SOME ASPECTS OF THE CYCLO-ADDITION REACTIONS OF NITRONES

by

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A Thesis Presented to the
University of Cape Town
for the Degree of
Doctor of Philosophy.

Department of Chemistry,
November, 1961.

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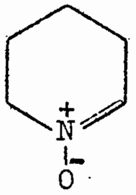
INTRODUCTION

In 1956, Thesing and Mayer[1] reported the synthesis of the dimer (II) of 1-piperideine 1-oxide (I), and they confirmed[1,2] that by analogy to the previously known non-cyclic nitrones[3], the nitrone function, (albeit somewhat masked in the dimeric state), behaved as a very reactive electrophile.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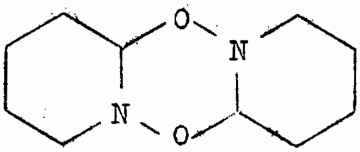
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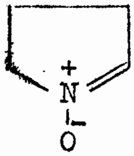
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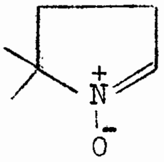
Shortly afterwards, Sir Alexander Todd and his co-workers[4] were successful in preparing monomeric derivatives of 1-pyrroline 1-oxide (III), whose diverse and fascinating properties have been made the object of a detailed study by the Cambridge School.[5,6,7,8,9,10]

Although these developments arise from very recent work, it should not be imagined that nitrones are by any means a novel class of substances. Even before the turn of the century, the so-called "N-ethers" of aldoximes and ketoximes were known and had attracted a certain amount of interest, culminating eventually in a review written with the collaboration of no less a person than Beckmann himself.[11]

The present author became interested in nitrone chemistry in 1958, when he undertook a brief study[12] of the reaction of Grignard reagents on 5,5-dimethyl-1-pyrroline 1-oxide (IV). The object in view was the preparation of isoxazolidines such as (VI) by cyclization of a reactive group

Y with the hydroxyl group of the N-hydroxy-pyrrolidine (V):



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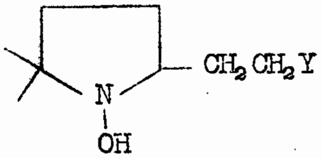

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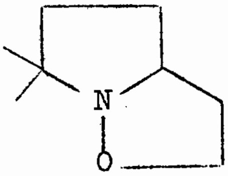


(VI)

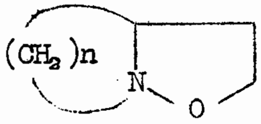
Although the addition of the Grignard reagents followed the expected course, the cyclizations which were attempted did not yield satisfactory results. From this preliminary work however, the author was convinced that the peculiarly reactive nature of the nitrone system could be utilized in novel general heterocyclic syntheses.

The problem studied in this thesis can be broadly divided into two parts:

(a) the use of nitrones in the synthesis of N-bridged polycyclic systems was to be investigated, and

(b) should novel heterocycles be synthesized, some of their more fundamental properties were to be examined.

However, the exact course of a protracted investigation cannot be predetermined. As events turned out, several authors reported results closely related to, and in some cases almost embodying work which was currently undertaken by the author. In the main, it can be emphatically stated that the nitrone function is admirably suited to form heterocycles of a novel type namely N-bridged isoxazolidines, (VII, $n = 3, 4$). The synthesis of such compounds, as well as degradative work leading up to the proof of their structures, will form the main



(VII)

topic of this thesis.

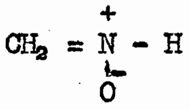
For convenience, the work reported here will be subdivided into four sections. In section I, the reactions which lead up to the formation of the new heterocycles will be introduced, followed by Section II, where degradative proof of their structure will be presented. In Section III, synthetic work relating to the degradation will be elaborated, and finally in Section IV the author will discuss theoretical implications raised by his results.

In addition, the author has thought fit to write what he hopes is a fairly comprehensive review of the chemistry of nitrones in general. This can be considered justified in the light of the fact that the last review on the subject is now more than twenty years out of date[13], in spite of the not inconsiderable amount of interest that these compounds have attracted in recent years.

THE CHEMISTRY OF
THE NITRONES

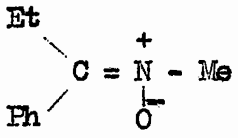
NOMENCLATURE:

For the purpose of this thesis, nitrones are considered to be C- and N-derivatives of the hypothetical substance "nitrone" (VIII).



$$CH_2 = \overset{+}{N} - H \atop \quad\;\;\; \overset{|}{O^-}$$

(VIII)



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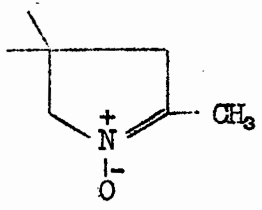
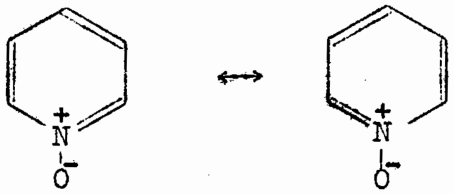


(X)

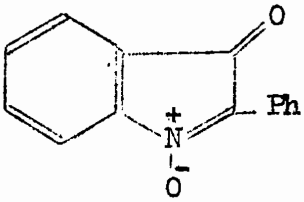
The carbon substituents are named without prefixes, but nitrogen substituents are indicated by the prefix -"N"-. Thus, (IX) is named ethyl-phenyl-N-methyl-nitrone. In the literature reference is occasionally made to aldonitrones, which have only one substituent on the carbon atom, and ketonitrones, which have two. Cyclic nitrones are named as oxides of the appropriate unsaturated heterocycle. For example, (X) is 2,4,4-trimethyl-1-pyrroline 1-oxide.

When the azomethine N-oxide system $>C = \underset{|}{\overset{+}{N}} - \overset{-}{O}$ is part of a cyclic fully conjugated system, the author prefers not to classify such compounds as true nitrones. Hetero-aromatic compounds[14] such as pyridine N-oxide (XI) have the azomethine linkage delocalized by resonance between Kekulé forms. Such compounds do not undergo general reactions of nitrones, although analogies based on the presence of an N-oxide link may be found.



(XI)

Similarly, isatogens (XII),[13] and the misnamed "cyclic nitrones" (XIII) of Köhler[15] are not considered to be nitrones. Chemically they are related to quinones[13]. Derivatives of isoxazoline 2-oxide (XIV)[16] and furoxan[17] (XV) have certain properties similar to nitrones, but are strictly speaking not derivatives of (VIII).



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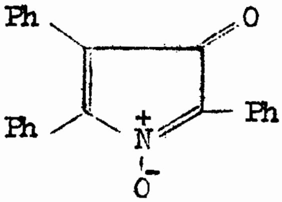

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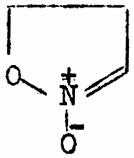

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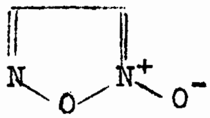

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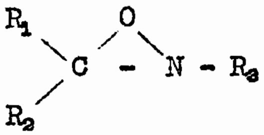
THE STRUCTURE OF NITRONES:

The early workers on nitrones formulated these compounds with a three-membered ring structure (XVI). This is more properly assigned to the newly discovered[18] oxaziranes, since no real evidence was led to substantiate such a structure in the nitrones. The chemistry of nitrones, which will be outlined in this review, more readily suggests the azomethine N-oxide structure (XVII).



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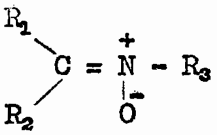


$$R_1R_2C=\overset{+}{N}(\overset{-}{O})-R_3$$

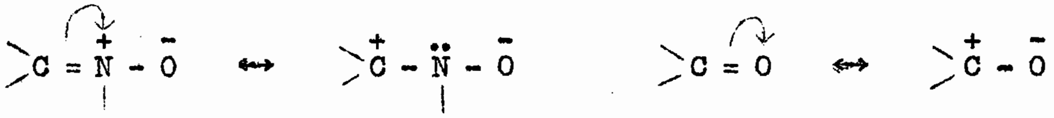
(XVII)

On stereochemical grounds alone, the oxazirane structure is untenable. Lindemann and Tschang[19] failed to resolve the bromocamphorsulphonate of "N-methyl-p-dimethylaminobenzaldoxime" (XVII, R_1 = p-dimethylaminophenyl, R_2 = H, R_3 = Me), which, on the basis of an oxazirane structure, should have an asymmetric carbon atom. The optical isomerism of the true oxaziranes has recently been established[20] by the resolution of 3-isobutyl-

3-methyl-2-propyl-oxazirane (XVI, R_1 = Me, R_2 = isoBu, R_3 = Pr).

The azomethine N-oxide group has an oxygen atom linked to nitrogen by a dative covalent bond, and this can be expected to lead to a considerable degree of polarity in the N-O link. The modern tendency is to write such N-oxide structures as $\equiv \overset{+}{N} - \overset{-}{O}$, and this will be adopted throughout this work, as opposed to the older $\equiv N \rightarrow O$ formulation.

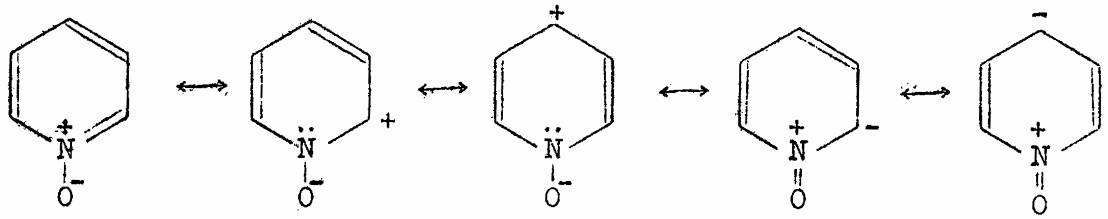
The polarity of the N-O link can be expected to be transmitted to the azomethine C = N bond. Indeed, the general reactions of nitrones suggest that the azomethine N-oxide system is a resonance hybrid of the two canonical extremes A and B, the mesomeric effect in the group tending to restore a lone pair of electrons on the nitrogen atom:



A B

There is a formal similarity between this effect and that which is found in the carbonyl group. Both the nitrone and carbonyl systems having, in the extreme, an electrophilic carbon atom, and a negatively charged oxygen atom. The lone pair of electrons on the nitrogen atom acts as an "electronic bridge" between the carbon and oxygen atoms, and the nitrone group may be regarded as an "extended carbonyl group". This similarity is not only formal, for as we shall see later, nitrones and aldehydes and ketones undergo closely analogous addition reactions.

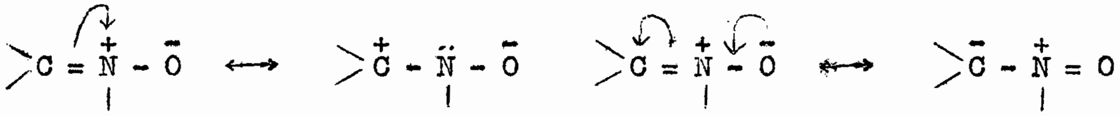
Certain reactions of nitrones have indicated that another kind of polarisation may take place, analogous to a "back-polarisation" which has been observed in pyridine oxides. Thus, electron distribution calculations[21] have shown that pyridine N-oxide (XI) is a resonance hybrid of the following structures (omitting obvious Kekulé variations):



(XI)

Similar conclusions have been reached by Katritzky and his co-workers as a result of dipole moment measurements on various pyridine N-oxides[22].

Thus, we can never exclude the possibility of nitrones reacting in two extreme forms, each of which a result of distinctly different mesomeric effects:



$$>C=\overset{+}{N}(-)-\overset{-}{O} \longleftrightarrow >\overset{+}{C}-\ddot{N}(-)-\overset{-}{O} \qquad >C=\overset{+}{N}(-)-\overset{-}{O} \longleftrightarrow >\overset{-}{C}-\overset{+}{N}(-)=O$$

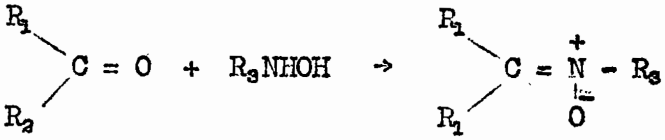
A B

THE SYNTHESIS OF NITRONES:

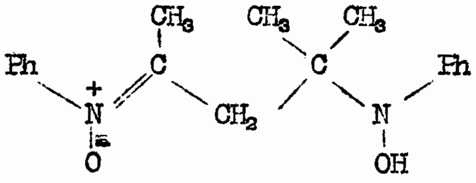
No account of the chemistry of nitrones would be complete without a summary of the principal reactions which are used in their preparation. However, since the chemical behaviour of the nitrone function is remarkably dependent on the groups which may be attached to it, wide generalisations are not always possible. In many cases the monomeric nitrones are not obtained, as they may spontaneously polymerise under even the mildest conditions. Bearing this in mind, some of the more important methods of nitrone synthesis are described below.

1. Condensation of Monosubstituted Hydroxylamines with Aldehydes and Ketones:

A considerable number of nitrones have been synthesised by the reaction of various hydroxylamines with aldehydes and ketones. The general reaction may be formulated:



It is analogous to the well-known formation of oximes from aldehydes and ketones by their condensation with hydroxylamine. Thus, N-substituted oximes are obtained from N-substituted hydroxylamines. The reaction however does not lend itself to general applications. For example, although both phenylhydroxylamine and methylhydroxylamine readily condense with aromatic aldehydes to form stable, monomeric nitrones[23], arylhydroxylamines generally react with acetone to give dimeric products[11]. Banfield and Kenyon[26] have formulated the product of the condensation of phenylhydroxylamine and acetone as (XVIII), and similar conclusions have been reached as to the structure of the compound obtained from n-butyraldehyde and phenylhydroxylamine[25]. A dimer of a different type is formed by the reaction of phenylhydroxylamine and formaldehyde[26].



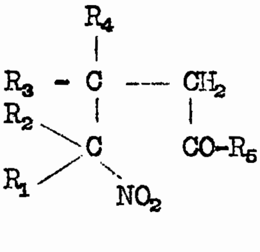
(XVIII)

The facile condensation of arylhydroxylamines and aldehydes is not generally duplicated with ketones, except as we have seen, with acetone. Beckmann and Scheiber failed to obtain products from phenylhydroxylamine and various aliphatic ketones[11]. Recently however, unstable nitrones have been prepared by the condensation of ketones or ketals with methylhydroxylamine hydrochloride under anhydrous conditions[27]. It must be pointed out that as far as a large number of nitrones is concerned, neither molecular weight determinations nor absorption spectra are available, thus leaving us in the dark as to the validity of a simple nitrone structure for these compounds.

2. Reduction of a Nitro Compound in the Presence of an Aldehyde or a Ketone:

This method can be considered as an experimental variation of the reaction described above, since the reduction is carried out in such a manner as to generate the hydroxylamine, which is the active intermediate[11].

Of particular interest is the extension of this reaction, which involves the cyclization of γ-hydroxylaminocarbonyl compounds (XX), obtained by reduction of γ-nitrocarbonyl compounds (XIX).



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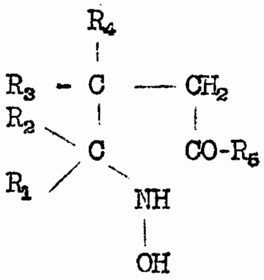

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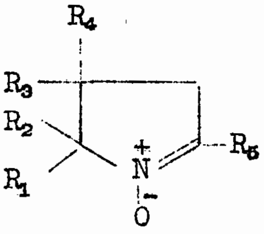


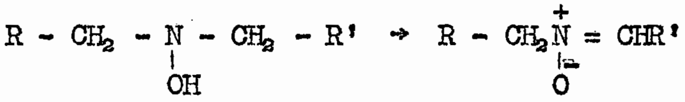
(XXI)

The products of such reductive cyclizations are the 1-pyrroline 1-oxides (XXI), which can be obtained in good yields by reducing the nitrocarbonyl compound with zinc dust and aqueous ammonium chloride solution[29,5]. The reduction should be carried out at temperatures preferably not exceeding 15°C., or high proportions of 1-pyrrolines may result[31]. Reduction of γ-nitroketones to 1-pyrroline 1-oxide has also been achieved by the use of hydrazine in the presence of Raney nickel[29].

The 1-pyrroline 1-oxides are the most convenient substances available to study the behaviour of the nitrone system in an isolated state, since the monomeric forms are stable. In addition, the γ-nitrocarbonyl compounds from which these cyclic nitrones are derived are readily available by Michael addition of nitroalkanes and αβ-ethylenic aldehydes and ketones, or even from nitro-olefines and aldehydes and ketones[32].

3. Oxidation of N,N-Dialkylhydroxylamines:

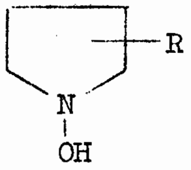
The oxidation of secondary alcohols to ketones has a parallel in the conversion of N,N-dialkylhydroxylamines to nitrones by a variety of oxidizing agents:



$$R - CH_2 - \underset{OH}{N} - CH_2 - R' \rightarrow R - CH_2\underset{O^-}{\overset{+}{N}} = CHR'$$

Mercuric oxide[33], lead dioxide[34], potassium ferricyanide[25,35,36], potassium permanganate[37], cupric acetate[38] and hydrogen peroxide[9,37] have all been found to be effective. If more gentle conditions are required, the oxidation may also be carried out using atmospheric oxygen, catalysed by $Ag(NH_3)_2^+$ or $Cu(NH_3)_4^{++}$ ions[25,39].

Oxidation of cyclic hydroxylamines results in the formation of cyclic nitrones. For example, 1-hydroxypyrrolidines (XXII) may be converted to 1-pyrroline 1-oxides (XXIII) in excellent yields by copper catalysed aerial oxidation[5] or by mercuric oxide[40].



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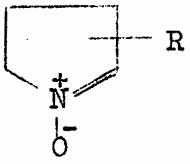
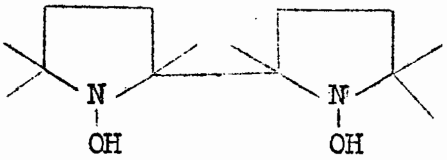


(XXIII)

If there are no hydrogen atoms on the carbon atoms adjacent to the hydroxylamino group, then C - C links may be broken. Thus, both 1,1'-dihydroxy-2,5,5,2'5'5'-hexamethyl-2,2'-bipyrrolidinyl (XXIV) and 1,5-dihydroxy-2,2,4a,6,6,8a-hexamethyl-1,5-diazadecalin (XXV) gave the same nitrone (XXVI) on oxidation with atmospheric oxygen in the presence of cuprammonium ions[9].



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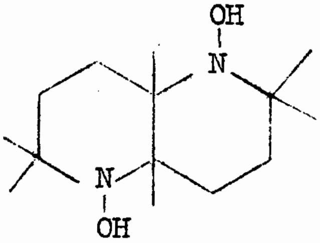

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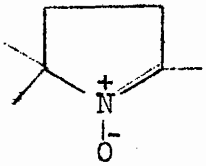
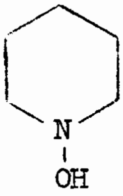


(XXVI)

In the six membered ring series, oxidation by various means does not generally give monomeric nitrones, and the product may to a certain extent depend on the nature of the reagent used to effect the oxidation. 1-Hydroxypiperidine (XXVII) gave the dimeric nitrone (II) on oxidation with cupric acetate[1], but oxidation with potassium ferricyanide[2] gave a trimer which has been formulated as (XXVIII).



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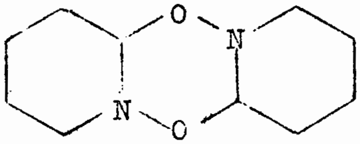

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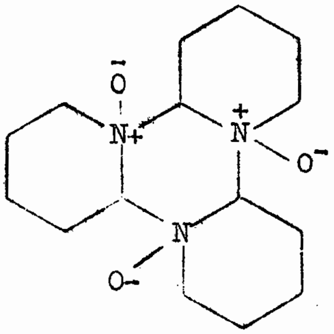
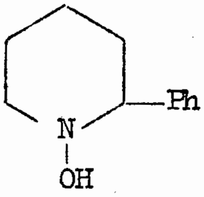


(XXVIII)

Unsymmetrical dialkylhydroxylamines with hydrogen atoms on both adjacent carbon atoms, can theoretically give rise to two isomeric nitrones. Few studies have been carried out in order to determine the factors influencing the orientation of the double bond, but Thesing and Mayer[2], in their work on the oxidation of 1-hydroxy-2-phenyl-piperidine (XXIX), have shown that the double bond did not enter into conjugation with the aromatic ring.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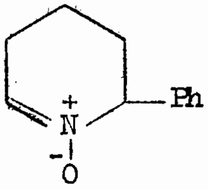
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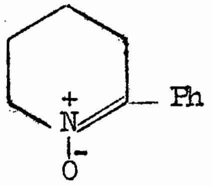
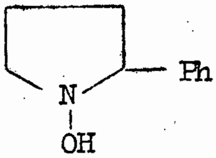

(XXXI)

Thus, the product of the oxidation was the dimer of (XXX), and not (XXXI) as expected. The results are different when 1-hydroxy-2-phenyl-pyrrolidine (XXXII) is oxidised[40], as in that case, the double bond enters into conjugation with the phenyl group to form monomeric 2-phenyl-1-pyrroline 1-oxide (XXXIII).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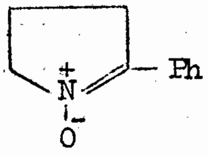
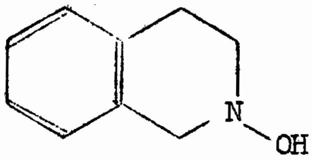
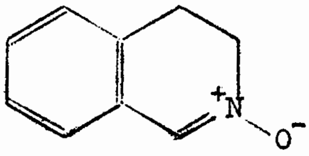

(XXXIII)

The difference between these results has been explained by Thesing and his co-workers[2,40] as being due to conformational effects in five and six membered rings. 2-Hydroxy-1,2,3,4-tetrahydro-iso-quinoline (XXXIV) has been oxidized[2] with mercuric oxide to the monomeric 3,4-dihydro-iso-quinoline 2-oxide (XXXV), thus providing us with yet another example of a stable cyclic nitrone:



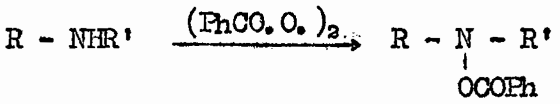
(XXXIV)



(XXXV)

The oxidation method for the synthesis of nitrones is limited in its usefulness by the availability of the parent hydroxylamines. It will not be out of place to list briefly here a few methods for their preparation:

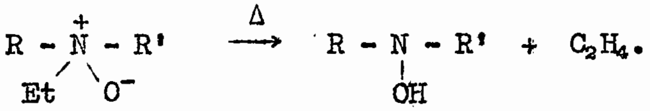
(i) Direct oxidation of secondary amines with hydrogen peroxide of various concentrations gives only low yields of hydroxylamines[41,42]. The oxidation may be carried out by the agency of benzoyl peroxide[43], which affords moderate yields of O-benzoylhydroxylamines:



$$R - NHR' \xrightarrow{(PhCO.O.)_2} R - \underset{\substack{| \\ OCOPh}}{N} - R'$$

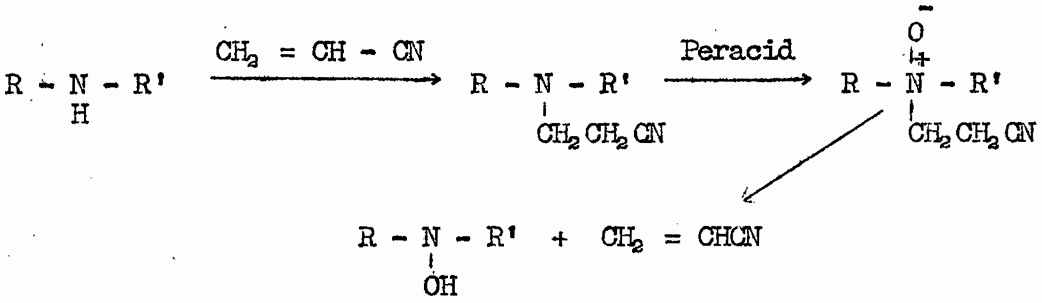
Another method makes use of hydrogen peroxide in the presence of ethyl formate[44]. Good yields have been claimed in the oxidation of pyrrolidine and piperidine to the corresponding N-hydroxy heterocycles, but the author has unfortunately not been able to duplicate these results, an experience which is shared by other workers in this field[40].

(ii) Certain tertiary amine oxides undergo pyrolysis to give olefins and hydroxylamines in varying yields[45]:



$$R-\underset{Et\ \ \ O^-}{\overset{+}{N}}-R' \xrightarrow{\Delta} R-\underset{OH}{N}-R' + C_2H_4.$$

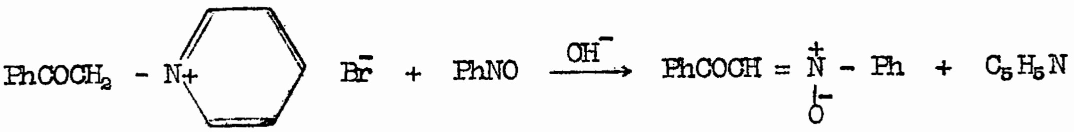
(iii) N-oxides of cyanoethylated or carbethoxyethylated secondary amines are alkali labile, and cleave to form hydroxylamines and acrylonitrile or ethyl acrylate[46].



(iv) The addition of Grignard reagents to nitrones, which results in the formation of more highly substituted hydroxylamines, often in very high yields, will be discussed later.

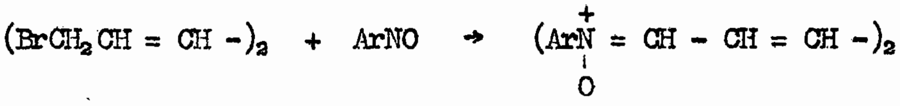
4. Reaction of Pyridinium Halides with Aromatic Nitroso Compounds:

Certain pyridinium halides, obtained from pyridine and reactive halogen compounds, react with aromatic nitroso compounds in the presence of alkali, to form N-aryl nitrones in good yields. This was first noticed by Kröhnke[47], who reacted phenacyl pyridinium bromide (XXXVI) with nitrosobenzene, and obtained benzoyl-N-phenyl nitrone (XXXVII):



(XXXVI) (XXXVII)

The halogen compounds which are suitably reactive include α-halo-carbonyl compounds, benzyl halides[48], and allyl halides. The use of the latter type may be suitably illustrated by the preparation[49] of the highly conjugated dinitrone (XXXIX, Ar = p-dimethylaminophenyl) from the dibromide (XXXVIII):

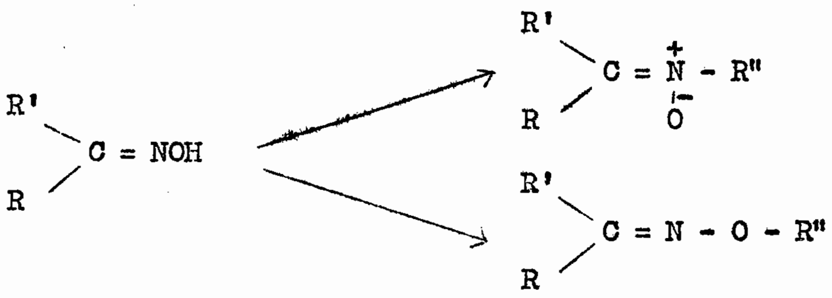


$$(\mathrm{BrCH_2CH = CH -})_2 \;+\; \mathrm{ArNO} \;\rightarrow\; (\mathrm{Ar}\underset{\substack{|\\ \mathrm{O}}}{\overset{+}{\mathrm{N}}} = \mathrm{CH - CH = CH -})_2$$

(XXXVIII) (XXXIX)

5. The Alkylation of Oximes:

The early nomenclature, which designated nitrones as N-ethers of aldoximes and ketoximes tried to differentiate between these and the isomeric O-ethers (XL), which are both produced by the alkylation of oximes.

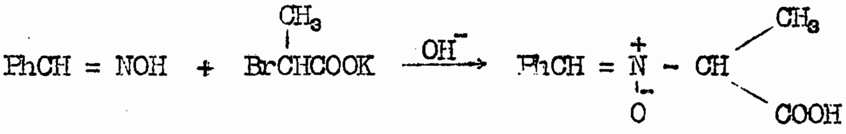


(XL)

The formation of a particular isomer, or its preponderance in a mixture containing both, is largely dependent on both experimental conditions and the nature of the alkylating agent. In general, the O-ethers are obtained exclusively when an oxime is alkylated with an alkyl iodide in the presence of silver oxide[13,50]. Aldoximes, on prolonged contact (about 5 months) with methyl iodide or dimethyl sulphate, have yielded hydriodides and methosulphates of nitrones[51].

When the alkylation is carried out under alkaline conditions, such as are met when the oxime is dissolved in a solution of sodium hydroxide, mixtures of O-ethers and nitrones are obtained. There appears to be a definite relationship between the acidity of the parent oxime, and the composition of the product mixture. Broadly, the higher the dissociation constant of the oxime, the higher the proportion of the O-ether[52,53].

The alkylation procedure, in spite of its obvious shortcomings, is of some preparative use, as witnessed by the synthesis of phenyl-N-(1-carboxyethyl) nitrone (XLI) from potassium bromopropionate and benzaldoxime in an alkaline medium[54]:

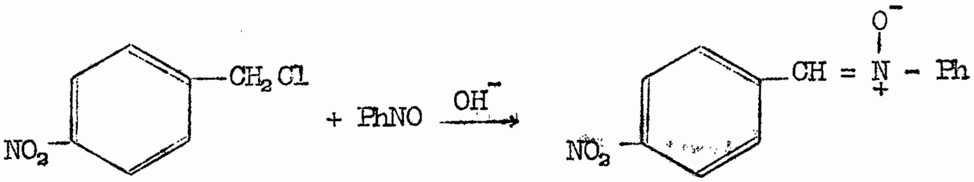


(XLI)

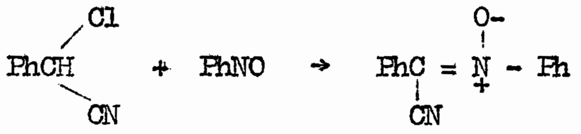
6. Miscellaneous Methods:

In the following discussion we will consider a number of reactions which have led to the formation of nitrones or modified nitrones, but which have not been developed sufficiently for general use, or which have only limited applications.

Under alkaline conditions, nitrobenzyl chlorides, which have a very reactive chloromethyl group, will react with aromatic nitroso compounds to yield nitrones[55,56]:

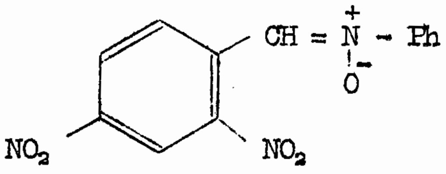


This reaction is clearly related to that which was discussed under 4. In a similar way, α-cyano-nitrones are readily obtained from α-chlorophenylacetonitrile (XLII) and aromatic nitroso compounds in the presence of alcoholic potassium hydroxide[57]:

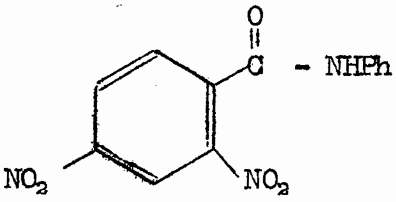


(XLII)

Aromatic nitro compounds which have an activated methyl group, can condense with nitroso compounds to form nitrones. Thus, 2,4-dinitrotoluene and nitrosobenzene give 2,4-dinitrophenyl-N-phenyl-nitrone (XLIII), together with the anilide (XLIV), formed by isomerisation of the nitrone under the alkaline conditions necessary for the condensation (see p. 37)[58]. Similar results were obtained by other authors[59].

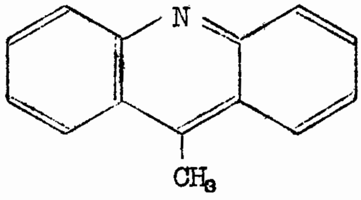


(XLIII)

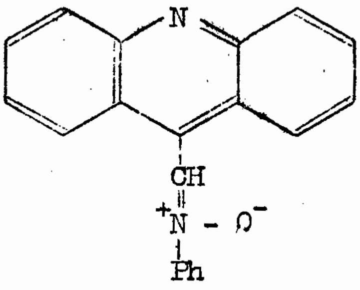


(XLIV)

9-Methyl-acridine (XLV) and its derivatives have been observed to condense with aromatic nitroso compound to form nitrones such as (XLVI), together with varying amounts of the related anils[60,61]:

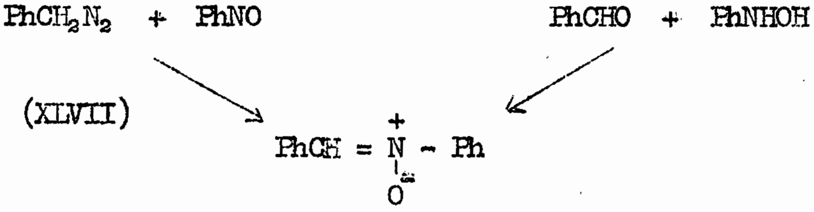


(XLV)



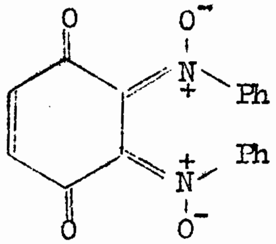
(XLVI)

Aliphatic diazo-compounds are found to react with aromatic nitroso compounds to yield nitrones[65]. This is exemplified by the reaction of phenyldiazomethane (XLVII) and nitrosobenzene to produce phenyl-N-phenyl nitrone (XLVIII), identical with the nitrone resulting from the condensation of benzaldehyde and phenylhydroxylamine[62]:



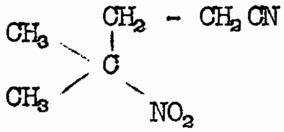
(XLVIII)

Aromatic nitroso compounds have also been found to undergo addition reactions with p-quinones. For example, the product of the addition of p-benzoquinone and nitrosobenzene[63] is the highly conjugated nitrone (XLIX):

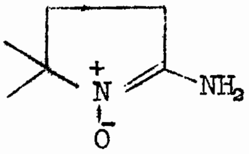


(XLIX)

The reduction of 3-methyl-3-nitrobutyl cyanide (L) with zinc dust and ammonium chloride solution has given 2-amino-5,5-dimethyl 1-pyrroline 1-oxide (LI), an amino-nitrone, which is in tautomeric equilibrium with the imino-hydroxylamine (LII)[64]:

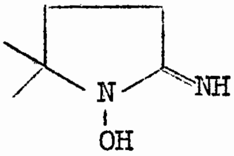


(L)



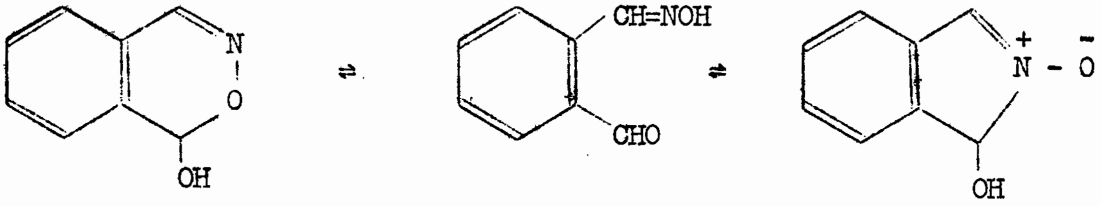
(LI)

⇌



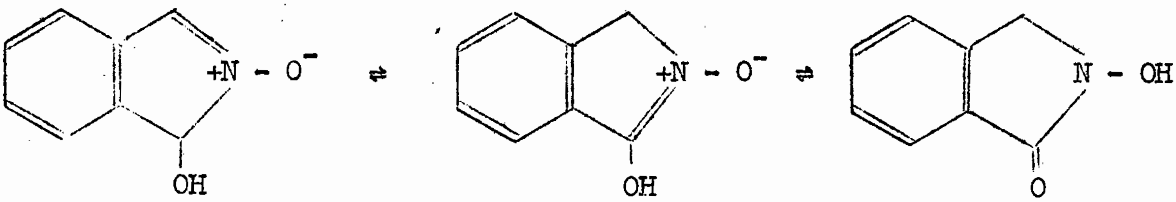
(LII)

Griffiths and Ingold[65] have made a study of the tautomeric system arising from the cyclisation of phthalaldehyde monoxime (LIII):



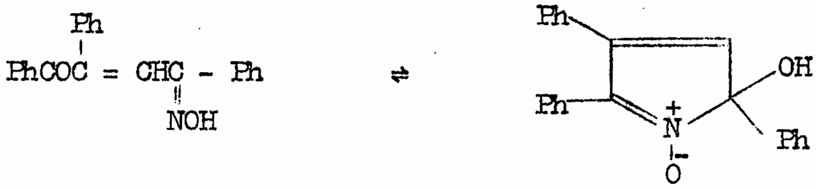
(LIV) (LIII) (LV)

Either 1-hydroxy-2,3-benzoxazine (LIV) or 1-hydroxy-*iso*indolenine 2-oxide (LV) could be obtained. There was strong evidence to suggest that the latter compound was itself a tautomer, the hydroxynitrone being interconvertible with the hydroxamic acid (LVI):



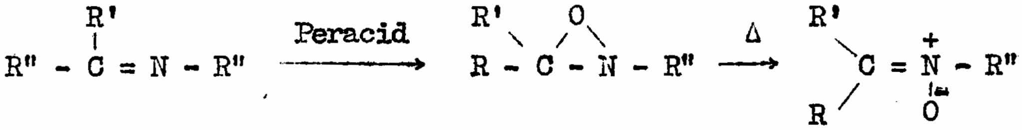
(LVI)

Another example of the intramolecular cyclisation of an oximino and carbonyl group concerns the monoxime of cis-dibenzoyl-phenylethylene (LVII), which is reversibly convertible into the cyclic hydroxy-nitrone[66,67] (LVIII):



(LVII) (LVIII)

The azomethine group C = N of N-substituted imines is susceptible to oxidation by peracids, which results in the formation of oxaziranes[18,20] :

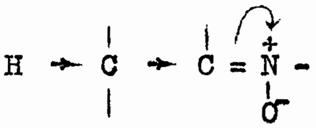


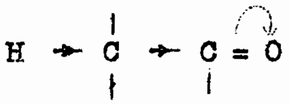
The nitrone is not obtained by such a procedure. However, it is sometimes possible to convert the oxazirans to the nitrones by heating, such changes being sometimes quantitative[68] . On the other hand, amides may also be formed[20] .

GENERAL COMMENTS ON THE CHEMICAL BEHAVIOUR OF NITRONES

It is in their general chemistry that the close similarity between the carbonyl and nitrone groups may be observed. The parallel that can be drawn between these groups is two-fold:

(a) The electromeric effects which are found result in the formation of an electrophilic carbon atom:



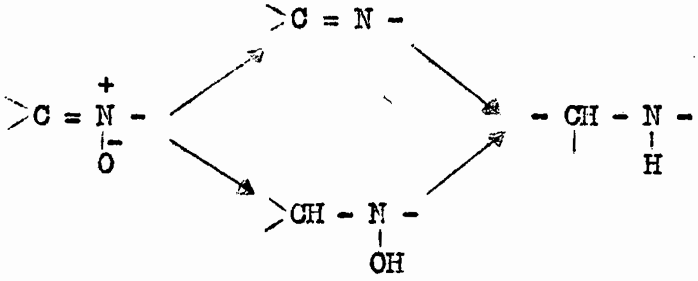


(b) The electrophilic carbon atom exerts in both cases a -I effect in neighbouring links, for example between C and H atoms.

The reader will easily be convinced of this astonishing similarity as he examines the main reactions in detail.

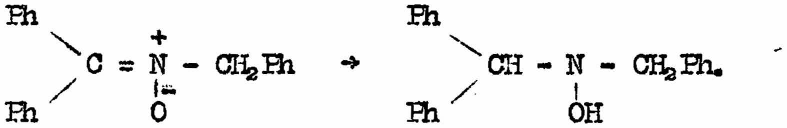
REDUCTION:

The nitrone group represents a high state of oxidation of the nitrogen atom, and it should thus be capable of stepwise reduction to less highly oxidized functional groups. In fact, a reduction sequence depicted below can be theoretically expected:



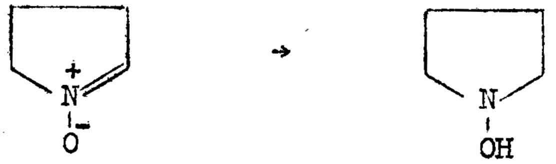
The above steps can be obtained by a judicious use of appropriate reducing agents, and such a sequence may be considered analogous to the reduction of the carbonyl group of ketones to secondary alcohols by various methods, or to paraffins by the well-known Clemmensen reduction[69].

In view of the electrophilic character of the nitrone system, it is hardly surprising to find that, like the carbonyl group, it will be vulnerable to attack by complex hydride reagents. Exner[70] appears to have been the first to have tried out such a reduction, and he reported than non-cyclic nitrones such as (LIX) were smoothly converted to the corresponding hydroxylamine (LX) by lithium aluminium hydride:

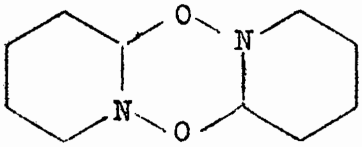


(LIX) (LX)

In the field of cyclic nitrones, this reagent behaves in a similar manner. 1-Pyrroline 1-oxide (LXI) can be reduced to 1-hydroxypyrrolidine (LXII) by lithium aluminium hydride in tetrahydrofuran:



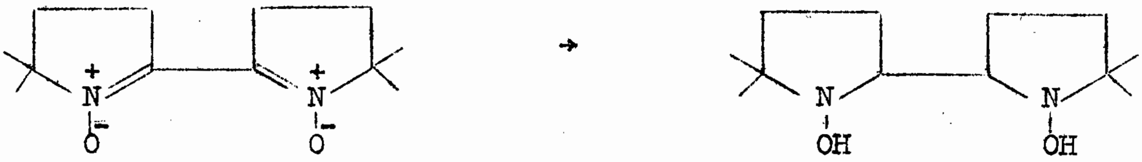
(LXI) (LXII)



(II)

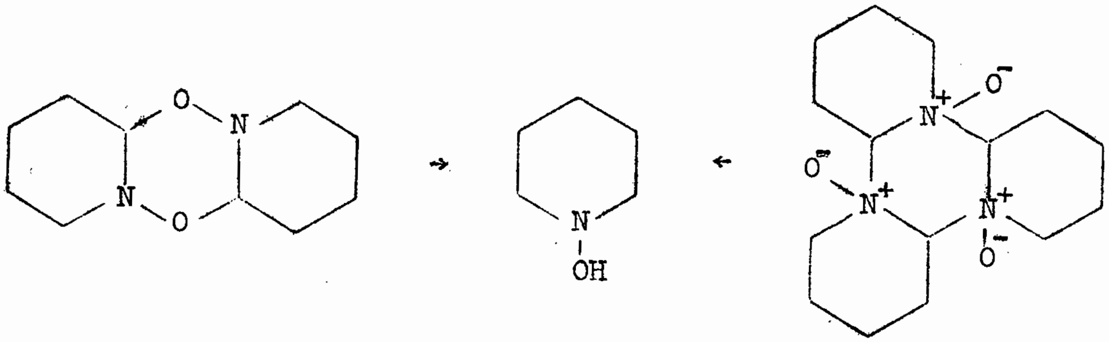
In spite of the fact that a relatively large excess of reagent was used, and that the time of reaction was fairly prolonged, the reduction did not appear to proceed further[40]. The dimeric nitrone (II) could not be reduced by lithium aluminium hydride in diethyl ether[1].

Sodium or potassium borohydrides afford a excellent method of converting nitrones to hydroxylamines[5,9]. For example, the dinitrone (LXIII) was reduced to the dihydroxylamine (LXIV) by sodium borohydride in aqueous solution[9]:



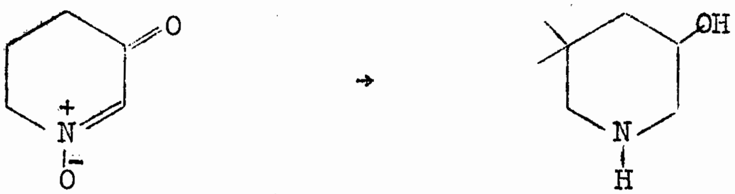
(LXIII) (LXIV)

The reduction of nitrones to hydroxylamines may also be effected by catalytic hydrogenation at pressures near atmospheric. The dimer (II) and trimer (XXVIII) were thus converted to 1-hydroxypiperidine (XXVII)[1,2]. Both platinum and palladium deposited on a barium sulphate support were found to be effective catalysts.



(II) (XXVII) (XXVIII)

The only recorded example of a nitrone system being fully reduced under conditions of catalytic hydrogenation occurred when 1,2,3,4-tetrahydro-3,3-dimethyl-5-oxopyridine 1-oxide (LXV) was hydrogenated in the presence of platinum. The product, 3-hydroxy-5,5-dimethylpiperidine (LXVI) was formed by total reduction of the nitrone to a secondary amine, with concomitant reduction of the ketonic system[7]:



(LXV) (LXVI)

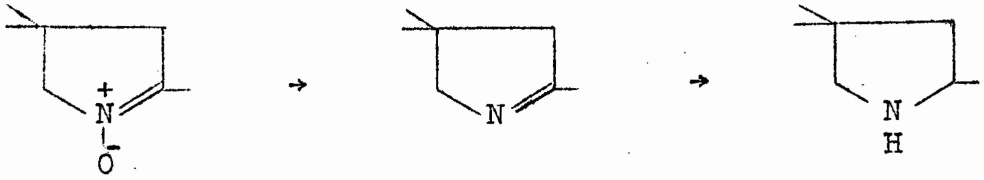
This unusual behaviour may well be ascribed to a mutual activation of the reducible groups.

In the field of acyclic nitrones, reduction by deoxygenation to the azomethine has been accomplished by the use of zinc and ammonium chloride. Phenyl-N-phenyl nitrone (XLVIII) was thus reduced to benzalaniline (LXVII)[71].

$$PhCH = \underset{\downarrow O}{\overset{+}{N}} - Ph \rightarrow PhCH = N - Ph$$

(XLVIII) (LXVII)

Such a reduction may also be carried out by the action of sulphur dioxide. Yields however are low, as in the reduction[5] of 2,4,4-trimethyl-1-pyrroline 1-oxide (X) to 2,4,4-trimethyl 1-pyrroline (LXVIII). Reduction to the pyrroline occurs more readily by the agency of zinc dust and glacial acetic acid[5], or with zinc dust alone[29].

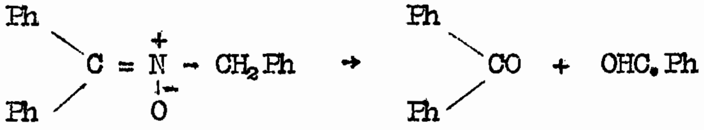


(X) (LXVIII) (LXIX)

Complete reduction of the nitrone system proceeds readily by the action of metals dissolving in strong acids. Tin and hydrochloric acid is a convenient medium for such a reduction. There is strong evidence that such a reduction proceeds via the intermediate azomethine, as witnessed by the fact that both the pyrrolidine (LXIX) and the pyrroline (LXVIII) are obtained by the reduction of the nitrone (X)[5].

OXIDATION:

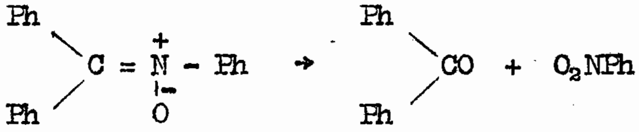
The nitrone function, being the highest state of oxidation of a secondary nitrogen atom, cannot be oxidized further without causing a breakdown of the molecule. Early work in this field[71] demonstrated that diphenyl-N-benzyl nitrone (LIX) was oxidized by chromic acid to a mixture of benzophenone and benzaldehyde.



$$\begin{matrix}Ph\\Ph\end{matrix}\!>C = \underset{\downarrow O}{\overset{+}{N}} - CH_2Ph \rightarrow \begin{matrix}Ph\\Ph\end{matrix}\!>CO + OHC.Ph$$

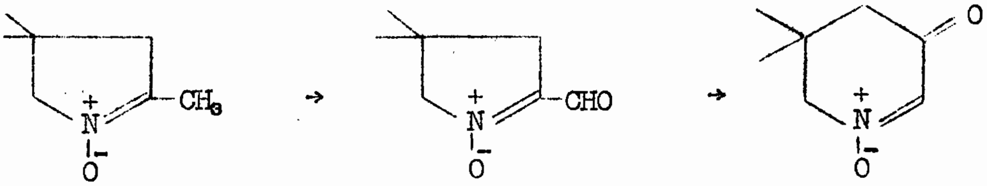
(LIX)

Ozonization of nitrones was carried out by Staudinger and Miescher[62], who showed that diphenyl-N-phenyl nitrone (LXX) gave benzophenone and nitrobenzene:



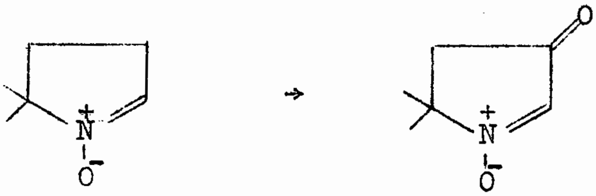
(LXX)

However, the nitrone group may influence the behaviour of neighbouring atoms towards oxidizing agents, with the formation of various more complex intermediate products. In general, it must be pointed out that comparatively little work has been carried out on this topic. Brown, Clark and Todd[7] found that treatment of 2,4,4-trimethyl-1-pyrroline 1-oxide (X) with selenium dioxide resulted in the formation of a dark oily material, which in the presence of dilute acid gave 1,2,3,4-tetrahydro-3,3-dimethyl-5-oxopyridine 1-oxide (LXV), evidently produced by ring enlargement of the intermediate nitrone-aldehyde (LXXI):



(X) (LXXI) (LXV)

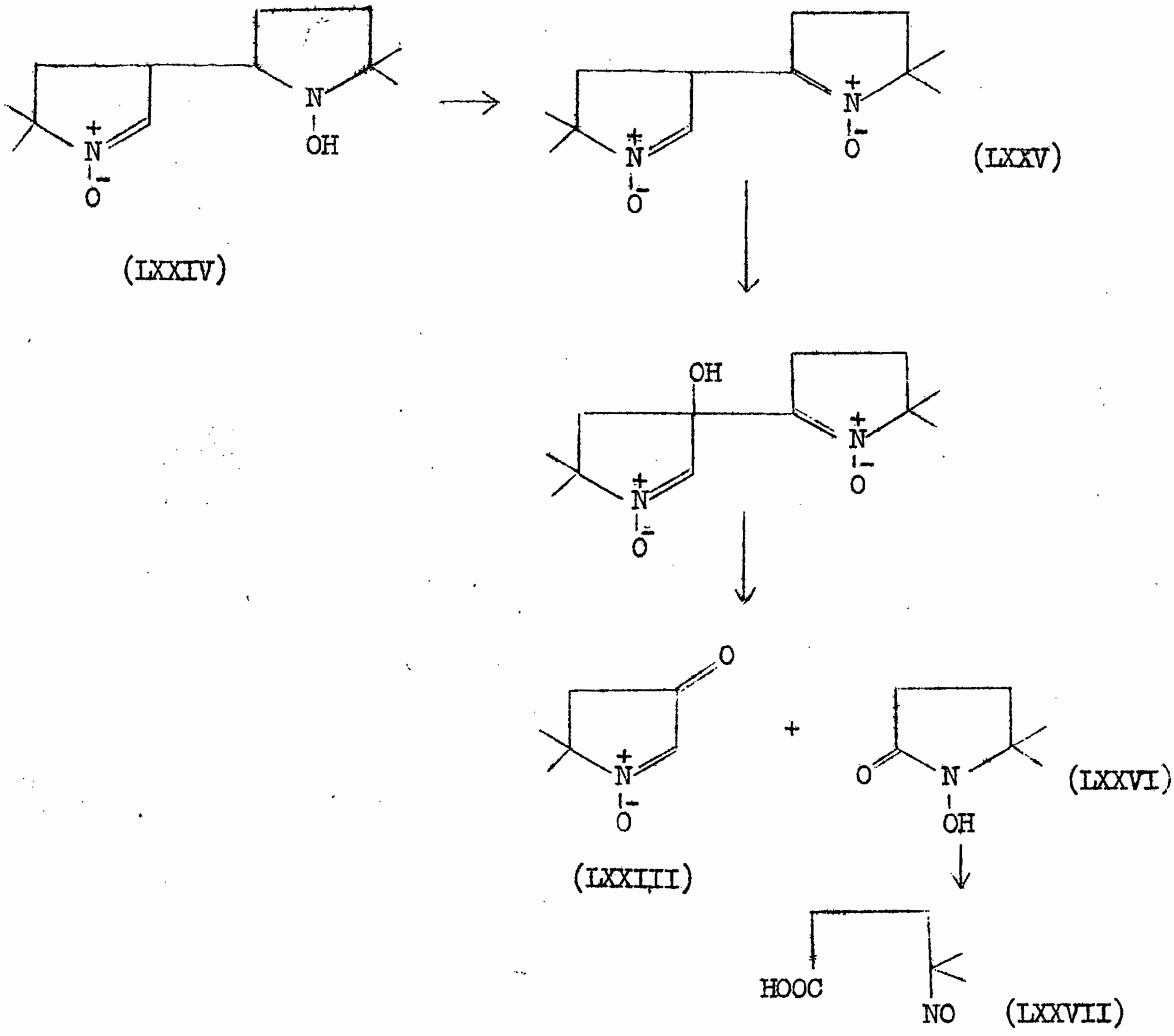
On the other hand, 5,5-dimethyl-1-pyrroline 1-oxide (LXXII) behaved normally when oxidized with selenium dioxide, to yield the cyclic α-ketonitrone (LXXIII)[10].



(LXXII) (LXXIII)

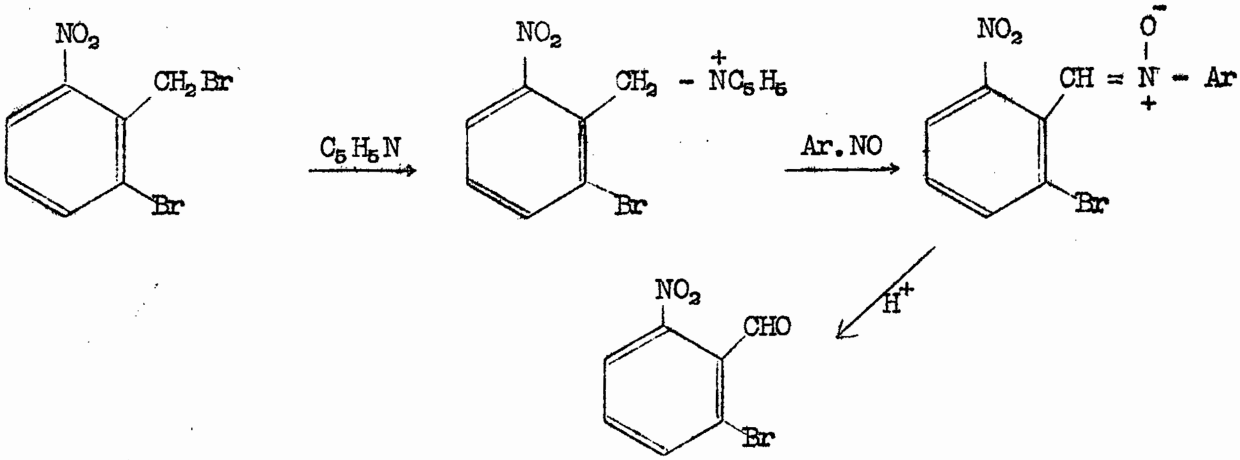
It is clear that the reaction is analogous to the formation of α-dicarbonyl compounds by the oxidation of active methylene groups with selenium dioxide[72].

Interesting results were obtained by Clark, Sklarz and Todd[10] in their study of the action of periodate on cyclic nitrones. These authors found, for example, that the dinitrone (LXXV) was converted to the nitroso acid (LXXVII). The nitrone hydroxylamine (LXXIV) also gave the same nitroso acid, but in this instance the keto nitrone (LXXIII) was also isolated. The course of the reaction is consistent with the following sequence where oxidative cleavage of the molecule occurs, followed by ring fission of the cyclic hydroxamic acid (LXXVI).



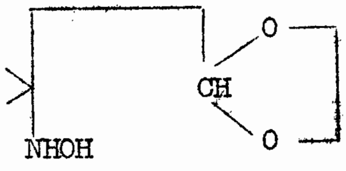
HYDROLYSIS:

Acyclic nitrones are readily susceptible to hydrolysis to yield a hydroxylamine and a carbonyl compound. This is a reversal of the reaction between carbonyl compounds and hydroxylamines which is used to synthesize nitrones (see page 7). It is stated[13] that acyclic nitrones are instantly hydrolysed by cold concentrated hydrochloric acid, while the reaction proceeds more slowly with cold dilute acids, and rapidly if warmed. The facile hydrolysis of some nitrones has been employed in the last step of the Kröhnke synthesis of aldehydes via the pyridinium halides (see page 14). A number of more inaccessible aldehydes may be synthesised by this method, such as, for example, 2,6-disubstituted benzaldehydes[73] :

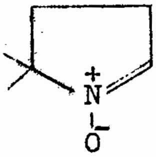


Many examples of this useful synthesis can be found in the literature.

The hydrolysis of cyclic nitrones does not appear to have been reported. Generally speaking, they seem to be much more stable than their acyclic counterparts. 5,5-Dimethyl-1-pyrroline 1-oxide (LXXII) is prepared by heating the hydroxylamino dioxolane (LXXVIII) in normal hydrochloric acid, and does not suffer appreciable hydrolysis during a prolonged evaporation under acid conditions.



(LXXVIII)



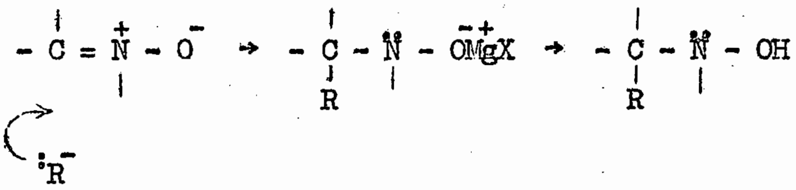
(LXXII)

Alkalis effect isomerisation of some acyclic nitrones to amides (see page 37) while others are hydrolysed[13]. On the other hand, 1-pyrroline 1-oxides are resistant to alkaline hydrolysis, as evidenced by the fact that ester and cyano groups on the pyrroline ring are hydrolysed in the usual way without attack of the nitrone function[5].

REACTION WITH NUCLEOPHILIC REAGENTS:

(i) Grignard reagents

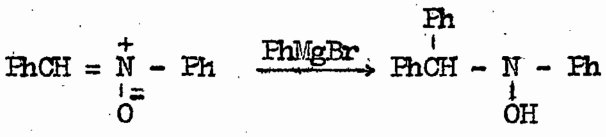
The behaviour of nitrones towards Grignard reagents is closely analogous to the well known addition reactions of these organometallic substances with carbonyl compounds. The reaction proceeds by a nucleophilic attack of a carbanion on the carbon atom, with the formation of a magnesium halide complex, which is readily hydrolysed to a hydroxylamine:



$$-\overset{|}{C}=\underset{|}{\overset{+}{N}}-\overset{-}{O} \rightarrow -\underset{R}{\overset{|}{C}}-\underset{|}{\ddot{N}}-\overset{-+}{OMgX} \rightarrow -\underset{R}{\overset{|}{C}}-\underset{|}{\ddot{N}}-OH$$

$$:\overset{-}{R}$$

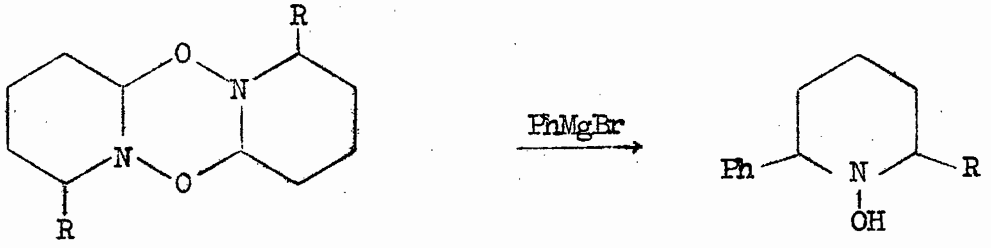
Early workers on this reaction[71] reacted phenyl-N-phenyl nitrone (XLVIII) with both methylmagnesium iodide and phenylmagnesium bromide, and obtained in each case the hydroxylamine:



$$PhCH=\underset{O^-}{\overset{+}{N}}-Ph \xrightarrow{PhMgBr} \overset{Ph}{PhCH}-\underset{OH}{N}-Ph$$

(XLVIII)

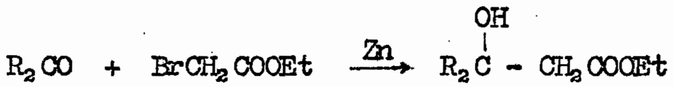
Cyclic nitrones react readily with Grignard reagents to form more highly substituted heterocycles. This is a powerful method for the synthesis of substituted pyrrolidines and piperidines, since virtually any group capable of functioning as the organic moiety of a Grignard reagent may be added to the nitrones, sometimes in excellent yields. Thesing and Mayer[132] for example, obtained phenyl piperidines by the action of phenylmagnesium bromide on dimeric 1-piperideine 1-oxides:



(i) R = H
(ii) R = Ph.

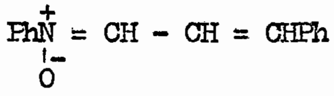
Addition of alkyl- and arylmagnesium halides to 1-pyrroline 1-oxides is also generally successful[5,12]. The reaction seems restricted only in the availability of the Grignard reagent.

The Reformatski reaction, which is akin to the Grignard reaction, is the condensation of α-bromoesters with carbonyl compounds under the influence of metallic zinc. An organozinc compound is first produced, and this adds to the carbonyl group in a nucleophilic manner, to yield ultimately a β-hydroxyester[74]:



$$R_2CO + BrCH_2COOEt \xrightarrow{Zn} R_2\overset{OH}{\overset{|}{C}} - CH_2COOEt$$

Only one example of an attempt at carrying out this reaction with nitrones appears to have been published. Utzinger and Regenass[25] found that the condensation between ethyl bromoacetate and styryl-N-phenyl nitrone (LXXIX) did not occur, and recovered the unchanged nitrone as the zinc bromide double salt. The present author has observed that 5,5-dimethyl-1-pyrroline 1-oxide and ethyl bromoacetate did not give stable products under Reformatski conditions[12].

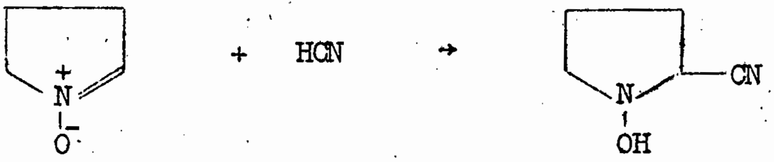


$$Ph\overset{+}{N}(\underset{O^-}{|}) = CH - CH = CHPh$$

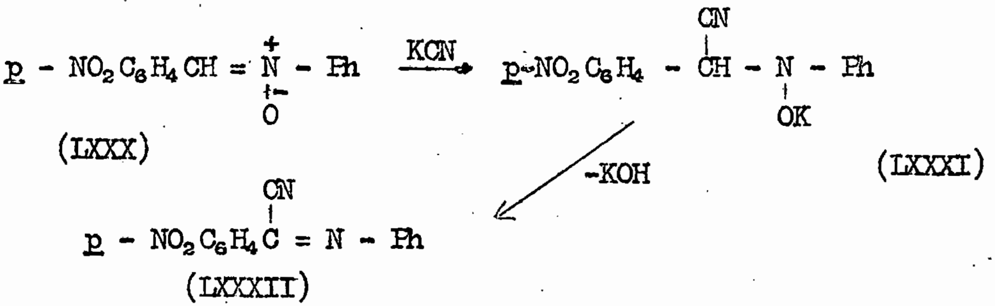
(LXXIX)

(ii) Other nucleophiles

Hydrogen cyanide has been found to react with 1-pyrroline 1-oxides to yield 1-hydroxy-2-cyanopyrrolidines in good yields[5], a reaction which is clearly analogous to the formation of cyanohydrins:



Cyanohydroxylamines have not been reported as a result of the addition of hydrogen cyanide on acyclic nitrones. However, Bellavita[75] has reacted potassium cyanide with p-nitrophenyl-N-phenyl nitrone (LXXX) to give a C-cyano substituted anil (LXXXII), which evidently has been produced via an intermediate such as (LXXXI), which was not isolated.



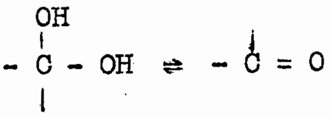
$$p\text{-}NO_2C_6H_4CH=\overset{+}{\underset{O^-}{N}}-Ph \xrightarrow{KCN} p\text{-}NO_2C_6H_4-\overset{CN}{CH}-\underset{OK}{N}-Ph$$

(LXXX) (LXXXI)

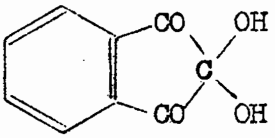
$$\xrightarrow{-KOH} p\text{-}NO_2C_6H_4\overset{CN}{C}=N-Ph$$

(LXXXII)

Water is a nucleophilic reagent, but it is well known that the hydrated carbonyl group is unstable, tending to lose water with extreme ease. The presence of electron attracting groups to some extent stabilizes the

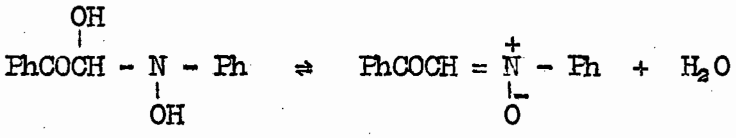


$$-\overset{OH}{\underset{|}{C}}-OH \rightleftharpoons -\overset{|}{C}=O$$



(LXXXIII)

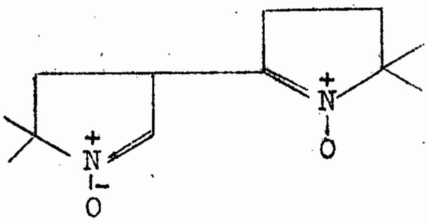
hydrated carbonyl group, as in chloral hydrate and ninhydrin (LXXXIII). Similarly, nitrone hydrates are unstable and lose water readily. When electron attracting groups are present, the nitrone hydrate system is stabilized. Thus, benzoyl-N-phenyl nitrone (LXXXV) is obtained as a stable hydrate (LXXXIV) by the reaction of phenylhydroxylamine on the hydrate of phenylglyoxal[76].



$$\mathrm{PhCO\overset{\overset{OH}{|}}{C}H - \underset{\underset{OH}{|}}{N} - Ph} \rightleftharpoons \mathrm{PhCOCH = \underset{\underset{O^{-}}{|}}{\overset{+}{N}} - Ph} + H_2O$$

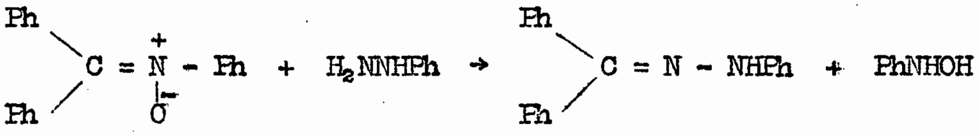
(LXXXIV) (LXXXV)

Heating in vacuo converts the hydrate into the anhydrous nitrone. 1-Pyrroline 1-oxides are generally very hygroscopic, and the presence of hydrates has been alluded to in explaining the weak OH absorption band in the infrared spectrum of 1-pyrroline 1-oxide itself[40]. The compound (LXXVI) has been obtained as a monohydrate[9].



(LXXVI)

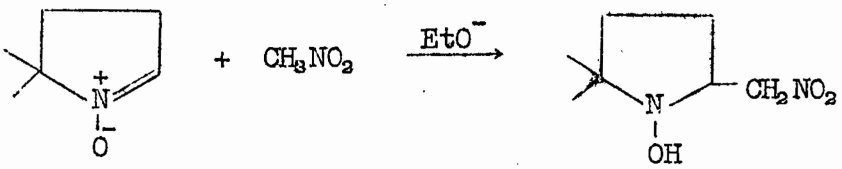
Phenylhydrazine, which readily reacts with aldehydes and ketones, also reacts with acyclic nitrones, with cleavage of the nitrone system. Thus, diphenyl-N-phenyl nitrone (LXXI) and phenylhydrazine form benzophenone phenylhydrazone and phenylhydroxylamine:



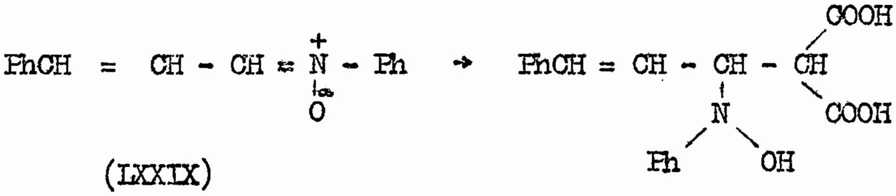
$$\begin{array}{l}\mathrm{Ph}\\ \mathrm{Ph}\end{array}\!\!>\mathrm{C = \underset{\underset{O^{-}}{|}}{\overset{+}{N}} - Ph} + \mathrm{H_2NNHPh} \rightarrow \begin{array}{l}\mathrm{Ph}\\ \mathrm{Ph}\end{array}\!\!>\mathrm{C = N - NHPh} + \mathrm{PhNHOH}$$

(LXXI)

Nitroalkanes are known to react with aldehydes and ketones under basic conditions to form α-nitroalcohols. The analogue of this reaction has been observed with 1-pyrroline 1-oxides, which form adducts with nitromethane[5] :

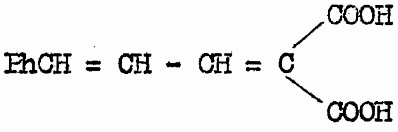


Malonic acid also reacts with some nitrones, as expected on grounds of analogy to the Knoevenagel reaction. Styryl-N-phenyl nitrone (LXXIX) and malonic acid gave phenylhydroxylamine and 4-phenyl-buta-1,3-diene-1,1-dicarboxylic acid (LXXXVII), by C - N cleavage of the intermediate (LXXXVI)[25].



(LXXIX)

(LXXXVI)



(LXXXVII)

POLYMERISATION AND BASE-CATALYSED CONDENSATIONS OF NITRONES.

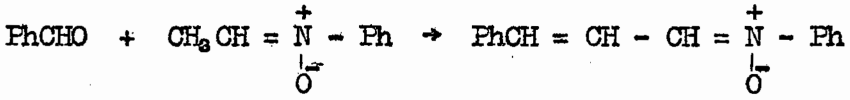
The analogy between carbonyl compounds and nitrones does not end at the reactions of the functional group, but extend over a series of base catalysed reactions.

The electron attracting character of both nitrone and carbonyl groups cause an inductive effect in neighbouring linkages, with the result that α-methylene groups become protogenic. In the case of nitrones, (and carbonyl compounds), loss of a proton results in the formation of a resonating anion (LXXXVIII) which may behave as a nucleophile in the presence of suitable reagents:

$$-\underset{|}{\overset{-}{C}}-\underset{|}{C}=\underset{|}{\overset{+}{N}}-\overset{-}{O} \longleftrightarrow -\underset{|}{C}=\underset{|}{C}-\underset{|}{\overset{\bullet\bullet}{N}}-\overset{=}{O}$$

(LXXXVIII)

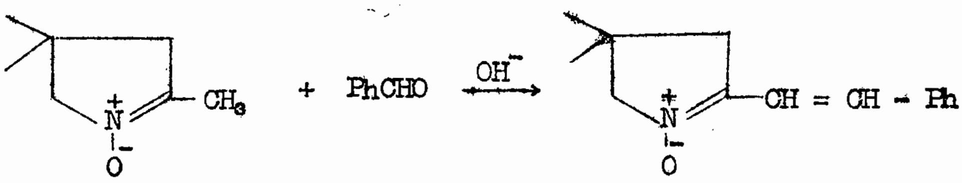
Certain nitrones condense with aromatic aldehydes in a manner reminescent of the Claisen-Schmidt reaction. This occurs when there is a methyl group directly attached to the nitrone system, as in the reaction of benzaldehyde and substituted benzaldehydes with methyl-N-phenyl nitrone (LXXXIX) to give derivatives of styryl-N-phenyl nitrone (LXXIX)[25] :



$$PhCHO + CH_3CH=\underset{\underset{O^-}{|}}{\overset{+}{N}}-Ph \rightarrow PhCH=CH-CH=\underset{\underset{O^-}{|}}{\overset{+}{N}}-Ph$$

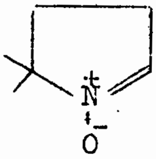
(LXXXIX) (LXXIX)

This reaction is not confined to acyclic nitrones as,2,4,4-trimethyl-1-pyrroline 1-oxide (X) has also been observed[5] to react with aromatic aldehydes, to form 4,4-dimethyl-2-styryl-1-pyrroline 1-oxide (XC):

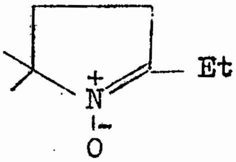


(X) (XC)

It appears that only the methyl group is reactive enough to undergo such condensations, since both 5,5-dimethyl-1-pyrroline 1-oxide (LXXII) and 2-ethyl-5,5-dimethyl-1-pyrroline 1-oxide (XCI) failed to give condensation products with benzaldehyde[6].

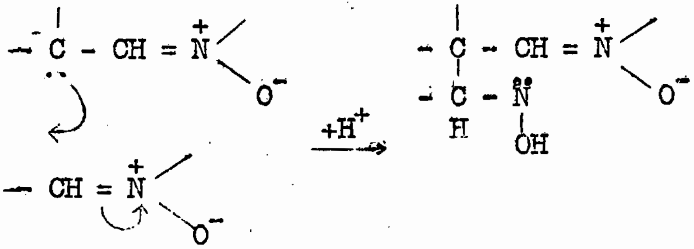


(LXXII)

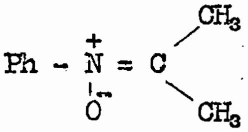


(XCI)

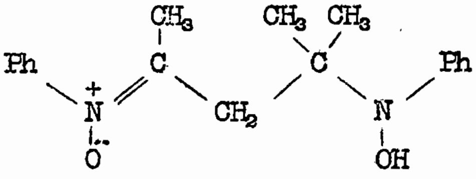
The base catalysed aldol condensation of aldehydes and ketones is duplicated by a variety of nitrones. Thus, the anion which is generated by loss of a proton from the -CH system is capable of nucleophilic attack on the nitrone group of another molecule:



The products of such aldol-type additions are β-hydroxylamino-nitrones. As expected, bases catalyse the reaction, but are not always essential. Thus, the product of the condensation of phenylhydroxylamine and acetone is not dimethyl-N-phenyl nitrone (XCII), but the aldol dimer (XVIII)[24]. Phenylhydroxylamine and n-butyraldehyde react in a similar way[19,25].



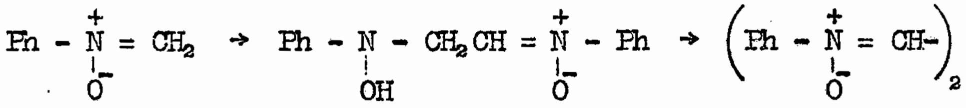
(XCII)



(XVIII)

The mechanism of this condensation is not yet fully understood, but it is believed that the nitrone group in its back-polarised form $>\bar{C} - \overset{+}{N} = O$ may play an important part[9]. In trimethylamine as solvent, sodamide gives rise to both aldol and benzoin type dimers[9,77], while a reductive dimerisation of (LXXII.) to (XCVI), akin to the formation of pinacols, occurs with sodium-potassium alloy in diglyme[10].

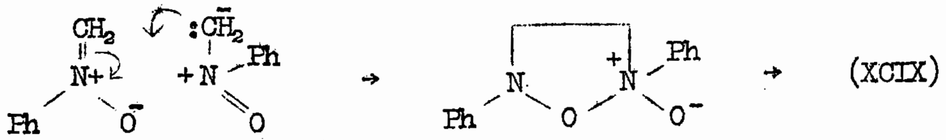
When formaldehyde is reacted with phenylhydroxylamine, the expected N-phenyl nitrone (XCVII) is not isolated. Instead, the dinitrone (XCIX) is obtained[1]. This has been explained on the basis of an oxidation of the benzoin-type dimer (XCVIII).



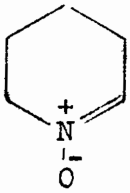
$$Ph-\underset{O^-}{\overset{+}{N}}=CH_2 \rightarrow Ph-\underset{OH}{N}-CH_2CH=\underset{O^-}{\overset{+}{N}}-Ph \rightarrow \left(Ph-\underset{O^-}{\overset{+}{N}}=CH-\right)_2$$

(XCVII) (XCVIII) (XCIX)

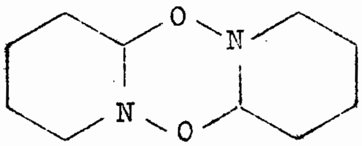
Thesing and Mayer[1] entertain the view that this dimerisation occurs by a cyclic addition mechanism, implying that the canonical form $-\underset{\overset{\|}{O}}{\overset{+}{N}}-\bar{C}-$ of the nitrone may be taking part:



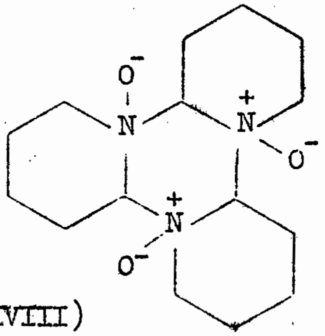
1-Piperideine 1-oxide (I) is unknown in the monomeric state, although a dimer (II) exists. This is most probably formed by mutual addition of extreme polar monomeric forms[1]. A trimer also exists, and it is believed to be (XXVIII)



(I)



(II)

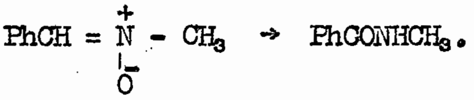


(XXVIII)

ISOMERISATION OF NITRONES

Nitrones as a class are found to be subject to isomerisations, although relatively few examples are known. Certain different types of isomerisations will be discussed in turn.

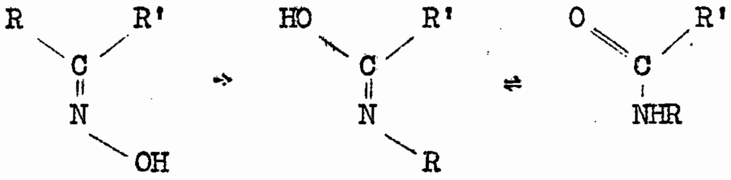
The action of certain substances cause some nitrones to "rearrange" to N-substituted amides, a reaction which is reminescent of the well-known Beckmann rearrangement of oximes[78]. Thus, phenyl-N-methyl nitrone (C) yields N-methylbenzamide on heating with phosphorus pentachloride[23]:



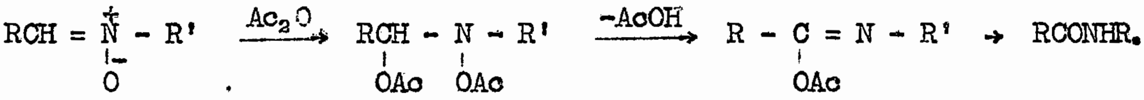
$$\mathrm{PhCH} = \underset{\mathrm{O}^{-}}{\overset{+}{\mathrm{N}}} - \mathrm{CH_3} \rightarrow \mathrm{PhCONHCH_3}.$$

(C)

Such a reaction proceeds very smoothly under the influence of acetic anhydride[79]. In contrast to the Beckmann rearrangment, which converts ketoximes into amides by trans-migration of groups undergoing rearrangement[78], the rearrangement of nitrones to amides involves no migration of



carbon atoms. Kröhnke[80] has reviewed this topic, and he has proposed a mechanism for the acetic anhydride catalysed isomerisation of nitrones to amides:



$$\mathrm{RCH} = \underset{\mathrm{O}^{-}}{\overset{+}{\mathrm{N}}} - \mathrm{R'} \xrightarrow{\mathrm{Ac_2O}} \underset{\mathrm{OAc}}{\mathrm{RCH}} - \underset{\mathrm{OAc}}{\mathrm{N}} - \mathrm{R'} \xrightarrow{-\mathrm{AcOH}} \mathrm{R} - \underset{\mathrm{OAc}}{\mathrm{C}} = \mathrm{N} - \mathrm{R'} \rightarrow \mathrm{RCONHR}.$$

Similarly, the isomerisation of some nitrones into amides under alkaline conditions[58,59] takes place by the intermediate formation of nitrone hydrates, which lose water to form lactims, tautomeric with amides:

CYCLO-ADDITION REACTIONS

Cyclo-addition reactions of nitrones will be discussed in detail in the next section of this thesis.

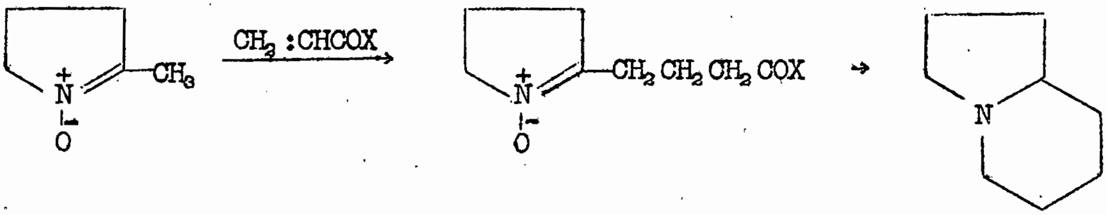
DISCUSSION

SECTION I

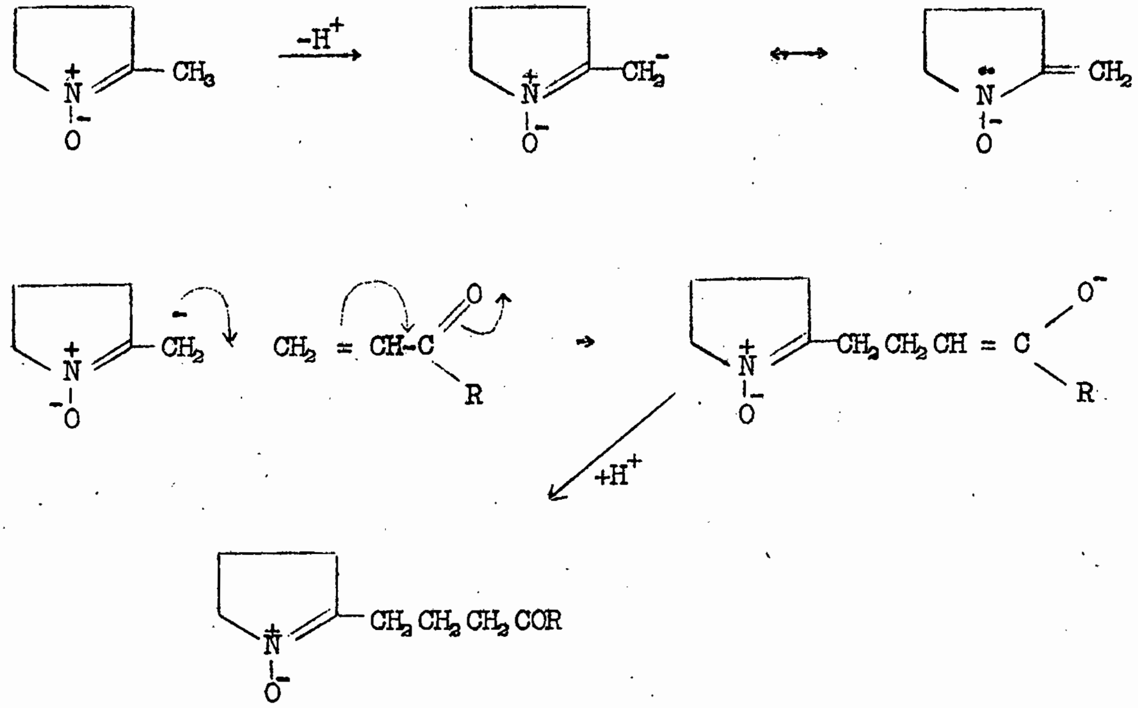
SECTION 1

The Cyclo-Addition Reactions of 1-Pyrroline 1-Oxides

The work described in this thesis was originally undertaken with the aim of developing a route to N-bridged bicyclic heterocycles, by making use of what was hoped would be a novel reaction of 1-pyrroline 1-oxides, namely a Michael addition of an αβ-unsaturated carbonyl compound on a reactive methyl group, to give a γ-nitrone carbonyl compound, whose cyclisation by various means was to be tried:

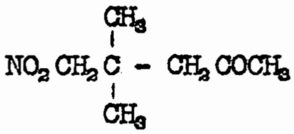


The addition of the unsaturated compound on a protogenic 2-methyl-1-pyrroline 1-oxide could be expected to follow a mechanism analogous to that which is generally believed[32] to take place in base catalysed Michael additions:



One might expect that the presence of strong bases which are necessary to catalyse Michael additions might well promote the base catalysed aldol-type dimerisations of pyrroline 1-oxides (see page 33), and low yields of Michael adducts might thus be expected.

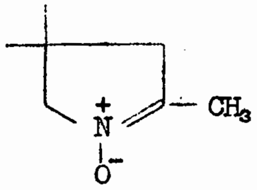
Preliminary investigations on the possibility or otherwise of the projected reaction was made with 2,4,4-trimethyl-1-pyrroline 1-oxide (II) as the Michael pseudo-acid, a choice based on its ready availability by reduction of 4,4-dimethyl-5-nitropentanone[5] (I), which in turn can be synthesised by the condensation of nitromethane and mesityl oxide[86,88].



$NO_2CH_2\overset{CH_3}{\underset{CH_3}{C}}-CH_2COCH_3$

(I)

→



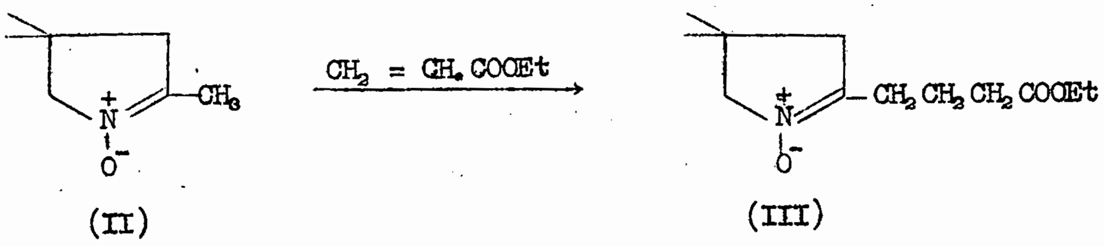
(II)

Furthermore, the nitrone (II) has a 2-methyl group of proved reactivity, since it is known to condense with aromatic aldehydes[5], and to undergo ready dimerisation by aldol-type reactions[8]. Ethyl acrylate was chosen as the unsaturated component in view of its volatility, and hence its ready removal from completed reactions if an excess was used, and also on account of its comparative freedom from polymerisation under normal conditions.

It was found that when 2,4,4-trimethyl-1-pyrroline 1-oxide (II) was heated for a day with ethyl acrylate, without any added catalysts, an oil was obtained by vacuum fractionation of the reaction mixture which was partially miscible with water, and completely soluble in excess 5 N hydrochloric acid, but separated out again on making the solution alkaline. The basic nature of this oil was further shown by the formation of a crystalline picrolonate. This salt analysed correctly for the picrolonate of a 1:1 nitrone-acrylate adduct. A picrate could not be formed.

Combustion analyses for the oil were unsatisfactory, as well as the saponification equivalent, which was too high. The infra-red absorption spectrum indicated the presence of a nitrone group, since there was a maximum at 1610 cm^{-1}, and a strong absorption at 1745 cm^{-1}, attributable to the presence of an ester group, was also present. Repeated vacuum distillation brought no appreciable change in the infra-red absorption spectrum.

On the above evidence, in spite of the unsatisfactory analysis of the oil, one might be tempted to believe that Michael addition to form the γ-nitrone-ester (III) had in fact taken place:



However, there was the questionable purity of the oil itself, which could be contaminated with unchanged nitrone, the latter co-distilling with the product, and so clouding the evidence at hand. Consequently, the author set about finding a method whereby the material could be purified further without having recourse to distillation. Having observed that the nitrone (II) was virtually insoluble in low boiling petroleum ether, whereas the addition product was readily soluble, partition between petroleum ether and water was tried. An oily residue was obtained on evaporation of the dried petroleum, and its infra-red absorption spectrum showed no absorption in the region where nitrones are known to absorb. This cast very strong doubts on the validity of a nitrone structure in the adduct. Combustion analyses and saponification equivalents for this purified substance were however in excellent agreement with the values theoretically required for a 1:1 nitrone-acrylate adduct.

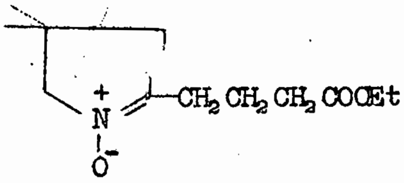
Methyl methacrylate reacted with (II) under similar conditions to give an analogous product, as shown by combustion analysis, saponification equivalent, formation and analysis of picrolonate, and infra-red spectrum.

It was observed that vacuum distillation of the adduct restored the nitrone absorption, and in one experiment, the adduct was partly decomposed into the parent nitrone (identified as its picrate), and ethyl acrylate (identified by its boiling point and infra-red spectrum). This clearly indicated the reversible nature of the reaction, and explained the presence of nitrone in the product, even after repeated attempts at fractionation. Rapid distillations of small quantities of material without noticeable decomposition could be carried out in a modified short-path still (see appendix).

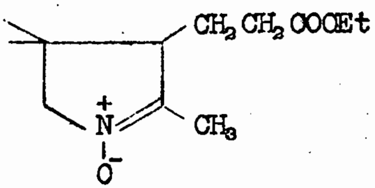
The Structure of the Adduct:

A variety of products may feasibly occur on reacting 2,4,4-trimethyl-1-pyrroline 1-oxide with ethyl acrylate. Some of these may be considered unlikely, but some cannot be dismissed out of hand. Structurally they may be broadly divided into two types.

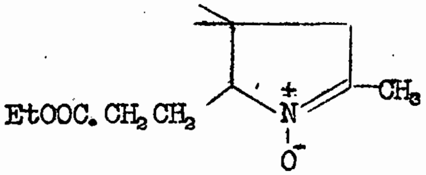
A. Michael-type aducts:



(IV)



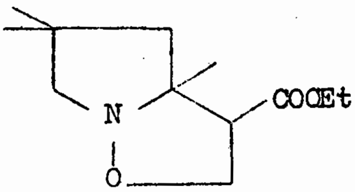
(V)



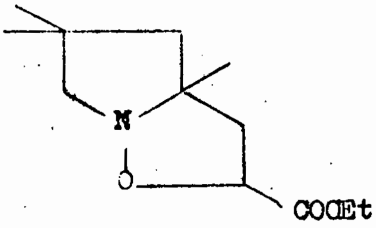
(VI)

(IV) can be regarded as the most probable of this group, and would occur by Michael addition of ethyl acrylate on the reactive 2-methyl group, by the mechanism discussed above. (V) must be considered less likely than (IV), in view of the known comparative reactivities of the methylene group at position 3 of the pyrroline ring and of the 2-methyl substituent[8]. The mechanism of addition would be similar to that proposed for (IV). The hydrogen atom in position 5 of the 1-pyrroline 1-oxide system is not known to be particularly activated, nor do the non-cyclic nitrones possess protogenic activity at a corresponding site. Structure (VI) can therefore be safely ruled out.

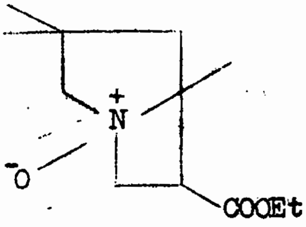
B. Cyclo-addition Products:



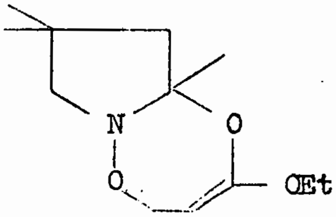
(VII)



(VIII)

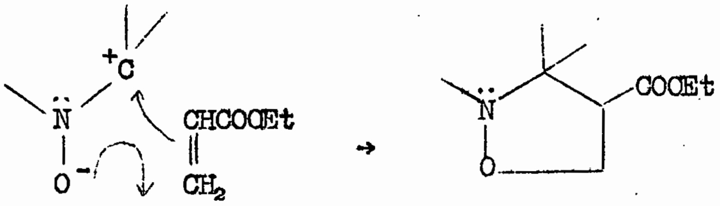


(IX)

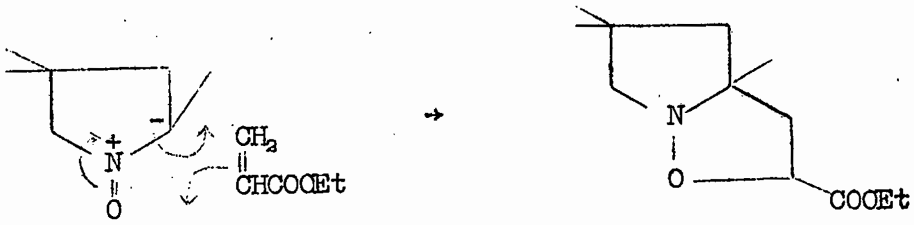


(X)

Structure (VII) could be expected to arise by a cyclo-addition reaction involving the nitrone system in its extreme dipolar form $-\overset{+}{\underset{|}{C}}-\overset{\bullet\bullet}{\underset{|}{N}}-\overset{-}{O}$ and the polarised double bond of ethyl acrylate:

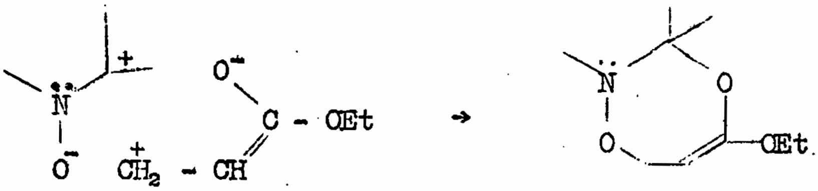


This reaction is analogous to the Diels-Alder reaction[87].
However, if the nitrone system undergoes an electromeric effect to give, at the instant of attack, the "back-polarised" extreme, $-\overset{-}{\underset{|}{C}}-\overset{+}{\underset{|}{N}}=O$ then cyclo-addition of ethyl acrylate would yield structure (VIII):



(VIII)

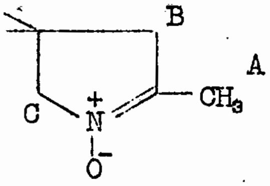
Structure (IX) must be considered unlikely, since it represents a cyclo-addition involving the C=N system of the nitrone. As discussed earlier, addition reactions of nitrones are generally 1,3 additions[13]. The compound (X) could arise by cyclo-addition of the extreme polar form of ethyl acrylate to the 1,3-dipolar nitrone system:



(X)

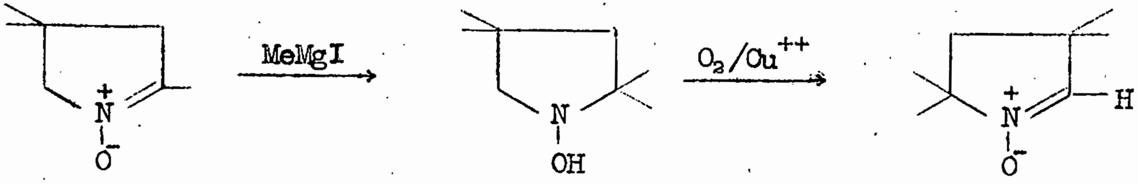
Exclusion of Michael-type additions:

As pointed out previously, the nitrone (II) possesses three positions where base-catalysed additions might conceivably take place. These are labelled A, B and C in the accompanying formula, in decreasing order of reactivity. In order to ascertain without doubt the necessity or otherwise of protogenic positions, it was decided to synthesise a monomeric cyclic nitrone which was devoid of hydrogen atoms which might be considered activated by the nitrone function.



(II)

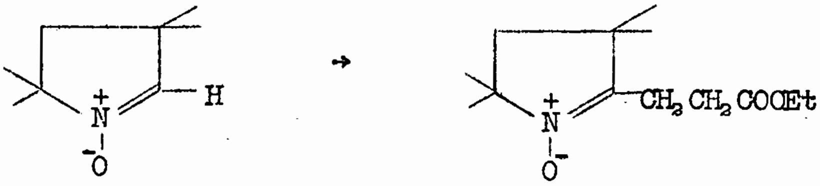
This requirement is met by 3,3,5,5-tetramethyl-1-pyrroline 1-oxide (XII), which has positions B and C blocked by gem-dimethyl systems, and which has no protogenic function A at position 2. This compound is readily synthesized from (II) by the sequence of steps shown below, in



(II) (XI) (XII)

which the hydroxylamine (XI) is oxidized by atmospheric oxygen in the presence of cuprammonium ions[5].

The nitrone (XII) may be considered as eminently suitable, but for the fact that it has a hydrogen atom at position 2, that is to say an aldonitrone hydrogen atom. It may well be argued that this raises an objection to the choice of (XII) as model compound, since we now have the possibility, which was previously absent, of an addition taking place to form a β-nitrone ester (XIII). Strongly basic conditions are, however, required for proton abstraction at this position[10], and although the possibility of this occurring under non-basic conditions can never be totally excluded, it must be considered reasonably unlikely.



(XII) (XIII)

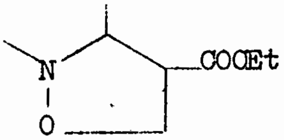
When 3,3,5,5-tetramethyl-1-pyrroline 1-oxide (XII) was heated with ethyl acrylate, the product had similar properties to the adducts obtained from 2,4,4-trimethyl-1-pyrroline 1-oxide. It analysed correctly for a 1:1 nitrone-acrylate adduct, and this was confirmed by analysis of its picrolonate. The infra-red spectrum was remarkably similar to that obtained from the adduct of ethyl acrylate on (II), any differences being centred in the "fingerprint region". In particular, the spectra showed the following features:

(a) There was no absorption maxima in the region 1570 - 1620 cm^{-1}, which is generally assigned to the C = N system of nitrones[5,40]. This also rules out the presence of C = C systems. On the basis of this evidence, all structures resulting from a Michael-type addition (which all contain a nitrone system), and structure (X) (which possesses a C = C system), can be excluded.

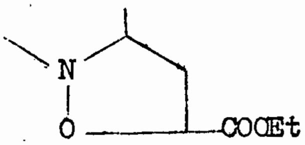
(b) Strong maxima at 1745 cm^{-1} were present and these may be safely attributed to the C = O stretching vibrations of esters. There seemed little doubt that the ethoxycarbonyl group of ethyl acrylate survived the addition.

(c) No maxima were observed in the region 950 - 970 cm^{-1}, which is expected[88] from tertiary aliphatic N-oxides. This would rule out structure (IX), which is a saturated N-oxide.

On spectral evidence therefore, it would appear that the adducts of ethyl acrylate and cyclic nitrones of the 1-pyrroline 1-oxide type are cyclo-addition products. More specifically, since in the formation of the adduct, the nitrone system and the ethylenic double bond of the unsaturated ester disappeared, they can be assumed to be involved. The three adducts should thus have the partial structures (A) or (B), which are recognised to be isoxazolidines.



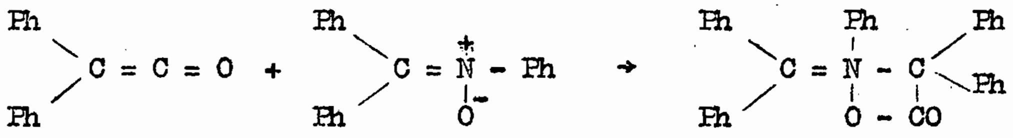
(A)



(B)

Cyclo-Additions of Nitrones: The state of the literature at the time of commencement of this Thesis:

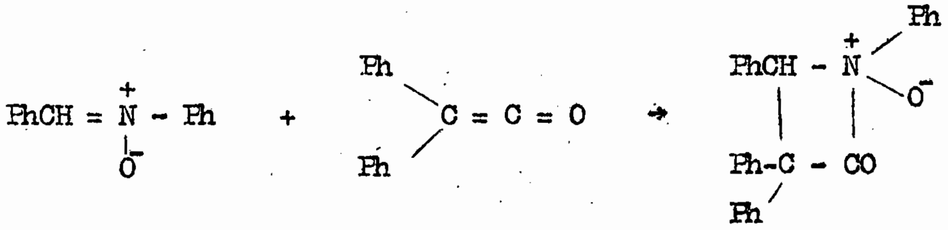
References to cyclo-additions of nitrones were very limited prior to the author's investigation. Staudinger and Miescher[62] had reacted diphenyl ketene (XIV) with diphenyl-N-phenyl nitrone (XV), and they obtained a 1:1 addition product which they formulated as a cyclo-addition product (XVI), without any plausible justification.



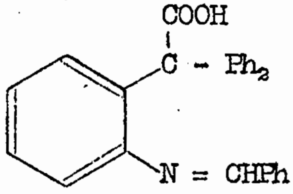
(XIV) (XV) (XVI)

These workers also isolated a product formed by addition of two moles of diphenyl ketene on (XV).

As the pentavalent formulation of certain nitrogen compounds generally fell into disfavour, the need for a reinvestigation into the nature of the reaction was clearly indicated. Consequently, Taylor, Owen and Whittaker[89] proposed a structure (XVIII) for the reaction product of diphenyl ketene and phenyl-N-phenyl nitrone, (XVII)



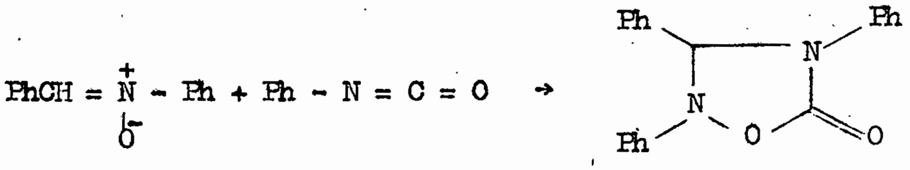
(XVII) (XIV) (XVIII)



(XIX)

Finally, Hassall and Lipmann[90] put paid to the cyclo-addition hypothesis, by demonstrating, on the basis of degradative studies, that this substance was wrongly formulated and was in fact (XIX).

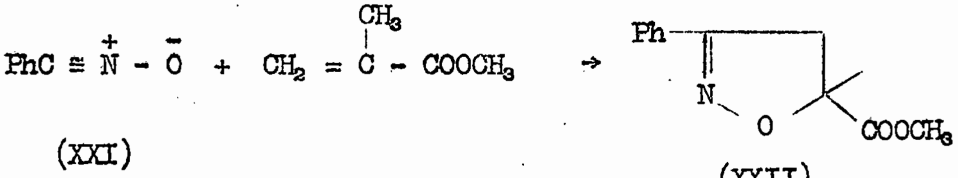
However, a true cyclo-addition reaction takes place with nitrones and isocyanates, which give rise to derivatives of 5-keto-1-oxa-2,4-diazoline[62,91]. Thus, phenyl-N-phenyl nitrone (XVII) and phenyl isocyanate form the compound (XX):



(XVII) (XX)

This reaction appears to be quite general, and has been observed to take place with cyclic nitrones[40].

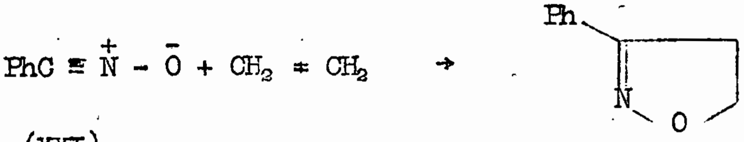
Although the literature on nitrone cyclo-additions was very scanty, an investigation into the literature of a related field, namely the nitrile oxides $R - C \equiv \overset{+}{N} - \overset{-}{O}$, proved to be most revealing. Thus, benzonitrile oxide (XXI) reacted[92] with methyl methacrylate to give an isoxazoline (XXII):-



(XXI)

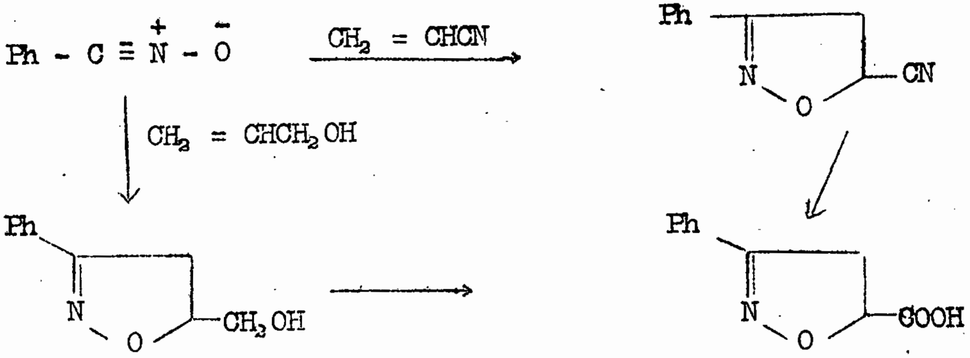
(XXII)

This reaction was later applied to other αβ-unsaturated esters, in all cases forming isoxazolines[93]. More interesting still, benzonitrile oxide (XXI) was found to react with a variety of olefinic systems, including ethylene itself[94]:



(XXI)

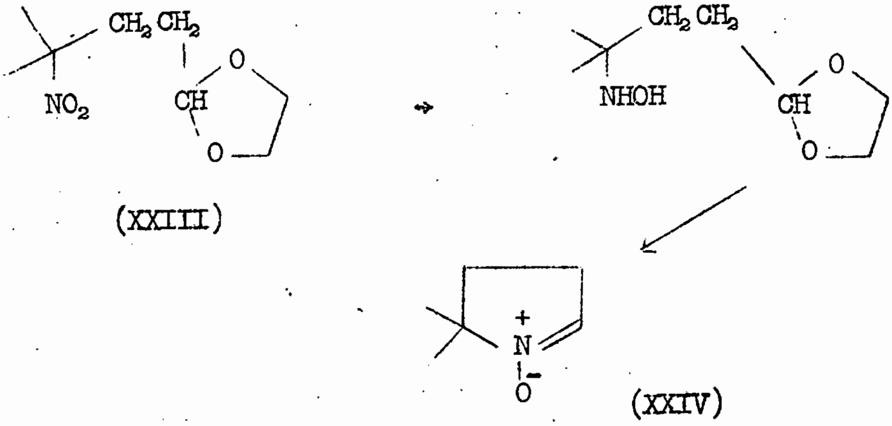
Although the authors concerned with this work carried out several interconversions of their adducts, positions of substituents on the ring appear to have been arbitrarily assigned. Thus, it was clearly shown[95] that both acrylonitrile and allyl alcohol reacted with benzonitrile oxide to give adducts with the same orientation of substituents, since both could be converted to the same isoxazoline carboxylic acid[92], with the substituent assigned to position 5. Similarly, reaction of (XXI) with allyl chloride, bromide, and iodide[95], propylene, isobutylene, pent-1-ene[94] and



styrene[96], are all supposed to give 5-substituted isoxazolines. The present author was unfortunately not able, at the time of writing, of obtaining the original references to the work mentioned, and so is not competent to judge the validity of the orientations.

Cyclo-Additions of 5,5-Dimethyl-1-pyrroline 1-oxide:

At this juncture, the author became convinced that nitrones would also duplicate the above series of reactions. In order to put this hypothesis to the test, he synthesised a somewhat simpler nitrone than those he had previously used, namely 5,5-dimethyl-1-pyrroline 1-oxide (XXIV), prepared by reduction of 2-(3-methyl-3-nitrobutyl)-1,3-dioxolan (XXIII) with zinc dust and ammonium chloride, followed by cyclisation in acid medium[5] :



(XXIII)

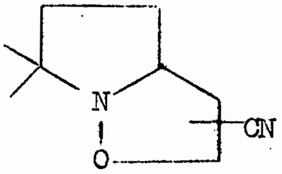
(XXIV)

This nitrone was chosen on account of the ease of its preparation, freedom from asymmetric centres, and comparative structural simplicity, an important factor as far as possible degradation of products was concerned.

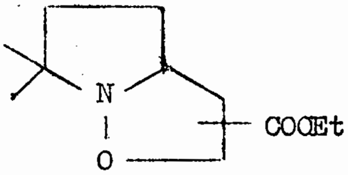
It was found that acrylonitrile reacted with (XXIV), to produce a solid compound with a characteristic infra-red absorption band attributable to a CN system. A picrolonate was readily formed by this compound. Similar results were obtained with ethyl acrylate, which gave analogous results to those previously obtained. More interesting however was the reaction of acrolein diethyl acetal on (XXIV), which formed a liquid, formulated as a 1:1 adduct on the basis of analytical data obtained from the adduct itself and its picrate.

This was most encouraging, as it provided a clear indication that a double bond unconjugated with a strong polarising function such as -COOEt or $-C\equiv N$, could in fact take part in the addition. This was immediately followed up by the synthesis of an adduct from (XXIV) and allyl alcohol. This adduct proved to be stable to heat, in contradistinction to the ethyl acrylate adducts, since it could be distilled in vacuo at 100°, the distillate readily crystallising to a nitrone free solid. This adduct formed a picrate.

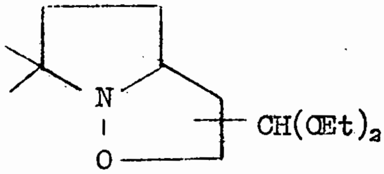
The results above, although constituting only a preliminary investigation into the problem of nitrone cyclo-addition, clearly foreshadowed the general feasibility of the reaction. Little objections could be raised against the formulations (XXV), (XXVI), (XXVII) and (XXVIII) for the acrylonitrile, ethyl acrylate, acrolein diethyl acetal and allyl alcohol adducts respectively.



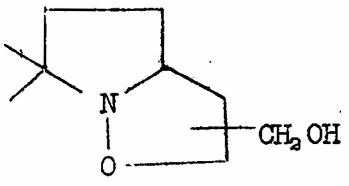
(XXV)



(XXVI)



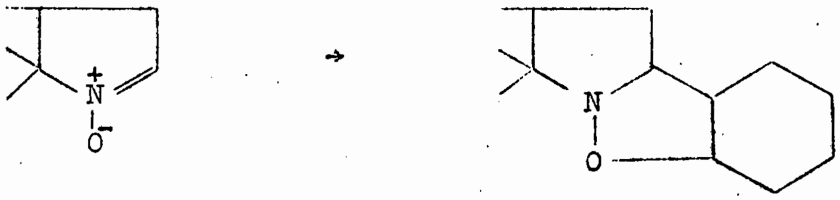
(XXVII)



(XXVIII)

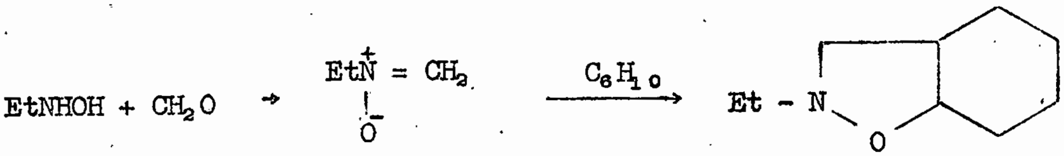
Recent Published Work on Nitrone Cyclo-Additions:

The author's view that the reaction between olefins and nitrones would prove to be general was borne out by the publication of Rogers and his collaborators[97], which in some aspects paralleled the author's investigations, and narrowly forestalled publication of his own work. The above workers found that isoxazolidines were produced by the reaction of olefins and nitrones. Thus, they reacted 4,5,5-trimethyl-1-pyrroline 1-oxide (XXIX) with cyclohexene, and obtained the tricyclic base (XXX):



(XXIX) (XXX)

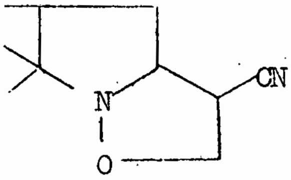
More elegant still, they discovered that the nitrones could readily be generated in situ, as in the case of the reaction between cyclohexene, paraformaldehyde and ethylhydroxylamine, which gave the isoxazolidine (XXXII), undoubtedly by way of the unstable N-ethyl-nitrone (XXXI):



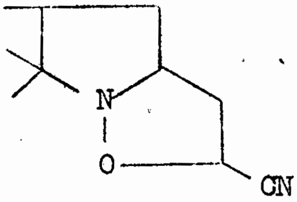
(XXXI) (XXXII)

Another point of interest in their paper, was the report that the reaction was probably reversible, but that their isoxazolidines could be distilled without decomposition.

With regard to the orientation of the substituents, these authors may be quoted:- "... In no case have we established the orientation of the adducts; e.g., that from the nitrone (XXIX) and acrylonitrile is thought to have structure (XXXIII), but (XXXIV) is not eliminated; other formulae in this communication are subject to the same qualification". (The numbering quoted is that following this thesis).

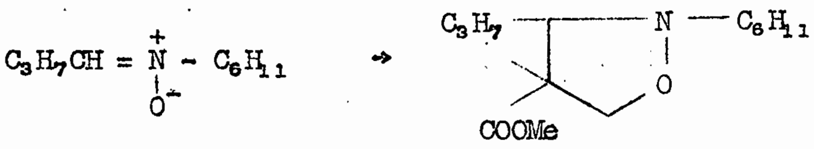


(XXXIII)



(XXXIV)

This interesting report was shortly followed by another communication[98], in which Huisgen and his co-workers announced further examples of cyclo-addition between nitrones and olefinic substances, and stressed the high yields which are frequently obtainable. These authors indicated some reactions in which they had degraded their adducts, but, they pointed out, in the case of the adduct of propyl-N-cyclohexyl nitrone (XXXV) and methyl methacrylate, the orientation of the adduct (XXXVI) awaited confirmation.

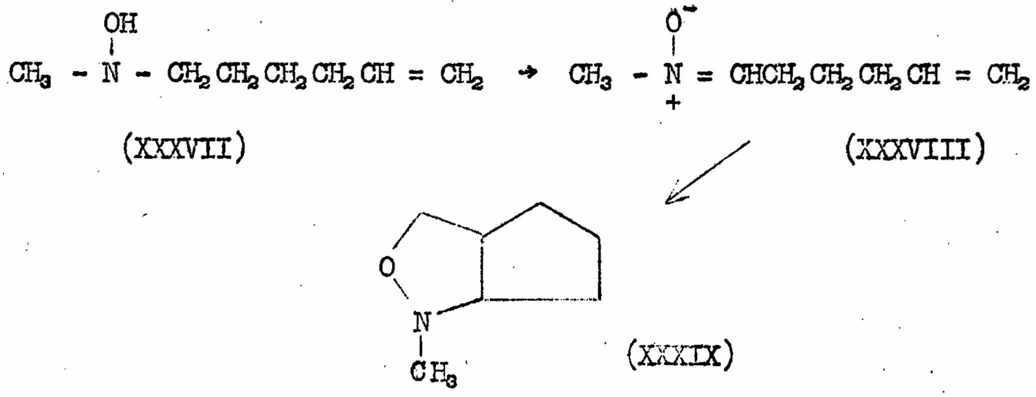


$C_3H_7CH = \overset{+}{\underset{|\atop O^-}{N}} - C_6H_{11}$

(XXXV) (XXXVI)

Professor Huisgen very kindly sent the author the reprint of a most informative lecture on cyclo-addition reactions[99], embodying results of a monumental piece of investigation on reactions of little-known systems.

Prior to the two communications mentioned above, Le Bel and Whang[100] announced the formation of an isoxazolidine (XXXIX), by oxidation of N-methyl-N-5-hexenyl-hydroxylamine (XXXVII), presumably formed by way of the intermediate nitrone (XXXVIII):



$$CH_3-\overset{OH}{\overset{|}{N}}-CH_2CH_2CH_2CH_2CH=CH_2 \rightarrow CH_3-\overset{O^-}{\overset{|}{\underset{+}{N}}}=CHCH_2CH_2CH_2CH=CH_2$$

(XXXVII) (XXXVIII)

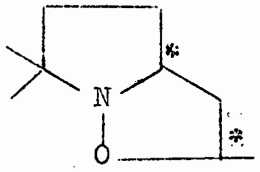
(XXXIX)

Degradative evidence substantiated this claim.

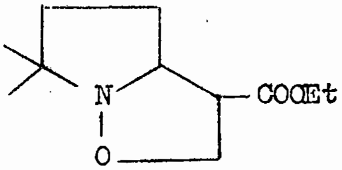
<u>Further Work on 5,5-Dimethyl-1-pyrroline 1-oxide:</u>

As soon as the above publications became known, it became obvious that the excellent work carried out by Rogers, Huisgen, and their collaborators, made any further investigation into the generality of the reaction quite superfluous. However, a point of major importance remained. Both Huisgen and Rogers assumed that in the reaction between nitrones and olefins, the addition of the olefin was most likely to take place across the ends of the nitrone system polarised in its $-\overset{+}{\underset{|}{C}}-\overset{\cdot\cdot}{\underset{|}{N}}-\overset{-}{O}$ form. That this must occur in many cases cannot be denied, and indeed, degradative work by Huisgen[99] has shown this to be so. However, the fact remains that there must be many cases where the direction of polarisation of an unsymmetrical olefin itself must be regarded as ambiguous. Furthermore, one cannot rule out the possibility of the nitrone functioning as its back-polarised extreme $>\overset{-}{C}-\overset{+}{\underset{|}{N}}=O$, which would give a different orientation of substituents in the adducts.

The present author decided to investigate fully the direction of addition of ethyl acrylate and allyl alcohol on to 5,5-dimethyl-1-pyrroline 1-oxide. In order to achieve this, degradative methods had to be developed, and the structure of key substances proved by synthesis. As events turned out, the whole problem belied its apparent simplicity. The sequence of events leading up to the elucidation of the problem will be elaborated further, as ~~this is~~ more properly discussed in the next two sections. However, in order to make this section more complete, it will suffice to indicate the results which have been obtained. 5,5-Dimethyl-1-pyrroline 1-oxide can react with ethyl acrylate to give two isomeric products, (XL) and (XLI). A mixture of these two compounds is obtained when the nitrone and an excess of ethyl acrylate are heated at 100°C for twenty four hours. The two isomers, although almost indistinguishable, having closely similar infra-red absorption curves, and refractive indices almost within experimental error, can nevertheless be obtained in a pure form, and their purity demonstrated. Further more, their formation takes place quantitatively



(XL)



(XLI)

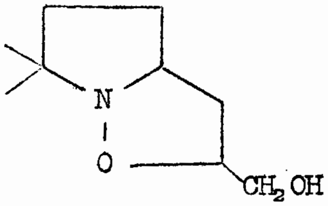
under suitable experimental conditions.

For example, (XL) is formed exclusively when the nitrone and an excess of ethyl acrylate are allowed to react for a day at room temperature. On the other hand, if the reactants are allowed to react for about four days at 100°C, then (XLI) is the only product. As expected from these results, (XL) is convertible into (XLI), by the simple expedient of allowing it to react at 100° with an excess of ethyl acrylate for a suitable period of time.

In addition to this, every indication points to the fact that (XL) is itself a mixture of the two possible racemates arising from asymmetry at the carbon atoms marked with an asterisk. (XLI), prepared by prolonged heating, seems to be a single racemate.

These results are the culmination of extensive degradative and synthetic work. It follows that the adducts of ethyl acrylate on 2,4,4-trimethyl-1-pyrroline 1-oxide and 3,3,5,5-tetramethyl-1-pyrroline 1-oxide, prepared before the above facts came to light, and whose syntheses were described earlier in this section, are probably mixtures of the two possible position isomers. The same can probably be said about the acrolein diethyl acetal adduct on 5,5-dimethyl-1-pyrroline 1-oxide. In the experimental section, the orientation of the substituent in these compounds is left purposely ambiguous.

In the case of the allyl alcohol adduct on 5,5-dimethyl-1-pyrroline 1-oxide, degradation has shown it to be pure (XLII)



(XLII)

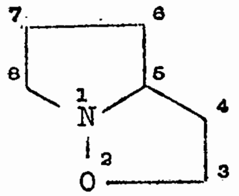
The acrylonitrile adduct, being a solid recrystallised to a constant melting point, is undoubtedly a pure position isomer, but the orientation of the cyano group has not been established.

SECTION II

SECTION II

The Degradation of the Ethyl-Acrylate and Allyl Alcohol Adducts on 5,5-Dimethyl-1-Pyrroline 1-oxide

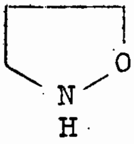
Preliminary Considerations



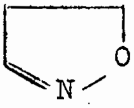
(I)

The isoxazolidines produced by the cyclo-addition reactions described in the previous section are derivatives of the saturated heterocyclic system 2-oxa-1-azabicyclo[3,3,0]octane (I), with numbering as shown in the accompanying formula. Before degradative experiments were undertaken, it seemed desirable to study in some detail the chemistry of compounds structurally related to (I), in order to obtain some insight into the best method of attack.

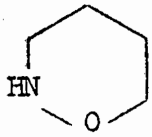
However, the fact soon came to light that comparatively little was known about the chemistry of non-aromatic heterocycles containing the N - O - C system. Representative of such substances are the derivatives of isoxazolidine (II), Δ^2-isoxazoline (III), and tetrahydro-1,2,2 H-oxazine (IV)



(II)



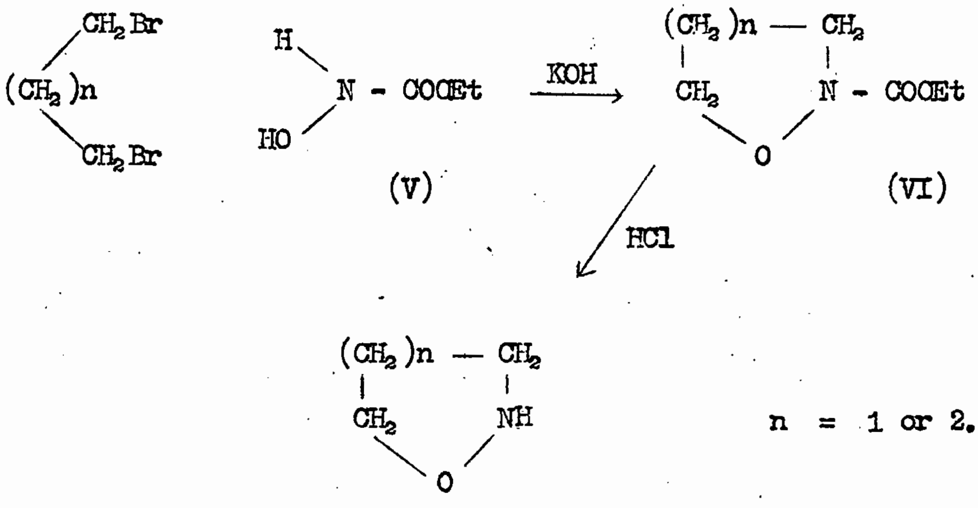
(III)



(IV)

Prior to the commencement of the work described in this thesis, only two isoxazolidines had been reported. Thus, King[101] prepared isoxazolidine

(II) and tetrahydro-1,2,2H-oxazine (IV) by condensation of terminal dibromides and N-hydroxyurethan (V) in the presence of 10% alcoholic potassium hydroxide:

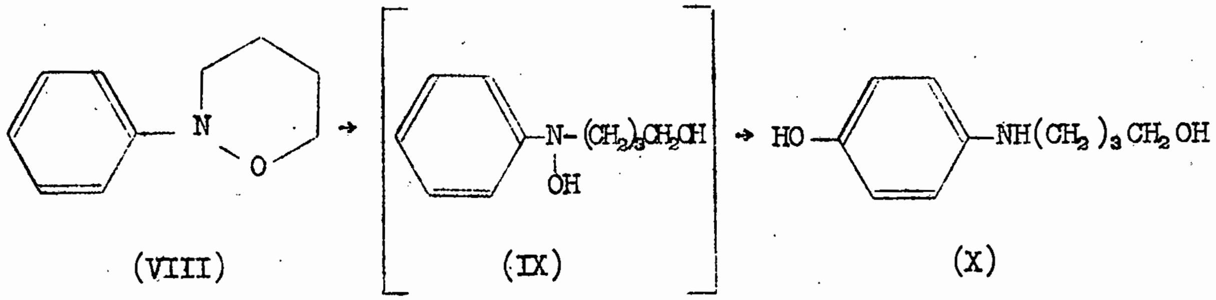


(V) (VI) (VII)

The intermediate urethan (VI) could be isolated, and was subsequently hydrolysed to the heterocycles (VII) with hydrochloric acid. These substances were reported as being strong bases, and were capable of being quaternized with methyl iodide. In view of their methods of synthesis, it is clear that the ring systems must be resistant to the action of both acids and bases.

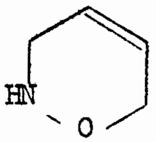
A somewhat larger body of evidence is available concerning the stability of Δ^2-isoxazolines. They are stable bases whose ring structure is retained during the hydrolysis of substituent cyano or carbalkoxy groups[95], or during the oxidation of certain substituents. Oxidation to the isoxazoles may sometimes occur[98].

In contrast to this, 2-phenyl-tetrahydro-1,2,2H-oxazine (VIII) can be converted[102] into 4-(p-hydroxyphenylamino)-butanol (X), evidently by acid catalysed rearrangement of an intermediate hydroxylamine (IX), upon treatment with cold 20% phosphoric acid:

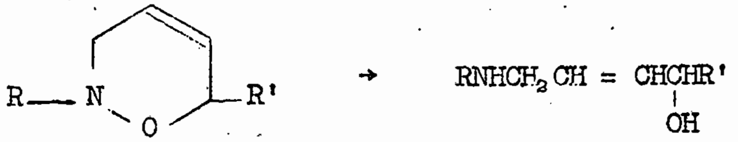


(VIII) (IX) (X)

The reductive cleavage of tetrahydro-1,2,2H-oxazines and 3,6-dihydro-1,2,2H-oxazines (XI) is perhaps the most thoroughly investigated reaction of these bases. It is known for example that the hydrogenated oxazine ring is readily cleaved by the agency of zinc and glacial acetic acid, even at room temperature. As examples of this may be quoted the reduction of 3,6-dihydro-1,2,2H-oxazine (XII, R = H, R' = H), and 2-ethyl-3,6-dihydro-1,2,2H-oxazine (XII, R = Et, R' = H) to the corresponding 4-amino-butenols (XIII)[103].



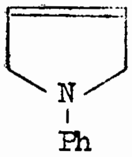
(XI)



(XII) (XIII)

This has also been observed with the 6-phenyl derivative (XII, R = H, R' = Ph)[104], and the saturated bases behave in an analogous manner.

Reductive cleavage may also be accompanied by cyclization of the product if the zinc-acetic acid reduction is carried out at a higher temperature, say on the water-bath. This has been found to be the case in the reduction of 2-phenyl-3,6-dihydro-1,2,2H-oxazine (XII, R = Ph, R' = H), which was converted[106] to 1-phenyl-Δ^3-pyrroline (XIV). When



(XIV)

$PhNHCH_2CH = CH - CH_3$

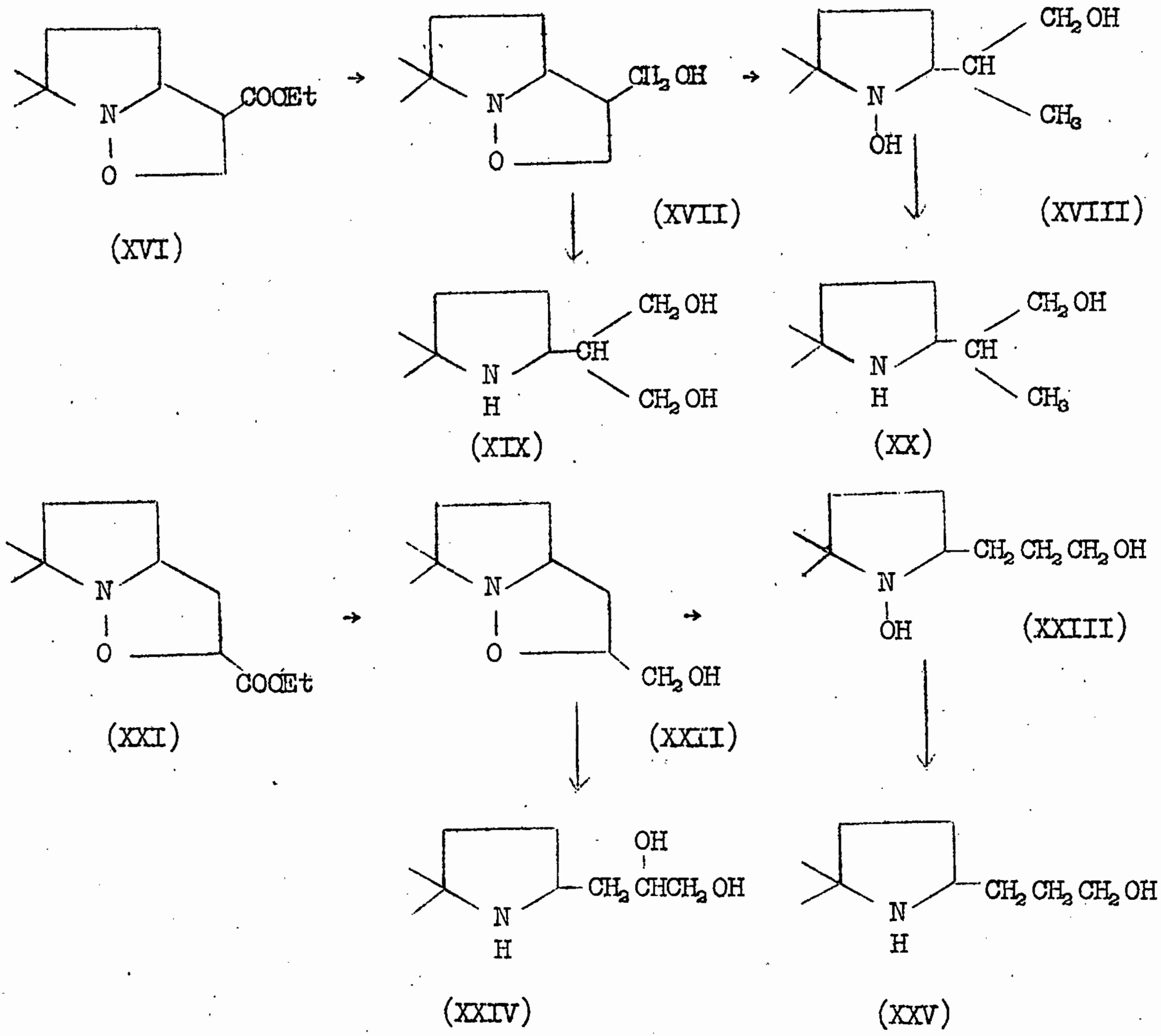
(XV)

the 3,6-dihydro-1,2,2H-oxazines are subjected to the action of sodium in ethanol, reductive cleavage occurs with loss of oxygen, but with retention of the olefinic double bond. Arbuzov[106,107] has shown this by converting both 2-phenyl- (XII, R = Ph, R' = H) and 2-(p-tolyl)-3,6-dihydro-1,2,2H-oxazine (XII, R = p-tolyl, R' = H) to the corresponding secondary amines (XV).

Projected Degradation of the Ethyl Acrylate Adduct on 5,5-Dimethyl-1-Pyrroline 1-Oxide

On the basis of the brief survey summarized above, it became clear that a reductive degradation was the answer to the author's structural problem. Thus, in the case of the adduct from ethyl acrylate and 5,5-dimethyl-1-pyrroline 1-oxide, which can be indicated by the formulae (XVI) or (XXI), reduction could give a variety of products, depending on both the exact nature of the isoxazolidine, and the extent and course of the reduction, the latter two factors being dependent on the nature of the reducing agent.

The alcohols (XVII) and (XXII) would arise by reduction of the ester groups without reduction of the ring. If ring cleavage at the N - O link were to occur, then (assuming reduction of the ester group), the amino-glycols (XIX) and (XXIV) would be thenproduced. If, on the other hand, the O - C link were to be cleaved, then the hydroxylamino-alcohols (XVIII) or (XXIII) would result. Since it is conceivable that



further reduction of the hydroxylamino function might be possible, the amino-alcohols (XX) or (XXV) might also be obtained. The amino-glycols and the hydroxylamino-alcohols are isomeric, and so would not be differentiated by analysis. Identification can be expected however on the basis of the test for hydroxylamines with 2,3,5-triphenyl-tetrazolium chloride[46] .

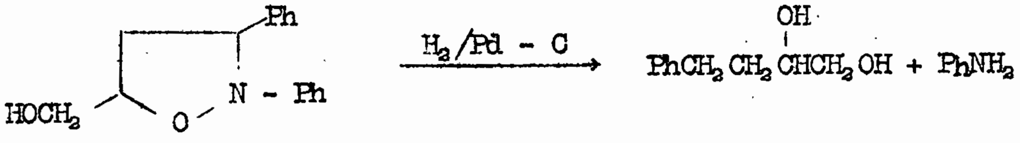
Preliminary Degradation:

The adduct used in the first experiments was that from ethyl acrylate and 5,5-dimethyl-1-pyrroline 1-oxide, obtained by heating the nitrone and ethyl acrylate on the water-bath for twenty four hours. As described in the experimental section, (page 119), analyses were in good agreement for a 1:1 adduct, and the material could however be distilled without decomposition to a constant refractive index in a short path still. The infrared spectrum indicated the absence of any nitrone, and the author had thus no reason to question its purity.

As a preliminary experiment, in which it was hoped to reduce both the ester group and the isoxazolidine ring by the agency of sodium in ethanol-toluene, did not give any results, it was decided, in view of the tremendous versatility of lithium aluminium hydride[108a], to employ this reagent. As confirmed subsequently by other authors[97,98,100], the choice proved to be a good one.

When the adduct was heated with an excess of lithium aluminium hydride in tetrahydrofuran, a good yield of a highly viscous hygroscopic base was obtained. This material failed to give a positive test for hydroxylamines with 2,3,5-triphenyl-tetrazolium chloride. A crystalline picrate of melting point 165 - 166° was obtained. Analysis of the picrate indicated on empirical formula $C_9H_{19}NO_2$ for the base. Analyses of the base itself, although in agreement with this, were rather unsatisfactory due to the hygroscopic nature of the substance. These results pointed out that there could be little doubt that the base was one of the two possible amino-glycols (XIX) or (XXIV).

At first glance, it would appear that the easiest way of establishing the correct structure for the amino-glycols would be a quantitative periodate uptake estimation. The glycol (XXIV), being a β-amino-α-glycol, should theoretically consume one mole of periodate, while (XIX), being a β-amino-β-glycol, should remain unaffected by this reagent. Unfortunately, when the periodate consumption of the degradation product was determined, results were obtained which gave no indication as to its possible structure. Later, when the pure compound (XIX) was at hand, it was observed that it reacted with periodate. It would appear that the presence of the amino group introduces side-effects which are as yet not understood. Uptake of periodate by dipyrrolidines, giving results not reconcilable with theoretical expectations, has been observed previously[109]. It is not unlikely that the periodate may partly oxidize the secondary amine to the hydroxylamine, which in turn may undergo oxidation by some sequence as outlined on page 26. Periodic acid has been successfully used to cleave the glycol (XXVIa) to hydrocinnamaldehyde. The above-mentioned glycol, which does not contain nitrogen, was obtained by catalytic reduction of the isoxazolidine (XXVI)[93].

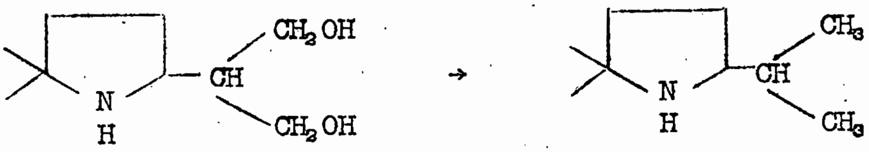


(XXVIa)

(XXVI)

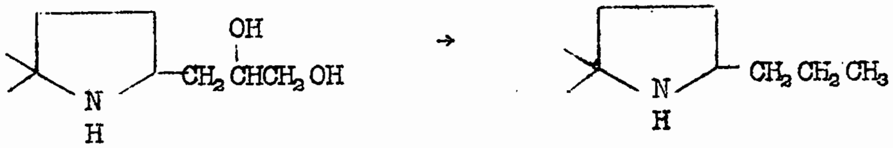
Further Structural Investigations:

Since the identification of the amino-glycols proved to be more complex than it had appeared, it was decided to convert them to the corresponding pyrrolidines:



(XIX)

(XXVII)

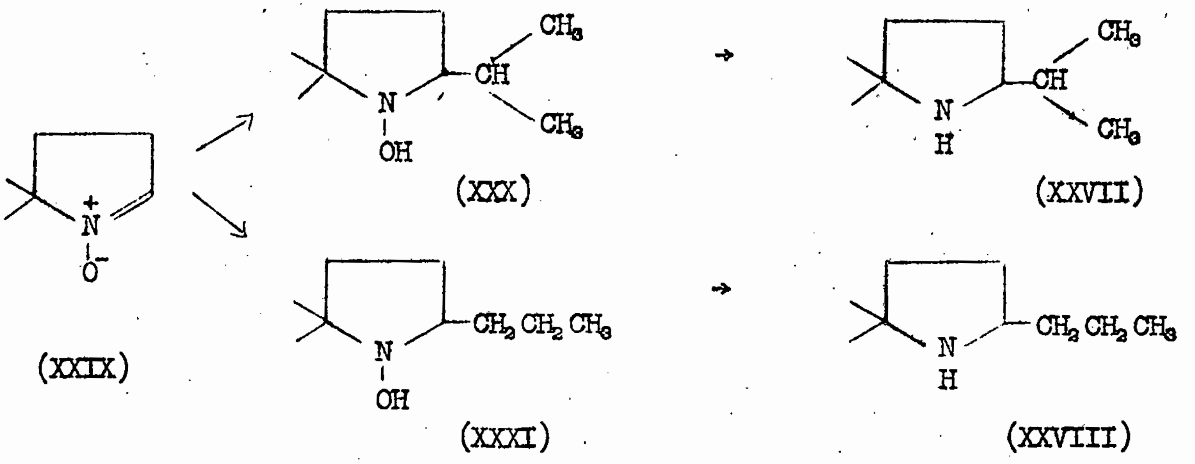


(XIV)

(XXVIII)

The compound (XIX) should be ultimately capable of conversion to the iso propylpyrrolidine (XXVII), while the isomer (XXIV) should be convertible to the n-propyl-pyrrolidine (XXVIII). The last two named compounds were not previously described in the literature, and thus it was necessary to synthesize them both by unambiguous means.

Since it was known that 5,5-dimethyl-1-pyrroline 1-oxide (XXIX) reacted readily with Grignard reagents (see page 28) to form cyclic hydroxylamines, and that these N-hydroxy heterocycles could be readily reduced to the secondary amines[2], the author decided to react the nitrone (XXIX) with the appropriate propylmagnesium bromides, and to reduce the resulting hydroxylamines to the required bases:

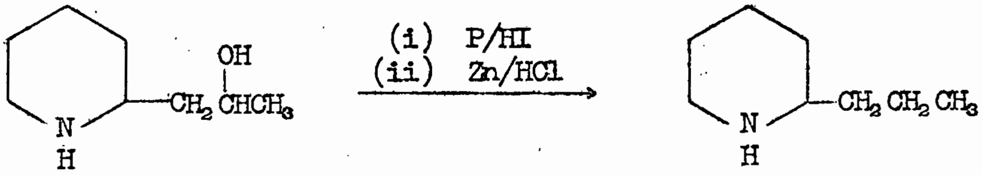


These projected syntheses were completely successful. Thus, treatment of (XXIX) with isopropylmagnesium bromide gave the hydroxylamine (XXX), an unstable solid, which formed an oxalate, and which, upon reduction with zinc and hydrochloric acid, gave 2-isopropyl-5,5-dimethyl-pyrrolidine (XXVII). This substance could be converted into a picrate, picrolonate, and oxalate. Similarly, (XXIX) and n-propylmagnesium bromide gave the hydroxylamine (XXXI) (which could be converted to its oxalate), and from which 2,2-dimethyl-5-n-propyl-pyrrolidine (XXVIII) was obtained by zinc-hydrochloric acid reduction. This base gave a picrolonate, and an oxalate, but did not form a picrate. The differences in melting points between the two above-mentioned oxalates, and between the picrolonates were sufficiently great to settle beyond question the identity of the projected degradation products by comparison of their derivatives with those of the synthetic pyrrolidines.

Of the methods which could be used to convert the amino-glycols to the pyrrolidines (these would include the reduction of p-toluene-sulphonyl esters[108b]), the author decided to make use of the well known reduction of alcohols by the agency of red phosphorus and hydriodic acid. This reagent converts the alcohol into the alkyl iodide, which in turn may be partially or totally reduced to the hydrocarbon. Any iodo compound formed is reduced to completion with zinc and hydrochloric acid.

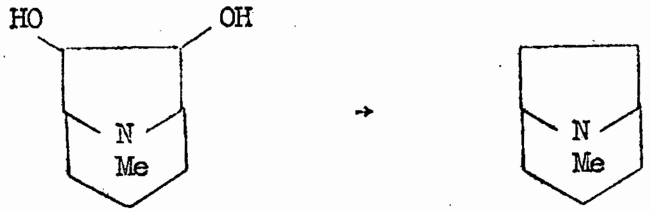
$$ROH \xrightarrow{P/HI} RH + RI \xrightarrow{Zn/HCl} RH$$

This procedure has met with considerable success in the field of hydroxy-bases related to piperidine and pyrrolidine. Hess and Weltzien[110], for example, were able to convert 3-(2-piperidyl)-propan-2-ol (XXXII) to coniine (XXXIII) in good yields; the first step in the reaction was carried out by heating (XXXII) at 150° - 170° for six hours in a sealed tube with fuming hydriodic acid (d 1.96) and a small quantity of red phosphorus.



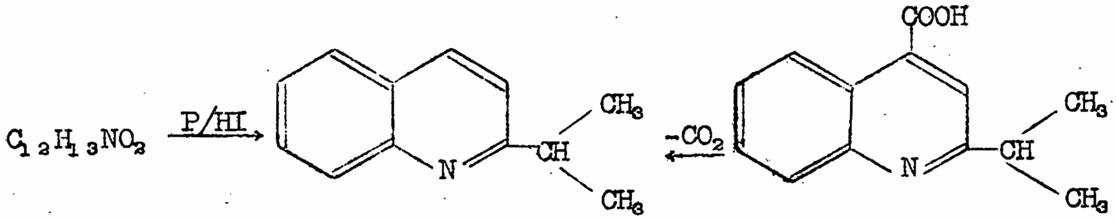
(XXXII) (XXXIII)

Glycols appeared to be similarly amenable to such a treatment. The so-called "hydroscopoline" (XXXIV) yielded tropane (XXXV) by the action of hydriodic acid, in the presence of phosphonium iodide, at temperatures near 200° for several hours[111].



(XXXIV) (XXXV)

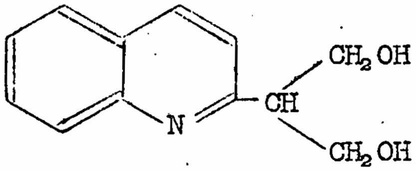
Koenigs[112] obtained a substance $C_{12}H_{13}NO_2$ by the reaction between quinaldine and formaldehyde. Upon heating at 150° - 160° for nine hours with hydriodic acid in the presence of red phosphorus, he obtained a base $C_{12}H_{13}N$, from which a picrate, melting at 155° - 157°, was obtained. This picrate was apparently identical with that of 2-<u>iso</u>propylquinoline (XXXVI), previously obtained by Doebner[113] by the decarboxylation of 2-<u>iso</u>propylquinonic acid (XXXVII):



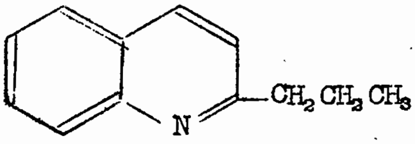
(XXXVI) (XXXVII)

Hence the compound $C_{12}H_{13}NO_2$ was formulated as 2-(2-quinolyl)-propan-1,3-diol (XXXVIII). This structure was further confirmed by the fact that

2-n-propyl-quinoline (XXXIX) has been synthesized by a variety of routes[114,115,116], and its picrate has a melting point reported as 162 - 164°.



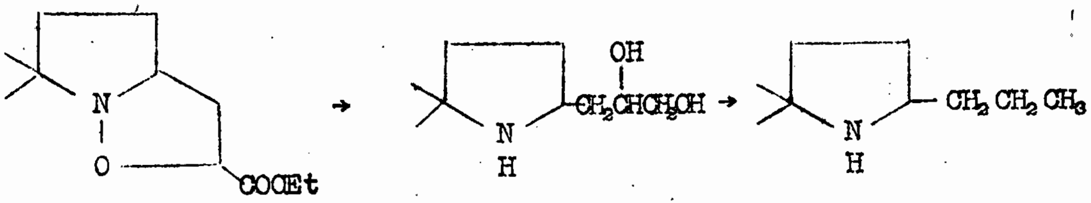
(XXXVIII)



(XXXIX)

Similarly[117], 2-(4-quinolyl)-propan-1,3-diol, (from lepidine and formaldehyde), reacted with phosphorus and hydriodic acid to a propylquinoline giving a picrate of melting point 172 - 173°. This compound must be 4-isopropylquinoline, since 4-n-propylquinoline forms a picrate melting with decomposition at 200°[118].

The above results indicated to the author not only that the projected reactions were perfectly feasible, but that there was no reason to fear that a rearrangement might occur on account of the rather drastic reaction conditions. The way seemed clear for the further degradation of the amino-glycol obtained from the ethyl acrylate adduct. Consequently, this material was heated with phosphorus and hydriodic acid, followed by zinc and hydrochloric acid reduction, to form a base in good yield. The oxalate and picrolonate of the base were identical with the corresponding derivatives of 2,2-dimethyl-5-n-propyl-pyrrolidine (XXVIII), whose synthesis was described earlier.



(XXI) (XXIV) (XXVIII)

The author had therefore no hesitation in formulating the adduct of ethyl acrylate and 5,5-dimethyl-1-pyrroline 1-oxide as (XXI), and the reduction product as the amino-glycol (XXIV). A preliminary communication of this work was published[119].

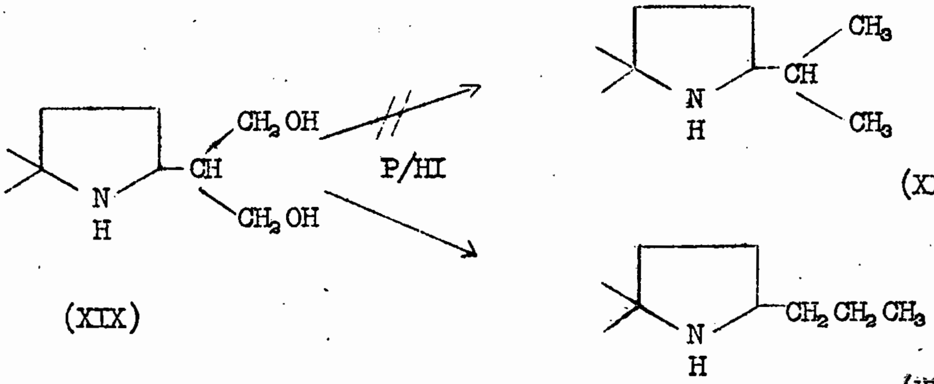
Degradation of the Allyl Alcohol Adduct on 5,5-Dimethyl-1-pyrroline 1-oxide.

In view of the ease of degradation of the isoxazolidine ester (XXI), the author decided to apply the same sequence to the adduct obtained from allyl alcohol and the nitrone (XXIX). This had an added interest in that, were the orientation of the substituent placed in position 4, the parallel degradation sequence would be obtained.

When the adduct was reduced with lithium aluminium hydride in tetrahydrofuran, an amino-glycol was obtained which was different from that formulated as (XXIV), obtained from the ethyl acrylate adduct (XXI). It was a low melting very hygroscopic solid, and secondly, it formed a picrate of melting point 125 - 126°. Reduction of the adduct with zinc and hydrochloric acid gave low yields of the same compound, whereas sodium borohydride had no effect. The possibility of this compound being a hydroxylamine-alcohol was eliminated on the grounds of its failure to reduce alkaline 2,3,5-triphenyl-tetrazolium chloride.

If the author's deductions concerning the structure of the ethyl acrylate adduct were correct, then, the new amino-glycol should have had structure (XIX). Reduction with phosphorus and hydriodic acid, followed by zinc and hydrochloric acid should then have given the isopropylpyrrolidine (XXVII).

To the author's amazement, the n-propyl pyrrolidine (XXVIII) was obtained, identified beyond doubt by direct comparison of its oxalate with the authentic material.



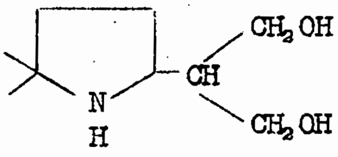
(XIX)

(XXVII)

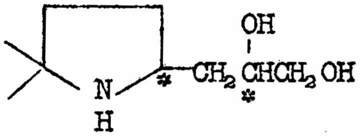
(XXVIII)

As a working hypothesis, the author considered that, with the evidence at hand, the anomaly could be best explained by assuming a rearrangement of the isopropyl side-chain in the glycol, which would result in an unusual unbranching of the isopropyl group. To complicate matters, the presence of such a postulated rearrangement now made invalid any conclusions as to the structure of <u>both</u> the allyl alcohol and ethyl acrylate adducts, since these were formulated on the basis of their conversion to the respective propylpyrrolidines. Clearly, a means of identifying the glycols had to be sought elsewhere, and thus it was decided to settle the problem by an unambiguous synthesis of both the glycols.

The work relating to the synthesis of these compounds will be fully described in Section III. For the purpose of the present discussion, the conclusions reached there will be mentioned here.



(XIX)



(XXIV)

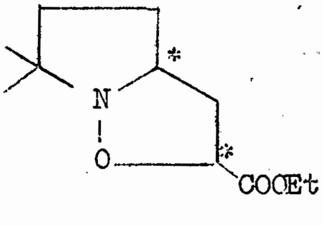
Synthesis of the glycol (XIX) showed that this structure should have been assigned to the compound obtained by reduction of the ethyl acrylate adduct, as discussed on page 63. The reduction of the allyl alcohol adduct gave the only other possible alternative (XXIV), which was also successfully synthesised.

However, with this last named compound, a certain discrepancy must be mentioned. Although the synthetic substance, obtained as a viscous oil by distillation, solidified to a solid of low and indefinite melting point upon seeding with the material obtained by degradation, it could not be recrystallized. The picrate of the synthetic material melted at 116 - 119° after one recrystallisation from n-butanol, but this melting point was not depressed by admixture with the picrate of melting point 125 - 126°, from the degradation product. Several recrystallizations of the low-melting picrate raised its melting point to 123 - 125°, again undepressed by admixture with the higher melting picrate. This phenomenon is ascribed to different proportions of the two possible racemates of the amino-glycol proportions.

Infra-red absorption spectra gave no clue to the answer, and even confused the issue, for the "cold" ester had a double absorption maximum, both peaks being of almost equal intensity, and with both absorption positions attributable to the C = O stretching vibrations of saturated esters. The one absorption maximum at 1757 $cm.^{-1}$ was just outside the commonly quoted range for such esters,[88,120] while the other, at 1740 $cm.^{-1}$, was well within the range (1735 - 1750 $cm.^{-1}$). The so-called "hot" ester had a virtually identical spectrum, with the only significant difference being noticeable in the C = O stretching vibrations, which now gave rise to a main peak with a shoulder.

On the above evidence, one might easily be led to believe that both the "hot" and the "cold" esters were in fact mixtures of the two position isomers, with varying composition. Consequently, attempts were made at separating the two ester components of the "cold" ester. Chromatography on magnesium silicate, which has been useful in the separation of ester mixtures[121a], did not result in either separation of, or enrichment of the components. A similar failure was experienced with acid-washed alumina. Partition between petroleum ether and water, (in which the esters are appreciably soluble), resulted in neither separation nor enrichment. Distillation, was out of the question, in view of the thermal instability of the compounds, even if appreciable differences in boiling points exist to permit fractionation.

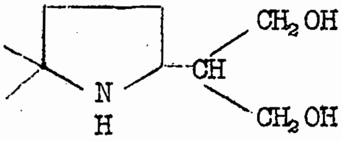
The above failures at separation led the author to the conclusion that the split ester infra-red absorption peak was due principally not to the presence of a mixture of the two position isomers, but to a mixture, in approximately equal proportions, of the two racemates arising from asymmetry at the carbon atoms marked with an asterisk. As discussed in Section IV of this thesis, the steric environment of the carbonyl grouping of the two racemates is quite different, and will be expected to cause an appreciable shift in the absorption maximum.



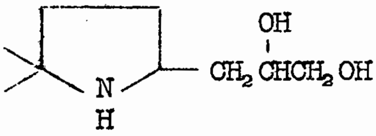
(XXI)

An Analytical Method for the Determination of the Presence of Individual Position Isomers in a Mixture.

In order to ascertain with certainty the presence of individual position isomers in a mixture, the author decided that the best method resided in the reduction of the esters to the amino-glycols (XIX) and (XXIV), and to separate these compounds by paper chromatography.



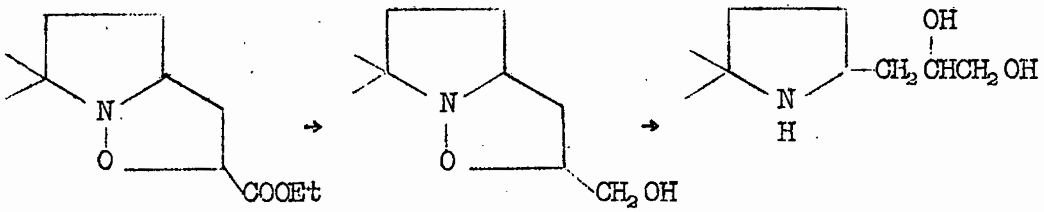
(XIX)



(XXIV)

Initially, the "cold" ester was reduced with lithium aluminium hydride in tetrahydrofuran, the time of reaction being about 5 - 6 hours. The product, obtained by vacuum distillation, was shown to consist of two components capable of separation by paper chromatography in an acidic solvent. The solvent, a mixture of butanol and aqueous acetic acid, was chosen in view of the fact that it has been shown to effect separation of amino-alcohols obtained by reduction of amino-acids[121b].

The slower moving component moved at the same rate as the amino-glycol (XXIV), obtained as mentioned previously by reduction of the allyl alcohol adduct on 5,5-dimethyl-1-pyrroline 1-oxide. The faster moving component was isolated by column chromatography on cellulose, and was purified by vacuum distillation. It was a viscous oil, which solidified to a low melting solid upon seeding with a sample of the pure allyl-alcohol adduct (XL). The picrate, of melting point 154 - 155° was not depressed by admixture with the picrate of melting point 151 - 152° obtained from the allyl alcohol adduct, and had the same analytical composition. In addition, reduction of this material with lithium aluminium hydride in tetrahydrofuran gave the amino glycol (XXIV), of picrate melting point 116 - 119°.



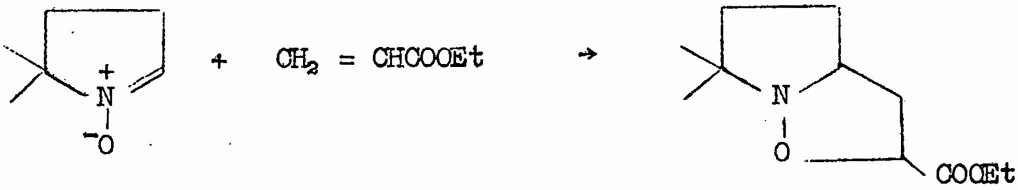
(XXI) (XL) (XXIV)

Thus, in spite of the small discrepancy in the melting points of the picrates, the material obtained by column chromatography must be regarded as being virtually identical to the allyl alcohol adduct, the differences in properties being most probably due to varying racemate compositions. This clearly shows that the orientation of the hydroxymethyl group in the allyl alcohol adduct and the ethoxycarbonyl group of one of the components of the "cold" ester, (still considering at this stage that it could be a mixture of the two possible position isomers), was identical. Since the amino-glycols were by then unambiguously synthesised, the sequence (XXI) → (XL) → (XXIV) was established.

At this juncture, it seemed highly likely that the "cold" ester was a pure position isomer, although of course, proof of this still awaited confirmation. In order to achieve this, it was essential to determine whether the solvent used effected separation of the isomeric amino-glycols by paper chromatographic methods. A small sample of the undoubtedly pure amino-glycol (XIX) was obtained on a micro-scale by treating a small quantity of the pure picrate with alkali, and extracting the base into ether, which was directly applied to the paper. It immediately became apparent that the solvent used was ineffective in separating the two glycols. However, a basic solvent (butanol-ammonia) readily effected a good separation. The time was now ripe for the investigation into the composition of the adducts.

The Preparation of the Pure Position Isomers:

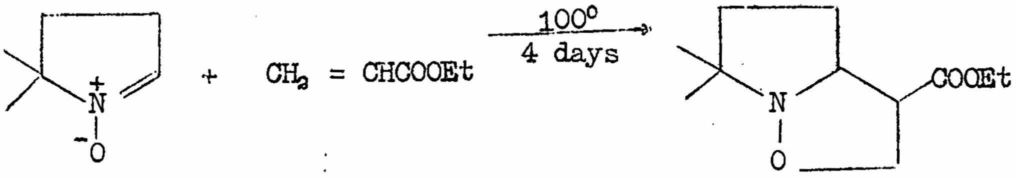
Reduction of the so-called "cold" ester to the corresponding amino-glycol, as described earlier, followed by paper chromatography in the manner elaborated above, revealed that only the amino-glycol (XXIV) was present. No traces of the isomer (XIX) could be detected, and so it must be concluded that, within the limitations of the experimental technique, reaction of 5,5-dimethyl-1-pyrroline 1-oxide (XXIX) with ethyl acrylate at room temperature gives, after about twenty four hours reaction time, a quantitative yield of pure 3-ethoxycarbonyl-8,8-dimethyl-2-oxa-1-azabicyclo[3,3,0]octane (XXI)



(XXI)

(XXIX)

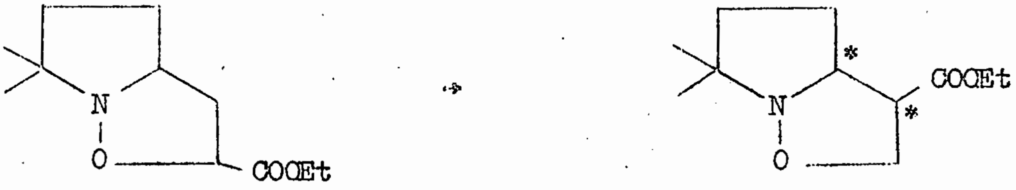
On the other hand, the so-called "hot" ester, prepared by heating the nitrone and ethyl acrylate at 100° for a day, was found to give on reduction, a mixture, in approximately equal proportions, of the two amino-glycols (XIX) and (XXIV). When the heating was carried out for four days, reduction of the adduct, which is formed in quantitative yield, showed that only the amino-glycol (XIX) was present, and so, again within the limitations of the analytical technique, it can be said that the reaction gives the pure isomer (XVI):



(XXIX) (XVI)

On a preparative scale, the adduct gave on reduction with lithium aluminium hydride, a 73% yield of pure (XIX), a very hygroscopic viscous liquid, forming a picrate of melting point 165 - 166°. This material, although being a amino-glycol, reacted with periodic acid in a manner not reconcilable with theory, thus showing that this reagent must be used with considerable caution in structural investigations of substances related to the amino-glycols here described.

The compound (XVI), 4-ethoxycarbonyl-8,8-dimethyl-2-oxa-1-azabicyclo [3,3,0]octane, had an infra-red absorption spectrum closely similar to that of the isomer (XXI), the only significant difference residing in the absorption characteristics of the ester group. Only a single, slightly unsymmetrical peak at 1742 cm.$^{-1}$ attributable to the C = O stretching vibrations was present. It is advanced as a working hypothesis that this compound is a single, or at least a very enriched racemate. Two racemates of this compound can theoretically exist, arising from asymmetry at the carbon atoms marked with an asterisk. This will again be discussed in Section IV of this thesis.



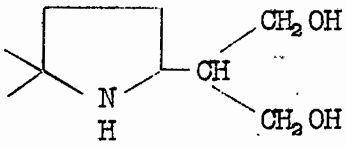
(XXI) (XVI)

In order to determine whether the ester (XXI) was convertible into the isomer (XVI), a small sample was heated for about twelve hours with ethyl acrylate. The ethyl acrylate was added in order to displace the probable decomposition equilibrium: (XXI) ⇌ nitrone + acrylate ⇌ (XVI) to the ester sides, a displacement which might not occur to the desired extent if the compound (XXI) alone was heated, as small quantities of ethyl acrylate produced by its decomposition would be present extensively in a vapour phase at 100°.

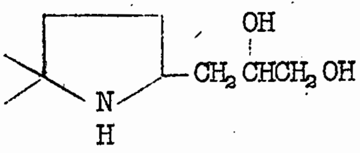
Reduction of the product after the heating treatment showed that the amino-glycols corresponding to the reduction of both (XVI) and (XXI) were present, clearly showing the partial interconversion of (XXI) into (XVI) under even the limited time of reaction.

The Rearrangement of the Amino-Glycol (XIX):

On page 69, the author mentioned how he was led to consider the possibility of a rearrangement of the amino-glycol (XIX) to the n-propyl-pyrrolidine (XXVIII) by the action of hot, fuming hydriodic acid. In the light of further work it was shown that the reaction was carried out on the reduction product of the so-called "hot" ester, which was in fact a mixture of the glycol (XIX), and the isomer (XXIV). Since the latter compound could alone be responsible for the formation of the pyrrolidine,



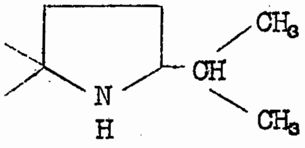
(XIX)



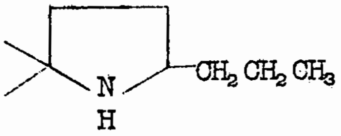
(XXIV)

any conclusions as to the existence of the suspected rearrangement had to be considered invalid.

In order to determine whether such a rearrangement did in fact occur, a sample of the pure glycol (XIX) was heated with hydriodic acid, and the reaction mixture reduced with zinc and hydrochloric acid. The basic product of the series of reaction gave an oxalate, identical with the oxalate of 2,2-dimethyl-2-propyl-pyrrolidine (XXVIII) as well as a small quantity of a picrolonate identical with the picrolonate of 5,5-dimethyl-2-*iso*propyl-pyrrolidine (XXVII). This must be regarded as clear evidence that the rearrangement formulated above does in fact occur. Lack of time unfortunately prevented the author's further investigations into this unusual reaction. However, in order to provide a reasonable explanation for this, the author would like to advance the following hypothesis.



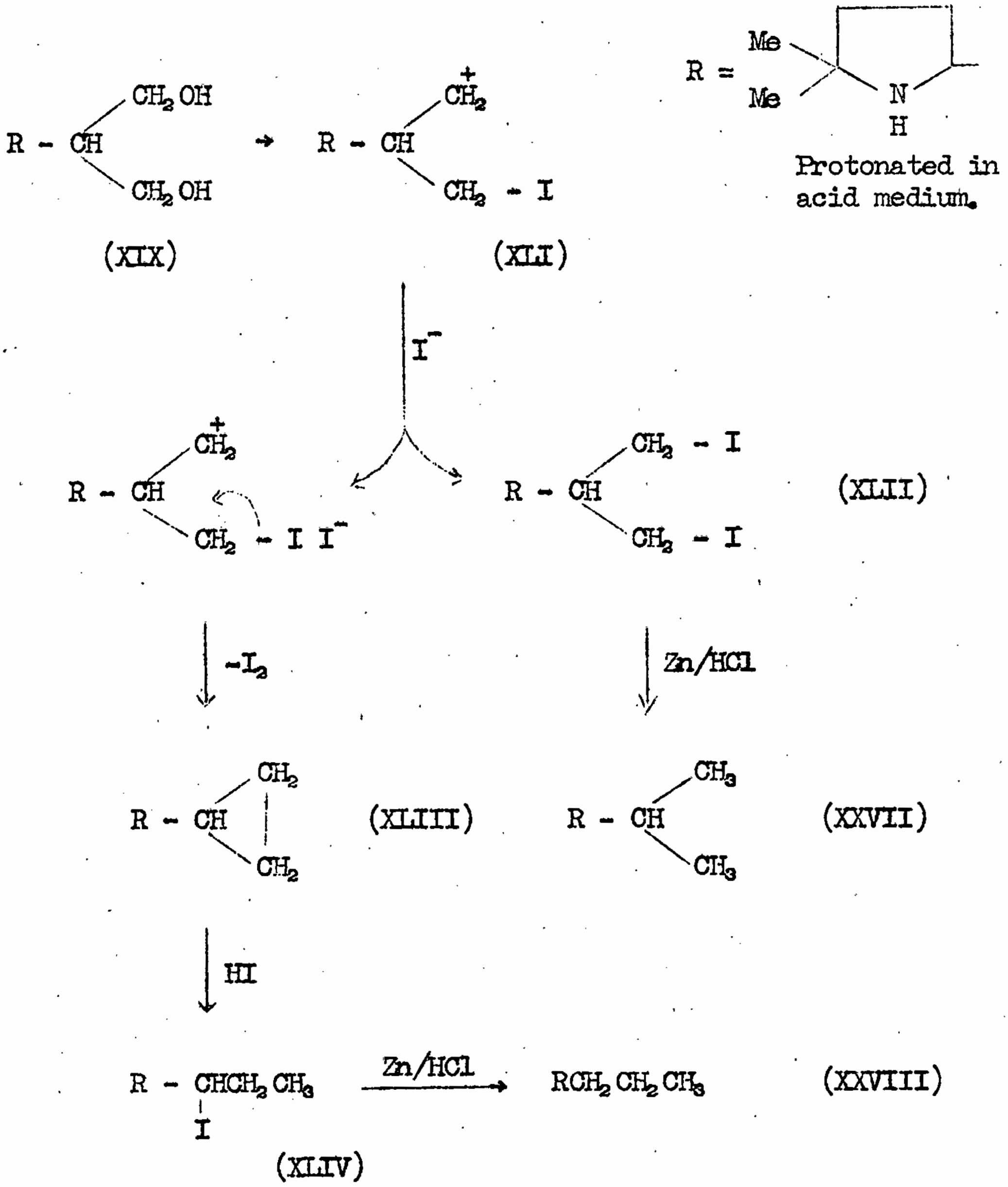
(XXVII)



(XXVIII)

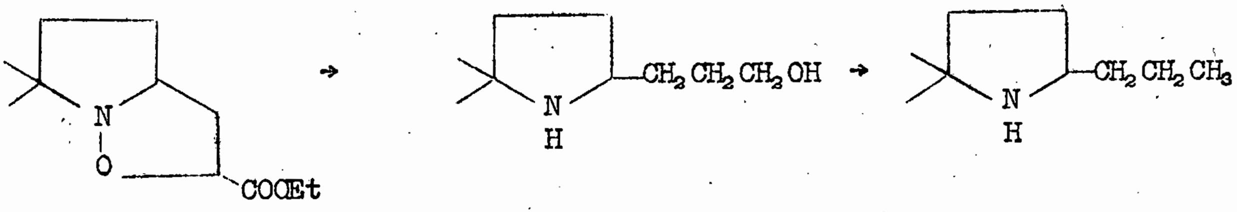
At some stage in the reaction, the glycol may well be converted to the species (XLI), an intermediate in the formation of the di-iodo compound

(XLII), which can be expected to be eventually converted to (XXVII). The



Protonated in acid medium.

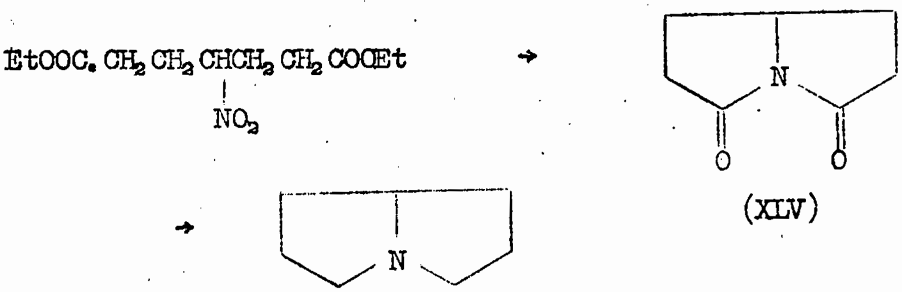
The ion (XLI), under the influence of iodide ion, or by some other mechanism, could conceivably lose iodine as an I^+ ion, (combining with I^- to form as for example the one described below.



(XXI) (XXVIII)

To this end, the ester (XXI) was hydrogenated for a prolonged period of time at elevated temperatures and pressures, using copper chromite as catalyst, and dioxan as solvent. A basic product was obtained, purified by distillation under reduced pressure, and analysed for $C_9H_{17-19}N$. A picrate was obtained from this base, and analyses corresponded closely to the picrate of a base $C_9H_{17}N$. This compound was not one of the two pyrrolidines (XXVII) or (XXVIII).

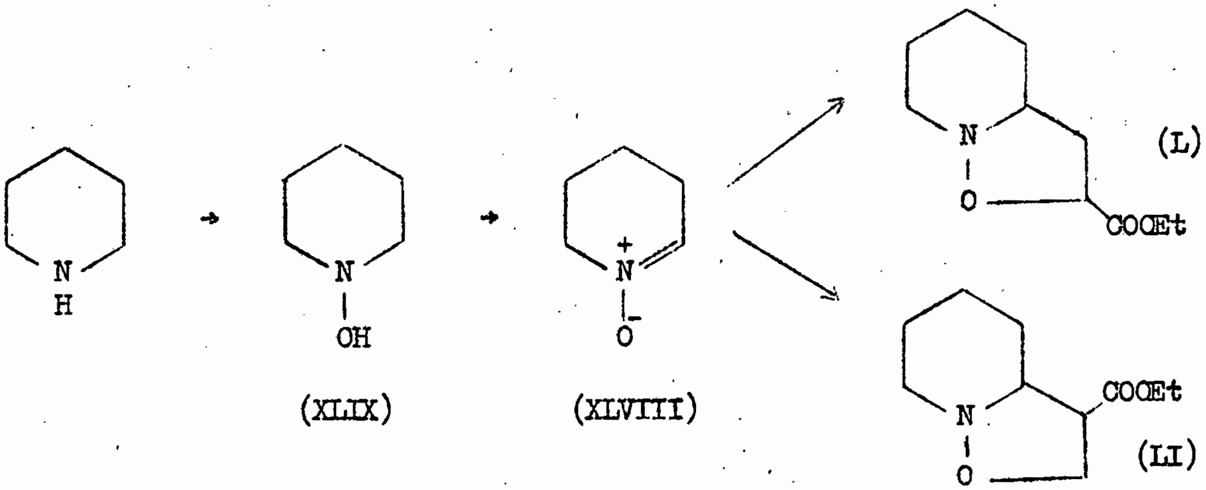
Formation of the pyrrolizidine (XLVI)ring system is known to take place by catalytic hydrogenation of γ-nitropimelic esters, using copper chromite in dioxan. This reaction is believed to occur by way of the intermediate imide (XLV)[123] :



(XLV)

(XLVI)

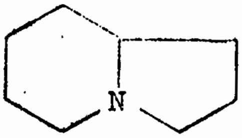
If one carried the analogy to the isoxazolidine ester (XXI), it seemed not unlikely that the hydrogenation would have given the pyrrolizidine (XLVII), by the following sequence:



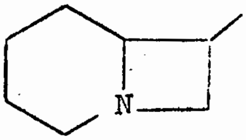
(XLIX) (XLVIII) (L) (LI)

Reaction of this nitrone trimer with ethyl acrylate at room temperature gave a 1:1 nitrone-acrylate adduct, which was not degraded, and whose exact structure is therefore unknown. It is tempting to assign to this compound the structure (L), on grounds of analogy to the corresponding compound prepared in the same way from ethyl acrylate and 5,5-dimethyl-1-pyrroline 1-oxide. Sufficient differences between the properties of five- and six-membered ring nitrones do however exist (see introductory review), to indicate the exercise of caution, and not to disregard entirely the possibility of the structure (LI).

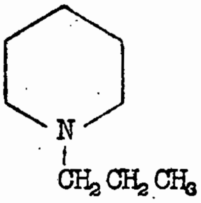
If the author's conjectures regarding the pyrrolizidine structure (XLVII) for the base $C_9H_{17}N$ obtained by hydrogenation of (XXI) were correct, then hydrogenation under the same conditions would yield (assuming structure (L) for the adduct) the known compound indolizidine (LII)[125]. On the other hand, should the structure of the adduct have been (LI), then hydrogenation could yield, as an initial product, the compound (LIII), 3-methyl-conidine, which has been previously described[126]. This material would not be expected to survive the severe hydrogenation conditions used, and would undergo hydrogenolytic cleavage of the four-membered ring, to give one or more of the bases (LIV), (LV), (LVI) or (LVII), which were either known, or could be fairly readily synthesised.



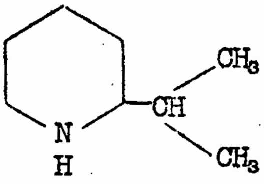
(LII)



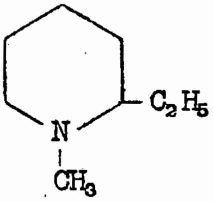
(LIII)



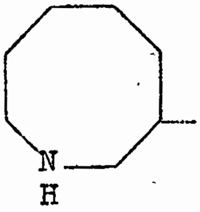
(LIV)



(LV)



(LVI)



(LVII)

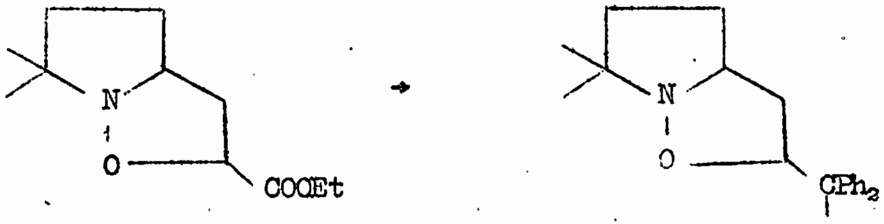
However, when the adduct was hydrogenated in dioxan over copper chromite, a substance analysing very closely for $C_8H_{15}N$ was obtained. It formed a picrate which analysed for the picrate of a base with the above empirical formula. This picrate had a melting point which did not correspond to the melting points of the known picrates of either (LII) or (LIII), although it definitely is isomeric with these compounds. A substance $C_8H_{15}N$, prepared by catalytic hydrogenation, can be no other compound than a saturated bicyclic amine.

This work is obviously far from complete, but as can be readily realized, a more thorough investigation lay rather beyond the scope of this thesis. It is highly likely that the severe conditions used in the hydrogenation resulted in some deep-seated rearrangement of the molecule. A detailed structural investigation of the bicyclic bases is under consideration.

The Reaction of 3-Ethoxycarbonyl-8,8-dimethyl-2-oxa-1-azabicyclo[3,3,0] octane with Phenylmagnesium Bromide.

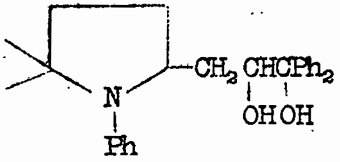
Since the author had shown that the isoxazolidine ring underwent N - O cleavage under the influence of the nucleophilic hydride ion from lithium aluminium hydride, he became interested in determining whether the ring might also not be cleaved by nucleophilic Grignard reagents.

Consequently, the ester (XXI) was treated with an excess (somewhat more than 3 moles) of phenylmagnesium bromide. The compound isolated corresponded to (LVIII), and not (LIX) or (LX), expected if the isoxazolidine ring had

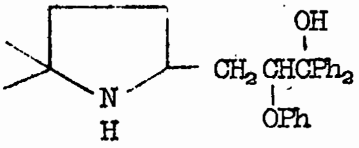


(XXI) (LVIII)

taken part in the reaction. It can be concluded therefore that the isoxazolidine ring appears to be stable to Grignard reagents, and in any case is far less reactive than the ester group. This is in agreement with the fact that the ester group is the first point of reduction of (XXI) with lithium aluminium hydride. (See page 74).



(LIX)



(LX)

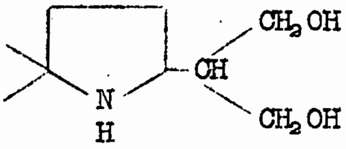
This failure of the isoxazolidine ring to react with phenylmagnesium bromide is by no means claimed to form a basis for generalisations, as more vigorous conditions, or a more reactive organometallic compound may achieve a ring cleavage.

SECTION III

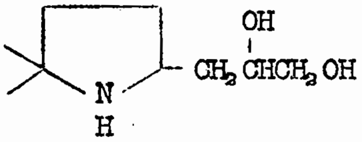
SECTION III

The Synthesis of the Amino-Glycols

The amino-glycols (XIX) and (XXIV) were found to present a number of interesting synthetic problems. It appeared desirable to employ known pyrrolidine syntheses, but the gem-dimethyl system present in both compounds afforded an impasse to any simple sequence based on the reduction of pyrroles[127a], while the complexity of the side-chain at position 2 of the pyrrolidine ring clearly introduced difficulty should it have been desired to synthesise the ring by the more usual cyclisation methods[127b].



(XIX)

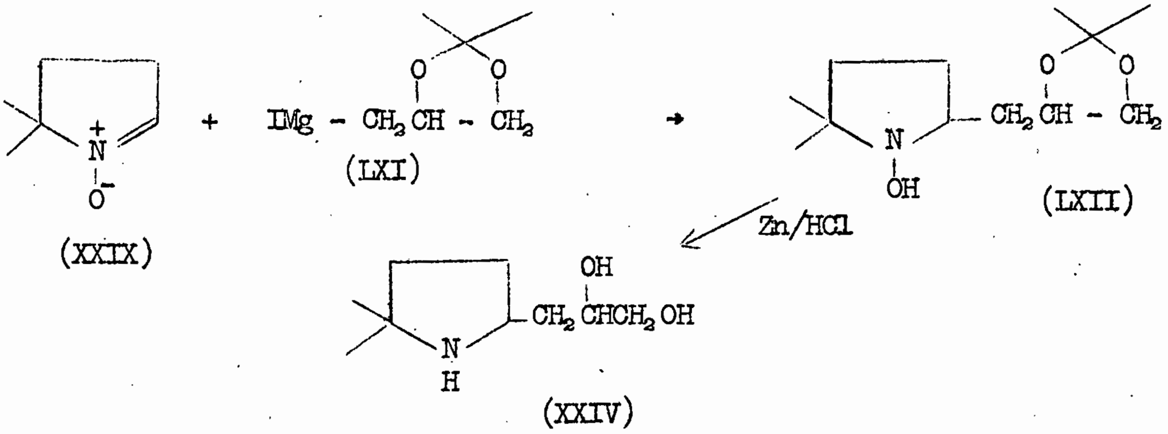


(XXIV)

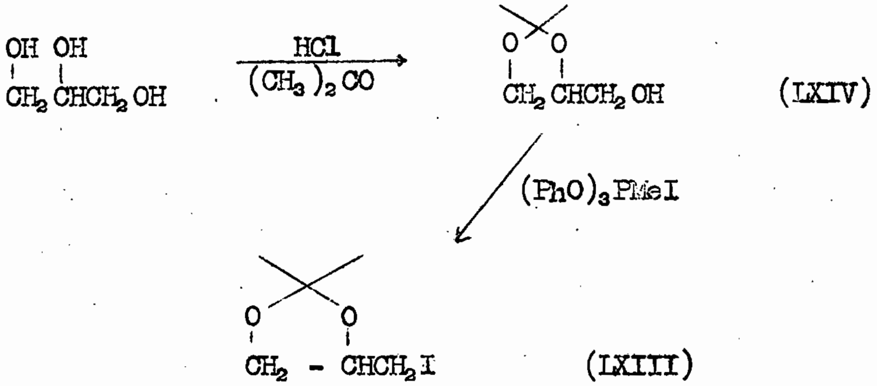
It was the author's opinion that the route to the desired compounds lay in the introduction or modification of side-chains on the pyrrolidine ring. Obviously, in order to achieve this, a suitably altered pyrrolidine system had to be utilised, and the author decided to make use of the reactive properties of the nitrone system, hoping thereby not only to synthesise the required amino-glycols, but also to demonstrate the suitability of cyclic nitrones for syntheses in the heterocyclic field.

Amino-Glycol (XXIV)

The first attempted route to the compound (XXIV) was as follows. The nitrone 5,5-dimethyl-1-pyrroline 1-oxide (XXIX), prepared as described earlier (page 51), was to be reacted with the Grignard reagent (LXI), to give, it was hoped, the hydroxylamino-ketal (LXII). The hydroxylamino group of this compound was to be reduced to the secondary amine by the action of zinc and hydrochloric acid, the ketal undergoing hydrolysis under these conditions to give ultimately, the desired amino-glycol (XXIV):

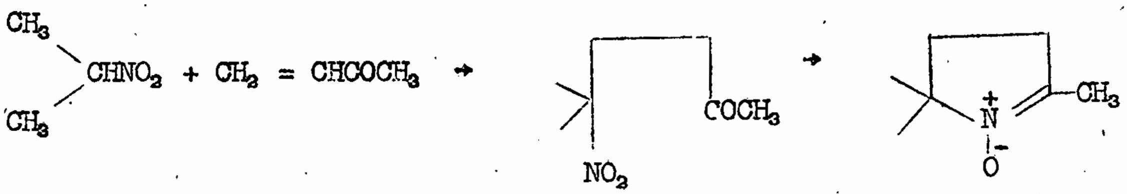


The iodo-compound (LXIII), required to form the Grignard reagent (LXI) was prepared by the reaction of triphenylphosphite methiodide[128] on αβ-propylidene glycerol (LXIV)[129], which in turn was prepared from glycerol and acetone by a known method[130].

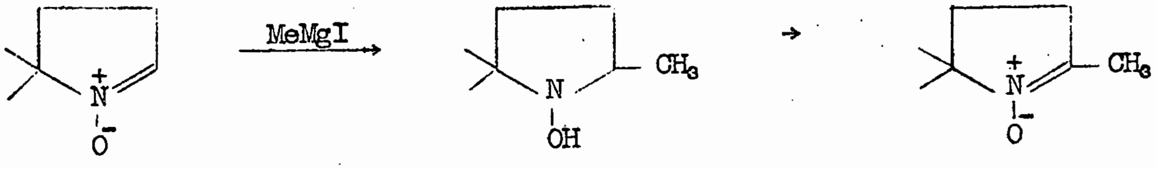


Unfortunately, the iodo-compound (LXIII) could not be converted to the Grignard reagent, in spite of repeated attempts using activated magnesium powder[131], tetrahydrofuran as "forcing" solvent[132], or a promising new method which makes use of ethylene dibromide as entraining agent[133].

The next line of approach was entirely different. 2-Nitropropane was condensed[134] with methyl vinyl ketone to give 5-methyl-5-nitro-pentan-2-one (LXV). This was then reduced with zinc dust and ammonium chloride, to the

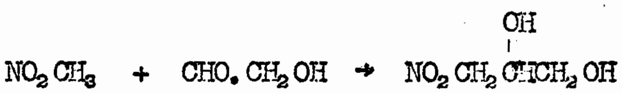

(LXV) (LXVI)

nitrone 2,5,5-trimethyl-1-pyrroline 1-oxide (LXVI), identical with that prepared by Todd and his co-workers[5], by oxidation of the corresponding hydroxylamine (LXVII), in turn prepared from 5,5-dimethyl-1-pyrroline 1-oxide (XXIX) and methylmagnesium iodide:


(XXIX) (LXVII) (LXVI)

The chemical properties of the 2-methyl group of 2-methyl-1-pyrroline 1-oxides are analogous to those of methyl ketones, (see page 33), and this methyl group can also be considered to be activated in a manner not unlike the methyl group of nitromethane.

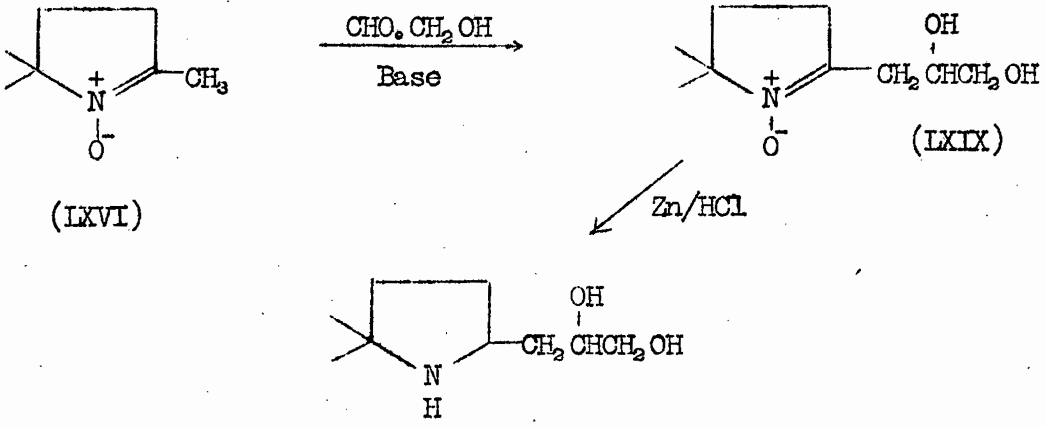
Since Pictet and Barbier[135] successfully managed to effect an aldol-type addition between glycollaldehyde and nitromethane, to yield initially, the nitro-glycol (LXVIII), the present author attempted the aldol addition



$$NO_2CH_3 + CHO.CH_2OH \rightarrow NO_2CH_2\overset{OH}{C}HCH_2OH$$

(LXVIII)

of glycollaldehyde (prepared from dihydroxymaleic acid[148,149]) to the nitrone (LXVI).



(LXVI)

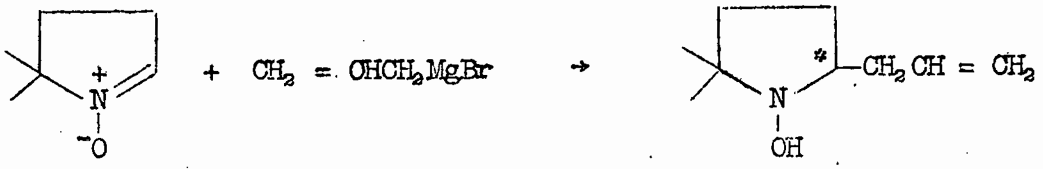
(LXIX)

(XXIV)

The intermediate nitrone-glycol (LXIX) was not to be isolated, but reduced with zinc and hydrochloric acid to the amino-glycol (XXIV).

However, since the next, and eventually successful synthesis was simultaneously concluded, only a preliminary attempt at reacting glycollaldehyde with (LXVI) was carried out. It was found that the basic catalyst used (sodium bicarbonate), caused the partial polymerisation of the glycollaldehyde to a mixture of sugars, and no compounds corresponding to an addition to the nitrone were isolated.

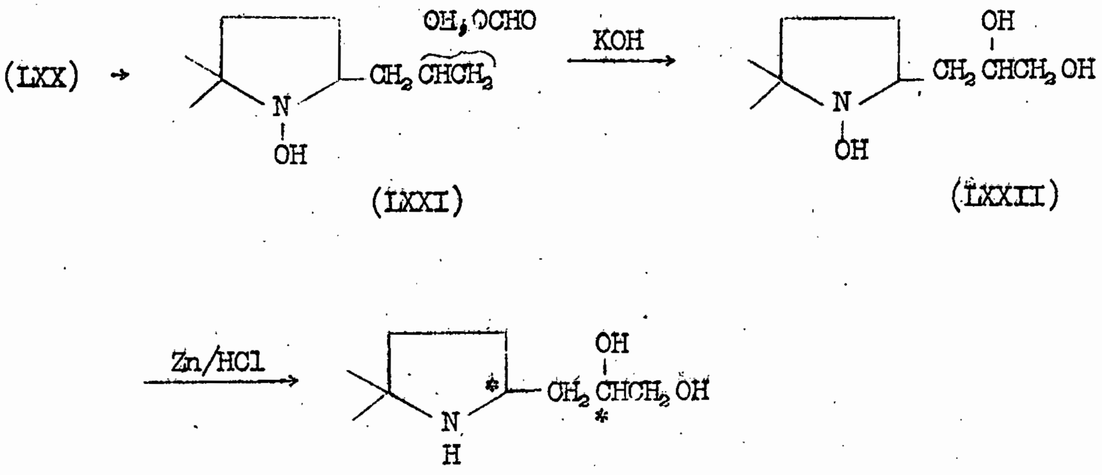
The successful synthesis made use of a compound previously synthesized by the author in a previous work[12]. This key substance was 2-allyl-1-hydroxy-5,5-dimethyl-pyrrolidine (LXX), which can be prepared by the addition of allylmagnesium chloride or bromide on the nitrone (XXIX).



(XXIX) (LXX)

The steric course of the reaction must be commented on; the compound (LXX), possesses only one asymmetric carbon atom (marked with an asterisk), and its method of synthesis from symmetrical precursors cannot be regarded as being stereospecific. Thus, (LXX) must be a mixture of two enantiomorphs.

It was decided to hydroxylate the double bond of (LXX) with performic acid, hydrolyse the resulting hydroxy-formyloxy hydroxylamine (LXXI) to the hydroxylamino-glycol (LXXII), and reduce the latter with zinc and hydrochloric acid to the amino-glycol (XXIV). The intermediates (LXXI) and



(LXXI) (LXXII)

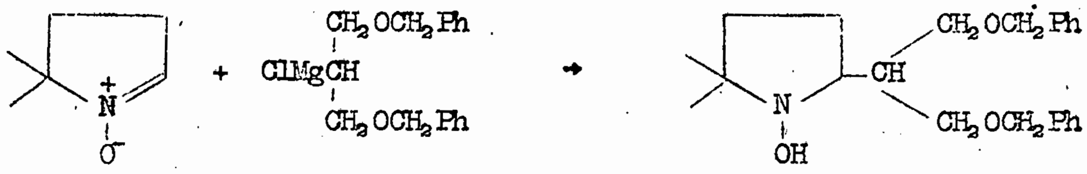
(XXIV)

(LXXII) did not need to be isolated. This projected sequence was successfully carried out. The product was a viscous liquid, which slowly crystallised on "seeding" with traces of the amino-glycols obtained by reduction (as described in the previous Section) of the "cold" ester and the allyl alcohol adduct on 5,5-dimethyl-1-pyrroline 1-oxide. The solid could not be recrystallised, but formed a picrate, of melting point 116 - 119° which was not depressed by admixture with the picrate, of melting point 116 - 119°, from the glycol obtained by reduction of the so-called "cold-ester". A mixed melting point with the picrate, of melting point 125 - 126°, from the glycol obtained by reduction of the allyl alcohol adduct, was not depressed below 116°. The low melting "synthetic" picrate could be recrystallised to a melting point 123 - 125°, which was not depressed on admixture with the picrate of melting point 125 - 126°.

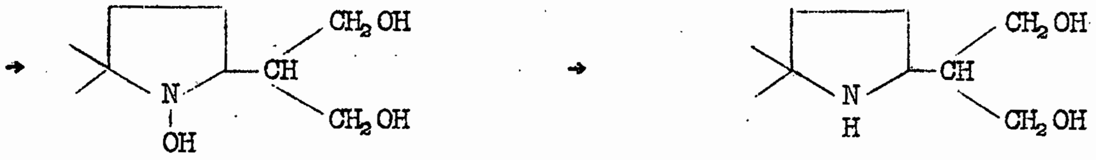
Again, the steric course of the reaction sequence must be discussed. The formation of the second asymmetric carbon atom, (i.e., the carbon atom 2 in the glycollic side-chain) is not stereospecific. Although it is fairly well established that hydroxylation with peracids is a trans-hydroxylation,[136] when such a reaction is carried out on the isolated allyl group, it must be a random process, and give eventually both the enantiomorphs of the asymmetric carbon atom bearing the hydroxyl group. Further, the reactions do not involve the carbon atom 2 of the pyrrolidine ring, which, as was pointed out, is asymmetric, and present in both enantiomorphic forms in the compound (LXX). Thus, the synthetic amino-glycol (XXIV) must be a mixture in nearly, if not totally, equal amounts of the two possible racemates arising from asymmetry at the carbon atoms marked with an asterisk.

Amino-Glycol (XIX)

As in the case of the former amino-glycol, (XXIV), a synthesis based on Grignard reagents was first attempted. It was hoped to react the Grignard reagent (LXXIII) with 5,5-dimethyl-1-pyrroline 1-oxide (XXIX), to yield the dibenzyl ether (LXXIV). This compound was then to be converted either to the desired amino-glycol (XIX), or the corresponding hydroxylamine (LXXV) by catalytic hydrogenolysis. This hydroxylamine was expected to reduce easily to the amino-glycol (XIX) by the agency of zinc and hydrochloric acid.

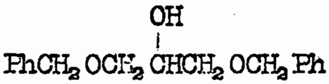


(XXIX) (LXXIII) (LXXIV)



(LXXV) (XIX)

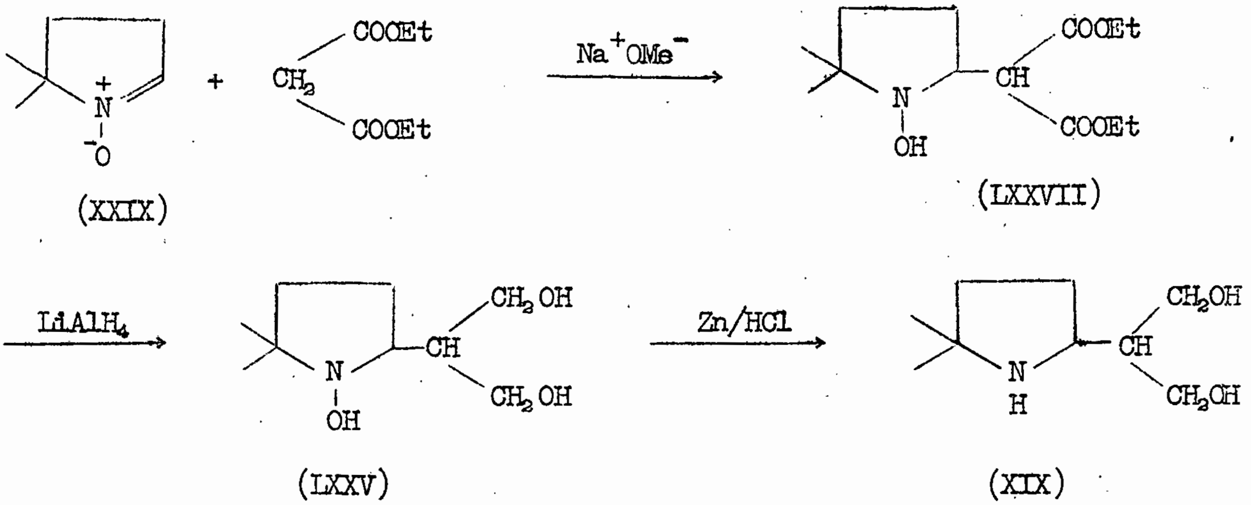
The chloro-compound required to form (LXXIII) was prepared by reacting glycerol 1,3-di-O-benzyl ether (LXXVI) with thionyl chloride in pyridine[137]. However, the conversion of this chloro-compound to the Grignard reagent failed, although especially forcing conditions were used.



$PhCH_2OCH_2CH(OH)CH_2OCH_2Ph$

(LXXVI)

A novel approach was obviously called for. As discussed in the introductory review, (page 34), nitrones undergo a series of base catalysed reactions akin to the aldol addition. It was argued that 5,5-dimethyl-1-pyrroline 1-oxide (XXIX) should then react with diethyl malonate under basic conditions to form the hydroxylamino-diester (LXXVII).



(XXIX) (LXXVII) (LXXV) (XIX)

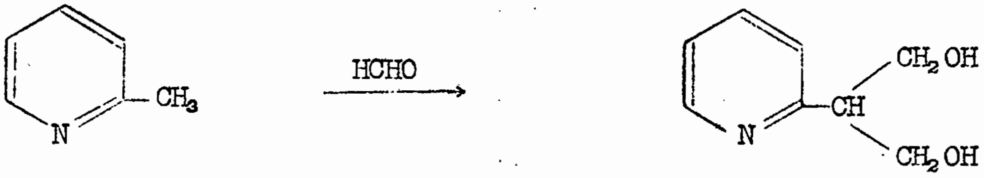
This compound was then to be reduced with lithium aluminium hydride to the hydroxylamino-glycol (LXXV), and hence to (XIX).

When the nitrone (XXIX) and diethyl malonate were reacted in the presence of sodium ethoxide, a water insoluble oil was obtained. This material gave a positive test for hydroxylamines when treated with 2,3,5-triphenyl-tetrazolium chloride, and showed a somewhat complex infra-red absorption spectrum in the region between 1600 and 1800 cm.$^{-1}$ Analysis of this oil indicated an empirical formula $C_{10}H_{17}NO_2$ and not $C_{13}H_{23}NO_5$, as required by the structure (LXXVII). Speculations as to the possible structure of this material must take into account that the analytical data cannot be considered reliable, in view of the fact that the substance was probably impure; this statement is based on the fact that the oil gave, upon treatment with oxalic acid, a substance analysing for the hydrogen oxalate of a base $C_{11}H_{21}NO$.

In addition to this, when piperidine was used instead of sodium ethoxide as the basic catalyst, in addition to the oil described above, a very small quantity of a solid was also obtained. This substance gave analytical values corresponding to a formula $C_{20}H_{28}N_2O_7$, which is difficult to reconcile with a simple reaction sequence.

In view of the above, the author prefers not to speculate upon the exact nature of the unidentified materials mentioned, but would however like to point out that the subject definitely merits further work.

The eventually successful attempt had its origin when the author noticed a possible similarity between the reactivity of the 2- and 4-methyl substituents in the pyridine and quinoline systems, which are known to be protogenic, and the 2-methyl group of 2-methyl-1-pyrroline 1-oxides. It was well known for example, that 2-picoline (LXXVIII) underwent aldol-type additions with formaldehyde^{138}, to yield 2-(2-pyridyl)-propan-1,3-diol (LXXIX):

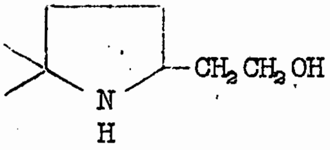


(LXXVIII) (LXXIX)

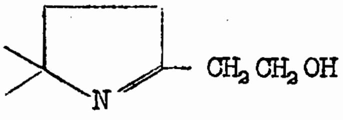
Quinaldine and lepidine react in an entirely analogous manner^{112,117}, and all indications are that this is a general reaction. With this observation in mind, it was not considered impossible that 2,5,5-trimethyl-1-pyrroline 1-oxide (LXVI) should undergo a similar reaction, to form the nitrone-glycol (LXXX). This was then to be converted to the amino-glycol (XIX).

(LXVI) (LXXX)

When (LXVI) was reacted with two moles of formalin, in the presence of aqueous alkali, and the product reduced, without prior isolation, a small quantity of a base was obtained, whose picrate did not give an entirely satisfactory analysis. The results indicated however that the reaction had yielded either the pyrrolidine (LXXXI) or the pyrroline (LXXXII), showing that only one mole of formaldehyde had reacted with



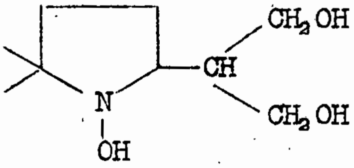
(LXXXI)



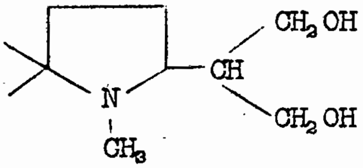
(LXXXII)

the nitrone.

Bearing this in mind, somewhat more vigorous reaction conditions were applied. The nitrone (LXVI) was heated with paraformaldehyde, and the product reduced directly with lithium aluminium hydride to the hydroxylamino-diol (LXXV), which again was not isolated.



(LXXV)



(LXXXIII)

The object behind this reduction step, which would appear unnecessary, since nitrones can be reduced directly to the amine with tin and hydrochloric acid, was to prevent the possibility of a reductive alkylation to the N-methyl-pyrrolidine (LXXXIII), such a reaction taking place on account of the presence of unreacted formaldehyde.

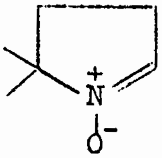
Reduction of the hydroxylamino-glycol (LXXV) with zinc and hydrochloric acid gave the desired amino-glycol, in a somewhat impure form, but from which could be obtained a picrate, m.p. 165 - 166°, identical with the picrate of the amino-glycol obtained by reduction of the ethyl acrylate adduct, as described on page 63.

SECTION IV

SECTION IV

Preliminary considerations.

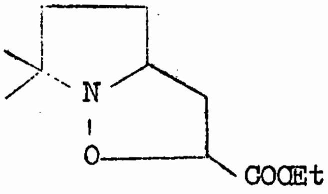
In attempting to formulate plausible mechanisms for the cyclo-addition reactions of 5,5-dimethyl-1-pyrroline 1-oxide (XXIX) involving ethyl acrylate and allyl alcohol, it will not be out of place to review the facts which transpire from the experimental work. These facts will be insufficient as far [illegible] constituting an exhaustive study of [illegible] reaction. This however, must be the case, as the author was primarily concerned with the complete proof of orientation of the adducts, and not with more subtle details of their formation.



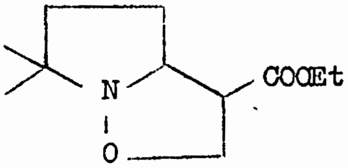
(XXIX)

(i) When ethyl acrylate reacts with 5,5-dimethyl-1-pyrroline 1-oxide (XXIX), an exothermic reaction takes place, with the exclusive and quantitative formation of the adduct (XXI).

(ii) When ethyl acrylate and (XXIX) react at 100°, a mixture of (XXI) and (XVI) occurs, the concentration of (XVI) increasing with time, until eventually it is formed quantitatively.



(XXI)

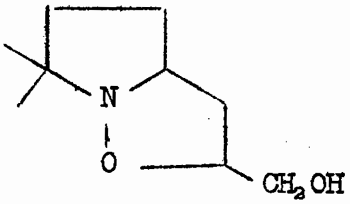


(XVI)

(iv) The adduct (XXI) can be converted to (XVI) by heating it at 100° with ethyl acrylate.

Points (iii) and (iv) thus clearly indicate that the adduct (XXI) is thermally less stable than the isomer (XVI). Furthermore, the fact that the latter is formed quantitatively under conditions where (XXI) is decomposed indicates that at 100°, the conversion of (XVI) into the nitrone and ethyl acrylate must either not occur, or be very slow with respect to its formation.

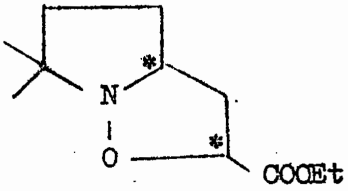
(v) When allyl alcohol is heated at 100° with the nitrone (XXIX), the adduct (XL) is the only product obtained, in 84% yield. It is not known whether the reaction proceeds quantitatively, in view of possible loss of material during its preparation. No reaction between (XXIX) and allyl alcohol appears to take place at room temperature.



(XL)

(vi) The adduct (XL) can be distilled without decomposition under conditions resulting in decomposition of (XXI). It is therefore clear that (XL) must be thermally more stable than (XXI).

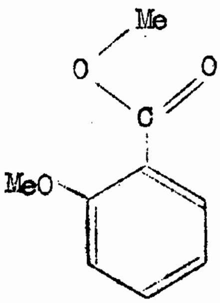
(vii) All evidence points to the fact that the adduct (XXI) is a mixture of the two possible racemates arising from asymmetry at the carbon atoms marked with an asterisk in the accompanying formula (XXI). This evidence can be summarised as follows.



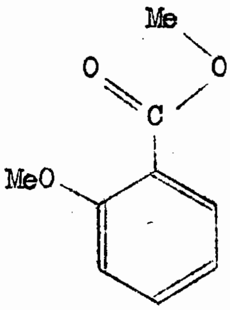
(XXI)

(a) The infra-red absorption spectrum of (XXI) shows two carbonyl absorption bands, at 1740 and 1757 cm^{-1}. Although little mention appears to have been made in the literature with regards to the relationship between steric environment and frequency shifts of certain groups, a recent paper on the subject may be mentioned.

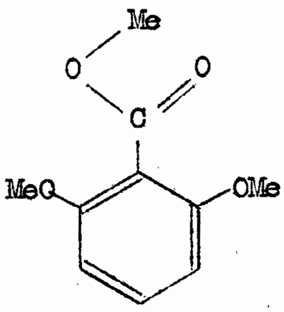
Brooks, Eglington and Morman[139], in their study on the infra-red spectra of carboxylic acids and their esters, observed that certain ortho-substituted methyl benzoates exhibited split carbonyl absorption bands in the infra-red. They ascribed this phenomenon to conformational isomerism. For example, o-methoxy methyl benzoate has two carbonyl bands. The one at 1723 cm^{-1} is assigned to the conformation A, while the other, at 1745 cm^{-1} is assigned to B.



A



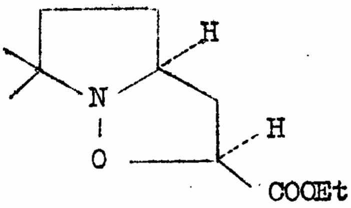
B



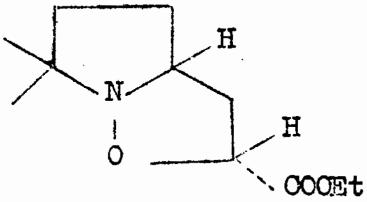
(LXXXIV)

2,6-Dimethoxy methyl benzoate (LXXXIV) shows only one carbonyl absorption band, as expected, since corresponding conformations A or B are identical. The difference between A and B (22 cm^{-1}) is of the same order as that noted for the adduct (XXI) (17 cm^{-1})

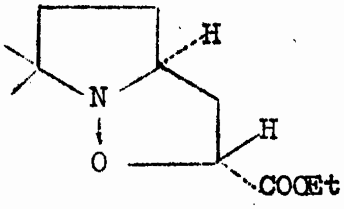
The compound (XXI), (the following discussion applies equally well to (XVI)), can exist in four stereoisomeric forms, represented below by the formulae (XXIa) - (XXId).



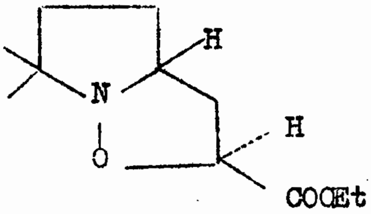
(XXIa)



(XXIb)



(XXIc)



(XXId)

The isomers (XXIa) and (XXIb) are enantiomorphs, and together they will, if present in equal amounts, constitute one racemic pair. The other two, (XXIc) and (XXId) will in the same way constitute the other racemate. Models clearly show that in the pair of isomers (XXIa) and (XXIb), the ethoxycarbonyl group is placed in such a way as to be partly included in the fold of the two five-membered rings, and this group experiences a totally different steric environment to that of the other pair of isomers. The models indicate that (XXIa) and (XXIb) have a sterically more compressed environment, and it may well be that this racemate is the least stable of the two. It is advanced by the author that the different steric environment found in the two racemates is responsible for the observed carbonyl frequency shift.

By a similar argument, it is most likely that (XVI), which exhibits a single absorption band (albeit unsymmetrical) even under conditions of high resolution, must be a pure racemate, or at least very enriched in one of the two possible racemates.

(b) The allyl-alcohol adduct is probably a pure or highly enriched racemate, in view of its readiness to solidify after vacuum distillation, to a low-melting solid of sharp melting point.

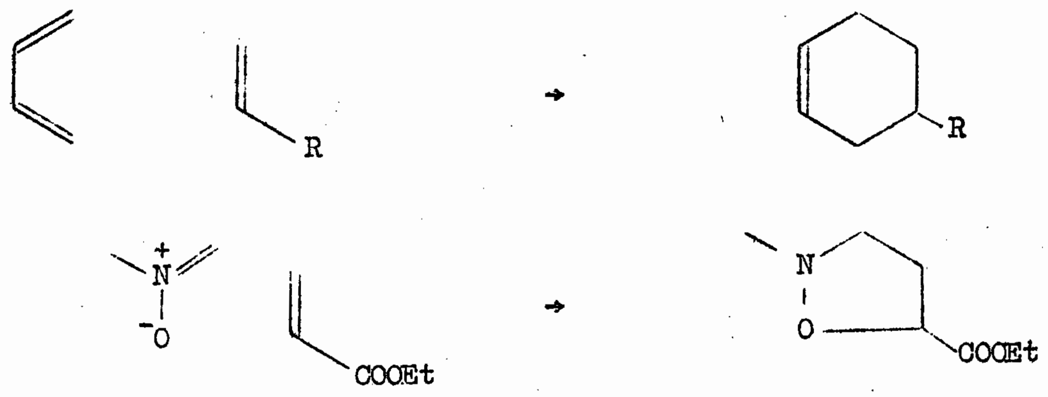
(c) Reduction of (XXI) gives an amino-glycol (XXIV), which is a solid of low and indefinite melting point, and which can be converted to a picrate of melting point 116 - 119°, analyses correctly for the picrate of the glycol, and yet can have its melting point raised by successive recrystallisations to 123 - 125°. The synthetic amino-glycol (XXIV), which cannot, in view of its method of synthesis, be anything else but a mixture of the two possible racemates, behaves similarly.

Reduction of the allyl alcohol adduct, which is probably a pure racemate, gives an amino-glycol (XXIV), which has a sharp melting point, and which gives a picrate of melting point 125 - 126°, which again analyses correctly as the picrate of (XXIV). This value is very close to the value to which the picrates of melting point 116 - 119° can be raised by successive recrystallisation.

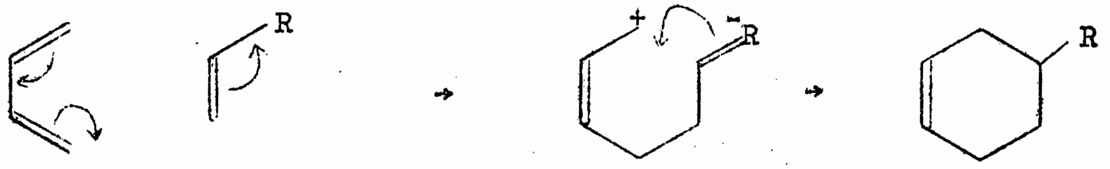
The above evidence does not conclusively and finally prove the presence in closely similar, if not equal amounts of the two possible racemates of (XXI), the single racemate of (XL), and the single, or at least highly enriched racemate of (XVI). The author is acutely aware of this, and considers that a final proof must be sought in the separation and complete characterisation of the four stereoisomers of (XXI), as well as the four stereoisomers of (XXIV). The suspected single racemates of both (XL) and (XVI) should be separated into only two, enantiomorphic components. However, it cannot be gainsaid that the evidence is sufficiently strong to give the author a reasonably secure basis for further stereochemical speculations.

Proposed mechanism for the reaction of ethyl-acrylate and 5,5-dimethyl-1-pyrroline 1-oxide:

The cyclo-addition of ethyl acrylate and 5,5-dimethyl-1-pyrroline 1-oxide, to form, at room temperature, exclusively (XXI), bears a formal similarity to the well known Diels-Alder reaction, which has been the subject of extensive investigations, and no small amount of mechanistical controversy[87,140].



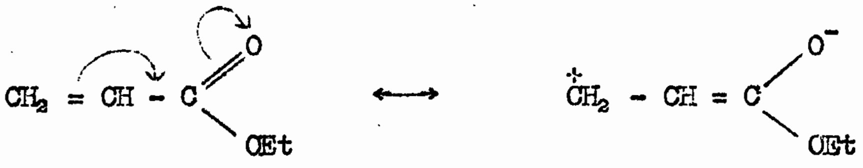
The restoration of the lone pair of electrons on the nitrogen atom of the isoxazolidine has its parallel in the formation of the double bond of the Diels-Alder adduct. Without going into details of the various possible mechanisms proposed for the Diels-Alder reaction, (recent work in this field include the contributions of Walling and Peisach[141], Woodward and Katz[142] and Newman[143]) it may be mentioned that the so-called ionic, two-step mechanism outlined below, is not generally favoured, as it fails



to account satisfactorily for the stereospecificity of the reaction, and the constancy of the observed rates, in both gaseous phase reactions and in solvents of widely differing polarity[141]. The present author however considers that the formation of (XXI) involves an ionic mechanism, which must be the easiest path of reaction between two highly polar substances such as the nitrone (XXIX) and ethyl acrylate, and also on account of the suspected non-stereospecificity of the reaction.

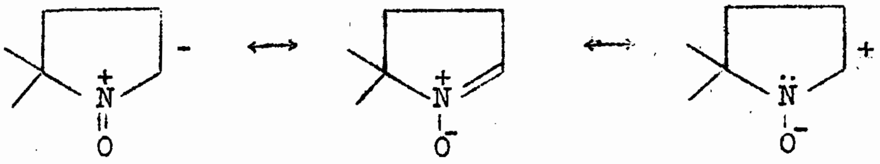
The mechanism proposed is entirely speculative, and will have to stand up to rigid physico-chemical studies, and conformational analysis.

The reactions of ethyl acrylate involve the polar extreme (B), which in view of the known general properties of αβ-unsaturated carbonyl compounds,



(A) (B)

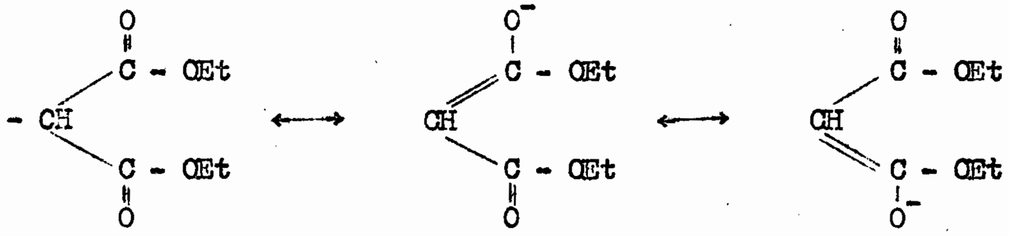
should generally behave as an electrophile[144]. The nitrone on the other hand, can polarise in two ways, to give the extremes (XXIXa) or (XXIXb).



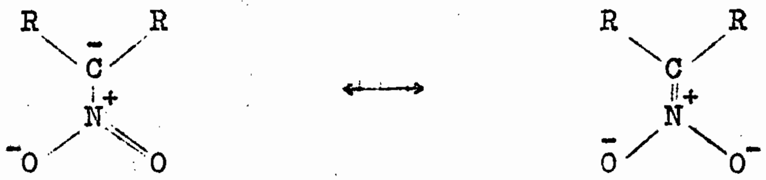
(XXIXa) (XXIXb)

The known electrophilic behaviour of nitrones is in accordance with the assumption that the nitrone should undergo an electromeric shift to (XXIXb) at the moment of attack by such species as Grignard reagents. There can be little doubt, in view of the close similarly between the nitrone and carbonyl groups, that the structure (XXIXb) contributes most to the actual structure of the hybrid. Nevertheless, to accommodate the fact that (XXIX) reacts spontaneously with ethyl acrylate to form only (XXI), one must take into account the possibility of an electromeric shift to (XXIXa) at the moment of attack by the ethyl acrylate in its polarised form. The nitrone would then react in the form that contributes least to the structure of the hybrid.

The above phenomenon should in no way be considered abnormal. It is well known, for example, that the ion derived from β-dicarbonyl compounds undergoes the Michael reaction with αβ-unsaturated carbonyl compounds[32]. The ion from diethyl malonate can resonate between the following canonical forms, in which the last two (which are identical) must contribute to the greater extent to the actual structure of the hybrid.

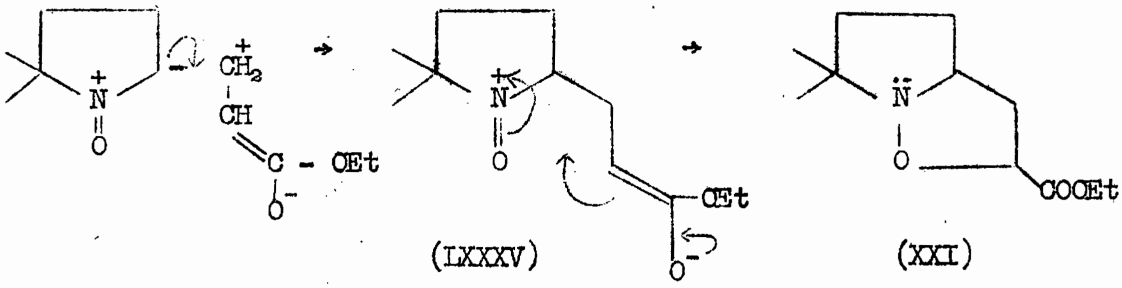


Yet, when diethyl malonate and its derivatives are reacted with electrophilic αβ-unsaturated esters, ketones, and nitriles, the products isolated are derived from the first canonical form. In an example more closely related to nitrones, the ion derived by proton abstraction from a nitro-paraffin must be a resonance hybrid of the two forms below, where again, the last form is considered to be the most important[146].



The structure which is operative in Michael reactions is the first one[34].

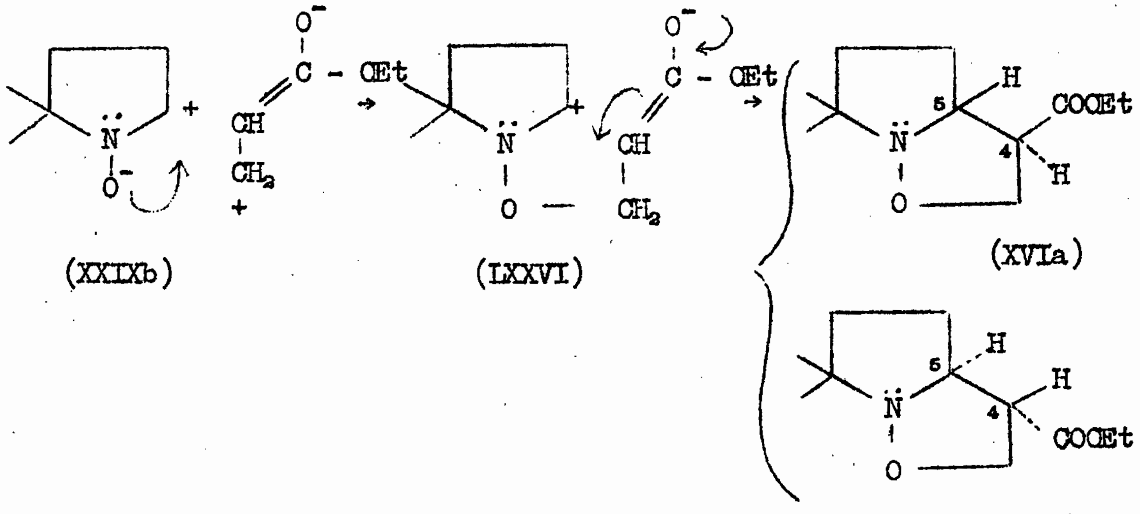
The first step in the reaction between the ethyl acrylate and the nitrone (XXIX) probably involves the formation of the zwitterionic intermediate (LXXXV):



(LXXXV) (XXI)

This intermediate then ring closes to the adduct (XXI). A mechanism such as the one above accounts for the probable non-stereospecificity of the reaction; the two asymmetric centres are formed at different times, and the first step cannot be conceived as having stereospecificity. In the second step, ring closure can take place by movement of the electrons equally well from either side of the plane of the "nascent" isoxazolidine ring. This would account for the random conformation of the carbon atom bearing the ester group.

As far as the formation of the ester (XVI) is concerned, an analogous mechanism can be postulated, involving, at the moment of initial attack, the nitrone polarised in the extreme (XXIXb):



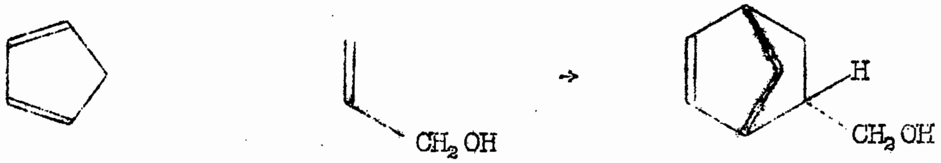
(XVIb)

The zwitterionic intermediate (LXXXVI) undergoes ring closure to give (XVI). It must be noted here that both carbon atoms 4 and 5 are rendered asymmetric simultaneously, and the bond formation could well be expected to possess stereochemical requirements which would make the formation of one racemate more likely than the other. Investigations with models seem to indicate that the formation of the racemic pair (XVIa) and (XVIb) would be favoured, but that has not been investigated by conformational studies, nor is the author certain, for that matter, that (XVI), as prepared, is a pure racemate, although, as mentioned earlier, this is a distinct possibility.

The fact that (XXI) only forms in the cold rather than (XVI) is expected in view of the fact that the compound (XXI) is formed by C^- coordinating on C^+, which process is attendant with a greater overall energy release than the rival process O^- on C^+. By an application of Le Chatelier's Principle, the exothermic character of the reaction leads one to expect its thermal reversal. That the adduct should be unstable at temperatures as low as 100° is however surprising. The author considers likely that (XVI), which slowly forms at 100°, does so by initial break-up of (XXI), and recombination of the liberated nitrone and ethyl acrylate, by the mechanism outlined above. The higher energy conditions which prevail at 100° allowing coordination of O^- on C^+.

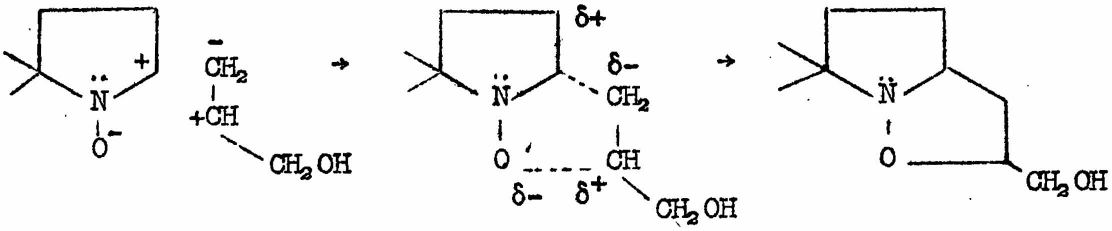
Whether the reversal of the cyclo-addition, i.e. the thermal decomposition of (XXI), takes place by a reversal of its formation mechanism, is not established.

As far as the reaction of 5,5-dimethyl-1-pyrroline 1-oxide and allyl alcohol is concerned, the author prefers to envisage a mechanism different to that of the ethyl acrylate additions. The reason for that is that the steric course of the reaction appears to be different, in that a single racemate is probably produced. As mentioned earlier, the ester (XXI), with identical group orientation, is a mixture of racemates. Possibly a mechanism similar to the reaction of cyclopentadiene with allyl alcohol, which is stereospecific[146], might operate:



Allyl alcohol is generally accepted to polarise in such a manner as to be open to attack by electrophiles[147] on the terminal carbon atom of the double bond. There lies the major difference between it and ethyl acrylate, which is open to attack by nucleophiles on its terminal olefinic carbon atom. Furthermore, in allyl alcohol, the absence of conjugation such as is found in ethyl acrylate must result in a less extensive polarisation, and hence the difference in reactivity towards the nitrone.

The demands of ethyl acrylate as an electrophilic reagent are sufficiently powerful to cause the nitrone to react in its least predominant extreme at room temperature. The demands of allyl alcohol, if at all significant, would be a nitrone polarised as (XXIXb). The polarisations of both nitrone and allyl alcohol are thus in such a mutually acceptable way as to allow dipole interactions to lower the energy of activation leading up to the transition state (LXXXII). Such an approach can be expected not only to determine the orientation of the addition, but, as in the case of Diels-Alder additions, to determine the stereochemistry of the adduct.



(XXIXb) (LXXXII) (XL)

In the absence of further information, the mechanisms suggested above must be considered as mere conjectures. Should they however stimulate further investigations into the kinetic, thermodynamic, and stereochemical aspects of nitrone cyclo-additions, the author will feel amply rewarded.

EXPERIMENTAL

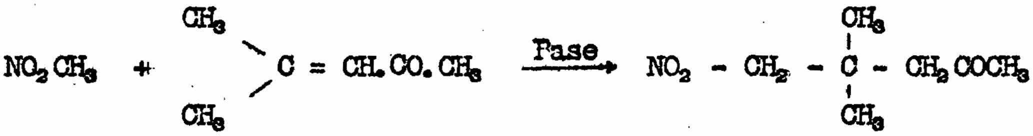
SECTION I

- SECTION I -

A. CYCLO-ADDITIONS OF 2,4,4-TRIMETHYL-1-PYRROLINE 1-OXIDE

(i) 4,4-Dimethyl-5-nitropentan-2-one:

Kloetzel, J.A.C.S., (1947), 69, 2271.
Smith and Engelhardt, J.A.C.S., (1949), 71, 2676.

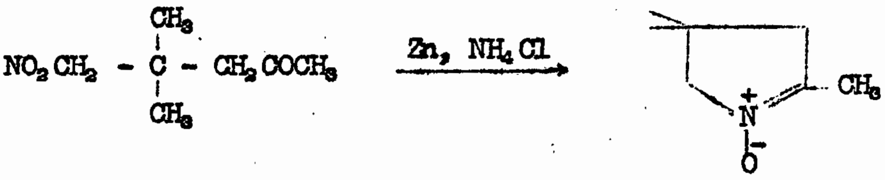

$$NO_2CH_3 + (CH_3)_2C=CH.CO.CH_3 \xrightarrow{\text{Base}} NO_2-CH_2-C(CH_3)_2-CH_2COCH_3$$

Kloetzel's method, which makes use of diethylamine as the basic catalyst, gave the author a 50% yield of product. The use of sodium ethoxide, as advocated by Smith and Engelhardt, gave a 68% yield, in a shorter reaction time, with the added advantage of being free from basic by-products.

4,4-Dimethyl-5-nitro-pentan-2-one had b.ps. 68° - 70°/0.4 mm., and 100° - 105°/9 mm. The semicarbazone had a m.p. 165° - 166° (decomp.). Kloetzel reports a m.p. 165° - 166° (decomp.) for the semicarbazone of 4,4-dimethyl-5-nitro-pentan-2-one.

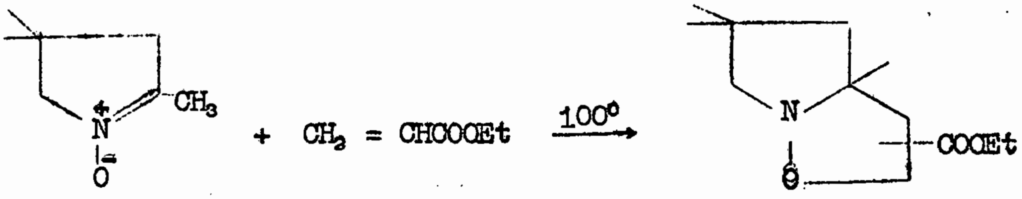
(ii) 2,4,4-Trimethyl-1-pyrroline 1-oxide:

Bonnett, Brown, Clark, Sutherland and Todd, J., (1959), 2094.



2,4,4-Trimethyl-1-pyrroline 1-oxide, b.p. 74°/0.4 mm. was obtained in 72% yield. The picrate had a m.p. 116° - 117° from butanol. The methiodide had a m.p. 105° - 106° (decomp.) from ethanol-ether. Bonnett et al reported m.ps. 111° for the picrate, and 106° (decomp.) for the methiodide of 2,4,4-trimethyl-1-pyrroline 1-oxide.

(iii) 3 or 4-Ethoxycarbonyl-5,7,7-trimethyl-2-oxa-1-azabicyclo[3.3.0]octane:



2,4,4-Trimethyl-1-pyrroline-1-oxide (2.00 g.) and ethyl acrylate (10 ml.) were heated on a steam bath for 24 hr. The unreacted ethyl acrylate was removed in vacuo at 100° bath temperature, and the residual oil shaken with water (10 ml.). Petroleum ether (b.p. 40° - 60°, 5 ml.). was added, the mixture shaken, and the aqueous layer discarded. The petroleum ether layer was washed with water (3 x 10 ml.), dried with anhydrous sodium sulphate, and evaporated. Rapid vacuum distillation (0.2 - 0.3 mm.) of the residual oil in a short path still, at a bath temperature of 100°C gave 3 or 4-ethoxycarbonyl-5,7,7-trimethyl-2-oxa-1-azabicyclo[3,3,0]octane as an almost colourless oil, n_D^{19} 1.4559. The yield was 2.19 g., (61%). ν_{max} 1745 cm.$^{-1}$ (ester >CO). No absorption at 1610 cm.$^{-1}$.

Distillation of larger quantities (10 g. or more) of product through a conventional vacuum distillation apparatus, leads to appreciable decomposition, with the formation of ethyl acrylate and 2,4,4-trimethyl-1-pyrroline-1-oxide.

To purify the product which may contain nitrone as a result of such decomposition, it was found advantageous to dissolve it in low boiling petroleum ether (b.p. 30° - 50°), and wash the solution with water to remove the nitrone. After drying and evaporation of the solvent, the residual oil had a refractive index identical with pure distilled material.

When 2,4,4-trimethyl-1-pyrroline 1-oxide and ethyl acrylate were reacted together in the presence of bases such as sodium ethoxide, either in pyridine or ethanol, highly viscous by-products were formed, and low yields of cyclo-addition product were obtained.

Analysis

Calculated for $C_{12}H_{21}NO_3$	Found
C 63.4%	C 63.4%
H 9.31%	H 8.95%
N 6.16%	N 6.76%

The saponification equivalent was determined by refluxing a known weight of ester with excess ethanolic potassium hydroxide, followed by titration of the remaining alkali with standard hydrochloric acid. Calculated for $C_{12}H_{21}NO_3$, 227. Found, 232.

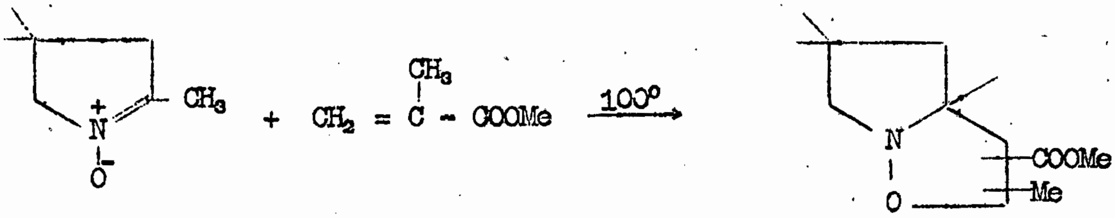
The picrate could not be obtained from saturated solutions of picric acid in ethanol or benzene. The picrolonate formed slowly from a saturated solution of picrolonic acid in ethanol, to which petroleum ether (b.p. 100° - 120°) was added. Recrystallisation from butanol gave yellow crystals, m.p. 134° - 136°.

Analysis

Calculated for $C_{22}H_{29}N_5O_8$	Found
C 53.8%	C 53.8%
H 5.95%	H 5.96%
N 14.3%	N 13.7%.

This picrolonate must be the picrolonate of a pure position isomer. The oil itself could be a mixture of the two position isomers. The same observation applies to other similar esters prepared in this section.

(iv) 3 or 4-Methoxycarbonyl-3 or 4,5,7,7-tetramethyl-2-oxa-1-azabicyclo [3,3,0]octane



2,4,4-Trimethyl-1-pyrroline 1-oxide (2.13 g.), and methyl methacrylate (stabilized with hydroquinone, 10 ml.) were heated on a steam bath for 24 hr. The unreacted methyl methacrylate was removed in vacuo, leaving a clear dark yellow oil, which appeared to be completely free from polymerized methyl methacrylate. Water (10 ml.) was added, and the mixture shaken. Petroleum ether (b.p. 30° - 50°, 5 ml.) was added, the mixture shaken again, and the aqueous layer discarded. The petroleum ether extract was washed by shaking with water (4 x 5 ml.) dried with anhydrous sodium sulphate, and evaporated. Short-path distillation in vacuo at a bath temperature of about 100° gave 3 or 4-methoxycarbonyl-3 or 4,5,7,7-tetramethyl-2-oxa-1-azabicyclo-[3,3,0]-octane as a almost colourless oil, n_D^{20} 1.4548. The yield was 2.07 g., (54.5%). ν_{max} 1750 cm.$^{-1}$, (ester C = O). No absorption at 1610 cm.$^{-1}$.

Analysis

Calculated for $C_{12}H_{21}NO_3$		Found	
C	63.4%	C	63.4%
H	9.31%	H	9.42%
N	6.16%	N	6.25%.

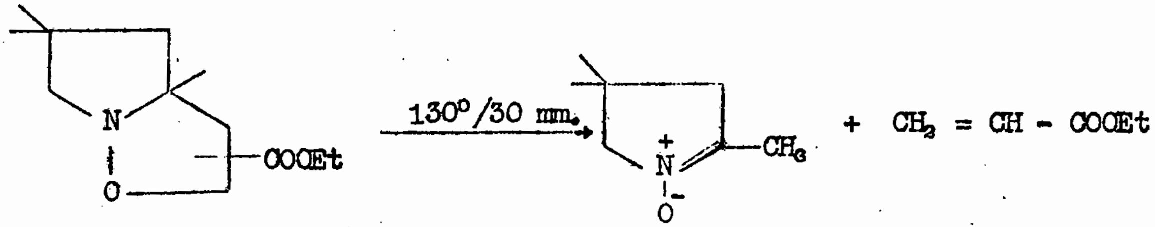
The saponification equivalent, determined as in the previous experiment was 228. Calculated for $C_{12}H_{21}NO_3$, 227.

The picrolonate formed readily from a solution of picrolonic acid in ethanol/petroleum ether (b.p. 100° - 120°). Recrystallisation from butanol gave pale yellow fluffy needles, m.p. 169° - 170° (decomp.).

Analysis

Calculated for $C_{22}H_{29}N_5O_8$	Found
C 53.8%	C 53.8%
H 5.95%	H 5.95%
N 14.3%	N 13.7%

(v) Thermal decomposition of 3 or 4 ethoxycarbonyl-5,7,7-trimethyl-2-oxa-1 azabicyclo[3,3,0]octane.



3 or 4-Ethoxycarbonyl-5,7,7-trimethyl-2-oxa-1-azabicyclo[3,3,0]octane (5.0 g.) was placed in a 50 c.c. two-necked flask fitted with a reflux condenser. The top of the condenser was connected to a filter pump by way of a dry-ice/acetone trap. The contents of the flask were heated to 120° - 130° while dry nitrogen was slowly led through the flask. The apparatus was thus kept under vacuum (about 2 - 3 mm.) for 1 hr.

The residual oil was dissolved in petroleum ether (b.p. 30° - 50°, 20 ml.) and shaken with water (20 ml.) to extract water-soluble materials. The water extract was evaporated in vacuo at a bath temperature of 70° to as low a volume as possible, and the remaining oil dissolved in absolute ethanol (5 ml.). A saturated solution of picric acid in ethanol (10 ml.) was added, and the precipitated crystals filtered.

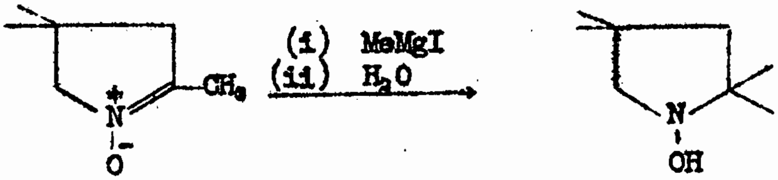
After one recrystallization from n-butanol, they had m.p. 116° - 117°, undepressed by admixture to the picrate of 2,4,4-trimethyl-1-pyrroline 1-oxide.

The liquid which had condensed in the dry-ice/acetone trap had a strong smell of ethyl acrylate and had b.p. 98° - 99°. Its infrared spectrum in the range 650 - 3650 $cm.^{-1}$ was identical to the spectrum of pure ethyl acrylate.

B. CYCLO-ADDITIONS OF 3,3,5,5-TETRAMETHYL-1-PYRROLINE 1-OXIDE

(i) 1-Hydroxy-2,2,4,4-tetramethylpyrrolidine:

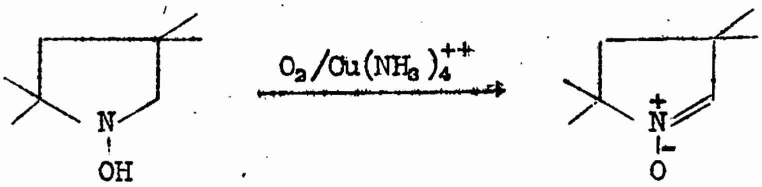
Bonnett, Brown, Clark, Sutherland and Todd, J., (1959), 2101.



1-Hydroxy-2,2,4,4-tetramethylpyrrolidine, m.p. 59 - 61° was obtained in 95% yield. Bonnett et al report m.p. 62° for this compound.

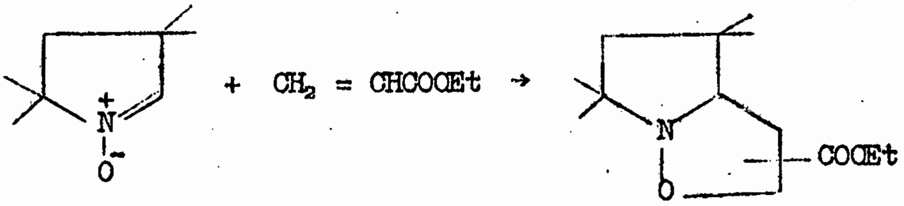
(ii) 3,3,5,5-Tetramethyl-1-pyrroline 1-oxide:

Bonnett, Brown, Clark, Sutherland and Todd, J., (1959), 2101.



3,3,5,5-Tetramethyl-1-pyrroline 1-oxide, m.p. 47-47° was obtained in 50% yield. The picrate had m.p. 140-142° from butanol. Bonnett et al report m.ps. 32° - 34° for 3,3,5,5-tetramethyl-1-pyrroline 1-oxide and 137° - 138° for the picrate.

(iii) 3 or 4-Ethoxycarbonyl-6,6,8,8-tetramethyl-2-oxa-1-azabicyclo[3,3,0]octane



3,3,5,5-Tetramethyl-1-pyrroline 1-oxide (2.68 g.) and ethyl acrylate (20 ml.) were heated on a steam bath for 26 hr. The unreacted ethyl acrylate was removed under reduced pressure, and the residual oil shaken with water (10 ml.). Petroleum ether (b.p. 30° - 50°, 10 ml.) was added, the mixture shaken, and the aqueous layer discarded. The petroleum ether layer was washed by shaking it with water (4 x 10 ml.), dried with anhydrous sodium sulphate, and evaporated. Distillation of the residual dark oil in a short-path still at 100° - 110°/0.2 - 0.3 mm. gave 3 or 4-ethoxycarbonyl-6,6,8,8-tetramethyl-2-oxa-1-azabicyclo[3,3,0]octane as a colourless oil, n_D^{20} 1.4600. The yield was 2.89 g., (65%). ν_{max} 1745 cm.$^{-1}$ (ester C = O). No absorption at 1575 cm.$^{-1}$.

Analysis

Calculated for $C_{13}H_{23}NO_3$		Found	
C	64.7%	C	64.3%
H	9.61%	H	9.61%
N	5.81%	N	6.22%.

The picrolonate was prepared by adding the ester to a saturated solution of picrolonic acid in ethanol, followed by addition of petroleum ether (b.p. 100° - 120°). Recrystallisation from butanol gave yellow crystals, m.p. 162° - 163° (decomp.).

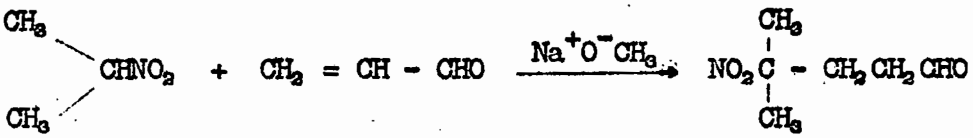
Analysis

Calculated for $C_{23}H_{31}N_5O_8$		Found	
C	54.6%	C	54.7%
H	6.18%	H	6.19%
N	13.9%	N	13.9%.

C. CYCLO-ADDITIONS OF 5,5-DIMETHYL-1-PYRROLINE 1-OXIDE

(i) 4-Methyl-4-nitropentanal:

Lamchen, private communication.

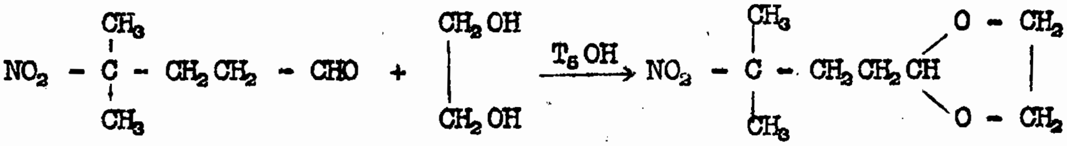


$$(CH_3)_2CHNO_2 + CH_2 = CH - CHO \xrightarrow{Na^+O^-CH_3} NO_2\overset{CH_3}{\underset{CH_3}{C}} - CH_2CH_2CHO$$

4-Methyl-4-nitropentanal, b.p. 65° - 68°/0.02 mm. was obtained in 52% yield.

(ii) 2-(3-Methyl-3-nitrobutyl)-1,3-dioxolan:

Bonnett, Brown, Clark, Giddey and Todd, J., (1959), 2090.

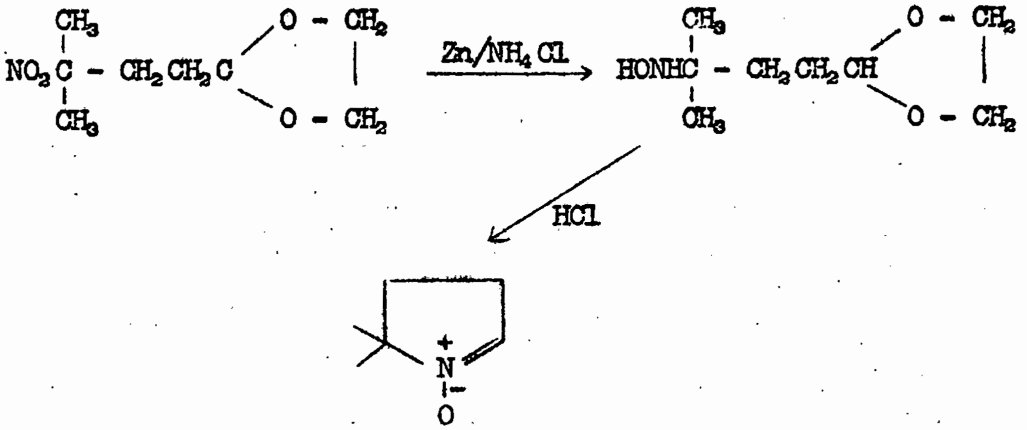


$$NO_2 - \overset{CH_3}{\underset{CH_3}{C}} - CH_2CH_2 - CHO + \begin{array}{c} CH_2OH \\ | \\ CH_2OH \end{array} \xrightarrow{T_sOH} NO_2 - \overset{CH_3}{\underset{CH_3}{C}} - CH_2CH_2CH\begin{array}{l} O - CH_2 \\ \quad\;\;\, | \\ O - CH_2 \end{array}$$

2-(3-Methyl-3-nitrobutyl)-1,3-dioxolan, b.p. 86° - 92°/0.2 mm. was obtained in 91% yield.

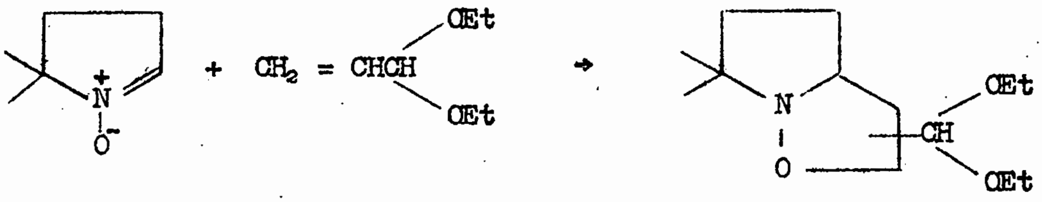
(iii) 5,5-Dimethyl-1-pyrroline 1-oxide:

Bonnett, Brown, Clark, Sutherland and Todd, J., (1959), 2095.



5,5-Dimethyl-1-pyrroline 1-oxide, b.p. 66° - 68°/0.2 mm., was obtained in 83% yield. The picrate had a m.p. 81° - 82° from butanol. Bonnett et al report a m.p. 81° for the picrate of 5,5-dimethyl-1-pyrroline 1-oxide.

(iv) 3 or 4-Diethoxymethyl-8,8-dimethyl-2-oxa-1-azabicyclo[3.3.0] octane:



5,5-Dimethyl-1-pyrroline 1-oxide (2.3 g.) and acrolein diethyl acetal (prepared by the method of VanAllan, Org. Synth., (1952), 32, 5; 5.0 ml.) were heated for 24 hrs. on the water bath. The excess of acrolein diethyl acetal was rapidly removed in vacuo, and water (10 ml.) added. The

insoluble oil was dissolved in petroleum ether (b.p. 30 - 50°, 10 ml.) and washed with water (3 x 10 ml.). The petroleum ether extract was dried with anhydrous magnesium sulphate, evaporated, and distilled in vacuo in a short-path still, at a pressure of 0.5 mm. and 100 - 110° bath temperature.
n_D^{24} = 1.4485. The yield was 2.81 g.

Analysis:

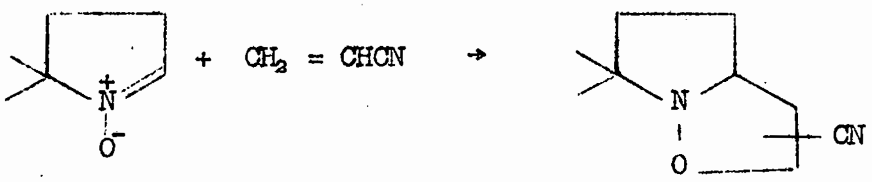
Calculated for $C_{13}H_{25}NO_3$	Found
C 64.2%	C 64.4%
H 10.4%	H 10.3%
N 5.76%	N 5.80%

The picrate formed readily from a saturated solution of picric acid in ethanol. Recrystallisation from butanol gave bright yellow needles, m.p. 102 - 103°.

Analysis:

Calculated for $C_{19}H_{28}N_4O_{10}$	Found
C 48.3%	C 48.9%
H 5.97%	H 6.21%
N 11.9%	N 12.0%

(v) 3 or 4-Cyano-8,8-dimethyl-2-oxa-1-azabicyclo[3,3,0]octane:



5,5-Dimethyl-1-pyrroline-1-oxide (2.0 g.) and acrylonitrile (10 ml.) were allowed to stand at room temperature for 24 hrs. The unreacted acrylonitrile was removed in vacuo at room temperature. Upon scratching and cooling, the residual oil solidified. Yield, 3.30 g., (100%). A sample, recrystallized from petroleum ether, (b.p. 100 - 120°) had m.p. 57 - 58°.

Analysis:

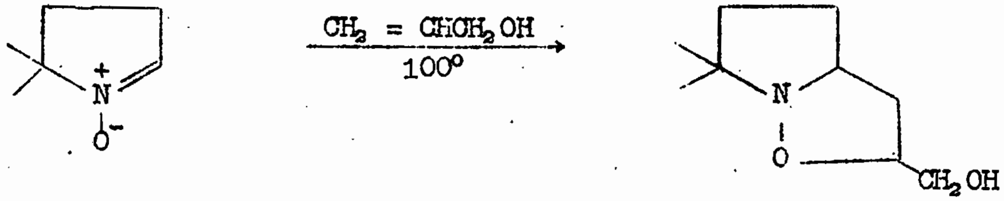
Calculated for $C_9H_{14}N_2O$	Found
C 65.0%	C 64.6%
H 8.47%	H 8.81%
N 16.9%	N 16.5%

The picrolonate readily separated from a saturated solution of picrolonic acid in ethanol. Recrystallisation from butanol gave dirty yellow crystals, m.p. 147°.

Analysis:

Calculated for $C_{19}H_{22}N_6O_3$	Found
C 53.0%	C 52.7%
H 5.12%	H 5.49%

(vi) 3-Hydroxymethyl-8,8-dimethyl-2-oxa-1-azabicyclo[3,3,0]octane:



5,5-Dimethyl-1-pyrroline 1-oxide (22 g.) and anhydrous allyl alcohol (100 ml.) were heated at 100° overnight. The unreacted allyl alcohol was removed in vacuo, and the residual oil dissolved in ether (50 ml.). The ether solution was washed with aqueous potassium carbonate, (30%, 5 x 25 ml.), dried with sodium sulphate, and evaporated. The residual oil was distilled in vacuo at 100 - 103° and 3 - 4 mm. The distillate solidified and weighed 28 g. (84%). A sample recrystallized from petroleum ether had a m.p. 43 - 44°. The material is highly hygroscopic.

Analysis:

	Calculated for $C_9H_{17}NO_2$		Found
C	63.1%	C	61.4, 60.9%
H	9.99%	H	9.65, 10.5%
N	8.18%	N	7.93%

The picrate formed from a solution of picric acid in ethanol. Recrystallisation from butanol gave bright yellow needles, m.p. 150 - 152°.

Analysis:

	Calculated for $C_{15}H_{20}N_4O_9$		Found
C	45.0%	C	45.1%
H	5.04%	H	5.13%
N	14.0%	N	14.7%
Eq. Wt.	400		399

(vii) Reaction of 5,5-dimethyl-pyrroline 1-oxide with ethyl acrylate:

(i) Preliminary investigation: Formation of a mixture of 3-ethoxycarbonyl- and 4-ethoxycarbonyl-8,8-dimethyl-2-oxa-azabicyclo[3,3,0]octane:

5,5-Dimethyl-1-pyrroline 1-oxide (26 g.) and ethyl acrylate (150 ml.) were heated on a boiling water bath for 24 hr. The unreacted ethyl acrylate was removed in vacuo, and the residual oil shaken with water (50 ml.). Petroleum ether (b.p. 30 - 50°, 50 ml.) was added to dissolve the water insoluble oil. The aqueous layer was discarded, and the petroleum ether layer washed with water (30 ml.). The infra-red spectrum of a dried sample of the extract showed no maximum at 1575 cm.$^{-1}$, thus showing that the washing process had removed all unchanged nitrone, if any was present. The bulk of the extract was dried with anhydrous magnesium sulphate, and the solvent removed in vacuo. Distillation by conventional vacuum-distillation gave 37.3 g., (76%) of product, b.p. 76 - 80° at 0.005 - 0.01 mm. This material was found to contain appreciable quantities of nitrone (peak at 1575 cm.$^{-1}$ in the I.R. absorption spectrum). This nitrone was removed by dissolving in a small quantity of petroleum ether, (b.p. 30 - 50°), washing with water, followed by drying and evaporating. The product could be distilled in a short-path still without noticeable decomposition, as witnessed by the constancy of the infra-red spectrum, which showed no nitrone absorption at 1575 cm.$^{-1}$.

In the preliminary stages of this work, the infra-red absorption curves were determined on a Perkin-Elmer "Infracord" instrument, which had a low resolution; only one ester carbonyl band (1745 cm.$^{-1}$) was registered. Later, the spectrum was determined on a Unicam S.P. 100 instrument, which had a much higher resolution. The spectrum showed a peak at 1740 cm.$^{-1}$, and a shoulder at 1755 cm.$^{-1}$.

The refractive index of this compound was constant in several fractions obtained by short-path distillation.

Analysis:

	Calculated for $C_{11}H_{19}NO_3$		Found
C	61.9%	C	61.2%
H	8.98%	H	9.13%
N	6.57%	N	6.74%

The saponification equivalent was found to be 217. The calculated value is 213.

The above material was degraded, and found to be a mixture of the 3-ethoxycarbonyl and 4-ethoxycarbonyl compounds in approximately equal quantities (see page 138).

A picrolonate separated after a period of several weeks from a solution of picrolonic acid in ethanol/petroleum ether (b.p. 100 - 120°C). Recrystallisation from butanol gave yellow crystals, decomposing at

SECTION II

SECTION II

Attempted Reduction of Ethyl Acrylate Adduct Prepared on page 118

The adduct (5.03 g) in a mixture of absolute ethanol (9.5 ml.) and dry toluene (15 ml.) was added to a stirred suspension of powdered sodium (3.5 g.) in dry toluene (75 ml.). The reaction mixture was stirred and heated at 85° - 95° during the addition (90 mins.), and refluxed for 2½ hrs. after. Water (5 ml.) was added, and the mixture stirred and refluxed for an additional 15 mins. Hydrochloric acid (5N, 75 ml.) was added, and after thorough shaking, the toluene layer was removed. The aqueous layer was evaporated in vacuo, saturated with anhydrous potassium carbonate, and extracted into chloroform. After drying and evaporating, a black tar remained, which could not be distilled.

Reduction of Ethyl Acrylate Adduct Prepared on page 118

The adduct (5.41 g.) in dry tetrahydrofuran (25 ml.) was added during 40 mins. to a well stirred suspension of lithium aluminium hydride (6.5 g.) in dry tetrahydrofuran. When the addition was complete, the mixture was refluxed for 10 hrs. The unreacted hydride was destroyed by cautious addition of dry methanol (25 ml.) and the tetrahydrofuran and methanol removed in vacuo. A saturated solution of sodium potassium tartrate (200 ml.) was then added, followed by a solution of potassium hydroxide (20 g.) in water (100 ml.). This solution was extracted continuously with ether for three days. The ethereal extract was dried with anhydrous sodium sulphate, evaporated, and the viscous residue distilled in a short-path still, at a bath temperature of 150 - 160° and pressure 2 - 3 mm. There was obtained 3.54 gm. of product, (80%), which failed to give a positive reaction for hydroxylamines when treated with an alkaline solution of 2,3,5-triphenyl-tetrazolium chloride.

The material is very hygroscopic. Periodic acid consumption was determined as described on page 142, and found to be .53 moles periodic acid per mole $C_9H_{19}NO_2$.

Analysis:

	Calculated for $C_9H_{19}NO_2$	Found
C	62.4%	60.9%
H	11.1%	10.7%
N	8.09%	8.44%

A *picrate* separated out from benzene-picric acid. Recrystallisation from n-butanol gave yellow-orange needles, m.p. 165 - 166°.

Analysis:

	Calculated for $C_{15}H_{22}N_4O_9$	Found
C	44.8%	45.1%
H	5.51%	5.61%
O	35.8%	35.5%
Equivalent weight	402	402

As described on page 138, the free base is a mixture of 3-(5,5-dimethyl-pyrrolidin-2-yl)-propan-1,2-diol and 2-(5,5-dimethylpyrrolidin-2-yl)-propan-1,3-diol. The picrate described above is the picrate of 2-(5,5-dimethylpyrrolidin-2-yl)-propan-1,3-diol.

Synthesis of 2-*iso*propyl-5,5-dimethyl-pyrrolidine

(a) 1-Hydroxy-2-*iso*propyl-5,5-dimethyl-pyrrolidine:

5,5-Dimethyl-1-pyrroline 1-oxide (11.7 g.) in dry ether (50 ml.) was added during 45 mins. to a stirred solution of isopropylmagnesium bromide, prepared in the usual way from magnesium (2.5 g.), isopropyl bromide (13 g.), and ether (75 ml.).

The mixture was stirred and refluxed for 5 hrs., and hydrolysed by addition of ammonium chloride (5N, 25 ml.). The ether layer was removed, and the aqueous layer extracted with ether (50 ml.). The combined ether layers were dried with anhydrous magnesium sulphate, evaporated, and the residual oil vacuum-distilled. There was obtained 7.42 g. (46%) of a colourless oil, b.p. 56 - 58° at 0.7 mm., which soon solidified in the receiver. This material gave a positive reaction for hydroxylamines upon treatment with alkaline 2,3,5-triphenyl-tetrazolium chloride.

A small sample was sublimed in vacuo, and had m.p. 36 - 38°C. It soon liquefied on standing in a desiccator, and turned yellow. This same phenomenon was observed with small samples kept in sealed tubes under dry nitrogen.

Analysis:

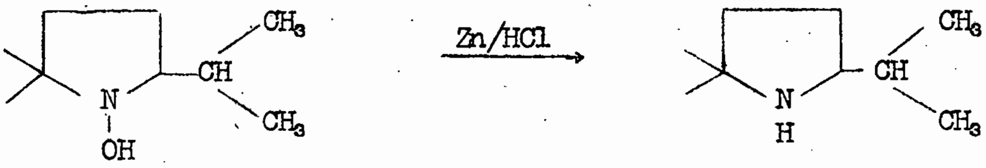
	Calculated for $C_9H_{19}NO$	Found
C	68.7%	67.8%
H	12.2%	12.3%
N	8.91	9.99%.

The oxalate was prepared by adding the base to a saturated solution of anhydrous oxalic acid in dry ether. Recrystallisation from butanol-dibutyl ether gave small white needles, m.p. 124 - 126°.

Analysis:

	Calculated for $C_{11}H_{21}NO_5$		Found
C	53.4%	C	53.5%
H	8.56%	H	8.55%
N	5.67%	N	5.60%.

(b) 2-*iso*Propyl-5,5-dimethyl-pyrrolidine:



1-Hydroxy-2-*iso*propyl-5,5-dimethyl-pyrrolidine (6.95 g.) and zinc dust (25 g.) in hydrochloric acid (20%, 75 ml.) were heated for 15 hrs. on a steam bath. The mixture was made strongly alkaline by addition of sodium hydroxide solution, and steam distilled. The steam distillate (150 ml.) was acidified with concentrated hydrochloric acid, and evaporated to dryness in vacuo. The solid hydrochloride was treated with enough concentrated sodium hydroxide solution to liberate the free base, and the resulting solution (about 10 ml.) was ether extracted, (2 x 50 ml.). The ether extract was dried with anhydrous calcium sulphate, and evaporated. Vacuum distillation gave the product as a colourless oil, b. p. 62 - 64°C at 23 mm. The yield was 4.54 g., (73%).

Analysis:

Calculated for $C_9H_{19}N$	Found
C 76.5%	C 77.1%
H 13.6%	H 13.8%
N 9.92%	N 10.1%

The picrate was prepared by adding the base to a hot solution of picric acid in benzene. Recrystallisation from benzene/petroleum ether (b.p. 100 - 120°C) gave yellow needles, m. p. 152 - 154°C.

Analysis:

Calculated for $C_{15}H_{22}N_4O_7$		Found	
C	48.6%	C	48.7%
H	5.99%	H	6.06%
N	15.1%	N	14.5%
Eq. Wt.	370		370

The picrolonate formed immediately from a saturated solution of picrolonic acid in ethanol. Recrystallisation from n-butanol gave yellow needles, decomposing at 245°.

Analysis:

Calculated for $C_{19}H_{27}N_5O_5$		Found	
C	56.3%	C	56.6%
H	6.71%	H	6.84%
N	17.3%	N	17.3%

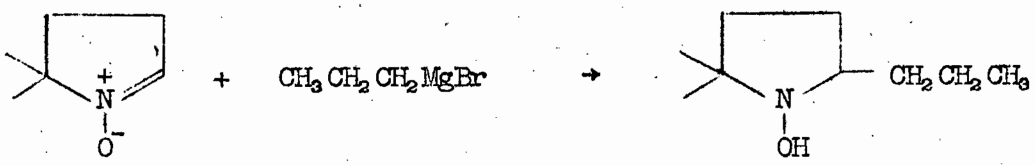
The oxalate formed readily as a white precipitate when the base was added to an ethereal solution of oxalic acid. Recrystallisation from butanol gave white fluffy needles, m.p. 221 - 222°C (dec.)

Analysis:

Calculated for $C_{11}H_{21}NO_4$		Found	
C	57.1%	C	57.1%
H	9.15%	H	9.16%
N	6.06%	N	6.06%

Synthesis of 2,2-dimethyl-5-propyl-pyrrolidine

(a) 1-Hydroxy-2,2-dimethyl-5-propyl-pyrrolidine:



5,5-Dimethyl-1-pyrroline 1-oxide (11.8 g.) in dry ether (50 ml.) was added to a solution of n-propylmagnesium bromide, prepared in the usual way from n-propyl bromide (13 g.) and magnesium (2.5 g.) in dry ether (75 ml.). The mixture was stirred and refluxed for 4 hrs., after which it was decomposed by the addition of a solution of ammonium chloride (10 g.) in water (30 ml.). The ether layer was separated, the aqueous layer extracted with ether, (50 ml.), and the combined extracts dried with anhydrous sodium sulphate. The ether was evaporated, and the residual oil distilled in vacuo. There was obtained 8.1 g. of a colourless oil b. p. 64 - 68°C at 3 - 4 mm. (49%). This material gave a positive test for hydroxylamines upon treatment with an alkaline solution of 2,3,5-triphenyl-tetrazolium chloride.

Analysis:

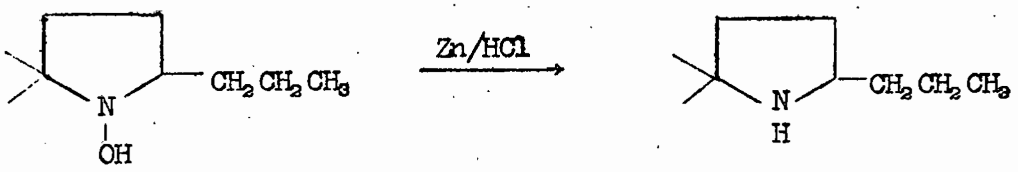
Calculated for $C_9H_{19}NO$	Found
C 68.7%	C 68.2%
H 12.2%	H 11.8%
N 8.91%	N 8.63%

The oxalate formed readily from a saturated solution of anhydrous oxalic acid in ether. Recrystallisation from di-n-butyl ether gave white needles, m.p. 116 - 117°C.

Analysis:

Calculated for $C_{11}H_{21}NO_5$	Found
C 53.4%	C 53.8%
H 8.56%	H 8.46%
N 5.67%	N 5.43%

(b) 2,2-Dimethyl-5-propyl-pyrrolidine:



1-Hydroxy-2,2-dimethyl-5-propyl-pyrrolidine, (5.84 g.) in hydrochloric acid (20%, 75 ml.) was heated on a steam bath with zinc dust (25 g.) for 9 hrs. The reaction mixture was made alkaline by addition of sodium hydroxide, (5 N, 400 ml.), and steam distilled. The steam distillate (about 250 ml.) was acidified with hydrochloric acid (30 ml.), and evaporated to dryness in vacuo. The solid hydrochloride was treated with a solution of sodium hydroxide (4 g.) in water (10 ml.), and extracted with ether (50 ml.). The solution was dried with anhydrous sodium sulphate, then with anhydrous calcium sulphate and evaporated. The residual oil was distilled in vacuo. There was obtained 3.79 g. (73%) of product, a colourless liquid b. p. 58 - 60° at 20 mm.

Analysis:

Calculated for $C_9H_{19}N$	Found
C 76.5%	C 76.3%
H 13.6%	H 13.5%
N 9.92%	N 10.6%

The picrate could not be formed by any of the usual methods. The picrolonate formed readily from ethanol. Recrystallisation from n-butanol gave yellow rods, m. p. 218 - 219°C.

Analysis:

Calculated for $C_{19}H_{27}N_5O_5$	Found
C 56.3%	C 56.2%
H 6.71%	H 6.80%
N 17.3%	N 17.3%

The oxalate formed readily as a white precipitate when the base was added to an ethereal solution of anhydrous oxalic acid. Recrystallisation from n-butanol gave white fluffy needles, m. pt. 201 - 202°C (dec.)

Analysis:

Calculated for $C_{11}H_{21}NO_4$	Found
C 57.1%	C 57.5%
H 9.15%	H 9.23%
N 6.06%	N 6.08%

Reduction of the suspected amino-glycol to the pyrroline:

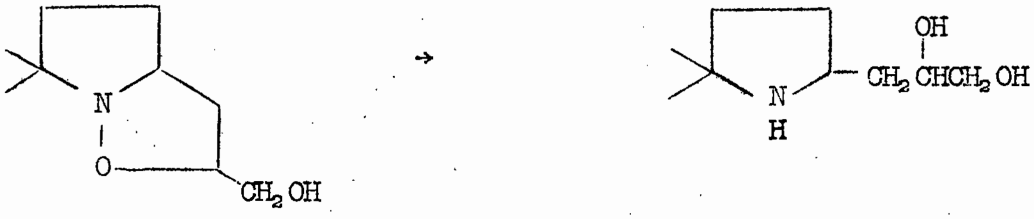
The product from page 121, (1.68 g.) in hydriodic acid (d. 1.96, 8 ml.) and red phsophorus (0.1 g.) were kept for 15 hrs. in a sealed tube at 170°C. The tube was then cautiously opened, the contents washed out by rinsing with ethanol, and filtered. The ethanol and hydriodic acid were removed by evaporation in vacuo, and the residual dark oil refluxed with hydrochloric acid (20%, 60 ml.) and zinc dust (2.5 g.). The mixture was then made strongly alkaline by the addition of sodium hydroxide (50 g.) in water (50 ml.) and steam distilled. The distillate (about 100 ml.) was acidified by the addition of concentrated hydrochloric acid, and the resulting solution evaporated to dryness in vacuo. The solid was dried overnight in vacuo over solid potassium hydroxide. The crude hydrochloride (1.04 g.) was treated with a solution of sodium hydroxide (1 g.) in water (2 ml.), extracted with ether (25 ml.), dried with anhydrous sodium sulphate and evaporated. The residual, strongly basic oil gave a picrolonate from a saturated solution of picrolonic acid in ethanol, as yellow needles, m. p. 218 - 219°C, from ethanol. This m. p. was undepressed when the picrolonate was mixed with the picrolonate m. p. 218 - 219°C of 2,2-dimethyl-5-propyl pyrrolidine.

The oxalate formed readily from a saturated solution of oxalic acid in ether, recrystallising from n-butanol as fluffy white needles, m. p. 201 - 202°C (dec.). This m. p. was undepressed on admixture with the oxalate of 2,2-dimethyl-5-propyl pyrrolidine m. p. 201 - 202°C (dec.). The infra-red adsorption spectra of these two oxalates were identical over the range 650 - 3650 cm.$^{-1}$, but the spectrum of the oxalate of 2-isopropyl-

5,5-dimethyl-pyrrolidine showed major differences.

Identical results were obtained without the addition of red phosphorus, but with all other experimental conditions unaltered.

Reductions of 3-hydroxymethyl-8,8-dimethyl-2-oxa-1-azabicyclo[3,3,0]octane: Preparations of 3-(5,5-dimethyl-pyrrolidin-2-yl)-propan-1,2-diol.



(a) With lithium aluminium hydride:

3-Hydroxymethyl-8,8-dimethyl-2-oxa-1-azabicyclo-[3,3,0]octane (6.44 g.) in dry tetrahydrofuran (25 ml.) was added during 30 minutes to a stirred slurry of lithium aluminium hydride (6.5 g.) in tetrahydrofuran (75 ml.). The mixture was stirred under reflux for about 1 hr., then refluxed for an additional 10 hrs. The excess hydride was decomposed by the addition of dry methanol (50 ml.), and the solvent removed in vacuo. The residual paste was dissolved in a mixture of potassium hydroxide (50 g.) and sodium potassium tartrate (50 g.) in water (200 ml.), and subjected to continuous ether extraction for 3 days. The extract was dried over anhydrous potassium carbonate, evaporated, and the residual viscous oil distilled in a short-path still at a pressure of 0.4 mm., and a bath temperature of 170 - 180°C. The viscous distillate soon solidified. Yield 4.91 g. (76%). A sample recrystallised from petroleum ether (b. p. 100 - 120°C) had a m. p. 64 - 66°, and did not give a positive test for hydroxylamines with alkaline 2,3,5-triphenyl-tetrazolium chloride. The material is hygroscopic.

Analysis:

Calculated for $C_9H_{19}NO_2$	Found
C 62.4%	C 61.8%
H 11.1%	H 11.0%
N 8.09%	N 8.00%

The picrate readily formed from a saturated solution of picric acid in ethanol. Recrystallisation from n-butanol gave bright yellow crystals, m. pt. 125 - 126°.

Analysis:

Calculated for $C_{15}H_{22}N_4O_9$	Found
C 44.8%	C 45.1%
H 5.51%	H 5.54%
O 35.8%	O 36.2%
Eq. Wt. 402	402

(b) With zinc and hydrochloric acid:

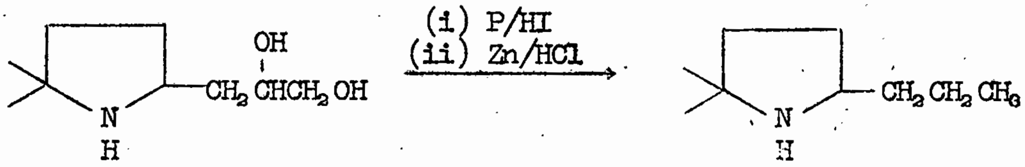
3-Hydroxymethyl-8,8-dimethyl-2-oxa-1-azabicyclo[3,3,0]octane (2.67 g.) was dissolved in water (5 ml.) and zinc dust (4 g.) was added. This mixture was stirred while concentrated hydrochloric acid (25 ml.) was slowly run in over a period of 3 hrs. A solution made up by dissolving potassium hydroxide (10 g.) and ammonium citrate (10 g.) in water (30 ml.) was added, and the resulting solution extracted continuously with ether for 48 hrs. The ether extract was dried with anhydrous sodium sulphate, evaporated, and the residue distilled in vacuo at 0.2 mm. and 150° (bath temperature) to give 0.17 g. of a viscous oil, which readily solidified on seeding with a small sample of the amino-glycol prepared above. The picrate, prepared from benzene, and recrystallized from n-butanol, had m.p. 124 - 125°.

(c) Attempted reduction with sodium borohydride:

3-Hydroxymethyl-8,8-dimethyl-2-oxa-1-azabicyclo[3,3,0]octane (2.0 g.) was dissolved in sodium hydrogen carbonate solution (2%, 15 ml.), and sodium borohydride (0.4 g.) was subsequently added. The mixture was allowed to stand for about 36 hrs., and then was acidified with glacial acetic acid. After all the borohydride had reacted, the solution was made strongly alkaline with sodium hydroxide, and then evaporated to a paste. Chloroform (50 ml.) was added, followed by a few lumps of dry ice, (to neutralize the sodium hydroxide).

After filtering, the chloroform layer was dried with anhydrous magnesium sulphate, and after evaporation, the remaining oil was distilled in a short-path still at about 1 mm., using a free flame. Paper chromatography (Whatman No. 1, BuOH : 3 N NH_3 ; 1 : 1) showed this product to be only unchanged starting material.

CONVERSION OF 3-(5,5-DIMETHYL-PYRROLIDIN-2-YL)-PROPAN-1,2-DIOL INTO 2,2-DIMETHYL-5-PROPYL-PYRROLIDINE:-



(a) 3-(5,5-Dimethyl-pyrrolidin-2-yl)-propan-1,2-diol (0.89 g.) in hydriodic acid (d. 1.96,5 ml.) and red phosphorus (0.05 g.) were heated at 170°C for 16 hrs. in a sealed tube. The contents of the tube were washed out with ethanol and the volume of the resulting solution reduced in bulk by evaporation in vacuo. The remaining dark material was heated on a water bath for 2 hrs. with zinc dust (10 g.) and hydrochloric acid (20%, 30 ml.). The mixture was made alkaline by addition of sodium hydroxide (25 g.) in water (50 ml.), and steam distilled. The distillate (150 ml.) was acidified by addition of hydrochloric acid

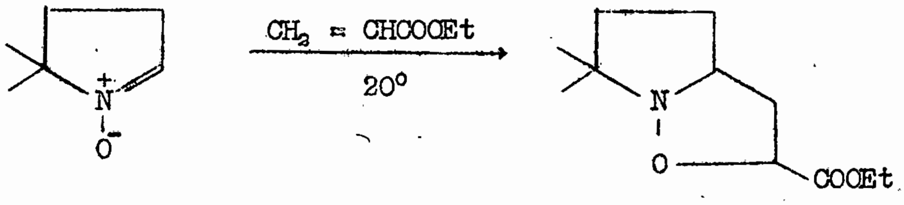
(5 ml.), and evaporated in vacuo. The residue was dried overnight in a vacuum desiccator over potassium hydroxide. The yield was 0.86 g. of crude hydrochloride. The base was liberated by addition of sodium hydroxide (1 g.) in water (2 ml.), extracted with ether (25 ml.), dried with anhydrous sodium sulphate and evaporated.

The base thus obtained was converted to the oxalate by addition to a saturated solution of oxalic acid in ether. The oxalate m. p. 200 - 201° (dec.) after one recrystallisation from n-butanol, showed no m. p. depression on admixture with 2,2-dimethyl-5-propyl pyrrolidine oxalate, m. p. 201 - 202° (dec.).

(b) 3-(5,5-Dimethyl-pyrrolidin-2-yl)-propan-1,2-diol (1.0 g.) in a mixture of hydrobromic acid (48%, 5 ml.) and concentrated sulphuric acid (4 ml.) were kept at room temperature for 24 hr. Water, (15 ml.) was added, and the mixture was kept on a boiling water bath while zinc filings (5 g.) were added in small portions over 1 hr. The solution was made alkaline with sodium hydroxide, and worked up as in (a). 2,2-Dimethyl-5-propyl pyrrolidine oxalate m.p. and mixed m.p. 201 - 202° dec. was obtained.

Preparation of Adducts from Ethyl Acrylate and 5,5-Dimethyl-1-pyrroline 1-oxide.

(i) 3-Ethoxycarbonyl-8,8-dimethyl-2-oxa-1-azabicyclo[3,3,0]octane.



5,5-Dimethyl-1-pyrroline 1-oxide (2.0 g.) and ethyl acrylate (10 ml.) were mixed and allowed to stand for 24 hr. at room temperature, 16°- 23°. The excess of ethyl acrylate was removed in vacuo at room temperature, to give 3.8 g. of product (100%), which was free from nitrone, as witnessed by the absence of absorption in the infra-red at 1575 cm^{-1}. A small sample was distilled in a short path still at 0.5 mm. and 110 - 120° bath temperature, without any noticeable decomposition. $n_D^{21} = 1.4671$. If the material was allowed to reflux at 110° in vacuo for about 1 hr., a strong nitrone absorption in the infra-red at 1575 cm^{-1} was observed.

The oil is appreciably soluble in water, and is also hygroscopic. No observable optical rotation was noticed when the optical rotation was determined on the pure liquid.

Analysis:

	Calculated for $C_{11}H_{19}NO_3$	Found
C	61.9%	60.2%
H	8.98%	8.94%
N	6.57%	6.22%

The infra-red absorption spectrum showed two strong peaks of almost equal intensity at 1740 and 1757 cm^{-1}, attributable to the carbonyl absorption of the two possible racemates. Unsuccessful attempts at separation of the two racemates were carried out as follows:

(a) Chromatography on magnesium silicate, using petroleum ether (A.R., b.p. 60 - 80°) as solvent. No appreciable adsorption occurred, and the various eluate fractions, when evaporated, left almost a quantitative recovery of the esters. These fractions (8 x 20 ml.), left residues of identical infra-red spectra, which was also identical with the spectrum of the distilled material.

(b) Chromatography on acid washed aluminium, using petroleum ether (A.R. b.p. 60 - 80°) gave results as above.

(c) Paper chromatography on Whatman No. 1 paper, using (i) butanol-acetic acid-water (77 : 6 : 17), and (ii) butanol-ethanol-water (4 : 1 : 5) showed only a single component revealed by a ninhydrin dip, followed by heating at 100° for about 5 minutes.

(d) About 2 gm. of the ester was dissolved in petroleum ether (b.p. 30 - 50°, 25 ml.), and shaken with water (25 ml.). The petroleum ether layer was dried ($MgSO_4$) and evaporated. The aqueous layer was saturated with sodium sulphate, and extracted into petroleum ether, which was dried and evaporated. The oil left in both cases showed identical infra-red spectra.

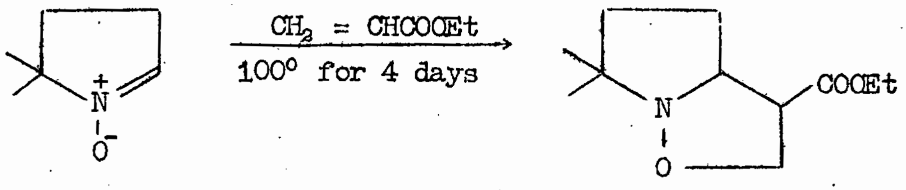
When the reaction between the nitrone and ethyl acrylate was carried out in the presence of small quantities of triethylamine or aqueous acetic acid, the direction and extent of the reaction did not appear to be affected. In one experiment, the nitrone (2.0 g.) and ethyl acrylate (3.0 ml.) were mixed at room temperature. The temperature rose to 55° within 5 mins. The reaction was allowed to stand 20 hr. at room temperature, petroleum ether (b.p. 30 - 50° 15 ml.) added, the extract washed with water (3 ml.), dried with anhydrous magnesium sulphate, and evaporated to give 3.4 g. of adduct.

The picrolonate was prepared from a saturated solution of picrolonic acid in ethanol-ether. Recrystallisation from butanol gave yellow crystals at m.p. 140 - 141°.

Analysis:

Calculated for $C_{21}H_{27}N_5O_8$	Found
C 52.8%	C 52.9%
H 5.69%	H 5.71%
N 14.7%	N 14.7%

(ii) 4-Ethoxycarbonyl-8,8-dimethyl-2-oxa-1-azabicyclo[3,3,0]octane



5,5-Dimethyl-1-pyrroline 1-oxide, (10 g.) and ethyl acrylate (60 ml.) were heated for 96 hr. at 100°. The excess ethyl acrylate was removed in vacuo on the water bath, and the residual oil dissolved in petroleum ether (b.p. 30 - 50, 60 ml.). This solution was washed with water (10 ml.) to remove any traces of nitrone which may have been present, dried with anhydrous magnesium sulphate, and evaporated to yield 18.5 g. (98%) of product. A small sample was distilled in a short path still at 0.5 mm. and 105 - 110° (bath temperature) to give a colourless oil, $n_D^{21} = 1.4676$.

Analysis:

Calculated for $C_{11}H_{19}NO_3$	Found
C 61.9%	C 61.4%
H 8.98%	H 9.00%
N 6.57%	N 6.39%

The infra-red spectrum exhibited a single strong unsymmetrical peak at 1742 cm^{-1}, attributable to the C = 0 stretching vibration of the ester A 30% solution of the adduct in ethanol showed no detectable optical rotation.

Analytical Method for the Detection of the Presence of Isomeric 3 and 4-Ethoxycarbonyl 8,8-Dimethyl-2-oxa-1-azabicyclo[3,3,0]octanes in a mixture:

(a) Initial Experiment:

The "cold" ester, (3-ethoxycarbonyl isomer, prepared as described on page 133 (1 g.) was dissolved in anhydrous tetrahydrofuran (10 ml.) and thus prepared had dimensions 38 x 180 mm.

A mixture of the two components obtained from the "cold" ester, as described before, (2.4 g.) was dissolved in the above-mentioned solvent (5 ml.) and introduced on the column. Elution was carried out using the same solvent. The presence or otherwise of ninhydrin-active substances in the eluate fractions was revealed by paper chromatography as described before, using the known 1,2-glycol as reference. Fractions I, II and III (each 50 mls.) showed no ninhydrin-activity. Fractions IV, V, VI, and VII contained only the fastermoving component. Fractions VIII, IX and X were not ninhydrin-active. The elution was discontinued at this stage.

Fractions IV to VII inclusive were evaporated in vacuo, and the residue mixed with a paste of anhydrous potassium carbonate (3 g.) and water (2 g.). Chloroform (30 ml.) was added, and the mixture stirred under reflux on the water bath for about 30 min. The chloroform extract was dried with anhydrous magnesium sulphate, evaporated, and the residue distilled in vacuo at 0.1 mm. in a short path still, using a free flame. The yield was 1.6 g. This material solidified on seeding with 3-hydroxymethyl-8,8-dimethyl-2-oxa-1-azabicyclo[3,3,0]octane (page 117).

The picrate was prepared from a saturated solution of picric acid in benzene. Recrystallisation from n-butanol gave yellow needles, m.p. 154 - 155°. Mixed m.p. with picrate, (m.p. 151 - 152°) of 3-hydroxymethyl-8,8-dimethyl-2-oxa-1-azabicyclo[3,3,0]octane, 151 - 152°.

<u>Analysis</u>:

	Calculated for $C_{15}H_{20}N_4O_9$	Found
C	45.0%	45.4%
H	5.04%	5.12%
N	14.0%	13.9%
Eq. Wt.	400	399

Reduction of the above material

The above suspected isoxazolidine (1.0 g.) in tetrahydrofuran (25 ml.) was briskly refluxed with lithium aluminium hydride (1.0 g.) for 14 hr. The reaction mixture was worked up as described on page 136. There was obtained 0.42 g. of a viscous oil, which solidified upon seeding with 3-(5,5-dimethyl-pyrrolidin-2-yl)-propan-1,2-diol. The picrate, m.p. 116 - 119°, was prepared from benzene-picric acid solution, and recrystallized from butanol. A mixed m.p. with the picrate (116 - 119°) from 3-(5,5-dimethyl-pyrrolidin-2-yl)-propan-1,2-diol, was not depressed.

(b) Further experiments

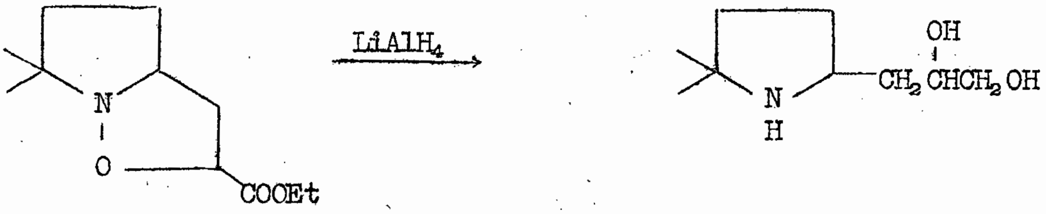
Reduction of the esters from 5,5-dimethyl-1-pyrroline 1-oxide and ethyl acrylate was carried out as described on page 136, except that the time of reduction was extended to 14 hr.

In the case of the "cold" ester (page 133), paper chromatography on Whatman No. 1 paper, using BuOH : AcOH : H_2O (77 : 6 : 17) showed the presence of a single component, corresponding to 3-(5,5-dimethyl-pyrrolidin-2-yl)-propan-1,2-diol.

To determine whether the two compounds 3-(5,5-dimethyl-pyrrolidin-2-yl)-propan-1,2-diol and 2-(5,5-dimethyl-pyrrolidin-2-yl)-propan-1,3-diol were separated by the BuOH : AcOH : H_2O solvent, a sample of pure 1,3-diol was obtained as follows:

The picrate (m.p. 165 - 166°) of 2-(5,5-dimethyl-pyrrolidin-2-yl)-propan-1,3-diol (page 162), (About 5 mgm.) was dissolved in a solution of potassium hydroxide (about 0.5 g.) in water (1 ml.). The resulting solution was shaken with ether (5 ml.) dried ($MgSO_4$), and this stock solution applied to the paper as required. BuOH : AcOH : H_2O (77 : 6 : 17) solvent did not separate the two glycols. Using BuOH : 3 N NH_3 (1 : 1), 2-(5,5-dimethyl-pyrrolidin-2-yl)-propan-1,3-diol had R_f 0.71, and 3-(5,5-dimethyl-pyrrolidin-2-yl)-propan-1,2-diol R_f 0.61. The reduction product prepared as described on page 121 was shown to consist of a mixture of the two amino-glycols in about equal proportions.

Reduction of 3-ethoxycarbonyl-8,8-dimethyl-2-oxa-1-azabicyclo[3,3,0]octane: Preparation of 3-(5,5-dimethyl-pyrrolidin-2-yl)-propan-1,2-diol



3-Ethoxycarbonyl-8,8-dimethyl-2-oxa-1-azabicyclo[3,3,0]octane (10 g.) in dry tetrahydrofuran (50 ml.) was added slowly with stirring to a suspension of lithium aluminium hydride (8 g.) in dry tetrahydrofuran (50 ml.). The mixture was stirred and refluxed for about 14 hr., after which the excess of lithium aluminium hydride was destroyed by the cautious addition of methanol (50 ml.).

The tetrahydrofuran and methanol were removed in vacuo, and the residual paste triturated with sodium potassium tartrate solution(saturated, 40 ml.). (If larger quantities of tartrate solution are employed, a slimy product is obtained which makes subsequent filtration extremely tedious). The granular solid was broken up with a spatula, and extracted with hot chloroform (5 x 25 ml. batches, under reflux for about 20 mins.). The chloroform extracts were combined, dried with anhydrous magnesium sulphate, evaporated and distilled in a short-path still at 150 - 180°, 0.5 - 1.0 mm. Yield 5.7 g. (70%). This compound solidified to a solid of indefinite melting point, about 125 - 150°. Paper chromatography on Whatman No. 1 paper, using BuOH : 3 N NH_3 (1 : 1) showed after treatment with ninhydrin, that this material was pure 3-(5,5-dimethyl-pyrrolidin-2-yl)-propan-1,2-diol. No traces of the 1,3-glycol were detected. The material is highly hygroscopic and this accounts for the unsatisfactory carbon values below. Attempts at recrystallisation, using petroleum ether (b.p. 100 - 120°, viz. page 129), were unsuccessful, in that only a slimy solid was obtained. The synthetic amino-glycol, page 156, behaves similarly.

<u>Analysis</u>:

Calculated for $C_9H_{19}NO_2$		Found	
C	62.4%	C	60.8%, 61.0%
H	11.1%	H	11.0%, 10.8%
N	8.09%	N	7.54%

The <u>picrate</u> was prepared from benzene-picric acid solution, and recrystallized from butanol. Yellow needles, m.p. 116 - 119°.

<u>Analysis</u>:

Calculated for $C_{15}H_{22}N_4O_9$		Found	
C	44.8%	C	45.2%
H	5.51%	H	5.67%
O	35.8%	O	36.7%
Eq. Wt.	402		403

The melting point of this picrate was not depressed when mixed with the picrate, (m.p. 116 - 119°) from synthetic 3-(5,5-dimethyl-pyrrolidin-2-yl)-propan-1,2-diol. Mixed m.p. with the picrate (m.p. 125 - 126°) from the product obtained by reduction of allyl alcohol adduct (see page 130). 116 - 120°. Several recrystallizations from butanol raised the m.p. of the picrate to 123 - 125°, undepressed when mixed with the picrate 125 - 126°.

The <u>picrolonate</u> was prepared from a saturated solution of picrolonic acid in ethanol. Recrystallisation from butanol gave dingy-yellow needles, m.p. 160 - 162°, undepressed when mixed with the picrolonate of the synthetic amino-glycol, prepared on page 156, of m.p. 160 - 162°.

<u>Analysis</u>:

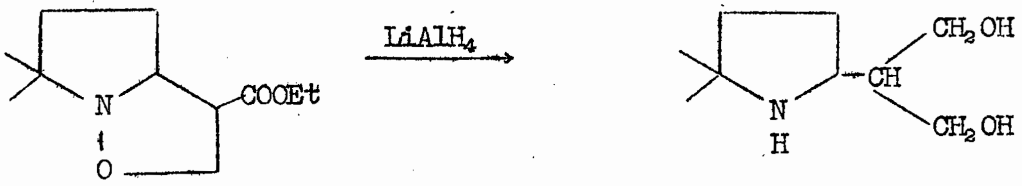
Calculated for $C_{19}H_{27}N_5O_7$		Found	
C	52.1%	C	51.2%
H	6.17%	H	6.04%
N	16.0%	N	15.6%

A tri-p-toluenesulphonyl derivative was prepared in the usual way from p-toluenesulphonyl chloride in pyridine, followed by recrystallisation from butanol-cyclohexane. White fluffy needles were obtained, of m.p. 153 - 154°.

Analysis:

Calculated for $C_{30}H_{37}NS_3O_8$	Found
C 56.7%	C 57.1%
H 5.86%	H 5.16%
S 15.1%	S 14.9%

Reduction of 4-ethoxycarbonyl-8,8-dimethyl-2-oxa-1-azabicyclo[3,3,0]octane: Preparation of 2-(5,5-dimethyl-pyrrolidin-2-yl)-propan-1,3-diol



4-Ethoxycarbonyl-8,8-dimethyl-2-oxa-1-azabicyclo[3,3,0]octane (10 g.) was reduced and subsequently worked up under conditions identical to those described on page 139. Distillation at 0.1 mm., 150 - 180° gave 5.9 g. (73%) of a highly viscous liquid. The hygroscopic nature of this material did not allow satisfactory analysis.

Analysis:

Calculated for $C_9H_{19}NO$	Found
C 62.4%	C 60.5%
H 11.1%	H 10.5%
N 8.09%	N 7.63%

The above amino-glycol was chromatographed on Whatman No. 1 paper, using butanol : 3 N NH_3 (1 : 1) as solvent, and its presence revealed by a ninhydrin dip. It moved at a rate identical to the amino-glycol obtained from the picrate, m.p. 165 - 166, as described on page 128. No traces of the isomeric glycol were observed.

Periodate uptake estimation:

The above amino-glycol (1.144 g.) was dissolved in water, and made up to 100 ml. 10 Ml. aliquots were treated with 20 ml. of periodic acid (C 0.05 M), and allowed to stand for 1 hr., 1½ hr., and 2 hr. Water was added (20 ml.), and sufficient solid sodium hydrogen carbonate added to saturate the solution. N/10 sodium arsenite solution was added (20 ml.) followed by potassium iodide solution (20%, 10 ml.). The mixture was then titrated with N/50 iodine. The titres were: after 1 hr., 7.80 ml.; 1½ hr., 7.80 ml.; 2 hr., 7.90 ml. A blank titration had titre 2.65 ml. This corresponds to an uptake of 0.16 moles of periodic acid per mole of glycol. The mixture of isomeric glycols described on page 121 under the same conditions, took up 0.53 moles periodic acid per mole of $C_9H_{19}NO_2$.

Reaction of 2-(5,5-dimethyl-pyrrolidin-2-yl)-propan-1,3-diol with hydriodic acid

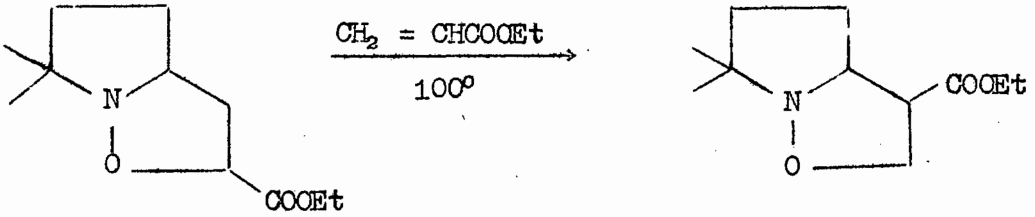
2-(5,5-Dimethyl-pyrrolidin-2-yl)-propan-1,3-diol (1.06 g.), was dissolved in fuming hydriodic acid (d. 1.96, 8 ml.) and heated at 165 - 175° for 14 hr., in a sealed tube. After cooling, the tube was cautiously opened, and the contents heated for 4 hr. with an excess of zinc and 20% hydrochloric acid. The mixture was cooled, made strongly alkaline with sodium hydroxide, and steam distilled. The steam distillate (c. 150 ml.) was acidified with hydrochloric acid, and evaporated to dryness in a tared flask, which was then kept 36 hr. in a vacuum desiccator over phosphorus pentoxide. The yield of hydrochloride was 0.93 g.

The hydrochloride was converted to the base by addition of sodium hydroxide (2 g.) in water (3 ml.), and extracted into ether (50 ml.) which was dried with anhydrous magnesium sulphate, and evaporated.

A portion of the base was treated with anhydrous oxalic acid in ether, to form an oxalate, m.p. 201 - 202 dec. (from butanol) undepressed when mixed with the oxalate m.p. 200 - 202 dec. of 2,2-dimethyl-5-n-propyl-pyrrolidine.

Another portion of the base, upon treatment with a saturated solution of picrolonic acid in ethanol, gave a picrolonate, dec. 244 - 246°. A mixture of this picrolonate and the picrolonate, (dec. 245°) of 5,5-dimethyl-2-isopropyl-pyrrolidine, decomposed at 244 - 246°.

Conversion of 3-ethoxycarbonyl-8,8-dimethyl-2-oxa-1-azabicyclo[3,3,0]octane into 4-ethoxycarbonyl-8,8-dimethyl-2-oxa-1-azabicyclo[3,3,0)octane



The 3-ethoxycarbonyl isomer[shown to be homogeneous,(1 g.)]was dissolved in ethyl acrylate (10 ml.) and heated 12 hr. at 100°. The excess of ethyl acrylate was removed in vacuo, the residue dissolved in petroleum ether (b.p. 30 - 50°, 10 ml.), shaken with water, (5 ml.), and dried with anhydrous magnesium sulphate. Evaporation of the solvent gave a 67% recovery of the esters. Reduction, followed by paper chromatography as described on page 136 showed the presence of 2-(5,5-dimethyl-pyrrolidin-2-yl)-propan-1,3-diol and 3-(5,5-dimethyl-pyrrolidin-2-yl)-propan-1,2-diol, the latter compound appearing to be in the largest amount.

Catalytic hydrogenation of 3-ethoxycarbonyl-8,8-dimethyl-2-oxa-1-aza-bicyclo[3,3,0]octane:

3-Ethoxycarbonyl-8,8-dimethyl-2-oxa-1-azabicyclo[3,3,0]octane (10.3 g.),in anhydrous, peroxide-free dioxane (100 ml.), was hydrogenated in a Baskerville and Lindsay bomb hydrogenator, over activated copper chromite. The initial temperature was 25°, and this was raised during about four hours to 230°. The pressure of the hydrogen, initially at 125 atms., rose to about 180 atms. The reaction mixture was maintained at 230° and 125 atms. for four hours, and then allowed to cool overnight under pressure. Mechanical agitation was maintained throughout the experiment.

The reaction mixture was filtered, acidified, and evaporated in vacuo on the steam bath. The viscous residue was then made alkaline, and steam distilled. The steam distillate was acidified, evaporated, and the residual syrup made strongly alkaline by the addition of sodium hydroxide solution (50% w/v, 25 ml.). The liberated base was extracted into ether, the extract dried with sodium sulphate, and evaporated. The residual oil was distilled to give 2.2 g. of product b.p. 65 - 69° at 25 mm. A forerun (1.2 g.) boiling below this range was collected. The main fraction was redistilled.

Analysis:

	Calculated for $C_9H_{17}N$;	$C_9H_{19}N$		Found
C	77.6%	76.5%	C	76.7%
H	12.2%	13.6%	H	12.9%
N	10.1%	9.92%	N	10.1%

A quantitative acylation was carried out as described in Vogel's "Elementary Practical Organic Chemistry", Part 3, p. 697 (Longmans 1958). The material above consumed an amount of acetic anhydride-pyridine reagent corresponding to 0.38 moles of acetic anhydride per mole of base (assuming a molecular formula $C_9H_{17}N$). Under identical conditions, 2,2-dimethyl-5-

propyl-pyrrolidine (prepared and purified as described on page 127) consumed an amount of acetic anhydride-pyridine reagent corresponding to 1.02 moles of acetic anhydride per mole of base.

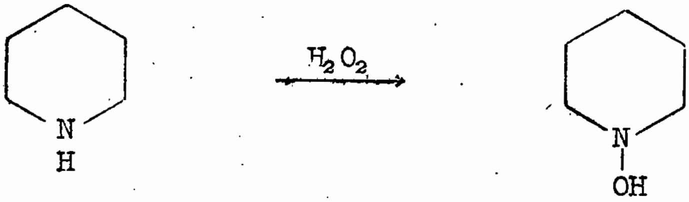
The picrate precipitated readily from an ethanolic solution of picric acid, and recrystallized from butanol, to give yellow needles, decomp. at 240 - 248°.

Analysis:

	Calculated for $C_{15}H_{20}N_4O_7$		Found
C	49.0%	C	48.8%
H	5.46%	H	5.43%
N	15.2%	N	15.0%
Eq. Wt.	368		368

(a) 1-Hydroxypiperidine

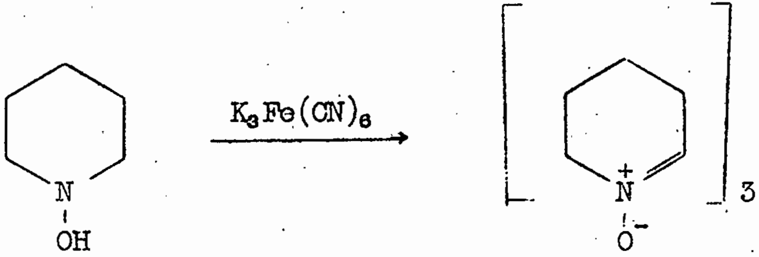
Wolffenstein, Ber., (1892), 25, 2777.



1-Hydroxypiperidine, b.p. 61 - 63° at 2 mm. was obtained in 25% yield. The oxalate, prepared from a solution of oxalic acid in acetone, and recrystallized from butanol, had m.p. 107 - 109°. Rogers, J., (1955), 769, reports a m.p. 104 - 106° for the oxalate of 1-hydroxypiperidine.

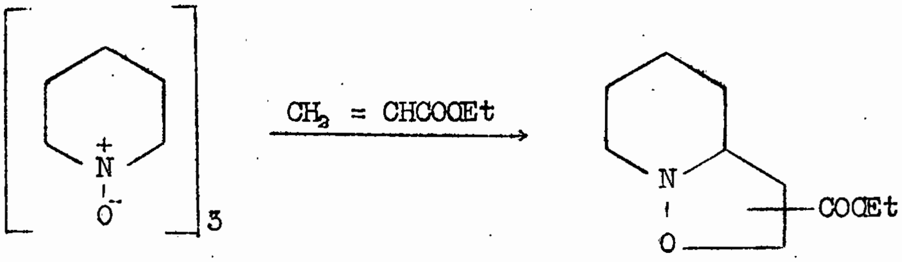
(b) Trimer of 1-piperideine 1-oxide

Thesing and Mayer, Ann., (1957), 609, 49.



A quantitative yield was obtained.

(c) 3 or 4-Ethoxycarbonyl-2-oxa-1-azabicyclo[4,3,0]-nonane



1-Piperideine 1-oxide trimer (5.0 g.), and ethyl acrylate (50 ml.) were mixed and allowed to stand for 24 hrs. The excess ethyl acrylate was removed in vacuo, and the residual oil dissolved in petroleum ether (30 - 50°, 50 ml.). The petroleum ether extract was washed with water (25 ml.), dried with magnesium sulphate, and evaporated. Yield 4.0 g. A sample was distilled in vacuo in a short-path still.

Analysis:

Calculated for $C_{10}H_{17}NO_3$		Found	
C	60.3%	C	60.5%
H	8.58%	H	8.81%
N	7.03%	N	6.75%

The picrolonate separated out from a saturated solution of picrolonic acid in ethanol. Recrystallization from n-butanol gave yellow needles, m.p. 161 - 162°.

Analysis:

Calculated for $C_{20}H_{25}N_5O_8$	Found
C 51.8%	C 53.0%
H 5.44%	H 5.69%
N 15.1%	N 14.9%

Catalytic hydrogenation of 3 or 4-ethoxycarbonyl-2-oxa-1-azabicyclo[4,3,0] nonane

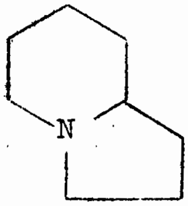
3 or 4-Ethoxycarbonyl-2-oxa-1-azabicyclo[4,3,0]nonane (17 g.) in anhydrous, peroxide-free dioxan, (150 ml.) were hydrogenated in a Baskerville and Lindsay bomb hydrogenator over activated copper chromite. The initial temperature was 20°, and was raised to about 250° in about 4 hrs. The pressure of the hydrogen rose during this heating process from 120 atms. to about 200 atms. The reaction mixture was maintained at 200 atms. and 250° for about 4 hrs., and then allowed to cool overnight under pressure. Mechanical agitation was maintained throughout the experiment.

The reaction mixture was worked up in the same manner as described on page 144, except that the final product, (10 g.) was purified by distillation at atmospheric pressure, and had b. pt. 158 - 161°.

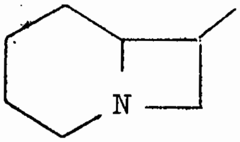
Analysis:

Calculated for $C_8H_{15}N$	Found
C 76.8%	C 76.8%
H 12.1%	H 12.4%
N 11.2%	N 11.2%

The picrate separated readily from ethanolic picric acid. Recrystallization from n-butanol gave yellow crystals, decomp. 201 - 203°.



has a picrate m.p. 226°
(Löffler and Kain, Ber.,(1909, 42, 105)



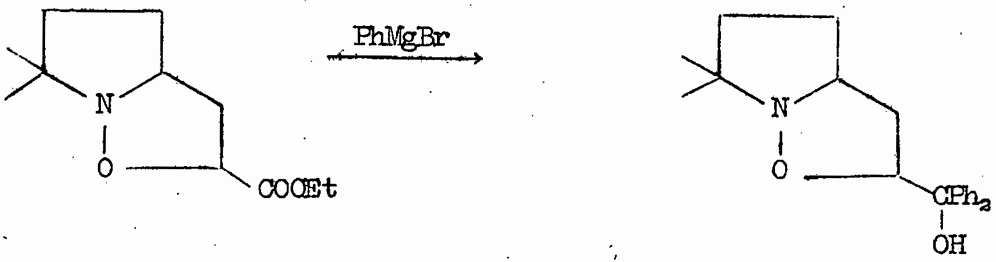
has a picrate m.p. 194 - 195°
(Loffler and Grosse, Ber., 1907, 40, 1333)

Analysis:

	Calculated for $C_{14}H_{18}N_4O_7$		Found
C	47.5%	C	47.5%
H	5.10%	H	5.07%
N	15.9%	N	15.8%
Eq. Wt.	354		352

Reaction of 3-Ethoxycarbonyl-8,8-dimethyl-2-oxa-1-azabicyclo[3,3,0]octane with Phenylmagnesium Bromide

8,8-Dimethyl-3-(hydroxy-diphenyl-methyl)-2-oxa-1-azabicyclo[3,3,0] octane



3-Ethoxycarbonyl-8,8-dimethyl-2-oxa-1-azabicyclo[3,3,0]octane, (11.2 g.) in ether (50 ml.) was slowly added with stirring to a solution of phenylmagnesium bromide (from magnesium, 3.9 g., and bromobenzene, 23.5 g., and ether, 100 ml.) prepared in the usual way. A highly viscous gum immediately precipitated, and this made stirring impracticable. The mixture was gently refluxed for 2½ hr., and a solution of ammonium chloride (25 g.) in water (75 ml.) was added. The ether layer was separated, dried with anhydrous sodium sulphate, and evaporated. The solid residue was recrystallized from petroleum ether (b. p. 60 - 80°), and had m.p. 134 - 135°. Yield 4.6 g.

Analysis:

Calculated for $C_{21}H_{25}NO_2$	Found
C 78.0%	C 77.4%
H 7.79%	H 7.80%
N 4.34%	N 4.27%

A picrate separated from ethanolic picric acid. Recrystallization from n-butanol gave pale yellow needles, decomp. 214 - 215°, with previous darkening.

Analysis:

Calculated for $C_{27}H_{28}N_4O_9$	Found
C 58.7%	C 58.5%
H 5.10%	H 4.97%
N 10.1%	N 9.75%

SECTION III

SECTION THREE

A: SYNTHESIS OF 3-(5,5-DIMETHYL-PYRROLIDIN-2-YL)-PROPAN-1,2-DIOL

(i) First attempt

(a) Triphenylphosphite methiodide:

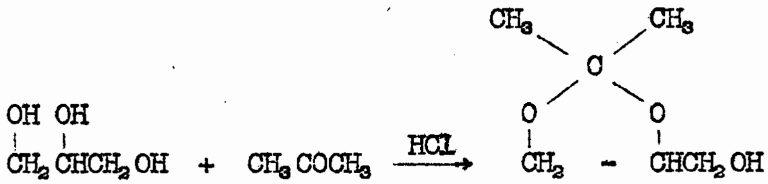
Landauer and Rydon, J., (1953), 2224.

$$(PhO)_3P + MeI \rightarrow (PhO)_3PMeI.$$

78 g. of crude triphenylphosphite methiodide were obtained from 75 g. triphenylphosphite. This crude material was used without further purification.

(b) αβ-Propylidene glycerol:

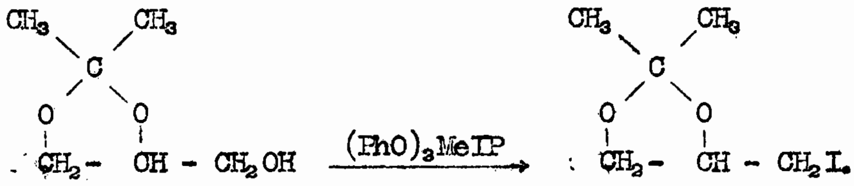
Malkin and Shurbagy, J., (1936), 1628.



αβ-Propylidene glycerol, b. pt. 49° at 0.2 mm., was obtained in 40% yield.

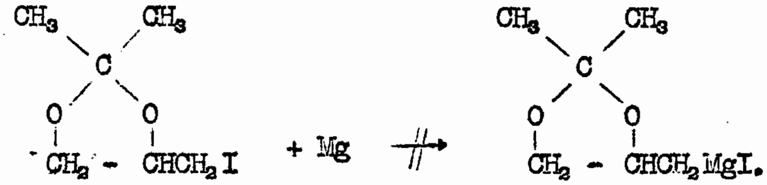
(c) 2,2-Dimethyl-4-iodomethyl-1,3-dioxolan:

Bevan and Malkin, J., (1955), 1383.



This compound had b.p. 70° at 0.2 mm. and was obtained in 55% yield.

(d) Attempted conversion of 3,3-dimethyl-4-iodomethyl-1,3-dioxolan into the Grignard reagent:



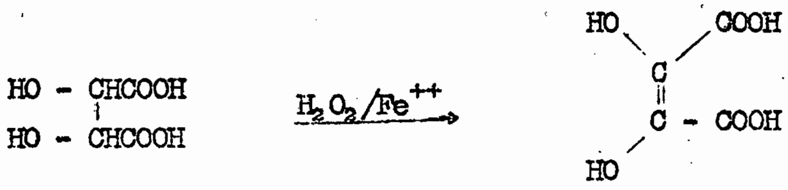
(i) 3,3-Dimethyl-4-iodomethyl-1,3-dioxolan (5.0 g.) in absolute tetrahydrofuran (50 ml.) was added to magnesium powder (0.6 g.) which had been activated by grinding and heating with powdered resublimed iodine (0.3 g.). No solution of the magnesium was observed, even on repeated heating and stirring. Eventually the reaction mixture was stirred and refluxed overnight without effecting the desired conversion.

(ii) 3,3-Dimethyl-4-iodomethyl-1,3-dioxolan (5.0 g.), magnesium turnings (0.5 g.) in ether (25 ml.) were refluxed and stirred while ethylene dibromide (4.1 g.) was slowly added during 14 hrs. During that time, the magnesium had dissolved. 5,5-Dimethyl-1-pyrroline 1-oxide (2.34 g.) in ether (25 ml.) was slowly added. A brown precipitate formed. Stirring and refluxing was continued for 2 hrs. The reaction mixture was decomposed by addition of excess ammonium chloride solution. Neither the aqueous or ethereal layers gave a positive test for hydroxylamine with triphenyl tetrazolium chloride.

(ii) Second attempt

(a) Dihydroxymaleic acid:

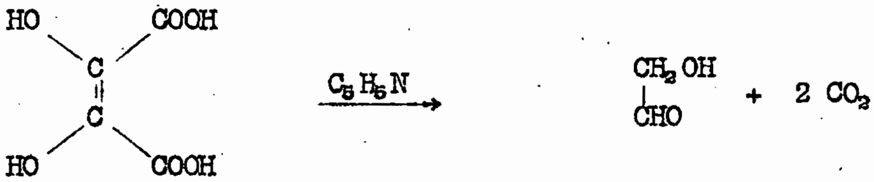
Fischer and Feldmann, Ber., (1929), 62, 865.



A 16% yield of crude dihydroxymaleic acid was obtained. This compound was used without further purification for the next preparation.

(b) Glycollaldehyde:

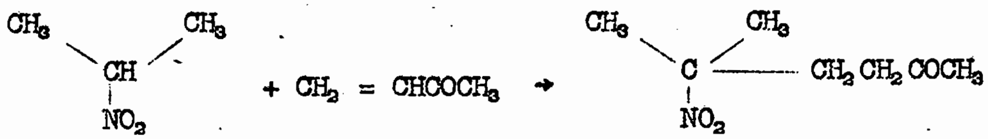
Fischer and Taube, Ber., (1927), 60, 1707.



Glycollaldehyde, m.p. 97 - 98°, was obtained in 42% yield. Heilbron's Dictionary of Organic Compounds report m.p. 96 - 97° for this compound.

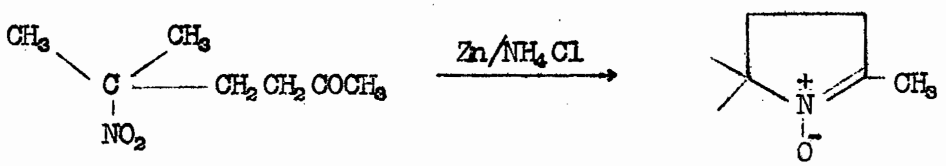
(c) 5-Methyl-5-nitro-hexan-2-one:

Schechter, Ley and Zeldin, J. Amer. Chem. Soc. (1952), 74, 3664.



5-Methyl-5-nitro-hexan-2-one, b. pt. 76 - 78° at 0.4 mm. was obtained in 60% yield. The 2,4-dinitrophenylhydrazone had a m. p. 130 - 131°. Schechter et al. (loc. cit.) quote a m. p. 130.5 - 131.5° for this compound.

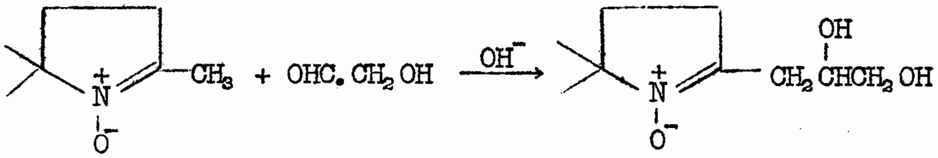
(d) 2,5,5-Trimethyl-1-pyrroline-1-oxide:



5-Methyl-5-nitro-hexan-2-one (94 g.) was stirred with a solution of ammonium chloride (26 g.) in water (710 ml.), while zinc dust (130 g.) was added over a period of two hours. The temperature was kept below 15° by maintaining the reaction in an ice bath, and occasional addition of crushed ice. After filtration, the residual cake of zinc oxide was well washed with hot water, and the combined washings and filtrate evaporated in vacuo at 70° - 75°. The residual viscous oil was saturated with potassium carbonate, and extracted with chloroform (4 x 100 ml.). After drying (Na_2SO_4), the chloroform was removed in vacuo, and the residue distilled. There was obtained 58 g. (77%) of product b.p. 71 - 72° at 2 mm.

The picrate readily formed from a saturated solution of picric acid in benzene or water. Recrystallization from butanol gave yellow needles m. p. 99° - 100°. Bonnett, Brown, Clark, Sutherland, and Todd, J., (1959), 2101, report a m. p. 98° for the picrate of 2,5,5-trimethyl-1-pyrroline 1-oxide, obtained by oxidation of 1-hydroxy-2,2,5-trimethylpyrrolidine.

(e) Preliminary attempt at reaction of glycollaldehyde with 2,5,5-trimethyl-1-pyrroline 1-oxide:



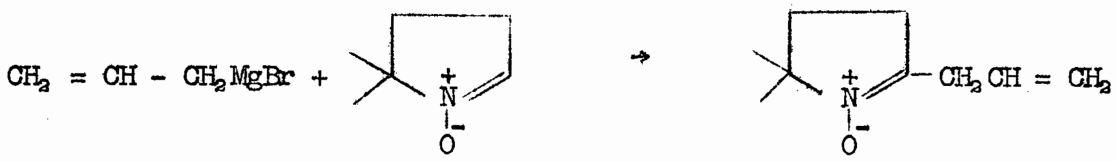
2,5,5-Trimethyl-1-pyrroline 1-oxide (2.0 g.) in water (5 ml.) and a solution of glycollaldehyde (0.60 g.) in water (5 ml.) were mixed. Sodium hydroxide solution (0.1 ml. N NaOH) was added, and the solution heated for 2½ hrs. at 50°- 55°. Paper chromatography on Whatman No. 1 paper in butanol-ethanol-water (4:1:5) followed by a p-anisidine hydrochloride spray revealed spots indicative of a sugar mixture, most likely corresponding to tetroses and hexoses, and unchanged glycollaldehyde. No desired product was isolated.

(iii) <u>Third and successful attempt</u>

(a) <u>2-Allyl-1-hydroxy-5,5-dimethyl-pyrrolidine</u>:

Improved preparation adapted from Delpierre, B.Sc. (Hons.) Research Report, University of Cape Town, 1958.

$$CH_2 = CH - CH_2Br + Mg \rightarrow CH_2 = CH - CH_2MgBr$$



Allyl bromide, (42 g.) in dry ether was added during 2 hrs. to a well stirred suspension of magnesium powder (50.5 g.) in dry ether (70 ml.). The reaction, which was quite vigorous, was completed by stirring for an additional 30 mins. at room temperature. The solution of allyl magnesium bromide was rapidly filtered from the excess magnesium, and transferred to another flask.

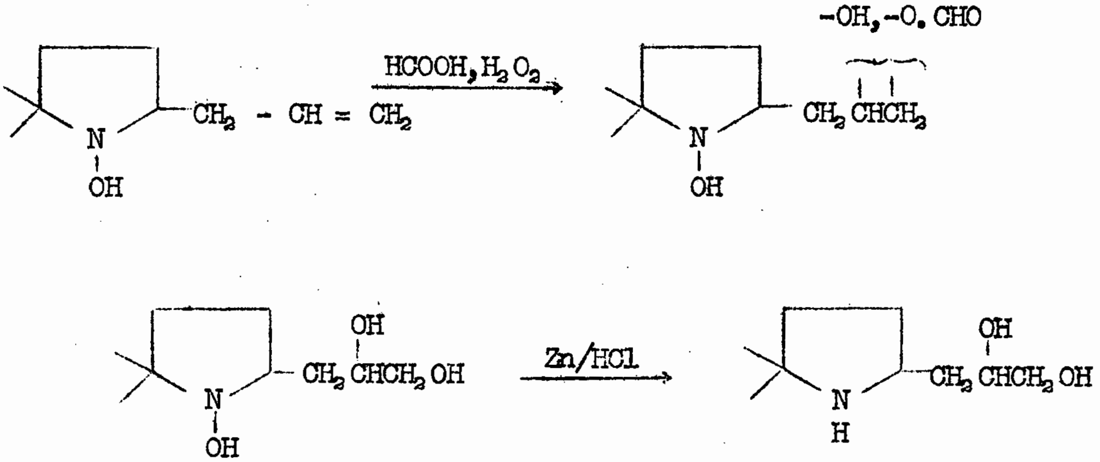
5,5-Dimethyl-1-pyrroline 1-oxide (32 g.), in dry ether (50 ml.), was added slowly to the allyl magnesium bromide, vigorous stirring being maintained throughout. A gummy white precipitate immediately formed. When the addition was complete

(30 mins.), the mixture was stirred under reflux for an additional two hours.

The complex was decomposed by the addition of ammonium chloride solution (5 N, 100 ml.). The ether layer was separated, and the aqueous layer extracted with a further quantity of ether (2 x 500 ml.). Drying the combined ether extracts with anhydrous sodium sulphate, followed by removal of the ether and vacuum distillation gave 16 g., (36%) of product, b. p. 80 - 82° at 5 mm.

This material has previously been correctly analysed. (Delpierre, loc. cit.).

(b) 3-(5,5-Dimethyl-pyrrolidin-2-yl)-propan-1,2-diol:



2-Allyl-1-hydroxy-5,5-dimethyl pyrrolidine (6.5 g.) in A.R. formic acid (99%, 50 ml.) was cooled in ice, and hydrogen peroxide (100 vols., 5.5 ml.) was added. The mixture was allowed to stand in ice for 10 mins., and then heated for 16 hrs. in a water bath thermostatically controlled at 40°. The formic acid was evaporated in vacuo, and ethyl alcohol (96%, 50 ml.) was added, followed by evaporation in vacuo.

A solution of potassium hydroxide (14 g.) in ethyl alcohol (96%, 80 ml.) was added, and the mixture refluxed for 1 hr. on the water bath. Glacial acetic acid (25 ml.) was added, and the mixture evaporated to a paste.

The paste, (which gave a positive tetrazolium test for hydroxylamines) was dissolved in hydrochloric acid (20%, 75 ml.) and heated overnight on the water bath with zinc dust (30 g.). The reaction mixture was filtered from the unreacted zinc, and rendered strongly alkaline by the addition of sodium hydroxide (100 g.) in water (100 ml.), followed by sodium potassium tartrate solution (saturated, 100 ml.). The clear solution was then extracted with ether continuously for four days.

The ether extract was dried with anhydrous potassium carbonate, and evaporated. The dark viscous residue was distilled in vacuo in a short path still to give 3.4 g. of a viscous liquid, which soon crystallized to a low melting solid upon seeding with suspected 3-(5,5-dimethyl-pyrrolidin-2-yl) propan-1,2-diol from reduction of the allyl alcohol adduct on 5,5-dimethyl-1-pyrroline 1-oxide.

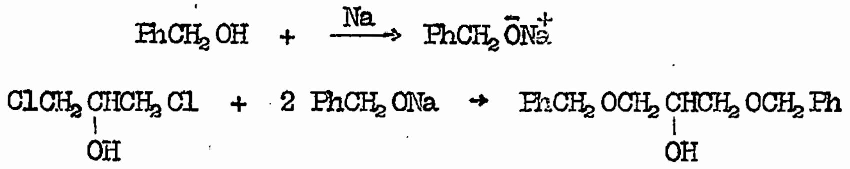
The picrate was prepared from a saturated solution of picric acid in benzene, and when recrystallized from butanol had m. p. 116 - 119° undepressed by admixture with the picrate, m.p. 116 - 119° obtained from the aminoglycol prepared on p.140. Several recrystallisations from n-butanol raised the melting point to 123 - 125°, undepressed by admixture with the picrate m.p. 125-120° obtained by reduction of the allyl alcohol adduct (see page 129). The picrolonate was prepared from ethanol/ether, and recrystallized from n-butanol had m. p. 160 - 162°, which showed no depression when mixed with the picrolonate m. p. 160 - 162°, prepared from the amino-glycol mentioned above.

B: SYNTHESIS OF 2-(5,5-DIMETHYL-PYRROLIDIN-2-YL)-PROPAN-1,3-DIOL

1. First attempt

(a) 1,3-Di-O-benzyl-glycerol

Tsatsas, Ann. Pharm. Franc., (1950), 8, 281.



$$PhCH_2OH + \xrightarrow{Na} PhCH_2\bar{O}\overset{+}{Na}$$

$$ClCH_2\underset{OH}{CH}CH_2Cl + 2\ PhCH_2ONa \rightarrow PhCH_2OCH_2\underset{OH}{CH}CH_2OCH_2Ph$$

A 43% yield of product was obtained, b. p. 180 - 182° at 1 mm.

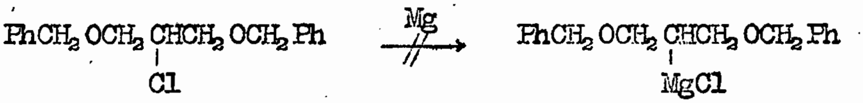
(b) 1,3-Dibenzyloxy-2-chloro-propane:

Tsatsas, Ann. Pharm. Franc., (1950), 8, 282.

$$PhCH_2OCH_2\underset{OH}{CH}CH_2OCH_2Ph \xrightarrow[C_5H_5N]{SOCl_2} PhCH_2OCH_2\underset{Cl}{CH}CH_2OCH_2Ph$$

A 52% yield of product was obtained, b. p. 160 - 162° at 0.2 mm.

(c) Attempted conversion of 1,3-dibenzyloxy-2-chloro-propane into the Grignard reagent:



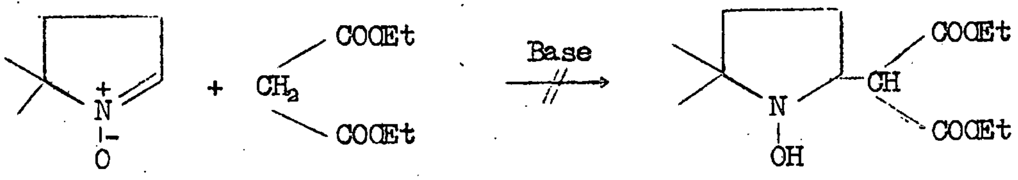
$$PhCH_2OCH_2\underset{Cl}{CH}CH_2OCH_2Ph \not\xrightarrow{Mg} PhCH_2OCH_2\underset{MgCl}{CH}CH_2OCH_2Ph$$

1,3-Dibenzyloxy-2-chloropropane (20 g.) in a mixture of dry ether (60 ml.) and dry tetrahydrofuran (40 ml.) was added to activated magnesium powder, (prepared by grinding magnesium powder (2.4 g.) and resublimed iodine (1.2 g.), and heating the mixture).

Since no observable reaction was taking place, even on intermittently raising the temperature, a few drops of methyl iodide were introduced, and although these immediately reacted, the reaction soon ceased. The mixture was stirred and refluxed overnight, but no magnesium was consumed. Virtually all the chloro-compound was recovered.

2. Second attempt

(a) Attempt at condensation of diethyl malonate and 5,5-dimethyl-1-pyrroline 1-oxide:



(i) Diethyl malonate, (40 g.) was added to a solution of sodium ethoxide, from sodium (5.8 g.) and absolute ethanol (400 ml.). The mixture was refluxed for 30 mins., and, after cooling, 5,5-dimethyl-1-pyrroline 1-oxide (24 g.) in absolute ethanol (100 ml.) was added. The solution was allowed to stand overnight at room temperature.

Glacial acetic acid (15 ml.) was added, and the ethanol removed on the water bath in vacuo. The residual paste was dissolved in an excess of water, and the precipitated oil dissolved in a mixture of petroleum ether (b. p. 60 - 80°) and ether, (1:1, 50 ml.).

After drying, with anhydrous sodium sulphate, and evaporation of the solvent, repeated fractionation in vacuo gave about 10 g. of a colourless, basic oil, b. p. 65 - 68° at 0.2 mm. This oil gave a positive test for hydroxylamines with triphenyl tetrazolium chloride. ν_{max} 1595, (s), 1610 (s), 1665 (s), 1740 (m), 1778 (w) cm^{-1}.

Analysis:

Calculated for	$C_{13}H_{23}NO_5$;	$C_{10}H_{17}NO_2$	Found
C	57.1%	65.6%	C 65.2%
H	8.48%	9.30%	H 9.29%
N	5.13%	7.65%	N 7.41%

On treating the above oil with a saturated solution of oxalic acid in butanol, a white solid separated, which, upon recrystallization from butanol had m. p. 112 - 113° (with decomposition).

Analysis:

Calculated for $C_{13}H_{21}NO_8$		Found	
C	48.9	C	48.4, 48.5
H	6.64	H	6.39, 6.38
N	4.39	N	4.27

(ii) 5,5-Dimethyl-1-pyrroline 1-oxide (6.0 g.), and diethyl malonate (10 ml.) were dissolved in anhydrous pyridine (25 ml.) and piperidine (0.5 ml.) was added. The mixture was heated for 14½ hrs. on a boiling water bath, and the pyridine then removed in vacuo. The yellow residual oil was shaken with an excess of water, dissolved in petroleum ether (b.p. 40 - 60°, 25 ml.), and shaken with water (2 x 25 ml.). After drying, the oil was distilled in vacuo, and appeared to be identical with that obtained above under (i) (comparison of infra-red spectra). The yield was of the same order as in the previous experiment. A crystalline residue remained in the distilling flask, and this, after recrystallisation from cyclohexane, had m. p. 97 - 98°. The yield of this material amounted to about 15 mg.

Analysis:

Calculated for $C_{20}H_{28}N_2O_7$		Found	
C	58.8%	C	58.6, 59.0%
H	6.86%	H	6.69, 7.03%
N	6.86%	N	6.81%

All the above materials were not investigated further.

3. Third Attempt.

(a) Attempt at addition of formaldehyde on 2,5,5-trimethyl-1-pyrroline 1-oxide, followed by reduction to 2-(5,5-dimethyl-pyrrolidin-2-yl) propan-1,3-diol.

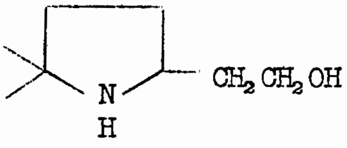
2,5,5-Trimethyl-1-pyrroline 1-oxide (2.0 g.) was dissolved in saturated sodium hydrogen carbonate solution (10 ml.), and the solution adjusted to pH 10 by addition of sodium hydroxide. Formaldehyde (40% aqueous solution, 10 ml.) was added, and the mixture allowed to stand overnight at room temperature. The solution was neutralized by the addition of glacial acetic acid, and evaporated in vacuo to about 5 ml.

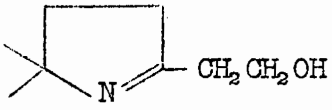
Concentrated hydrochloric acid (15 ml.) and zinc dust (5 g.) were added, and the mixture heated for 6 hr. on the water bath. After making alkaline by adding concentrated ammonia, the zinc was precipitated as sulphide by passing hydrogen sulphide through the solution. After filtration, the solution was evaporated in vacuo under alkaline conditions (to remove any 2,2,5-trimethyl-pyrrolidine and 2,5,5-trimethyl-1-pyrroline obtained by reduction of the unreacted nitrone), and the residual paste extracted with chloroform (50 ml.). The chloroform solution was dried with anhydrous magnesium sulphate to give a small quantity of a brown oil, which was converted directly to the picrate by addition of a saturated solution of picric acid in benzene. An oil initially precipitated, and this solidified after decanting the benzene, and triturating with cyclohexane. Recrystallization of the resulting solid from n-butanol gave dark yellow rods, m.p. 99 - 100°. The yield of the pure picrate was 0.52 g.

Analysis:

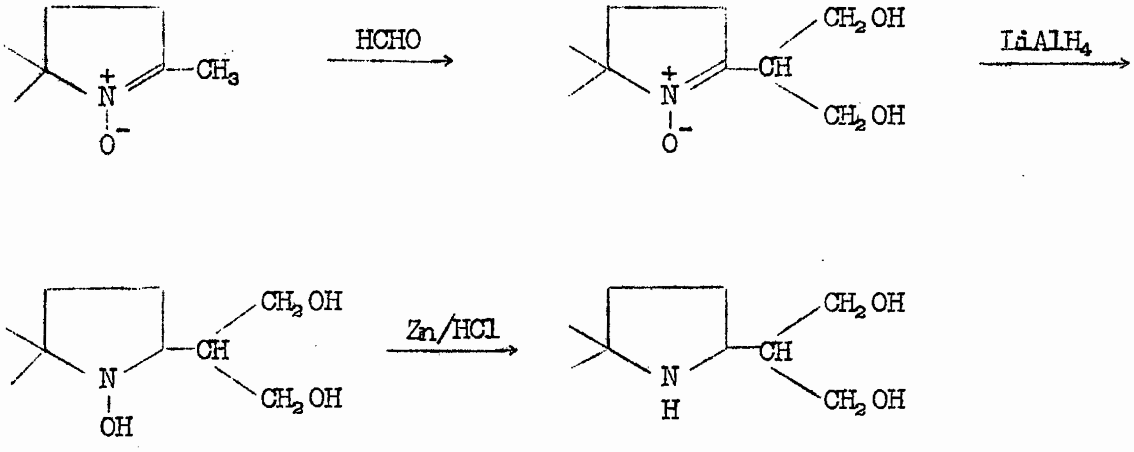
	Calculated for $C_{14}H_{20}N_4O_8$	Found
C	45.2%	44.1%
H	5.43%	5.13%
O	34.4%	35.8%
Eq. Wt.	372	370, 376

(This analysis could fit $C_{14}H_{18}N_4O_8$. The picrate then most likely corresponds to either 2-(5,5-dimethyl-pyrrolidin-2-yl)-ethanol (A) or 2-(5,5-dimethyl-1-pyrrolin-2-yl)-ethanol (B).


(A)


(B)

(b) 2-(5,5-Dimethyl-pyrrolidin-2-yl)-propan-1,3-diol.



Freshly distilled 2,5,5-trimethyl-1-pyrroline 1-oxide (20 g.), and paraformaldehyde (9.2 g.) were heated for 18 hrs. at 100°. The thick brown gum was dissolved in anhydrous tetrahydrofuran (100 ml.), and this solution was slowly added to a suspension of lithium aluminium hydride (10 g.) in tetrahydrofuran (100 ml.). The reaction mixture was stirred and refluxed for 6 hrs. The unreacted lithium aluminium hydride was destroyed by the addition of anhydrous methanol, and the mixture evaporated in vacuo to a paste. Hydrochloric acid (20%, 100 ml.) was added, followed by zinc dust (50 g.), and the mixture heated overnight at 100°.

The unreacted zinc was filtered, and the solution made strongly alkaline by addition of potassium hydroxide (50 g.) in water (50 ml.) and sodium potassium tartrate (saturated, 100 ml.). The liberated bases were extracted continuously with ether for about four days. The ether extract was dried with anhydrous magnesium sulphate, and evaporated. The thick, viscous, brown oil which remained was distilled through a short-path still, at a pressure of about 1 mm., and a bath temperature 120 - 180°. A viscous liquid was obtained (6.8 g.). This was shown by paper chromatography on Whatman No. 1 paper using butanol-acetic acid-water (77 : 6 : 17) as solvent, to consist mainly of 2-(5,5-dimethyl-pyrrolidin-2-yl)-propan-1,3-diol, although there were appreciable quantities of a faster moving, unidentified component.

Treatment of the product with a saturated solution of picric acid in benzene gave a picrate, m.p. 165 - 166°, after three recrystallizations from n-butanol. The melting point of this picrate was not depressed when mixed with the picrate m.p. 165 - 166°, obtained from the amino-glycol whose preparation is described on pages 122 and 142.

APPENDIX

APPENDIX

A Modified Short-Path Still

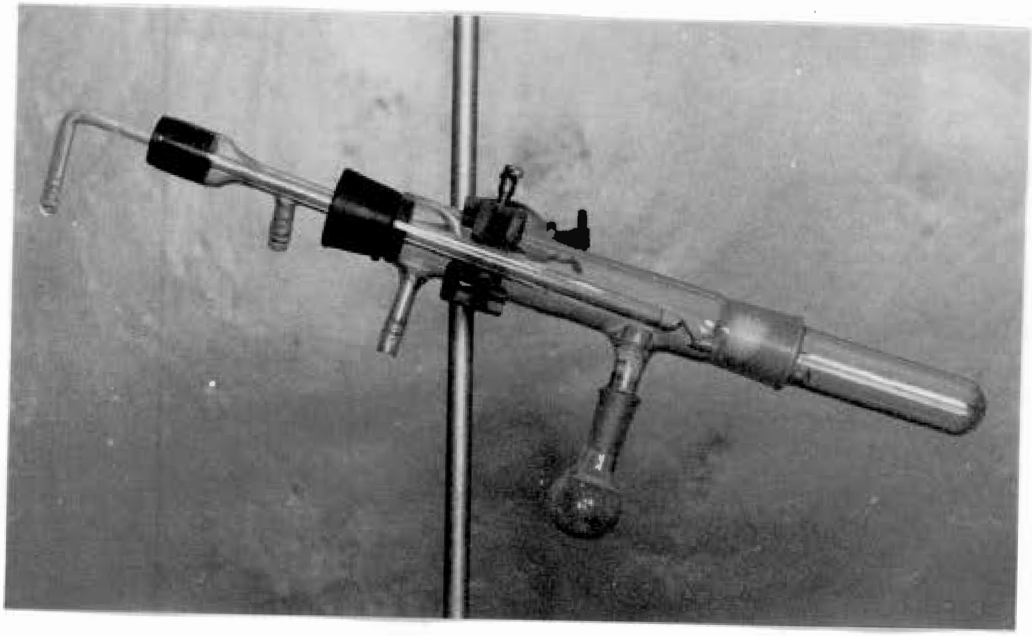


Fig. I

While carrying out the experimental work reported in this thesis, the author was often faced with the problem of distilling in vacuo small quantities of liquids, which were either too viscous to handle in conventional apparatus, or apt to decompose if heated for an appreciable time.

Very often, the scale of materials to be distilled was in the range 0.3–6 g., and there was a great need for a versatile piece of glassware. The author consequently designed a modified vacuum short-path still, which has proved itself invaluable not only to him, but also to his colleagues.

The most obvious requirements of a small-scale distillation apparatus are as follows:

(i) It must be capable of operation both at atmospheric and under low pressures.

(ii) The loss of materials by hold-up should be as small as possible. This implies that the surface of glass in contact with the liquid must be as small as possible.

(iii) Some means of determining the temperature of the vapour is useful, but not essential.

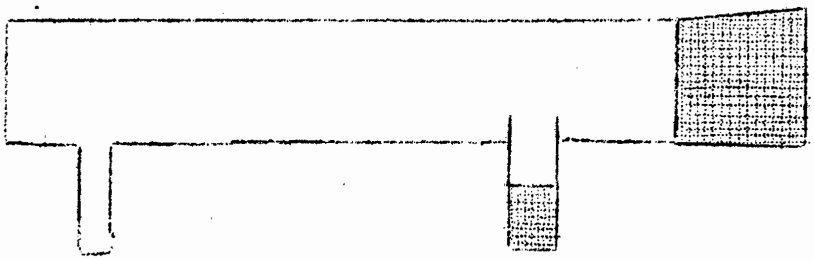
(iv) Liquids falling within a wide range of boiling points and viscosities must be capable of being handled.

(v) Some means of collecting a number of fractions must be included.

The apparatus is illustrated in Fig. I. The details of its construction are described below. All glass parts are made of borosilicate glass.

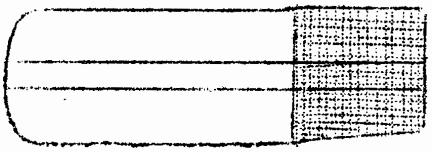
The apparatus consists of the following parts:

(a) A chamber A, made from a tube about 200 mm. long, 32 mm. O.D., carrying at one end a B29 standard socket. A vacuum connection is provided about 20 mm. from the open, unground end. A tube, (about 12 mm. O.D., and about 60 mm. in length, joint included) is fused into the chamber about 30 mm. from the B29 joint, in such a manner that the tube protrudes 8 mm. into the chamber. The external end of the small tube ends in a B14 standard cone.



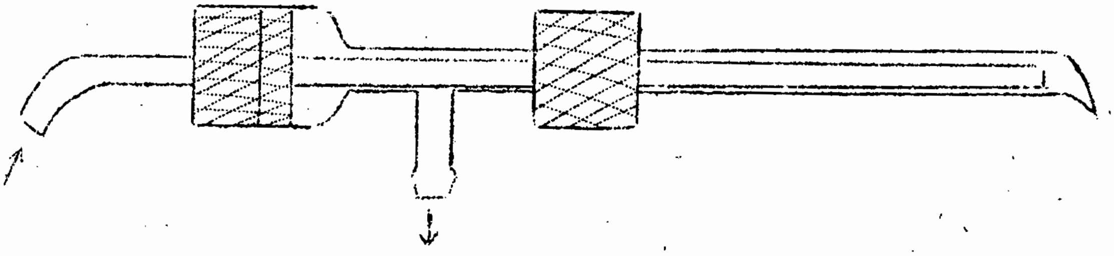
A

(b) A receiver holder B, made from a tube (about 28 mm. O.D.) carrying a B29 cone. The tube is closed at its unground end, and into this is sealed a centre rod (6 mm.). The whole length of the receiver is not critical. The author used a receiver about 100 mm. in length, joint included. The centre rod should not protrude beyond the open mouth of the tube.

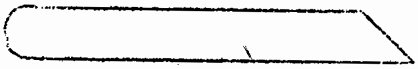


B

(c) A cold finger condenser, fitted with a rubber bung to enable it to be inserted into the unground end of the chamber A. The tip of the condenser is drawn to a "beak", as shown in the diagram. The length of the condenser which is inserted into the chamber is about 150 mm., but it can be adjusted at will by altering the position of the rubber bung. The condenser tube is about 9 mm. O.D.



(d) The receivers are small tubes, about 7 mm. O.D., cut to various suitable lengths, and conveniently have a capacity of about 1 ml. The open end is ground at an angle, as illustrated in the diagram below. These tubes may be etched with some distinguishing mark, and are conveniently weighed before and after filling, thus providing a measure of the yield of each fraction. Five such tubes fit into the receiver holder B.



Mode of Operation.

The liquid to be distilled is placed in a small B14 flask (5 - 25 ml.), a few chips of pumice added, followed by a small wad of glass wool. The joint is lubricated, and connected to the B14 joint of the chamber A.

The receiver tubes are placed in the holder B, and held in place by a wad of glass or cotton wool. The ground ends of the tubes are oriented in such a way that the lowest end of the bevel is directed towards the centre rod. The photograph (Fig. II) clearly indicates this. The B29 joint is lubricated, and inserted into the chamber.

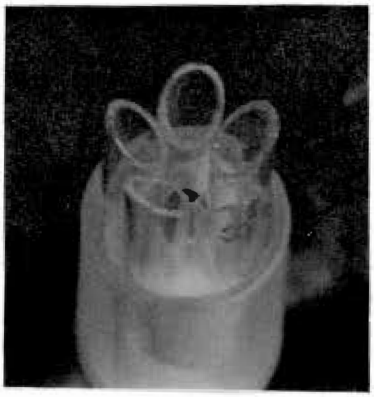


Fig. II

The rubber bung on the cold finger condenser is adjusted so that when it is inserted into the chamber, the "beak" overhangs directly over the open mouths of the receivers. The whole apparatus is inclined in such a way that the bevel of the lowest tube is horizontal. The photograph (Fig. III) shows the arrangement just before a fraction is collected.

Fig. III

The water and vacuum are connected. The flask can be heated by water or oil baths, or by a free flame, as desired. If "bumping" occurs, the glass wool prevents spattering onto the cold finger. One observes a "ring" of condensed vapour rising in the tube. A dew usually appears on the cold finger at this stage, and it is advisable to gently heat the chamber A with a free flame, to avoid condensation on it. As the distillation proceeds, drops of liquid formed on the cold finger fall into the receiver; when the tube is full, or another fraction must be collected, the receiver holder B is rotated so as to orient the next receiver tube in the operative position.

The apparatus described above was found to operate satisfactorily both at atmospheric pressure, and at pressures as low as 0.1 mm. Quantities of material of the order of 0.5 g., can be distilled with only a small loss. Purification of liquids for combustion analysis can readily be carried out with as little as three drops although of course, the loss is relatively greater.

No means of observing boiling points are included. However, this is of little consequence, as exact boiling points at low pressures on a small scale are of little significance. The author used the bath temperature as a rough guide, but preferred to rely on refractive index measurements, infra-red spectra, or paper chromatography, to establish the identity or otherwise of random fractions. In a typical experiment, when an isoxazolidine was distilled, on the five gram scale, five random fractions with a range of refractive indices falling within the limits ±0.0002 were obtained. The same material, under the same conditions of temperature and pressure (0.1 mm., 110 - 120° bath temperature) decomposed appreciably in a distillation carried out in a conventional apparatus.

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INDEX

SUMMARY

SUMMARY

When αβ-unsaturated esters reacted with nitrones of the 1-pyrroline 1-oxide type, a cyclo-addition reaction took place, with formation of bicyclic, N-bridged isoxazolidines. Thus, ethyl acrylate and 5,5-dimethyl-1-pyrroline 1-oxide reacted at room temperature to give a quantitative yield of 3-ethoxycarbonyl-8,8-dimethyl-2-oxa-1-azabicyclo[3,3,0]octane, whose structure was proved by reduction to 3-(5,5-dimethyl-pyrrolidin-2-yl)-propan-1,2-diol, also obtained by an unambiguous synthetic route. If the nitrone and ethyl acrylate were heated at 100° for four days, a quantitative yield of 4-ethoxycarbonyl-8,8-dimethyl-2-oxa-1-azabicyclo[3,3,0] octane was obtained. The structure of this compound was established by reduction to 2-(5,5-dimethyl-pyrrolidin-2-yl)-propan-1,3-diol, whose structure was proved by synthesis.

If the nitrone and ethyl acrylate were heated for only one day, then a mixture of the isomeric esters was formed. The 3-ethoxycarbonyl compound could be converted into the 4-ethoxycarbonyl isomer by heating with ethyl acrylate. Evidence regarding the thermal instability of some of the adducts was obtained.

Acrylonitrile, acrolein diethyl acetal, and allyl alcohol were also found to react with 5,5-dimethyl-1-pyrroline 1-oxide to form isoxazolidines. The allyl alcohol adduct was proved to be 3-hydroxymethyl-8,8-dimethyl-2-oxa-1-azabicyclo[3,3,0]octane, since it could also be produced by the partial reduction of 3-ethoxycarbonyl-8,8-dimethyl-2-oxa-1-azabicyclo

[3,3,0]octane, and also by its reduction to 3-(5,5-dimethyl-pyrrolidin-2-yl)-propan-1,2-diol.

3-(5,5-dimethyl-pyrrolidin-2-yl)-propan-1,2-diol reacted with phosphorus and hydriodic acid to give, after further reduction with zinc and hydrochloric acid, a base shown to be 2,2-dimethyl-5-propyl-pyrrolidine.

A similar treatment of the isomeric amino-glycol, 2-(5,5-dimethyl-pyrrolidin-2-yl)-propan-1,3-diol, unexpectedly gave rise to a rearrangement, as 2,2-dimethyl-5-propyl-pyrrolidine was also obtained, as the major product. Only a small quantity of the expected base, 2-*iso*propyl-5,5-dimethyl-pyrrolidine was formed. The structures of the two propylpyrrolidines were established by unequivocal synthetic paths.

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ACKNOWLEDGEMENTS

ACKNOWLEDGEMENTS

The author would like to take the opportunity to place on record his sincere and heartfelt thanks to his Supervisor, Dr. M. Lamchen, for his guidance, keen interest, and never-failing enthusiasm at all stages of this work, and also to Professor F.G. Holliman, for the facilities of his Department, enlightened advice, and constructive criticisms.

Thanks are also due to other members of the Chemistry Department Staff, for their help, and in particular to Dr. A.M. Stephen, for many helpful and stimulating discussions.

Grateful mention must also be made of Messrs. R. von Holdt and E.G. Marshall, for some of the micro-analyses, Mr. H.H.D. Hollemann, for infra-red spectra, and Mr. W.C. Lewis, for his skilful glass-blowing.

Finally, the author wishes to thank his wife, to whom this thesis is dedicated, for her encouragement and help at all times.