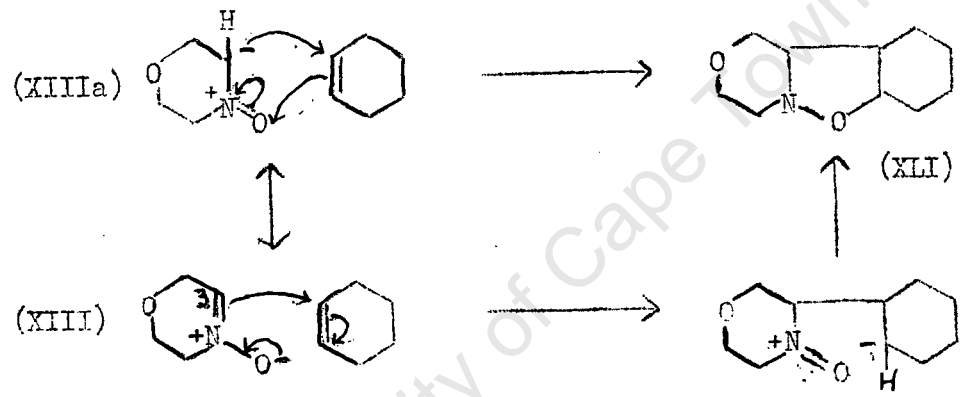
If the reaction were considered as a two-step process (Mechanism 1), the initial step would be nucleophilic attack by the equatorial electron pair at C-3 in the nitrone (XIIIb) on to the β-carbon atom of the olefin. In the intermediate (XLV) the ethoxycarbonyl group can only be directed to the same side of the nitrone ring plane as the exocyclic oxygen or to the opposite side prior to the second step, i.e. prior to nucleophilic attack by the α-carbon atom on the exocyclic oxygen atom. (Chart 1)

An aspect of these cycloadditions requiring comment arises from the observation that the heterocyclic nitrone (XIII) gave only the one ester (XLIII) with ethyl acrylate and none of the structural isomer (XLIV) even at elevated temperatures. This means that the nitrone (XIII) reacts only in its "back-polar" form which would appear, even at elevated temperatures, to be thermodynamically favoured over the "normal" polar structure (XIII) in these cyclo-additions. This is in contrast to the nitrone (Ia) which can react in either of the canonical forms shown, depending upon the reaction temperature,[44] as discussed earlier.



(Ia)

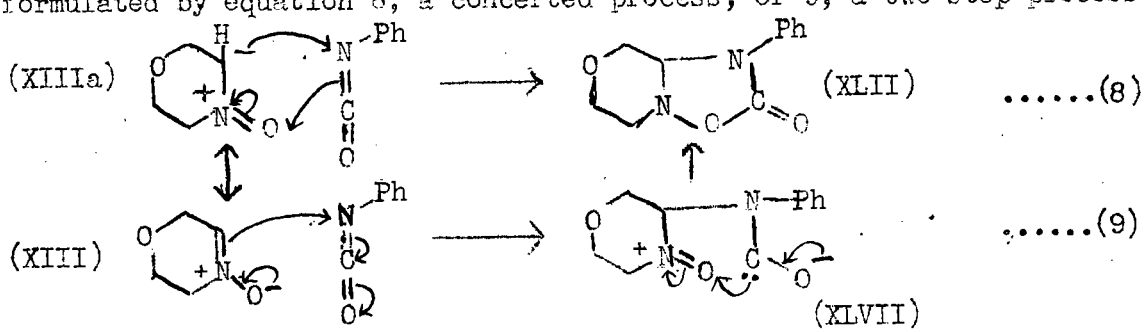
The addition of the heterocyclic nitrone (XIII) to cyclohexene can now be formulated as a single step process (Equation 6) or a two-step process (Equation 7). In the former case, the nitrone must be "prepared" in its "back-polar" state (XIIIa) prior to cyclization with the olefin.



(XLVI)

In the two-step process (equation 7), the exocyclic oxygen atom in (XIII) provides the driving force for the reaction, resulting in nucleophilic attack by C-3 on the olefin to yield the intermediate zwitterion (XLVI) as shown. The positive charge on the nitrogen atom in (XLVI) provides the driving force which completes the cyclization process.

In the same way, the addition of phenyl-isocyanate to (XIII) can be formulated by equation 8, a concerted process, or 9, a two step process.



(XLVII)

In equation 9, an intermediate carbene-containing zwitterion (XLVII) is suggested which can cyclize in the manner shown to yield the morpholino-oxadiazolidinone (XLII).

It should be stressed that it may be incorrect to suggest that the "back polar" mechanism which operates in the cyclo-addition of (XIII) with ethyl acrylate must also be the modus operandi in all other cyclo-additions, for it is reported that under different conditions and with different reagents, different mechanisms for the cyclo-addition of olefins to nitrones may be operative.[9]

It is clear that the present evidence is insufficient to deduce whether the foregoing cyclo-additions occurred in one or two steps. Reference has been made to Huisgen's report in a review article on kinetic data which support his argument for a one-step mechanism.[48] It is unfortunate that his results are not yet available. Indeed kinetic studies in this particular field are scant,[9,48] and the author intends upon completing the present work to examine the kinetics of the above cyclo-additions since the mechanistic path can really only be decided on the basis of entropy of activation measurements.[9]

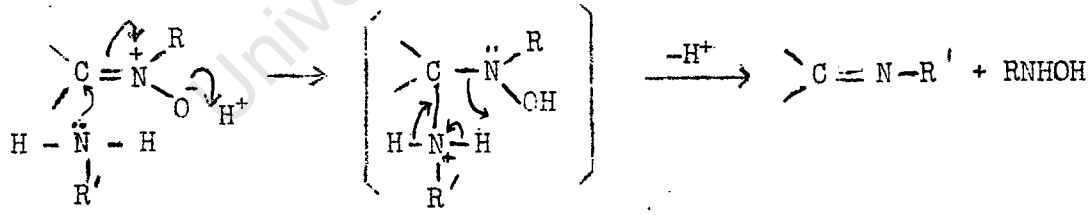
In concluding this discussion, the author admits to having taken undue liberty to speculate on the detailed structures of certain cyclo-adducts and drawing inferences from rather limited experimental data and from models which, although helpful in understanding the steric course of a

reaction, may yet mislead one's judgment. While wild speculation can rarely be justified, the speculation which lies within the bounds of reason and logic and leads to results which can ultimately be tested is a necessary adjunct of every research student for it is this speculation which provides the stimulus to advance his understanding in his particular field.

Oxidations of Δ^3-dihydro-1,4-oxazine 4-oxide.

Reaction with phenylhydrazines.

Nitrones are cleaved by reacting with the usual carbonyl reagents and the products are derivatives of the parent carbonyl compound.[15,16,52,55] The mechanism of this reaction is uncertain. Initial nucleophilic attack by the carbonyl reagent on the nitrone-carbon atom is considered as one possibility.[9] The intermediate adduct (XLVIII), which has not been isolated, is then considered to lose the hydroxylamino-residue.

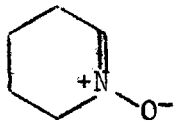


(XLVIII)

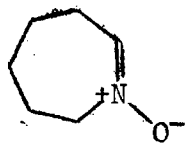
Initial hydrolysis of the nitrone to the parent carbonyl and N-substituted hydroxylamine has been suggested as an alternative mechanism.[9] The carbonyl compound can then react with the reagent.

While acyclic nitrones react readily with carbonyl reagents,[9] cyclic

nitrones appear to be less reactive. Thus the 1-pyrroline 1-oxides have not been reported to yield derivatives with acidic solutions of 2,4-dinitrophenylhydrazine. Piperideine 1-oxide (XVI) and its higher homologue (XLIX), however, are reported to yield 2,4-dinitrophenylhydrazones (D.N.P.s) with the same reagent.[37]

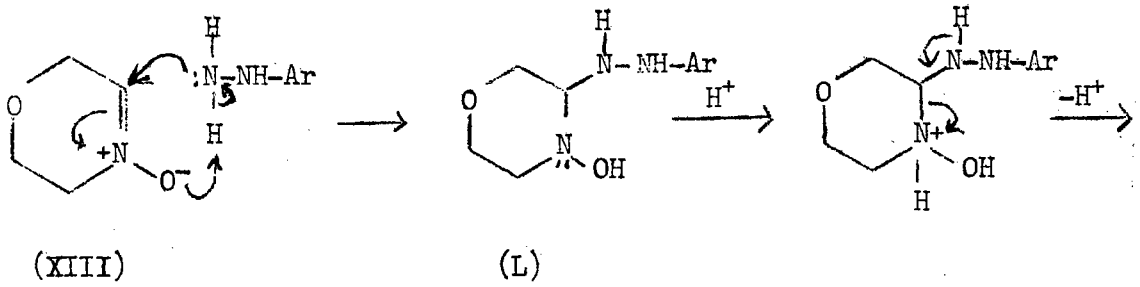


(XVI)

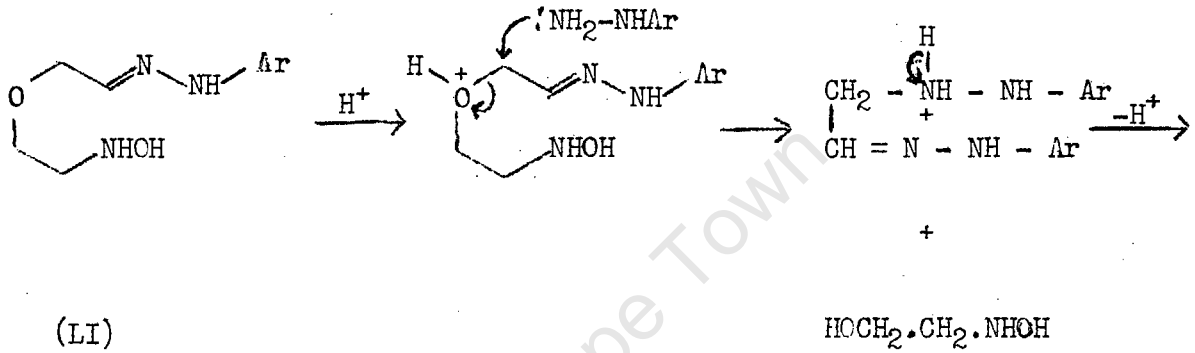


(XLIX)

Aqueous solutions of the dihydrooxazine 4-oxide (XIII) were observed to react rapidly with either a hot aqueous solution of phenylhydrazine hydrochloride containing sodium acetate or a hot acidic solution of 2,4-dinitrophenylhydrazine in ethanol to form the corresponding glyoxal phenylosazone (LIV) in nearly quantitative yields. From the phenylhydrazine reaction mixture were recovered both aniline and the equivalent of 1 mole of ammonia per mole of nitrone. Ammonia was also recovered from the reaction with 2,4-dinitrophenylhydrazine, but in much smaller yield (about 0.2 mole per mole nitrone). Clearly oxidative cleavage of the nitrone ring occurred in both cases and a mechanism for the reaction is suggested in the scheme overleaf (Chart 2).



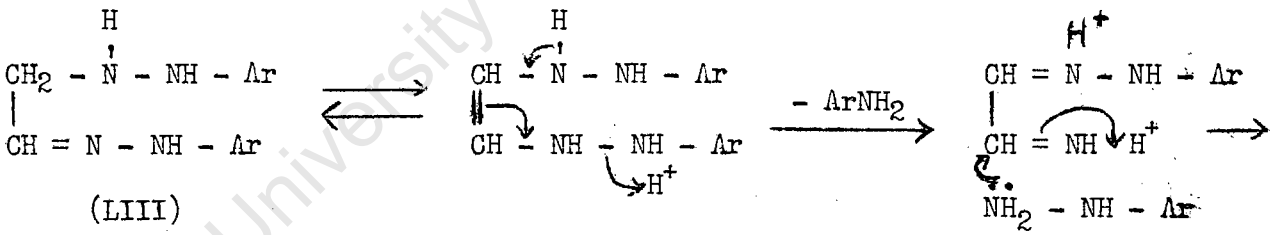
(XIII) (L)



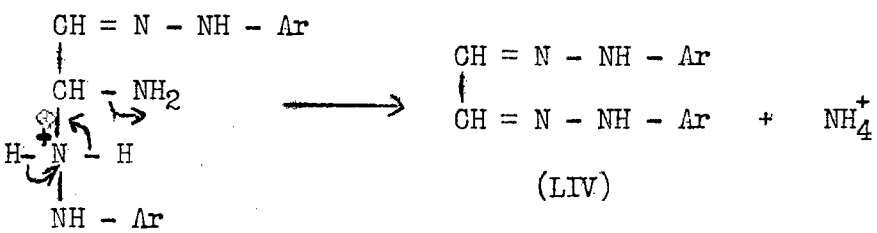
(LI)

$HOCH_2.CH_2.NHOH$

(LII)



(LIII)



(LIV)

Ar = Ph, O_2N-

CHART 2.

Initial nucleophilic addition to the nitrone (XIII) is shown to yield the substituted 4-hydroxymorpholine (L) which undergoes prototropic rearrangement to the phenylhydrazone (LI). This glycolaldehyde derivative would now be expected to undergo oxidation by more of the carbonyl reagent, a reaction well known to glycolaldehydes, aldoses and ketoses, to form phenyl- and substituted-phenylosazones. This oxidation could occur by the mechanism shown in Chart 2.

Protonation of the ether oxygen atom facilitates nucleophilic displacement of this atom by a second molecule of the substituted hydrazine to yield β-hydroxyaminoethanol (LII) and the hydrazino-hydrazone (LIII). Oxidative rearrangement of the intermediate (LIII) following the mechanism postulated by Weygand for the formation of sugar oxazones,[56] involving successively the loss of arylamine, nucleophilic attack by a third molecule of the substituted hydrazine and loss of ammonium ion, leads to the corresponding osazone of glyoxal (LIV). Attempts to isolate the hydroxylamine (LII) were unsuccessful owing to the formation of tarry products. Further, the fact that the reaction mixture readily reduced alkaline triphenyltetrazolium chloride (TTC) to the red formazan, was not satisfactory evidence for the presence of this hydroxylamine,[57] since it was observed that phenylhydrazines also behave similarly towards alkaline TTC. It is worthy of mention that the reaction with either phenylhydrazine or the 2,4-dinitro compound proceeded equally readily in the absence of air so that an alternative mechanism postulated for the formation of sugar osazones in which air is required to effect oxidation of an intermediate enol form of the sugar phenylhydrazone[58] would not apply in this case. The author is unable to account for the consistently

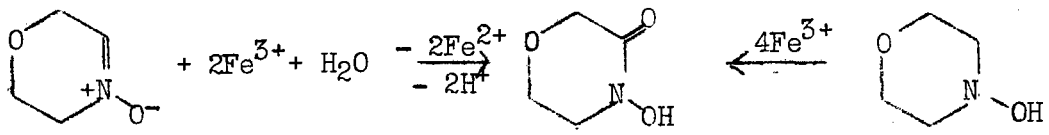
low yield of ammonia recovered from the reaction between (XIII) and 2,4-dinitrophenylhydrazine, although the 2,4-D.N.P.-osazone was obtained in almost quantitative yields.

Reaction with ferric chloride.

Aqueous solutions of Δ^3-dihydro-1,4-oxazine 4-oxide, of its polymer and of 4-hydroxymorpholine were all observed to give intense wine-red colours upon treatment with ferric chloride. This parallels the reports of the action of ferric chloride upon the dimer (XVIII) of 1-piperideine 1-oxide,[20] and the products formed when secondary hydroxylamines were subjected to catalytic aerial oxidation.[21] The author observed that the intensity of the colour increased to a limiting value as the concentration of the ferric ion increased. The visible spectrum showed a maximum near 500 mμ (ε 740). The solutions gave a positive qualitative test for ferrous ion. Furthermore, stoichiometric studies showed that 2 moles of ferric ion were reduced very rapidly per mole of nitrone, while 4 moles of ferrous ion were formed equally rapidly by each mole of 4-hydroxy-morpholine.

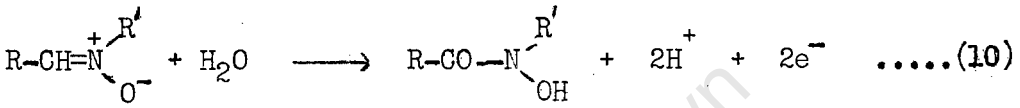
It would therefore appear that since the heterocyclic nitrone (XIII) is an oxidation product of 4-hydroxymorpholine, that both these compounds undergo further oxidation by ferric ions to the same product.

From nitrone (XIII) was isolated a product, analysing for $C_4H_7NO_3$ to which the author assigns the structure of the cyclic hydroxamic acid, 4-hydroxy-3-morpholone (LV) on the following grounds:

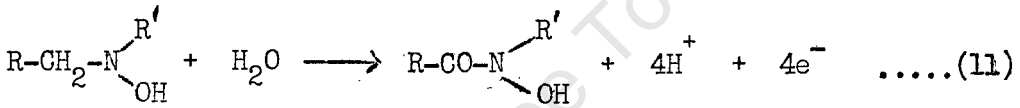


(XIII) (LV) (XV)

(i) The stoichiometric proportions require a product having the same oxidation state as that of a hydroxamic acid grouping, as determined by the partial equations (10) and (11):



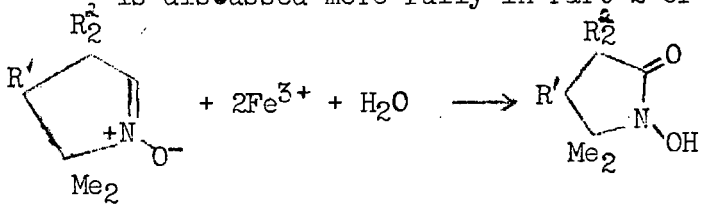
.....(10)



.....(11)

(ii) Hydroxamic acids have long been known to yield coloured complexes with ferric ions, absorbing in the visible spectrum over the range 480 - 540 mμ. [59,60,61,62]

(iii) Finally the isolation of the 1-hydroxy-2-pyrrolidones (LVI a, b, and c) from the oxidation of the corresponding cyclic nitrones (Ia), (Ib) and (Ic) by ferric chloride lends conclusive support to the hydroxamic acid structure (LV) assigned. (This work, which resulted in a publication [63] is discussed more fully in Part 2 of this Thesis.)



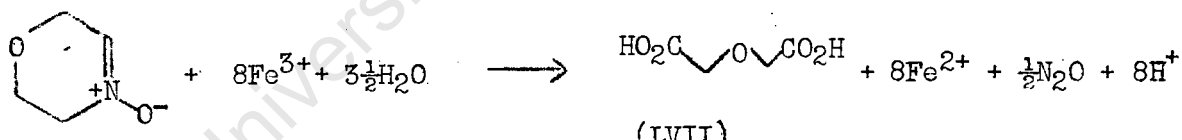
(I) (LVI)

	R'	R''
a:	H	H
b:	Me	H
c:	H	Me

The IR spectrum of (LV) revealed the following bands some of which are reported to be characteristic for hydroxamic acids:[64,65]

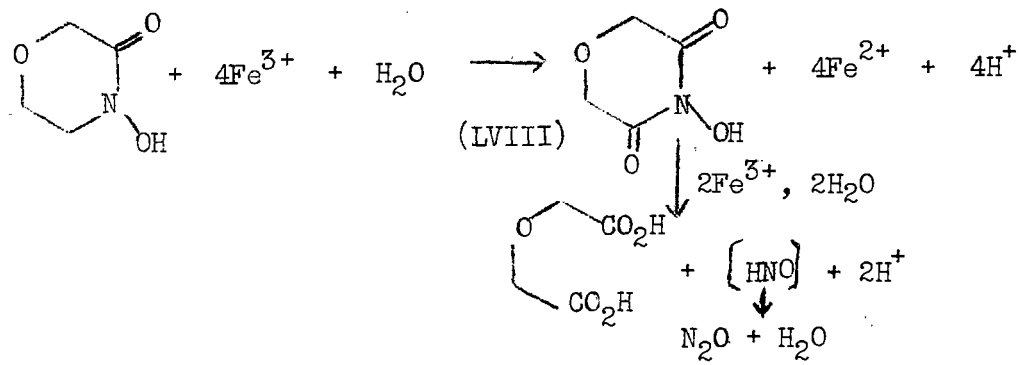
3030 and 2790 (bonded OH), 1670 (C=O), 1518, 1106 (C-O-C),[32b] 994 and 880 $cm.^{-1}$ (N-O stretch).

It was noticed that further oxidation of the hydroxamic acid (LV) continued when the solution either was allowed to stand for a prolonged period or was heated on a steam bath. The amounts of ferric ion reduced per mole of the heterocyclic nitrone (XIII) and of 4-hydroxymorpholine were 8 and 10 moles respectively. In addition, nitrous oxide gas was isolated from the solutions and characterised by the IR absorption spectrum having multiple bands at 2220 and 1290 $cm.^{-1}$ (lit.[32e,66] 2220 and 1290 $cm.^{-1}$). From the solution of (XIII), after removal of the iron as insoluble hydroxides, was recovered a colourless crystalline solid, identified as diglycollic acid (LVII).[54] These facts are consistent with the stoichiometric requirements represented in the following equation:

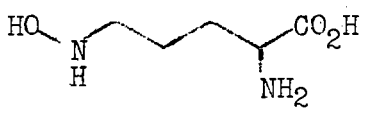


(LVII) .....(12)

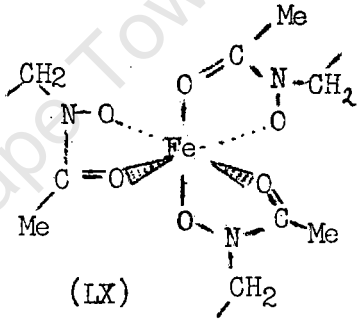
The reaction most probably passes through the intermediate diketo-compound (LVIII) which upon oxidation and hydrolysis would yield the products shown.



This reaction demonstrates that a methylene group adjacent to the N-O group is capable of undergoing facile oxidation by ferric ion. While the mechanism of the oxidation of a carbon atom adjoining a N-O group will be discussed more fully in Part 2, there is an interesting biogenetic aspect of this reaction in relation to those members of the Aspergillaceae which yield metabolites termed "fungal siderochromes".[67] These contain hydroxamic acid systems derived from δ-N-hydroxyornithine (LIX). In particular the structure of ferrichrome has been elucidated.[68,69] The N-hydroxy group is acetylated and three such hydroxamic acid residues are co-ordinated octahedrally around a central ferric ion (LX).

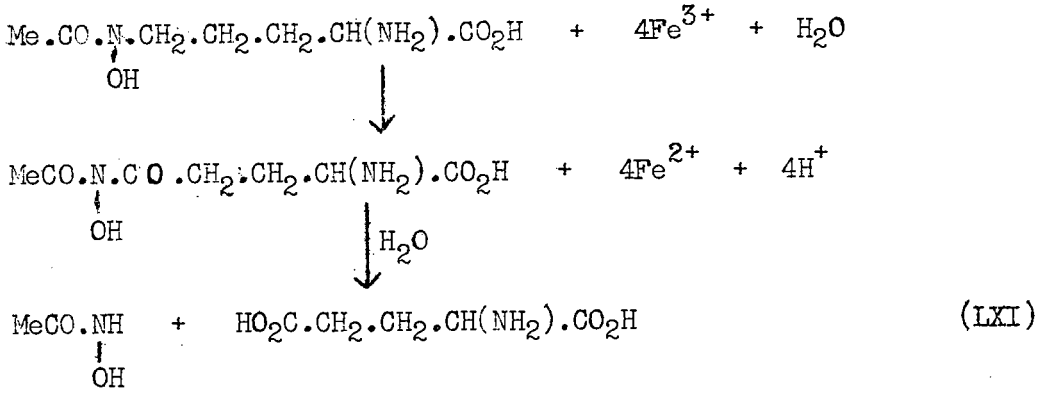


(LIX)



(LX)

Since a methylene group adjoins the N-O group of each hydroxamate residue, it becomes apparent from the following equation that further oxidation by excess of ferric ion followed by hydrolysis would yield glutamic acid (LXI):



(LXI)

Ferrochrome may thus serve as a source of glutamic acid in the organism, its release being controlled by the ferric ion available.

PART 2.

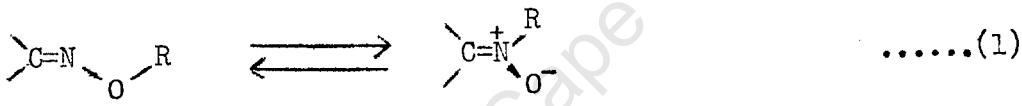
OXIDATIONS OF CYCLIC NITRONES BY FERRIC CHLORIDE.

PART 2

OXIDATIONS OF CYCLIC NITRONES BY FERRIC CHLORIDE.

1. Introduction.

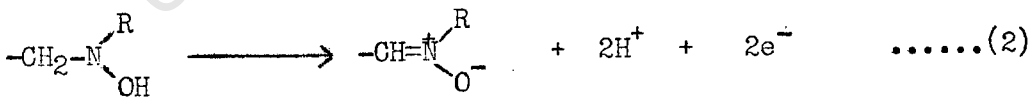
The tautomeric expression (equation 1) demonstrates that the oxidation level of the nitrone group is equivalent to the oxime O-ether group. In fact, nitrones have been referred to as "oxime N-ethers",[70,71] although not for this reason.



.....(1)

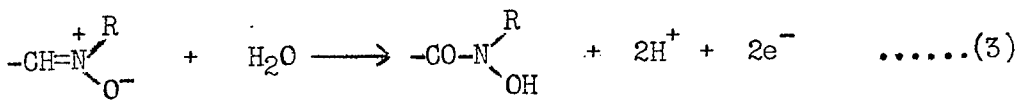
oxime O-ether nitrone (oxime N-ether)

The oxidation level is intermediate between substituted hydroxylamines (I) at a lower oxidation state, and hydroxamic acids (II) at a higher oxidation state. The relationships are shown in the following two equations:



.....(2)

(I)



.....(3)

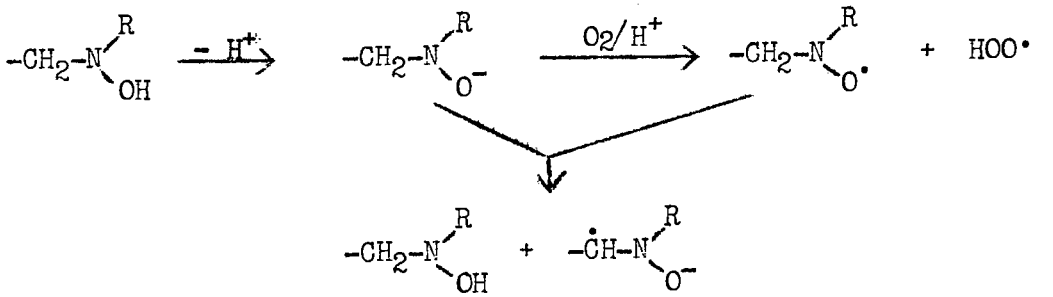
(II)

The oxidation level of the hydroxamic acid group (II) cannot be raised without rupturing the C-N bond.

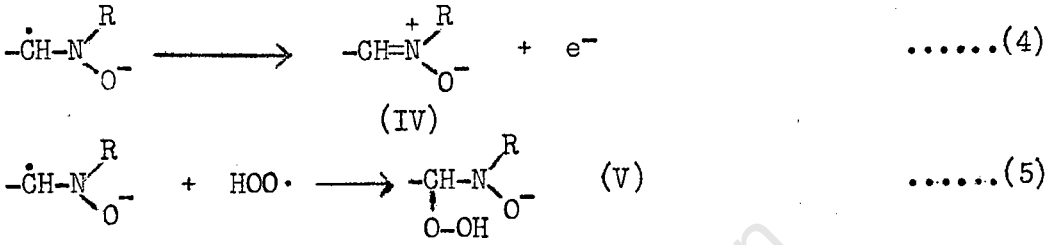
In a discussion on the oxidation of nitrones it will be necessary to refer to these allied structures. For this reason it is considered apposite to review at the outset the literature relating to oxidations of cyclic nitrones and related secondary hydroxylamines.

Review on Oxidations of Secondary Hydroxylamines.

It is a well attested fact that one of the important methods for preparing nitrones is by the use of mild oxidising agents on corresponding secondary hydroxylamines.[8,9] Thus aeration of ammoniacal solutions of secondary hydroxylamines containing catalytic amounts of cupric ion leads to high yields of nitrones with few side products.[2,27,55] Rogers and his co-workers, in a study of the mechanism by polarographic analysis of the resulting solutions, identified peroxidic products though only in small yield.[27] In their mechanism it was postulated that through an auto-oxidation process, the radical ion (III) together with peroxide radical was generated. The subsequent behaviour of the radical ion (III) depended upon its stability. Unstable radicals yielded nitrones (IV) on further oxidation (4) while more stable radicals gave both nitrones and peroxidic products (V) (5).



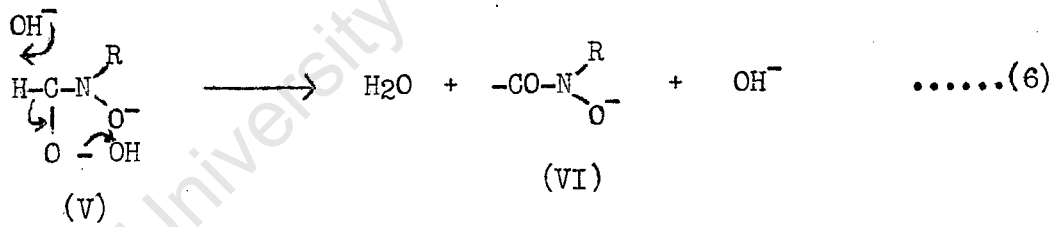
(III)



(IV)

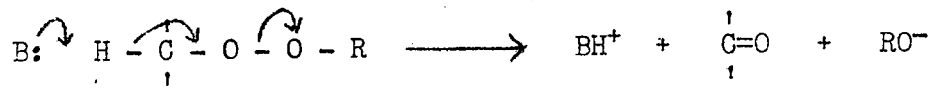
(V)

The author would suggest that the reason for the products giving intense colours with ferric chloride may be due to the facile hydrolysis of the peroxidic ion (V) to yield hydroxamate ion (VI) (6) which would yield the intense red colours with ferric ion.[59]



(V) (VI)

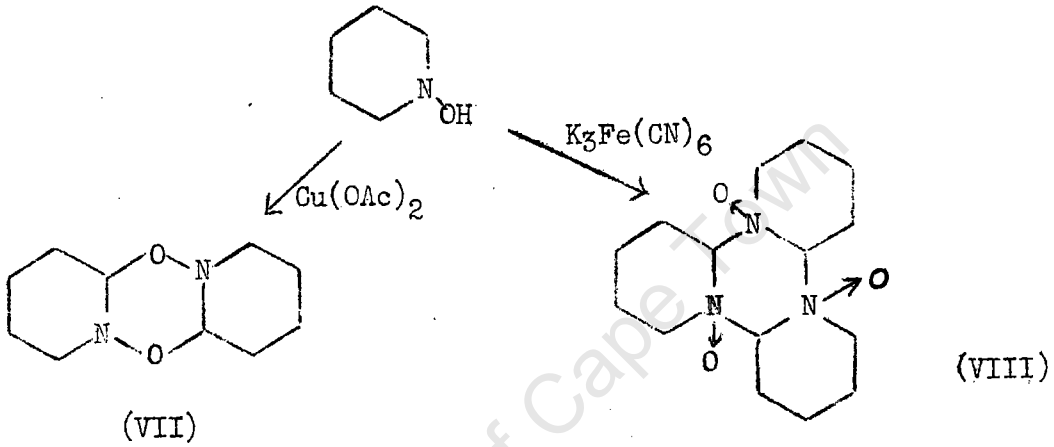
This reaction finds its parallel in the base-catalysed carbonyl-forming elimination reactions <u>via</u> peroxide intermediates.[72]



The silver ion, Ag^+, is also capable of catalysing the aerial oxidation of secondary hydroxylamines to nitrones[55] though less efficiently.[21]

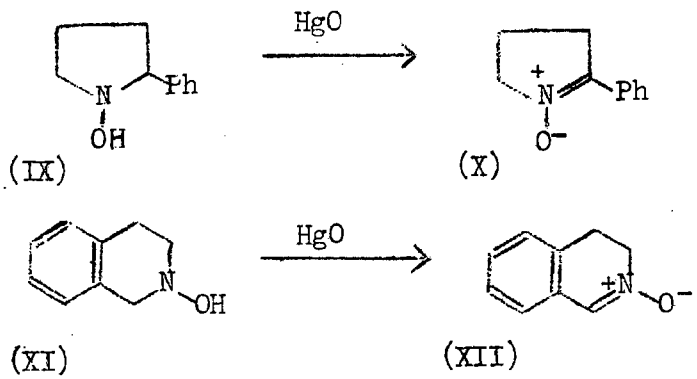
Metallic oxides and salts in a high state of oxidation are effective

in oxidising secondary hydroxylamines to nitrones. Thus yellow mercuric oxide,[28,29,30] lead dioxide,[73] cupric acetate,[20,74] potassium permanganate[75] and potassium ferricyanide[21,76] have been employed in this reaction. The products, however, may depend upon the experimental conditions. For example 1-hydroxypiperidine with cupric acetate yielded the nitrone dimer (VII)[20] whereas the same hydroxylamine with potassium ferricyanide yielded the nitrone trimer (VIII).[21]



(VII) (VIII)

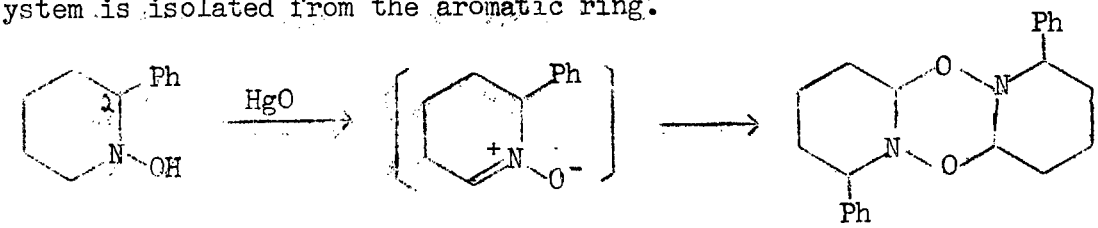
Furthermore the site of formation of the nitrone C=N bond may be electronically and sterically influenced by the substituents present. Thus, 2-phenyl-1-hydroxypyrrolidine (IX) and N-hydroxy-tetrahydroisoquinoline (XI) on treatment with mercuric oxide yielded the respective cyclic nitrones (X)[30] and (XII)[21] in which the C=N system is in conjugation with the aromatic ring.



(IX) (X)

(XI) (XII)

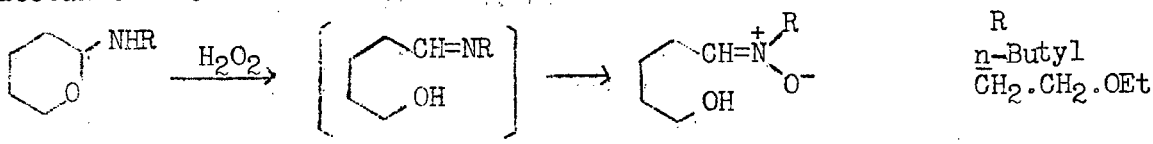
1-Hydroxy-2-phenyl-piperidine (XIII) however, on similar oxidation yielded the dimer of cyclic nitrone (XIV) in which latter compound the nitrone system is isolated from the aromatic ring.[21]



(XIII) (XIV)

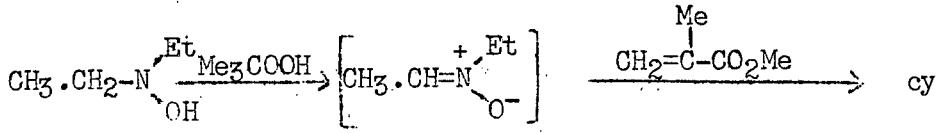
The explanation offered[21] is that, whereas conjugation of the C=N bond with the aromatic ring is favoured on electronic grounds, only an equatorial hydrogen atom on the carbon adjacent to the nitrogen atom is capable of being removed. In structure (XIII) the thermodynamically stable conformation would be a chair form with the phenyl and hydroxyl substituents equatorial. Consequently the hydrogen at C-2 would be axial. This situation does not arise in the former two hydroxylamines (IX) and (XI).

Peroxides have limited use in the oxidation of secondary hydroxylamines to nitrones. The use of hydrogen peroxide in the preparation of secondary hydroxylamines from secondary amines[22,23,24] would naturally preclude its use in the further oxidation to nitrones. However, hydrogen peroxide is reported to effect the oxidation of an aldehyd-amine hemiacetal to the nitrone[77] as follows:

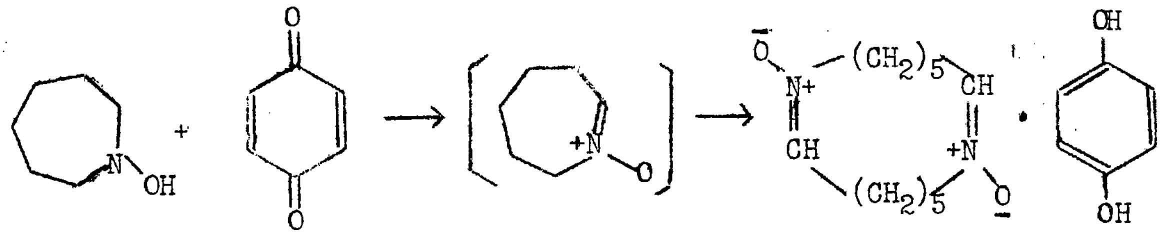


R
n-Butyl
$CH_2.CH_2.OEt$

A better peroxidic reagent is tertiary butyl hydroperoxide. Thus unstable nitrones have been prepared and trapped in situ by a reactive olefin such as methyl methacrylate.[46]

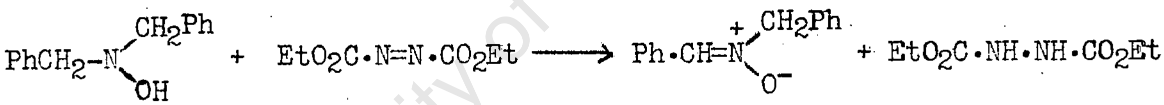


Among organic oxidising agents, high-potential quinones have been used.[37,78] The nitrone product, however, may complex with the hydroquinone formed as in the following example:[37]



It was suggested[37] that the monomeric nitrone intermediate in this oxidation dimerised and that the dimer rearranged by the mechanism referred to earlier (page 13) to the macrocyclic dinitrone structure shown.

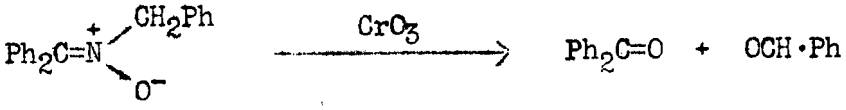
Diethylazodicarboxylate has recently been reported to be effective in the following oxidation:[79]



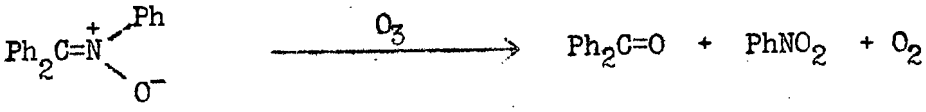
The literature contains many more references to oxidations of hydroxylamino compounds by other reagents in which the products are not nitrones. These fall outside the scope of this discussion.

Review on Oxidations of Nitrones.

Early work on the oxidations of nitrones was directed to a study of the products of oxidative cleavage using vigorous oxidising conditions. Chromic acid oxidised the nitrone (XV) to acetophenone and benzaldehyde[80] while ozone oxidised C,C,N-triphenylnitrone (XVI) to acetophenone and nitrobenzene:[81]

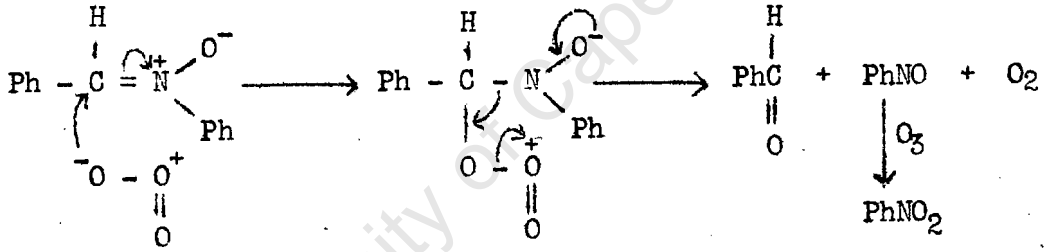


(XV)

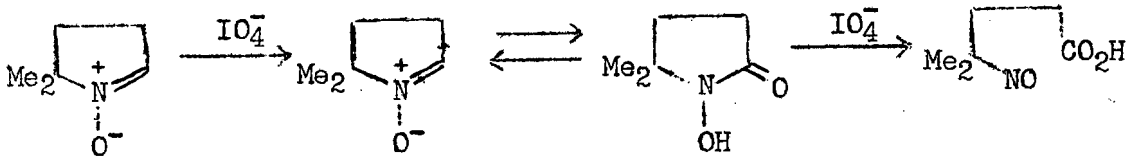


(XVI)

A more detailed study of the latter reaction has shown that the mechanism involved the formation of an intermediate nitroso compound which was then oxidised further to the nitrocompound:[82,83]

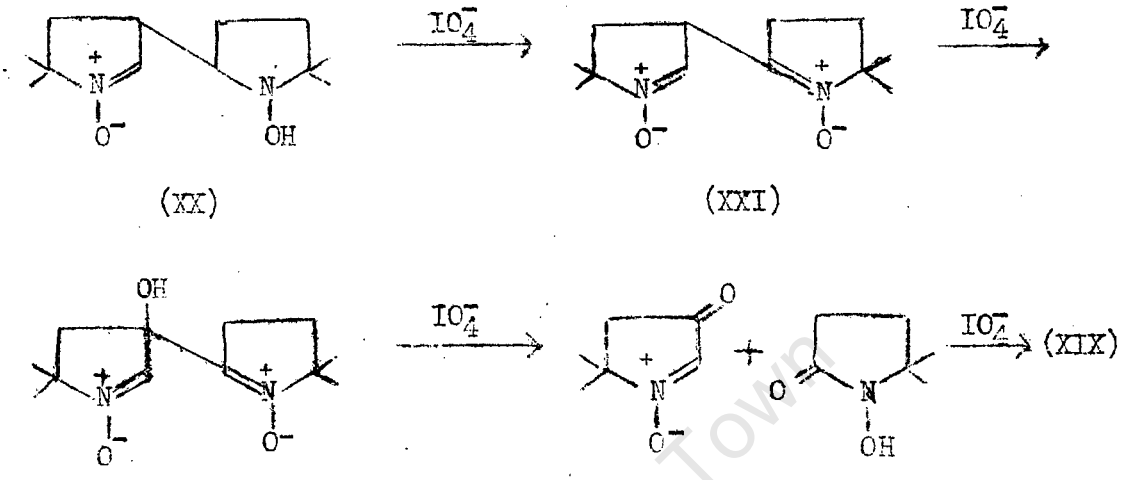


Periodate has been shown to cleave the C=N bond in cyclic nitrones.[7,75] 5,5-Dimethyl-1-pyrroline 1-oxide (XVIIb)[84] has been shown to yield the nitroso acid (XIX). The mechanism is assumed to proceed via the intermediate hydroxamic acid (XVIII).[75]



(XVIIb) (XVIII) (XIX)

Periodate is also capable of oxidising a secondary hydroxylamine to a nitrone prior to further oxidation as was observed in the following sequence.[7]

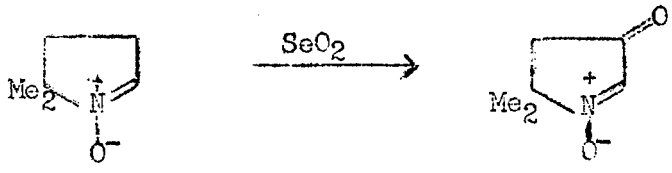


(XX) (XXI)

(XXII) (XVIII)

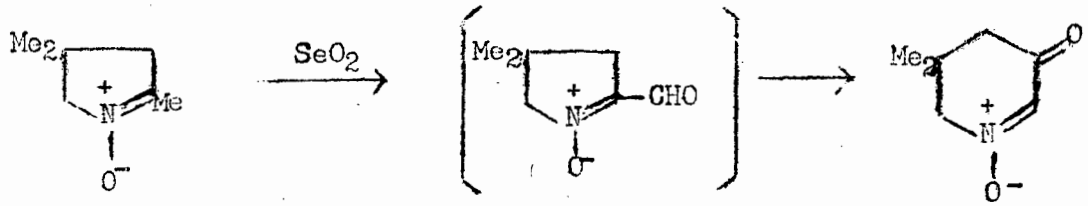
The nitrone-hydroxylamine (XX) was initially oxidised to the dinitrone (XXI). Further oxidation of the ∝-tertiary carbon resulted in cleavage into two fragments (XXII) and (XVIII). The hydroxamic acid underwent further oxidative cleavage to the nitroso acid (XIX) as before.

Selenium dioxide, known to yield ∝-dicarbonyl compounds by the oxidation of ∝-methylene groups in aldehydes and ketones,[85] oxidises the nitrone (XVIIb) to the keto-nitrone (XXII)[4] in which the carbonyl group is conjugated with the nitrone system. The same compound is one of the fission products resulting from the action of periodate on the dinitrone (XXI) referred to above.



(XVIIb) (XXII)

From 2,4,4-trimethyl-1-pyrroline 1-oxide, however, the 6-ring keto-nitrone (XXIII) and not the expected nitrone-aldehyde (XXIV) was the product.[4] It has been suggested that the ring-expanded product is an artefact resulting from acid treatment of the reaction mixture.[9]



(XXIV) (XXIII)

From the foregoing review, the following facts emerge:-

(i) Mild oxidants can effect oxidation either of a nitrone group to a hydroxamic acid grouping, or of a reactive site on the nitrone to a higher oxidation level without cleaving the C-N bond.

(ii) More powerful oxidising agents cleave the C-N bond and yield fission products.

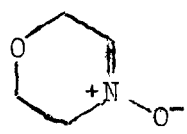
(iii) Whereas the oxidising action of high potential transition metal ions such as cobalt$^{(III)}$, cerium$^{(IV)}$ and vanadium$^{(V)}$ on a wide range of oxygen-containing organic compounds has been examined in detail, the mechanisms in many cases having been elucidated chiefly by the research school under Waters,[86a] the nitrones however, have not been included in these studies.

(iv) None of the oxidations of the nitrones has as yet been examined kinetically. Clearly this approach could prove extremely fruitful in providing a clearer understanding of the mechanisms involved.

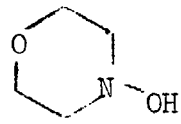
The author has selected the ferric ion for the present studies. It is a milder oxidising agent than the above-mentioned ions, having a lower oxidation potential ($Fe^{3+} + e^- \rightleftharpoons Fe^{2+}$, 0.74 volts). In this Part are presented the results of both product and kinetic studies on the oxidation of cyclic nitrones and related compounds by ferric chloride and a general mechanism is deduced therefrom.

2. Product Studies on the Oxidation of Cyclic Aldonitrones by Ferric Chloride.

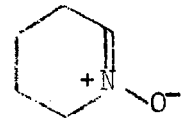
The present work had its origin in the author's observation that the heterocyclic nitrone (XXV) and its related hydroxylamine (XXVI) gave intense wine colours with dilute aqueous ferric chloride solutions (Part 1). Mention has already been made of the report that the dimer of the nitrone (XXVII) gave a red colour with the same reagent, with no further comment.[20] Arising from this observation, the author found that a 5% aqueous ferric chloride solution served as a very suitable spray reagent for detecting cyclic nitrones on both thin layer and paper chromatograms. Thus the 1-pyrroline 1-oxides (XVIIb, c and d) immediately gave intense mauve spots, though the 2-methyl-1-pyrroline 1-oxides (XXVIIIa, b and c) gave less characteristic brown or yellow-brown spots.



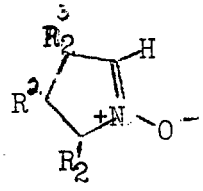
(XXV)



(XXVI)

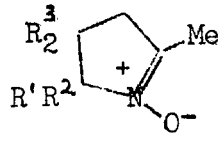


(XXVII)



(XVII)

	R^1	R^2	R^3
a:	H	H	H
b:	Me	H	H
c:	Me	Me	H
d:	Me	H	Me



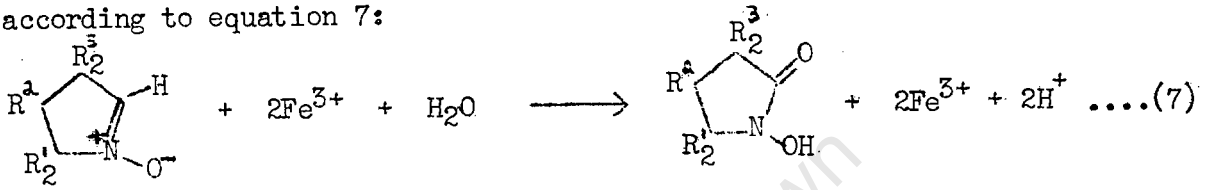
(XXVIII)

	R^1	R^2	R^3
a:	Me	H	H
b:	Me	Me	H
c:	H	H	Me

The reagent, however, was not specific since secondary hydroxylamines often gave similar colours. Nevertheless in the solvent systems employed, the parent cyclic hydroxylamines were observed to move faster on chromatograms than the corresponding nitrones. Ferric chloride was found to be a more sensitive chromatographic reagent for most of the nitrones used than p-dimethylaminocinnamaldehyde, a reagent reported to be successful for a wide range of aryl-substituted nitrones.[87]

Qualitative tests on solutions of cyclic aldonitrones, both 5- and 6-membered rings incorporating the group: $-CH=\overset{+}{N}\!\!\swarrow_{O^-}$, after treatment with ferric chloride showed the presence of ferrous ion. This indicated that the nitrone system had undergone oxidation. The treated solutions rapidly developed purple colours, having a broad absorption band near 540 mμ, or wine-red colours, absorbing near 500 mμ. The former colours were produced by those cyclic nitrones having the partial structure $-CH=\overset{+}{N}\!\!\swarrow^{CMe_2}_{O^-}$, e.g. (XVIIb), (XVIIc) and

(XVIId), whereas the wine-red colours arose from those cyclic nitrones having the partial structure $-CH=\overset{+}{N}\begin{smallmatrix}CH_2\\ O^-\end{smallmatrix}$, e.g. (XVIIa), (XXV) and (XXVII). When the colours had reached maximum intensity, titrimetric examination of the solutions established that two moles of ferric ion had been reduced per mole of nitrone. These results are consistent with oxidation of the cyclic nitrone to a cyclic hydroxamic acid structure (XXIX) according to equation 7:



(XVII) (XXIX)

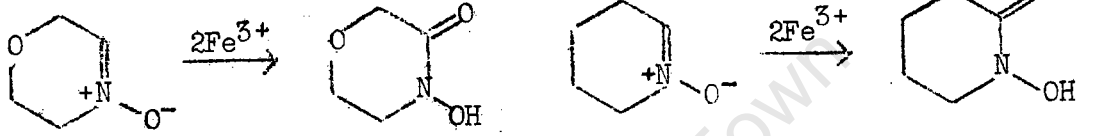
	R'	R²	R³
b:	Me	H	H
c:	Me	Me	H
d:	Me	H	Me

The resulting colours and absorption bands also point to the formation of ferric hydroxamate complexes which absorb in the range 480 - 525 mμ, depending on the nature of the ligand, pH and solvent used.[60,61,62]

The inferences were confirmed by isolating the known 1-hydroxy-2-pyrrolidones (XXIXb) and (XXIXc)[2] as colourless crystalline solids from the oxidation of the respective nitrones (XVIIb) and (XVIIc) by ferric chloride and characterising them by analysis, melting points and IR spectra. In addition the pyrrolidone (XXIXb) was synthesised by a standard method[2] for comparison and its identity with the oxidation product from (XVIIb) was established. From the tetramethyl-pyrroline

oxide (XVIId) was isolated the new cyclic hydroxamic acid (XXIXd) as a colourless, soft, crystalline solid, characterised by analysis and its IR spectrum as compared with those of (XXIXb) and (XXIXc).

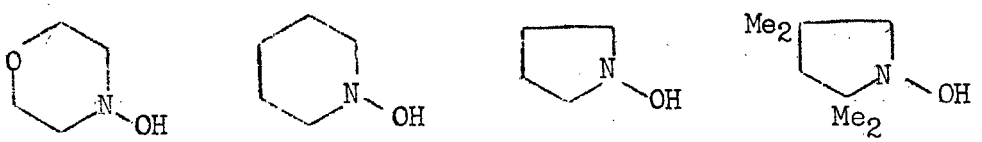
The isolation and characterisation of the cyclic hydroxamic acid (XXX) from the heterocyclic nitrone (XXV) has already been referred to in Part 1, and the analogous 6-membered cyclic hydroxamic acid (XXXI)[88] has been isolated by treating the cyclic nitrone (XXVII) with 2 moles of ferric ion.



(XXV) (XXX) (XXVII) (XXXI)

Because the complex ferric salt, potassium ferricyanide (redox potential + 0.49 volt) has been used to oxidise cyclic hydroxylamines to nitrones,[21,76] one would expect that ferric ions ($Fe^{3+} + e^- \longrightarrow Fe^{2+}$, redox potential + 0.74 volt) should oxidise secondary hydroxylamines to the corresponding hydroxamic acids either directly or <u>via</u> nitrone intermediates. This expectation has been demonstrated in the following:

(i) The cyclic hydroxylamines (XXVI), (XXXII), (XXXIIIa) and (XXXIIIb) on treatment with ferric chloride solutions gave colours identical with those obtained from their respective nitrones (XXV), (XXVII), (XVIIa) and (XVIId).



(XXVI) (XXXII) (XXXIIIa) (XXXIIIb)

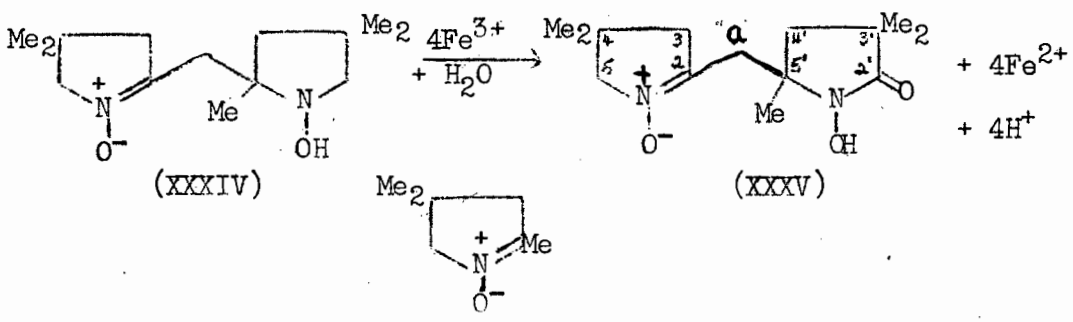
(ii) A solution of the tetramethyl-hydroxypyrrolidine (XXXIIIb) reduced 4 moles of ferric ion per mole of the substrate to yield the same cyclic hydroxamic (XXIXd) isolated from the nitrone (XVIId). Hence a 4-electron transfer had occurred, i.e. equations (2) and (3) (Page 43) have occurred together. This clearly indicates the difference between the oxidising powers of the aquocomplexed ferric ion and the cyano-complexed species towards hydroxylamines.

The oxidation of hydroxylamines to hydroxamic acids by ferric ions appears to pass through a nitrone intermediate because a solution of 4-hydroxymorpholine (XXVI) on treatment with the equivalent of 2 moles ferric ion per mole substrate, showed the presence of both the hetero-cyclic nitrone (XXV) and hydroxamic acid (XXX) as well as unchanged hydroxylamine (XXVI) on T.L.C. examination of the crude product. Since two oxidation products are formed, this result also leads to the inference that the second step as represented by equation (3) occurs more rapidly than the first step, equation (2). Rate studies, however, show that hydroxylamines are oxidised to hydroxamic acids at almost the same rate as the corresponding nitrones (see Experimental section). This will be discussed in more detail (see Section 4 of this Part).

The following example presents a striking illustration of the difference in the ease of oxidation of hydroxylamines and ketonitrones (2-substituted nitrones). 2,4,4-Trimethyl-1-pyrroline 1-oxide (XXVIIIc) undergoes slow, spontaneous dimerisation to form a colourless, crystalline solid for which the nitrone-hydroxylamine structure (XXXIV) had been tentatively assigned.[5] The dimer was observed to reduce very rapidly

four moles of ferric ion and produce the characteristic colour of the ferric hydroxamate complex. A colourless crystalline solid, m.p. 171 - 172° and analysing for $C_{14}H_{24}N_2O_3$, was isolated. The nitrone-hydroxamic acid structure (XXXV) is assigned to this compound on the following facts:

The IR spectrum showed absorption bands at 3360 (hydrogen bonded OH), 1688 (hydroxamic C=O) and 1620 $cm.^{-1}$ (2-substituted nitrone[2]). In the UV region it showed the E-band absorption of monocyclic nitrones, $\lambda_{max.}$ 237 mμ (ε 9700).[9] Finally, the hydrogen integrated p.m.r. spectrum revealed singlets at τ 8.82 ($>CMe_2$), 8.76 ($>CMe_2$), 8.60 (Me at C-5') and 8.11 ($>CH_2$ at C-4' in the pyrrolidone moiety) together with one unresolved band centred at τ 7.35 (two methylene groups at 'a' and C-3) and a second multiplet band at τ 6.2 (methylene group at C-5). The assignment of the multiplets to the pyrroline moiety is consistent with the p.m.r. data available for 1-pyrroline 1-oxides[34] and in particular for the nitrone (XXVIIIc), in which the methylene protons at C-3 and C-5 gave rise to multiplets at τ 7.4 and 6.5[34], and the 2-methyl group also appears as at multiplet at τ 8.2.[34]



(XXXIV) (XXXV)

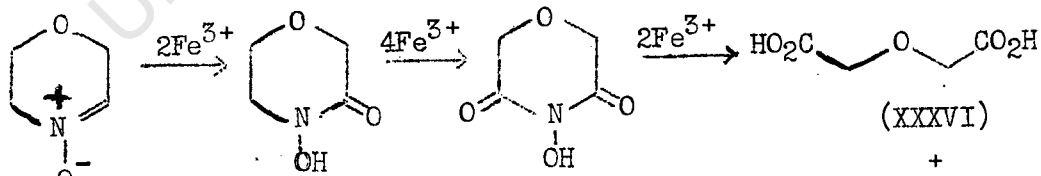
(XXVIIIc)

Characterisation of this compound (XXXV) provides confirmation of structure (XXXIV) suggested[5] for the dimer of nitrone (XXVIIIc) and it indicates that it is possible to oxidise the hydroxylamine residue of the molecule without affecting the 2-substituted nitrone group. (See, however, Section 3 of this Part.)

Since the hydroxylamine system, $-CH_2-N\langle_{OH}$, is capable of oxidation to the hydroxamic acid system, $-CO.N\langle_{OH}$, it seems probable that those hydroxamic acids which possess the system $-CH_2-N\langle^{CO-}_{OH}$ should undergo further oxidation to the partial structure $-CO.\underset{OH}{N}.CO-$. That this in fact appears to happen has been observed in the case of the heterocyclic nitrone (XXV). On prolonged oxidation or on heating with ferric chloride it reduced 8 moles of ferric ion to yield diglycollic acid (XXXVI) and nitrous oxide (see Part 1). Clearly the nitrous oxide resulted from the ferric oxidation of hydroxylamine by the known reaction[89]

$$2NH_2OH + 4Fe^{3+} \longrightarrow N_2O + H_2O + 4Fe^{2+} + 4H^+ ,$$

the hydroxylamine originating from the hydrolysis of an intermediate N-hydroxy-diglycollic imide (XXXVII) which was not isolated.

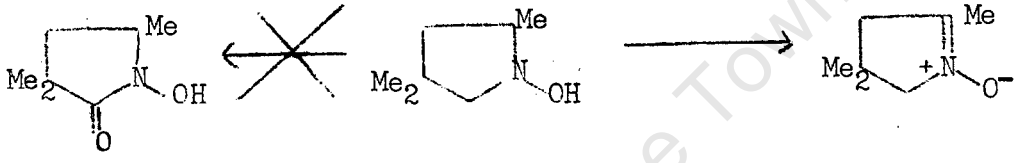


(XXV) (XXX) (XXXVII) (XXXVI) + $\frac{1}{2}N_2O$

Thus the cyclic hydroxamic acids having the partial structure $-CH_2.N\langle^{CO-}_{OH}$ indeed do undergo further oxidation and this may well account for the observation that the colour and visible spectra of solutions of the cyclic nitrones (XVIIa), (XXV) and (XXVII) with ferric chloride are

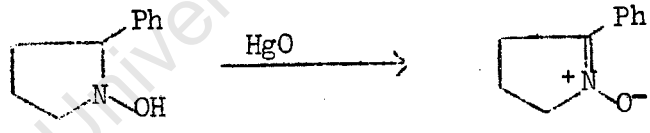
different from those of the nitrones (XVIIb), (XVIIc) and (XVIId) which, having a gem-dimethyl group at C-5, cannot undergo such further oxidation.

It is of interest to note that the hydroxylamine (XXXIIIc) which possesses two oxidisable positions adjacent to the hydroxylamine grouping, on treating with ferric chloride gave no colour characteristic of the hydroxamic acids. It was thought that it might give rise to the cyclic hydroxamic acid (XXIXe), whereas in fact the cyclic hydroxylamine (XXXIIIc) rapidly reduced two moles of ferric ion and the nitrone (XXVIIIc) was recovered.



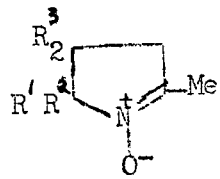
(XXIXe) (XXXIIIc) (XXVIIIc)

Aerial oxidation of the same hydroxylamine (XXXIIIc) was reported to give the same result[a] and a parallel result was observed in the action of mercuric oxide on 1-hydroxy-2-phenylpyrrolidine:[30]



3. Product Studies on the Oxidation of Cyclic Ketonitrones by Ferric Chloride.

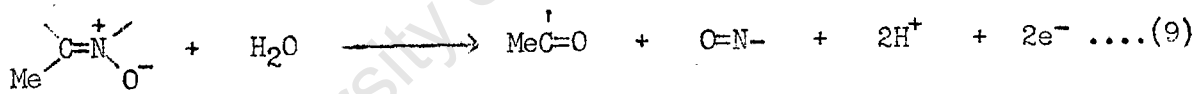
Whereas cyclic aldonitrones undergo facile oxidation with ferric chloride to yield cyclic hydroxamic acids, the cyclic ketonitrones (XXVIII) are not expected to undergo oxidation at C-2 since the methyl group blocks this position. To attempt to raise the oxidation level



(XXVIII)

	R^1	R^2	R^3
(a)	Me	H	H
(b)	Me	Me	H
(c)	H	H	Me

of the nitrone system can only lead to its cleavage. This may be represented by the equation:



$$\text{Me}\overset{+}{\text{C}}\text{=N}\overset{O^-}{} + H_2O \longrightarrow MeC(=O)^{\cdot} + O{=}N^{\cdot} + 2H^+ + 2e^- \quad \ldots\ldots(9)$$

and the final products will depend on the behaviour of the resultant nitroso-ketone.

The cyclic ketonitrones (XXVIII) do in fact undergo this mode of oxidative cleavage with ferric chloride. However the rate of oxidation, which can be followed by the titrimetric determination of ferrous ion, is very slow, requiring several days to weeks, at ordinary temperatures

for complete oxidation. The reactions however can be completed in a matter of hours by heating solutions. At no stage did the solutions acquire any characteristic intense colour. All these ketonitrones (XXVIIIa), (XXVIIIb) and (XXVIIIc) on complete oxidation gave nitrous oxide as one product.

2,5-Dimethyl-1-pyrroline 1-oxide (XXVIIIa). The cyclic nitrone (XXVIIIa), in addition gave, after reducing 4 moles of ferric ion, 2,5-hexanedione (XXXVIII), characterised by comparison of its IR spectrum and bis-2,4-DNP with those of the authentic material available. The reaction may be represented as follows:

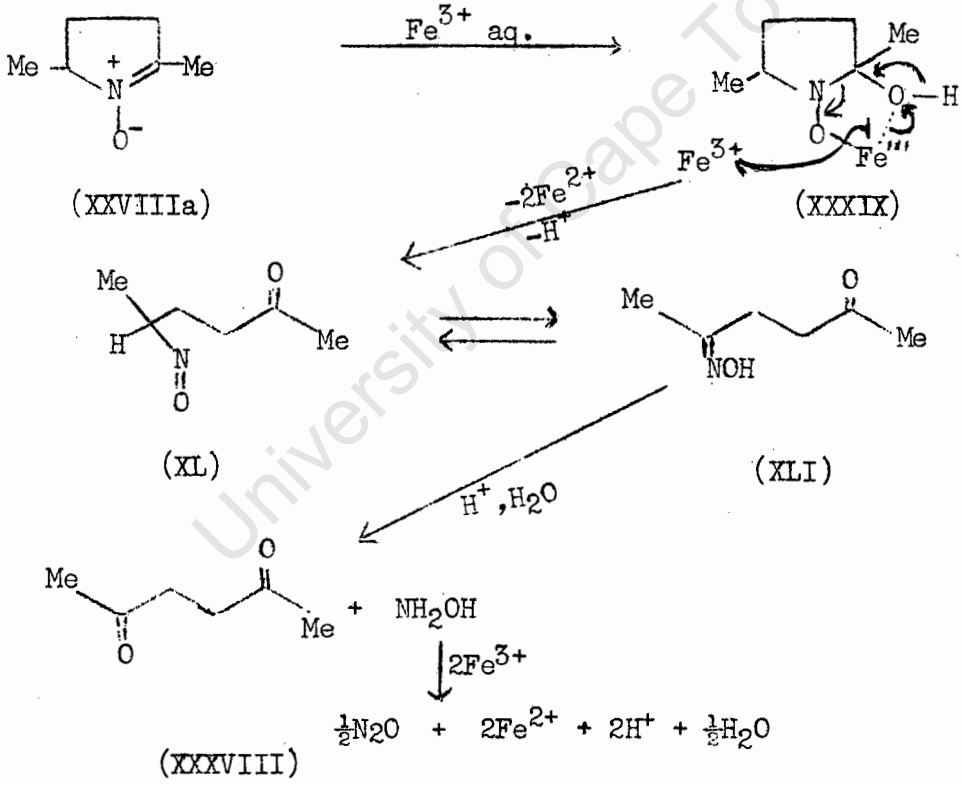
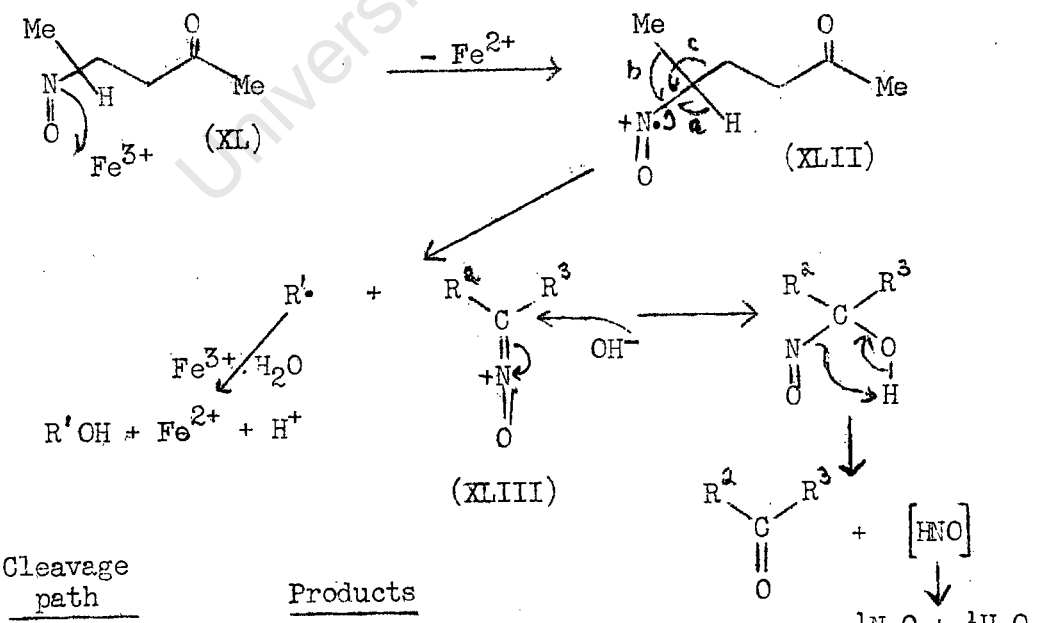


CHART 1.

The first step is probably the formation of a nitrone-ferric complex (XXXIX). (Evidence that this type of formation with the aldonitrones is a slow step will be presented in Section 4 of this Part.) A two-electron abstraction followed by cleavage of the C-N bond as shown would yield the nitroso ketone (XL) which on tautomerisation to the monoxime of hexane-2,5-dione (XLI) followed by hydrolysis would yield the dione (XXXVIII) and free hydroxylamine. Oxidation of the latter would account for the production of nitrous oxide.[87]

G.L.C. examination of the ethereal extract containing the oxidation products showed, in addition to the dione (XXXVIII) the presence of acetaldehyde and methanol and two further components, unidentified as yet.

These results require a modification of the scheme in Chart 1 and would suggest that a radical mechanism resulting in fragmentation of the molecules is operative. Such a mechanism is proposed in the following Chart.



Cleavage path	Products	
a.	$H^+ + CH_3.CO.CH_2.CH_2.CO.CH_3$	(XXXVIII)
b.	$MeOH + OHC.CH_2.CH_2.CO.CH_3$	(XLIV)
c.	$Me.CHO + HOCH_2.CH_2.CO.CH_3$	(XLV)

CHART 2.

In the above chart the abstraction of one electron from the nitroso ketone (XL)(formed as in Chart 1) would yield the iminoxy ion (XLII). Similar iminoxy radicals have been observed by e.s.r. studies on the oxidation of oximes by ceric salts.[90] It is suggested that the radical ion (XLII) rearranges with concomitant homolysis by any one of the steps a, b and c to yield a radical, $R'\cdot$ and the cation (XLIII). Oxidation of the radical, $R'\cdot$, followed by hydroxylation would yield an alcohol $R'OH$. Thus the formation of methanol, via the homolytic step b, is accounted for. At the same time the pentanonal (XLIV) should be a product. Although not yet proved this may well be one of the unidentified components.

Homolysis via a is seen to yield acetonylacetone (XXXVIII) as identified, while homolysis via c would yield acetaldehyde, a product observed by G.L.C. analysis, together with the butanonol (XLV), as yet unidentified.

Rearrangement of the primary radical (XLVI) formed by path c, to a secondary radical (XLVII) prior to oxidation also requires consideration. The subsequent reactions may be represented by the equations (10) and (11):-

$$\underset{\text{(XLVI)}}{\cdot CH_2 \cdot CH_2 \cdot CO \cdot Me} \longrightarrow \underset{\text{(XLVII)}}{CH_3 \cdot \dot{C}H \cdot CO \cdot Me} \qquad \ldots\ldots(10)$$

$$CH_3 \cdot \dot{C}H \cdot CO \cdot Me + Fe^{3+} + H_2O \longrightarrow \underset{\text{(XLVIII)}}{CH_3 \cdot CH(OH) \cdot CO \cdot Me} + Fe^{2+} + H^+ \quad \ldots(11)$$

Thus two butanonols, (XLV) and (XLVIII) could both be present in the oxidation products.

The nett stoichiometry of the reactions in Chart 2 requires 4 moles of ferric ion per mole of the nitrone (XXVIIIa). This accords with the experimental facts.

In support of the suggestion that fragmentation had occurred, G.L.C. examination of the product from the oxidation of acetoxime by two moles of ferric chloride showed that, in addition to nitrous oxide, methanol and acetaldehyde were the main products with only a very small proportion of acetone. Clearly the reaction cannot be represented by the simple stoichiometric equation (12):

$$Me_2C{=}NOH + 2Fe^{3+} + \tfrac{1}{2}H_2O \longrightarrow Me_2CO + \tfrac{1}{2}N_2O + 2H^+ + 2Fe^{2+} \quad .....(12)$$

The following mechanism is therefore suggested:-

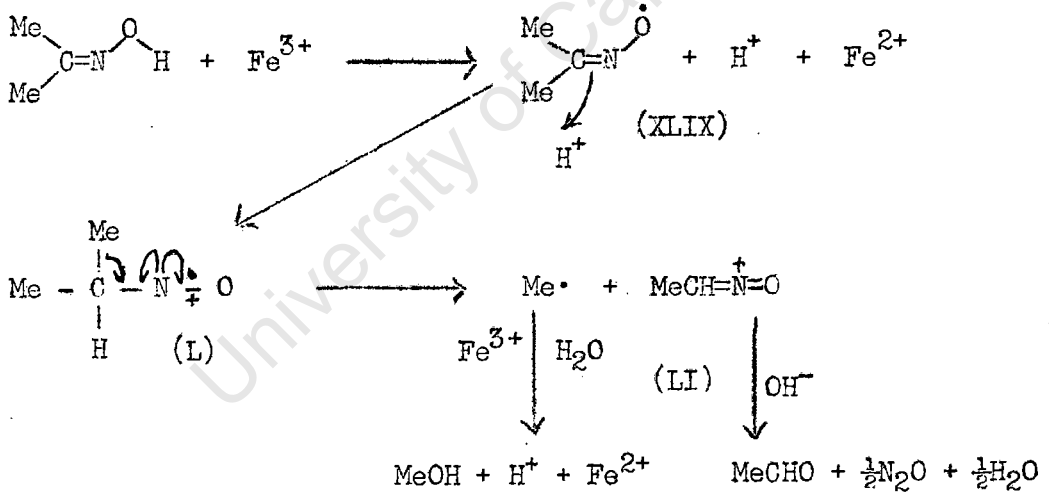


CHART 3.

It is suggested that the iminoxy radical (XLIX) formed by the abstraction of one electron from the oxime adds a proton to form an iminoxy ion (L) which fragments in the manner shown. Oxidation of the methyl radical would yield methanol and from hydrolysis of the cation (LI)

acetaldehyde and nitrous oxide would result. The mechanism here closely parallels that presented in Chart 2 and therefore lends support to the fragmentation mechanism suggested in that scheme.

2,4,4-Trimethyl-1-pyrroline 1-oxide. One mole of the cyclic nitrone (XXVIIIc) was observed to reduce 6 moles of ferric ion. From the final mixture both mesitonic acid (LII) and nitrous oxide were isolated. Since the attempts to isolate the acid (LII) from the dark oily product failed, it was isolated as its 2,4-DNP and semicarbazone. The identity of these was established by analysis and by comparison of the melting points and IR spectra with those of authentic samples prepared by known methods.[91,92] The oxidation product was not examined by G.L.C.

The formation of the products is readily accounted for by an ionic mechanism (Chart 4) although a free radical mechanism similar to that in Chart 2 could equally well be employed.

In Chart 4 the initial step would probably require hydroxylation of the nitrone to form the structure (LIII) similar to (XXXIX) but with the coordinated metal ligand omitted. Oxidative cleavage would yield the nitroso-ketone (LIV) which is then shown to isomerise to the oxime (LV). Since the oxidation level of oximes is the same as that of nitrones (Section 1 of this Part), the further oxidation of the oxime group in (LV) is possible. The resulting nitroso-ketonol (LVI) is shown to tautomerise to the hydroximic structure (LVII). Further oxidation of (LVII) by a process identical with the previous step would yield the analogue of an ortho-carboxylic structure (LVIII) which breaks down to yield mesitonic acid (LII) and nitrous oxide.

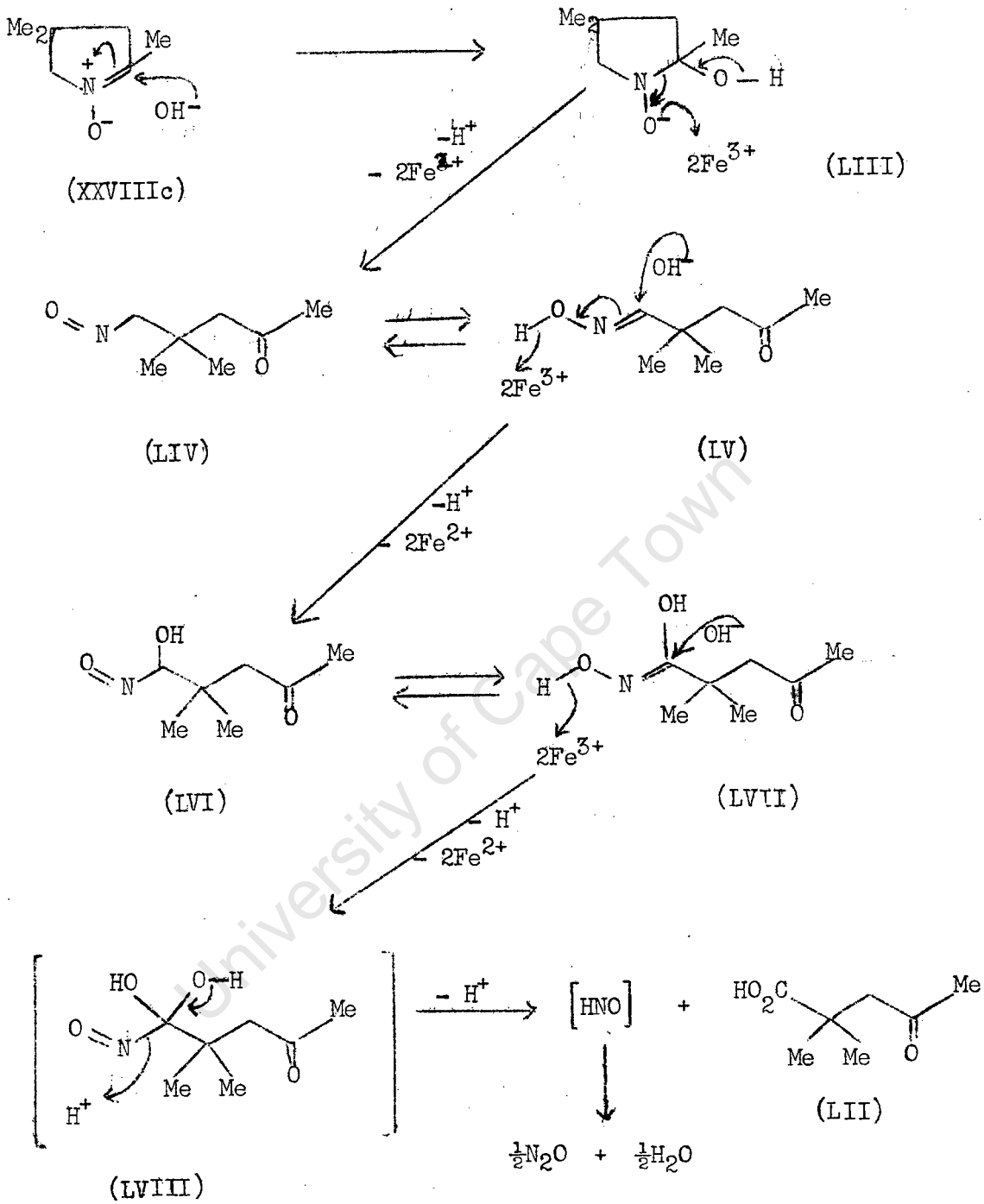


CHART 4.

An alternative mechanism in which it is suggested that the oxime (LV) suffered acid hydrolysis to mesitonaldehyde (LIX) and hydroxylamine with the subsequent oxidation of these two products occurring separately (Chart 5) is ruled out as the author has observed that aqueous solutions of aldehydes, e.g. formaldehyde, acetaldehyde and butyraldehyde failed to reduce ferric ion, even after many days.

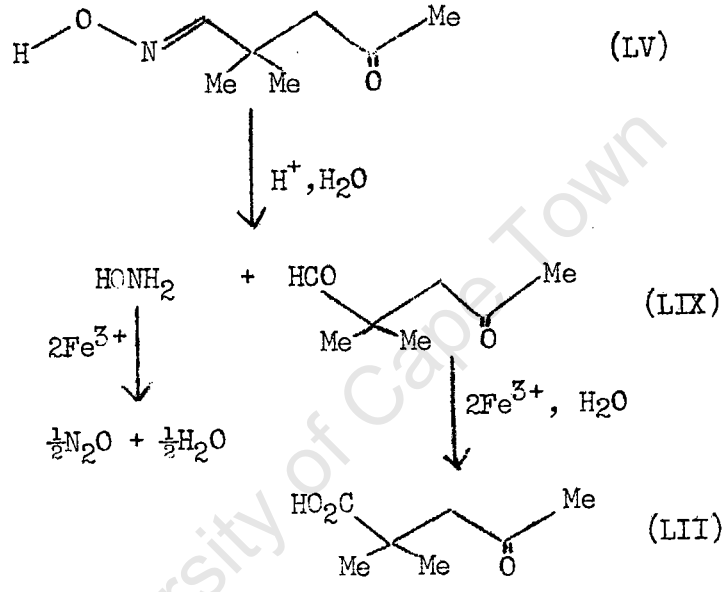
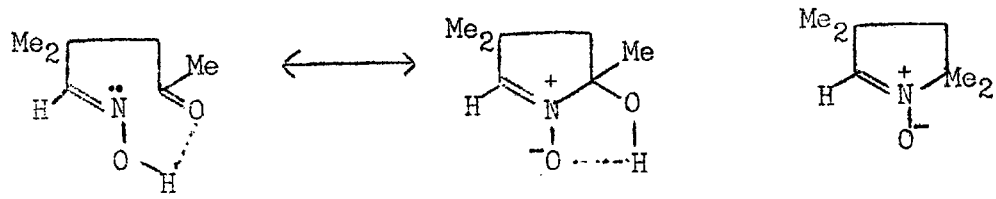


CHART 5.

Semi-quantitative rate studies showed that the reduction of the first two moles of ferric ion was noticeably faster than for the subsequent steps. An attempt was therefore made to isolate the intermediate aldoxime-ketone (LV)(Chart 4) by stopping the reaction after two moles of ferric ion had been reduced by the nitrone (XXVIIIc). A colourless, crystalline solid analysing for $C_7H_{13}NO_2$ was isolated. The UV spectrum of the compound in ethanol had a single strong absorption band at 231 mμ (ε 10,000), typical of the nitrone chromophore.[2,9] The IR spectrum showed a broad band at 2730 $cm.^{-1}$ (chelately bonded -OH[3af])

and a moderately strong band at 1635 cm.$^{-1}$ There was no C=O absorption. These results are inconsistent with the expected oximino-ketone structure (LVa) but they can be reconciled with an alternative canonical form, the novel hydroxy-nitrone structure (LVb).

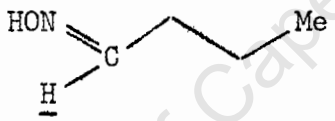


(LVa) (LVb) (XVIId)

A Drieding model of the structure (LVb) showed considerable strain in the -OH bonded ring. While increased strain in the ring of which the nitrone chromophore forms a part is known to lower the stretching frequency,[32a] it is uncertain how the strain in the fused "ring" with hydrogen bonding would affect the C=N stretch absorption. The author has not been able to find a parallel in the literature. The typical examples involve hydrogen bonding and double bond formation within the same cyclic system as, for example, in the β-diketones.[32g] In such cases the C=C stretching mode is lowered.[32g] The author would suggest that in structure (LVb) the strain in the nitrone ring would be somewhat alleviated by the exocyclic intramolecular hydrogen bond and hence the absorption signal due to the C=N stretching mode should be raised with a possible decrease in its intensity. Thus, by comparison, the cyclic nitrone (XVIId) which involves no hydrogen-bonding showed the nitrone-stretching frequency at 1575 cm.$^{-1}$ as the most intense band in the spectrum.[2,9] The absorption band at 1635 cm.$^{-1}$ in (LVb)

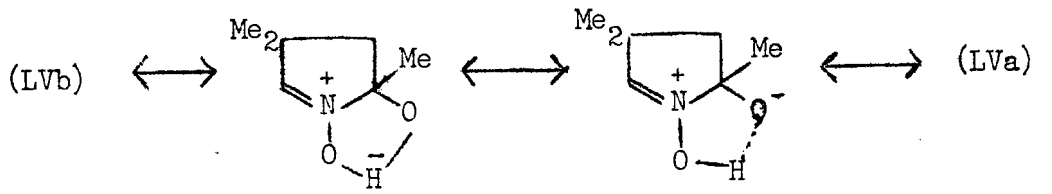
however was only moderate in comparison with other bands in the spectrum, the strongest occurring at 1150 cm.$^{-1}$ (tertiary OH [32k]).

The p.m.r. spectrum of the product can account equally well for both structures. Thus the singlets at τ 8.85 (6H) and 7.55 (2H) are readily assigned respectively to $>CMe_2$ and $-CH_2-$ groups in either structure and the broad singlet at τ 4.92 (1H) to either the aldoxime proton in (LVa) or the aldonitrone proton in (LVb). This signal, however, though high when compared with the corresponding signal of τ 3.53 for the aldonitrone (XVIId),[34] is yet very much higher than τ 2.55, the resonance signal assigned to the aldehydic proton in n-butanaldoxime (LX).[93] The low field signal (0.6H) at



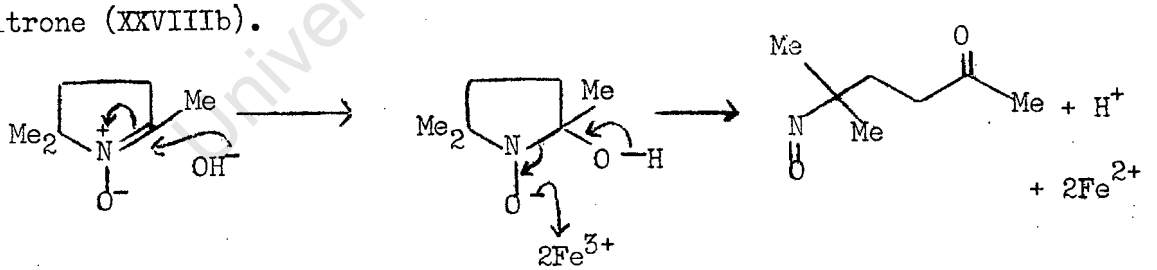
(LX)

τ -0.25 is assigned to the intramolecularly bonded OH proton[26b] in either structure. It is difficult to explain the appearance of the quartet at τ 7.94 (3.5H, J = 1.5 c.p.s.). While the single methyl group in either structure would be expected to give a resonance signal near τ 8.0,[26c, 34] it should be a singlet in either case as there are no protons on the adjacent carbon atom for spin-coupling. The magnitude of the coupling constant would suggest that long range coupling of the kind found associated with aromatic rings[26d] had possibly occurred. This would infer some delocalisation of the charge in the hydrogen-bonded ring and would therefore favour structure (LVb) for which various canonical forms can be written:-



While a resonance hybrid would appear to be the most likely structure for the intermediate oxime (LV), it can only be regarded as tentative until model compounds have been prepared and examined.

2,5,5-Trimethyl-1-pyrroline 1-oxide. It was anticipated that the third cyclic keto-nitrone (XXVIIIb) would reduce only two moles of ferric ion and yield only the nitroso ketone (LXI) in the light of the foregoing mechanism, since the nitroso group, being attached to a tertiary carbon atom, could not tautomerise to an oxime structure. The isolation of such a compound would provide strong evidence for the nitroso intermediates postulated in the earlier charts. It was surprising, therefore, to observe that four moles of ferric ions were reduced per mole of the nitrone (XXVIIIb).



(XXVIIIb) (LXI)

Nitrous oxide was isolated and characterised as before. The iron-free solution after working up consistently yielded dark oils which on T.L.C. examination were observed to consist of a mixture of products. Attempts at both distillation of, and isolation of 2,4-DNP's from the

oils were unsuccessful. The reaction mixture, after removal of the iron salts, was subjected to ether extraction. G.L.C. examination of the concentrated extract revealed some ten to twelve products among which were recognised acetaldehyde, methanol and acetone. Hexane-2,5-dione (XXXVIII) was absent.

These facts are interesting because, as far as the author is aware, the oxidation of tertiary aliphatic nitroso compounds by transition metal ions has not been reported. Aromatic nitroso compounds, on the other hand, can be prepared and isolated by the action of ferric chloride on aromatic hydroxylamines.[94] Furthermore the oxidation of tertiary carbon atoms is difficult and leads to fragmentation. Waters has shown, for example, that tertiary alcohols,[95,96] ketones[97] and carboxylic acids[98] can be oxidised by high potential transition metal ions such as the cobaltic ion.[86a] His school has shown by kinetic and product studies that radicals are produced as intermediates.

An ionic mechanism (Chart 6 below), could account for the formation of acetone by oxidation of the nitroso-ketone (LXI) which would require the reduction of a total of four moles of ferric ion. The butanonol (XLV) would also be a product though yet unproven, of this oxidation.

It should be mentioned that oxidation resulting in C-methyl fragmentation at the tertiary carbon atom in the nitroso-ketone (LXI) can be disregarded because the hexane-dione (XXXVIII), a product expected by this oxidation, was not detected by G.L.C.

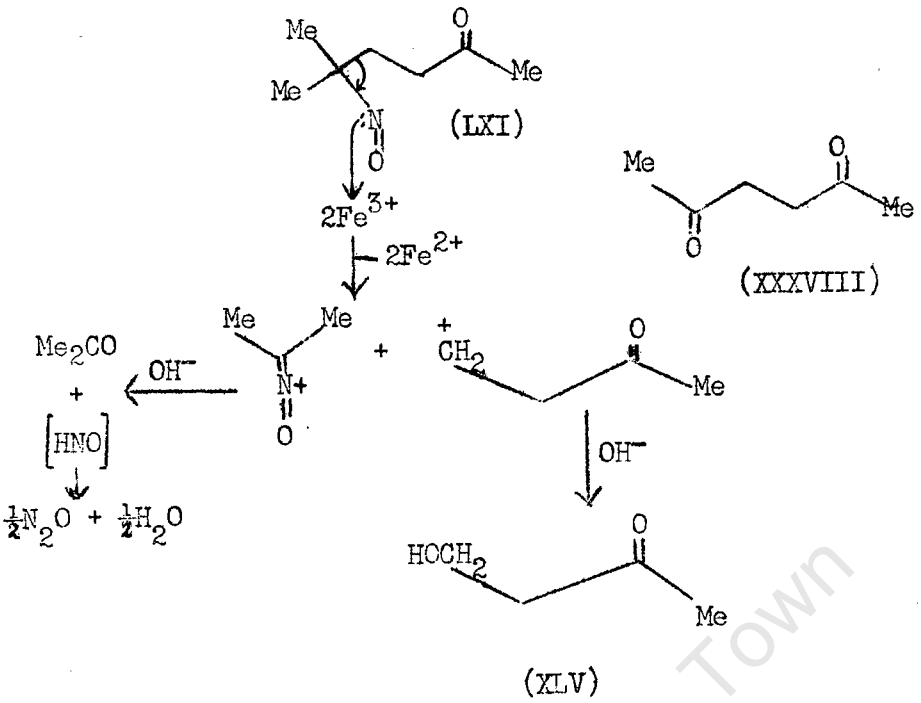


CHART 6.

The mechanism represented in Chart 6, however, cannot account for the large number of products obtained in this oxidation and for this reason a radical mechanism is to be preferred. One such mechanism, analogous to that outlined earlier in Chart 2 is offered in Chart 7.

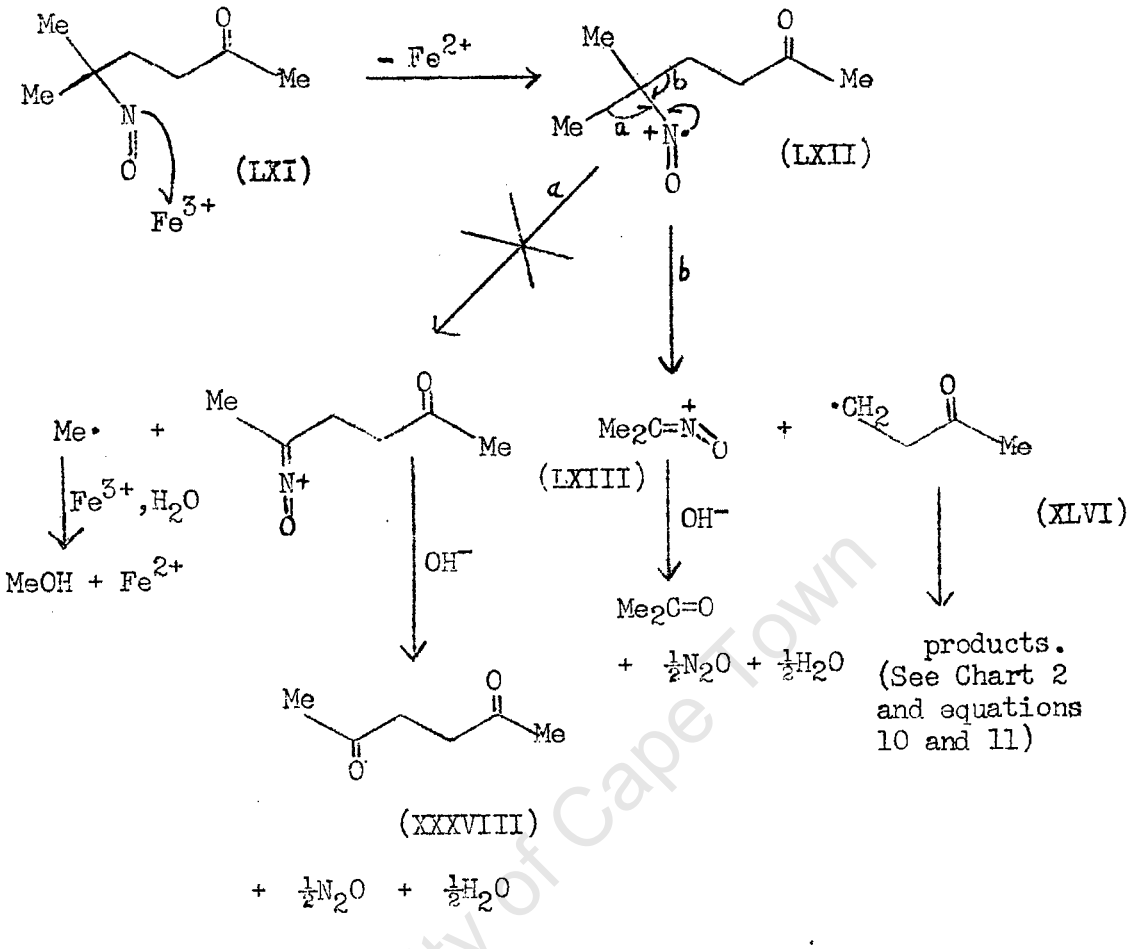


CHART 7.

Abstraction of one electron from the nitroso-ketone (LXI)(Chart 7) would yield the radical ion (LXII) which could fragment by the homolytic steps a or b. The former mode of fragmentation would be expected to yield the hexane-dione (XXXVIII) and since this was not observed in the products by G.L.C., this path need not be considered. Fragmentation by path b would yield acetone and the radical (XLVI) which, as shown earlier (Chart 2, equations 10 and 11) could give rise to two butanonols, $HOCH_2 \cdot CH_2 \cdot CO \cdot CH_3$ (XLV) and $CH_3 \cdot CH(OH) \cdot CO \cdot CH_3$ (XLVIII).

In order to account for the appearance of acetaldehyde and methanol, a possible modification of the mechanism in Chart 7 incorporating an earlier suggestion (Chart 3) for the fragmentation of acetoxime is shown below.

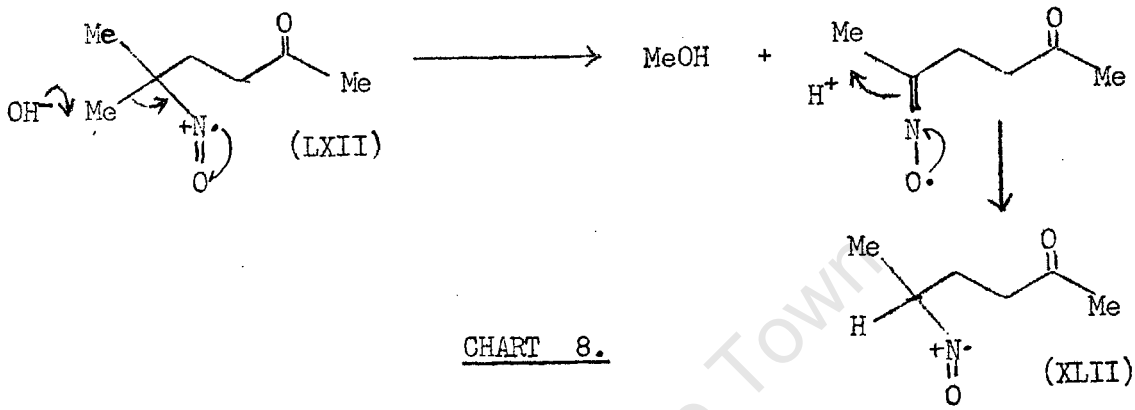


CHART 8.

The nett result in this process is electrophilic substitution by a proton and the resulting iminoxy ion (XLII) could then fragment according to the method shown in Chart 2. The above scheme, however, would require that hexane-2,5-dione (XXXVIII) be one of the products. Since this was not observed on G.L.C. examination this scheme cannot be seriously considered.

An alternative approach is to consider the following unusual mode of hydrolysis of the ion (LXIII) formed by path b in Chart 7.

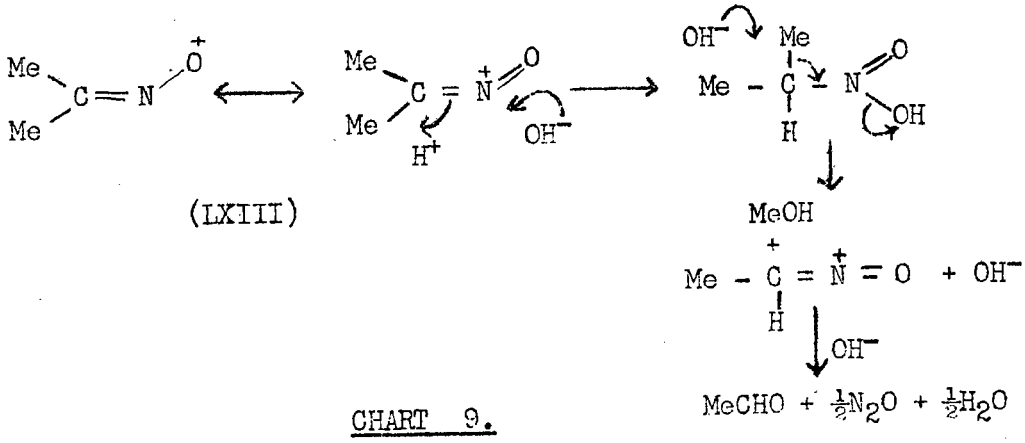


CHART 9.

The charge on the ion (LXIII) could be stabilised partly by delocalisation over the N-O bond and partly by hydration. The steps suggested involve electrophilic substitution as in Chart 8. Hydrolysis of the resulting ion would then yield acetaldehyde and nitrous oxide.

The nett stoichiometry of the above reactions would require four moles of ferric ion to be reduced per mole of nitrone (XXVIIIb). The observation that 4.2 moles Fe^{3+} were reduced suggested that some further oxidation of one or more of the products had occurred. Until a more thorough investigation of this reaction has been carried out, an explanation for this is not possible.

Conclusions.

While it must be stressed that the inferences drawn are the result of only preliminary G.L.C. studies so far and hence some of the mechanisms advanced must be viewed with some scepticism, nevertheless the following facts clearly emerge from these studies:-

(i) Cyclic ketonitrones are oxidised by ferric ion to give open chain intermediate nitroso-ketones as represented by equation 9 (page 60).

(ii) The N-O group plays an important role in raising the oxidation level of the carbon atom to which it is attached. This is probably due to the stability of the intermediate radical formed when one electron has been abstracted by an oxidant ion.[90,99,100,101]

(iii) Subsequent to the step (ii) is fragmentation with the production of a radical. This is in keeping with Waters' observation that the oxidation of tertiary alcohols,[95,96] ketones[97] and carboxylic acids[98] by cobaltic salts leads to radical production through homolysis of C-C bonds. These radicals yield alcohols according to the general equation

$$R\cdot + H_2O + Fe^{3+} \longrightarrow ROH + H^+ + Fe^{2+} \qquad \ldots\ldots(13)$$

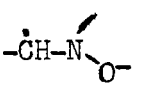
(iv) The N-O group is finally eliminated as the hypothetical hyponitrous acid, $(HNO)_2$, which breaks down to nitrous oxide and water.

Finally it may be added that a project is planned to utilise Preparative G.L.C. to determine the relative proportions of the oxidation products from the cyclic nitrones (XXVIIIa) and (XXVIIIb) and to isolate and characterise the components. The results of these projected studies will be used either to confirm the mechanisms proposed or to lead to some modification of them.

4. The Mechanism for the Oxidation of Cyclic Aldonitrones by Ferric Chloride.

Since the products of oxidation of the 1-pyrroline 1-oxides (XVII), give coloured complexes with ferric ions, it follows that if the structure and behaviour of the resulting ferric hydroxamate complex can be determined, then the rate of formation of this complex should be measurable spectrophotometrically. Furthermore rate measurements under a variety of controlled conditions may provide valuable information as to the mechanism of oxidation of aldonitrones by one-electron abstracting oxidants. While this field has not yet been examined from the kinetic angle, the mechanism of oxidation of the closely related hydroxylamines and oximes by one-electron abstractors has been the subject of several papers during the last two years.[90,99,100,101] The findings, which are based mainly on the results of the application of electron spin resonance (e.s.r.) spectroscopy, all point to the formation of short-lived radical ion intermediates containing the resonance structures (LXIV) or related protonated species.

(LXIV)



(III)

This would appear to support the ion-radical mechanism proposed for the autoöxidation of secondary hydroxylamines in which the radical ion with the partial structure (III) was proposed as an intermediate. (See page 45 .)[27] Waters, in recognising the unique behaviour of such systems, concluded a review as follows:

"The whole mechanism of oxidation, reduction and coupling together of nitrogen compounds needs reconsideration, but for this detailed kinetic

studies will be required."[102a]

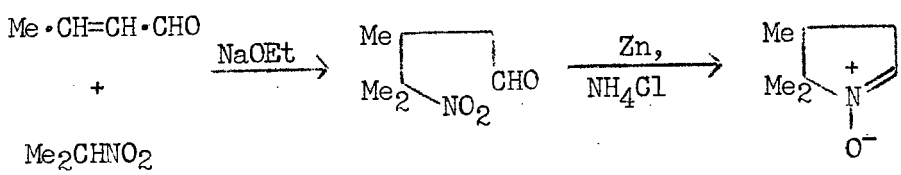
In the overall reaction for the oxidation of the cyclic nitrones to cyclic hydroxamic acids clearly two processes occur. They are:

(a) the oxidation step, the stoichiometry of which has been shown earlier to accord with the partial equation (14):

$$-CH=\overset{+}{N}\!\!\swarrow_{O^-} + 2Fe^{3+} + H_2O \longrightarrow -CO-N\!\!\swarrow_{OH} + 2Fe^{2+} + 2H^+ \quad \ldots\ldots(14)$$

(b) the formation of a coloured ferric hydroxamate complex.

To formulate a mechanism for the whole reaction it is necessary to establish whether formation of the complex precedes or follows the oxidation step and what the structure of this complex is. Evidence obtained from both spectral and kinetic studies has enabled the author to postulate a mechanism for the oxidation. Most of the spectral and kinetic studies were carried out on 4,5,5-trimethyl-1-pyrroline 1-oxide (XVIIc) and its related hydroxamic acid (XXIX c) for the reason that the nitrone itself was readily prepared by the zinc-ammonium chloride reduction of the nitro-aldehyde (LXV) obtained from base-catalysed condensation of 2-nitropropane with crotonaldehyde.[2]



(LXV) (XVIIc)

Kinetic studies on other cyclic nitrones, hydroxylamines and related compounds were carried out for comparative purposes.

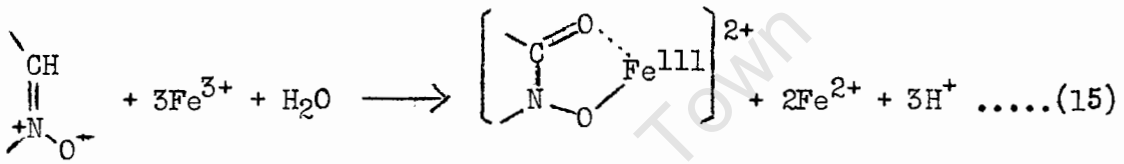
Spectral studies.

The ferric-hydroxamate complex (hereafter referred to by the abbreviation Fe^{III}.Am) was first examined to determine both its structure and stability. The complex appeared to possess a 1 : 1 structure for the following reasons:

(a) Howsmon[61] has examined the structures of various Fe^{III}.Am complexes and has found them to be dependent on pH. At low pH (1 - 2), 1 : 1 complexes were formed and gave rise to purple solutions. The purple solutions of the hydroxamic acid (XXIX c) with ferric ion were found to have a pH between 1 - 2 (measured electrometrically).

(b) A series of solutions of the nitrone (XVIIc) and ferric chloride having various initially fixed molar compositions were examined spectrally at intervals over a period of 24 days. The pattern of the change in absorbance of these solutions is shown in Fig. 3 (App.1). After $^3/_4$ hr. the solution corresponding to 1 : 1 proportions was observed to have the greatest absorbance, thus pointing to the initial formation of a 1 : 1 complex between the nitrone and ferric ion. With the passing of time, however, the colour intensity slowly diminished in those solutions having less than 75 mole-% ferric ion, and it had disappeared altogether after 8 days in solutions having less than 40 mole-% ferric ion. In the case of those solutions having more than 75 mole-% ferric ion, the intensity continued to increase with time. After 24 days, the highest absorption corresponded with 76 mole-% Fe^{3+}. For comparison, a series of solutions of the cyclic hydroxamic acid (XXIX c) with ferric ion was prepared so that the composition of each of the

solutions with respect both to hydroxamic acid and to ferric ion would correspond with the composition of each of the nitrone (XVIIc)-ferric solutions examined above, assuming oxidation to be complete in the latter solutions. In this series, the solution having maximum absorbance corresponded with the solution above, obtained from the nitrone. This maximum at 76% lay close to the stoichiometric 75 mole-% Fe^{3+} required by equation (15) in which a 1 : 1 ferric-hydroxamate complex (LXVI) is formed:



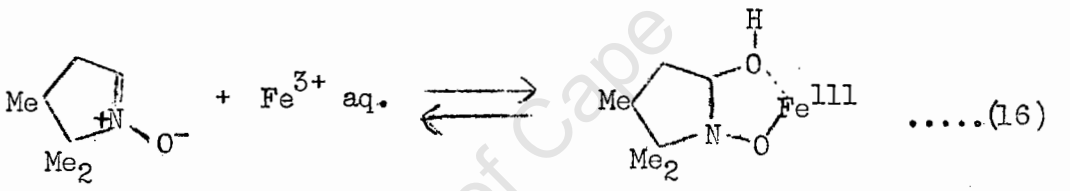
(LXVI)

The final ferric-hydroxamate complex could not comprise 2 or 3 hydroxamate residues co-ordinated to the ferric ion as the corresponding maximum absorbance would have occurred at 71.4 or 70.0 mole-% Fe^{3+} respectively, and not at 75%. The reason for the maximum absorbance occurring near 76 mole-% Fe^{3+}, i.e. with the ferric concentration in slight excess of stoichiometric requirements, is due to the fact that when $[Fe^{3+}] \approx [HAm]$, the solutions do not obey the Beer-Lambert Law and the effect of a small increase in $[Fe^{3+}]$ on raising the absorbance is greater than the depressing effect of a small reduction in $[HAm]$. (See Table 5, page 174.) Indeed in Table 5 the calculated absorbance values are shown to have a maximum at 76 mole-% Fe^{3+}, which is in good agreement with the observed value.

The diminution of the colour intensity in those solutions having

less than 75 mole-% Fe^{3+} would be expected if the nitrone were oxidised initially by non-complexed or "free" ferric ions. On depletion of this oxidising source, the ferric ions which are bound up in the coloured complex, Fe^{III}.Am must then continue the oxidation of the excess of nitrone with consequent loss of colour since the author has observed that ferrous salts gave no colour with either the cyclic nitrone (XVIIc) or the corresponding hydroxamic acid (XXIX c).

The evidence from kinetic studies (next section) points to the formation of an initial 1 : 1 nitrone-ferric complex in a slow, rate-determining step, and this may now be represented by the reversible equation:



.....(16)

(LXVII)

The ferric-nitrone complex (LXVII) (which will be abbreviated for convenience to Fe^{III}.Nn) appears to be colourless for the reason that the rate of reduction of Fe^{3+} as determined titrimetrically approximately paralleled the rate of increase in colour intensity i.e. the rate of formation of Fe^{III}.Am. Moreover, the ketonitrones (XXVIII) which have also been shown to undergo oxidation by ferric ions, although at a much slower rate, gave no characteristic colours with ferric chloride. Therefore any initial complex of the type Fe^{III}.Nn formed in this reaction must be colourless. It is important to establish this fact

that the intermediate complex (LXVII) is colourless, since kinetic studies involved the measurement of the rate of increase in intensity of the colour which is attributed entirely to the final product, $Fe^{III}.Am$.

Before rate measurements could be made, it was first necessary to ascertain the conditions under which solutions of the hydroxamic acid (XXIX c) obeyed the Beer-Lambert Law and to determine the stability constant. Figure 5 (Append. 1) shows that for solutions of constant HAm concentration, as the concentration of Fe^{3+} is increased, the absorbance, as measured at the maximum 540 mμ, increased to a constant value. In general it was found that the Beer-Lambert Law was obeyed when $[Fe^{3+}] > 10$ times the maximum $[HAm]$ under investigation. (Figure 5, Appendix 1)

The stability of the ferric-hydroxamate complexes in general is dependent on the pH. This may be represented by the reversible equation 17 in which the nett charge on the complex $Fe^{III}.Am$ is omitted

$$Fe^{III}.Am + H^{+} \rightleftharpoons HAm + Fe^{III} \qquad \ldots\ldots(17)$$

for clarity. Clearly the extent of dissociation would increase at lower pH's with consequent diminution in the colour intensity. In the particular system under investigation, the colour could be completely discharged by addition of strong mineral acid. The stability constant, K, for the complex $Fe^{III}.Am$, is defined by the equation:[103a]

$$K = [Fe^{III}.Am] / [Fe^{3+}][Am^{-}] \qquad \ldots\ldots(18)$$

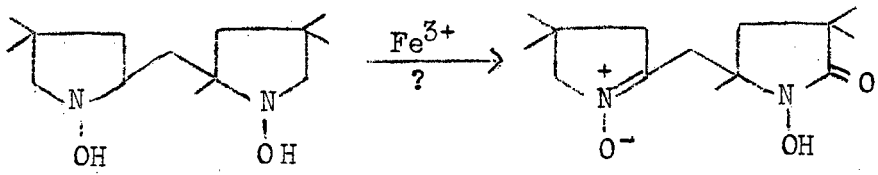
where $[Fe^{3+}]$ and $[Am^{-}]$ are the equilibrium molar concentrations of the uncomplexed ferric ion and hydroxamate anion respectively. From the results obtained (Table 4, page 171) the value of 3.7×10^{9} l. $mole^{-1}$

was found. This is comparable to the 1 : 1 complex formed between ferric ion and the acetylacetone anion ($K = 2 \times 10^9$ l. mole^{-1}).[103b]

The molar absorbances, ε, of the hydroxy-pyrrolidones (XXIX b, c and d) as obtained from the constant absorbance values for solutions of the respective nitrones (XVIIb, c and d) treated with a large excess of ferric chloride, were very similar at 1075, 1070 and 940 respectively (Table 3, page 169). This similarity would be expected since the skeletal structures of the Fe^{III}.Am complex in the three cases only differ in their substituents. The much lower value of $\varepsilon = 203$ which tended to decrease slowly in the case of the unsubstituted nitrone (XVIIa) corroborates the earlier suggestion that the resulting hydroxamic acid (XXIXa) is capable of further oxidation and hence the Fe^{III}.Am complex would be different. The results presented in Table 3 (page 169) also show that since the molar absorbances of cyclic nitrones and their corresponding hydroxylamines are in reasonable agreement (within 5%), the products of oxidation of corresponding pairs are the same. Confirmation of this by the isolation of the same cyclic hydroxamic acid from the nitrone (XVIId) and its hydroxylamine has been mentioned earlier (page 56).

The dihydroxylamine (LXVIII), a colourless, crystalline, water-insoluble solid isolated by the action of sodium borohydride on the nitrone-hydroxylamine (XXXIV), on treatment with ferric chloride gave a solution whose spectrum was similar to that resulting from the nitrone-hydroxylamine (XXXIV) on identical treatment. This would imply oxidation of one of the pyrrolidine rings to a cyclic hydroxamic acid structure and the other ring to a nitrone, with the nitrone system forming on the

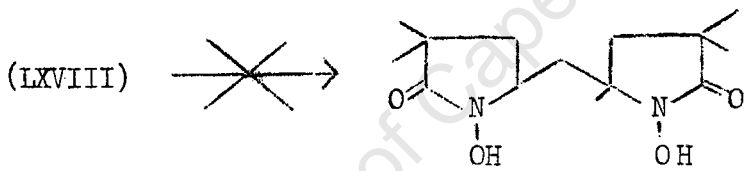
substituted carbon atom ∝ to the N atom, as shown in equation 19.



.....(19)

(LXVIII) (XXXV)

This would be agreement with the earlier observation that the nitrone double bond tends to form on the more substituted carbon atom (page 59) If the dihydroxamic system (LXIX) had formed in this reaction instead, the molar absorbance would be expected to be much higher than 1000, due to the presence of two hydroxamic moieties.



(LXIX)

The product of this reaction, however, was not isolated.

Kinetic Studies.

In the previous section it was shown that the Beer-Lambert Law applied in those solutions when the ratio of the molar concentrations of ferric ion to hydroxamic acid was at least 10 : 1. Thus it was feasible to use the measurement of the rate of increase of intensity of colour of a reaction mixture as a measure of the rate of reaction, provided $[Fe^{3+}]$ was never less than 10 x $[HAm]$ formed. Now since the oxidation of 1 mole of nitrone, Nn, to HAm has been shown to require 2 moles of

ferric ions, in order to minimise or eliminate the effect of the partial reduction of $[Fe^{3+}]$ on rate studies, two courses were available:

(a) by using relatively large molar proportions in those reactions to be followed to completion, the ferric ion concentration $[Fe^{3+}]$ may be assumed to remain constant and a pseudo-first order rate constant can be measured.[136]

(b) the determination of initial rates could be applied.[104a] This method would have to be used in those reactions where the molar ratios of ferric ion : nitrone are less than 10 : 1 in which case the disappearance of ferric ion would influence the rate.

Both these methods were adopted and will be discussed.

Consider a reacting solution containing nitrone, Nn, and a relatively very large excess of $[Fe^{3+}]$. Readings of the absorbance A at 540 mμ are recorded at frequent intervals of time until the reaction is complete. Then at any instant of time, t,

$$[Fe^{III}.Am]_t \propto (A_t - A_o) \qquad \ldots\ldots(20)$$

where $[Fe^{III}.Am]_t$ = molar concentration of ferric hydroxamate, $Fe^{III}.Am$, at time t, and

A_t, A_o = absorbance at times = t and o respectively.

When the oxidation is complete, then

$$[Fe^{III}.Am]_\infty \propto (A_\infty - A_o) \qquad \ldots\ldots(21)$$

Because the stoichiometry requires that the disappearance of 1 mole of nitrone, Nn, yields 1 mole of the hydroxamic acid in its complex, $Fe^{III}.Am$, this may be expressed in the equation:

$$[Nn]_o = [Fe^{III}.Am]_\infty$$

Therefore at any time t, the molarity of the nitrone will be given by the expression

$$[Nn]_t = [Fe^{III}.Am]_\infty - [Fe^{III}.Am]_t.$$

Thus $[Nn]_t \propto (A_\infty - A_o) - (A_t - A_o)$, which simplifies to:

$$[Nn]_t \propto (A_\infty - A_t) \qquad \ldots\ldots(22)$$

Thus the rate of increase in absorbance will be proportional to the rate of disappearance of nitrone. This will be true provided that the final reading, A_∞ is not unduly delayed, for it was observed in practice that over a period of days, solutions slowly became turbid. This was particularly noticeable in those reactions carried out at temperatures of 38° and above. All rate measurements were therefore completed within a period of 10 - 20 half lives.

The evaluation of the rate constants from the results is discussed in the Experimental Part, Section 2.32(page 175).

Discussion of Results.

All rate measurements were carried out at constant ionic strength due to the influence of this factor upon the first order rate constant. (Figure 8, Appendix 1.) Constant ionic strength was maintained by the addition of potassium chloride. This avoided introducing other anions which themselves might introduce other undesirable effects.

At the outset of mechanistic studies of this kind, it was necessary to attempt to identify the species of Fe^{3+} involved in complex formation with the nitrone. In ferric chloride aqueous solutions, three equilibria have to be considered with their respective equilibrium constants:[105a]

$$Fe(OH_2)_6^{3+} + Cl^- \rightleftharpoons FeCl(OH_2)_5^{2+} + H_2O \text{ , } K \sim 30 \quad \ldots\ldots(23)$$

$$FeCl(OH_2)_5^{2+} + Cl^- \rightleftharpoons FeCl_2(OH_2)_4^{+} + H_2O \text{ , } K \sim 5 \quad \ldots\ldots(24)$$

$$FeCl_2(OH_2)_4 + Cl^- \rightleftharpoons FeCl_3(OH_2)_3 + H_2O \text{ , } K \sim 0.1 \quad \ldots\ldots(25)$$

Since an increase in $[Cl^-]$ was observed to raise the first order rate constant, in all probability either the $FeCl^{2+}$ or the $FeCl_2^{+}$ species will be the active oxidant in this reaction. Using the equilibrium constants quoted,[105a] calculations show that if the ionic strength μ were increased from 0.197 to 0.460, the molar percentage change in each of the species present would be that shown in the table below:

	$[Fe^{III}$ species$]$, x 10^2M		
Species	$\mu = 0.197$	$\mu = 0.460$	molar % age change
Fe^{3+}	0.500	0.118	- 76
$FeCl^{2+}$	2.16	1.37	- 37
$FeCl_2^{+}$	1.56	2.65	+ 70
$FeCl_3$	0.02	0.106	+ 430

For the same increase in the total ionic strength the pseudo-first order rate constant k' (as calculated from the data in Figure 8, Appendix 1) actually increased from 0.0628 to 0.0790 $min.^{-1}$ representing a 26% increase. This would suggest that both the mono- and dichloro-ferric complexes probably participate equally in this reaction. For convenience and practical purposes, however, only the monochloro-ferric complex $Fe^{III}Cl(OH_2)_5^{2+}$, (LXX) will be used in the ensuing discussion and all ionic strength values, μ, due to ferric solutions will be based on this ionic species, i.e.

$$\mu_{Fe^{3+}} = \tfrac{1}{2}\left[Fe^{3+}\right].2^2, = 2\left[Fe^{3+}\right] \qquad \text{.....(26)}$$

or $\mu_{FeCl_3} = 3\left[FeCl_3\right]$.

It may be assumed that the ionic strength remained unchanged throughout the reaction since the amount of oxidant reduced in the course of the reaction would be negligible in comparison with the large excess of ferric chloride used initially.

An increase in the acid concentration initially increased the rate to a maximum value at about 0.08 M-HCl (Figure 10, Appendix 1), but at higher acid concentrations the rate decreased again to an approximately constant value. The following equilibria applied to the ionic species (LXX) must be considered in the interpretation of these results:

$$\left\{Fe^{III}Cl(OH_2)_5\right\}^{2+} \rightleftharpoons \left\{Fe^{III}Cl(OH)(OH_2)_4\right\}^{+} + H^{+} \qquad \text{.....(27)}$$

(LXX) (LXXI)

$$\{Fe^{III}Cl(OH)(OH_2)_4\}^{2+} \rightleftharpoons \{Fe^{III}Cl(OH)_2(OH_2)_3\} + H^+ \quad \ldots\ldots(28)$$

(LXXI) (LXXII)

$$2\{Fe^{III}Cl(OH_2)_5\}^{2+} \rightleftharpoons \{(H_2O)_3ClFe^{III}(OH)_2Fe^{III}Cl(OH_2)_3\}^{2+} + 2H^+ \quad \ldots\ldots(29)$$

(LXX) (LXXIII)

Each of these equilibria has its parallel in the ionisation of chloride-free aquoferric complexes, derived from $Fe^{III}(OH_2)_6^{3+}$, for which ionisation constants are known.[105a] Since data on the ionisation constants for the equilibria (27), (28) and (29) are not available, one can only offer a qualitative interpretation at this stage for the change in rate as a result of increasing the acid concentration. Initially, the pH (as measured) of the reacting solutions was about 2. In such solutions it is possible that there was a significant proportion of the inactive dinuclear species (LXXIII). This suggestion is advanced on the report that the analogous non-chloro-dinuclear species $\{(H_2O)_4Fe^{III}(OH)_2\ Fe^{III}(H_2O)_4\}^{4+}$ is formed in solutions at pH $\geq$ 2 - 3.[105a] Now if the main effect of the addition of small amounts of acid was the reversal of the equilibrium (29), then the concentration of the non-hydroxylated species (LXX) would be increased. Since the equivalent non-chloro-species, $Fe^{III}(OH_2)_6^{3+}$, undergoes extensive hydrolysis at pH $\sim$ 2,[105a] it is reasonable to assume that the species (LXX) would also suffer significant hydrolysis (equation 27). Thus if an increase in $[H^+]$ were to reverse the equilibrium (29) to a greater extent than equilibrium (27), the nett result of a small increase in the acid concentration would be an increase in concentration of the ionic species (LXXI).

Further hydrolysis of (LXXI) to the uncharged dihydroxylated species (LXXII) is also expected, but if the ionisation constants for equilibria (27) and (28) are of the same order as those for the following parallel equilibria (30) and (31), [105a] viz.,

$$\{Fe(OH_2)_6\}^{3+} \rightleftharpoons \{Fe(OH)(OH_2)_5\}^{2+} + H^+ \; ; \; K, \; 10^{-3.05} \quad \ldots(30)$$

$$\{Fe(OH)(OH_2)_5\}^{2+} \rightleftharpoons \{Fe(OH)_2(OH_2)_4\}^{+} + H^+ \; ; \; K, \; 10^{-3.26} \quad \ldots(31)$$

one is led to infer that the proportion of the complex (LXXII) in the solutions investigated would be insignificant.

It is realised that the foregoing hypothesis is very liable to error since it has been assumed that the equilibrium constants for the hydrolysis of the monochloro-ferric species, for which no data are available as yet, would closely parallel the known data for the hydrolysis of the non-chloro ferric species. Nevertheless it can explain why the addition of a small amount of acid increased the first order rate constant. As a result it also points to the complex ion (LXXI) as being the oxidant species in this reaction.

Moreover the above treatment can account for the effect of increasing the acid concentration. As a result, a state would be reached when the dinuclear species (LXXIII) was reduced to insignificant proportions in which case continued increase in the concentration of the acid would reverse equilibrium (27) and so reduce the concentration of the ion (LXXI) and hence the rate constant would be retarded.

From the foregoing discussion it would therefore appear that the monohydroxylated complex ion (LXXI) was most likely the active oxidant

ion in this reaction. The author, however, would stress the point that the inference drawn can only be regarded as tentative because a possibly over-simplified treatment has been accorded here to the ferric chloride system which is known to contain a wide range of complex structures which complicate the equilibrium picture.[105a, 106] Nevertheless it would appear that the rate determining step is governed by the concentration of the monohydroxylated species (LXXI) and this finds close parallels in the non-chloro complex, $\{Fe^{III}(OH)(OH_2)_5\}^{2+}$, (LXXIV), the oxidising species in redox reactions of inorganic ions,[107] and in the cobaltic ion, $\{Co^{III}(OH)(OH_2)_5\}^{2+}$, which has been shown to be the active ion in the oxidation of organic molecules by cobaltic perchlorate.[86b, 95, 102b] It should be obvious that the aquocomplex (LXXIV) cannot be considered to be the oxidising ion in the reaction under discussion since, from its structure, it cannot be reconciled with the observation that the measured rate constant increased with increase in ionic strength, i.e. chloride concentration.

The results of rate measurements, both initial and overall, (Tables 10 and 11, pages 183, 184) showed that the rate determining step was first order in nitrone and first order in ferric ion. This would be consistent with a slow stage in one of the steps (32), (34) and (35) below:

$$Fe^{3+} + Nn \rightleftharpoons Fe^{III}.Nn \qquad \ldots\ldots(32)$$

in which the 1 : 1 ferric-nitrone complex, cf. (LXVII), was formed. This would be expected to be followed by a very rapid step (33) in which an electron was transferred intramolecularly from the nitrone

molecule to the ferric ion to form a ferrous-nitrone radical complex, represented as $Fe^{II}.N'$:

$$Fe^{III}.Nn \xrightarrow{\text{fast}} Fe^{II}.Nn' \qquad \text{.....(33)}$$

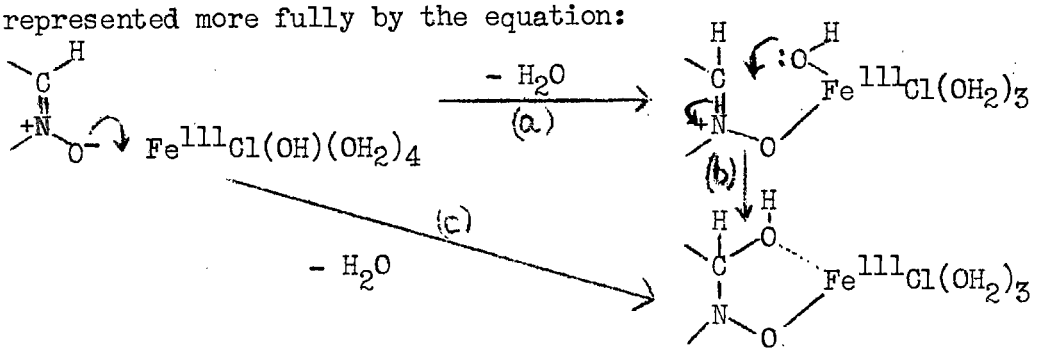
The subsequent steps (34) and (35) would complete the oxidation:

$$Fe^{III}.Nn' + Fe^{3+} \longrightarrow Fe^{II}.Am + Fe^{2+} \qquad \text{.....(34)}$$

$$Fe^{II}.Am + Fe^{3+} \longrightarrow Fe^{III}.Am + Fe^{2+} \qquad \text{.....(35)}$$
(coloured)

Identification of the slow step was possible from a comparative study of the pseudo-first order rate constants for a series of nitrones under identical conditions. If equation (32) represented the slow step and the subsequent oxidation steps were fast, then the inductive and steric effects of substituents on the pyrroline ring would be expected to alter the rate of formation of the nitrone-ferric complex, $Fe^{III}.Nn$, depending on the substitution pattern. The results contained in Table 15 (page 188) show that this was indeed the case and therefore merit closer examination.

Now the formation of the nitrone-ferric complex (LXVII) may be represented more fully by the equation:

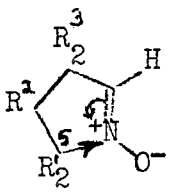


.....(36)

(LXVII)

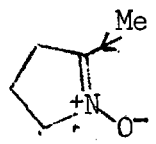
The formation of the ferric-nitrone complex (LXVII) may occur in a single step by a concerted cyclic process (c), but the two step scheme shown (a, b) is preferred on the evidence considered as a whole.

If we start with the assumption that the second step (b) in equation (36) was the slow or rate-determining step, all other steps being very much faster, then it should follow that electron-repelling substituents at C-5, e.g. a gem-dimethyl group at C-5, would tend to oppose the shift of the π-electrons on to the nitrogen atom and would therefore reduce the observed rate constant. Thus the substituted



(XVII)

	R'	R^2	R^3	10^2k^* (l. mole^{-1}sec.$^{-1}$)
a:	H	H	H	22.4
b:	Me	H	H	3.1
c:	Me	Me	H	3.0
d:	Me	H	Me	0.22



(XXVIII)

* Rate constants measured at 30°.

nitrones (XVIIb) and (XVIIc) have similar rate constants as expected, which are much smaller than that for the unsubstituted nitrone (XVIIa). The effect of electron-repelling substituents on the carbon atom of the nitrone system, while enhancing the π-electron shift on to the nitrogen atom, will at the same time reduce the electrophilicity of the carbon atom towards the attacking nucleophilic hydroxyl ligand, as shown in the second step (b) of equation (36). It is probably for this reason that the 2-methyl-1-pyrroline 1-oxides (XXVIII) undergo very much slower oxidation (Table 17, page 191). The gem-dimethyl group at C-3 in the nitrone (XVIId), due to its inductive effect would

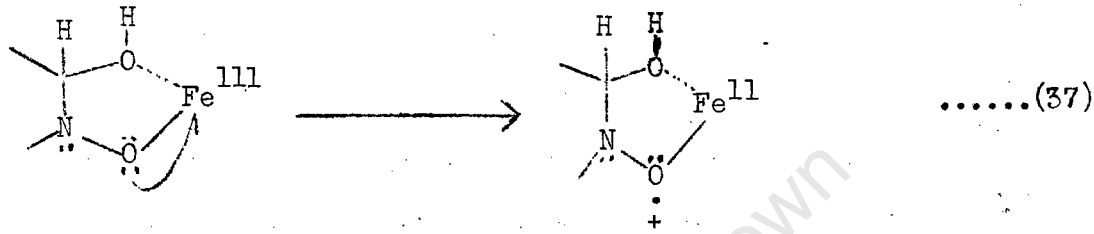
be expected to exert a similar but much weaker effect on the nitrone-carbon atom and this would account for the rate constant being much smaller than that for the nitrone (XVIIb). An examination of a model of (XVIId) showed that the spatial arrangement of the gem-dimethyl groups at C-3 should not sterically hinder a nucleophilic hydroxyl group attacking C-2, so that the observed slower rate could only be the result of an inductive effect.

The moderate decrease observed in the entropy of activation, - 6.6 e.u. (Table 13, page 186) would appear to indicate that the second step (b) in equation (36) was the rate-determining step in the reaction since it would involve a loss of rotational freedom in the intermediate complex. If the slow step were either the first step (a) in equation (36) or a concerted cyclization (c), then the loss of translational and rotational freedom of the uniting pairs would be expected to lead to a lower entropy of activation relative to the second step (b) in equation (36).[108] It is possible, however, that a moderate gain in entropy resulting by the expulsion of a solvent molecule from the ferric ion may offset the lower entropy expected so that the actual observed entropy could be attributed to any one of the three possible steps. The entropy criterion alone, therefore, cannot predict a particular mechanism but must be viewed alongside the other experimental data.[108]

It now follows that the subsequent oxidation of the nitrone within the complex is a very fast reaction. This behaviour is the opposite of the results reported for the oxidation of oxygen-containing organic compounds by cobaltic salts where the oxidation step, the

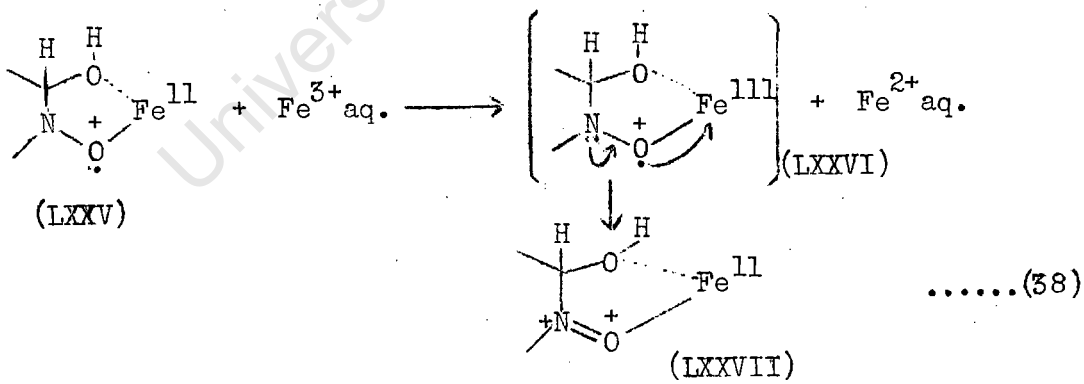
abstraction of an electron from the organic molecule, is the slow step which follows the formation of an intermediate complex.[86a, 102b] The oxidation of nitrones must therefore occur by a different mechanism.

In the oxidation of the partial complex (LXVII) the first step envisaged is the transfer of an electron to the metal ion, the fast reaction referred to earlier as equation (33):



(LXVII) (LXXV) .....(37)

The resulting radical ion complex (LXXV) would have the same charge as the initial complex (LXVII). Re-oxidation of the co-ordinated ferrous ion by free solvated ferric ions would follow and the radical intermediate (LXXVI) would transfer a second electron to the



(LXXV) (LXXVI) (LXXVII) .....(38)

ferric ion to form the complex (LXXVII). The first step in equation (38) would be expected to be a rapid step since the following exchange is known to occur very rapidly:[107]

$$^{*}Fe^{2+} + Fe^{3+} \rightleftharpoons {}^{*}Fe^{3+} + Fe^{2+}$$

(* indicates a radioisotope.)

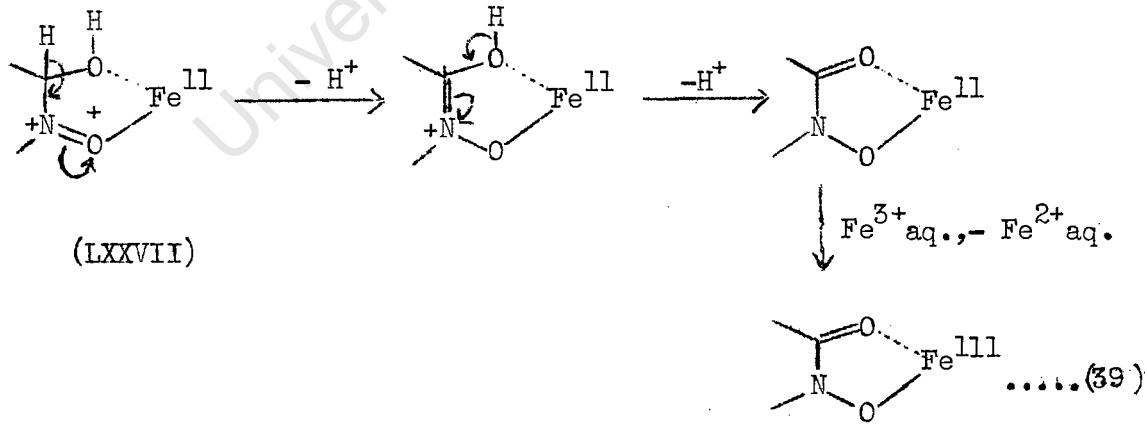
The inter-ionic transfer of the electron in (38) may proceed by any one of the three mechanisms postulated for transfer from a ferric to a ferrous ion:-[107,109a]

(i) an inner-sphere mechanism involving a water molecule bridging the two metal ions by participation in both hydration shells;

(ii) an outer sphere mechanism involving the interpenetration of the orbitals of two water molecules, one liganded to the free metallic ion, the other to the complexed ion.

(iii) hydrogen transfer mechanism in which a hydrogen atom is transferred from the hydration shell of the ferrous ion to the hydration shell of the oxidising ion.

The organic moiety of the complex (LXXVII) has the same oxidation level as the hydroxamic acid. By the loss of two protons in the mechanism shown (39) and re-oxidation of the co-ordinated ferrous ion by a rapid step as before, the final coloured ferric-hydroxamate structure (LXVI) is formed:

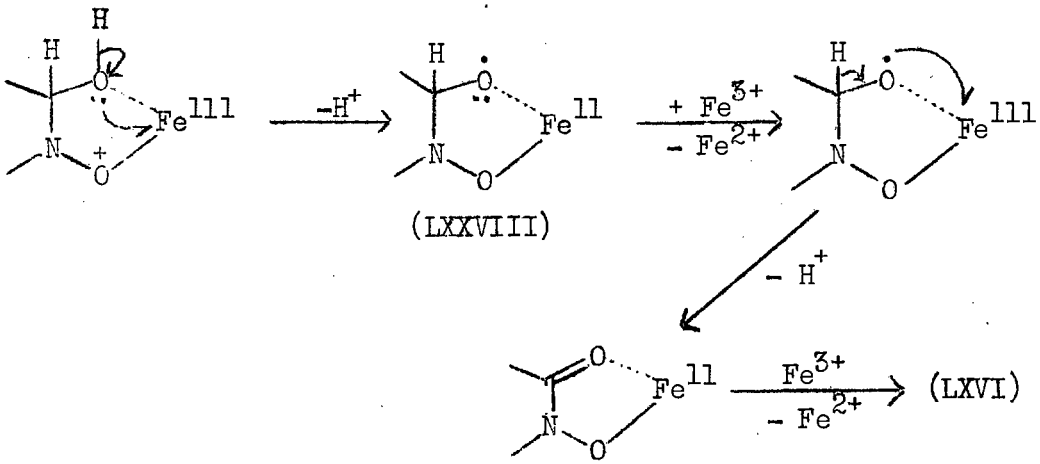


(LXXVII)

.....(39)

(LXVI)

Two possible alternative mechanisms for the oxidation of the nitrone-ferric complex (LXVII) are presented for consideration:



(LXXVIII)

...(40)

(LXXIX)

...(41)

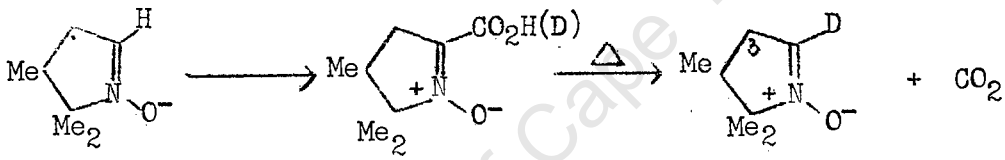
The author considers both of these to be unlikely for two reasons:-

(i) in the oxidation of alcohols by high potential transition metal ions, e.g. Co^{3+}, the abstraction of an electron from a C-H bond constitutes the rate determining step.[110] Hence one would expect the formation of the radical (LXXIX) in (41) to be the slow step.

(ii) reference has been made earlier to the results of e.s.r. studies on the oxidation of hydroxylamines and oximes by ceric salts, in which it has been shown that the first electron is abstracted from the N-O bond.[96,99,100,101] The resulting radical is stabilised by sharing of the electron

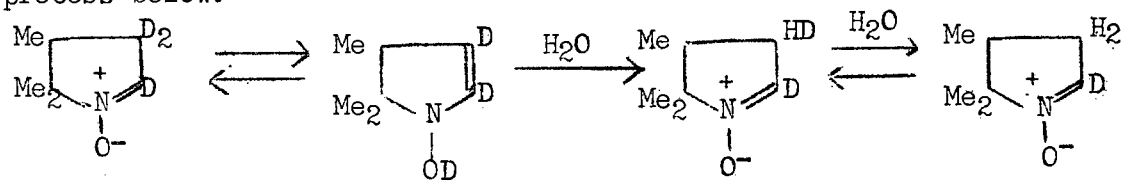
between the N and O atoms. Such stabilisation cannot occur in the C-O radical system. Hence the removal of an electron from the oxygen atom attached to the nitrogen to yield the radical complex (LXXV) in (38) should be thermodynamically more favourable than the formation of either of the radical complexes (LXXVIII) and (LXXIX).

For kinetic isotope studies, the deuterated nitrone (LXXX) was prepared from the nitrone (XVIIc).[35] Deuterium exchange was carried out on the intermediate carboxynitrone (LXXXI) which was then pyrolysed to yield (LXXX).[35]



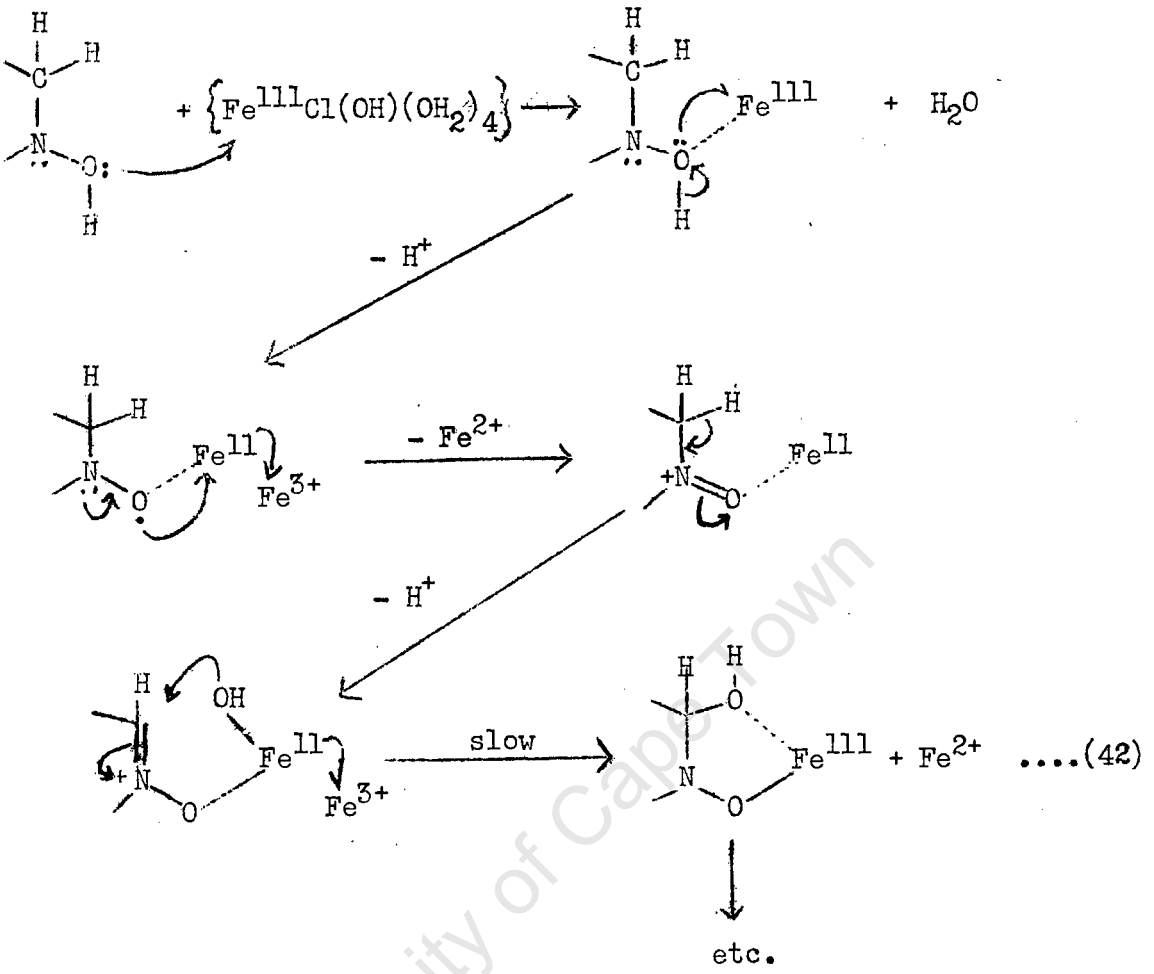
(XVIIc) (LXXXI) (LXXX)

Mass spectral analysis of the deuterated nitrone (LXXX) showed the presence of considerable amounts of di- and tri-deuterated nitrone. The significance of this has been discussed elsewhere (page 12). For rate studies in aqueous solvents it was reasonable to suppose that any influence on the rate constant would be due to the D-atom at C-2 in (LXXX) since the one or two D-atoms at C-3 would be expected to exchange out with protons from the aqueous medium by the tautomeric process below:



The fact that a significant secondary isotope effect[111,112] in the first order rate constants was observed (Table 16, page 189 shows k_H/k_D = 0.86) is inconsistent with C-H(D) fission as being the rate determining step. Primary isotope effects in which k_H/k_D values are very much greater than unity have been reported for the oxidation of alcohols and aldehydes by cobaltic ions[110,113] and are regarded as evidence for C-H(D) fission. The secondary isotope effect observed in the nitrones (XVIIc) and (LXXX) can be reconciled more satisfactorily with the formation of the complex (LXVII) as being the slow step. The higher rate constant observed for the deuterated nitrone (LXXX) may possibly arise from the stronger +I effect of the C-D bond,[114] and this effect in assisting the shift of the π-electrons on to the N-atom in equation (36) may be greater than its effect in reducing the susceptibility of the carbon atom to nucleophilic attack, thus enhancing the cyclization process in equation (36).

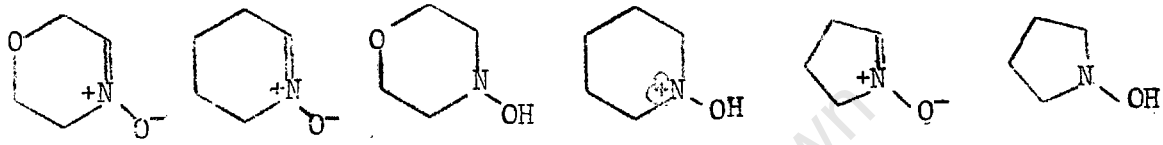
The foregoing mechanism for the oxidation of cyclic aldonitrones to hydroxamic acids can, with slight modification, readily explain the ease of oxidation of cyclic secondary hydroxylamines to hydroxamic acids. Table 15 (page 180) shows that corresponding hydroxylamines and nitrones have closely similar rates of oxidation and hence the manner of formation of the complex, the slow step in each case, must be similar. This may be represented in the scheme below:



The slow step would be the cyclization step, while the preceding steps i.e. the formation of the N-O to metal bond and the oxidation of the C-N bond to the nitrone level by abstraction of 2 electrons, would all be fast steps for the reasons advanced earlier in the discussion on the oxidation process in nitrones. It should be mentioned, however, that detailed kinetic studies on hydroxylamines in order to determine entropy of activation data have not been carried out yet. If such studies were to show that the entropy of activation was of the same order as that for the nitrones, this could be taken as conclusive proof that the same mechanism operated in the oxidation of both classes of

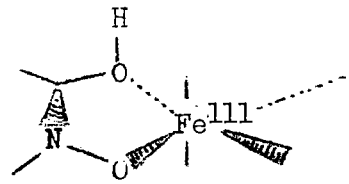
compounds, and that the slow step was the completion of the cyclization to yield the nitrone ferric complex (LXVII).

It is of interest to note that the 6-membered cyclic nitrones (XXV) and (XXVII) and their respective hydroxylamines (XXVI) and (XXXII) have immeasurably fast rate constants as compared with the unsubstituted 5-membered nitrone (XVIIa) and its hydroxylamine (XXXIIIa)(Table 15, page 188).



(XXV) (XXVII) (XXVI) (XXXII) (XVIIa) (XXXIIIa)

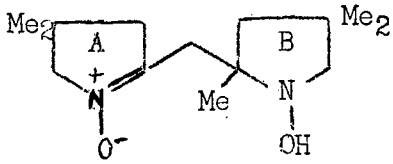
An explanation can be found in a study of the model of the nitrone ferric complex (LXVII) using Drieding models. The cyclic system incorporating the ferric ion showed strain due to the long Fe-O bond (2.0 Å) and the small O-Fe-O angle (90°) in the octahedral complex. The strain, however, was noticeably less in the complex formed on a 6-membered ring than on a 5-membered ring and hence cyclization, the rate determining step, would be expected to occur more readily, as observed, with the 6-membered rather than with the 5-membered cyclic nitrones.



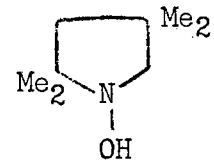
(LXVII)

A modification of this same explanation can account for the nitrone-hydroxylamine (XXXIV) having a rate constant not only much larger than that of the hydroxylamine (XXXIIIb) but also larger than

those of the pyrroline 1-oxides (XVIIb), (XVIIc) and (XVIId).

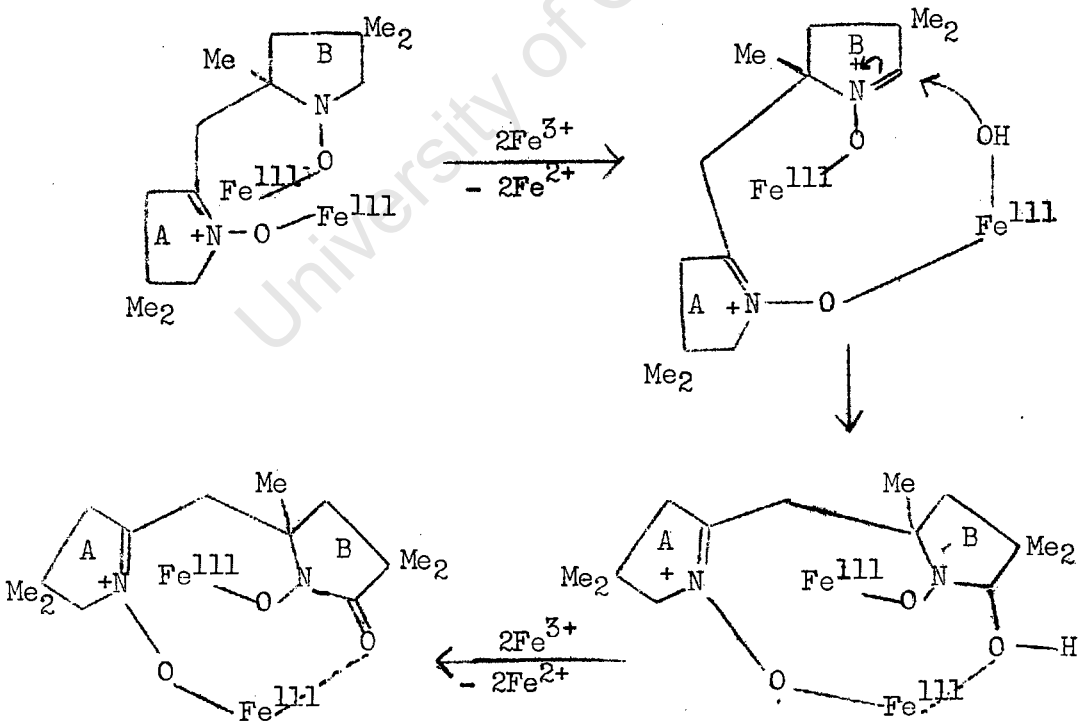


(XXXIV)



(XXXIIIb)

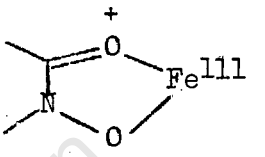
The author would suggest that both oxygen atoms of the structure (XXXIV) can, and do, enter the co-ordination shells of two aquoferric ions. When the oxidation level of the hydroxypyrrolidine ring B in (XXXIV) has been raised to that of a nitrone, nucleophilic attack on the newly-formed nitrone system in ring B by a hydroxyl ion liganded to the ferric ion attached to the original nitrone ring A would occur preferentially since models show that no ring strain will occur in the resulting 9-membered ring complex (LXXXII).



(LXXXIII)

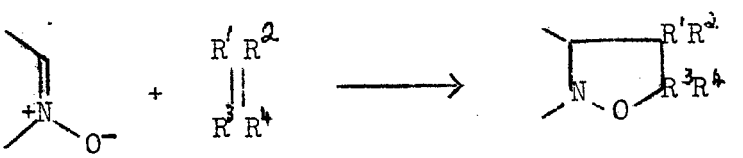
(LXXXII)

The structure (LXXXII) can only be regarded as tentative for the present as it is unsupported by entropy of activation data. An argument which may be levelled against it is that the visible spectrum of the resulting ferric-hydroxamate complex (LXXXIII) should be different from the spectrum of the complex (LXVI), whereas in fact their solution spectra are identical, both structures absorbing strongly near 540 mμ and having molar absorbances of the same order. The colour, however, may be attributed to d-orbital splitting in the ferric ion[105b, 115] by the hydroxamate ligand and not delocalisation of the charge within the complex. This postulate, however, is advanced with caution because no theory for the colour of ferric-hydroxamate complexes has yet been advanced. Should the above be true then the resulting spectrum would not be influenced by the size of the ring incorporating the complex.



(LXVI)

In conclusion, it may be added that while much of the kinetic data presented may be empirically useful, what is of value is the establishment that the rate determining step is the formation of a cyclic structure and that the cyclization is accompanied by a moderate negative entropy of activation (approx. - 7 e.u.). This cyclization may be compared with the addition of reactive olefins to nitrones to yield isoxazolidines:



The mechanism of the cyclo-addition has not been elucidated fully. In fact opinions as to whether the addition is a 1-step or 2-step process are at variance.[9,48] Though thermodynamic data on these cycloadditions is scanty, the high negative entropy of activation observed by Huisgen for the 1,3-addition of methyl methacrylate to C-phenyl-N-methyl nitrone (- 32 e.u.) would support his argument in favour of a concerted mechanism.[48] It would appear therefore that it may be an easy matter to distinguish between the two mechanisms since the activation entropies are widely different. Further extensive kinetic studies in this field would be justified and the results could shed much light on what at present is largely speculation.

PART 3.

EXPERIMENTAL.

All melting points, which are uncorrected, were recorded on a Fischer melting point stage unless otherwise stated. Ultraviolet spectra were obtained on a Beckman DB self-recording spectrophotometer coupled with a scale expander. This latter apparatus was used to determine more precisely the position of maximum absorption in solutions absorbing in the visible range. Solutions for UV examination were contained in cuvettes of 1 cm. path length. Infrared spectra were obtained on a Perkin-Elmer IR 237 Infracord. Proton magnetic resonance (p.m.r.) spectra were recorded in the National Chemical Research Laboratory of the Council for Scientific and Industrial Research, Pretoria, on a Varian A 60 N.M.R. Spectrometer. Samples were dissolved in deuteriochloroform with tetramethyl-silane (TMS) as internal reference for p.m.r. spectra. Mass spectra were also recorded in the same laboratory on an Atlas MS 9 mass spectrometer. Micro-analyses were performed in this laboratory.

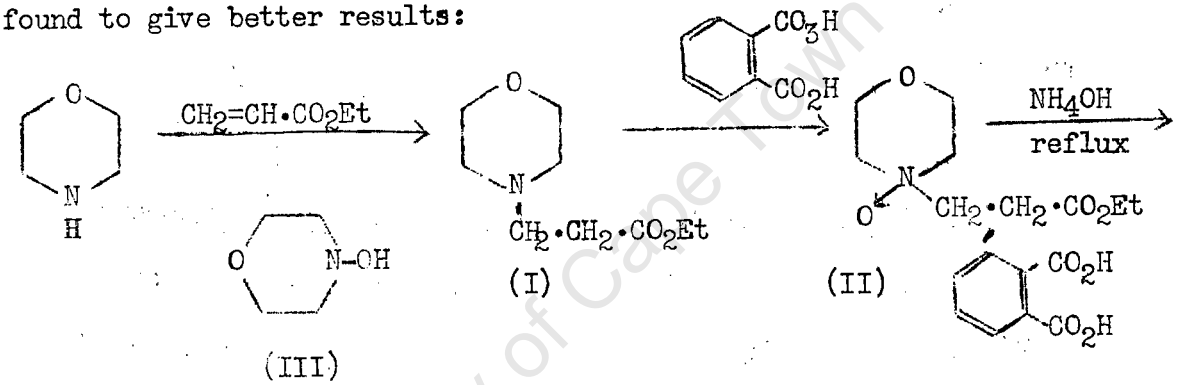
For G.L.C. studies, use was made of an Aerograph Autoprep Model 700, containing a 4 metre column packed with polyethyleneglycol-succinate, 20M, on Chromasorb B with hydrogen as carrier-gas flowing at approximately 200 ml. $sec.^{-1}$ Retention times were measured from the instant the sample was injected on to the column.

SECTION 1: STUDIES ON Δ^{2}-DIHYDRO-1,4-OXAZINE 4-OXIDE.

1.1. Preparation of Δ^{2}-Dihydro-1,4-oxazine 4-oxide (IV).

1.11. Preparation of 4-Hydroxymorpholine (III).

The direct oxidation of morpholine using 30% hydrogen peroxide[22,23] gave very low yields of (III). Repeated fractionation of the product failed to remove last traces of morpholine. The following method was found to give better results:



(III) (I) (II)

The method of Adamson[25] was modified slightly by the use of 20% molar excess of ethyl acrylate, and shorter reflux time (4 hr.) on a steam bath. This resulted in an improved yield (93%) of ethyl 4-morpholinopropionate (I), b.p. 76 - 78°/0.5 mm. (lit.[25] 118°/16 mm.). The picrate had m. p . 107 - 108° (ex n-butanol).

The morpholinopropionic ester (I) was oxidised to the 4-oxide phthalate (II) using monoperphthalic acid following the method of Rogers:-

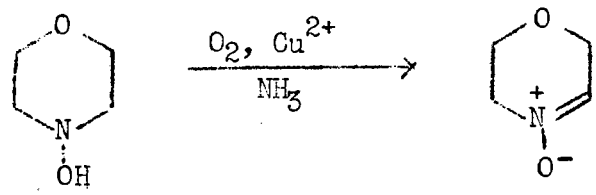
Ethyl 4-morpholinopropionate (42.6 g, 0.23 mole) in diethyl ether (100 ml.) was cooled in an ice bath. To the vigorously-stirred solution was added an ice-cold, dry, ethereal solution (1 l.)

containing monoperphthalic acid (41.2 g, 0.23 mole) (prepared according to a standard procedure[116] and incorporating Roger's modification[24]). The crude N-oxide phthalate settled out as a syrup. Stirring was continued for 5 - 10 minutes after the addition was complete. The ether layer was decanted off and the syrup was washed with ether (3 x 200 ml.). During this washing the syrup suddenly crystallised exothermically as beautiful white needles of the N-oxide phthalate (II), the yield being almost quantitative. This product was used in the next stage without further purification. A small sample on recrystallisation, (from ethanol), had m. p . 126 - 128° (lit.[24] 129 - 130°).

The N-oxide phthalate obtained above was treated with 2N-ammonium hydroxide (445 ml.) and heated under reflux for 5½ hr. in a fume cupboard owing to the release of ethyl acrylate. After cooling, the dark solution was acidified (conc. HCl), and concentrated in a rotary vacuum evaporator to approx. 200 ml. The solution was then basified (25% ammonium hydroxide) and subjected to continuous chloroform extraction (2 days). After this time the aqueous layer gave only a very weak red colour when a drop was added to an alkaline solution of triphenyltetrazolium chloride. The organic phase was separated off, dried ($MgSO_4$), and the residue, after removal of the solvent, on fractional distillation, gave pure 4-hydroxymorpholine (13.60 g, 58% yield based on the ester (I)), b.p. 54°/0.6 mm. The hydrogen oxalate was obtained as colourless needles (ex 95% ethanol), m. p. 137 - 138° (lit.[23] 136 - 137°) [$C_4H_9NO_2.H_2C_2O_4$ requires C, 37.7; H, 5.70; N, 7.25. Found: C, 37.3; H, 5.69; N, 7.14%].

1.12 Oxidation of 4-Hydroxymorpholine.

1.121 Aerial catalysed oxidation.



(IV)

(a) 4-Hydroxymorpholine (464 mg, 4.50 mmole) dissolved in a buffer solution of pH 9 (7.5 ml.) with crystalline copper sulphate 10 mg) was shaken in a 50 ml. flask in the presence of oxygen at room temperature (24°). The oxygen uptake was recorded. After 22 hr., 59.3 ml. oxygen was absorbed. (The equivalent of $\frac{1}{2}$-mole oxygen per mole of 4-hydroxymorpholine at 24° and 754 mm. was 57.0 ml.).

Paper chromatography of the resulting solution (Whatman No. 4 in butanol-ethanol-water, 4 : 1 : 5, followed by drying and spraying with a 5% aqueous ferric chloride solution) showed only a trace of the hydroxylamine (R_F 0.69) and an intense purple spot at R_F 0.38 tending to streak to R_F 0.58, attributed to the heterocyclic nitrone (IV).

(b) In a second approach, a solution containing 4-hydroxymorpholine (1.05 g, 10.2 mmole), copper sulphate (45 mg) and 25% ammonia (5 ml.) in water (30 ml.) was aerated for 4 hr. During the period of aeration, ammonia solution was added (1 - 2 ml.) at approximately hourly intervals. The solution, spotted on a chromatoplate (silica gel) and eluted with a chloroform-iso-

propanol-acetic acid (4 : 4 : 1) solvent, showed an elongated spot (R_F 0.36), attributed to the heterocyclic nitrone (IV), and only a trace of the hydroxymorpholine (R_F 0.69) upon development in iodine vapour.

The bulk of the solvent was removed by freeze drying and the residue was saturated with anhydrous potassium carbonate, extracted into chloroform and dried (Na_2SO_4).

The yield of nitrone recovered was estimated by the following procedure:

A portion of the solution (0.123 g)(total wt. of dry chloroform solution: 325.8 g) was transferred to a 200 ml. volumetric flask with distilled water and the chloroform was removed by subjecting the contents to water vacuum (15 mm.) with vigorous shaking for 15 min. The aqueous solution containing the nitrone, on dilution to volume, exhibited a peak at $\lambda_{max.}$ (water) 232 mμ, absorbance 0.080. Using the value of ε_{232} = 7900 (section 1.122 b), the yield of the nitrone recovered in the chloroform solution was 53%.

The dry chloroform solution, on removal of the desiccant and solvent at room temperature, yielded an oil which, when left over P_2O_5 and evacuated (1 - 2 mm.), puffed up to yield a white, gummy, extremely hygroscopic resin which dissolved readily in polar solvents (water, ethanol) but was insoluble in dry ether and other non-polar solvents. The addition of any of these latter solvents to an ethanolic solution of the resin precipitated the latter as a floc.

1.122. Oxidation by yellow mercuric oxide.

(III) (IV)

(a) In chloroform.

To a solution of 4-hydroxymorpholine (4.12 g, 41 mmole) in A.R. chloroform (160 ml.) was added yellow mercuric oxide (17.3 g) and the mixture was shaken mechanically. The solution rapidly became green, and then darkened to grey-black. The temperature tended to rise initially. After one hour, TLC of the resulting solution eluted in chloroform-iso-propanol-acetic acid (4 : 4 : 1) on spraying with 5% ferric chloride solution, showed the presence of a small proportion of the parent hydroxy compound (III) (R_F 0.70) with mainly a purple spot (R_F 0.36) attributed to the cyclic nitrone (IV). The insoluble material was filtered off using a thick pad of cellulose powder, and was washed with A.R. chloroform (4 x 20 ml.) and the combined washings and filtrate were dried ($MgSO_4$). The infra-red spectrum of the solution showed bands at $\nu_{max.}$($CHCl_3$) 3350, 1628, 1155, 1109, 986 and 874 $cm.^{-1}$ (cf. the cyclic nitrone (XXXI), Section 2.11(i)).

(b) In water.

A stock aqueous solution of 4-hydroxymorpholine (0.1006 g, 0.977 mmole/100 ml.) was prepared. Into a clean, dry stoppered flask was pipetted the solution (25 ml., 0.244 mmole) and yellow mercuric oxide (119 mg, 0.55 mmole) was added. The mixture on shaking rapidly turned

grey-green and finally grey-black. After shaking for ½ hr the mixture was centrifuged. The centrifugate was examined as follows:-

(i) TLC (in chloroform-iso-propanol-acetic acid, 4 : 4 : 1), showed a single spot on spraying with 5% ferric chloride; the parent hydroxylamine (III) was absent;

(ii) in order to ascertain the extent of recovery for further spectral studies, a 1.272×10^{-3} M- solution was prepared by pipetting the above solution (3.26 ml.) into a 25 ml. stoppered flask and diluting to mark. Into a clean, dry cuvette was pipetted this prepared solution (1.00 ml.), and 0.0763 M-$FeCl_3$ (2.00 ml.) and the solution carefully mixed. At the same time into a second cuvette was pipetted 1.272×10^{-3} M-4-hydroxymorpholine solution [prepared from the stock solution above] (1.0 ml.) and 0.0763 M-$FeCl_3$ (2.00 ml.). After ¼ hr. the visible spectrum of each solution was examined with the aid of the scale expander against a reference cell containing water (1.00 ml.) and 0.0763 M-$FeCl_3$ (2.00 ml.). Both solutions showed a broad band at $\lambda_{max.}$ 506 - 508 mμ. The absorbance at this wavelength for each solution was as follows:

Solution	Absorbance*
4-hydroxymorpholine	0.312
Δ^3-dihydro-1,4-oxazine 4-oxide	0.313

* Corrected for cuvette blank.

These figures confirm that the cyclic nitrone (IV) was completely recovered. Since the concentration of the

nitrone in the cuvette was 4.24×10^{-4}M, the molar absorbance $\varepsilon = \underline{738}$.

(iii) the 1.272×10^{-3} M-nitrone solution [prepared as described in (ii) above] (1.0 ml.) was diluted to 50 ml. The solution showed a single UV absorption band at $\lambda_{max.}$ 232 mμ, absorbance 0.205, i.e. molar absorbance = 7900.

Preparation of the picrate.

Method 1.

The dry chloroform solution from 4-hydroxymorpholine (0.5 g) and yellow mercuric oxide (2.2 g) was concentrated to approx. 20 ml. in a rotary vacuum evaporator at room temperature. To this was added a dry chloroform solution (50 ml.) saturated with picric acid. The deep yellow solution soon deposited Δ^3-dihydro-1,4-oxazine 4-oxide picrate (0.8 g) as fine, dark yellow needles, m. p. 87.5 - 88° (decomp.) after washing with dry chloroform and vacuum drying (Found: C, 36.7; H, 3.1; N, 17.03. Calc. for $C_4H_7NO_2.C_6H_3N_3O_7$: C, 36.4; H, 3.03; N, 17.0%). Equivalent wt. (determined spectrophotometrically[41]): found, 334. Calc., 330.

Method 2.

The chloroform solution from 4-hydroxymorpholine (1.0 g) and yellow mercuric oxide (4.3 g) was concentrated as in the previous method to about 5 ml. and was treated with a saturated aqueous solution of picric acid (150 ml.). The residual chloroform was removed under

water vacuum and the aqueous solution, on leaving in the refrigerator overnight, deposited the picrate (1.06 g) as bright yellow needles, m. p.. 94 - 94.5° (decomp.)(Found: C, 36.4; H, 3.1; N, 17.0. Calc. for $C_4H_7NO_2.C_6H_3N_3O_7$: C, 36.4; H, 3.03; N, 17.0%). Equivalent wt. (determined spectrophotometrically[41]): found, 335. Calc., 330.

Mixed m. p . of the two picrates: 89 - 89.5° (decomp.). The IR spectra of the two picrates were identical and both samples gave identical X-ray powder diffraction diagrams.

Both picrates dissociated extensively on attempting to recrystallise them from alcohol, water or chloroform, and they were insoluble in benzene and other non-polar solvents. On storage they slowly changed to tarry products.

1.123. Oxidation by potassium ferricyanide.

To a vigorously stirred solution of 4-hydroxymorpholine (2.06 g, 20 mmole) and potassium hydroxide (5.6 g, 100 mmole) in water (45 ml.) at room temperature was added a solution of A.R. potassium ferricyanide (13.2 g, 40 mmole) in water (40 ml.) over 45 min. T.L.C. examination (silica gel chromatoplate in chloroform-iso-propanol-acetic acid 4 : 4 : 1, developed in iodine vapour) indicated that approx. 50% of the starting compound (R_F 0.64) had undergone oxidation to the nitrone (R_F = 0.32). After stirring for a further 2½ hr., T.L.C. examination indicated the above two compounds present in roughly equal proportions, with a third unidentified spot at R_F 0.20, present in a significant

amount.

This route to the nitrone (IV) was not followed further as it appeared to be unsatisfactory.

1.13. Polymeric Δ^3-dihydro-1,4-oxazine 4-oxide.

Preparation. 4-Hydroxymorpholine (1.82 g, 17.7 mmole) in A.R. chloroform (20 ml.) was shaken together with yellow mercuric oxide (8.0 g, 37 mmole) for ½ hr. The insoluble mercury compounds were filtered off and the filtrate dried (Na_2SO_4). Removal of the desiccant and evaporation of the solvent left a clear yellow-brown gum. T.L.C. showed the nitrone (IV) to be the major component, together with some unchanged 4-hydroxymorpholine. Trituration of the gum with dry ether with discard of the supernatant left a cream yellow solid (1.17 g) insoluble in all solvents, but readily soluble in dil. hydrochloric acid and aqueous ferric chloride. With the latter solution it gave an intense wine-red colour. After careful washing with small amounts of water and drying under high vacuum over P_2O_5, the polymer had m. p. 156 - 165° (decomp.) (Found: C, 47.4; H, 7.1; N, 13.5. Calc. for $(C_4H_7NO_2)_n$: C, 47.5; H, 6.93; N, 13.86%) $\nu_{max.}$ (KCl) 1270, 1120, 1022, 930 and 872 $cm.^{-1}$ Shoulders at 1140, 1130, 1115 and 1100 $cm.^{-1}$ (N-C-O).[39]

Attempt to determine molecular weight.

Because it was observed to dissolve slowly in chloroform, attempts were made to determine the molecular weight by an ebullioscopic method.

The apparatus and method employed was that of Sucharda, Bobranski and Schmidt.[117]

58.29 mg polymer refluxed with 8.90 g A.R. chloroform raised the b. p. irregularly to a maximum value of 0.240°. This corresponded with a mol. wt. of 106. [Calc. for $C_4H_7NO_2$: 101]. In a second run 52.64 mg polymer in 8.90 g chloroform raised the boiling point again irregularly(Fig. 1, App.1) to a maximum value of 0.304, corresponding with a mol. wt. of 77. Two inflexions were observed at approximately 0.112° and 0.242° elevation, corresponding with the mol. wts. of 205 [calc. for $(C_4H_7NO_2)_2$: 202] and 99 [calc. for $C_4H_7NO_2$: 101] respectively.

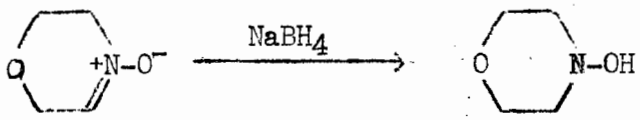
The IR spectrum of the resulting solution after drying ($MgSO_4$) showed absorption bands at $\nu_{max.}$($CHCl_3$) 1754, 1680 and 1630 $cm.^{-1}$ Paper chromatography (cf. 1.121) showed a mixture of products.

Hydrogenation of polymer. The polymer (0.353 g) was added to a mixture of platinum black (from 90 mg $H_2PtCl_6.xH_2O$) in M-HCl (20 ml.) and hydrogenated at room temperature and atmospheric pressure. Within 20 hr. 3.66 mmole hydrogen had been absorbed (Theory for 1 mole: 3.48 mmole). The catalyst was filtered off and the filtrate concentrated to low volume, saturated with anhydrous potassium carbonate and extracted with ether. The dry (Na_2SO_4)extract gave, on removal of the solvent an oil (0.336 g) which gave an intense red colour with alkaline triphenyltetrazolium chloride.

T.L.C. examination showed it to be almost entirely 4-hydroxymorpholine with a trace of morpholine. The oil distilled in a short path still at oil bath temp. 120°/16 mm. The distillate with oxalic acid in ethanol gave 4-hydroxymorpholine oxalate (from absolute ethanol) m.p. 136 - 137°, undepressed by admixture with an authentic sample.

1.2. Reductions of Δ^3-Dihydro-1,4-oxazine 4-oxide.

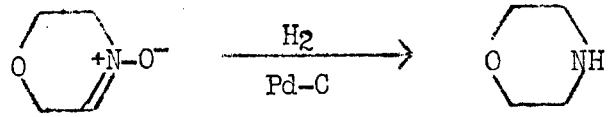
1.21. Reduction by sodium borohydride.



(IV)

A solution of the cyclic nitrone (IV) (2.0 g) in chloroform (80 ml.) was evaporated under water vacuum at room temp. in the presence of a 1% aqueous solution of sodium hydrogen carbonate (10 ml.). By this method the organic solvent was removed and the nitrone extracted completely into the aqueous phase. The latter was treated with sodium borohydride (0.5 g). After 2 days at room temperature, the excess borohydride was carefully destroyed by addition of a slight excess of acetic acid. The solution was saturated with anhydrous potassium carbonate and extracted with chloroform (4 x 20 ml.). The organic phase was dried ($MgSO_4$) and after removal of both desiccant and solvent, the residual dark oil (1.20 g) was distilled in a short path still. 4-Hydroxymorpholine (1.0 g) distilled as a colourless, slightly viscous liquid at a bath temp. 50 - 70°/18 mm. The picrate formed readily from picric acid-benzene and gave bright yellow needles (from n-butanol), m. p. 138 - 139°, undepressed by admixture with an authentic sample of 4-hydroxymorpholine picrate.

1.22. Catalytic reduction.



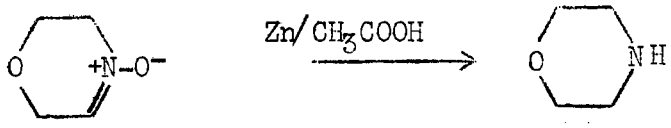
(IV)

The aqueous solution of the cyclic nitrone (IV) obtained by the aerial catalysed oxidation of 4-hydroxymorpholine (464 mg) [from section 1.121] was transferred to a pressure bottle using approx. 30 ml. water for rinsing. 5%-Palladium-charcoal catalyst (approx. 0.2 g) was added and the solution was hydrogenated at 32 p.s.i. on a Parr hydrogenator. When no further fall in pressure was observed, the solution was filtered free of the catalyst. Two paper chromatograms (Whatman No. 4) were run: P.C. 1 (in n-butanol-ethanol-water, 4 : 1 : 5) on drying and spraying with 5% $FeCl_3$ solution gave no reaction, indicating the absence of both 4-hydroxymorpholine and the cyclic nitrone (IV).

P.C. 2 (in n-butanol-acetic acid-water, 4 : 1 : 5) on drying and spraying with 0.5% ninhydrin in n-butanol revealed a single pink spot at R_F 0.27 corresponding with morpholine.

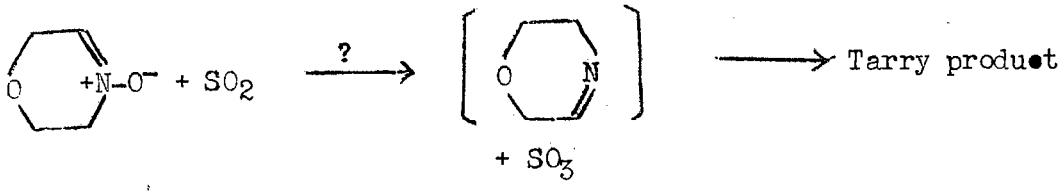
The filtrate was steam-distilled until the distillate no longer gave an alkaline reaction with litmus (approx. 700 ml. distillate were collected). To the distillate was added picric acid (1 g). The solution was evaporated in a rotary vacuum evaporator below 40° to approx. 30 ml. On standing and scratching morpholine picrate (0.69 g) crystallised out. It was obtained as bright yellow needles (2 recrystallisations from n-butanol-cyclohexane), m. p . 148 - 149.5°C, undepressed by admixture with an authentic sample of morpholine picrate.

1.23. Reduction by Zinc - Acetic Acid.



4-Hydroxymorpholine (0.50 g, 4.9 mmole) in water (16 ml.) was shaken mechanically with yellow mercuric oxide (2.40 g, 11 mmole) for 1 hr. After filtering off the insoluble material and washing the same with water (total of 80 ml.), the combined filtrates were refluxed together with zinc dust (5 g) and glacial acetic acid (4 ml.) overnight. The mixture was basified with NaOH and steam distilled. The steam distillate (600 ml.) was neutralised with an aqueous picric acid and the solution was evaporated to low volume and allowed to crystallise. The picrate on two recrystallisations from n-butanol gave bright yellow rhombs, m. p. 146 - 147°, undepressed by admixture with morpholine picrate. The IR spectrum of the picrate recovered was also identical with that of morpholine picrate.

1.24. Reduction by Sulphur Dioxide.



4-Hydroxymorpholine (0.51 g, 5.0 mmole) in dry A.R. chloroform (20 ml.) was mechanically shaken together with yellow mercuric oxide (2.38 g, 11 mmole) at room temp. for 1 hr. The insoluble material was filtered off over a cellulose pad and washed with small amounts of chloroform

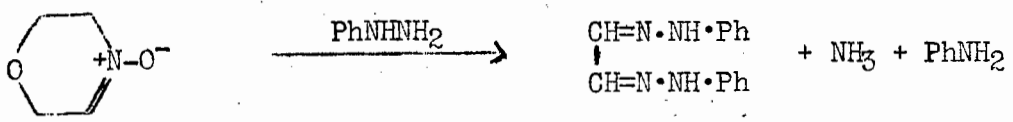
(50 ml.). The combined filtrates were dried (Na_2SO_4), freed of desiccant and then saturated with a slow stream of sulphur dioxide. The solution became warm and turbid after 5 min. and a white flocculant precipitate began to form. After one hour the floc. was rapidly filtered off at the filter pump, washed with dry ether and transferred immediately to a desiccator where it was kept over P_2O_5 at 0.5 mm. pressure. Freshly isolated the solid proved to be extremely hygroscopic, but on keeping this characteristic disappeared. On heating, the solid slowly darkened from about 70° and was a charred mass at 100°. The solid dissolved readily in water, its aqueous solution showing weak absorbance in the far UV, $\lambda_{max.}$(water) 213 mμ ($E^{1\%}_{1\ cm.}$, 8.9) $\nu_{max.}$(nujol) 3390, 1625 weak, broad (C=C ?), 1190 cm^{-1} (C-O-C).

The aqueous solution on treatment with hot, dilute hydrochloric acid and barium chloride gave a white precipitate of barium sulphate. Aqueous solutions of the solid gave no red colour with alkaline triphenyltetrazolium chloride and no wine-red colour with ferric chloride solution.

On basifying and extracting into chloroform, the dry (Na_2SO_4) extract gave only a tarry product in which neither morpholine nor 4-hydroxymorpholine was detected.

1.3. Oxidations of Δ^3-Dihydro-1,4-Oxazine 4-Oxide.

1.31. Reaction with Phenylhydrazine.



(VI)

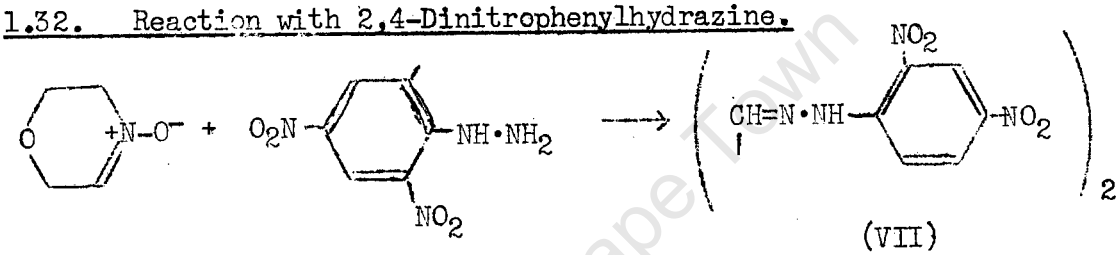
4-Hydroxymorpholine (0.50 g, 4.8 mmole) in water (20 ml.) was shaken with yellow mercuric oxide (2.40 g, 11.1 mmole) for 40 min. at room temperature. The mixture was filtered through a cellulose pad and the insoluble material was washed with water (80 ml.). To the filtrate and washings were added freshly recrystallised phenylhydrazine hydrochloride (5.1 g) and crystalline A.R. sodium acetate (7.7 g) and the solution under nitrogen was heated by immersion in a boiling water bath for 5 hr. Yellow glyoxal phenylosazone precipitated out. The mixture after cooling was filtered and the osazone washed with small amounts of cold water (0.62 g, 54% theory). Three recrystallisations from dilute ethanol gave glyoxal phenylosazone (VI) as yellow needles, m. p. 166 - 167° (lit. 169 - 171°[118], 175°[119], 176 - 177°[120]), identical with an authentic sample by mixed m. p. and comparison of the infrared spectra. [$C_{14}H_{14}N_4$ requires N, 23.5. Found N, 23.3%].

The filtrate from above was cautiously basified and steam distilled quantitatively into 0.245 M-hydrochloric acid (35.0 ml.). The residual hydrochloric acid required 41.4 ml. 0.101 M-sodium hydroxide (electrometric titration). Hence ammonia produced = 4.41 mmole (91% theory for 1 mole ammonia/mole nitrone). Aniline is reported to have no

effect upon this determination.[121]

The titration solution was treated with 5M-NaOH (20 ml.), extracted with ether (2 x 150 ml.) and the organic phase was dried ($CaCl_2$). Removal of the ether gave aniline (crude wt. 0.5 g) which was distilled off in a short path still and converted under Schötten-Baumann conditions to benzanilide, white needles (from ethanol) m. p. 162 - 163° (lit.[122] 162°).

1.32. Reaction with 2,4-Dinitrophenylhydrazine.



(VII)

4-Hydroxymorpholine (0.2193 g, 2.13 mmole) in water (16 ml.) was mechanically agitated with yellow mercuric oxide (1.0 g) for half an hour. The solution of Δ^3-dihydro-1,4-oxazine 4-oxide thus formed was filtered through a cellulose pad. The turbid filtrate with the washings (95% ethanol, 80 ml.) was clarified by a second filtration. The filtrate was added to a mixture of A.R. 2,4-dinitrophenylhydrazine (3.5 g) in 95% ethanol (175 ml.) and the whole was just brought to the boil and allowed to cool slightly before adding concentrated hydrochloric acid (10 ml.). The mixture was magnetically stirred and allowed to boil gently under reflux overnight. An orange-red precipitate formed very rapidly soon after the addition of the acid. This was filtered off after cooling the reaction flask. (2.97 g crude, dry wt.). After 2 - 3 recrystallisations from dimethylformamide, glyoxal-2,4-dinitro-

phenylosazone (VII) was obtained as red needles, m. p. 323 - 324° (decomp.)(lit. 318°,[123] 322 - 324°,[124] 326 - 328°,[125] 329 - 331°,[120]) undepressed by admixture with an authentic sample. [$C_{14}H_{10}N_8O_8$ requires C, 40.2; H, 2.39; N, 26.8. Found: C, 40.6; H, 2.58; N, 26.43%]. The IR spectrum was found to be identical with that of authentic glyoxal-bis-2,4-dinitrophenylhydrazone.

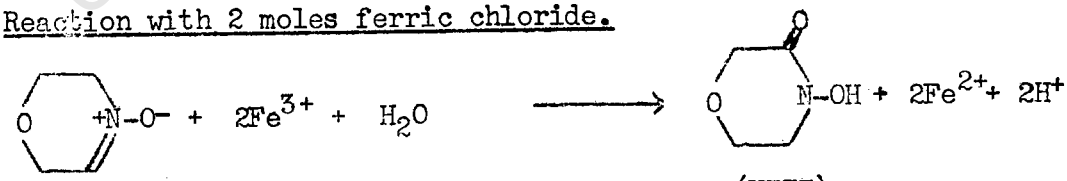
The filtrate from above was basified (20 ml. 50% sodium hydroxide) and steam distilled quantitatively into 0.245 M-hydrochloric acid (30.0 ml.). The residual acid required 68.35 ml. 0.102 M-sodium hydroxide for neutralisation (electrometric titration). This was equivalent to 0.16 mole ammonia per mole nitrone.

In a repeat experiment, 0.20 mole ammonia per mole nitrone was recovered.

4-Hydroxymorpholine on treatment with 2,4-dinitrophenylhydrazine as above failed to show any reaction.

1.33. Reaction with Ferric Chloride.

(a) Reaction with 2 moles ferric chloride.

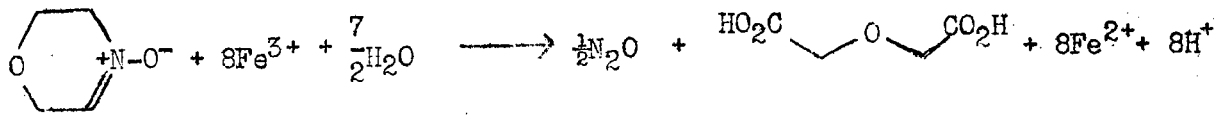


(VIII)

4-Hydroxymorpholine (1.294 g, 12.6 mmole) in water (20 ml.) was shaken together with yellow mercuric oxide (5.7 g) for ½ hr, and the mixture was filtered through a cellulose pad. The insoluble residue was washed with water (100 ml.) and the combined filtrates were treated

with 0.335 M-$FeCl_3$ (112.5 ml., 37.8 mmole). The solution, which immediately became intensely purple on mixing, was allowed to stand for 2 hr with stirring. After this time 1.0 ml. of the solution (total vol. 350 ml.) was found to require 0.072 ml. 0.1000 N-$K_2Cr_2O_7$ for complete oxidation of the ferrous ion, i.e. total ferrous ion in the solution = 25.2 mmole (2 mole Fe^{3+} reduced per mole nitrone). The residual solution was treated with 5N-NaOH (25 ml.) and the iron hydroxides were removed by centrifugation and washed with 0.5N-NaOH (5 x 70 ml.), each washing being followed by centrifugation. The combined centrifugates were brought to pH 6, vacuum evaporated nearly to dryness, acidified with 5N-HCl (30 ml.) and the acidic solution was finally subjected to continuous chloroform extraction. The dry (Na_2SO_4) organic extract on evaporation gave a dark oil (0.43 g) which slowly formed clusters of needles when the flask was left in the refrigerator. The residual oil was soaked up on a porous plate and the crystalline solid on two sublimations (60 - 70°/25 mm.) gave 4-hydroxy-3-morpholone (VIII) as colourless, waxy needles, m. p. 120 - 121°. (Found: C, 41.1; H, 6.2; N, 11.74. $C_4H_7NO_3$ requires: C, 41.0; H, 5.98; N, 11.96%.) $\nu_{max.}$(nujol) 3350 (bonded OH), 1670 (hydroxamic C=O), 1645, 1138, 1106 (C-O-C), 994 and 880 $cm.^{-1}$ The solid gave an intense wine-red colour with 5% ferric chloride solution. Visible spectrum of the ferric chloride solution contained a broad band at $\lambda_{max.}$ 505 mμ.

(b) Reaction with Excess of Ferric Chloride.



(IX)

4-Hydroxymorpholine (1.217 g, 11.8 mmole) in water (25 ml.) was mechanically shaken together with yellow mercuric oxide (5.8 g) for ½ hr. The filtered solution was treated with 60% A.R. ferric chloride solution (60 ml., 216 mmole), diluted to 500 ml. and heated on a steam bath. 1 ml. aliquots were removed at intervals and titrated against 0.1000N-$K_2Cr_2O_7$ for Fe^{2+} content.

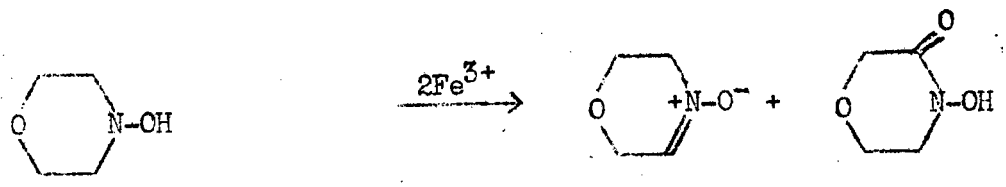
After 6 hr at 94°, 1 ml. required 1.83 ml. (corrected for temp.) of the $K_2Cr_2O_7$ solution, hence $[Fe^{2+}]$ = 0.183 M. (Calculated $[Fe^{2+}]$ for $[Fe^{2+}]$/initial (IV) = 8, 0.189M).

Gas which was extracted from the hot solution (for method of extraction, see App. 2) was dried over $CaCl_2$ and transferred to a gas cell (NaCl plates, path length 10 cm.). The IR spectrum showed absorption bands at 2230 and 1275 $cm.^{-1}$ (N_2O).[32e,66]

The cooled solution was treated with 50% sodium hydroxide solution (45 ml.) and the precipitated iron salts were centrifuged down and washed several times with 0.2M-sodium hydroxide (500 ml. in all). The combined centrifugates were adjusted to pH 2 (conc. hydrochloric acid), evaporated $<60°$ to low volume and extracted continuously into ether for 2 days. The dry (Na_2SO_4) extract gave crude diglycollic acid (IX) (0.40 g) as pale yellow needles. On heating with pure aniline (1 g) 180 - 200° for 2 hrs., from the mixture was isolated

diglycollic acid dianilide, as colourless needles (ex ethanol - light pet. ether), m. p. 152 - 153° (lit.[64] 152°) [$C_{16}H_{16}N_2O_3$ requires N, 9.86. Found: N, 9.80%].

1.34. Reaction of 4-Hydroxymorpholine with 2 moles of Ferric Chloride.

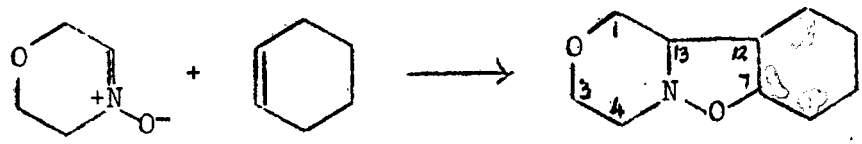


(III) (IV) (VIII)

To 4-hydroxymorpholine (1.093 g, 10.6 mmole) was added 0.331M-$FeCl_3$ (64.2 ml., 21.2 mmole). The purple solution after ½ hr was basified with 5N-NaOH (25 ml.) and the iron hydroxides were centrifuged off and washed with 0.5N-NaOH (24 ml.) as before. The combined centrifugates were adjusted to pH 4 (conc. HCl), evaporated $\lesssim 60°$ to low volume and extracted overnight into chloroform. T.L.C. of the solution showed 5 spots in iodine vapour. Three of the spots gave purple colours on spraying with 5% ferric chloride. These corresponded with the nitrone (IV), the cyclic hydroxamic acid (VIII) and unchanged (III).

1.4. Cycloadditions of Olefins to Δ^3-Dihydro-1,4-Oxazine 4-Oxide.

1.41. Reaction with cyclohexene.



(X)

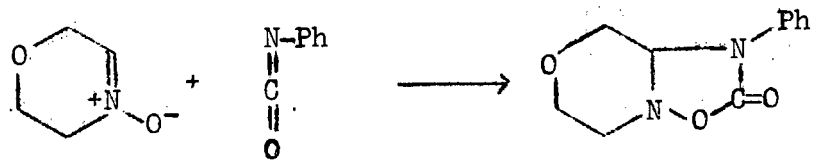
A chloroform solution (90 ml.) containing Δ^3-dihydro-1,4-oxazine 4-oxide [prepared from 4-hydroxymorpholine (2.06, 20 mmole) by the method described in section 1.122 and dried over $MgSO_4$], was treated with cyclohexene [previously treated to remove peroxides, dried ($CaCl_2$) and redistilled] (20 ml.) and the mixture was evaporated to low volume (approx. 20 ml.) in a rotary vacuum evaporator at a temperature below 40°. A further quantity of cyclohexene (20 ml.) was added, followed by evaporation as before. By this process, much of the chloroform was removed. A third quantity of cyclohexene (20 ml.) was now added and the solution was heated on a steam bath under reflux for 36 hr. The yellow supernatant was decanted off and on evaporation gave a crude oil (1.75 g) which was distilled in a short path still. A colourless, oily liquid (1.55 g) passed over at a bath temp. of 80 - 90°/0.3 mm. The liquid crystallised in the micro-receivers, m. p . 13 - 18°, and had a strong mouse-like odour. Further direct purification of the free base was unsuccessful.

The picrate formed readily from ethanol-picric acid, giving bright yellow crystals m. p . 180 - 181° (from butanol-cyclohexane).

[Found: C, 46.3; H, 4.56; N, 13.5. Calc. for $C_{10}H_{17}NO_2.C_6H_3N_3O_7$: C, 46.6; H, 4.85; N, 13.6%]. Equivalent wt. (determined spectrophotometrically[44]) 418. Calc. for $C_{16}H_{20}N_4O_9$: 412.

The free base was obtained in a pure form by decomposition of the picrate.[126] The above picrate (1.05 g) in a 50 ml. flask was treated with liquid ammonia (10 ml.) and dry A.R. chloroform (10 ml.). The ammonia was allowed to evaporate at room temperature, after which the chloroform solution was filtered free of the insoluble ammonium picrate, and dried (Na_2SO_4). Removal of first the desiccant then the solvent gave a basic oil (0.62 g) which on distillation gave pure 2,6-dioxa-3-aza-tricyclo[7,4,$0^{3,8}$] tridecane (X), b.p. 96 - 98°/1 mm. (0.50 g) [Found: C, 65.3; H, 9.5; N, 7.41. Calc. for $C_{10}H_{17}NO_2$: C, 65.6; H, 9.29; N, 7.65%] $\nu_{max.}$(film) 1462, 1273, 1129 and 861 $cm.^{-1}$ The free base solidified, m. p. 29 - 30°. The p.m.r. spectrum (Figure 2c, Appendix 1) showed five unresolved multiplets centred at τ 8.4 (8H), 7.4 (1H), 7.0 (3H), 6.2 (2H) and 5.6 (1H).

1.42. Reaction with phenylisocyanate.

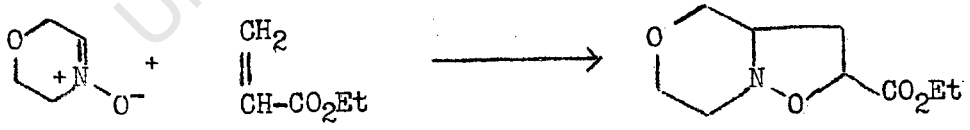


(XI)

To a chloroform solution (80 ml.) containing Δ^3-dihydro-1,4--oxazine 4-oxide (2.2 g) [prepared by the method described in section 1.122 (a) and dried ($MgSO_4$)] was added phenylisocyanate (2.2 g) in dry

A.R. chloroform (17 ml.) and the mixture was gently refluxed for 3 hr. on a hot water bath. The chloroform and unreacted phenylisocyanate were removed by initially evaporating the mixture in the rotary vacuum evaporator ($\leq 40^{\circ}$) and finally under high vacuum ($\sim$ 1 mm.). A yellow-brown oil (3.68 g) remained. The oil was dissolved in dry ether which, on spontaneous evaporation, slowly deposited a crystalline mass. The supernatant ether was filtered off and the mass on recrystallisation from 96% ethanol gave 7-phenyl-4,9-dioxa-1,7-diaza-bicyclo [4,3,0] nonan-8-one (XI) (1.95 g) as colourless needles, m. p. 117 - 118° [Found: C, 59.6; H, 5.67; N, 12.72. Calc. for $C_{11}H_{12}N_2O_3$: C, 60.0; H, 5.45; N, 12.72%] $\nu_{max.}$ ($CHCl_3$) 1770 (δ-lactone), 1600 (phenyl ring), 1496, 1149 (C-O-C), 1097 and 866 $cm.^{-1}$ The p.m.r. spectrum revealed signals at τ 2.63 (5 aromatic H), 4.90 triplet (J = 1.5 c.p.s.)(1H), and complex unresolved multiplets in the range 5.8 - 6.8 (6H).

1.43. Reaction with ethyl acrylate.



(XII)

Ethyl acrylate (10 ml.) was added to a dry chloroform solution (160 ml.) containing Δ^3-dihydro-1,4-oxazine 4-oxide (4.1 g) prepared as described in Section 1.122(a). The mixture, which became slightly warm, was allowed to drop slowly into a distilling flask containing a further quantity of ethyl acrylate (20 ml.) heated on a steam bath.

Most of the chloroform distilled off and carried off some of the acrylic ester. At the end of the addition, a third quantity of ethyl acrylate (20 ml.) was added and the mixture was heated on a steam bath under reflux for 12 hr. The residual solvent and excess of ethyl acrylate were removed at room temperature, first under moderate vacuum and finally under high vacuum. Distillation of the residual oil yielded 8-ethoxycarboryl-3,7-dioxa-6-aza-bicyclo[4,3,0]nonane (XII) (4.50 g) as a colourless oil, b. p. 118°/1 mm. [Found: C, 53.5; H, 7.65; N, 6.77. Calc. for $C_9H_{15}NO_4$: C, 53.7; H, 7.46; N, 6.96] $\nu_{max.}$ (film) 1745 (C=O ester), 1210 (C-O-C ester), 1128, 1116 (C-O-C), 862 cm^{-1}. P.m.r. spectrum (Figure 2b, Appendix 1) showed the ethyl ester signals at τ 5.75 (quartet, J = 7.0 c/s) and 8.69 (triplet, J = 7.0 c/s). Other signals were multiplets at τ 5.25 (1H) and 7.48 (2H), together with a complex series in the range τ 5.5 - 7.2 (7H). Weak ethyl ester signals at τ 5.78 (quartet, J = 7.0 c/s) and 8.72 (triplet, J = 7.0 c/s) became relatively more intense when the reflux conditions used in the preparation above were extended over 4 days. The bicyclic morpholino-isoxazolidine (XII) on treatment with an ethanolic solution of picrolonic acid immediately precipitated the picrolonate as dull yellow needles (from ethanol), m. p. 148 - 149° [Found: C, 49.2; H, 4.8: N, 15.0. Calc. for $C_{19}H_{23}N_5O_9$: C, 49.0; H, 4.95; N, 15.05%.].

The equivalent wt of the picrolonate was measured spectrophotometrically.[51,127] For ethanolic solutions of a series of picrolonates, the molar absorbances at 370 mμ gave a mean value of 19,970 ± 2%. An ethanolic solution of the picrolonate of the bicyclic isoxazolidine

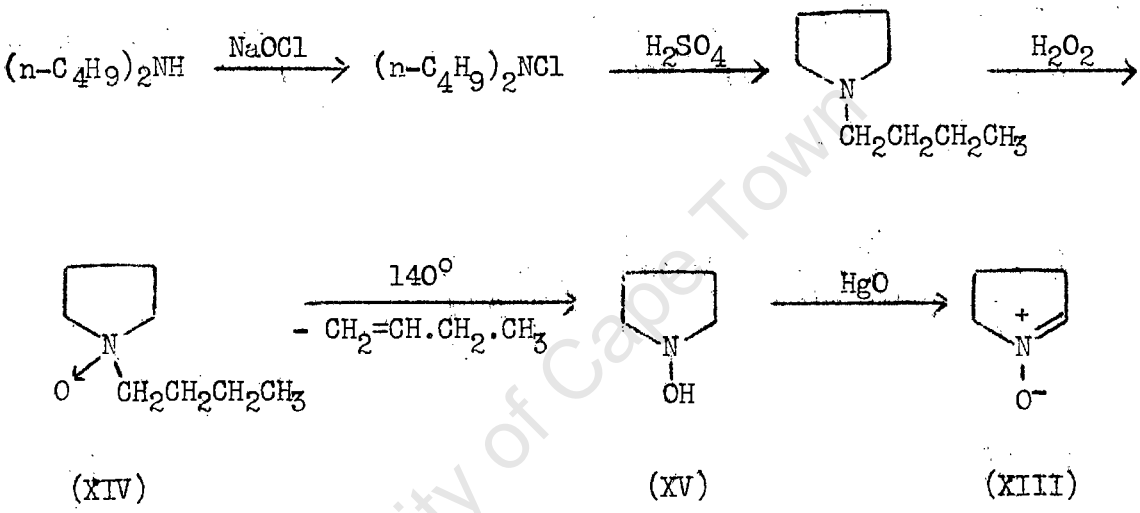
(XII) at the same wavelength exhibited an absorbance of 0.339 for a concentration of 7.99 mg/l. Hence equivalent wt.: Found, 471. Calc. for $C_{19}H_{23}N_5O_9$: 465.

SECTION 2: OXIDATION STUDIES.

2.1. Preparation of the Compounds Required.

2.11. Preparation of Cyclic Nitrones.

2.11 (a) 1-Pyrroline 1-Oxide (XIII).



(XIV) (XV) (XIII)

1-Butylpyrrolidine, prepared by the method of Coleman and his collaborators,[128] was obtained in 65% yield, b. p.. 154 - 155° (lit.[128] 154 - 155°).

1-Butylpyrrolidine 1-oxide (XIV). A homogeneous mixture containing 1-butyl pyrrolidine (6.35 g, 50 mmole), water (5 ml.) and 96% ethanol (15 ml.) was cooled in ice. Vigorous stirring was applied while 30% hydrogen peroxide (11.2 ml., 100 mmole) was added dropwise, the temperature being maintained at about 6°. The ice-bath was removed at the end of the addition and stirring was continued for 1 hr. at room temperature and for a further 16 hr. at 60°. The excess of hydrogen

peroxide was decomposed with platinum black (50 mg. prepared from $H_2PtCl_6.xH_2O$[129]) added as an aqueous suspension (2 ml.). After 15 min. the cloudy mixture, which gave a negative test with starch-iodide paper, was evaporated to a syrup to remove all the alcohol, diluted to approx. 110 ml. with water and extracted with ether (200 ml.) to remove unchanged amine.

The aqueous phase (1 ml.) on treatment with saturated aqueous picric acid (7.3 ml.) gave a bright yellow precipitate of crude picrate (117 mg, 69% yield of amine-oxide). Pure 1-butylpyrrolidine 1-oxide picrate was obtained as prisms (from butanol) m. p. 96 - 97° [Found: C, 45.1; H, 5.61; N, 14.70. Calc. for $C_8H_{17}NO.C_6H_3N_3O_7$: C, 45.2; H, 5.38; N, 15.05%].

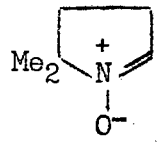
1-Hydroxypyrrolidine. The aqueous solution of the 1-butylpyrrolidine 1-oxide from above was concentrated in a rotary vacuum evaporator to a syrup, which was then transferred to a vacuum distillation flask arranged so that dry nitrogen entered the apparatus via the capillary bleed. The distillation flask was immersed in an oil bath whose temperature was maintained from 60- 75°. Most of the water was removed at a pressure of 25 mm. The pressure was then lowered to 14 mm. and the bath temp. slowly raised (at a rate of about 2°/min.). At a bath temp. of 115° the amine oxide solidified in the flask. When the external temperature rose to approx. 135 - 140°, the solid melted and decomposed, with 1-hydroxypyrrolidine (XV) distilling over at about 43° initially. When the bath temp. was 145°, pyrolysis occurred more rapidly with the hydroxylamine distilling over as a colourless liquid,

b. p. 59 - 62°/14 mm. The heating was stopped when, near the end, the residue started to bump. The crude distillate (2.3 g, 53%) was dissolved in ether (50 ml.), dried (Na_2SO_4) and distilled after removal of both the desiccant and solvent. The hydroxylamine distilled at 75 - 76°/20 mm. (lit.[30] 65 - 65.5°/12 mm.) as a colourless liquid (1.66 g, 38%) having a strong mouse-like odour. The hydrogen oxalate, obtained from acetone-ether solution of anhydrous oxalic acid, had m. p. 123 - 124°(from methanol)(lit.[30] 123 - 124°) [$C_4H_9NO.C_2H_2O_4$ requires: C, 40.67; H, 6.26; N, 7.90. Found: C, 41.0; H, 6.5; N, 7.6%]. Addition of 1 drop of 1-hydroxypyrrolidine to a dry, saturated ethereal solution of picric acid (5 ml.) immediately gave the picrate as yellow needles which were filtered off and washed with dry ether, m. p. 142 - 142.5° (decomp.) after sintering at about 136° (lit.[30] 146°). The hydroxypyrrolidine gave a deep red colour with alkaline triphenyltetrazolium chloride.[57]

1-Pyrroline 1-Oxide. (XIII). Following the method of Thesing and Sirrenberg,[30] 1-hydroxypyrrolidine (1.65 g) with yellow mercuric oxide gave 1-pyrroline 1-oxide (0.53 g, 30%), as a colourless oil (distilled in a short path still at a bath temp. 80 - 90°/0.3 mm.) which crystallised when left in the refrigerator, the solid, m. p. 100 - 101°,(sealed tube) being extremely hygroscopic. The picrate formed readily from picric acid in ether and was obtained as dull yellow needles (from n- butanol-cyclohexane), m. p. 123.5 - 124.5° (lit.[30] 124.5 - 125.5°). [$C_4H_7NO.C_6H_3N_3O_7$ requires: C, 38.2; H, 3.24; N, 17.83. Found: C, 38.4; H, 3.6; N, 17.8%] $\lambda_{max.}$(water) 225 mμ (ε 8500).

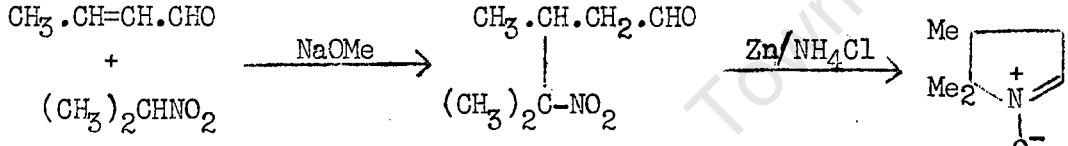
2.11 (b) 5,5-Dimethyl-1-Pyrroline 1-Oxide. (XVI).

The compound was available in this laboratory. The author is grateful to Prof. Lamchen for providing this. It was redistilled (b. p. 78 - 80°/0.7 mm.) before use. The picrate after recrystallisation (n-butanol) had a m. p. 81 - 82° (lit.[2] 82°).



(XVI)

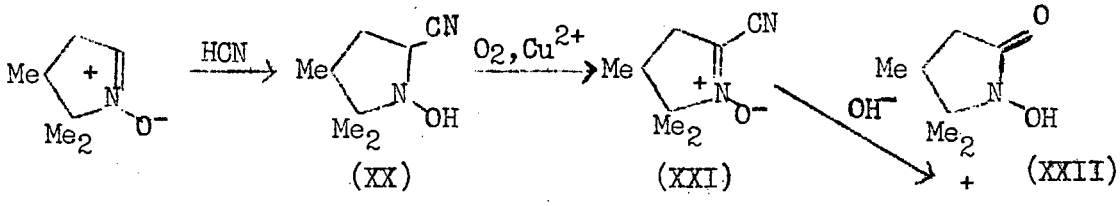
2.11 (c) 4,5,5-Trimethyl-1-Pyrroline 1-Oxide. (XVII).



(XVII)

The method described by Sir A. Todd and his co-workers was used.[2] 3,4-dimethyl-4-nitropentanal was obtained in 46% yield, b. p. 66°/0.2 mm. (lit.[2] 80°/0.5 mm.). From this, 4,5,5-trimethyl-1-pyrroline 1-oxide was obtained as a colourless, hygroscopic oil in 51% yield, b. p. 70°/0.6 mm. (lit.[2] 85°/1 mm.); the picrate (from n-butanol) was obtained as yellow needles, m. p. 111 - 112° (lit.[2] 112°).

2.11. (d) 2-d-4,5,5-Trimethyl-1-Pyrroline 1-Oxide. (XVIII).



(XX) (XXI) (XXII)

(XVIII) (XIX)

4,5,5-Trimethyl-2-carboxy-1-pyrroline 1-oxide. (XIX).

Bonnett, Brown, Clark, Sutherland and Sir A. Todd.[2]

The yield of cyanohydroxylamine (XX) was improved when sodium carbonate instead of sodium hydroxide was used to basify the mixture after the addition of hydrochloric acid was complete. The product was obtained in 89% yield, m. p . 108 - 109° (ex ether - light petrol ether)(lit.[2] 109°). Aerial oxidation gave the cyanonitrone (XXI) which recrystallised as plates more readily from cyclohexane than from ethyl acetate-pet. ether,[2] m. p . 86 - 87° (lit.[2] 86 - 87°) in 72% yield. Alkaline hydrolysis of the latter cyanonitrone gave, by the method[2] described, the cyclic hydroxamic acid (XXII) (Section 2.132) in 58% yield as needles (ex cyclohexane), m. p . 101 - 102° (lit.[2] 101 - 102°) and the carboxynitrone (XIX) as needles (ex cyclohexane) m. p . 40 - 41° (lit.[2] 40 - 41°) in 39% yield.

2-Deutero-4,5,5-Trimethyl-1-pyrroline 1-oxide. (XVIII).

Brown, Clark and Lord Todd.[35]

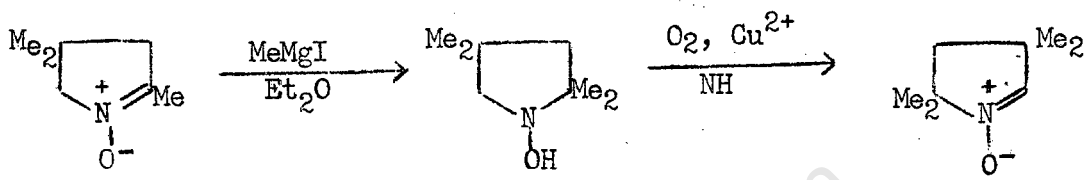
The carboxynitrone (XIX)(1.3 g) dried by azeotropic distillation with benzene, was treated with 99.5% deuterium oxide (7.5 g) in anhydrous tetrahydrofuran (20 ml.) added in 7 portions to the acid and evaporated slowly in a rotary vacuum evaporator at 16 mm. pressure while being heated with an infrared lamp. After removal of excess of solvent and exchange reagent, the residual oil was decarboxylated by placing in an oil bath at 155° for 10 mins. It was then twice distilled in a micro-distillation set at an oilbath temperature 80 - 100°/0.2 mm. (lit.[35] 78 - 80°/0.8 mm.) $\nu_{max.}$(film) 1570, 1370 and 1250 cm. , $\lambda_{max.}$(water)

227 mμ (ε 8400). Analysis of the mass spectrum gave the percentage incorporation of deuterium as follows:

D_0, 28.7; D_1, 52.2; D_2, 16.7; D_3, 2.5 (?)%

2.11 (e) 3,3,5,5-Tetramethyl-1-Pyrroline 1-oxide. (XXIII).

Bonnett, Brown, Clark, Sutherland and Sir A. Todd.[2]

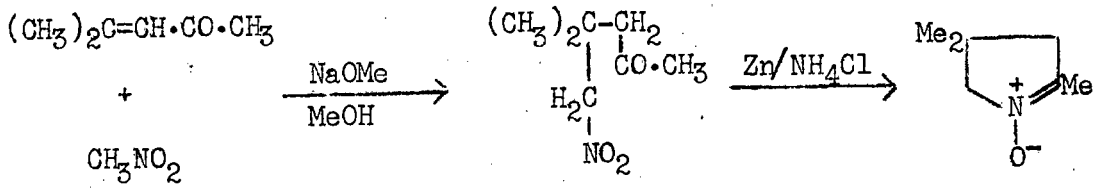


(XXIV) (XXIII)

2,2,4,4-Tetramethyl-1-hydroxypyrrolidine (XXIV) was obtained in 87% yield as colourless needles, m. p. 61 - 62° (lit.[2] 62°) on sublimation, by the action of ethereal magnesium iodide upon 2,4,4-trimethyl-1-pyrroline 1-oxide [Section 2.11 (f)]. The freshly sublimed product gave an immediate deep red colour with alkaline triphenyltetrazolium chloride,[57] showed a weak absorption band at $\nu_{max.}$ (nujol) 1570 cm.$^{-1}$ and, in aqueous solution, absorbed at $\lambda_{max.}$ 226 mμ (ε 2170). These facts indicate that the compound contained about 20% of the nitrone (XXIII).

Aerial oxidation of an ammoniacal solution of the hydroxylamine in the presence of copper sulphate gave 3,3,5,5-tetramethyl-1-pyrroline 1-oxide (XXIII) as a colourless oil (50%) which crystallised on standing, m. p. 46 - 47° (lit. 32 - 34°,[2] 47 - 48°[52]). The picrate, recrystallised from n-butanol, had a m. p. 140 - 140.5° (lit.[44] 140 - 140.5°).

2.11 (f) 2,4,4-Trimethyl-1-Pyrroline 1-Oxide. (XXV).

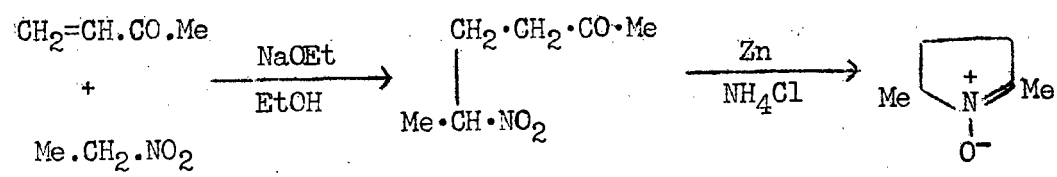


(XXVI) (XXV)

4,4-Dimethyl-5-nitropentanone (XXVI) was obtained by the method of Smith and Engelhard[130] in 60% yield as a colourless oil, b. p. 84 - 85°/2 mm. (lit.[130] 109 - 110°/11mm)which became pale yellow on standing. The 2,4-DNP had a m. p. 111 - 112° (from dil. ethanol).

The nitropentanone (XXVI) upon reduction by the method of Bonnett, Brown, Clark, Sutherland and Todd[2] yielded 2,4,4-trimethyl-1-pyrroline 1-oxide, b. p. 70°/0.4 mm. (lit.[2] 72°/0.4 mm.) in 72% yield. The picrate (ex n-butanol) had m. p. 110 - 111°(lit.[2] 111°).

2.11 (g) 2,5-Dimethyl-1-Pyrroline 1-Oxide. (XXVII).

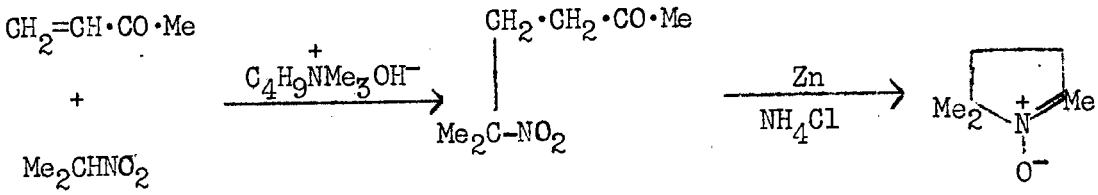


(XXVIII) (XXVII)

Following the method of Schechter, Ley and Zeldin,[131] 5-nitro-2-hexanone (XXVIII) was obtained in 38% yield as an almost colourless liquid, b. p. 112 - 114°/6 mm., 82°/1 mm. (lit.[131] 115 - 117.5°/10 mm.). The 2,4-DNP (recrystallised from 96% ethanol) had a m. p. 96.5 - 97.5° (lit.[131] 95.5 - 96°).

The nitro-hexanone (20.3 g, 0.14 mole) and ammonium chloride (6.1 g) in water (180 ml.) were vigorously stirred with external cooling while zinc dust (30.4 g) was added over a period of 2 hr, the temperature being kept below 15°. After stirring for a further 2 hr, the zinc oxide was filtered off and washed with warm water (200 ml.). The combined filtrates were concentrated in a rotary vacuum evaporator below 40° to a pale yellow oil. This latter oil was taken up in chloroform (100 ml.) and dried (Na_2SO_4). After removing both desiccant and solvent, fractional distillation yielded 2,5-dimethyl-1-pyrroline-1-oxide as a pale yellow oil (9.98 g, 63%) b. p. 72°/0.7 mm. [Found: C, 63.3; H, 9.9; N, 11.9. Calc. for $C_6H_{11}NO$: C, 63.3; H, 9.7; N, 12.4%] $\lambda_{max.}$ (ethanol) 229 mμ (ε 9000), $\nu_{max.}$ (film) 1610, 1231 $cm.^{-1}$ The most satisfactory method for preparing the picrate was by treating the nitrone (0.90 g) with a saturated aqueous picric acid solution (113 ml., 1 mole equivalent) and evaporating to dryness $<40°$. The dark oil on trituration with n-butanol crystallised. Several recrystallisations from the same solvent gave the picrate, m. p. 58 - 58.5°. [Found: C, 42.4; H, 4.3; N, 16.1. Calc. for $C_6H_{11}NO.C_6H_3N_3O_7$: C, 42.1; H, 4.1; N, 16.4%].

2.11 (h). 2,5,5-Trimethyl-1-Pyrroline 1-Oxide. (XXIX).

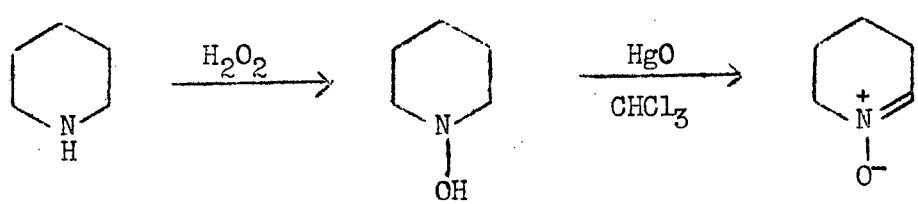


(XXX) (XXIX)

5-Methyl-5-nitro-2-hexanone (XXX) was obtained in 75% yield following the method of Shechter and his co-workers[131] as a pale yellow liquid, b. p. 65 - 66.5°/0.3 mm., from methyl vinyl ketone (redistilled before use and collecting the fraction boiling at 36 - 38°/160 mm.) and 2-nitropropane (b. p. 118 - 118.5°). The 2,4-DNP (recrystallised from ethanol) had m. p. 128 - 129° (lit.[131] 130.5 - 131.5°).

Reduction of the nitro-hexanone (XXX) according to the procedure of Delpierre and Lamchen[44] gave 2,5,5-trimethyl-1pyrroline 1-oxide (XXIX), b. p. 58 - 60°/0.4 mm. (lit. 71 - 72°/2 mm.) in 81% yield. The picrate, from aqueous picric acid and recrystallised from n-butanol-cyclohexane, had a m. p. 99.5 - 100.5° (lit.[44] 98°).

2.11 (i). Δ^1-3,4,5,6-Tetrahydropyridine 1-Oxide. (XXXI).



(XXXII) (XXXI)

1-Hydroxypiperidine, b. p. 53 - 55°/1 mm., was obtained in 9% yield from piperidine (170 g) and 30% hydrogen peroxide (227 ml.).[132] This was purified by converting to the hydrogen oxalate (m. p. 74 - 76°), decomposing the latter with excess of sodium hydroxide and subjecting the aqueous solution to continuous ether extraction for 24 hr after which time the aqueous phase gave no red colour with alkaline triphenyltetrazolium chloride reagent.[57] The dried (anhyd. K_2CO_3) ether solution on evaporation yielded pure 1-hydroxypiperidine (5.6 g, 3%) as a colourless oil, b. p. 80 - 81°/15 mm. (lit. 93°/15 mm.,[132] 89°/23 mm.[20]), which crystallised to a white solid, m. p. 38 - 39° (lit.[20] 39 - 40°).

Oxidation of 1-Hydroxypiperidine.

(i) In chloroform.

An A.R. chloroform solution (40 ml.) containing 1-hydroxypiperidine (1.00 g, 10 mmole) was treated with yellow mercuric oxide (4.50 g, 21 mmole) and mechanically agitated. After 30 minutes, the insoluble material was filtered off and washed with A.R. chloroform and the IR spectrum of the dried ($MgSO_4$) solution showed bands at 3320, 1624, 1100, 992 and 886 $cm.^{-1}$ (cf. the heterocyclic nitrone (IV), Section 1.122).

(ii) In water.

An aqueous solution containing redistilled 1-hydroxypiperidine (53.3 mg, 0.528 mmole/100 ml.) was prepared, i.e. 5.28×10^{-3} molar.

Into a dry stoppered flask was pipetted the solution (50 ml., 0.264 mmole) and yellow mercuric oxide (0.120 g, 0.56 mmole) was added.

After mechanically agitating the mixture for 2 hr, the grey-green mercury compounds were centrifuged out.

Thin layer chromatography of the clear supernatant [see Section 1.122 (b)] showed the oxidation to be complete. The clear supernatant was pipetted (8.69 ml.) into a 25.0 ml. flask and diluted to mark with water. This solution was examined as follows:

(α) Percentage recovery.

Into a clean, dry cuvette were pipetted the solution (1.00 ml.) and 0.0382 M-$FeCl_3$ solution (2.00 ml.). At the same time, into a second cuvette was pipetted 1.272×10^{-3} M-1-hydroxypiperidine solution obtained from (ii) above (1.0 ml.) and 0.0382 M-$FeCl_3$ solution (2.00 ml.). Each solution was carefully mixed and after half an hour the visible spectrum of each was examined with the aid of the scale expander against a reference cell containing water (1.0 ml.) and 0.0382 M-$FeCl_3$ (2.00 ml.). Both solutions showed a broad band at $\lambda_{max.}$ 500 mμ. The absorbance at 500 mμ for each solution was as follows:

Solution:	Absorbance*
1-hydroxypiperidine	0.362
Δ^1-tetrahydropiperidine 1-oxide	0.363

* Corrected for cuvette blank.

These figures indicated 100% recovery of the cyclic nitrone (XXXI), and the second value gives the molar absorbance at 500 mμ as 85(6).

(β) UV spectrum of the cyclic nitrone (XXXI) alone.

1.00 ml. of the solution was diluted to 50 ml. The solution showed a single absorption band at $\lambda_{max.}$ 229 mμ, (absorbance 0.215, whence $\varepsilon = 8400$).

2.11 (j). Δ^3-Dihydro-1,4-Oxazine 4-Oxide. (IV).

Aqueous solutions of the heterocyclic nitrone (IV) were prepared as described in section 1.122 (b).

2.12. Preparation of Cyclic hydroxylamines.

The preparations of the following cyclic hydroxylamines have been referred to in the sections indicated:-

1-Hydroxypyrrolidine (XV), see section 2.11 (a).

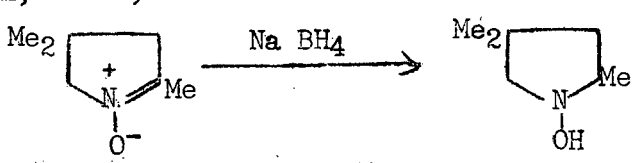
2,2,4,4-Tetramethyl-1-hydroxypyrrolidine (XXIV), see section 2.11 (e).

1-Hydroxypiperidine (XXXII), see section 2.11 (i).

4-Hydroxymorpholine (III), see section 1.11.

2,4,4-Trimethyl-1-hydroxypyrrolidine. (XXXIII).

Bonnett, Brown, Clark, Sutherland and Sir A. Todd.[2a]

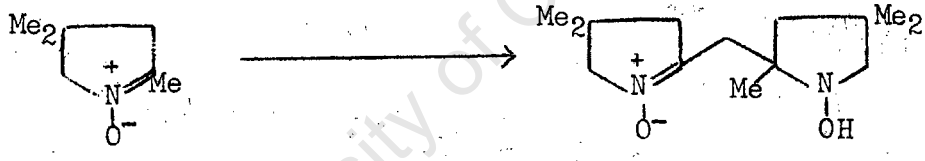


(XXV) (XXXIII)

2,4,4-Trimethyl-1-pyrroline 1-oxide (2.0 g) in water (10 ml.) was treated with sodium borohydride (0.8 g). After 2 days at room temp.

the excess sodium borohydride was destroyed by chilling the solution in an ice bath and adding glacial acetic acid dropwise. The solution was saturated with anhydrous potassium carbonate and extracted with ether. The dried (Na_2SO_4) ether extract gave an oil (1.6 g) from which 3 fractions were collected in a short path still, over an oil bath temperature range 65 - 75°/0.3 mm. The fractions each gave a deep red colour with alkaline TTC reagent.[57] The second fraction was redistilled before use. The cyclic nitrone (XXV) was shown to be absent by T.L.C. on silica gel in chloroform-isopropanol-acetic acid (4 : 4 : 1) and exposing the chromatoplate to iodine vapour.

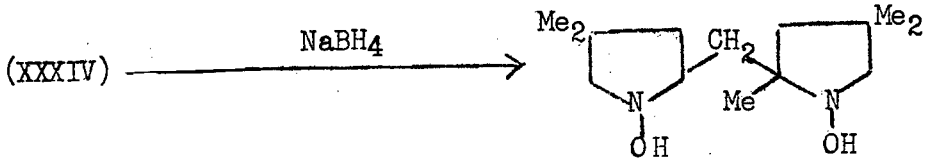
2-(1-Hydroxy-2,4,4-trimethylpyrrolidin-2-ylmethyl)-4,4-dimethyl-1-pyrroline 1-oxide. (XXXIV).



(XXXIV)

The nitrone-hydroxylamine (XXXIV) was isolated from an old sample of 2,4,4-trimethyl-1-pyrroline 1-oxide which had largely undergone spontaneous dimerisation,[5] by filtering off the crystalline solid and washing with a 1 : 1 solution of benzene-pet. ether (b. p. 40 - 60°). Recrystallisation from the same solvent gave needles, m. p. 110 - 111° (lit.[5] 115°).

2(1-Hydroxy-2,4,4-trimethylpyrrolidin-2ylmethyl)-4,4-dimethyl-1-hydroxypyrrolidine. (XXXV).

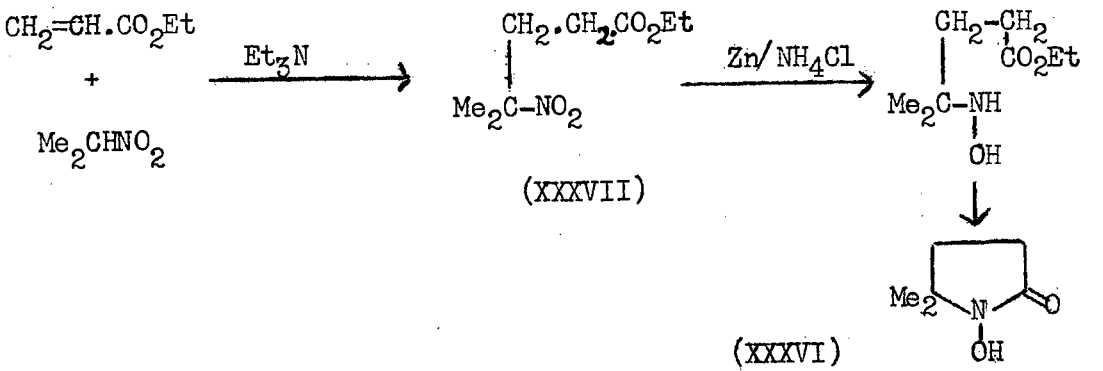


(XXXV)

The nitrone-hydroxylamine (XXXIV)(1.00 g, 4 mmole) in water (30 ml.) was treated with sodium borohydride (1.00 g). The crystalline dihydroxylamine separated out of solution after 2 hr. After 4 days, the crystalline material (0.55 g, 55%) was filtered off and washed with ice cold water. From several recrystallisations (pet. ether, 40 - 60°) was obtained the dihydroxylamine (XXXV) as a mixture of diastereoisomers, m. p. 151 - 155°. [Found: C, 65.7; H, 11.0 ; N, 10.7. Calc. for $C_{14}H_{28}N_2O_2$: C, 65.6; H, 10.9; N, 10.9%].

2.13. Preparation of cyclic hydroxamic acids.

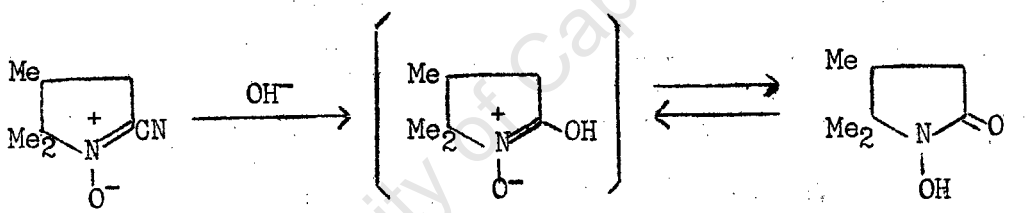
2.131. 1-Hydroxy-5,5-dimethyl-2-pyrrolidone. (XXXVI).



(cf. Bonnett, Brown, Clark, Sutherland and Sir A. Todd.[2])

Using ethyl acrylate instead of the methyl ester, ethyl 4-methyl-4-nitro-pentanoate (XXXVII) was isolated in 80% yield (b. p. 96 - 98°/ 1.5 mm.). Reduction of this nitro-ester by zinc dust in aqueous solution buffered with ammonium chloride gave the cyclic hydroxamic acid (XXXVI), m. p. 81 - 82° (from benzene-cyclohexane)(lit.[2] 83°) in 35% yield [$C_6H_{11}NO_2$ requires N, 10.9. Found: N, 10.85%] $\nu_{max.}$ (nujol) 3375, 1703, 1667 $cm.^{-1}$; the compound gave a deep red colour with 5% aqueous ferric chloride.

2.132. 1-Hydroxy-4,5,5-trimethyl-2-pyrrolidone. (XXII).



(XXI) (XXII)

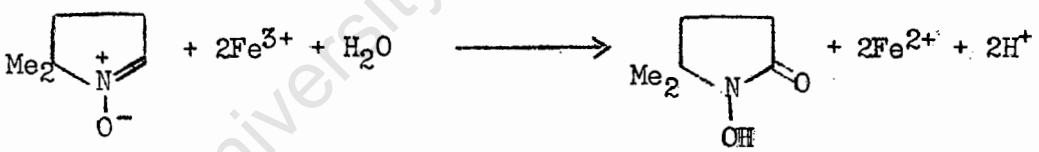
Alkaline hydrolysis of the cyano-nitrone (XXI) resulted in some nucleophilic displacement of the cyano group, yielding the cyclic hydroxamic acid (XXII) [section 2.11 (d)] as plates (from benzene-cyclohexane) m. p. 101 - 102° (lit.[2] 101 - 102°) $\nu_{max.}$ (nujol) 3370, 1707 and 1667 $cm.^{-1}$, which gave a deep red colour with 5% aqueous ferric chloride.

2.2. Oxidation of Cyclic Nitrones and Related Compounds by Ferric Chloride: Stoichiometric and Product Studies.

In this section reagent grade ferric chloride hexahydrate was used in all oxidations, and the extent of oxidation of each compound was determined by titrating a suitable aliquot of the reacting solution for ferrous ion concentration. The colour of the solutions in all cases disappeared on adding to 20% sulphuric acid, and the solution was titrated against 0.1000N-$K_2Cr_2O_7$ solution (prepared from oven-dried, reagent grade potassium dichromate), using barium diphenylamine sulphonate as indicator.[133] Titration figures quoted have been corrected for a blank titration of the ferric chloride solution alone.

2.21. Oxidation of Cyclic Aldonitrones by Ferric Chloride.[63]

2.211. 5,5-Dimethyl-1-Pyrroline 1-Oxide. (XVI).

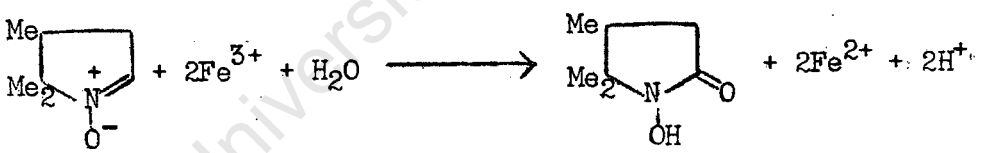


(XVI) (XXXVI)

5,5-Dimethyl-1-pyrroline 1-oxide (0.313 g, 2.77 mmole) and 60% ferric chloride (7.5 ml., 27.7 mmole) were diluted to 100 ml. and heated at 60° on a water bath for 1 hr. A 5 ml. aliquot was titrated for Fe^{2+}. [Fe^{3+} reduced: Found, 5.71 mmole. Theory, 5.54 mmole]. The intense blue-green solution ($\lambda_{max.}$ 543 mμ) was cooled and treated with an excess of 5N-NaOH and the precipitated iron hydroxides were centrifuged off. The insoluble material was washed with 0.4N-NaOH

(6 x 25 ml.), each washing being followed by further centrifugation. The combined centrifugates were concentrated $<60^{\circ}$ (rotary vacuum evaporator) to approx. 30 ml., acidified (conc. HCl) and continuously extracted with chloroform overnight, after which time the aqueous phase gave no blue colour with ferric chloride. The dried (Na_2SO_4) chloroform extract on removal of the desiccant and solvent yielded a dark oil which crystallised out on leaving in the refrigerator. The crude mass was transferred to a porous plate to soak up oily material, and, on recrystallisation from n-hexane, gave 1-hydroxy-5,5-dimethyl-2-pyrrolidone (0.286 g, 80%), m. p. 85 - 86°, undepressed by admixture with an authentic sample[2] (section 2.132). The IR spectrum, $\nu_{max.}$ (nujol) 3375, 1703 and 1667 $cm.^{-1}$, was identical with that of the authentic material.

2.212. 4,5,5-Trimethyl-1-Pyrroline 1-Oxide. (XVII).

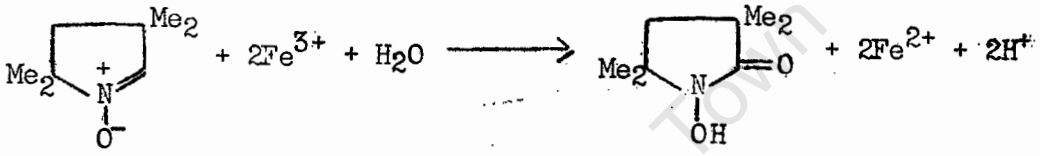


(XVII) (XXII)

A solution of 4,5,5-trimethyl-1-pyrroline 1-oxide (1.52 g, 12 mmole) and ferric chloride (120 mmole) diluted to 500 ml. rapidly became intensely blue. The solution was left 1½ hr. at room temp. [Fe^{3+} reduced: Found, 24.0 mmole. Theory, 24.0 mmole.] The solution, on working up as described in section 2.211, yielded a dark oil which crystallised overnight in the refrigerator.

Recrystallisation (pet. ether, b. p. 40 - 60°) gave 1-hydroxy-4,5,5-trimethyl-2-pyrrolidone (0.93 g, 68%), m. p. 101 - 102°. [$C_7H_{13}NO_2$ requires: C, 58.9; H, 9.10; N, 9.80. Found: C, 58.7; H, 9.32; N, 9.3%] $\nu_{max.}$ (nujol) 3370, 1707 and 1667 cm.$^{-1}$ The product was shown to be identical with the authentic material[2] (section 2.132) by mixed melting point and by comparison of IR spectra.

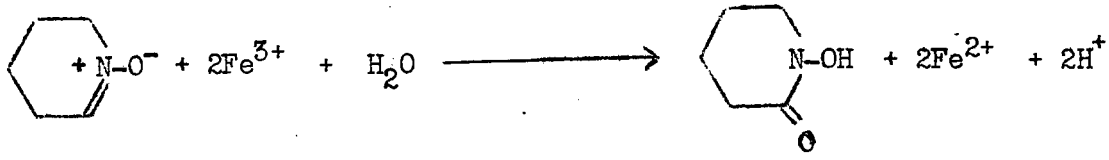
2.213. 3,3,5,5-Tetramethyl-1-Pyrroline 1-Oxide. (XXIII).



(XXIII) (XXXVIII)

3,3,5,5-Tetramethyl-1-pyrroline 1-oxide (0.56 g, 4.0 mmole) and ferric chloride (40 mmole) were diluted to 250 ml. The solution was left overnight at room temperature. [Fe^{3+} reduced: Found, 8.0 mmole. Theory, 8.0 mmole.] Upon working up the solution as before [section 2.211], pure 1-hydroxy-3,3,5,5-tetramethyl-2-pyrrolidone (XXXVIII) was obtained (0.39 g, 69%) as prisms (from n-hexane) which change to feather-like crystals at 90 - 95°, finally melting 111 - 112°. [Found: C, 61.3; H, 9.5; N, 8.7. Calc. for $C_8H_{15}NO_2$: C, 61.2; H, 9.5; N, 8.9%] $\nu_{max.}$ (nujol) 2720, 2670, 2615 (bonded -OH)[3a,f], and 1680 cm.$^{-1}$ (hydroxamic C=O).[64,65] The compound gave an immediate intense purple colour with ferric chloride.

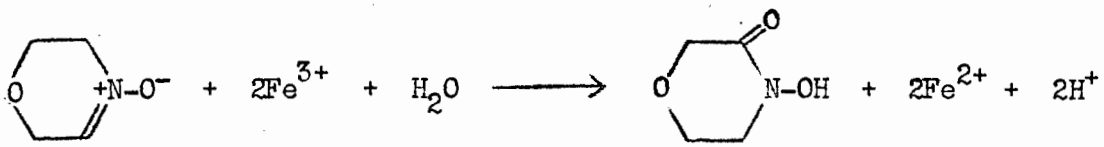
2.214. Δ^1-3,4,5,6-Tetrahydropyridine 1-Oxide.



(XXXI) (XXXIX)

1-Hydroxypiperidine (1.238 g, 12.3 mmole) in water (50 ml.) was shaken with yellow mercuric oxide (5.5 g) for ½hr. The insoluble material was filtered off and washed with water (50 ml.). The combined filtrates were treated with 60% $FeCl_3$ (35 ml., 123 mmole). The intensely purple solution was stirred for 1 hr. The resulting solution was treated with 5N-NaOH (80 ml.) and the iron hydroxides removed by centrifugation and washed with 0.5N-NaOH (3 x 50 ml.). The combined centrifugates were neutralised (HCl) and vacuum evaporated nearly to dryness. 5N-HCl was added (to pH 2) and the solution extracted overnight into chloroform. The dried (Na_2SO_4) extract yielded a dark oil (0.84 g) which deposited crystals after several weeks when the flask was left in the refrigerator. The crude mass was transferred to a porous plate and the crystalline solid was re-sublimed twice (60°/20 mm.) to give 1-hydroxy-2-piperidone (XXXIX) as colourless needles, m. p. 57 - 58° (lit.[88] 55 - 57°). [$C_5H_9NO_2$ requires C 52.2; H, 7.83; N, 12.2. Found: C, 52.4; H, 7.9; N, 12.1%] $\nu_{max.}$ (nujol) 3340, 3120, 1635, 1332, 1160, 1090, 920 $cm.^{-1}$ The compound gave an intense wine-red colour with 5% ferric chloride solution.

2.215. Δ^3-Dihydro-1,4-Oxazine 4-Oxide.

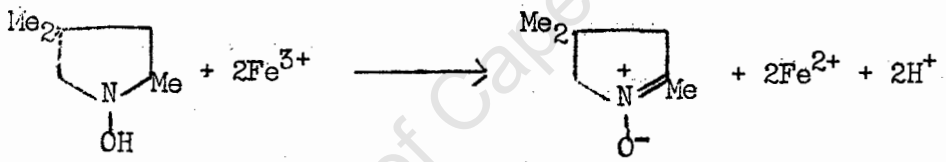


(IV) (VIII)

(see section 1.33 of this Part).

2.22. Cyclic Secondary Hydroxylamines.

2.221. 1-Hydroxy-2,4,4-trimethylpyrrolidine.

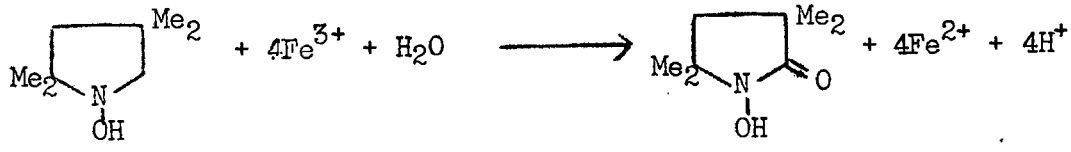


(XXIV) (XXV)

1-Hydroxy-2,4,4-trimethylpyrrolidine (0.1947 g, 1.53 mmole) and 60% A.R. ferric chloride solution (5 ml.) were diluted together to 25 ml. and left at room temperature. [Fe^{3+} reduced: Found, (5 min.), 2.88; (25 min.) 3.06 mmoles. Theory, 3.06 mmoles]. The solution, which had a slight green colour, was treated with 25% ammonia solution (9 ml.) and the precipitated iron hydroxides were centrifuged off and washed once with 5N-NH_4OH (20 ml.). The combined centrifugates were concentrated to about 10 ml., saturated with potassium carbonate (anhydrous) and extracted with chloroform for 2 days. The dried (Na_2SO_4) extract on evaporation gave a dark oil which on distillation in a short path still yielded 2,4,4-trimethyl-1-pyrroline 1-oxide

(0.10 g)(oil bath temp. 120°/0.2 mm.), characterised as its picrate, m. p. and mixed m. p. 110 - 111°, which gave an IR spectrum (nujol) identical with the authentic picrate of (XXV).

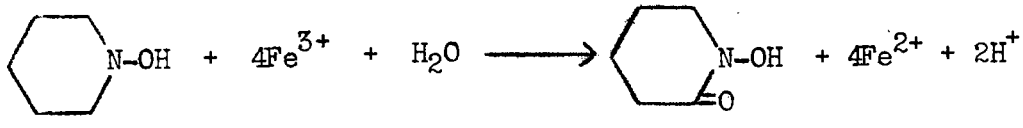
2.222. 1-Hydroxy-2,2,4,4-tetramethylpyrrolidine. (XXIV).



(XXIV) (XXXVIII)

1-Hydroxy-2,2,4,4-tetramethylpyrrolidine (0.7697 g, 5.38 mmole) suspended in water (50 ml.) was warmed to 70° with ferric chloride (107 mmole) in water (29 ml.) for 3 hr. The blue green solution was diluted to 100 ml. [Fe^{3+} reduced: Found, 21.2 mmole. Theory, 21.5 mmole]. The iron salts were precipitated as their hydroxides and removed, and the solution worked up as described earlier [section 2.212]. 1-Hydroxy-3,3,5,5-tetramethyl-2-pyrrolidone (XXXVIII)(0.50 g) was obtained as prisms (from n-hexane) m. p. 111 - 112°, undepressed by admixture with the cyclic hydroxamic acid obtained from the similar oxidation of 3,3,5,5-tetramethyl-1-pyrroline 1-oxide [section 2.213] $\nu_{max.}$ (nujol) 2720, 2670 and 2620 (bonded -OH), 1680 $cm.^{-1}$ The IR spectra of the two samples of (XXXVIII) were identical.

2.223. 1-Hydroxypiperidine (XXXII).



(XXXII) (XXXIX)

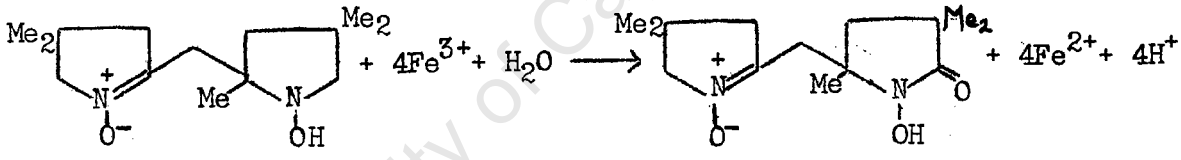
1-Hydroxypiperidine (1.279 g, 12.7 mmole) and ferric chloride (127 mmole) were diluted to 500 ml. and left at room temperature. The solution rapidly developed a reddish-purple colour. [Fe^{3+} reduced after 1 hr.: Found, 49.3 mmole. Theory, 50.8 mmole].

The product of the oxidation, presumed to be the hydroxypiperidone (XXXIX) was not isolated.

2.224. 4-Hydroxymorpholine. (III).

[See section 1.33.].

2.225. 2(1-Hydroxy-2,4,4-trimethylpyrrolidin-2-ylmethyl)-4,4-dimethyl-1-pyrroline 1-oxide. (XXXIV).

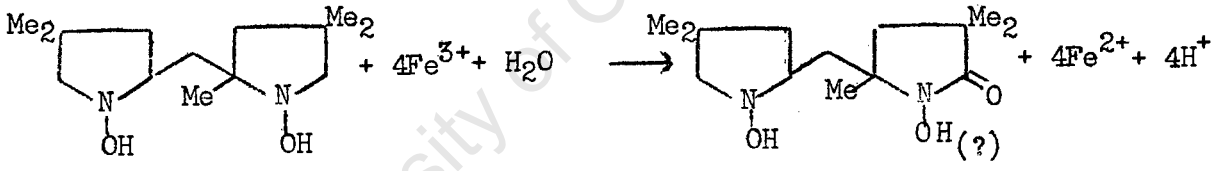


(XXXIV) (XL)

The nitrone-hydroxylamine (XXXIV)(1.089 g, 4.29 mmole) and ferric chloride (83.8 mmole) were diluted to 500 ml. and left at room temperature. A purple colour developed rapidly. [Fe^{3+} reduced: Found, 11.5 mmole ($\frac{1}{2}$ hr.), 18.0 mmole (26 hr.). Theory, 17.2 mmole.] The solution (235 ml.) was worked up as before (section 2.212) and the dry (Na_2SO_4) chloroform extract yielded on vacuum evaporation an oil (0.52 g) which slowly crystallised in the refrigerator. The oily crystalline mass was transferred to a piece of porous plate. The solid residue on recrystallisation (from ethyl acetate) yielded 2(1-hydroxy-2,4,4-trimethyl-5-oxopyrrolidin-2-ylmethyl)-4,4-dimethyl-1-pyrroline 1-oxide

(XL) as plates, m. p. 171 - 172° [Found: C, 62.8; H, 8.73; N, 10.4. Calc. for $C_{14}H_{24}N_2O_3$: C, 62.7; H, 8.95; N, 10.44%.] [Mol. wt.: (Sucharda-Bobranski-Schmidt ebullioscopic method[117]) 13.00 mg in A.R. chloroform (8.94 g) raised the b. p. 0.022°. Found: 256. Calc. for $C_{14}H_{24}N_2O_3$: 268] $\lambda_{max.}$ (95% ethanol) 237 mμ (ε 9700) $\nu_{max.}$ (nujol) 3360 (intramolecular bonded -OH)[32f], 1698 (hydroxamic acid C=O),[64,65] and 1620 cm.$^{-1}$ (nitrone $C=\overset{+}{N}\langle$ $\overset{}{O}^-$).[29] Proton magnetic resonance spectrum showed singlets at τ 8.82 (6-H), 8.76 (6-H), 8.60 (3-H), and 8.11 (2-H), and two unresolved multiplets centred at τ 7.35 (4-H) and 6.2 (2-H).

2.226. 2(1-Hydroxy-2,4,4-Trimethylpyrrolidin-2ylmethyl)-4,4-Dimethyl-1-Hydroxypyrrolidine. (XXXV).



(XXXV) (XLI)

The dihydroxylamine (XXXV)(51.30 mg, 0.201 mmole) was shaken with A.R. ethanol (200 ml.) until the solid had dissolved, and the solution diluted to 500 ml. Aliquots (25 ml.) of the solution were pipetted into flasks together with 0.30 M-$FeCl_3$ (3.26 ml.) and water (5.0 ml.), the time of addition being recorded in each case. After intervals of time, 20% sulphuric acid (about 20 ml.) and 85% phosphoric acid (1 ml.) were added to each flask and the contents were rapidly titrated against 0.1000 N-$K_2Cr_2O_7$ as before. In each case the solution rapidly turned

blue after addition of the oxidant. The results from the titrations obtained were as follows:-

Initial (XXXV) in each flask, 0.0100 mmoles.

Time (min.):	1	2	5	10	60	120	(18 hr.)
Fe^{3+} reduced, 10^2 x mmoles:	2.8	3.6	3.8	3.9	3.9	4.4	4.9

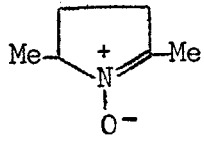
Theory for equation above, 0.040 mmoles Fe^{3+}.

A total of 0.0603 mmoles Fe^{3+} would be required for complete oxidation to the nitrone-hydroxamic acid (XL)(Section 2.225).

The oxidation product was not isolated.

2.23. Cyclic Ketonitrones and Related Compounds.

2.231. 2,5-Dimethyl-1-Pyrroline 1-Oxide. (XXVII).



$$+ 4Fe^{3+} + 1\tfrac{1}{2}H_2O \longrightarrow \underset{\text{(XLII)}}{Me.CO.CH_2.CH_2.CO.Me} + 4Fe^{2+} + \tfrac{1}{2}N_2O + 4H^+$$

(XXVII)

2,5-Dimethyl-1-pyrroline 1-oxide (5.32 g, 47.1 mmole) and ferric chloride (370 mmole) were diluted (1 l.), mixed and left at 30°. 5 ml. aliquots were titrated at intervals. The results are shown in the table below.

Initial [nitrone] = 0.0471M

Time (hr.)	$[Fe^{2+}]$ formed M	$[Fe^{2+}]$/initial [nitrone]
1	0.021	0.46
2.5	0.038	0.80
18	0.096	2.04
44	0.119	2.52
(6 days)	0.142	3.02
(16 days)	0.160	3.86 (Theory: 4.00)

Isolation of nitrous oxide:

From the solution which showed gas bubbles was extracted a sample of the gas (see Appendix 2 for experimental details). This was dried over anhydrous calcium chloride. The dry sample was then drawn into a highly evacuated IR gas cell (10 cm) fitted with sodium chloride plates. The IR spectrum showed bands at 2230 and 1270 $cm.^{-1}$ (N_2O).[32e,66] The spectrum of an authentic sample of nitrous oxide in the same gas cell had identical bands.

Isolation of hexane-2,5-dione, (XLII).

The solution (775 ml.) after removal of the nitrous oxide was treated with 5N-sodium hydroxide and the precipitated iron hydroxides were centrifuged and washed. The combined centrifugates were subjected to continuous ether extraction for 2 days. The dried (Na_2SO_4) ether extract on evaporation yielded a dark oil from which was recovered by fractional distillation hexane-2,5-dione (1.54 g), b. p. 78 - 80°/15 mm. (lit.[134] 78 - 79°/15 mm.). The bis-2,4-DNP had m. p. 256 - 257°

(from dimethylformamide-ethanol) undepressed on admixture with the bis-2,4-DNP from an authentic sample of hexane-2,5-dione. The IR spectra (nujol) of the two bis-2,4-DNP- samples were also shown to be identical.

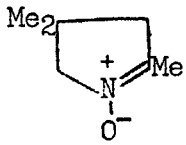
Examination of the products by Gas Liquid Chromatography (G.L.C.)

In a second similar experiment in which the reaction solution was kept at 50 - 55°, the equivalent of 4.05 mole Fe^{3+} had been reduced per initial mole of nitrone (XXVII). The solution was worked up as before and the dried ether extract was concentrated to 3 ml. by distilling off the ether through a 10" fractionating column packed with porcelain "saddles". A sample of the concentrate was examined cursorily by G.L.C. analysis on the column described earlier (page 105) at two different temperatures. The retention times of the significant peaks are shown, together with assignments made by comparison with the retention times of the authentic samples obtained on the same column under identical conditions.

Column temp. 55°		Column temp. 150°	
Retention time.	Assignment	Retention time.	Assignment
min. sec.		min. sec.	
2 . 4	CH_3CHO		
3 . 40 (v.wk.)	$CH_3.CO.CH_3$	6 . 3	$Me{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}Me$
5 . 25	CH_3OH	7 . 57	?
12 . 28	?		

(v.wk.) = very weak signal.

2.232. 2,4,4-Trimethyl-1-Pyrroline 1-Oxide. (XXV).



$$+ 6Fe^{3+} + 2\tfrac{1}{2}H_2O \longrightarrow Me_2C(CO_2H).CH_2.CO.CH_3 + \tfrac{1}{2}N_2O + 6Fe^{2+} + 6H^+$$

(XXV) (XLIII)

A solution containing 2,4,4-trimethyl-1-pyrroline 1-oxide (XXV) (3.8 g, 30 mmole) and ferric chloride (200 mmole) diluted to 250 ml. was heated on a steam bath. Aliquots (1 ml.) were withdrawn at occasional intervals and were titrated for ferrous ion concentration. The results are shown in the table below.

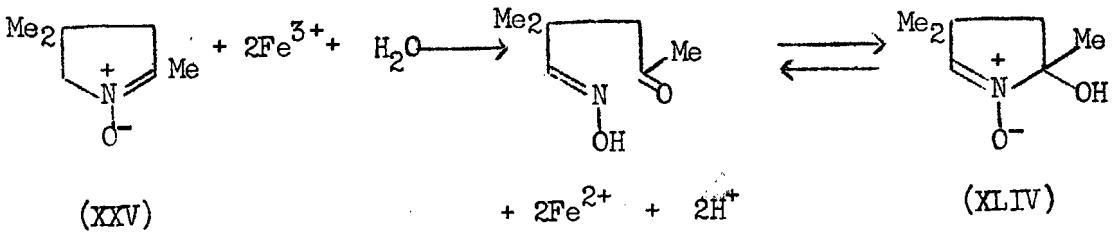
Initial [nitrone] = 0.120M

Time (hr.)	$[Fe^{3+}]$ reduced (M)	$[Fe^{2+}]$ / initial [nitrone]
0.5	0.360	3.0
1.0	0.456	3.8
2.0	0.576	4.8
3.5	0.672	5.6
5.0	0.720	6.0
6.0	0.732	6.1 (Theory, 6.0)

After 6 hr. gas isolated from the solution (see Appendix 2 for details) after drying ($CaCl_2$) was introduced into a gas cell (NaCl plates) having a 10 cm. path length. The IR spectrum showed bands at 2220 and 1275 $cm.^{-1}$, characteristic for nitrous oxide.[32e,66] The solution was concentrated in a rotary vacuum evaporator to approx. 40 ml., basified with 5N-sodium hydroxide and centrifuged.

The centrifugates and washings were finally clarified by filtration through a cellulose pad. The filtrate was extracted with ether (3 x 80 ml.) to remove organic basic products, the aqueous phase acidified (conc. hydrochloric acid), vacuum evaporated to approx. 50 ml. and subjected to continuous ether extraction overnight. The dry (Na_2SO_4) ethereal extract yielded a dark oil on evaporation which failed to crystallise when left in the refrigerator and on trituration. A portion of the oil (approx. 0.5 g) on heating with an ethanolic solution of 2,4-dinitrophenylhydrazine containing hydrochloric acid, deposited a crude 2,4-DNP on cooling. On recrystallisation from dimethylformamide-ethanol, mesitonic acid-2,4-DNP was obtained as orange needles, m. p. 214 - 215°. Its identity was established by the melting point of the admixture with the 2,4-DNP of an authentic sample of mesitonic acid (XLIII)[91,92] which showed no depression, and by the comparison of the IR spectra of the two samples. Furthermore, the oil (0.25 g) on addition to a solution of semicarbazide hydrochloride (0.5 g) and crystalline sodium acetate (0.75 g) in water (5 ml.), followed by heating and cooling deposited the semicarbazone of mesitonic acid, which gave needles (from 96% ethanol), m. p. 191 - 192°, undepressed when mixed with an authentic specimen.[91,92] [$C_8H_{15}N_3O_3$ requires N, 20.9%. Found: N, 20.7%]. The IR spectrum of the isolated semicarbazone was identical with that of synthetic mesitonic acid semicarbazone.

Isolation of the intermediate oxime.



(XXV) + $2Fe^{2+}$ + $2H^{+}$ (XLIV)

2,4,4-Trimethyl-1-pyrroline 1-oxide (2.88 g, 22.7 mmole) and ferric chloride hexahydrate (63 g, 23 mmole) were dissolved in water (100 ml.) and diluted to 250 ml. at 40°. 1 ml. aliquots were titrated at intervals for ferrous ion concentration.[133] The results obtained are shown below:

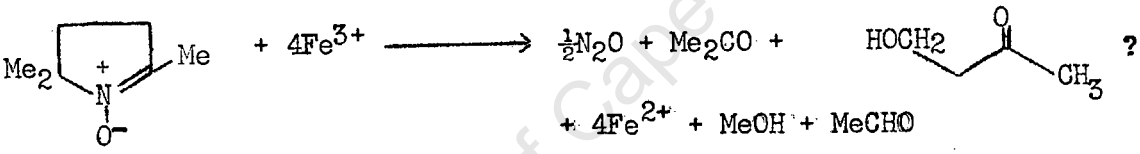
Initial $[(XXV)] = 0.0908M$

Time (hr.)	$[Fe^{3+}]_{reduced}$ (M)	$[Fe^{2+}]$ / initial $[(XXV)]$
2	0.044	0.48
21	0.121	1.33
46	0.165	1.82
55	0.178	1.96 (Theory, 2.00)

The reaction was stopped by adding 5M-ammonium hydroxide in excess of that required to precipitate all the iron salts as hydroxides (170 ml.). The insoluble hydroxides were centrifuged off and washed with 0.5M-NH_4OH (total 1 l.). The combined centrifugates were concentrated (130 ml.) in a rotary vacuum evaporator and extracted with chloroform (200 ml.). The dried (Na_2SO_4) organic phase on evaporation gave a yellow-brown oil (1.96 g) which on cooling crystallised as needles spontaneously and exothermically. The cooled mass was transferred to a porous plate.

The white solid on recrystallisation (from ethyl acetate-light pet. ether, b. p. 40 - 60°) gave 5'-hydroxy-3,3,5-trimethyl-1-pyrroline 1-oxide (XLIV) as colourless rhombs, m. p. 136 - 137° [Found: C, 58.9; H, 9.2; N, 9.96. Calc. for $C_7H_{13}NO_2$: C, 58.75; H, 9.09; N, 9.79%] $\nu_{max.}$ (nujol) 2730 broad (chelated -OH), 1635 $cm.^{-1}$ (hydrogen bonded? $-\overset{|}{C}=\overset{+}{\underset{|}{N}}-O^-$), $\lambda_{max.}$ (95% ethanol) 231 mμ (ε 10,000). P.m.r. spectrum showed signals at τ 8.85. (6H), 7.94 quartet (J = 1.5 c.p.s., 3.5H), 7.55 m (2H), 4.92 (H), and 0.75 (0.6H).

2.233. 2,5,5-trimethyl-1-pyrroline 1-oxide. (XXIX).



(XXIX)

2,5,5-Trimethyl-1-pyrroline 1-oxide (XXIX)(1.086 g, 8.55 mmole) and 60% ferric chloride solution (48 ml., 170 mmole) were diluted together to 250 ml. and the solution was placed in a water bath maintained between 50 and 55°. The course of the reaction was followed titrimetrically[133] and the results obtained are reported below.

Initial [(XXIX)] = 0.0342M

Time (hr.)	$[Fe^{3+}]$ reduced (M)	$[Fe^{2+}]$/initial [nitrone]
22	0.067	1.96
69	0.087	2.56
117	0.116	3.4
141	0.127	3.7
165	0.145	4.25

After 7 days, a sample of gas was isolated from the solution (method described in Appendix 2), dried ($CaCl_2$) and introduced into an evacuated IR gas cell (NaCl plates) of path length 10 cm. Absorption bands at 2220 and 1275 $cm.^{-1}$ confirmed the presence of N_2O.[32e, 66]

The residual solution was treated with 25% ammonium hydroxide (50 ml.) and centrifuged. The supernatant was subjected to continuous ether extraction for 2 days. The dried (Na_2SO_4) extract was concentrated by distilling off the ether *via* a 10" fractionating column packed with porcelain "saddles". The concentrate (4 ml.) was examined by G.L.C. (for details, see page 105) at two different temperatures. The retention times of the significant peaks obtained are recorded below. Assignments were made by comparison of retention times of the known samples on the same column under identical conditions.

Column temp: 55°		Column temp: 150°	
Retention time.	Assignment	Retention time.	Assignment
min. sec.		min. sec.	
1.. 53	?	1 . 6	$CH_3.CO.CH_3$
2 . 3	CH_3CHO	2 . 19	?
3 . 42	$CH_3.CO.CH_3$	4 . 35	?
5 . 42	CH_3OH	7 . 0	?
12 . 48	?	12 . 56	?

2.234. Oxidation of Acetoxime by Ferric Chloride.

Acetoxime (0.76 g, 10.4 mmole) and 60% A.R. ferric chloride (29 ml., 104 mmole) were mixed and diluted to 250 ml. and placed in a water bath at 40°. After 3 hr. the equivalent of 2 moles ferric ion had been reduced per mole of oxime. Nitrous oxide gas, $\nu_{max.}$ (10 cm. gas cell, NaCl plates) 2220 $cm.^{-1}$ was isolated from the solution which showed considerable gasification. The solution was treated with 25% ammonium hydroxide (40 ml.) and the iron hydroxides were removed by centrifugation. The supernatant was extracted overnight with ether. The organic layer was dried (Na_2SO_4) and concentrated to 3 ml. by distilling off the ether via a 10" fractionating column packed with porcelain "saddles".

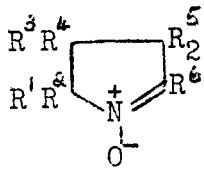
A sample of the concentrate was examined qualitatively by G.L.C. analysis (see page 105 for details). The retention times of the significant peaks together with preliminary assignments were as follows:

Column temp: 55°	
Retention time.	Assignment
min.sec.	
2 . 4	$CH_3.CHO$
3 . 35 (very small)	$CH_3.CO.CH_3$
5 . 24	CH_3OH
12 . 34	?

2.3. Oxidation of Cyclic Nitrones and Related Compounds by Ferric Chloride: Spectral and Kinetic Studies.

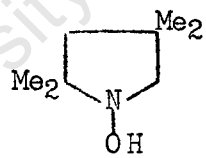
Symbols and Abbreviations used.

In this and the subsequent sections the compounds having the formulae below will be referred to by the Roman numerals shown:-

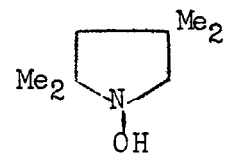


	R^1	R^2	R^3	R^4	R^5	R^6
(I)	H	H	H	H	H	H
(II)	Me	Me	H	H	H	H
(III)	Me	Me	Me	H	H	H
(IV)	Me	Me	Me	H	H	D
(V)	Me	Me	H	H	Me	H
(VI)	Me	H	H	H	H	Me
(VII)	Me	Me	H	H	H	Me
(VIII)	H	H	Me	Me	H	Me

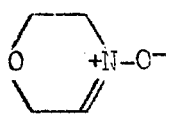
(IX)



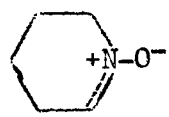
(X)



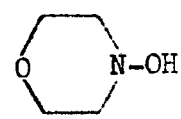
(XI)



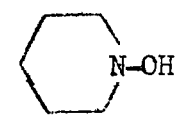
(XII)



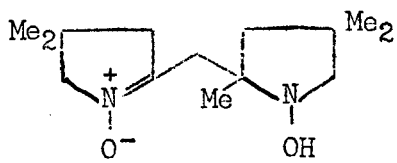
(XIII)



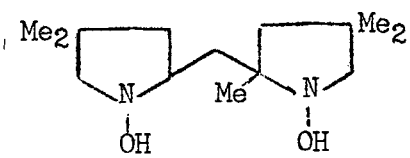
(XIV)



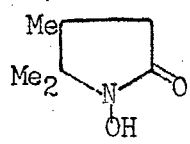
(XV)



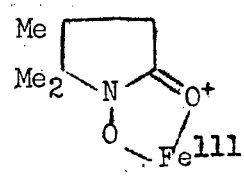
(XVI)



(XVII)



(XVIII)



(XIX)

The following abbreviations will be used:

Nitrone . . . . . Nn

Hydroxamic acid . . . . . HAm

Hydroxamate anion . . . . . Am^-

Ferric-nitrone complex . . . . . $Fe^{III}.Nn$

Ferric-hydroxamate complex . . . $Fe^{III}.Am$

Preparation of Standard Solutions and Apparatus used.

All liquids were redistilled before use, while solids were recrystallised to constant melting point from appropriate solvents. Stock aqueous solutions of the compounds were prepared by weighing out a suitable quantity of the compound and diluting to a given volume using water which had been redistilled in pyrex glassware. Solutions of the cyclic nitrones (XII) and (XIII) had to be prepared according to the procedure outlined in sections 1.122 and 2.11 (i). Solutions of all the nitrones showed little change in absorbance after several months storage in a cool, dark cupboard. Since solutions of hydroxylamines tended to oxidise over a long period of time, they were prepared as required in freshly boiled redistilled water and stored under nitrogen.

A stock solution of approx. 5% A.R. ferric chloride was prepared from the B.D.H. 60% A.R. ferric chloride solution. The dilute solution was standardised at intervals by reducing an aliquot (5.0 ml.) using

the Jones' reductor method,[135] and determining the resultant ferrous ion concentration titrimetrically using 0.1000 N-potassium dichromate solution,[133] the determination being carried out in duplicate.

1.000 M-potassium chloride (A.R.) solution was used in studies on the influence of ionic strength, and 1.000 N-hydrochloric acid was used to determine the effect of acid concentration on rate of oxidations.

Solutions were prepared in Grade B volumetric pyrex ware. Pipettes were checked for errors. 1 ml. graduated pipettes tended to deliver 0.5 - 0.9% in excess. All other graduated pipettes tended to over-deliver by less than 0.3%. All glassware, including cuvettes, was cleaned in chromic acid, well rinsed with distilled water and dried at room temperature before use.

Solution spectra were recorded on a Beckman DB self-recording spectrophotometer fitted with a scale expander to facilitate the determination of the position of maximum absorption, the solutions being contained in matched cuvettes having a path length of 1 cm. Rate measurements were obtained manually on a Unicam SP 500 spectrophotometer fitted with an Adkins thermostatted cell-holder and controller capable of maintaining the temperature within a range of $\pm 0.1^{\circ}$. Temperatures were recorded using a Grade A (N.P.L. certificated) thermometer.

2.31. Spectral Studies.

2.311. Variation in Absorbance of solutions of ferric chloride with hydroxamic acid: Conditions for obedience to the Beer-Lambert Law.

A stock aqueous solution of the cyclic hydroxamic acid (XVIII) was prepared. From this was prepared a series of solutions the molarity of which ranged from 1.5 to 7.5 x 10^{-4} M-HAm; in similar manner was prepared a series of ferric chloride solutions ranging in molarity from 0.75 to 15 x 10^{-3} M-$FeCl_3$. Into a dry cuvette were pipetted one of the solutions of the hydroxamic acid (1.00 ml.) and one of the ferric chloride solutions (2.00 ml.). The solutions were well mixed using a micro-stirrer (made from a melting point capillary tube, sealed and bent into a suitable shape by heating in a flame) and after 5 - 10 min. the absorbance at 540 mμ was recorded against a matched reference cell containing the same ferric chloride solution (2.00 ml.) in water (1.00 ml.).

A straight line passing through the origin was obtained for each series of ferric chloride solutions when the absorbance, A, was plotted against the molar concentration of the hydroxamic acid (Table 1). (See also Figure 4, Appendix 1.) From the slope of each line the "apparent" molar absorbance, ε', was calculated and Table 2 shows that with increase in $[FeCl_3]$, these values of ε' increase to a maximum constant value, 1070, which represents the true molar absorbance, ε. (Figure 5, Appendix 1.) It follows, therefore, that in a given solution under examination containing ferric and either hydroxamic acid or potential hydroxamate substrate such as aldonitrone, when $[FeCl_3] > 0.008M$ then total $[HAm] \propto$ absorbance.

TABLE 1.

Variation in absorbance for solutions of the cyclic hydroxamic acid (XVIII) with ferric chloride at 540 mμ.

Series 1. Initial $[FeCl_3]$, M x 10^3 = 1.00.

$[HAm]$, M x 10^4	0.50	1.00	1.50	2.00	2.50
Absorbance (540 mμ).....	0.043	.085	.126	.165	.206

Apparent molar absorbance, ε'_{540} (calculated from slope) = 815.

Series 2. Initial $[FeCl_3]$, M x 10^3 = 5.00.

$[HAm]$, M x 10^4	0.50	1.00	1.50	2.00	2.50
Absorbance (540 mμ).....	0.078	0.105	0.131	0.208	0.233

Apparent molar absorbance, ε'_{540} = 1055.

(See Figure 4, Appendix 1, for plot of each series.)

TABLE 2.

Solutions of the hydroxamic acid (XVIII) with ferric chloride: relationship between apparent molar absorbance, ε', and ferric ion concentration.

$[HAm]$, M x 10^4	range 0.50 to 2.50				
Initial $[FeCl_3]$, M x 10^3...	0.50	1.00	2.50	5.00	10.00
ε'_{540}	620	815	970	1055	1070

The variation of the apparent molar absorbance, ε', with $[FeCl_3]$ is shown graphically in Figure 5 (Appendix 1). From the graph was evaluated the mole-fraction of the total HAm present as the complexed (coloured) species, $Fe^{III}.Am$. For example Table 2 shows that at $[FeCl_3]$ = 5 x 10^{-4}M, ε' = 620 and hence the mole-fraction of HAm

present as the complex $Fe^{III}.Am$ is 620/1070 = 0.58. It therefore becomes possible to evaluate the stability constant, K, for the formation of the coloured complex, $Fe^{III}.Am$. (Section 2.313.)

2.312. Visible spectra of solutions of cyclic nitrones and related compounds with ferric chloride.

Suitable aliquots of standard stock solutions of the various cyclic nitrones or hydroxylamines were measured each into a 20 ml. volumetric flask together with a fixed quantity of ferric chloride added in large excess. When the colour reached a maximum value, representing completion of oxidation, the visible spectrum was recorded. Since all solutions of the compounds capable of oxidation to cyclic hydroxamate systems showed very broad absorption bands, a more precise value for $\lambda_{max.}$ was obtained by using the scale expander. The reference cell contained ferric chloride solution alone, having the same molarity as that initially present in each solution. The results are tabulated in Table 3.

TABLE 3.

Substrate		Initial Concentration ($M \times 10^4$)	$\lambda_{max.}$ ($m\mu$)	Absorbance	ε
Cyclic aldonitrone	(I)	6.36	520	0.129[b]	203
do.	(II)	3.18	544	0.342	1075
do.	(III)	3.18	544	0.340	1070
do.	(IV)	3.18	543	0.342	1075
do.	(V)	3.18	544	0.299[c]	940
do.	(XII)	3.18	500	0.238	750
do.	(XIII)	3.18	508	0.295	930
Cyclic ketonitrone	(VI)	15.7	540	0.011[c]	7
do.	(VII)	15.7	560	0.006[c]	3.5
do.	(VIII)	15.7	525 - 535	0.057[c]	36
Cyclic hydroxylamine	(IX)	6.36	523	0.132[b]	207
do.	(XI)	5.85	556	0.079[c]	135
do.	(X)	3.18	544	0.289[c]	910
do.	(XIV)	3.18	500	0.248	780
do.	(XV)	3.18	508	0.295	930
Nitrone-hydroxylamine	(XVI)	3.18	540	0.308	970
Dihydroxylamine	(XVII)	1.60[a]	545	0.157	980
Cyclic aldonitrone	(III)	3.18[a]	547	0.270	850

Notes. (a) Since the dihydroxylamine (XVII) was only sparingly soluble in water, the original stock solution was prepared by adding 200 ml. ethanol and diluting with water to 500 ml. The final solution contained 16% ethanol. For the purpose of comparison, a solution of the cyclic nitrone (III) in 16% ethanol was used.

(b) These values decrease by 10 ~ 20 absorbance units after 4 - 5 hr.

(c) After 30 hr.

2.313 Effect of acid concentration on the absorbance of solutions of the cyclic nitrone (III) with ferric chloride: Calculation of the stability constant for the ferric-hydroxamate complex (XIX).

The experimental conditions were those described in section 2.323. The absorbance at the end of the reaction for each solution is recorded in Table 4. The variation in the absorbance with added [HCl] (Figure 6, Appendix 1) shows that the coloured ferric-hydroxamate complex, $Fe^{III}.Am$, the final product of oxidation of the cyclic nitrone, is acid-labile and the dissociation may be represented by the reversible equation:

$$Fe^{III}.Am + H^{+} \rightleftharpoons Fe^{3+} + HAm$$

where HAm represents the free, colourless species of the hydroxamic acid. The formation of the complex is represented by the reversible equation

$$Fe^{3+} + Am^{-} \rightleftharpoons Fe^{III}.Am$$

for which the stability constant, K, is given by the expression:[103a]

$$K = \left[Fe^{III}.Am\right] / \left[Fe^{3+}\right]\left[Am^{-}\right]. \qquad \ldots\ldots(1)$$

The ionisation constant, K_a, for the hydroxamic acid under discussion is reported[a] to be 1.4×10^{-9}, whence

$$\left[Am^{-}\right] = K_a \left[HAm\right] / \left[H^{+}\right],$$

and substitution of this term in equation (1) gives the equation for

the stability constant:

$$K = 10^9.[H^+][Fe^{III}.Am]/1.4[HAm][Fe^{3+}]. \quad .....(2)$$

Each of these quantities is calculable. Thus the third row in Table 4 below represents the mole-fraction of the hydroxamic acid present in the complexed state (coloured), based on the reasonable assumption that the absorbance of 0.519 in the first column represents all the hydroxamic acid, HAm, as being fully complexed. From these mole fractions, the actual molar concentration of the coloured species, $Fe^{III}.Am$, is given by $[Fe^{III}.Am]$ = mole-fraction x (initial $[Nn]$) and the values are shown in the fourth row. The fifth row gives the molar concentration of the free, uncomplexed hydroxamic acid, HAm and the sixth row, the molar concentration of the residual free Fe^{3+}, given by

$$[Fe^{3+}]_{residual} = [Fe^{3+}]_{initial} - 2[Nn]_{initial} - [Fe^{III}.Am]$$

since 2 moles Fe^{3+} are reduced by each mole of nitrone, Nn, and 1 mole Fe^{3+} is bound up in each mole of the complex. In the seventh row, for practical purposes, $[H^+]$ is taken as being the same as $[HCl]$ added. The stability constant K has been calculated by substituting the data from each column in equation (2).

TABLE 4.

Initial $[Nn]$ = 4.28×10^{-4}M; initial $[FeCl_3]$ = 0.042M.

$[HCl]$ added, M x 10^2.....	0	6	8	10	12	14	16	18
Final absorbance	.519	.396	.377	.356	.334	.320	.303	.276
$100[Fe^{III}.Am]$/initial $[Nn]$.	100	76.3	72.6	68.6	64.4	61.6	58.4	53.2
$[Fe^{III}.Am]$, M x 10^4	4.28	3.27	3.11	2.94	2.76	2.64	2.50	2.28
$[HAm]$, M x 10^4	0.00	1.01	1.17	1.34	1.52	1.64	1.78	2.00
$[Fe^{3+}]_{residual}$, M x 10^2...	4.12	4.12	4.13	4.13	4.13	4.13	4.13	4.13
log K	-	9.53	9.57	9.58	9.58	9.59	9.59	9.55

Mean log K = 9.57, or K = 3.7×10^9 l. mole^{-1}.

2.314. Variation in absorbance for solutions of cyclic nitrone (III) with ferric chloride: Determination of optimum molar proportions.

(a).

Stock solutions of the cyclic nitrone (III) and of ferric chloride, both having the same molarity, 1.43×10^{-2}M, were prepared. Into each of a series of 50 ml. flasks were pipetted the ferric chloride solution (ν ml.) and the nitrone solution, (10 - ν ml.), where ν had the values: ν = 1, 2, 3, 4, 5, 6, 7, 7.14, 7.5, 8 and 9.

It followed that the molar-percentage composition with respect to ferric ion in each solution = 10ν initially, and that the total molarity is given by $[Fe^{3+}] + [Nn] = 2.86 \times 10^{-3}$M,

where $[Nn]$ = initial molar concentration of the nitrone.

The time of mixing of the two solutions was noted and each solution, after diluting to mark and thoroughly mixing, was allowed to stand at room temperature. After approximately the same time lapse, samples were transferred to cuvettes and the absorbance at 540 mμ in each case was measured against water as reference. The absorbance of each solution was noted after $^3/_4$ hr, 3 hr, 21 hr, and 24 days. The change in absorbance of the solutions with time is shown graphically in Figure 5 (Appendix 1).

(b).

In a second allied study, in order to determine more precisely the optimum composition for complete reaction, a series (A) of solutions of the cyclic nitrone (III) and ferric chloride were prepared in similar manner, the initial composition of the solutions ranging from

70 - 90 mole-% Fe^{3+}, and the total molarity being $2.54(4) \times 10^{-3}$M. The absorbance at 540 mμ for these solutions was then measured after 8 days.

In parallel with the above, a second series (B) of solutions of the corresponding cyclic hydroxamic acid (XVIII) with ferric chloride was prepared in such concentrations as to correspond with those finally expected in series (A) (above) at the completion of the oxidation. For example, the initial concentration of each species in the solution in Series A having the initial composition 70 mole-% Fe^{3+} was calculated as:

$$[Nn] = 7.63 \times 10^{-4}\text{M and } [Fe^{3+}] = 1.781 \times 10^{-3}\text{M.}$$

At the completion of the oxidation, since 1 mole of Nn would be oxidised by 2 moles of ferric ion to yield 1 mole of HAm, (Section 2.212), it follows that the final molar concentrations of each species would be

$$[HAm] = 7.63 \times 10^{-4}\text{M; residual } [Fe^{3+}] = 2.55 \times 10^{-4}\text{M.}$$

These latter values were then used in preparing the corresponding solution in series B above.

The composition of the pairs of corresponding solutions for Series A and Series B is shown in Table 5, together with the absorbance values for the Series A solutions after 8 days, and the Series B solutions. A graphical representation of these values gave the maximum absorbance at 77 mole-% Fe^{3+}.

TABLE 5.

Comparison of Absorbance values at 540 mμ of solutions of the nitrone (III) and ferric chloride after 8 days (Series A), with solutions of the hydroxamic acid (XVIII) and ferric chloride (Series B).

Series A:-

Init. compstn., Mole-% Fe^{3+} ...	70	71.3	75	77.5	80	90
Initial [Nn], M x 10^4	7.63	7.27	6.36	5.72	5.09	2.54
Initial $[Fe^{3+}]$, M x 10^4....	17.81	18.17	19.08	19.72	20.35	22.90
Absorbance, 8 days	0.291	0.316	0.370	0.387	0.380	0.233

Series B:-

[HAm], M x 10^4	7.63	7.25	6.36	5.73	5.09	2.54
$[Fe^{3+}]$, M x 10^4	2.55	3.69	6.36	8.25	10.17	17.81
Absorbance (observed)	0.293	0.353	0.430	0.432	0.420	0.242
Absorbance (calculated)[a] ...	(b)	(b)	0.436[c]	0.433	0.412	-[b]

(a) The absorbance was calculated by first obtaining the apparent molar absorbance, ε', for the value of $[Fe^{3+}]$ in each solution by interpolation in the values in Table 2, whence

$$\text{Absorbance (calculated)} = \varepsilon' \times [HAm].$$

(b) Calculated values are unreliable since the values of ε' are unreliable at low $[Fe^{3+}]$.

(c) Absorbance values calculated to correspond with Series A solutions of 76 and 77 mole-% Fe^{3+} are 0.440 and 0.433 respectively.

2.32. Oxidation of Cyclic Nitrones by Ferric Chloride: Kinetic Studies.

General Procedure.

For all rate measurements, freshly prepared solutions of a nitrone (or other substrate) and ferric chloride of appropriate concentrations were used. Into a cuvette was pipetted a solution of the reductant (1.00 ml.) and diluent (water or potassium chloride solution of appropriate molarity or hydrochloric acid of appropriate molarity)(1.00 ml.), and the cuvette was placed in the thermostatted cell holder supported in the Unicam SP 500 spectrophotometer and previously set to a given temperature. After 15 - 20 mins. had elapsed (sufficient time to allow the cuvette and its contents to equilibrate to the selected temperature), the small microstirrer (described in section 2.311)was introduced into the solution and the appropriate ferric chloride solution (1.00 ml.) previously equilibrated in a water bath whose temperature was 0.1 - 0.2° above that of the cuvette temperature, was rapidly introduced using a 1 ml. pipette graduated to the tip, the pipette itself having also been previously warmed to the same temperature in the same water bath. When approximately half of the ferric chloride solution had run in, a stop-watch was started. At appropriate intervals of time the absorbance (A_t) at 540 mμ was recorded, using water in the reference cell. The final reading (A_∞) was taken after a period equal to 10 - 20 half-lives. In most cases, measurements were performed in duplicate to obtain concordant results.

Evaluation of rate constants from the results.

The rate equation for the oxidation of nitrone to hydroxamic acid may be represented as

$$v = d[Fe^{III}.Am]/dt = -d[Nn]/dt = k[Fe^{3+}]^r[Nn]^s \quad \ldots\ldots(3)$$

where v(mole.l.$^{-1}$min.$^{-1}$) = rate of formation of the coloured complex, $Fe^{III}.Am$

and = rate of disappearance of the nitrone, Nn,

$[X]$ = molarity of species X,

k = rate constant for the reaction,

r, s = reaction order with respect to the species Fe^{3+} and Nn respectively.

If initially $[Fe^{3+}] \gg [Nn]$, then equation (3) simplifies to

$$v = k'[Nn]^s, \quad \ldots\ldots(4)$$

$$\text{where } k' = k[Fe^{3+}]^r. \quad \ldots\ldots(5)$$

(a) Evaluation of the pseudo-first order rate constant, k'.[136]

Earlier it was shown (page 86) that

$$[Nn]_t \propto (A_\infty - A_t), \quad \ldots\ldots(6)$$

where A_t = absorbance at time t,

and A_∞ = absorbance at completion of reaction.

Hence the pseudo-first order rate constant k' may be evaluated directly by plotting log $(A_\infty - A_t)$ against t when a straight line should be obtained if s = 1, whence k' = - 2.303 x slope (Figure A). Fig.7 (App.1) shows the result for the nitrone (III) with ferric chloride in a typical run over two half-lives. k' will have the units min.$^{-1}$ if r = s = 1, i.e. if the slow step is first order in nitrone and in ferric ion. This will be demonstrated (Section 2.324).

(b) Evaluation of k' from initial rate measurements.[104b]

k' may also be evaluated from the plot of absorbance, A, against t, which gives a curve flattening out to a constant value, A_∞ (Figure B). The rate of formation of Fe^{III}.Am at any particular instant, v_t, will be proportional to the slope of the tangent to the curve at that particular instant, v'_t, and it will have the units: absorbance. $min.^{-1}$

$$\text{i.e. } v'_t \propto v_t$$

$$\text{or } q v'_t = v_t$$

where q (mole.$l.^{-1}$ $absorbance^{-1}$) is a conversion factor.

If the tangent is constructed to the curve at t = 0, then its slope, v'_o, will be proportional to the initial rate of the reaction v_o:

$$q v'_o = v_o ,$$

But from equation (4)

$$v_o = k'[Nn]_o,$$

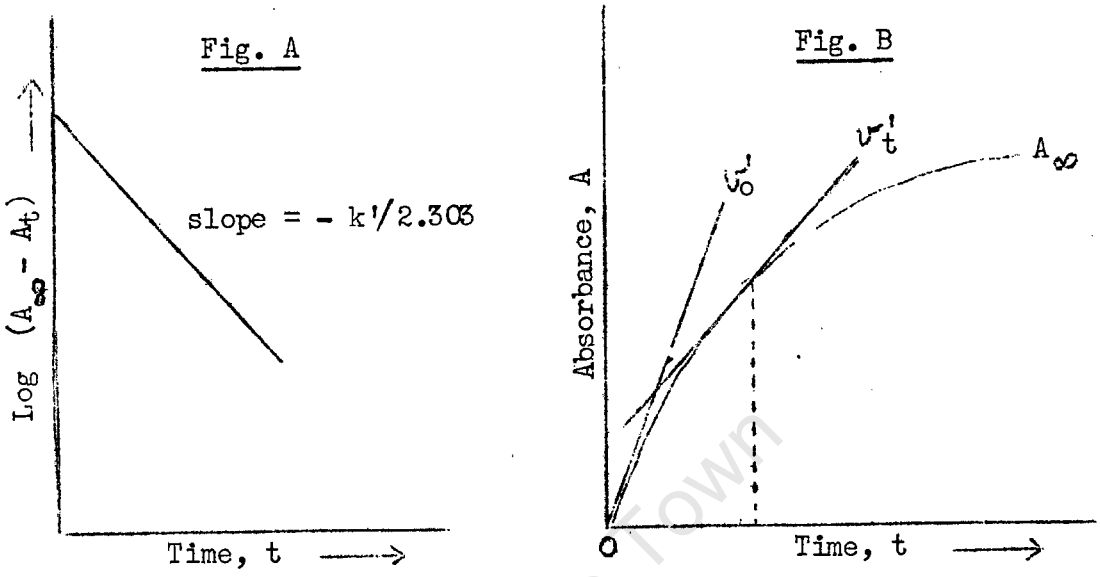
where $[Nn]_o$ = molarity of Nn at the commencement of reaction, whence $k'[Nn]_o = q v'_o$. .....(7)

Thus the conversion factor, q, can be evaluated by plotting the results of a series of runs in two ways:

(i) by evaluating k' using the first method outlined above,

(ii) by plotting absorbance A against time and measuring the slope v'_o of the tangent drawn at t = 0. The mean value of q so obtained may then be applied to those systems in which $[Fe^{3+}] \sim [Nn]$ where only initial rate measurements can be considered valid.

Figure 11 (Appendix 1) shows a typical curve used for evaluating initial rates.



2.321. Oxidation of 4,5,5-trimethyl-1-pyrroline 1-oxide by ferric chloride:/ pseudo-first order rate constant, k', at 30°.

The general procedure (section 2.52)was followed using 0.00045M-nitrone (2.00 ml.) and 0.0800M-$FeCl_3$ (1.0 ml.). No potassium chloride was added as the aim of the experiment was only to establish that the rate of formation of the hydroxamic acid, as determined by the rate of production of colour, in the presence of a large molar excess of ferric ion, gave a first order plot. The results of a typical run are shown in Table 6. The plot of log $(A_\infty - A_t)$ against time t, in which A_∞ and A_t are the absorbances at times ∞ and t respectively, is seen to give a straight line (Figure 7, Appendix 1) of slope -0.0166, whence the/ pseudo-first order rate constant, k' = -2.303 x slope = 0.0382 $min.^{-1}$

TABLE 6.

Initial $[\text{nitrone}]$ = 3.00×10^{-4}M, initial $[FeCl_3]$ = 3.00×10^{-2}M; temperature = 30.0°.

Time (min.)	1	3	6	9	12	15	18	21	24
Absorbance, A	.035	.059	.093	.123	.150	.174	.195	.213	.230
log $10(A_\infty - A_t)$	.522	.490	.439	.389	.338	.288	.238	.190	.140

30	40	∞
.258	.290	.361
.041 $\bar{1}$	.892	-

2.522. Influence of ionic strength on the rate of oxidation of the cyclic nitrone (III).

The total ionic strength, μ, was calculated from the expression:

$$\mu = \mu_{FeCl_3} + \mu_{KCl}$$

Since the ferric ion in the aqueous chloride solution contains essentially the species $\{FeCl(OH_2)_5\}^{2+}$ (see page 88), in which the ionic charge is 2+, then

$$\mu_{FeCl_3} = \tfrac{1}{2}([Fe^{3+}].2^2 + [Cl^-].1^2) \quad {}^{109b}$$
$$= 3[FeCl_3].$$

Into a cuvette were pipetted 0.0127M-nitrone (1.0 ml.), KCl solution (ν ml.), and water (1 - ν ml.). In the first series M-KCl was used, whereas 0.696M-KCl was used in the second series. 0.1272M-$FeCl_3$ (1.0 ml.) was added to each cuvette and the rate constant measured in the usual way. The results of each series are tabulated below and the plot of log k' (from both series) against $\mu^{\frac{1}{2}}$ gave a straight line of positive

slope (Figure 8, Appendix 1). Application of the method of least squares gave the equation of the slope as:

$$\log k' = 0.432(\mu)^{\frac{1}{2}} - 1.39.$$

TABLE 7.

Initial [nitrone] = 4.24×10^{-4}M; initial [$FeCl_3$] = 0.0424M; μ_{FeCl_3} = 0.127; temp. 30.0°.

Series A: M-KCl added.

Vol. KCl (v ml.)	0.00	0.30	0.60	0.75	1.00
μ(total)	0.127	0.227	0.327	0.377	0.460
$k' \times 10^2$ (min.$^{-1}$)	5.78	6.47	7.19	7.51	7.88

Series B: 0.696 M-KCl added.

Vol. KCl (v ml.)	0.00	0.30	0.60	0.75	1.00
μ(total)	0.127	0.197	0.266	0.301	0.359
$k' \times 10^2$ (min.$^{-1}$)	5.71	6.31	6.72	7.01	7.33

2.323 Influence of acid concentration on rate of oxidation of the cyclic nitrone (III).

Into a series of 20 ml. flasks were pipetted 0.00857M-nitrone (1.5 ml.) M-HCl (v ml.), M-KCl (6 - v ml.) and water was added to the mark. Rate measurements were obtained for each solution (2.0 ml.) mixed with 0.127M-$FeCl_3$ (1.0 ml.) in the usual way. The first order plots gave straight lines, but in those solutions having higher concentration of acid, there was a significant decrease in the rate after a short time lapse (Figure 9, Appendix 1). The values of the first order rate

constant, k', given in Table 8 are those calculated from the initial slope. The variation of k' with added [HCl] is shown in Figure 10 (Appendix 1). The effect of the acid concentration on the absorbance at the end of the reaction has been referred to (Table 4).

TABLE 8.

Initial [nitrone] = 4.28×10^{-4}M; initial [$FeCl_3$] = 0.042M; ionic strength = 0.327; temperature = 30.0°.

M-HCl dild. to 20 ml.(v ml.)	0.0	1.8	2.4	3.0	3.6	4.2	4.8	5.4
Added [HCl] in reaction, (M)	0.0	0.06	0.08	0.10	0.12	0.14	0.16	0.18
$k' \times 10^2$, ($min.^{-1}$)	7.28	9.58	10.04	9.74	8.84	8.77	8.80	8.57

2.324. Initial rate measurements on the oxidation of the cyclic nitrone (III).

To determine the relationship between the pseudo-first order rate constant, k', and the initial slope of the tangent, v'_o in equation (7).

For a series of rate measurements, a plot of the absorbance against time was made in each case, and the tangent to the curve at t = 0 min. was constructed by a visual method. (Figure 11, Appendix 1). The slope of this tangent, v'_o, (absorbance. $min.^{-1}$) was proportional to the initial rate of reaction. Each was compared with the value of the first order rate constant, k', obtained from the same set of results,

as described in section 2.52. Table 9 shows a constant relationship between v'_o and k'.

TABLE 9.

Initial $[\text{nitrone}] = 4.24 \times 10^{-4}$M; temperature = 30.0°.

Run	$[FeCl_3]$ (M x 10^2)	$10^2 v'_o$ (Absorbance units. min.$^{-1}$)	$10^2 k'$ (min.$^{-1}$)	k'/v'_o
1.	2.54	2.12	4.54	2.14
2.	3.39	2.75	5.80	2.11
3.	4.24	3.26	7.15	2.19
4.	5.30	3.87	8.38	2.17
5.	6.36	5.07	10.92	2.15

The last column gives a mean value for $k'/v'_o = 2.15$.

By substituting this value together with the original concentration of the nitrone in equation (7) the conversion factor, q, can be calculated:

$$q = [Nn]_o . k'/v'_o$$
$$= 4.24 \times 10^{-4} \times 2.15;$$
$$\text{i.e.} \quad q = 9.12 \times 10^{-4} \text{ mole. lit.}^{-1} \text{ absorbance}^{-1}.$$

The expression for converting the slope of a tangent at time t = 0 for any run into a first order rate constant thus becomes:

$$k' = 9.12 \times 10^{-4} v'_o / [Nn]_o \qquad \ldots\ldots(8)$$

where $[Nn]_o$ is the initial molar concentration of nitrone in a given run.

Application of initial rate measurements to determine the effect of concentration of nitrone on the oxidation rate.

Two aqueous solutions were prepared:- 0.01272 M-nitrone (III) and a solution containing both ferric chloride (0.01272M) and potassium chloride (0.800M).

Into a cuvette were pipetted the nitrone solution (v ml.) and water (2 - v ml.). The mixed solution containing the oxidant was added (1.0 ml.) and the rate was measured in the usual manner. The results are tabulated below, the initial pseudo-first order rate constant k' being calculated from v'_o, the tangent slope at time = 0, using equation (8) above. The plot log v'_o against log $[Nn]$ gave a straight line for which the method of least squares gave the slope = 0.99, i.e. the reaction is first order in nitrone.

TABLE 10.

Initial $[FeCl_3]$ = 4.24×10^{-3}M; ionic strength = 0.279; temperature = 30.0°.

Initial [Nitrone], M x 10^3	2.14	4.24	6.36	8.48
Initial slope, $v'_o \times 10^3$ (absorb.$min.^{-1}$).	1.45	2.88	4.25	5.78
Rate constant, k' x 10^3 ($min.^{-1}$)	6.27	6.22	6.12	6.24

The values given in the third row give a mean value to the first order rate constant, k' = 6.22×10^{-3} $min.^{-1}$, from whence

$$k = k'[FeCl_3]$$
$$= 6.22 \times 10^{-3} / 4.24 \times 10^{-3}$$
$$= 1.46 \text{ l.mole.}^{-1}\text{min.}^{-1}$$
$$= 0.0244 \text{ l.mole.}^{-1}\text{sec.}^{-1}$$

This latter agrees reasonably with the value of 0.0278 obtained elsewhere (Section 2.235) where rates were measured at higher ionic strengths.

2.325. Effect of concentration of oxidant on the oxidation rate of the cyclic nitrone (III).

In addition to the 0.00127M-nitrone solution, a complementary series of ferric chloride and potassium chloride solutions was prepared having such concentrations that 1.0 ml. of the one when mixed with 1.0 ml. of the second gave a solution of constant ionic strength. The molarities of these solutions are shown in Table 11. The rate of oxidation of the nitrone solution (1.0 ml.) mixed with the appropriate potassium chloride solution (1.0 ml.) and ferric chloride solution (1.0 ml.) was determined as before (section 2.32). The pseudo-first order rate constants obtained for each run are presented in the Table below.

TABLE 11.

Initial $[\text{nitrone}] = 4.24 \times 10^{-4}$M; ionic strength = 0.326; temperature = 30.0°.

Solutions prepared:

$FeCl_3$, (M)	0.0763	0.1018	0.1272	0.1590	0.1908
KCl, (M)	0.750	0.672	0.597	0.501	0.405
Reaction: Initial $[FeCl_3]$, $(M \times 10^2)$	2.54	3.39	4.24	5.30	6.36
$k' \times 10^2 (min.^{-1})$	4.19	5.55	7.19	8.91	10.40

The plot of log k' against log $[FeCl_3]$ (Figure 12, Appendix 1) gave a straight line of slope = 1.0, i.e. the reaction was first order in ferric ion. The second order rate constant, k, calculated by applying the method of least squares, was found to be: 1.61 l.mole $^{-1}$min.$^{-1}$ or 0.0278 l.mole $^{-1}$sec.$^{-1}$ (cf. section 2.324).

2.326. Oxidation of 4,5,5-trimethyl-1-pyrroline 1-oxide by ferric chloride: influence of temperature on the rate constants: the derivation of thermodynamic data.

The method described in section 2.325 to obtain kinetic data at 30.0°C. was followed using the identical solutions at different temperatures, viz. 26°, 34°, 38°, and 42°. It was noticed that the reacting solutions at temperatures of 38° and higher, after several hours, became turbid, due to an increase in the rate of hydrolysis of ferric ion. At these temperatures, therefore, the final absorbance, A_∞, was taken after a lapse of 10 - 12 half-lives. The plots of log k' against log $[FeCl_3]$ for each temperature are shown graphically in Figure 12 (Appendix 1). The Least Squares method was used to calculate the second order rate constant, k, for each temperature and the slope (= order in ferric ion), the values of which are shown in the Table below.

TABLE 12.

Initial [nitrone] = 4.24×10^{-4}M; total ionic strength = 0.326.

Temperature (°C)	26.0	30.0	34.0	38.0	42.0
Temperature (T°K)	299	303	307	311	315
10^2k (l.mole^{-1}sec.$^{-1}$)	1.73	2.78	4.16	5.93	9.06
Order in Fe^{3+}(= slope)	0.98	1.00	1.00	0.99	1.00

The plot of log k against $10^3/T$ gave a straight line (Figure 13, Appendix 1) whose slope and intercept were evaluated using the method of least squares. From these were evaluated the Arrhenius parameters, the activation energy, E_a (= - 4.57 x slope) and the frequency factor A (log A = intercept).[1046] These values are shown in Table 13. The

entropy of activation $\Delta S^{\ddagger}$ was evaluated from the rate equation for a bimolecular reaction:-[104c]

$$k = e^2 \frac{kT}{h} . e^{\Delta S^{\ddagger}/R} . e^{-E_a/RT},$$

and the free energy of activation, $\Delta G^{\ddagger}$, was calculated from the equation[104d]

$$k = \frac{kT}{h} . e^{-\Delta G^{\ddagger}/RT} .$$

TABLE 13.

Energy of activation, E_a	19.1± 0.2 kcal.mole^{-1}
Log A (l.mole^{-1}sec.$^{-1}$)	12.21 ± 0.01
Free energy of activation, $\Delta G^{\ddagger}$	19.9 kcal.mole^{-1}
Entropy of activation, $\Delta S^{\ddagger}$	-6.6 e.u.

The plots of log k' against $10^3/T$ for each solution gave parallel lines of negative slope (Figure 14, Appendix 1). A mean value of the activation energy, E_a, could also be calculated from the slopes of the lines. The values are shown in Table 14 and the mean value for E_a shows satisfactory agreement with the value in Table 13.

TABLE 14.

Initial [III] = 4.24 x 10^{-4}M; total ionic strength = 0.326.

Temperature (°K)	299	303	307	311	315
E_a (kcal.mole^{-1})	18.6	18.9	19.1	18.7	18.8

Mean E_a = 18.8 ± 0.2 kcal.mole^{-1}

2.327. Comparison of Pseudo -First Order Rate Constants, k', of cyclic Aldonitrones and some Hydroxylamines by Ferric Chloride.

Since it had been shown that in large excess of the oxidant the pseudo-first order rate constant, k', was independent of the concentration of the nitrone, it followed that comparative studies could be made using ferric chloride of given molarity (0.1272M), and solutions of the reductant of suitable molarity in order to give a value for the final absorbance (A_{∞}) in the range 0.3 - 0.5. In most cases where the molar absorbances of the resulting hydroxamic acids were of the same order, equimolar solutions of the nitrones and related compounds were used (see Table 15). In the case of the nitrone (I) and its related hydroxylamine (IX), higher molarities were employed.

All measurements were performed on solutions having the same ionic strength, μ, at the same temperature and at a wave-length corresponding with $\lambda_{max.}$ for each solution (see Table 3). In each case, the pseudo-first order rate constant, k', was evaluated as before. The results are presented in Table 15.

Since the reaction has been shown to be first order in ferric chloride and nitrone, it follows that the true rate constant, k, can be calculated using equation (5) , i.e.

$$k = k'/\left[Fe^{3+}\right], \text{ l. mole}^{-1}\text{min.}^{-1}$$

$$\text{or } k = k'/60\left[Fe^{3+}\right], \text{ l. mole}^{-1}\text{sec.}^{-1}$$

TABLE 15.

Pseudo-first order rate constants for cyclic nitrones and related compounds.

Initial $[FeCl_3]$ = 4.24 x 10^{-2}M; ionic strength = 0.359; temperature = 30°C

Reductant		Initial [reductant] (10^4M)	10^2k' (min.$^{-1}$)
Pyrroline oxide	(I)	13.6	57(1)
Hydroxypyrrolidine	(IX)	13.6	52(1)
Dimethylpyrroline oxide	(II)	4.24	7.95
Trimethylpyrroline oxide	(III)	4.24	7.37
2-d-Trimethylpyrroline oxide	(IV)	4.24	8.38
Tetramethylpyrroline oxide	(V)	4.24	0.57
Hydroxytetramethylpyrrolidine	(X)	4.24	0.45
Tetrahydropyridine oxide	(XIII)	4.24	very fast(2)
Hydroxypiperidine	(XV)	4.24	very fast(2)
Piperidine		-	0.0
Dihydroöxazine oxide	(XII)	4.24	very fast(3)
Hydroxymorpholine	(XIV)	4.24	very fast(3)
Morpholine		-	0.0
Nitrone-hydroxylamine	(XVI)	4.24	41.7

Notes: (1) the reaction showed a retardation after ca. 3 mins. i.e. about 2 - 3 half-lives. k' was evaluated from the initial portion of the plot which was a straight line.

(2) and (3): these reactions, too rapid for measurement, were respectively approximately 85% and 96% complete after $\frac{1}{2}$ min.

2.328. Kinetic isotope effect in the rate of oxidation of 4,5,5-trimethyl-1-pyrroline 1-oxide.

0.001272M- solutions of the cyclic nitrone (III) and of 2-d-4,5,5-trimethyl-1-pyrroline 1-oxide (IV) were prepared. Each solution (1.0 ml.) was treated with 0.1272M-$FeCl_3$ (1.0 ml.) and 0.750M-KCl (1.0 ml.) and the rate of reaction was followed in the usual way, at two different temperatures. From the first order rate constants (Table 16), the ratio k'_H/k'_D was calculated for each temperature.

TABLE 16.

Initial $[\text{nitrone}]$ = 0.000424M; initial $[FeCl_3]$ = 0.0424M; ionic strength = 0.377.

Nitrone	30.0°		35.0°	
	$10^2k'$ (min.$^{-1}$)	k'_H/k'_D	$10^2k'$ (min.$^{-1}$)	k'_H/k'_D
(III)	7.21	0.860	12.44	0.869
(IV)	8.38		14.22	

2.33. Semi-quantitative rates of oxidation of some cyclic ketonitrones and related compounds by ferric chloride.

General Procedure.

Aqueous solutions of the given compounds were prepared with known molarities. An aliquot of one solution was measured into a volumetric flask, together with an appropriate aliquot of 30% ferric chloride solution, the molarity of which had been determined. The mixed solution was diluted to volume and left in a constant temperature water bath. Convenient aliquots were withdrawn and titrated for their ferrous ion content (section 2.2). A blank correction was subtracted from each titration value. For each titration the ratio

$$\left[Fe^{2+}\right] \text{ formed / initial } \left[\text{reductant}\right]$$

was calculated, and from the plot of these values against time, the approximate time taken for 1, 2, 3, ... etc. moles of ferric ion to be reduced per mole of nitrone was estimated. The results are recorded in the table below. In order to draw comparable conclusions, the solutions examined were all initially of the same concentration. Furthermore, since in some cases the solutions were kept for several weeks, the air in each flask was displaced with nitrogen after removing a sample for each titration.

In order to compare these results with the oxidation rate of the cyclic aldonitrones, 4,5,5-trimethyl-1-pyrroline 1-oxide was examined in the same way.

TABLE 17.

Initial $\left[\text{reductant}\right]$ = 0.00300M; initial $\left[FeCl_3\right]$ = 0.30M; temperature, 30.0°.

Reductant	Time taken to form n moles Fe^{2+}/mole nitrone*					
n =	1	2	3	4	5	6
Dimethylpyrroline oxide (VI)	0.08 d.	0.23 d.	0.63 d.	8.3 d.	-	-
Trimethylpyrroline oxide (VIII)	0.3 d.	0.95 d.	2 d.	4.2 d.	12 - 13 d.	-
Trimethylpyrroline oxide (VII)	1.1 d.	3.4 d.	8 d.	-	-	-
Hydroxylamine	3 min.	5 min.	-	-	-	-
Acetoxime	4 min.	28 min.	-	-	-	-
Trimethylpyrroline oxide (III)	1 min.	30 min.	-	-	-	-

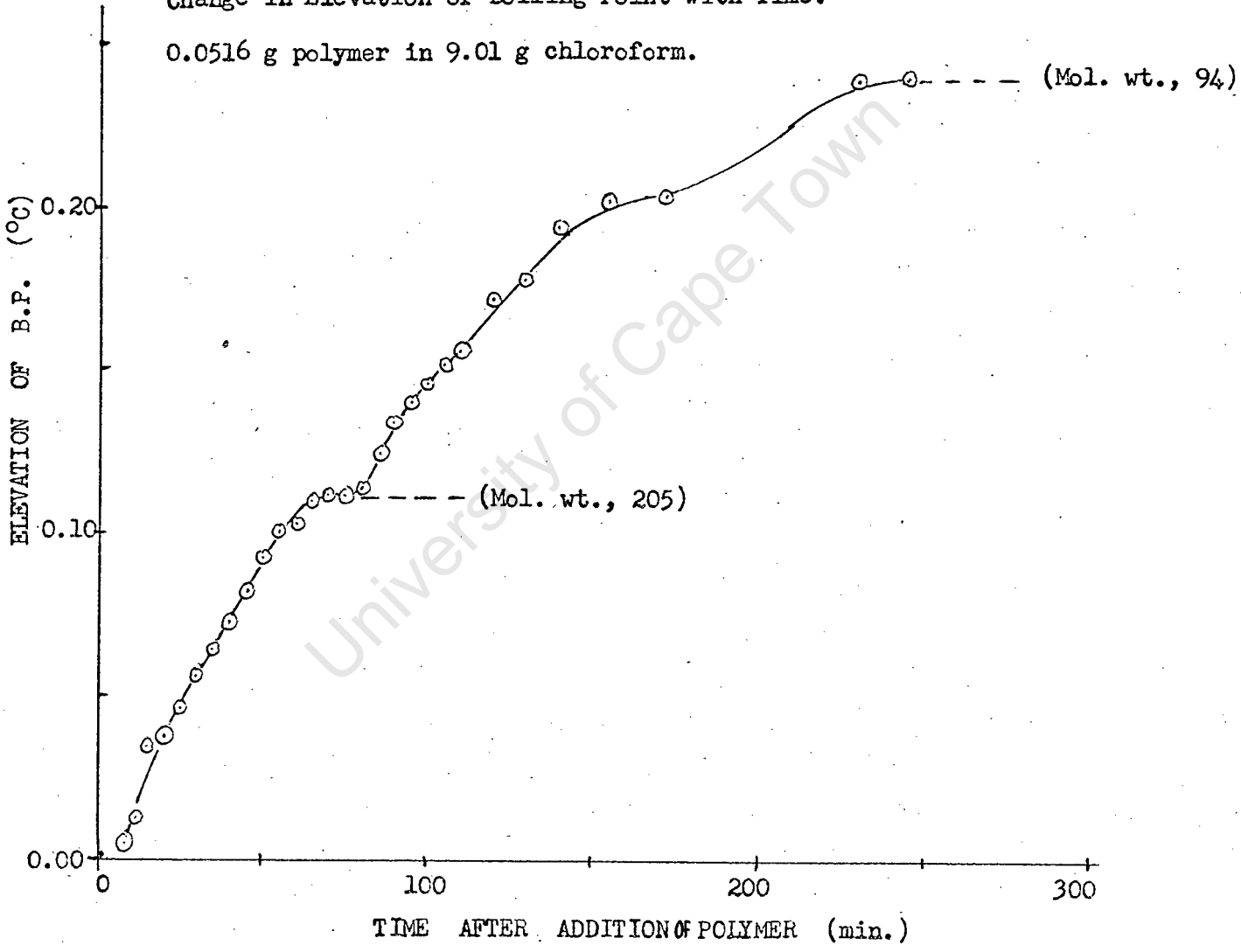
d = day(s).

APPENDIX 1.

FIGURES.

Figure 1. Determination of Mol. Wt. of Polymer.
Change in Elevation of Boiling Point with Time.

0.0516 g polymer in 9.01 g chloroform.



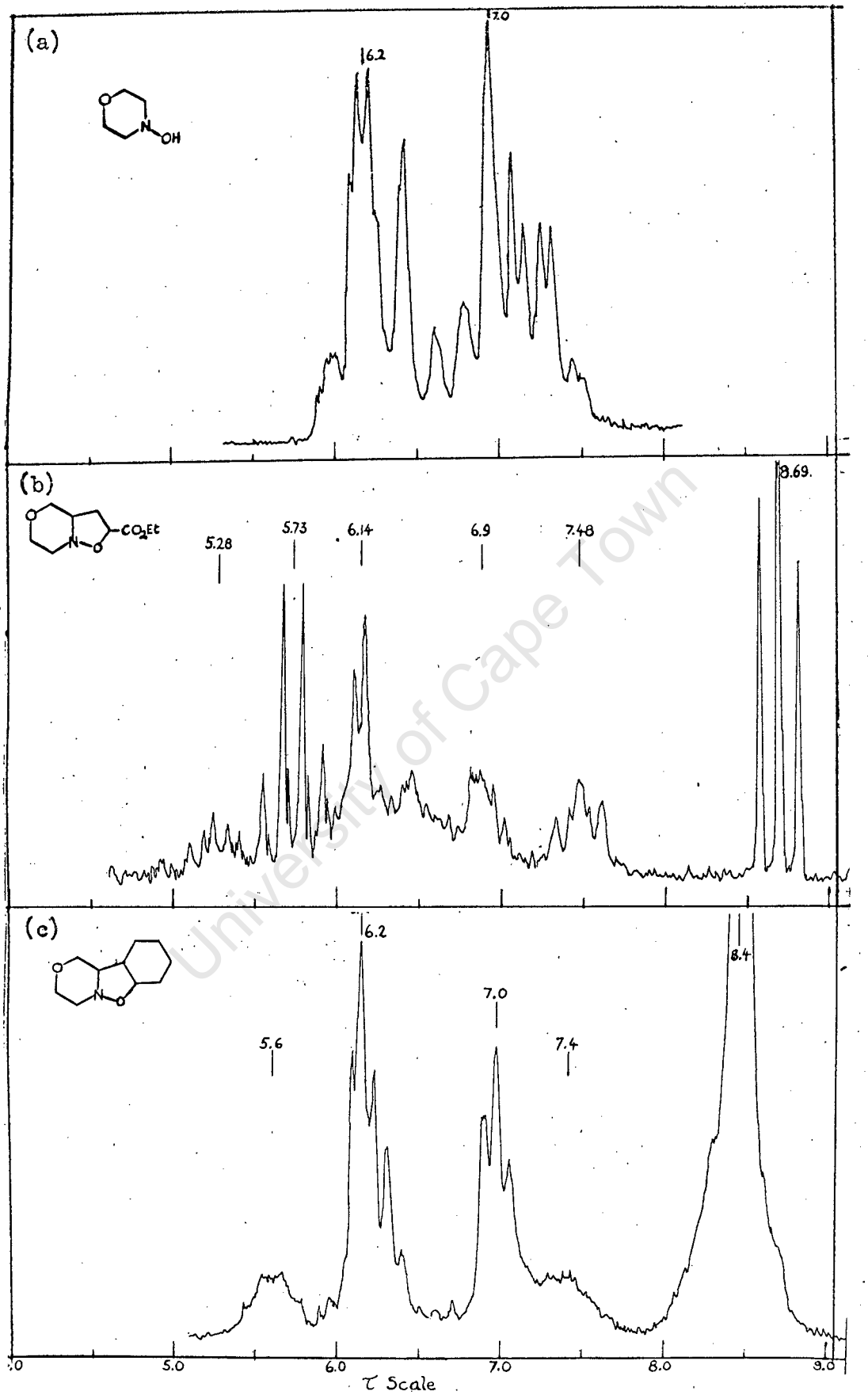


Fig. 2. P.M.R. SPECTRA.

Figure 3. Effect of Molar Composition of Solutions of Cyclic Nitrone (III) and Ferric Chloride on the Change in Absorbance with Time. (Section 2.314).

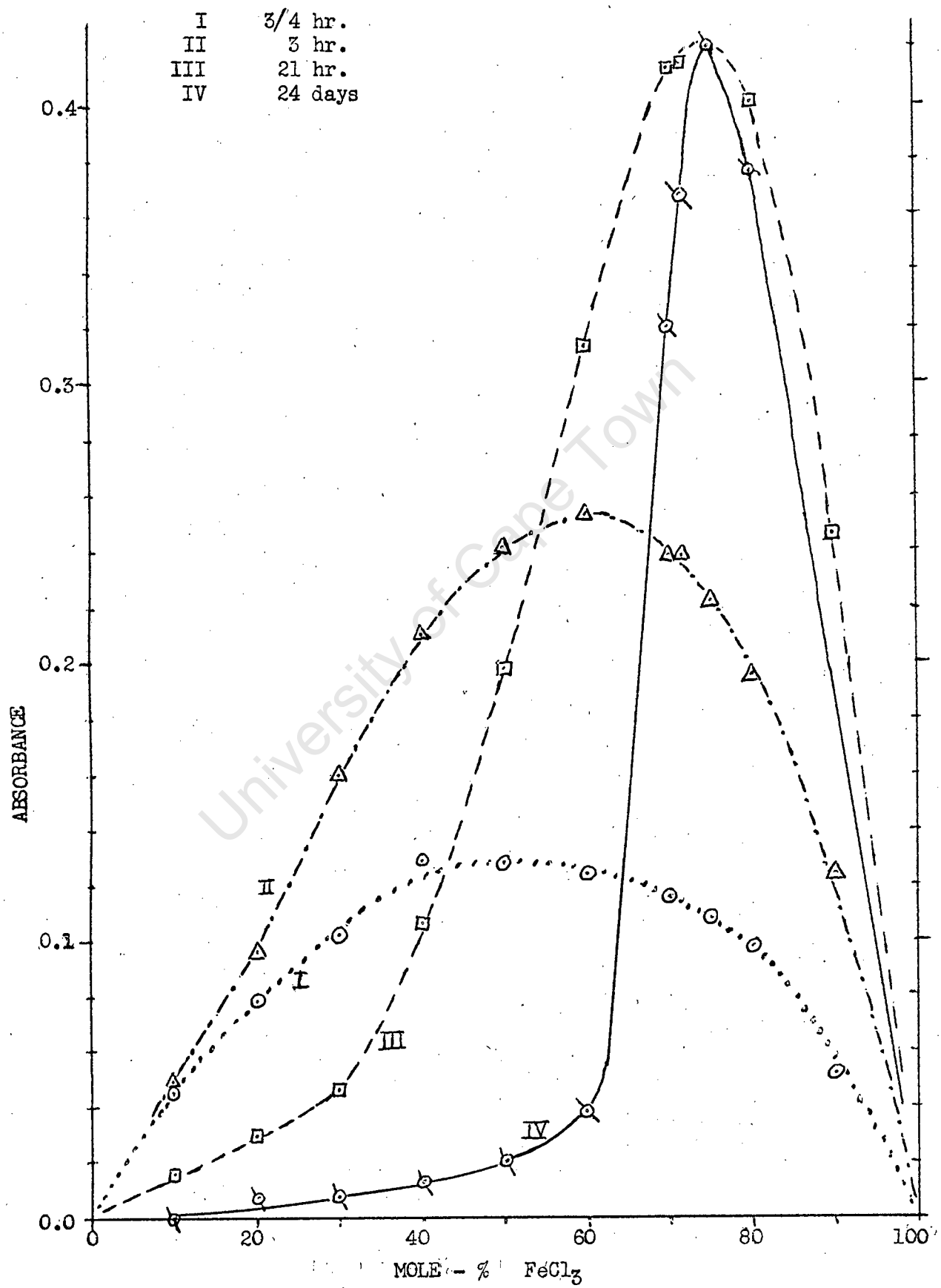


Figure 4._ Plots of Absorbance against [HAm], the concentration of cyclic hydroxamic acid (XVIII), using different concentrations of ferric chloride. (Section 2.311).

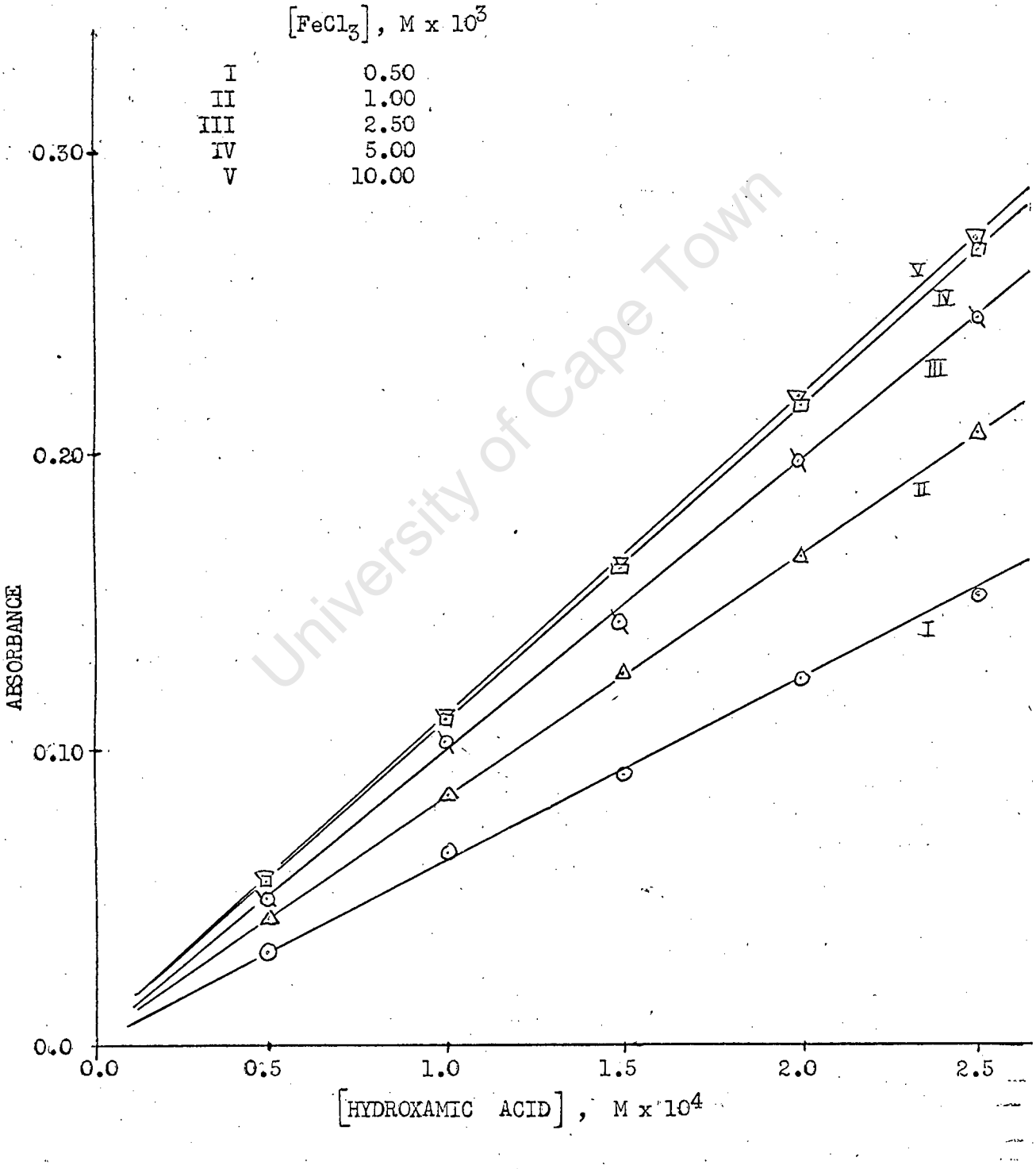


Figure 5. Plot of Apparent Molar Extinction, ε', against $[FeCl_3]$. (Section 2.311).

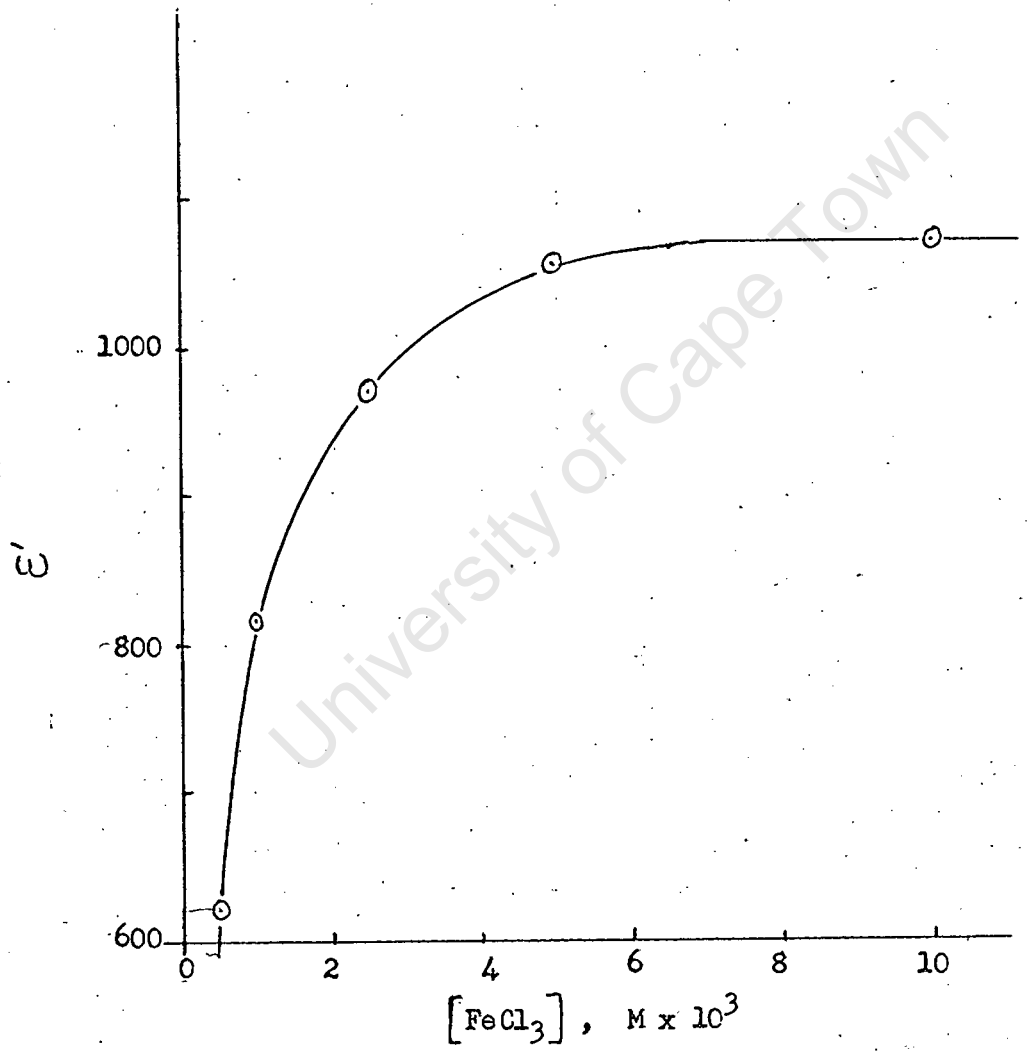


Figure 6. Effect of [HCl] on Absorbance of a Solution of Cyclic Nitrone (III) on Completion of Oxidation by Ferric Chloride. (Section 2.313).

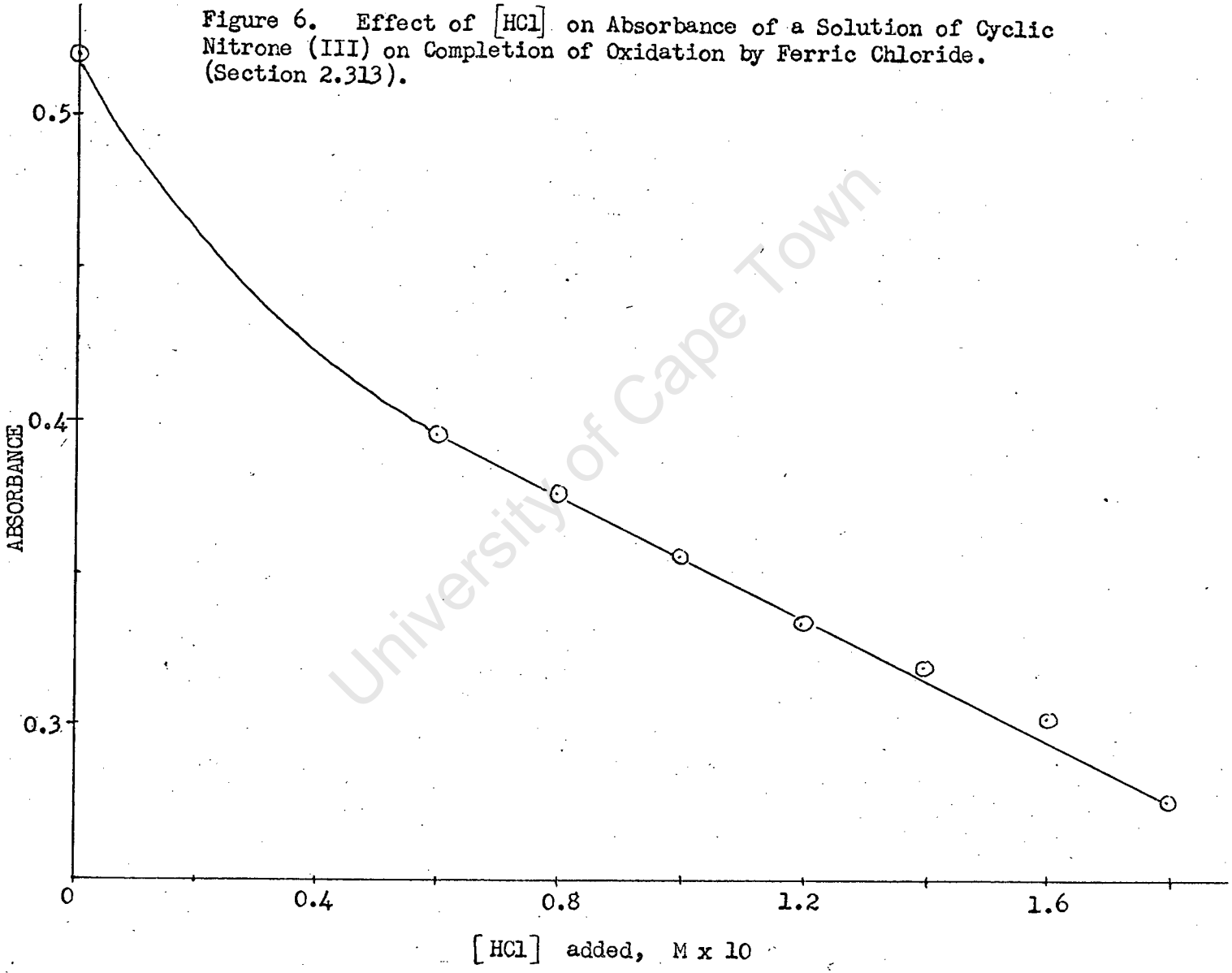


Figure 7. Plot of Log ($A_\infty - A_t$) against Time to obtain the Pseudo-First Order Rate Constant, k', at 30°, for the Oxidation of Cyclic Nitrone (III) by Ferric Chloride. (Section 2.321).

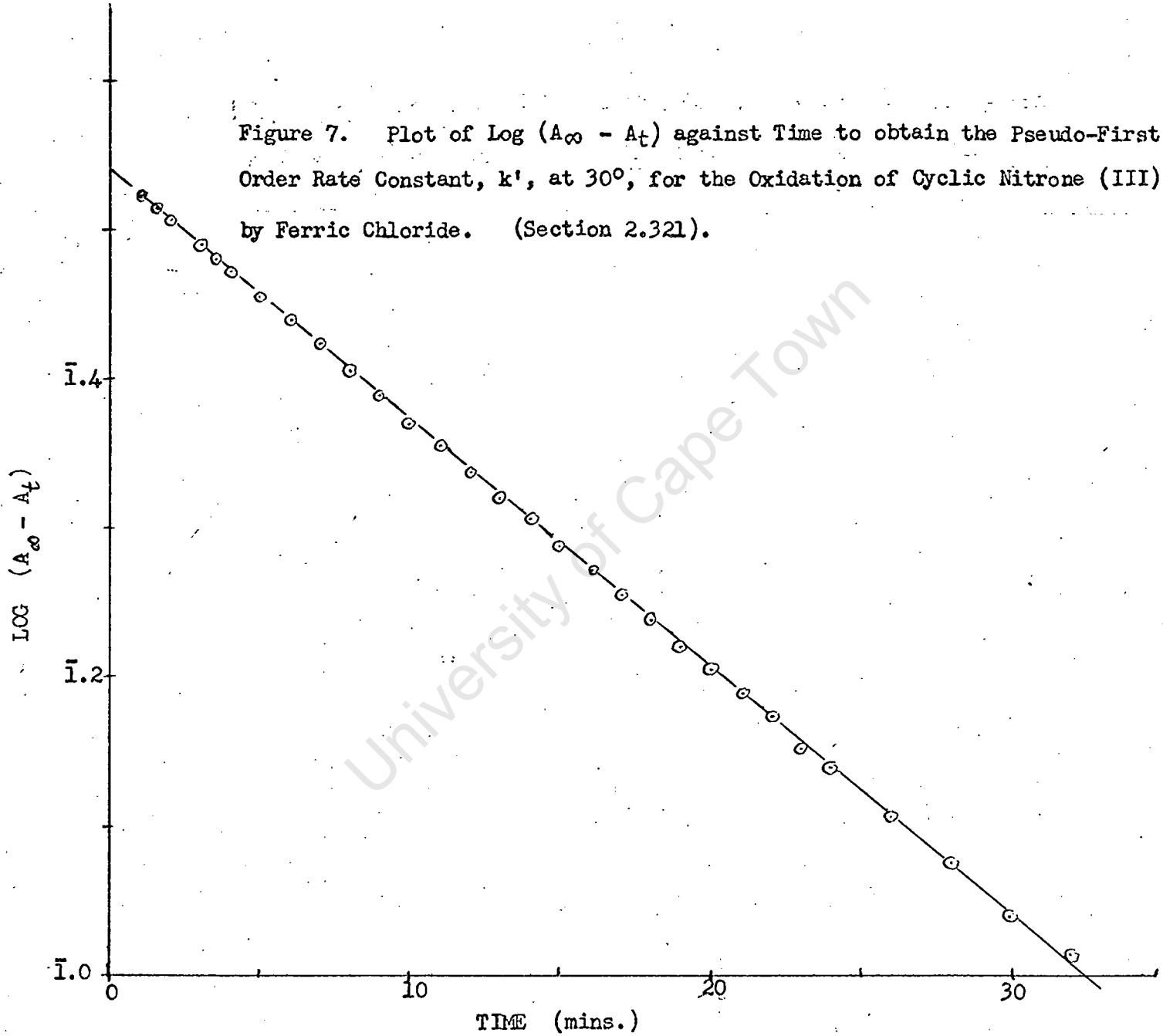


Figure 8. Effect of Ionic Strength, μ, on the Pseudo-First Order Rate Constant, k' ($min.^{-1}$), for the Oxidation of Cyclic Nitrone (III) by Ferric Chloride at 30°. (Section 2.322).

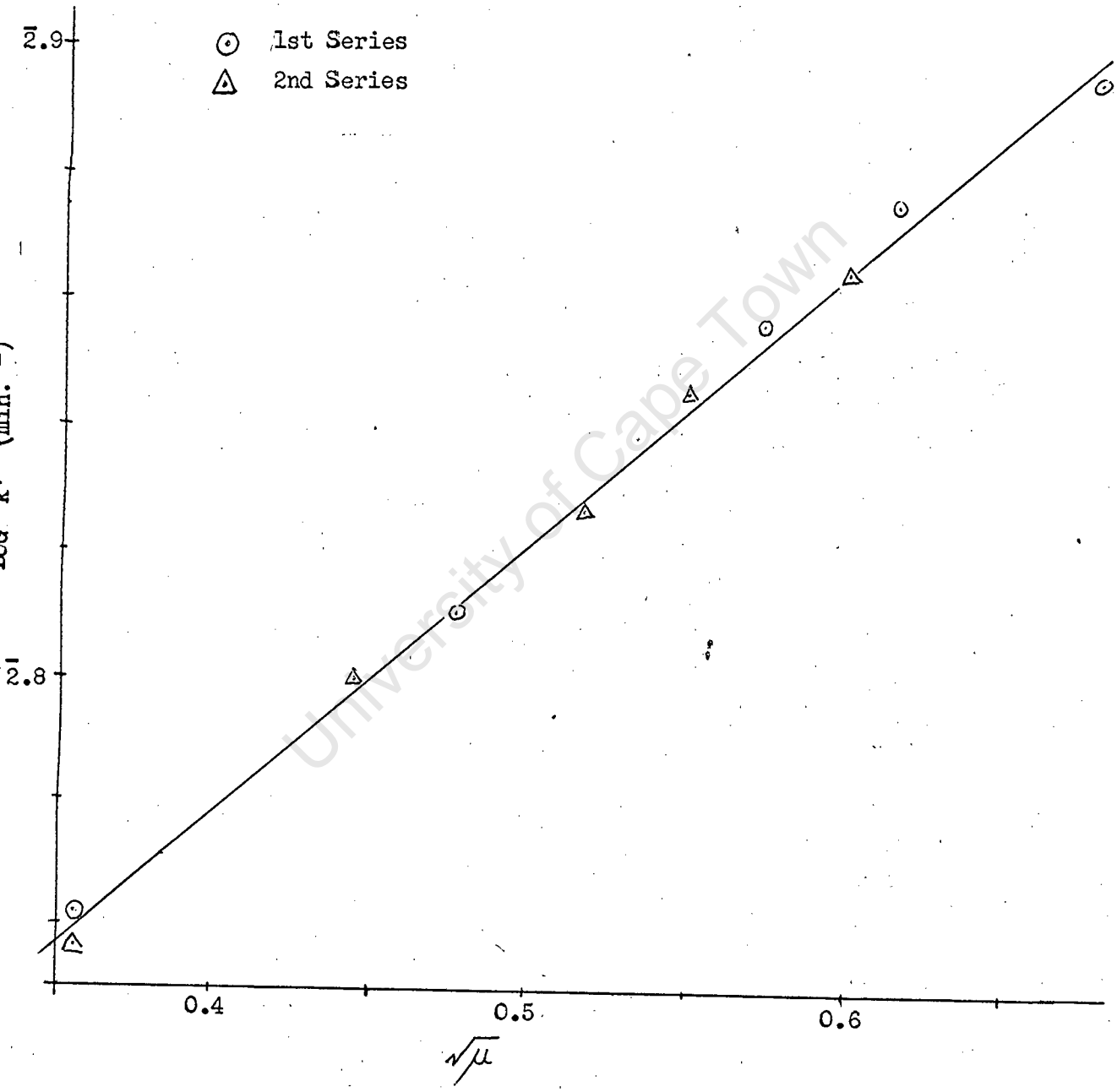
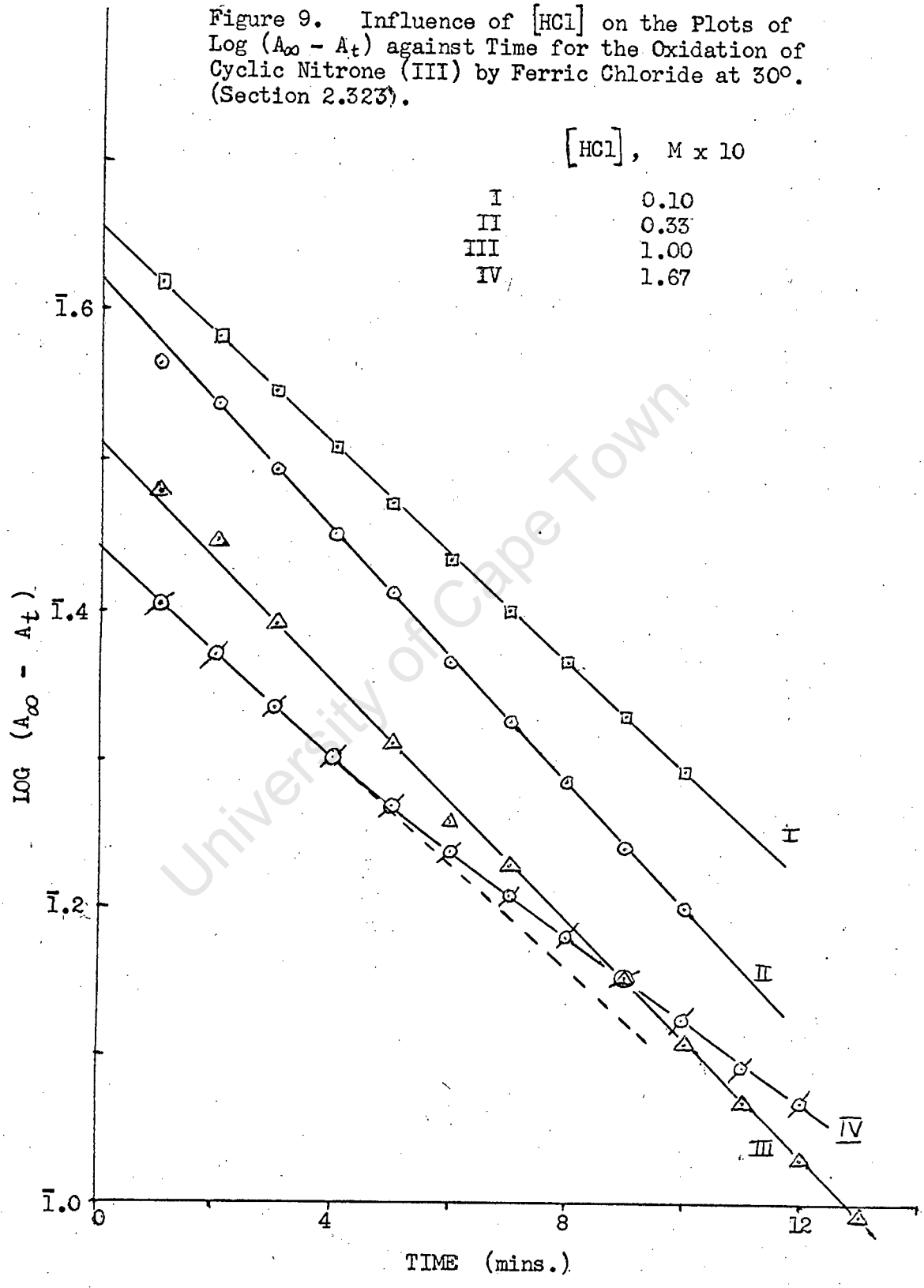


Figure 9. Influence of [HCl] on the Plots of Log ($A_\infty - A_t$) against Time for the Oxidation of Cyclic Nitrone (III) by Ferric Chloride at 30°. (Section 2.323).



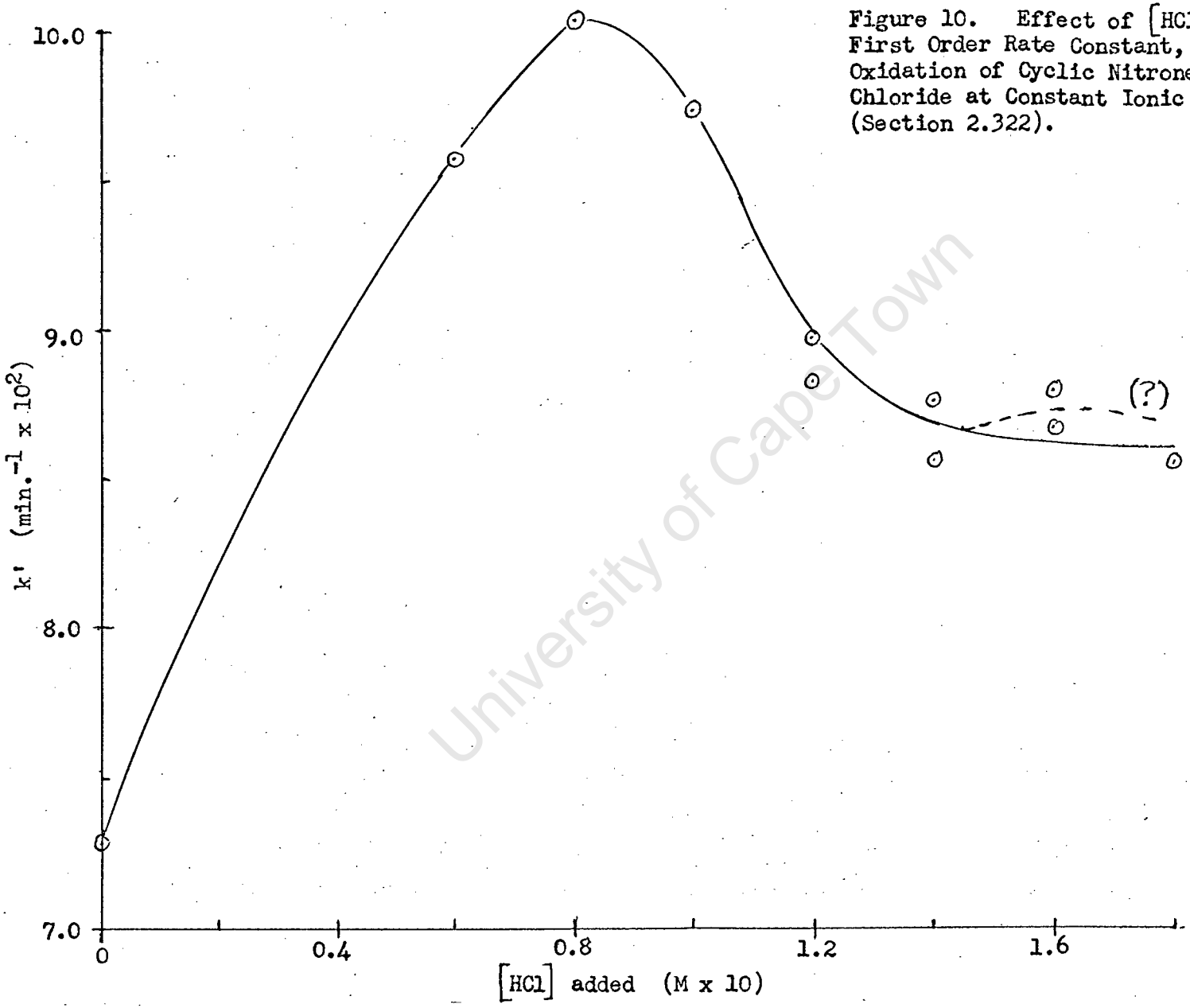


Figure 10. Effect of [HCl] on the Pseudo-First Order Rate Constant, k', for the Oxidation of Cyclic Nitrone (III) by Ferric Chloride at Constant Ionic Strength and 30°. (Section 2.322).

Figure 11. Plot of Absorbance against Time to measure Initial Rate for Oxidation of Cyclic Nitrone (III) by Ferric Chloride. (Section 2.324).

Initial (III) = 6.36×10^{-3}M; initial $[FeCl_3] = 4.24 \times 10^{-3}$M; $\mu = 0.279$; temperature = 30.0°.

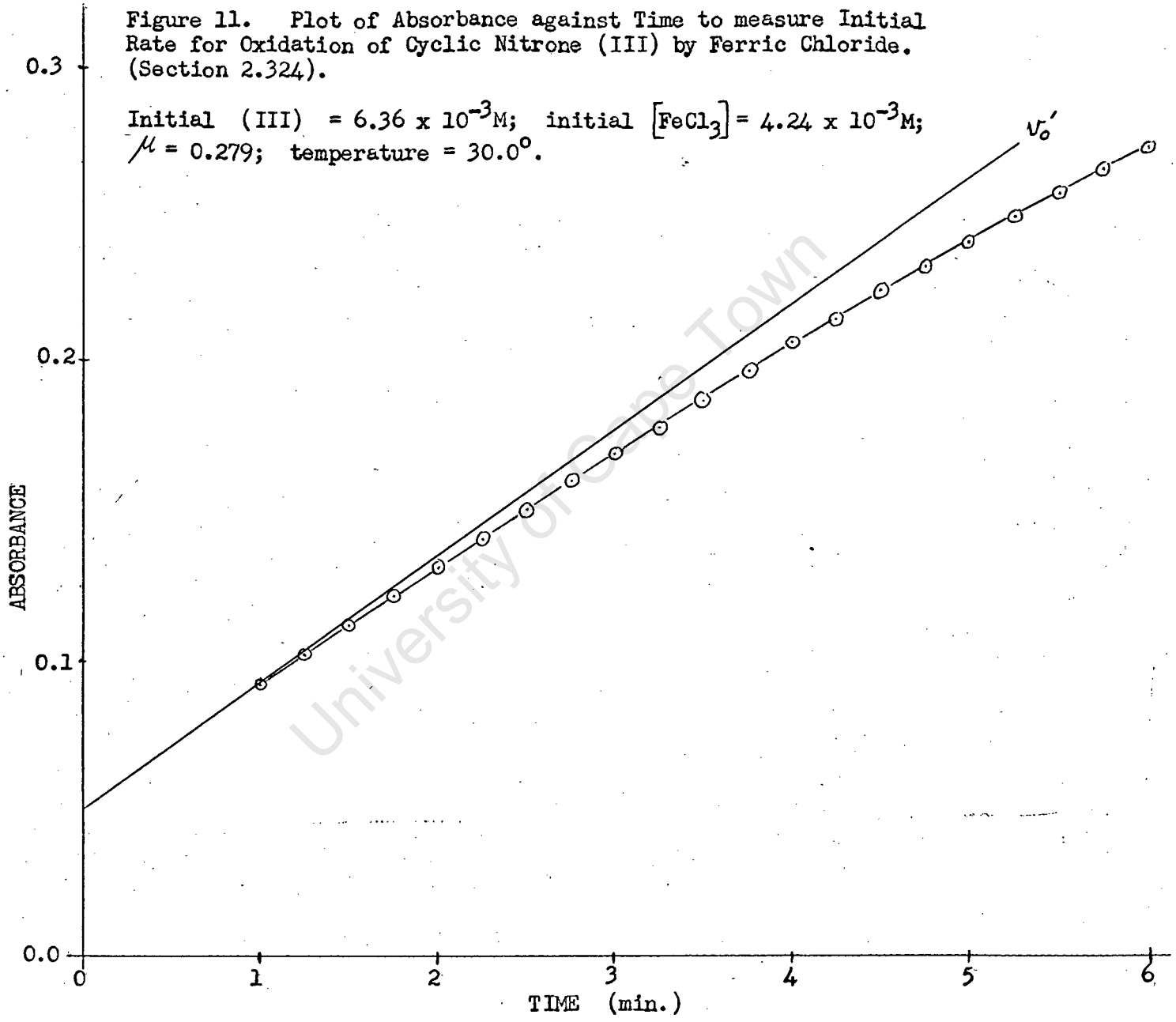


Figure 12. Influence of [$FeCl_3$] on Pseudo-First Order Rate Constant, k' ($min.^{-1}$), for Oxidation of Cyclic Nitrone (III) at constant Ionic Strength and different Temperatures.
(Sections 2.325 and 2.326).

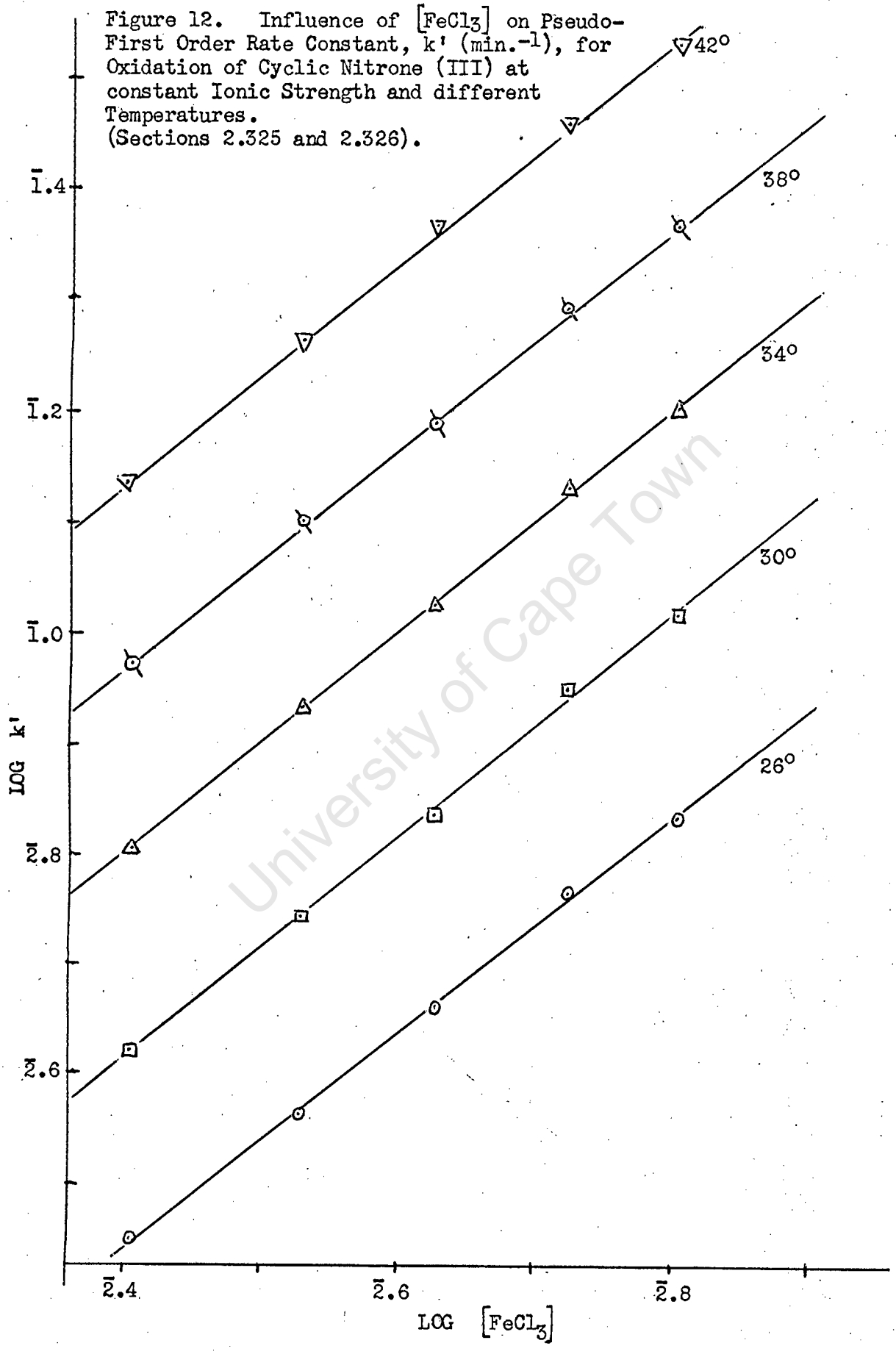
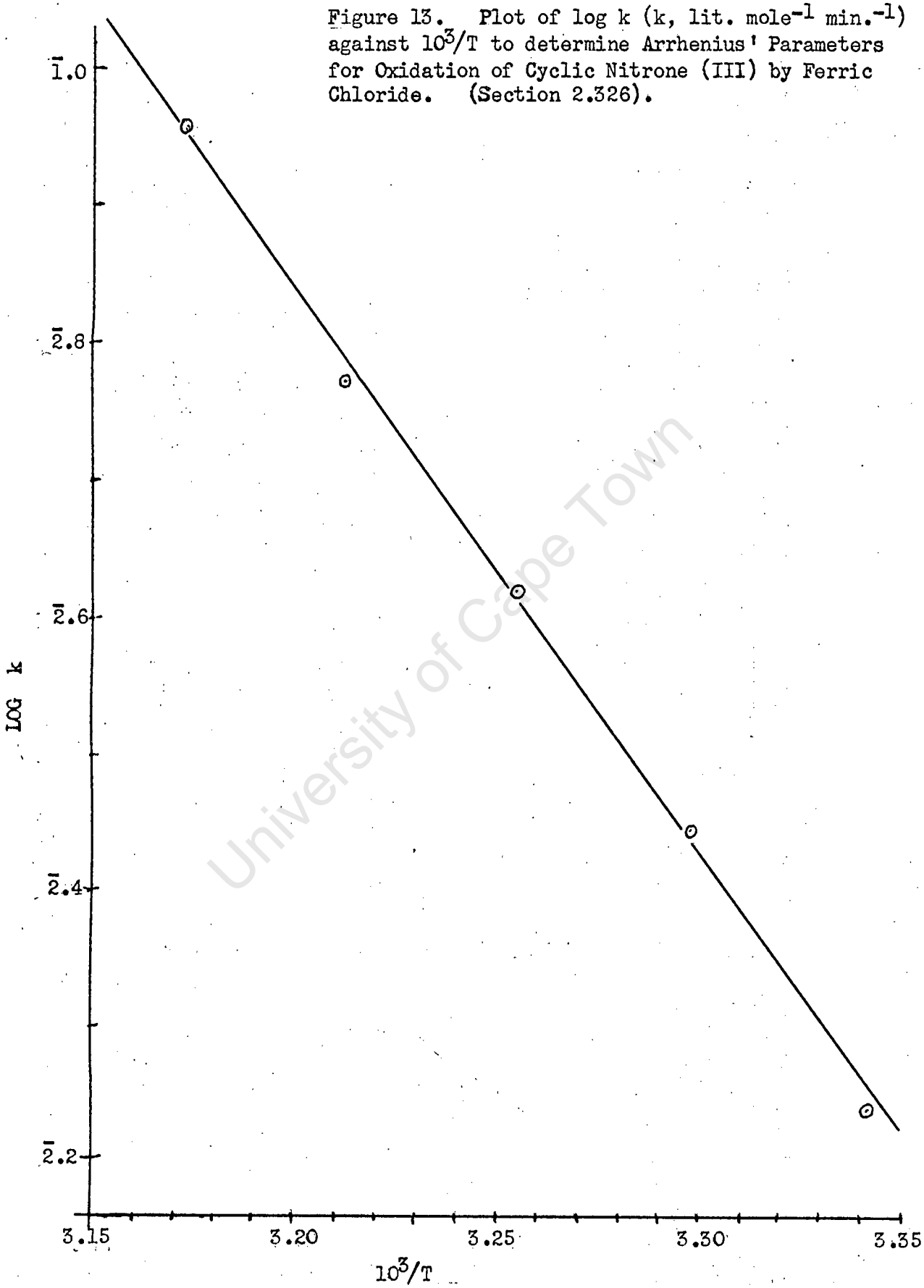


Figure 13. Plot of log k (k, lit. mole^{-1} min.$^{-1}$) against $10^3/T$ to determine Arrhenius' Parameters for Oxidation of Cyclic Nitrone (III) by Ferric Chloride. (Section 2.326).



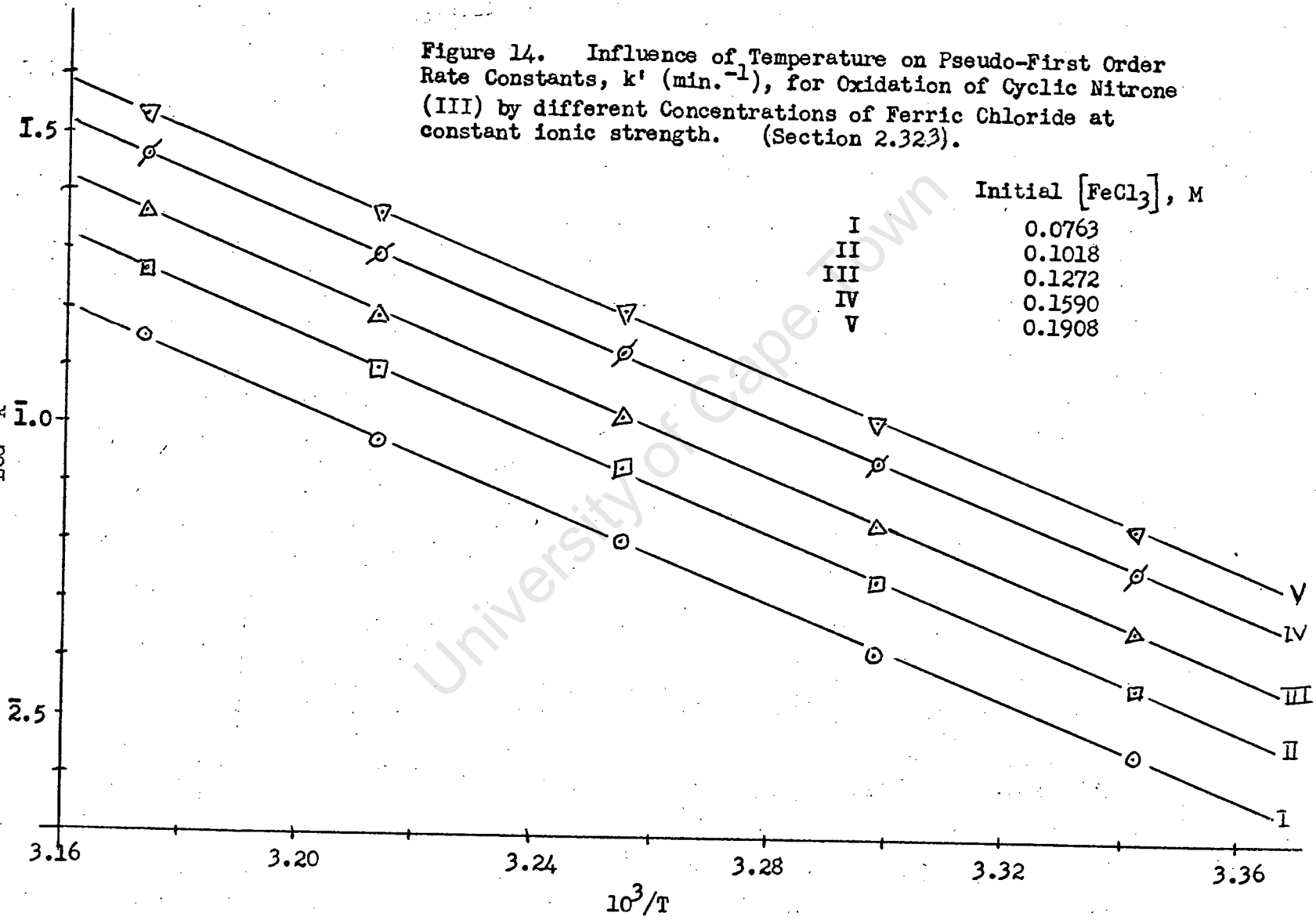


Figure 14. Influence of Temperature on Pseudo-First Order Rate Constants, k' ($min.^{-1}$), for Oxidation of Cyclic Nitrone (III) by different Concentrations of Ferric Chloride at constant ionic strength. (Section 2.323).

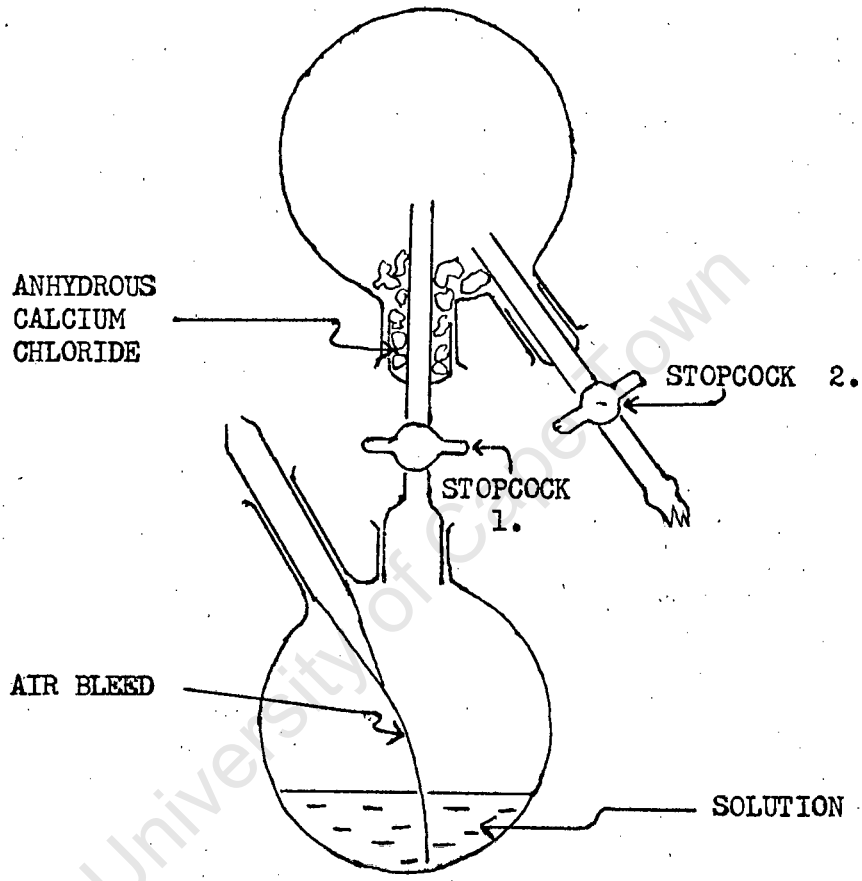


Figure 15. Apparatus for isolation of nitrous oxide from reaction solution.

APPENDIX 2.

Method used to isolate nitrous oxide from solutions of cyclic nitrones oxidised by ferric chloride.

The apparatus is that shown in Figure 15 (Appendix 1).

The solution was introduced into the lower flask into which a fine "bleed" passed. Taps 1 and 2 were opened and the apparatus was carefully evacuated at the water pump *via* Tap 2. When the solution began to "boil" vigorously, Tap 1 was closed and the upper flask was evacuated as completely as possible at the water pump (15 mm. Hg). Tap 2 was then closed and Tap 1 was cautiously opened. As the vigour of the air stream decreased, Tap 1 was gradually fully opened. The apparatus was left until only a small stream of air bubbles passed through the solution. Tap 1 was then shut and the upper flask removed together with Tap 1. This flask would contain a mixture of nitrous oxide and air.

The socket carrying Tap 1 was removed, anhydrous calcium chloride (10 - 20 g) was rapidly introduced and a ground-glass stopper was inserted. The gas in the flask, after drying overnight, was then transferred to an IR gas cell using standard equipment.

A blank run, in which ferric chloride solution alone was present in the lower flask, showed, upon IR examination, that it was not necessary to remove possible impurities in the air entering the bleed.

INDEX

**Indicates the compound has not been reported in the literature.

Diglycollic acid 124

Equivalent weight, determination of, picrates 112
picrolonates 129

Glyoxal, phenylosazone 120
2,4-dinitrophenylosazone 121

Hexane-2,5-dione 155
bis-2,4-dinitrophenylhydrazone 155

Mesitonic acid, 2,4-dinitrophenylhydrazone 158
semicarbazone 158

Morpholine, picrate 117

Morpholine, 4-hydroxy-, 106
oxalate 107
picrate 116
p.m.r. spectrum Fig. 2a

**3-Morpholone, 4-hydroxy-, 123

**bicyclo [4,3,0] Nonane, 3,7-dioxa-6-aza,
8-ethoxycarbonyl-, 129
picrolonate 129
p.m.r. spectrum Fig. 2b

**bicyclo [4,3,0] Nonan-8-one, 4,9-dioxa-1,7-diaza-,
7-phenyl 128

**1,4-Oxazine 4-oxide, Δ^3-dihydro-, 110
cycloaddition with cyclohexene 126
ethyl acrylate 128
phenylisocyanate 127
oxidation by 2,4-dinitrophenylhydrazine 121
ferric chloride 122,124
phenylhydrazine 120
picrate 112
polymer 114
reduction by catalytic hydrogenation 115,117
sodium borohydride 116
sulphur dioxide 118
zinc-acetic acid 118
spectral studies 110,111

Δ^{1}-Piperideine 1-Oxide 139

Piperidine, 1-Hydroxy-, 139

2-Piperidone., 1-hydroxy-, 149,151

Pyrrolidine, 1-butyl-, 131
1-hydroxy-, 132
hydrogen oxalate 133
picrate 133
** 4,4-dimethyl-2(1-hydroxy-2,4,4-trimethylpyrrolidin-2-ylmethyl) 144
2,2,4,4-tetramethyl 136
2,4,4-trimethyl 142
** 1-oxide, 1-n-butyl 131
picrate 132

2-Pyrrolidone, 1-hydroxy-, 5,5-dimethyl 144,146
** 3,3,5,5-tetramethyl 140,151
4,5,5-trimethyl 135,147

1-Pyrroline 1-oxide 133
picrate 133
** 2,5-dimethyl 137
picrate 138
5,5-dimethyl, picrate 134
** 4,4-dimethyl-2-(1-hydroxy-2,4,4-trimethyl-5-oxo-pyrrolidin-2-ylmethyl) 152
4,4-dimethyl-2-(1-hydroxy-2,4,4-trimethylpyrrolidin-2-ylmethyl) 143
5-hydroxy-2,5,5-trimethyl 159
3,3,5,5-tetramethyl 136
picrate 136
2,4,4-trimethyl 137,150
picrate 151
2,5,5-trimethyl 139
picrate 139
4,5,5-trimethyl 134
picrate 134
2-d-4,5,5-trimethyl 135

**tricyclo [7,4,0 ^{3,8}] Tridecane, 2,6-dioxa-5-aza-, 127
picrate 126
p.m.r. spectrum Fig.2c

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