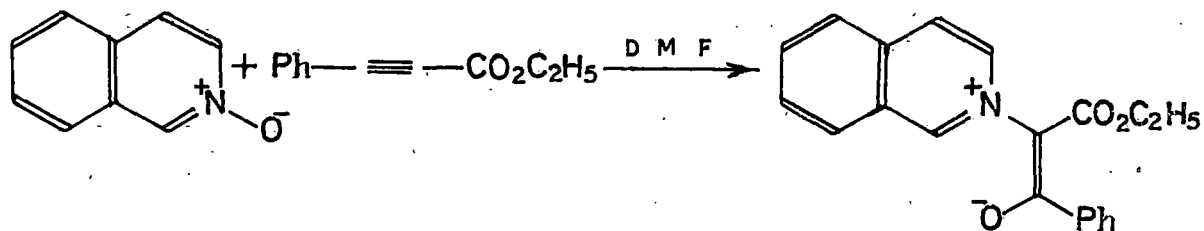


CHAPTER - II

Reactivity of Aromatic N-oxides with Electrophilic Acetylenes

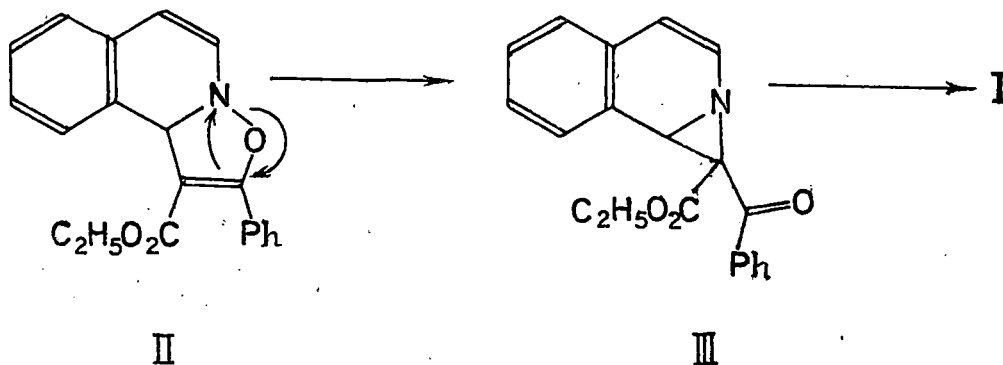
As has already been discussed in the previous chapter aromatic N-oxides constitute a class by themselves and undergo a wide variety of reactions One of the least understood mechanistically, however, is the reaction of aromatic N-oxides with electrophilic acetylenes such as phenylpropionic acid ethyl ester. Niessen et al.⁵⁵ have established that the product is an ylid (I).



I

Although no mechanism of this reaction has been given by the above authors, a priori cycloaddition may be assumed to be the first step. The cycloadduct (II)

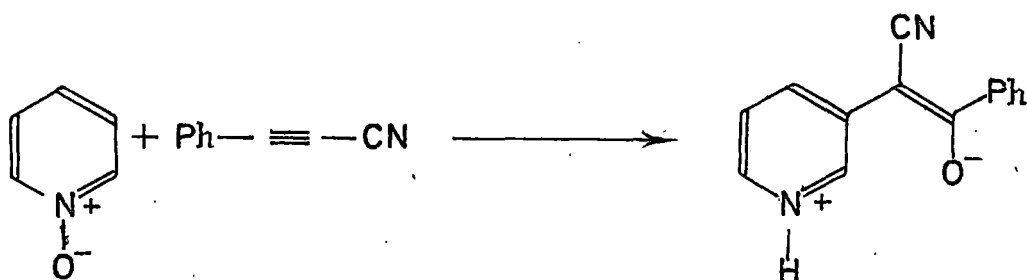
may, then, undergo ring contraction to furnish the aziridine (III) which undergoes further transformation to the ylid (I).



It must be emphasized here that the above mechanism is a hypothetical one and there is no experimental evidence of the formation of either (II) or (III).

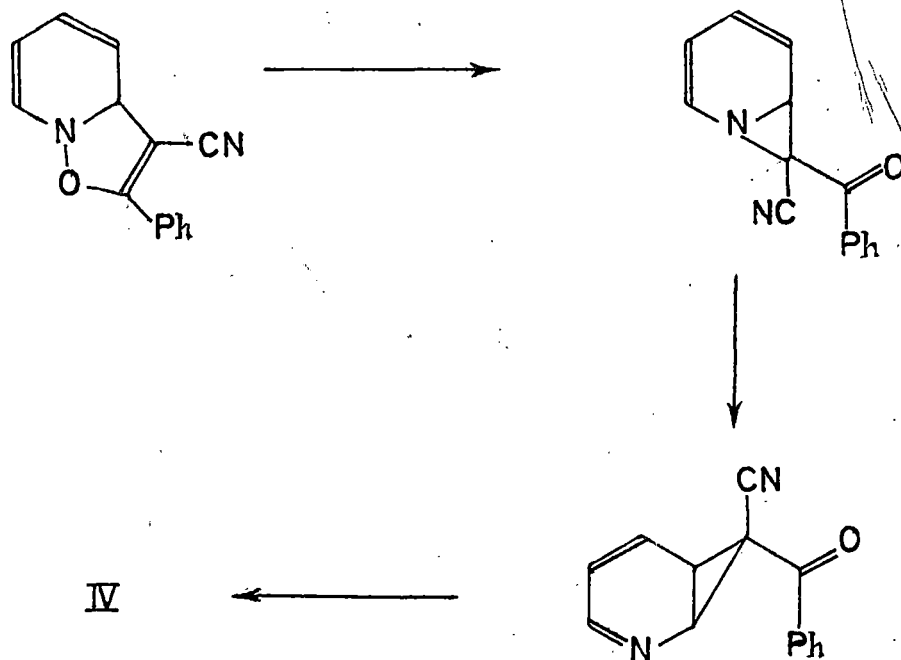
Abramovitch et al⁵⁶ have more recently described the reaction of pyridine N-oxide with phenyl propiolonitrile. In this reaction the 3-substituted product (IV)

has been formed almost exclusively, although there is no evidence of the formation of a cycloadduct as the first step of the reaction.



IV

If, once again, we assume a concerted cycloaddition as the first step of the reaction, formation of (IV) can be explained by a multistep process (Scheme I).

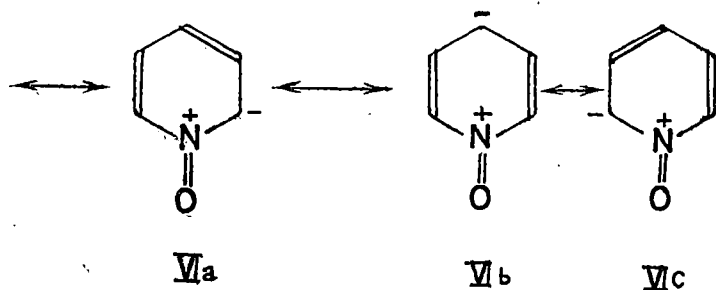
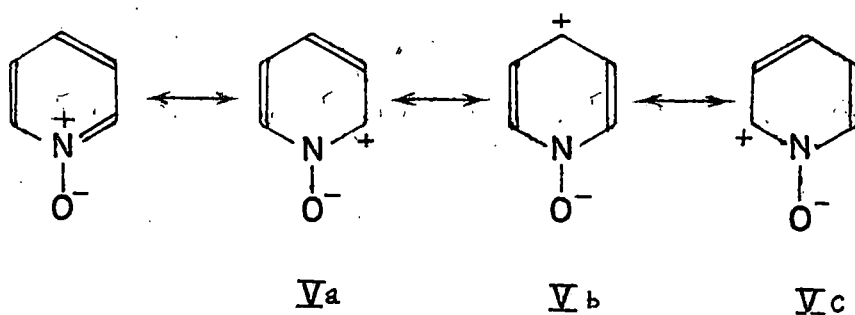


S C H E M E I

Although cycloadducts are quite reasonable hypothetical intermediates in the above reactions, we wonder whether some other reaction pathways would be operative here. Such a pathway should not only be allowed on symmetry and energy grounds but also be a shorter one.

In order to find out such a shorter pathway we should once again look back into the general nature of the electronic structure of aromatic N-oxides and the reactivity patterns that such structures furnish.

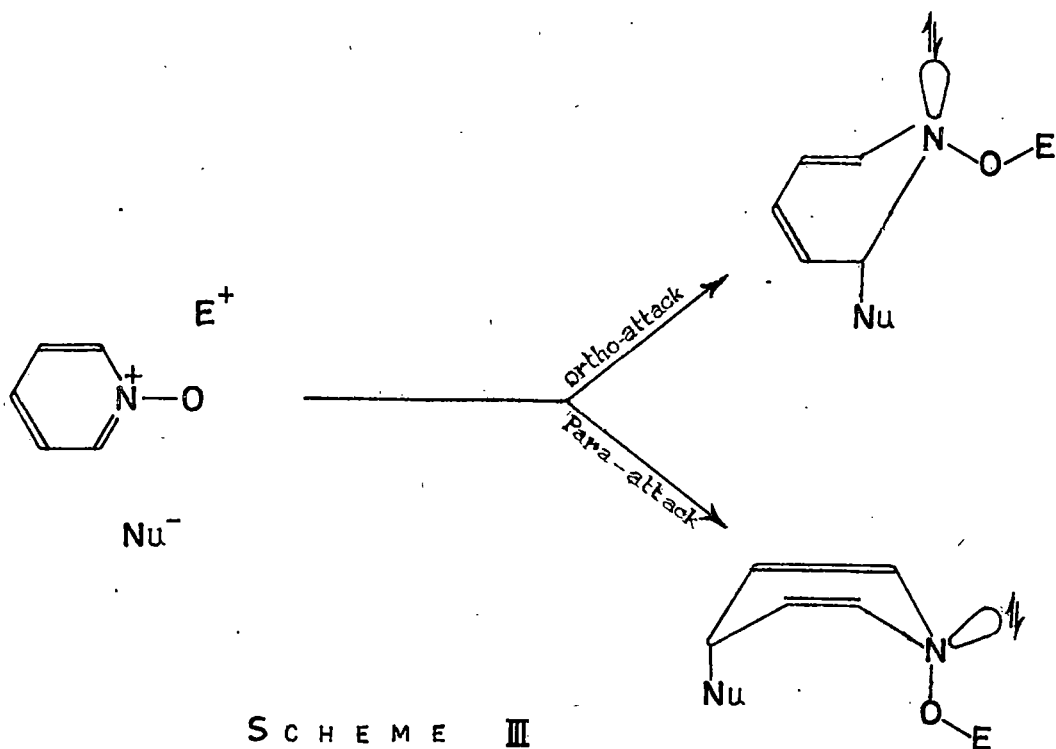
Pyridine N-oxide, the simplest of the aromatic N-oxides, can be described as a resonance hybrid of seven structures (Scheme II). Of those structures (VIa, b and c) make major contribution to the resonance hybrid



S C H E M E II

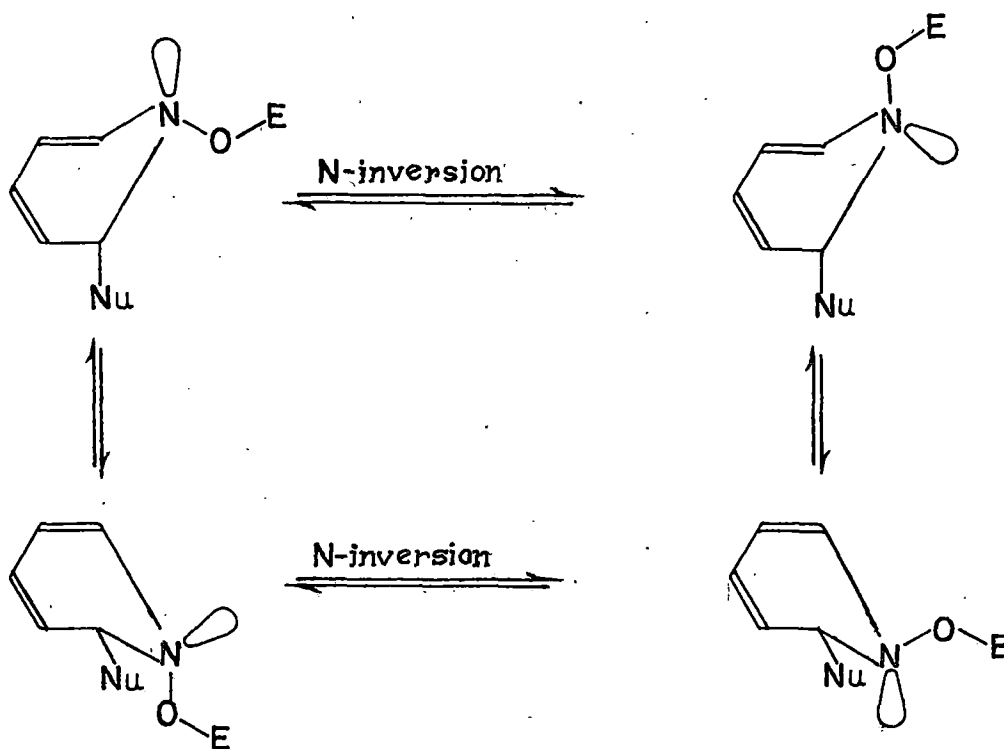
as is evidenced from the nitration of pyridine N-oxide which takes place exclusively at the para position. The structures (Va, b and c) make only a minor contribution, as the repulsive interaction between oxy-anion and the adjacent nitrogen lone-pair is quite appreciable in these structures. However, as we shall see shortly, these minor structural contributions can play a major role in reaction dynamics.

It was first pointed out by Katritzky³⁷ that a nucleophile (Nu^-) would attack the ortho- or para-positions of the pyridinium moiety of pyridine N-oxide if an electrophile (E^+) was available to interact at the oxy-anionic end. This idea is schematically represented in Scheme III. From the view point of conformational



analysis the entry of the nucleophile is axial and anti-periplanar with respect to the developing lone-pair at nitrogen.

The situation is not so simple as described in Scheme III. More detailed model study would reveal that there are possibilities of conformational change and nitrogen inversion which make the situation complicated. A complete picture of such changes is given in Scheme IV

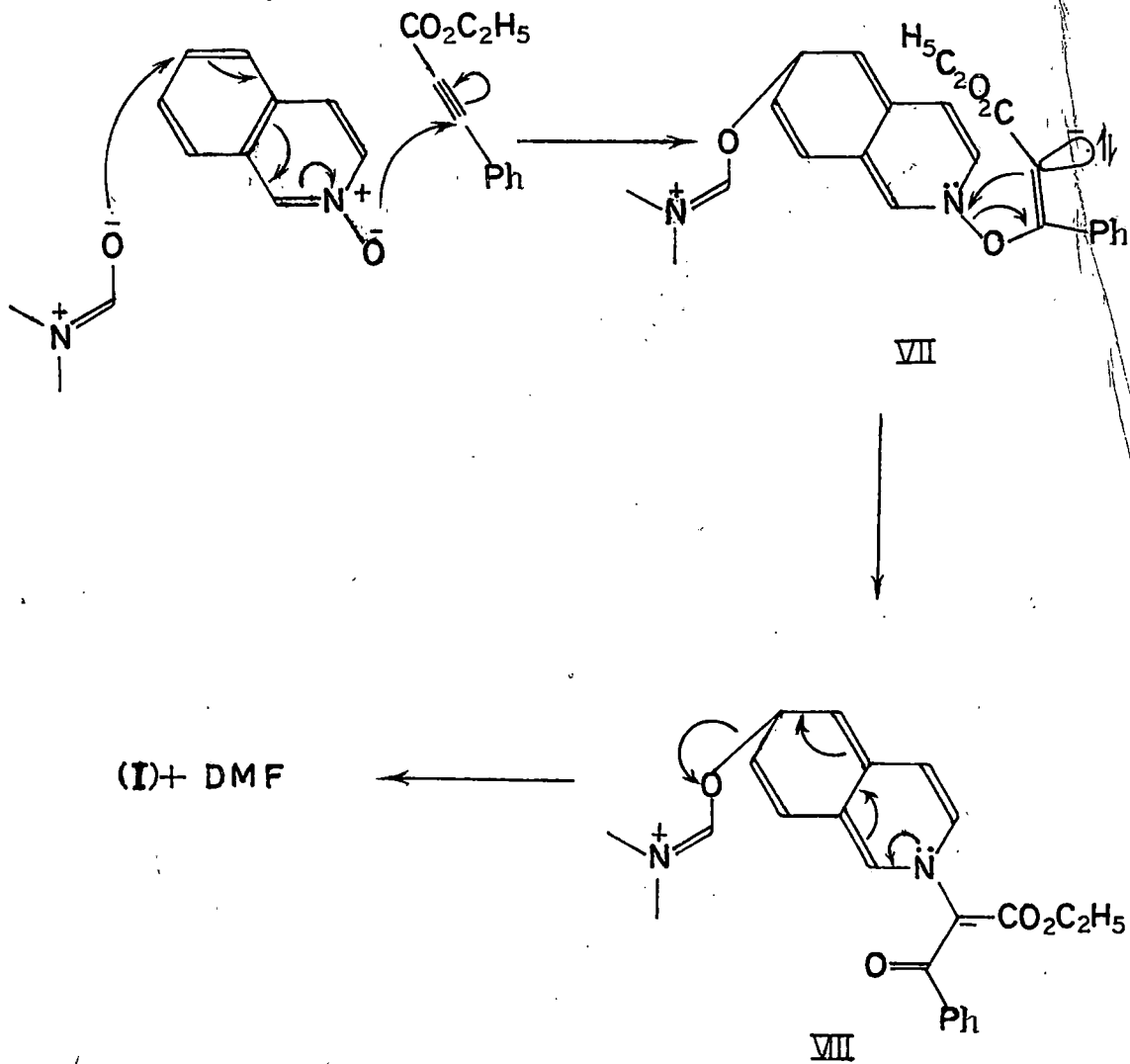


S C H E M E I V

with the product from the ortho-attack of the nucleophile. A similar scheme may also be drawn with the product from the para-attack of the nucleophile.

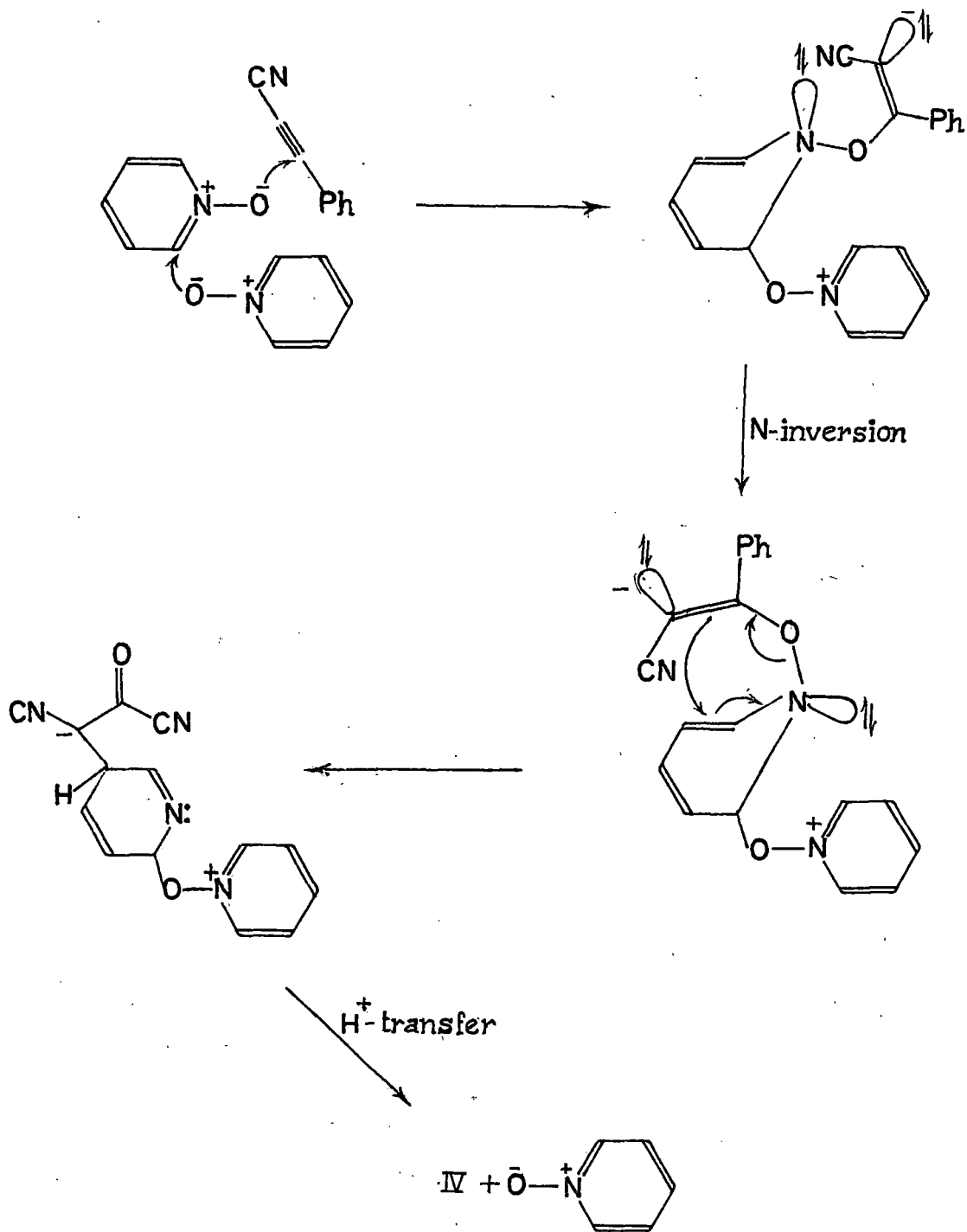
On the basis of the above model studies it is now evident that such a three-body mechanism can be operative in the reactions of aromatic β -oxides with electrophilic acetylenes such as phenylpropionic acid ethyl ester and phenyl propiolonitrile. These acetylene compounds play the role of electrophiles while a second molecule of aromatic β -oxide would act as a nucleophile. When the reactions are carried out in nucleophilic solvents such as dimethyl-formamide, the solvent molecule may also act as a nucleophile.

We are now in a position to explain the formation of (I) on the basis of the above model with R1P acting as the nucleophile (Scheme V). The most important step in this case is the conversion of (VII) to (VIII). This is a symmetry-allowed $6\sigma + \pi_2$ process and is expected to be a facile one as the average bond-energy of the >N-O bond in (VII) is quite low (48 Kcal/mole), whereas that of the carbonyl group in (VIII) is exceptionally high.



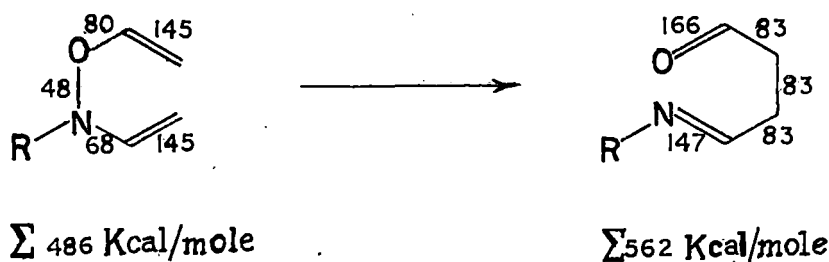
S C H E M E V

The formation of the product (IV) can also be explained on the basis of a similar mechanism. In this case, a second molecule of pyridine N-oxide will act as



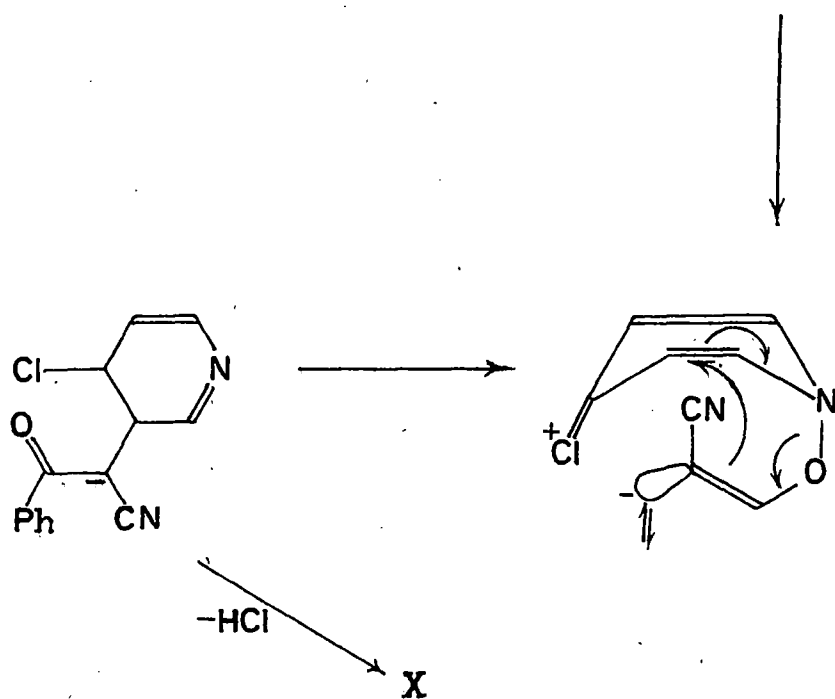
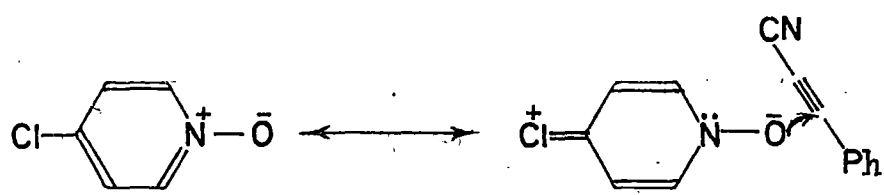
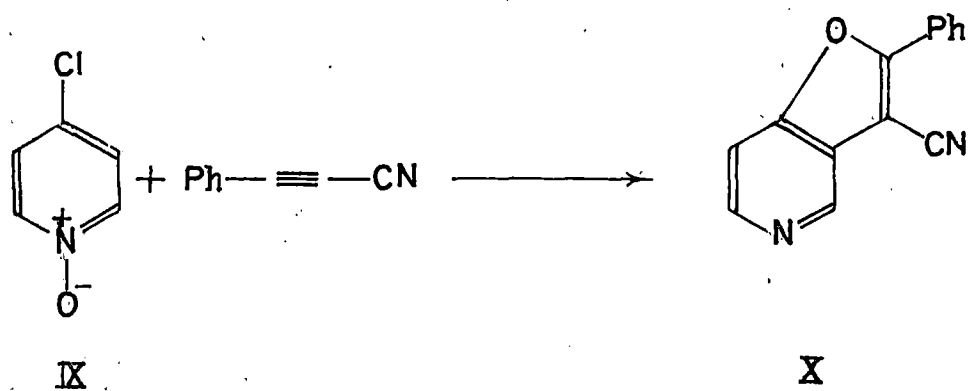
S C H E M E VI

the nucleophilic catalyst (Scheme VI). The most important step in this case is the *ortho-para*-Claisen rearrangement. An ordinary Claisen rearrangement requires a temperature as high as 300°. But here, due to the weakness of the $\text{N} = \text{O}$ bond, the balance of average bond-energy is 76 Kcal/mole towards the right hand side (Scheme VII) and the reaction should run smoothly at a much lower temperature.



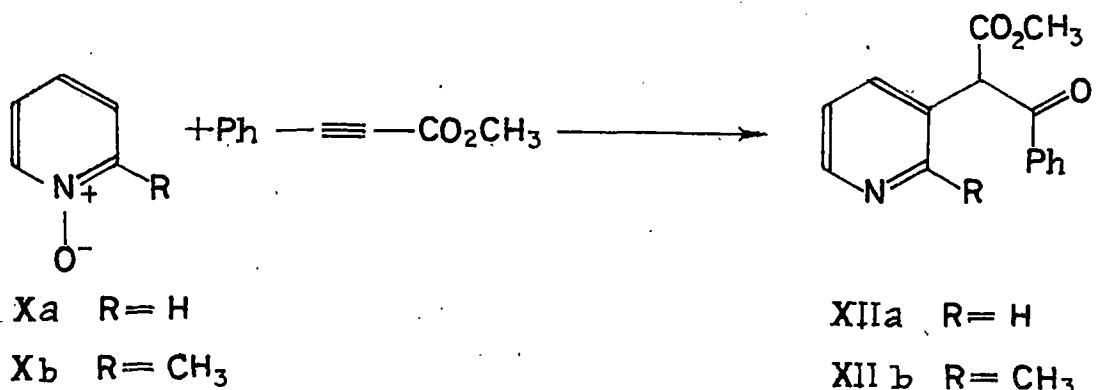
S C H E M E VII

So far we have discussed cases in which a molecule of DMP or pyridine N-oxide act as nucleophilic catalyst. There are also cases in which a heteroatom incorporated into the ring structure is able to play a similar role. The reaction of 4-chloro pyridine N-oxide (IX) with phenyl propiolonitrile may be considered as an example. In this case the chlorine atom plays the trick (Scheme VIII).



S C H E M E VIII

In order to find out which of the two mechanisms — cycloaddition vis-a-vis three-body mechanism — is valid we undertook the following experiments with pyridine N-oxide and 2-methyl pyridine N-oxide as the starting materials. For the electrophilic acetylene we chose phenylpropionic acid methyl ester. A mixture of N-oxide and methyl ester was refluxed in boiling benzene or toluene, when the 3-substituted product was formed exclusively (Scheme IX). The reaction mixture was cooled to room temperature, diluted with ether and washed with water to remove the unreacted N-oxide. The organic layer



S C H E M E IX

was then extracted with 10% hydrochloric acid to remove the basic product which was then liberated by making the solution alkaline with sat. sodium bicarbonate solution and subsequent extraction with ether. The residual acetylene compound was also recovered from the organic layer and weighed to find out the amount of it consumed during the reaction. This gave us the exact amount of the product formed.

If concerted cycloaddition was operative in the first step of the reaction, this step would be reversible, whereas the steps leading to the product (XIIa, b) would be irreversible. Therefore, from the amount of the product formed a kinetic study could be made. This was done in detail and it was apparent from these kinetic studies that the cycloaddition pathway was indeed operative in this case.