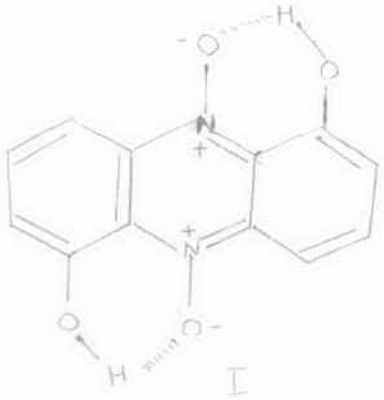
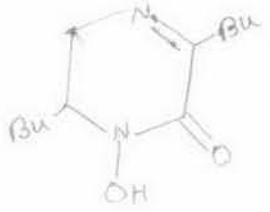
Though the first heteroaromatic N-Oxide were prepared a century ago, they were just chemical curiosities for the next Seventy years. In the early 1940 the Japanese began their extensive studies of the chemistry of N-Oxides but due to the intervention of the Second World War their work was not known until 1951. Since then the N-Oxides have been actively studied and their manifold reactions have already found extensive application in synthetic work; their reactivity pattern is of considerable theoretical interest. The discovery that the antibiotics iodinin[1] (I), aspergillic acid[2] (II), 1, 6, dihydroxy phenazine 5-oxide[3] (III), mixin which is the 6-methoxy derivative of Iodinin[4-5] (IV), hydroxy aspergillic acid (V), mutaaspergillic acid (VI), neo-aspergillic acid[6] (VII), Pulcherinic acid[7] (VIII), mycelliananide[8] (IX) and emiroycin[9] (X) has given further impetus to this study of the general chemistry of N-Oxides.

More recently Abramovitch and Singer[10] have discovered that Pyridine and Quinoline N-Oxides react with Phenyl Propiolonitrile to give largely 3-substituted pyridine and quinoline. This is a very valuable synthetic method for the preparation of substituted homo nicotinic acids which may have some therapeutic applications.

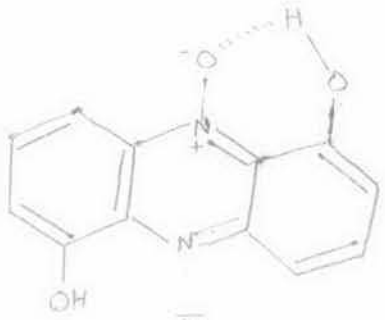
N-Oxides have been prepared by a number of methods, the most common are those involving the oxidation of the heterocycles by organic per acids.



I



II



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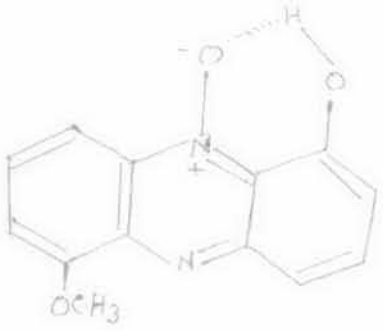
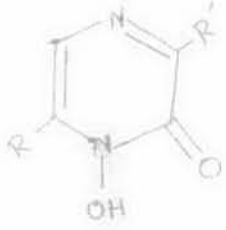


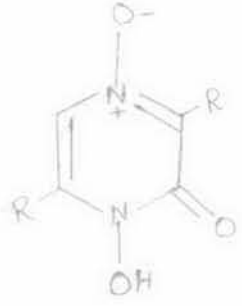
IV



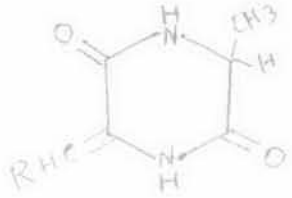
V R = C(OH)(CH$_3$)C$_2$H$_5$
R' = CH$_2$CH(CH$_3$)$_2$

VI R = C(OH)(CH$_3$)$_2$
R' = CH$_2$CH(CH$_3$)$_2$

VII R = R' = CH$_2$CH(CH$_3$)$_2$

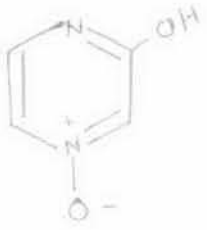


VIII



IX

R = Bu.

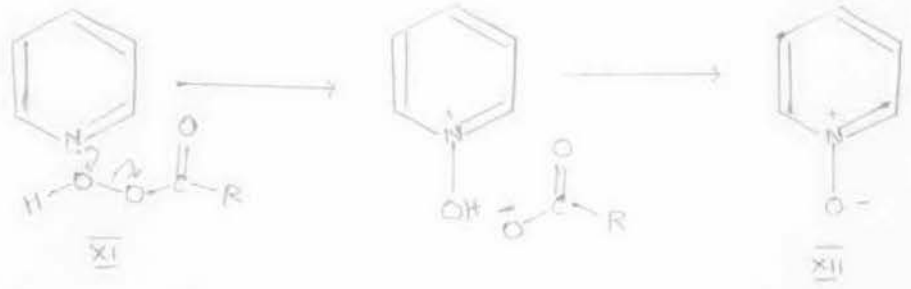


X

Although simple and efficient process in many instances, N-oxidation may suffer from the serious disadvantages of ambiguity in the position of oxidation, competitive of exclusive oxidation at

desired position, and occasionally even the loss of a substituent. Furthermore, direct oxidation is sensitive both to steric and to electronic factors, which often militate successfully against the reaction and unequivocal methods for the preparation number of heterocyclic N-oxides have been developed and an excellent review of the methods has been made by Taylor[11].

A Kinetic study[12] showed that the reaction of Pyridine with per benzoic acid in aqueous dioxan is second order and involves Pyridine as free base and the per acid as such. The rate falls off at low pH values due to the formation of per acid anion. Electron donating alkyl groups enhance the reaction rate constant measured under standard condition at 25° which correlate with pK_a values of Pyridine as bases. These findings are in accord with a mechanism of the type illustrated (XI → XII)



XI XII

However steric effects are also reflected in the lower than expected rate found for collidine[13].

Pyridine	K x 10^3 Sec^{-1} $mole^{-1}$/Litre	pK_a value
....	4.80	5.17
4-methyl	7.25	6.02
2,4,dimethyl	10.2	6.79
2,4,6, Collidine	10.2	6.50

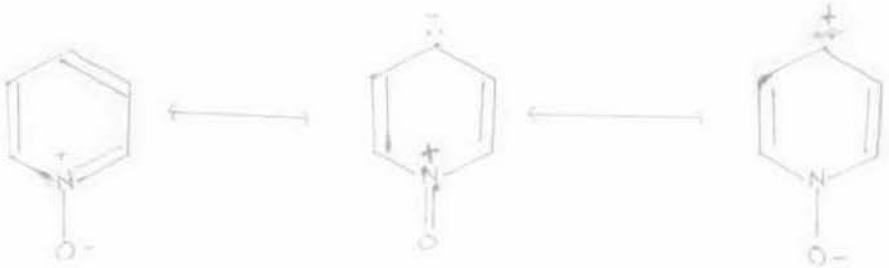
More recently the kinetics of perbenzoic acid N-oxidation have been extended to cover a wide variety of alkyl substituted Pyridines and also the monochloro Pyridines[14]. Linear relationships were found between the second order rate constants and the Hammet Sigma constants for the mono substituted compounds. Rho for the reaction has as expected a large negative value of - 2.35. For all the compounds studied a satisfactory linear relationship was found between the second order rate constants and the pK_a values, except for 2,6 disubstituted derivatives, where the steric hindrance obviously interferes with N-oxidation.

An analogous kinetics study has been concerned with the N-oxidation of Quinoline, isoquinoline and aza-phenanthrene. The N-oxidation reaction is less sensitive to steric effect than is the formation of Quaternary salts with methyl iodide[15]. Although no Kinetic work has been reported for the peracetic acid N-oxidation of Pyridines, rate study of oxidation of ring substituted aniline gave a Hammet Rho value of -1.86 indicating that the lone pair of electrons on nitrogen attack the outermost oxygen atom of per acetic acid. It was concluded that the mechanism of heteroaromatic bases in peracetic

acid is similar to that shown in the scheme (XI → XII).

Structure and Reactivity relation in aromatic N-oxides:

Fundamental to the chemistry of N-oxides is the fact that the dipolar N-oxide group is both an electron donar and electron acceptor by the resonance effect. Taking Pyridine N-oxide (XIII) as an example, this push pull character is expressed by the fact that canonical forms of type (XIV) and (XV) contribute to the resonance hybrid.



XIII XIV XV

This situation is in fundamental contrast to that appertaining to Pyridine (XVI) where significant resonance is limited to canonical forms (XVI ⟷ XVIa)

XVI XVIa

In its dual role as an electron donor or acceptor, the N-oxides group resembles the nitroso group[16]. Much evidence has been amassed from physical measurements regarding the electron donating and electron accepting properties of the N-oxide group in pyridine-1-oxide and these data are discussed by Katritzky and Lagowski[17].

1,3-dipolar cycloaddition is a well known principle in organic chemistry. Huisgen and co-workers have explored a number of these reactions[18]. Although, the 1,3, dipole formation is quite useful in predicting the results of a reaction, the evidence of the mechnaism of many of the reactions suggest that this cycloaddition proceeds via isopolar transition state.

1,3 dipoles can be broadly divided into three groups.

XVII

XVIII

XIX

Examples of each of the groups of 1,3-dipoles are given in tables 2,3 and 4.

Table 2

Type : $\overset{+}{a} = b - \overset{-}{c} \longleftrightarrow a \equiv \overset{+}{b} - \overset{-}{c}$

Atom system	1,3-Dipolar Form	Alternate Form	Name
CNC	$-\overset{+}{C} = N - \overset{-}{C}<$	$-C \equiv \overset{+}{N} - \overset{-}{C}<$	Nitrile ylide
CNN	$-\overset{+}{C} = N - \overset{-}{N}-$	$-C \equiv \overset{+}{N} - \overset{-}{N}-$	Nitrile imine
CNO	$-\overset{+}{C} = N - \overset{-}{O}$	$-C \equiv \overset{+}{N} - \overset{-}{O}$	Nitrile oxide
NNC	$\overset{+}{N} = N - \overset{-}{C}<$	$:N \equiv \overset{+}{N} - \overset{-}{C}<$	Diazoalkane
NNN	$\overset{+}{N} = N - \overset{-}{N}-$	$:N \equiv \overset{+}{N} - \overset{-}{N}-$	Azide
NNO	$\overset{+}{N} = N - \overset{-}{O}$	$N \equiv \overset{+}{N} - \overset{-}{O}$	Nitrous oxide

Table 3

Type : $\overset{+}{a} - b - \overset{-}{c} \longleftrightarrow a = \overset{+}{b} - \overset{-}{c}$

Atom system	1,3-Dipolar form	Alternate form	Name
CHC	$>\overset{+}{C} - \overset{\|}{N} - \overset{-}{C}<$	$>C = \overset{\|+}{N} - \overset{-}{C}<$	Azomethine ylide
CHN	$>\overset{+}{C} - \overset{\|}{N} - \overset{-}{N}-$	$>C = \overset{\|+}{N} - \overset{-}{N}-$	Azomethine imine

Contd.....

Table 5 (Contd.)

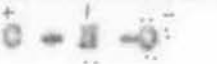
Atom system	1,3-Dipolar form	Alternate form	Name
CNO			Nitrone
NNC			Azoxy
ONO			Nitro
COC			Carbonyl ylide
CON			Carbonyl imine
COO			Carbonyl oxide
NON			Nitrosimine
NOO			Nitroso oxide
OOO			Ozone

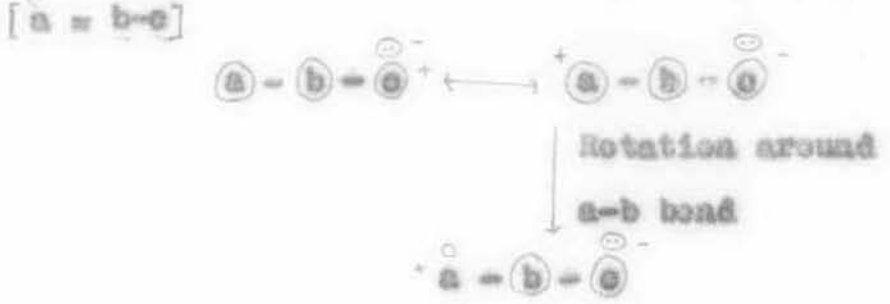
Table 4

Type : $\overset{+}{a} = b - \overset{-}{\underset{\cdot\cdot}{c}} \longleftrightarrow \overset{\cdot\cdot}{a} - b = c$

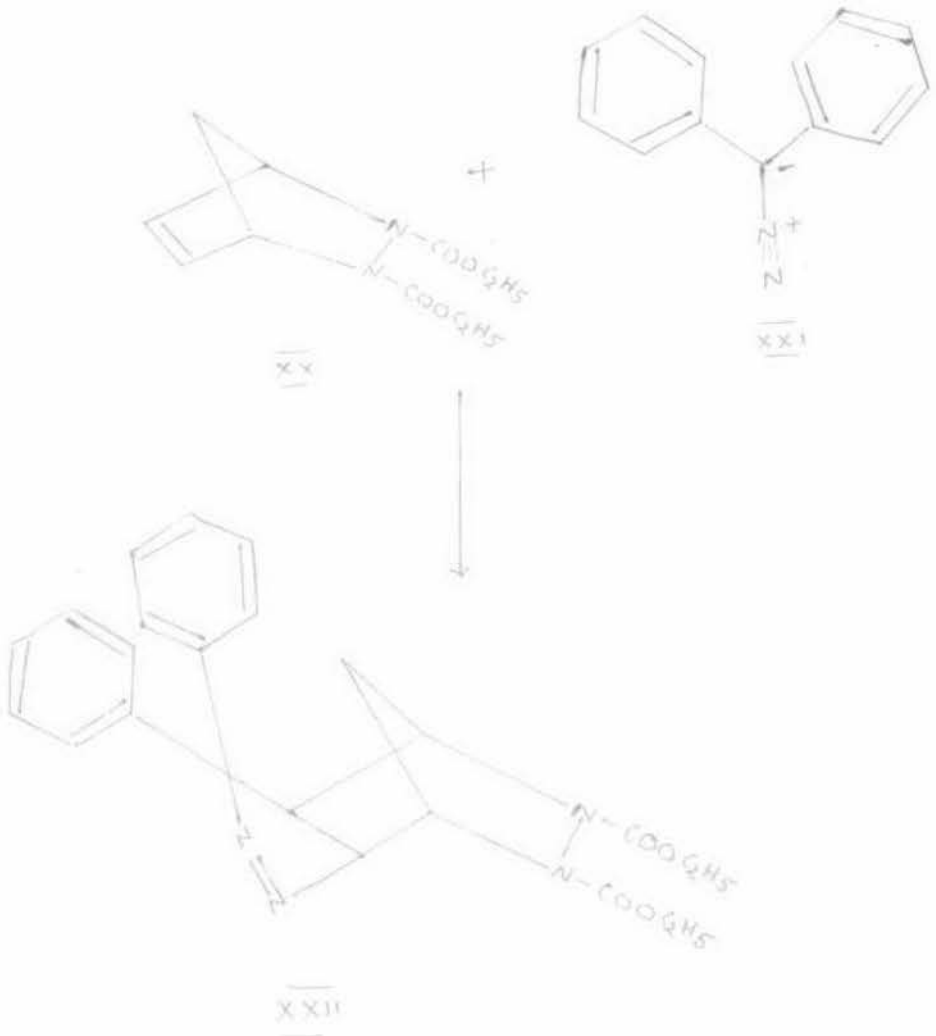
Atom system	1,3-Dipolar form	Alternate form	Name
CCC	$-\overset{+}{C} = C - \overset{-}{C}<$	$-\overset{\cdot\cdot}{C} - C = C<$	Vinylmethylene
CCN	$-\overset{+}{C} = C - \overset{-}{N}-$	$-\overset{\cdot\cdot}{C} - C = N-$	Iminomethylene
CCO	$-\overset{+}{C} = C - \overset{-}{\underset{\cdot\cdot}{O}}:$	$-\overset{\cdot\cdot}{C} - C = O$	Ketomethylene
NCC	$:\overset{+}{N} = C - \overset{-}{C}<$	$:\overset{\cdot\cdot}{N} - C = C<$	Vinylnitrene
NCN	$:N = C - \overset{-}{N}-$	$:\overset{\cdot\cdot}{N} - C = N -$	Iminonitrene
NCO	$:N = C - \overset{-}{\underset{\cdot\cdot}{O}}:$	$:\overset{\cdot\cdot}{N} - C = O$	Ketonitrene

Of these three groups of 1,3 dipoles, it is possible one group reacts with the development of considerable charge separation in the transition state. But unfortunately there is no information on the mechanism of reaction because all of the members of these group are unstable intermediates that are generated in the same medium in which they are consumed. For the other two groups there is little to suggest that the separation charge is augmented in the transition state. For example solvent effect is usually quite small. Therefore these reactions ar preferably labelled (2+3) cycloadditions and the general equation might be written

The last group (XIX) bears a some what dubious relationship to the other dipoles. It can be seen that it is necessary to rotate a p-orbital 90° in order to attain a true 1,3 dipole.



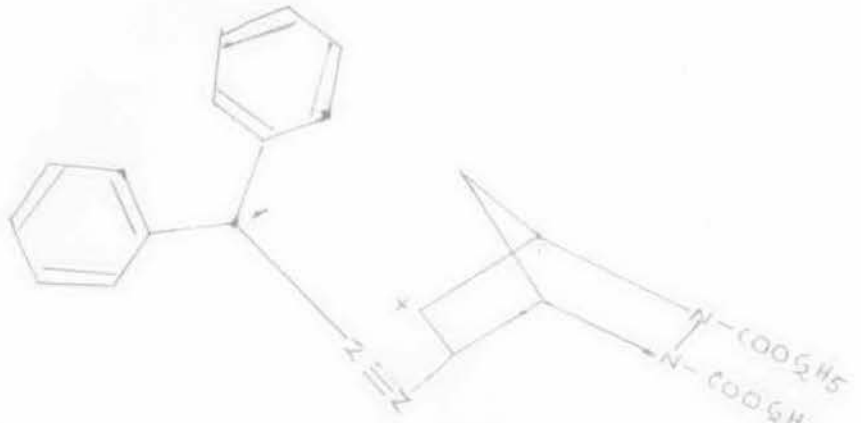
An important clue to the nature of (2+3) cycloaddition is found in the medium insensibility of the rate of the reaction of 1,3-dipole of the type XVII with a strained alkene. The reaction of diphenyl-diazomethane (XX) with 5,6 dicarbethoxy 5,6 diazobicyclo (2,2,1) heptene-2 (XXI) may be written.



XX XXI XXII

An intermediate with a structure of an ion pair (XXIII) would have arisen from a transition state with much more separation of charge than the initial state, and a solvent effect would have been observed for the rate constant. (The dipole moment of diazomethane is about 1,5D, the local dipole for the strained double bond is small

and the dipole moment for the ion pair is 11 -12D).



XXIII

The data in Table 5[19] indicate that the reaction (XX+XXI → XXII) is insensative to solvent over a polarity range. A rate factor of 10^4 might have been expected if the transition state were (XXIII).

Table 5

Reaction of XXX with XX

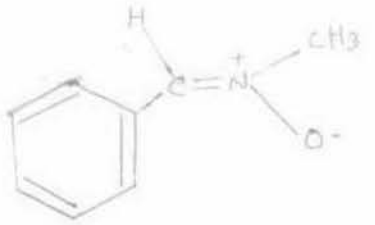
Solvent	Z Value[20]	10^4k, l.mole^{-1}sec^{-1}
Benzene	54	2.43
Dioxane	-	2.93
Ethyl acetate	-	2.27

(Contd..)

Table 5 (Contd.)

Solvent	Z Value[20]	10^4k, $l.mol^{-1}sec^{-1}$
1,2 dimethoxy ether	-	3.64
Acetone	65.7	2.38
Acetonitrile	71.3	2.61
Dimethyl formamide	68.5	2.30

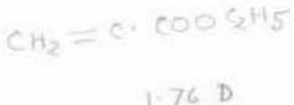
The reaction of the nitrone (XXIV) with ethyl acrylate (XXV) is also insensitive to change in solvent polarity. Thus the reaction is faster in ethanol than in toluene by a factor of 5[12]. The rate increase which might have been anticipated for this solvent change (ΔZ about 26) for the formation of an ion pair intermediate would be about 10^6 and one must conclude that the transition state to product has about same charge separation as the initial state.



3.5 D

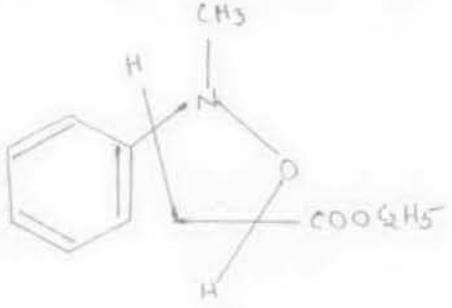
XXIV

+



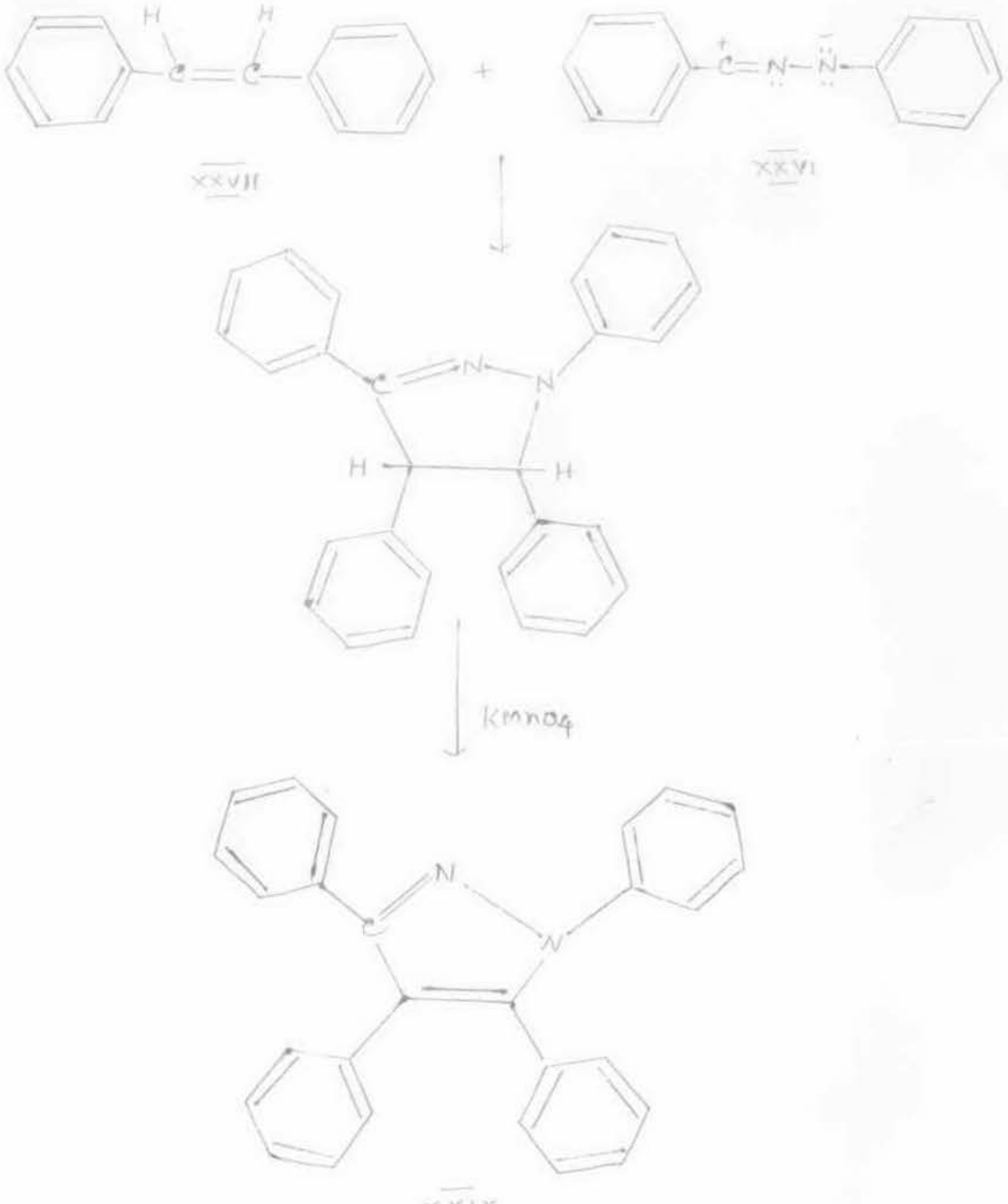
1.76 D

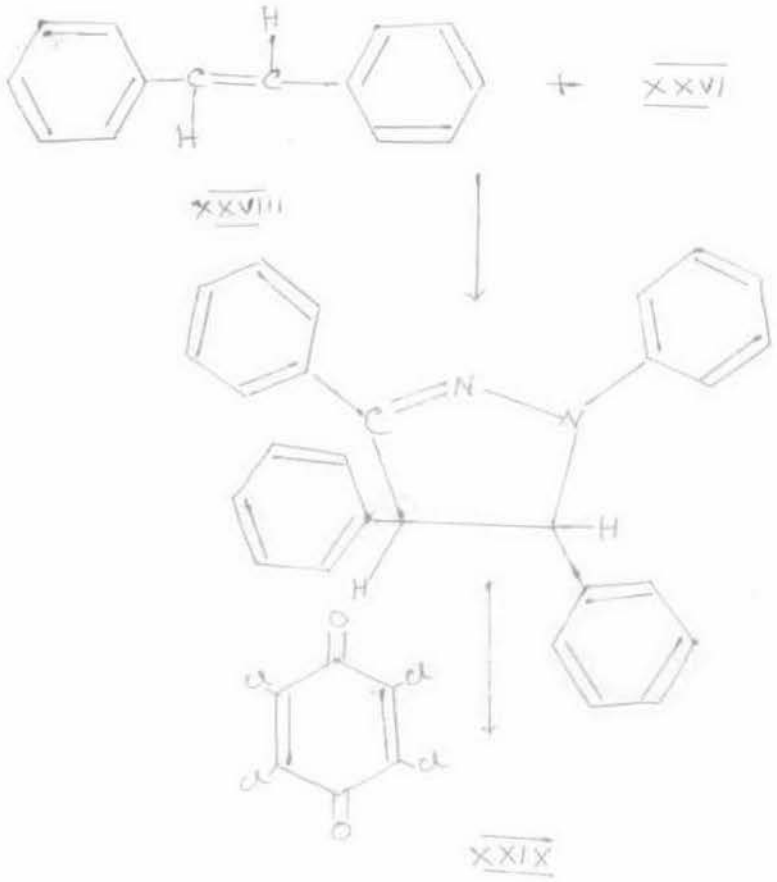
XXV



2.42 D

A second significant aspect of the (2+3) cycloaddition is the stereospecificity of the reaction as shown by formation of different isomer from diphenyl nitrile imine (XXVI) and isomeric stilbene as (XXVII) and trans (XXVIII). The isomeric products may be oxidised to the same tetraphenyl pyrazole (XXIX)





XXVIII + XXVI → XXIX

The stereospecificity of the (2+3) cycloaddition distinguishes it from the (2+2) cycloaddition which involves an intermediate diradical. The absence of solvent effect excludes ion pair intermediate which might preserve the stereo-chemical relationship of the reactant through the product-forming step. According to the available information it looks that concerted formation of the product occurs.

Molecular orbital co-relation digrams constructed for each of the two groups of 1,3-dipoles in reaction with an alkene show that the orbitals of the products are co-related with those of the reactants. The identical symmetries of initial and final orbitals are easily seen in this diagram (Fig. i , Fig. ii).

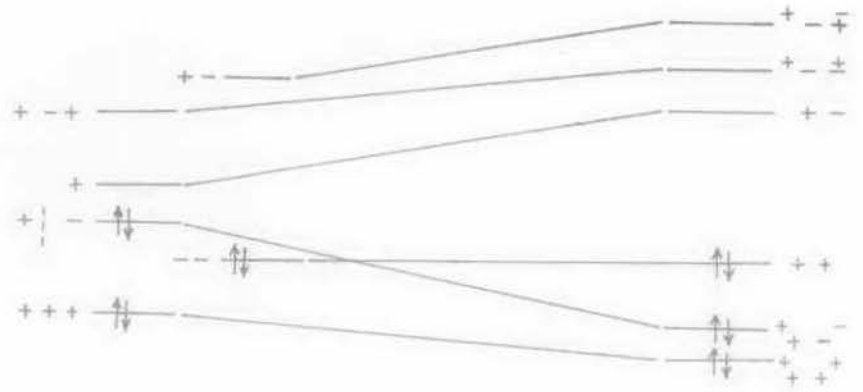


Fig.(1) A molecular orbital correlation diagram for a (2 3) cycloaddition, applicable to the cases $\dot{a}-\ddot{b}-\ddot{c}^{-} \longleftrightarrow a=\dot{b}-\ddot{c}^{-}$ listed in Table 2, The signs refer to that portion of a wavefunction on the side of the molecular plane toward the second reactant. Thus, a bonding π -orbital would be shown as + +.

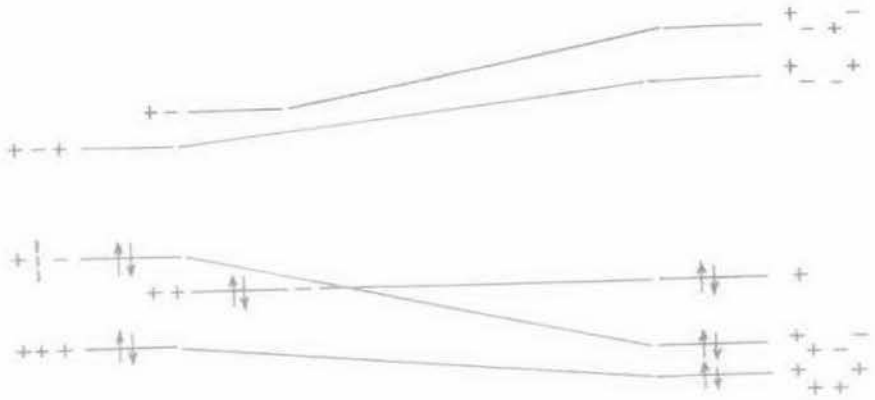


Fig.(11) A molecular orbital correlation diagram for a (2 + 3) cycloaddition, applicable to the cases $\dot{a}-\ddot{b}-\ddot{c} \longleftrightarrow a=b^{+}-c^{-}$ listed in Table 5. The signs refer to the wave function on one side of the molecule. A bonding π -orbital would be shown as $+\,+$, and a nonbonding p-orbital as $+\;\;-$.

A molecular orbital formulation of the course of the reaction in somewhat different terms has been advanced by Huisgen[21].

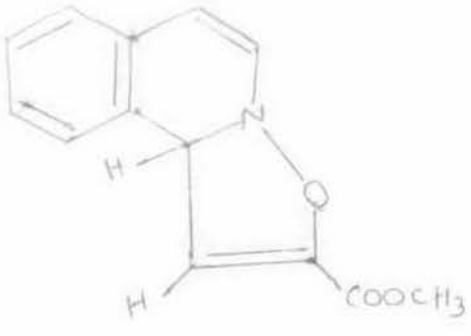
The general view presented by Huisgen is probably valid but there is much scope for detailed mechanistic investigation in the field as exemplified by the cautionary remarks in the literature[22].

New heterocyclic N-Oxides have been treated with activated acetylenes, examples are the 1-methyl[23], 1,2 dimethyl benzimidazole 3-oxide[24], certain 1-Pyrolin-1-oxides[25], isoquinoline 2-oxide[26], its 3,4 dihydro derivatives[27], 6-methyl phenanthrene 5-oxide[28], Pyridine-1-oxide and quinoline-1-oxide[29].

Huisgen et al treated isoquinoline 2-oxide (XXX) with methyl Propiolate (XXXI) in Dimethyl formamide at room temperature and obtained in 70% yield a 1:1 adduct to which they assigned the structure (XXXII)

XXX

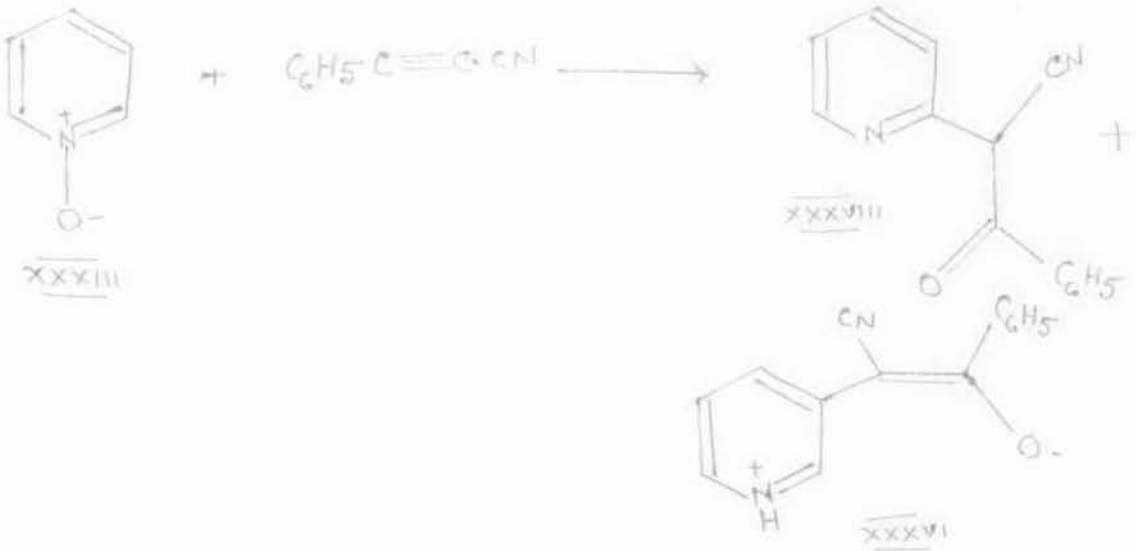
XXXI



XXXII

On the other hand treatment of Pyridine-1-oxide (XXXIII) and Quinoline-1-oxide (XXXIV) with Phenyl propiolic nitrile (XXXV) in boiling ethylene chloride gave re-arranged 3-alkylated derivatives (XXXVI) and (XXXVII) as the main product together with minor amounts of the expected 2-alkylation (XXXVIII) and (XXXIX) products[29].

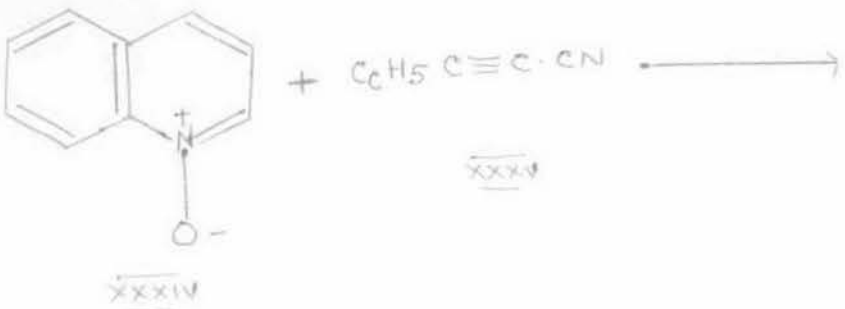
Huisgen, Seidl and Wolff have reported the formation of the ylid (XLI) from Isoquinoline 2-oxide and ethyl phenyl propiolate (XL) but they have not reported the formation of any c-alkylation product nor have they proposed any mechanism for the formation of (XLI).



XXXIII

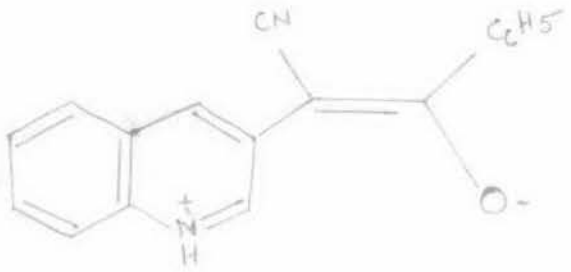
XXXVIII

XXXVI

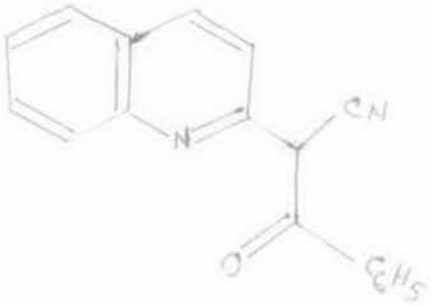


XXXIV

XXXV

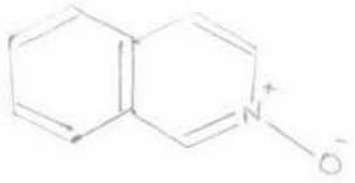


XXXVII



XXXIX

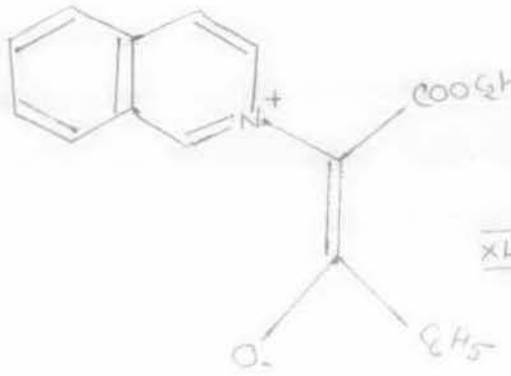
Abramovitch has proposed the following mechanism to account for 3-substituted products and the ylid. Assuming the first step of the reaction to be the addition of the N-oxide to the triple bond to give (XLII), the intermediate (XLIIa) can either undergo intermolecular cyclisation and ring opening to give 2-substituted products (alternatively these could arise by 1,3 dipolar addition) or heterolysis to give the highly electrophillic benzoylcyano (or carboethoxy) carbene (XLIII) which on recombination could give the ylid. Two routes can then be envisioned to 3-substituted products (i) cyclisation of the ylid followed by a 1,5 Sigmatropic shift and (ii) addition of the carbene to C_2-C_3 of the heterocyclic ring of Pyridine and quinoline followed by ring opening similar to the formation of 3-benzen sulphonyl aminopyridine from benzene sulphonylnitrine[30].



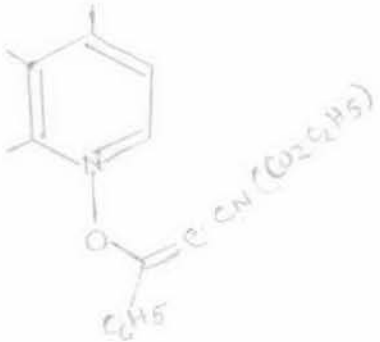
XXX

+ $C_6H_5C{\equiv}C\cdot COOC_2H_5$ ⟶

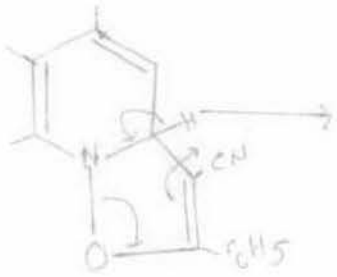
XL



XLI



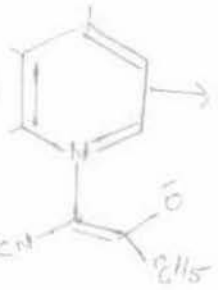
XLII

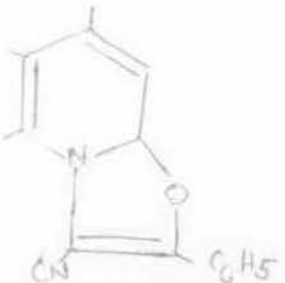


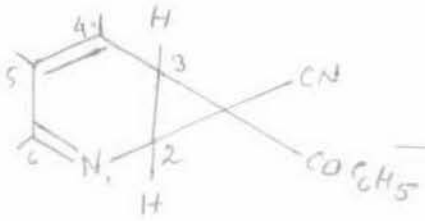
XLII a ⟶ XXXVIII or XXXIX

+ $C_6H_5\ddot{C}\cdot\ddot{C}CN(CO_2C_2H_5)$ ⟶

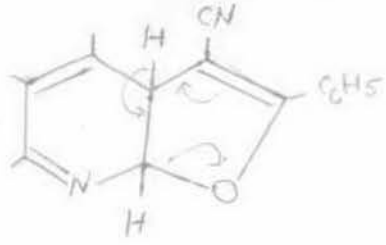
XLIII



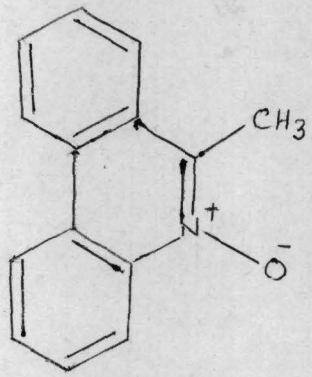




XXXVI or XXXVII



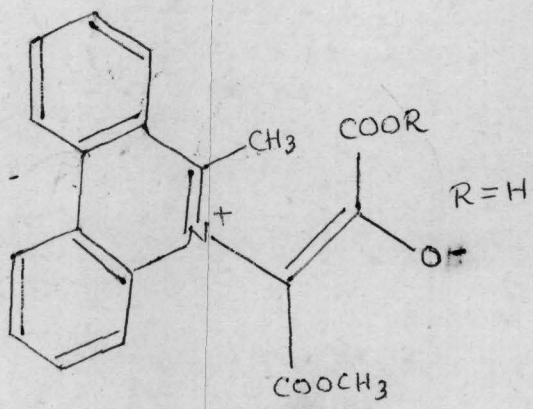
Acheson et al[31] have studied the reaction of Phenanthridine 5-oxides with dimethyl acetylene dicarboxylate and other acetylic esters. They found that if a 6-alkyl group is present, the initially formed phenanthridinium-5-vinyl oxide readily cyclises to methoxy carbonyl pyrrolo (1,2-f) phenathridine. Typically 6-methyl phenanthridine-5-oxide (XLIV) with dimethyl acetylene dicarboxylate (XLVI) in benzene or methanol gave a 1:1 adduct with ultraviolet spectrum similar to that of the hydroxide (XLVIa)[31].



XLIV

$CH_3OOC \cdot C \equiv C \cdot COOCH_3$

XLVI

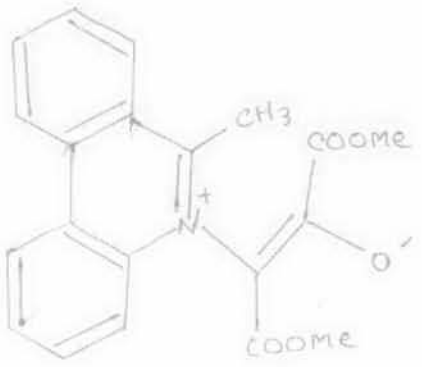


XLVIa

Its infrared spectrum showed two ester carbonyl absorptions, and a strong band at 6.45 μ often associated with the carbonyl oxygen stretching with enolate anion[24,26].

The nuclear magnetic resonance spectrum showed three proton singlets at τ 6.00, τ 6.39 and τ 6.72 and two broad multiplets (eight aromatic protons) the low field portion of which is probably due to the 1,4 and 10 protons.

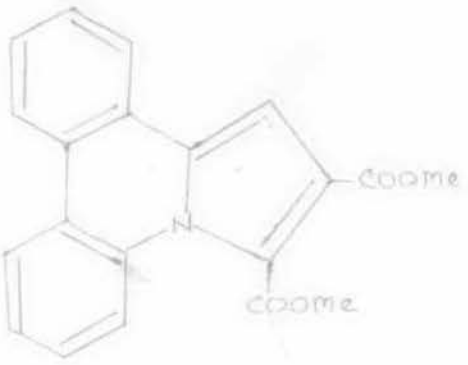
The 6-methyl phenanthridinium structure (XLVIb) (R = Me) best accommodates the observed values and other properties. Analogous



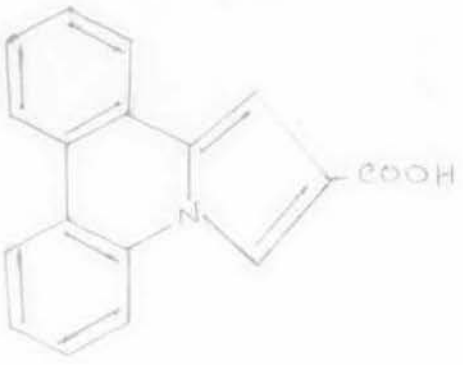
XLVIc

compounds were prepared by the authors from phenanthridine 5-oxide and 6-methyl derivative. Vacuum sublimation of the Vinyl oxide (XLVIb) gave the Pyrrolo phenanthridine (XLVII).

Cyclisation of the vinyl oxide must proceed by proton transfer from the 6-methyl group to the alpha-carbon or the oxygen atom of the N-substituent - followed by ring formation. All the peaks in the mass spectrum of Pyrrolo Phenanthridine were present in that of vinyl-oxide (XLVIb). Acidic or basic hydrolysis of the vinyl oxide caused the expected cyclisation with the loss of the hindered carboxy group and formation of the pyrrolo (1,2 f) Phenanthridine 2-carboxylic acid (XLVIII), which could also be obtained on basic hydrolysis of the diester (XLVII)



XLVII



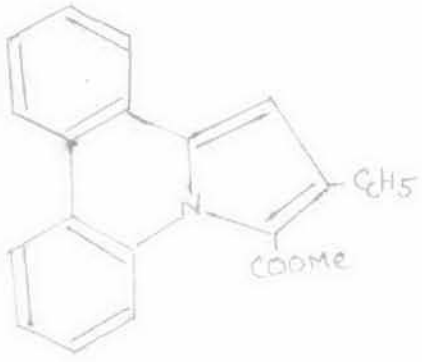
XLVIII

6-methyl phenanthridine 5-oxide did not combine with methyl phenyl propiolate (XLIX)

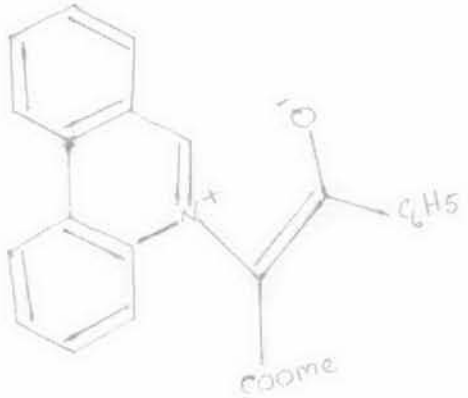
$C_6H_5C\equiv C\cdot COOMe$

XLIX

under conditions successful for the more reactive dimethyl acetyline dicarboxylate. However at 100° in dimethyl formamide methyl 2-phenyl pyrrolo (1,2 f) Phenanthridine 3-carboxylate (LI) was formed presumably through a vinyl oxide intermediate (L).



LI

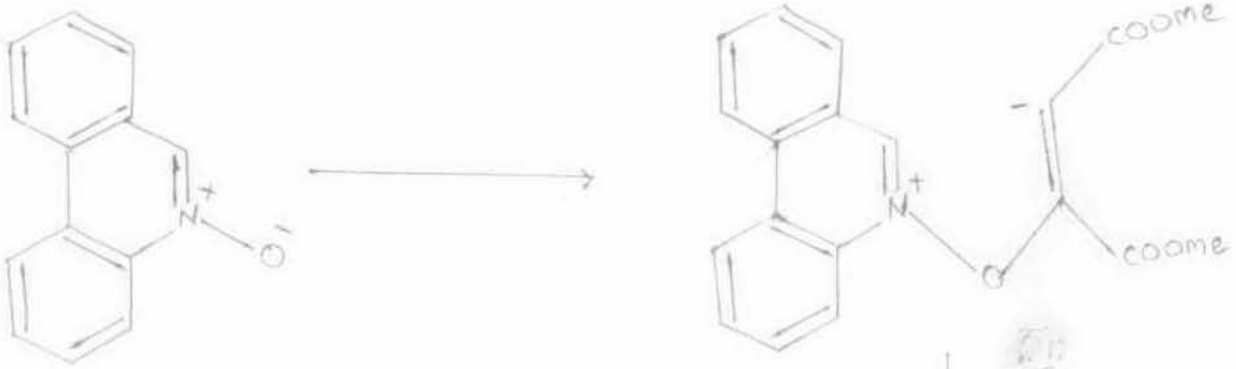


L

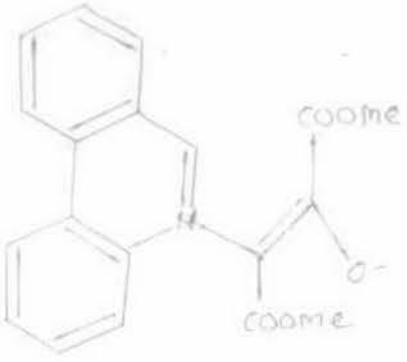
Phenanthridine 5-oxide on the other hand gave 1:1 adduct with methyl propiolate and methyl phenyl propiolate, their U.V., I.R. and N.M.R spectra were similar to the other oxide.

Acheson has proposed a mechanism for the formation of the vinyl oxide from the corresponding N-oxide. The intermediate (LII) could give the vinyl oxide (LIII) by a 1,2, shift of C3-carbon atom from position 3a to position 12 and cleavage of N-O bond, nucleophillic attack at position 3 by the nitrogen atom would give the aziridine (LIV) which could cleave to the oxide (LIII). Examples of the opening of an aziridine ring between the carbon atom are known[32].

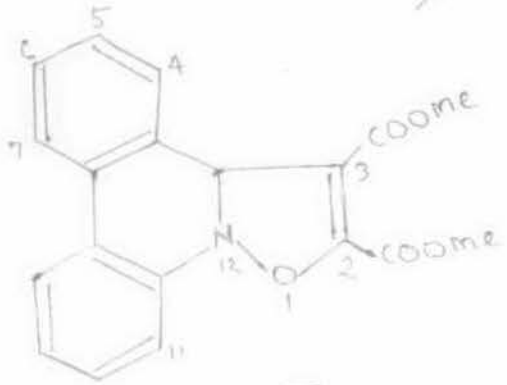
A fourth scheme could involve oxygenation of the phenanthridine 5-oxide by the acetylene to give the phenanthridine and the appropriate oxirene which should be stable enough to act as an intermediate[33], followed by opening of the three membered ring on nucleophillic attack by the heterocyclic N-atom. The possibility of the phenanthridine 5-oxide photocyclising to an oxarirene prior to combination with acetylene[34], was considered unlikely because of the high yield and the non isolation of phenanthridine in appropriate cases, but this possibility was not rigorously excluded.



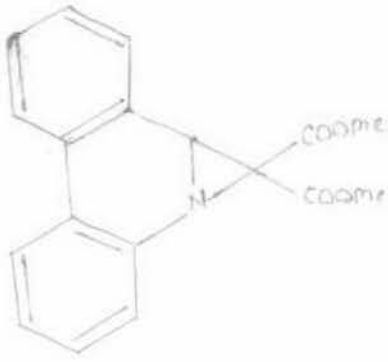
LII



LIII



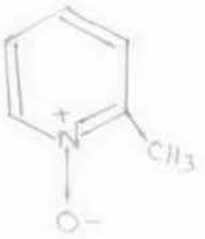
LII



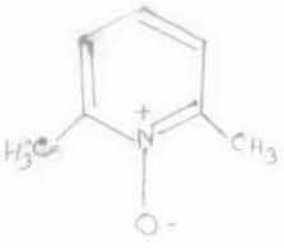
LIV

A chemically well documented fact is that the methyl protons of picoline, Lutidine, Collidine, Quinaldine, as also their N-oxides are sufficiently acidic to take part in a wide variety of reactions. Assuming that the reaction of aromatic N-oxides proceeds through a two step cycleaddition as has been proposed by Huisgen via the intermediate Zwitterion, we were tempted to speculate a series of transformations involving a 2-methyl proton as shown in the chart-(i).

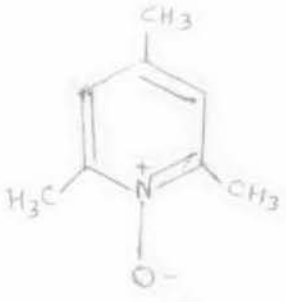
For preliminary studies we chose the N-oxides of 2-picoline (LV), 2,6 Lutidine (LVI) and 2,4,6 Collidine (LVII) and methyl phenyl propiolate (LVIII) as the acetylenic compound.



LV



LVI



LVII

$C_6H_5C\equiv C\cdot COOCH_3$

LVIII

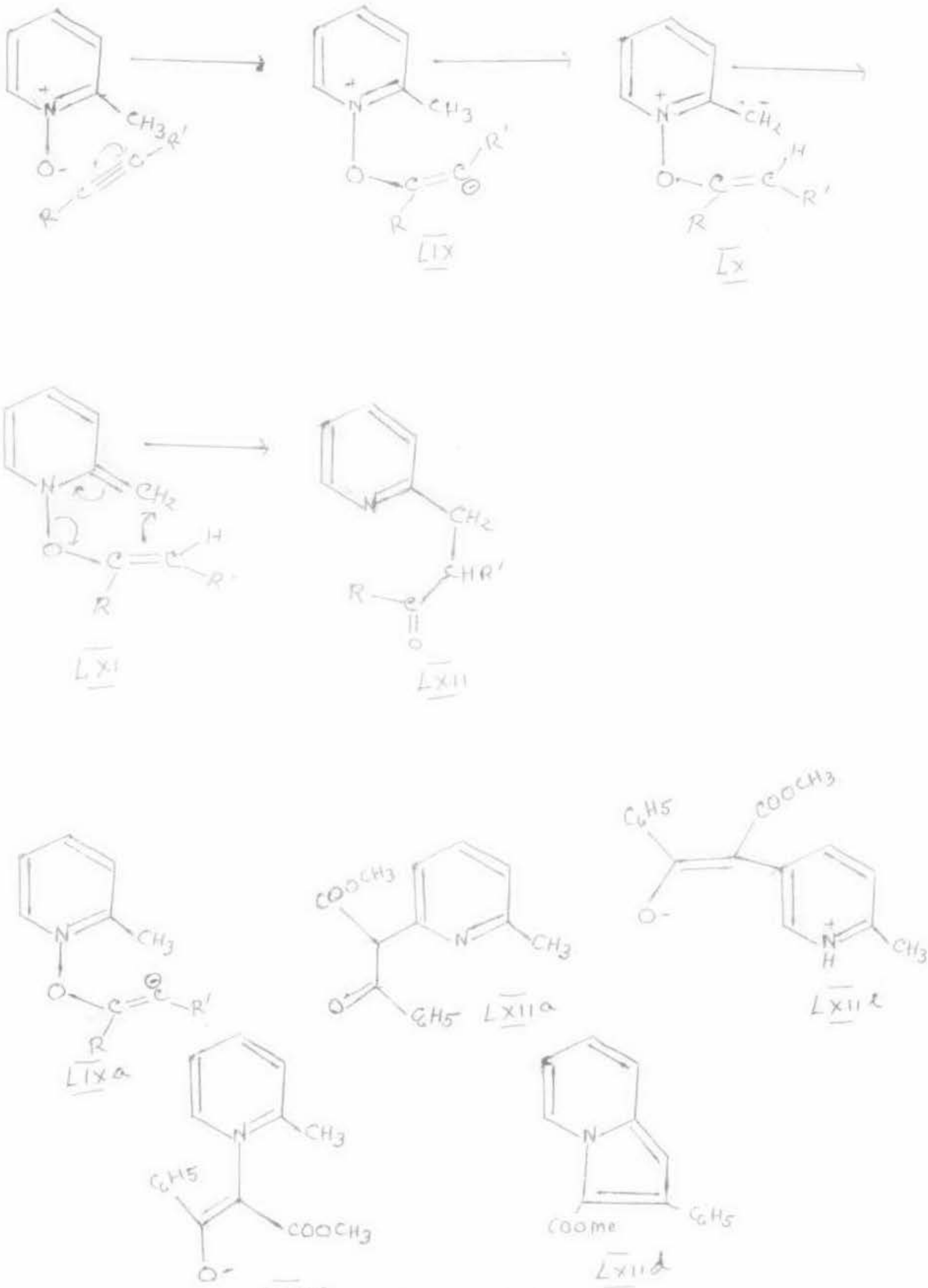

CH3
R'
R
CH3
R'
R
LIX
CH2
H
R'
R
LX
CH2
H
R'
R
LXI
CH2
CHR'
R
LXII
CH3
R'
R
LIXa
COOCH3
CH3
C6H5
LXIIa
C6H5
COOCH3
CH3
LXIIb
CH3
C6H5
COOCH3
LXIIc
COOMe
C6H5
LXIId

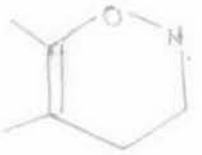
Chart (i)

The reason for the choice of this particular acetylene was the previously established fact that it reacts with aromatic N-oxides comparatively slowly in contrast with acetylene dicarboxylate or propiolate. We had in mind that a slow reaction would certainly give us a chance of experimental control over the kinetic course of the reactions under study.

The inversion of the Carbanion (LIX ⟶ LIXa) is an essential prerequisite for the proton abstraction and cycloaddition. Abstraction of the methyl proton gives the (LX).

From a chemical stand point the fact that N-O bond is sufficiently weak (average bond energy value in this case only 48 K cal/mole[35]. This is due to conjugative distabilisation[36] between adjacent lone pair which constitute a two centre four electron π-system)in systems like (LXIII) and (LXIIIa) has been utilised by

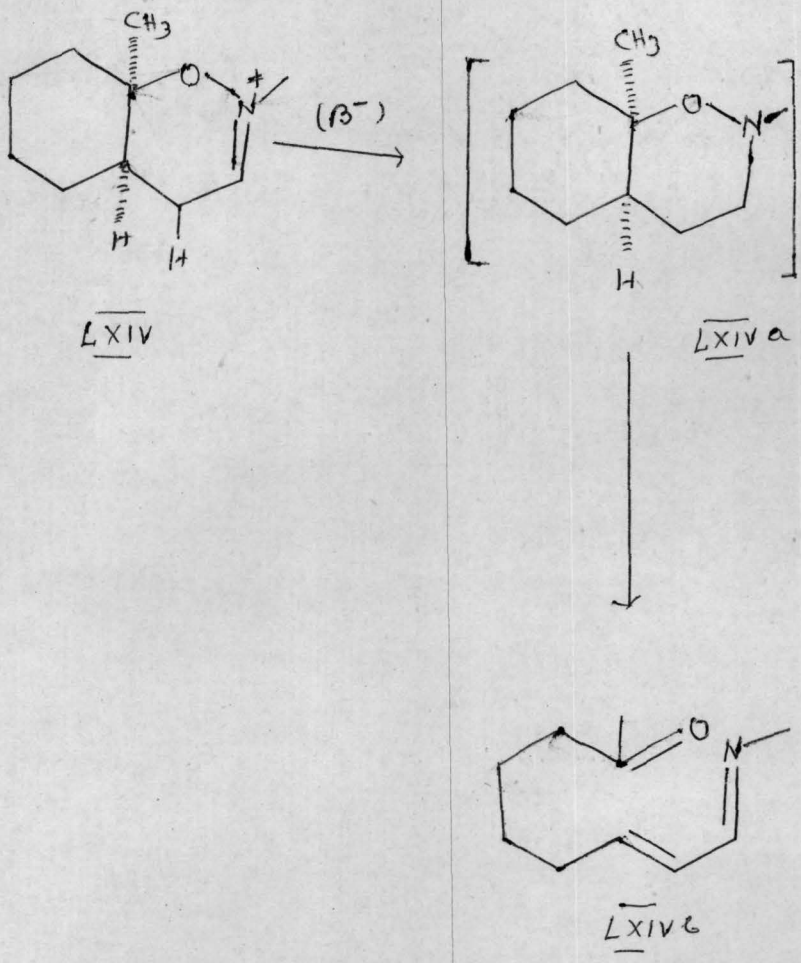
LXIII



LXIIIa

Eschenmoser et al[37] in a series of synthetic reactions,for example enamine derivative (LXIV) generated by deprotonation of immonium tetraphenyl borate (LXIVa) undergoes smooth thermal reversion to

furnish the imine (LXIVb) at 0°-40°C in a few hours. This fact also been demonstrated in aromatic N-oxide chemistry by Schiess et al[38].



LXIV

LXIVa

LXIVb

These authors have shown that the Grignard adduct of Pyridine N-oxide with phenyl magnesium bromide, contrary to the earlier assumptions[39] in favour of structure (LXIV), exists mainly in the open valence tautomeric form (LXIVb) in which repulsion between non bonded pairs of electrons on adjacent heteroatoms has been greatly minimised. We therefore presumed that if the intermediate (LXI) is formed it would smoothly undergo oxa-aza-claisen rearrangement to give (LXII). On the other hand cycloaddition followed by rearrangement of the cyclo adduct could give rise to Abramovitch, Huisgen or Acheson products (LXIIa), (LXIIb), (LXIIc) and (LXIId).

2-Picoline-1-oxide (LV) was prepared from redistilled picoline following the method described in literature[40] (b.p 123°-24°/15 mm). Methyl phenyl propiolate (LVIII) was prepared according to the method described in literature[41]. Ethyl cinnamate (LXV) was brominated to give the dibromo compound (LXVI) (M.P 66°-71°). Dehydrobromination with alcoholic potassium hydroxide followed by acidification gave phenyl propiolic acid (LXVII) (M.P 75°). Esterification of phenyl propiolic acid with diazomethane gave methyl phenyl propiolate (LVIII) (b.p. 133°-35°/16 mm)[42].

LXV

LXVI

LXVII

Methyl phenyl propiolate and 2-picoline-1-oxide were mixed in 1:1 molar ratio in dimethyl formamide and kept at 80° for 60 hours, a single product in approximately 10% yield was obtained. Utmost caution was taken to run the experiment under strictly anhydrous conditions and under nitrogen atmosphere. It was observed that there was a considerable drop in yield when the experiment was run without this precaution. The reaction was studied in other solvents under a wide range of time and temperature. It was observed that the yield was maximum in toluene and xylene.

The results are tabulated below:

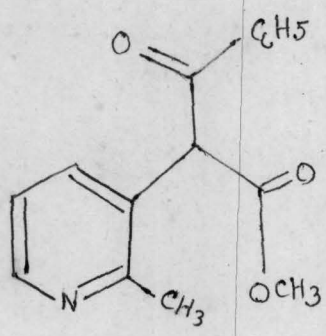
Table 6

Reaction between 2-picoline-1-oxide with methyl phenyl propiolate.

Molar ratio	Solvent	Temperature	Time	Yield
1:1	Dimethyl formamide	80°C	60 hrs.	10%
1:1	Diglyme	80°C	60 hrs.	10%
1:1	Benzene	Reflux	60 hrs	17%
1:1	Toluene	Reflux	13 hrs	27%
1:1	Xylene	Reflux	1 hr. 45 min.	26%
2:1	Dimethyl formamide	80°C	60 hrs.	20%
2:1	Diglyme	80°C	60 hrs.	20%
2:1	Benzene	Reflux	60 hrs.	30%
2:1	Toluene	Reflux	13 hrs.	44%
2:1	Xylene	Reflux	1 hr. 45 min.	50%

The experimental procedures have been described in detail in the experimental Section.

The product (LXVIII) crystallised from a mixture of petroleum ether (60°-80°) and benzene as yellow crystals m.p. 93°-94°C. The I.R. spectrum (Fig. 1) of the product showed bands at 1745 cm^{-1} (-C-O CH_3) and at 1680 cm^{-1} (-C - C_6H_5). The N.M.R. spectrum (Fig. 2) showed bands at δ 2.54 (singlet, 3H), δ 3.70 (singlet, 3H) δ 5.45 (singlet, 1H) and a complex multiplet at δ 6.8 -8.35 (8H). The band at 2.54 is due to the methyl group attached to the



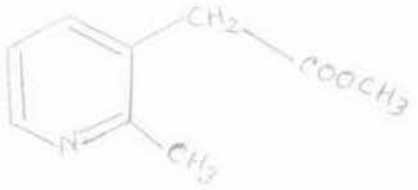
LXVIII

Pyridine nucleus, at δ 3.70 is due to the methoxy group of ester (-C-OCH_3). The band at δ 5.45 disappears on exchange with D_2O, hence this proton must be very labile and is possibly the proton of -CH(COC_6H_5)($COOCH_3$) group. The multiplet at δ 6.8 - 8.35 arises from the eight aromatic protons (three from pyridine and five from benzene nuclei). These spectral data are in good accord with structure assigned to the product.

The product (LXVIII) was extremely labile and slowly hydrolysed in air to furnish two compounds as is evidenced primarily from TLC studies.

In order to characterise the hydrolysis products and to study the mechanism an efficient chromatographic hydrolysis procedure has been developed. A benzene solution of the compound was adsorbed on a deactivated alumina column and after 50 hrs, eluted with benzene.

The eluant after removal of the solvent and distillation under reduced pressure gave two compounds. The major product (LXIX) b.p 122°-25° (Bath)/1 mm, showed I.R. (Fig. 3) 1740 cm^{-1} (Ester carbonyl group). The band at 1680 cm^{-1} of the original compound (LXVIII) disappeared, indicating that a portion containing the



LXIX

conjugated carbonyl group (-C(=O)-Ph-) was lost from the parent molecule in forming this compound (LXIX). The N.M.R spectrum (Fig. 4) showed bands at δ 2.47 (singlet, 3H), δ 3.47 (singlet, 2H), δ 3.61 (singlet, 3H), δ 6.98 (doublet J = 8Hz, 1H), δ 8.27 (doublet J = 2Hz,

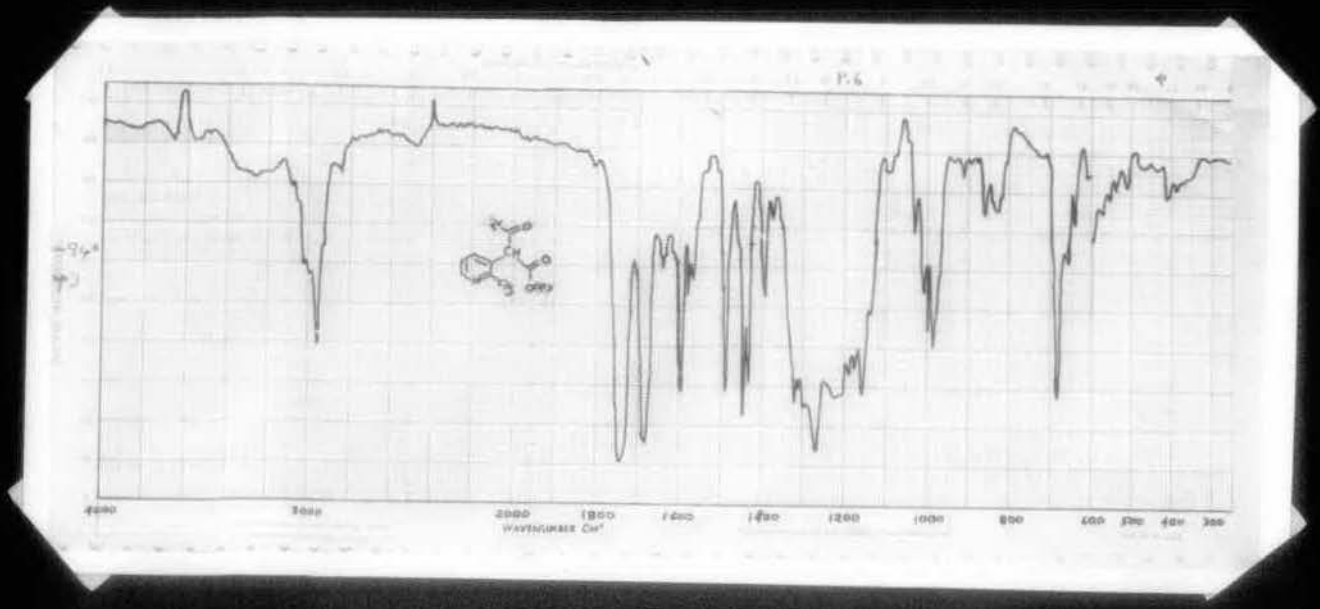


Fig. 1 IR spectrum of (XVIII)

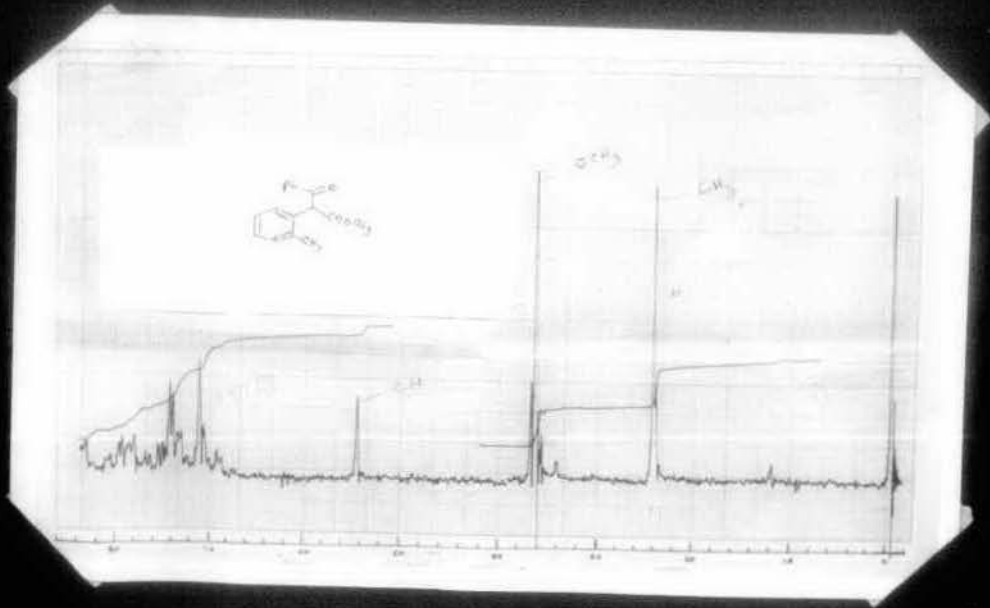


Fig. 2 NMR spectrum (LXVIII)

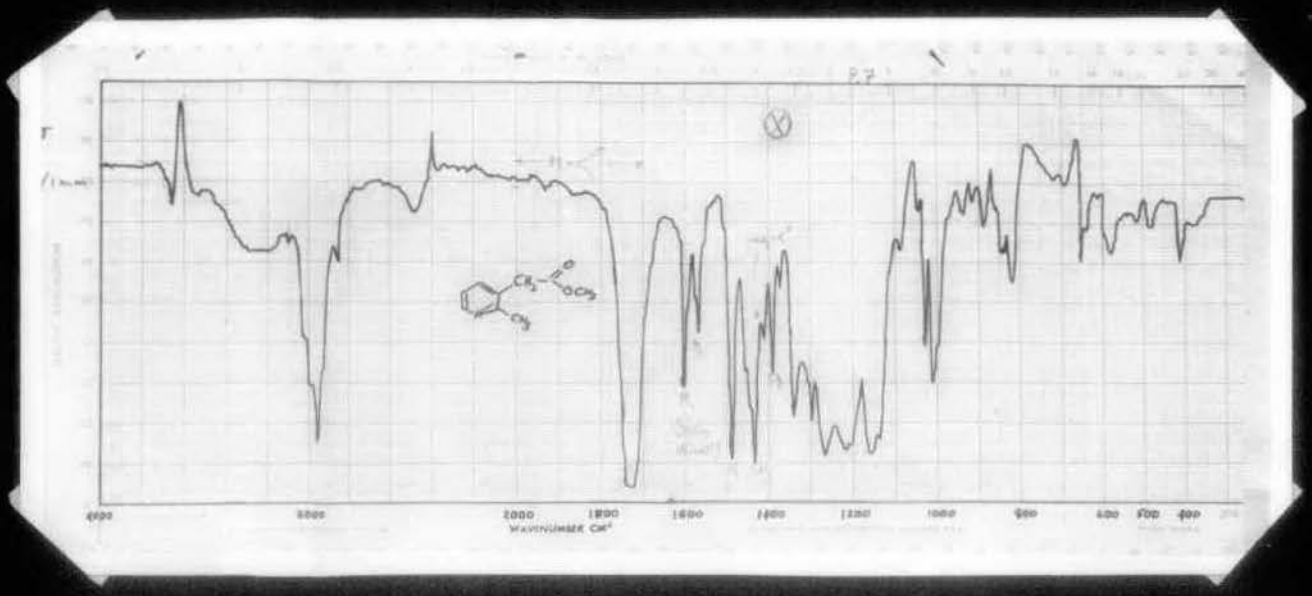


Fig. 3 IR spectrum of (LXIX)

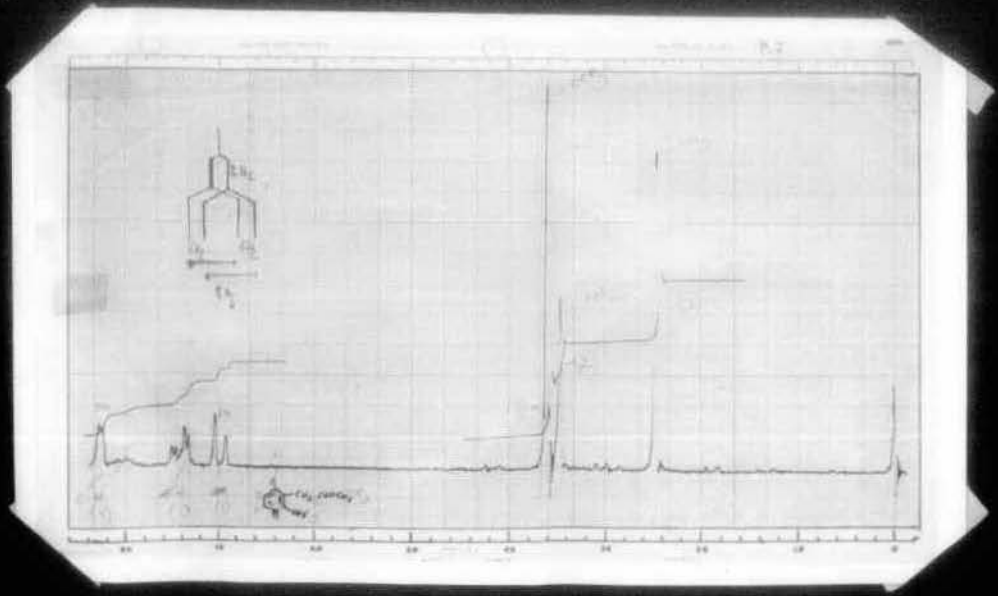
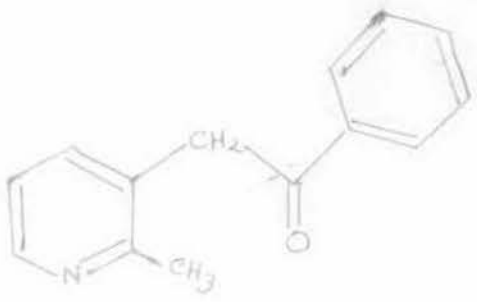


Fig. 4 NMR spectrum of (LXIX)

1H) and δ 7.43 (quartet J =8Hz,2Hz, 1H). The band at δ 2.47 is due to the methyl group attached to the pyridine nucleus, at δ 3.47 is due to the $-CH_2$ and δ 3.61 for $-OCH_3$ of the ester group. The last three bands were ascribed to the pyridine protons at C_4, C_6 and C_5 respectively.

Apart from the major product, trace amount of a second product (LXX) was isolated from the benzene eluate, b.p 176° (bath)/ 1 mm, shows I.R (Fig. 5) 1680 cm^{-1} (carbonyl group conjugated with the benzene ring). Like compound LXIX the band at 1745 cm^{-1} of the original compound is absent in (LXX). Hence this compound must arise



LXX

from (LXVIII) by the loss of ester group.

The mass spectrum (Fig. 6) of the above hydrolysis products Chart ii) was measured and it has been observed that it contained all the peaks characteristic of (LXIX) and a trace amount of (LXX), having the molecular ion peak M^+ 165. It will be observed from chart ii that in addition to the abundant peak at m/e 106 i.e. $[M^+ - 59$ i.e. $M^+ - CH_3 - O - C \overset{+}{=} O]$, there is an intense peak at m/e 59 i.e $[M^+ - 106$

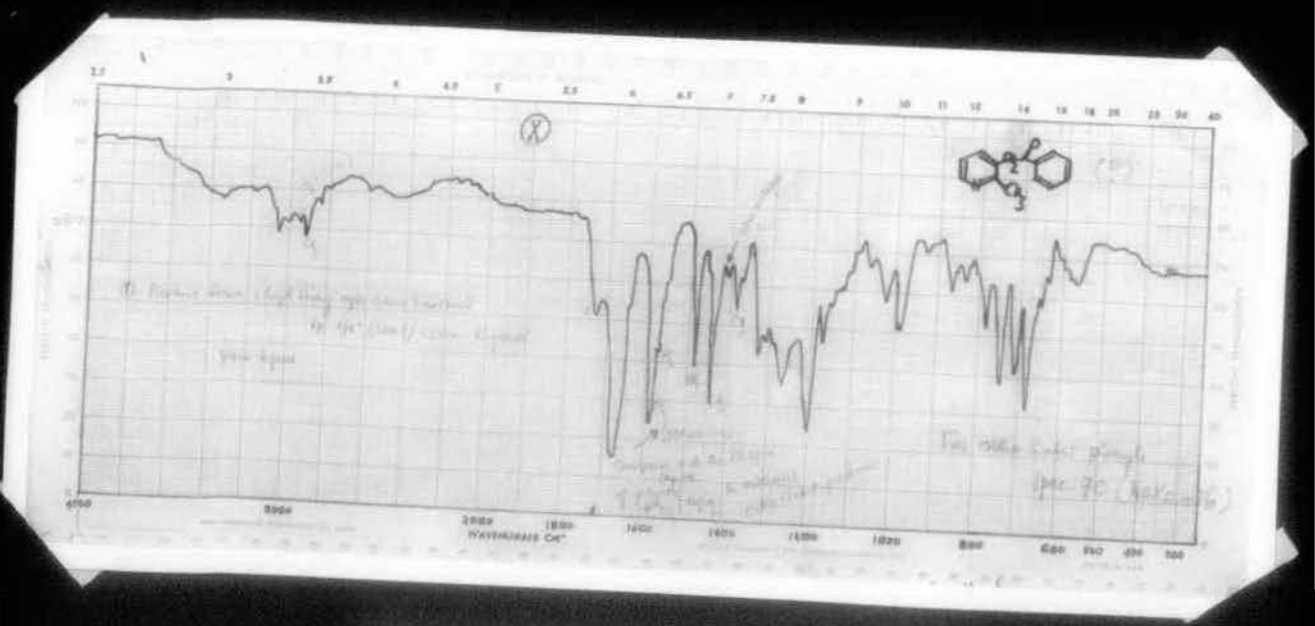


Fig. 5 IR spectrum of (LXX)

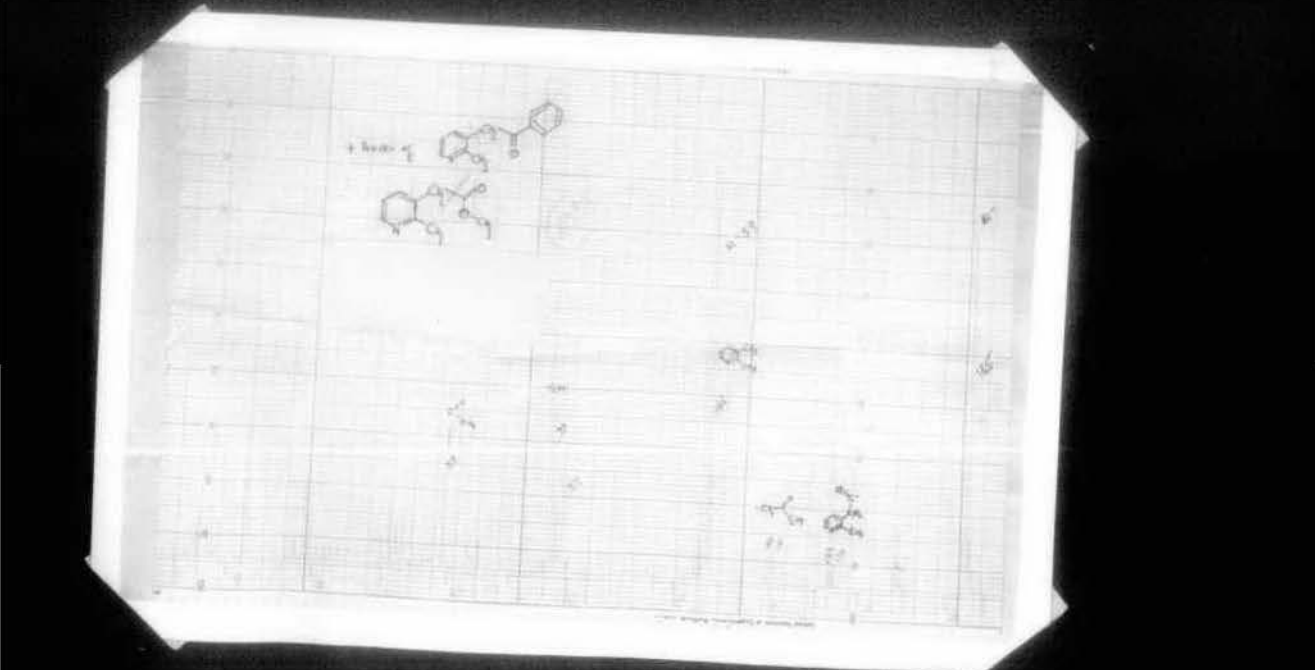
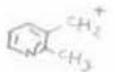
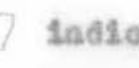


Fig. 6 Mass spectrum of (LXIX) and (LXX)

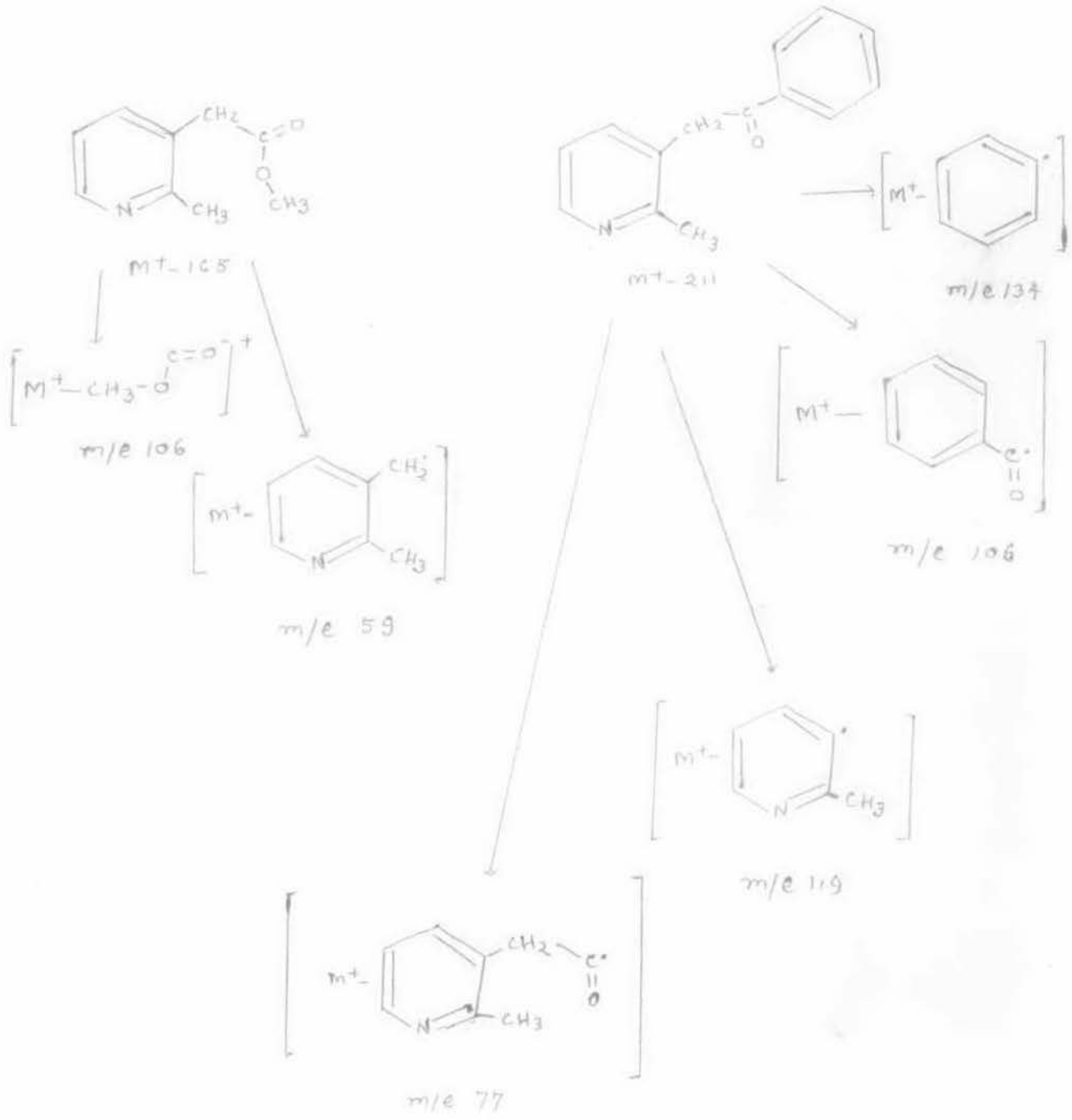
viz. $M^+ -$  indicating that the compound has the structure (LXIX).

In addition to the other peaks m/e 134 explained as $[M^+ - 77$ i.e. $M^+ -$  along with intense peak m/e 77 is coming from $M^+ - 134$ i.e. $[M^+ -$  and m/e 106 can be explained as $M^+ - 105$ $[M^+ -$  and peaks at m/e 119 coming from $M^+ - 92$ i.e. $[M^+ -$  indicate the presence of another new trace compound (LXX) whose original molecular ion peak was not observed in the mass region due to cleavage of (LXX). The mass peak m/e 106 is more abundant than molecular ion peak M^+ 165 in the mass regions probably because the same fragment came from both the compound (LXIX) and (LXX).

These mass spectral studies afforded convincing proof to the structures (LXIX) and (LXX) attributed respectively to the major and minor products of hydrolysis.

Chart 11

Mass fragmentation pattern



The reaction of 2,6 Lutidine N-oxide and methyl phenyl propiolate in different solvents was studied. The results are summarised in Table 7 (Detailed experimental procedures are furnished in the experimental section).

Table 7

Reaction between 2,6 lutidine-1-oxide and methyl phenyl propiolate.

Molar Ratio	Solvent	Temp.	Time	Yield
1:1	D.M.F	32°-33°	60 hrs.	3.1%
1:1	Benzene	Reflux	60 hrs.	4.4%
1:1	Toluene	Reflux	13 hrs.	3.4%
1:1	Xylene	Reflux	1 hr 45 min.	6%
2:1	D.M.F	32±1°C	60 hrs.	6.8%
2:1	Benzene	Reflux	60 hrs.	9%
2:1	Toluene	Reflux	13 hrs.	7.6%
2:1	Xylene	Reflux	1 hr. 45 min.	12%

In this case also a single product was obtained. The product (LXXI), a light pink gum b.p 160°-65° (Bath)/0.6 mm, showed I.R. bands (Fig. 7) at 1740 cm^{-1} (Ester carbonyl) and 1660 cm^{-1} (conjugated carbonyl group). The N.M.R spectrum (Fig. 8) of the compound showed bands at δ 2.47 (singlet, 3H), δ 2.61 (singlet, 3H), δ 3.75 (singlet, 3H) δ 5.74

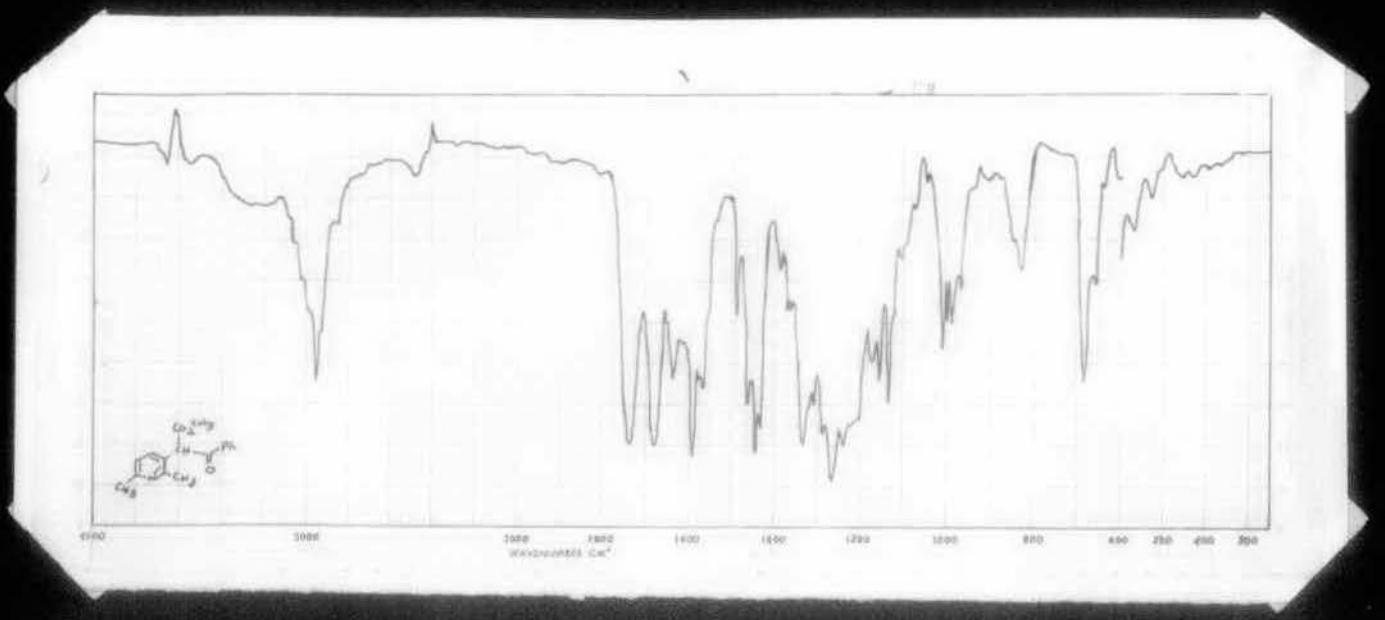


Fig. 7 IR spectrum of (LXXI)

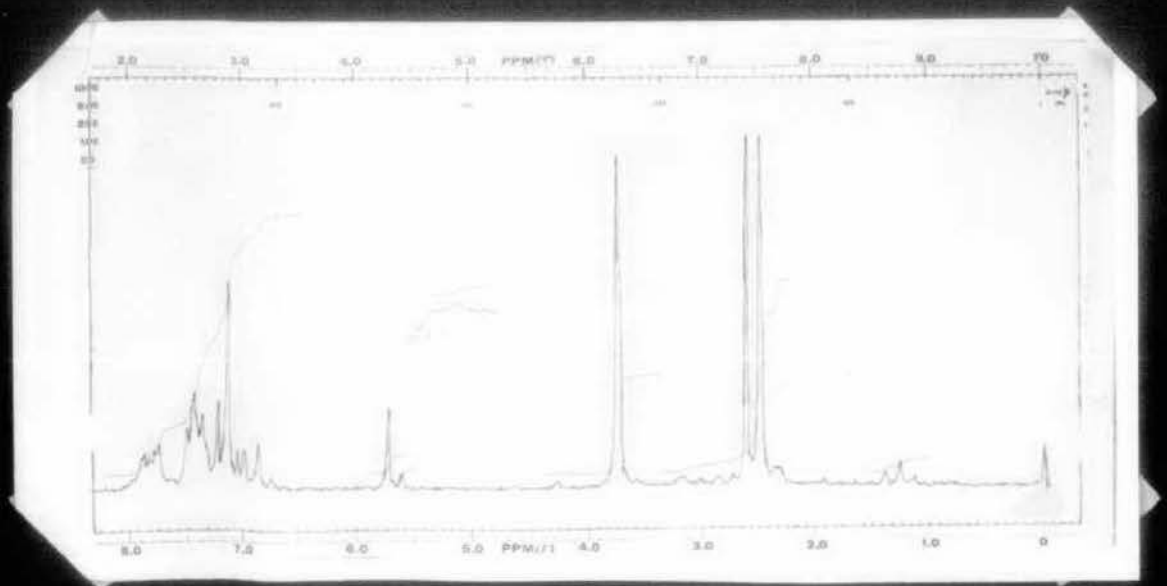
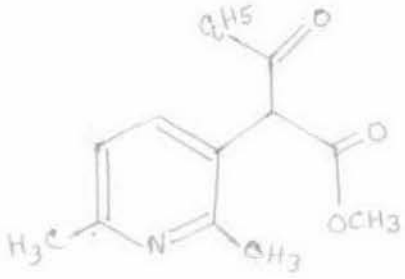


Fig. 8 NMR spectrum of (LXXI)

(singlet, 1H) and a complex multiplet in the region δ 6.85-7.9 corresponding to seven protons. From the I.R and N.M.R and by analogy with the picoline series, structure (LXXI) is assigned to this product.



LXXI

This product LXXI is also very labile and hydrolyses on long exposure to air. As in the picoline series, chromatographic hydrolysis was carried out on this compound and two products were isolated.

The major product (LXXII) yellow oil b.p 140°-45° (bath)/ 1 mm showed I.R (Fig. 9) band at 1730 cm^{-1} ($-\overset{O}{\overset{\|}{C}}-OCH_3$). The minor product, a yellow viscous liquid b.p 180° (Bath)/1 mm showed I.R (Fig. 10) bands at 1670 cm^{-1} ($-\overset{O}{\overset{\|}{C}}-C_6H_5$). From this spectral evidence and by analogy with the picoline series, the structure (LXXII) and (LXXIII) can be attributed to the major and minor products respectively.

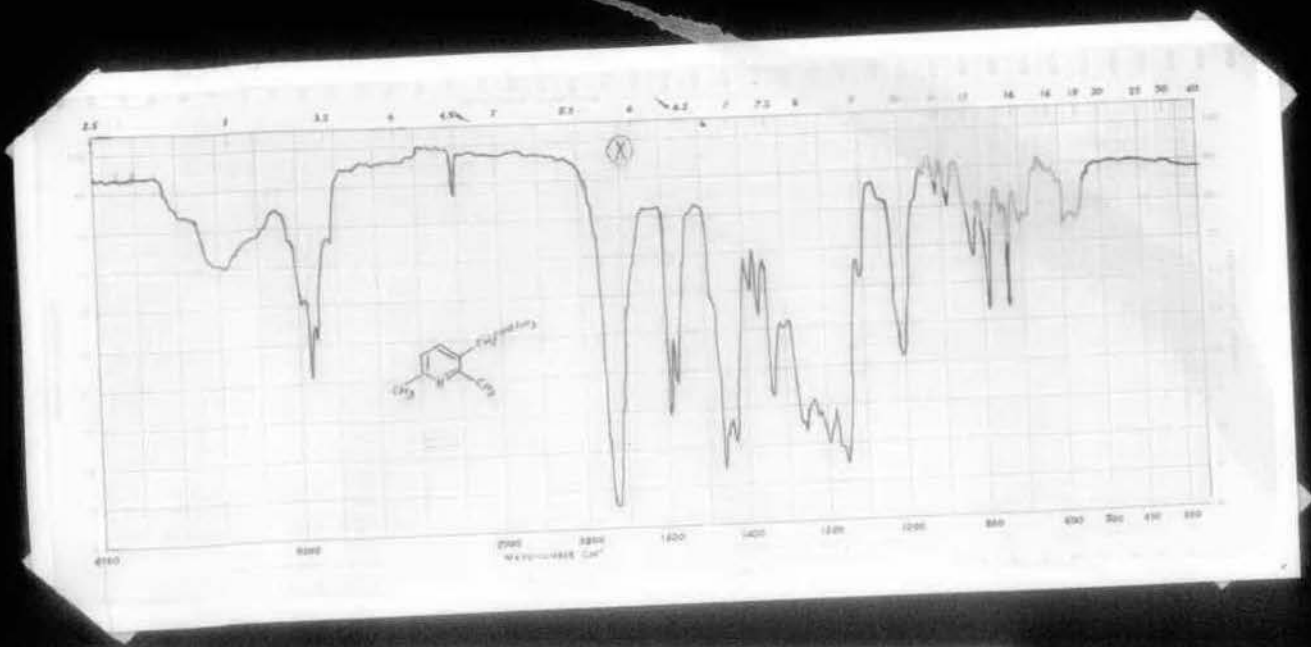


Fig. 9 IR spectrum of (LXXII)

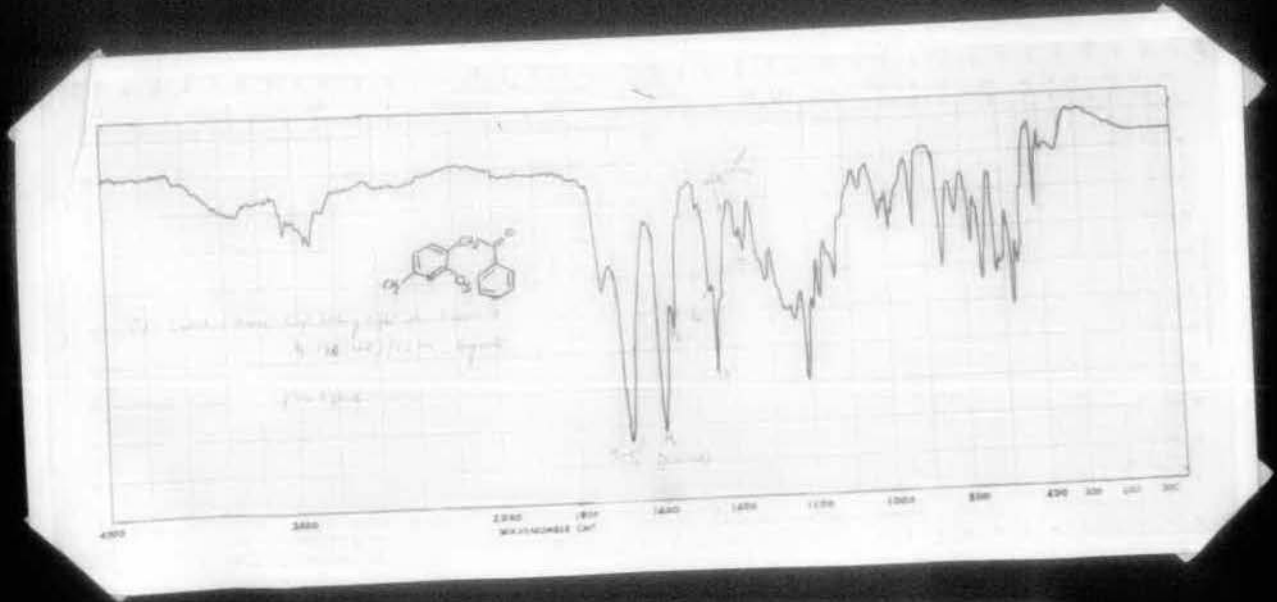
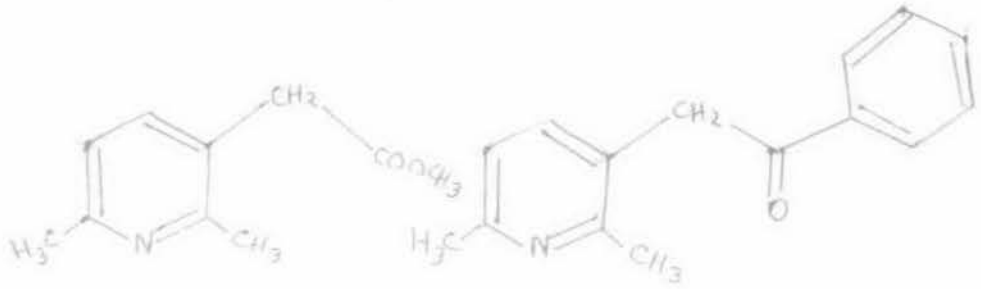


Fig. 10 IR spectrum of (LXXIII)



LXXII

LXXIII

Unlike the picoline series, adsorption on alumina column for 50 hrs. leads to incomplete hydrolysis. This was evident from T.L.C. studies, which showed three spots, one spot due to the starting material (LXXI) and other two due to the two products LXXII and LXXIII. Hence the rate of hydrolysis of LXXI is much slower than that of LXVIII (picoline series). Complete hydrolysis of LXV required 72 hours.

Investigation was also carried out on 2,4,6-Collidine-i-oxide and methyl phenyl propiolate. The molar proportion, temperature, solvent used and yields obtained are summarised in table 8.

Table 8

Reaction between 2,4,6 Collidine-1-oxide and methyl phenyl propiolate.

Molar ratio	Solvent	Temp.	Time	Yield
1:1	D.M.F	30±1°c	59 hrs.	3.3%
1:1	Benzene	Reflux	60 hrs.	6.8%
1:1	Toluene	Reflux	13 hrs.	8.5%
1:1	Xylene	Reflux	1 hr. 45 min.	13%
2:1	D.M.F	30±1°c	59 hrs.	8%
2:1	Benzene	Reflux	60 hrs.	13%
2:1	Toluene	Reflux	13 hrs.	17%
2:1	Xylene	Reflux	1 hr. 45 min	27.4%

Like the picoline and Lutidine series only one compound was obtained. The product was a deep yellow viscous liquid b.p 178-180°/bath 0.6 mm. In I.R. (Fig. 11) it absorbs at 2800-3100 cm^{-1} (broad) and 1685 cm^{-1}. The I.R. data,at a glance, is confusing, since the product obtained in picoline and lutidine series all showed a band near 1730 cm^{-1} which is absent in this case. But we could not expect a dramatic change in the mechanism of the reaction and accordingly structure of the product by a simple substitution of methyl group at C_4 of the pyridine nucleus.

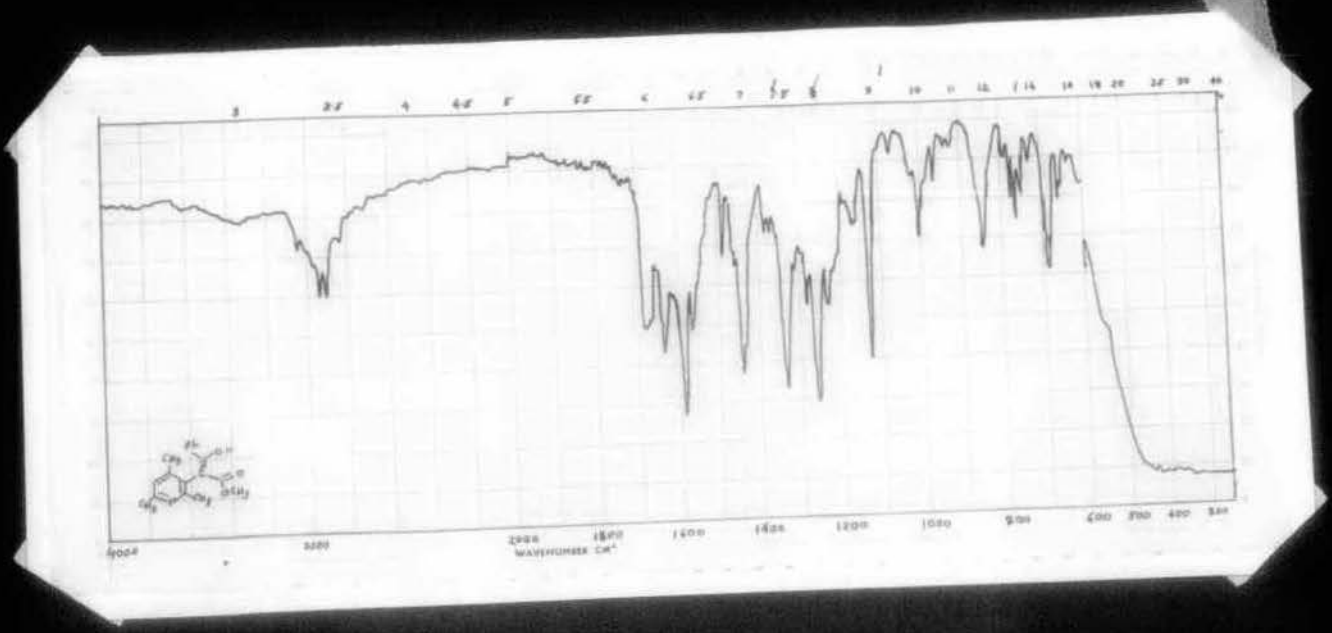


Fig. 11 IR spectrum of (LXXV)

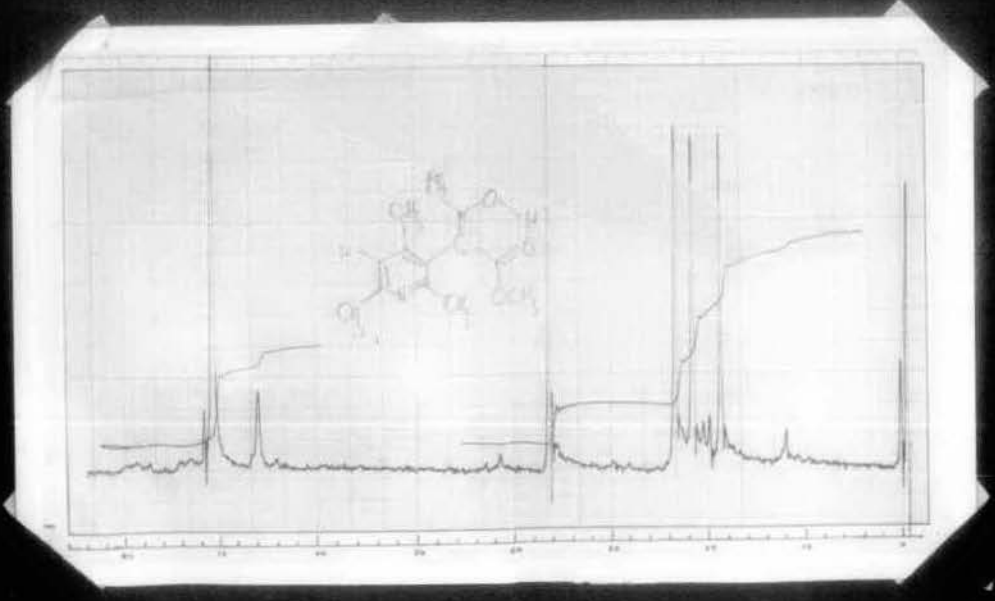
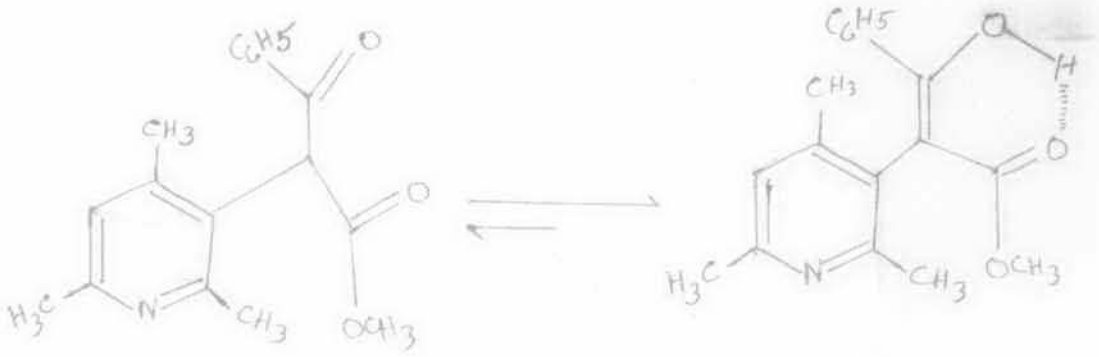


Fig. 12 NMR spectrum of (LXXV)

In analogy with the picoline and lutidine series our expected product would have structure (LXXIV). But (LXXIV) would absorb at 1730 cm^{-1} ($-\overset{O}{\overset{\|}{C}}-OCH_3$) and a 1680 cm^{-1} ($-\overset{O}{\overset{\|}{C}}-C_6H_5$). The tautomeric form (LXXV) of the beta keto ester is likely to absorb at 1680-85 cm^{-1} with a broad band at 2800-3100 cm^{-1}. The I.R. spectrum clearly shows that this compound exists mostly if not exclusively in the enolic form (LXXV)

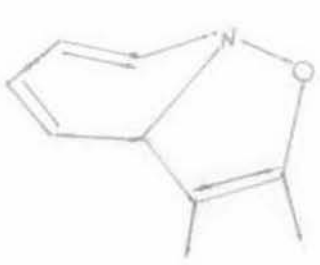


LXXIV LXXV

Convincing proof for (LXXV) as the structure of our product was afforded by N.M.R (Fig. 12) studies. In N.M.R the compound absorbs at δ 1.9 (singlet, 3H), δ 2.18 (singlet, 3H), δ 2.38 (singlet, 3H) due to the 2,4 and 6-methyl groups of the pyridine nucleus, δ 3.7 (singlet, 3H) due to ester methyl group, δ 6.65 (singlet, 1H) due to enolic proton (-O-H), δ 7.16 (6H) due to aromatic proton. This N.M.R data is in good agreement with the structure (LXXV). Compound (LXXV) had sufficient life time and very stable. Adsorption on

alumina column and elution even after 72 hours showed that hydrolysis had not occured.

As all the reactions we have studied have been found to be extremely sensitive to the solvent medium, it was rather difficult to view these reactions as 1:3 dipolar cycloaddition reactions which are known to be insensitive to the solvent changes. This led us to believe that the reactions did not proceed via a two step mechanism. The intermediates of the type(XXXII) and(XLIIa) which have been proposed by Huisgen and Abramovitch to account for 2-substituted and 3-substituted products should exist in the conformation (LXXVI) just at the moment of formation if concerted approach is maintained.



LXXVI

LXXVII

In this conformation the nitrogen lone pair which is part of dihydro pyridine π-system is energetically in an unfavourable situation due to interaction with the adjacent lone pair of oxygen atom. Conformational flip to (LXXVII) is, of course, possible and the unfavourable interaction may be eliminated to some extent. Now, if the 2 p non-bonded pair of oxygen in an aromatic N-oxide could be diverted to interact with an electrophile (E^+), a nucleophile (Nu^-) might interact complementarily with the aromatic ring at either ortho or para position. Smooth reaction would then proceed with simultaneous conformation change resulting in orientation of the nitrogen lone-pair in a position of minimum overlap with the dihydropyridine π-system. All of the possible complementary processes with pyridine N-oxide as model system are shown in Fig. 13.

On the basis of these possibilities and as an alternative to 1,3-dipolar cycloaddition, one could think of complementary pathway for the reaction of aromatic N-oxides with electrophilic acetylenes leading either to an oxa-aza-claisen (path i) or to a $\sigma_2+\pi_2$ process[43] (path ii) according to steric possibilities (Fig. 14). Such a process would possibly be autocatalysed with a second molecule of aromatic N-oxide acting as the nucleophile. In this way, a one-step conversion of aromatic N-oxide to Huisgen product (XLI) or a precursor (a in Fig. 14) of Abramovitch product (XXXVI) could be envisaged.

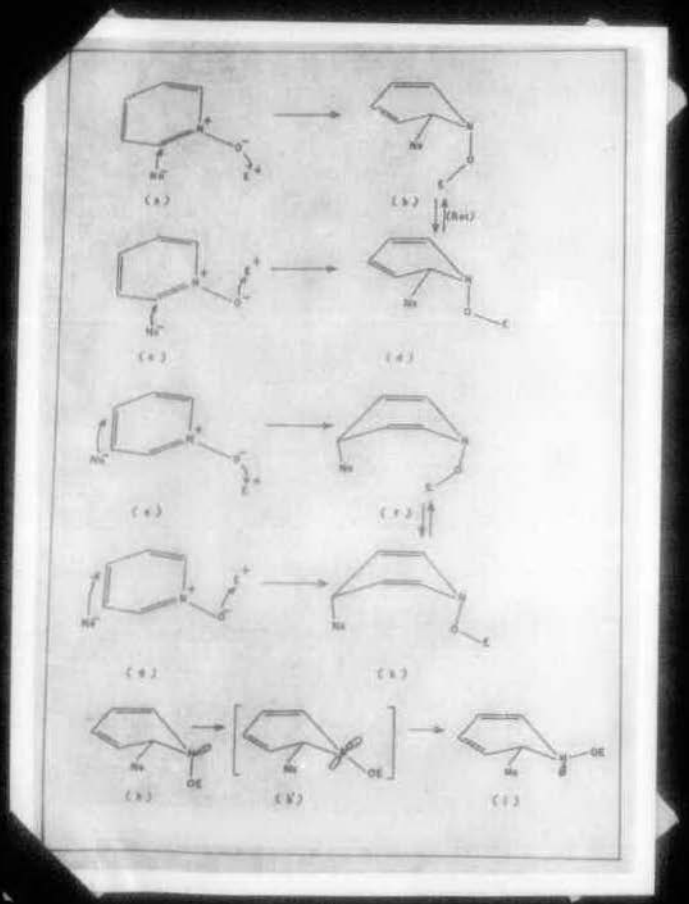


Fig. 13

A few aspects of this model need special mention. First of all, the approaching nucleophile and the developing lone-pair of nitrogen are shown to be trans in all cases; this is to some extent in agreement with current ideas. That the Sp^2-anion generated from the acetylene is trans with respect to the incoming oxy-anion is also a reasonable supposition[44], although this anion may have only fleeting stability. Secondly, due to smooth conformational change an appropriate distance between the developing vinyl carbanion and the pyridinium moiety can be maintained throughout the entire course of reaction so that there is a scope for considerable charge-transfer interaction between them. In this way, charge separation may not change to an appreciable extent from starting material till attainment of the transition state. On the other hand, in the alternative ortho-model (Fig. 13c) this type of charge-transfer interaction is not possible, and charge separation will greatly increase during the reaction course resulting in considerable increase in dipole moment in the transition state.

The above discussion may be summarised in the following manner: Symmetry-allowed co-operative interaction between (i) N-oxide π -HOMO and acetylene π-LUMO and (ii) acetylene π'-HOMO and σ_{N-O}-LUMO at positions of the highest HOMO and LUMO densities[44a], facilitated by concomitant attack of a nucleophile at the ortho (or para) positions of the N-oxide and subsequent conformational change, guide the course of the reaction. How a third species can catalytically assist an energetically or symmetrically disfavoured process to take place has been discussed by Fukui et al[44b]. At the

moment, we do not have any data in support of our alternative mechanism but experiments are in progress to test this possibility.