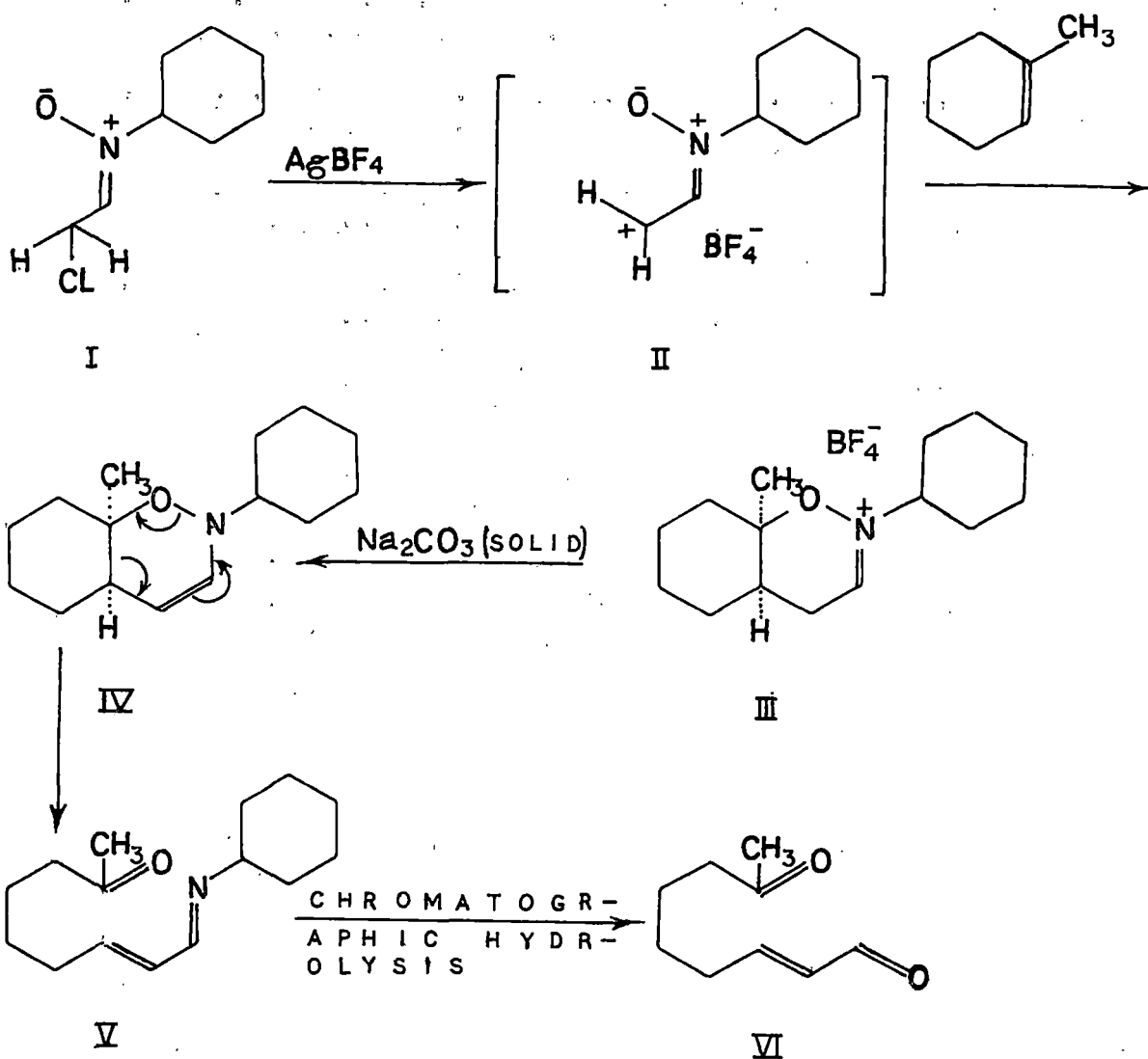


## **PART II**

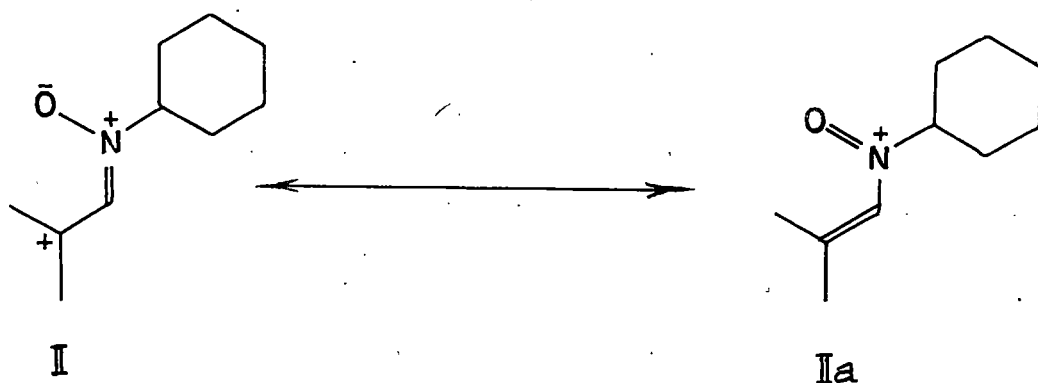
## CHAPTER - I

### Chemistry of the $\alpha$ -Amino Nitrones

Current chemistry of the  $>\ddot{N}-\ddot{O}$  bond has received great impetus from the work of Eschenmoser et al. Due to repulsive interaction between the adjacent lone-pairs this bond is very weak, having the average bond-energy value of only 49 kcal/mole and takes part in different chemical transformations which have great synthetic potentialities. For example, the following transformation may be considered<sup>1</sup>.

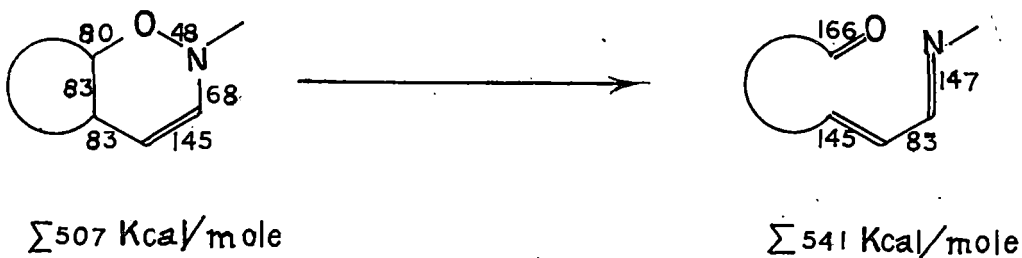


This is one of the striking examples of the synthetic potentiality of the Eschenmoser chloro-nitrene method. The nitrene (I), when treated with silver tetrafluoroborate furnishes the cation (II) which may be considered as a resonance hybrid of the structures shown below.



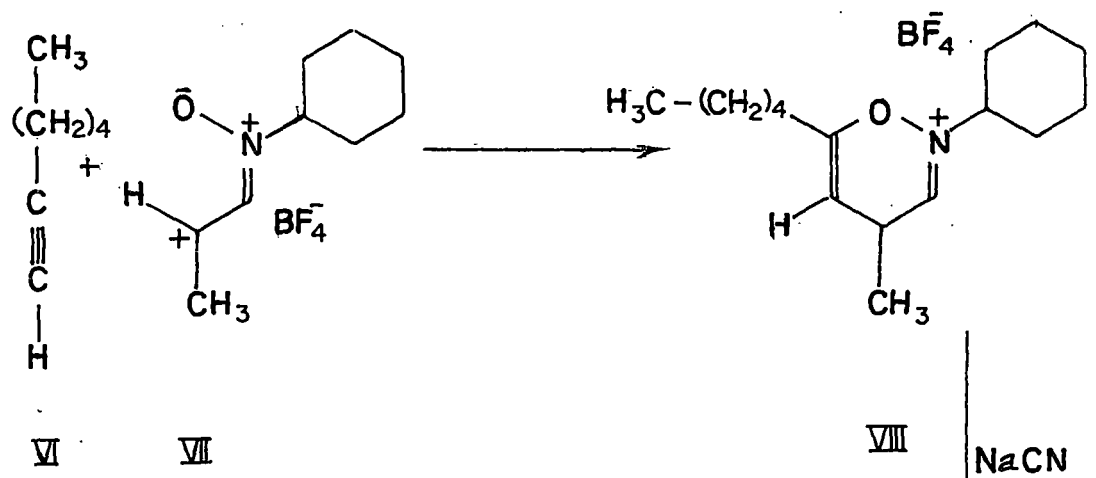
The vinyl nitrosonium ion (IIa) undergoes facile cycloaddition in a stereo- and regio-specific way with 1-ethyl cyclohex-1-ene to furnish the cycloadduct (III). The latter on stirring with powdered sodium carbonate in an organic solvent loses one of the 4-H atoms to furnish the 1-oxa-2-aza-5-ene system (IV) containing the weak  $\text{O}=\text{N}$  bond. The system (IV), then, undergoes smooth transformation to (V) at 40°C. Average bond-energy calculations show that this should be, because the balance

of energy is 34 Kcal/mole towards the right-hand side.

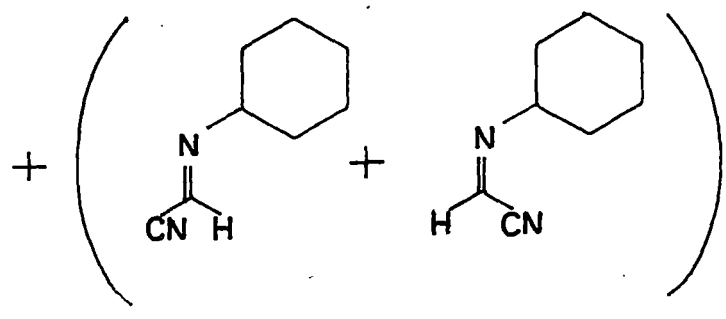
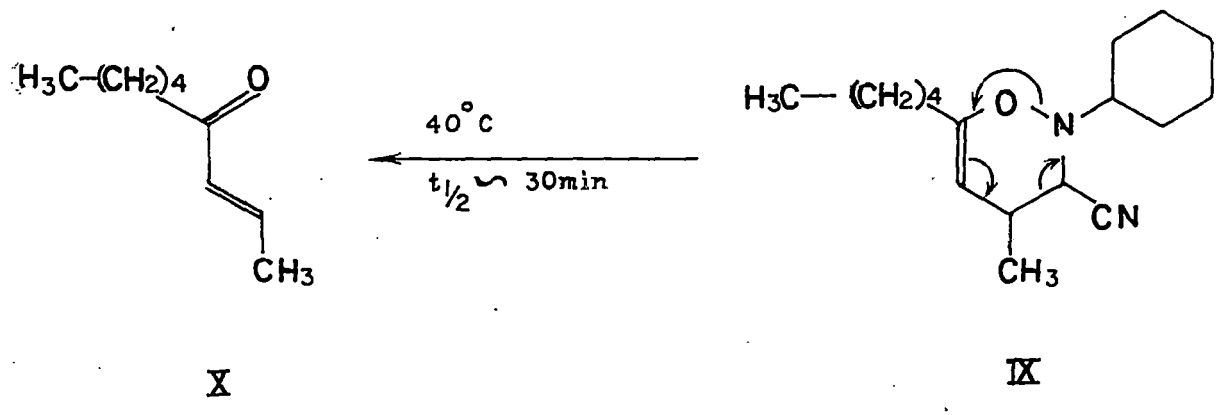


It must be mentioned that not only the weakness of the  $\text{C}=\text{N} - \ddot{\text{O}}$  bond, but also the force of "Carbonylisation" drives the reaction towards the right hand side. A carbonyl group is quite a strong bond, having the average bond-energy value of 168 Kcal/mole which is considerably higher than other double bonds.

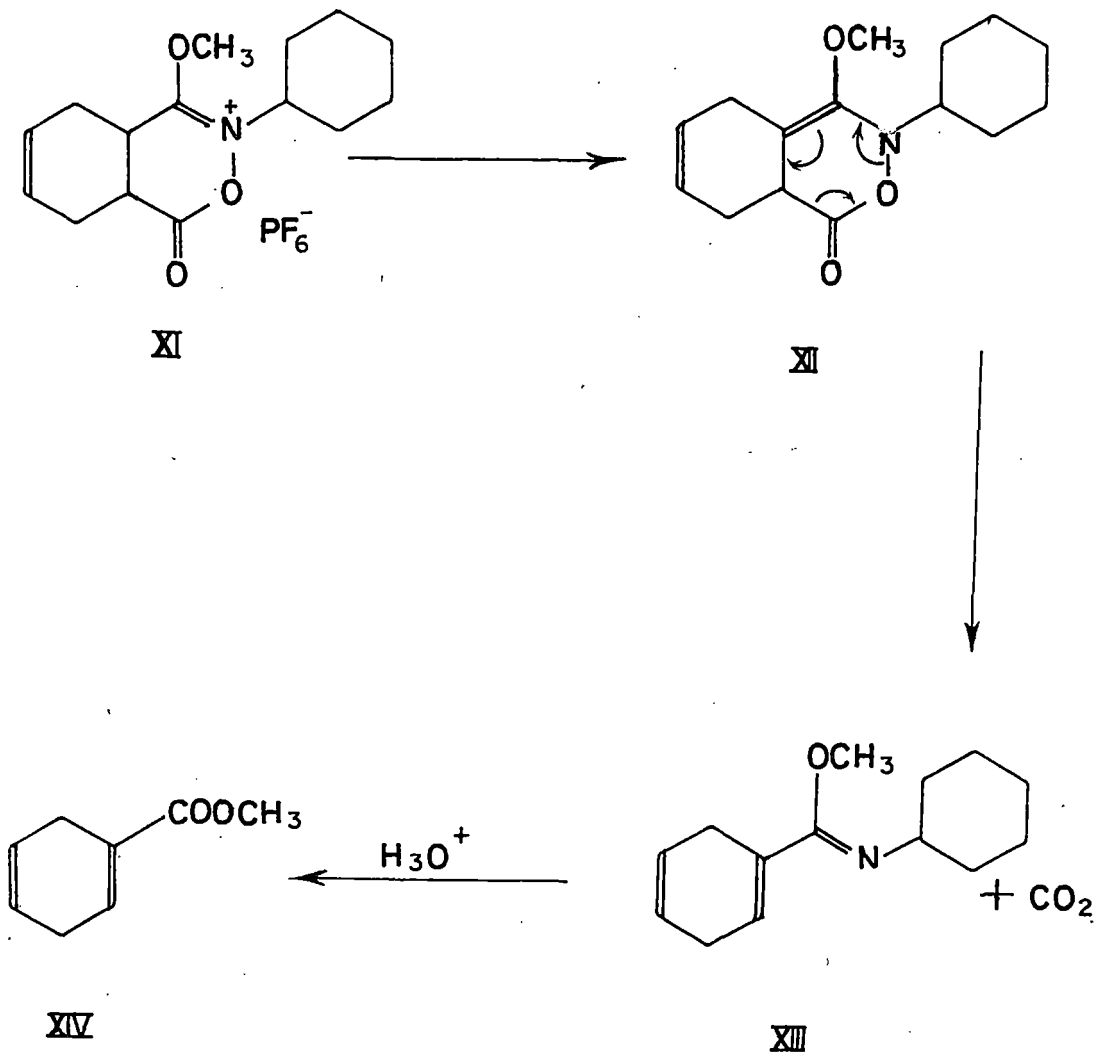
A second example is the reaction of vinyl nitrosonium ion with acetylene<sup>2</sup>. Here also, due to similar reasons, the nitrile (IX) undergoes smooth transformation to the  $\alpha, \beta$ -unsaturated ketone (X).



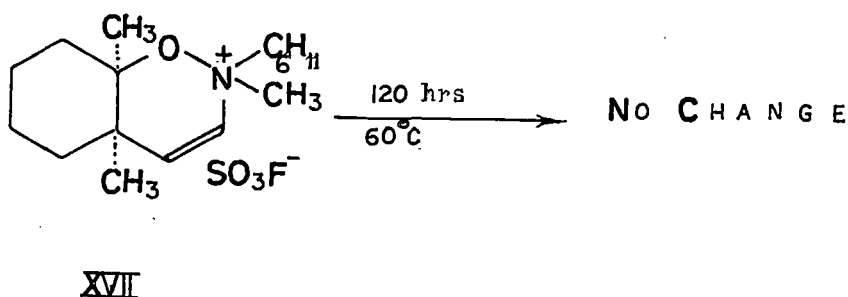
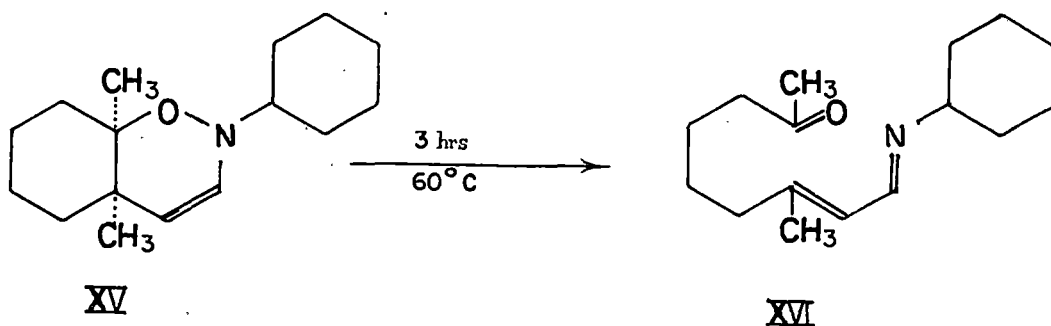
NaCN



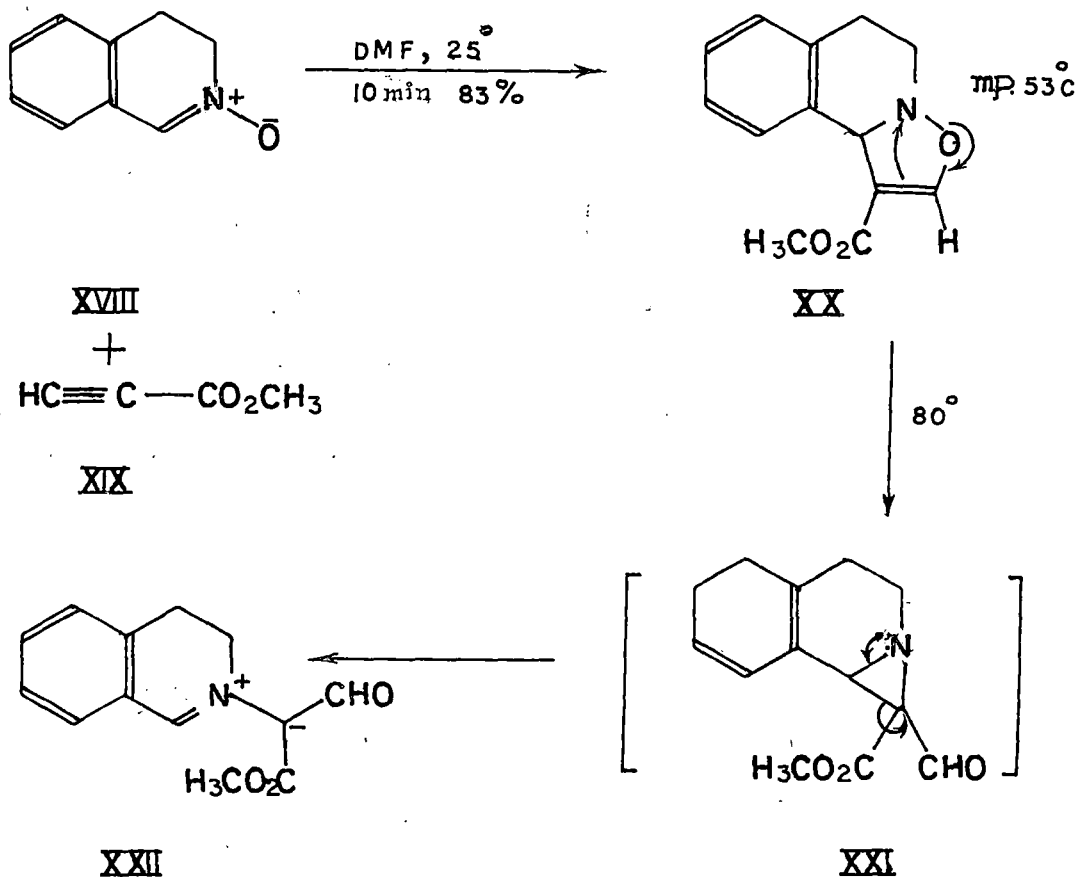
A third example<sup>5</sup> is the transformation of (XI) via oxo-aza-one system (XII) to 1,6-cyclohexadiene-2-carboxylate (XIV).



That the weakness of the  $>\ddot{N}-\ddot{O}$  bond is the driving force behind all these transformations has been elegantly established by Dr. P. Gyax in his Ph.D. dissertation<sup>4</sup>. If the nitrogen atom of the above bond is alkylated, one arrives at the system  $>\overset{+}{N}-\ddot{O}$ . Here, due to alkylation, the lone pair of the nitrogen is used up, so that the repulsive interaction between the heteroatoms is no longer present. As a result, the average bond energy of the alkylated species is much higher than that in which lone-pairs are present at adjacent heteroatoms. Gyax has established that, while the oxo-aza-one system (XV) undergoes smooth transformation to (XVI) in 3 hrs at 60°C, the N-alkylated system (XVII) remained unchanged when left at 60°C for 120 hrs.

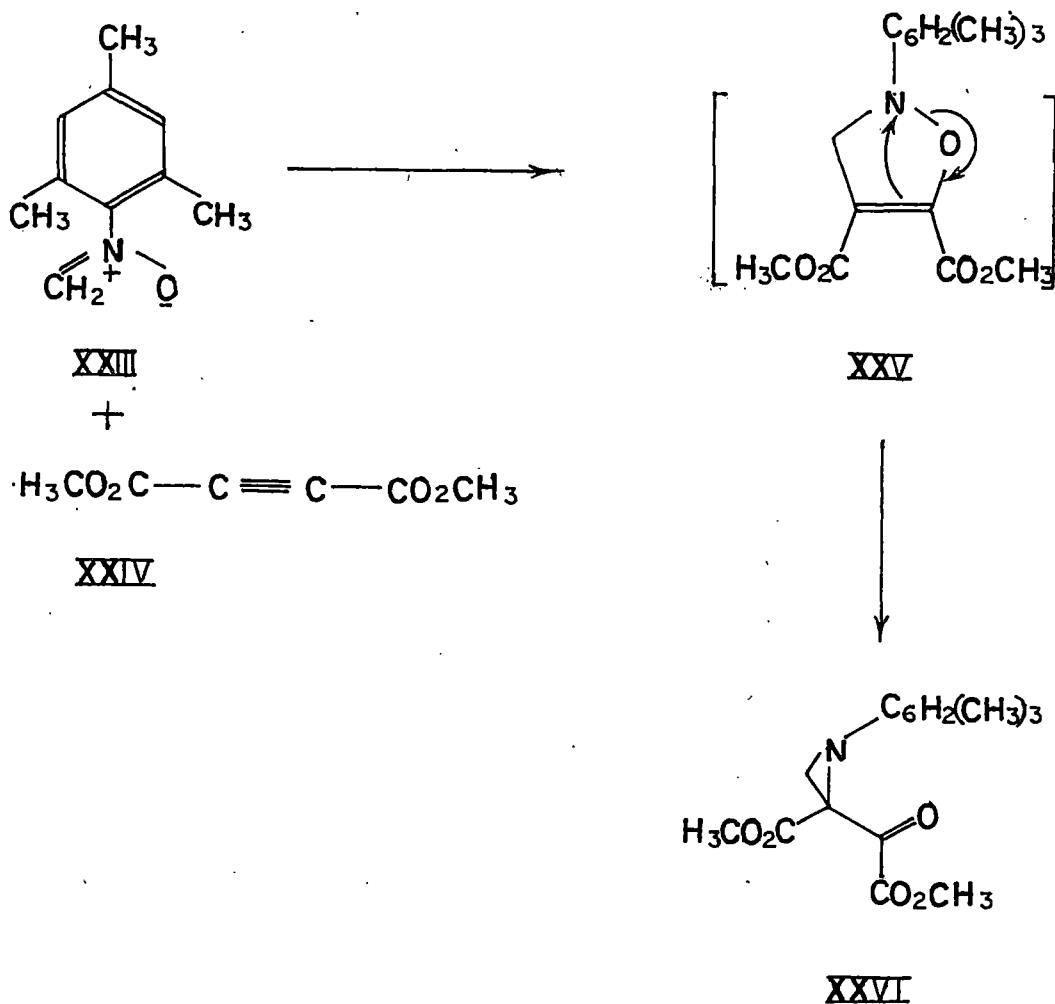


In all the above cases the oxo-azo-ene systems are contained in six-membered rings. Formation of five-membered oxo-azo-ene systems and their facile chemical transformations have been demonstrated by Huisgen et al.<sup>6</sup> These authors have shown that 5,6-dihydro-isoquinolino N-oxide (XVIII) undergoes facile cycloaddition reaction with the acetylene compound (XIX) in DMF at 83° furnishing the cycloadduct (XX) as colorless crystals in high yield. At 80°, however, the cycloadduct (XX) undergoes further transformation to the ylid (XXI) probably via an aziridine ring-system (XXI).

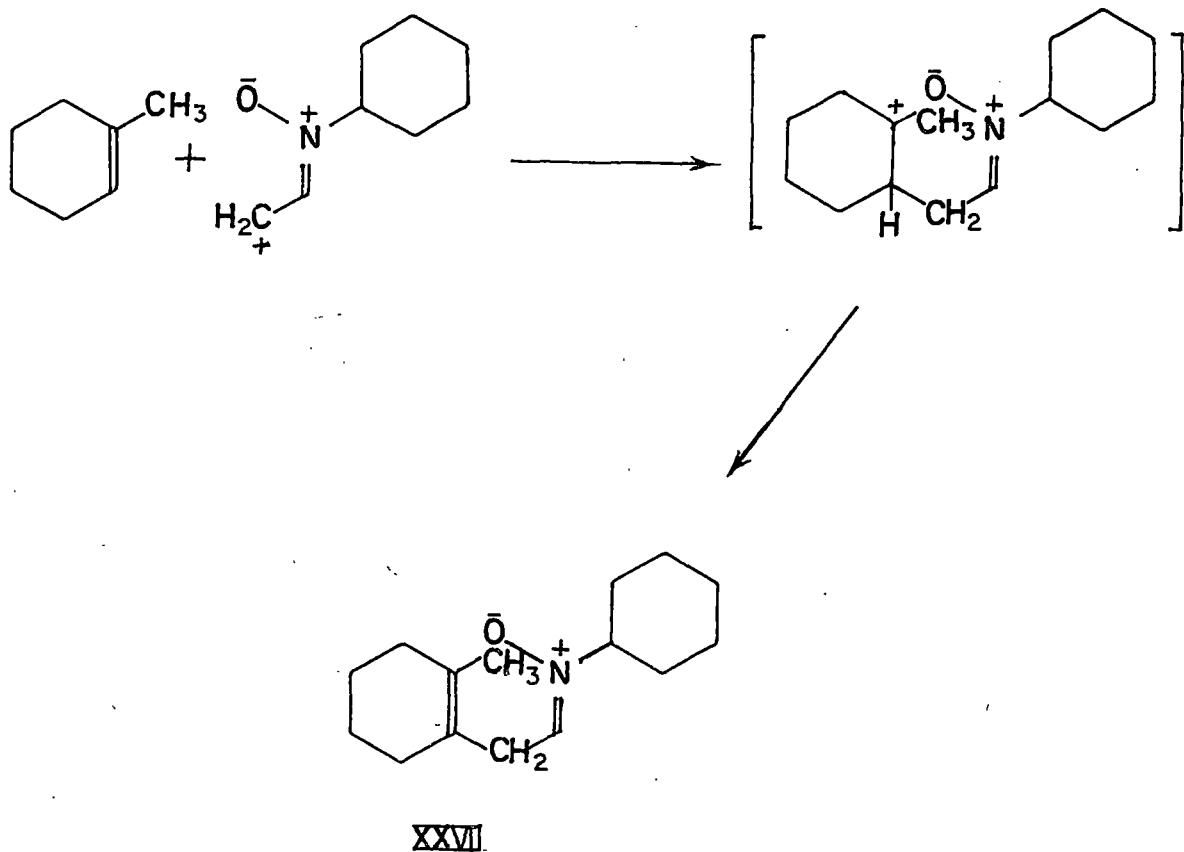




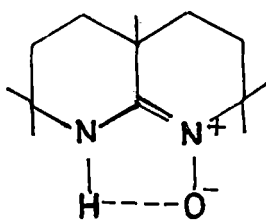
That the aciridino ring, indeed, is formed has been demonstrated in a separate example by Baldwin et al.<sup>6</sup> Thus the nitron (XXIII) undergoes cycloaddition with diethylacetylene dicarboxylate (XXIV) furnishing the transient cycloadduct (XXV) which is automatically transformed into the acylaciridino (XXVI).



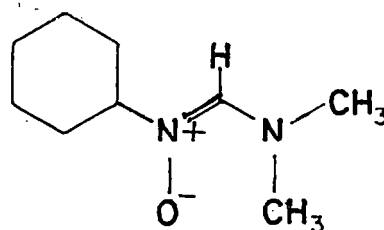
It has now been firmly established that a cation,  $\text{---}$  and only a cation,  $\text{---}$  can be formed  $\alpha$  to the nitrene group. Thus, Beckenboser et al.<sup>7</sup> have shown that the reaction between unsymmetrically substituted olefins and vinyl nitrosonium cation (II  $\leftrightarrow$  III) produces not only the cycloadduct, but also a substitution product (XXVII)



It was, therefore, very striking on the light of these observations that  $\alpha$ -amino nitrones<sup>3</sup> could be prepared as stable compounds (XXVIII and XXIX). From the



XXVIII



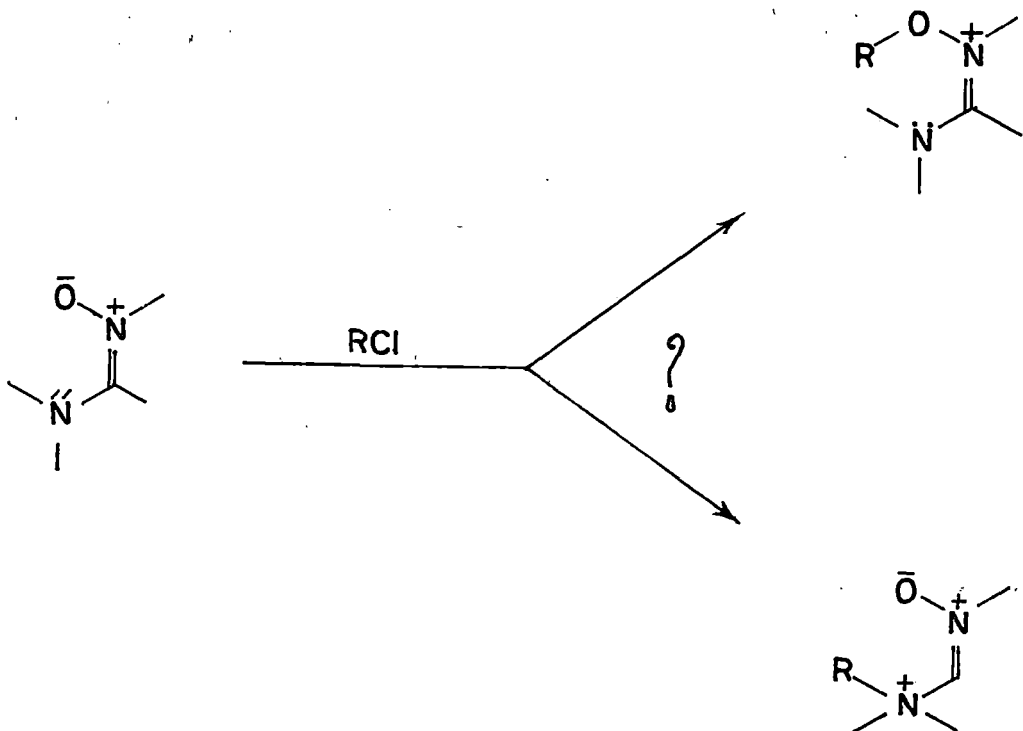
XXIX

theoretical standpoint on the basis of simple MO theory the formation of vinyl nitrosonium ion is quite logical, the system being butadiene-like 4-centred-4-electron

system in which both the bonding MO's are filled up and the antibonding MO's vacant. This, therefore, acts as the diene component in (hetero-) Diels-Alder reaction with olefins ( $4\pi + 2\pi$ -cycloaddition) furnishing cycloadducts of type (III). On the other hand,  $\alpha$ -aminonitrones constitute a 4-centred-6-electron  $\pi$ -system in which the lower lying antibonding orbital is also filled up. As a result, the system is expected to be comparatively unstable. That the system is not so, has been demonstrated

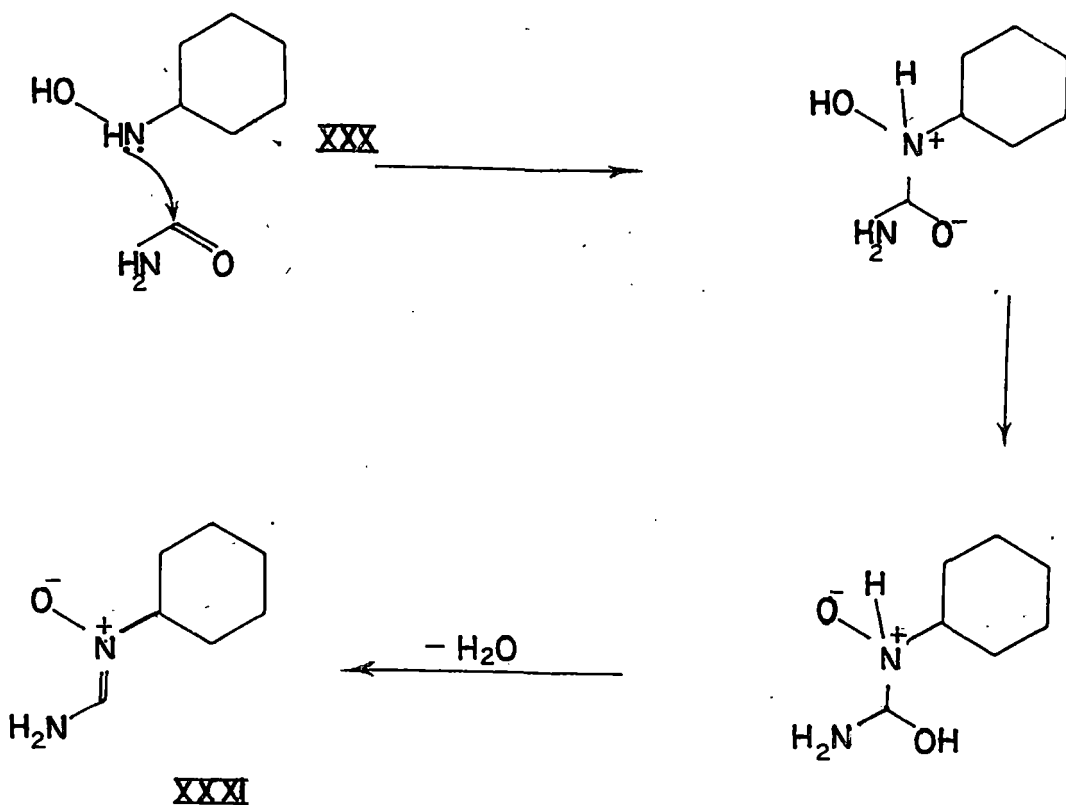
by the preparation of the stable  $\alpha$ -aminoitrone (XXVIII and XXIX).

From the above discussions one thing is apparent, that the  $\alpha$ -aminoitrone should be very reactive due to presence of a filled up antibonding MO, and, indeed, should act as a powerful nucleophile. There are two electron-rich centres, one at the oxy-anion and the other at the  $\alpha$ -nitrogen. But the density of electrons being more at the oxy-anion end (three electron pairs) and steric hindrance minimum, this end should preferably act as a powerful nucleophilic centre in  $S_N2$  reactions. Simple nitrones are not known to act as nucleophiles in this fashion.



S C H E M E I

In order to verify this possibility we first of all undertook the preparation of the nitrene from the simplest of the amides, formamide, and N-cyclohexyl hydroxylamine. The choice of formamide rested on the fact that it not only had sufficient carbonyl functionality but also could function as a good solvent when used in excess. A plausible mechanism of the possible formation of the nitrene is given below.



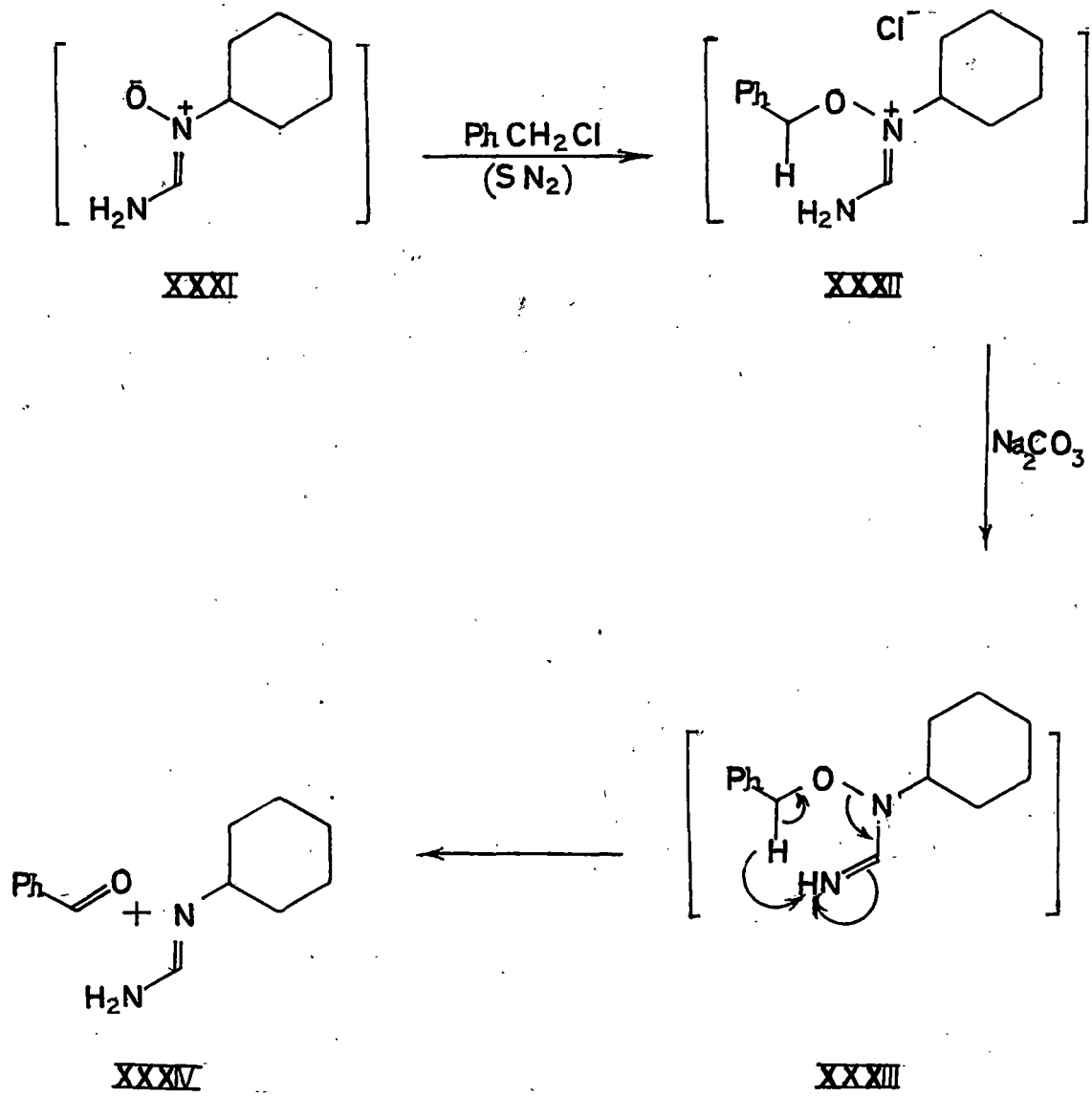
The most important step in the formation of the nitrene (XXXI) is a dehydration process, so that efficient execution of the preparative method needed the use of a dehydrating agent. Anhydrous magnesium sulphate was chosen for that purpose.

N-cyclohexyl hydroxylamine was found to be insoluble in formamide, but as the former was a very light compound, it floated on the surface of the latter. This provided the possibility of a nice experimental observation. The hydroxylamine (XXX) was added to excess of dry, freshly distilled formamide under nitrogen atmosphere and strictly anhydrous conditions at 5°C, anhydrous magnesium sulphate was added, which settled at the bottom, and the mixture was stirred for 3 hours. It was observed that during this period the hydroxylamine (XXX) went into solution, possibly due to formation of the nitrene (XXXI).

In order to characterize the nitrene (XXXI) the reaction mixture was taken in ether and washed several times with water to remove formamide. The ether layer was dried over anhydrous magnesium sulphate and the ether removed carefully at room temperature under vacuum. This

left behind a very unstable white solid which showed in the infrared a strong stretching frequency at  $1630\text{ cm}^{-1}$  characteristic of the nitroso group. Another strong broad band was observed at  $3240 - 3600\text{ cm}^{-1}$ , which could not be removed even after keeping the sample under 0.5 mm pressure for several hours. This band had arisen possibly due to the presence of occluded water which was found to be difficult to remove. The nitrone (XXXI) slowly decomposed on keeping to furnish the hydroxylamine (XXX). Two things were apparent from the above observations, viz. (a) the nitrone (XXXI) was highly hygroscopic and it was difficult to remove the absorbed water and (b) it was unstable. No attempt was, therefore, made to crystallize and further characterize the nitrone (XXXI) and it was used in situ for further reactions.

In order to find out the synthetic potentiality of the  $\alpha$ -amino nitrone (XXXI) we, first of all, made a simple scheme (Scheme II) as shown below.

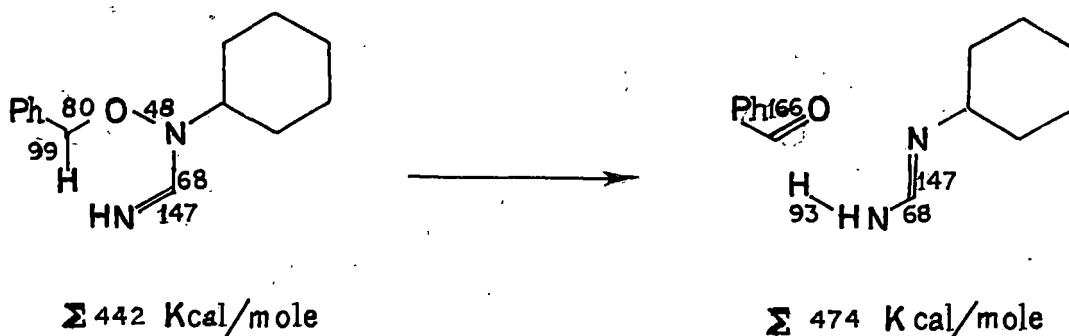


S C H E M E II



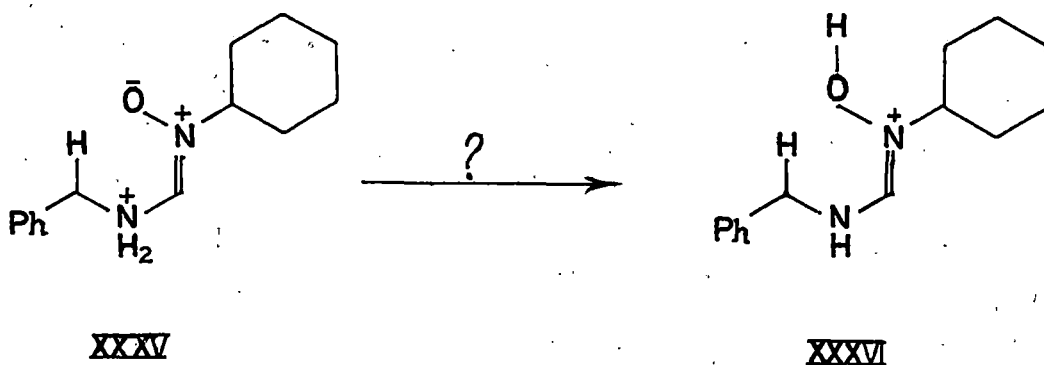
In this scheme the nitrene (XXXI) was supposed to undergo facile  $\text{S}_\text{N}2$  reaction with benzyl chloride, a primary halide, at its oxy-anionic end to furnish the  $\alpha$ -amino immonium compound (XXXII). A proton at the position  $\alpha$  to the immonium group is supposed to be acidic. In this particular case, the acidic proton is attached to the nitrogen atom of the amine group. As has already been stated at the beginning of this discussion, in the conversion of (III) to (IV), this type of acidic proton belonged to a carbon atom, which could be removed by stirring (III) with solid sodium carbonate in an organic solvent. Here, in fact, we had in mind to extend this experimental observation by Bechmoser et al<sup>1</sup> to cases where the acidic proton belonged to a nitrogen atom.

If the conversion of (XXXII) to the imine (XXXIII) was possible, this would not only extend the principle to a generality but would furnish a synthetic tool for the generation of aldehydes also. The imine (XXXIII) is expected to be unstable on energy grounds because of the presence of a very weak  $>\text{N} - \ddot{\text{O}}$  bond. This would, therefore, undergo a thermal pericyclic reaction to furnish benzaldehyde and the amidine (XXXIV). Simple average bond-energy calculations indicate that the reaction is favoured by 32 Kcal/mole towards the right hand side (Scheme III).



S C H E M E III

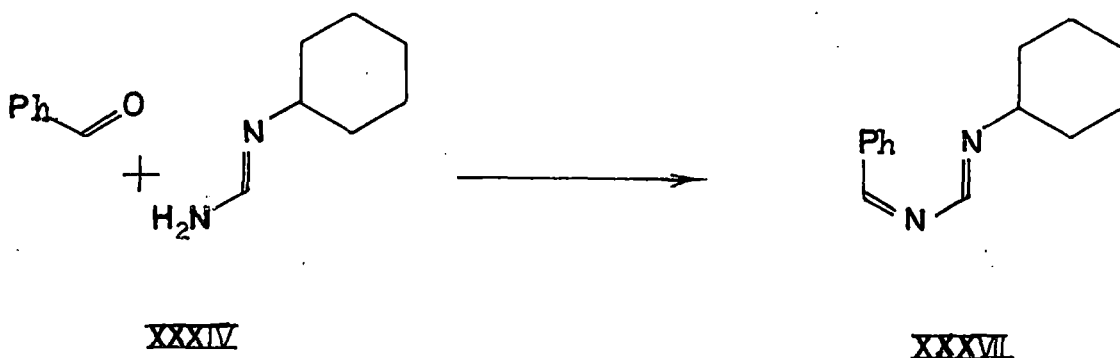
If, on the other hand, reaction of the nitro compound (XXI) with benzyl chloride took place at the amino-nitrogen end of the former to furnish (XXV), no formation of benzaldehyde could be envisaged. The compound (XXV) would be expected to give rise to (XXVI) by a proton-transfer. Therefore the feasibility of the Scheme II rests on the isolation of benzaldehyde from the reaction mixture.



In order to verify the Scheme II, the nitrene (XXXV) was generated in excess formamide at 5°C and then equimolar amount of benzylchloride was added to it at room temperature under nitrogen and anhydrous conditions with stirring. Benzyl chloride was found to be sparingly soluble in formamide; but on stirring it went slowly into solution. Stirring was continued for 9 hours, when in the TLC a new spot appeared. To the reaction mixture powdered sodium carbonate was added with vigorous stirring.

and stirring was continued for 9 hours at room temperature, when the formation of benzaldehyde was observed by TLC studies. The reaction mixture was then poured into ether and washed several times with water to remove the formamide. The ether extract was dried over anhydrous magnesium sulphate and concentrated under vacuum at room temperature. The residual oily liquid exhibited a carbonyl band at  $1700\text{ cm}^{-1}$  characteristic of benzaldehyde.

The situation was further complicated by the fact that benzaldehyde condensed with the amidine (XXXIV) to form (XXXVII). This was confirmed by chromatography over



100 times aluminium oxide deactivated by adding 10% water. The compound (XXVII) was isolated and showed in the infra red the stretching frequency at  $1650\text{ cm}^{-1}$ . In the TLC it showed a single spot. Benzaldehyde was also isolated by chromatography.

Chromatography was, however, found not to be a suitable experimental method for the characterization of these compounds because a number of unknown decomposition products were formed in the column. A direct method was acid hydrolysis of the crude reaction product. On hydrolysis the imine (XXVII) was converted into benzaldehyde. This was isolated by extraction with ether and usual work up. The ether extract formed readily an orange coloured NPH having the melting point  $237^{\circ}\text{C}$ . Mixed melting point with the authentic NPH of benzaldehyde showed no depression. Formation of benzaldehyde was also confirmed by IR spectroscopy.