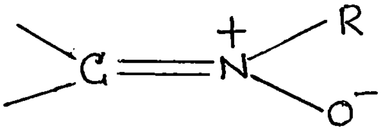
CHAPTER II
CHEMISTRY OF NITRONE

1. INTRODUCTION:

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



2. NOMENCLATURE :

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

α, N diphenyl nitrone.

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

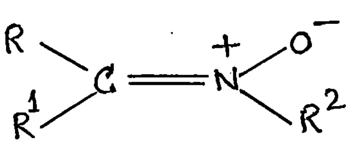
The cyclic nitrones are named according to the parent-heterocyclic structure, e.g. 2,4 dimethyl - Δ^1 - pyrolidine N - oxide; Δ^1 - tetra hydropyridine N - oxide etc. Of late nitrones have also been named as C - cyclopropyl N - methyl nitrone, C,C dicyclopropyl - N - methyl nitrone etc.

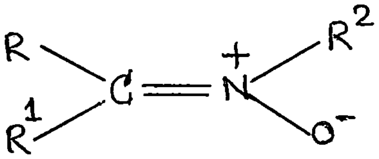
The general terms, aldonitrones and Keto nitrones have been employed occasionaly. Aldonitrones - contain a proton on the α - carbon atom, $RCH = \overset{+}{N}(O)R^{1}$. While in Keto nitrones contain the α - carbon fully substituted with alkyl and or aryl groups.

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

3. GEOMETRICAL ISOMERISM :

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





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

4. Synthesis of Nitrones

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

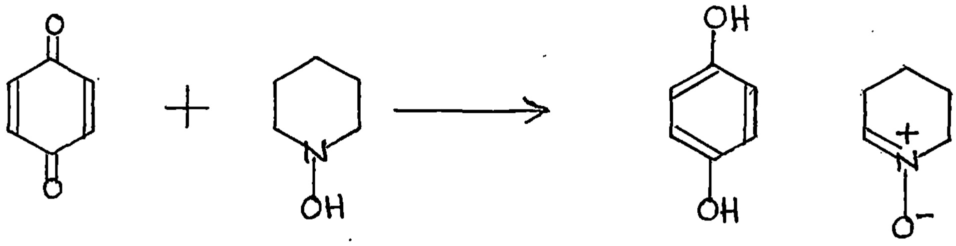
(A)

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

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

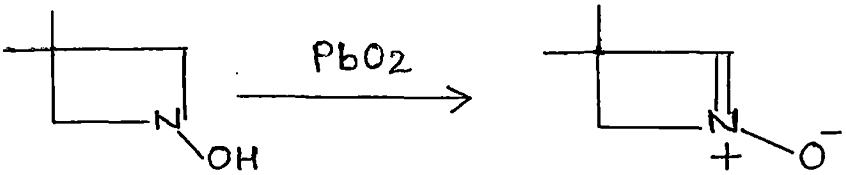
Both cyclic and acyclic nitrones were prepared by this method. Different oxidizing agents were used, e.g. molecular oxygen (42-46) , yellow mercuric oxide (38, 47-49), active lead oxide (50), pottasium ferricyanide (43,47,49,51), hydrogen peroxide (52,53), pottasium permanganate (53), t-butyl hydroperoxide,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

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



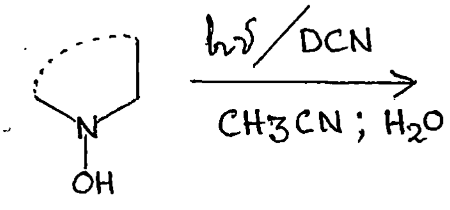
Formation of nitrone from N, N disubstituted and N-Substituted hydroxyl amines using Palladium Catalyst were also reported (56).

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



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

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



(B) From Oximes :

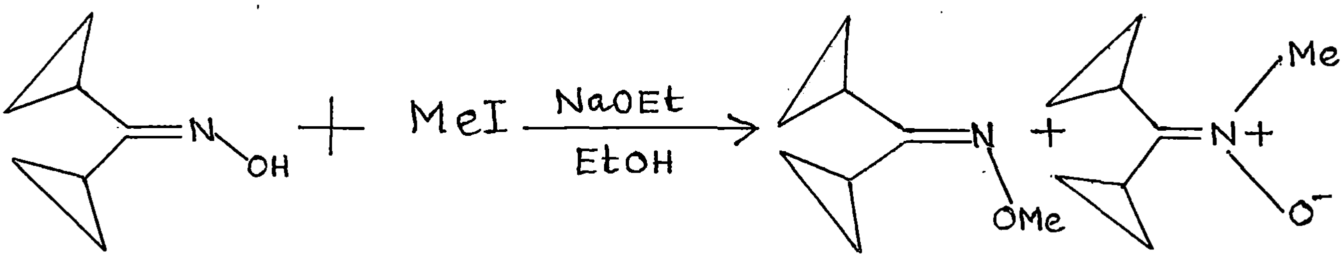
The alkylation of oximes were reviewed in 1938 (35). A disadvantage of the method was that, nitrone were produced along with oxime ether.

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

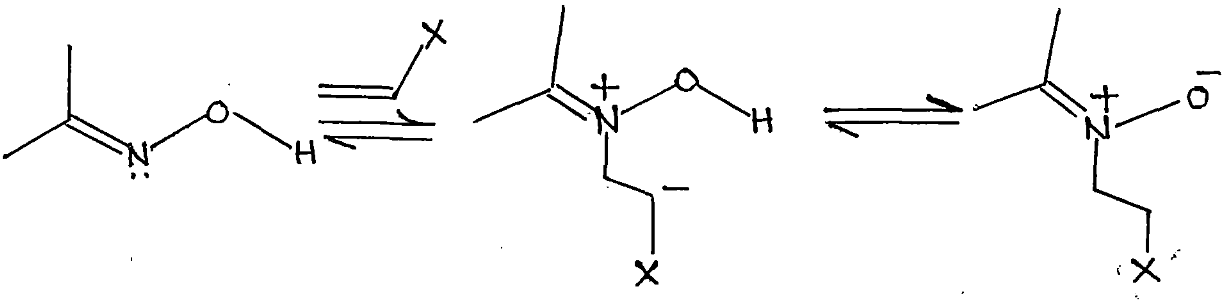
Li, Na, K or tetramethyl ammonium oxime Salts did not alter the products ratio of oxime ether to nitrone significantly. Electron withdrawing group in p ,p' disubstituted benzophenone oxime Salts markedly promoted the formation of nitrones, while electron donating group favours oxime-ether formation.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

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

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

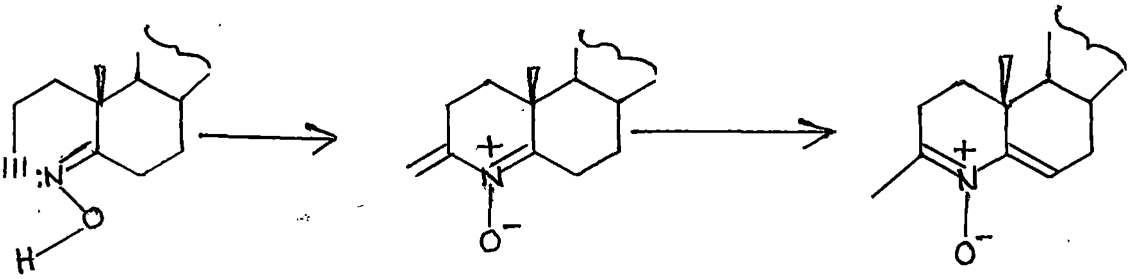


Formation of nitrones were also reported by the intra molecular Michael addition of aldoximes and Ketoximes to electronegative olefines (62).



Recently oxime -O -allyl ethers were converted to the corresponding N - allyl nitrones on treatment with 10 mole % $PdCl_2(MeCN)_2$ by a formal [2,3] sigmatropic shift (63).

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



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

$$PhCH=N(O)SiMe_3 \xrightarrow{\text{Me-triflate}} PhCH=\overset{+}{N}(\overset{-}{O})Me$$

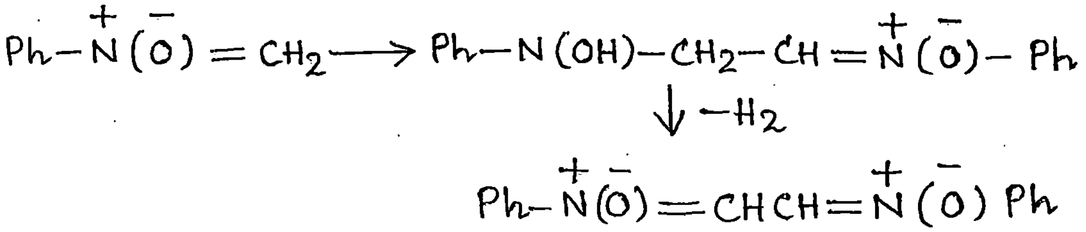
α - Nitroso - nitrones have been prepared from nitrile oxide and nitroso-arene (66).

(C)

From N - Substituted Hydroxylamine :

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

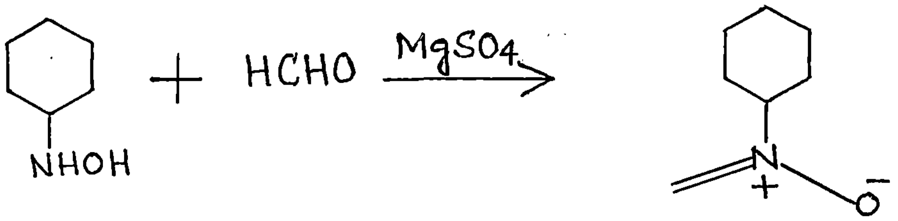
This reaction proceeds smoothly and in high yield when R is an alkyl or aryl group and R^1 and R^2 are of small size. When R^1 and R^2 are bulky groups the reaction does not proceed to any extent(67). This is one of the best method for the preparation of aldonitrones. N- phenyl-hydroxyl amine has been treated with a variety of aldehydes and Ketones. With n- butylaldehyde, 80 % yield, α- propyl-N-phenyl nitrone was obtained (51). With benzal dehyde a 90 % yield of the nitrone (68 , 69) with o , m and p - nitro benzaldehyde good yield (70) with p-N, N-dimethyl amino benzaldehyde a 79% yield (71) and good yield with other substituted benzaldehydes (72).N-phenyl nitrone formed from hydroxyl amine and formaldehyde insitu and finally dinitrone (43).



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

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

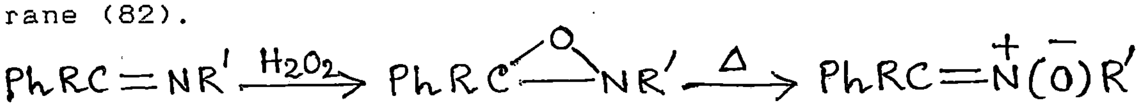
N -cyclohexyl methelene nitrone similar to N -phenyl methelene nitrone (2) can be prepared by passing HCHO gas through N- cyclohxyl hydroxyl amine in CH_2Cl_2 and anhydrous $MgSO_4$.



(D)

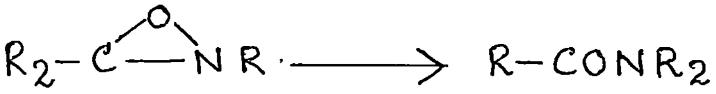
From Oxaxiranes :

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



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

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



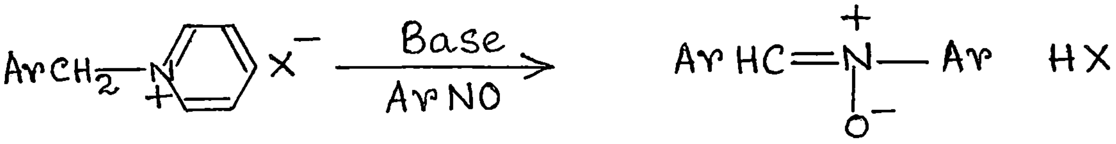
This is not general method for the preparation of nitrones since the oxaxiranes are generally prepared by the photochemical isomerisation of nitrones or by the reaction between imine and hydrogen peroxide , moreover, some other rearranged products also encountered.

The oxidation of N- alkyl imines by dimethyl dioxirane (82) (DMD) in CH_2Cl_2 -acetone solution yielded nitrones without evidence of oxaziridine formation. The yields of isolated nitrones were higher for C, C diaryl imines and for imines bearing less bulky N- alkyl subsitituents.

(E)
From Aromatic Nitroso Compounds :

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

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



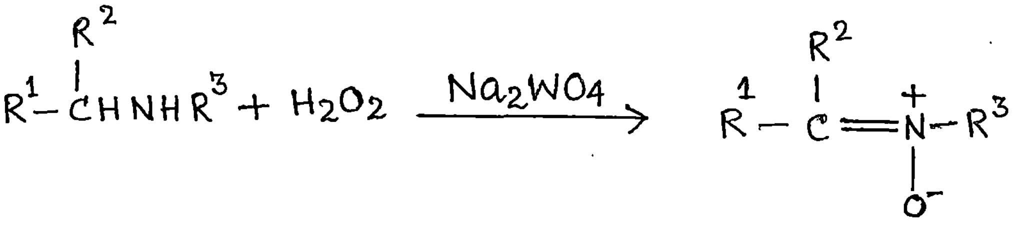
Pyridinium salt may be prepared by King reaction (89,90). This reaction is specially helpful for preparing pyridinium salts of methyl - substituted hetero cyclic aromatic compounds, α - methyl Ketones (67) etc.

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

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

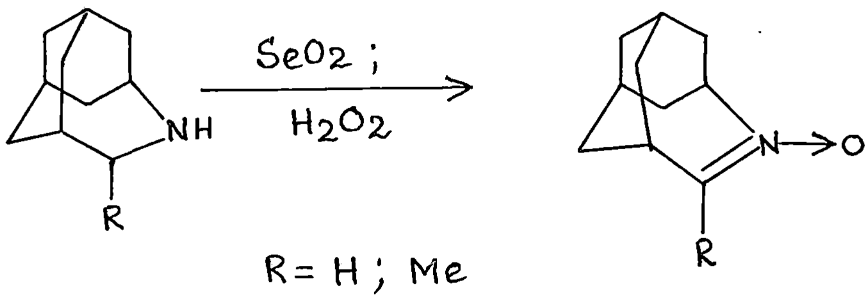
(F)
From Secondary Amines :

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



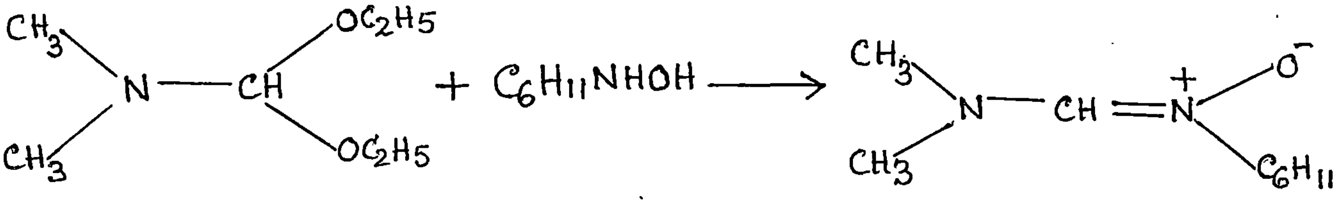
$$R^1\text{-}CH(R^2)NHR^3 + H_2O_2 \xrightarrow{Na_2WO_4} R^1\text{-}C(R^2)=\overset{+}{N}(O^-)\text{-}R^3$$

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



(G)
From acetal and amides :

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

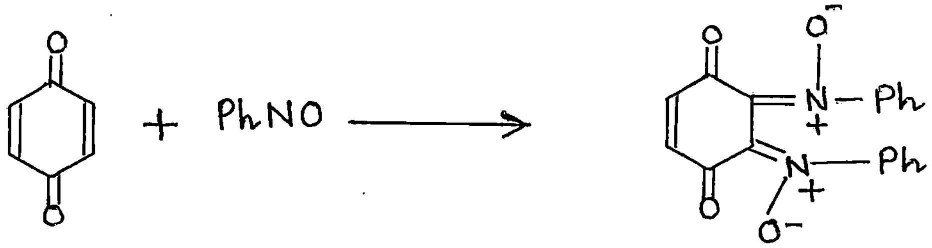


Finally the work has been extended after a slight change in methodology (101).

(H)

Some Other Miscellaneous Methods :

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

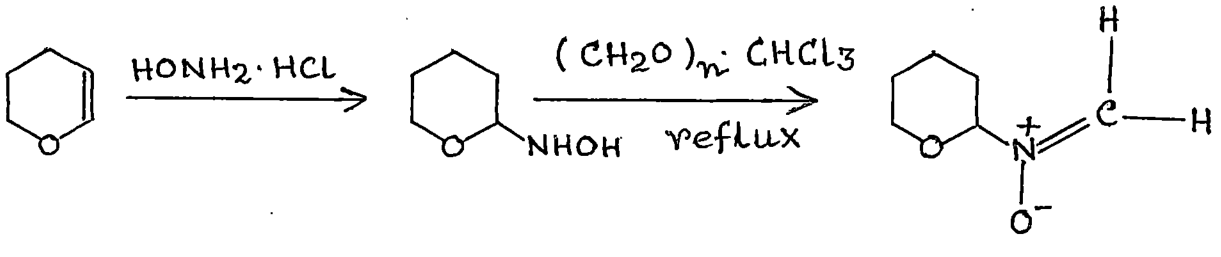


Some thiazolium salt partially reduce nitro-benzene with benzaldehyde to nitrone (103).

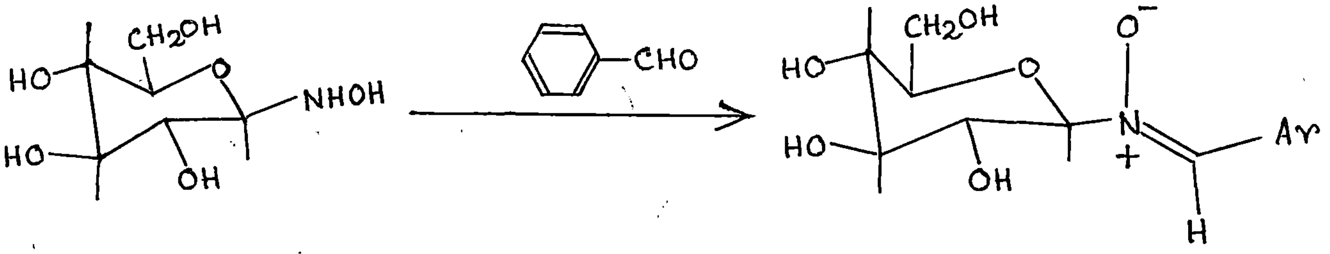
The adduct silyl enol ether with nitrobenzene can be oxidized to α - aryl - N - phenyl nitrone by Ag_2O (104).

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

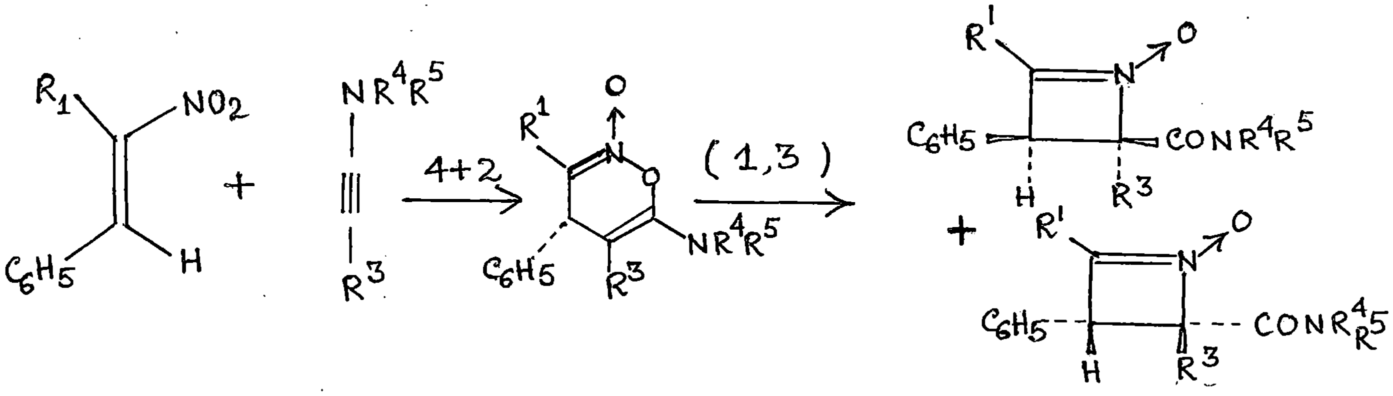
N - tetrahydro pyran 2-yl nitrone (106) was also generated insitu and finally characterised by PMR .



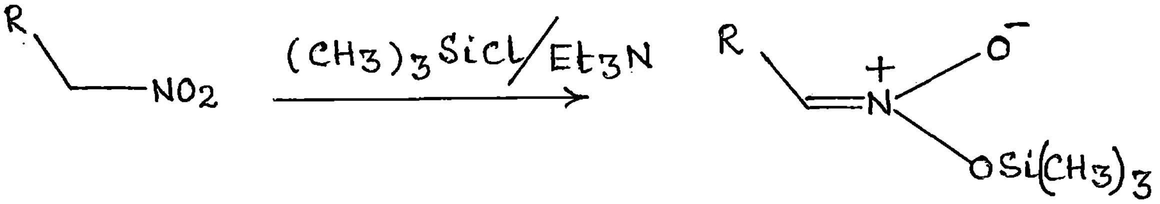
Nitrones (107) can also be isolated in pure state from D - glucose oxime and benzaldehydes without employing any protection of hydroxyl group.



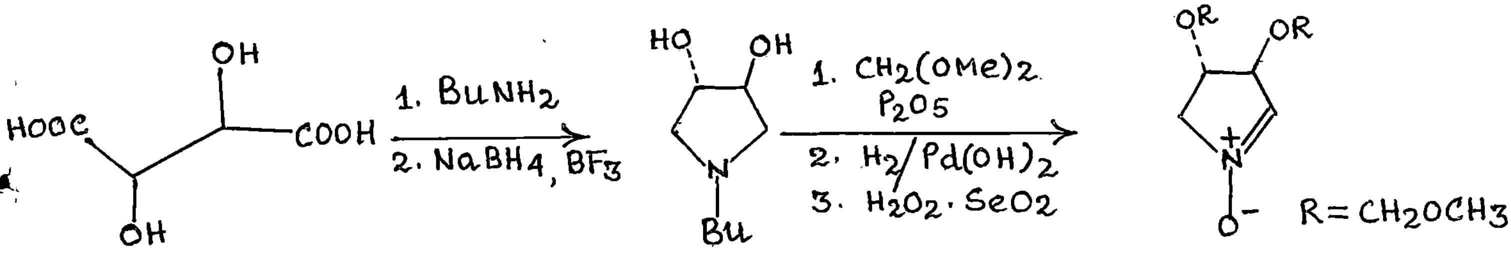
Chiral 4 - membered cyclic nitrones (108) were synthesized by the asymmetric (4 + 2) cycloaddation of nitroalkenes and chiral ynamines.



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



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



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

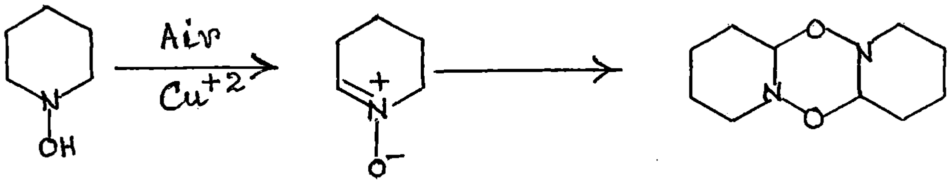
Ketone intermediate was reported in the early 1994.

5. Reactions of Nitrones :

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

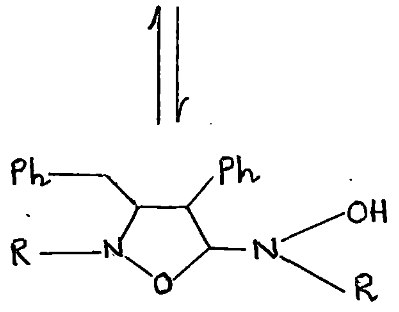
(A) Dimerisation :

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



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

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

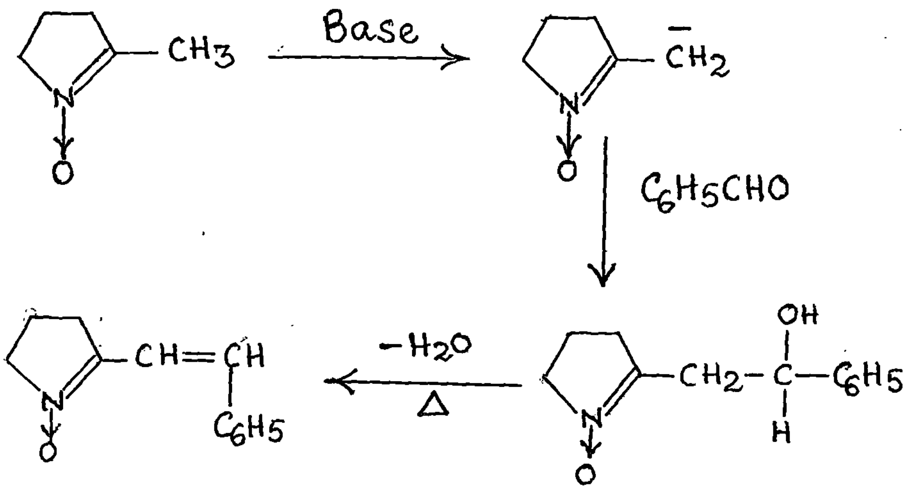


R= CH3; Ph; p-MePh

(B) Aldol Condensations :

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

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



(C)

Addition of Grignard Reagents :

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

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

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

(D)

Addition of Hydrogen Cyanide :

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

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

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

(E)

Rearrangement :

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

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

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

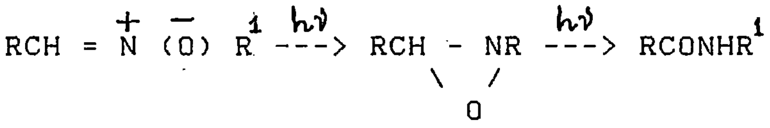
$$Ph_2C = \overset{+}{N}(\overset{-}{O}) - CHPh_2 \dashrightarrow Ph_2C = N - O - CHPh_2$$

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

(G)

Some Other Transformations of Nitrones :

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



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

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

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

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

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

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

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

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

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

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

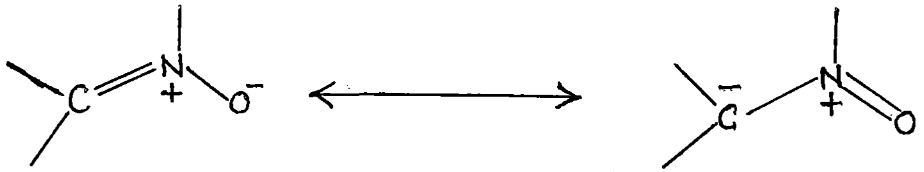
Deoxygenation of nitrohas been accomplished by zinc, iron, tin, phosphine, sulfur dioxide, sulfur and catalytic hydrogenation (44, 76-78,142).

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

(143).

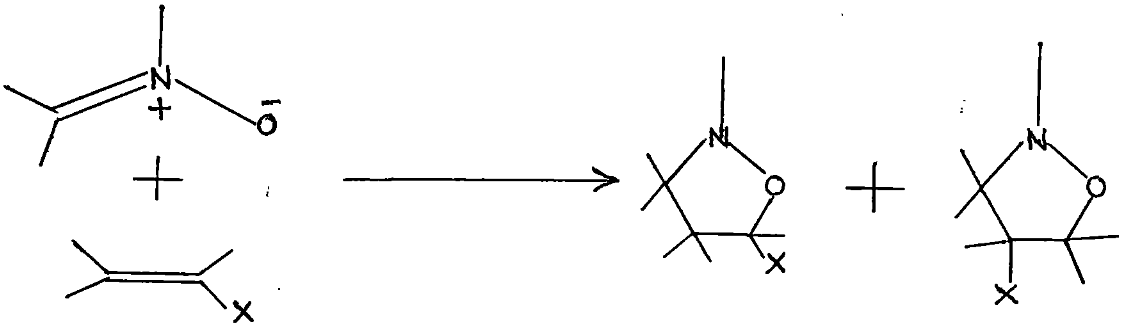
(H)
Cycloaddition Reactions of Nitrones :

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



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

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



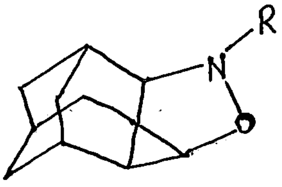
The cycloaddition reactions of Nitrones can be classified in two major catagories ;

1) Intramolecular 1,3 dipolar cycloadditions.

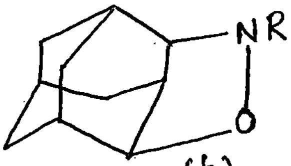
2) Intermolecular 1,3 dipolar cycloadditions.

1) Intramolecular 1,3 dipolar cycloadditions.:

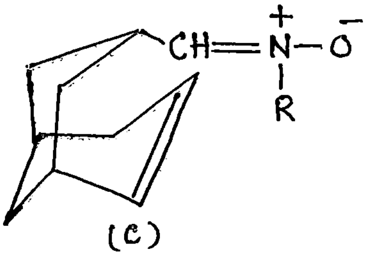
Intramolecular 1,3 dipolar cycloadditions have proved to be of considerable value in the synthesis of noble fused ring heterocycles (145-148). Sasaki-etal (145) have reported to convenient stereo specific synthesis of 2,4 diaxial adamantane [a] and 2,4 di-endo-proto adamantane derivatives [b] via an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



(a)

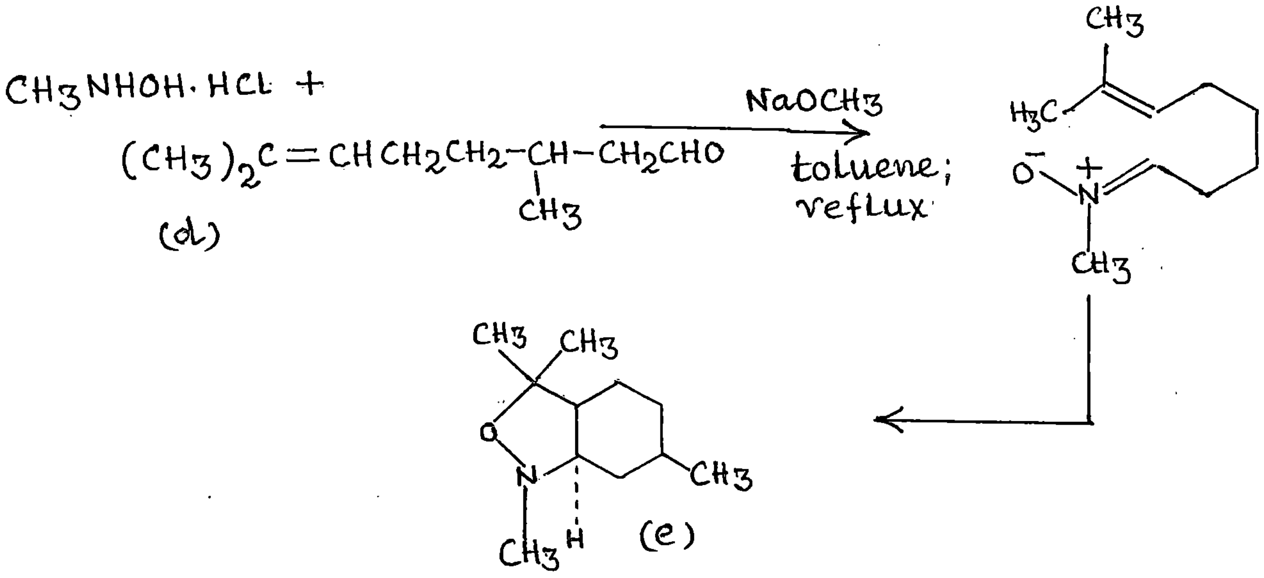


(b)



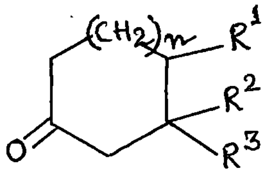
(c)

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

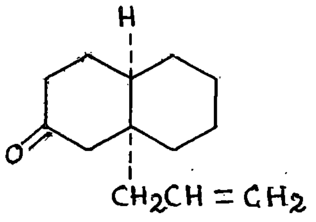


Scheme-III.

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

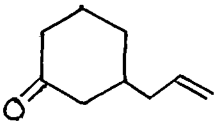
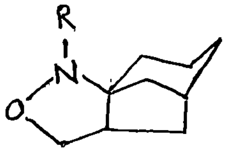
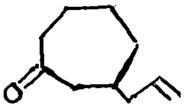
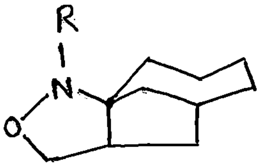
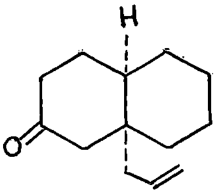
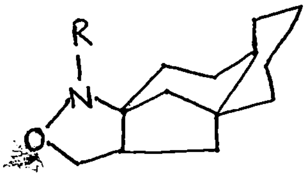
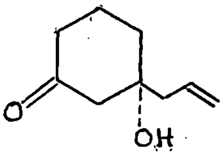
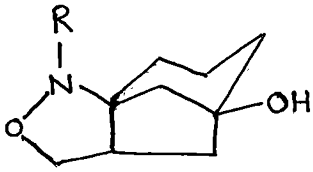
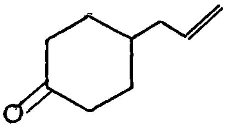
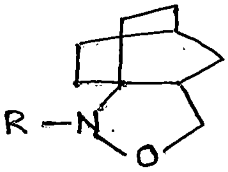
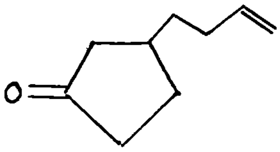
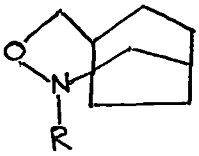
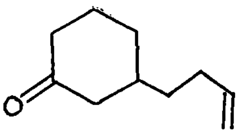
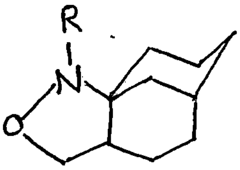


(f)



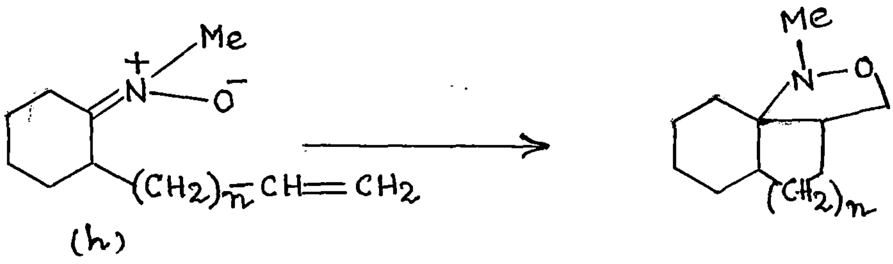
(g)

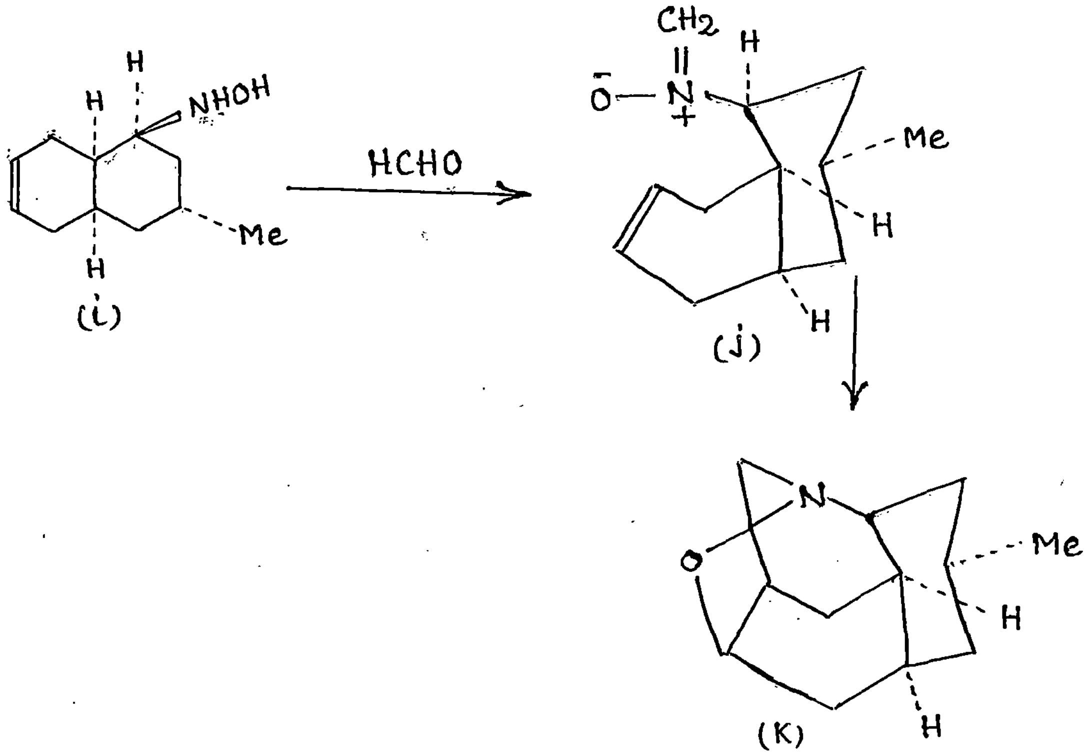
Table - 5 :

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

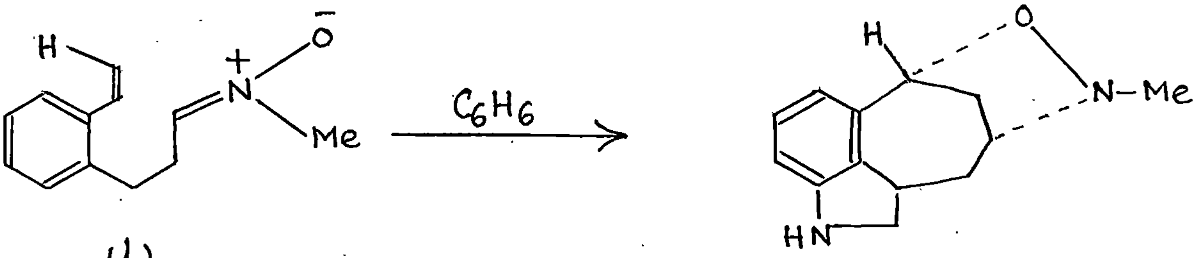
The annelation by intramolecular 1,3 dipolar addition of nitrones [h] and the factors controlling the case of reaction have been investigated by Kusurni etal (149). Structural and medium effects on the intramolecular 1,3 dipolar cycloadditions of nitrones have been studied (150).

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



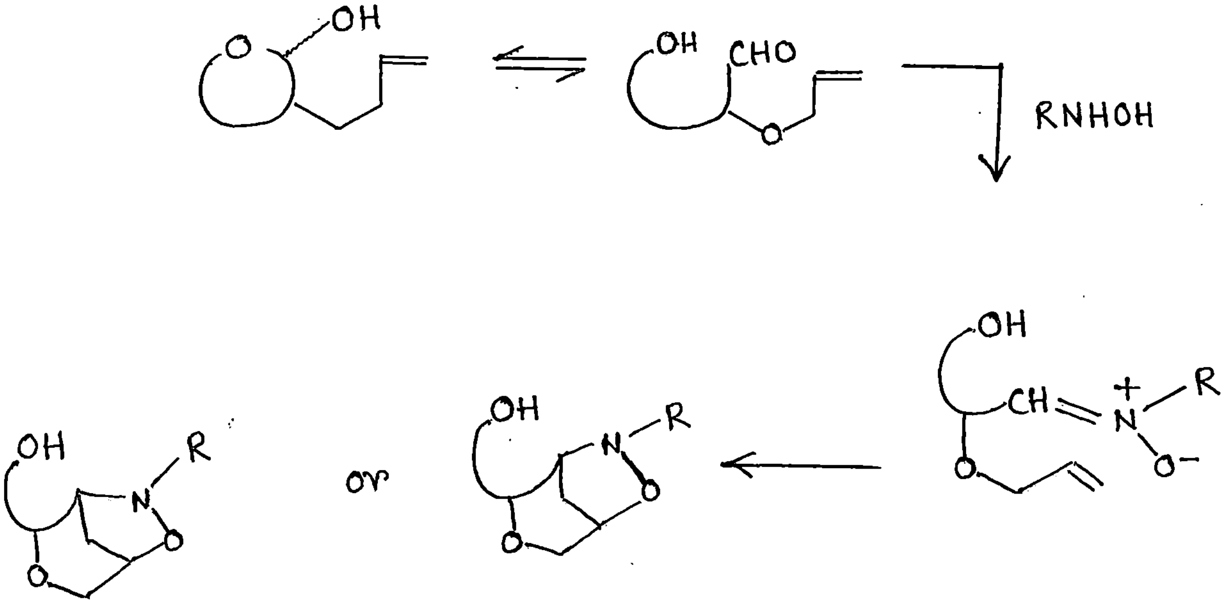


The clavive alkaloids have been synthesised (151) Stereo Selectively from indole 4- carboxaldehyde. One of the steps involved a transient nitrone (l) which underwent a kinetically controlled regio and stereoselective intramolecular cycloaddition to a 1,2 disubstituted olefinic bond to give cycloadduct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

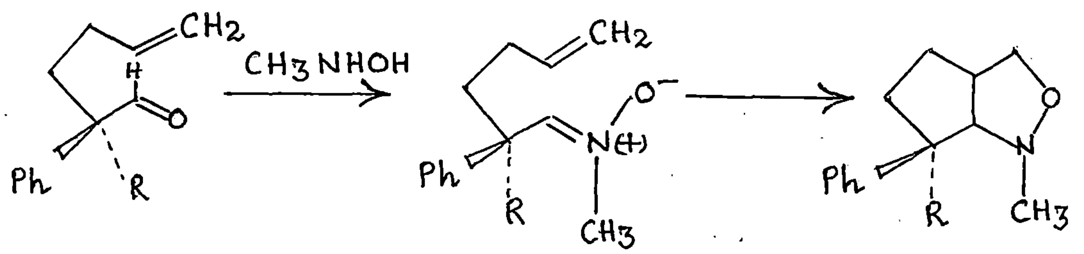


(l) (m)

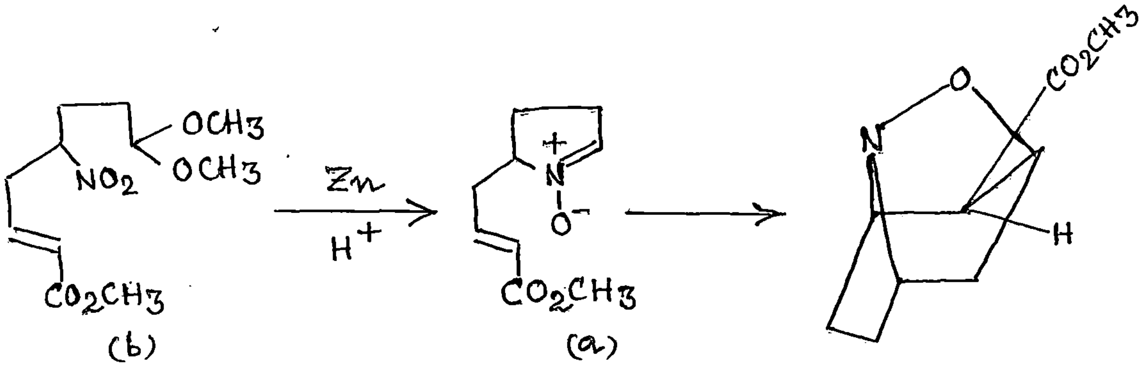
The intramolecular 1,3 dipolar cycloaddition of the N-benzylnitrone of 3 - O - allyl D (+) glucose (153) yielded a chiral oxepane derivative, potentially useful for the synthesis of other chiral systems.



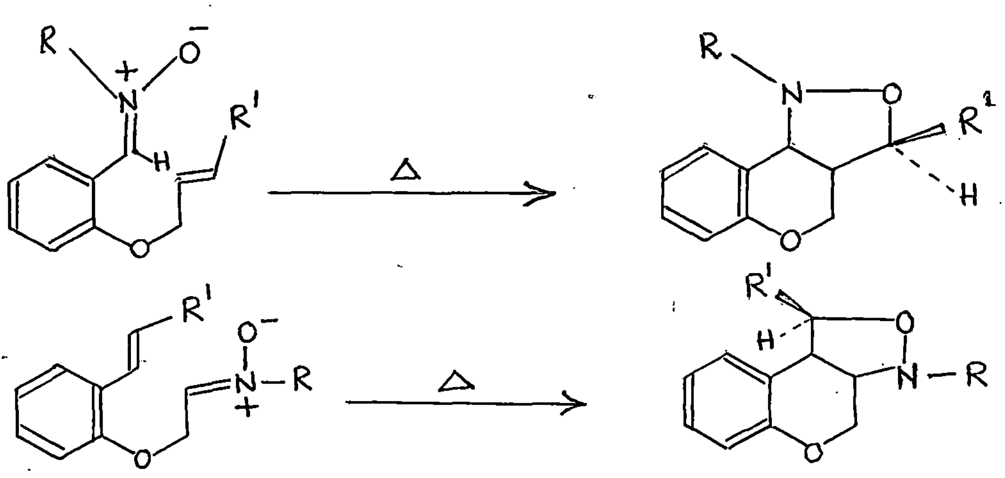
Vinick et. al (154) reported that cyclopentanone ring with three asymmetric centre's was stereo specially constructed in a single step from an acyclic precursor by means of intramolecular 1,3 dipolar cycloaddition reactions.



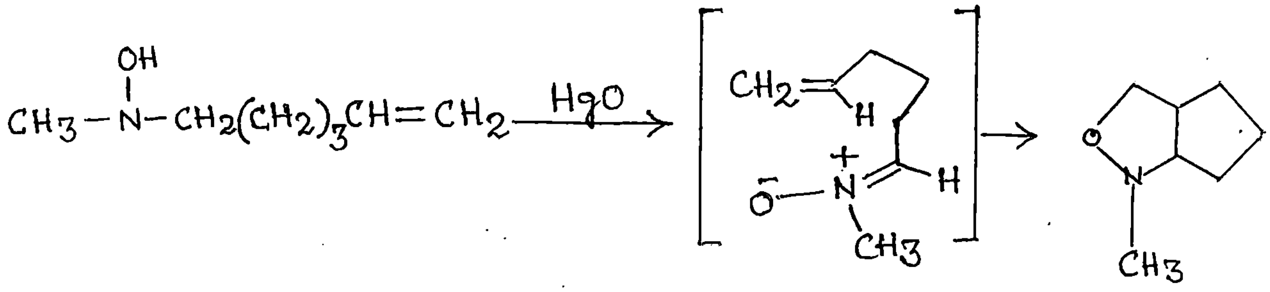
A very interesting application of intramolecular nitrone cycloaddition was reported by Tufariellow (155, 156) in the synthesis of dl-cocaine. The synthesis was developed by the generation of nitrone ester [a] as the key precursor of the natural product which was accomplished by reduction of acetal [b]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



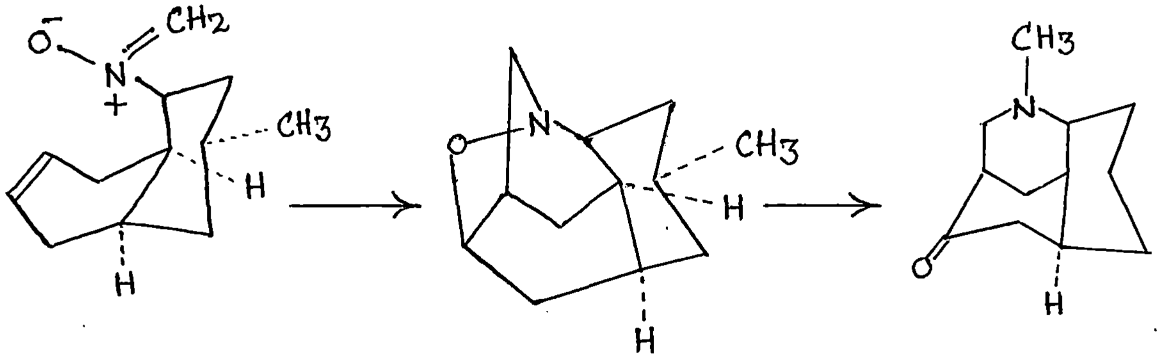
Oppolzer and co-workers (157, 158) had extended the intramolecular 1,3 dipolar cycloaddition to incorporate a benzene ring and a hetero atom containing isoxazolidines.



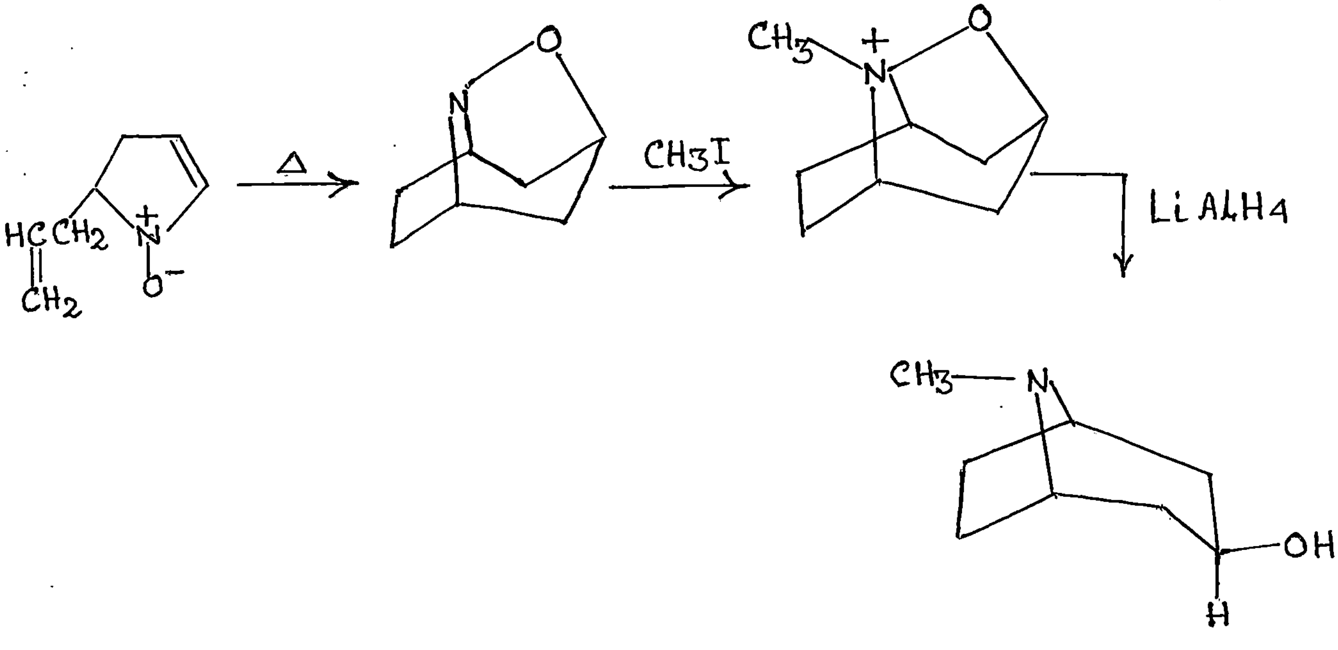
Formation of bicyclic isoxazolidine (159) was also reported, in a situation when alkene and nitrone moieties were suitably arranged in the same molecule.



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

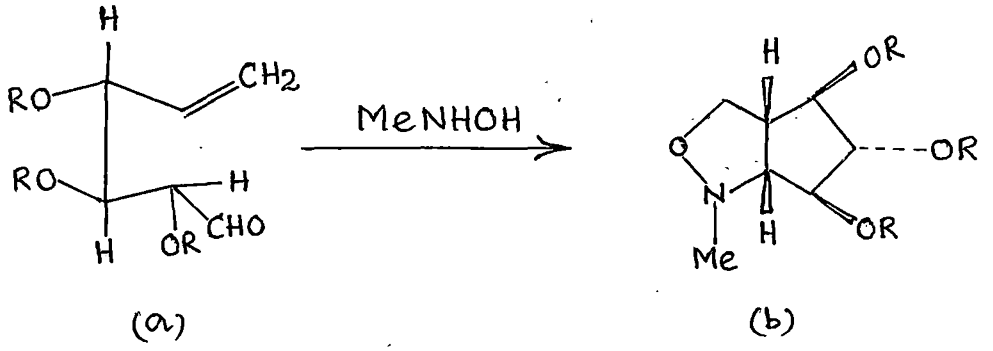


The intramolecular 1,3 dipolar addition of 5 allyl 1, pyrroline N- oxide was reported to give a cycloadduct which was a useful precursor of tropane-skeleton (160).

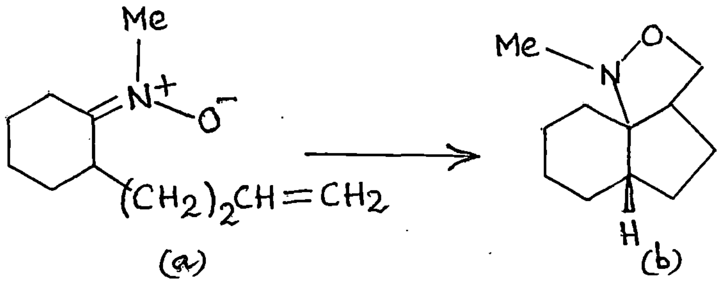


A series of intramolecular nitrone cycloadditions (161) to chiral allyl ethers was studied in order to evaluate the influence on the stereochemical out come exerted by several factors, including the nature of the substituents at the stereo centre and electronic features of the double bond.

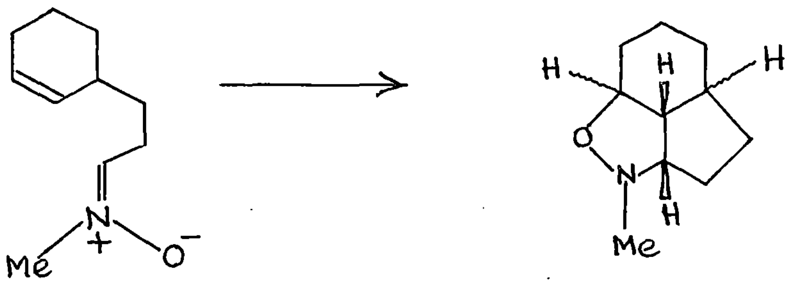
Pentasubstituted cyclopentanes have been prepared from mono saccarides (162). The reductive fragmentation of 5-bromo-5 deoxy glucosides with Zn produces 5,6 deoxy hex 5-enones, [a] which upon treatment with N-methyl amine followed by intramolecular cyclization afford the chiral isoxazolidine [b] in good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



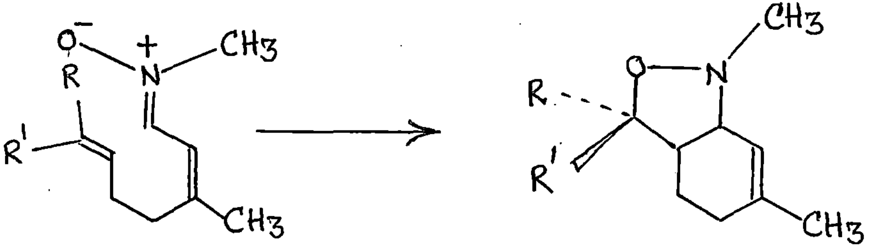
Annelation of nitrone [a] at room temp. led quantitatively to the hydrindane [b] whose stereochemistry was tentatively assigned as depicted (163).



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

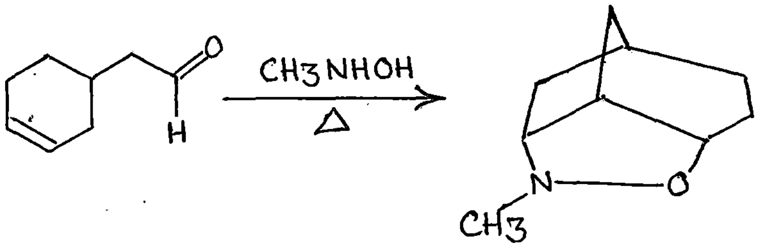


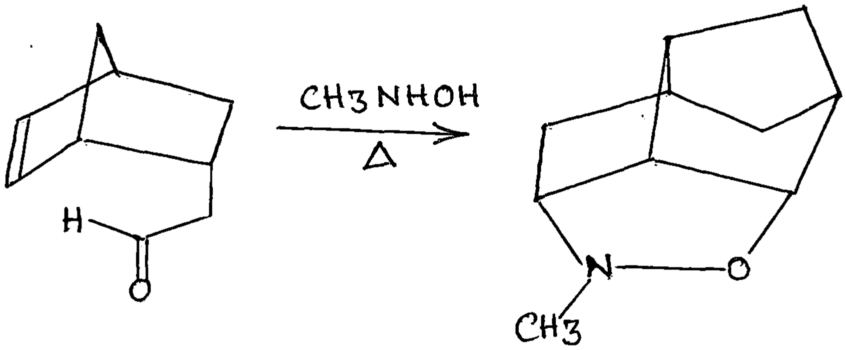
Nitrone [a] derived from farnesal was found to undergo ready thermal cycloaddition to give isoxazolidine (165,166) [b] using intramolecular 1,3 dipolar cycloaddition, with complete retention of configuration.

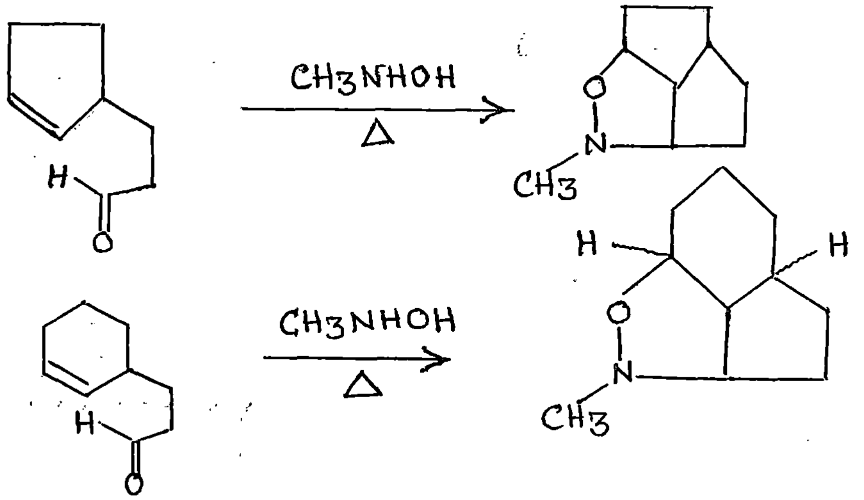


(a) (b)

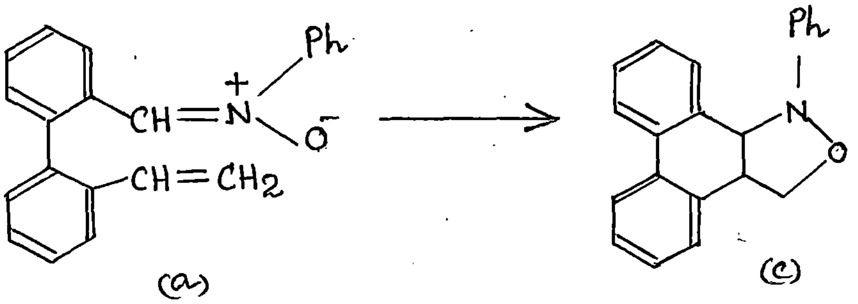
LeBel and co-workers further demonstrated the utility and synthetic scope of the intra modecular 1,3 dipolar cyclo addition of nitrones by preparing a variety of polycyclic isoxazolidines (164, 167-169) e.g.

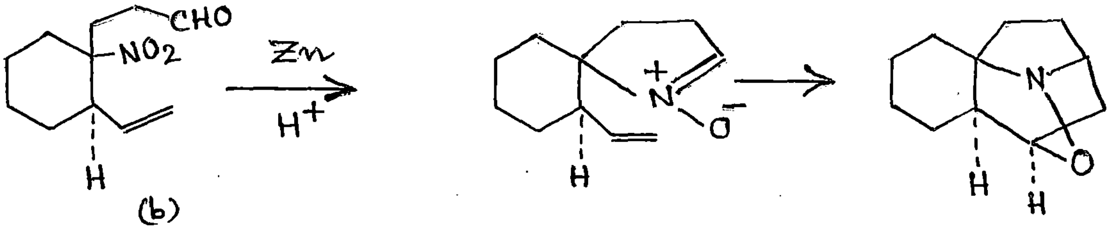




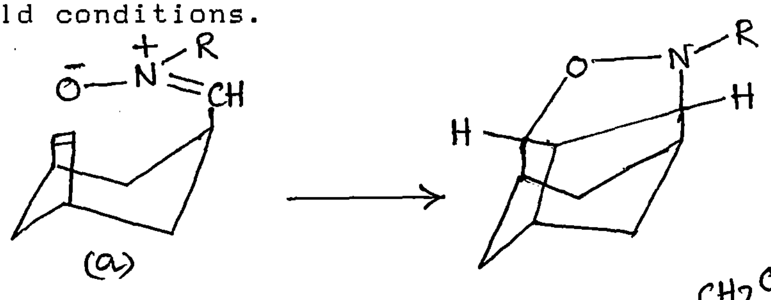


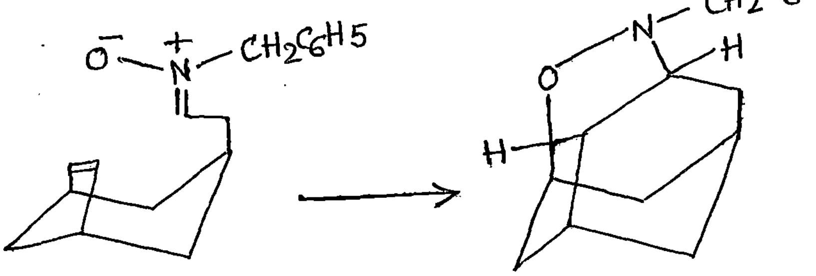
Other systems that undergo intramolecular 1,3 dipolar cycloaddition include N[O(O- Vinyl phenyl)-benzylidine] aniline N- oxide [a] (170) and the nitrone derived from the Zn reduction of nitro aldehyde [b] (171). The exclusive formation of [c] is especially interesting in the light of Huisgen's work dealing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

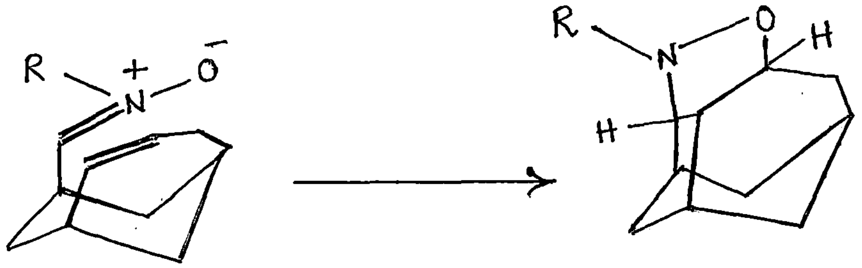




Intramolecular cycloaddition of nitrones to olefines are kinetically controlled process (173 - 175).The intramolecular 1,3 dipolar cycloadditions at C- bicyclo alkenyl nitrones [a],[b],[c], proceed smoothly at 25°-80° c affording the expected cycloaducts in high yield (176). These intramolecular cycloadditions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







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

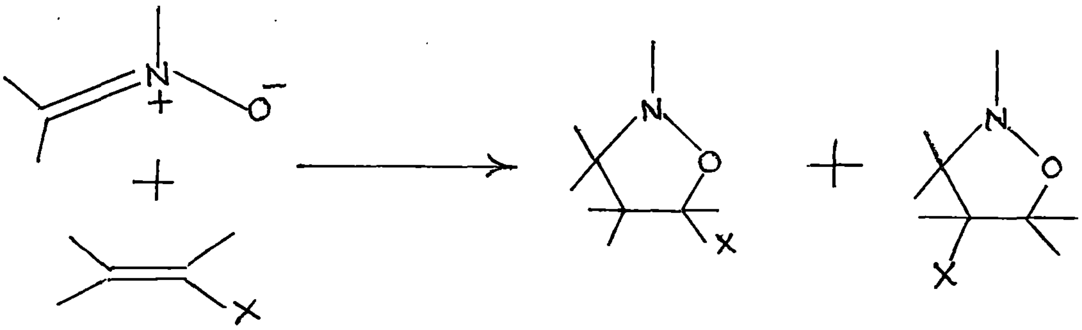
[2]

Intermolecular 1,3 dipolar Cycloadditions. :

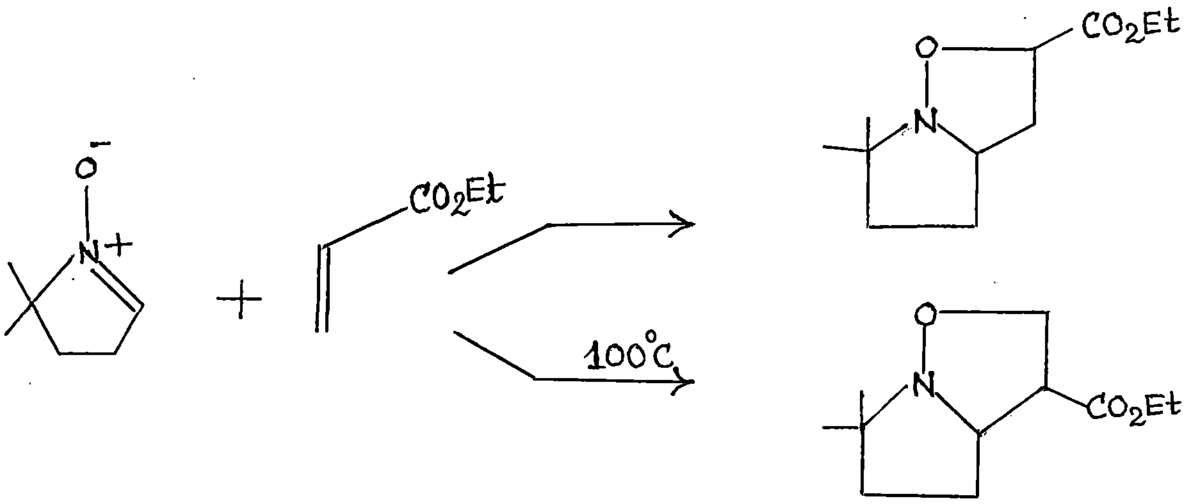
A very wild range of intermolecular 1,3 dipolar cycloadditions are known. Important cyclo additions are systematically reviewed here.

[a] 1. Addition to alkenes :

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



The direction of nitrone addition can be reversible and therefore subject to both thermodynamic and kinetic control (177). For instance, the addition of ethyl acrylate to 5,5 dimethyl - N - oxide at room temperature yields 100 % of one structural isomer and at 100^{0}c yields 98 % of the other.



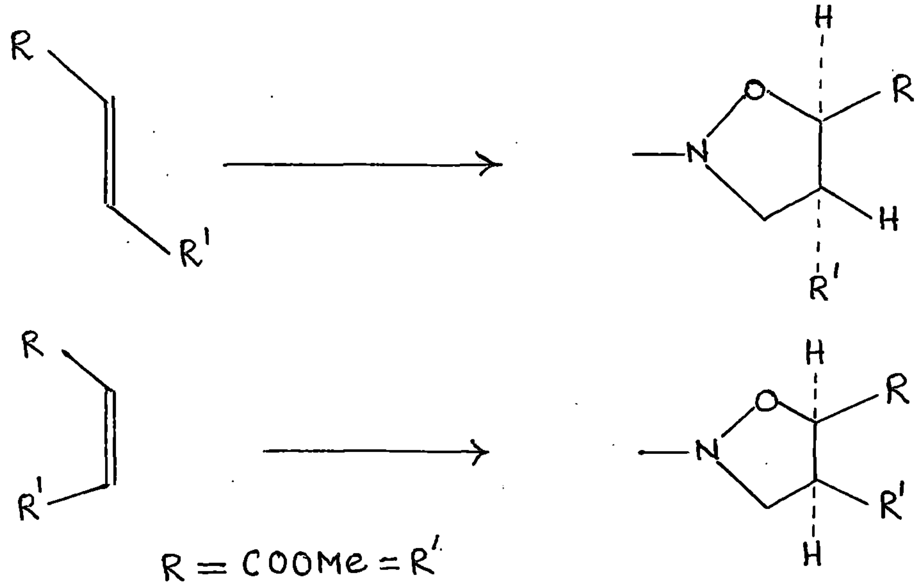
Regio selectivity applies to addition under conditions of kinetic control.Both steric and electronic factors are important [1(a)],(8) .In general the more hindered end of the electrophile adds to the oxygen atom of the nitrone to give 5-substituted adducts reversal of regio selection was also observed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

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

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

[a] 2. Stereochemistry of Addition :

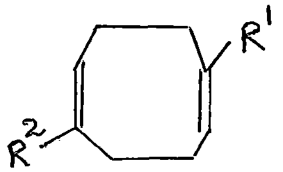
Studies of addition of dimethyl maleate and dimethyl fumarate to a variety of nitrones (181, 182) have established stereo specific cis addition by the production of mutually uncontaminated dia-stereomeric adducts.

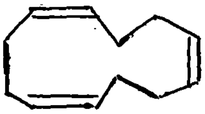
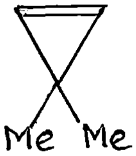
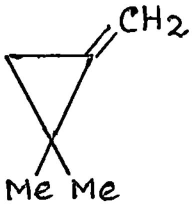
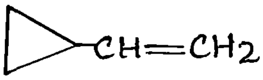
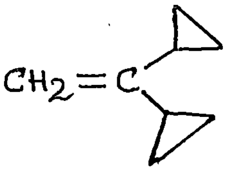
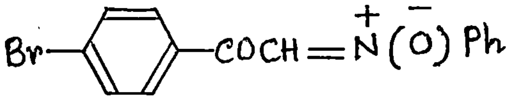
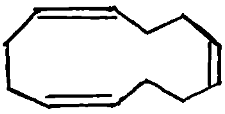
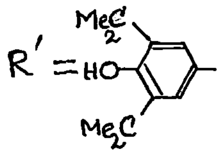
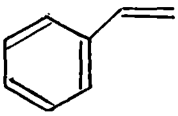


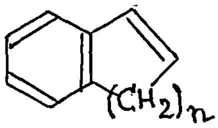
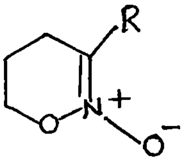
$R = COOMe = R'$

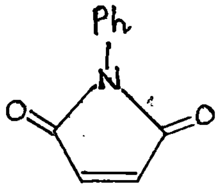
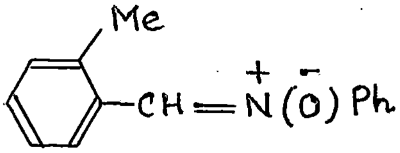
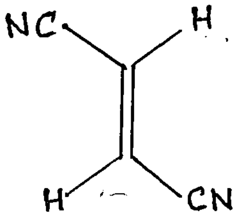
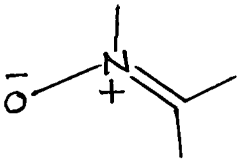
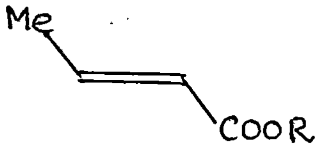
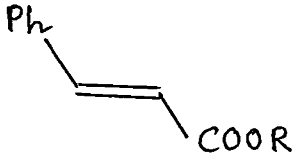
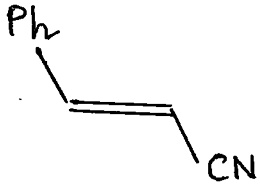
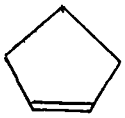
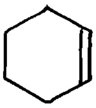
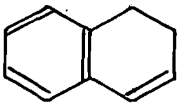
This general principal has been confirmed in many other cases of cycloadditions (177, 183, 182). Cis - trans - isomerism of dipolarophile substituent with respect to the nitrone substituents has been noted in many cases and is caused by the fact that the nitrone can approach the dipolarophile from two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

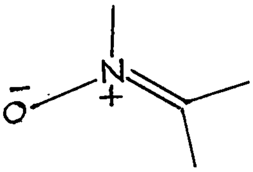
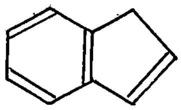
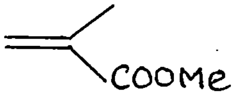
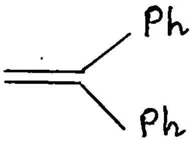
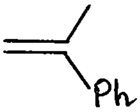
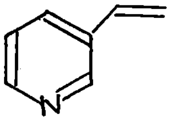
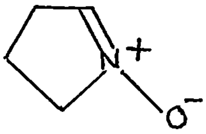
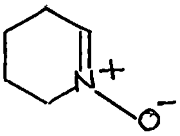
TABLE :1
Cycloadditions of Nitrone to olefins / Alkene

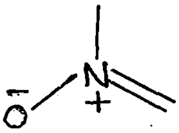
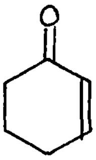
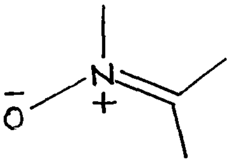
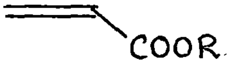
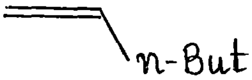
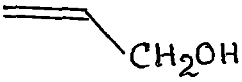
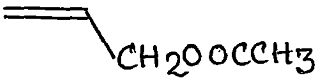
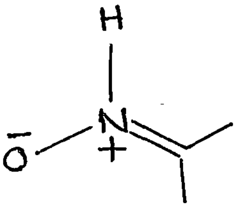
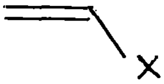
Nitrones	Olefin / alkene	References
$PhCH_2\overset{+}{N}(\overset{-}{O})=CHCO_2Et$	$Me_2CH=CH_2$	185
"	$CH_2=CHCO_2Me$	"
"	$MeCH=CHCO_2Me$	"
$PhNHCOCH=\overset{+}{N}(\overset{-}{O})Ph$	$RCH=CHR'$ $R=R'=CO_2Me; CO_2H$ $R=CHO; R'=Ph$ $R=H; R'=CHO$ $RR'=-CO-O-OC-$	186
" "	 $R^1,R^2=H;H: H,Me;$	187

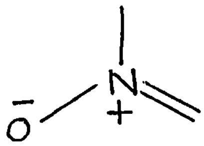
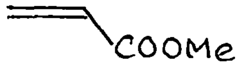
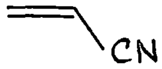
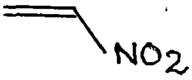
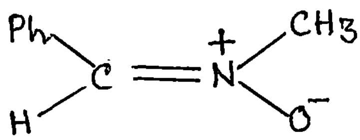
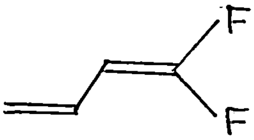
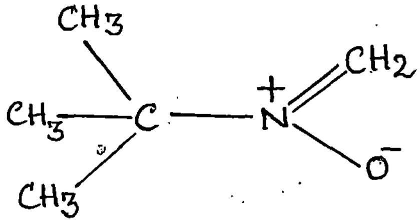
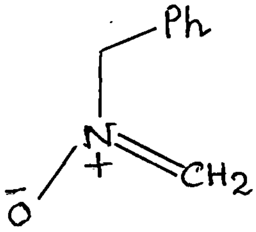
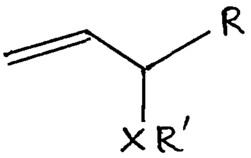
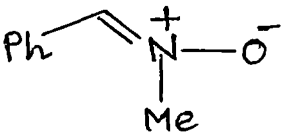
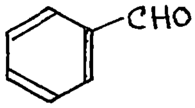
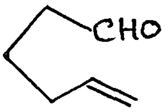
Nitrones	Olefin / alkene	References
$PhNHCOCH{=}\overset{+}{N}(\overset{-}{O})Ph$		187
"		188
"		188
"		"
"		"
3. 		187.
4. $R'{-}Z{-}CH{=}\overset{+}{N}(\overset{-}{O})R$ R = Ph ; R' =  Z = NHCO ; CO	$CH_2{=}CHCN$	189
" "		"

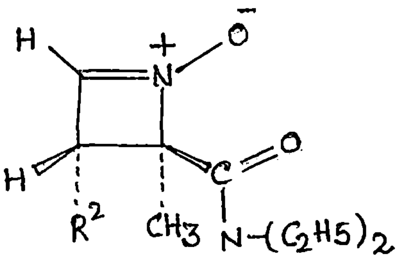
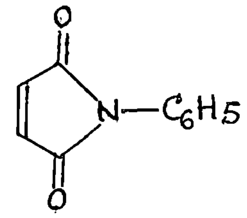
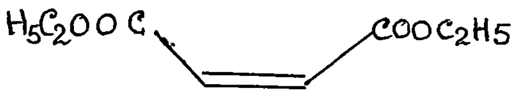
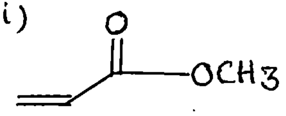
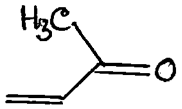
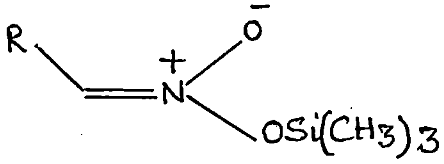
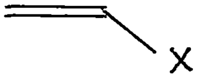
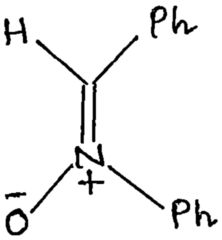
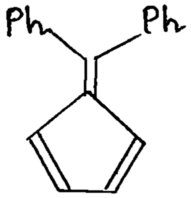
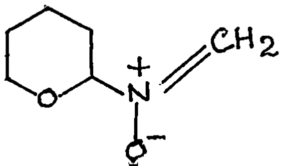
	Nitrones	**Olefin / alkene**	**References**
	$PhCH=\overset{+}{N}(\overset{-}{O})R$ (i) $R = Ph$; Me	(R)-4-$MeC_6H_4S(O)CH=CH_2$	190
	(ii) $R = Me$	 $n = 1, 2$	191
	$R\overset{+}{N}(\overset{-}{O})=CR^1R^2$ $R = Me, Bu, PhCH_2, Ph_2CH,$ 4-MeC_6H_4, $R' = CO_2$ (1R, 3R, 4S)- (–) menthyl	$Ph(R^3)C=CH_2$ $R^3 = H, Ph$	192
	$R\overset{+}{N}(\overset{-}{O})=CPh_2$ $R = Me, PhCH_2$	$CH_2=CHCO_2R'$ $R' =$ (1R, 3R, 4S)- (–) menthyl	"
	$(MeO_2C)_2C=\overset{+}{N}(O)Me$	$CH_2=CRR'$	56, 193
9.		$R'CH=CH_2$ $R' = Ph, COOMe, CN$	194
10.	$PhCOCH=\overset{+}{N}(\overset{-}{O})Ph$	$CH_2=CHPh(O)(OMe)_2$	1, 8

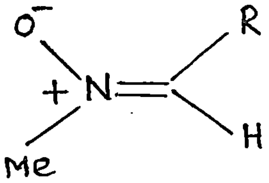
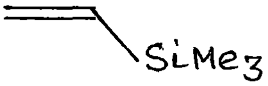
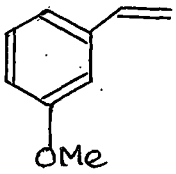
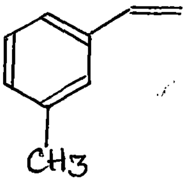
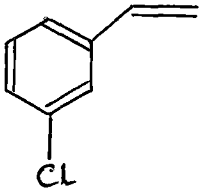
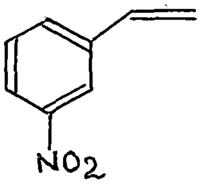
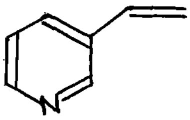
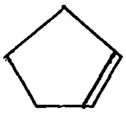
	Nitrones	Olefin / alkene	References
11.	$RCH=\overset{+}{N}(\overset{-}{O})\,Ph$ R = o- or m-tolyl		195
12.			195
13.			196–198 ; 177, 199.
14.	" "		177, 199 ; 182.
15.	" "		182
16.	" "		1
17.	" "		1
18.	" "		1

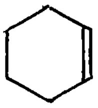
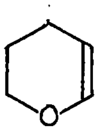
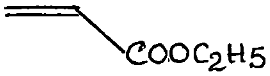
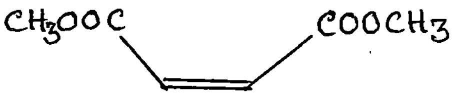
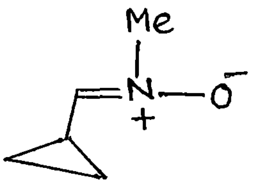
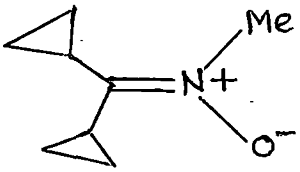
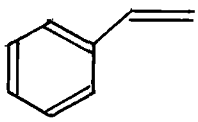
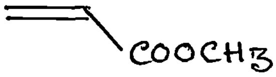
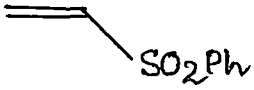
	Nitrones	**Olefin / alkene**	**References**
19.			200
20.	" "		177
21.	" "		200
22.	" "	(i)  (ii) 	200
23.	 ; 	 (i) $R = OEt$ (ii) $= CH_2OH$ (iii) $= CH_2OSi{}^tBu(CH_3)_2$ (iv) $=CH_2OAc$. (v) $= Ph$ (vi) $= CO_2CH_3$ (vii) $= CN$ (viii) $= CHO$	178

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

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

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

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

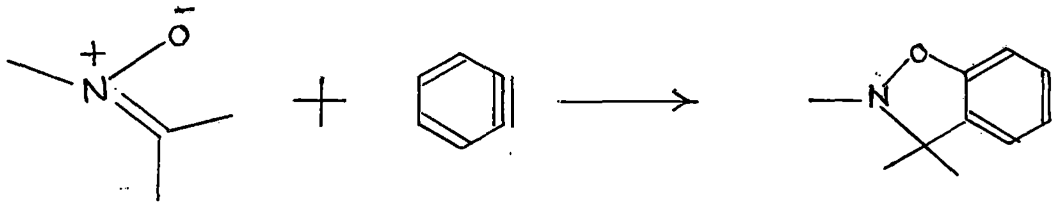
	Nitrones	Olefin / alkene	References
39.	α- Phenyl N- methyl nitrone		7
	"		"
	"	$CH_2=CH—CH_2OH$	"
	"		7, 8
	"		8
40.	 ; 	(i) 	25
		(ii) 	"
		(iii) 	"
		(iv) 	"
		(v) — ≡ —$COOCH_3$	"

[b] Addition to Alkynes :

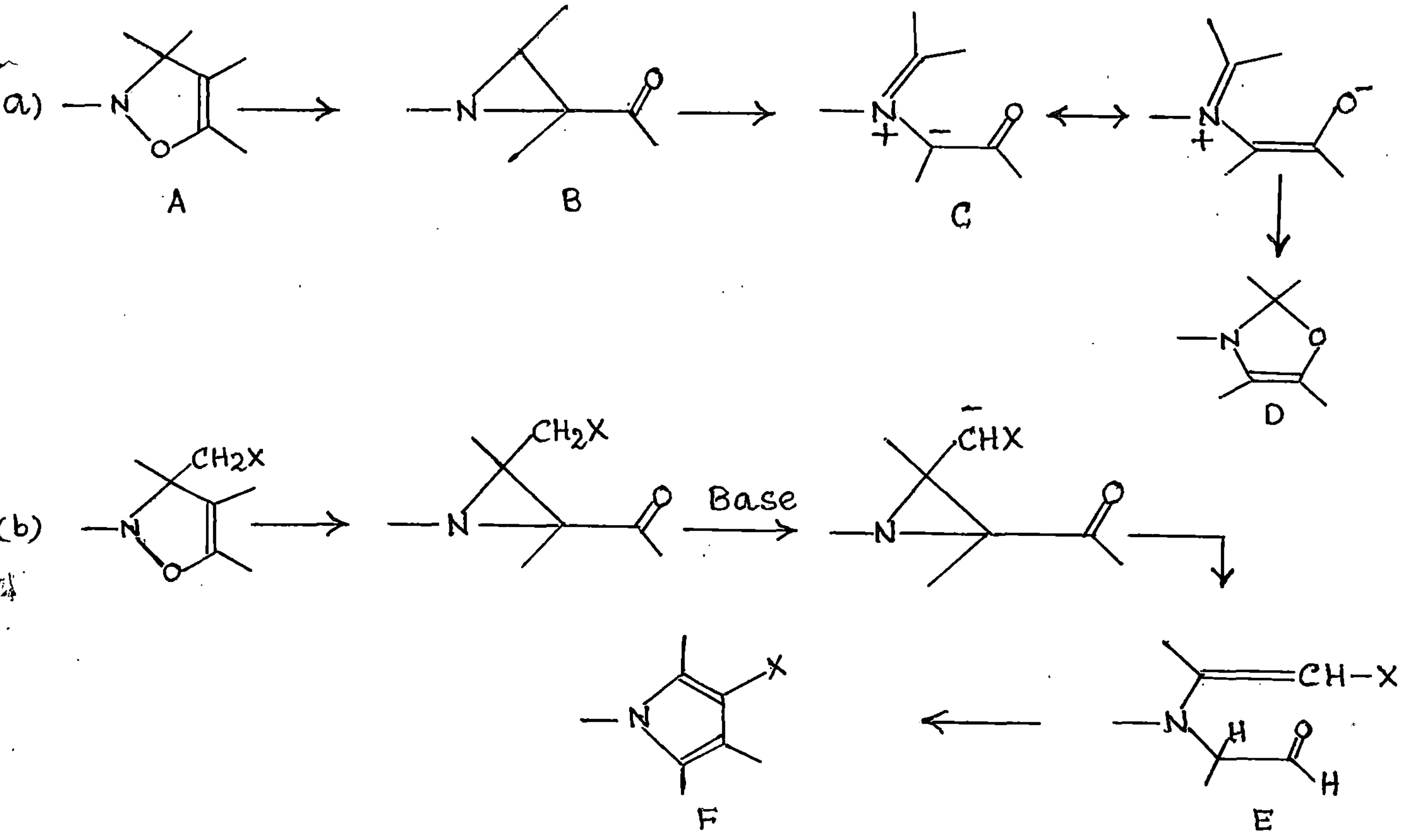
Acetylenic compounds reacts smoothly with nitrones to give 4 - isoxazolines. But very seldom the adduct has been isolated. In major cases some rearranged products are found. The instability of the isoxazoline system is most plausibly responsible for the rearrangement (207). Depending on the nature of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

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

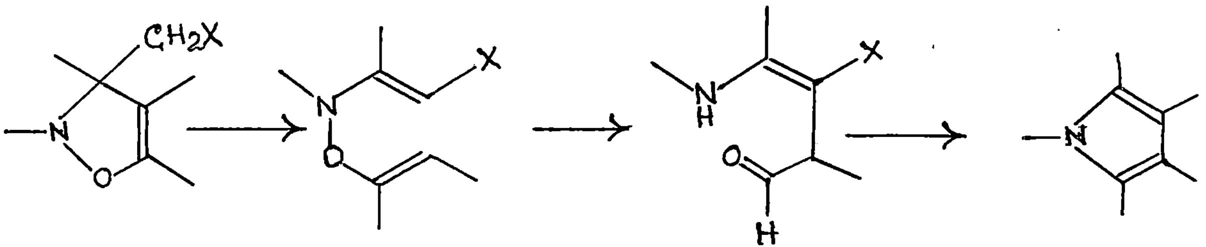
Benzynes form stable adducts with simple nitrones (208) but those derived from hetero aromatic N- oxides cannot be detected and are postulated to undergo rearrangement to phenolic derivatives (211,212).



Scheme - V

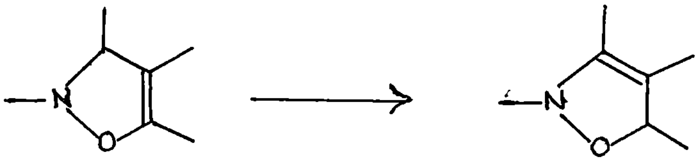


(c)



G F

(d)

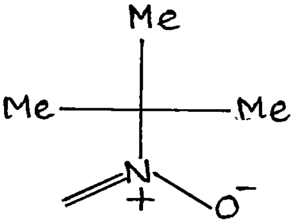
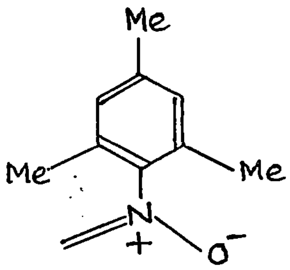


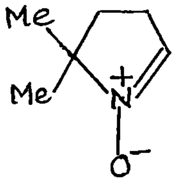
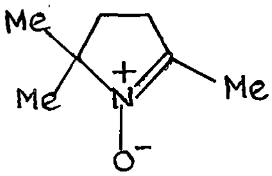
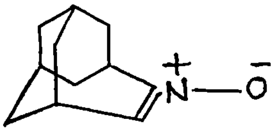
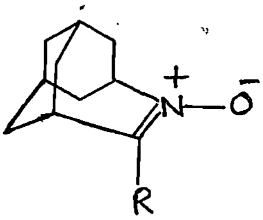
H

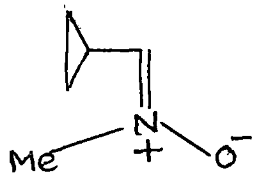
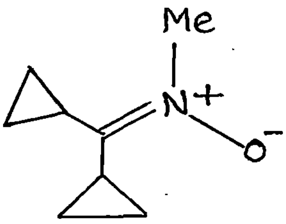
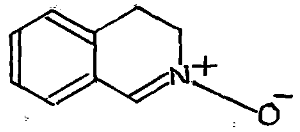
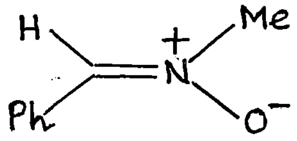
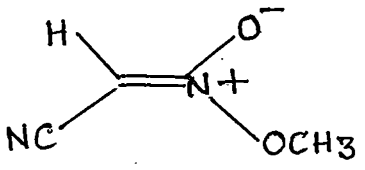
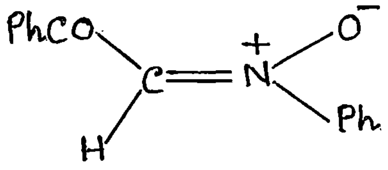
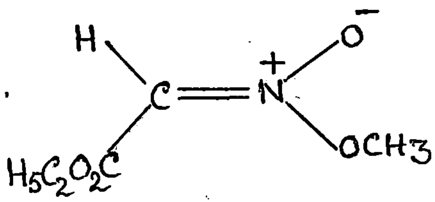
Allenes and Ketenes also give different products which arises presumably from rearrangements of the initial adducts (142, 213-215).

Table 2 :

Cycloaddition of Nitrones to alkynes :

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

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

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

(C) Addition to Carbon - Nitrogen Bonds :

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

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

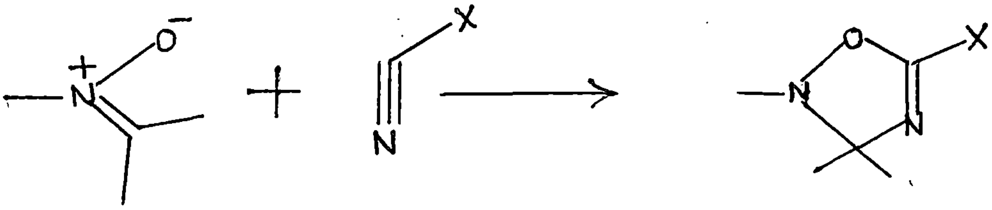
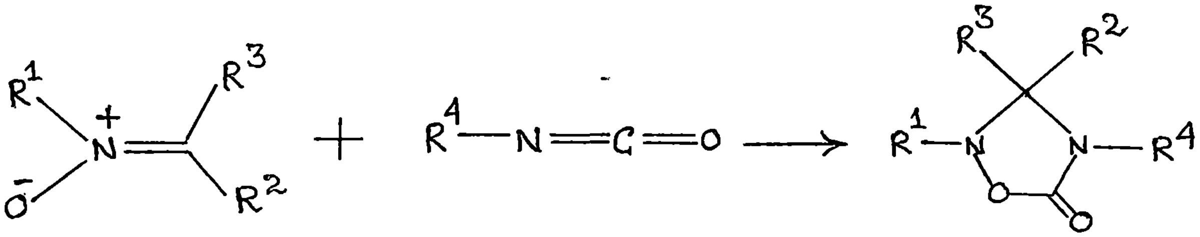
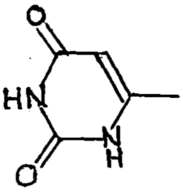
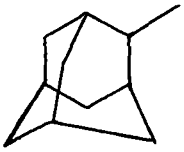


Table 3



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

	R^1	R^2	R^3	Ref.
(iv)	Ph	Ph–CH_2–CH–	H	230
(v)	Ph	Ph	Ph	43
(vi)	Ph		H	196
(vii)	Alkyl; Aryl	H	H	231, 232, 226, 233.
(viii)		Aryl	H	234
(ix)	"	Alkyl	H	235

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