1,3 - DIPOLAR CYCLOADDITION OF α - AMINO NITRONE

THESIS SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY (SCIENCE)
OF THE
UNIVERSITY OF NORTH BENGAL
JUNE, 1993

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PREFACE

The work entitled "1,3-Dipolar Cycloaddtion Of α-Amino Nitrone" corresponds to the systematic investigation of 1,3-dipolar cycloaddition reactions of α-Amino-N-Cyclohexyl Nitrone with a variety of alkenes and a few alkynes and the SN_2 reactions of the nitrone with benzyl chloride and iso-propyl bromide.

Chapter-I (Theoretical Approach), deals with the theoretical aspects of the nitrone as 1,3-dipole. Approximate HMO calculation for N-cyclohexyl methylene nitrone and α-amino-N-cyclohexyl nitrone were done to find the existance and approximate stability of the α-amino nitrone. In the same chapter, the mechanistic view point of 1,3-dipolar cycloaddition were also discussed.

Chapter-II, deals with the chemistry of nitrone. Actually this chapter is the review of the previous works.

Chapter-III, is the experimental section.

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

Chapter-V, deals with the further scope and objective of the present work.

For cycloaddition reactions, different types of alkenes viz., normal, conjugated, moderately electron deficient and moderately electron rich alkenes were chosen. Reaction conditions, regioselectivity and stereospecificity of cycloaddition reactions of the nitrone with different alkenes and a few alkynes were studied.

The strong nucleophilic character of the nitrone was also studied.

Structures of all the products were assigned on the basis of 2D-NMR, ^1H NMR, Mass and IR spectras.

ACKNOWLEDGEMENT

The author would like to express his deep gratitude to his teacher Dr.A.R.Ghosh, Senior Lecturer, Department Of Chemistry, Sikkim Government College. Throughout the research work, author has received expart criticism, valuable comments and above all his loving care.

The author is highly indebted to Dr.T.K.Das Gupta, Department Of Chemistry, University Of North Bengal, for important comments and constructive ideas.

The author also acknowledges Prof. A.Eschenmoser, ETH, Zurich, for valuable comments and Dr. D.Felix of the same institute for supplying an authentic sample of N-cyclohexyl hydroxylamine hydrochloride and a few fine chemicals as gift.

Thanks are also due to Dr.C.B.Sunwar, Head and Reader, Department of Chemistry, Sikkim Government College for his enthusiastic support and to Dr.Fr.M.J.Moolel, Principal, Sikkim Government College for his keen interest and for providing laboratory facility.

The author is highly indebted to Dr.P.S.Ray, Head and Dr.S.Das, Senior Scientific Officer, Department Of Chemistry, University Of North Bengal and Dr.T.S.Basu and Mr.Dey of RSIC, North Eastern Hill University (NEHU), Shillong, for providing analytical facility.

The author is thankful to Mr.K.K.Pradhan, Head, Department Of History and to Dr.M.P.Thapa, Department Of Zoology, Sikkim Government College, for scrutinising the whole manuscript.

The author is equally thankful to Mrs.S.Ghosh, Dr.J.P.Tamang, Mr.B.Bhowmik, Mr.S.N.Tiwari, Mr.B.Chakraborty and Mr.Chhetri for their help during the research work.

Thanks are also due to RSIC, C.D.R.I., (Lucknow), RSIC (NEHU), RSIC, Indian Institute Of Technology (Bombay) and RSIC, Indian Institute Of Science (Bangalore) for providing C,H,N analysis and IR, NMR, Mass etc.

The author is indebted to University Grants Commission, New Delhi for financial support and to the Council Of Scientific and Industrial Research, New Delhi for the award of a Junior Research Fellowship to the author.

The author would like to express his profound gratitude to his parents, brothers (Munna and Pappa) and sister (Bonu) for their affections and encouregement.

Finally the author is taking this opportunity to acknowledge his teachers who taught him at defferent levels and also to his friends and well-wishers.

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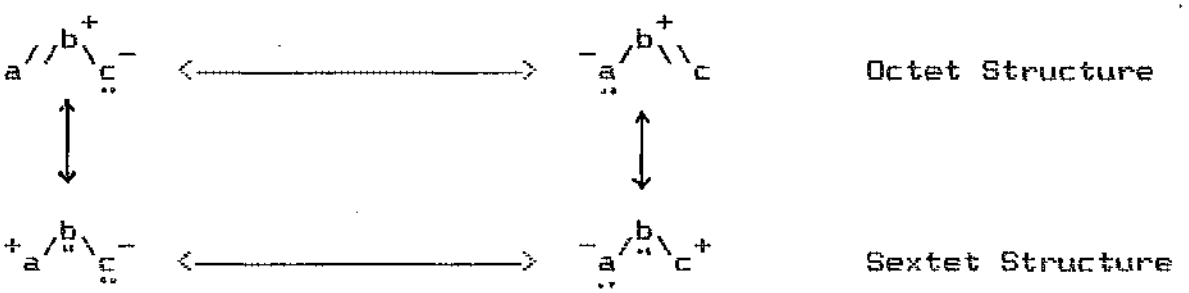
CONTENTS

CHAPTER-I (THEORETICAL APPROACH)

1. GENERAL :

The "1,3-Dipole", $a\text{-}b\text{-}c$, 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-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.,

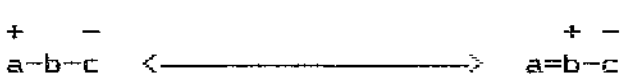


1,3-Dipoles can be further stabilised by internal octet stabilisation.

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:

(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:



1,3-Dipoles can be classified among two types,viz., with double bond and without double bond and 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 stabilisation 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.

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:

(a) (b)

Approximate HMO calculation of the structure (a):

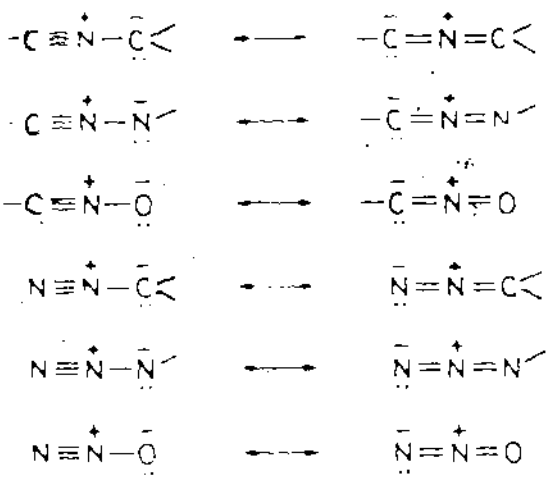
The secular determinant could be set up using the suggested parameter values[3] for hetaroatoms for use with simple LCAO treatment, viz., $h_N^+=2$; $h_O^-=2$; $K_{C-N}=1.1$; $K_{N-O}=0.7$; ect.

$$\begin{vmatrix} \alpha_O - \varepsilon & \beta_{12} & \beta_{13} \\ \beta_{21} & \alpha_O - h_N^+\beta_O - \varepsilon & \beta_{23} \\ \beta_{31} & \beta_{32} & \alpha_O + h_O^-\beta_O - \varepsilon \end{vmatrix} = 0$$

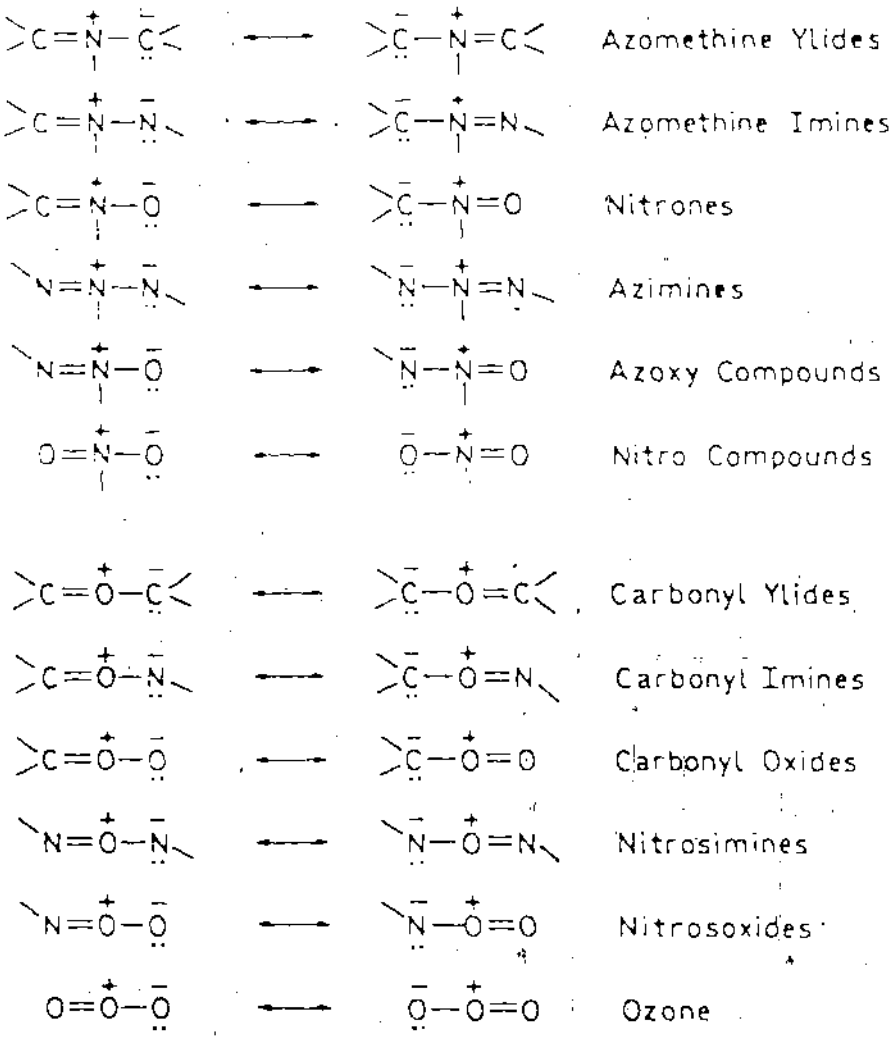
Putting the above values and $X = \alpha_O - \varepsilon / \beta_O$,

Table 1
Classification of 1,3-Dipoles Consisting of
Carbon, Nitrogen, and Oxygen Centers

A. Propargyl-Allenyl Type



B. Allyl Type



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

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

i.e., X = 0.5175, −1.58775 and −2.9297.

Therefore, $\varepsilon_1 = \alpha_0 + 2.9297\beta_0$

$\varepsilon_2 = \alpha_0 + 1.58775\beta_0$

$\varepsilon_3 = \alpha_0 - 0.5175\beta_0$

And the total Π-energy of the system (a) was $4\alpha_0 + 9.0349\beta_0$.

Similar treatment on the system (b) gave the following values:

$\varepsilon_1 = \alpha_0 + 3.035\beta_0$

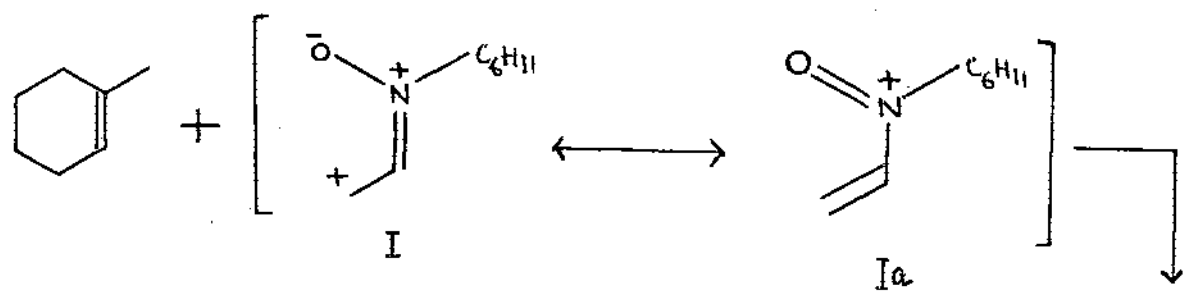
$\varepsilon_2 = \alpha_0 - 0.3304\beta_0$

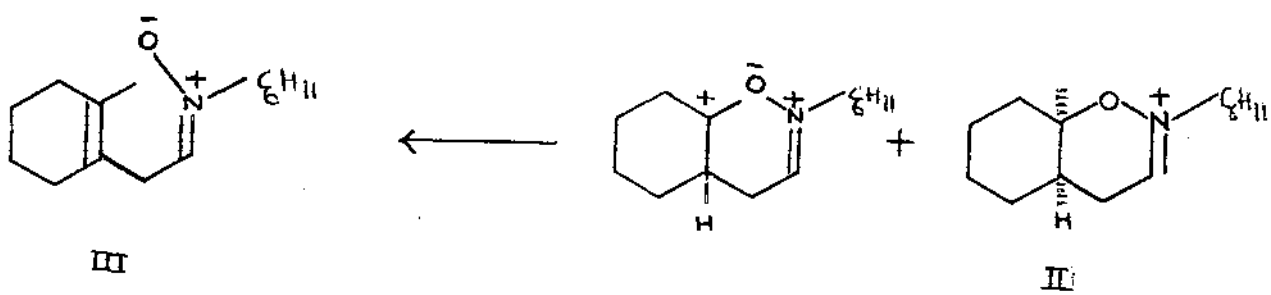
$\varepsilon_3 = \alpha_0 - 1.295\beta_0$

And the total Π-energy of the system (b) was $4\alpha_0 + 5.4092\beta_0$.

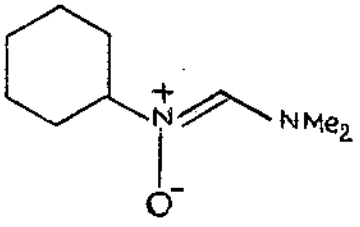
From the calculated result, it is evident that the canonical form (a) is more favourable on energy ground and this is also in agreement with the existing principle.

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

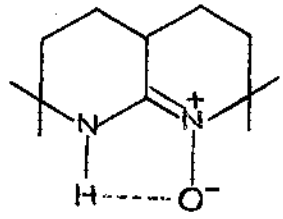




It was therefore, very striking on the light of these observations that α-Amino Nitrone could be prepared as stable compounds (IV and V)[6].



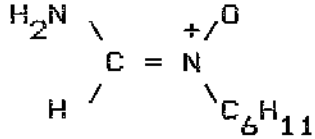
(IV)



(V)

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 MOs are filled up and the antibonding MOs are vacant and acts as a diene component in the hetero Diels-Alder reaction with olefins (4Π + 2Π-cycloaddition). But α-amino nitrones are 4-centered-6-electrons-Π-system in which the lower lying antibonding orbital is also filled up resulting the system to be comparetively unstable. But the system is not so, has been demonstrated by the synthesis of α-amino nitrones (IV and V)[6].

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



(VI)

The secular determinant for α-amino-N-cyclohexyl nitrone was as follows:

$$\begin{vmatrix} \alpha_O + h_N\beta_O - \varepsilon & \beta_{12} & \beta_{13} & \beta_{14} \\ \beta_{21} & \alpha_O - \varepsilon & \beta_{23} & \beta_{24} \\ \beta_{31} & \beta_{32} & \alpha_O + h_N\beta_O - \varepsilon & \beta_{34} \\ \beta_{41} & \beta_{42} & \beta_{43} & \alpha_O + h_O\beta_O - \varepsilon \end{vmatrix} = 0$$

By putting, $X = \alpha_0 - \varepsilon / \beta_0$,

$$\begin{vmatrix} X + 1.5 & 0.8 & 0 & 0 \\ 0.8 & X & 1.1 & 0 \\ 0 & 1.1 & X + 2 & 0.7 \\ 0 & 0 & 0.7 & X + 2 \end{vmatrix} = 0$$

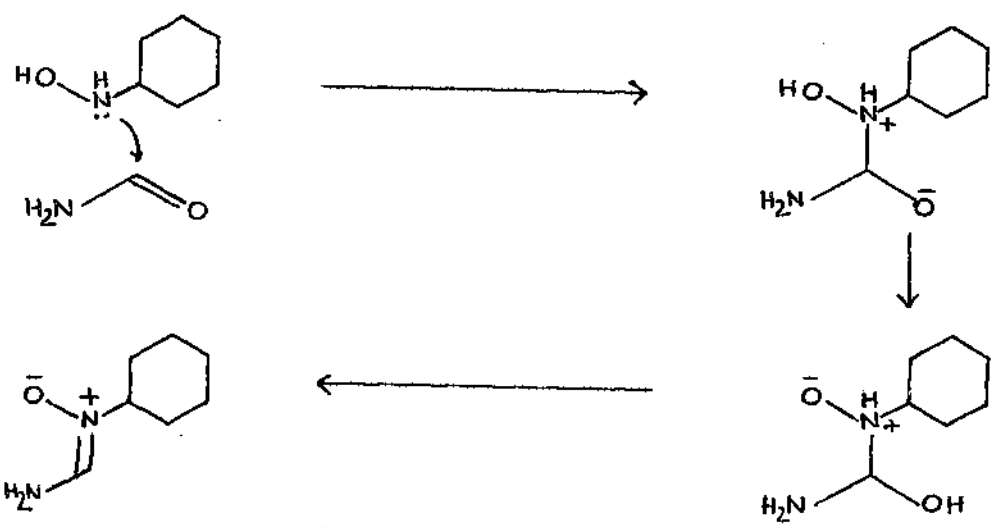
Thus solving, X = −2.96; −1.97; −1.32 and 0.75.

The energy levels were :

$$\varepsilon_1 = \alpha_0 + 2.96\beta_0$$
$$\varepsilon_2 = \alpha_0 + 1.97\beta_0$$
$$\varepsilon_3 = \alpha_0 + 1.32\beta_0$$
$$\varepsilon_4 = \alpha_0 - 0.75\beta_0$$

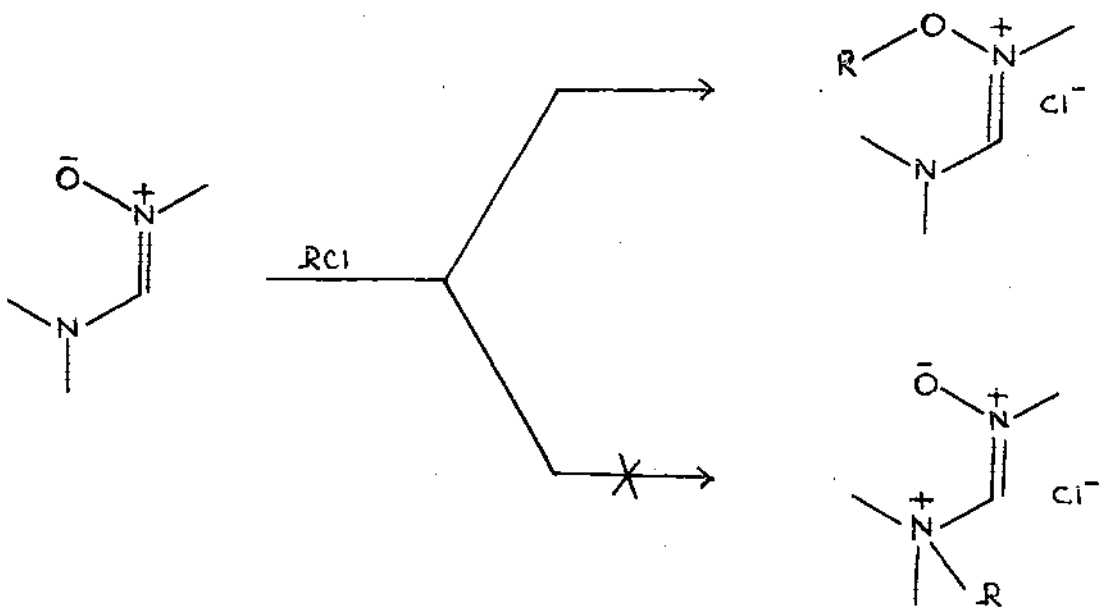
The total Π-energy was $6\alpha_0 + 12.5\beta_0$.

Considering the calculated energy levels associated with both the nitrones, viz., N-cyclohexyl methylene nitrone and α-amino-N-cyclohexyl nitrone (VI), it was also evident that the latter one was not so unstable. Keeping the above observations in mind, finally the **α-Amino-N-Cyclohexyl Nitrone** was synthesised directly from the simplest of the amide, formamide, and N-cyclohexyl hydroxylamine. The choice of formamide rested on the fact that it not only has sufficient carbonyl functionality but also could function as a good solvent when used in excess. A plausible mechanism of the possible formation of the nitrone is given bellow:



The most important step in the formation of the nitrone (VI) was the dehydration process, so the eficient execution of the preparative method needed the use of dehydrating agent. Anhydrous Magnesium sulphate was chosen for this purpose.

From the above discussion one thing was apparent that the α-amino nitrone should be very reactive due to the presence of a filled up antibonding MO, and indeed should act as a powerful nucleophile. There are two electron rich centers, one at the oxy-anion and the other at the α-nitrogen. But the density of the electrons being more at the oxy-anion end (three electron pairs) and steric hindrence is minimum, this end should preferebly act as a powerful nucleophilic centre in SN_2 reactions. Simple nitrones are not known to act as nucleophile in this fashion.



The above assumption could also be rationalised on the basis of Fukui's Frontier Orbital Theory. The Sustman Classification Of 1,3-dipoles (details discussed in Chapter-I/2) strictly holds only for the parent species, could be adapted qualitatively to substituted 1,3-dipole as well. Electron donor group in 1,3-dipole shifts the 1,3-dipolar character towards the Type-1, i.e., HOMO controled or nucleophilic 1,3-dipole. Whereas an electron acceptor shifts the behavior towards Type-3, i.e., electrophilic character.

α-Amino-N-cyclohexyl nitrone (VI) has an amino group at C-terminus which is a strong electron donor. Therefore, this nitrone should be nucleophilic in character. In general, nitrones are HOMO-LUMO controlled 1,3-dipoles skewing towards LUMO-controlled side, and do not react as nucleophiles.

The high reactivity of α-amino nitrone could also be explained on the basis of Perturbation Theory[7] wherein the HOMO level of a parent (unsubstituted) nitrone is raised in energy by the introduction of an amino group on the α-carbon atom and the corresponding LUMO level of the nitrone is stabilised. Thus the stabilisation of the dipole LUMO level should increase the interaction with the dipolarophile HOMO level, thereby providing relative stabilisation to the transition state for the cycloaddition and consequently increasing the rate of reaction.

2. 1,3-DIPOLAR CYCLOADDITION (MECHANISTIC APPROACH) :

According to Huisgen et.al., a cycloaddition of type 3+2——>5 leading to an uncharged 5-membered ring cannot possibly occur with octet stabilised reactants which have no formal charges. Combination of a 1,3-dipole with a multiple bond system d=e, termed the dipolarophile, is refer to as a 1,3-dipolar cycloaddition[1,8].

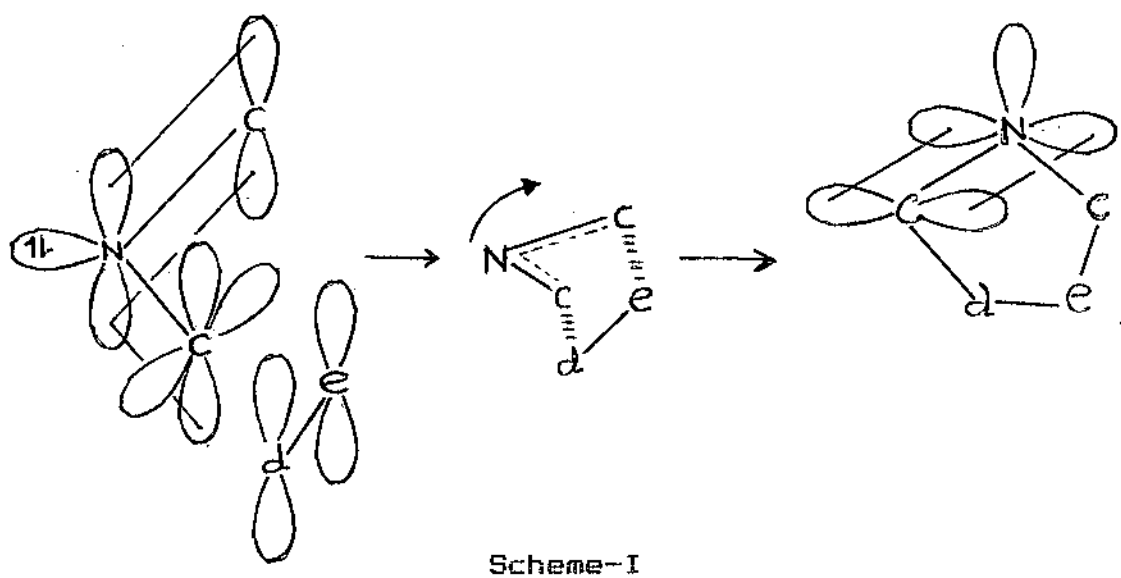
1,3-Dipolar cycloadditions are concerted reactions, i.e., both the σ-bonds are formed simultaneously and the reaction profile passes through a maxima[1,9]. Such type of single step reactions sometimes referred to as no mechanism reactions. A 1,3-dipole is always an ambivalent compound, which either displays electrophilic or nucleophilic activity in position 1 and 3. The mesomerism of the octet and sextet resonance structures of the 1,3-dipole results in charge compensation and charge exchange, respectively which makes it impossible to identify unequivocally an

electrphilic and nucleophilic centers. In other words, the question whether the cyclic electron shifts in Fig-A takes place clockwise or anti-clockwise is meaningless. Furthermore, though both the σ-bonds are formed simultaneously there is no reason to consider that the bonds at transition state be formed to the same extent.

Fig-A

The evidence in favour of the concerted process[1] in 1,3-dipolar cycloaddition came from their independence of solvent polarity[10,11], the negative entropies of activation[12] and the stereospecificity and regioselectivity[8].

Taking nitrile as a model system Huisgen described the cycloaddition according to the Scheme-I



Scheme-I

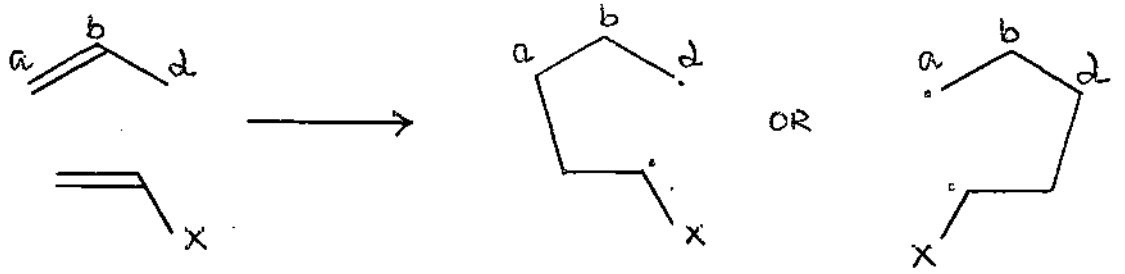
1,3-Dipoles "without a double bond" are already bent in the ground stable state, but the 1,3-dipoles "with a double bond" i.e., propagyl-allenyl type, the linear bond system a-b-c must necessarily bend in order to place centres "a" and "c" in contact with the Π-bond system of the dipolarophile. Calculation[13] shows that the resonence energy of the allyl anion is not disturbed by bending. The gradual transformation of p-orbitals into SP^2 or SP^3 orbitals of the new σ-bonds is accompanied by an interesting change of configaration. The nitrogen moves upwards until it reaches the plane of the remaining four centers in the adduct. In the course of this continuous transition, the orbital of the lone pair at nitrogen attains P-character; the σ-bond of the product originates from this pair of electrons. For 1,3-dipoles "without a double bond", the nitrogen at the transition state needs not to be shifted to the plane of the remaining four atoms and rather will shift in such a way that the product conformation at ground state can be achieved.

R.A.Firestone[14,15,16] observed some discrepancies in the mechanism proposed by Huisgen et.al. and suggested an alternative two-step mechanism for the 1,3-dipolar cycloadditions (Scheme-II).

Firestone considered three principal canonical forms of a typical 1,3-dipole (A,B and C in Scheme-II). These are all octet structures which have the same number of bonding electrons. All other forms such as sextet structures, have fewer bonding electrons and are therefore, discounted. Form "C" is drawn according to Linnett's method and is quantum-mechanically equivalent to "A" and "B". Since the dipole moment of most 1,3-dipoles are small compared to the theoretical values for full charge separation, Firestone stressed that the expression "C" may usually be accepted as the principal representation of the 1,3-dipole.

He considered all the modes of addition of the dipole and the dipolarophile and selected two possible regioisomeric products 3 and 4 respectively. Diradical 5 and 6 expected to be less important because they do not utilize the radical- stabilizing power of the substituent "X". For any individual 1,3-dipole, a preference for either 1 or 2 is expected, and this preference

should be the same whether the substituent "X" in the dipolarophileis electron attracting or electron releasing and expectedly this preference will govern the regioselection of the addition.



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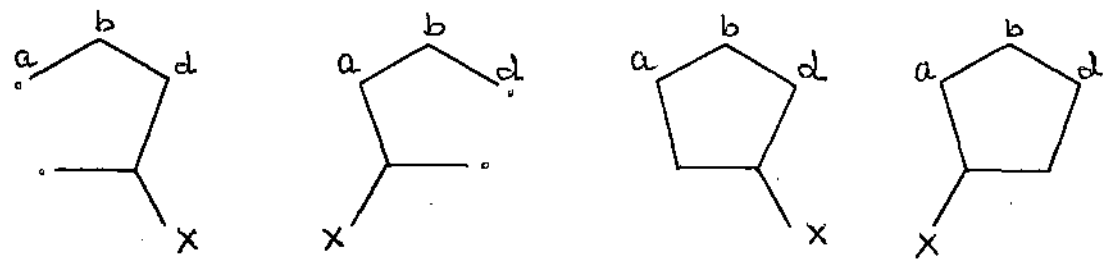
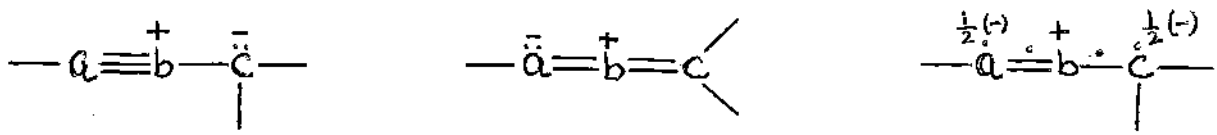


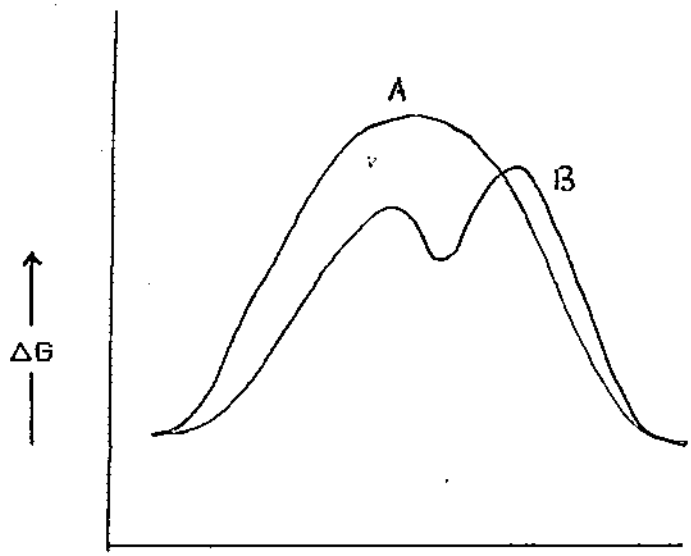
5 6 3 4



A B C

Scheme-II

For two step process, the first step is the rate determining step and the activation energies for both advance and retrograde motion along the reaction co-ordinate is very small, smaller in fact than that for rotation around a single bond (Fig-B).



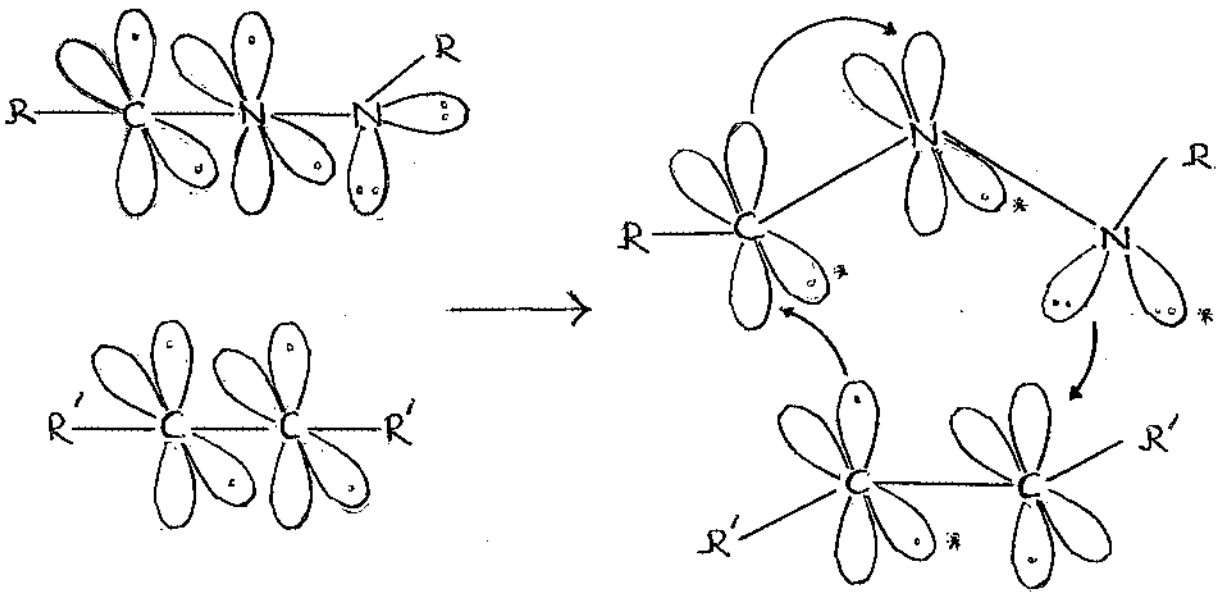
A-Reaction profile for concerted reaction.
B-Reaction profile for two-step reaction.

Fig-B

Firestone thought that when the dipolarophiles bears a substituent with appreciable conjugation energy, which is lost in the transition state in concerted process and this would retard the reaction relative to one with unsubstituted dipolarophile. But the fact is that all substituents in the dipolarophile strongly accelarate 1,3-dipolar cycloadditions.

Furthermore, a number of 1,3-dipoles react with acetylenes to produce aromatic system directly e.g., nitrile imine, nitrile oxide and azides. In a concerted reaction, a portion of this aromatic stabilisation should exist in the transition state on this basis. Firestone formulated a planer transition state as Scheme-III.

Although the observed fact of low activation energy for the 1,3-dipolar cycloaddition seems to contradict two step process, Firestone explained on the basis of bond energy calculations that actually the energy defferences for the two processes is very low. He tried to rationalize all other general characteristics of these type of reactions.



The orbitals marked with asterstiks constitute developing aromatic Π-cloud.

Scheme-III

But Huisgen strongly refuted[17] the above diradical mechanism. He argued that the greatest obstacle for the assumption of a diradical intermediate is the stereospecifisity observed in the cycloadditions of the 1,3-dipole with cis- and trans dipolarophiles; energy calculations of diradical intermediate are not adequate and planer transition state as propossed by Firestone is not in accord with the Woodward-Hoffman Rules[21].Lots of other discrepancies had also been pointed out by Huisgen in the Firestone model of 1,3-dipolar cycloadditions and he ultimately concluded that all mechanistic criteria underline the superiority of the concerted mechanism over the diradical hypothesis.

Houk et.al., pointed out that mechanistic investigations have shown that cycloadditions of 1,3-dipole to alkenes are stereospecificaly suprafacial; solvent polarity has little effect on reaction rates, and small activation enthalpies and large negative entropies are generaly found. These facts, along with

reactivity and regioselectivity phenomenon, have been considered totally compatible only with a concerted five-center mechanism. Orbital symmetry consideration have provided permissive, though not obligatory, theoretical evidence for the concerted mechanism and the observation of [$\pi^4s + \pi^6s$] cycloaddition but not [$\pi^4s + \pi^4s$] cycloadditions of 1,3-dipoles to triene has provided further evidence for the concerted mechanism[18,19]. But the experimentally observed regioselectivity 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 Moleculer Orbital Theory.

Qualitative orbital energies and co-efficients are of great imporance here. For this purpose frontier orbitals of representative alkenes are shown in Table-II and III. In each figure, (-)ve of the ionisation potential (IP) of alkene is given under the horizontal line for the HOMO (Highest Occupied Moleculer Orbital) and the (-)ve of the electron affinity is given under LUMO (Lowest Unoccupied Moleculer Orbital) level. The units are electron volt (eV). The AO (Atomic Orbital) co-efficients for the frontier MOs 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 donor.The conjugated alkenes (Table-III) raise HOMOs and lower LUMOs as compared to ethylene. Frontier MOs of some 1,3-dipoles (Table-IV) show relatively small gap in their HOMO-LUMO levels and therefore their reactivity are quite high. Houk et.al. further proposed that bending of either terminus can reverse these generalisations[20].

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[21]. And the allowed process can be of three types as proposed by Sustman[22,23] (Fig-C). the Type-1 involves dominent interaction between HOMO(dipole) and LUMO (dipolarophile). Type-3 involves LUMO(dipole)-HOMO(dipolarophile).

TABLE - II

The frontier MO's of electron-rich alkenes.

		Cl	Me	OMe	SMe	NMe_2
LUMO	·71, -71 +1·5	·67, -54 ~+5	·67, -65 +1·8	·66, ·72 +20	·63, -48 -10·	·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

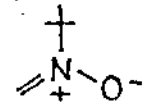
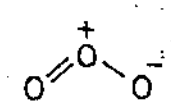
TABLE - III

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

	COOMe	CN	NO_2		Ph
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.

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

But in type-2, both the LUMO(dipole)-HOMO(dipolarophile) and the HOMO(dipole)-LUMO(dipolarophile) are important in determining reactivity and regiochemistry.

Type-1 dipoles are those having high lying HOMOs and LUMOs and refered as HOMO controlled or nucleophilic 1,3-dipoles. Type-3 are having low lying FMOs and refered as LUMO controlled or electrophilic dipoles. The type-2 1,3-dipoles are refered 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.

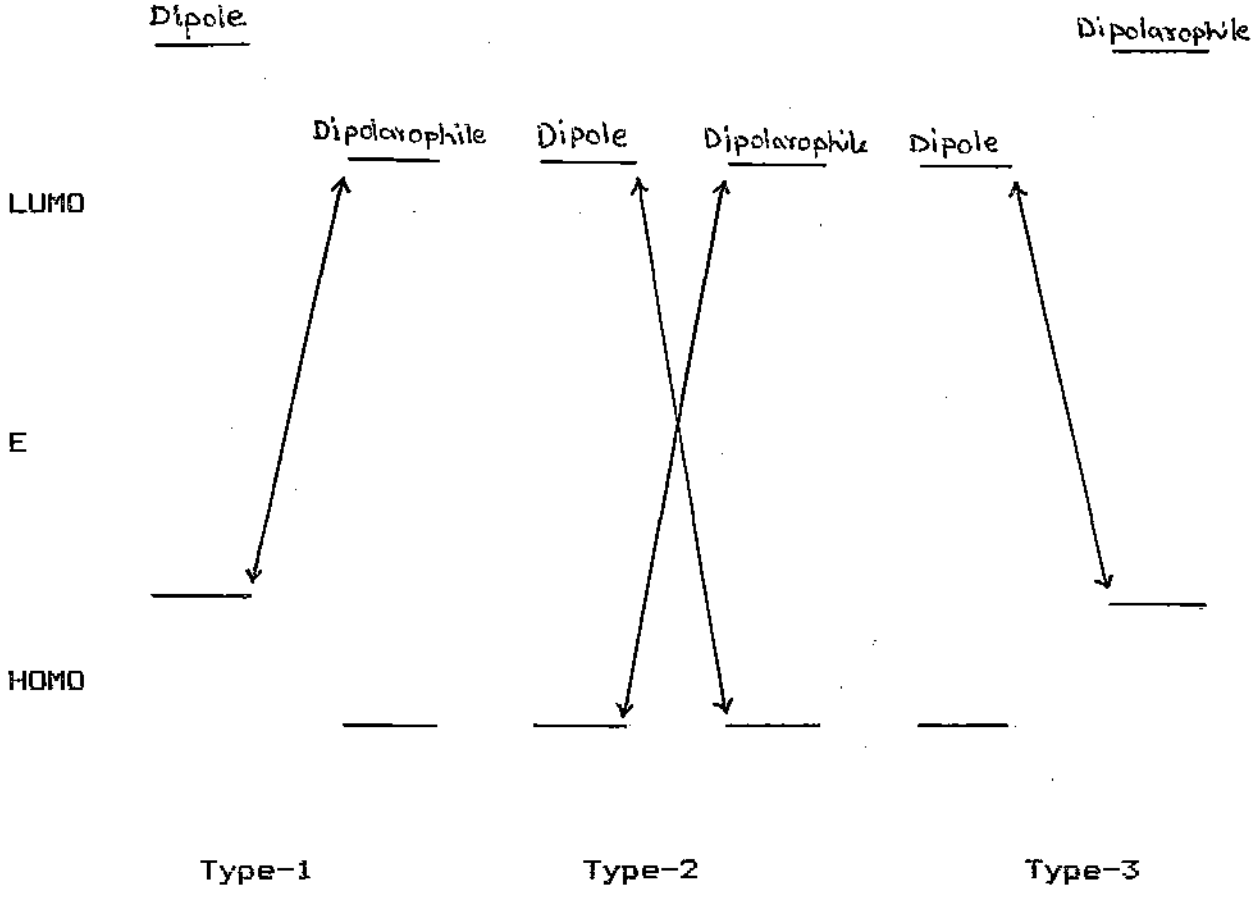
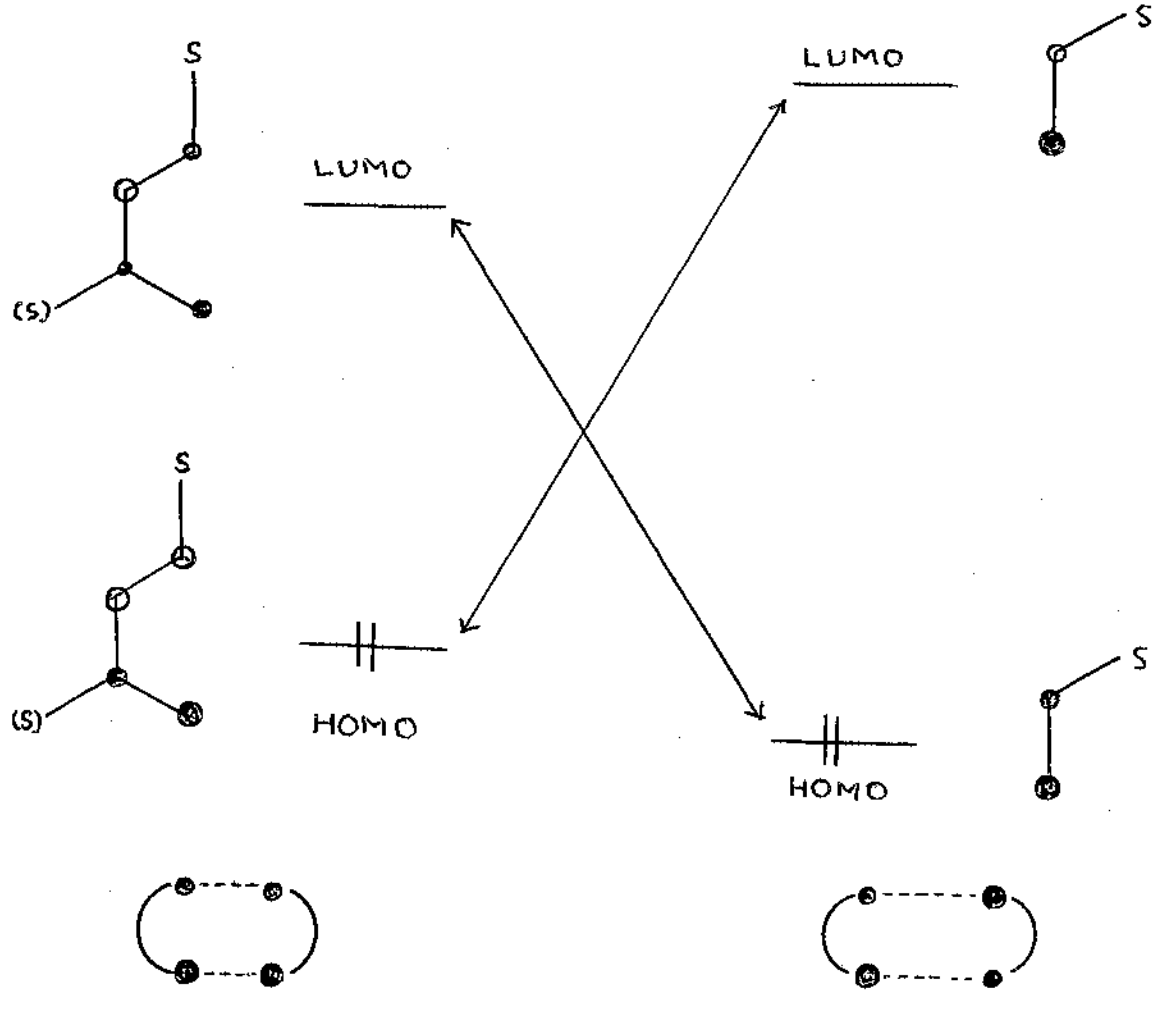


Fig-C

The nitrile ylides, diazoalkenes 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.



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

Fig-D

Nicety of Houk's model lies specially in its general applicability in the prblem of regioselection. Fig-D summerizes the frontier MOs of monosubstituted alkenes and 1- and 2-substituted dienes. In the case of a donor or conjugatively substituted diene , the acceptor substituent at the 1-possition of a diene or alkene will enlarge the co-efficient at the most remote position in the LUMO. In the case of donor diene and acceptor alkene, the diene HOMO - dienophile LUMO interaction will be the largest when the transition state involves bond formation leading to the "ortho" or (Z) adduct This is because the stabilisation energy will be larger when the larger terminal co-efficients and the smaller terminal co-efficient of the two interacting orbitals overlap, which gives a larger net overlap, and thus larger transition state stabilisation, than if a large co-efficient on one orbital interacts with a small on the second at both bond forming centers.

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

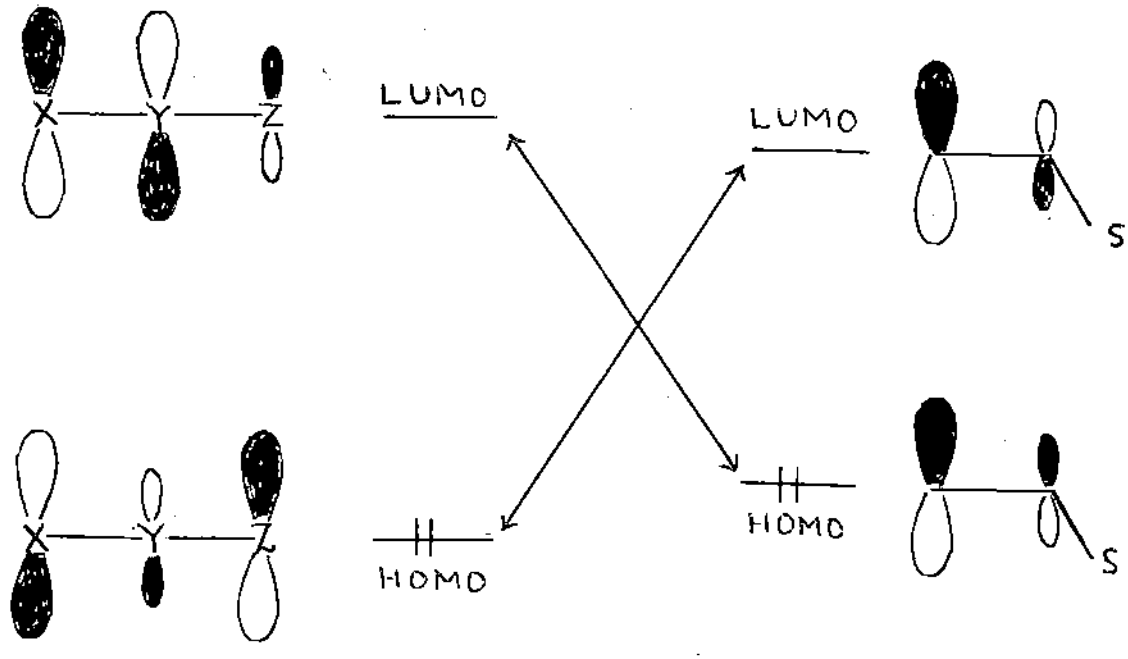


Fig-E

The HOMOs of the 1,3-dipolar system generally have the larger terminal co-efficient on the group "Z", while the LUMOs have the larger co-efficientat the opposite terminus, "X". The HOMOs and LUMOs 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 the 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.

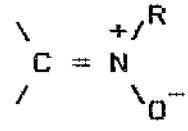
Nitrile oxide and nitrones react to give mainly the 5-substituted adduct with weakly electron deficient alkenes such as acrylonitrile and acrylate. The HOMOs and LUMOs of these electron deficient alkenes both iteract fairly strongly with the LUMOs and HOMOs of the nitrile oxides or nitrones, so that orientation is influenced by both the iteractions. The experimental results show that the dipole LUMO - dipolarophile HOMO interaction has more influence on regioselectivity. 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 dipolarophiles are less reactive than expected on the basis of their IP's[28]. Since alkynes have larger HOMO-LUMO gap than the analogous 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 acual 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 regiochemistry in the former case is stil controlled by the LUMO(dipole) - HOMO(dipolarophile) interaction. Therefore, in the case of alkyne, the dipole HOMO - dipolarophile LUMO interaction becomes so much 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 :

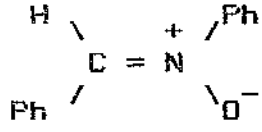
The name NITRONE is given to the compounds having the group :



to indicate a chemical relationship between nitrone and carbonyl compound[29].

2. NOMENCLATURE :

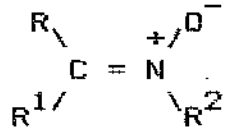
The nomenclature employed by the Chemical Abstract is as follows : the following compound is named as α,N-diphenyl nitrone.

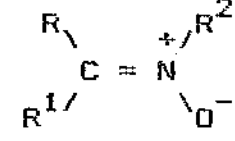


Cyclic nitrones are named according to parent heterocyclic compound, e.g., 2,4-dimethyl-Δ^1-pyrrolidine-N-oxide and Δ^1-tetra hydro pyridine-N-oxide. Nitrone have also named as C-cyclopropyl-N -methyl nitrone, etc. The general terms, aldonitrones and keto nitrones have been employed occasionally. Aldonitrones contain a proton on the α-carbon atom, $RCH = N(O)R^1$, while in ketonitrones contain the α-carbon fully substituted with alkyl and/or aryl groups, $RR^1C = N(O)R^2$.

3. GEOMETRICAL ISOMERISM :

Nitrone exhibit geometrical isomerism due to the presence of





double bond in the nitrone group. The existance of geometrical isomerism was first demonstrated in 1918 for α-phenyl-α-(p-tolyl) -N-methyl nitrone[30]. The configurations of the isomers were established by dipole moment studies. The cis-forms of some nitrones were converted readily into the trans-form by heating[31]. Generaly, aldonitrones exist in stable trans-forms and this has been established by UV, IR and NMR studies[32]. The only example of geomtrical isomerism is known for α-phenyl-N-^{t}butyl nitrone[33]. Therefore, in such cases , where geometrical isomerism are possible, E/Z notion may be employed in naming.

4. SYNTHESES OF NITRONES :

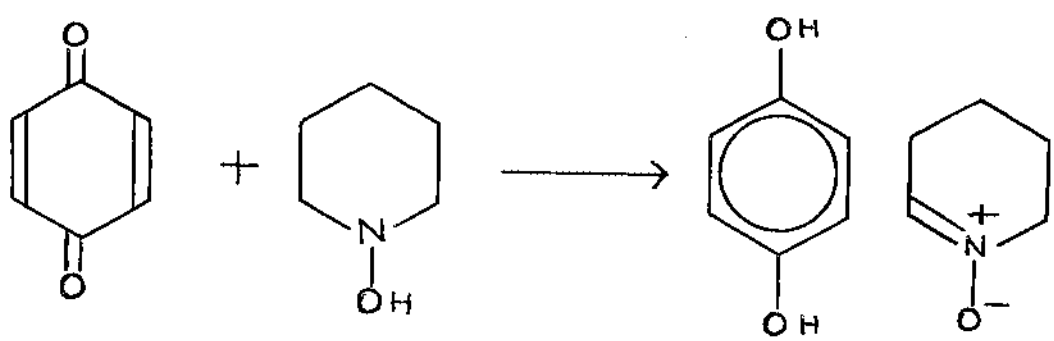
The chemistry and syntheses of nitrones were reviwed[29,34,35]. The general methods of syntheses of nitrones are briefly discussed here.

[A] By Oxidation Of N,N-Disubstituted Hydroxylamine :

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

Cyclic and acyclic nitrones were prepared by this method. Different oxidizing agents were used, e.g., molecular oxygen[36-40], yellow mercuric oxide[32,41-43], active lead oxide[45], pottasium ferricyanide[37,41,43,46], hydrogen peroxide[47,48], pottasium permanganate[48], t-butyl hydroperoxide[49], diamine silver nitrate[37], etc.

The formation of a nitrone salt was reported from the reaction between p-bezoquinone and 1-hydroxy piperidine[50].



[B] From Oximes :

The alkylation of oximes were reviewed in 1938[29]. A disadvantage of the method is that, nitrone are produced along with oxime ether.

$$R^1R^2C{=}NOH + XR \longrightarrow R^1R^2C{=}NOR + R^1R^2C{=}\overset{+}{N}(O^-)R$$

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.

Heptanal oxime when treated with benzyl chloride in solution of ethanol and sodium ethoxide yielded 77% of α-hexyl-N-benzyl nitrone[51]. Dimethyl sulfonate was employed in the alkylation of various keto-oxime[52,53].

C,C-dicyclopropyl-N-methyl nitrone has been prepared by this method[25].

O-trimethyl silyl oximes converted to nitrones conveniently by N-alkylation[54]:

$$PhCH{=}NOSiMe_3 \xrightarrow{\text{Me-triflate}} PhCH{=}\overset{+}{N}(O^-)Me$$

α-Nitrso nitrones have been prepared from nitrile oxide and nitrosoarene[55].

[C] From N-Substituted Hydroxylamine :

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

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[56].

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-butyraldehyde, 80% yield of α-propyl-N-phenyl nitrone was obtained[46]. With benzaldehyde a 90% yield of the nitrone[57,58], with o-, m- and p-nitro benzaldehyde good yield[59], with p-N,N-dimethyl amino benzaldehyde a 79% yield[60] and good yield with other substituted benzaldehydes[61]. N-phenyl nitrne formed from hydroxyl amine and formaldehyde in situ and finally dinitrone[37].

$$Ph\text{-}\overset{+}{N}(O)^{-}=CH_2 \longrightarrow Ph\text{-}N(OH)\text{-}CH_2\text{-}\overset{+}{C}H\text{-}\overset{-}{N}(O)\text{-}Ph \xrightarrow{-H_2} PhN(O)=CHCH=N(O)Ph$$

A similar 2:1 products were observed in the reaction between N-phenyl hydroxyl amine and α-bromo crotonaldehyde[37]. A number of sesitive nitrones have been prepared by this method and have been trapped in-situ[62,63]. The bisulphite addition compounds of aldehydes and ketones may be used instead of the aldehydes or ketones[64]. Five membered cyclic nitrones have been prepared in yields ranging 50-80% by reductive cyclization of γ-nitro ketones[65-67] or γ-nitro nitriles by employing zinc dust and aqueous ammonium chloride.

[D] From Oxaziranes :

The smooth thermal rearrangement of 3-phenyl oxaxirane derivatives to the corresponding nitrones were reported by various workers[33,68-70] in yields 50-100%. Other imine also gave nitrone on oxidation by peroxy acids or dimethyl dioxirane[71].

$$PhRC=NR^1 \xrightarrow{H_2O_2} PhRC\overset{O}{\diagup\diagdown}NR^1 \xrightarrow{\Delta} PhRC=\overset{+}{N}(O)^{-}R^1$$

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

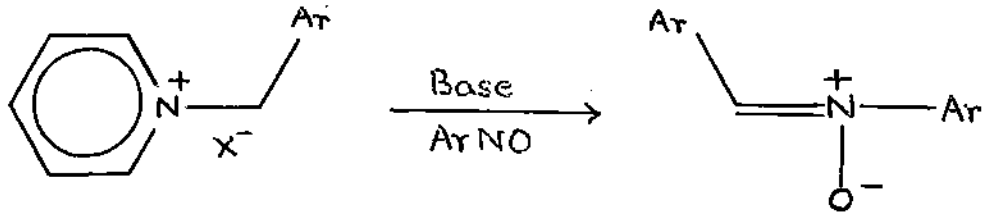
$$R_2C\overset{O}{\diagup\diagdown}NR \longrightarrow R\text{-}CO\text{-}NR_2$$

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

[E] From Aromatic Nitroso Compounds :

Aromatic nitroso compounds react with a variety of compounds to form nitrones. 2,4,6-Trinitro toluene 9-methyl acridine, with sufficiently active methylene group react with aromatic nitroso compounds to form nitrones but may often forms anils also[72-75]. The reaction usually catalised by trace amount of base, e.g., pyridine, pipyridine and sodium carbonate.

Such type of reactions are also known with lepidine-N-oxide[76], quinaldine-N-oxide[76,77] and 2- and 4-picoline[72,73] 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[80,81]. This reaction is specially helpful for preparing pyridinium salts of methyl-substituted heterocyclic aromatic compounds, α-methyl ketones[56], etc.

Aromatic nitroso compounds react with benzyl derivative such as benzyl chloride[82,83] and fluorene[84] and similar compounds[85-87] in presence of some suitable base to yield nitrones.

Lot of other compounds like diazo compounds, sulphar ylides, alkenes and alkynes can react with aromatic nitroso compounds to yield nitrones[34].

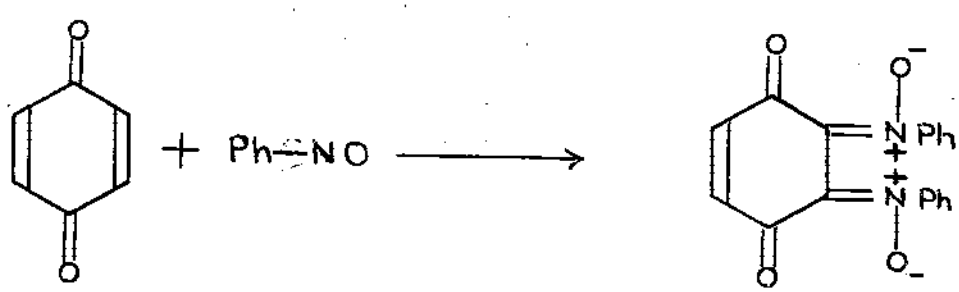
[F] Some Other Miscellaneous Methods :

N,N-Disubstituted and N-substituted hydroxyl amine gave the corresponding nitrones by the palladium catalised reaction. The former reaction was performed in the presence of alkene to give the cycloadduct[88].

$$RCH_2\text{-}N(OH)R^1 \longrightarrow RCH{=}\overset{+}{N}(O^-)R^1 + H_2$$

Quarternary Mannich bases when treated with an aromatic nitroso compound yielded nitrones[34].

Quinone yielded dinitrones upon treatment with nitroso benzene[89].



Oxidation of secondary amine by hydrogen peroxide in presence of catalytic amount of Na_2WO_4 yielded corresponding nitrone[90] and also oxidation by dimethyl dioxirane of secondery amine yielded nitrone[55].

Some thiazolium salt partially reduce nitrobenzene with benzaldehyde to nitrone[91].

The adduct silyl enol ether with nitrobenzene can be oxidised to α-aryl-N-phenyl nitrone by silver oxide[92].

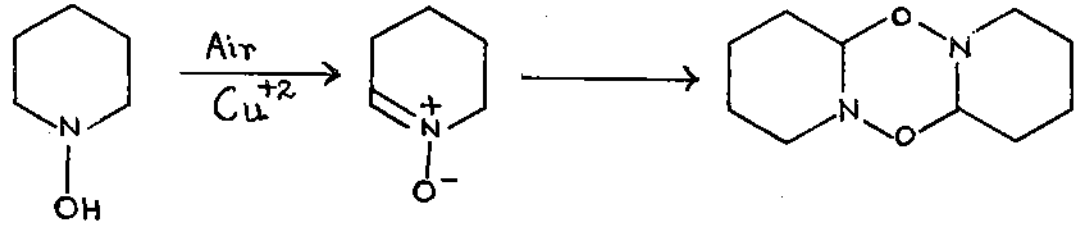
N-methyl nitrones can be generated in good to excellent yields from aldehydes and ketones with stoichiometric amount of N-methyl-N,O-bis(trimethyl silyl) hydroxyl amine[93].

5. REACTIONS OF NITRONES :

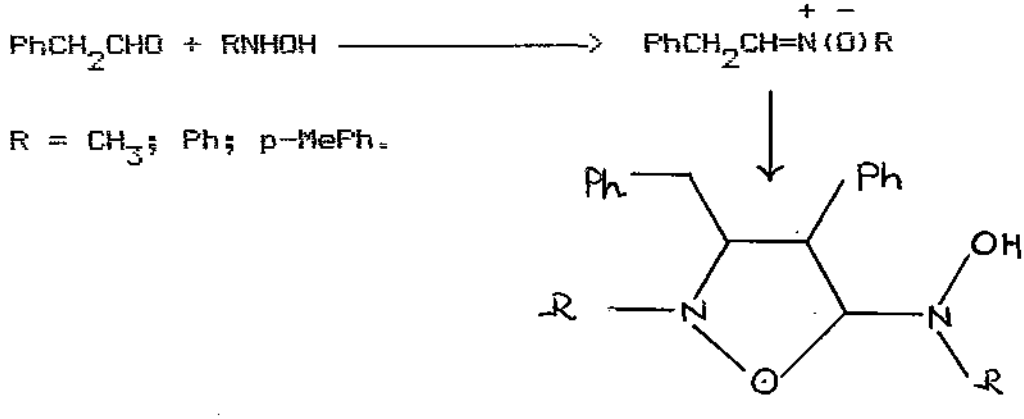
The reactions of nitrones were reviewed in 1964 by J.Hamer and A.Macaluso[34]. The major reactions of nitrones are their cycloadditions with a variety of multiple bonds. Reactions are briefly reviewed here.

[A] Dimerisation :

Nitrones are sometimes very susceptible to dimerisation, e.g., N-hydroxy piperidine did not give the expected cyclic nitrone but the dimer[40] and the trimer[41]. The corresponding five membered nitrones were found to be monomeric[38].

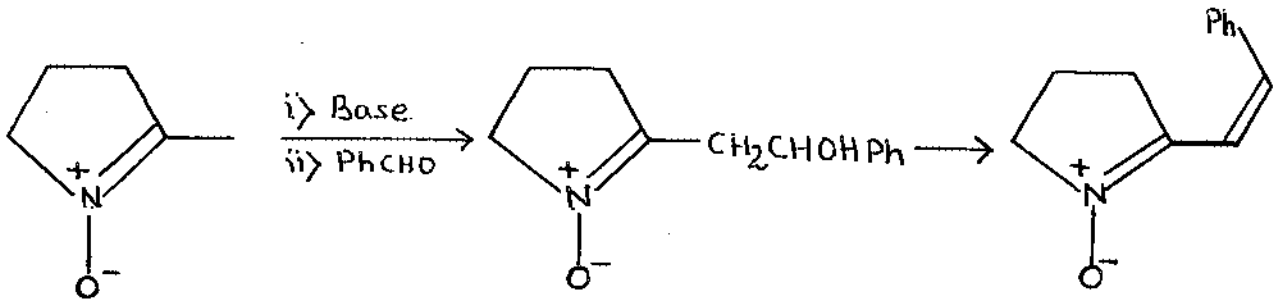


2-Phenyl-N-hydrxy piperidine also yielded a cyclic dimer upon oxidation. Acetone and N-phenyl hydroxyl amine yielded an aldol type of dimer[65]. N-butyraldehyde and N-phenyl hydroxyl amine also yielded same type of dimer. Dimerisation with a loss of hydrogen molecule for a methyl nitrone was also reported[37]. For aliphatic nitrones following type of cyclodimerisation was reported[142].



[B] Aldol Condensations :

The nitrone group bears a marked resemblace to the carbonyl group in facilitating the removal of a proton from adjacent carbon under basic condition[94,95,102]. Benzaldehyde and α-styryl-N-methyl nitrone in presence of base yielded α-styryl-N-phenyl nitrone[97]. This reaction was observed employing p-nitro or p-chloro benzaldehyde[97].



[C] Addition Of Grignard Reagents :

Grignard reagents were added to aldonitrones in a 1,3-fashion but the reaction with ketonitrones led to imines[97-100,32,37,38].

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

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

[D] Addition Of Hydrogen Cyanide :

Nitrones formed a 1,3-adduct with hydrogen cyanide[38,101-105]. In presence of base the adduct readily lose water to yield a cyanomine.

$$RCH=\overset{+}{N}(O)\overset{-}{R^1} + HCN \longrightarrow RCH(CN)-N(OH)R^1 \longrightarrow RC(CN)=NR^1$$

Other type of miscellaneous additions are also known[37-39].

[E] Rearrangement :

Aldonitrones rearrange to isomeric amides by treatment with a variety of reagents, e.g., $POCl_2$, PCl_3, PCl_5, $SOCl_2$, SO_2, CH_3COCl, $(CH_3CO)_2O$ and solution of base in ethanol[53,103,106-112].

$$PhCH=\overset{+}{N}(O)\overset{-}{C}H_3 \longrightarrow PhCONHCH_3$$

Under the influence of heat[44,103] or acid[114-116,117] nitrones may rearrange to o-ethers.

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

Ketonitrones may rearrange to aldonitrones by base[113,118,119] and such type of rearrangement also observed in the synthesis of nitrones[114,118] and is known as Behrend Rearrangement.

[F] 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[57,70,120].

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

On pyrolysis nitrones split into anils, with traces of other products[121-123] e.g.,

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

Ozonolysis of nitrones is very rapid. Formation of green or blue colour indicates nitroso compounds[121,124].

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

Nitrones readily hydrolyses to an aldehyde or a ketones[115,78] and an N-substituted hydroxyl amine. Arylnitrones are less readily hydrolyse than alkylnitrones.

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

Treatment of $LiAlH_4$ or $NaBH_4$ on nitrones in ether yielded the corresponding hydroxylamines, in high yield[92,93,106,125,126].

$$R^1R^2C{=}\overset{+}{N}(O^-)R^3 \xrightarrow[NaBH_4]{LAH\ or} R^1R^2CH{-}NH(OH)R^3$$

α-Hexyl-N-benzyl nitrone with sodium in alcohol yielded N-heptyl-N-benzyl amine[51].

Deoxygenation of nitrone has been accomplished by zinc, iron, tin, phosphine, sulfur dioxide, sulfur and catalytic hydrogenation[38,65-67,127].

[G] Cycloaddition Reactions Of Nitrones :

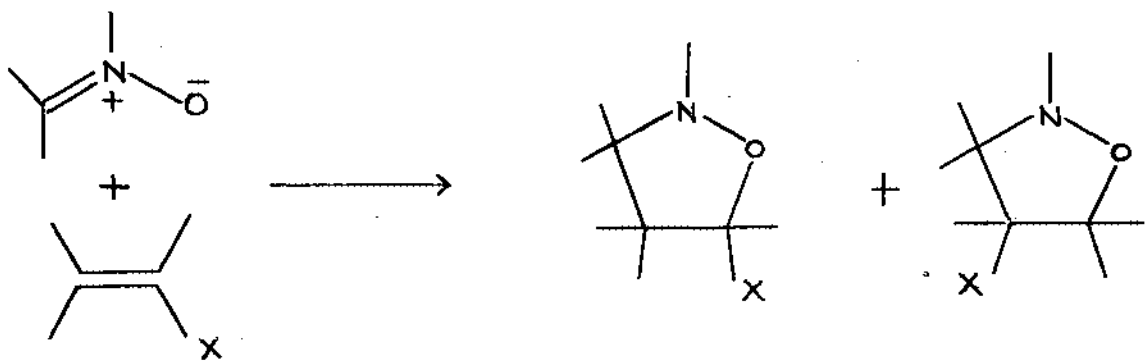
Nitrones readily undergo 1,3-dipolar cycloaddition reactions with a variety of multiple bonds. The nitrone addition were comprehensively rwviewed[34,35,128]. In nitrones, four Π-electrons are distributed over three atoms like allyl anion systems. In valence bond theory, such compounds can only be described in terms of dipolar resonance contributors, thus the term 1,3-dipole arose.

Dipolarophiles are substrates having at least two Π-electrons and can undergo cycloaddition with 1,3-dipoles. Only the 1,3-dipolar cycloadditions are systematically are reviewed here.

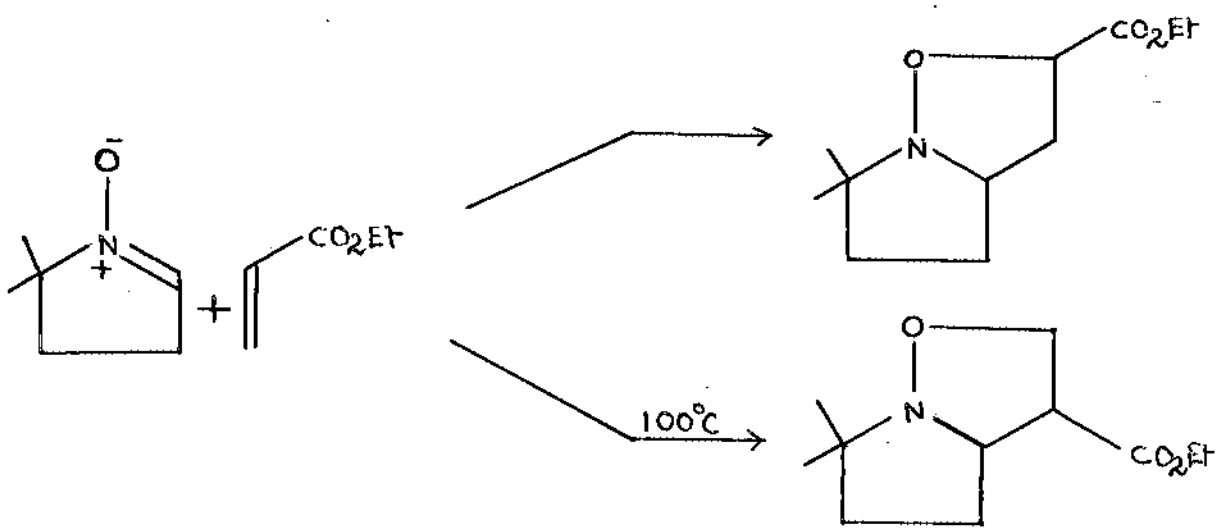
(G1) Addition With alkenes :

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-defficient dipolarophiles react with nitrones smoothly. With unsymmetrical system, two orientations are possible.



The direction of nitrone addition can be reversible and therefore, subject to both thermodynamic and kinetic control[129]. 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^{0}C yields 98% of the other.



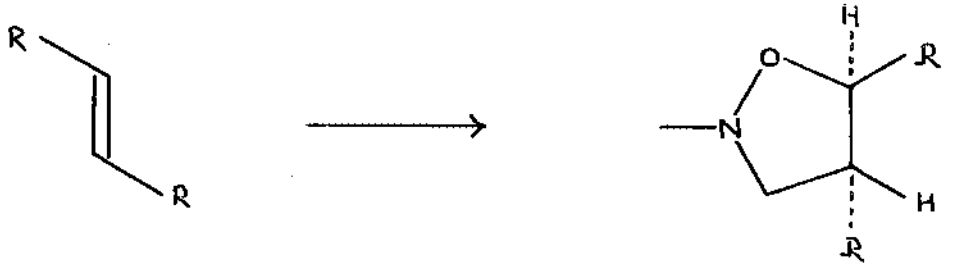
Regioselectivity applies to addition under conditions of kinetic control. Both steric and electronic factors are important[1a,9]. In general the more hindered end of the electrophile adds to the oxygen atom of the nitrone to give 5-substituted adducts. However this generalisation does not hold good for all

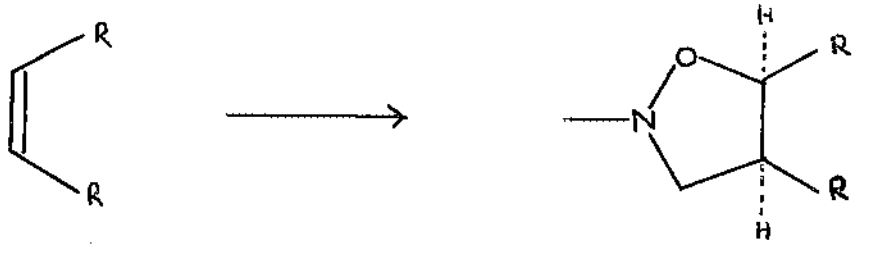
cases. The reversal of regioselection was also observed with nitrones of very high ionization potential[27] or with very electron deficient dipolarophiles[26]. Table-V illustrates how the regioselection changes with the different dipolarophiles and with different type of nitrones. Other reported cycloadditions are given in Table-VI, VII and VIII.

Only 5-substituted isoxazolidines are generaly formed in nitrone addition with 1,1-disubstituted alkenes. But a recent study shows that 4-substituted adduct was also formed[133]. Most addition of trisubstituted alkenes to nitrones yield 4,5,5-trisubstituted isoxazolidines, but in some cases 4,4,5-tri substituted isoxazolidines[130,131]. Cycloaddition of tetra substituted alkenes to nitrones are not common and regioselectivity factors are similar to those discussed for unsymmetrical 1,2-disubstituted alkenes.

(62) Stereochemistry Of Addition :

Studies of addition of dimethyl maleate and dimethyl fumarate to a variety of nitrones[135,136] have established stereospecific cis-addition by the production of mutually uncontaminated diastereomeric adducts.





R = CO_2Me

TABLE-V

Ratio of 5-substituted:4-substituted adducts from nitrone cycloadditions of electron-deficient dipolarophiles.

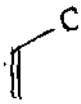
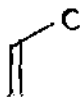
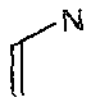
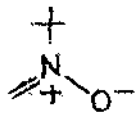
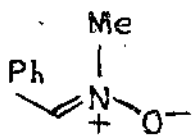
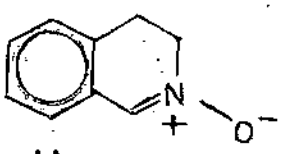
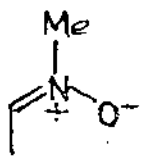
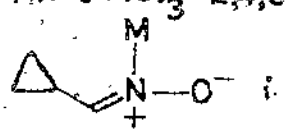
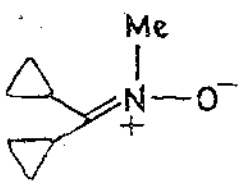
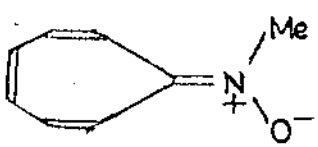
Dipolarophiles:						
Nitrones:						
	100:0	100:0	100:0	70:30	70:30	50:50
	100:0	100:0	0:100	32:68	42:58	0:100
	100:0	20:80	-	-	0:100	0:100
	50:50	15:85	0:100	0:100	0:100	0:100
 i	80:20	66.6:33.3	-	37:63	20:80	-
	50:50	25:75	-	0:100	0:100	-
	-		-	0:100	-	-

TABLE - VI

Monosubstituted alkene dipolarophiles in nitrone cycloadditions

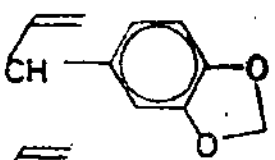
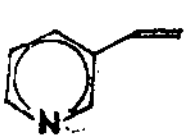
Dipolarophiles	Yield(%) of adducts	References
	57 - 100	27, 148-154
$C_6H_4X(p)$		
	64 - 93	153, 155.
n-But		
	75 - 100	152, 155.
CH_2OH		
	93	155.
n-Am		
	65 - 93	148, 153.
CH_2Cl		
	76	155.
CH_2OOCCH_3		
	97	155.
	98	155.
$(CH_2)_2COOCH_3$		
	67	155.
$(CH_2)_8COOC_2H_5$		
	100	152, 156.
	12	157.
	50	157.

TABLE-VI (Cont.)

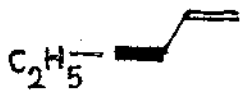
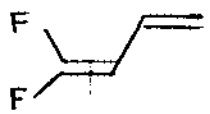
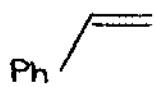
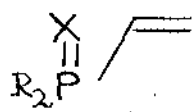
Dipolarophiles	Yield(%) of adducts	References
	50	157.
	61 - 100	66, 155, 27, 153, 152, 158-161.
	34 -100	155, 27, 148, 153, 158, 160, 161-164.
	75 - 79	151, 160, 165, 183.
	95	184.
	89	185.
	52-93.	186.

TABLE-VII

1,1-disubstituted alkenes in nitrone cycloaddition.

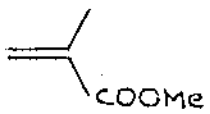
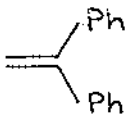
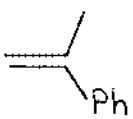
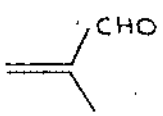
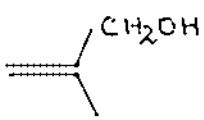
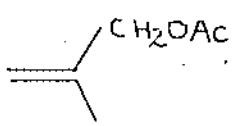
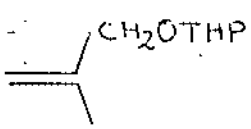
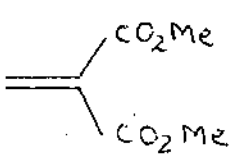
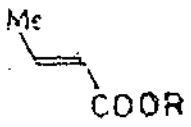
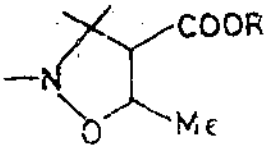
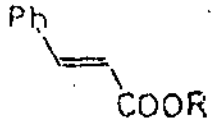
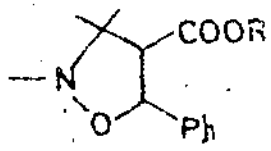
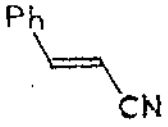
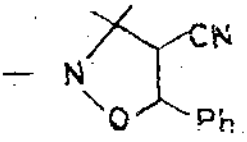
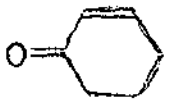
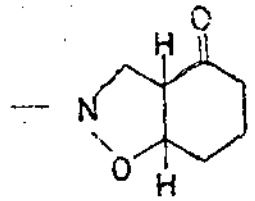
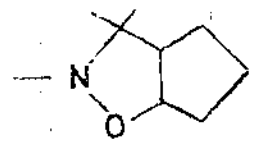
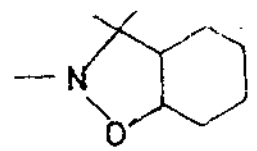
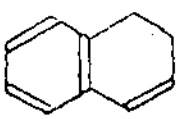
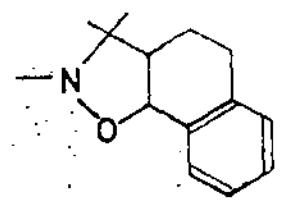
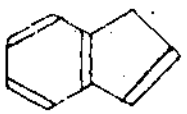
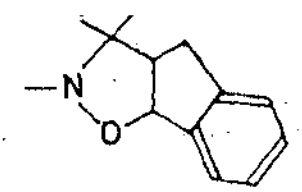
Dipolarophiles	Yield(%)	References
	90-100	155
	65-86	156
	70-85	156
	94-95	133
	70-77	133
	66-72	133
	50-58	133
	74-90	133

TABLE-VIII

Unsymmetrical 1,2-Disubstituted Alkene Dipolarophiles in Nitrone Cycloadditions.

Dipolarophiles	Adducts	Yields (%)	Ref.
		63 -96	152-155, 166.
		70 - 100	136, 155, 166.
		50 - 78	136.
		-	166.
		-	1.
		-	1.
		97	1.
		70 - 92	156.

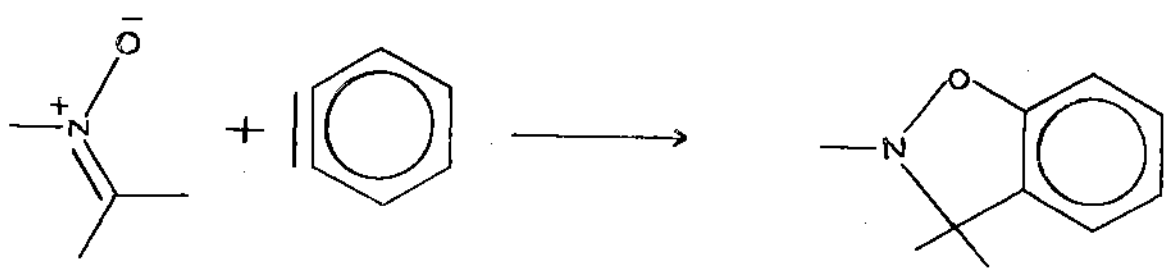
This general principle has been confirmed in many other cases of cycloadditions[129,134,136]. Cis-trans isomerism of dipolarophile substituent with respect to the nitrone substituents has been noted in many cases and is caused by the fact that the nitrone can approach the dipolarophile from two different sides. Isomer ratio ranging from 50:50 to 100:0 have been observed. There is a good evidence[137] 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 increases the stereospecificity and vice-versa.

(63) Addition To Alkyne :

Acetylenic compounds react 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[138]. Depending on the nature of substituents, a number of different rearranged products may be formed as shown in Scheme-IV. Products isolated in different cases are summarised in the Table-IX.

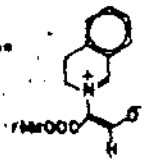
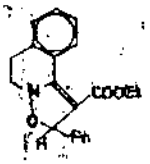
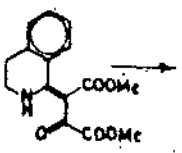
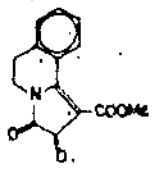
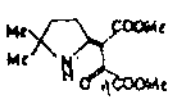
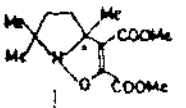
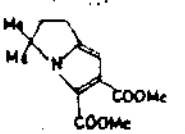
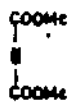
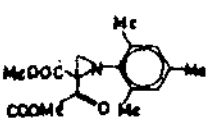
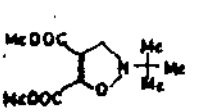
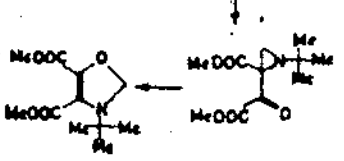
Relatively stable 4-isoxazoline adducts have been prepared from 2-phenylisatogen[139] and from phenylacetylene[140],diphenylacetylene, cyanoacetylenes[26] and enamines[141].

Benzyne forms stable adducts with simple nitrones[139], but those derived from heteroaromatic N-oxides cannot be detected and are postulated to undergo rearrangement to phenolic derivatves[142,143].



Allenes and ketenes also give different products which arises presumably from rearrangements of the initial adducts[127,144-146].

TABLE-IX

DIPOLAROPHILES	DIPOLES	ADDUCTS	TYPE	Ref.
	3,4-dihydro isoquinoline N-oxide.		C	139,167.
	" "		B	139,167.
			D	139,167.
			G	172.
			A	172.
			F	
			B	173.
			A	
			B	173.
Alkynes	1,2-dimethyl benzimidazole N-oxide, Isoquinoline N-oxide, Phenanthridine N-oxide.		C	142,168-171.

(G4) Addition to Carbon-Nitrogen Bonds :

Isocyanate add spontaneously with a wide variety of nitrones to give stable products as reported in Table-X.

Similar cycloaddition reactions with iso thiocyanates, carbodimides, aziridinium and azitidinium salts are also reported and reviewed[128]. Other examples of nitrone additions to carbon-sulfur, carbon-phosphorus and nitrogen-phosphorus multiple bonds are also reveiwed[128].

Recently 1,3-dipolar cycloaddition reactions of nitriles with a variety of nitrones has been studied and showed that nitrone-nitrile cycloadditions mechanistically not different from nitrone-alkene cycloadditions[132,147].

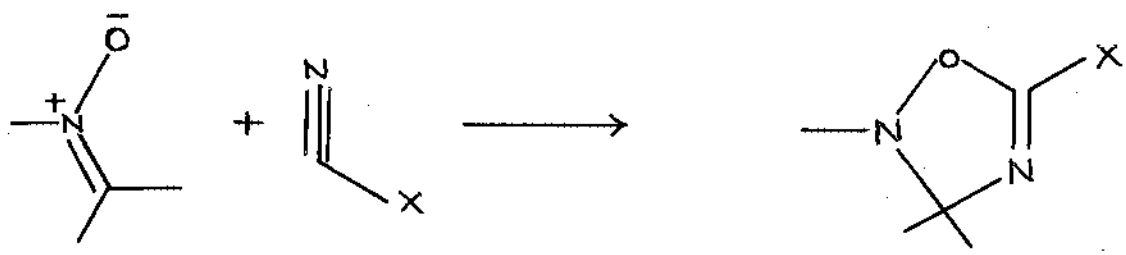
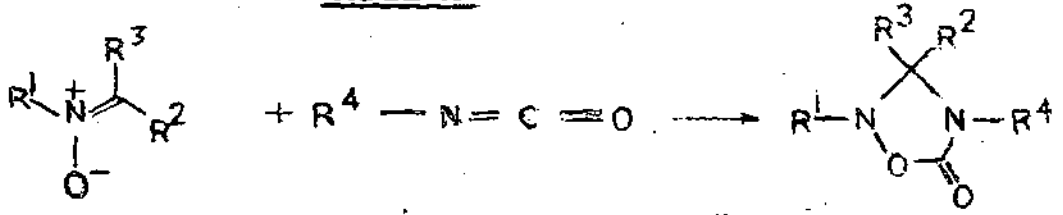
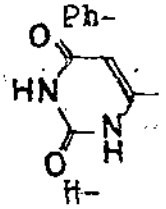


TABLE-X



R^1	R_2	R_3	Yield(%)	Ref.
$Ph-CH_2-$	Ph-	H-		174-176
Ph-	Ph-	H-	71 - 100	177-179
Me-	Ph-	H-	56 - 100	177-179
Ph-	Ph-CH CH-	H-	89	96
Ph-	Ph-	Ph-	92	97
Ph-		H-	62	152
Alkyl, Aryl,	H-	H-	98	149,150, 176,180
	Aryl	H-	81 - 83	181
	Alkyl	H-	47 - 91	182

CHAPTER-III (EXPERIMENTAL)

IR spectra were recorded as film in solution or in nujol by Perkin Elmer-297 or Beckman IR-20 instruments. Absorption maxima stated in cm^{-1}; abbreviations : s = strong, m = medium, w = weak, b = broad.

Proton NMR spectra were recorded by Varian EM-390 (90MHz) or Brucker WM-300 (300MHz) or 270MHz instruments, TMS as internal standard. Generally $CDCl_3$ was used as solvent or otherwise mentioned. Abbreviations: s = singlet; d = doublet; t = triplet; q = quertet; b = broad; m = multiplet.

Mass spectra were recorded by Jeol SX-300 (Electron Impact) spectrometer. Major mass fragments are reproduced.

Varian-2390 instrument was used for UV-visible spectra.

All melting points are uncorrected. TlC of the reaction mixture and that of the the pure compounds were compared. Hand drawn silicagel plates of 0.5-0.7mm thickness and benzene ethyl acetate (10:1) as solvent were used for TLC studies. Silicagel (60-200 mesh, Loba) and alumina (BDH) were used for column chromatography. All the solvents and most of the reagents were purified before use.

(A) Preparation Of N-Cyclohexyl Hydroxylamine : [187]

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 vacuum.

To a slution of pyridine hydrochloride (65.9g,0.57mol) suspended in dry pyridine (150ml), a solution of sodium boro hydride (22.24g,0.58mol) in dry pyridine (575ml) was added dropwise under dry nitrogen atmosphere. The reaction mixture was filtered quickly under suction and the filtrate was concentrated at 50^{0}C/5mm, when pyridine borane remain 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,0.05mol) and pyridine borane (25ml,0.25mol) in ethanol (25ml)was stirred at 5^{0}C for 30 minutes, rendered alkaline with saturated aqueous sodium bicarbonate and extracted with ether (25mlx3). The combined ether layer was washed with water (15mlx3) and dried ($MgSO_4$). Upon removal of ether, N-cyclohexyl hydroxylamine was obtained as a white solid (5.2g,91%), which recrystallise from ethanol as white needles.

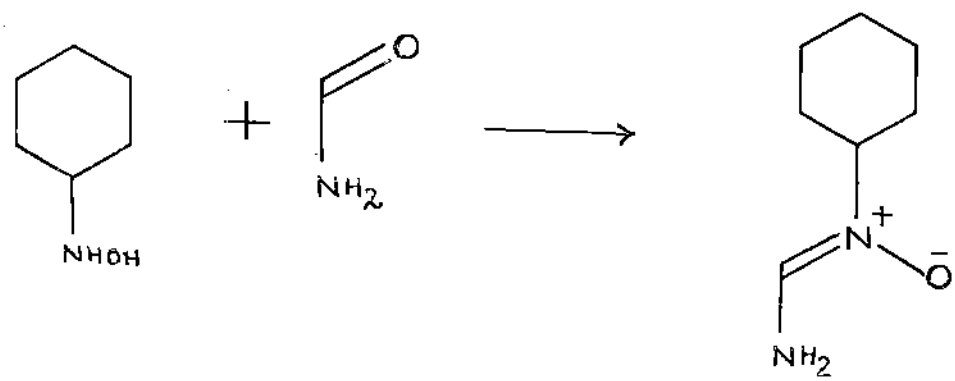
M.P. = 140^{0}C.

IR (Nujol): 3220(s); 3120(sb); 1515(s); 1345(m); 1310(s); 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) Synthesis Of α-Amino-N-Cyclohexyl Nitrone :

A mixture of N-cyclohexyl hydroxylamine (1g,8.7mmol) in dry freshly distilled formamide (25ml) with $MgSO_4$ (2g) in a 100ml conical flask fitted with a $CaCl_2$ guard tube and a nitrogen balloon was stirred at room-temperature ($8-10^{0}$C) for 24hrs. N-cyclohexyl hydroxylamine which floated over formamide in the begining gradually went into the solution with the formation of nitrone. The reaction mixture was filtered quickly on suction and

the filtrate was extracted with ether (25mlx3) and the combined ether layer was washed with water (25mlx3) and dried ($MgSO_4$) and cocentrated in vacuum to furnish the nitrone as white solid (0.52g,42.9%) which recrystallised from hexane (60-80^{0}C) to get a needle shaped crystal. The nitrone showed a characteristic band in IR at 1680 cm^{-1}.



M.P. = 81^{0}C

UV : λ_{max} 220 nm.

IR (Nujol): 3400-3280(bs); 1680(s); 1600(w); 1390(s); 1340(w); 790(w).

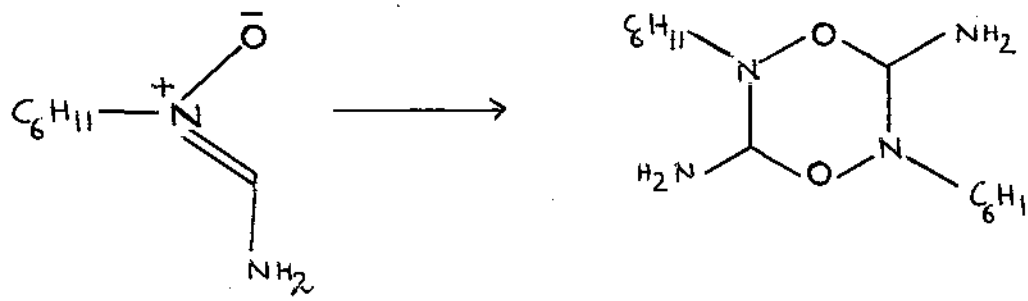
^{1}H NMR (90MHz,δ): 8.1(s,1H); 3.5(b,1H); 2.4(b,2H); 1-2(m,10H).

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

(C) Reaction Of Nitrone With Triphenyl Phosphine :

128.3mg (0.9mmol) purified nitrone was mixed with 335mg triphenyl phosphine in 25ml dry benzene under anhydrous nitrogen atmosphere and kept at room temperature for 24hrs. TLC of the reaction mixture showed no change. Then the reaction mixture was refluxed under the same condition for 8hrs. Again no change was recorded by TLC of the reaction mixture. Therefore,nitrone did not react with triphenyl phosphine.

(D) Convertion Of The Nitrone To Dimer :



A mixture of N-cyclohexyl hydroxylamine (270mg,2.34mmol), $MgSO_4$ and formamide (0.3ml) in 15ml dry methylene chloride was stirred at room temperature under anhydrous nitrogen atmosphere for 24hrs. The reaction mixture was kept at room temperature under the same condition for 192hrs. Then the reaction mixture was filtered and the solvent methylene chloride was removed under reduced pressure from filtrate to get a white solid. The product was purified by column chromatography (50g alumina deactivated with 5% water, hexane 60-80^{0}C as eluent) to get a white crystal (104mg).

R_f : 0.39

UV : λ_{max} 222.2 nm.

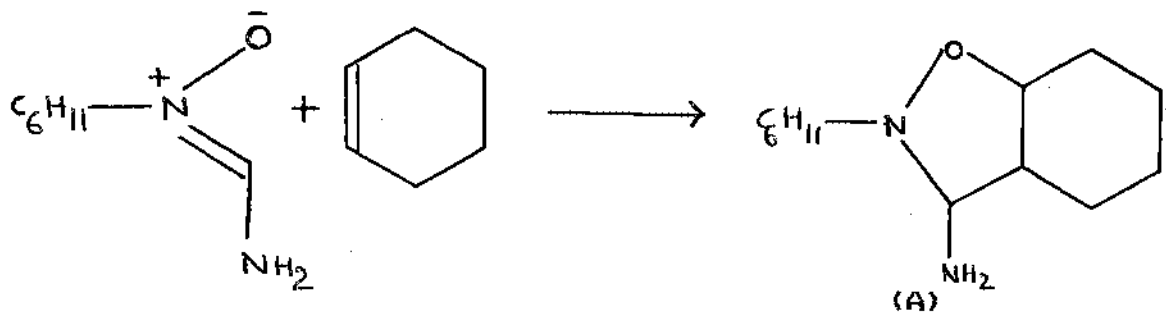
IR (CCl_4): 3500-3200(b); 2980(s); 2920(s); 1640(s); 1470(s); 1430(s); 1235(s); 1120(w); 1090(w); 970(s); 950(s).

^1H NMR (270MHz,δ): 3.9-4.1(bm,2H,N-C<u>H</u>(NH_2)-O); 2.47-2.52(m,2H, N-CH cyclohexyl); 1-2.2(m,24H).

Mass: 284(M^+); 282; 227; 202; 172; 171; 143; 142; 126; 125; 120; 113; 82; 70; 67; 58; 57; 56; 55(100%); 54.

(D) Reaction Of The Nitrone :

1. Reaction With Cyclohexene :



(A)

(a) At Room-Temperature (8-19^{0}C) :

Nitrone was generated in formamide from 542.1mg (4.71mmol) of N-cyclohexyl hydroxylamine mixed with 1ml freshly distilled cyclohexene and stirred at room temperature under anhydrous nitrogen atmpsphere for 48hrs. Then the reaction mixture was extracted with ether (25mlx3) and the combined ether layer was washed with water (15mlx3) and dried ($MgSO_4$). The solvent ether was removed under reduced pressure. Yield : 193.1mg(18.29%). The product was purified by column chromatography (50g alumina deactivated with 5% water and hexane 60-80^{0}C as eluent) to get a white crystal.

(b) On Water Bath :

Nitrone generated in formamide from 457.3mg(3.97mmol) N-cyclohexyl hydroxylamine was mixed with 1ml freshly distilled cyclohexene and refluxed on water bath under dry nitrogen atmosphere for 24hrs. The reaction mixture was extracted with ether (25mlx3) and the combined ether layer was washed with water (15mlx3) and dried ($MgSO_4$). The solvent was removed under reduced pressure. Yield : 163mg(18.3%). The product was purified by column chromatography (50g alumina deactivated with 5% water and hexane 60-80^{0}C as eluent) to get white crystal.

R_f : 0.27

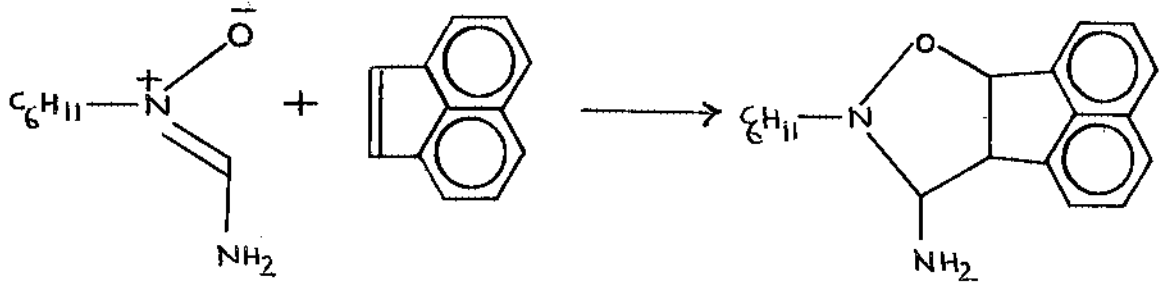
UV : λ_{max} 213.4 nm.

IR (CCl_4): 3500-3300(b); 3392(s); 2927(s); 1499(s); 1483(s); 1446(s); 1336(s); 1260(s); 1118(s); 993(s); 942(s); 697(s); 659(s); 627(s).

^1H NMR (270MHz,δ): 4.3(bm,1H,C_5); 3.5(q,1H,C_3); 2.8(m,1H,N-CH); 2.5(bm,1H,C_4); 0.6-2.2(m,20H).

Mass: 224(M^+); 221; 183; 141; 126; 125; 114; 113; 111; 110; 98; 83; 82; 70; 67; 60; 59; 57; 56; 55(100%); 54; 43.

2.<u>Reaction With Acenapthalene</u> :



(D)

The nitrone was generated in formamide from 440mg (3.82mmol) N-cyclohexyl hydroxylamine and refluxed on water bath with 474.7mg (3.12mmol) acenapthalene for 72hrs. Then the reaction mixture was extracted with ether (25mlx5) and the combined ether layer was washed with water (15mlx3) and dried ($MgSO_4$). Yield: 568mg(50.5%). The product was purified by column chromatography (200g alumina deactivated with 2.5% water and hexane (60-80^{0}C) benzene (4:1) as eluent) to get 60mg white crystal.

R_f : 0.24

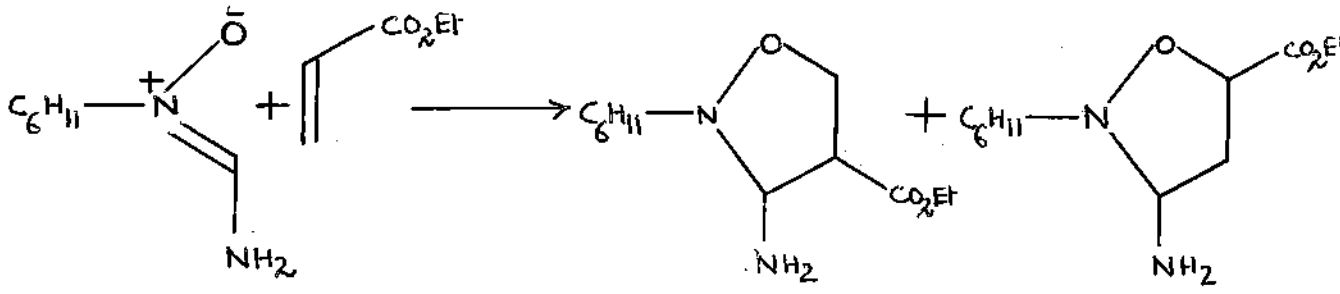
UV : λ_{max} 220 nm.

IR (CCl_4): 3488-3202(b); 3135(s); 2919(s); 2853(s); 2798(s); 2108(s); 2068(s); 1783(s); 1635(s); 1485(s); 1325(w); 1242(s); 1098(b); 777(s); 758(s).

^1H NMR (270MHz,δ): 7.1-7.9(m,6H); 4.9(d,1H,C_5); 3.6(bm,1H,C_3); 3.3(t,1H,C_4); 2.8(m,1H); 2.5(b,2H,NH_2); 0.9-1.8(m,10H).

Mass: 294(M^+); 171; 168; 158; 153; 152; 126; 125; 114; 113; 98; 83; 82; 70; 67; 60; 59; 57; 56; 55(100%); 54; 46; 43.

3. Reaction With Ethyl Acrylate :



(I) (J)

A mixture of N-cyclohexyl hydroxylamine (516.2mg,4.49mmol), $MgSO_4$ (1g) and ethyl acrylate (1.5ml) was stirred in formamide (15ml) at room temperature under anhydrous nitrogen atmosphere for 36hrs. Then the reaction mixture was filtered on suction and the filtrate was extracted with ether (25mlx3). The combined ether layer was washed with water (15mlx3) and dried ($MgSO_4$). The solvent ether was removed under reduced pressure. Yield: 644.2mg, 59.3%. TLC showed two products.Products were separated by column chromatography (200g alumina deactivated with 2.5% water).Eluent: hexane (60-80^{0}C): Pure product (J) 83.7mg and (I) 560.3 mg. Both the products were yellowish gummy liquid.

Physical data of (J):

R_f : 0.224

IR (Neat): 3500-3300(b); 2920(s); 2870(s); 1730(b); 1570(b); 1460(b); 1380(s); 1180(s); 1030(s).

^{1}H NMR (270MHz.,δ): 4.15-4.22(q,2H,-COOCH_2-); 3.9-3.98(t,1H,C_5, J=6.3 and 3.7 Hz); 3-3.1(t,1H,C_3); 2.59-2.68(m,1H); 2.44-2.59 (t,2H,NH_2); 1.08-2.17(m,15H).

Mass: 242(M^+); 199; 198; 169; 142; 128; 126; 116; 114; 101; 100; 98; 83; 82; 73; 70; 67; 60; 59; 57; 56; 55(100%); 54; 45; 43.

Physical data of (I):

R_f : 0.442

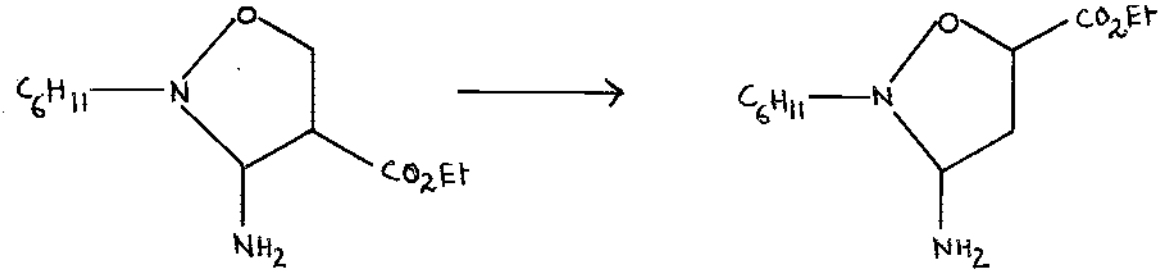
IR (Neat): 3500-3300(b); 2930(s); 2850(s); 1730(s); 1440(s);

1370(b); 1350(w); 1310(w); 1260(s); 1180(s); 1030(s).

^{1}H NMR (270MHz,δ): 4.11-4.19(q,2H,-COOCH$_2$-); 3.82-3.86(t,2H,ABX, C_5,J = 6.17 and 3.85 Hz); 3-3.1(m,1H,C_3); 2.84-3(m,1H): 2.39-2.56 (m,3H,C_4 and NH_2); 1.19-2.23(m,13H).

Mass: 242(M^+); 199; 198; 186; 169; 156(100%); 142; 129; 128; 126; 117; 116; 114; 113; 101; 100; 84; 82; 73; 70; 67; 60; 59; 57; 56; 55; 54; 45; 44; 43.

4. Cycloconvertion Of 4-Substituted Adduct To 5-Substituted Adduct Of Ethyl Acrylate :



(I) (J)

4-Substituted adduct of of ethyl acrylate (200mg) was taken in dry benzene (25ml)and refluxed under dry nitrogen atmosphere for 8hrs. By TLC it was found that 4-substituted adduct was completely converted into 5 substituted adduct along with a few decomposed products. Then the solvent benzene was removed under reduced pressure to get a red liquid. The product thus obtained was chromatographed using 40g alumina deactivated with 5% water and hexane 60-80^{0}C as eluent. Yield : 146.4mg.

R_f : 0.224

IR (Neat): 3500-3300(b); 2920(s); 2870(s); 1730(b); 1570(b); 1460(b); 1380(s); 1180(s); 1030(s).

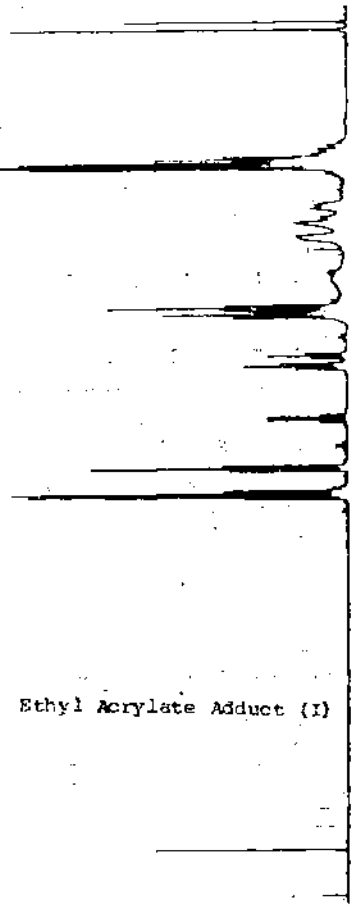
^{1}H NMR (270MHz,δ): 4.1-4.2(q,2H,-COOCH$_2$-); 3.9-4(t,1H,C_5,J = 6.3 and 3.7 Hz); 3-3.1(t,1H,C_3); 2.6-2.68(m,1H): 2.4-2.58(t,2H,NH_2); 1-2.1(m,15H).

Mass: 242(M^+); 198; 169; 142; 128; 126; 114; 114; 113; 101; 100; 98; 83; 82; 73; 70; 67; 60; 59; 57; 56; 55(100%); 54; 45; 43.

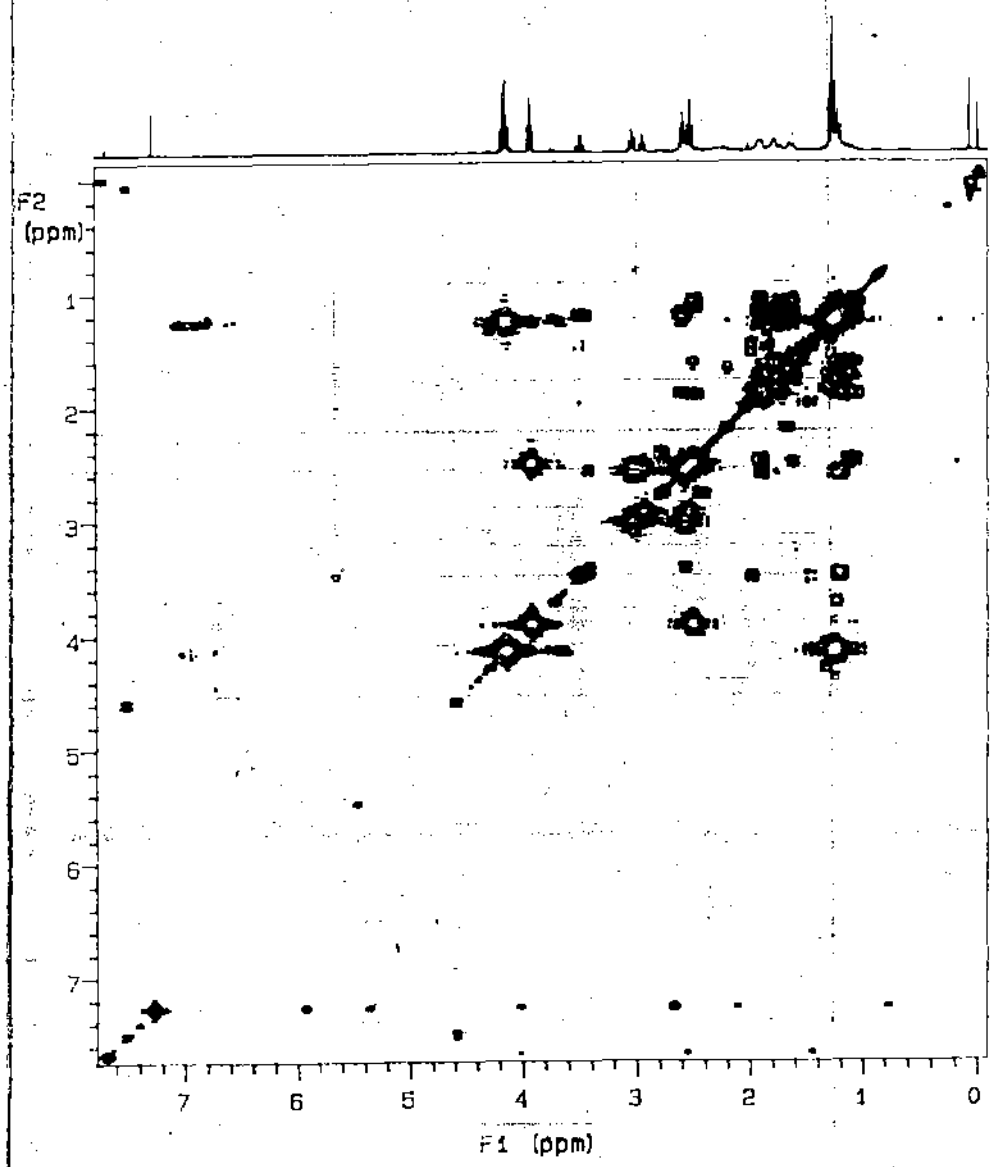
JHG-2B

H1_data are in file H1

Pulse sequence relayh
OBSERVE H1
Frequency 299.949 MHz
Spectral width 2516.4 Hz
2D Spectral width 2516.4 Hz
Acquisition time 0.203 sec
Relaxation delay 1.500 sec
Pulse width 90.0 degrees
First pulse width 90.0 degrees
Temperature 25.0 deg. C / 298.1 K
No. repetitions 24
No. increments 256
Double precision acquisition
DATA PROCESSING
Sine bell 0.101 sec
FT size 1024
F1 DATA PROCESSING
Sine bell 0.048 sec
FT size 1024
Total acquisition time 3.0 hours



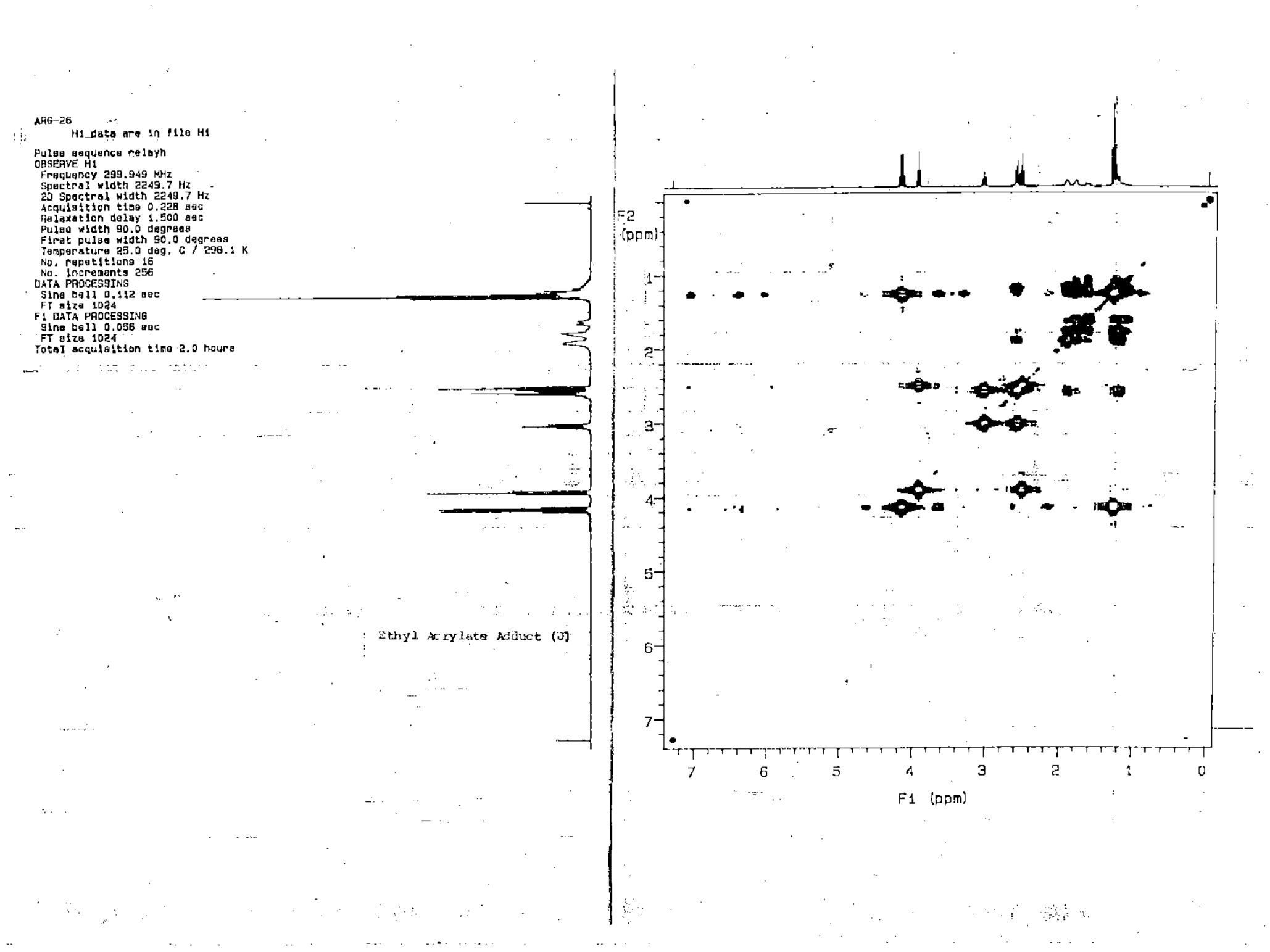
Ethyl Acrylate Adduct (I)



ARG-26

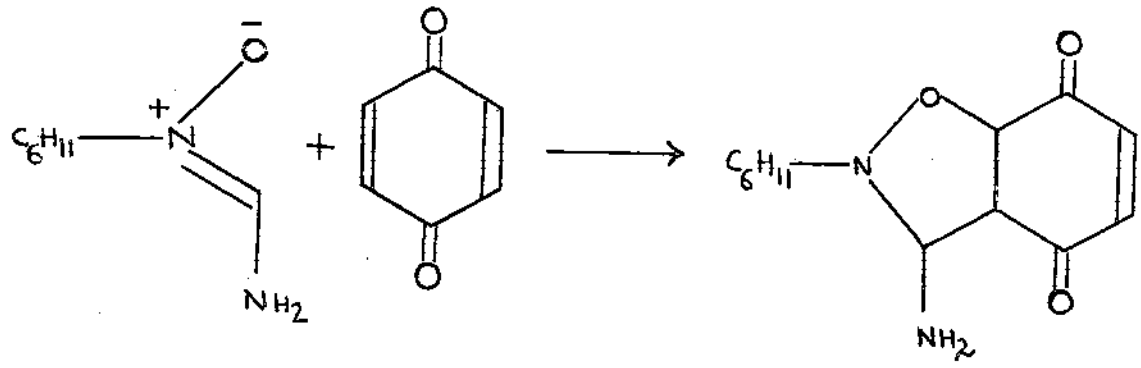
H1_data are in file H1

Pulse sequence relayh
OBSERVE H1
Frequency 299.949 MHz
Spectral width 2249.7 Hz
2D Spectral width 2249.7 Hz
Acquisition time 0.228 sec
Relaxation delay 1.500 sec
Pulse width 90.0 degrees
First pulse width 90.0 degrees
Temperature 25.0 deg. C / 298.1 K
No. repetitions 16
No. increments 256
DATA PROCESSING
Sine bell 0.112 sec
FT size 1024
F1 DATA PROCESSING
Sine bell 0.056 sec
FT size 1024
Total acquisition time 2.0 hours



Ethyl Acrylate Adduct (J)

5. Reaction With p-Benzoquinone :



(F)

Nitrone was generated in formamide from 590mg (5.13mmol) of N-cyclohexyl hydroxylamine and stirred with freshly sublimed p-benzoquinone (546.6mg,5.06mmol) under anhydrous nitrogen atmosphere at room temperature in dark for 24hrs. Then the reaction mixture was extracted with ether (25mlx3). The combined ether layer was washed with water (15mlx3) and dried ($MgSO_4$). The solvent ether was removed under reduced pressure to get 430mg (33.45%) product. The product was purified by column chromatography using 100g alumina deactivated with 5% water and benzene as eluent. to get a yelloish solid.

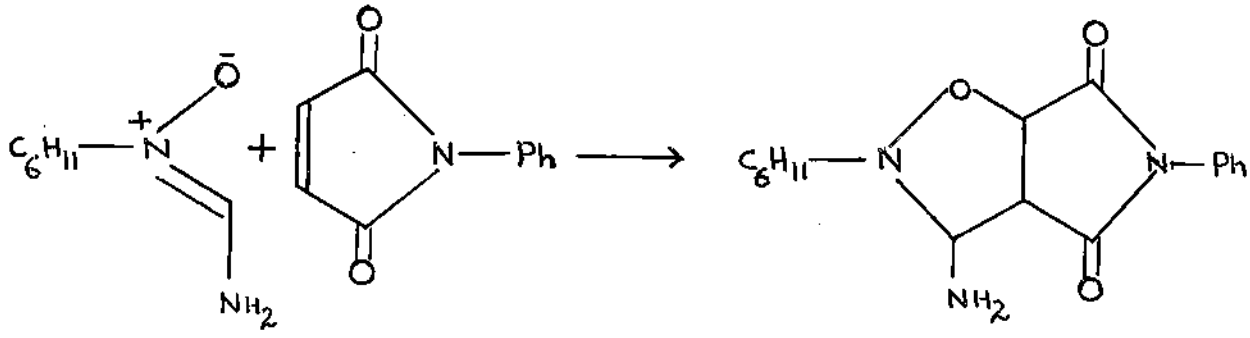
R_f : 0.24

IR (CCl_4): 3474(b); 3389(b); 3257(b); 2924(s); 2850(s); 2737(s); 2680(s); 2646(s); 1822(w); 1778(s); 1719(s); 1698(w); 1539(s); 1443(s); 1369(s); 1246(s); 990(s).

^1H NMR (270MHz,δ): 5(m,3H,C_5H and -CH=CH-); 3.8(b,1H,C_4); 3.2(m,1H,C_3); 2.9(m,1H); 2.5-2.6(m,2H,NH_2); 0.8-2.2(m,10H).

Mass: 250(M^+); 142; 137; 135; 126; 125; 124; 123; 114; 113; 112; 109; 108; 107; 96; 83; 82; 81; 80; 70; 68; 67; 60; 59; 57; 56; 55(100%); 52; 43.

6. Reaction With N-Phenyl Maleimide :



(D)

A mixture of N-cyclohexyl hydroxylamine (500mg,4.34mmol), $MgSO_4$ (1g) and N-phenyl maleimide (593mg,3.43mmol) in formamide (15ml) was stirred at room-temperature under anhydrous nitrogen atmosphere for 48hrs. Then the reaction mixture was filtered. The filtrate was extracted with ether (25mlx6). The combined ether layer was washed with water (15mlx3) and dried ($MgSO_4$). On concentration, the ether layer , a white solid was separated out. It was filtered and washed with cold ether. Separeted solid was identified as pure product by TLC.

Yield : 509.3mg (37.2%).

M.P. 162^{0}C.

R_f : 0.12

IR (CCl_4): 3300(b); 2890(s); 2840(s); 1680(s); 1450(s); 1380(s); 1290(w); 1200(s); 1120(s); 1080(s).

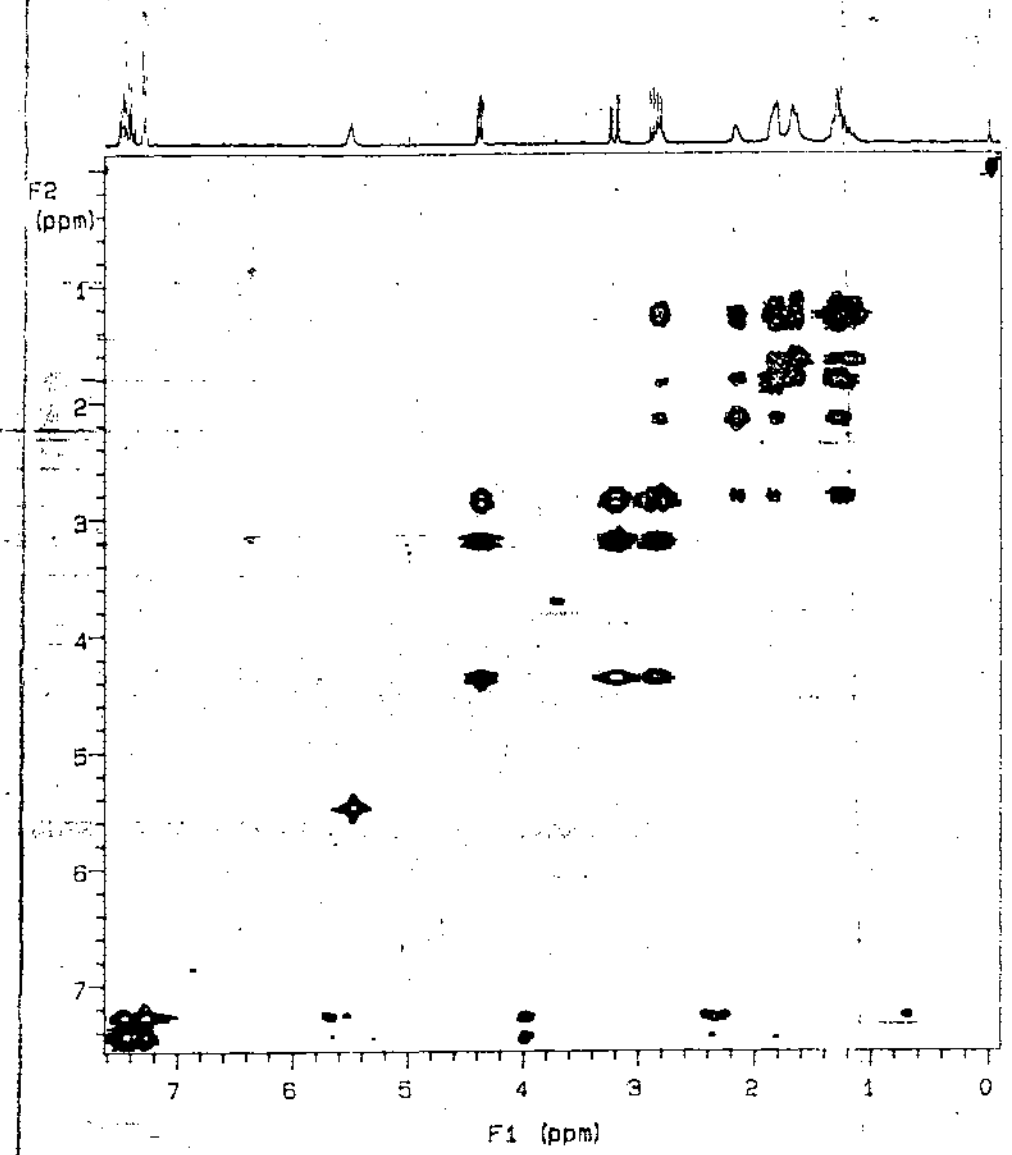
^{1}H NMR (300MHz,δ): 7.2-7.5(m,5H,Ph); 5.53(b,1H,C_5); 4.36-4.41(m, 1H,C_4); 3.17-3.26(q,1H,C_3); 2.8-2.9(m,3H,NH_2 and N-CH cyclohexyl); 1-2.17(m,10H).

Mass: 315(M^+); 272; 202; 174(100%); 173; 156; 141; 137; 125; 114; 113; 96; 83; 82; 77; 70; 67; 60; 59; 57; 56; 55; 54; 43; 42.

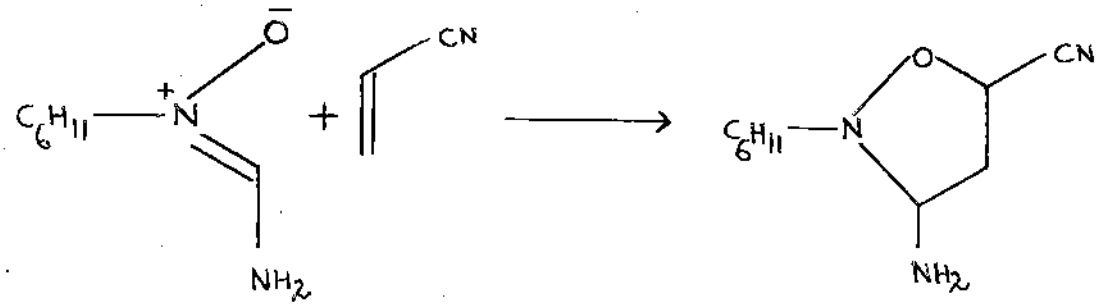
H1_data are in file H1

Pulse sequence relayh
OBSERVE H1
Frequency 299.949 MHz
Spectral width 2483.9 Hz
F2 Spectral width 2483.9 Hz
Acquisition time 0.206 sec
Relaxation delay 1.500 sec
Pulse width 90.0 degrees
First pulse width 90.0 degrees
Temperature 25.0 deg. C / 298.1 K
No. repetitions 16
No. increments 256
DATA PROCESSING
Sine bell 0.100 sec
FT size 1024
F1 DATA PROCESSING
Sine bell 0.046 sec
FT size 1024
Total acquisition time 2.0 hours

N-Phenyl Maleimide Adduct (D)



7. Reaction With Acrylonitrile :



(K)

A mixture of N-cyclohexyl hydroxylamine (471mg,4.1mmol), $MgSO_4$ (1g) and acrylonitrile (0.35ml) in formamide (15ml) was stirred under dry nitrogen atmosphere for 48hrs. Then the reaction mixture was filtered on suction and the filtrate was extracted with ether (25mlx5). The combined ether layer was washed with water (15mlx2) and dried ($MgSO_4$). The solvent ether was removed under reduced pressure to get a redish liquid (689mg,86.31%). The product was chromatographed using 40g silicagel to get only 103mg product (K) (red liquid), eluent: ether-benzene (4:1). Continued elution with ether afforded the second fraction, a red gummy liquid (339.3mg), which contained the hydrolysed product as identified by different instrumental analysis.

Physical data of the cycloadduct (K):

R_f : 0.3

IR (Neat): 3500-3300(b); 2930(s); 2860(s); 2250(w); 2200(w); 1770(s); 1650(b); 1440(s); 1380(w); 1340(w).

^1H NMR (270MHz,δ): 3.5-3.7(bm,1H,C_3); 3.42(t,1H,J = 7.2 and 5.4 Hz); 2.71(m,1H,N-CH cyclohexyl); 0.9-2.5(m,14H).

Mass: 196(M+1); 195(M^+); 194(M-1); 169; 152; 141; 139; 138; 127; 125; 126; 114; 113; 98; 82; 81; 70; 69; 68; 67; 60; 59; 57; 56; 55(100%); 54; 53; 43.

Physical data of the hydrolysed product :

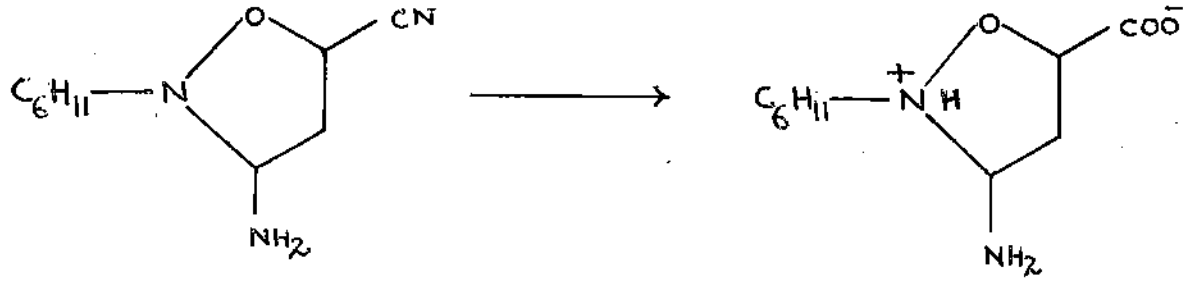
R_f : 0.01

IR (Neat): 3500-3300(b); 2920(s); 2860(s); 1650(w); 1575(s); 1450(b); 1420(w); 1380(w); 1080(b); 1040(s).

^{1}H NMR (270MHz,δ): 8.12-8.17(d,1H,N^+H); 5.67-5.79(b,1H,C_5); 3.9(m, 1H,N-CH cyclohexyl); 3.55-3.69(q,1H,C_3); 3.12-3.16(s,2H,NH_2); 0.9-2.1(m,10H).

Mass: 214(M^+); 198; 196; 171; 170; 169; 142; 126; 114; 113; 101; 100; 98; 83; 82; 73; 72; 70; 67; 60; 59; 57; 56; 55(100%); 54; 43.

8.Hydrolysis Of Acrylonitrile Adduct :



2-Cyclohxyl-5-cyano-1,2-isoxaxlidine (acrylonitrile adduct) 102mg was dissolved in 40% hydrochloric acid (25ml) and refluxed on water bath for 4hrs. After completion of hydrolysis the solvent water was removed by heating on water bath till the residue separated out. The product was purified by column chromatography using 10g silicagel and ether as solvent to get a red gummy liquid (86mg). TLC and other instrumental analysis showed that the product was identical with the product obtained during the purification of acrylonitrile adduct by column chromatography.

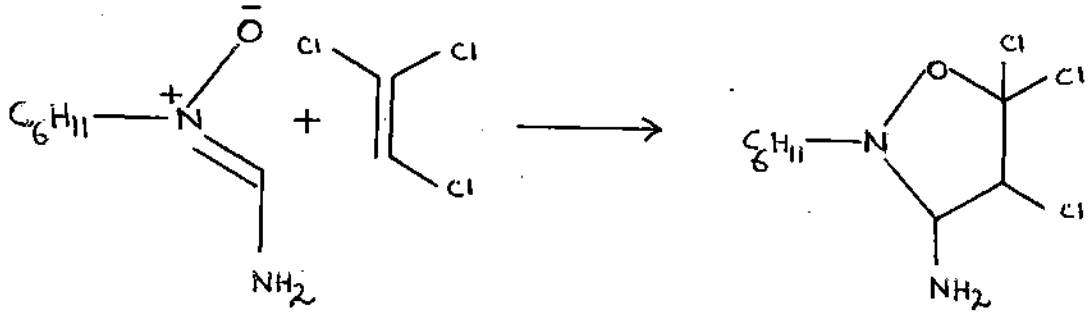
R_f : 0.01

IR (Neat): 3500-3300(b); 2920(s); 2860(s); 1650(s); 1575(s); 1450(b); 1420(w); 1380(w); 1080(b); 1040(s).

^{1}H NMR (270MHz,δ): 8.12-8.17(d,1H,N^+H); 5.67-5.79(b,1H,C_5); 3.9(m, 1H,N-CH cyclohexyl); 3.55-3.69(q,1H,C_3); 3.12-3.16(s,2H,NH_2); 0.9-2.1(m,10H).

Mass: 214(M^+); 198; 196; 171; 170; 169; 142; 126; 114; 113; 101; 100; 98; 83; 82; 73; 72; 70; 67; 60; 59; 57; 56; 55(100%); 54; 43.

9. Reaction With Trichloro Ethylene :



(M)

A mixture of N-cyclohexyl hydroxylamine (498mg,4.33mmol), trichloro ethylene (0.45ml) and $MgSO_4$ (1g) was stirred under anhydrous nitrogen atmosphere at room temperature for 72 hrs. Then the reaction mixture was filtered on suction and the filtrate was extracted with ether (25mlx5). The combined ether layer was washed with water (25mlx3) and dried ($MgSO_4$). The solvent ether was removed under reduced pressure 117mg (9.86%) to get a redish liquid. The product was purified by column chromatography using 20g silicagel and benzene/ether (1:1) as eluent to get a red liquid which on freezing gave a red crystal.

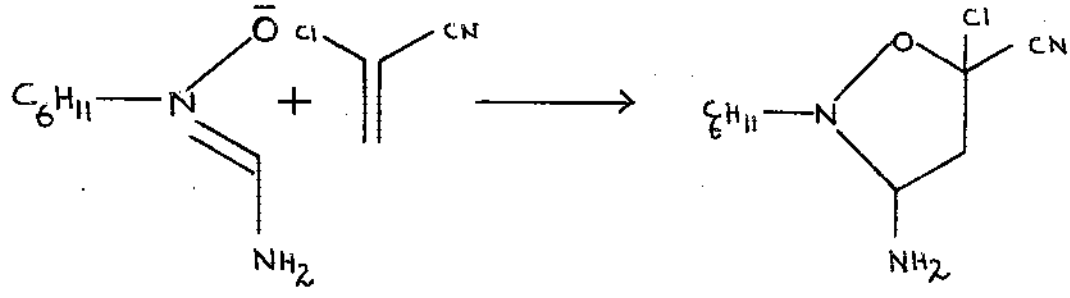
R_f : 0.04

IR (Neat): 3400-3200(b); 2920(s); 2850(s); 1730(b); 1650(s); 1480(s); 1450(s); 1380(s); 1320(s); 1240(s); 1220(s); 1100(s); 990(s); 960(s); 900(s); 850(s).

^1H NMR (270MHz,δ): 4.1(d,1H,C_4); 3.4(m,1H,C_3); 2.95(m,1H,N-CH cyclohexyl); 0.9-2.3(m,12H).

Mass: 273(M^+); 225; 114; 113; 112; 83; 82; 81; 72; 67; 59; 56; 55(100%); 54; 43; 42.

10. Reaction With 2-Chloro Acrylonitrile :



(L)

Nitrone was generated in formamide from 508mg (4.4mmol) of N-cyclohexyl hydroxylamine and was kept in freezing mixture. 2-Chloro acrylonitrile was added dropwise under dry nitrogen atmosphere with constant stirring to the solution of nitrone in formamide. The reaction mixture was kept at room temperature and kept for 24 hrs was extracted with ether (25mlx5). The combined ether layer was washed with water (15mlx3) and dried ($MgSO_4$). The solvent ether was removed under reduced pressure to get a red viscous liquid (335mg,33%). The product was purified by column chromatography using 20g silicagel and benzene-ether (3:2) as eluent to get a colourless viscous liquid (236mg).

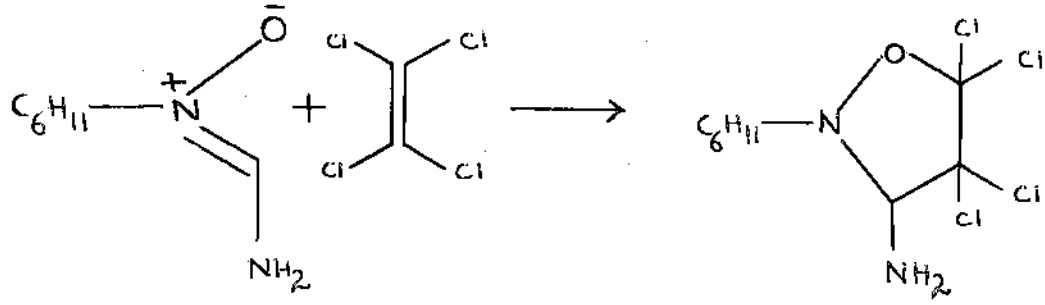
R_f : 0.11

IR (Neat): 3400-3300(b); 3100(w); 2920(s); 2860(w); 1650(w); 1520(w); 1445(s); 1410(w); 1390(s); 1180(s).

^1H NMR (270MHz,δ): 3.1-3.2(m,1H,C_3); 2.8-2.97(m,1H,N-CH cyclohexyl); 2.3-2.5(m,4H,NH_2 and C_4); 0.9-2.2(m,10H).

Mass: 230(M+1); 229(M^+); 228(M-1); 212; 194; 172; 142; 126; 125; 116; 115; 114; 113; 98; 88; 87; 83; 82; 70; 67; 60; 59; 57; 56; 55(100%); 54; 43.

ii. Reaction With Tetrachloro Ethylene :



(N)

A mixture of N-cyclohexyl hydroxylamine (500mg,4.34mmol), tetra chloro ethylene (1.1ml) and $MgSO_4$ (1g) in formamide (15ml) was stirred at room temperature under anhydrous nitrogen atmosphere for 24 hrs. The reaction mixture was kept under same condition for additional 48 hrs. Then the mixture was filtered and the filtrate was extracted with ether (25mlx5). The combined etherlayer was washed with water (15mlx3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to get a white crystal (144mg,10.78%). The product was purified by column chromatography using 15g silicagel and benzene as eluent.

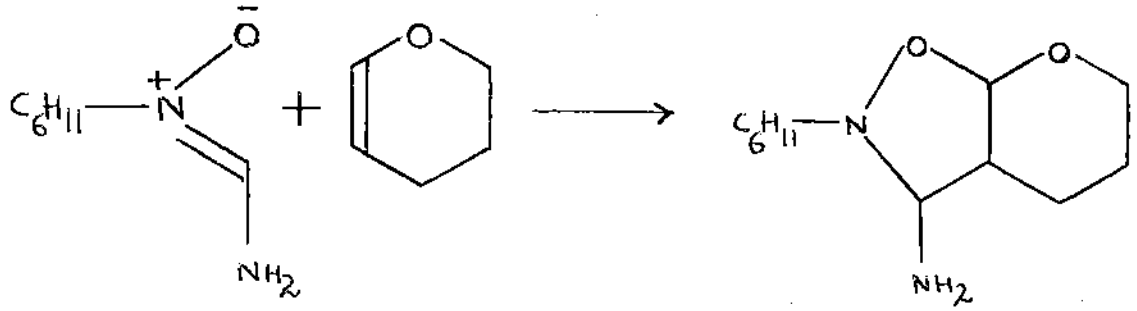
R_f : 0.23

IR (CCl_4): 3500-3300(b); 3200(s); 2920(s); 2854(w); 1735(w); 1658(w); 1541(s); 1443(s); 1365(w); 1248(s); 1216(s); 990(s); 889(s); 777(b).

^1H NMR (270MHz,δ): 3.1(t,1H,C_3); 2.8(m,1H,N-CH cyclohexyl); 2.4-2.5(b,2H,NH_2); 1.1-2.16(m,10H).

Mass: 308(M^+); 286; 225; 193; 165; 143; 126; 125; 114; 113; 112; 98; 83; 82; 81; 70; 67; 60; 57; 56; 55(100%); 54; 43; 41.

12. Reaction With 3,4-Dihydro-2H-Pyran :

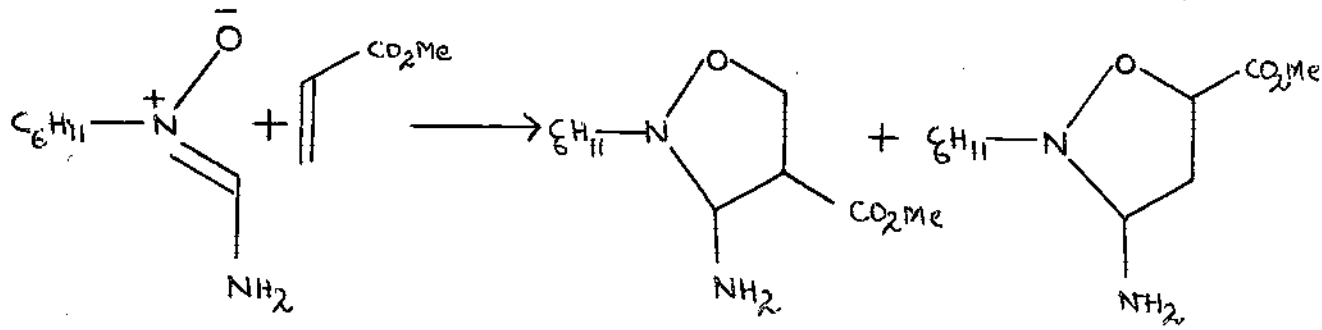


(B)

Nitrone was generated in formamide from 507mg (4.4mmol) of N-cyclohexyl hydroxylamine and was heated on water bath with 3,4-dihydro-2H-pyran (0.4ml) under dry nitrogen atmosphere for 24 hrs. The reaction mixture was extracted with ether (25mlx3). Combined ether layer was washed with water (15mlx3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford the product (128mg,12.8%) as a colourless liquid. The product was purified by column chromatography using 5g silicagel and benzene as eluent.

R_f : 0.29
IR (Neat): 3475-3199(b); 2987(w); 2914(s); 2775(s); 2305(s); 2445(s); 2392(w); 1761(s); 1650(s); 1399(s); 1272(s); 982(s).
^1H NMR (270MHz,δ): 4.4(bd,1H,C_5); 4(b,2H,O-C_5-O-CH_2-); 3.6(m,1H,C_3); 2.9(m,1H,N-CH cyclohexyl); 2.4(m,1H,C_4); 1-2.2((m,16H).
Mass: 226(M^+); 225(M-1); 199; 183; 171; 169; 144; 142; 141; 127; 126; 125; 114; 113; 112; 101; 100; 99; 85; 84; 83; 82; 70; 67; 62; 60; 59; 57; 56(100%); 55; 54; 43.

13. Reaction With Methyl Acrylate :



(G) (H)

A mixture of N-cyclohexyl hydroxylamine (473mg,4.12mmol), methyl acrylate (0.5ml) and $MgSO_4$ (1g) in formamide (15ml) was stirred at room temperature under anhydrous nitrogen atmosphere for 48 hrs. The reaction mixture was filtered and filtrate was extracted with ether (25mlx3). Combined ether layer was washed with water (15mlx3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford the product (745mg,79.4%) as a redish viscous liquid. Two products were identified by TLC and separated by column chromatography using 25g silicagel: product (G), 373mg, redish liquid, [eluent benzene] and product (H), 128mg, red gummy, [eluent benzene-ether (10:1)].Physical data of product (G):

R_f : 0.07

IR (Neat): 3500-3300(b); 2920(s); 2860(s); 1770(s); 1730(s); 1620(s); 1450(s); 1380(s); 1240(w); 1180(w); 1150(w); 1120(w); 1010(w); 890(s).

^1H NMR (300MHz,δ):3.9(s,3H); 3.48-3.69(b,1H,C_5); 3.1-3.3(m,1H,C_3); 2.8-2.9(m,1H,N-CH cyclohexyl); 2.6-2.8(b,2H,NH_2); 2.27-2.5(m,1H,C_4); 1.2-1.96(m,10H).

Mass: 228(M^+); 226(M-2); 211; 185; 183; 171; 142; 126; 115; 114; 113; 98; 87; 82; 70; 60; 59; 57; 56; 55(100%); 43; 31.

ARG-B2

H1_data are in file H1

Pulse sequence relayh
OBSERVE H1
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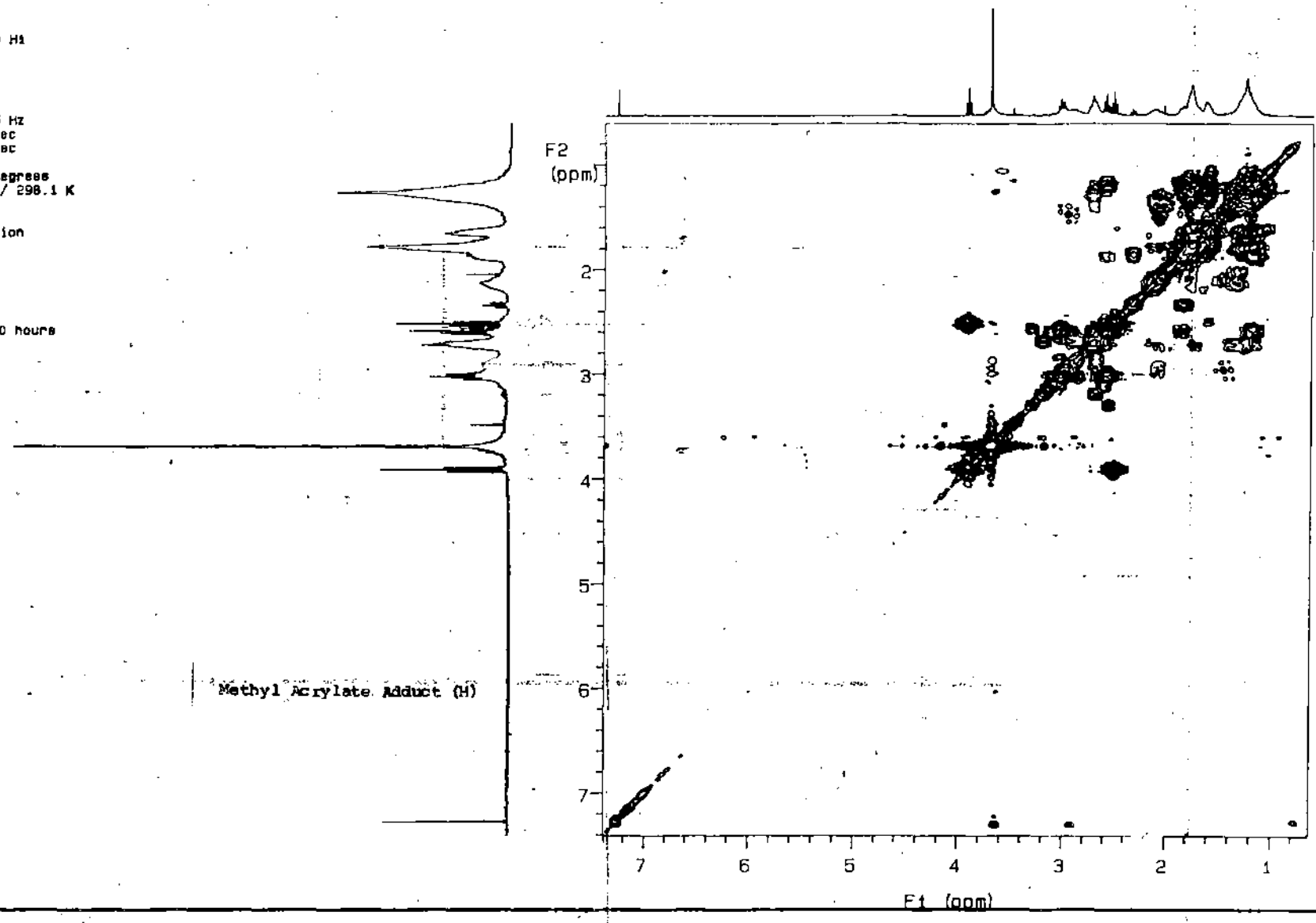
2D Spectral width 2405.6 Hz
Acquisition time 0.213 sec
Relaxation delay 1.500 sec
Pulse width 90.0 degrees
First pulse width 90.0 degrees
Temperature 25.0 deg. C / 298.1 K
No. repetitions 16
No. increments 256
Double precision acquisition
DATA PROCESSING
Sine bell 0.082 sec
FT size 1024
F1 DATA PROCESSING
Sine bell 0.043 sec
FT size 1024
Total acquisition time 2.0 hours



Methyl Acrylate Adduct (H)

OBSERVE: Nucleus ____ Freq ____ MHz; Spec Width ____ Hz; Offset ____ Hz; Acq. Time ____ sec; Delay ____ sec; Pulse Width ____ μsec; Transients ____

DECOUPLE: Nucleus ____ Offset ____ Hz; Mode ____ Power ____ db; Modulation Mode ____ Freq ____ Hz; Pulse Width ____ μsec; Power Mode ____

PLOT/PROCESSING: FN ____ K; RE ____ sec; CD ____ sec; LB ____ Hz; AF ____ sec; CCD ____; Width ____ Hz/ppm; Start ____ Hz/ppm; Reference ____

EXPERIMENT: Pulse Sequence ____; Tube O.D. ____ mm; Temp ____ °C; Solvent ____

SAMPLE

Number ____; File ____; Date ____; H1 ____

varian

Physical data of product (H):

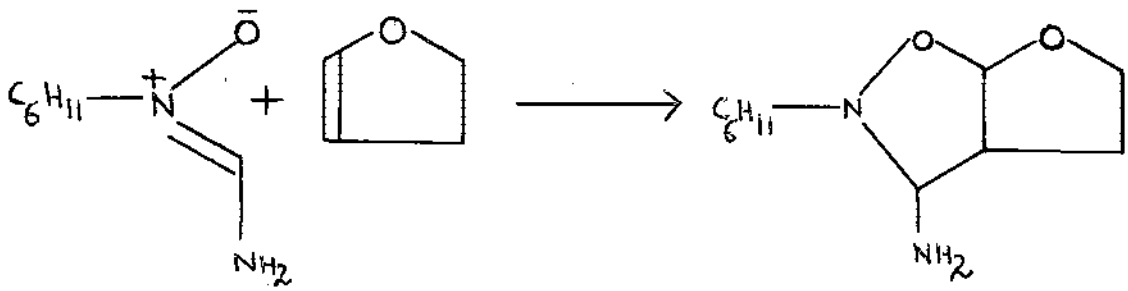
R_f : 0.49

IR (Neat): 3500-3300(b); 2940(s); 2860(s); 1770(b); 1450(s); 1380(s); 1250(w); 1220(w); 1180(s); 1150(s); 1120(s); 960(s).

^1H NMR (300MHz,δ): 3.8(t,1H,C_5); 3.6(s,3H); 2.9-3.1(m,1H,C_3); 2.5-2.6(m,3H,NH_2 and N-CH cyclohexyl); 1-2(m,12H).

Mass: 228(M^+); 185; 184; 183; 142; 126; 125; 114; 113; 102; 98; 87; 86; 83; 82; 71; 70; 67; 60; 59; 57; 56; 55(100%); 54; 43; 31.

14. Reaction With 2,3-Dihydro furan :



(C)

Nitrone was generated in formamide from 503mg (4.4mmol) of N-cyclohexyl hydroxylamine and was heated on water bath with 2,3-dihydro furan under dry nitrogen atmosphere for 72 hrs. The reaction mixture was extracted with ether (25mlx3). The combined ether layer was washed with water (15mlx3) and dried ($MgSO_4$). The solvent ether was removed under reduced pressure to afford the product as a light red liquid (378mg,41%). The product was purified by column chromatography using 12g silicagel and benzene as eluent.

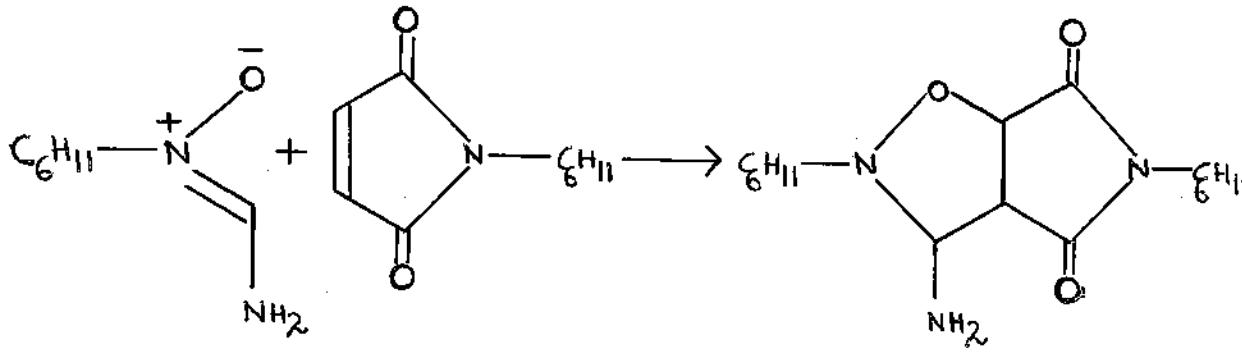
R_f : 0.21

IR (Neat): 3500-3200(b); 2940(s); 2860(s); 1650(s); 1530(s); 1450(s); 1380(s); 1260(m); 1030(s); 1080(s).

^1H NMR (270MHz,δ): 5.4(b,1H,C_5); 3.9-4(bt,2H); 3.4(d,1H,C_3); 3.2(m,1H,N-CH cyclohexyl); 2.4(m,1H,C_4); 0.65-2.2(m,14H).

Mass: 214(M+2); 212(M^+); 184; 144; 141; 128; 127; 126; 125; 113; 112; 99; 98; 97; 96; 87; 86; 85; 84; 83; 82; 81; 71(100%); 70; 67; 57; 56; 55; 54; 43.

15. Reaction With N-Cyclohexyl Maleimide :



(E)

A mixture of N-cyclohexyl hydroxylamine (486mg,4.2mmol), N-cyclohexyl maleimide (600mg,3.35mmol) and $MgSO_4$ (1g) in formamide (15ml) was stirred at room temperature under anhydrous nitrogen atmosphere for 48 hrs. The reaction mixture was filtered and the filtrate was extracted with ether (25mlx6). The combined ether layer was washed with water (15mlx3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford the product (367.3mg,27%) as a gray solid. The product was purified by column chromatography using 12g silicagel and benzene as eluent.

M.P. = 144^{O}C.

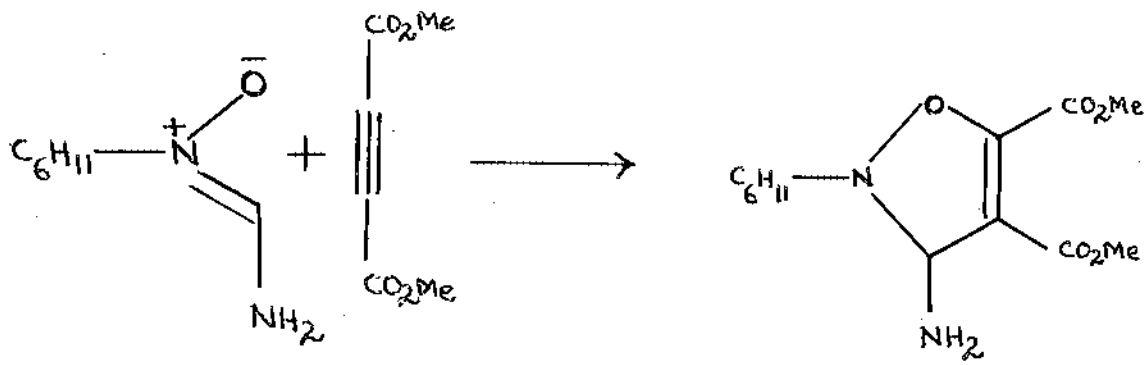
R_f : 0.26

IR (CCl_4): 3500-3400(b); 2920(s); 2850(s); 1760(s); 1680(s); 1450(s); 1380(s); 1250(s); 1190(s).

^1H NMR (270MHz,δ): 6.2(b,1H,C_5); 4.1(b,1H,C_4); 3(d,1H,C_3); 2.2-2.9(m,4H,N-CH cyclohexyl and NH_2); 0.6-2.1(m,20H).

Mass: 321(M^+); 278; 180; 179; 141; 125; 114; 113; 98; 96; 83; 70; 67; 60; 59; 57; 56; 55(100%); 43.

16. Reaction With Dimethyl Acetylene Dicarboxylate :



(P)

Nitrone was generated in formamide from 500mg (4.34mmol) of N-cyclohexyl hydroxylamine and was mixed with dimethyl acetylene dicarboxylate (0.65ml) kept at room temperature under dry nitrogen atmosphere with constant stirring for 24 hrs. The reaction mixture was extracted with ether (25mlx5). Combined ether layer was washed with water (15mlx3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford the product as a yellow solid (496mg). The product was purified by column chromatography using 20g silicagel and benzene as eluent.

Yield = 80.95%

M.P. : $56^{O}C$.

R_f : 0.55

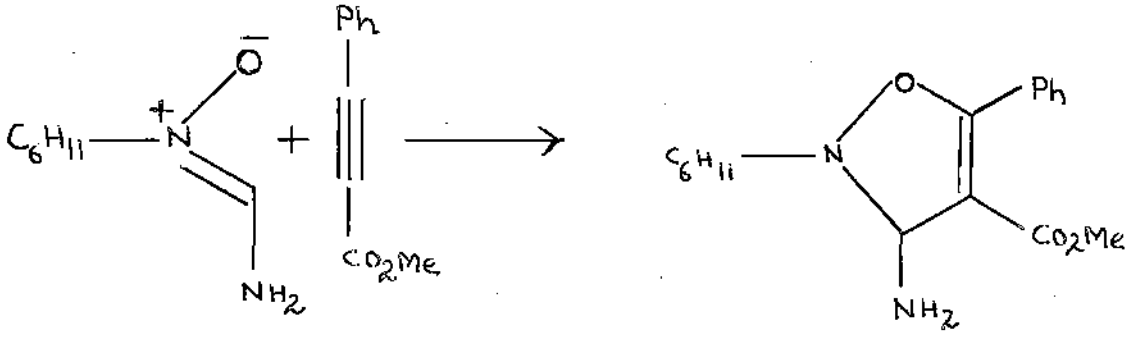
IR (CCl_4): 3440-3420(b); 3350(s); 2920(s); 2850(s); 1740(s); 1720(s); 1505(s); 1430(s); 1400(s); 1380(s); 1350(s); 1305(s); 1280(s); 1210(w); 1160(w); 1140(w); 1120(s); 1040(s).

^1H NMR (270MHz,δ): 5.4(b,1H,C_3); 3.9(s,6H,$-COOCH_3$); 3.6(d,2H,NH_2); 1-2(m,11H).

Mass: 284(M^+); 283(M-1); 241; 198; 166; 143; 98; 83; 82; 67; 59; 57; 56; 55(100%); 54; 43; 42.

The cycloadduct of dimethyl acetylene dicarboxylate (50mg) was refluxed in 20ml of dry benzene under dry nitrogen atmosphere for 4 hrs. But no change was recorded by TLC of the reaction mixture.

17. Reaction With Methyl Phenyl Propiolate :



(Q)

Nitrone was generated in formamide from 507.9mg (4.4mmol) of N-cyclohexyl hydroxylamine and was mixed with methyl phenyl propiolate (0.5ml) and kept at room temperature under dry nitrogen atmosphere with constant stirring for 24 hrs. The reaction mixture was extracted with ether (25mlx3). The combined ether layer was washed with water (15mlx3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford the product (414.9mg, 73.9%) as a red solid. The product was purified by column chromatography using 20g silicagel and benzene-ether (4:1) as eluent.

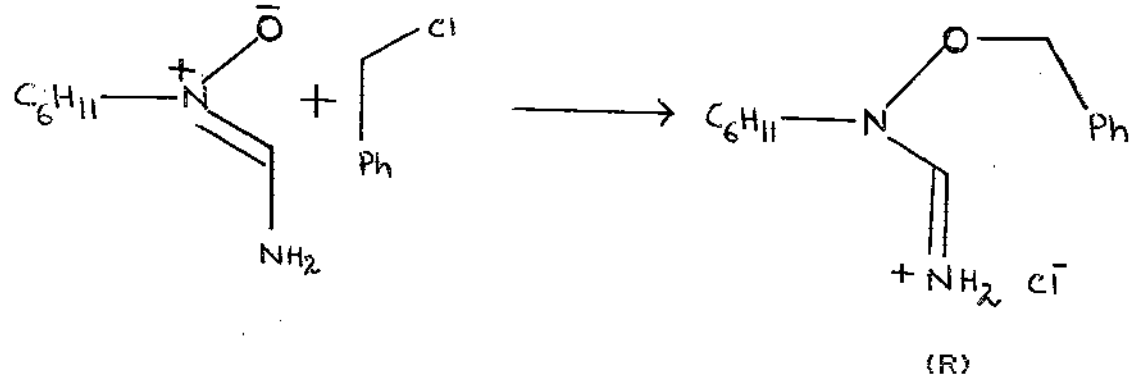
R_f : 0.28

IR (CCl_4): 3300-3100(b); 2940-2900(b); 2600-2500(b); 1660(s); 1570(w); 1470(w); 1450(s); 1380(w); 1320(w); 1250(s); 1220(s); 1110(s); 990(s); 950(s).

^1H NMR (270MHz,δ): 7.33-7.58(m,5H,Ph); 3.8(s,3H,$-COOCH_3$); 3.5-3.6 (m,1H,C_3); 2.94(m,1H,N-CH cyclohexyl); 1-2.2(m,12H).

Mass: 302(M^+); 301(M-1); 271; 197; 189; 188; 176; 161; 160; 142; 126; 113; 105(100%); 98; 83; 82; 70; 67; 60; 59; 56; 55; 54; 43.

18. Reaction With Benzyl Chloride :

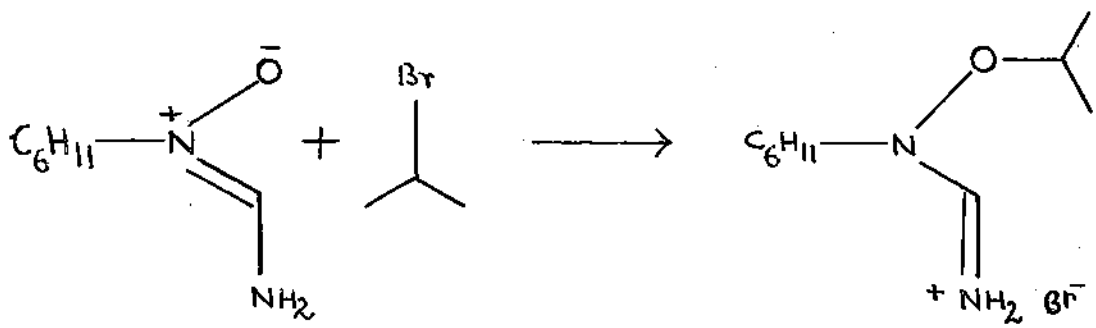


(R)

Purified α-Amino-N-cyclohexyl nitrone (113.6mg,0.8mmol) was dissolved in dry benzene (10ml) with benzyl chloride (0.1ml) and kept at room temperature under dry nitrogen atmosphere for 18 hrs. Then the solvent was removed under reduced pressure to afford the product (200.2mg,93.2%) as a white crystal.

R_f : 0.625 (Benzene-Ethylacetate = 19:1).
IR (CCl_4): 2920(b); 2840(s); 2720(w); 2510(w); 2600(w); 2360(s); 2160(w);
2080(w); 2000(w); 1890(s); 1840(w); 1450(s); 1380(s); 1150(m); 1130(m); 1040-1010(b); 960(s); 910(w).
^1H NMR (90MHz,δ): 8.1(s,2H,N^+H_2); 6.4(b,1H,N-C<u>H</u>=N^+H_2); 4(s,2H, -O-CH_2-Ph); 2.95(m,1H,N-CH cyclohexyl); 1-2.3(m,10H).

19. Reaction With 2-Propyl Bromide :



(8)

Purifird α-amino-N-cyclohexyl nitrone (202.5mg,1.4mmol) was dissolved in dry benzene (25ml) with 2-propyl bromide (0.6ml) and was stirred at room temperature under dry nitrogen atmosphere for 24 hrs. The solvent benzene was removed under reduced pressure to get the product as a yellow liquid (237mg,89.57%).

R_f : 0.73

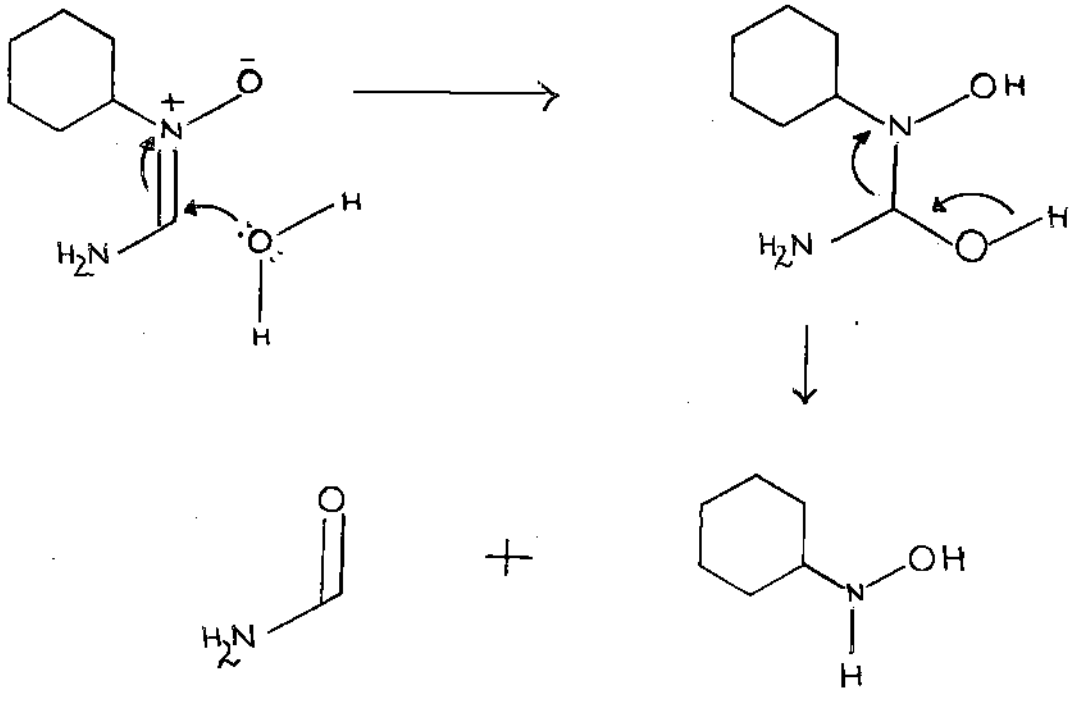
IR (Neat): 2917(s); 2847(s); 2752(s); 2308(s); 2254(s); 2029(s); 2079(s); 1639(s); 1610(s); 1453(s); 1373(s); 1247(s); 1092(s); 1066(w); 1022(w); 983(s); 751(s).

^{1}H NMR (90MHz,δ): 8(s,2H,N^+H_2); 6.6(b,1H,-N-C<u>H</u>=N^+H_2); 3.5(bm,1H, -O-C<u>H</u>Me_2); 2.69(m,1H,N-CH cyclohexyl); 1-2.1(m,16H).

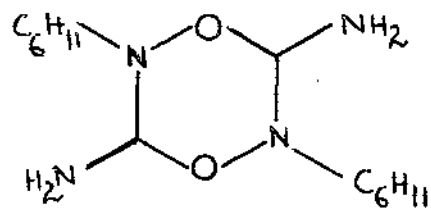
CHAPTER-IV (RESULTS AND DISCUSSION)

A. General Discussion :

α-Amino-N-cyclohexyl nitrone was prepared directly from formamide and N-cyclohexyl hydroxylamine. The nitrone was isolated as colourless solid, recrystallised from hexane (60^0–80^0C), mp.81^0C. The nitrone was found to be hygroscopic and slowly decomposed in presence of traces of moisture to the corresponding N-cyclohexyl hydroxylamine.



Structure of the nitrone was confirmed by spectroscopic data (reproduced in Experimental Section). In IR spectra, a broad peak (3500–3300 cm^{-1}) due to intramolecular H-bonding was observed which was unaffected even by changing the dilution, indicating a trans structure of the nitrone. The nitrone was stable at 5^0C up to 4 days. While keeping, it was changed gradually to (3+3——>6) dimer after 8 days, to a colourless crystalline solid. The structure of the dimer was confirmed by IR, NMR and Mass spectra.



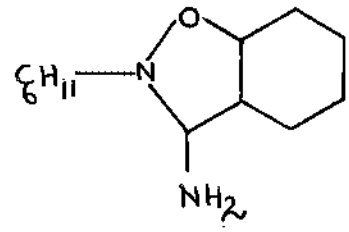
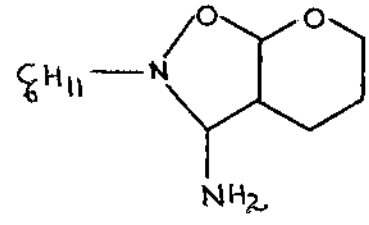
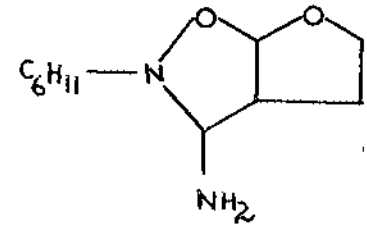
Cyclorevertion (6——>3+3) of the dimer to monomer and finally to the corresponding cycloadduct was also observed while keeping the dimer in cotact with electron deficient dipolarophiles.

The nitrone on refluxing with triphenyl phosphine in dry benzene remained unchanged. Which indicates that the negative charge is not so localised on the oxygen atom like aromatic N-oxides.

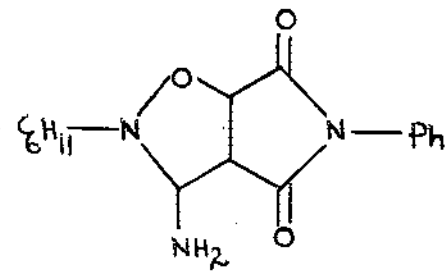
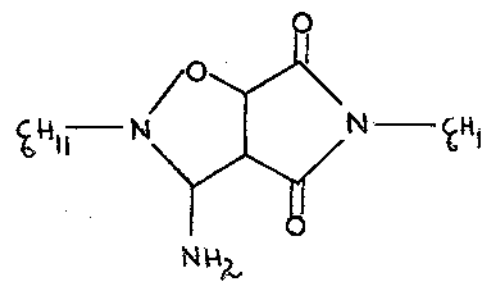
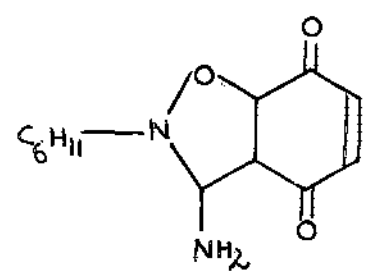
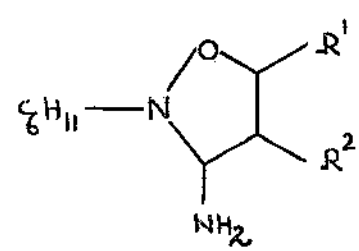
1,3-Dipolar cycloaddition reaction of α-amino -N-cyclohexyl nitrone with different dipolarophiles were studied. The nitrone reacted with most of the olefins, even with cyclohexene adduct, smoothly at room temperature. In the case of cyclohexene, no appreciable change of yield was observed at water bath temperature. In the Table-XI, the reaction condition , major products, nature etc., are summarised. The addition of acrylonitrile, chloro acrylonitrile, 3,4-dihydro-2H-pyran and 2,3-dihydro furan with the nitrone were found to be regiospecific. Only 5-substituted adducts were obtained. A red viscous liquid was obtained during the chromatographic purification of acrylonitrile adduct. The same product was also obtained after hydrolysis of the acrylonitrile adduct by aqueous HCl and was characterised by IR,NMR and Mass spectra. With highly electron deficient dipolarophile , viz., N- phenyl maleimide, N-cyclohexyl maleimide and p-benzoquinone, cycloadducts were obtained spontaneously at room temperature.

Reactions with normal or moderately electron rich olefins, viz., 3,4-dihydro-2H-pyran, 2,3-dihydro furan and acenapthalene were not facile even at water bath temperature.

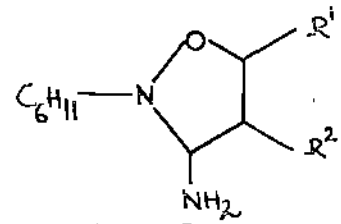
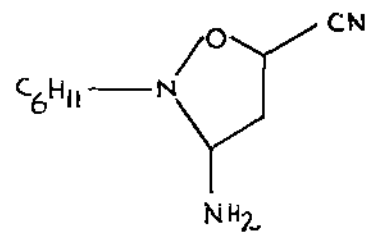
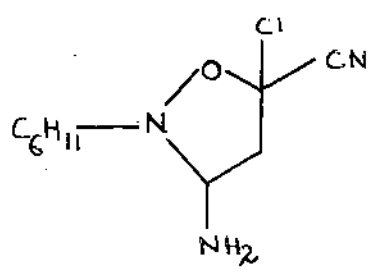
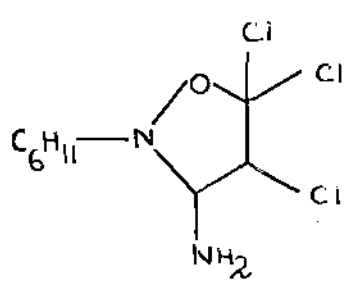
TABLE-XI.

Dipolarophiles	Solvent, Reaction Condition	Nature of Products	Structures of Products
Cyclohexene	Formamide, R.T., 48 Hrs. Reflux / Water Bath, 24 Hrs.	White Crystalline Solid.	 (A)
3,4-Dihydro-2H-pyran	Formamide, Reflux on Water Bath, 24 Hrs.	Colourless liquid	 (B)
2,3-Dihydro Furan	Formamide, Reflux on Water Bath, 72 Hrs.	Light Red Liquid	 (C)

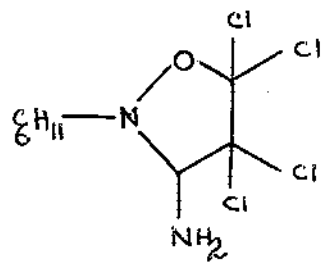
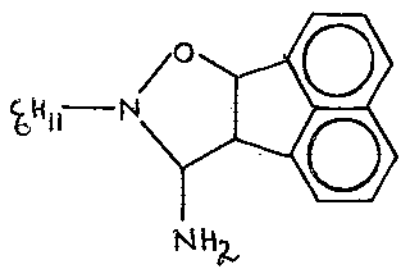
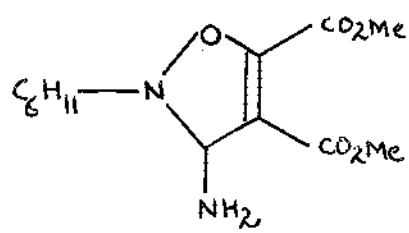
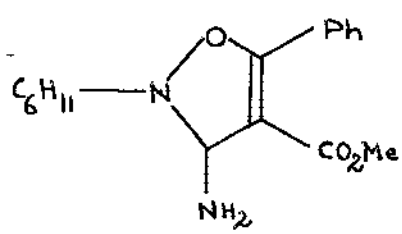
Cont.

N-phenyl maleimide	Formamide, R.T., 24 Hrs.	White Solid	 (D)
N-cyclohexyl maleimide	Formamide, R.T., 24 Hrs.	Gray Solid	 (E)
P-benzo-quinone	Formamide, R.T., 24 Hrs., Stirring in Dark	Yellowish Solid	 (F)
Methyl-acrylate	Formamide, R.T., 24 Hrs.	G-Redish Liquid H-Red Gum	 (G): R^1=H, R^2=COOMe. (H): R^1=COOMe, R^2=H.

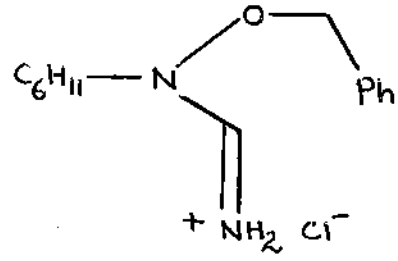
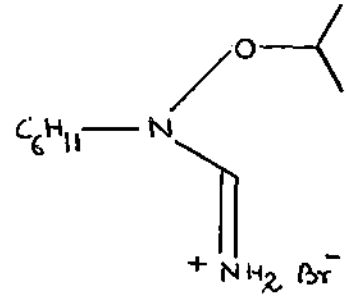
Cont.

Ethyl-acrylate	Formamide, R.T., 24 Hrs.	Yellow Gummy Liquid	 (I): R^1=H, R^2=COOEt. (J): R^1=COOEt, R^2=H.
Acrylo-nitrile	Formamide, R.T., 24 Hrs.	Red Liquid	 (K)
2-Chloro acrylo nitrile	Formamide, 5°C, 12 Hrs.	Colourless Viscous Liquid	 (L)
Trichloro erhylene	Formamide, R.T., 48 Hrs.	Red Crystal	 (M)

Cont.

Tetrachloro ethylene	Formamide,R.T., 48 Hrs.	White Crystal	 (N)
Acenapthalene	Formanide, Reflux on Water Bath, 72 Hrs.	White Crystal	 (O)
Dimethyl acetylene dicarboxy -late	Formamide,R.T., 24 Hrs.	Yellowish White Solid	 (P)
Phenyl methyl propio -late	Formamide,R.T., 24 Hrs.	Red Crystal	 (Q)

Cont.

Alkyl Halide	Solvent, Reaction Condition	Nature of Products	Structures
Benzyl Chloride	Dry Benzene, R.T., 18 Hrs.	Redish White Crystal	 (R)
2-Propyl bromide	Dry Benzene, R.T., 24 Hrs.	Yellow Viscous Liquid	 (S)

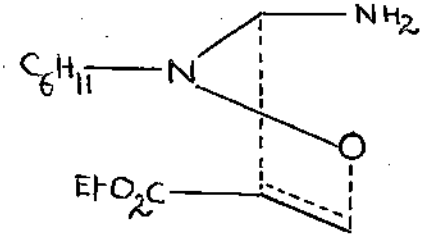
In the case of methyl and ethyl acrylate, both the regioselective products were obtained. The Table-XII shows the ratio of the separated 4- and 5-substituted products

Dipolarophiles	Adducts(4-:5-substituted)
(a) Methylacrylate	2.9 : 1
(b) Ethylacrylate	1 : 6.6

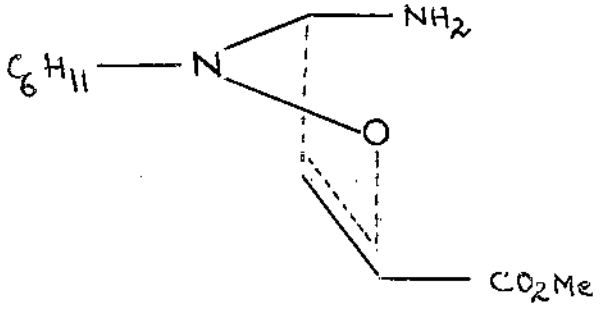
Table-XII

When 4-substituted adduct of ethylacrylate was kept at room temperature for a few weeks, the product was partially converted to 5-substituted adduct. The cycloconvertion was studied by refluxing 4-substituted adduct in dry benzene for 8 hrs where complete convertion to 5-substituted adduct was observed. But such type of convertion was not found in the case of methylacrylate adducts. These interesting observations remind once again of Ali's[133] work.

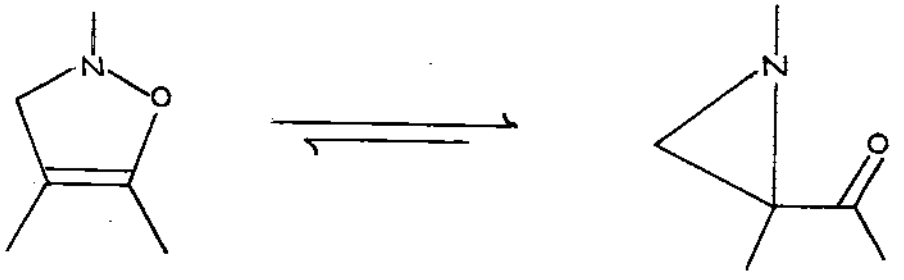
Another aspect of the cycloaddition reactions is their preference for the endo-addition over the exo-addition. To examine the fact whether endo- or exo-addition occured, 2D NMR (COSY) of some of the adducts were studied. In the case of ethylacrylate adducts (I and J), a strong interaction between methylene protons of ester group and protons of cyclohexyl group was observed. Therefore, endo-addition was expected in this case.



But in the cases of methylacrylate and N-phenyl maleimide adducts, no such interactions between protons were observed. Therefore, additions in these cases were expected via exo transition state.



Alkynes, viz., methyl phenyl propiolate and dimiethyl acetylene ducarboxylate were studied as dipolarophiles for 1,3-dipolar cycloaddition with α-amino-N-cyclohexyl nitrone. Cycloadducts (P and Q) were obtained at room temperature in satisfactory yields upon purification. The formation of adduct Q is due to secondary orbital effect between the carbon of the nitrone (HOMO) and the adjacent atom of the electron withdrawing group of the dipolarophile (LUMO). Here the transition state was further stabilised by secondary orbital interaction. Both the cycloadducts were thermally stable, but, while studing the mass-fragmentation pattern, base peak (m/e) at 105 (cf. PhCO) for methyl phenyl propiolate adduct was found. Thus during mass-fragmentation, the adduct underwent rearrangement to Aziridine ring.



In order to find out the synthetic potentiality of α-amino-N-cyclohexyl nitrone, SN_2 reactions were studied with benzyl chloride and 2-propyl bromide. Purified nitrone was directly used for this purpose and was mixed with equimoler amount of alkyl halide in dry benzene at room temperature. Both the products were isolated (yield: 93.2% and 89.57% respectively) and characterised by NMR and IR. The reaction indicates that α-amino-N-cyclohexyl nitrone behaved as a powerful nucleophile in SN_2 reaction. Other nitrones are not known to act as a nucleophile in this fashion.

B. Interpretation Of Mass Spectra :

All the compounds possess 2-cyclohexyl-3-amino-1,2-isoxazoli-dine moiety in common. Therefore, it was very usual to expect some rationalization in the mass fragmentation patterns of the compounds. On electron impact mass fragmetation 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-V). The fragmentation pattern of all the adducts were discussed on the light of this fission pattern. In the case of cyclic amine, the major fission pattern of such a molecular ion would be due to α-cleavege. Among the probable modes of α-cleavege, viz., C_3-C_4 and C_6-C_7, the C_6-C_7 cleavege was most probable as this leads to highly substituted bond cleavege. C_3-C_4 bond was also cleaved and further transformation led to a number of fragments with m/e, M-142 (Type-B); 125; 82; 70; 57; 56; 55 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-cleavege in which at first the C_5-O bond cleaved to lead the ion with m/e M-141 (Type-F).

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

Other major fragmentation might occur with the ionisation of free amino group on C_3 and subsequent α-cleavege leading to m/e 113 and 111 (Type-I).

Occurence of this common fragments are shown in Table-XIII. The other peaks were dependent on the nature of substituent on 4- and 5-possition of the 1,2-isoxazolidines.

In the fragmentation patter of the N-phenyl maleimide adduct, in addition to the common expected fragments, other prominent peaks at m/e 156; 96; 60; and 77 were found (Type-J).

For tri- and tetra-chloro ethylene adducts some of the expected ion fragments were absent. But the other peaks were prominent e.g.,m/e 113; 98; 82; 60; 57; 55(100% for both the adducts). Following peaks were prominent (Type-K_1) m/e 225 and 93 and (Type-K_2) m/e 225; 112; 83, for trichloro ethylene and tetra chloro ethylene adducts respectively.

The fragmentation pattern of 3,4-dihydro-2H-pyran adduct followed the general pattern with some special peaks at m/e 127; 99 and 85 (Type-L_1).

2,3-Dihydro furan adduct also followed the same fragmentation pattern like cyclohexene adduct with some special peaks at m/e 127; 71 (100%) and 85 (Type-L_2).

P-Benzoquinone adduct fragmented following the same pattern with some typical peaks at m/e 112; 96 and 82 (Type-M).

The fragmentation patterns of both the methyl and ethyl acrylate adducts followed the general pattern with some typical peaks for methyl and ethyl ester, e.g., CH_3O (31); CH_3OCO (59); C_2H_5O (45); C_2H_5OCO (73) and a prominent peak for both the cases at m/e 198 probably due to the ion M-31 for methyl and M-45 for ethyl acrylate adducts respectively (Type-N).

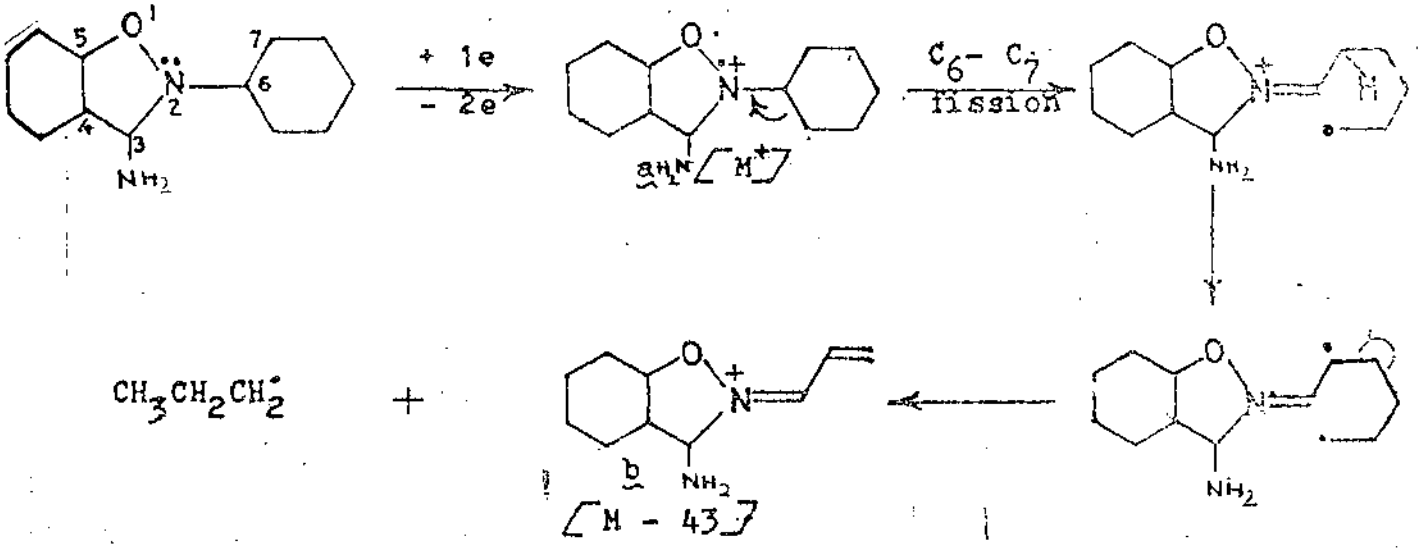
Fragmentation pattern of acenapthalene adduct was similar to the general pattern. Some weak peaks at m/e 126 and 168 were found (Type-O).

Fragmentation pattern of 2-chloro acrylonitrile adduct was also in accordance with the general pattern. The molecular ion peak was associated with M+1 and M-1 peaks. Very weak peaks at m/e 212 (M-CN) and 194 (M-Cl) were also found.

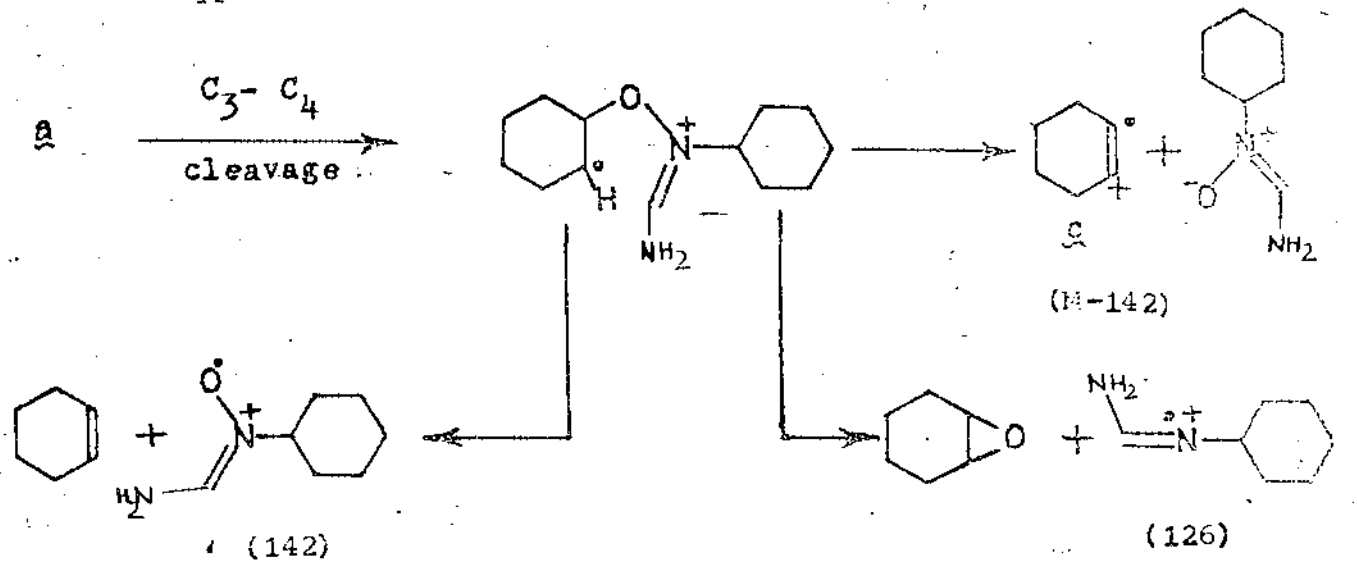
SCHEME - I

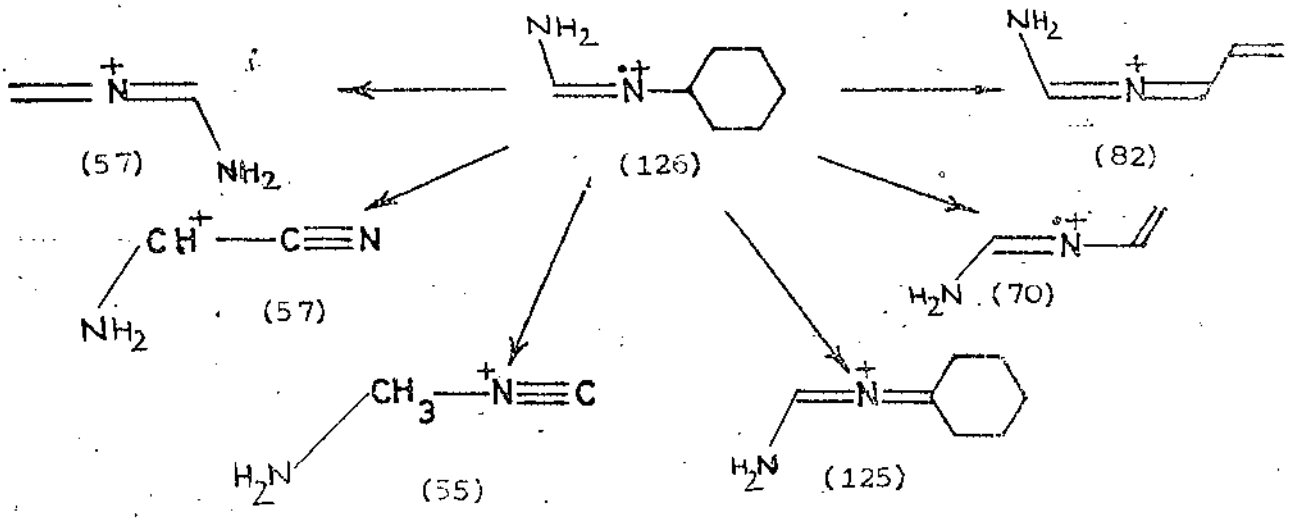
General patterns of mass fragmentation

Type-A

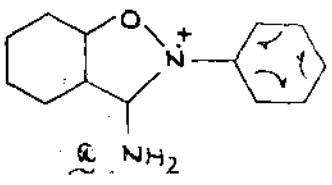


Type-B

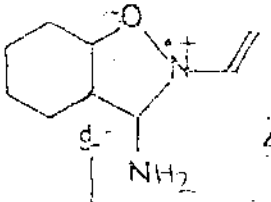




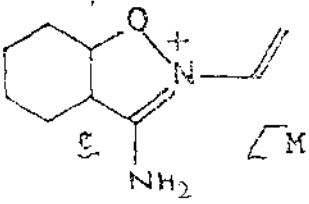
Type -C



Sigmatropic rearrangement

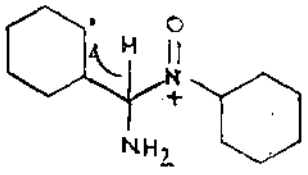


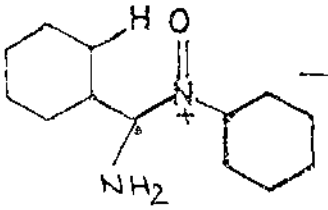
[M - 56]

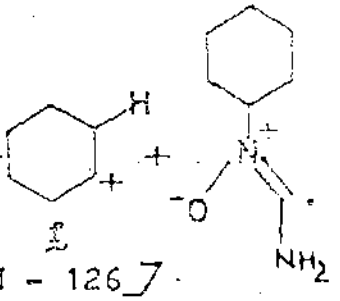


[M - 57]

Type -F

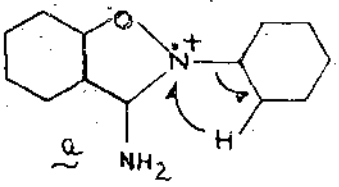




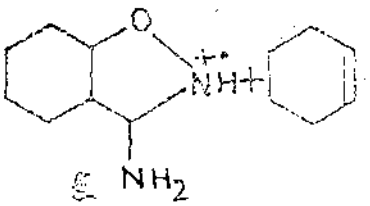


[M - 126]

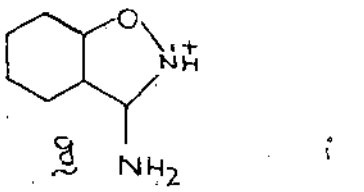
Type -G

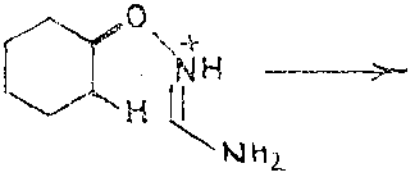


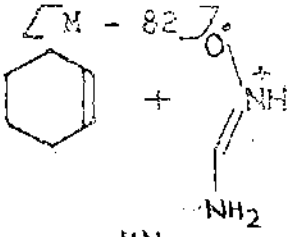
β- H rearrangement with Cδ- N bond cleavage



[M - 82]

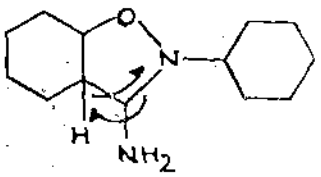




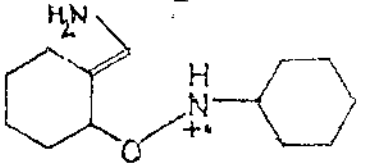


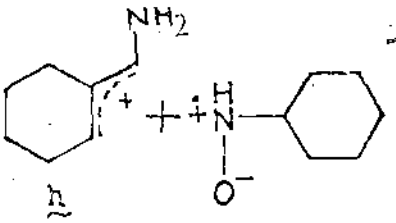
(60)

Type -H

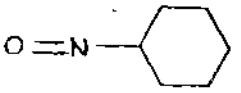


β- H rearrangement with C_3- N bond cleavage





[M -114]



(113)

Table-XIII

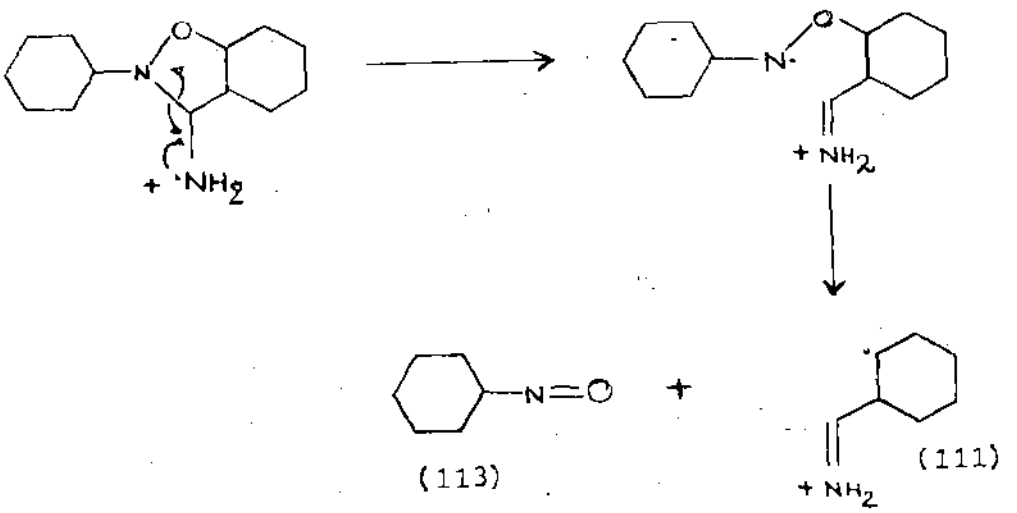
Adducts	M	M-1	M-43	M-56	M-57	M-113	M-114	M-141	M-142
(A)	+	—	—	—	—	+	+	+	+
(B)	+	+	+	—	—	+	+	+	+
(C)	+	—	—	—	—	+	+	+	+
(D)	+	—	+	—	—	+	—	+	+
(E)	+	+	—	—	—	—	—	+	+
(F)	+	—	—	—	—	+	—	+	+
(G)	+	—	+	—	+	+	+	+	—
(H)	+	—	+	—	—	—	+	+	+
(I)	+	—	+	—	—	—	+	+	+
(J)	+	—	+	+	—	+	+	+	+
(K)	+	+	+	+	+	+	+	+	+
(L)	+	+	—	—	—	+	+	—	+
(M)	+	—	—	—	—	—	—	—	—
(N)	+	—	—	—	—	—	—	—	—
(O)	+	—	—	—	—	—	—	—	+
(P)	+	+	+	—	—	—	—	+	—
(Q)	+	+	—	—	—	+	+	+	+

+ and − sign indicates presence and absence of the ion fragments.

Table-XIII (Continued)

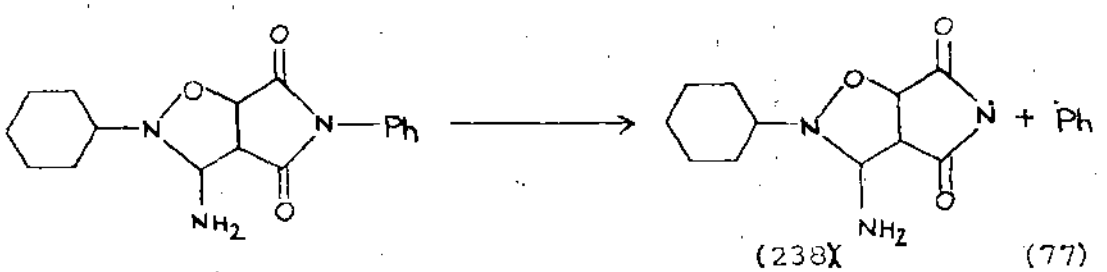
	142	141	126	114	113	98	82	70	60	57	56	55
(A)	—	+	+	+	+	+	+	+	+	+	+	+
(B)	+	+	+	+	+	—	+	+	+	+	+	+
(C)	—	+	+	—	+	+	+	+	—	+	+	+
(D)	—	+	—	+	+	—	+	+	+	+	+	+
(E)	—	+	—	+	+	+	—	+	+	+	+	+
(F)	—	—	+	+	+	—	+	+	+	+	+	+
(G)	+	—	+	+	+	+	+	+	+	+	+	+
(H)	+	—	+	+	+	+	+	+	+	+	+	+
(I)	+	—	+	+	—	+	+	+	+	+	+	+
(J)	+	—	+	+	+	—	+	+	+	+	+	+
(K)	—	+	+	+	+	+	+	+	+	+	+	+
(L)	+	—	+	+	+	+	+	+	+	+	+	+
(M)	—	—	—	+	+	—	+	—	—	—	+	+
(N)	—	—	+	+	+	+	+	+	+	+	+	+
(O)	—	+	+	+	+	+	+	+	+	+	+	+
(P)	—	—	—	—	—	+	+	—	—	+	+	+
(Q)	+	—	+	—	+	+	+	+	+	—	+	+

Type -I



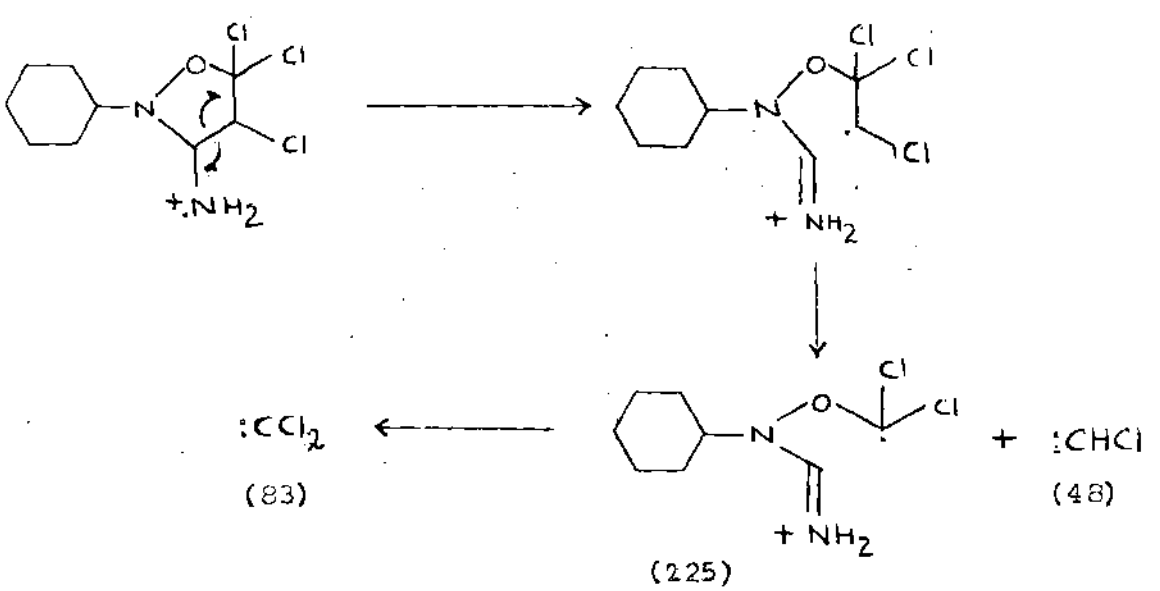
(113) (111)

Type -J

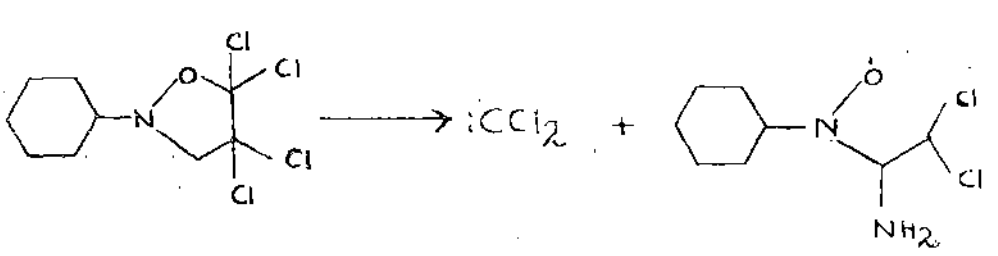


(238) (77)

Type -K_1 and K_2



(83) (48) (225)



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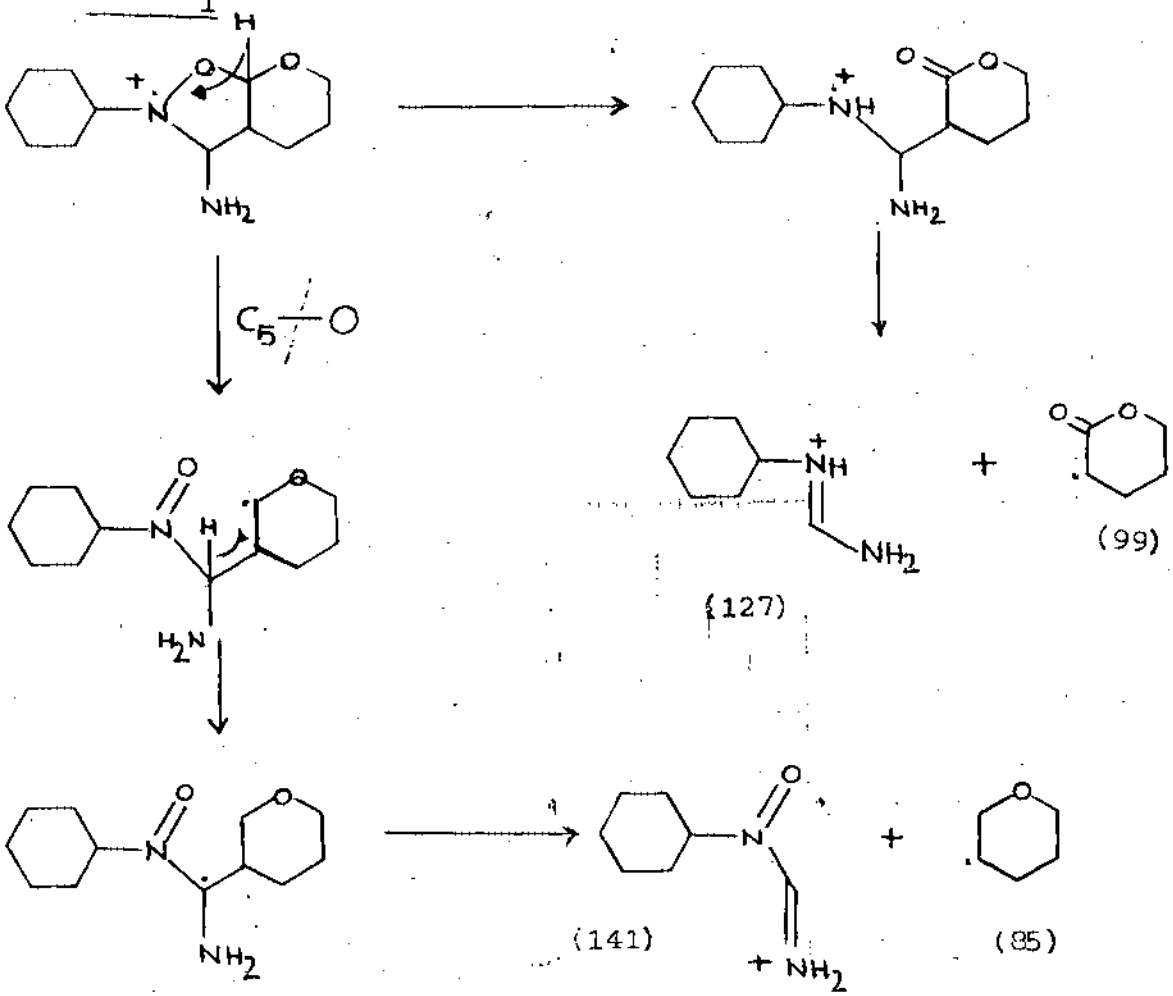
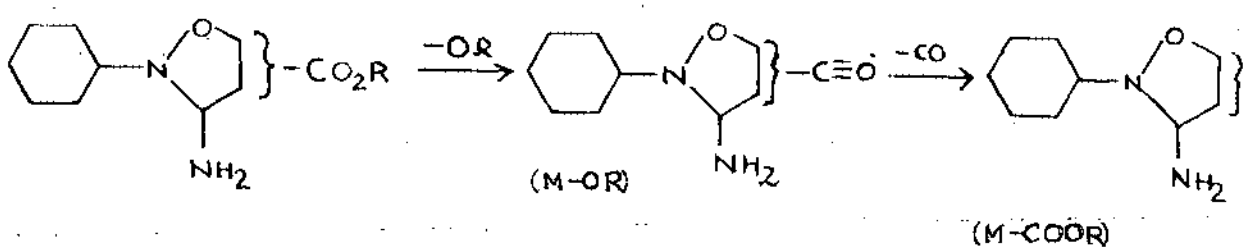
Type-L_1

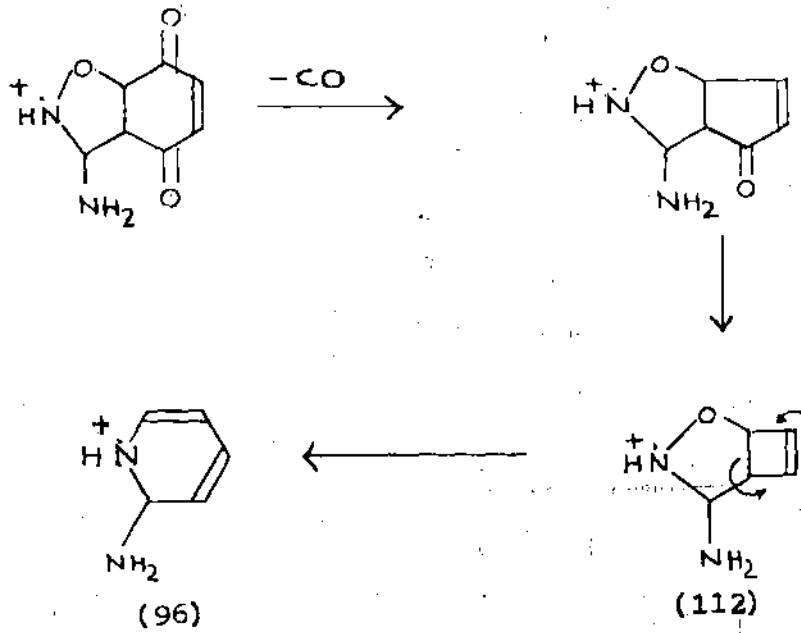


Type-L_2 (same as Type-L_1)

Type-N



Type-M



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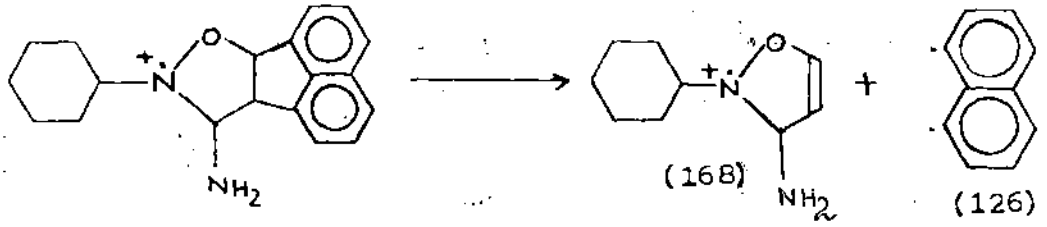
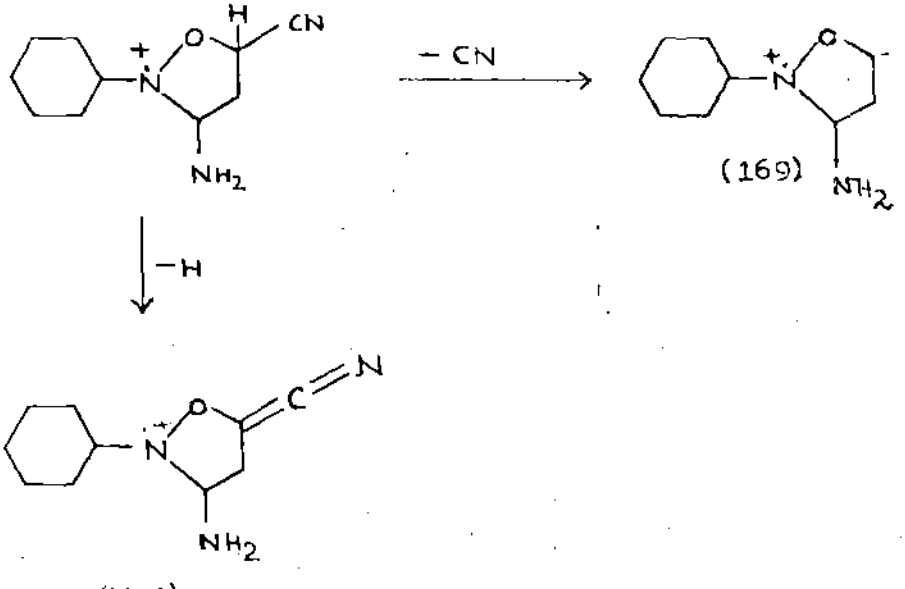
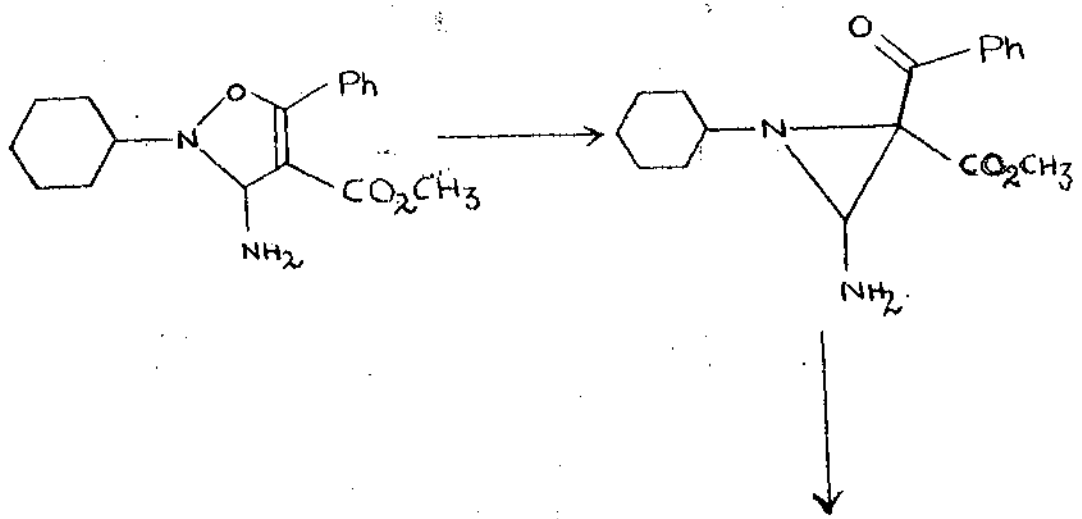
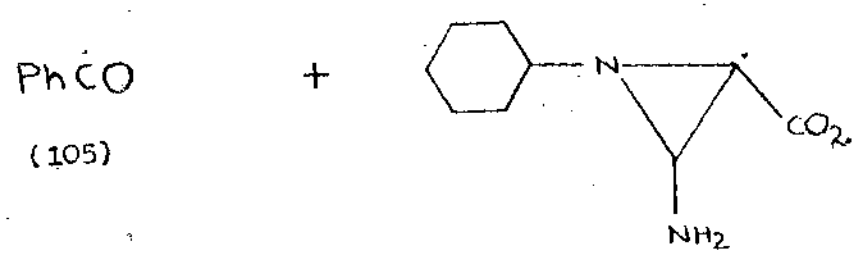


Type-P



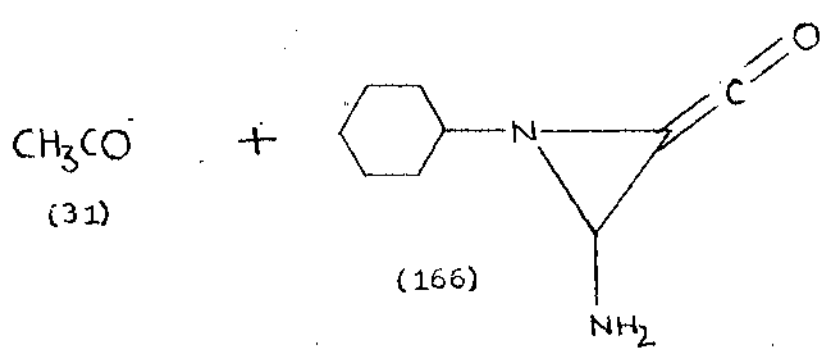
Type-Q





(105)

(M-105)



(31)

(166)

Acrylonitrile adduct similarly followed the general pattern. Some peaks at m\e 169; 127; 68; 54 and M-1 were explained in type-P.

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

C. Interpretation Of NMR Spectra :

On interpreting the NMR spectra of the nitrone adducts, the chemical shifts and coupling constant for the C_5 protons, wherever possible, were studied, as well as the dihedral angle between C_4-C_5 protons. In addition to that, the band width i.e., the distance between the first and the last line of the multiplet of of the signals, of the C_5 protons in Hz was also measured. Bauman et.al.[188] used this method to elucidate the conformations of the cis- and trans-cyclopentane-1-carbomethoxy-2-ol and found that for trans isomer the band width was 18 C/S and for cis isomer 11 C/S for C_1 proton. Similarly, 13.5-15 C/S for cis compound and 20-22.5 C/S for trans compound were found in the case of α-amino -N-cyclohexyl nitrone adducts (Table-XIV).

Adducts	C_5-Protons (δ in ppm)	Band Width (Hz)	Coupling Constant (Hz)
(A)	4.3(q)	15	—
(B)	4.4(b)	14	—
(C)	5.4(b)	—	—
(D)	5.5(b)	14	—
(E)	6.2(b)	13.5	—
(F)	5(b)	—	—
(G)	3.48-3.69(b)	—	—
(H)	3.81-3.86(d)	—	—
(I)	3.82-3.86(t)	22.5	6.17 and 3.85
(J)	3.90-3.98(b)	21.6	6.30 and 3.70
(K)	3.42(t)	20.25	7.20 and 5.40
(O)	4.9(b)	13.5	—

Table-XIV

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

From the coupling constant values of C_5-protons of the nitrone adducts with ethyl acrylate (I and J), acrylonitrile (K) and hydrolised product of acrylonitrile adduct, the dihedral angles between C_5 and C_4 protons were calculated from standard graph. From these calculated values and with general assumption that at normal condition 2-cyclohexyl-1,2-isoxazolidine preferred the "envelope" (Fig-XV), the C_5-C_4 projections with the corresponding dihedral angles (Fig-XVI) were constructed for I,J,K and the hydrolised product of acrylonitrile.

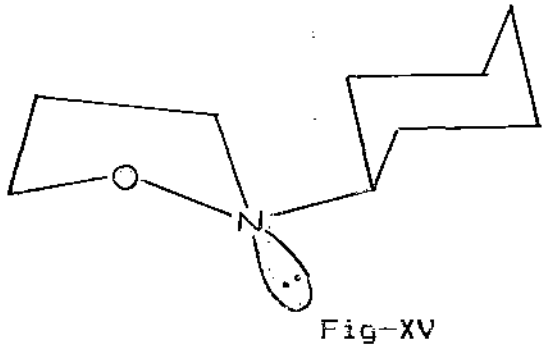


Fig-XV

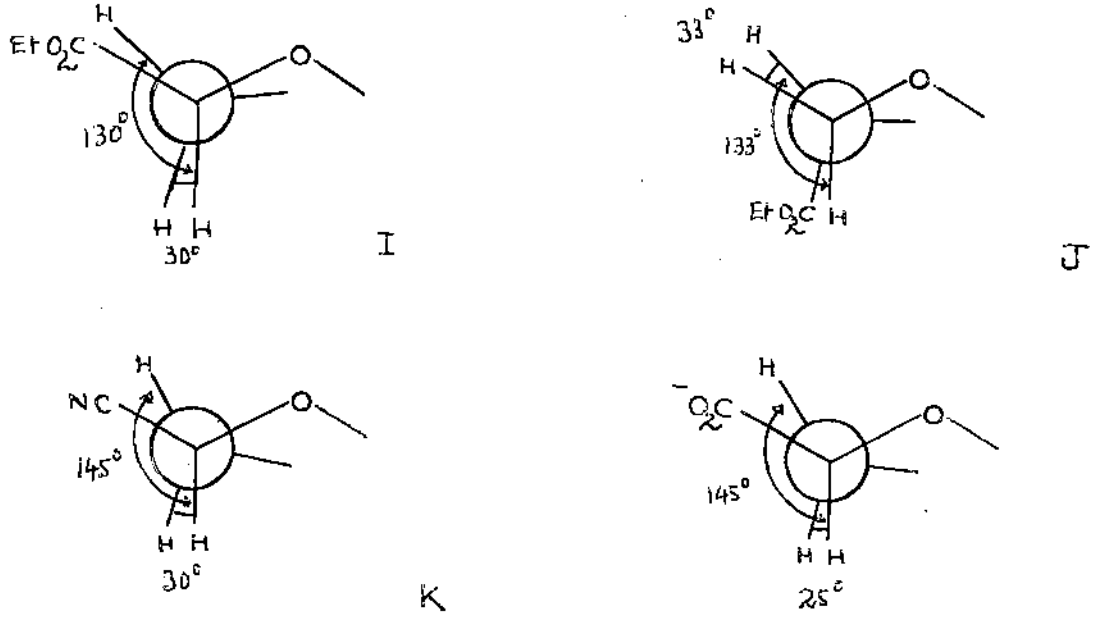


Fig-XVI

As the C_5-proton in the other cycloadducts were either absent or the splitting of the signal were not prominent so the dihedral angle between C_4-C_5 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 the amine protons were appeared at 1-2.2 δ. C_3-Proton in all adducts appeared in the region 2.7-3.6 (δ). N-CH proton of cyclohexyl group gave signal in region 2.6-3 (δ). C_4 and C_5 proton signals depended on the substituent at C_4 and C_5 possitions.

To compare the the proton signals, cycloadducts were devided into a number of groups having similar type of structures.

Cycloadducts (A), (B) and (C) :

Signals for C_4-proton were found at 2.5(b); 2.4(m) and 2.4(m) for (A), (B) and (C) respectively and that of C_5-protons were at 4.3(b), 4.4(b) and 5.4(b). C_5-Proton signal for (C) was slightly in lower field probably due to two fused five membered rings.

Cycloadducts (D), (E) and (F) :

C_4-Proton signals were found at 4.36-4.41(m), 4.1(b) and 3.8(b) for the adducts (D), (E) and (F) and that of C_5-protons were at 5.35(b), 6.2(b) and 5(m) respectively. In p-benzoquinone adduct (F), signals due to C_4 and C_5 protons and two olefinic protons were marged together at 4.5-5, to give a broad peak.

Cycloadducts (G) and (I) :

Signals for C_4-protons found at 2.27-2.5(m) and 3.82-3.86(t) and for C_5-protons at 3.48-3.69(b) and 3.9-4(t) for (G) and (I) respectively.

Cycloadducts (H) and (J) :

C_4-Proton signals for both the adducts were merged with the signals due to cyclohexyl methylene protons at 1-2.2(m). Signals for the C_5-protons were found at 3.8(t) and 3.9-3.98(t) respectively for (H) and (J).

Cycloadducts (K) and (L) :

C_4-Proton signals for (L) were found at 2.3-2.5(m) and that of (K) were merged with the signals due to the protons of the cyclohexyl methylene group protons. C_5-Proton signals for (K) found at slightly lower than expected, probably due to the anisotropic effect of the cyano group at C_5-possition.

Cycloadducts (P) and (Q) :

In the case of acetylenic adducts C_4 and C_5 protons were absent. The C_3-proton signals were found at lower field between 4-5.5(δ) due to the presence of a double bond between C_4 and C_5 possition.

Products (R) and (S) :

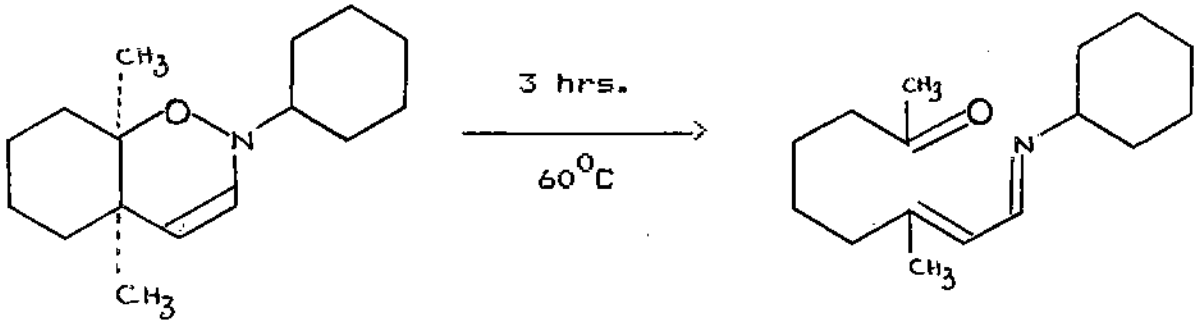
A singlet of two protons for each case were found at 8.1 and 8 (δ) for N^+H_2 respectively for (R) and (S). The olefinic protons were found at 6.4(b) and 6.6(b) respectively.

CHAPTER-V (SCOPE AND OBJECTIVE)

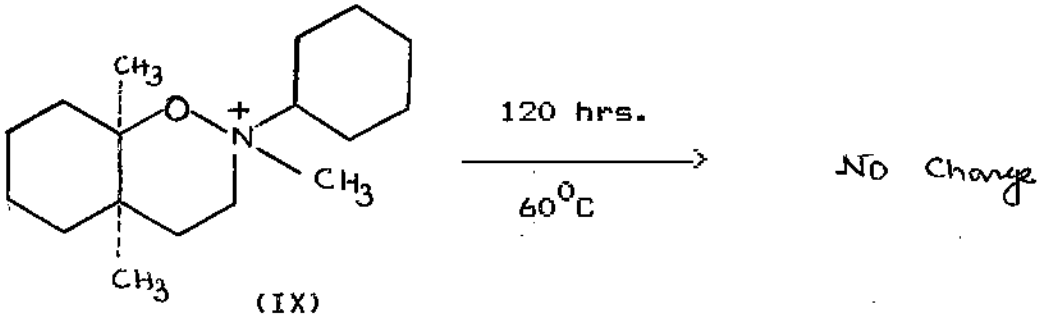
Among plethora of functional groups, the nitrone functionality has secured an important place in the arsenal of synthetic chemists. This was possible largely owing to the brilliant efforts of Huisgen and his group in Munich have resulted in major advances in the entire panorama of 1,3-dipolar cycloaddition rections. Houk and his co-workers are responsible for the pioneering investigations of regioselectivity and stereospecifi -city associated with the 1,3-dipolar cycloaddition. Finally Eschenmoser and his collaborator in Zurich made a brilliant contribution by discovering the α-chloro nitrone[189-191]. Another new vista of the nitrone chemistry is the α-amino nitrone[2,192]. The molecule constitutes 4-centered-6-electrons-Π-system and is expected to be unstable, therefore, an attempt has been made (in Chapter-I) to investigate the stability by HMO approximation. Although this simple theory has provided a qualitative guide for the preparation and the reactivity phenomena of the nitrone. Yet for the prediction of regioselectivity in 1,3-dipolar cycloaddition reaction, CNDO/2 or ab initio SCF calculations have tremendus scope. Theoretical work field in this field now in progress.

Direct synthesis of α-amino-N-cyclohexyl nitrone from formamide is interesting because Eschenmoser et.al. prepared the DMF nitrone by an indirect route. Now there is an ample scope to improve the yield of the nitrone. Lately, the nitrone was purified and used for the substitution reactions with alkyl halides.

P.Gygax[193] in his Ph.D. dissertation, elegantly established that the oxa-aza-ene (VII) in six membered ring, undergoes smooth transformation to (VIII) in 3 hrs at 60°C, while the N-methylated system (IX) remained unchanged.

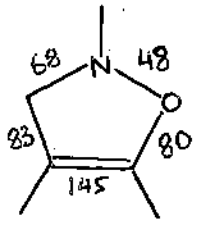


(VII) (VIII)

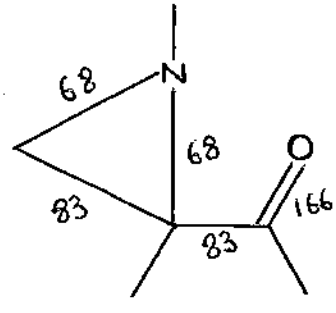


(IX)

Formation of five membered oxa-aza-ene system and their facile transformation were first demonstrated by Huisgen and later the formation of aziridine ring was confirmed by Baldwin[173] in a separate example. The average bond energy calculation also supports the above facts, because the balance of energy is 44 Kcal/mole towards the right side:



Σ 424 K.cal/mole



Σ 468 K.cal/mole

Though no such change was observed in the five membered oxa-aza-ene of α-amino-N-cyclohexyl nitrone, yet, extensive investigation is needed.

Another important aspect of the α-amino-N-cyclohexyl nitrone is the facile displacement reaction at room temperature with alkyl halides. Here the lone pair of the N-atom, α- to the nitrone group plays a trick. The new nitrone has a tremendus scope, to study the pericyclic reactions. Similarly, one can also study the formation of Meisenheimer complex by the nitrone to the electron deficient ring systems.

While studing the 1,3-dipolar cycloaddition reactions of α-amino-N-cyclohexyl nitrone with ethyl and methyl cinnamate it was found that both the cycloadducts were unstable and dissociated probably due to (3 + 2 $\rightleftharpoons$ 5) cyclorevertion.

Finally, a thorough study of the (3 + 3 $\rightleftharpoons$ 6) dimerisation-cyclorevertion of α-amono-N-cyclohexyl nitrone could open the question as to whether the cycloaddition reactions are concerted or a two-step process.

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