PART I

CHAPTER - I.

Basic Principles of Aromatic N-Oxides

If we consider the field of heterocyclic chemistry as one unit, it is difficult to understand the many different experimental results, the electronic and steric factors guiding the reactions, and the important features responsible for the physical and chemical properties of the compounds. Since many experimental facts have been collected and assembled without looking for general basic principles, heterocyclic N-Oxide chemistry did not develop systematically for many years.

We shall start our discussion with a hypothetical model. First we shall expand a few axioms on which the model is based, and then we shall see how far the model conforms to changes demanded by possible interactions between relevant orbitals guided once again by symmetry over and above energy. In fact, what we actually want to do is to derive as much informations from the model as possible on the basis of those axioms and then see how far experimental results agree with those informations.

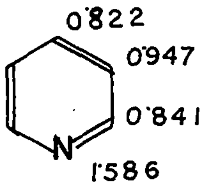
For a better understanding of the matter, we should keep in mind a few elementary facts concerning the most widely known aromatic compounds we know, benzene. Benzene is no doubt an outstanding example of a molecule in which electron delocalization is the most important feature. According to Huckel rule[1] a cyclic substance is aromatic if all the π-electrons are delocalized around the ring forming a closed electron shell. But this is a property of the substance in its ground state, whereas chemical reactivity is dependent on the difference in free energy between the ground state and that of the transition state for the chemical change involved. Valid criteria for aromaticity are such properties as a lower energy content than would be predicted by comparison with an appropriate acyclic analog, the presence of c-c bonds that are intermediate in lengths between those usual for single and double bonds, and above all, the ability of the system to sustain an induced ring current of π-electrons.

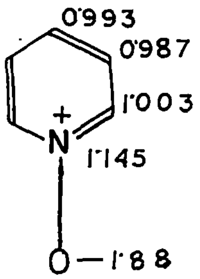
The replacement of a CH-group by a nitrogen atom that is more electronegative than carbon leads to a disturbance of the symmetry of the π-electron system so that the bonds are not all equivalent, and consequently the quantitative theoretical approach to the hybrid state is difficult and frequently ambiguous. A quite satisfying qualitative understanding of the bond properties, however, can be obtained if the same simple rules of resonance of the aromatic hydrocarbons are applied to the resonance systems with heteroatoms. Since we are discussing six-membered nitrogen heterocycles, we should like to give an idea of the modifications required in changing from benzene to pyridine and so forth. In general, the bond system of the pyridine ring remains the same since the ring nitrogen is bonded with its adjacent atoms by two Sp^2 hybrid bonds, like the methine group. Therefore, pyridine has formal properties of a benzene-like aromatic substance reflected in the stabilization energy as well as in the bond lengths which average 1.39 Å. Although the original aromatic character of both substances are much alike, the fine structure of the electronic system shows typical differences due to the greater electronegativity of the nitrogen atom. Since this attraction has an effect on the mobile π-electrons, which are partially shifted towards nitrogen, the dipole moment of 2.21D in pyridine demonstrates to some extent partial localization of π-electrons.

Qualitative informations about the non-uniform electron distribution of electric charge in pyridine could be obtained by applying the resonance method to this system. In contrast to benzene, where the molecule is described by the most important Kekule structures and to some minor extent by the three Dewar structures, we have to take into consideration in pyridine also the dipolar resonance structures bearing the negative charge at the nitrogen atom. Structural consideration of this kind give a rather good picture of the electron distribution, which naturally becomes even better if electron density diagrams based on molecular orbital calculations are in hand.

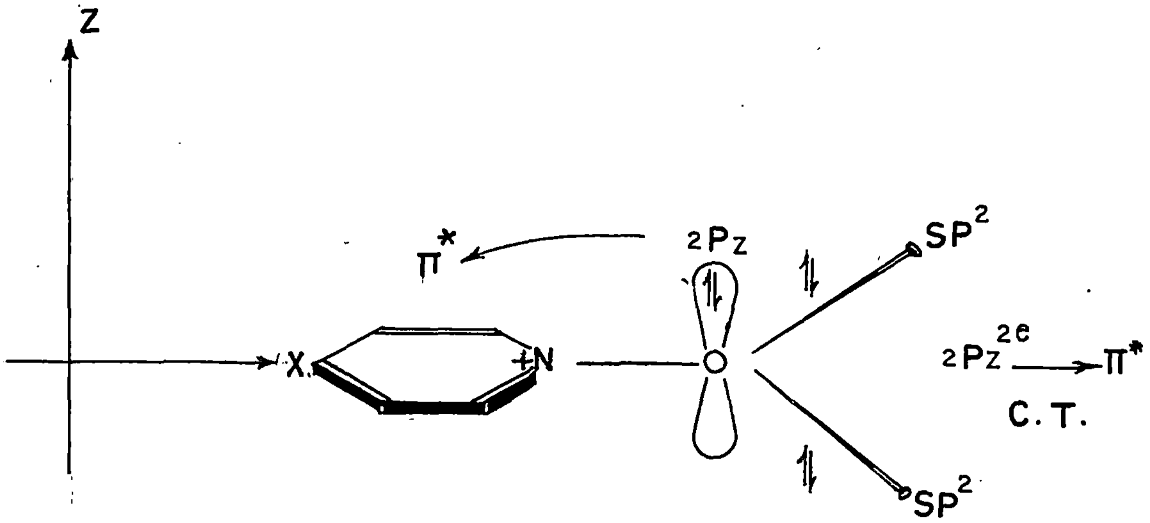
However, more essential for synthetic work is the reactivity of such heterocycles, since success of synthesis always depends on the question where and when the reaction takes place and under what conditions. Looking at the experimental results, one finds the surprising phenomenon pointing to a parallel of electron distribution in the ground state and reactivity. Especially if we take pyridine as a standard example, one tends to assume that the electron distribution of the ground state gives information on the reactivity of the molecule, since electrophilic substitutions take place with much more difficulty compared with benzene, the position of the attack being β to the ring nitrogen. If there is really such a relationship, this would mean that the decisive factor would be the electrostatic orientation of the heterocycle and the attacking reagent.

If we slowly want to extend our topic more elegantly we would now simply introduce an N-Oxide grouping. Here we would like to draw some attention and to correlate the electron distribution of pyridine[2a] and that of the pyridine N-Oxide[2b].





Recent calculations indicate that the introduction of an N-Oxide group increases the aromaticity of pyridine[2c]. That is the ring electrons are much more delocalised than our reference compound pyridine. So there must be some other possible way of interactions to achieve this extra stabilising energy by different electronic rearrangement. It is clear that feasible symmetry-allowed interactions is possible only when two electrons from $2P_z$ orbitals of the oxygen atom through longitudinal way of through space charge-transfer[3] process of interaction with the π^* of the pyridinium electron localised ring system and thereby regain the extra aromatic character of the ring of pyridine N-Oxide.



Although it seems that the electrons are some how symmetrically distributed yet there are predominant dipolar character of the molecule. Here intermolecular forces plays an unique as well as a vital role. The dipole that arises from the unequal sharing of electrons, associates each molecule with the so called dipole-dipole attraction[4]. So <u>dimeric-association</u> rather than dimerisation is a rule in aromatic N-Oxide Chemistry. Remembering that the electronic energies of bound states of atoms, molecules and ions are "quantised"[5], this simple hypothetical approach has tremendous importance in chemistry.

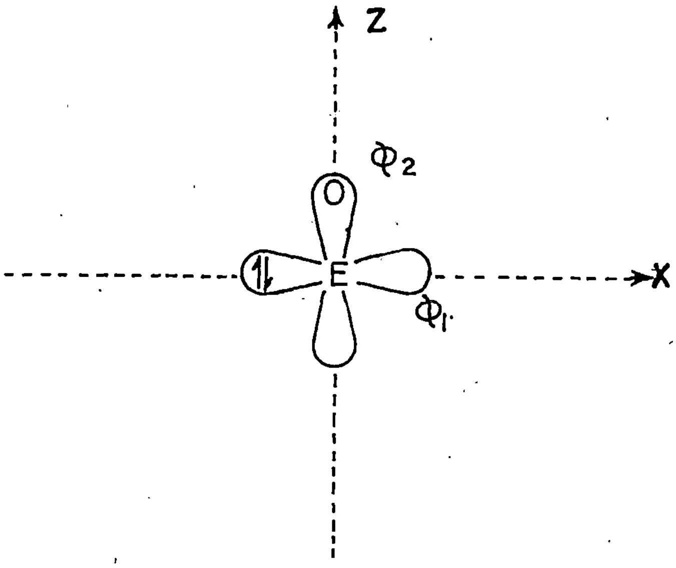
Schematic Representation of Oxeno-transfer.

Choice of E

Let us start a priori with an undefined cation E^+ (a, b, c, ...) in which a, b, c, are ligands. These ligands may be other atoms bonded with E or non-bonded electron pairs belonging to E.

E^+(a, b, c, ...) may be formally thought to have arisen by heterolytic fission of X-E bond in the original species X-E (a, b, c, ...) in which X leaves with the bonded pair of electrons. This leaves a bonding orbital in E^+(a, b, c, ...) vacant. So the general undefined cationic species we constructed is:

E^+(and a, b, c, ... are ligands, may be other atoms bonded with E or non-bonded electron pairs). More precisely E^+can be formally represented as:

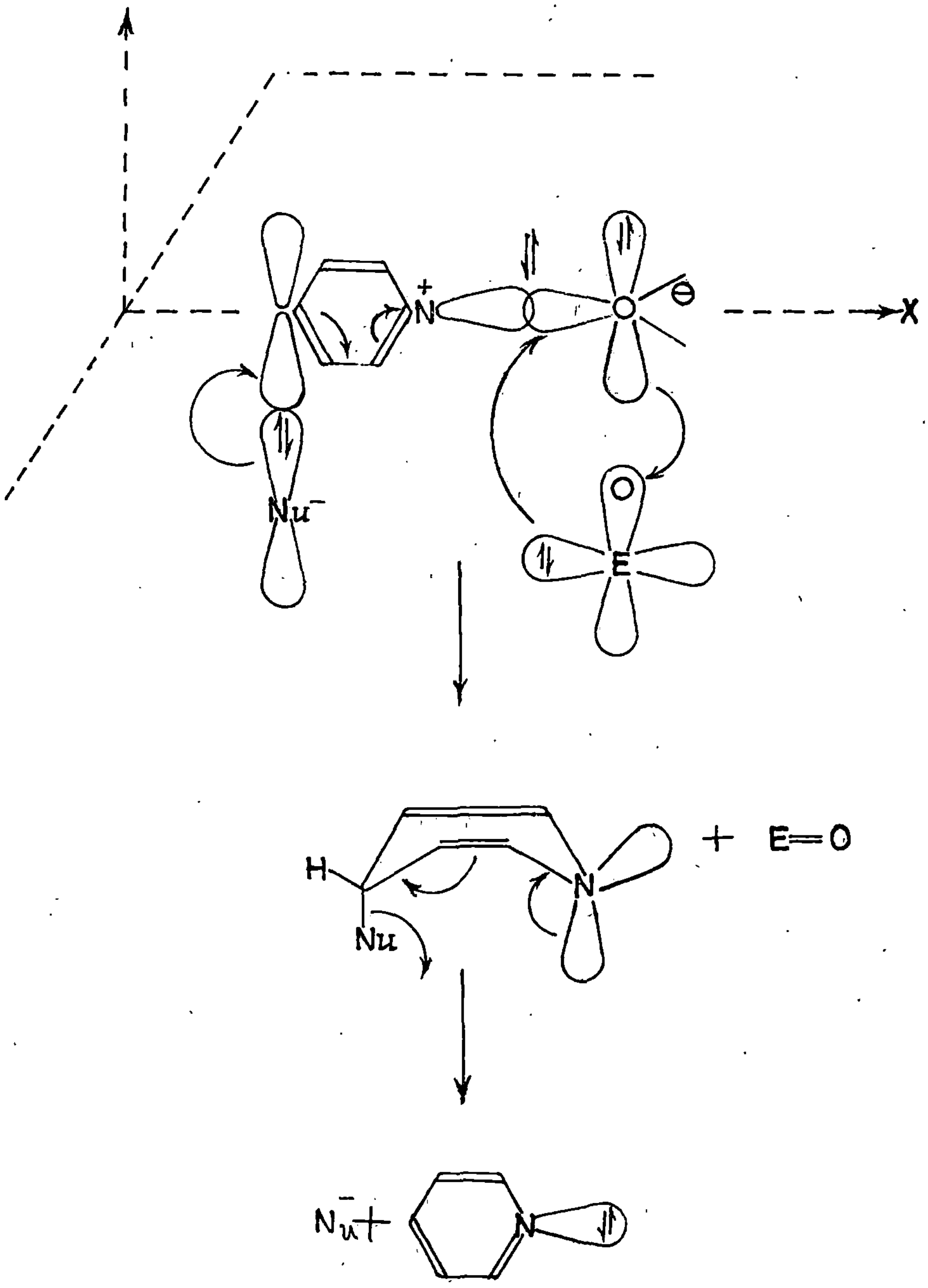


where, $\Phi_1 \rightarrow$ orbital containing non-bonded electron pair,
taking from undefined parameters a, b, c.....
$\Phi_2 \rightarrow$ vacant orbital.
and Φ_1 and Φ_2 are mutually orthogonal.

As a chemical change mainly involves interactions of electrons. Our axiocentric structure defines the primary interactions as:

$$2P_z^{2e}\,(\text{Oxygen}) \text{ —— } \dot{\Phi}_2(E^+)$$

Mutual co-operative interactions of symmetry allowed orthogonal orbital Φ_1 then guided the over all reaction in a feasible energetic pathway. This courageous interpretation of the $\sigma_2 \longrightarrow \Pi_2$ interaction can be pictorially represented in Scheme I.



SCHEME I

Reactions of PCl_3 with pyridine N-Oxide[6] is a very good example for the proposed hypothesis. Here PCl_3 molecule acting as an electrophile due to the presence of 'vacant' d-orbitals and only the appropriate d-orbitals[7] which is symmetrically suitable for the interaction can play the part among the five degenerate, or almost degenerate d-orbitals. The total electronic interactions covering the entire reactions can be formulated as:

$$2P_z^{2e}(\bar{O}) \longrightarrow d^{\circ}(P) \; ; \; nb^{2e}(P) \longrightarrow \delta^{*}(>\overset{+}{N}-\bar{O})$$

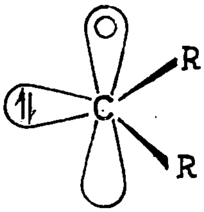
with co-operative interactions of

$$2P_z^{2e} \; (Cat.\bar{O}) \longrightarrow \pi^{*}(Py^{+})$$

Here generalised and characteristic interpretation can be rationalised from Fukui Frontier-Orbital Theory[8] approach. Symmetry-allowed co-operative interactions between (i) N-Oxide - HOMO and Electrophile - LUMO and (ii) Electrophile-HOMO and N-Oxide-LUMO at the position of highest HOMO and LUMO densities, facilitated by concomitant attack of the second N-Oxide molecule as a nucleophile at the ortho (or para) position of the N-Oxide and subsequent conformational change, guide the course of the reaction.

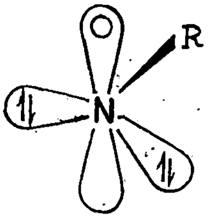
Here comes 'OXENE' the non-de-plume of oxygen species which included the complimentarity principle in chemical reaction dynamics. 'Oxene' can be defined, as an oxygen atom having complimentary electrophilic and nucleophilic properties, i.e. can simultaneously act with an external electrophile (E^+) and nucleophile (Nu^-) in a concerted fashions. One can place 'Oxene' with 'Carbene' and 'Nitrene' as all have complimentary electrophilic and nucleophilic properties.

Carbene



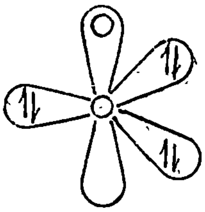
$:CR_2$

Nitrene



$:\ddot{N}R$

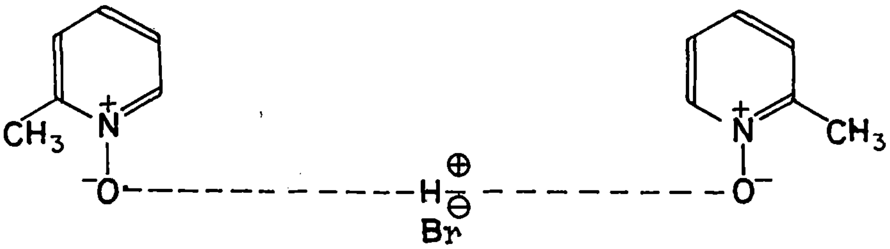
Oxene



$:\ddot{O}:$

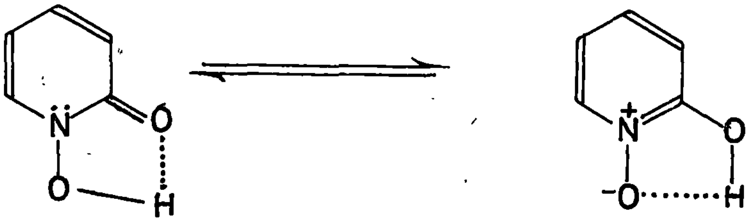
Reactivity of Aromatic N-oxides.

The extensive development of the heterocyclic N-oxide chemistry in the past 15 to 20 years may be attributed to their unique reactions of synthetic and mechanistic interest. Although Meisenheimer[9] in 1926 reported a facile oxidative procedure for the preparation of pyridine N-oxide and related compounds, the chemistry of the heterocyclic N-oxide lay dormant until 1940. At that time Linton[10] reported an unexpected low dipole moment (4.32D) for pyridine N-oxide, which indicated a considerable back-polarisation of electrons into the pyridine ring from the N-oxide group. Ochiai, realising that this might facilitate electrophilic substitution and ultimately discovered the nitration of pyridine N-oxide[11]. He also quickly recognised the increased stability of aromatic N-oxides which sharply differentiates them from their aliphatic analogue (i.e. the 'nitrones'). The aromatic N-oxides are often hygroscopic, probably because of the ease with which they form hydrogen bonds. Sometimes they may be isolated as hydrates, e.g. 6-methyl-quinoline-1-oxide. The symmetrically hydrogen bonded structure (I) has been suggested for the hemihydrobromide of 2-picoline N-oxide on the basis of infrared spectral data and X-ray studies.



I

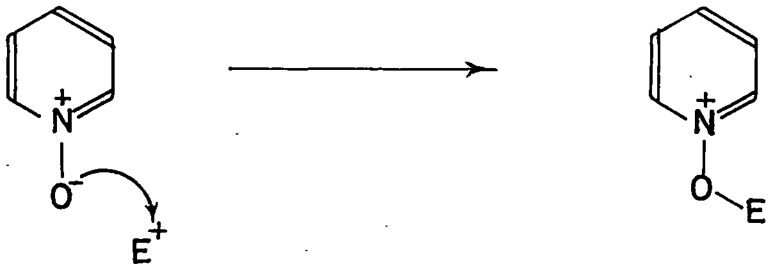
Strong intramolecular hydrogen bonds have been shown to exist in the tautomeric compound 2-hydroxy-pyridine N-oxide (IIa ⇌ IIb) by infrared spectroscopy.



IIa IIb

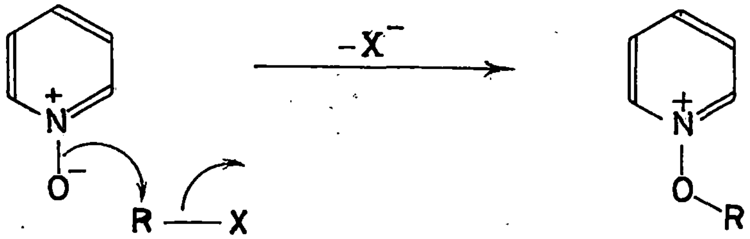
Reactivity Pattern of Aromatic N-Oxides:

N-oxides can react with a variety of electrophilic reagents (E^+) to give adducts (III), which according to the reagent and reaction conditions, may be stable or react further.

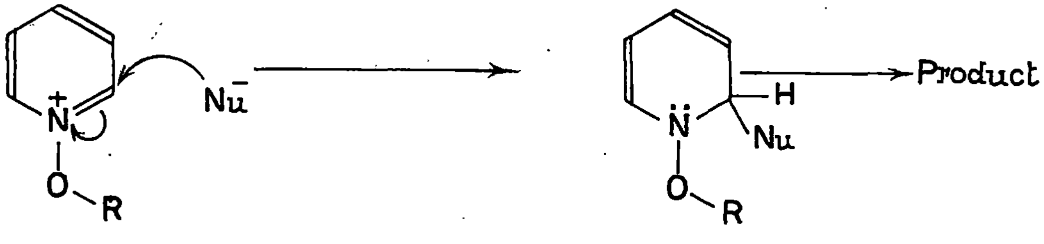


III

N-oxides undergo S_N2 reactions with reactive halides and similar compounds. The quaternary salts (IV), derived from alkylhalides, sulphonates, etc. can often be isolated, but this is seldom the case for reactions involving acyl halides. Quaternary derivatives of the type (IV) are highly reactive, even when R is a alkyl group, and they readily undergo further reactions at either the ring carbon atoms (e.g. IV ⟶ V) or the substituents (VI ⟶ VII).

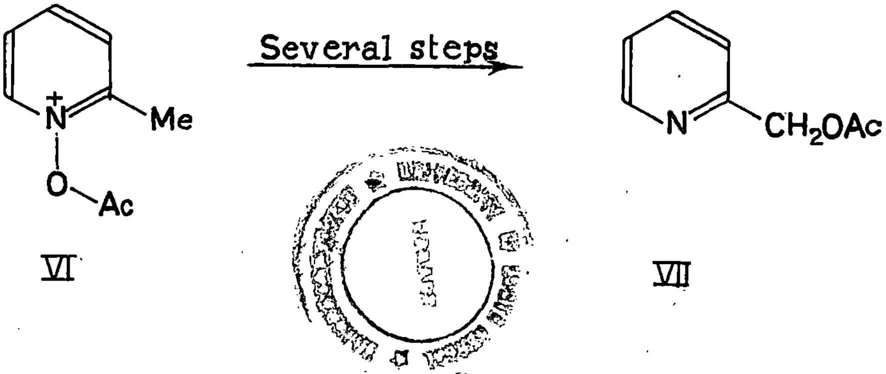


IV



IV

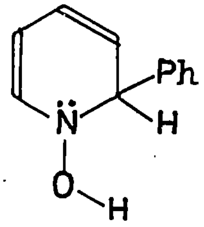
V



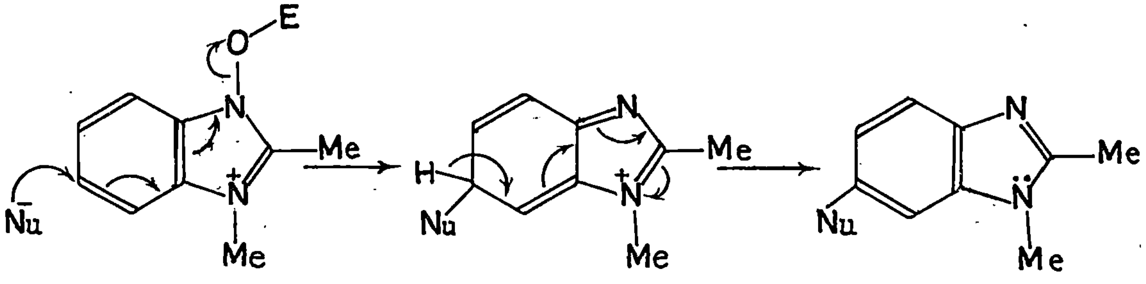
VI

VII

Addition products which have been isolated (e.g VIII from the reactions of pyridine N-oxide with phenylmagnesium bromide) sometimes show surprising stability and are versatile reaction intermediates as well[12]. These reactions generally occur preferentially at the α-position, but if this is blocked the γ-position is attacked. If positions on the heterocyclic ring are not open, reaction can sometimes occur on a fused benzenoid ring (Scheme II)[13].



VIII

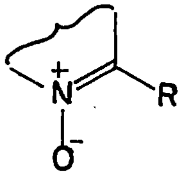


SCHEME II

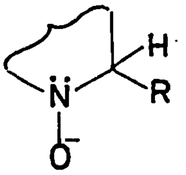
Ideal examples of the different types of reactions can be summarised as follows:

Reactions with Grignard Reagents:

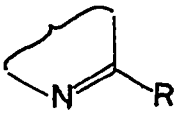
Grignard reagents react with heterocyclic N-oxides to give α-alkyl or α-aryl heterocyclics (XI). The intermediates (X) are generally converted into the aromatic products (XI), or oxidised by the unreacted N-oxide in the reaction mixture to form α-substituted N-oxides (IX) as by-products. Yields are generally poor, but can be improved by carrying out the reaction in tetrahydrofuran as solvent when the intermediates (X) are more stable and are protonated to give isolatable hydroxy compound[14] (VIII), which on heating readily lose water to give the aromatic compound (XI).



IX

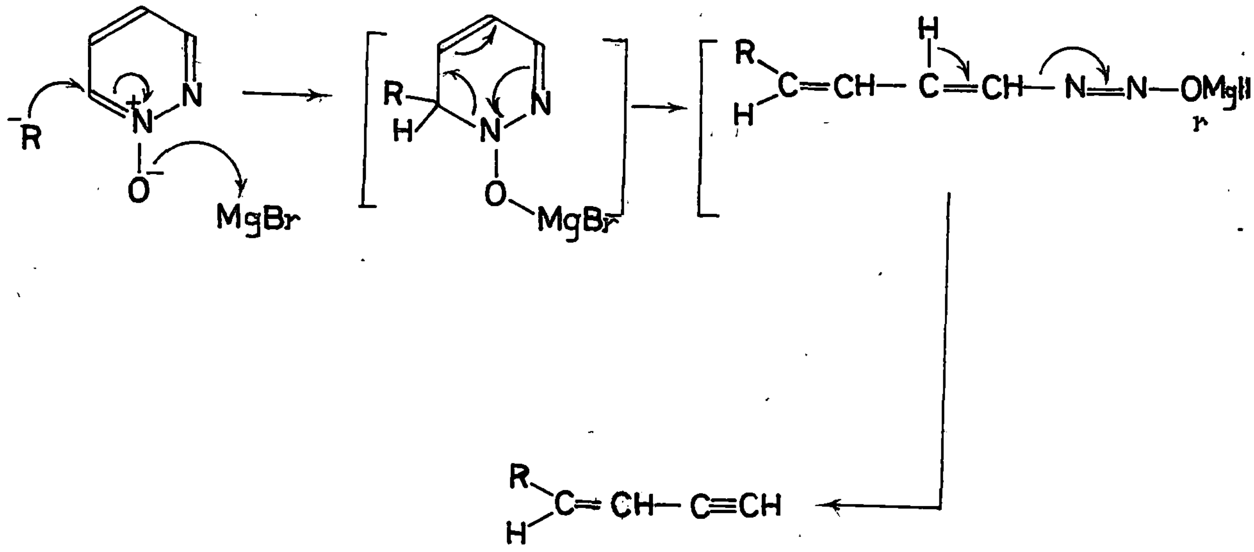


X



XI

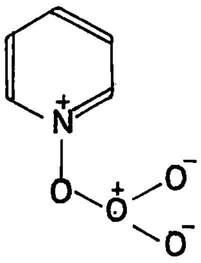
With pyridazine 1-oxide, the reaction takes an extraordinary course (Scheme III) to yield vinylacetylene[15]. Some butadienes are formed as by-products in reactions involving two moles of Grignard reagent:



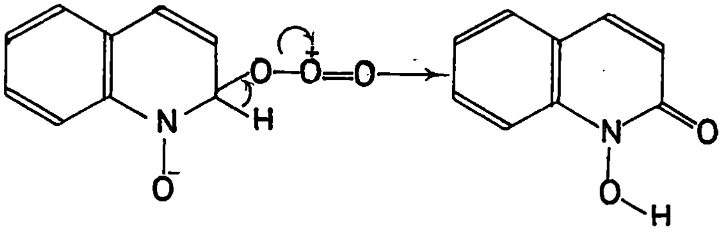
SCHEME III

Reactions with oxidising agents:

The reaction between ozone and pyridine N-oxide in methylene dichloride solution is considered to proceed through the unstable intermediate[16] (XII). The ozonolysis of 3-methylisoquinoline 2-oxide to phthalic acid[17] and 3,4-diphenylfuroxan to benzoic acid[18] are known, here ozone is acting as an electrophile. But initial nucleophilic attack by ozone at the α-position of the N-oxide was also proposed by Moriconi, et al.[19] (Cf. formation of 1-hydroxy-2-quinolone (XIII) from quinoline 1-oxide).

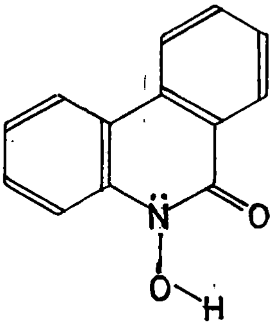


XII

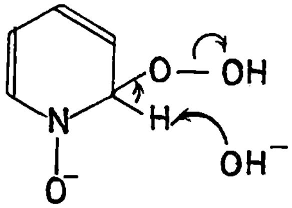


XIII

Alkaline hydrogen peroxide[20] also converts phenanthridine-5-oxide to 6-hydroxy phenanthridone (XIV), and the formation of N-oxides from heterocyclic bases by peracid oxidation sometimes form ring-oxidised compounds as by-products. These reactions probably involves nucleophilic attack by the hydroperoxide ions in the α-position of the N-oxide followed by cleavage of the intermediate (XV)



XIV

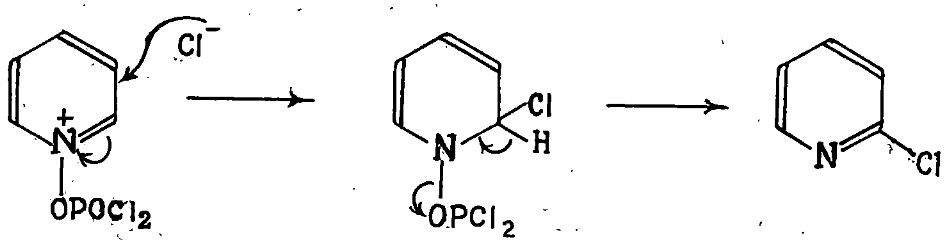


XV

Leadtetraacetate and tetrabenzoate can also oxidise quinoline 1-oxide to 1-hydroxy 2-quinolone (XIII)[21].

Formation of a carbon-halogen bond by nucleophilic attack:

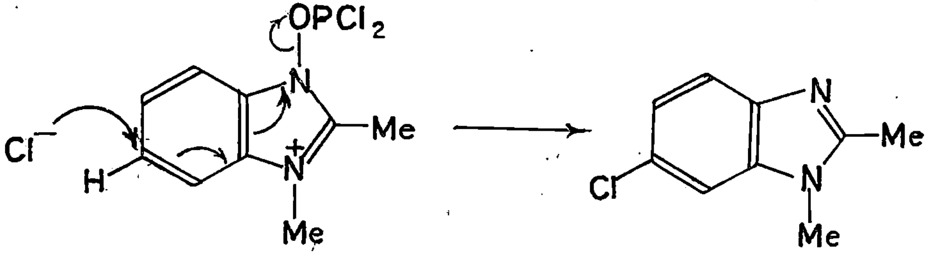
α and γ-chloro heterocyclics are formed by the action of phosphorus oxychloride, phosphorus pentachloride or sulphurylchloride with heterocyclic N-oxides. In typical reactions of this type the N-oxide and sulphurylchloride are heated at 110° for 2 hours with phosphorus oxychloride, temperatures ranging from 40° to the boiling point of the mixture and times of 0.5 - 5 hours have been used, sometimes with chloroform as solvent. The mechanism of the reaction with phosphorus oxychloride and the other reagents is almost certainly of the type illustrated for the conversion of pyridine N-oxide into 2-chloropyridine[22] (XVI) in Scheme IV.



XVI

S C H E M E IV

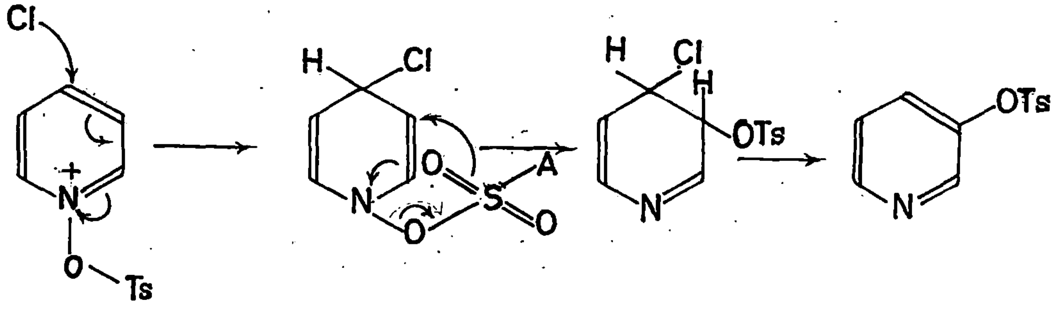
Formation of 6-chloro compound[23] (XVII) from 1,2-dimethylbenzimidazole-3-oxide probably involves a mechanism of the type shown in Scheme V.



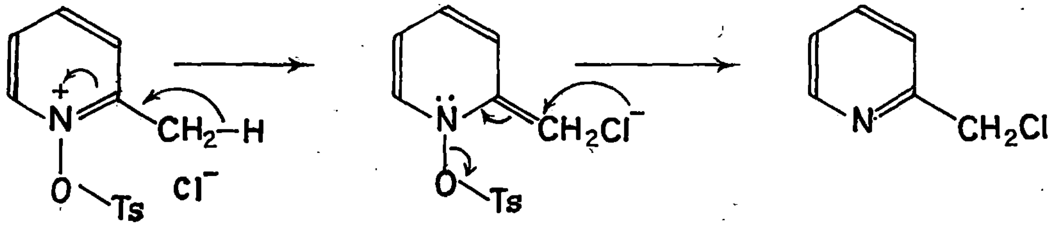
XVII

SCHEME V

Isolated examples of the use of tosylchloride are known[24]. But this reagent also gives several other types of products. On heating with tosylchloride, pyridine N-oxide yields 3-tosyloxy pyridine (XVIII)[22,25]. 3-picoline N-oxide similarly gives 3-methyl-5-tosyloxy-pyridine[26,27], but with 2-picoline-N-oxide and other α-alkyl N-oxide reactions occurs at the methyl group to yield 2-chloromethylpyridine (XIX) with simultaneous loss of N-oxide oxygen atom:

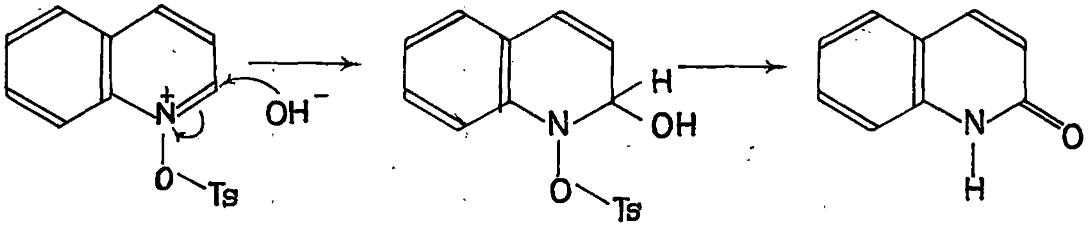

Cl
N
O
Ts
H
Cl
N
O
S
O
O
A
H
Cl
H
OTs
N
OTs
N

XVII


N
O
Ts
CH₂—H
Cl⁻
N
O
Ts
CH₂Cl⁻
N
CH₂Cl

XIX

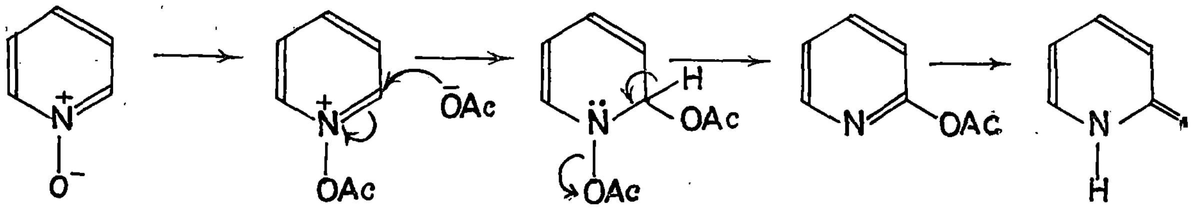
Reactions of N-oxide with tosylchloride in an aqueous alkaline medium is perhaps the best known reaction involving nucleophilic attack by hydroxide ion on N-oxide rings. The hydroxide ion adds to the initial adduct to give an α-oxo compound (Scheme VI)[28]. The main limitation of this reaction is its failure in the pyridine N-oxide series.



S C H E M E VI

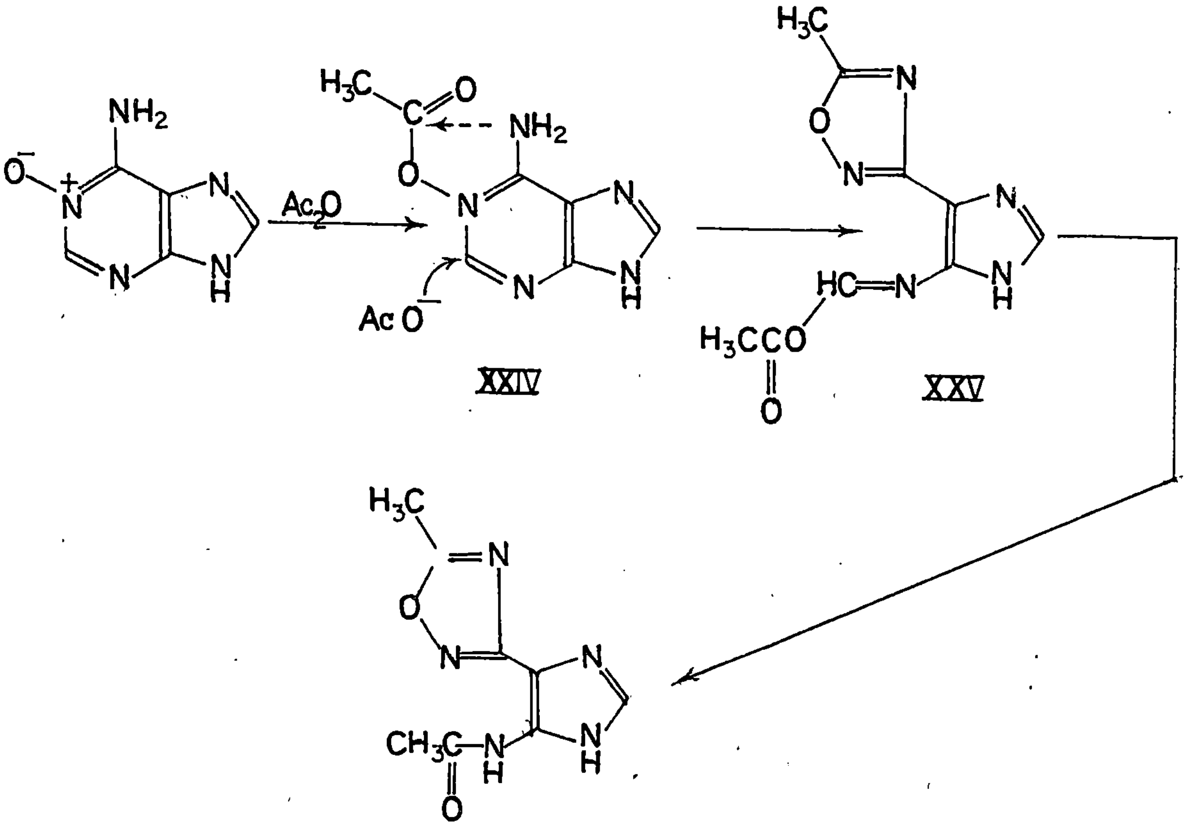
Reactions with acetic anhydride:

The first reaction of heterocyclic N-oxides with acylating reagents was reported in 1947 by Katada[29], who isolated 2-pyridone (XXIII) from the reaction of pyridine N-oxide with acetic or benzoic anhydride. However, the initial product of reaction is 2-acetoxy pyridine (XXII) which is ultimately hydrolysed on work-up to produce the 2-pyridone (XXIII). Although there is a very strong tendency for the reaction to occur at the α-position, if both the -positions are occupied, reaction occurs at the γ-position e.g., at the 9-position with acridine -10-oxides[30], and if all the positions on the hetero-ring are substituted, reaction can occur in a fused benzene ring:



XX XXI XXII XXIII

In a typical reaction the N-oxide is heated under reflux with excess acetic anhydride as solvent for 0.5 - 5 hours. Other anhydrides e.g., benzoic anhydride behaves similarly to acetic anhydride[29], whereas trifluoroacetic anhydride effects the rearrangement under very mild conditions[31]. An alternative reaction path was also observed in the reaction of adenine-1-oxide with acetic anhydride. The initial N-acetoxy acetate salt (XXIV) undergoes cleavage of the pyrimidine ring to give the imidazole (XXV)[32]. Subsequent reactions of (XXV) led to the isolated product (XXVI).

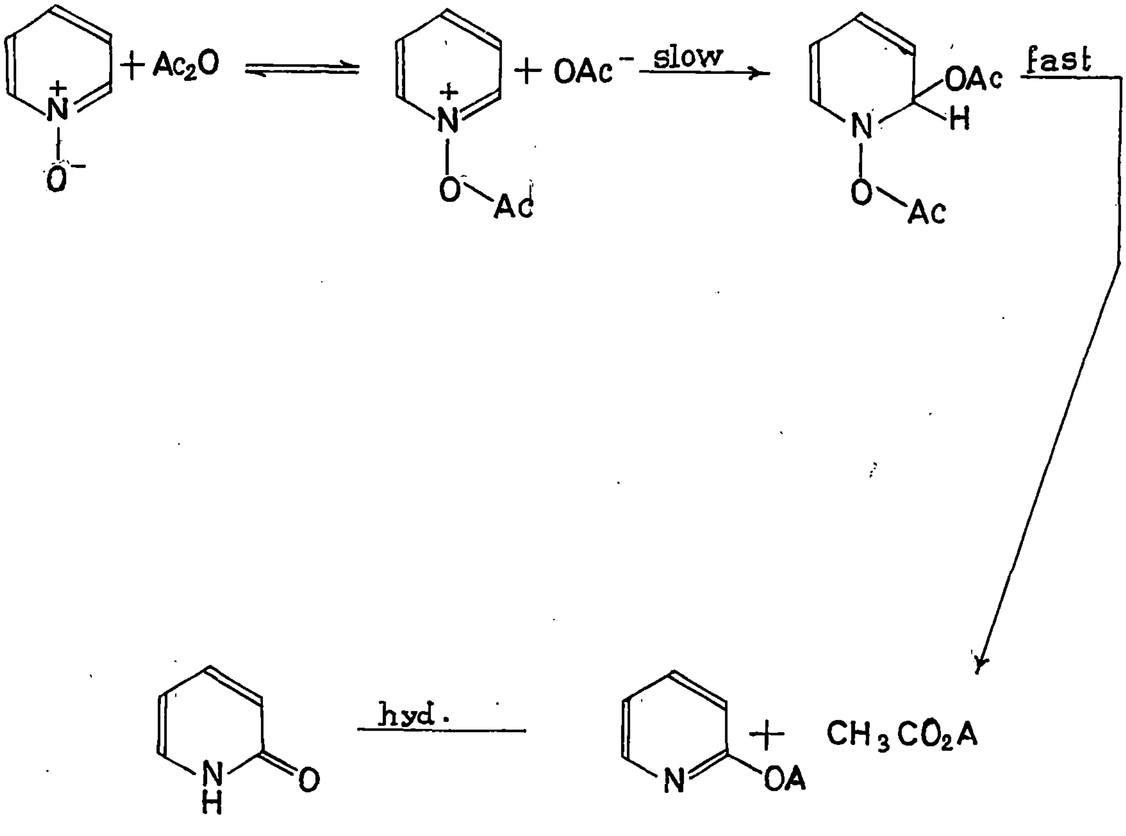


XXIV

XXV

XXVI

Although Ochiai and Okamoto[33] has proposed the general mechanism for the reaction of pyridine N-oxide and acetic-anhydride in 1948, the refinements of this mechanism along with supporting evidence are only recently given by Markgraf[34] and Oae[35,36] (Scheme VII):



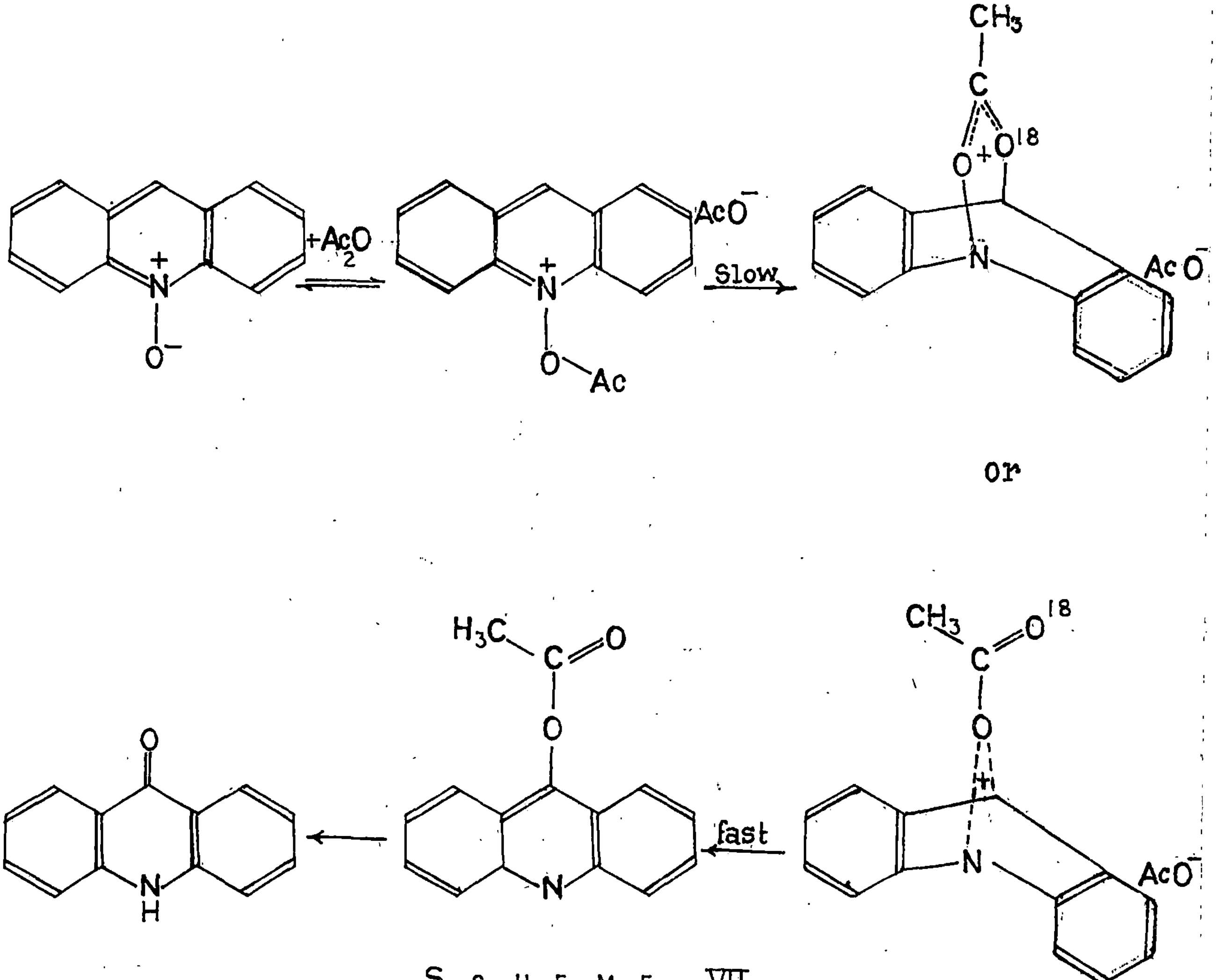
XXIII

SCHEME VII

The rearrangement of 3-picoline N-oxide to 2-and 6-acetoxy-3-methylpyridine using ^{18}O-labelled acetic anhydride was investigated; the results strongly support the intermolecular ionic reaction pathway.

The experimental approach in the mechanistic study of the reaction of acridine N-oxide with acetic anhydride parallels closely that for the pyridine N-oxide case. Markgraf and Ahn[37] observed pseudo-first-order kinetics for the reaction of acridine N-oxide in excess acetic anhydride and reported the following paramete $\Delta H^{\ddagger}$ 12.2 ± 0.1 Kcal/mole, $\Delta S^{\ddagger}$ -32.2 ± 0.6 eu. In addition a small positive salt effect was found with sodium perchlorate and tetrabutylammonium acetate.

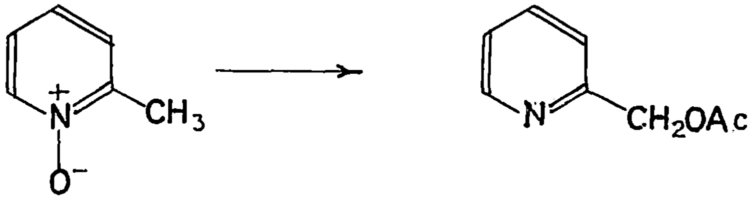
A subsequent report by Markgraf and Carson[38] showed no kinetic isotope effect ($K_H/K_D = 1$) for this reaction. These data are rationalized by the mechanistic path way given in Scheme VIII



S C H E M E VII

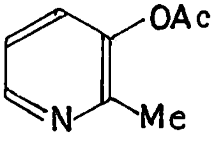
A comparison of the reaction rates of acridine N-oxide and pyridine N-oxide with acetic anhydride at 25° shows $K_{\text{acridine-N-oxide}}/K_{\text{pyridine N-oxide}} = 4 \times 10^{6}$. This striking difference in reaction rate along with a comparison of activation parameters for the two reactions is not surprising in view of the mechanistic differences for these reactions.

Reactions of 2-picoline N-oxide with acetic anhydride was independently discovered by four groups[39-42]. This side-chain acyloxylation (XXVII) by acid anhydrides has since been shown to be a general reaction for the N-oxides of quinoline, isoquinoline, pyridazine, pyrimidine, pyrazine, quinoxaline, thiazole and other heterocyclic systems provided they are substituted at an α or γ-position by practically any alkyl group; a saturated carboxylic ring fused to a heterocyclic N-oxide behaves as an alkyl group. In typical reactions, the N-oxide is heated with an excess of the acid anhydride for 1-6 hours at 100°; yields are often in the range of 50-70%.

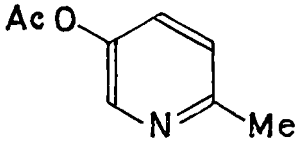


XXVII

Kobayashi and Furukawa[39] isolated a by-product from the reaction of 2-picoline N-oxide with acetic anhydride. It was originally thought to be 6-methyl-2-pyridone, but was latter shown to be a mixture of (XXVIIIa) and (XXVIIIb) (ca 3% yield of each isomer[43-45]). 4-picoline N-oxide similarly yields 3-acetoxy-4-picoline as a by-product.

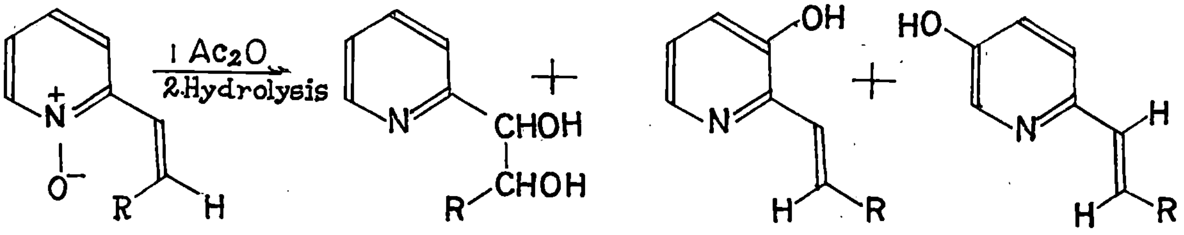


XXVIIIa



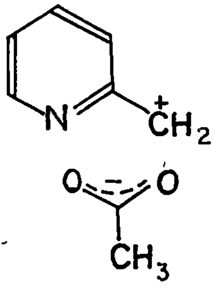
XXVIIIb

Reactions with a variety of 4-substituted-2-picoline N-oxides and 2,6-lutidine-N-oxide were described by Furukawa[46,47], who also noted the rearrangement of 2-styrylpyridine N-oxide (XXIX) by acetic anhydride to (XXIXa), (XXIXb) and (XXIXc).

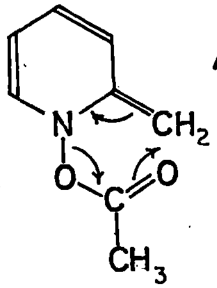


XXIX XXIXa XXIX b XXIX c

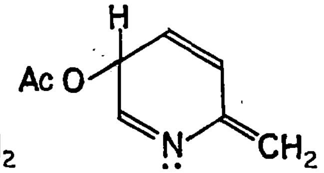
It was suggested[39,43] that the reaction mechanism involves ionization and anionotropic rearrangement, but Bullitt and Maynard proposed that the reaction proceeds though a rearrangement of the anhydro-base (XXX). Not only does rearrangement of the anhydro-base account for the formation of the major α-acetoxymethyl product (XXXII), but analogous rearrangement to intermediates of type (XXXI) are logical routes to the β-acetoxy by-products (XXVIIIa & XXVIIIb). However, Boekelheide and Harrington proved that the reaction mixture contains free-radicals and proposed a radical-chain mechanism



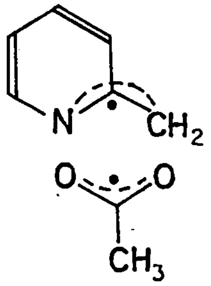
XXXa



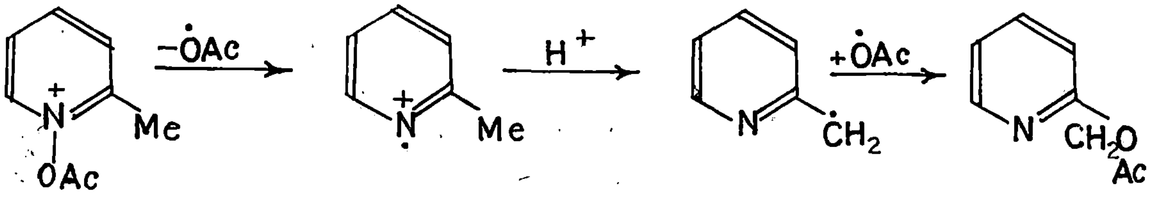
XXX



XXXI



XXXb



VI

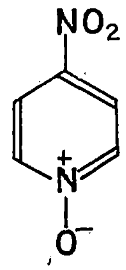
XXXII

Decisive evidence against the cyclic rearrangement (XXX) mechanism was provided by the ^{18}O-labelling work of Oae and his co-workers[48,49]. They demonstrated that the rearrangement of 1-acetoxy-2-picolinium anhydro-base is indeed intramolecular, but that the two oxygen atoms of the acetoxy group become equivalent in the product. Oae interpreted these results in terms of a radical-pair mechanism (XXXb) in which the radicals are enclosed in a solvent cage and cannot react intermolecularly.

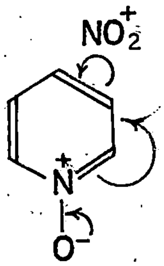
Taking the evidence as a whole, it now seems conclusively proved that 2-picoline N-oxide reacts with acetic anhydride via ion-pair intermediates (XXXa).

Electrophilic Substitution Reaction of Aromatic N-Oxides:

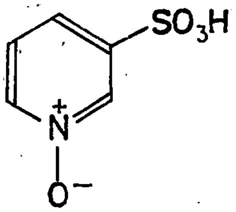
The facile nitration of pyridine N-oxide in the 4-position (XXXIII) was first discovered by Ochiai[11,50], and independently by den Hertog[51]. Both of whom correctly reasoned that the N-oxide oxygen atom would release electrons to the 4-position thereby promoting the reaction. However, the fact that sulphonation of pyridine N-oxide under some condition gives a good yield of the 3-sulphonic acid[52] (XXXIV) had to be explained. It was early postulated that this difference in orientation is a reflection of the fact nitration occurs on the free base (XXXIIIa), whereas sulphonation involves the conjugate acid (XXXIVa)[53]. Recently, good evidence has been obtained that electrophilic reactions in strongly acidic media yield γ-substituted products when the free base is attacked, and β-substituted derivatives when reaction proceeds through the conjugate acid.



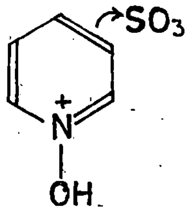
XXXIII



XXXIIIa

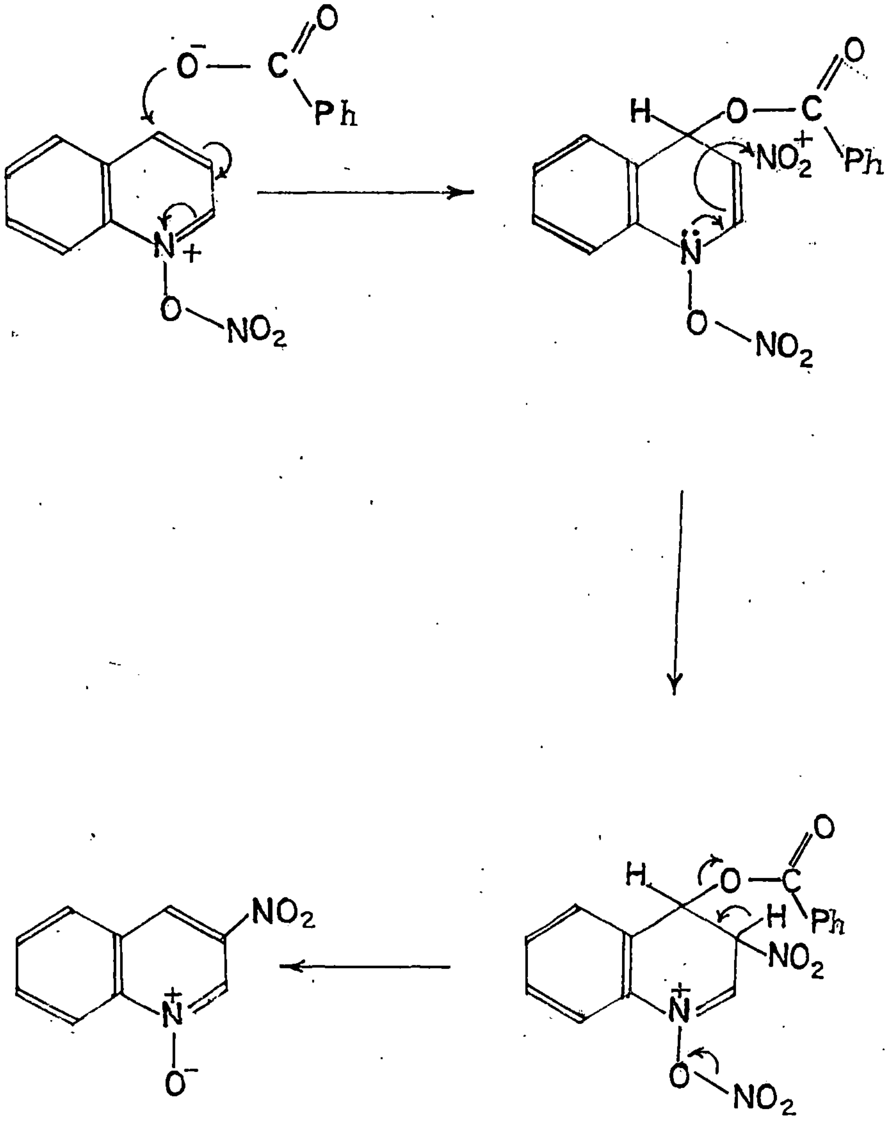


XXXIV



XXXIVa

Pyridine N-oxide can be converted into 4-nitropyridine N-oxide (XXXIII) in 80-90% yield on heating with concentrated sulphuric acid and fuming nitric acid at 100°[50,51]. Ochiai and Kaneko[53], reported that quinoline N-oxide could be nitrated with benzoyl nitrate to give 3-nitroquinoline N-oxide (XXXV) (Scheme IX).



XXXV

SCHEME IX