STUDIES OF 1,3 DIPOLAR CYCLOADDITION REACTIONS WITH N-CYCLOHEXYL NITRONES.

THESIS SUBMITTED FOR THE DEGREE OF DOCTOR
OF PHILOSOPHY (SCIENCE) OF THE
UNIVERSITY OF NORTH BENGAL
MAY 1995

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PREFACE

The nitrone moiety can be regarded as a 3 centered dipolar 4π System, which enables 1,3 dipolar cycloaddition reactions with dipolarophilic reagents to occur. 1,3 Dipolar cycloadditions are susceptible to electronic and Steric influences.

The question of reactivity and substituent effects in 1,3 dipolar cycloaddition reactions has been rationalised successfully using the 'Perturbation Molecular Orbital Theory' which provides the relative interaction energies of the frontier orbitals of 1,3 dipole and dipolarophile. Conjugating Substituents, electron attracting groups or electron releasing moieties influence the atomic orbital coefficients and have a significant influence on the regio selectivity of the reaction.

In 1,3 dipolar cycloaddition reactions, alkenes & alkynes with electron withdrawing groups are highly reactive where as alkenes with electron releasing substituents are moderately reactive.

But recently known nitrile-nitrone cycloadditions are allowed under thermal as well as under high pressure conditions with complete regio selectivity. Therefore, though it is generally accepted that in 1,3 dipolar cycloaddition of nitrones to alkenes are single step concerted reaction but polarized dipolaro philes (e.g nitriles) may undergo concerted but not necessarily synchronous cycloadditions.

The present work entitled " Studies of 1,3 Dipolar cycloaddition Reactions with N- Cyclohexyl Nitrones " describes the theoritical study as well as a systematic investigation of 1,3 dipolar cycloaddition reactions of two different N-Cyclohexyl nitrones with a variety of alkenes and a few alkynes along with some interesting results of the nitrone - nitrile cycloaddition.

Chapter - I is an attempt to find out the existence and approximate stabilities of different N- cyclohexyl nitrones. Special emphasis has been given to theoritical HMO calculation for such nitrones to study the mechanistic course of 1,3 dipolar cycloaddition reactions.

Chapter - II deals with the chemistry of intra & inter molecular 1,3 dipolar cycloadditions of nitrones. Attempts have been made in this chapter to cover a complete review of the literature & the latest developements upto 1994 in a more comprehensive manner.

Chapter - III is the experimental section. In this section, cycloaddition reactions with different alkenes viz, normal, conjugated, moderately electron deficient and moderately electron rich along-with few alkynes and their reaction conditions are given.

Chapter - IV deals with the results and discussion, along with spectral interpretation viz, PMR and Mass.

Chapter - V deals with the further scope and objectives of the present work in brief.

Structures of all the products were assigned on the basis of PMR, Mass and IR Spectra's .

ACKNOWLEDGEMENT

The author would like to express his deep gratitude to his esteemed teacher Dr. A.R. Ghosh, Senior Lecturer, Dept. of Chemistry, Sikkim Govt. College. Through out the research work, author has received expert criticism, valuable comments and above all his best loving care.

The author is highly indebted to Dr. T.K. Das-Gupta, and Dr. G.S.S. Murthi, Dept. of Chemistry, University of North Bengal for constructive ideas. The author also acknowledges Prof. A. Brandi Universita Di Firenze, for valuable comments and Dr. D. Felix ETH, Zurich, for supplying an authentic Sample of N-Cyclohexyl hydroxyl amine hydrochloride and a few chemicals as gift.

Thanks are also due to Dr. C.B. Sunwar Principal, Sikkim Govt. College, for his enthusiastic support and constant co-operation. The author is highly indebted to Dr. P.S. Roy, former Head, and Dr. B. Basu Dept. of Chemistry, University of North Bengal and Dr. T.S. Basu of RSIC, North Eastern Hill University (NEHU) Shillong, for providing analytical facility.

The author is thankful to Mr. Partha Pratim Chakraborty, NIIT Siliguri, for typing the whole manuscript.

The author is equally thankful to Mr. A.K. Nanda, Mrs, S. Ghosh, Mr. B. Bhoumik, Mr. S.N. Tiwari, Mr. P. Saha and Mr. K. Chhetri for their help during the research work.

Thanks are also due to RSIC, C.D.R.I. (Lucknow), RSIC (NEHU), for providing IR; NMR; Mass Spectra's. The author is highly indebted to University Grants Commission, New-Delhi for financial support. The author is highly indebted to Dr. M. Murthi and all his teachers who taught him at different levels and also all his relatives, friends and well-wishers.

Finally, author would like to express his deep gratitude, to his beloved parents and dearest Rosy. Their affections ever encouraged the author for the entire research work.

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7. Published Paper entitled "1,3 Dipolar cycloaddition reactions of N- cyclohexyl nitrone."

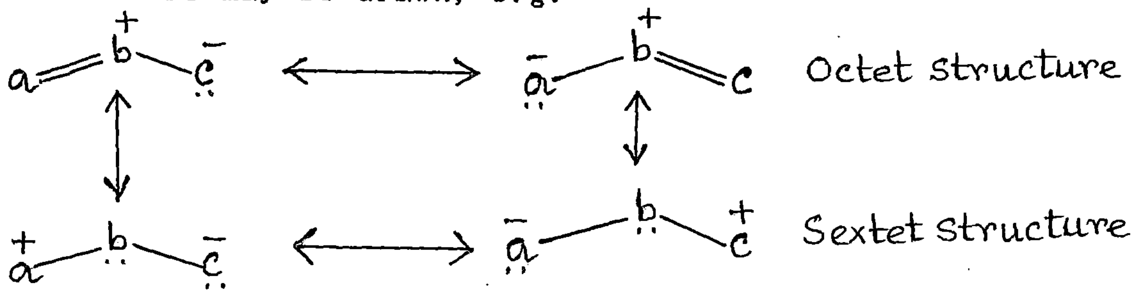
8. Paper on N- cyclohexyl chloro nitrone has been communicated in Indian Journal of Chemistry.

THEORETICAL APPROACH

1.General :

The " 1,3 dipole ", $\overset{+}{a} - b - \overset{-}{c}$, may be defined such that atom 'a' possesses an electron sextet, i.e. an incomplete valence shell combined with a formal positive charge and that atom 'c',the negatively charged centre, has an unshaired pair of electrons and which undergoes 1,3 dipolar cycloaddition to a multiple bond system, the 'dipolarophile '(1).

Since compounds with six electrons in the outer - shell of an atom are usually not stable, the a - b - c system is actually one canonical form of a resonance hybrid, for which at least one other structure may be drawn, e.g.



1,3 Dipoles can be further stabilized by internal octet stabilization.

1,3 Dipolar compounds can be devided into two main types :

(1) Propagyl - Allenyl Type :

Those in which the dipolar canonical form has a double bond on the sextet atom and the other canonical form a triple bond on that atom.

$\overset{+}{a} = b - \overset{-}{c}$ <--------------> $a \equiv \overset{+}{b} - \overset{-}{c}$

(2) Allyl Type :

Those in which the dipolar canonical form has a single bond on the sextet atom and the other form a double bond.

$\overset{+}{a} - b - \overset{-}{c}$ <-------------> $a = \overset{+}{b} - \overset{-}{c}$

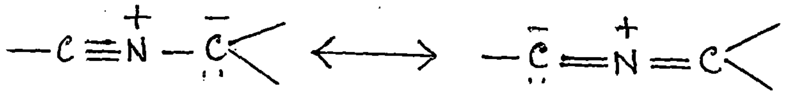
1,3 - Dipoles can be classified between two types viz, with double bond and without double bond and are represented in the **Table-I** .

In this 1,3 Dipoles the central atom is never a carbon atom. If the central atom be a carbon function then internal octet stabilization is prevented by lack of an available free electron pair. Such system are therefore extremely reactive and short lived. Example of this type are the unsaturated carbenes and azenes.

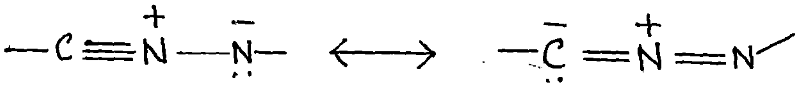
Table I

Classification of 1,3 Dipoles consisting of carbon, nitrogen and oxygen centres :

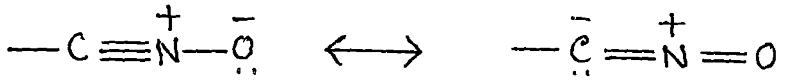
[A] Propagyl - Allenyl Type :



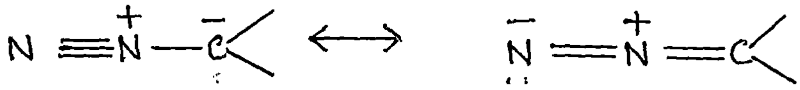
Nitrile Ylides.



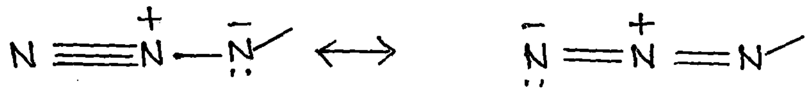
Nitrile Imines.



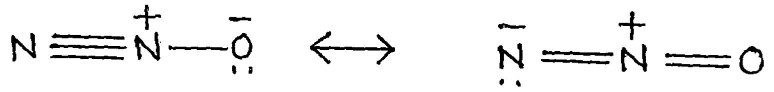
Nitrile Oxides.



Diazo alkanes

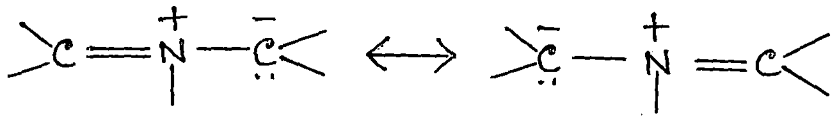


Azides.

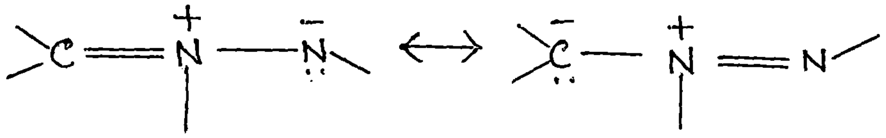


Nitrous Oxide.

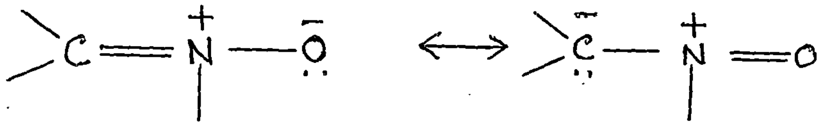
[B] Allyl Type :



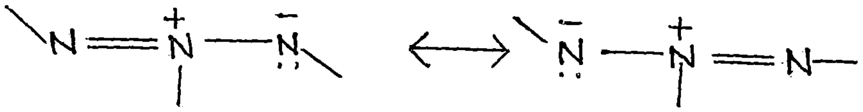
Azomethine Ylides.



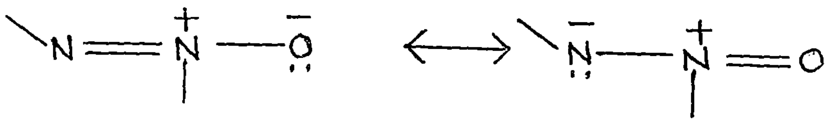
Azomethine Imines.



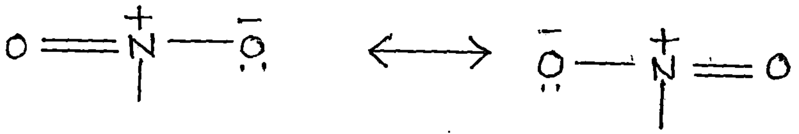
Nitrones.



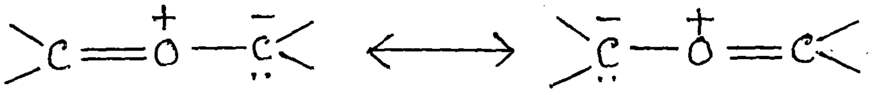
Azimines.



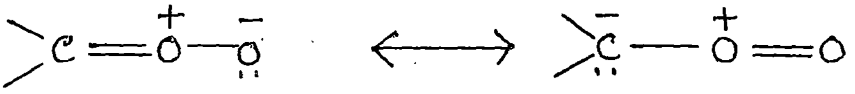
Azoxy Compounds.



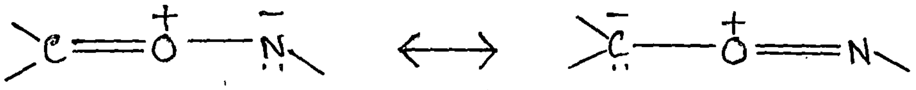
Nitro Compounds.



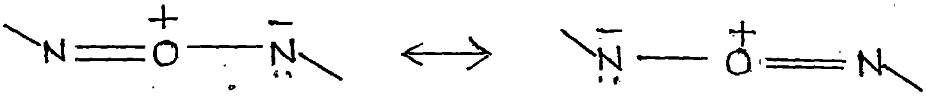
Carbonyl Ylides.



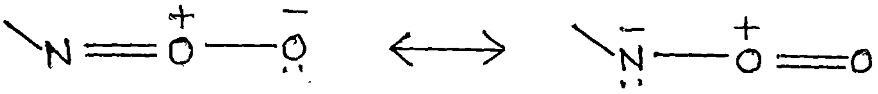
Carbonyl Oxides.



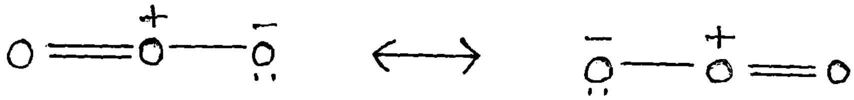
Carbonyl Imines.



Nitrosoimines.

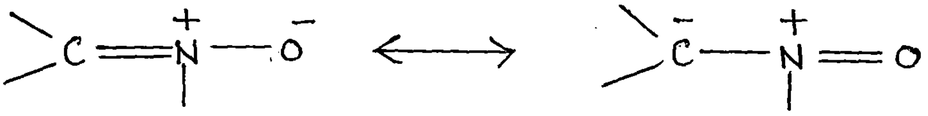


Nitrosoxides.

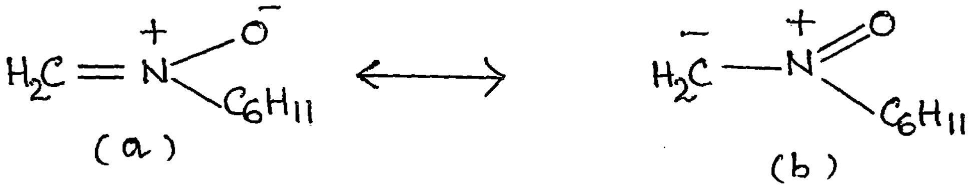


Ozone.

In allyl type of 1,3 dipole, if one restricts the atom a, b and c to carbon, nitrogen and oxygen, results Nitrone.



In order to verify the energies associated with the two canonical forms, N- cyclohexyl methylene - nitrone was taken as an ideal example (2). Approximate qualitative information of the non - uniform distribution of electronic charge of the nitrone could be obtained by applying the HMO method. The canonical forms of the nitrone are :



In 1971, Sustmann classified 1,3 dipoles into 3 main types (23). This classification was based on perturbation treatments of cycloaddition reactivity described earlier by Fukui (29), Salem (30), and Herndon (31) and also described generally by several authors (32).

According to this theory, the intermolecular interactions that occur in the transition state of a cycloaddition are divided into destabilizing closed shell- replusions, stabilizing or destabilizing coulombic interactions and stabilizing charge - transfer interactions. The charge transfer stabilization arises from the overlaps of filled orbitals on one molecule with vacant orbitals on the other.

Sustmann showed the reactivity trends expected for various relative energies of the frontier orbitals (23) starting from the case where both 1,3 dipole and dipolarophile have similar frontier orbital energies (Fig. F)

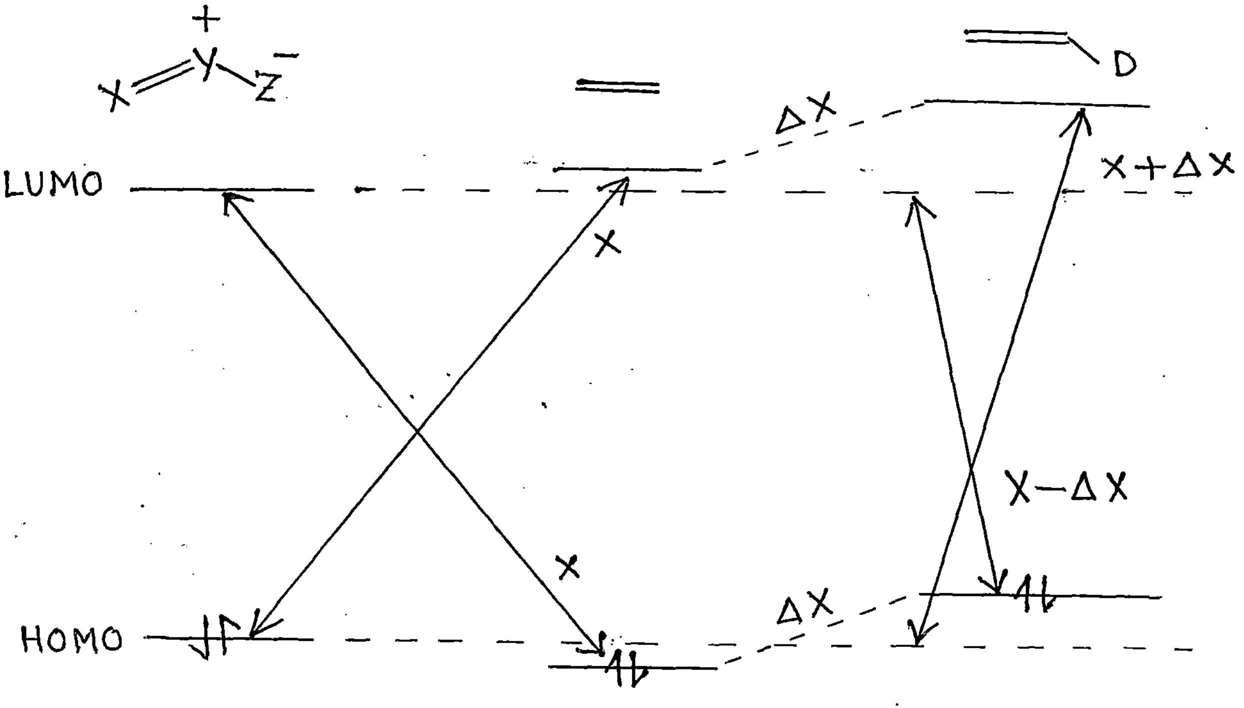


Fig. F.

Pattern of frontier molecular orbitals for a type II (ambiphilic) 1,3 dipole demonstrating the sustmann approximation.

Our one of the nitrones i.e. N- cyclohexyl 5- hydroxy - nitrone (245) belongs to type II i.e. ambiphilic in nature and the nature of frontier molecular orbitals are same as shown in the Fig. F.

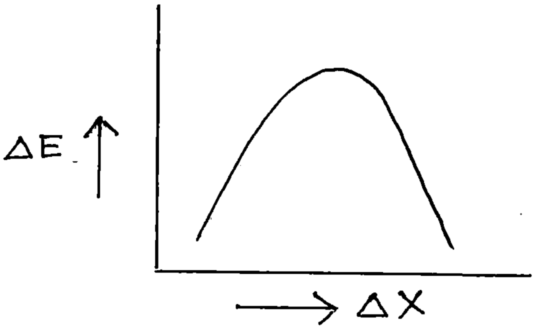
Sustmann made the following approximations in order to facilitate the analysis of interactions between the HOMO of the dipole and the LUMO of the dipolaro phile. For ambiphillic 1,3 dipole, both frontier energy gaps are assumed to be equal with a value X with these assumptions, the stabilization becomes,

$$\Delta E_{\text{frontier}} \cong \frac{1}{X} + \frac{1}{X}$$

When the dipolaro phile is substituted, the HOMO and LUMO of this species are assumed to change by an equal amount, ΔX. This decreases one frontier orbital gap to $X - \Delta X$, and increases the other to $X + \Delta X$, as indicated for a donar - substituted alkene in Fig. F. The new Stabilization energy is :

$$\Delta E'_{frontier} \cong \frac{1}{X-\Delta X} + \frac{1}{X+\Delta X}$$

The term $\frac{1}{X-\Delta X}$ increases faster than $\frac{1}{X+\Delta X}$ decreases and if ΔE is plotted versus ΔX, a parabola results.



Type I dipoles are those that have relatively high lying HOMO's and LUMO's . An increase in the narrowest frontier molecular orbital gap will decelerate the reaction. This is termed as HOMO controlled or neocleophilic 1,3 dipoles.

Finally a type III , LUMO - controlled or electrophilic 1,3 dipole is one with low - lying frontier molecular orbitals. Electron donars on the dipolaro- phile accelerate reaction, whereas acceptors slow the reaction. These are indicated schematically in Fig. G.

Type of 1,3 - Dipole.

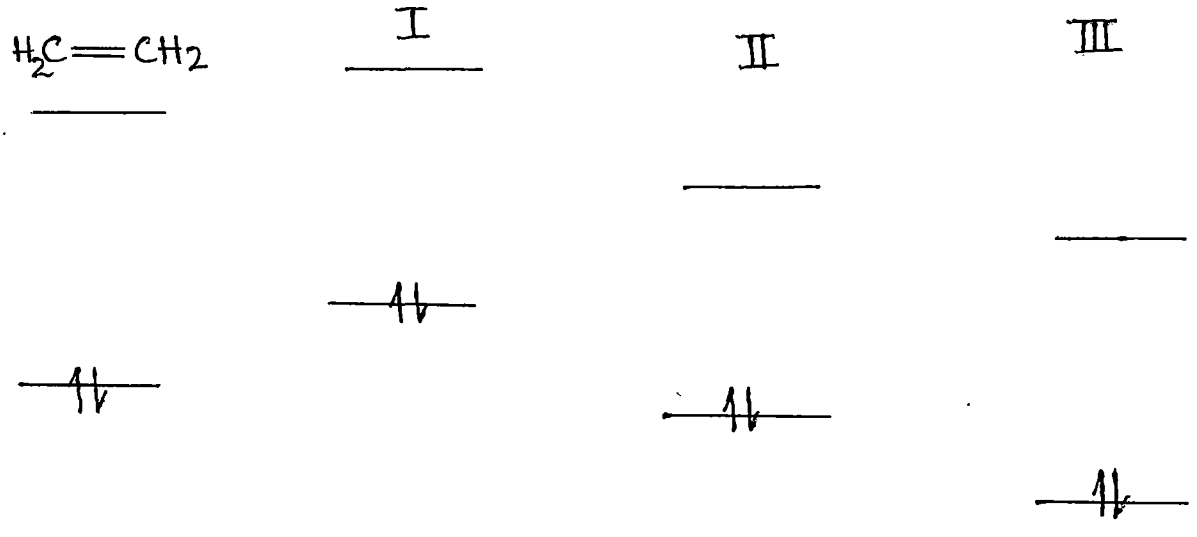


Fig G.

Types I,II,III, dipoles are also known as HOMO, HOMO - LUMO and LUMO controlled 1,3 dipoles or nucleophilic, ambiphilic and electrophilic 1,3 dipoles.

Our second nitrone, N- cyclohexyl chloro nitrone belongs to the type III i.e. LUMO controlled 1,3 dipoles or electrophilic 1,3 dipoles. In these type of nitrones the frontier molecular orbitals are placed low lying compared to the type I & II in the energy level diagram as shown in Fig. G.

Effect of Substituents on the dipolarophiles

According to Sustmann (22), electron attracting substituents on the dipolaro philes will lower both the Ψ_A and Ψ_B in energy Fig. I. Therefore the interaction leading to Ψ_2 will become stronger, resulting in a stabilization of the transition state. Although Ψ_B and Φ_A will now interact less strongly this effect will be smaller owing to the higher difference in orbital energy already present in the molecule. As a result, the LUMO - ethylene - HOMO - allyl anion interaction will exist. Experimentally an increase in reactivity due to electron attracting substituents for most 1,3 dipolar cycloadditions, for instance with nitrile imines (33), azides (9) and sydnones (34).

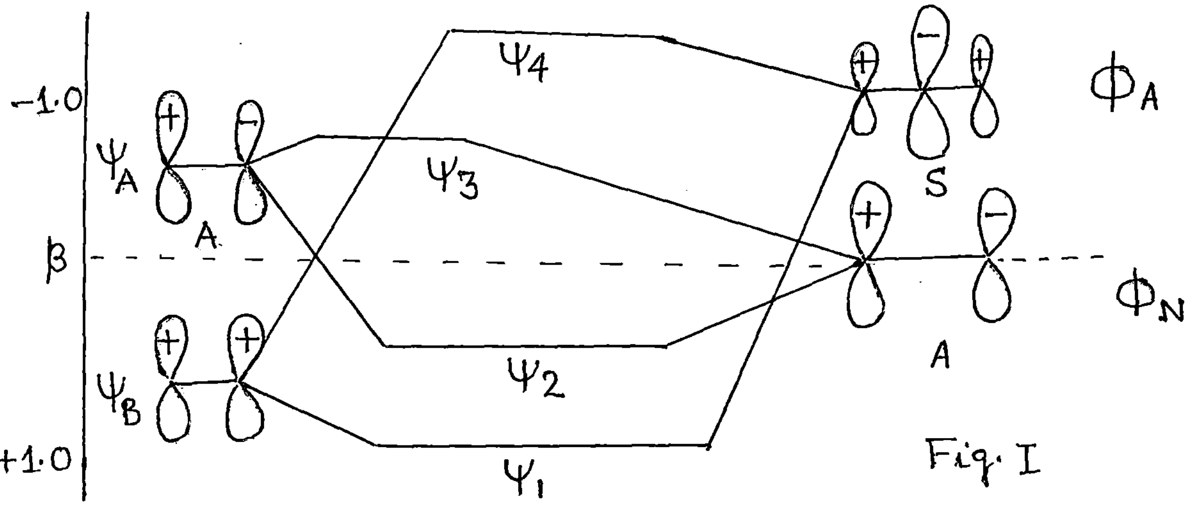


Fig. I

On the other hand electron relaeasing substituents on the dipolaro phile will raise the energy of Ψ_B and Ψ_A . As a consequence Ψ_A and Φ_B will show smaller and Ψ_B and Φ_A stronger interaction.

Approximate HMO calculation of the structure (a)

The secular determinant could be set up using the suggested parameter values (3) for hetero atoms for use with simple LCAO treatment, viz, $h_{N^+} = 2$; $h_{O^-} = 2$; $K_{C-N} = 1.1$; $K_{N-O} = 0.7$ etc.

$$\begin{vmatrix} \alpha_0 - \epsilon & \beta_{12} & \beta_{13} \\ \beta_{21} & \alpha_0 - h_N + \beta_0 - \epsilon & \beta_{23} \\ \beta_{31} & \beta_{32} & \alpha_0 + h_0 - \beta_0 - \epsilon \end{vmatrix} = 0$$

putting the above values and $X = \alpha_0 - \epsilon/\beta_0$

$$\begin{vmatrix} X & 1.1 & 0 \\ 1.1 & X+2 & 0.7 \\ 0 & 0.7 & X+2 \end{vmatrix} = 0$$

The secular polynomial of the system was :

$$X^3 + 4X^2 + 2.3X - 2.4 = 0$$

i.e. $X = 0.5175, -1.58775,$ and -2.9297

Therefore the energy levels are :

$$\epsilon_1 = \alpha_0 + 0 \cdot 5175 \beta_0$$
$$\epsilon_2 = \alpha_0 - 1 \cdot 58775 \beta_0$$
$$\epsilon_3 = \alpha_0 - 2 \cdot 9297 \beta_0$$

And the total π - energy of the system [a] was $E_\pi = 4\alpha_0 + 5 \cdot 03495 \beta_0$

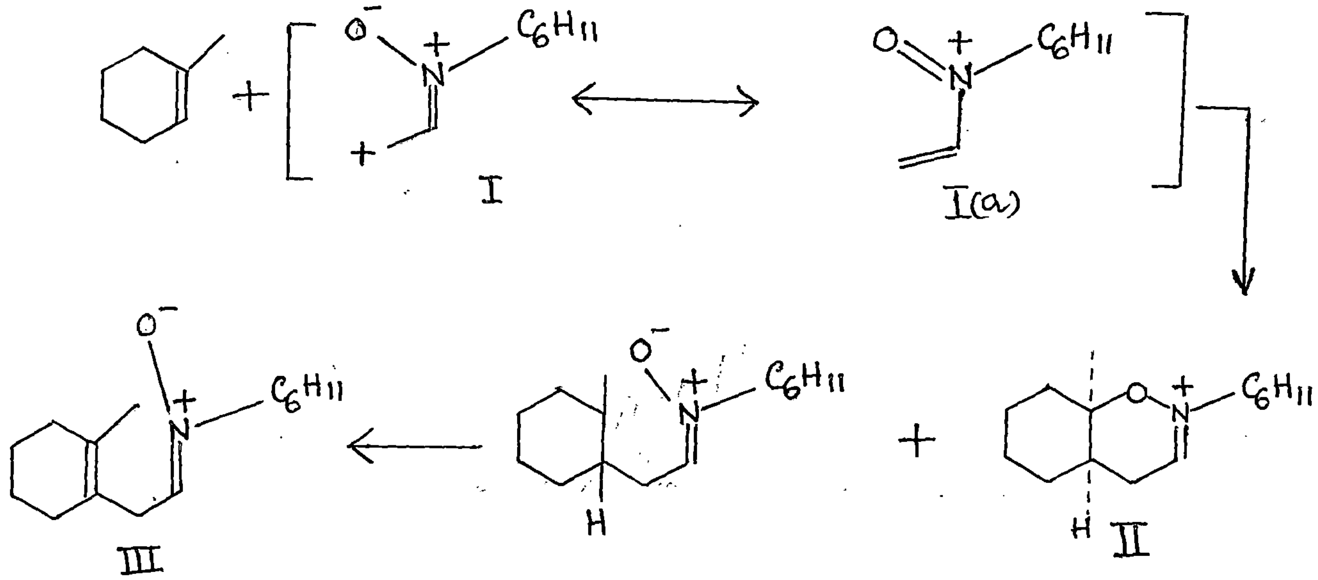
Similar treatment on the system [b] gave the following values.

$$\epsilon_1 = \alpha_0 + 3 \cdot 035 \beta_0$$
$$\epsilon_2 = \alpha_0 - 0 \cdot 3304 \beta_0$$
$$\epsilon_3 = \alpha_0 - 1 \cdot 295 \beta_0 .$$

The total π - energy of the system [b] was $E_\pi = 4\alpha_0 + 4{\cdot}6604\beta_0$

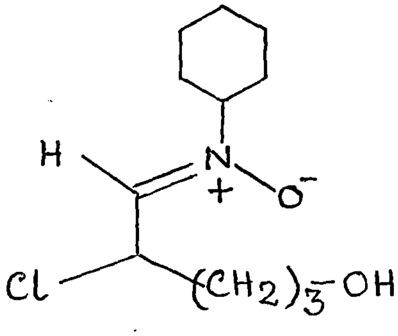
From the calculated result, it is evident that the canonical form [a] is more stable and favourable on energy ground and this is also in agreement with the existing principle.

Eschenmoser et al (4) has shown that, a certain cation and only a cation can be formed α to the nitrone group. The reaction between unsymmetrically substituted olefins and vinyl nitrosonium cation (I <--> Ia) produces not only cycloadduct but also a substitution product (III) (5).



On the basis of qualitative Molecular Orbital (MO) theory, the formation of vinyl nitrosonium ion is quite logical, it is butadiene like 4 - centered - 4 - electron π - system having both bonding MO'S are filled and the antibonding MO'S are vacant and acts as a diene component in the hetero Diels - Alder reaction with olefins (4π + 2π - cycloaddition).

In order to verify the stability of such type of nitrones, N - cyclohexyl chloro - nitrone (IV) was taken as example for approximate HMO calculation.



(IV)

The Secular determinant for nitrone (IV) could be studied in two ways, viz. C & D :

(C) :

$$\begin{vmatrix} \alpha_0+2\beta_0-\epsilon & \beta_{12} & \beta_{13} & \beta_{14} \\ \beta_{21} & \alpha_0-\epsilon & \beta_{23} & \beta_{24} \\ \beta_{31} & \beta_{32} & \alpha_0+2\beta_0-\epsilon & \beta_{34} \\ \beta_{41} & \beta_{42} & \beta_{43} & \alpha_0+2\beta_0-\epsilon \end{vmatrix} = 0$$

$$\begin{vmatrix} x+2 & 0.4 & 0 & 0 \\ 0.4 & x & 1.1 & 0 \\ 0 & 1.1 & x+2 & 0.69 \\ 0 & 0 & 0.69 & x+2 \end{vmatrix} = 0$$

Thus solving X = 0.578 ; -1.5607 ; -2.9436 ; -2.0656 .

The energy levels were :

$$\epsilon_1 = \alpha_0 - 0.578\,\beta_0$$
$$\epsilon_2 = \alpha_0 + 1.5607\,\beta_0$$
$$\epsilon_3 = \alpha_0 + 2.9436\,\beta_0$$
$$\epsilon_4 = \alpha_0 + 2.0656\,\beta_0$$

The total π energy of the system was = $4\alpha_0 + 7.1479\,\beta_0$

(D) :

$$\begin{vmatrix} \alpha_0+2\beta_0-\epsilon & \beta_{12} & \beta_{13} & \beta_{14} & \beta_{15} \\ \beta_{21} & \alpha_0-\epsilon & \beta_{23} & \beta_{24} & \beta_{25} \\ \beta_{31} & \beta_{32} & \alpha_0+2\beta_0-\epsilon & \beta_{34} & \beta_{35} \\ \beta_{41} & \beta_{42} & \beta_{43} & \alpha_0+2\beta_0-\epsilon & \beta_{45} \\ \beta_{51} & \beta_{52} & \beta_{53} & \beta_{54} & \alpha_0+2\beta_0-\epsilon \end{vmatrix} = 0$$

$$\begin{vmatrix} x+2 & 0{\cdot}4 & 0 & 0 & 0 \\ 0{\cdot}4 & x & 0{\cdot}9 & 0 & 0 \\ 0 & 0{\cdot}9 & x & 1{\cdot}1 & 0 \\ 0 & 0 & 1{\cdot}1 & x+2 & 0{\cdot}69 \\ 0 & 0 & 0 & 0{\cdot}69 & x+2 \end{vmatrix} = 0$$

Solving ; X = 1.129; X = =1.20; X = -.555; X = -2.954;
X = - 2.4195 .

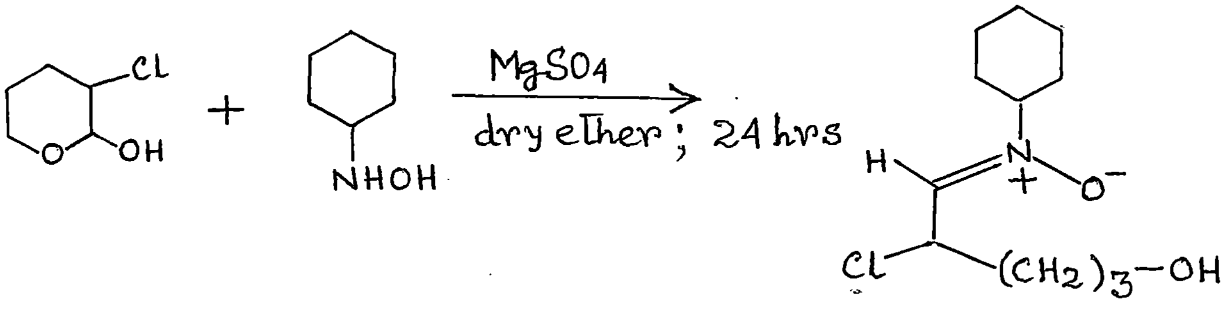
The energy levels were :

$$\epsilon_1 = \alpha_0 - 1{\cdot}129\beta_0$$
$$\epsilon_2 = \alpha_0 + 1{\cdot}20\beta_0$$
$$\epsilon_3 = \alpha_0 + 0{\cdot}555\beta_0$$
$$\epsilon_4 = \alpha_0 + 2{\cdot}954\beta_0$$
$$\epsilon_5 = \alpha_0 + 2{\cdot}4195\beta_0$$

Total π - energy of the system was = $5\alpha_0 + 8{\cdot}2575\beta_0$.

Considering the calculated energy levels associated with nitrone (IV) it was expected to be unstable.

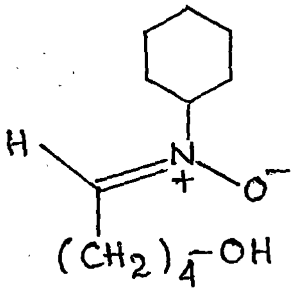
Keeping in mind the nitrone was synthesised from chlorohydrin (240)and N-cyclohexyl hydroxyl amine and was quickly chromatographed with Al_2O_3 . Nitrone was highly hygroscopic in nature.



The above assusmption could also be rationalised on the basis on the Fukui's Frontier Orbital Theory. The Sustman classification of 1,3 dipoles (details discussed in this chapter already) strictly holds only for the parent species, could be adapted qualitatively to substituted 1,3 dipole as well. Electron donar gr in 1,3 dipole shifts the 1,3 dipolar character towards the type - I i.e. HOMO controlled or nucleophilic 1,3 dipole. Where as an electron acceptor shift the behavior towards type-III i.e. electrophilic character.

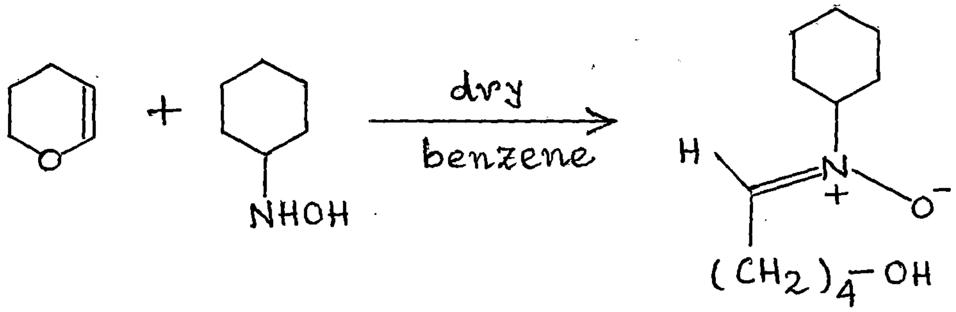
N - cyclohexyl chloro nitrone has a chlorine group at the β position of the nitrone which has a strong electron with drawing nature. Therefore, this nitrone should be electrophilic in character. In general nitrones are HOMO - LUMO controlled 1,3 dipoles skewing towards LUMO - controlled side. The high reactivity of N - cyclohexyl chloro nitrone could also be explained on the basis of Perturbation Theory (6), where in the HOMO level of a parent nitrone is raised in energy by the introduction of an chlorine group on the β - carbon atom and the corresponding LUMO level of the nitrone is stabilized. Thus the stabilization of the dipole LUMO level, thereby providing relative stabilization to the transition state for the cycloaddition and consequently increasing the rate of reaction.

On the other hand, N- cyclohexyl 5- hydroxy nitrone (V) do not have any withdrawl or electron donar group and therefore this nitrone is more or less neutral in character.



(V)

Keeping in mind N- cyclohexyl 5-hydroxy nitrone (245) was synthesised directly by refluxing Dihydropyran and N - cyclohexyl hydroxyl amine in dry benzene for 24 hours.



2. 1,3 Dipolar Cycloaddition

Houk et al (18) pointed out that mechanistic investigations have shown that cycloadditions of 1,3 dipole to alkenes are stereo specifically suprafacial; solvent polarity has little effect on reaction rates, and small activation enthalpies and large negative entropies are generally found. These facts, along with reactivity and regio selectivity phenomenon, have been considered totally compatible only with a concerted five centre mechanism. Orbital symmetry consideration have provided permissive, though not obligatory, theoretical evidence for the concerted mechanism and the observation of ($4\pi s + 6\pi s$) cycloaddition but not ($4\pi s + 4\pi s$) cycloaddition of 1,3 dipoles to triene has provided further evidence for the concerted mechanism (19,20). But the experimentally observed regio selectivity of most 1,3 dipolar cycloadditions has been the most difficult phenomenon to explain.

Houk et al. solved this vexing problem with the use of generalised frontier orbitals of 1,3 dipoles and dipolarophiles within the frame work of qualitative Perturbation Molecular Orbital Theory .

Qualitative orbital energies and co efficients are of great importance here. For this purpose frontier orbitals of representative alkenes are shown in Table - II and Table - III. In each fig. (-ve) of the ionisation potential (IP) of alkene is given under the horizontal line for the HOMO (Highest Occupied Molecular Orbital) and the (-ve) of the electron affinity is given under LUMO (Lowest Unoccupied Molecular Orbital) level. The units are electron volt (ev) . The AO (Atomic Orbital) co efficients for the frontier MO'S are also given. For the electron rich alkenes (Table - II), the trend of decreasing HOMO - co efficients as the IP decreases results from the greater admixture of substituent orbitals with the ethylene π - orbitals as the group becomes a better donar. The conjugated alkene (Table - III) raise HOMO'S and lower LUMO'S as compared to ethylene. Frontier MO'S of some 1,3 dipoles (Table IV) show relatively small gap in their HOMO - LUMO levels and therefore their reactivity are quite high. Hauk et al. further proposed that bending of either terminus can reverse these generalisations (21).

Now whether an 1,3 dipolar cycloaddition to be allowed or forbidden may be judged according to the symmetry properties of the HOMO and LUMO orbitals of the dienes and dipolarophiles as proposed in Woodward - Hoffman rule (17). And the allowed process can be of three types as proposed by Sustman (Fig. - C) (22,23). The type - I involves dominent interaction between HOMO (dipole) and LUMO (dipolarophile). Type - III involves LUMO (dipole)-HOMO (dipolarophile) .

Table - II

The frontier MO'S of electron rich alkenes.

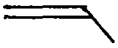
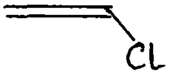
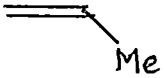
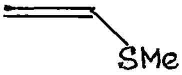
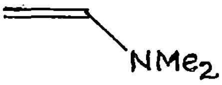
						
LUMO	·71, −·71 +1·5	·67, −·54 ~ +5	·67, −·65 +1·8	·66 − ·72 +2·0	·63, −·48 −1·0	·62, −·69 2·5
HOMO	·71, ·71 −10·52	·44, ·30 −10·15	·67, ·56 −9·88	·61, ·39 −9·05	·34, ·17 −8·45	·50, ·20 −8·0

Table - III

The frontier MO'S of electron - deficient and conjugated alkenes.

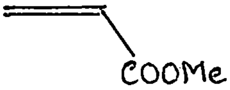
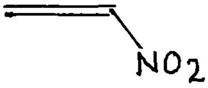
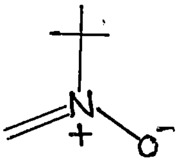
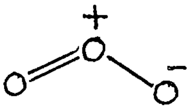
					
LUMO	·69, −·47 ~0·0	·66, −·54 ~0·0	·54, −·32 ~ −0·7	·56, −·42 1·0	·48, −·35 +0·8
HOMO	·43, ·33 −10·72	·60, ·49 −10·92	·62, ·60 ~ −11·4	·57, ·41 −9·03	·49, ·32 −8·48

Table - IV

The frontier MO'S of 1,3 dipoles :

	$N\equiv\overset{+}{N}-\overset{-}{C}H_2$	$H-C\equiv\overset{+}{N}-\overset{-}{O}$		
LUMO	·50, −·70, −·51 ~ +·2	·68, −·67, −·30 ~0	·58, −·67, ·41 −·5	·53, −·67, ·53 −2
HOMO	·61, −·13, ·78 −8·99	·56, ·21, −·80 −10·5	·69, ·15, −·70 −8·64	·71, 0, ·71 −13·02

But in type-II both the LUMO (dipole) - HOMO (dipolarophile) and the HOMO (dipole) - LUMO (dipolarophile) are important in determining reactivity and regio-chemistry.

Type - I dipoles are those having high lying HOMO'S and LUMO'S and referred as HOMO controlled or nucleophilic 1,3 dipoles. Type III are having low lying FMO'S and referred as LUMO controlled or electrophilic dipoles. The type-II, 1,3 dipoles are referred as HOMO - LUMO controlled dipoles.

Houk et al (24) have treated all common 1,3 dipoles, according to this simple model and have shown that the prediction nicely explains the experimental results.

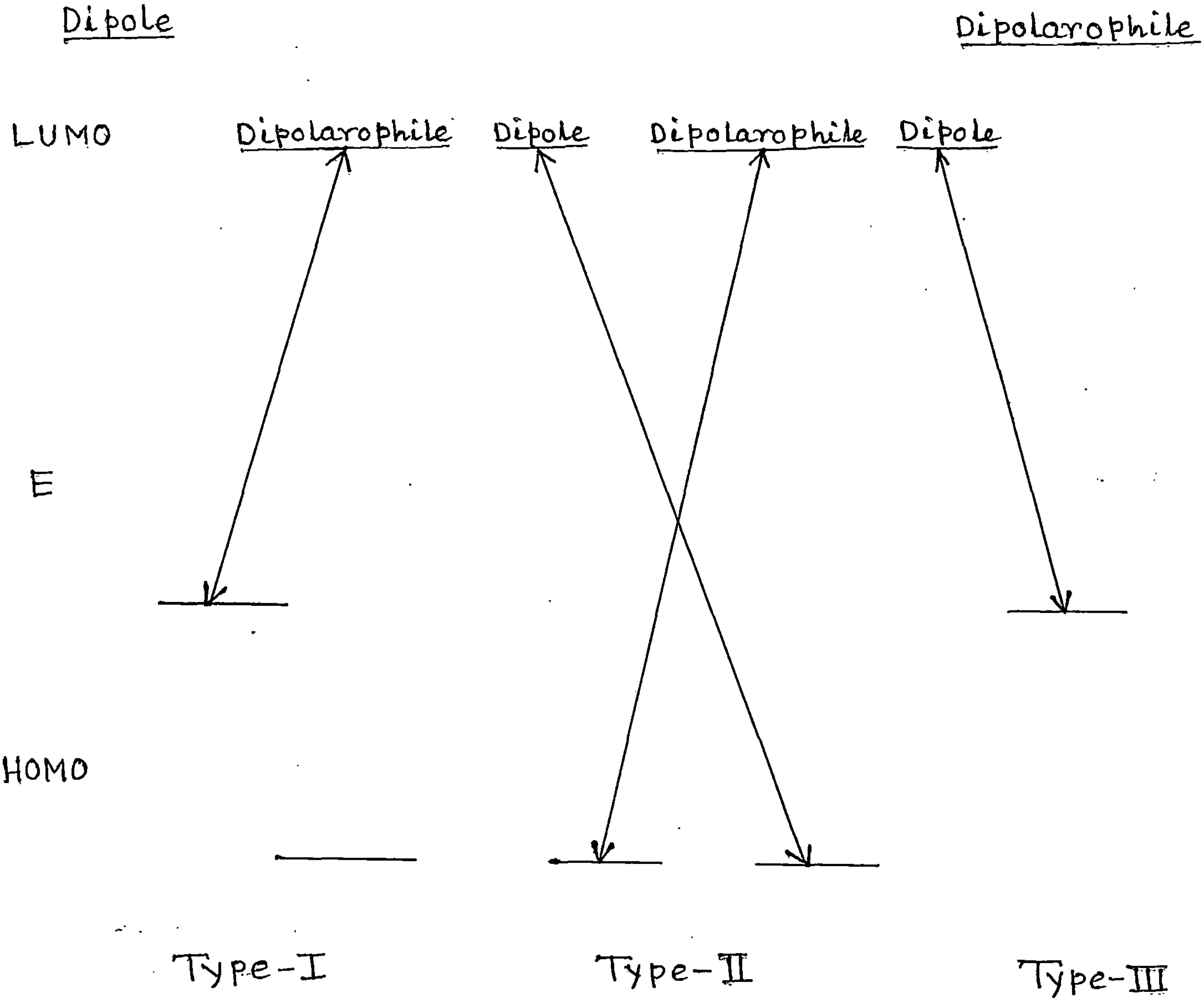


Fig-C.

The nitrile ylides, diazoalkanes and azomethine ylides are HOMO controlled 1,3 dipoles, reacting fastest with alkenes having one or more electron withdrawing substituents. The nitrile imines, azides and azomethine imines are HOMO - LUMO controlled dipoles react rapidly with both electrone rich and electron deficient dipolarophiles. The nitrile oxides and nitrones are also HOMO - LUMO controlled dipoles but these species are skewed toward the LUMO controlled side. Finally species with several electronegative atoms are LUMO controlled 1,3 dipoles, e.g. nitrous oxide, ozone.

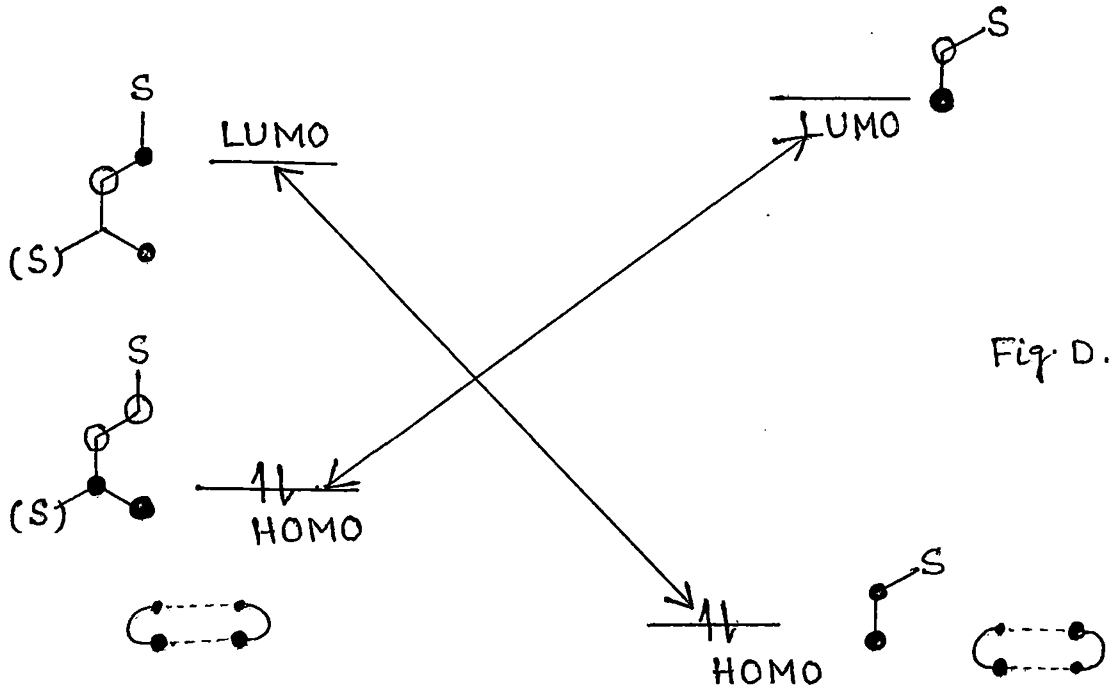


Fig. D.

$\Delta E \propto L^2+S^2$ is better than $\Delta E \propto 2LS$; L and S are larger and smaller co efficient at the concerning c - atom respectively.

Nicety of Houk's model lies specially in its general applicability in the problem of regio selection. Fig. D summerises the frontier MO'S of monosubstituted alkenes and 1 & 2 substituted dienes. In the case of a donar or conjugatively substituted diene, the acceptor substituent at the 1 - position of a diene or alkene will enlarge the co efficenent at the most remote position in the LUMO. In the case of donar diene and acceptor alkene, the diene HOMO - dienophile LUMO interaction state involves bond formation leading to the 'ortho' or (Z) adduct. This is because the stabilization energy will be larger when the larger terminal co efficients and the smaller terminal coefficient of the two interacting orbitals overlap, which gives a larger net overlap, and thus larger transition state stabilization, than it a large co efficient on one orbital interacts with a small on the second at both bond forming centre.

Calculation on all of the common parent and a number of substituent 1,3 dipoles have lead to the generalization about the frontier orbitals of 1,3 dipoles (Fig. E) .

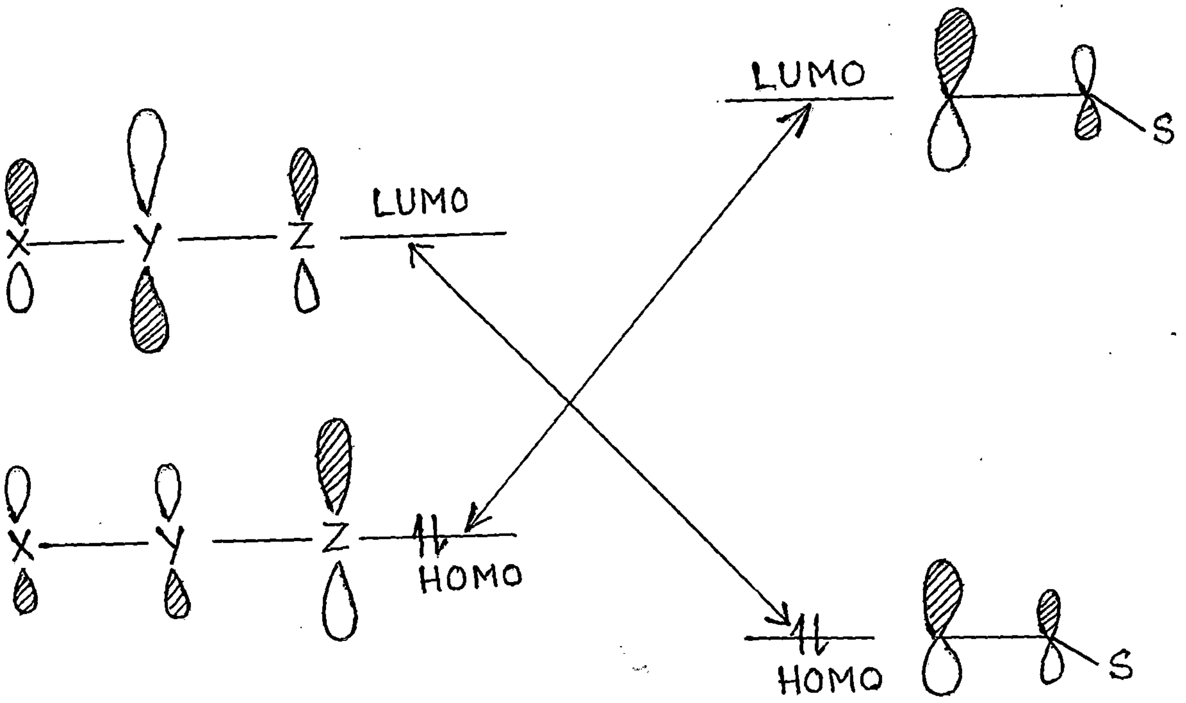


Fig. E

The HOMO'S of the 1,3 dipolar system generally have the larger terminal co-efficient on the group 'Z', while the LUMO'S have the larger co efficient at the opposite terminus 'X'. The HOMO'S and LUMO'S of the 1,3 dipoles are qualitatively similar to those of an allyl anion but are distorted in unsymmetrical systems. The greater differences in terminal co efficients occur when two termini differ greatly in electronegativity.

The interaction of the dipole LUMO with dipolarophile HOMO favours the formation of the product with the substituent on carbon adjacent to 'Z' , while the opposite frontier orbital interaction favours the opposite regioisomer.

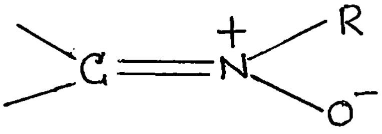
Nitrile oxides and nitrones react to give mainly the 5 - substituted adduct with weakly electron deficient alkenes such as acrylonitrile and acrylates. The HOMO'S and LUMO'S of these electron deficient alkenes both interact fairly strongly with the LUMO'S and HOMO'S of the nitrile oxides of nitrones, so that orientation is influenced by both the interactions. The experimental results show that the dipole LUMO-dipolarophile HOMO interaction has more influence on regio selectivity. Houk et al. has studied a number of such reactions with different nitrones (25, 26, 27) and has shown that all of them are in accordance to the predicted results.

From the plots of rates versus IP of dipolarophiles Huisgen observed that acetylenic dipolaro philies are less reactive than expected on the basis of their IP'S (28). Since alkynes have larger HOMO - LUMO gap than the analogues alkenes, one would expect that in reactions where interaction with the alkyne LUMO is of most important, the alkyne will be less reactive than expected. The actual fact is that though the reactivity of nitrones with both electron deficient alkenes and alkynes are determined by the HOMO dipole - LUMO dipolarophile interaction, the regio chemistry in the former case is still controlled by the LUMO (dipole)-HOMO (dipolarophile) interaction. Therefore, in the case of alkyne, the dipole HOMO - dipolarophile LUMO interaction becomes so such more important than the dipolarophile HOMO-dipole LUMO interaction, that the former completely dominates the reaction and leads to the formation of only the 4 - substituted adducts.

CHAPTER II
CHEMISTRY OF NITRONE

1. INTRODUCTION:

The term 'nitrone' was coined from nitrogen ketone (azomethine oxide) in order to keep its resemblence to the carbonyl group in its several reactions (35).



2. NOMENCLATURE :

The nitrones were known since 1887. The nomenclature employed by chemical abstract is as follows.

α, N diphenyl nitrone.

α - phenyl - α - (p-tolyl) - N - methyl nitrone.

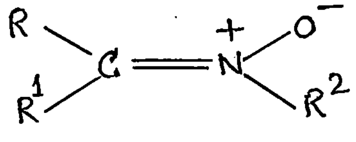
The cyclic nitrones are named according to the parent-heterocyclic structure, e.g. 2,4 dimethyl - Δ^1 - pyrolidine N - oxide; Δ^1 - tetra hydropyridine N - oxide etc. Of late nitrones have also been named as C - cyclopropyl N - methyl nitrone, C,C dicyclopropyl - N - methyl nitrone etc.

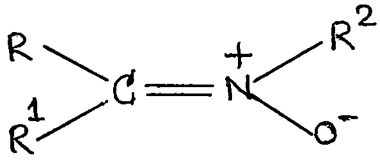
The general terms, aldonitrones and Keto nitrones have been employed occasionaly. Aldonitrones - contain a proton on the α - carbon atom, $RCH = \overset{+}{N}(O)R^1$. While in Keto nitrones contain the α - carbon fully substituted with alkyl and or aryl groups.

$$R\,R'^{1}\,C = \overset{+}{N}\,(\overset{-}{O})\,R^{2}$$

3. GEOMETRICAL ISOMERISM :

Nitrones may exhibit geometrical isomerism because of the double bond in the nitrone moiety.





The existence of geometrical isomerism was first demonostrated in 1918 for α -phenyl α (p-tolyl) - N - methyl nitrone (36). The configuration of the isomers were established by dipole-moment studies (35). The cis - forms of some nitrones were converted readily into the trans-form by heating (37). Generally, aldonitrones exist in stable trans-forms and this has been established by UV, IR and PMR Studies (38). The only example of geometrical isomerism is known for α - phenyl - N - t-butyl nitrone (39). Therefore in such cases, where geometrical isomerism are possible, E-Z notation may be employed in naming.

4. Synthesis of Nitrones

The chemistry and synthesis of nitrones were reviewed (35,40, 41). The general methods of synthesis of nitrones are briefly discussed here.

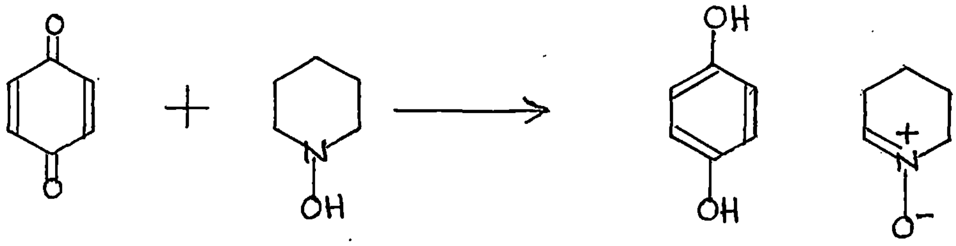
(A)

By the oxidation of N, N- Disubstituted Hydroxyl amine :

$$R - N(OH) - CHR^{1}R^{2} \text{-------}> R - \overset{+}{N}(\overset{-}{O}) = CR^{1}R^{2}$$

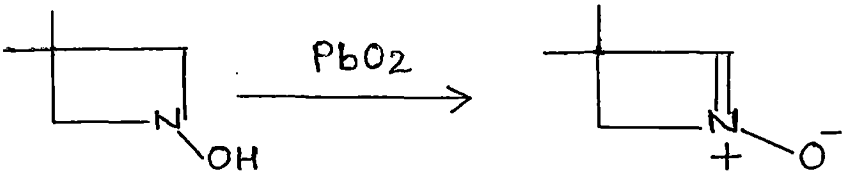
Both cyclic and acyclic nitrones were prepared by this method. Different oxidizing agents were used, e.g. molecular oxygen (42-46) , yellow mercuric oxide (38, 47-49), active lead oxide (50), pottasium ferricyanide (43,47,49,51), hydrogen peroxide (52,53), pottasium permanganate (53), t-butyl hydroperoxide, (54) diamine Silver nitrate (43), etc.

The formation of a nitrone Salt was reported from the reaction between p-benzoquinone and 1-hydroxy piperidine (55) .



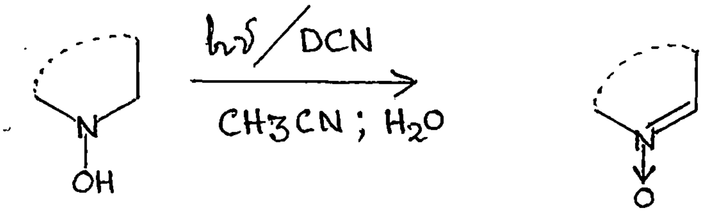
Formation of nitrone from N, N disubstituted and N-Substituted hydroxyl amines using Palladium Catalyst were also reported (56).

Recently 4 membered cyclic nitrones were also reported by the oxidation of 1 - OH - azetidines with PbO_2(57)



Some other oxydative methods were also known, e.g. diamino silvernitrate was used as the reagent for the preparation of α - Styryl α -benzyl-N-phenyl nitrone from the corresponding hydroxyl amine (43).

Photolysis of N - hydroxylamines in presence of 1,4 di cyano napthalene (DCN) as an electron acceptor gave high yields of nitrones (58) .



(B) __From Oximes :__

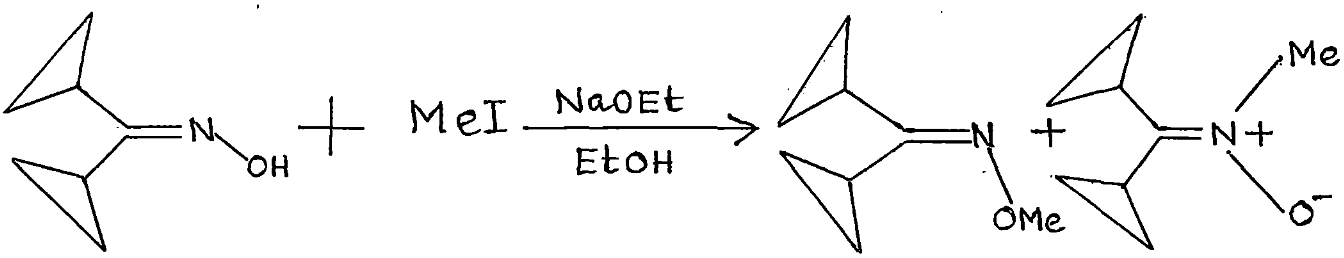
The alkylation of oximes were reviewed in 1938 (35). A disadvantage of the method was that, nitrone were produced along with oxime ether.

$$R^1R^2C = N - OH + XR \text{-------}> R^1R^2C = NOR + R^1R^2C = \overset{+}{N}(\overset{-}{O})R$$

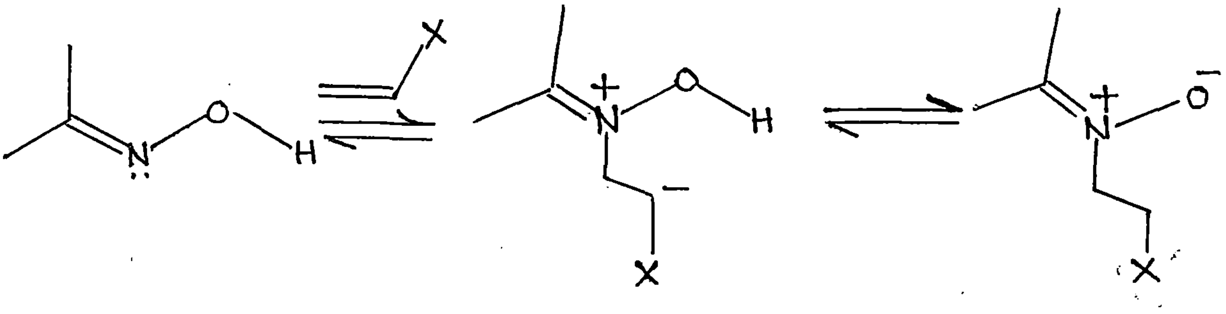
Li, Na, K or tetramethyl ammonium oxime Salts did not alter the products ratio of oxime ether to nitrone significantly. Electron withdrawing group in p ,p′ disubstituted benzophenone oxime Salts markedly promoted the formation of nitrones, while electron donating group favours oxime-ether formation. A pronounced steric effect was observed by comparing the reaction between benzophenone oxime Sodium Salt with methyl bromide or benzyl bromide. The smaller size of the alkylating reagent favours nitrone formation - whereas larger size favours oxime - ether formation.

Heptanol oxime when treated with benzyl chloride in solution of ethanol and Sodium ethoxide yielded 77 % of α - hexyl - N - benzyl nitrone (59). Dimethyl Sulfonate was employed in the alkylation of various Keto-oxime (60,61) .

C , C dicyclopropyl N - methyl nitrone has been prepared by this method (25) .

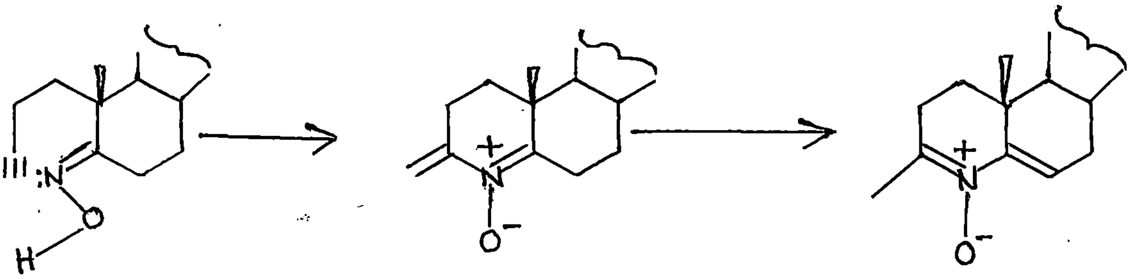


Formation of nitrones were also reported by the intra molecular Michael addition of aldoximes and Ketoximes to electronegative olefines (62).



Recently oxime -O -allyl ethers were converted to the corresponding N - allyl nitrones on treatment with 10 mole % Pd $Cl_2(Me\ CN)_2$ by a formal [2,3] sigmatropic shift (63).

Formation of cyclic N- vinyl nitrones were also reported from δ - alkynyl oximes by a concerted $2n + 2\pi + 2\delta$ 1,3 azaprotio cyclotransfer (APT) reaction (64).



O-trimethyl silyl oximes converted to nitrones conveniently by N -alkylation (65).

$$Ph\,CH = N\,(\,O\,)\,Si\,Me_3 \xrightarrow{\text{Me-triflate}} PhCH = \overset{+}{N}\,(\,\overset{-}{O}\,)\,Me$$

α - Nitroso - nitrones have been prepared from nitrile oxide and nitroso-arene (66).

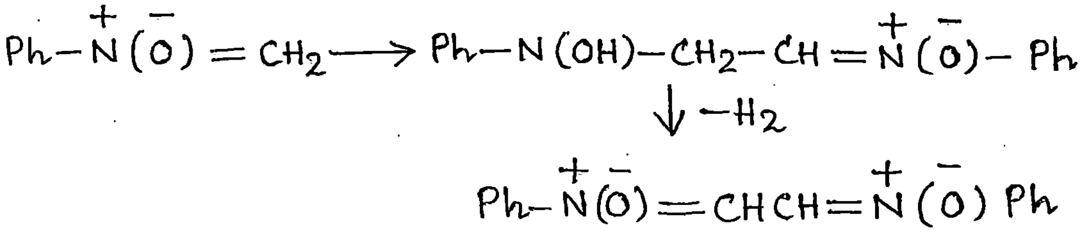
(C)

From N - Substituted Hydroxylamine :

$$R^1R^2C = O + R\,NH\,OH \longrightarrow R^1R^2C = \overset{+}{N}\,(\overset{-}{O})\,R + H_2O$$

This reaction proceeds smoothly and in high yield when R is an alkyl or aryl group and $R^1$and R^2 are of small size. When $R^1$and R^2 are bulky groups the reaction does not proceed to any extent(67). This is one of the best method for the preparation of aldonitrones. N- phenyl-hydroxyl amine has been treated with a variety of aldehydes and Ketones. With n- butylaldehyde, 80 % yield,

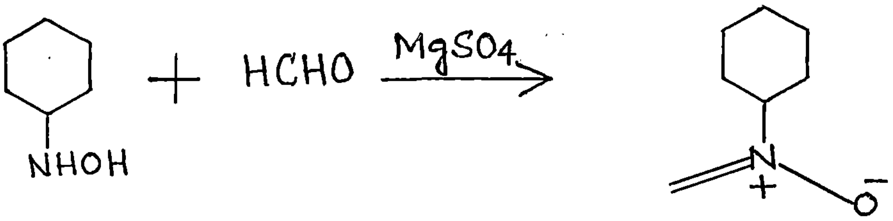
α- propyl-N-phenyl nitrone was obtained (51). With benzal dehyde a 90 % yield of the nitrone (68 , 69) with o , m and p - nitro benzaldehyde good yield (70) with p-N, N-dimethyl amino benzaldehyde a 79% yield (71) and good yield with other substituted benzaldehydes (72).N-phenyl nitrone formed from hydroxyl amine and formaldehyde insitu and finally dinitrone (43).



$$Ph-\overset{+}{N}(\overset{-}{O})=CH_2 \longrightarrow Ph-N(OH)-CH_2-CH=\overset{+}{N}(\overset{-}{O})-Ph \xrightarrow{-H_2} Ph-\overset{+}{N}(\overset{-}{O})=CHCH=\overset{+}{N}(\overset{-}{O})Ph$$

A similar 2 : 1 products were observed in the reaction between N-phenyl hydroxyl amine and α - bromo crotonaldehyde (43). A number of sensitive-nitrones have been prepared by this method and have been trapped in-Situ (73,74). The bisulphite addition compounds of aldehydes or ketones may be used instead of the aldehyde or ketones (75). Five membered cyclic nitrones have been prepared in yields ranging 50 - 80 % by reductive cyclization of γ - nitro Ketones (76-78) or γ - nitro nitriles by employing Zinc dust and aqueous NH_4Cl.

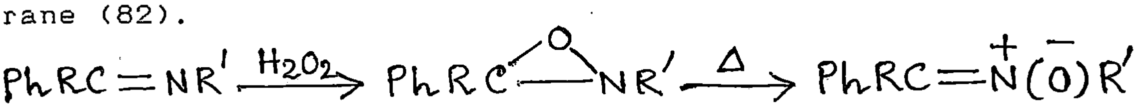
N -cyclohexyl methelene nitrone similar to N -phenyl methelene nitrone (2) can be prepared by passing HCHO gas through N- cyclohxyl hydroxyl amine in CH_2Cl_2 and anhydrous $MgSO_4$.



(D)

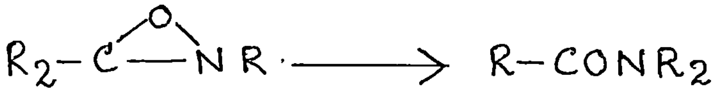
From Oxaxiranes :

The smooth thermal rearrangement of 3 phenyl oxaxiranes derivatives to the corresponding nitrones were reported by various workers (39, 79-81), in yields 50 - 100 % other imine also gave nitrone on oxidation by peroxy acids or dimethyl dioxirane (82).



$$PhRC=NR' \xrightarrow{H_2O_2} PhRC\overset{O}{—}NR' \xrightarrow{\Delta} PhRC=\overset{+}{N}(\overset{-}{O})R'$$

The thermal isomerisation of oxaxiranes other than 3 - phenyl oxaxirane did not lead to nitrone but to various rearranged products, mainly amides.



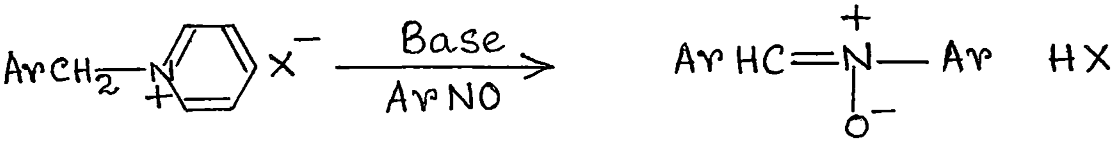
This is not general method for the preparation of nitrones since the oxaxiranes are generally prepared by the photochemical isomerisation of nitrones or by the reaction between imine and hydrogen peroxide , moreover, some other rearranged products also encountered.

The oxidation of N- alkyl imines by dimethyl dioxirane (82) (DMD) in CH_2 Cl_2 -acetone solution yielded nitrones without evidence of oxaziridine formation. The yields of isolated nitrones were higher for C, C diaryl imines and for imines bearing less bulky N- alkyl subsitituents.

(E)
From Aromatic Nitroso Compounds :

Aromatic nitroso compounds react with a variety of compounds to form nitrones. 2,4,6 - tri - nitro - toluene, 9 methyl acridine, with sufficiently active methylene group react with aromatic nitroso compounds to form nitrones but may often forms anils also (83-86). The reaction usually catalysed by trace amount of base, e.g. pyridine, pipyridine and Na_2CO_3.

Such type of reactions are also known with lepidine - N - oxide (87), quinaldine - N - oxide (87,88), and 2 and 4 - picoline (83,84) in which aromatic nitroso compounds react in presence of base with pyridinium salt to give nitrones. Quinolinium and isoquinolinium salts were used occassionaly.



Pyridinium salt may be prepared by King reaction (89,90). This reaction is specially helpful for preparing pyridinium salts of methyl - substituted hetero cyclic aromatic compounds, α - methyl Ketones (67) etc.

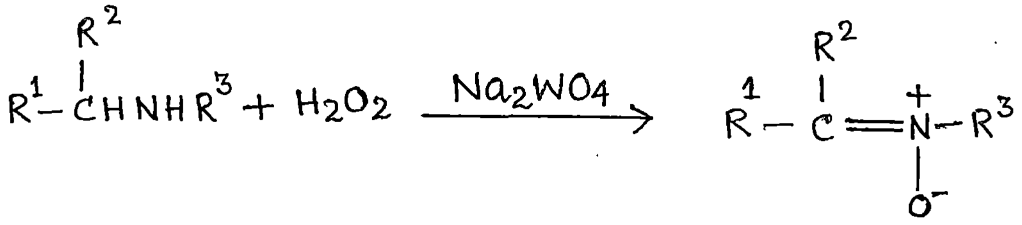
Aromatic nitroso compounds react with benzyl derivative such as benzyl choloride (91,92) and fluorene (93) and similar compounds (94-96) in presence of some suitable base to yield nitrones.

Lot of other compounds like diazo compounds, Sulpher yields, alkenes and alkynes can react with aromatic nitroso compounds to yield nitrones(40).

(F)

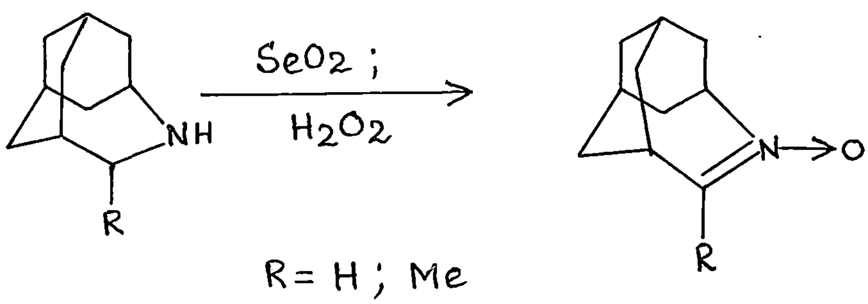
From Secondary Amines :

The sodium tungstate catalyst oxidation of secondary amines with hydrogen peroxide gives the corresponding nitrones (97) . Acyclic and cyclic nitrones can be obtained from secondary amines in a single step in good to excellent yields.



$$R^1-\overset{\overset{R^2}{|}}{C}HNHR^3 + H_2O_2 \xrightarrow{Na_2WO_4} R^1-\overset{\overset{R^2}{|}}{C}=\underset{\underset{O^-}{|}}{\overset{+}{N}}-R^3$$

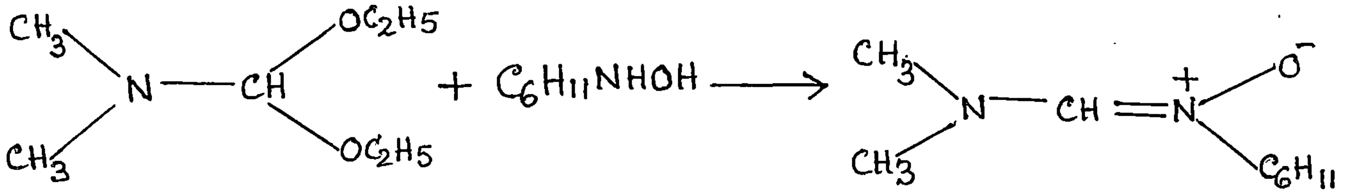
Oxidation of secondary amines with H_2O_2 in the presence of SeO_2 catalyst at room temperature give nitrones (98). This is an excellent method for the preparation of nitrones at room temperature. The bridging nitrones (99) formation by the oxidation of 4- azahomoadamantane with SeO_2 / H_2O_2 has been recently reported.



(G)

From acetal and amides :

The most recent additions are Amino-nitrones. The Synthesis of first α - amino nitrone from DMF diacetal was possible owing to the brilliant affords of Eschenmoser and his co-workers (100).

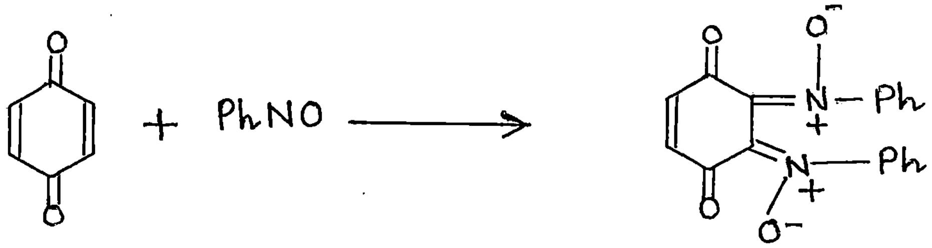


Finally the work has been extended after a slight change in methodology (101).

(H)

Some Other Miscellaneous Methods :

Quinones yielded dinitrones upon treatment with nitroso benzene (102).

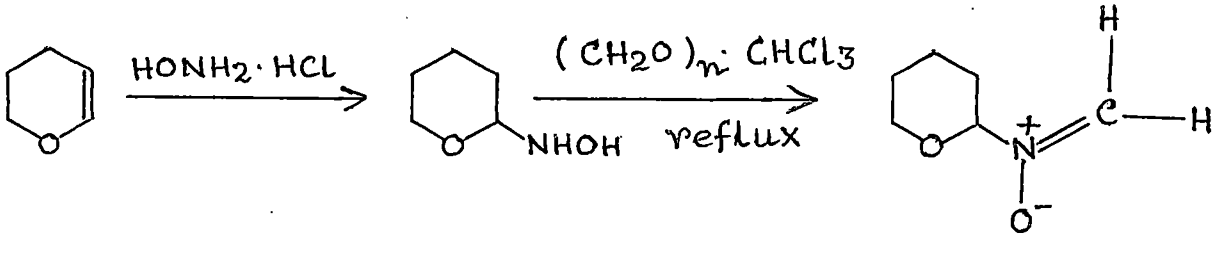


Some thiazolium salt partially reduce nitro-benzene with benzaldehyde to nitrone (103).

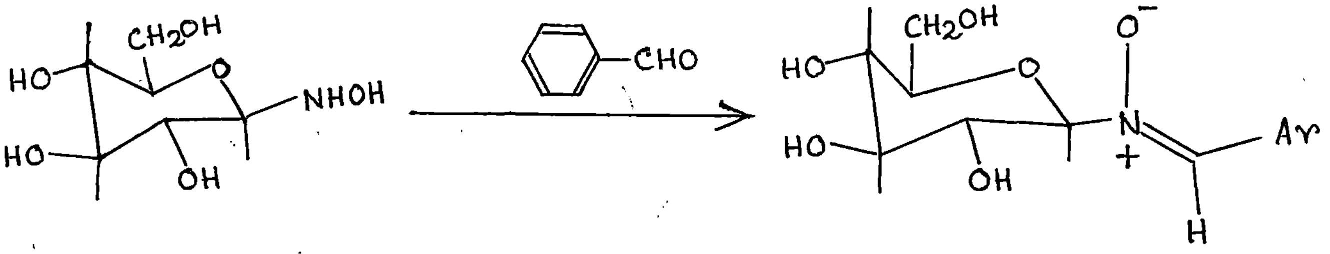
The adduct silyl enol ether with nitrobenzene can be oxidized to α - aryl - N - phenyl nitrone by Ag_2O (104).

N- methyl nitrones can be generated in good to excellent yields from aldehydes and ketones with stoichiometric amount of N - methyl N, O bis (trimethyl Silyl) hydroxyl amine (105).

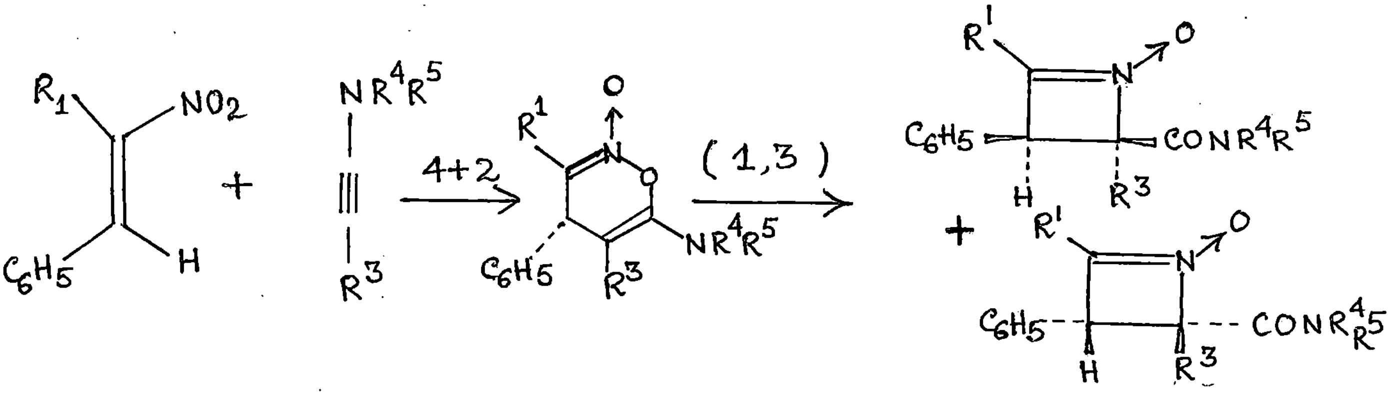
N - tetrahydro pyran 2-yl nitrone (106) was also generated insitu and finally characterised by PMR .



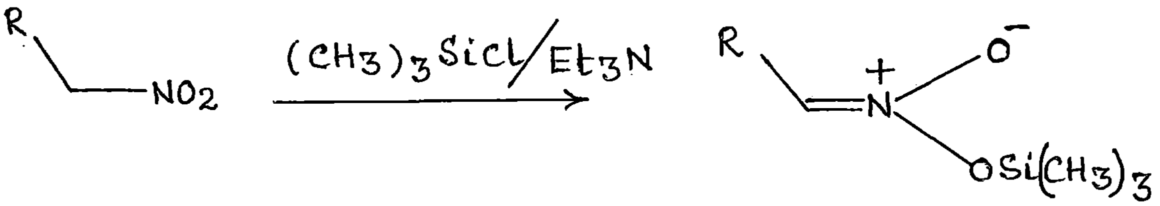
Nitrones (107) can also be isolated in pure state from D - glucose oxime and benzaldehydes without employing any protection of hydroxyl group.



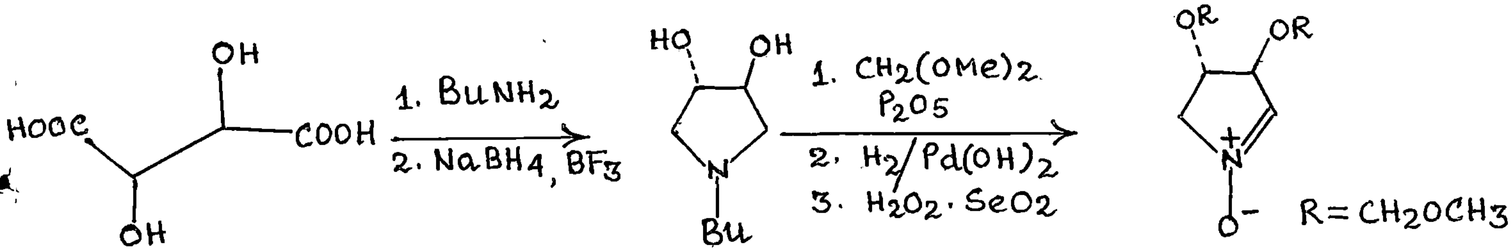
Chiral 4 - membered cyclic nitrones (108) were synthesized by the asymmetric (4 + 2) cycloaddation of nitroalkenes and chiral ynamines.



Nitrones (109) can be obtained by the treatment of trimethyl Silyl chloride and triethyl amine on nitro alkanes.



A new Synthesis of five-membered cyclic Nitrone from tartaric acid was reported recently (152) .



A Novel Synthesis of cyclic Nitrones (242) via a Nitroso

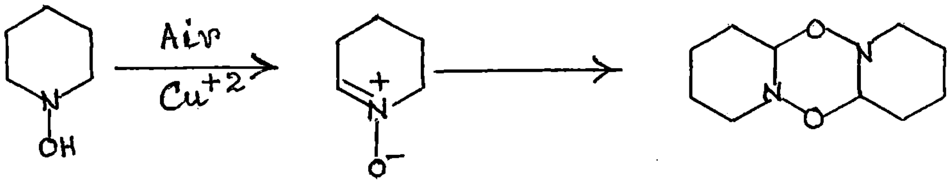
Ketone intermediate was reported in the early 1994.

5. Reactions of Nitrones :

The reactions of nitrones were reviewed in 1964 by J. Hamer and A. Macaluso (40). The major reactions of nitrones are their cycloadditions with a variety of multiple bonds. Reactions are briefly reviewed here.

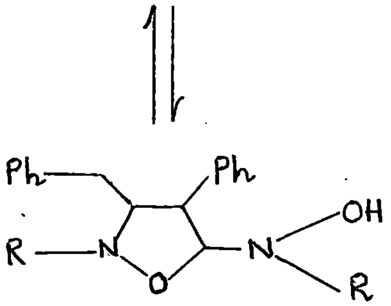
(A) Dimerisation :

Nitrones are sometimes very susceptible to dimerisation e.g. N- hydroxy piperidine did not give the expected cyclic nitrone but the dimer (46) and the trimer (47). The corresponding five membered nitrones were found to be monomeric (44).



2 - phenyl N- hydroxy piperidine also yielded a cyclic dimer upon oxidation. Acetone and N- phenyl hydroxyl amine yielded an aldol type of dimer (76). N- butyraldehyde and N- phenyl hydroxyl amine also yielded some type of dimer. Dimerisation with a loss of hydrogen molecule for a methyl nitrone was also reported (43). For alifatic nitrones following type of cyclodimerisation was reported (110).

$$Ph\ CH_2CHO + R\ NHOH \dashrightarrow PhCH\ CH = \overset{+}{N}\ (\overset{-}{O})\ R\ .$$

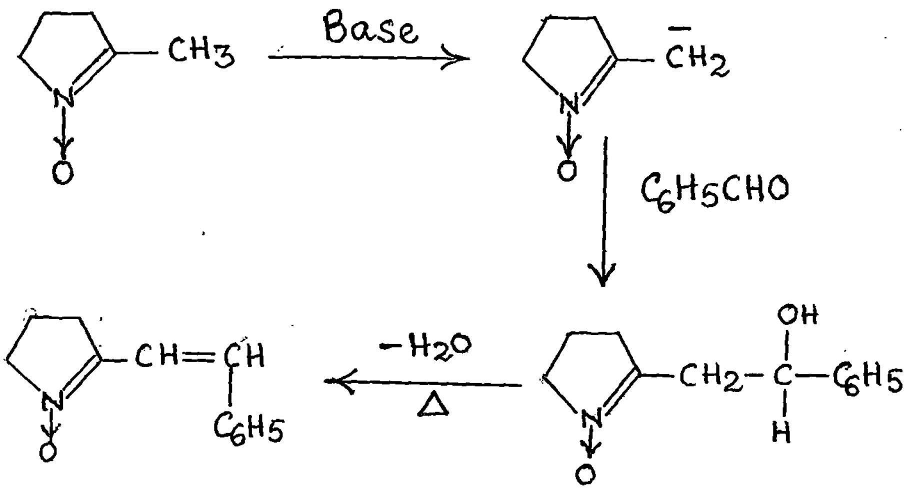


R= CH3 ; Ph ; p-MePh

(B) Aldol Condensations :

The nitrone group bears a marked resemblance to the carbonyl group in facilitating the removal of a proton from adjacent carbon under basic condition (111, 112, 70).

Benzaldehyde and α - Styryl - N - methyl nitrone in presence of base yielded α styryl -N-phenyl nitrone (43). This reaction was observed employing p-nitro or p-chloro benzaldehyde.



(C)

Addition of Grignard Reagents :

Grignard reagents were added to aldonitrones in a 1,3 fashion but the reaction with Ketonitrones led to imines (43, 113-115, 38, 43, 44).

$$RCH = \overset{+}{N}\ (\overset{-}{O})\ R^1 + R^2 MgBr \text{ -----> } RR^2\text{-}CH\text{-}N\text{-}(OH)\text{-}R^1$$

$$RR^1 C = \overset{+}{N}\ (\overset{-}{O})\ R^2 + R^3 MgBr \text{ ------> } RR^1 C = N\ R^2$$

(D)

Addition of Hydrogen Cyanide :

Nitrones formed a 1,3 adduct with hydrogen cyanide (44, 116, 70, 117, 118, 119). In presence of base the adduct readily lose water to yield a cyanomine.

$$RCH = \overset{+}{N}\ (\ \overset{-}{O}\ )\ R^1 + HCN \text{ ---> } RCH(CN) - N\ (OH)\ R^1 \text{ ---> } \underset{\substack{\vdots \\ (CN)}}{RC} = NR^1$$

Other types of miscellaneous additions are also known (43-45).

(E)

Rearrangement :

Aldonitrones rearrange to isomeric amides by treatment with a variety of reagents, e.g. $POCl_2$, PCl_5 , $SOCl_2$, SO_2 , CH_3COCl, $(CH_3CO)_2O$ and solution of base in ethanol (61 , 117 , 120-126).

$$PhCH = \overset{+}{N}\ (\overset{-}{O})\ CH \text{ -----> } PhCONHCH_3$$

Under the influence of heat (127, 117) , or acid (128-130, 131) nitrones may rearrange to O- ethers.

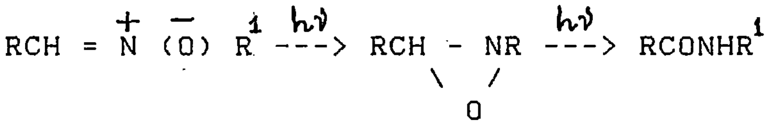
$$Ph_2C = \overset{+}{N}\ \overset{-}{(O)} - CHPh_2 \longrightarrow Ph_2C = N - O - CHPh_2$$

Ketonitrones may rearrange to aldonitrones by base (132, 133, 134) and such type of rearrangement also observed in the synthesis of nitrones (128, 133) and is known as 'Behrend Rearrangement' .

(G)

Some Other Transformations of Nitrones :

Irradiation of nitrones was found to lead to the isomeric oxaziranes, which were further rearrange thermally to the nitrones or photochemically to amides (68, 81,135).



$$RCH = \overset{+}{N}\ \overset{-}{(O)}\ R^1 \xrightarrow{h\nu} RCH - NR \xrightarrow{h\nu} RCONHR^1$$

On pyrolysis nitrones split into anils with traces of other products (136-138) e.g.

$$Ph_2C = \overset{+}{N}\ \overset{-}{(O)}\ Ph \longrightarrow Ph_2C = NPh + Ph_2CO + PhNO + O_2$$

Ozonolysis of nitrones is very rapid. Formation of green or blue colour indicates nitroso compounds (136, 139).

$$PhCH - \overset{+}{N}-\overset{-}{(O)}-R + O_3 \longrightarrow PhCHO + RNO + O_2$$

Nitrones readily hydrolysis to an aldehyde or a ketones (129,140) and an N- substituted hydroxyl-amine. Aryl nitrones are less readily hydrolyse than alkylnitrones.

$$RR^1C = \overset{+}{N}\ \overset{-}{(O)}\ R^2 + H_2O \longrightarrow RR^1CO + R^2NHOH$$

Treatment of LiAlH$_4$ or NaBH$_4$on nitrones in either yielded corresponding hydroxyl amines, in high yield (104, 105,120,141).

$$R^1R^2C = \overset{+}{N}\ \overset{-}{(O)}\ R^3 \xrightarrow{\text{LAH or NaBH}_4} R^1R^2CH - NH(OH)R^3$$

α - hexyl - N - benzyl nitrone with Sodium in alcohol yielded N - heptyl - N - benzyl amine (59).

Deoxygenation of nitrohas been accomplished by zinc, iron, tin, phosphine, sulfur dioxide, sulfur and catalytic hydrogenation (44, 76-78,142).

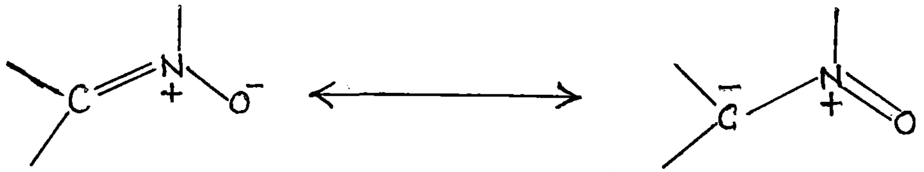
Addition of trimethly silyl cyanide to N- alkyl C- phenyl nitrones affords cyano - O - Silylhydroxyl amines. Reaction of these species with silver fluoride regenerates the nitrone in quantitative yield there by providing a useful nitrone blocking gr

(143).

(H)

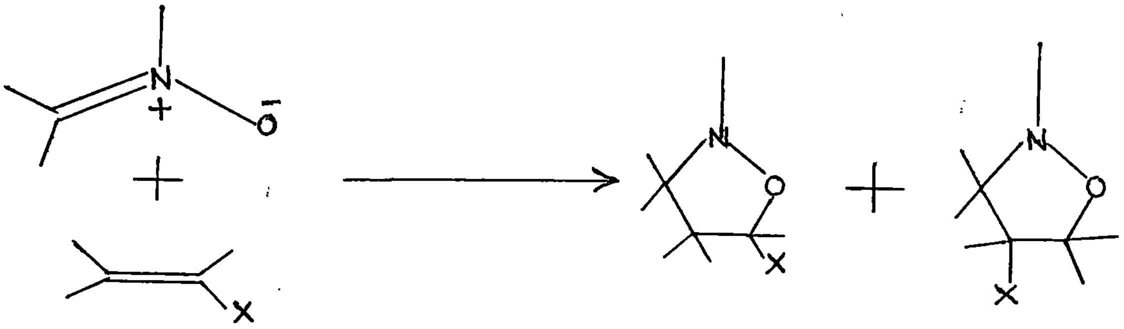
Cycloaddition Reactions of Nitrones :

Nitrones readily undergo 1,3 dipolar cycloaddition reactions with a variety of multiple bonds. The nitrone additions are comprehensively reviewed in 1964 (40), 1975 (144) and 1984 (41) respectively. Nitrones are a system of three atom, over which are distributed four π - electrons as in the allyl anion system. The term " 1,3 - dipole" arose because of in valence - bond theory such compounds can only be described in terms of dipolar resonance - contributors.



And dipolarophiles are the substrates having at least two π- electrons and can undergo cycloadditions with 1,3 dipoles.

Addition of a nitrone to a carbon - carbon double bond gives rise to an 1,2 isoxazolidine, which is usually quite stable.



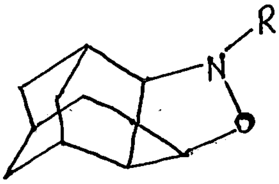
The cycloaddition reactions of Nitrones can be classified in two major catagories ;

1) Intramolecular 1,3 dipolar cycloadditions.

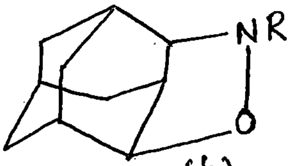
2) Intermolecular 1,3 dipolar cycloadditions.

1) Intramolecular 1,3 dipolar cycloadditions.:

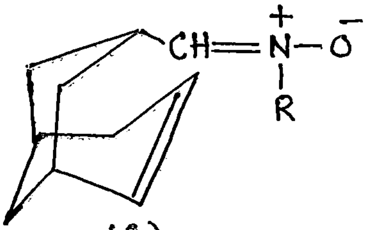
Intramolecular 1,3 dipolar cycloadditions have proved to be of considerable value in the synthesis of noble fused ring heterocycles (145-148). Sasaki-etal (145) have reported to convenient stereo specific synthesis of 2,4 diaxial adamantane [a] and 2,4 di-endo-proto adamantane derivatives [b] via an intramolecular cycloaddition of the bicyclo [3,3] - non - 6 - enenitrone [c] .



(a)

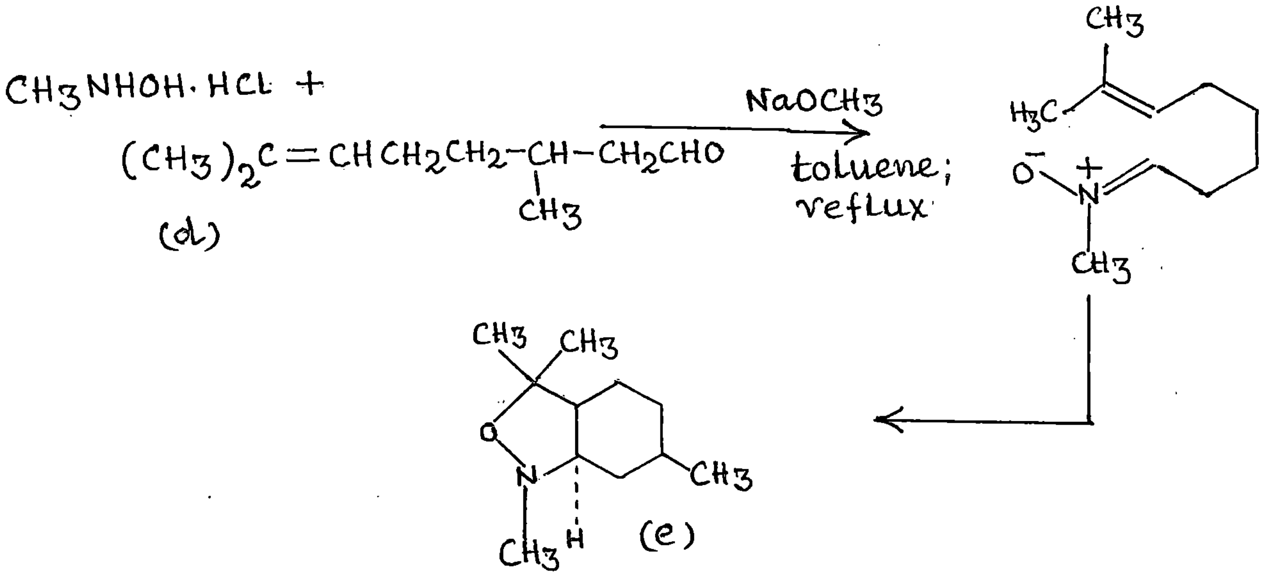


(b)



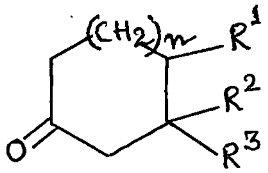
(c)

Cyclo condensation of [d] with N- methyl hydroxyl amine in refluxing toluene - methanol with azeotropic distillation of water and methanol gave the benzisoxazoline [e] (146) in 64-67 % yield. This intramolecular variation represents a useful synthetic approach as a carbocyclic ring is generated together with a five membered isoxazolidine. (Scheme - III).

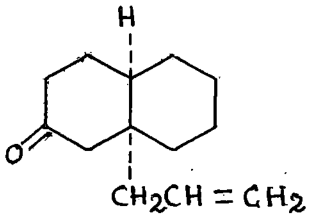


Scheme-III.

Exocyclic nitrones prepared from alkexylcyclo alkanones e.g. [f] (n = 0, 1, 2, $E^1 = R^2$ = H, allyl, $CH_2 = CHCH_2CH_2$, R^3 =H, OH) [g] and hydroxyl amines (RNHOH) : R = Ph, $PhCH_2$,Me) undergo smooth intramolecular cycloaddition reaction to give bridged bicyclo alkanes. Table - [5] (147).

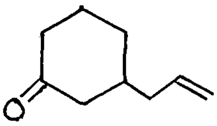
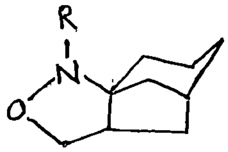
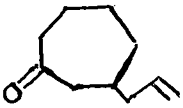
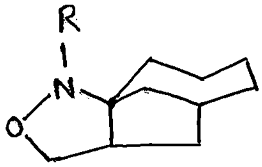
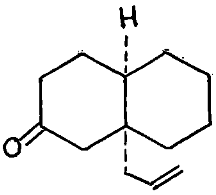
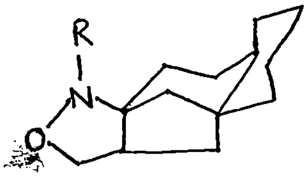
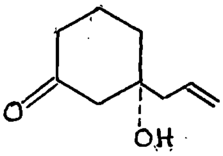
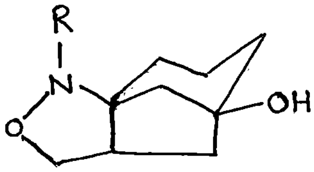
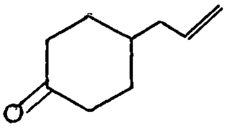
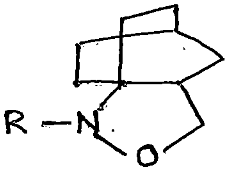
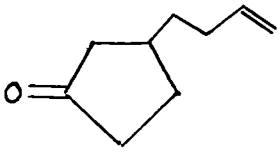
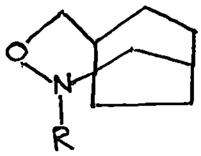
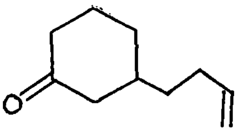
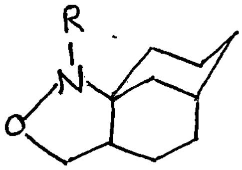


(f)



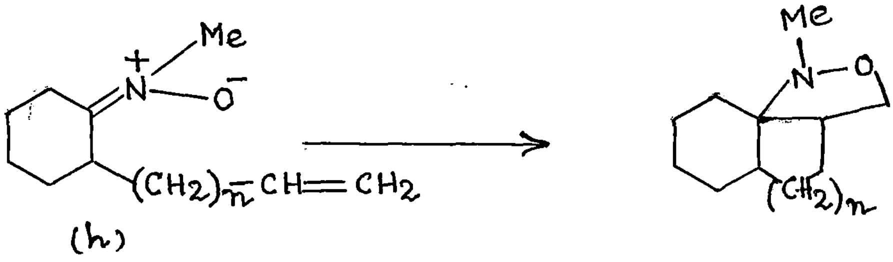
(g)

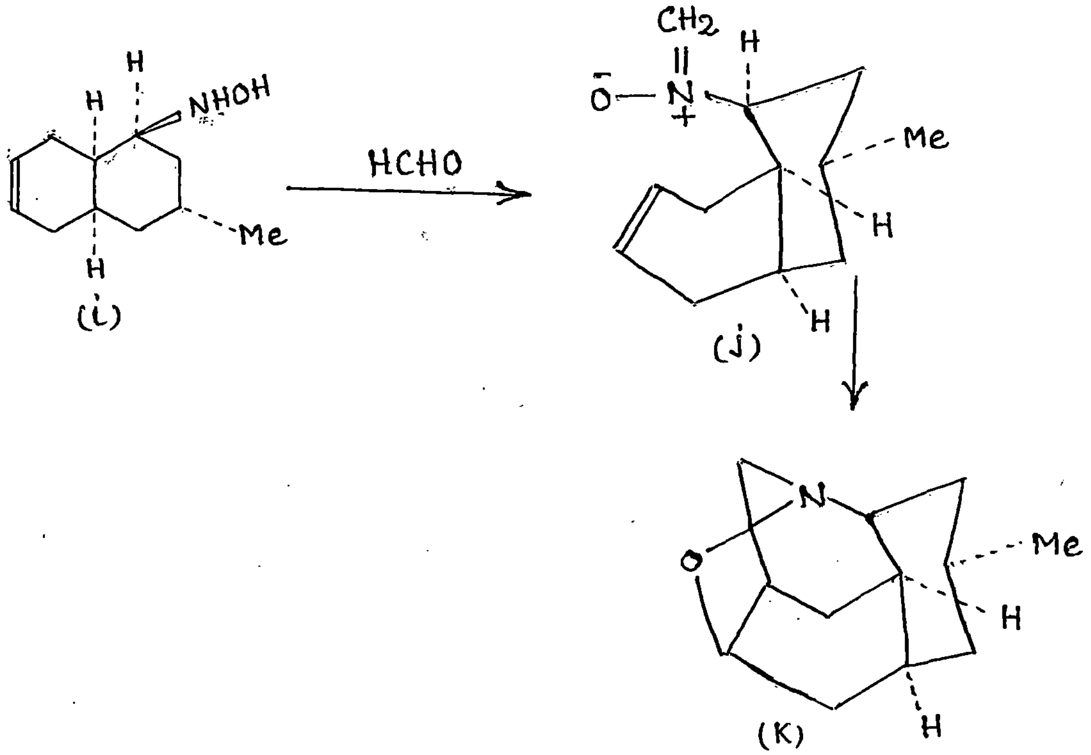
Table - 5 :

Cycloalkanone	bridged bicyclo alkane	yield
		84 (Me) 100 (Bz) 74 (Ph)
		84 (Me) 82 (Bz)
		94 (Bz)
		55 (Me) 70 (Bz)
		48 (Bz)
		50 (Bz)
		46 (Me)

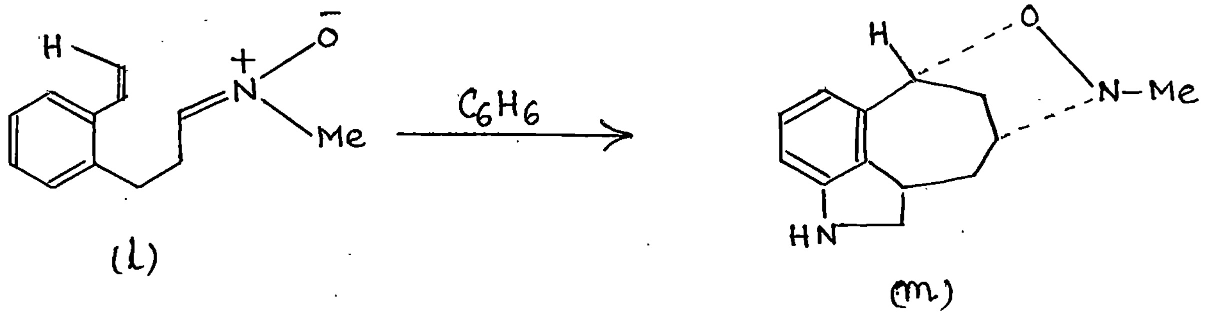
The annelation by intramolecular 1,3 dipolar addition of nitrones [h] and the factors controlling the case of reaction have been investigated by Kusurni etal (149). Structural and medium effects on the intramolecular 1,3 dipolar cycloadditions of nitrones have been studied (150).

On reaction with formaldehyde at 115° c, [i] affords the transient N-lakenyl nitrone [j] which gives the isoxazolidine derivative [k] Stereo Specifically (148).

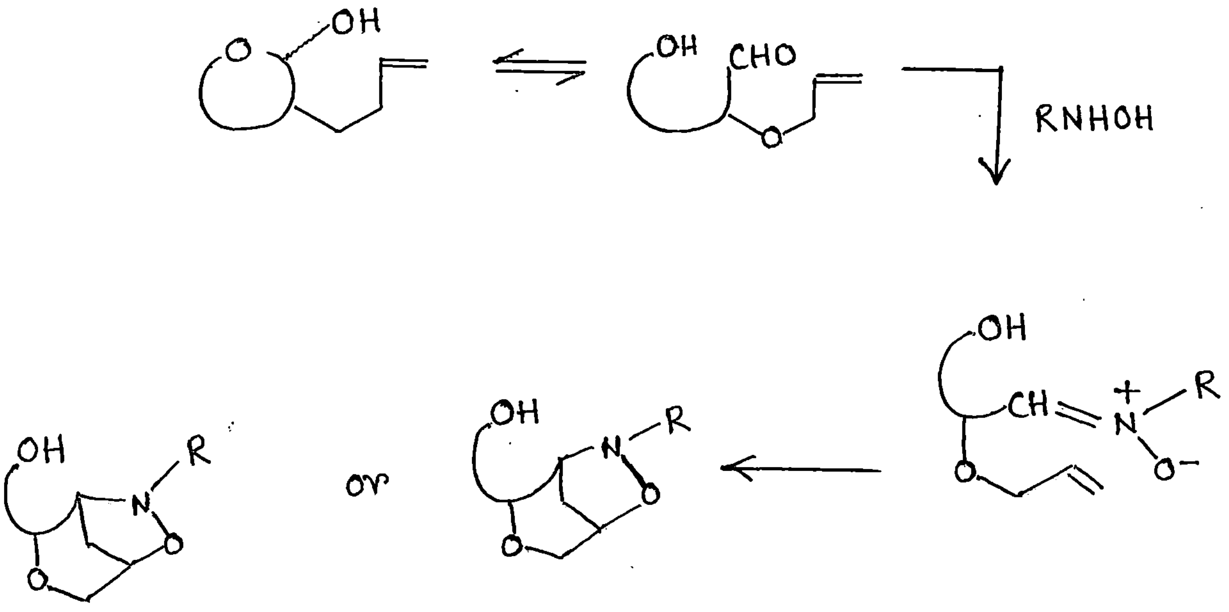




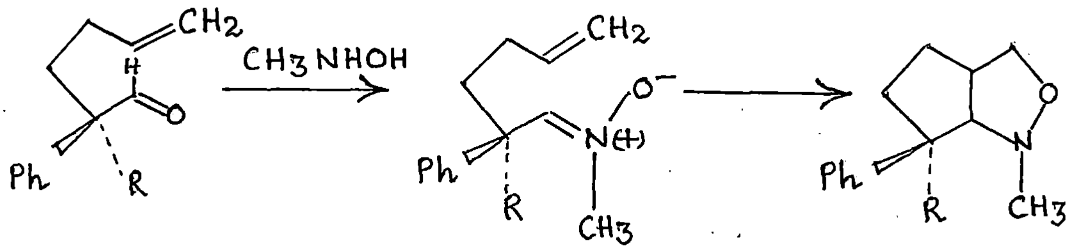
The clavive alkaloids have been synthesised (151) Stereo Selectively from indole 4- carboxaldehyde. One of the steps involved a transient nitrone (l) which underwent a kinetically controlled regio and stereoselective intramolecular cycloaddition to a 1,2 disubstituted olefinic bond to give cycloadduct [m] (Scheme - IV)



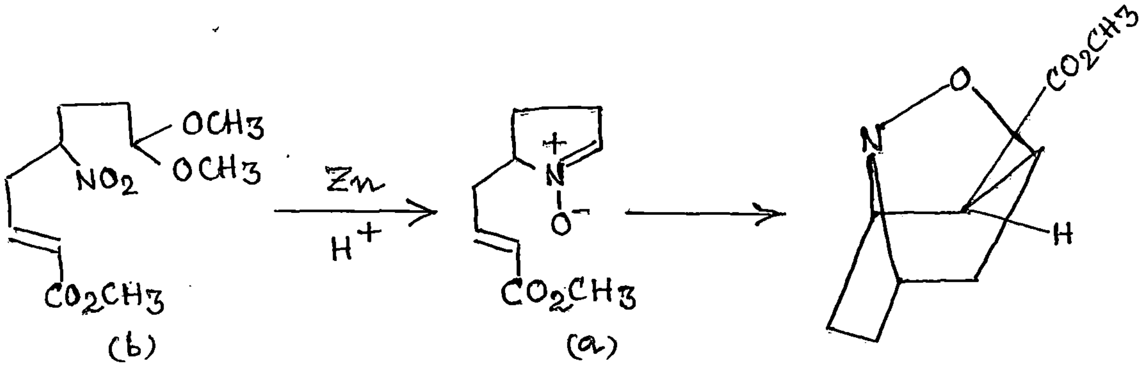
The intramolecular 1,3 dipolar cycloaddition of the N-benzylnitrone of 3 - O - allyl D (+) glucose (153) yielded a chiral oxepane derivative, potentially useful for the synthesis of other chiral systems.



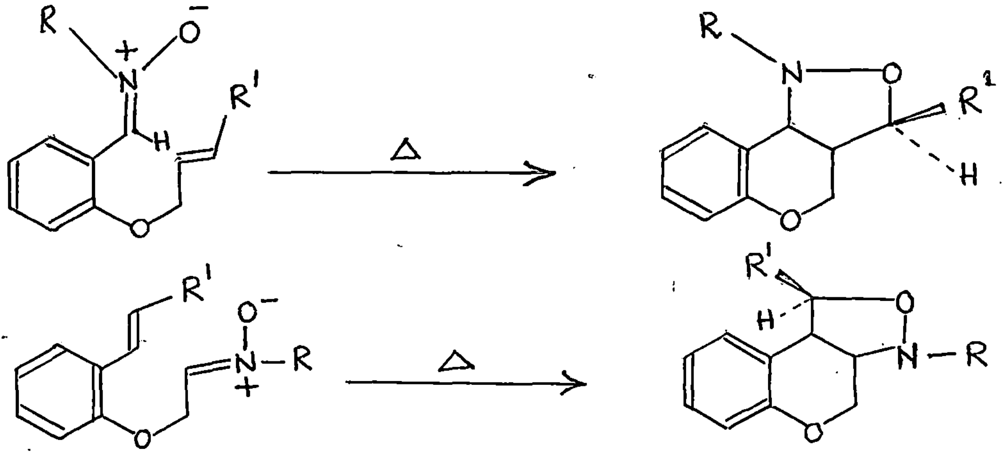
Vinick et. al (154) reported that cyclopentanone ring with three asymmetric centre's was stereo specially constructed in a single step from an acyclic precursor by means of intramolecular 1,3 dipolar cycloaddition reactions.



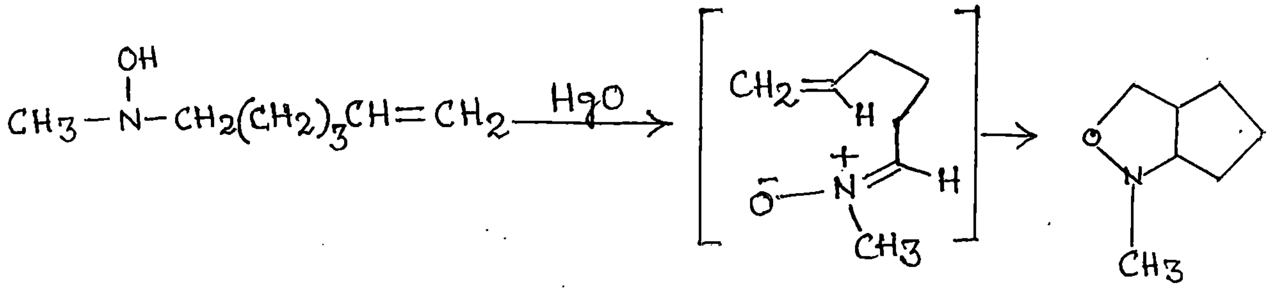
A very interesting application of intramolecular nitrone cycloaddition was reported by Tufariellow (155, 156) in the synthesis of dl-cocaine. The synthesis was developed by the generation of nitrone ester [a] as the key precursor of the natural product which was accomplished by reduction of acetal [b] with Zn.



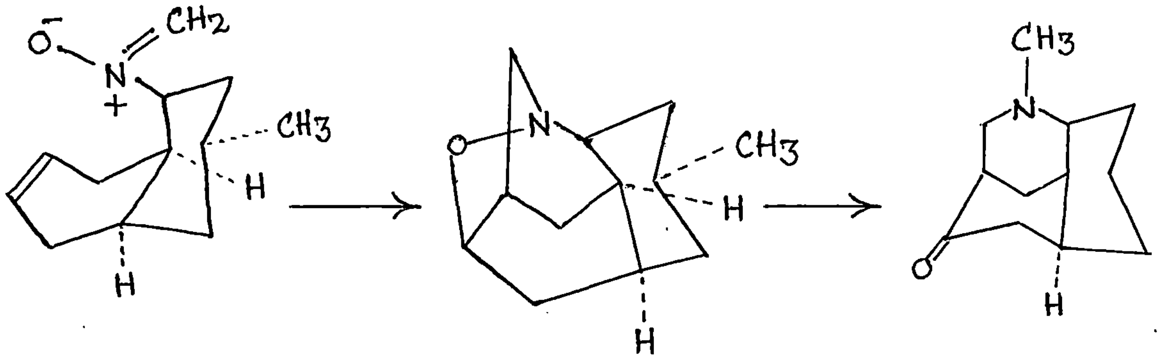
Oppolzer and co-workers (157, 158) had extended the intramolecular 1,3 dipolar cycloaddition to incorporate a benzene ring and a hetero atom containing isoxazolidines.



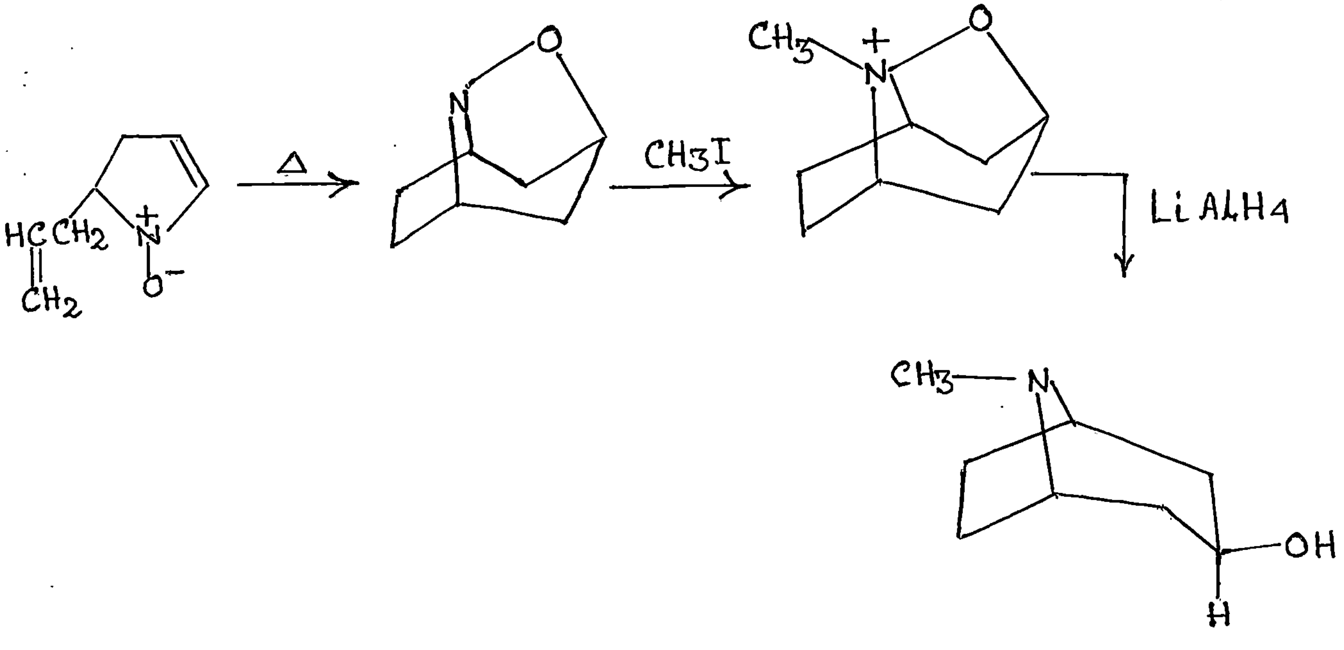
Formation of bicyclic isoxazolidine (159) was also reported, in a situation when alkene and nitrone moieties were suitably arranged in the same molecule.



Synthesis of lycopodium alkaloid dl-luciduline from N-alkenyl nitrone was also reported by W. oppolzer (148).

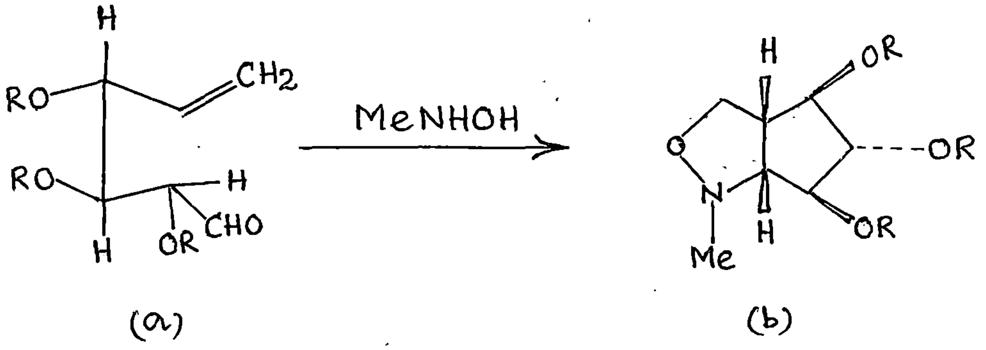


The intramolecular 1,3 dipolar addition of 5 allyl 1, pyrroline N- oxide was reported to give a cycloadduct which was a useful precursor of tropane-skeleton (160).

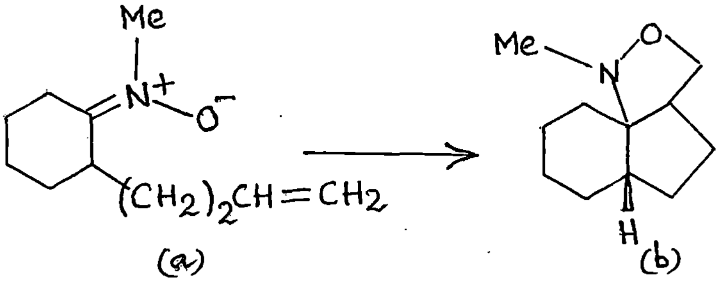


A series of intramolecular nitrone cycloadditions (161) to chiral allyl ethers was studied in order to evaluate the influence on the stereochemical out come exerted by several factors, including the nature of the substituents at the stereo centre and electronic features of the double bond.

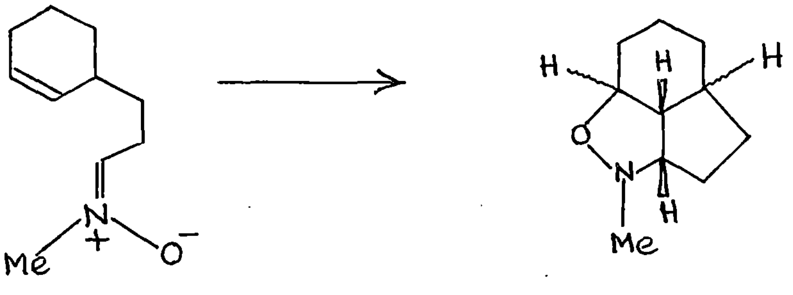
Pentasubstituted cyclopentanes have been prepared from mono saccarides (162). The reductive fragmentation of 5-bromo-5 deoxy glucosides with Zn produces 5,6 deoxy hex 5-enones, [a] which upon treatment with N-methyl amine followed by intramolecular cyclization afford the chiral isoxazolidine [b] in good yields (162) [a].



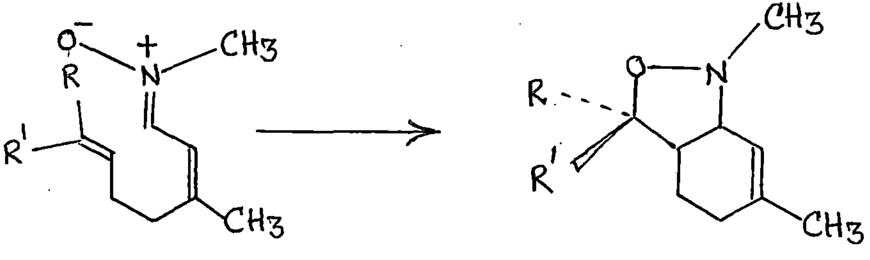
Annelation of nitrone [a] at room temp. led quantitatively to the hydrindane [b] whose stereochemistry was tentatively assigned as depicted (163).



Intramolecular nitrone cyclizations leading to bicyclo (3,3,0) octyl skeleton has been known for sometime (164).

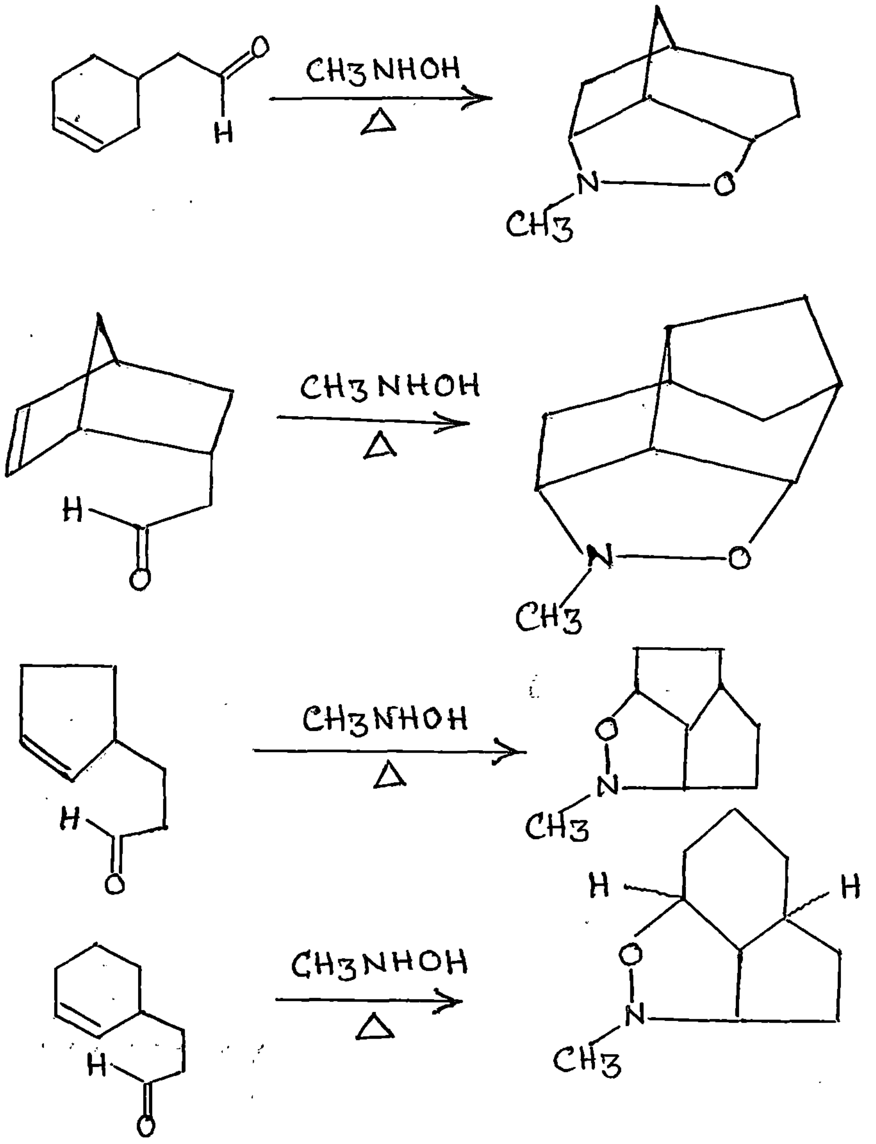


Nitrone [a] derived from farnesal was found to undergo ready thermal cycloaddition to give isoxazolidine (165,166) [b] using intramolecular 1,3 dipolar cycloaddition, with complete retention of configuration.

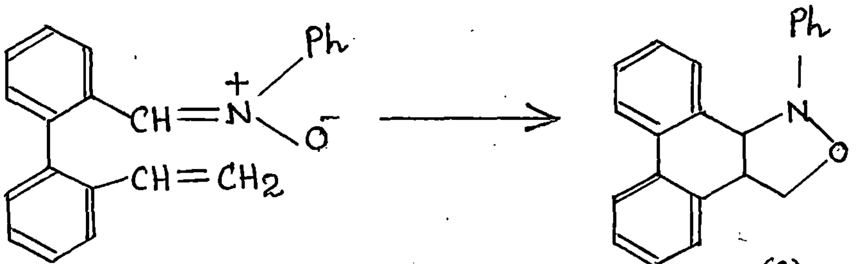


(a) (b)

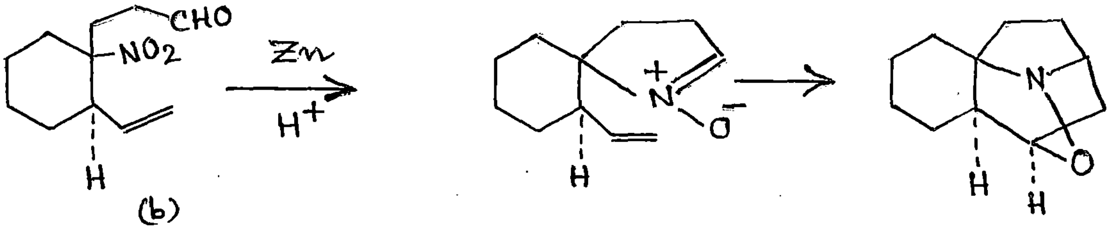
LeBel and co-workers further demonstrated the utility and synthetic scope of the intra modecular 1,3 dipolar cyclo addition of nitrones by preparing a variety of polycyclic isoxazolidines (164, 167-169) e.g.



Other systems that undergo intramolecular 1,3 dipolar cycloaddition include N[O(O- Vinyl phenyl)-benzylidine] aniline N- oxide [a] (170) and the nitrone derived from the Zn reduction of nitro aldehyde [b] (171). The exclusive formation of [c] is especially interesting in the light of Huisgen's work dealing with the bimolecular reaction of N- phenyl benzal nitrone with styrene which affords the alternative regio isomer (172).

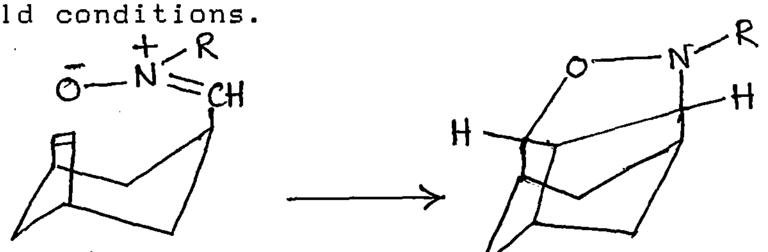


(a) (c)

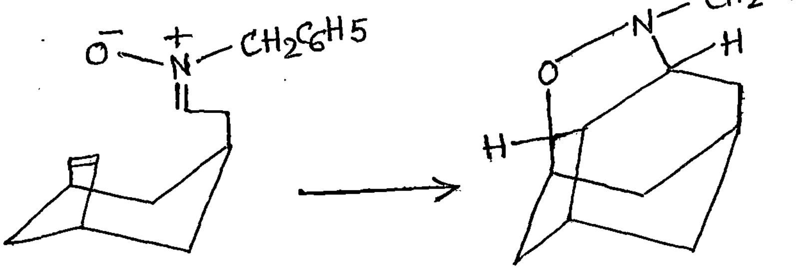


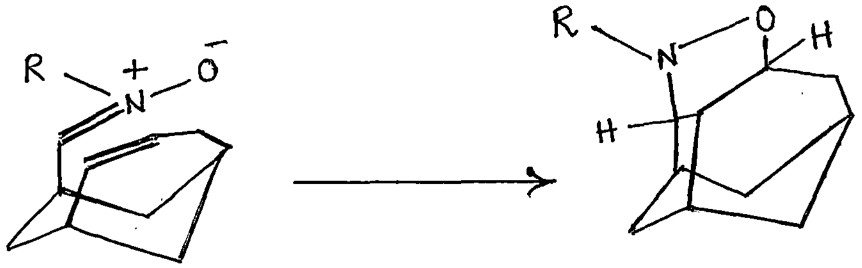
(b)

Intramolecular cycloaddition of nitrones to olefines are kinetically controlled process (173 - 175).The intramolecular 1,3 dipolar cycloadditions at C- bicyclo alkenyl nitrones [a],[b],[c], proceed smoothly at 25°-80° c affording the expected cycloaducts in high yield (176). These intramolecular cycloadditions proceed under very mild conditions.



(a)





Very recently the ring - selective synthesis of homo chiral oxepanes and tetrahydro pyranes from carbohydrates via intra molecular Nitrone or nitrile - Oxide cycloadditions have been reported (243).

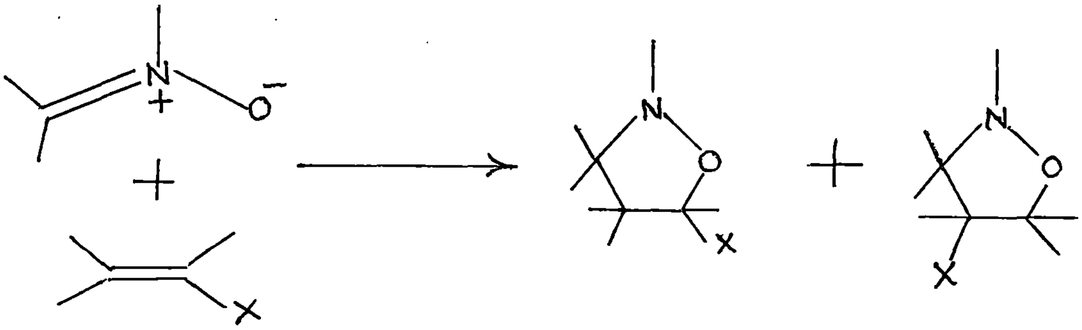
[2]

Intermolecular 1,3 dipolar Cycloadditions. :

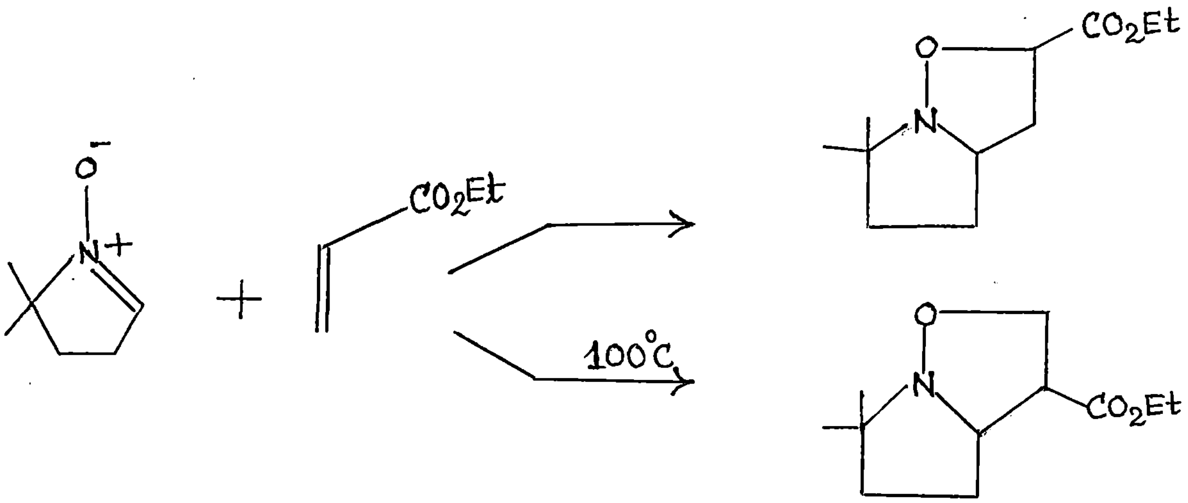
A very wild range of intermolecular 1,3 dipolar cycloadditions are known. Important cyclo additions are systematically reviewed here.

[a] 1. Addition to alkenes :

Addition of nitrones to C = C double bond give rise to an 1,2 isoxazolidine, which is usually quite stable. Conjugated unsaturated system readily react with nitrones but unconjugated alkenes react considerably slowly and required drastic condition sometimes. Electron deficient dipolarophiles react with nitrones smoothly. With unsymmetrical systems two orientations are possible.



The direction of nitrone addition can be reversible and therefore subject to both thermodynamic and kinetic control (177). For instance, the addition of ethyl acrylate to 5,5 dimethyl - N - oxide at room temperature yields 100 % of one structural isomer and at 100°c yields 98 % of the other.



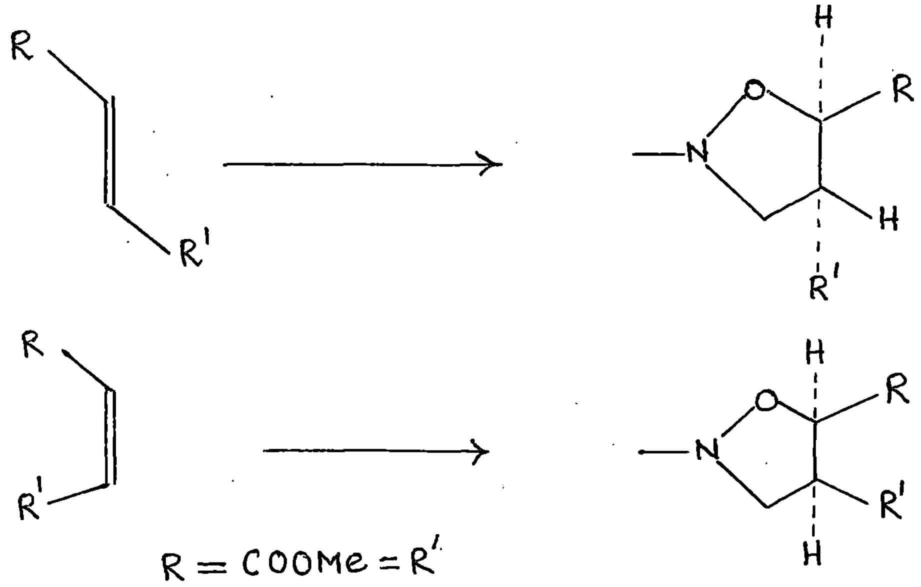
Regio selectivity applies to addition under conditions of kinetic control.Both steric and electronic factors are important [1(a)],(8) .In general the more hindered end of the electrophile adds to the oxygen atom of the nitrone to give 5-substituted adducts reversal of regio selection was also observed with nitrones of very high ionization potential (27) or with very electron deficient dipolarophiles (26).

Only 5- substituted isoxazolidines are generally formed in nitrone addition with 1,1 disubstituted alkenes. But a recent study shows that 4 - subsitituted adduct was also formed (178). Most addition of trisubstituted alkenes to nitrones yield 4,5,5 - trisubstituted isoxazolidines, but in some cases 4,5,5 - tri-substituted isoxazolidines (179,180).

Cycloaddition of tetra-substituted alkenes to nitrones are not common and regio selectivity factors are similar to those discussed for unsymmetrical 1,2 - disubstituted alkenes.

[a] 2. Stereochemistry of Addition :

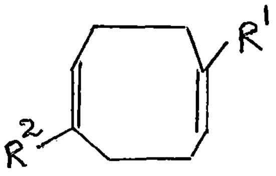
Studies of addition of dimethyl maleate and dimethyl fumarate to a variety of nitrones (181, 182) have established stereo specific cis addition by the production of mutually uncontaminated dia-stereomeric adducts.

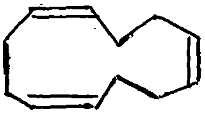
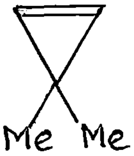
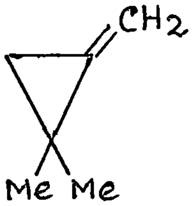
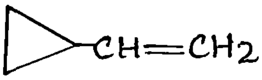
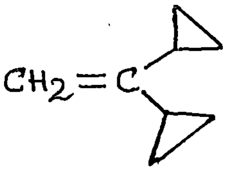
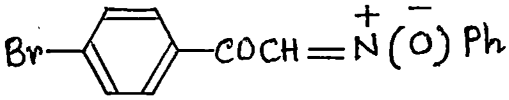
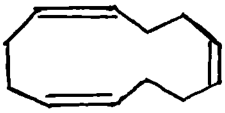
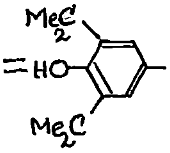
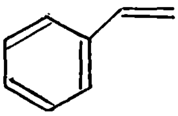


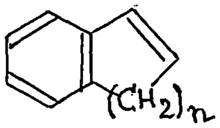
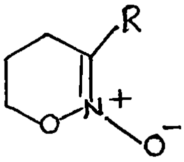
$R = COOMe = R'$

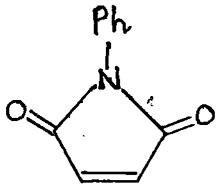
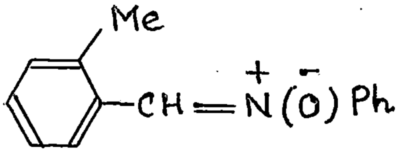
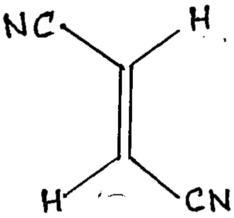
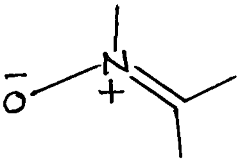
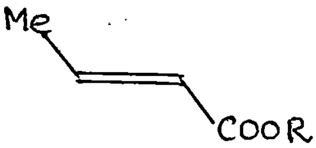
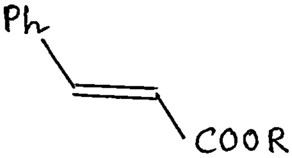
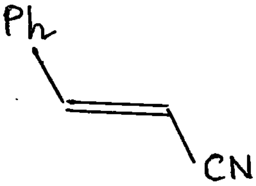
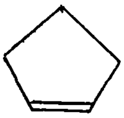
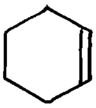
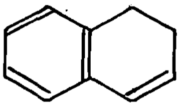
This general principal has been confirmed in many other cases of cycloadditions (177, 183, 182). Cis - trans - isomerism of dipolarophile substituent with respect to the nitrone substituents has been noted in many cases and is caused by the fact that the nitrone can approach the dipolarophile from two different sides. Isomer ratio ranging from 50 : 50 to 100 : 0 have been observed . There is a good evidence (184) that the more favoured transition state is the one in which the dipole of the reactants are opposed and that an increase in dipole moment increses the stereo specificity vice-versa.

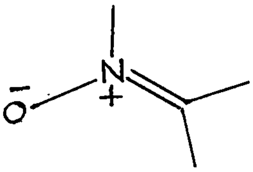
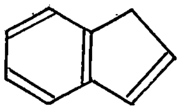
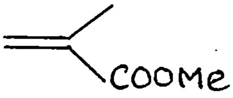
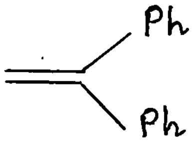
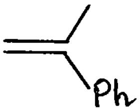
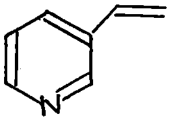
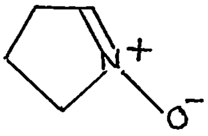
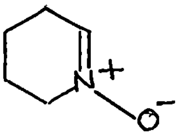
TABLE :1
Cycloadditions of Nitrone to olefins / Alkene

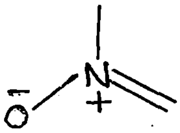
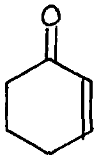
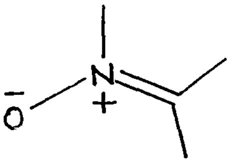
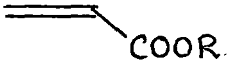
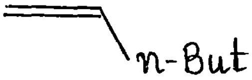
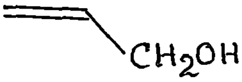
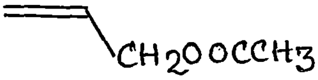
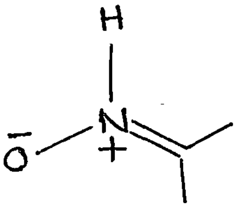
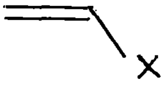
Nitrones	**Olefin / alkene**	**References**
$PhCH_2\overset{+}{N}(\overset{-}{O})=CHCO_2Et$	$Me_2CH=CH_2$	185
"	$CH_2=CHCO_2Me$	"
"	$MeCH=CHCO_2Me$	"
$PhNHCOCH=\overset{+}{N}(\overset{-}{O})Ph$	$RCH=CHR'$ $R=R'=CO_2Me$; CO_2H $R=CHO$; $R'=Ph$ $R=H$; $R'=CHO$ $RR'=-CO-O-OC-$	186
" "	 $R^1, R^2 = H; H:$ $H, Me;$	187

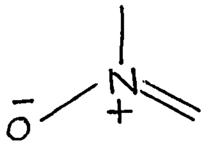
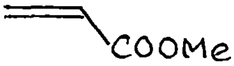
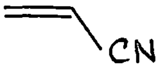
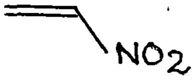
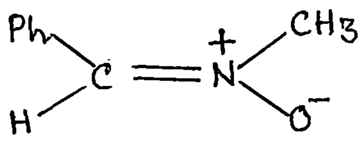
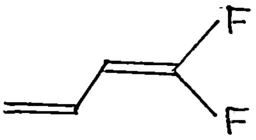
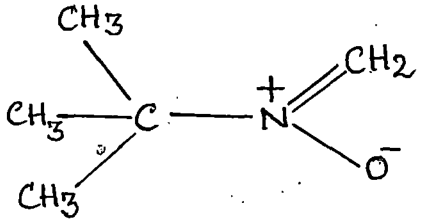
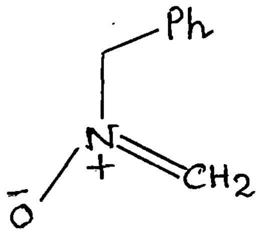
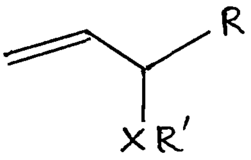
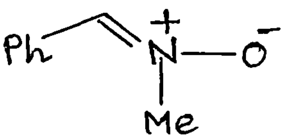
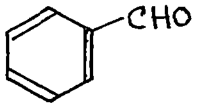
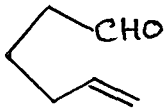
	Nitrones	**Olefin / alkene**	**References**
	$PhNHCOCH=\overset{+}{N}(\overset{-}{O})Ph$		187
	"		188
	"		188
	"		"
	"		"
3.			187.
4.	$R'-Z-CH=\overset{+}{N}(\overset{-}{O})R$ R = Ph ; R' =  Z = NHCO ; CO	$CH_2=CHCN$	189
	" "		"

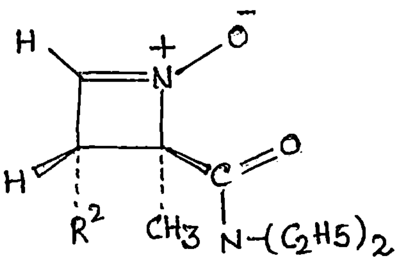
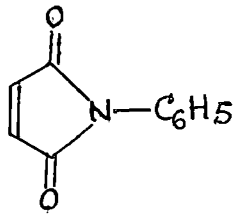
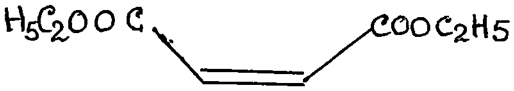
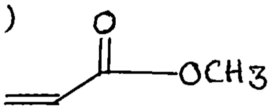
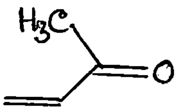
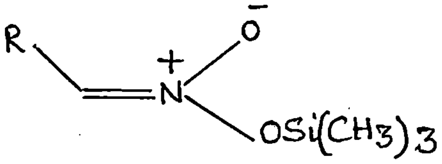
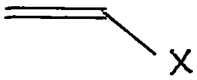
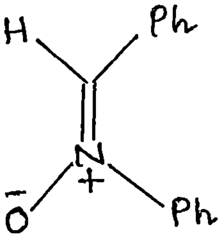
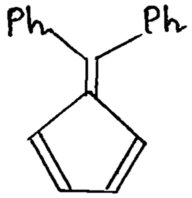
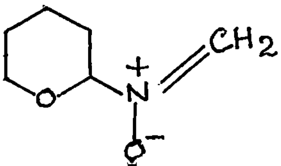
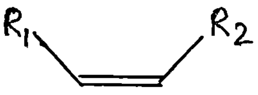
	Nitrones	**Olefin / alkene**	**References**
.	$PhCH=\overset{+}{N}(\overset{-}{O})R$ (i) R = Ph ; Me	$(R)-4-MeC_6H_4S(O)CH=CH_2$	190
	(ii) R = Me	 n = 1 , 2	191
.	$R\overset{+}{N}(\overset{-}{O})=CR^1R^2$ R = Me, Bu, $PhCH_2$, Ph_2CH, 4-Me C_6H_4, R′ = CO_2 (1R, 3R, 4S)-(–) menthyl	$Ph(R^3)C=CH_2$ R^3 = H, Ph	192
.	$R\overset{+}{N}(\overset{-}{O})=CPh_2$ R = Me , $PhCH_2$	$CH_2=CHCO_2R'$ R′ = (1R, 3R, 4S)-(–) menthyl	"
.	$(MeO_2C)_2C=\overset{+}{N}(O)Me$	$CH_2=CRR'$	56, 193
9.		$R'CH=CH_2$ R′ = Ph, COOMe, CN	194
10.	$PhCOCH=\overset{+}{N}(\overset{-}{O})Ph$	$CH_2=CHPh(O)(OMe)_2$	1, 8

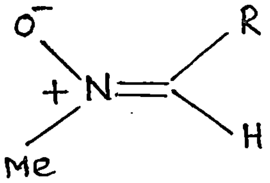
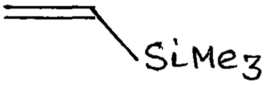
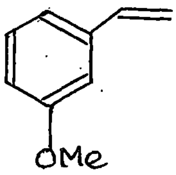
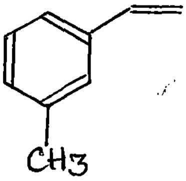
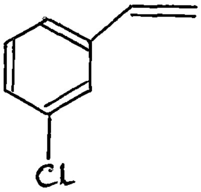
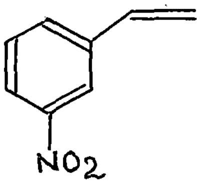
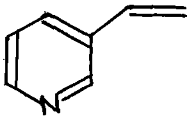
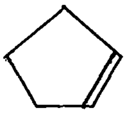
	Nitrones	Olefin / alkene	References
11.	$RCH=\overset{+}{N}(\overset{-}{O})\,Ph$ R = o- or m-tolyl		195
12.			195
13.			196–198 ; 177, 199.
14.	" "		177, 199 ; 182.
15.	" "		182
16.	" "		1
17.	" "		1
18.	" "		1

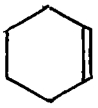
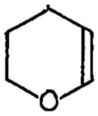
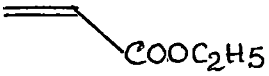
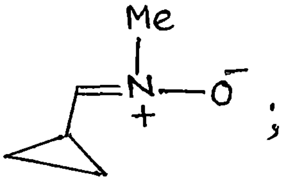
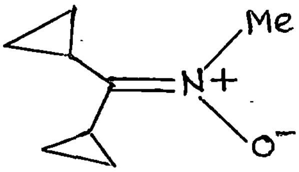
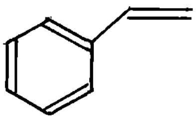
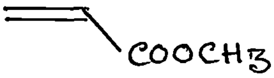
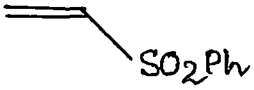
	Nitrones	Olefin / alkene	References
19.			200
20.	" "		177
21.	" "		200
22.	" "	(i)  (ii) 	200
23.	; 	 (i) R = OEt (ii) = CH_2OH (iii) = $CH_2OSi\,{}^{t}Bu(CH_3)_2$ (iv) = CH_2OAc. (v) = Ph (vi) = CO_2CH_3 (vii) = CN (viii) = CHO	178

	Nitrones	Olefin / alkene	References
24.			199
25.			177
26.	" "		"
27.	" "	(i) 	"
		(ii) 	"
		(iii) 	"
		(iv) 	"
28.		 $X = SO_2Ph$ $= CO_2CH_2Ph$ $= COCH_3$	62(c)

	Nitrones	Olefin / alkene	References
29.		(i)  (ii)  (iii)  (iv) 	199
30.			201
31.		"	"
32.		 $X = O$ $R = Me$, iPr, $R' = H$, TBS.	202
33.		(i)  (ii) 	105

	Nitrones	Olefin / alkene	References
34.		(i)  (ii)  (iii)  (iv) 	203
35.	 R = CH_3, C_2H_5 ; C_4H_9, C_6H_5,		109
36.	α- N- Diphenyl Nitrone	(i) Norbornene (ii) Ethyl Crotonate	8
37. (a)			205
(b)		 $R_1 = H$; $R_2 = Ph$	204

Nitrones	Olefin / alkene	References
38. 		206
39. α- Phenyl N- methyl nitrone.		1; 8
"		" "
"		" "
"		" "
"		" "
"		7

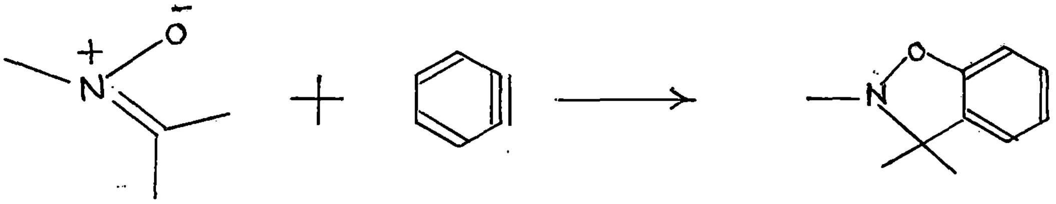
Nitrones	Olefin / alkene	References
39. α- Phenyl N- methyl nitrone		7
"		"
"	$CH_2=CH-CH_2OH$	"
"		7, 8
"		8
40.  ; 	(i) 	25
	(ii) 	"
	(iii) 	"
	(iv) 	"
	(v) $-\equiv-COOCH_3$	"

[b] Addition to Alkynes :

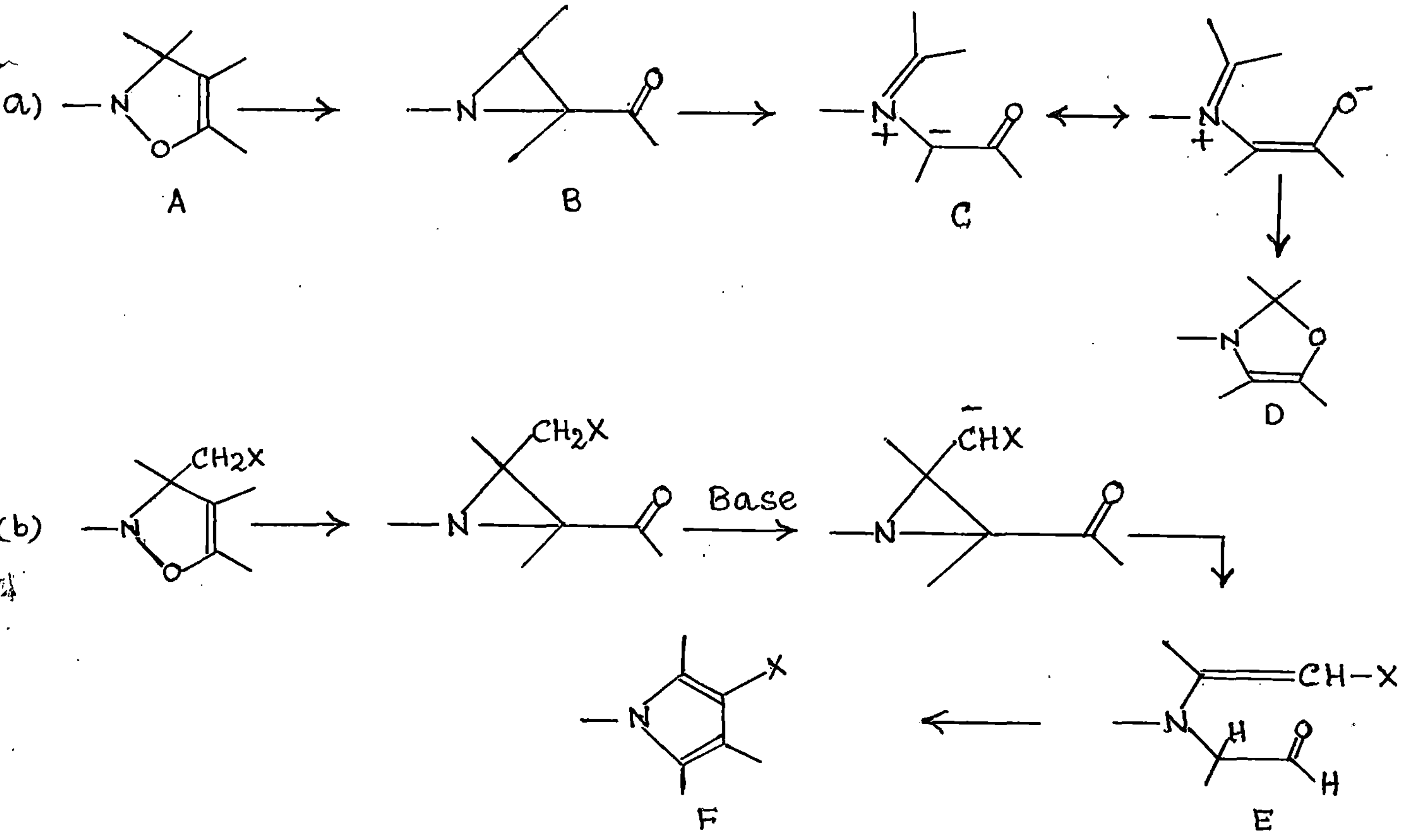
Acetylenic compounds reacts smoothly with nitrones to give 4 - isoxazolines. But very seldom the adduct has been isolated. In major cases some rearranged products are found. The instability of the isoxazoline system is most plausibly responsible for the rearrangement (207). Depending on the nature of substituents, a number of different rearranged products may be formed as shown in Scheme - V .

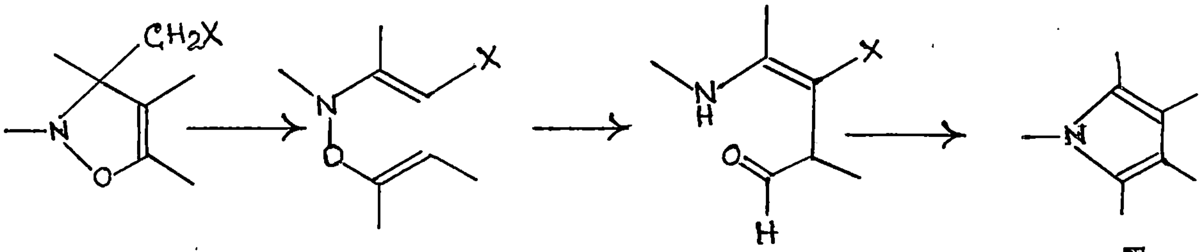
Relatively stable 4- isoxazoline adducts have been prepared from 2- phenyl isatogen (208), and from phenyl - acetylene (209), diphenyl acetylene, cyano acetylenes (26) and enamines (210).

Benzynes form stable adducts with simple nitrones (208) but those derived from hetero aromatic N- oxides cannot be detected and are postulated to undergo rearrangement to phenolic derivatives (211,212).

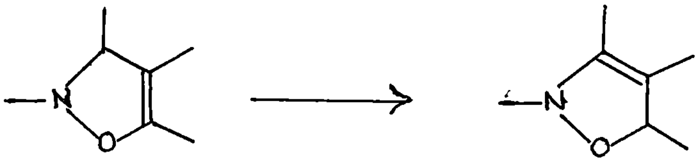


Scheme - V



(c) 

G F

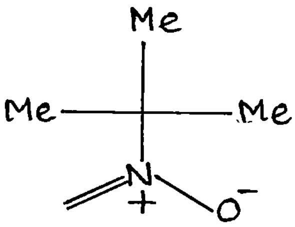
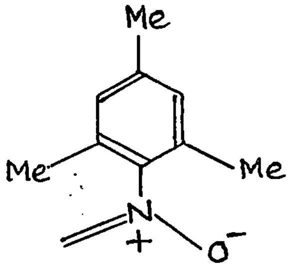
(d) 

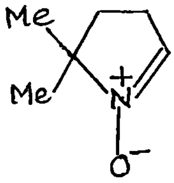
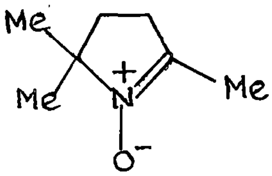
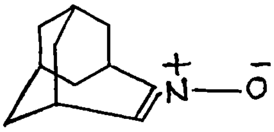
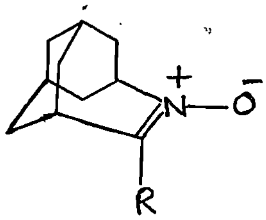
H

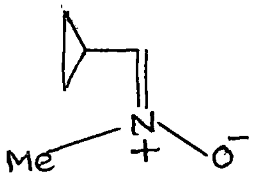
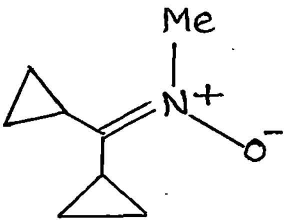
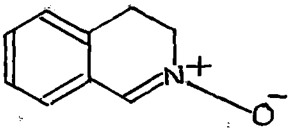
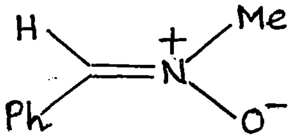
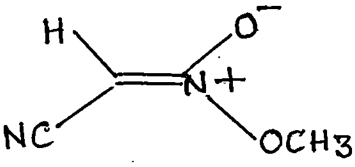
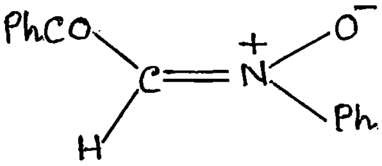
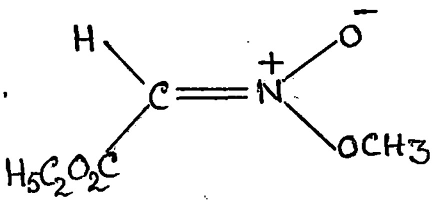
Allenes and Ketenes also give different products which arises presumably from rearrangements of the initial adducts (142, 213-215).

Table 2 :

Cycloaddition of Nitrones to alkynes :

	Nitrone	Alkyne	References
1.		$MeOOC-C\equiv C-COOMe$	216
2.		" "	"

	Nitrone	Alkyne	References
3.		$MeOOC—C\equiv C—COOMe$	217
4.		" "	"
5.		$PhC\equiv CH$	99
6.	 R = H ; Me	$R^1C\equiv CR^2$ (i) $R^1 = COOCH_3$; $R^2 = H$ (ii) = CN ; = H (iii) $= CO_2CH_3$; $= CO_2CH_3$ (iv) = H ; = Ph	99

	Nitrone	Alkyne	References
7.		$H-C\equiv C-COOC_2H_5$	25
8.		" "	"
9.		(i) $MeOOC-C\equiv C-COOMe$	198
		(ii) $Ph-C\equiv C-COOEt$	"
10.		$HC\equiv C-CO_2Me$	"
11.		$PhCO-C\equiv CH$	221
12.		$Ph-C\equiv CH$	219
13.		$Ph-C\equiv CH$	220

(C) Addition to Carbon - Nitrogen Bonds :

Iso cyanate add spontaneously with a wide variety of nitrones to give stable products as reported in Table - 3. Similar cycloaddition reactions with iso-thiocyanates , Carbodimides, aziridinium and azitidium salts are also reported and reviewed (144). Other examples of nitrone additions to carbon-sulpher , carbon-phosphorus and nitrogen-phosphorus multiple bonds are also reviewed (144).

Recently 1,3 dipolar cycloaddition reactions of nitriles with a variety of nitrones has been studied and showed that nitrone - nitrile cyclo additions mechanistically not different from nitrone - alkene cycloadditions (222, 223).

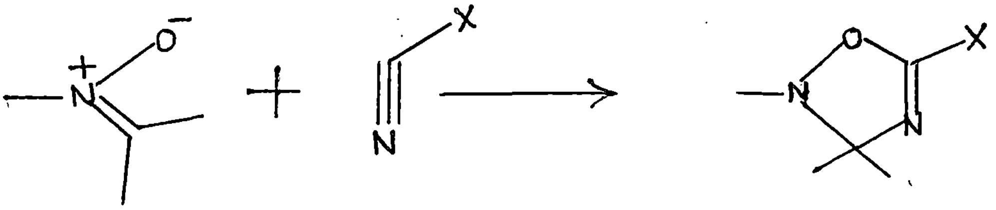
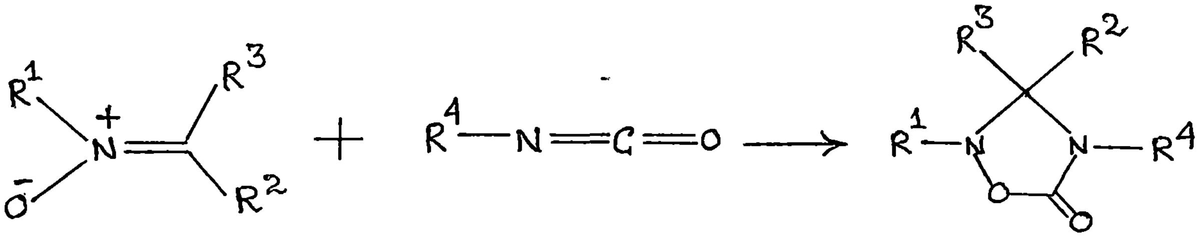
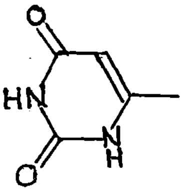
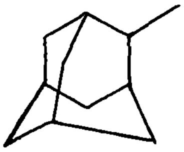


Table 3



	R^1	R^2	R^3	Ref.
(i)	PhCH$_2$	Ph	H	224- 226
(ii)	Ph	Ph	H	227 - 229
(iii)	Me	Ph	H	" "

	R^1	R^2	R^3	Ref.
(iv)	Ph	Ph–CH$_2$–CH–	H	230
(v)	Ph	Ph	Ph	43
(vi)	Ph		H	196
(vii)	Alkyl; Aryl	H	H	231, 232, 226, 233.
(viii)		Aryl	H	234
(ix)	″	Alkyl	H	235

Synthesis of Lentiginosine by stereoselective chiral Nitrone cycloaddition and thermal rearrangement of stained spiro isoxazolidine was reported recently by A.Brandi et al (244).

CHAPTER III
EXPERIMENTAL

IR spectra were recorded as film or in solution or in nujol by Perkin - Elmer 1800 (FR - IR) and Perkin - Elmer 881 or Perkin - Elmer 557 machine. Absorption maxima stated were in cm^{-1} ; abbreviations used were ;

S = Strong, m = medium, w = week, b = broad .

Proton NMR spectra were recorded by Bruker WM 400 (400 MHZ, FT NMR),varian EM-360 L (60 MHZ) and EM 390 (90 MHZ) instruments. TMS as internal standard. Solvents were specified in each case. Abbreviations used were :

S = singlet, d = boublet, t = triplet, q = quartred ,
b = broad, m = multiplet .

Mass spectra were recorded by Jeol D - 300 (CI) spectrometer. All melting points are uncorrected. TLC of the reaction mixture and that of pure compounds were compared. Hand drawn silica gel(E.Merck) plates of 0.5-0.7 mm thickness were used for TLC studies. Silica gel (Loba;60-200 mesh) alumina (BDH) were used for column chromatography. All the solvents and most of the reagents were purified before use.

(A) Preparation of the N- cyclohexyl hydroxyl amine (246):

Pyridine hydrochloride was prepared by passing dry hydrogen chloride through a solution of dry and distilled pyridine, in dry ether, till white precipitation of pyridine hydrochloride was completed. The precipitate was quickly filtered, washed with dry ether and dried under vaccum.

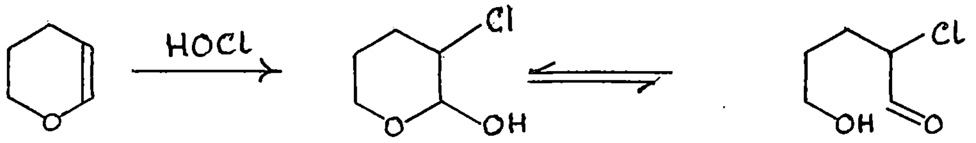
To a solution of pyridine hydrochloride (65.9g, 0.57mole) suspended in dry pyridine (150 ml), a solution of soddium - borohydride (22.24g , 0.58 mole) in dry pyridine (575 ml) was added dropwise under nitrogen atmosphere. The reaction mixture was filtered quickly under suction and the filtrate concentrated at 50° c / 5mm , when pyridine borane remained in the flask as a pale yellow liquid (49g , 93 %). The reagent was used in the next step without further purification.

A solution of cyclohexanone oxime (5.6g , 0.05 mole) and pyridine borane (25ml ,0.25mole) in ethanol (25ml) was stirred at 5° c for 30 minutes, rendered alkaline with ether saturated aquous sodium bicarbonate and extracted with ether (25 X 3)ml. The combined ether layer was washed with H_2O (25 X 3)ml and anhydrous $MgSO_4$. Upon removal of ether, N- cyclohexyl hydroxyl amine was obtained as a white solid (5.2g 91 %), which was recrystallized from ethanol as white needles.

M.P - 140° c

IR (Nujol) : 3220 (s); 3120 (s,b); 1515 (s); 1345 (m); 1310 (m); 1270 (w); 1245 (w); 1210 (s); 1150 (s); 1120 (m); 1075 (s); 1065 (s); 1030 (s); 970 (s); 930 (s); 920 (s); 900 (s); 840 (s); 830 (s); 810 (s); 790 (s) .

(B) Preparation of "Chloro - hydrin" (Communicated):



Dihydropyran (1 equivalent) was taken with water (2 - equivalent) at 10° c . With stirring hypochlorous acid (HOCl), (produced by passing dry Cl_2 in a saturated $NaHCO_3$ solution) was added in one portion and the reaction mixture was cooled to 0-5° c. It was followed by-quenching the reaction mixture into water and finally the product was isolated with ether extraction (25ml X 3).

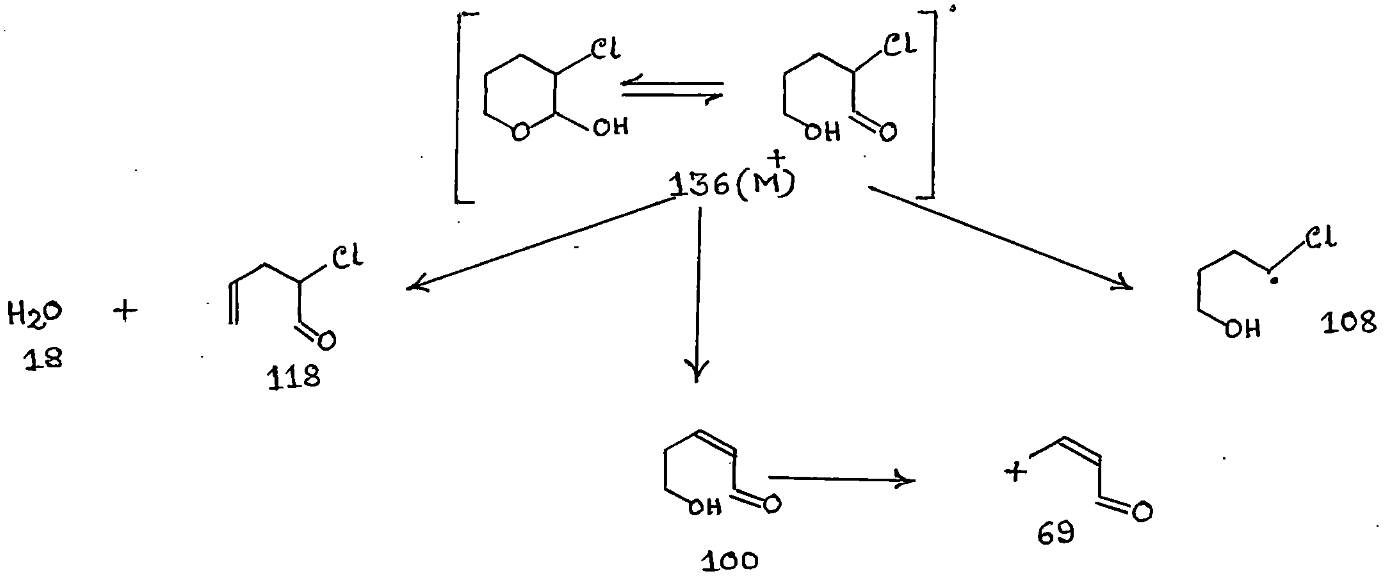
IR : 3300 - 3480 (b); 2940 - 2960 (s); 1640 (m); 1450 (w); 1360 (w); 1280 (w) .

PMR : ($CDCl_3$) : δ (5.2 - 5.1; b, 1H; -OH) δ 9.1 (1H, $\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\underline{\mathrm{H}}$)
5 - 4.9 (C-1, $>\underset{H}{C}$ - O) ; d, J = 6Hz; 1H)
4.1 - 3.9 (C-2, $>\underset{H}{C}$ - Cl) ; m, 1H, - $\underset{|}{C}$H - Cl).

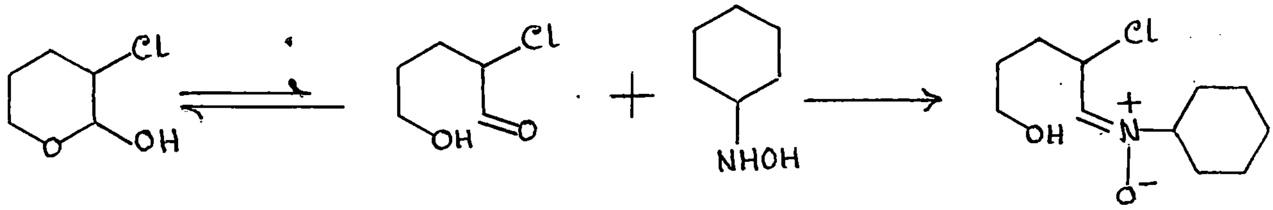
3.8 - 3.4 (m, 2H, - O - CH_2 -).
2.4 - 0.7 (m, 4H, - CH_2 -).

Mass(m/z) : 136(M^+); 118; 108; 102; 85; 78; 69; 52; 49; 35; 32; 18.

The major mass fragmentation patterns of "chloro hydrin" was explained as follows :



(C) Preparation of N-cyclohexyl chloro- nitrone (Communicated):



N - cyclohexyl hydroxyl amine, 0.500g (4.34 m. mole) was added to a solution of 0.6167g (4.52 m.mole) chlorohydrin in dry ether (150 ml) and anhydrous $MgSO_4$, under nitrogen atmosphere and was kept at R.T. for 24 hrs, while the formation of nitrone was monitored by TLC(Silica gel ; ethyl acetate / Benzene = 1:10). The nitrone was isolated as colourless crystal by column chromatography using 10g Al_2O_3 (5 % deactivated) and ether as eluent. Nitrone was highly hygroscopic and showed characteristic IR bands at 1610 (s) cm^{-1}.

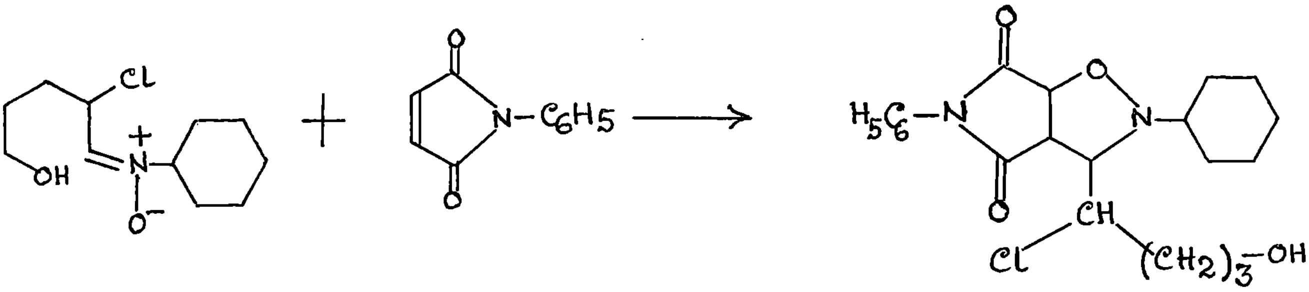
M.P. - 58°c

IR : 3200 - 3400 (b); 2930 (s); 2880 (w); 1660 (m); 1610 (s);
(Neat) 1450 (s); 1390 (m); 1340 ; 1300 ; 1230 ;1150 ;
1100 ; 1080 ; 1020 ; 1000 ; 940 ; 900 ; 870;

PMR ($CDCl_3$);
90 MHZ :
δ 7.0-6.8 (d, 1H; $\mathrm{H}{>}\mathrm{C}=\overset{+}{\mathrm{N}}{<}$; J = 7.5 HZ)
4.3 - 4.1 (m, 1H; $-\underset{|}{\mathrm{C}}\mathrm{H}-\mathrm{Cl}$; J = 4.5 HZ)
3.7 - 3.6 (m, $>\underset{\mathrm{H}}{\mathrm{C}}-\overset{\mathrm{O}-}{\underset{+}{\mathrm{N}}}=$)
2.2 - 1.0 (m, 16H)

The nitrone was generated by the above method and used in-situ for the following reactions.

1. Reaction of Nitrone With N- Phenyl maleimide :



N- cyclohexyl hydroxyl amine 0.250g (2.17 m. mole) was added to a solution of 0.298g (2.17 m. mole) chlohydrin in dry ether(100 ml) with anhydrous $MgSO_4$, under nitrogen atmosphere and was kept at R.T. for 24 hrs, while the reaction was monitored by TLC (Silica gel ; ethyl acetate / Benzene = 1 : 10).

N- phenyl maleimide, 0.375g (2.17 m. mole) was added at this stage and the reaction mixture was again kept at R.T. for further 48 hrs. The solvent was evaporated off to afford the cyclo adduct as gray white solid (o.398g).. The product was purified by column chromatography using 20g. Silica gel and Benzene : ether = 5 : 1 eluent.

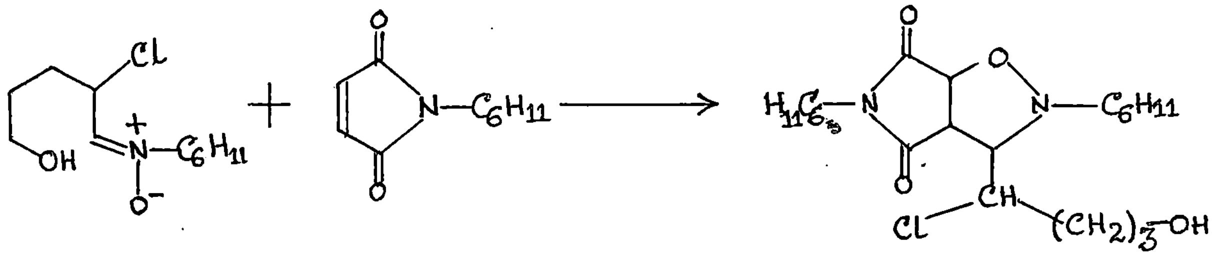
Yield: 45.14 %
M.P. : 150° c
Rf : 0.20 (Benzenel/ethyl acetate = 10 : 1)

IR (KBr) : 3520(s); 3360(s); 2840(s); 1700(s); 1690(s); 1600(s); 1500(s); 1395; 1190.

Mass : (m/z) : $407(M^{+})$; 391; 366; 323; 306; 299; 289; 273; 245; 191; 172; 133; 117; 98; 69; 52; 35; 18.

PMR :δ 7.7 - 7.3 (m, 5H, C_6H_5) .
($CDCl_3$) 5.7 - 5.4 (b, 1H, C(5)H, D_2O exchanged).
5 - 4.43 (d, 1H, J = 5.25 Hzs. C(4)H).
4.39 - 4.33 (d, 1H, J = 5.25 Hzs, $H - \overset{|}{\underset{|}{C}} - Cl$)
3.39 - 3.1 (dd, 1H, J = 5.25 Hzs, C(3)H) .
3 - 2.65 (m, 1H, $>N - CH<$).
2.3 - 1 (m, $- CH_2 -$) .

2. Reaction of Nitrone With N- Cyclohexyl maleimide :



N- cyclohexyl hydroxyl amine , 0.2639g (2.29 m. mole) was added to a solution of 0.312g(2.29 m. mole) chlorohydrin in dry ether (100 ml) with anhydrous $MgSO_4$, under nitrogen atmosphere and was kept at R.T. for 24 hrs, while the reaction was monitored by TLC (Silica gel; ethyl acetate / Benzene = 1 : 10).

N- cyclohexyl maleimide (0.428g), 2.39 m. mole was added at this stage and the reaction mixture was again kept at R.T. for further 48 hrs. The solvent was evaporated off to afford yellowish white solid (o.6487g) as product. The product was purified by column-chromatography using 20g. Silica gel and Benzene : ether = 2 : 1 as eluent .

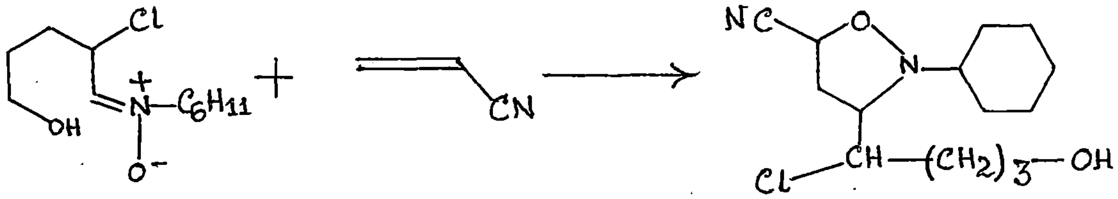
Yield: 67.55 %
M.P. : 77° c
Rf : 0.60 (Benzene / ethyl acetate = 10 : 1)

IR : ($CHCl_3$) : 3580(b); 2920(S); 2840(m); 1760; 1700(b); 1440; 1380.

Mass : (m/z) : 412($\overset{+}{M}$); 408; 399; 366; 344; 321; 283; 260; 220; 208; 178; 171; 142; 126; 110; 102; 96; 79; 52; 35; 18.

PMR ($CDCl_3$):
δ 4.63 - 4.57 (d, J = 6.06 Hzs, 1H, C(5)H),
4.05 - 3.93 (m, 1H, - $\overset{|}{C}HCl$)
3.38 - 3.77 (q, J = 6.06 Hzs, 1H, C(4)H]
3.19 - 3.11 (d, J = 6.06 to 7.75, 1H, C(3)H)
2.7 - 2.59 (b, 2H, >N - CH<)
2.2 - 1.1 (m, 26H, $-[CH_2]_{13}$].

3. Reaction of Nitrone With Acrylonitrile :



N- cyclohexyl hydroxyl amine 0.274g (2.38 m. mole) was added to a solution of 0.3103g (2.28 m. mole) chlorohydrin in dry ether (100 ml) with anhydrous $MgSO_4$, under nitrogen atmosphere and was kept at R.T. for 24 hrs, while the reaction was monitored by TLC (Silica gel; ethyl acetate / Benzene = 1 : 10) .

Acrylonitrile, 0.248g (4.679 m. mole) was added at this stage and the reaction mixture was again kept at R.T. for further 48 hrs. The solvent was evaporated off to afford the cycloadduct as dark yellow gummy liquid (0.4713g). The product was purified by column chromatography using 20g Silica gel and Pet ether :

Benzene = 1:1 as eluent.

Yield : 71.52 %

Rf : 0.65 (Benzene / ethyl acetate = 10 : 1)

IR : 3450-3400 (b); 2880 (s); 2840 (s); 1620 (br); 1440 (s); 1360 ;

Mass (m/z) : 286(M^{+}); 195; 168; 151; 142; 124; 98; 85; 82; 60; 41 .

PMR : ($CDCl_3$) :

δ 5.49 (dd, J = 2.7 & J = 4.05 Hzs, X part of ABX spectrum, 1H, C(5)H).

4.7-4.6 (dd, J = 4.05 & J = 8.1 Hzs, X part of ABX spectrum, 1H, C(3)H).

3.9-3.8 (m, J = 4.05, 5.4, 2.7, X part of ABMX spectrum, 1H, $-\underset{|}{C}HCl$

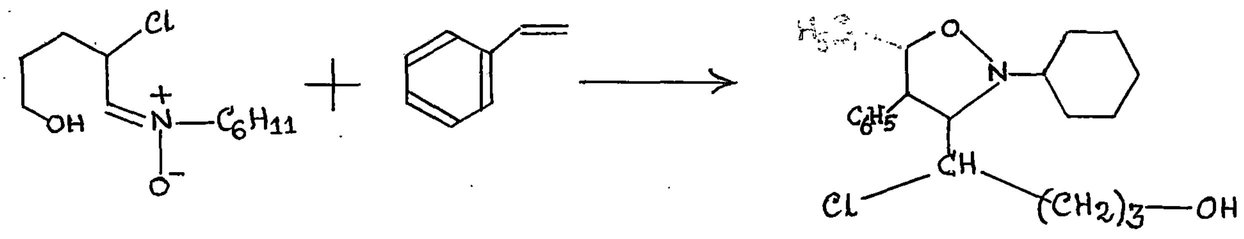
3.55-3.3 (m, AB part of MABX, 2H, C(3)H, $C(4)H_2$, C(5)H)

2.85-2.7 (m, 1H, $>N-CH<$)

2.3 - 1.1 (m, 16H, $-(CH_2)_8-$)

Configuration of the compound is Syn C(5) with respect to C(3) via exo Transition State.

4. Reaction of Nitrone With Styrene :



N- cyclohexyl hydroxyl amine 0.2492g(2.16m.mole) was added to a solution of 0.3123g (2.29 m. mole) chlorohydrin in dry ether (100 ml) with anhydrous $MgSO_4$, under nitrogen atmosphere and was kept at R.T for 24 hrs, while the reaction was monitored by TLC (Silica gel; ethyl acetate / Benzene = 1 : 10) .

Styrene (2.63 m. mole), 0.274g was added at this stage and the reaction mixture was again kept at R.T for further 48 hrs.

The solvent was evaporated off to afford the cycloadduct as white crystalline solid (0.320g). The product was purified by column chromatography using 20g. Silica gel and Benzene / pet ether = 1:1 as eluent .

Yield : 43.89 %

M.P. : 97°c.

Rf : 0.23 (Benzene / ethyl acetate = 1 : 10)

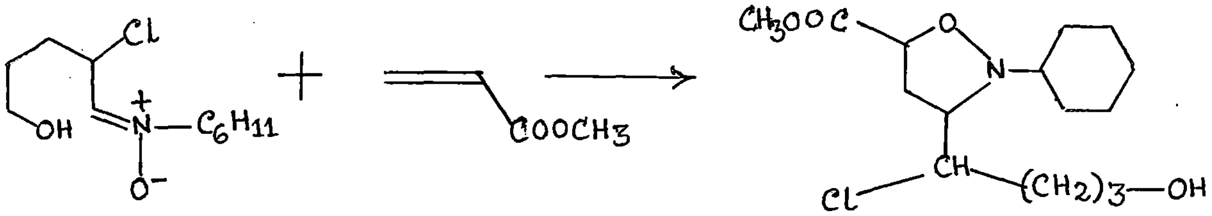
IR : 3580(s); 3320-3180(br); 2960-2840(b); 2400(m); 1700(m); 1650(m); 1435(m); 1310; 1230-1210(b) .

Mass (m/z) : 338(M^+); 219; 142; 114; 96 .

PMR ($CDCl_3$) :

δ 7.6 - 7.35 (m, 5H, C_6H_5) ,
3.55 - 3.43 (q, J = 7.57, 7.57, 13.63, X part of ABX Spectrum, 1H, C(4)H ,)
2.58 - 2.44 (t, J = 6.06, AB part of ABX Spectrum 2H, C(5)H_2)
2.4 - 2.33 (m, 1H, $>$N - CH$<$)
2.285 - 2.145 (t, J = 6.06 Hz, 1H C(3)H)
2.9 - 0.75 (m, 16H, -$(CH_2)_8$ -) .

5. Reaction of Nitrone With Methyl Acrylate



N - Cyclohexyl hydroxyl amine 0.276g (2.40 m. mole) was added to a solution of 0.327g (2.40 m. mole) chlorohydrin in dry ether (100 ml) with anhydrous $MgSO_4$, under nitrogen atmosphere and was kept at R.T for 24 hrs, while the reaction was monitored by TLC (Silica gel ; ethyl acetate / Benzene = 1 : 10) .

Methyl acrylate, 0.206g (2.39 m. mole) was added at this stage and the reaction mixture was again kept at R.T for further 48 hrs. The solvent was evaporated off to afford the cyclo adducts as dark red gummy liquid (0.422g) . The product was purified by column chromatography using 20g Silicagel and Benzene : ether = 2 : 1 as eluent.

Yield : 55.264 %

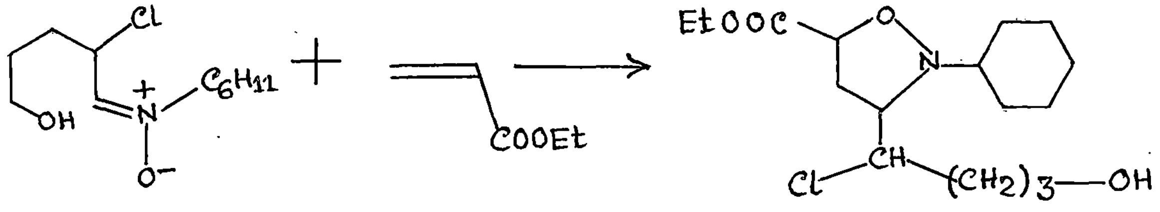
Rf : 0.09 (Benzene / ethyl acetate = 10 : 1)

IR ($CHCl_3$) : 3360-3340 (b); 2930(s); 2850(m); 1625(b); 1440; 1100 .

Mass (m/z) : 319(M^+); 309; 294; 288; 278; 262; 253; 226; 216; 212; 207; 200; 194; 186; 184; 170; 152; 112; 98; 90; 73; 55; 44 .

PMR ($CDCl_3$) :
δ 4.0-3.9 (m, 1H, $-\overset{Cl}{\overset{|}{C}}H-$);
3.87-3.6 (b, X part of ABX spectrum, 1H, C(5)H)
3.53- (s, 3H, $-CH_3$).
3.05-2.9 (dd, J = 6.06 Hz; M part of MABX spectrum, 1H, C(3)H).
2.80-2.63 (b, 1H, $>N - CH<$)
2.60-2.30 (m, AB part of MABX spectrum, $C(4)H_2$
2.2 - 1 (m, 16H, $-(CH_2)_8$ -)

6. Reaction of Nitrone With ethyl Acrylate



N- cyclohexyl hydroxyl amine, 0.264g (2.29 m. mole) was added to a solution of 0.313g (2.30 m. mole) chlorohydrin in dry ether (100 ml) with anhydrous $MgSO_4$, under nitrogen atmosphere and was kept at R.T for 24 hrs, while the reaction was monitored by TLC (Silica gel ; ethyl acetate / Benzene = 1 : 10) .

Ethyl acrylate 0.230g (2.30 m. mole) was added at this stage and the reaction mixture was again kept at R.T for further 48 hrs. The solvent was evaporated off to afford the cycloadduct as yellow gummy liquid (0.407 g). The product was purified by column chromatography using 20g silica gel and Benzene as eluent.

Yield : 61.541 %

Rf : 0.11 (Benzene / ethyl acetate = 10 : 1)

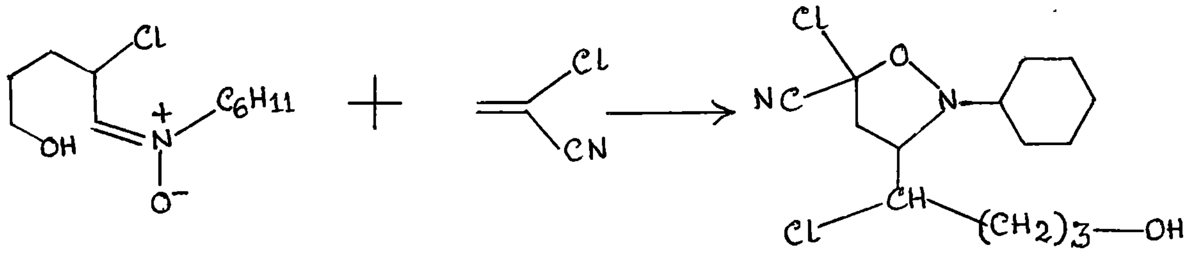
IR ($CHCl_3$) : 3340-3360(b); 2930(s); 2850(m); 1720(s); 1440 .

Mass (m/z) : 333(M^+); 323; 322; 316; 312; 296; 284; 276; 270; 269; 260; 242; 231; 226; 216; 214; 200 (B.P); 187; 180; 170; 161; 145; 131; 114; 102; 100; 52; 35; 18 ;

PMR ($CDCl_3$) :
δ 4.25-4.12 (q, 2H, $-COCH_2.CH_3$)
3.95-3.87 (t, J = 6.06 Hz, 1H, >CH-Cl)
3.6-3.5 (b, X part of ABX Spectrum, 1H, C(5)H).
3.18-3.0 (m, M part of MABX Spectrum, 1H, C(3)H)
2.67-2.43 (m, 1H, >N - CH<)
2.37-2.13 (m, AB part of MABX Spectrum, 2H, $C(4)H_2$)
1.93-0.8 (m, 19H, $-(CH_2)_8-$ & $-CH_3$).

Sturcture is syn with respect to. >CH - Cl via exo Transition State .

7. Reaction of Nitrone With Chloro Acrylo-nitrile



N- cyclohexyl hydroxyl amine 0.237g (2.06 m. mole) was added to a solution of 0.281g (2.06 m. mole) chloro hydrin in dry ether (100 ml) with anhydrous $MgSO_4$, under nitrogen atmosphere and was kept at R.T for 24 hrs, while the reaction was monitored by TLC (Silica gel ; ethyl acetate/ Benzene = 1 : 10) .

Chloro acrylonitrile, 0.180g (2.06 m. mole) was added at this stage and the reaction mixture was again kept at R.T for further 48 hrs. The solvent was evaporated off to afford the cycloadduct as yellow gummy liquid (0.326g). The product was purified by column chromatography, using 20g. Silica gel and

Benzene : Pet ether = 1 : 1 as eluent.

Yield : 49.29 %

Rf : 0.83 (Benzene / ethyl acetate = 10 : 1)

IR ($CHCl_3$): 3384(b); 2932(s); 2856(s); 2337(m); 1603(b); 1451; 1383; 1153;

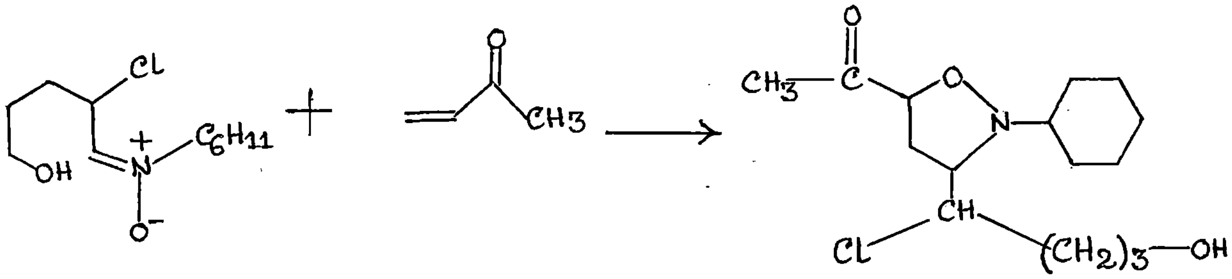
Mass (m/z) : 321(M^+); 308(B.P); 297; 288; 260; 248; 241; 231; 227; 210; 202; 193; 186; 184; 145; 131; 119; 117; 114; 102; 52; 35; 18 .

PMR ($CDCl_3$) δ :

5.9-5.8 (b, 1H, -OH);
4.1-3.9 (m, 1H, -CH-Cl) ;
3.45-3.36 (q, J = 6.06, X part of ABX spectrum, 1H, C(3)H)
3.0-2.86 (dd, J = 6.06 Hzs & J = 15.15 Hzs, AB part of ABX spectrum, 2H, $C(4)H_2$)
2.78-2.68 (m, 1H, >N - CH<)
2.3-0.8 (m, 16H, $-(CH_2)_8$ -)

Structure is expected to be Syn with respect to - CH - Cl .

8. Reaction of Nitrone With Methyl Vinyl Ketone:



N- cyclohexyl hydroxyl amine, 0.253g (2.20 m. mole) was added to a solution of 0.300g (2.20 m. mole) of chlorohydrin in dry ether (100 ml) with anhydrous $MgSO_4$, under nitrogen atmosphere and was kept at R.T for 24 hrs, while the reaction was monitored by TLC (Silica gel; ethyl acetate / Benzene = 1:10).

Methyl Vinyl Ketone, 0.154g (2.20 m. mole) was added at this stage and the reaction mixture was again kept at R.T for further 48 hrs. The solvent was evaporated off to afford the cycloadduct as oily greenish liquid (0.586g). The product was purified by column chromatography, using 20g Silica gel, and Benzene as eluent.

Yield : 87.76%

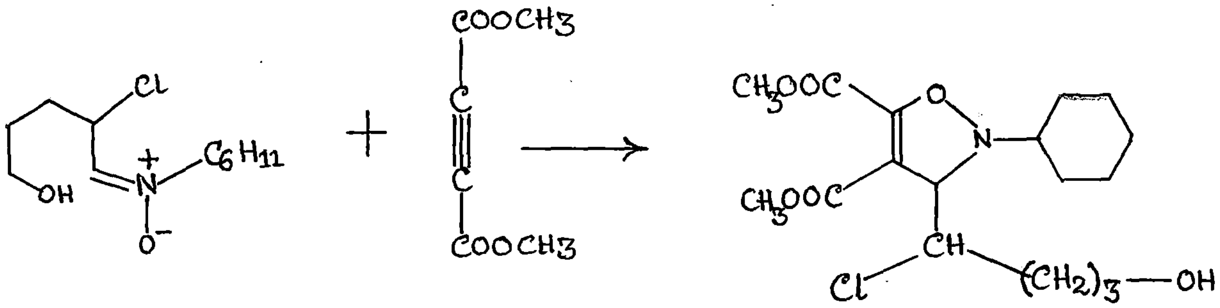
Rf : 0.24 (Benzene / ethyl acetate = 10 : 1)

IR (Neat) : 3440(br); 2920(s); 2840(s); 1710(s); 1440; 1320.

Mass (m/z): 303(M^+); 298; 281; 274; 260; 246; 236; 228; 211; 206; 186; 176; 169; 158; 148; 141; 119; 102; 85; 52; 35(B.P); 18.

PMR ($CDCl_3$): δ 4.9-4.8 [t, J = 6.06 Hzs, X part of ABX spectrum, 1H, C(5)H]
4.15-4.07 (b, 1H, >CH-Cl)
4.07-3.9 [m, 1H, J = 6.06, J = 9 Hzs, X part of MABX spectrum C(3)H]
3.6-3.5 [q, J = 6.06 Hzs, 1H, AB part of MABX spectrum, C(4)H]
2.54-2.48 [b, 1H, >N-CH<]
2.1 [s, 3H, CH_3-]
2-0.8 (m, 16H)

9. Reaction of Nitrone With Dimethyl Acetylene di carboxylate:



N- cyclohexyl hydroxyl amine 0.263g (2.28 m. mole) was added to a solution of 0.312g (2.29 m. mole) chlorohydrin in dry ether (100 ml) with anhydrous $MgSO_4$, under nitrogen atmosphere and was kept at R.T. for 24 hrs, while the reaction was monitored by TLC (Silica gel; ethyl acetate / Benzene = 1:10) .

Dimethyl acetylene dicarboxylate 0.325g (2.28 m. mole) was added at this stage and the reaction mixture was again kept at R.T. for further 48 hrs. The solvent was evaporated off to afford the cycloadduct as oily yellow liquid (0.698g). The product was purified by column chromatography using 20 g Silica gel and Benzene : ether = 5:1 as eluent.

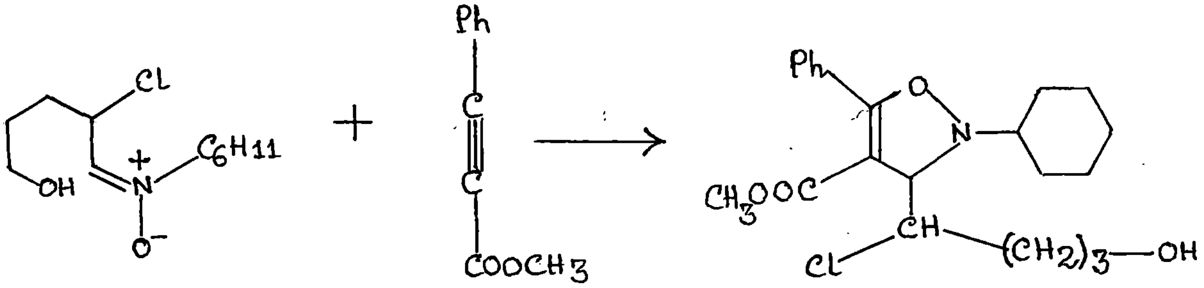
Yield : 81.09 %

Rf : 0.56 (Benzene/Ethyl acetate = 10 : 1)
IR : 3600-3316(b); 2960(s); 2940(s); 1740(s); 1720(s); 1520(s); 1440(m); 1320; 1080;

Mass (m/z) : 375(M^+); 369; 367; 351; 345; 331; 328; 312;
306(B.P); 298; 284; 275; 270; 258; 242; 236;
234; 219; 203; 189; 172; 158; 139; 131; 122;
117; 100; 69;.

PMR ($CDCl_3$) : δ 5-4.9 (d, J = 4.5Hz, 1H, C(3)H)
3.8-3.7 (d, J = 2,Hz 1H, -CHCl)
3.63 (S, 3H, - CO_2Me)
3.59 (S, 3H, -CO_2Me)
2.7-2.5 (b, 1H, - N - CH<)
2.3-0.9 (m, 16H, -$(CH_2)_8$ -).

10. Reaction of Nitrone With Phenyl - methyl propiolate



N - cyclohexyl hydroxyl amine 0.251g (2.18 m. mole) was added to a solution of 0.298g (2.19 m. mole) chlorohydrin in dry ether (100 ml) with dry $MgSO_4$, under nitrogen atmosphere and was kept at R.T for 24 hrs, while the reaction was monitored by TLC (Silica gel; ethyl acetate/Benzene = 1:10).

Phenyl - methyl - propiolate, 0.348g (2.18 m. mole) was added at this stage and the reaction mixture was again kept at R.T for further 48 hrs. The solvent was evaporated off to afford the cycloadduct as Red liquid (0.573g) . The product was purified by column chromatography using 20g Silicagel and Benzene : ether = 4 : 1 as eluent .

Yield : 66.79 %

Rf : 0.42 (Benzene / ethyl acetate = 10 : 1)

IR : 3620-3540(b); 2940(s); 2920(s); 1760(s); 1440; 1360; 1240; 1120; 1080; 960 ;.

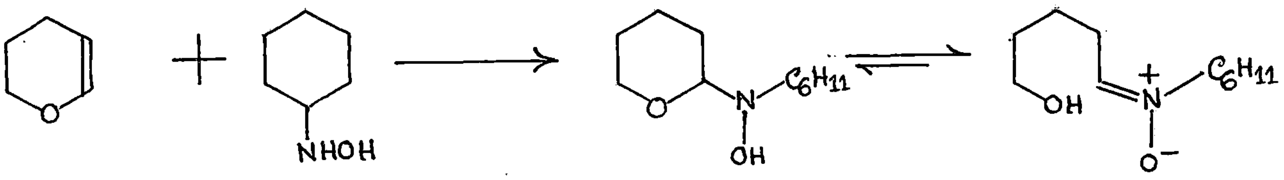
Mass (m/z) : 393(M^+); 385; 378; 372; 354; 336; 344; 336; 324;
319; 316; 302; 299; 288; 275; 361; 260; 253; 234;
217; 204; 195; 186; 178; 119; 102; 69 ;.

PMR ($CDCl_3$):

δ 7.85-7.35 (m, 5H, $-C_6H_5$)
4.55-4.45 (q, J = 6.06 Hzs, 1H, C(3)H)
3.9 -3.8 (b, 1H, - CHCl)
3.7 (S, 3H, $-CO_2CH_3$)
2.8-2.75 (m, 1H, $>N - CH<$)
2.3-0.8 (m, 16H, $-(CH_2)_8-$)

Preparation of N- cyclohexyl 5 - hydroxy Nitrone (245)

N- cyclohexyl hydroxyl amine 0.250g(2.17 m. mole) was added to a solution of 2,3 dihydro -4H- pyran 0.2 ml [0.182g; 2.17 m. mole] in dry benzene (20 ml) under nitrogen atmosphere and was refluxed for 124 hrs, while the reaction was monitored by TLC (Silica gel , Ethyl acetate / Benzene = 1:10). The solvent was evaporated off and the soild nitrone was isolated by column chromatography, (Benzene / Pet - ether (60° - 80°).



IR :(KBr) : 3603(S); 3272(b); 3012(S); 2927(S); 2854(S); 2397(S); 743(m) .

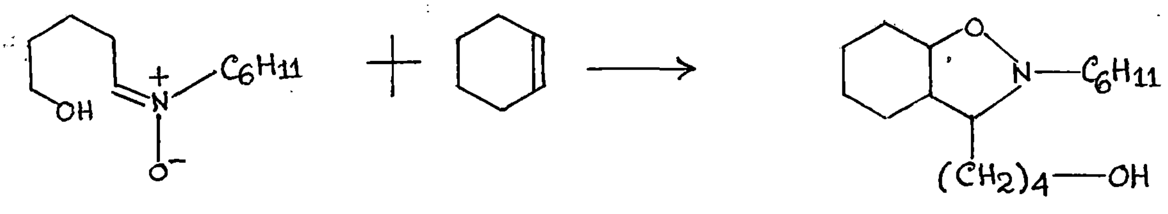
PMR ($CDCl_3$) :δ **6.0-5.8 (b, m, $\underset{O^-}{\overset{+}{=N}}$ - CH)**

2.5-2.3 (m, $(CH_2)_4$ -OH),

1.9-1.2 (m, 10H).

The nitrone was generated from dihydropyran by the above method and used in-situ for the following reactions.

1. Reaction of Nitrone With Cyclohexene :



N- cyclohexyl hydroxyl amine, 0.252g (2.19 m. mole) was added to a solution of 2,3 dihydro -4H- Pyran (0.1846g = 2.21 m. mole) in dry benzene (20 ml) under nitrogen atmosphere and was refluxed for 24 hrs, while the reaction was monitored by TLC (Silica gel, ethyl acetate / Benzene = 1:10) .

Cyclohexene 0.177g (2.15 m. mole) was added at this stage and the reaction mixture was further refluxed for 24 hrs. The solvent was evaporated off to afford the cycloadduct as gray solid (0.207g). The product was purified by column chromatography using 20g Silica gel and Benzene as eluent.

Yield : 34.26 %

M.P. : 106° c

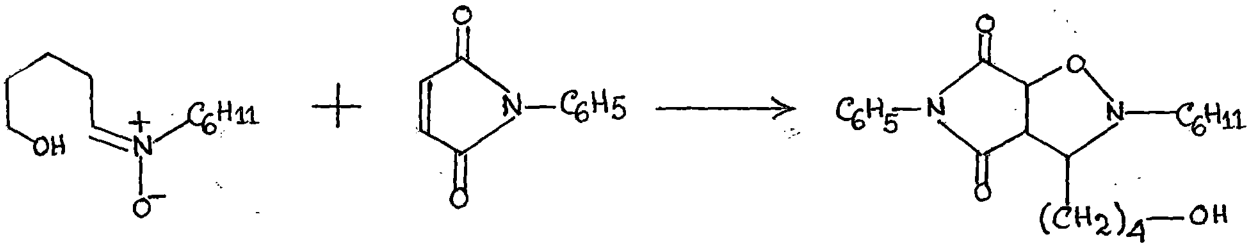
Rf : 0.30 (Benzene : ethyl acetate = 10 : 1)

IR ($CHCl_3$) : 3264(br), 2924, 2851, 1540, 1443, 1248 .

Mass (m/z) : 281(M^+); 113(b.p); 98; 42; 18;.

PMR ($CDCl_3$): δ
3.80-3.7 (d, 1H, J = 4.5Hz, C(5)H)
3.10-3.06 (b, 1H, >CH - N<)
2.63-2.46 (q, 1H, J = 7.5Hz, C(3)H)
2.36-2.16 (dd, 1H, J = 4.5, J = 7.5Hz, C(4)H)
2.00-0.50 (m, 26H)

2. Reaction of Nitrone With N- phenyl maleimide :



N- cyclohexyl hydroxyl amine, 0.250g (2.17 m. mole) was added to a solution of 2,3 -dihydro -4H- pyran, 0.1822g (2.17 m. mole) in dry benzene (20 ml) under nitrogen atmosphere and was refluxed for 124 hrs, while the reaction was monitored by TLC (Silica gel, ethyl acetate / Benzene = 1:10) .

0.3514g (2.13 m. mole) N- phenyl maleimide was added at this stage and the reaction mixture was further refluxed for 24 hrs. The solvent was evaporated off to afford the cyclo adduct as yellowish white solid (0.210g). The product was purified by column chromatography using 20g Silica gel and Benzene as eluent.

Yield : 30.4 %

M.P. : 132° c

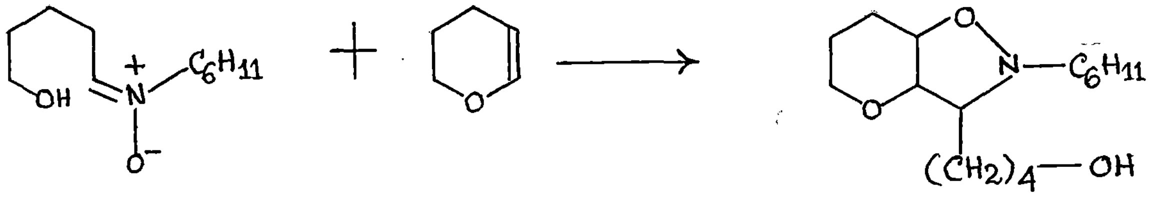
Rf : 0.34 (Benzene : ethyl acetate = 10 : 1)

IR ($CHCl_3$): 3460(br), 2940; 2840; 1700; 1690; 1480; 1395; 1190 ;.

Mass (m/z): 372(M^+), 299, 289, 242, 173, 117, 113, 78.

PMR: ($CDCl_3$): δ
7.8-7.3 (m, 5H, C_6H_5).
5.7-5.46 (b, 1H, C(5)H, exchanged in D_2O shake)
4.5-4.26 (dd, 1H, J = 6Hz, C(4)H)
3.38-3.1 (dd, 1H, J = 6.0Hz, C(3)H).
3.0-2.83 (m, 1H, $>$CH - N$<$)
2.16-0.43 (m, 18H).

3. Reaction of Nitrone With Dihydropyran :



N- cyclohexyl hydroxyl amine, 0.261g (2.36 m. mole) was added to a solution of 2,3 - dihydro - 4H - pyran 0.3964g (4.72 m. mole) in dry benzene (20 ml) under nitrogen atmosphere and was refluxed for 48 hrs, while the reaction was monitored by TLC (Silica gel, Ethylacetate / Benzene = 1:10). The solvent was evaporated off to afford the cycloadduct as brown solid, (0.212g). The product was purified by column chromatography, using 15g Silica gel and Benzene as eluent.

Yield : 31.74 %

M.P. : 103° c

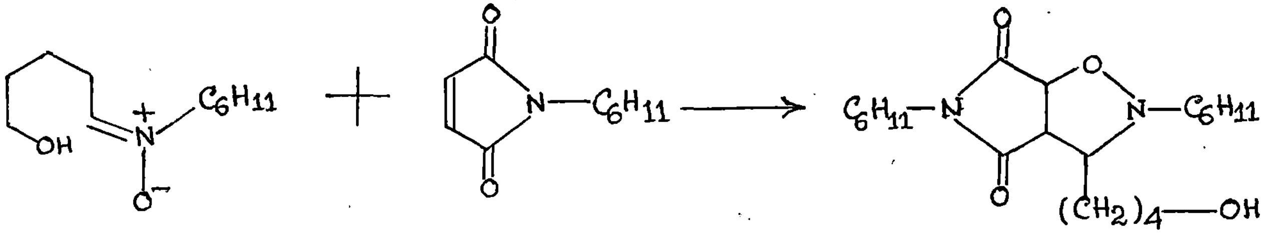
Rf : 0.42 (Benzene : ethyl acetate = 10 : 1)

IR ($CHCl_3$): 3580(s); 3300-3160(b); 2880(s); 2740(m); 1660(s); 1440(b); 1360(m); 1310; 1240-1190(b); 1130; 1100(s); 980;.

Mass (m/Z) : 283(M^+); 227; 209; 193; 182; 168; 152; 142; 114; 98;.

PMR ($CDCl_3$): δ 2.5-2.4 (C-5, 1H, t,)
2.3-2.2 (C-4, 1H, d,)
2.2-2.1 ($>$N - CH, m,)
1.7-1.6 (C3 - 1H, m,)
1.6- 1.5 (m, 24H).

4. Reaction of Nitrone With N- cyclohexyl maleimide :



N- cyclohexyl hydroxyl amine, 0.251g (2.17 m. mole) was added to a solution of 2,3 dihydro -4H- pyran, 0.182g (2.17 m. mole) in dry benzene (20 ml) under nitrogen atmosphere and was refluxed for 24 hrs, while the reaction was monitored by TLC (Silica gel, ethyl acetate Benzene = 1:10) .

N- cyclohexyl maliemide, 0.3884g (2.16 m. mole) was added at this stage and the reaction mixture was further refluxed for 24 hrs. The solvent was evaporated off to afford the cycloadduct as yellow solid (o.242g). The product was purified by column chromatography using 20g Silica gel and Benzene as eluent.

Yield : 29.50 %

M.P. : 114° c

Rf : 0.38 (Benzene : ethyl acetate = 10 : 1)

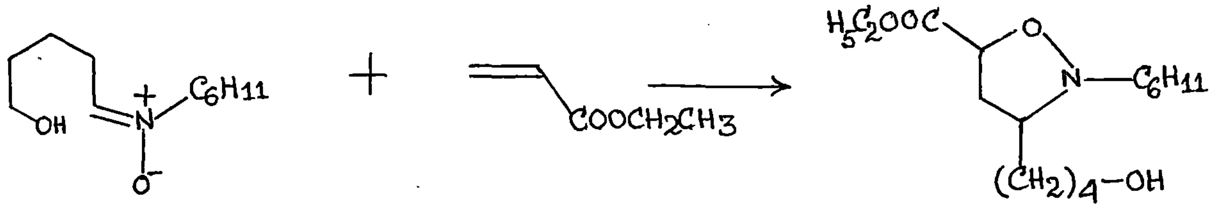
IR ($CHCl_3$): 3580, 2920(br), 1775, 1690, 1440, 1390, 1140, 890.

Mass (m/z): 378(M^+), 323, 305, 295, 277, 267, 251, 208, 196, 170, 114, 83 .

PMR ($CDCl_3$) : δ

5.75-5.0 (b, 1H, C(5)H, exchanged in D_2O shake).
4.15-3.93 (dd, 1H, J = 6.06 Hz, J = 6.06, C(4)H).
3.20-3.10 (m, 1H, $>CH - N<$)
3.06-2.94 (dd, 1H, J = 6.06Hz, C(3)H)
2.93-2.84 (m, 1H, $>CH - N\overset{O}{<}$)
2.20-1.03 (m, 28H)

5. Reaction of Nitrone With Ethyl acrylate :



N- cyclohexyl hydroxyl amine 0.255g (2.20 m. mole) was added to a solution of 2,3 dihydro 4H - Pyran, 0.182g (2.17 m. mole) in dry benzene (20 ml) under nitrogen atmosphere and was refluxed for 24 hrs, while the reaction was monitored by TLC (Silica gel, ethyl acetate / Benzene = 1:10) .

Ethyl acrylate, 0.217g (2.17 m. mole) was added at this stage and the reaction mixture was further refluxed for 24 hrs. The solvent was evaporated off to afford the cyclo adduct as dark red liquid (0.363g). The product was purified by column chromatography using 25g Silica gel and Benzene : Pet ether = 1:2 as eluent.

Yield : 55.94 %

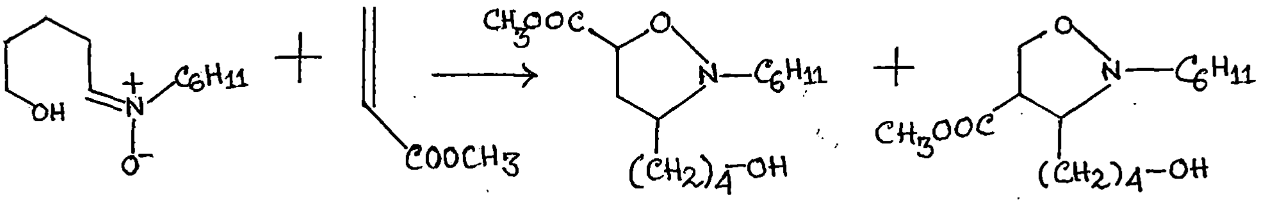
Rf : 0.46 (Benzene : ethyl acetate : 1:10).

IR ($CHCl_3$) : 3340(br), 2930, 2850, 1725, 1440.

Mass (m/z) : 299(M^+); 296; 242; 226; 204; 187; 142; 131(b.p).

PMR ($CDCl_3$) : δ
4.77-4.64 (b, 1H, C(5)H, exchanged in D_2O shake).
4.20 (q, 2H, - O CH_2CH_3).
3.10-2.98 (t, 1H, J = 8.1Hz, C(3)H).
2.98-2.80 (b, 1H, $>$CH - N$<$).
2.80-2.60 (q, 2H, J = 8.1Hz, C(4)H_2).
2.35-0.60 (m, - CH_3 and remaining protons).

6. Reaction of Nitrone With Methyl Acrylate :



(A) (B)

N- cyclohexyl hydroxyl amine, 0.254g (2.18 m. mole) was added to a solution of 2,3 dihydro -4H- pyran, 0.182g (2.17 m. mole) in dry benzene (20 ml) under nitrogen atmosphere and was refluxed for 24 hrs, while the reaction was monitored by TLC (Silica gel, ethyl acetate/Benzene = 1:10) .

Methyl acrylate, o.1866g (2.16 m. mole) was added at this stage and the reaction mixture was further refluxed for 24 hrs. The solvent was evaporated off to afford two cycloadducts as yellow liquids (0.400 g) identified by TLC. The products were purified and separated by column chromatography using 20g silica gel.

Benzene : Pet ether = 1 : 2 (eluent for product A)
Benzene : Pet ether = 1 : 1 (eluent for product B)

Yield : 64.67 % (total)

Physical Data for Product A :

Rf : 0.47 (Benzene : ethyl acetate = 10:1)

IR (Neat) : 3360(b); 2960(s); 2940(m); 1760(s); 1440; 1400; 1320; 1300; 1160; 1120; 880;.

Mass (m/z) : $285(M^+)$; 278; 267; 262; 252; 236; 221; 211; 196; 180; 169; 151; 154; 128; 126; 113; 98; 83; 55;.

PMR ($CDCl_3$) : δ 3.7 (C-5, 1H, b)
3.1-2.9 (C-4, 2H, b, m,)
2.7 (- $\overset{O}{\overset{\|}{C}}$ - OCH_3 , 3H,)
2.2-2.1 (>N - CH< , m)
1.8-1.6 (C-3, 1H, m,)

1.4-1.2 (m, 14H) ;

Physical Data for Product B

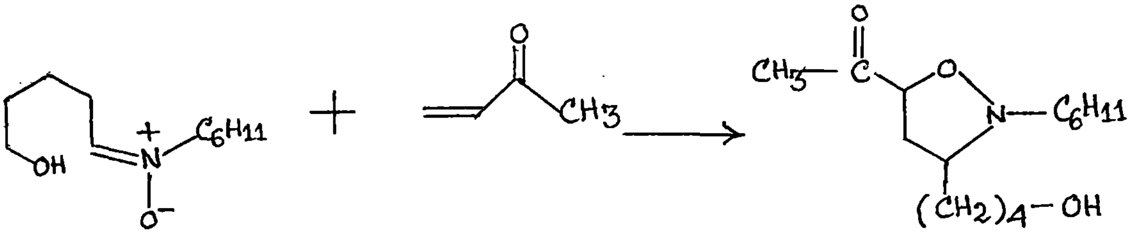
Rf = 0.38

IR (Neat) : 3360(b); 2940(s); 2920(m); 1740(s); 1435; 1400; 1250; 1130; 860;

Mass (m/z) : 287 (M+2); 285(M^+; 267; 242; 229; 211; 209; 183; 178; 165; 102.

PMR ($CDCl_3$) :δ 3.75-3.6 [s,3H,-OCH_3]
3.1-2.8 [m, 2H, C(5)H_2 AB part of ABX spectrum, J = 12.3 Hzs]
2.8-2.6 [m, X part of ABX spectrum, 1H, C(4)H & 1H of$>$CH - N$<$]
2.4-2.3 [q, 1H, J = 6.06 Hzs, C(3)H]
1.9-1.1 [m, 18H,]

7. Reaction of Nitrone With Methyl Vinyl Ketone :



N- cyclohexyl hydroxyl amine, 0.250g (2.17 m. mole) was added to a solution of 2,3 dihydro -4H- Pyran, 0.182g (2.17 m. mole) in dry benzene (20 ml) under nitrogen atmosphere and was refluxed for 124hrs, while the reaction was monitored by TLC (Silica gel, ethyl acetate / Benzene = 1:10).

Methyl Vinyl Ketone, 0.151g (2.17 m. mole) was added at this stage and the reaction mixture was further refluxed for 24 hrs. The solvent was evaporated off to afford the cycloadduct as crystalline white solid (0.453g). The product was purified by column chromatography using 25g Silicagel and Benzene : Pet ether = 2:1 as eluent.

Yield : 77.60 %

M.P. : 140° c

Rf : 0.30 (Benzene : ethyl acetate = 10:1)

IR : 3200(b); 2960(s); 2940(s); 1700; 1650; 1480; 1440; 1240; 1120; 1000; 960; 920;.

Mass (m/z) : 269(M^+); 254; 242; 225; 206; 183; 168; 156; 142; 114; 96; 41;.

PMR ($CDCl_3$): δ

2.6-2.5 (C-5, 1H, m,)

2.4 (- $\overset{O}{\overset{\|}{C}}$ -CH_3 , 3H, S)

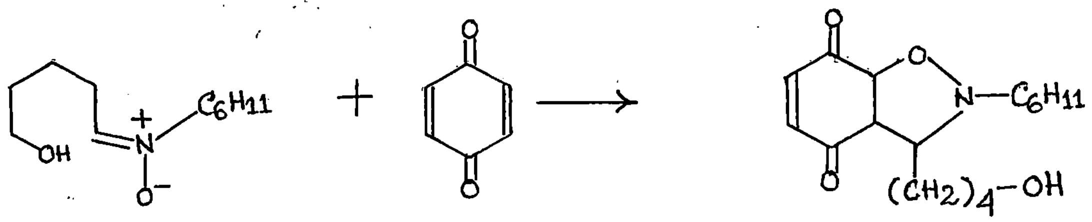
2.3 (C-4, 2H, m)

2.2 ($>$CH - N$<$, m)

1.7 (C-3, 1H, m,)

1.5 (m, 18H),

8. Reaction of Nitrone With P-benzoquinone :



N- cyclohexyl hydroxyl amine, 0.250g (2.17 m. mole) was added to a solution of 2,3 dihydro -4H- Pyran, 0.182g (2.17 m. mole) in dry benzene (20 ml) under nitrogen atmosphere and was refluxed for 24hrs, while the reaction was monitored by TLC (Silica gel, ethyl acetate / Benzene = 1:10) .

P-benzoquinone, 0.234g (2.16 m. mole) was added at this stage and the reaction mixture was further refluxed for 24 hrs. The solvent was evaporated off to afford the cyclo adduct as brown solid (0.417g). The product was purified by column chromatography using 20g Silicagel and Benzene : Pet-ether = 4:1 as eluent.

Yield : 62.65 %

M.P. : 143° c.

Rf : 0.45 (Benzene / ethyl acetate = 10:1)

IR : 3200(b); 2960(s); 2940(m); 1660; 1480; 1440; 1240; 1120; 960; 920 ;.

Mass (m/z) : 307(M^+); 302; 285; 251; 224; 202; 169; 126; 113; 110; 98; 72;.

PMR ($CDCl_3$) :

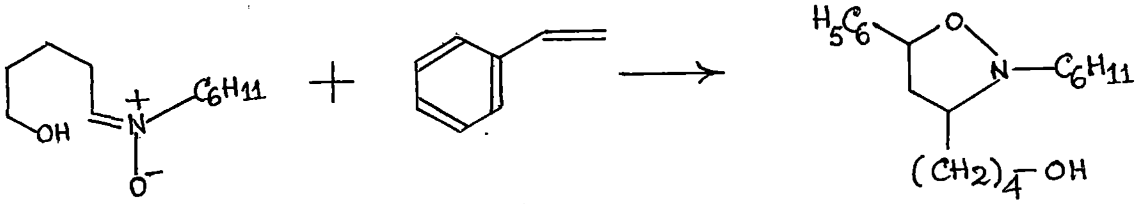
δ 6.7 (O =C–CH=CH–C= O, 2H, S,)

2.5 (C-5, m, 1H,)
2.3 (C-4, m, 1H,)

2.2 ($>$N - CH$<$, 1H, m)

1.7 (C-3, 1H, m)
1.6 (m, 18H)

9. Reaction of Nitrone With Styrene :



N- cyclohexyl hydroxyl amine, 0.255g (2.18 m. mole) was added to a solution of 2,3 dihydro -4H- Pyran, 0.182g (2.17 m. mole) in dry benzene (20 ml) under nitrogen atmosphere and was refluxed for 124 hrs, while the reaction was monitored by TLC (Silica gel, ethyl acetate / Benzene = 1:10).

Styrene, 0.2256g (2.44 m. mole) was added at this stage and the reaction mixture was further refluxed for 24 hrs. the solvent was evaporated off of afford the cyclo adduct as Brown solid (0.3027g). The product was purified by column chromatography using 20g Silicagel and Benzene : ether = 5:1 as eluent.

Yield : 46.03 %
M.P. : 137° c

Rf : 0.52 (Benzene / ethyl acetate = 10:1)

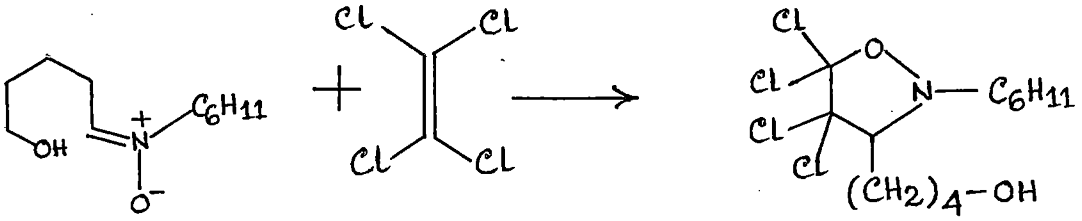
IR : 3580(s); 3200-3180(b); 2920(s); 2840(s); 1650(m); 1440(b); 1350(s); 1310; 1230-1180(b); 1130; 1100; 990(s); 930(s); 880(s);.

Mass (m/z) : 303(M^+); 299; 260; 232; 204; 154; 142; 114; 96;.

PMR : δ
($CDCl_3$)

7.5-7.00	(5H, m, C_6H_5)
2.6-2.5	(1H, m, C_5H , J = 6.06 Hz)
2.3-2.2	(2H, dd, C_4H)
2.1-2.0	(1H, m, C_3H)
1.8-1.7	($-\underset{\mid}{N}-\underset{\mid}{C}H$, m)
1.6-1.4	(m, 18H).

10. Reaction of Nitrone With Tetra-Chloro-ethylene



N- cyclohexyl hydroxyl amine, 0.249g (2.16 m. mole) was added to a solution of 2,3 dihydro -4H- Pyran, 0.182g (2.17 m. mole) in dry benzene (20 ml) under nitrogen atmosphere and was refluxed for 24hrs, while the reaction was monitored by TLC (Silica gel, ethyl / Benzene = 1:10) .

Tetra-chloro-ethylene was added, 0.36g (2.17 m. mole) at this stage and the reaction mixture was further refluxed for 24 hrs. The solvent was evaporated off to afford cycloadduct as brown solid (0.276g). The product was purified by column chromatography using 20g Silicagel and Benzene:ether = 5:1 as eluent.

Yield : 34.84 %

M.P. : 99° - 102° c

Rf : 0.34 (Benzene : ethyl acetate = 10:1)

IR : 3580(s); 3320-3140(b); 2900(s); 2840(m); 1660(s); 1440-1400; 1360; 1310(s); 1220-1190(b); 1130; 1100; 980; 930; 880;.

Mass (m/z) : 365(M^+); 227; 211; 194; 168; 152; 142; 114; 98;.

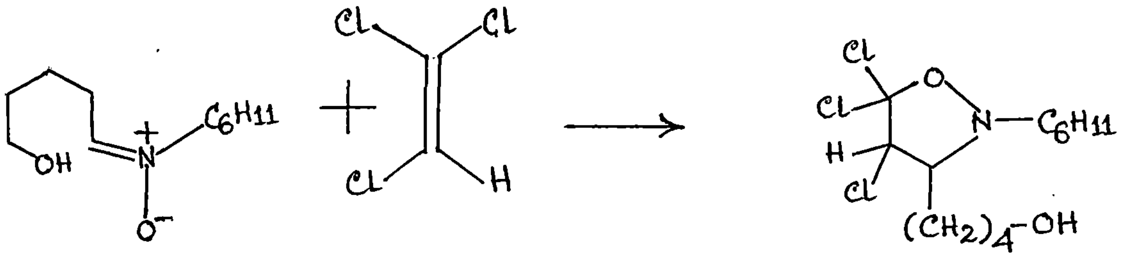
PMR ($CDCl_3$)

δ 2.6-2.5 (m, >N - CH< ;)

2.3-2.2 (m, C-3, 1H)

1.7-1.5 (m, 18H);

11. Reaction of Nitrone With Trichloro ethylene :



N- cyclohexyl hydroxyl amine, 0.253g (2.18 m. mole) was added to a solution of 2,3 dihydro -4H- Pyran, 0.182g (2.17 m. mole) in dry benzene (20 ml) under nitrogen atmosphere and was refluxed for 24hrs, while the reaction was monitored by TLC (Silica gel, ethyl acetate / Benzene = 1:10).

Trichloro ethylene, 0.287g (2.19 m. mole) was added at this stage at the reaction mixture was further refluxed for 24 hrs. The solvent was evaporated off to afford the cyclo adduct as yellowish white solid (0.2713g). The product was purified by column chromatography using 20g. Silicagel and Benzene : Pet-ether = 1:1 as eluent.

Yield : 37.82 %

M.P. : 98° c

Rf : 0.31 (Benzene : ethyl acetate = 10:1)

IR : 3580(s); 3300-3200(b); 2920(s); 2840(m); 1660(m); 1440(m); 1360; 1310; 1250-1190(b); 1130(s); 1100(s); 980(s); 930; 880;.

Mass (m/z) : 330(M^+); 283; 233; 207; 190; 163; 147; 114; 96; 69; 61;.

PMR ($CDCl_3$):

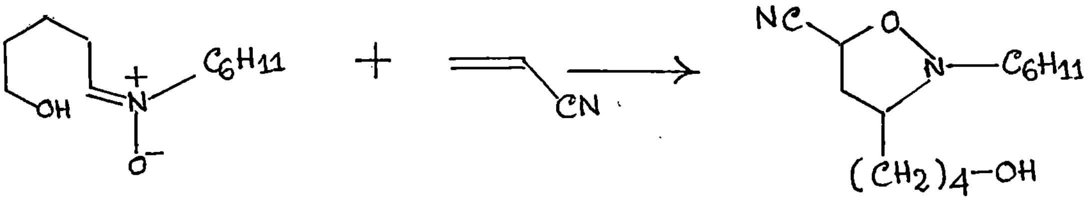
δ 2.5 (m, C-4, 1H,)

2.3 (m, $>$N - CH$<$;)

2.2 (m, C-3, 1H ;)

1.6 (m, 18H);.

12. Reaction of Nitrone With Acrylonitrile :



N- cyclohexyl hydroxyl amine, 0.260g (2.26 m. mole) was added to a solution of 2,3 dihydro -4H- Pyran, 0.1997g (2.36 m. mole) in dry benzene (20 ml) under nitrogen atmosphere and was refluxed for 124hrs, while the reaction was monitored by TLC (Silica gel, ethyl acetate / Benzene = 1:10). Acrylonitrile, 0.134g (2.46 m. mole) was added at this stage and the reaction mixture was further refluxed for 24 hrs. The solvent was evaporated off to afford the cyclo adduct as dark yellow gummy liquid (0.443g). The product was purified by column chromatography using 20g Silicagel and Benzene : Pet-ether = 5:1 as eluent.

Yield : 77.78 %

Rf : 0.25 (Benzene : ethyl acetate = 10:1)

IR : 3222(b); 2934(s); 2857(m); 1664(m); 1449; 1437; 1385; 1350; 1225; 1138; 1073; 993; 899;.

Mass (m/z) : 252 (M^+); 227; 187; 170; 142; 131(B.P); 114; 52;.

PMR ($CDCl_3$) :

δ 3.7-3.5 (C-5- 1H, m;)

3.1-2.9 (C-4, -2H, m;)

2.5 (m, $>N - CH<$;)

2.2 (m, C-3, 1H ;)

1.7-1.5 (m, 18H);

CHAPTER IV
RESULTS & DISCUSSION

General Discussion :

Eschenmoser et al (236-238) have shown the synthetic potentiality of α -chloro nitrone in 1,4 dipolar cycloaddition reactions with an unactivated double bonds. We wish to report an application of α - chloro - nitrone in 1,3 dipolar cycloaddition reactions with different dipolarophiles.

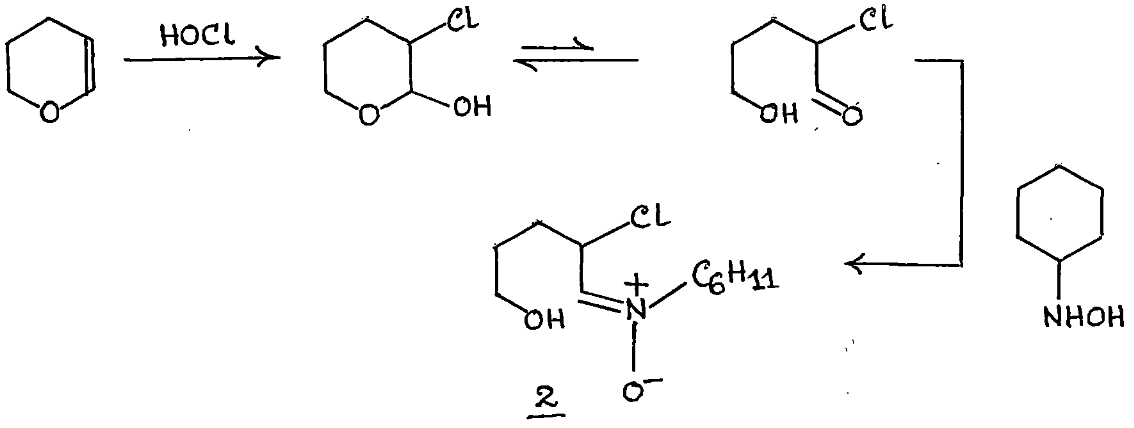
N- cyclohexyl chloro nitrone was synthesised from a mixture of chlorohydrin and its toutomer with N- cyclohexyl hydroxyl amine in dry ether and anhydrous $MgSO_4$ with constant stirring for 24 hours, under N_2 - atmosphere at room temperature.

Chlorohydrin (240) and its tautomer were obtained when 2,3 dihydro -4H- pyran was subjected to chloro hydrination with HOCl.

The nitrone was a colourless crystalline solid, M.P., 58°c (uncorrected).

IR (Nujol) : 1660 (m); 1610 (s) ; 1155 (m).

PMR ($CDCl_3$): δ 7.05-6.65 (b, 1H); 4.3-4.15 (d, J=4.5Hz, 1H)
90 Mhz 3.7-3.5 (b, 1H);
2.6-0.5 (m, 16H)



Nitrone 2, was very unstable, therefore it was generated insitu and trapped with different dipolarophiles at room - temperature in a 1,3 dipolar cycloaddition reaction to furnish cyclo adducts in satisfactory yields. With methyl vinyl ketone and acrylonitrile, the reaction was found to be highly regio selective to form solely 5-substituted isoxazolidines respectively. The regio selectivity in these reactions were rationalised by use of the frontier-orbital theory. Nitrone 2 has considerably higher ionization potentials than normal nitrones due to the electron with drawal effect of chlorine. So Nitrone (LUMO) - Dipolarophile (HOMO) interactions were so important that it completely dominates the reaction and leads to the formation of only 5- substituted adducts.

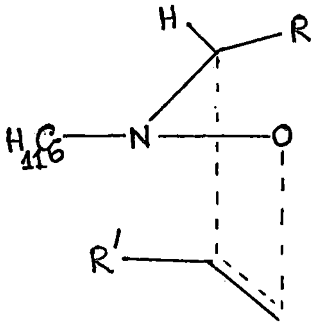
1,3 dipolar cyclo additions of nitrone 2 were not only regio selective but also stereo selective. The relative configurations of C-3; C-4; C-5 protons of the cycloadducts formed in most often cases were syn. Since most of the nitrones were exist exclusively in the Z- configuration, therefore the cycloadducts were formed from Z- nitrone through an exo-transition state.

In table VI, the reaction condition, major products, nature etc. are summarised.

In the case of methyl acrylate adduct both the regio selective products were obtained. When the 4, substituted adduct of methyl acrylate was kept at room temperature for few weeks, the products were partially converted to 5-substituted adducts. These interesting cyclo reversion observations remind once again of Ali's work (178).

With highly electron deficient dipolarophiles viz, N- phenyl maleimide, N- cyclohexyl maleimide and p- benzoquinone cyclo adducts were obtained spontaneously at room temperature.

In the case of 'chloro acrylonitrile', 'methyl vinyl ketone' of N-cyclohexyl chloro nitrone and 'methyl acrylate' of N-cyclohexyl 5-hydroxy nitrone, the cyclo adducts were expected to form via endo Transition State,



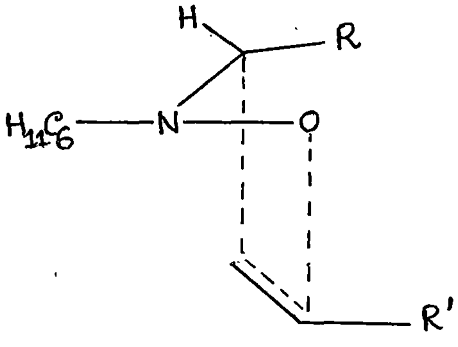
$R = (CH_2)_4-OH$

$= -\underset{Cl}{CH}-(CH_2)_3-OH$

$R' = -COCH_3$.

$= -COOCH_3$.

While N-phenyl-maleimide, ethyl acrylate etc. the cycloadducts were expected to form via exo Transition State.



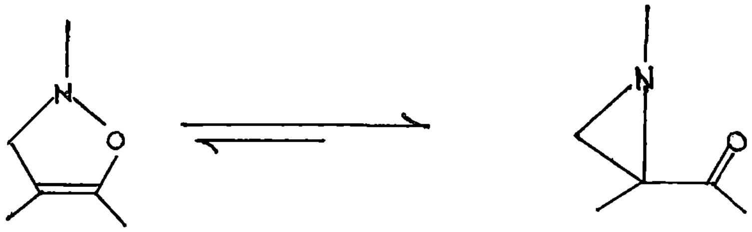
$R = (CH_2)_4-OH$

$= -\underset{Cl}{CH}-(CH_2)_3-OH$

$R' = -COOCH_2CH_3$.

Alkynes, viz, methyl phenyl propiolate and dimethyl acetylene dicarboxylate were studied as dipolarophiles for 1,3 dipolar cyclo addition with N- cyclohexyl chloro-nitrone. Cyclo adducts were obtained at room temperature in satisfactory yields upon purification. Here, the adduct formation can be explained due to secondary orbital effect between the carbon of the nitrone (HOMO) and the adjacent atom of the electron withdrawing group of the dipolaro phile (LUMO).

Both the cycloadducts were thermally stable but while studing the mass fragmentation pattern, base peak (m/e) at 105 (i.e. due to PhCO) for methyl phenyl propiolate adduct was found. Thus during mass fragmentation, the adduct under went the rearrangement to Aziridine ring.



In all the cases number of products formed were explained on the basis of TLC and the major products were isolated in each case. However for the addition of nitrone with some dipolarophiles, the polarity of both the products were so close that the separation was not possible, and both the products were isolated from the reaction mixture and was distinguished from PMR integration curve of the mixture for the respective C-5 protons.

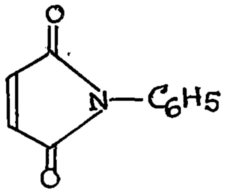
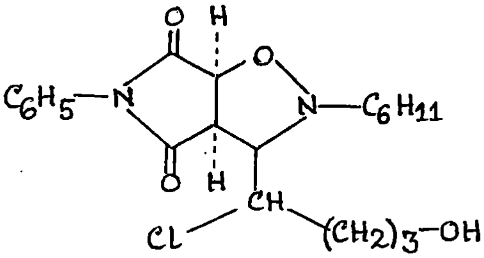
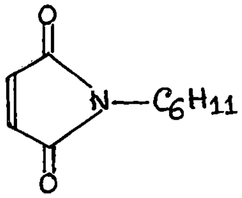
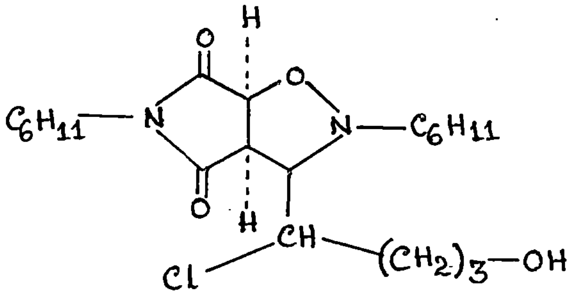
The mode of regio selections in all the cases can be well explained on the basis of qualitative frontier orbital model treatment of nitrone and the dipolaro philes. In qualitative treatment for 1,3 dipolar cyclo additions two major aspects are stressed. One is the energy levels of the dipoles and the dipolarophiles and the other is the HOMO & LUMO coefficients on the concerning atoms of the dipoles and the dipolarophiles. The HOMO - LUMO energy gap of the reactants indicates the fastness of the addition. This gap is low for the additions of the nitrone with moderately electron deficient dipolaro philes and therefore the reactions are comparatively fast.

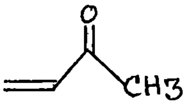
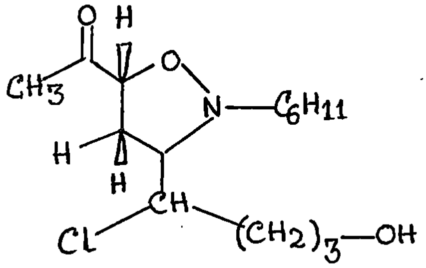
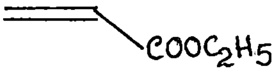
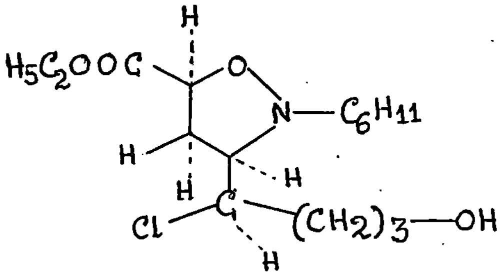
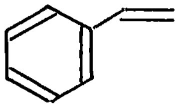
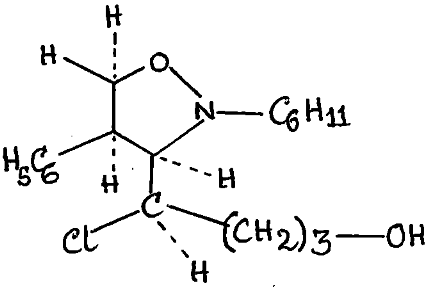
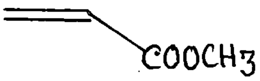
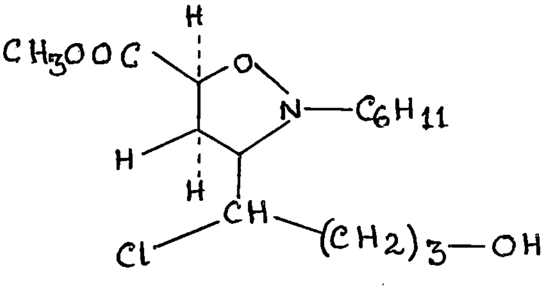
However, the question of regio selection is only applicable for the cases where the kinetically controlled products are considered. The thermodynamic product may be the next product as expected from the regio selection rule (177).

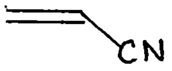
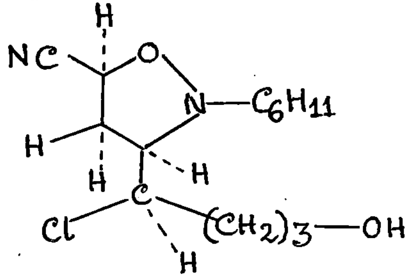
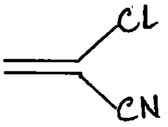
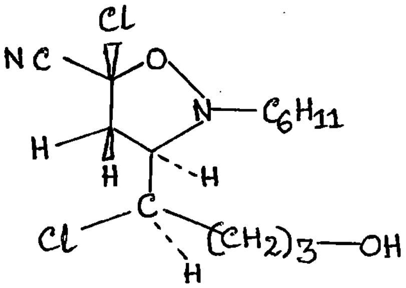
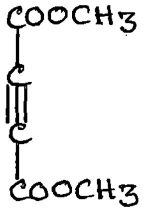
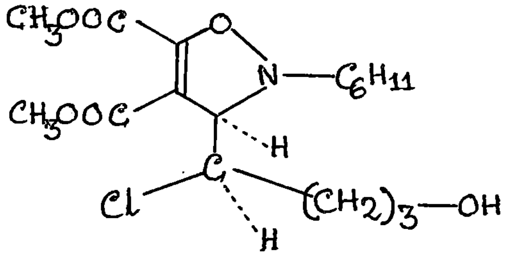
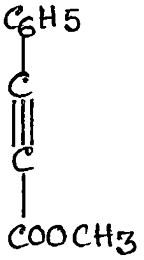
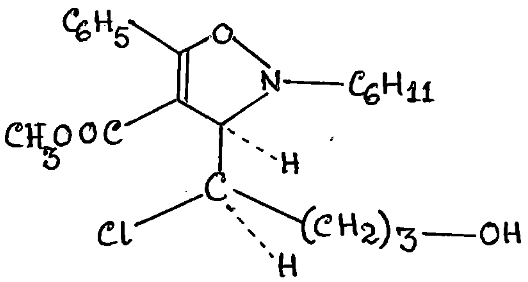
All the olefines considered so far undergo cycloadditions with N- cyclohexyl chloro nitrone at room temperature, but the cycloaddition with styrene which is a electron rich olefin was not facile unless some drastic conditions were applied. For that purpose, styrene was heated with the nitrone for 24 hours, the 4-substituted adduct was obtained and in accordance with the regio selection rules.

Another aspect of the cycloaddition reactions is their preference for the <u>endo</u> addition over the <u>exo</u> addition. In the present cases of cycloadditions of N- cyclohexyl chloro-nitrone , the question cannot be answered from the inspection of the product structure since in such a case either the <u>endo</u> or <u>exo</u> addition affords the some product. But in as such as these cyclo additions hold all the criteria of other cyclo additions,there is no reason to expect that the secondary orbital interactions will be absent in such cases. Houk et al have proposed that the preference for the endo transition state will only be large in these cycloadditions when the dipole - LUMO and dipolaro phile - HOMO inter action will be important which are also in accordance with P.Deshong et. al (206).

Table-VI

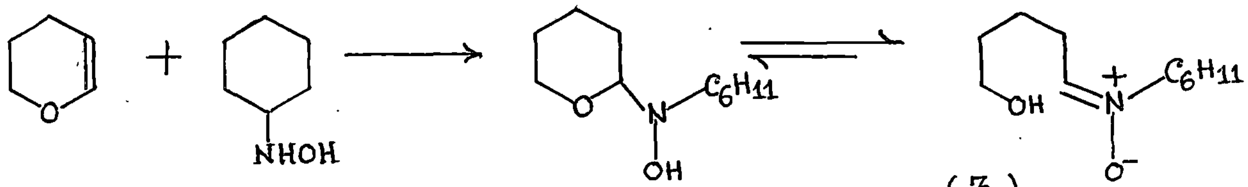
	Dipolarophiles	Solvent/Reaction Condition	Nature of Products	Str. of Products
1.		Ether; R.T. 72 hours	Grayish white Solid	
2.		Ether; R.T. 72 hours	Yellowish white Solid	

	Dipolarophiles	Solvent/Reaction Condition	Nature of Products	Str. of Products
3.		Ether; R.T. 72 hours	Oily greenish Liquid	
4.		Ether; R.T. 72 hours	Yellow Oily Liquid	
5.		Ether; R.T. 72 hours,	White crystalline Solid	
6.		Ether; R.T. 72 hours	Dark Red Gummy Liquid	

	Dipolarophiles	**Solvent/Reaction Condition**	**Nature of Products**	**Str. of Products**
7.		Ether; R.T. 72 hours	Dark Yellow Gummy Liquid	
8.		Ether; R.T. 72 hours	Yellow Gummy Liquid	
9.		Ether; R.T. 72 hours	Yellow Oily Gummy Liquid	
10.		Ether; R.T. 72 hours	Pale Yellow Liquid	

N-cyclohexyl 5-hydroxy nitrone (245) was generated by refluxing N-cyclohexyl hydroxyl amine and 2,3 dihydro-4H pyran in dry benzene for 24 hours

The nitrone was obtained as crystalline solid, M.P. - 77° c (uncorrected).



(3)

IR (KBr) : 3603(s); 3272(b); 3012(s); 2927(s); 2854(s); 2397(s); 743(m);.

PMR (CDCl$_3$): δ :

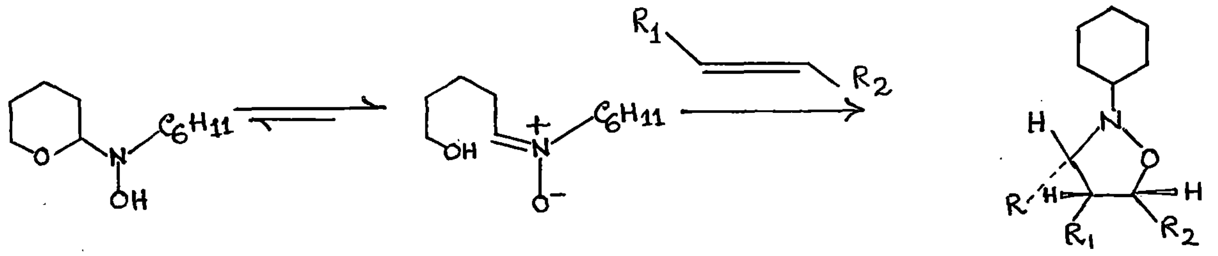
6.0-5.8 (b, m, $=\overset{+}{N}(O^-)-CH$)

2.5-2.3 (m, $(CH_2)_4$ - OH)

1.9-1.2 (m, 10H).

Like that of nitrone (2); nitrone (3) was also very unstable, and hygroscopic in nature and therefore it was generated insitu and trapped with different dipolarophiles in 1 , 3 dipolar cycloaddition reaction to furnish cyclo adducts in satisfactory yields. Dimerisation of the nitrone can also be controlled under this condition.

The concerted nature of cycloaddition reactions with nitrone (245)as 1,3 dipole was generally accepted . The regio selectivity in this relations were rationalised by the use of the frontier - orbiral theory. The ethyl acrylate adduct corresponds to this theory.Therefore the 5- substituted adduct for ethyl acrylate is due to LUMO (nitrone) - HOMO (dipolaro phile) interaction.



II

II (a) $R_1R_2 = -(CH_2)_4-$

(b) $R_1R_2 = -CONPhCO-$

(c) $R_1R_2 = -CONC_6H_{11}CO-$

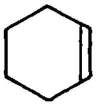
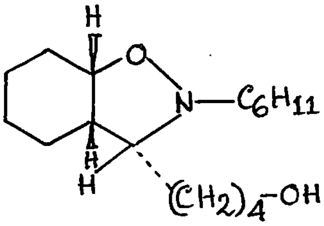
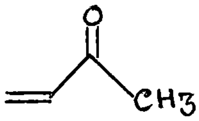
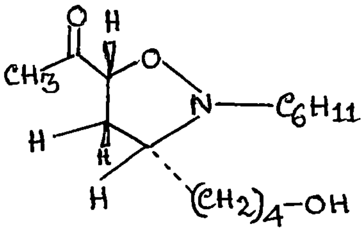
(d) $R_1 = H$, $R_2 = -CO_2CH_2CH_3$

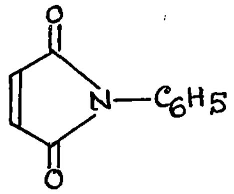
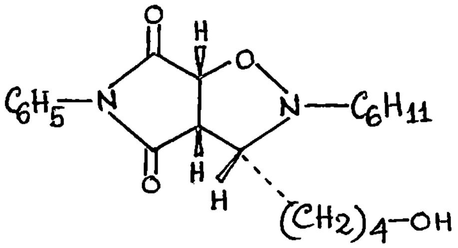
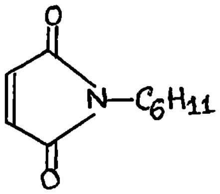
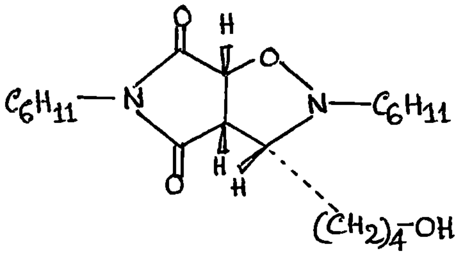
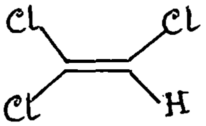
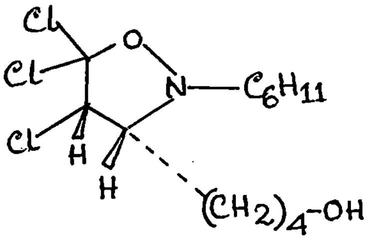
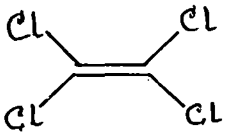
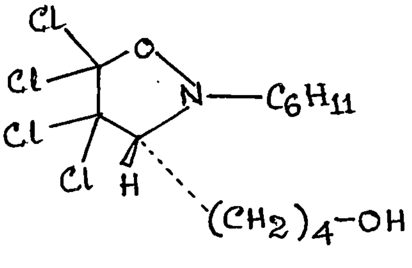
R = $-(CH_2)_3-CH_2OH$

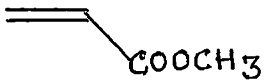
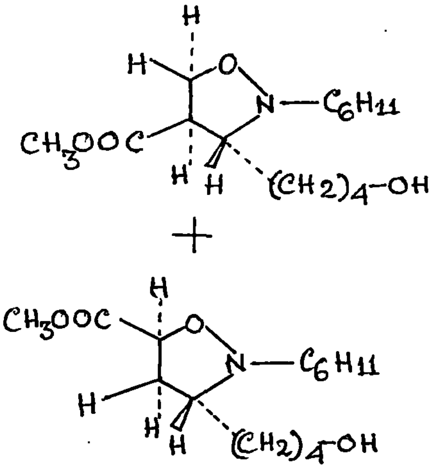
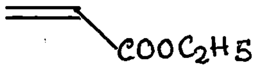
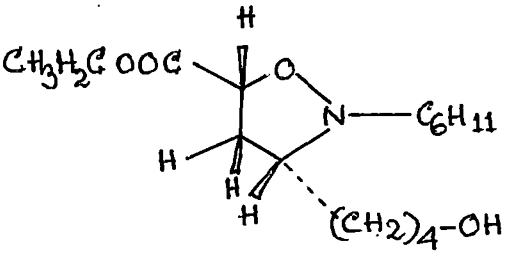
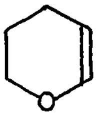
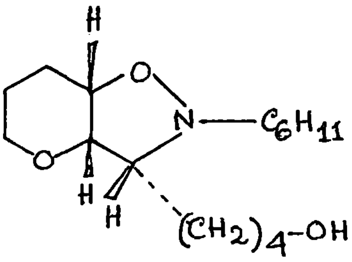
Cyclo addition of Z- nitrone via an exo - transition state results in the formation of syn isoxazolidines. The relative configuration of C3, C4 and C5 in the adducts were in favour of exo-transition state geometry. The proton at C3 and C4 were syn in II-(b) and II-(c) and their coupling constants (J = 6 Hz) were also indicative of this stereo chemical relationship, whilst a D_2O shake revealed the presence of one rapidly exchangeable proton at C-5. Stereo chemistry of II-(a) and II-(d) at C-3, C-4 and C-5 on the isoxazolidine ring were also determined from PMR spectrum. The coupling constant values viz, J = 7.5-8 Hz, were revealed the formation of syn-isoxazolidine in both the cases vis exo transition state.

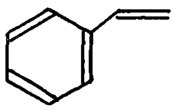
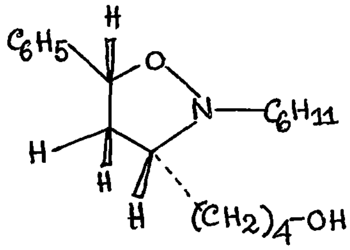
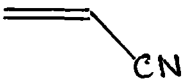
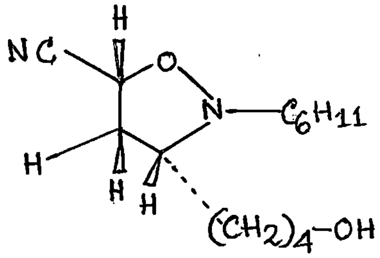
In table VII, the reaction condition, major products and its nature are summarised.

Table-VII

	Dipolarophiles	**Solvent/Reaction Condition**	**Nature of Products**	**Str. of Products**
1.		Benzene; reflux 48 hrs	Gray Solid	
2.		Benzene; reflux 48 hrs	Crystalline White Solid	

	Dipolarophiles	Solvent/Reaction Condition	Nature of Products	Str. of Products
3.		Benzene; reflux 48 hrs	Yellowish White Solid	
4.		Benzene; reflux 48 hrs	Yellow Solid	
5.		Benzene; reflux 48 hrs	Yellowish White Soild	
6.		Benzene; reflux 48 hrs	Brown Solid	

	Dipolarophiles	Solvent/Reaction Condition	Nature of Products	Str. of Products
7.		Benzene; reflux 48 hrs	Yellow Liquid	
8.		Benzene; reflux 48 hrs	Red Liquid Gummy	
9.		Benzene; reflux 48 hrs	Brown Solid	

	Dipolarophiles	Solvent/Reaction Condition	Nature of Products	Str. of Products
10.		Benzene; reflux 48 hrs	Brown Solid	
11.		Benzene; reflux 48 hrs	Yellowish White Crystalline Solid	

2. Interpretation of Mass Spectra:

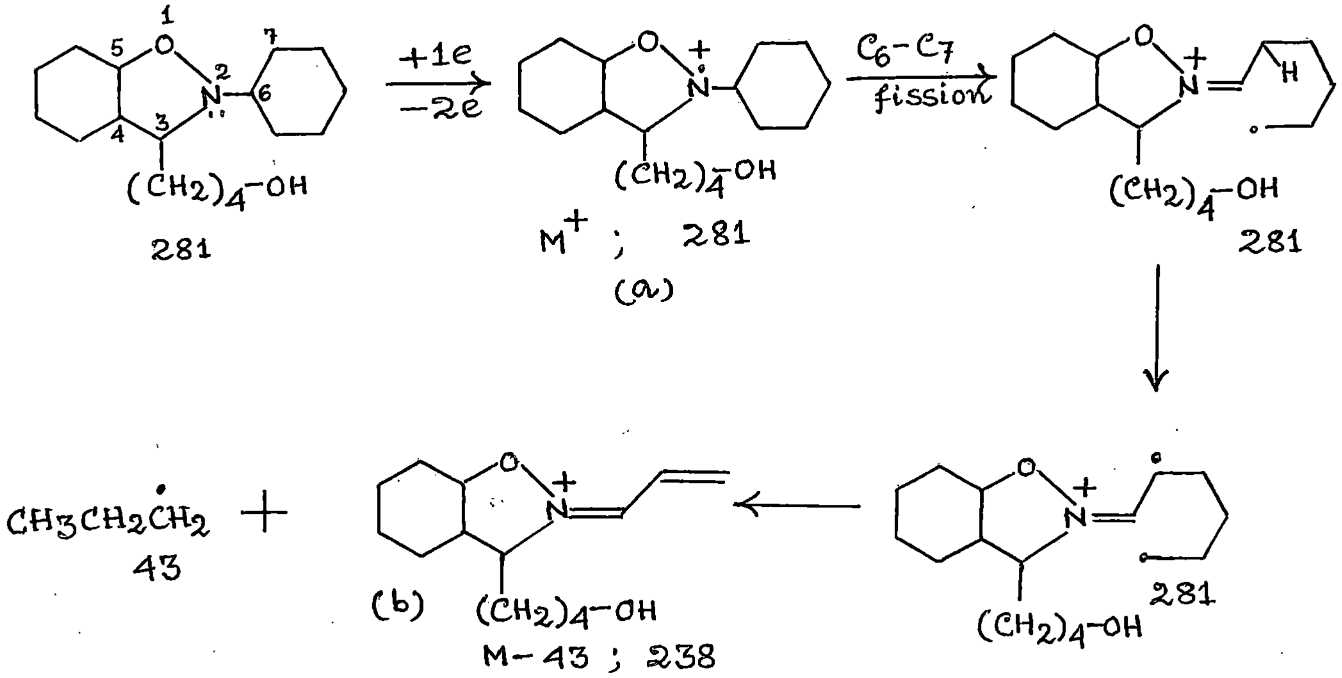
For both the N- cyclohexyl chloro nitrone and N- cyclohexyl 5- hydroxy nitrone, all the cyclo adducts formed possess 2-cyclohexyl 3 chloro butanol 1,2 isoxazolidine moiety or 2- cyclohexyl 3- butanol 1,2 isoxazolidine moiety in common.Therefore,it was very usual to expect some rationalization in the mass fragmentation patterns of the compounds. On electron impact mass fragmentation of a molecule would generate, generally, a radical ion and expectedly one of the non bonding electrons of nitrogen atom of 1,2 isoxazolidine ring would be removed as this nitrogen was tertiary in nature. Thus, taking cyclohexene adduct as example, a general scheme was formulated. (Scheme VI) .

The fragmentation pattern of all the adducts were discussed on the light of this fission pattern.

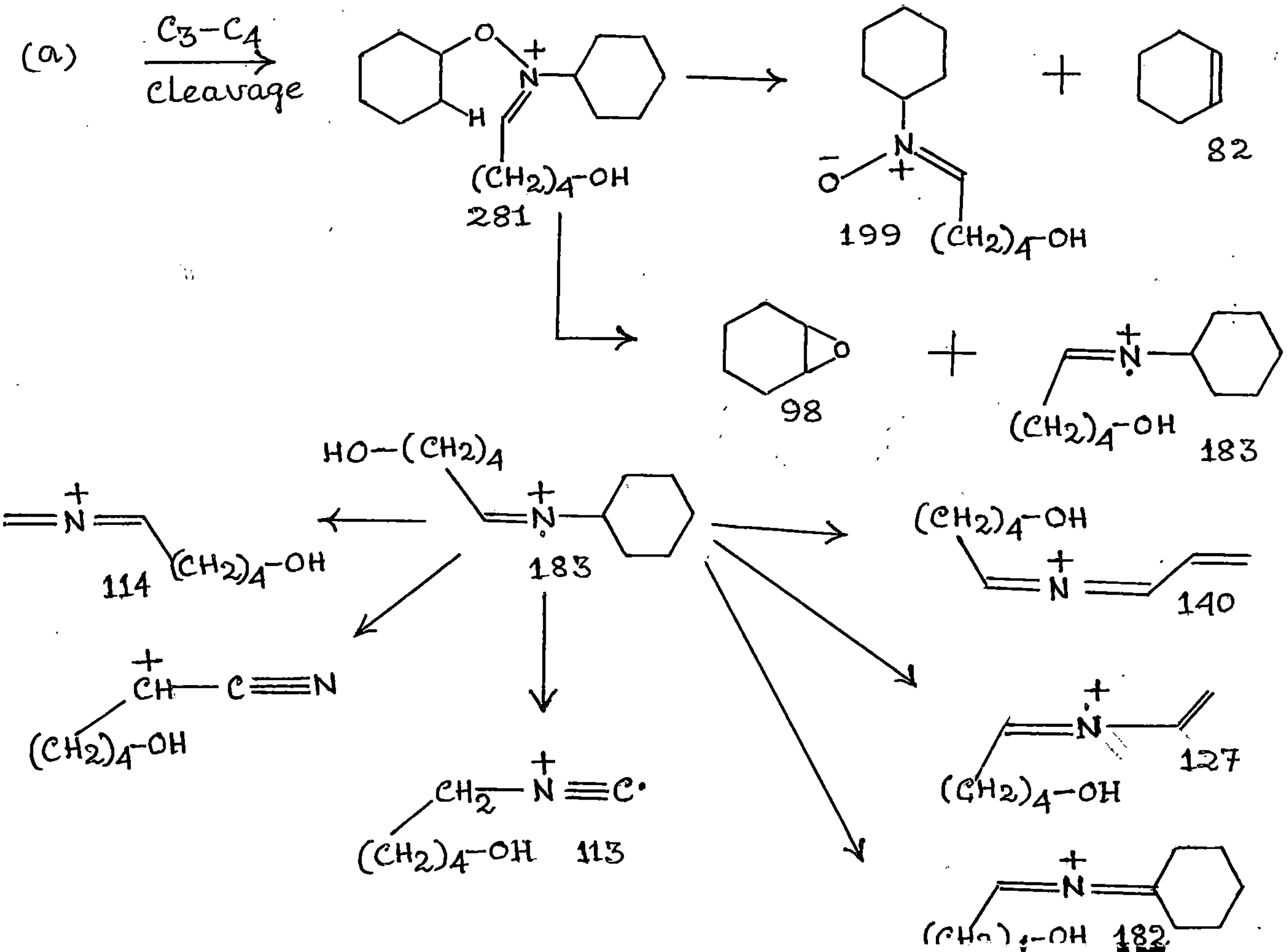
Scheme - VI

General Pattern of mass fragmentation

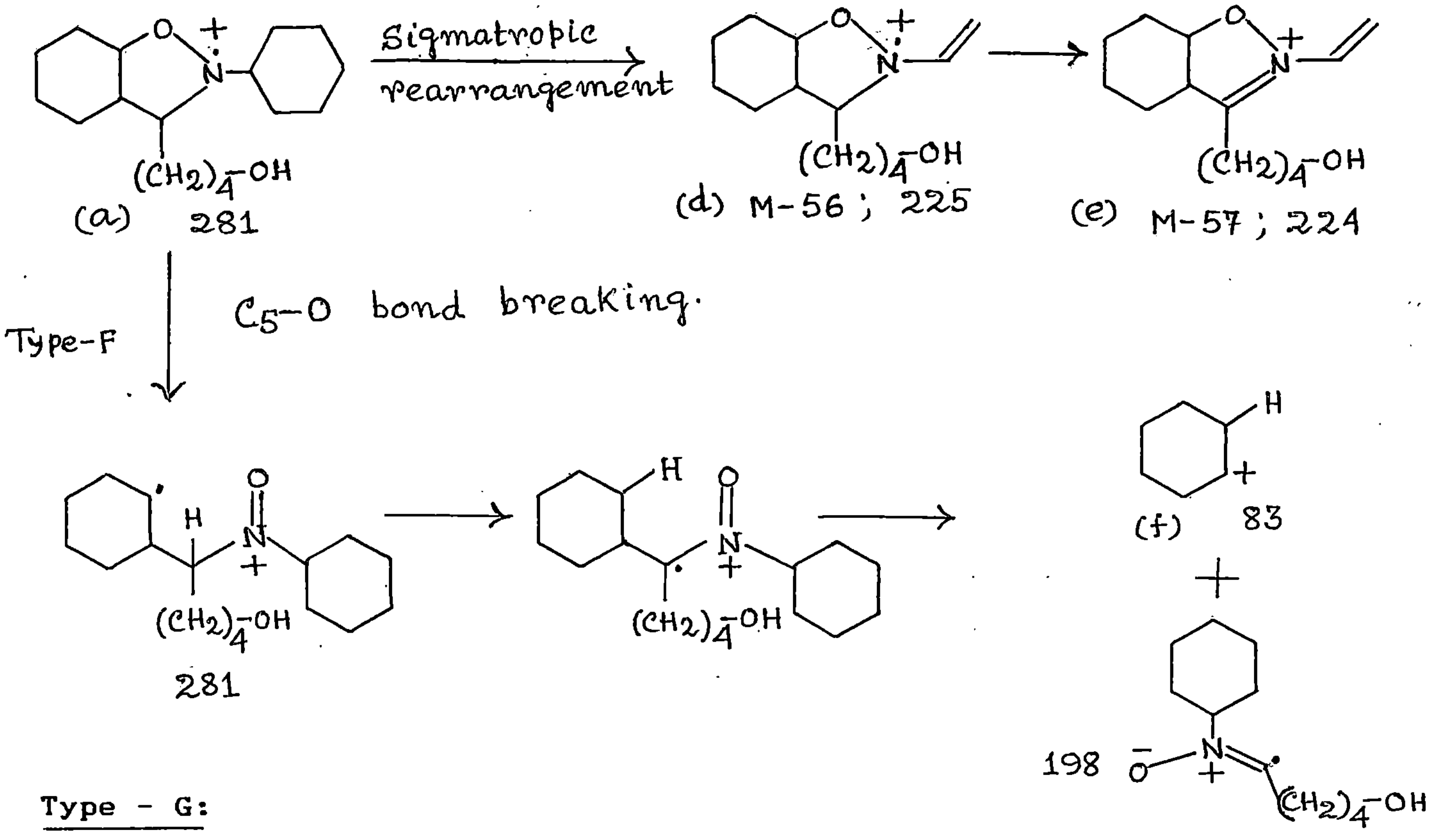
Type - A:



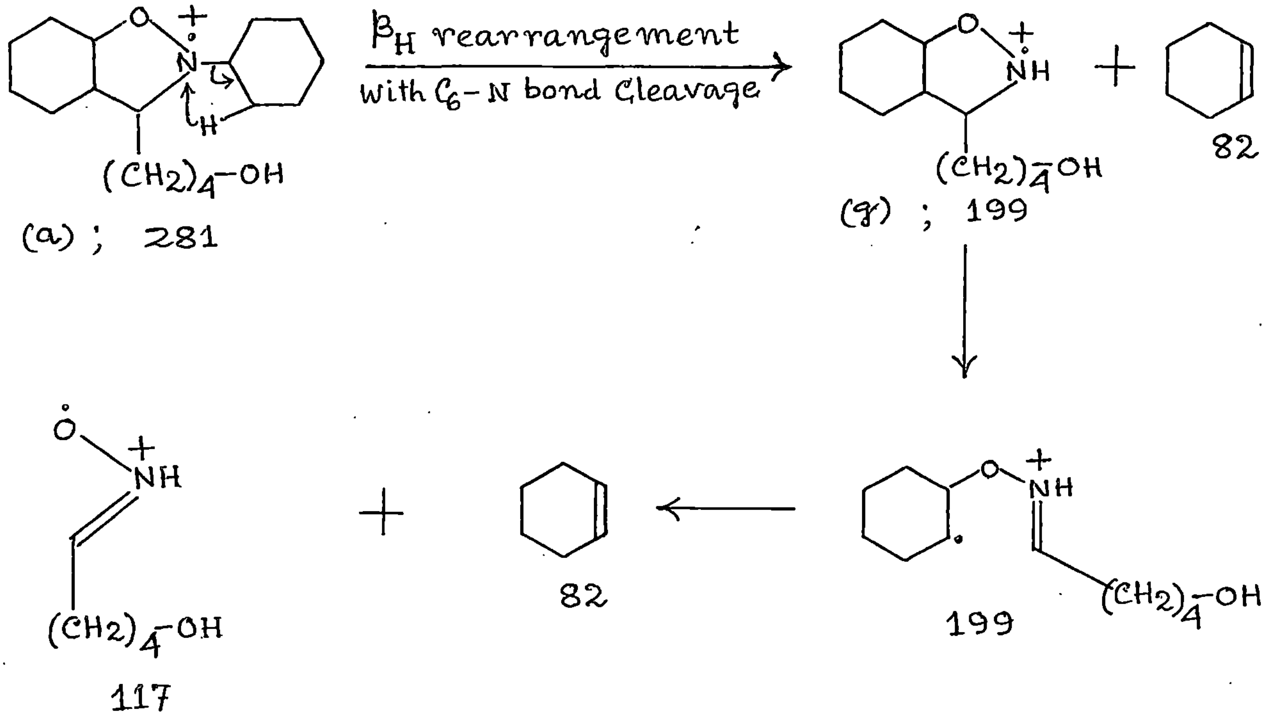
Type - B:



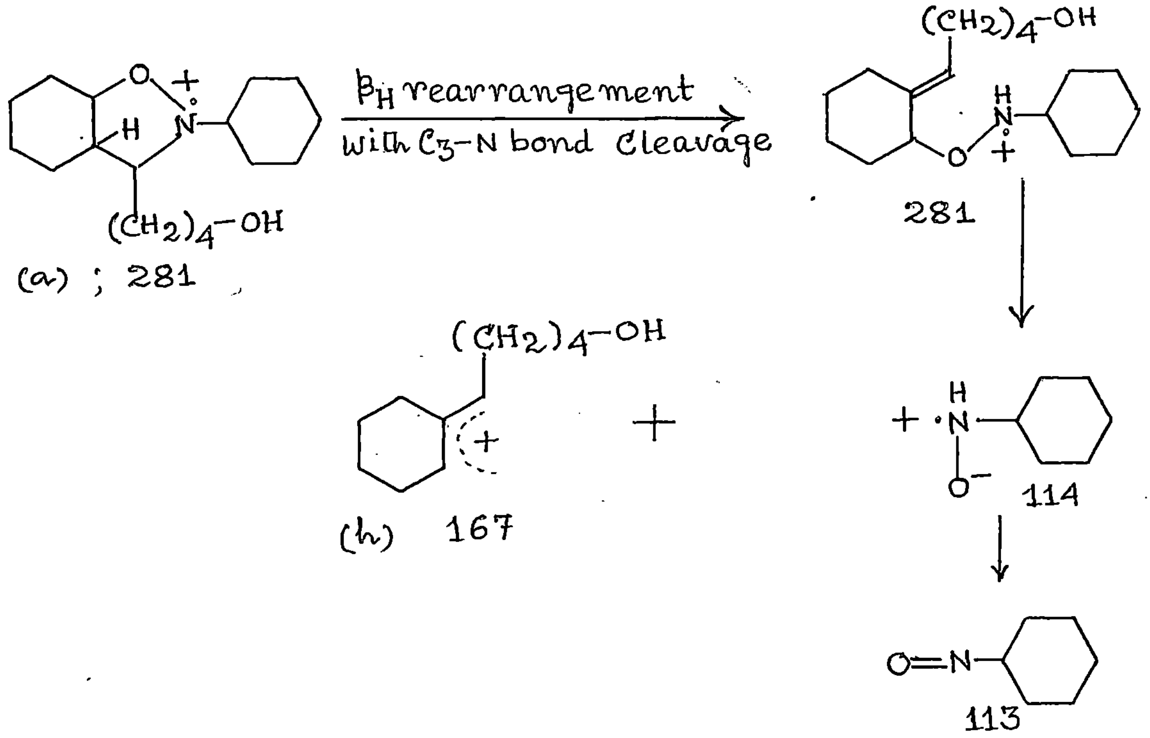
Type - C:


Sigmatropic rearrangement
$(CH_2)_4-OH$
(a) 281
(d) M-56 ; 225
(e) M-57 ; 224
Type-F
C_5-O bond breaking.
H
281
(f) 83
198

Type - G:


β_H rearrangement
with C_6-N bond Cleavage
$(CH_2)_4-OH$
(a) ; 281
(g) ; 199
82
199
82
117

Type - H:



In the case of cyclic amine, the major fission pattern of such a molecular ion would be due to α - cleavage. Among the probable modes of α - cleavage, viz, C3 - C4 and C6 - C7, the C6 - C7 cleavage was most probable as this leads to highly substituted bond cleavage. C3 - C4 bond was also cleaved and further transformation led to a number of fragments with m/e, M - 199; (type - B) 82; 182; 140; 127; 114; 113; 112, were explained.

Another process of concerted homolytic fission of cyclohexyl ring might lead to a fragment with m/e, M-56 (type - C).

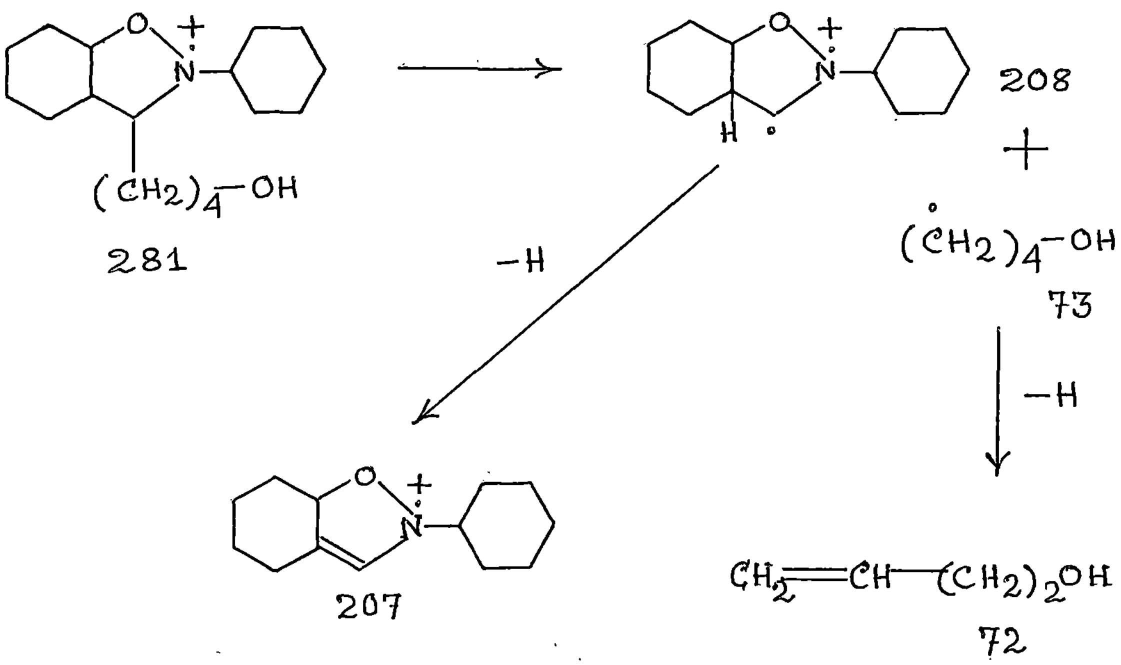
Another type of α - cleavage in which at first the C5 - O bond cleaved to lead the ion with m/e M-198. (type - F).

The process of β - hydrogen rearrangement with C - N bond cleavage might occur in two ways leading to the type - G with m/e M - 82 and type H with m/e M - 114. The ions produced in this process may further be fragmented (not shown).

Other major fragmentation might occur with the ionization of free butanol or chloro butatol gr at C3 and subsequent α - cleavage leading to m/e 208; 207; 72 in the case of N- cyclohexyl 5- hydroxy nitrone while different m/e, fragmentation values are obtained in the case of cycloadducts with N- cyclohexyl - chloro - nitrone.

Type I for cyclohexene adduct with N- cyclohexyl 5-OH-nitrone:

Type I



Occurance of common fragments are shown in Table - X & XI.

Table-X

Cycloadducts With N-cyclohexyl 5-OH-nitorne :

Adduct	M	M-1	M-43	M-56	M-57	M-113	M-114	M-199	M-198
1.Cyclohexene.	+	-	-	-	+	+	+	+	+
2.Ethyl acrylate.	+	-	+	+	+	+	-	+	-
3.Methyl acrylate.	+	-	+	+	+	+	+	+	+
4. Methyl Vinyl Ketone	+	-	+	-	-	+	+	-	-
5.P-benzoquinone	+	-	-	+	-	+	-	+	-
6. Acrylonitrile	+	-	-	-	-	-	-	+	-
7. Dihydro Pyran	+	-	-	+	+	-	+	+	-
8.N-cy-male imide.	+	-	-	+	-	-	-	+	-
9.N-ph-male imide.	+	-	-	+	+	+	+	+	+
10.Styrene.	+	-	+	-	-	-	-	+	-
11.Trichloro ethylene	+	-	-	-	-	+	+	+	-
12.Tetra Chloro ethylene	+	-	-	-	-	-	-	+	-

'(+)' and '(-)' sign indicates the presence and absence of the ion fragments.

Table-X Contd.

Adduct	267	225	168	142	114	113	98	169	227	196	226
1.	+	-	-	-	+	+	+	-	-	-	-
2.	-	-	-	+	-	-	-	-	-	-	+
3.	+	-	-	-	-	+	-	+	-	+	-
4.	-	+	+	+	+	-	+	+	-	-	-
5.	-	-	-	-	-	+	+	+	-	-	-
6.	-	-	-	+	+	-	-	-	-	-	+
7.	-	-	+	+	+	+	+	-	-	-	-
8.	+	-	-	+	+	-	+	-	-	-	-
9.	-	+	-	-	-	-	-	-	-	-	-
10.	-	-	-	+	+	-	-	-	-	-	-
11.	-	-	-	+	+	+	-	-	-	-	-
12.	-	-	+	+	+	+	+	-	-	-	-

The '+' and '-' sign indicates the presence and absence of ions

Table-XI
Cycloadducts With N-cyclohexyl Chloro nitrone

Adduct	M	M-1	M-43	M-56	M-57	M-113	M-114	M-233	M+1
N-Ph-maleimide	+	-	-	-	-	+	+	+	+
N-cy-maleimide	+	-	-	-	-	+	-	+	-
Methyl Vinyl ketone	+	-	+	+	+	+	+	-	-
Styrene	+	-	-	-	-	-	-	+	-
Ethyl Acrylate	+	-	+	+	+	+	-	+	-
Methyl Acrylate	+	-	+	+	+	+	-	+	-
Acrylonitrile	+	-	-	-	-	-	-	+	-
Chloro Acrylonitrile	+	-	-	-	+	-	-	+	+
Phenyl Methyl Propiolate	+	-	-	-	-	-	-	+	-
Dimethyl Acetylene dicarboxylate	+	+	+	+	-	+	+	+	-

The '+' and '-' sign indicates the presence and absence of ion.

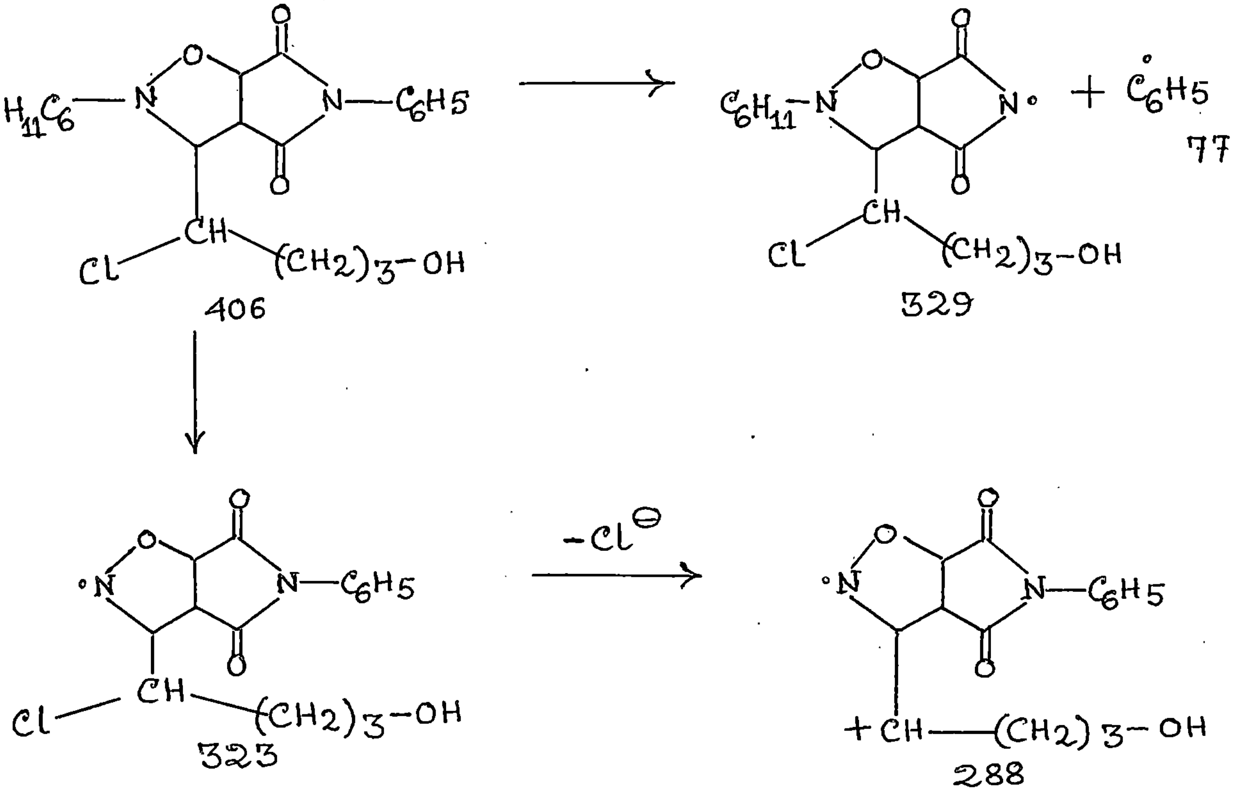
Table-XI Contd.

Adduct	298	288	226	186	187	172	142	114	102	98
1. Methyl Acrylate	-	+	+	+	-	+	-	-	-	+
2. Ethyl Acrylate	+	-	+	-	+	-	-	+	-	-
3. Styrene	-	-	-	-	-	-	+	+	-	-
4. Methyl vinyl Ketone	+	-	-	-	-	-	-	-	-	-
5. N-Cy maleimide	-	-	-	-	-	-	+	-	-	-
6. N-Ph maleimide	-	+	-	-	-	-	-	-	-	+
7. Dimethyl acetylene dicarboxylate	-	-	-	-	-	+	-	-	-	-
8. Phenyl Methyl propiolate	-	-	-	+	-	-	-	-	+	-
9. Acrylo-nitrile	-	-	-	-	-	-	+	-	-	+
10. Chloro-Acrylo-nitrile.	-	-	-	-	-	-	+	-	-	+

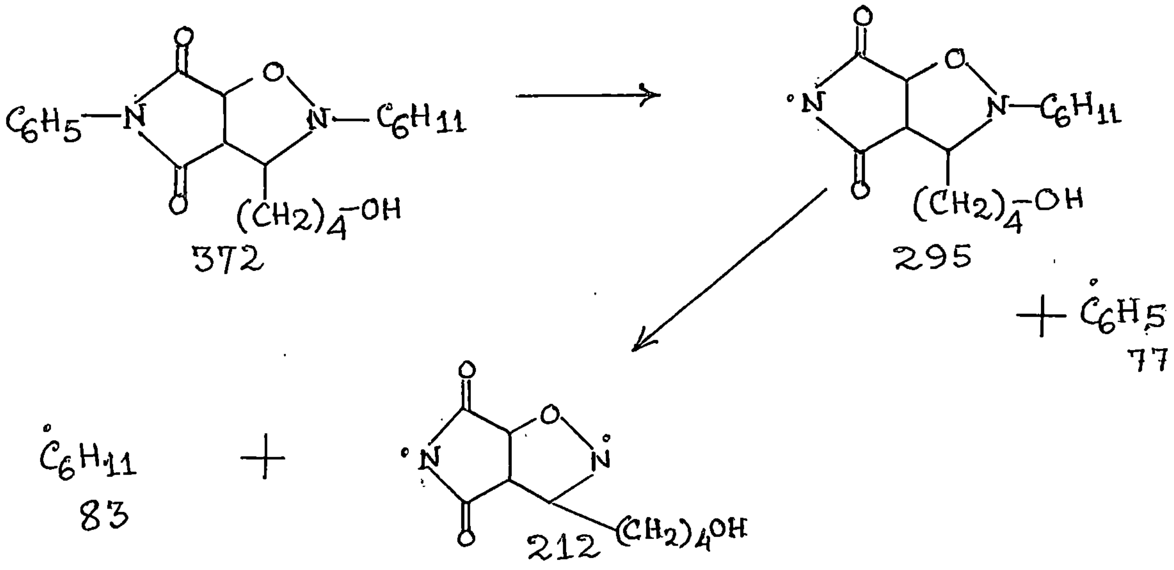
The '+' and '-' sign indicates the presence and absence of ions.

In the fragmentation pattern of N- phenyl maleimide of both the nitrones in addition to the common expected fragments, other prominent peaks at m/e 77; 329; 323; 288 in N- cyclohexyl chloro nitrone and m/e 77; 295; 212 in N- cyclohexyl 5- OH nitrone were found. (type - J)

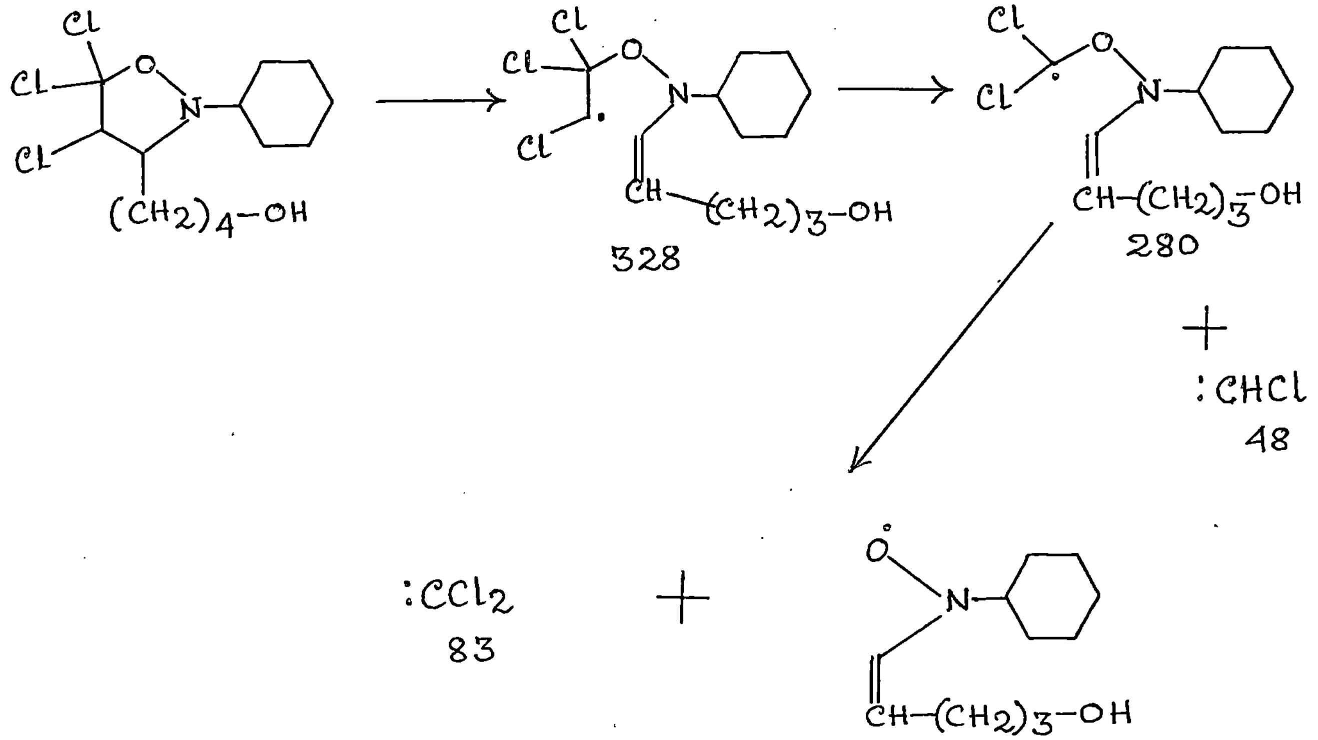
(i)

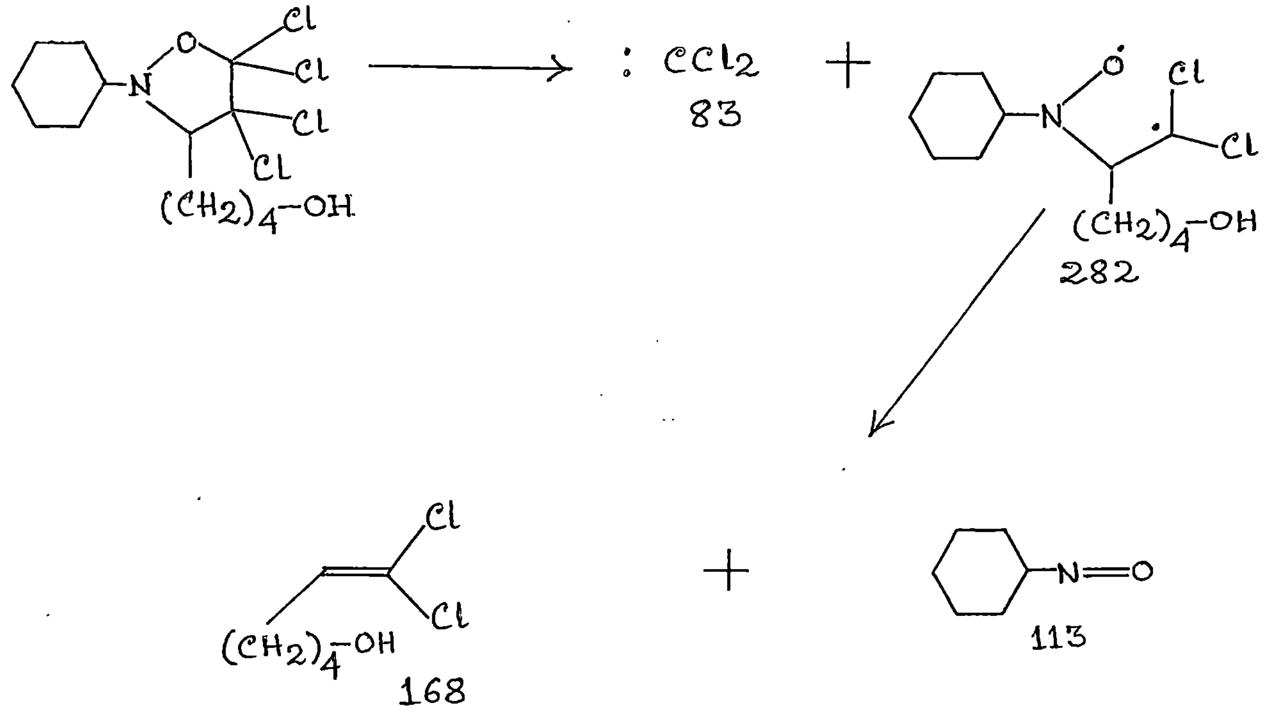


(ii)



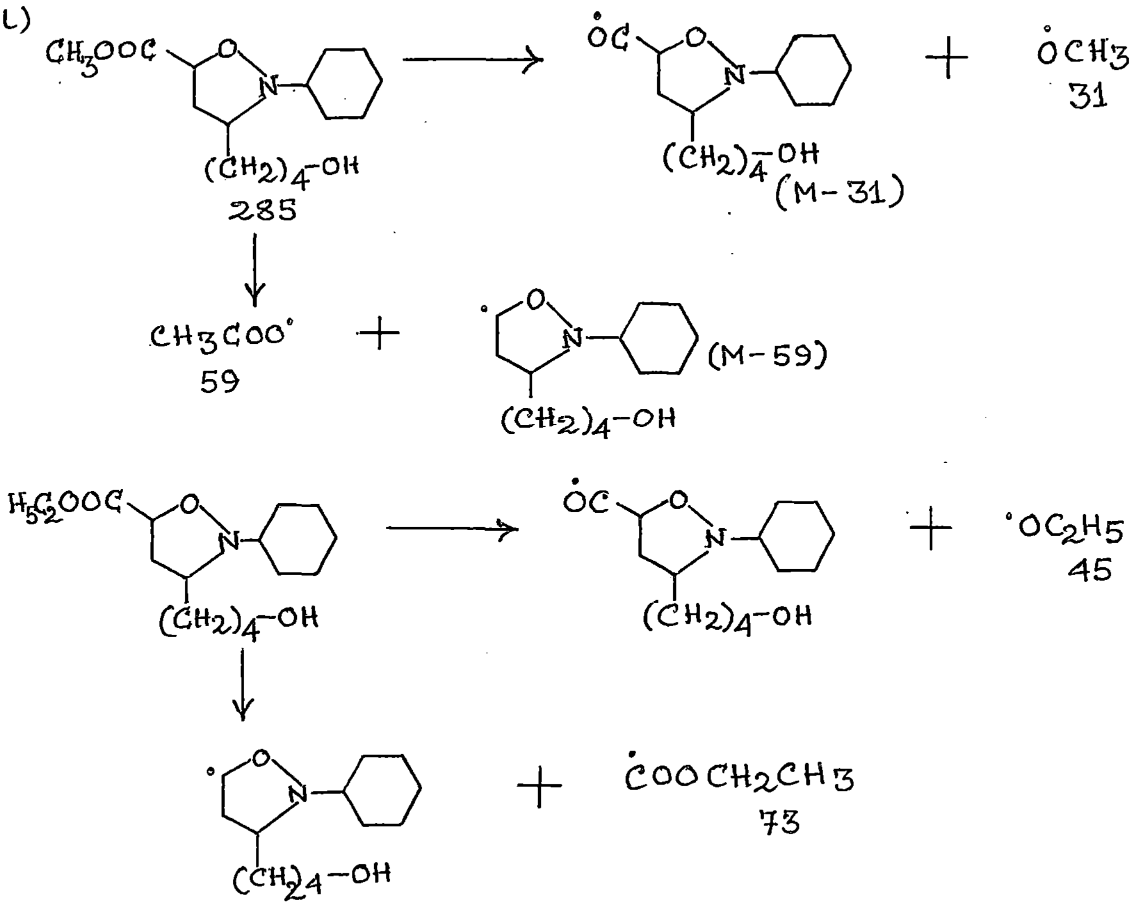
With N- cyclohexyl 5- OH nitrone and trichloro & tetrachloro ethylene adducts some of the expected ion fragments were absent. But the other peaks were prominent. e.g. 280; 48; 83; in the case trichloro ethylene while 282; 83; 168 in the case of tetra chloro ethylene (Type K1 and K2):



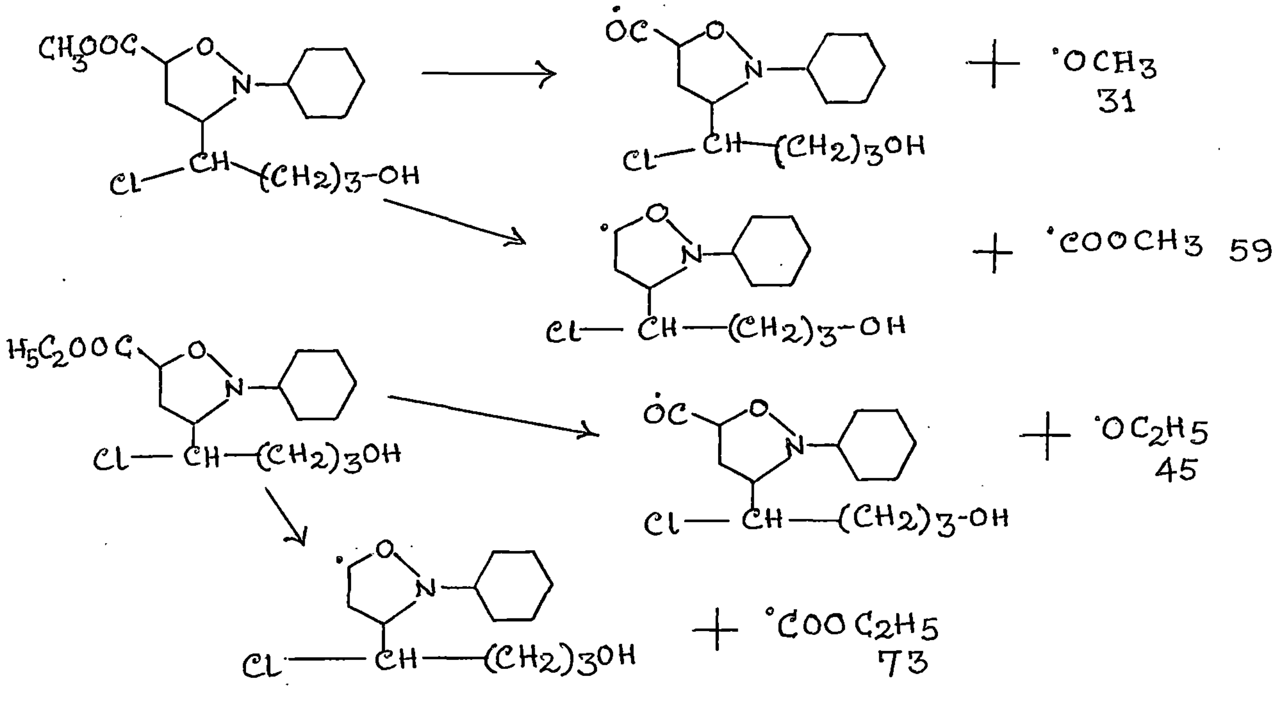


The fragmentation patterns of both the methyl and ethyl acrylate adducts with both the nitrones followed the general pattern with some typical peaks for methyl and ethyl ester e.g. CH_3O (31); CH_3COO (59); CH_3CH_2O (45); CH_3CH_2COO (73) and prominent peaks for both the cases (at m/e 254,) probably due to the ion M-31 for methyl and M-45 for ethyl acrylate adducts respectively. (type L)

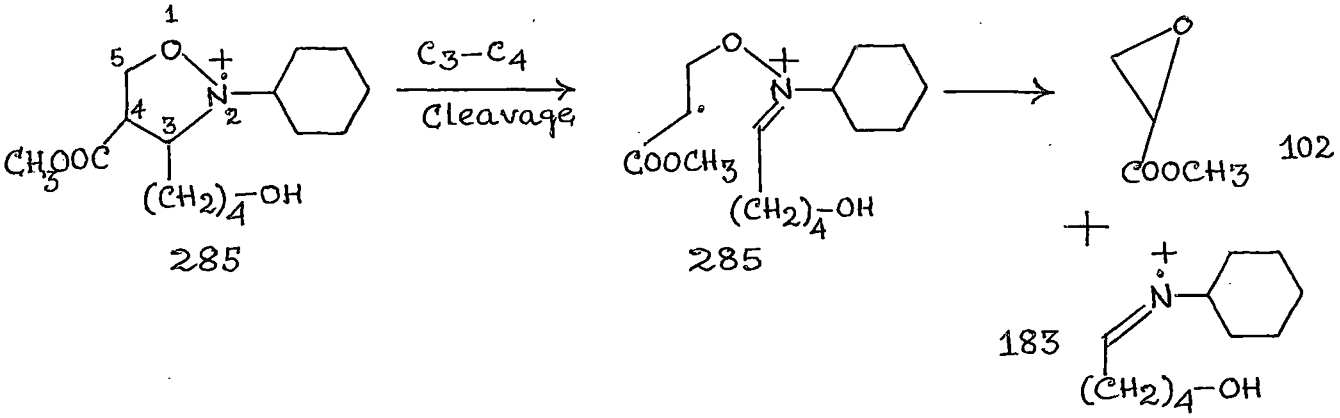
(i)



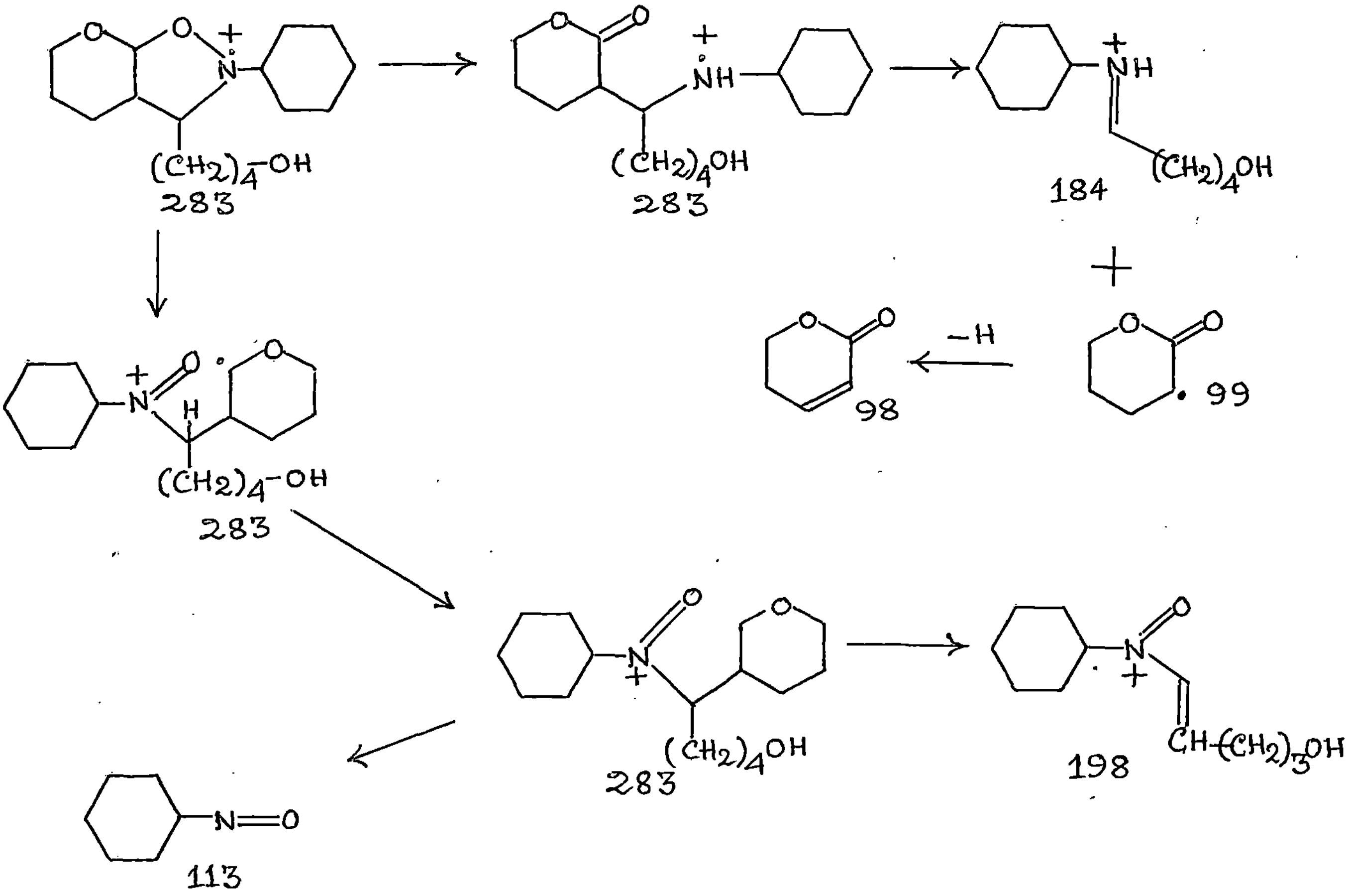
(ii)



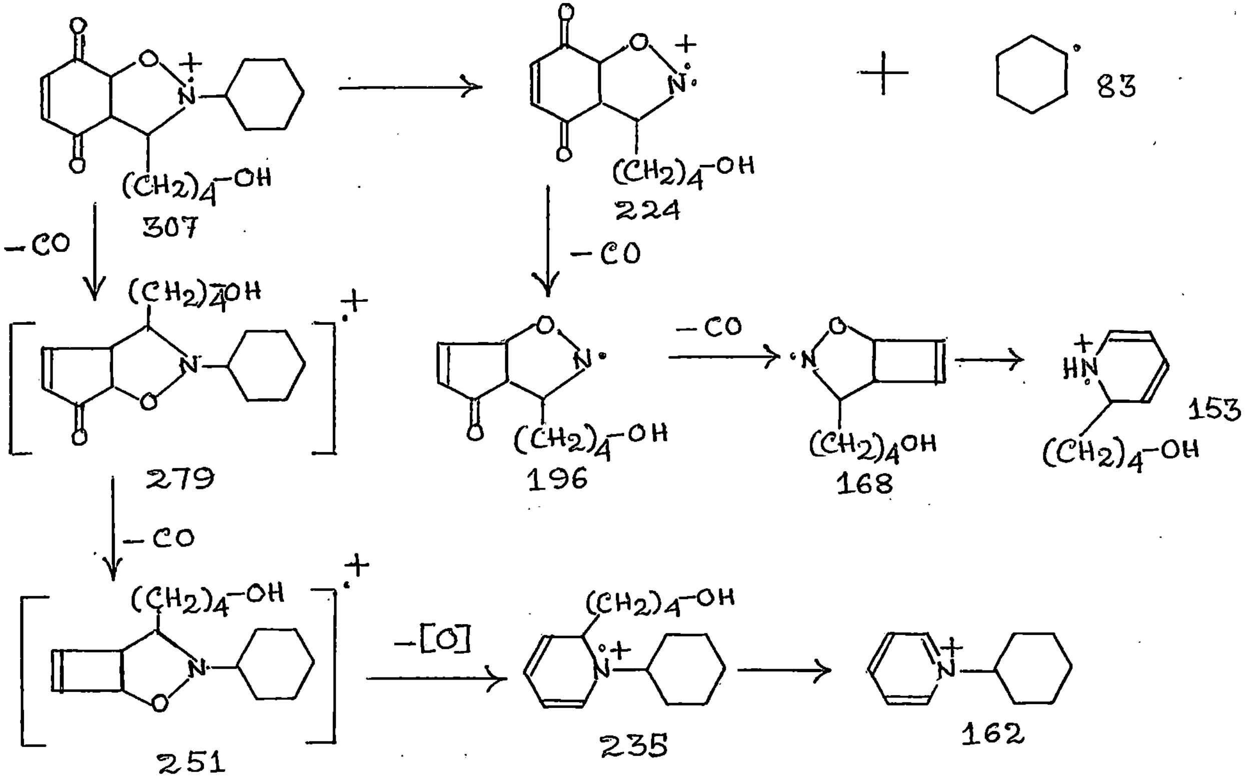
In the case of methyl acrylate adduct with N- cyclohexyl 5-hydroxy nitrone, from mass spectro scopic analysis we can cite strong evidence in favour of 4- substituted cycloadd over that of 5- substituted adduct.



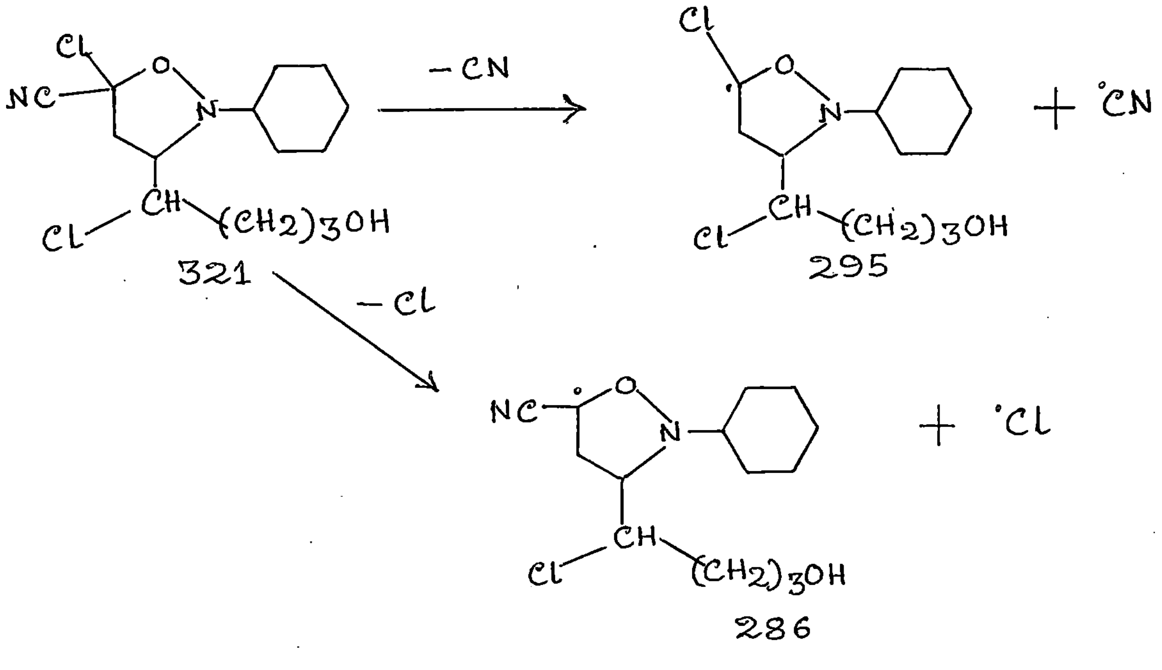
The fragmentation pattern of dihydro pyran with N- cyclohexyl 5 - OH - nitrone followed the general pattern with some special peaks at 184 and 99. (type M)



P- benzoquinone adduct formed from N- cyclohexyl 5- hydroxy nitrone fragmented following the same pattern with some typical peaks at 196, 168, 153, 251, 162. (type N).



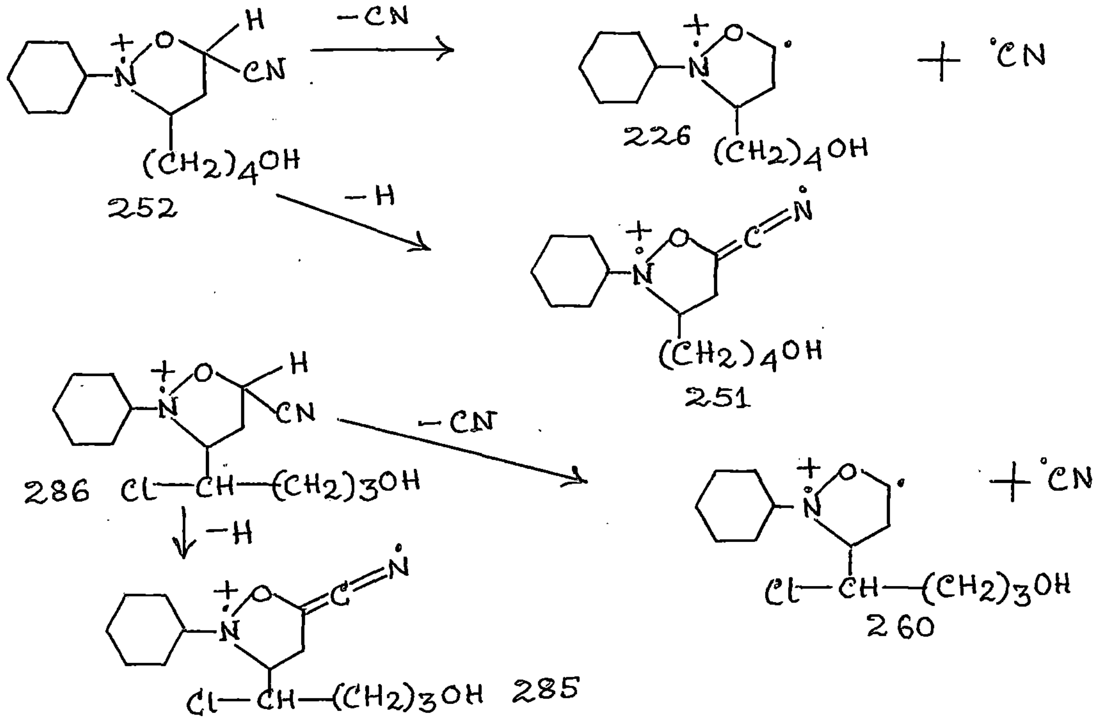
Fragmentation pattern of 2-chloro-acrylonitrile formed from N- cyclohexyl chloro nitrone was also in accordance with the general pattern. The molecular ion peak was associated with M+1 peak. Very weak peaks at 295 (M-26) and 286 (M-35) due to (M-CN) and (M-Cl) were also found. (type O)



Acrylonitrile adduct for both the N- cyclohexyl chloro-nitrone and N- cyclohexyl 5- hydroxy nitrone follwed the same general pattern with some special peaks at 251, 226 and 260, 285. (type P)

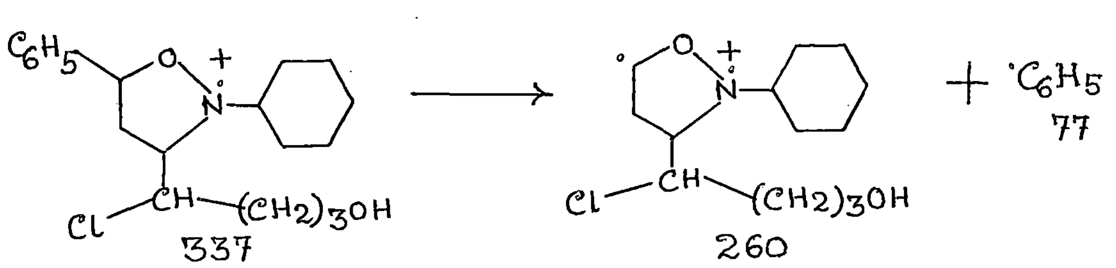
(i)

(ii)

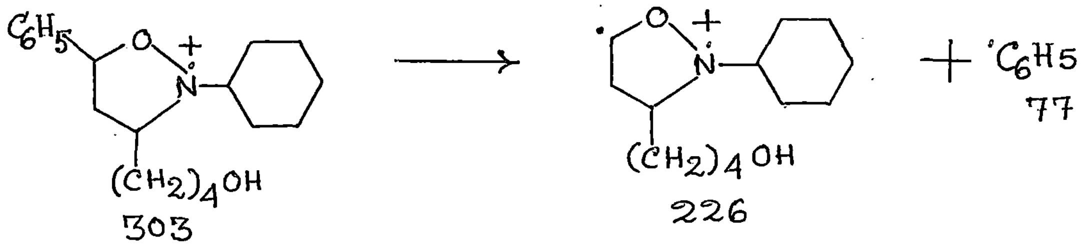


The cycloadduct of styrene with both N- cyclohexyl chloro nitrone and N- cyclohexyl 5- hydroxy nitrone also followed the same fragmentation pattern with some weak peaks (M-77) due to the loss of phenyl gr. (type Q)

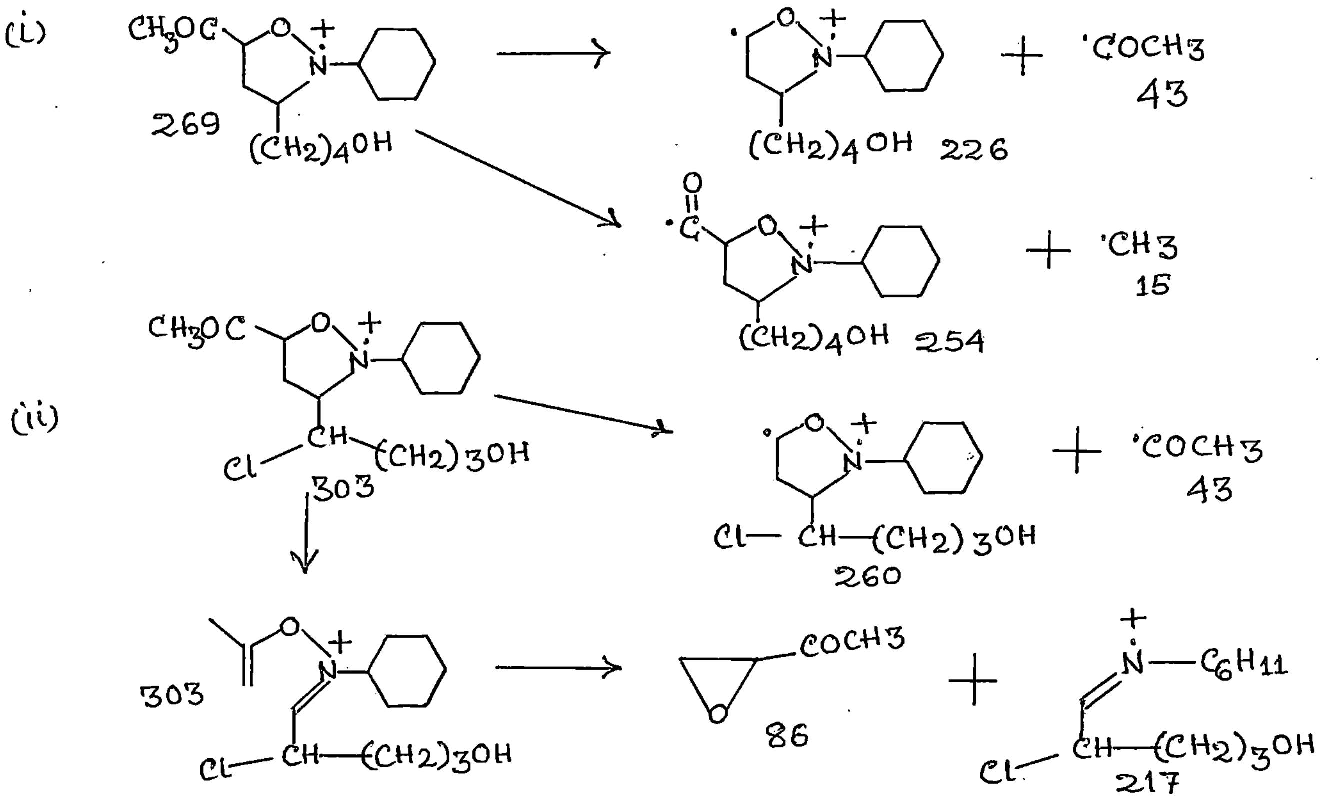
(i)



(ii)

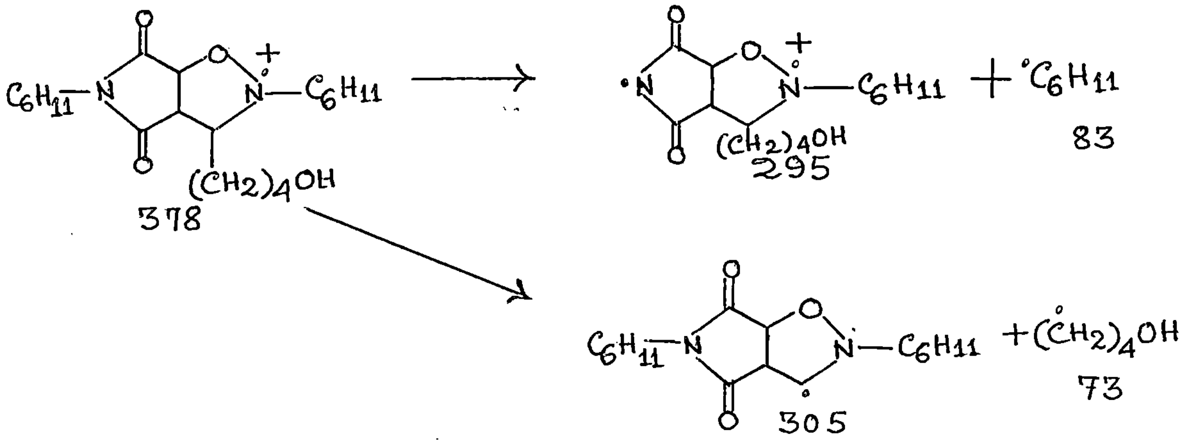


The fragmentation patterns of methyl vinyl ketone adduct with both the nitrones were also in accordance with the general pattern with some special peaks in both the cases. (type R)

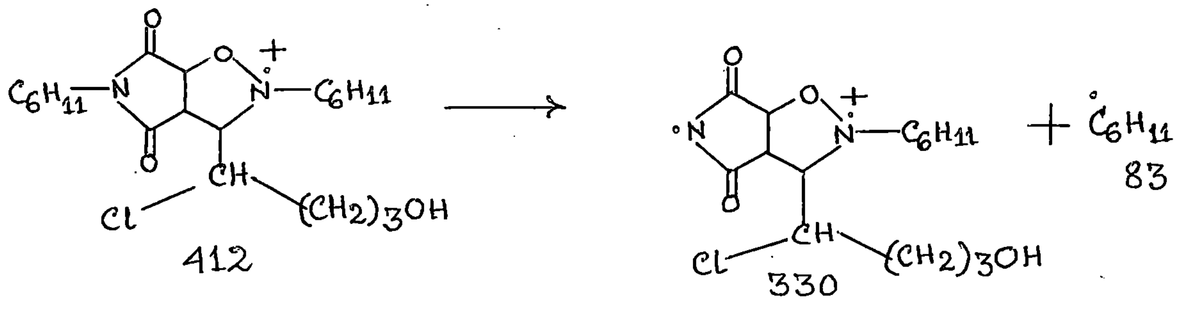


In addition to the general pattern of mass fragmentation, some special peaks of N- cyclohexyl maleimide adduct with both the nitrones were explained (type S).

(i)

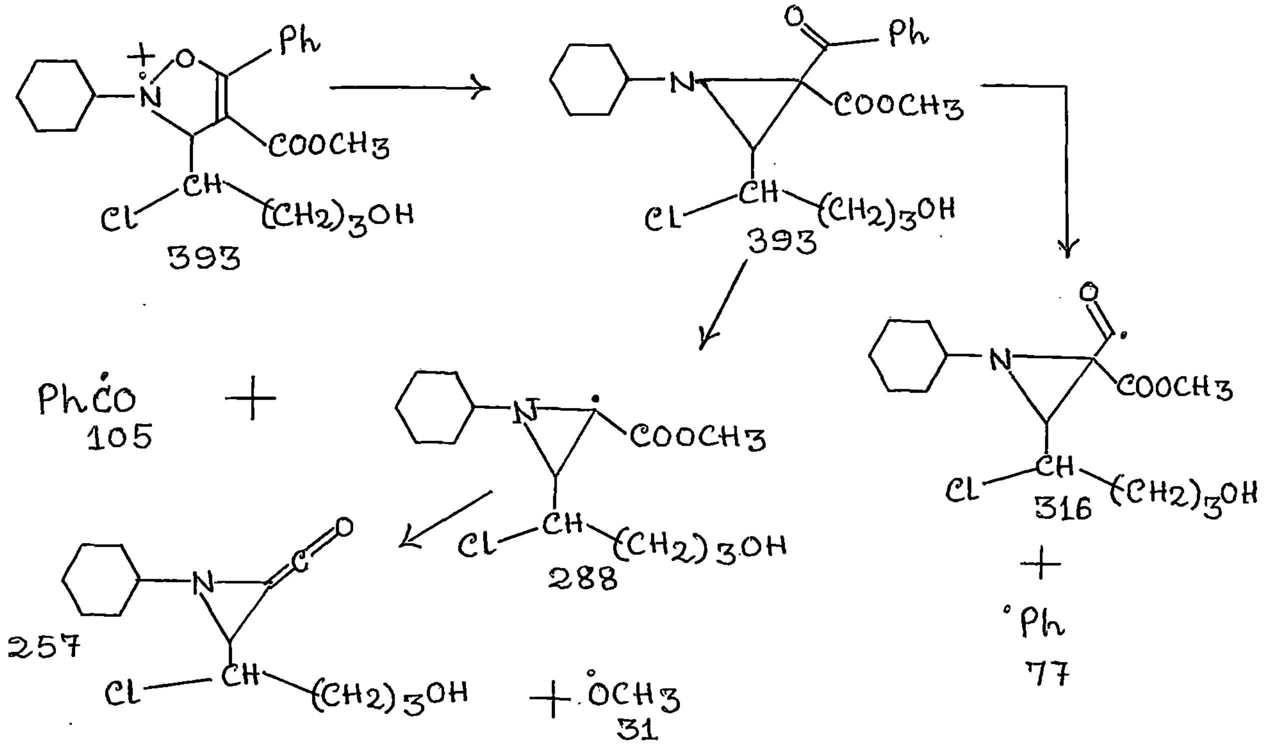


(ii)

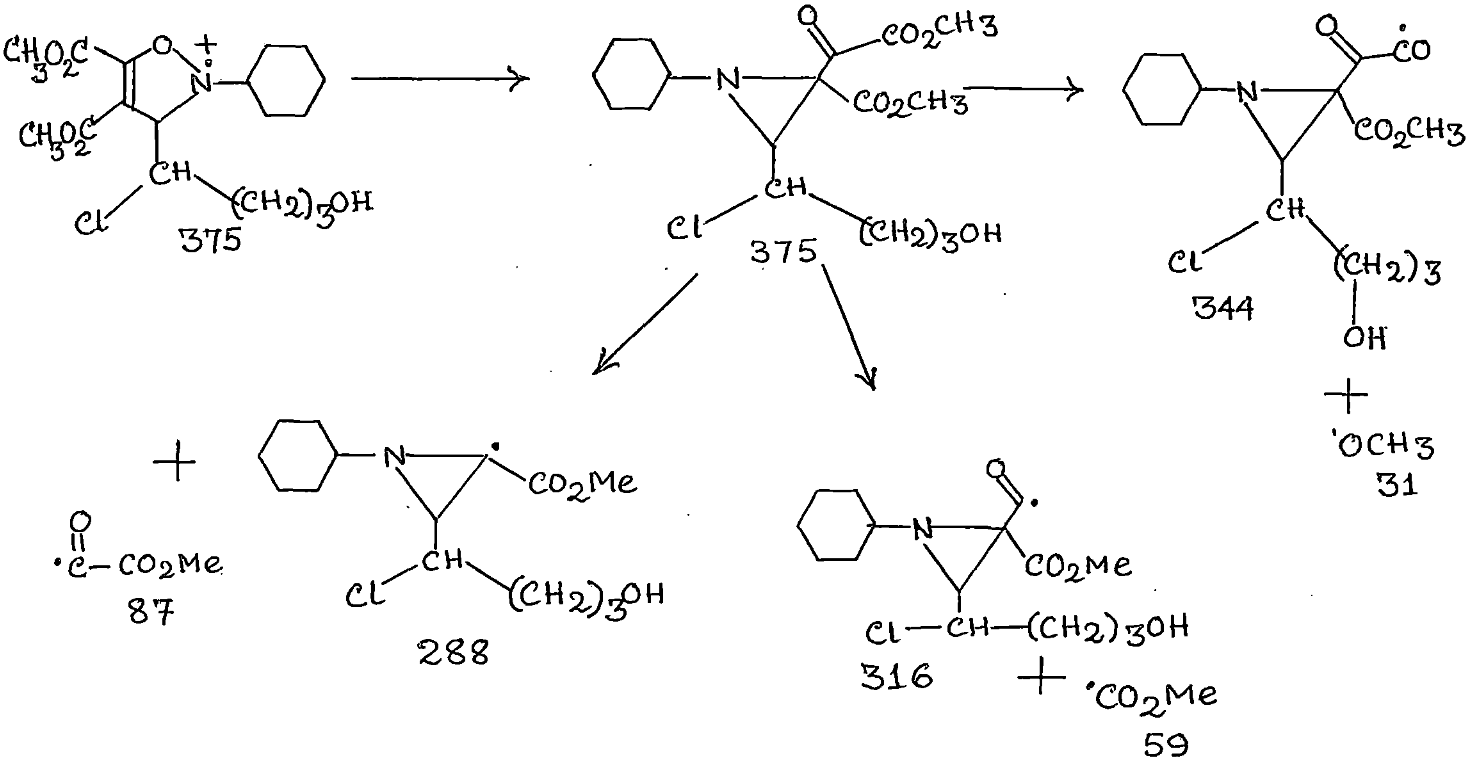


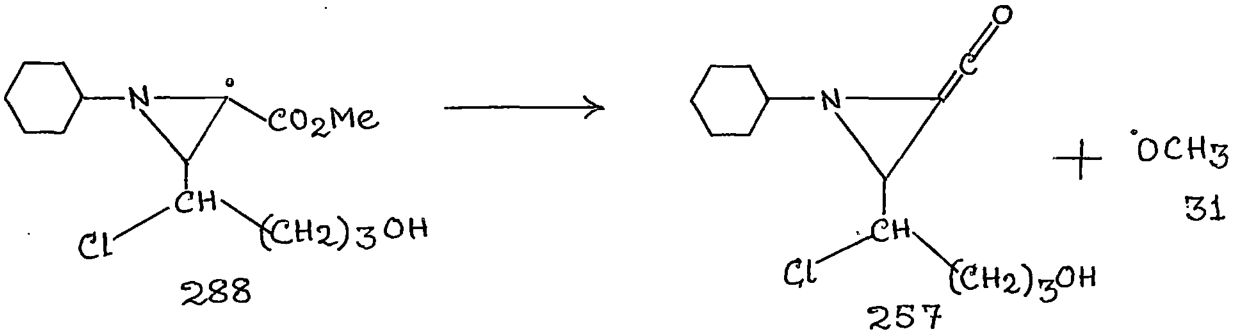
The fragmentation pattern of acetylene adducts were different and explained in type T.

i) Phenyl methyl propiolate adduct :



ii) Dimethyl acetylene dicarboxylate :





3. Interpretation of PMR Spectra

On interpreting the NMR Spectra of the nitrone adducts, the chemical shifts and coupling constant for C5 protons, wherever possible were studied, as well as the dihedral angle between C4-C5 protons. In addition to that, the "band-width" i.e. the distance between the first and the last line of the multiplet of the signals, of the C5 protons in Hz was also measured. Bauman et al (241) used this method to elucidate the conformations of the cis and trans cyclopentane 1 - carbo methoxy - 2 - ol and found that for trans isomer the band width was 18 Hzs and for cis isomer 11 Hzs. (Table XII).

Table-XII
Cyclo adducts with N-cyclohexyl-chloro-nitrone

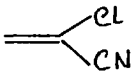
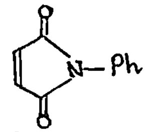
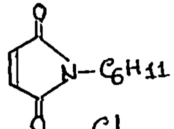
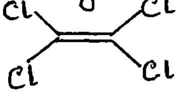
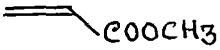
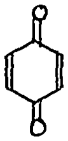
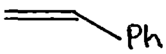
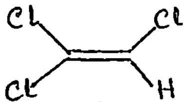
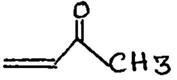
Adduct	C5-H in ppm	Band-Width (Hz)	Coupling Const(J) in(Hz)
N-Cy-maleimide.	4.63-4.57 (d)	9 Hz	6.06 Hz
. Styrene.	2.58-2.44 (t)	10 Hz	6.06 Hz
Me-Vinyl Ketone.	4.9-4.8 (t)	8 Hz	6.06 Hz
N-Ph-maleimide.	5.7-5.4 (b)	11 Hz	---
·$MeO_2C-C\equiv C-CO_2Me$	—	—	—
. Acrylonitrile.	5.0-4.9 (dd)	9 Hz	4.05; 2.7
7. Ethyl Acrylate.	3.6-3.5 (b)	10 Hz	
8. Methyl Acrylate.	3.87-3.6 (b)	12 Hz	
9. 	—	—	—
10. $Ph-C\equiv C-CO_2Me$	—	—	—

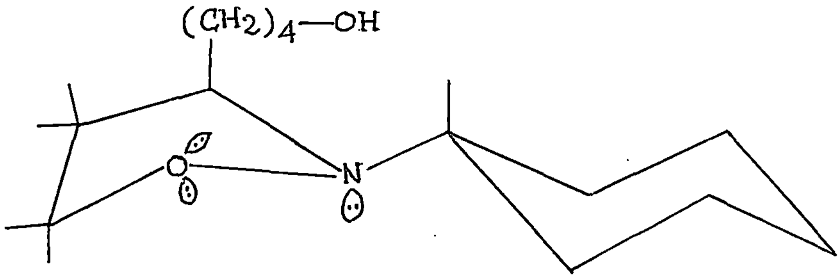
Table-XIII

Cyclo adducts with N-cyclohexyl 5-hydroxy nitrone(245)

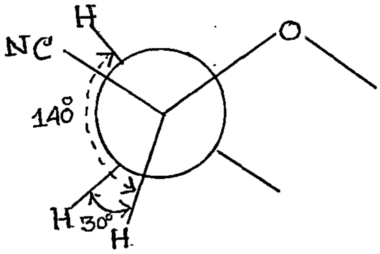
Adduct	C5-H (d ppm)	Band-Width (Hz)	Coupling Const(J) in(Hz)
	4.9 (q)	10 Hz	4.5; 4.5
	5.6 (b)	9 Hz	3
	5.75-5.00 (b)	12 Hz	
	—	—	—
	3.1-2.8 (m)	12 Hz	12.3
	4.77-4.64 (b)	10 Hz	
	9-8.65 (b)	12 Hz	
	2.6-2.5 (m)	9 Hz	6.06 Hz
	—	—	—
	2.6-2.5 (t)	9 Hz	
	3.7-3.5 (t)	10 Hz	4.05; 2.7
	2.5 (m)	12 Hz	

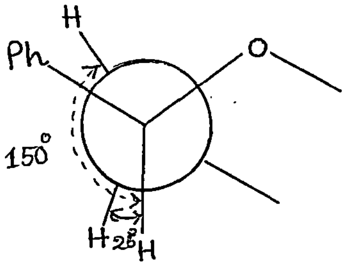
It may be concluded from these band-width values that the dipolarophiles with cis configurations about the double bond gave rise to cis-adducts and therefore, the nitrone additions were stereospecifically cis.

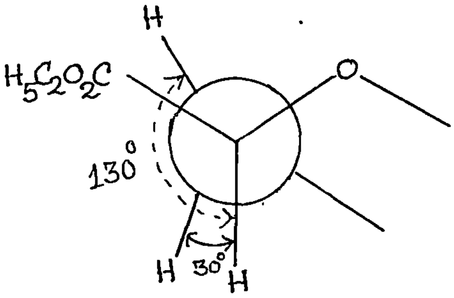
From the coupling constant values for C-5 protons of the nitrone adducts with (i) acrylo nitrile;(ii) styrene, in the case of N- cyclohexyl 5- hydroxy nitrone (245) we have calculated the dihedral angles between C5 - C4 protons from standard graph. From these calculated values along with the assumption that 2-cyclohexyl 1,2 isoxazolidine at normal condition will prefer the envelop configuration with N- cyclohexyl group at equatorial position, (Fig V), and the free butanol group will also be in equatorial position at C3 .



We have constructed the C5-C4 with the corresponding dihedral angles (fig VI) for the compounds acrylonitrile; styrene and ethyl acrylate for N- cyclohexyl 5- hydroxy nitrone (245).

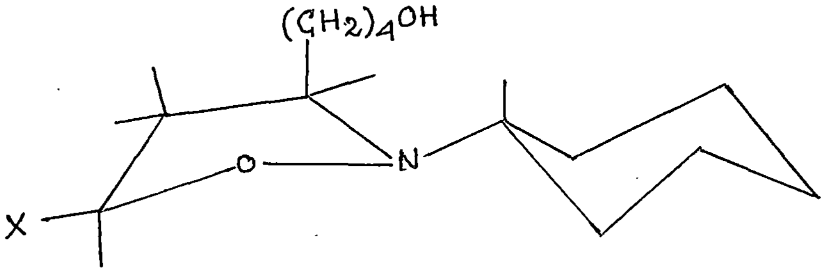






From these figures it is clear that the substituents at the C-5 position tries to have the equatorial position from the quasi - equatorial position of the envelop form. As a result, the 1,2 isoxazolidine conformation shifts from envelop to half chair form - depending on the bulkiness of the C-5 substituents.

The conformation of acrylonitrile has less bulky gr and is close to the envelop form and that of methyl acrylate and styrene are close to the half chair form. The pseudo-rotation of the five-memered ring is restricted by the substituents in all these compounds.



This indicates that in each of the compounds C5 proton and C4 proton couple in the same way and comparison of the corresponding dihedral angle suggests that the dihedral angle of the proton is 50°. The normal dihedral angles for cyclohexene in perfect chair form are 60° for cis proton and 180° for trans protons. The deviation is due to the strain of the five membered ring.

As the C5 proton in the other cyclo adducts were either absent or the splitting of the signal were not prominent, so the dihedral angle between C4 - C5 protons and the coupling constant could not be calculated. Therefore nothing could be infered about their conformational structures.

For most of the cases cyclohexyl protons along with -n-butanol protons as well as chloro butanol protons were appeared at 0.75 - 2.3 δ. C3 protons in all adducts appeared in the region 2.7 - 3.6 δ. N - CH - proton of cyclo hexyl group gave signal in region 2.6 - 3.3 δ. C4 & C5 proton signals depended on the substituent at C4 and C5 positions.

'Syn' cyclo adducts were formed via " exo Transition State " in the case of cyclohexene; N- phenyl - maleimide ; N- cyclohexyl maleimide; ethyl acrylate; acrylonitrile etc. with N- cylohexyl 5-hydroxy-nitrones.The "Band-Width" values and J values were also in support of them.

The coupling constant, J values calculated for 'chloro - acrylonitrile', and 'methyl vinyl ketone' of N- cyclohexyl chloro nitrone were found to be 15.15 & 9 Hzs respectively while it was 12.3 Hzs for methyl acrylate of N- cyclohexyl 5- hydroxy nitrone (245) and were in favour of anti-cycloadducts formed via endo transition state (206).

In the case of methyl acrylate adduct of N- cyclo hexyl 5-hydroxy nitrone (245), the major product was confirmed as 4-substituted one and not the 5- substituted one also explained from mass spectral analysis.

'Syn' cycloadducts were formed via exo- transition - state in the case of acrylonitrile; chloro acrylonitrile; ethyl acrylate etc. with N- cyclohexyl chloronitrone. Band-Width values and coupling constant (J) values were also in support of them.

In the case of di-methyl acetylene dicarboxylate & phenyl-methyl propiolate, both the cyclo adducts were 'Syn' considering C_3H and $-\underset{\underset{Cl}{|}}{CH}-$ protons.

SCOPE & OBJECTIVE

Among the plethora of functional groups, the nitrone functionality has secured an important place in the arsenal of synthetic chemists. This was possible largely owing to the brilliant efforts of Huisgen and his group in Munich .

K. N. Houk and his co-workers are responsible for the pioneering investigations of regio selectivity and stereo specificity associated with the 1,3 dipolar cyclo addition.

The discovery of α- chloronitrone and its reactions paved a new avenue in the nitrone - chemistry. The chemistry of α- chloro - nitrones was originated and developed by Prof. A. Eschenmoser and his school (236-238).

Another new vista of the nitrone chemistry is the intramolecular cyclo additions. Such type of reactions have been reviewed by A. Padwa (173) and W. oppolzer (174) . Due to these vast synthetic potentiality of the nitrones, a number of natural products and other biologically active substances have been designed and synthesized via nitrone routes (239). Therefore the scope of the nitrone chemistry is abundant. One of the objective of our present work is due to these vast potentiality of "chloronitrone" , and we have tried to elucidate the cycloaddition patterns of both N- cyclohexyl chloronitrone and N- cyclohexyl 5- hydroxy nitrones with a wide variety of dipolarophiles. Among the numerous nitrones that have been studied so far, majority of them bear at least one C-Substituent.

For the prediction of regio selectivity in 1,3 dipolar cyclo addition reaction, CNDO/2 or ab initio SCF calculations have tremendus scope for our new nitrones. Theoritical work in this field now in progress.

N- cyclohexyl chloro nitrone has been prepared by the treatment of chlorohydrin (240) on an etherial solution of N-cyclohexyl hydroxyl amine along with anhydrous $MgSO_4$.

On the other hand N- cyclohexyl 5- hydroxy nitrone has been prepared by the direct heating of dihydro pyran and N- cyclohexyl hydroxyl amine in dry benzene.

Both the nitrones are very interesting on synthetic point of view because

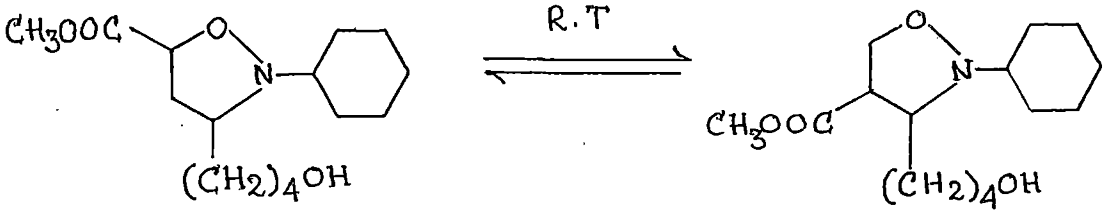
i) It is quite a new approach from such hemiacetal.

ii) It has tremendous synthetic potentiality.

The reactions of both N- cyclohexyl chloro nitrone and N-cyclohexyl 5- OH nitrones with moderately electron deficient dipolaro philes are abserved to smooth and invariably all the reactions do occur at room temperature in the case of N-cyclohexyl chloro - nitrone, while heating required in the case of N-cyclohexyl 5- hydroxy nitrone, yielding mainly the 5- substituted adducts.

The cycloaddition reactions of N-cyclohexyl chloro nitrone with 'acrylonitrile', 'chloro acrylonitrile', 'methyl acrylate', 'ethyl acrylate', 'methyl vinyl ketone' results both 5 and 4 substituted products but the regio selection prefers the 5 substituted adducts over 4 substituted adducts and this has been established from PMR and Mass spectral analysis.

An interesting observation was noticed in the case of Methyl acrylate cycloadducts. It has been found that there is an inter conversion of 5- substituted and 4- substituted cyclo adducts on keeping them at room temperature i.e. cyclo reversion occurs.



N-cyclo hexyl 5-hydroxy nitrone results mainly 5-substituted cycloadducts,even in the case of ethyl acrylate and acrylonitriles etc.All the additions are found to be stereo speciafically cis in nature (245).

N- cyclohexyl chloro - nitrone reacts smoothly with the activated acetylenes viz, dimethyl acetylene dicarboxylate, phenyl - methyl propiolate resulting 5- substituted cyclo adducts.

N- cyclohexyl chloro-nitrone is equally significant and important for the synthesis of many unnatural cyclic amino acids and lactones.

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Indian Journal of Chemistry
Vol. 33B, December 1994, pp. 1113-1114

Communications

1, 3-Dipolar cycloaddition reactions of N-cyclohexylnitrone

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Received 6 July 1994; accepted 15 September 1994

1, 3-Dipolar cycloaddition reaction of nitrone **1**, derived from 2, 3-dihydro-4*H*-pyran with different dipolarophiles, have been studied. The reactions have been found to be highly regio- and stereo-selective.

Nitrones are versatile synthetic intermediates and excellent spin trapping reagents[1]. Nitrones are prepared either by condensation of aldehydes and ketones with hydroxylamines[1] or by oxidation of the corresponding N, N-disubstituted hydroxylamines[2].

In the present study the formation of nitrone **1** has been achieved (Scheme I) by refluxing N-cyclohexylhydroxylamine[3] and 2, 3-dihydro-4*H*-pyran in dry benzene which were then trapped *in situ* by different dipolarophiles in a 1, 3-dipolar cycloaddition reaction with high regio- and stereoselectivity giving **2** (cf. Table I). Dimerization of nitrone could also be controlled under this condition[4].

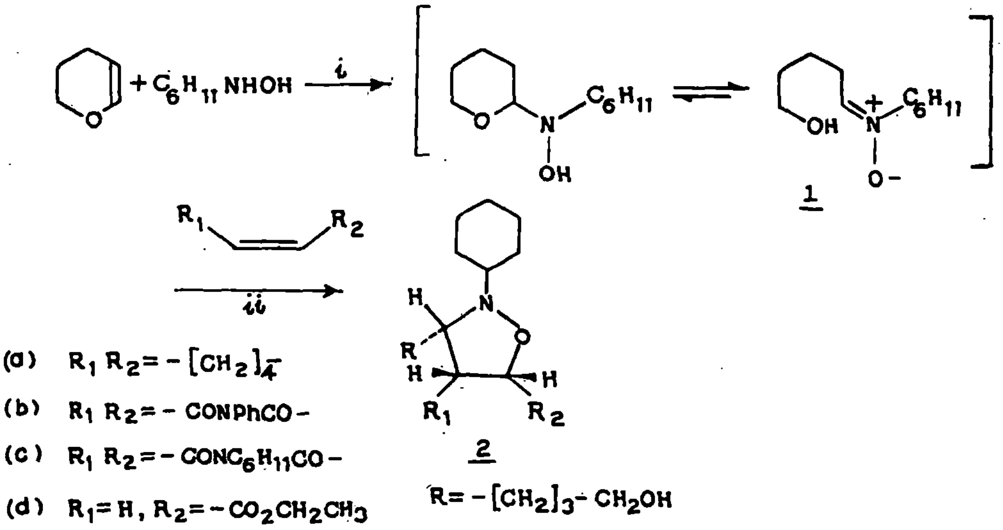
The concerted nature of these cycloaddition reactions with nitrone as 1, 3-dipole was generally accepted. The regioselectivity in these reactions was rationalized by using the frontier-orbital theory[5]. The ethyl acrylate adduct corresponded to this theory. Therefore, the 5-substituted adduct for ethyl acrylate is due to LUMO (nitrone)-HOMO (dipolarophile) interaction.

Cycloaddition of *Z*-nitrone via an *exo*-transition state results in the formation of *syn*-isoxazolidine[6]. The relative configurations of C-3, C-4 and C-5 in the adducts were in favour of the *exo*-transition state geometry. The proton at C-3 and C-4 were *syn* in **2b** and **2c** and their coupling constants ($J_{3,4}=6$ Hz) were also indicative of this stereochemical relationship, whilst a D_2O shake revealed the presence of one rapidly exchangeable proton at C-5. The stereochemical assignments of **2a** and **2d** at C-3, C-4 and C-5 on the isoxazolidine ring were also determined from ^1H NMR spectra. The coupling constant values ($J_{3,6}=7.5$-8.0 Hz) revealed the formation of *syn*-isoxazolidine in both the cases via *exo*-transition state.

Further study of the reaction in various systems is in progress.

Table I—Physical data of the cycloadducts (**2**)

Cycloadduct	Yield (%)	R_f	m.p. °C
2a	33.63	0.30	106
2b	26.01	0.34	132
2c	29.50	0.38	114
2d	55.94	0.41	Dark red gummy liquid



Scheme I

Experimental

General procedure for cycloaddition

N-Cyclohexylhydroxylamine (2.17 mmoles) was added to a solution of 2, 3-dihydro-4*H*-pyran (1 equivalent) in dry benzene (20 ml) under nitrogen atmosphere and the reaction mixture refluxed for 24 hr. The reaction was monitored by TLC [silica gel; ethyl acetate-benzene (1:10)]. Dipolarophiles were added (1 equivalent) at this stage and the reaction mixture was further refluxed for 24 hr. The solvent was evaporated off and the cycloadducts [cf., Table 1] were isolated by column chromatography using benzene-pet. ether (60°-80°) as eluant.

Compound 2a: MS: m/z 281 (M^+), 113, 98; IR ($CHCl_3$): 3264 (br), 2924, 2851, 1540, 1443, 1248 cm^{-1}; PMR ($CDCl_3$): δ 3.80-3.7 (d, 1H, $J=4.5$ Hz, C_5-H), 3.10-3.06 (br, 1H, $>CH-N<$), 2.63-2.46 (q, 1H, $J=7.5$ Hz, C_3-H), 2.36-2.16 (dd, 1H, $J=4.5$, $J=7.5$ Hz, C_4-H), 2.00-0.5 (m, 26H).

Compound 2b. MS: m/z 372 (M^+), 299, 289, 242, 173, 117, 113, 78; IR ($CHCl_3$): 3460 (br), 2940, 2840, 1780, 1700, 1690, 1480, 1395, 1190 cm^{-1}; PMR ($CDCl_3$): δ 7.80-7.30 (m, 5H, C_6H_5), 5.70-5.45 (br, 1H, C_5-H, exchangeable with D_2O), 4.50-4.26 (dd, 1H, $J=6$ Hz, C_4-H), 3.38-3.10 (dd, 1H, $J=6$ Hz, C_3-H), 3.00-2.83 (m, 1H, $>CH-N<$), 2.16-0.43 (m, 18H).

Compound 2c: MS: m/z 378 (M^+), 323, 305, 295, 277, 267, 251, 208, 196, 170, 114, 83; IR ($CHCl_3$): 3580, 2920 (br), 1775, 1690, 1440, 1390, 1140, 890 cm^{-1}; PMR ($CDCl_3$): δ 5.75-5.0 (br, 1H, C(5H)H, exchangeable, with D_2O), 4.15-3.93 (dd, 1H, $J=6.06$ Hz, $J=6.06$, C_4-H), 3.20-3.10 (m, 1H, $>CH-N<$), 3.06-2.94 (dd, 1H, $J=6.06$ Hz, C_3-H), 2.93-2.84 (m, 1H, $>CH-N<O$), 2.20-1.03 (m, 28H).

Compound 2d: MS: m/z 299 (M^+), 296, 242, 226, 204, 187, 142, 131; IR ($CHCl_3$): 3340 (br), 2930, 2850, 1725, 1440 cm^{-1}; PMR ($CDCl_3$): δ 4.77-4.64 (b, 1H, C(5)H, exchangeable with D_2O), 4.20 (q, 2H, $-OCH_2Me$), 3.10-2.98 (t, 1H, $J=8.1$ Hz, C_3-H), 2.98-2.80 (br, 1H, $>CH-N<$), 2.80-2.60 (q, 2H, $J=8.1$ Hz, C_4-H_2),, 2.35-0.60 (m, $-CH_3$ and remaining protons).

Acknowledgement

The authors are thankful to the Principal, Sikkim Govt College, for providing laboratory facilities. Thanks are also due to CDRI, Lucknow, IIT, Bombay and RSIC, North Eastern Hill University, Shillong for providing spectral data. Financial support from UGC, New Delhi is also gratefully acknowledged.

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