SOME ASPECTS

OF

CYCLIC ADDITION REACTIONS

A thesis presented by

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ABSTRACT

A review on molecular mechanisms is followed by an account of reactions, mainly cyclic additions, that have been studied with special reference to carbon-carbon bond formation.

The pyrolysis of oxalates has been briefly studied and in an attempted azo-ester synthesis an interesting rearrangement has been found.

A conversion of diphenyl furoxan to dibenzyl is reported and the mechanism of the degradation of diphenyl furoxan by hydrazine and by alkali has been elucidated.

Nitrones have been studied and one cyclic addition reaction of diphenyl nitrone is reported.

Benzonitrile oxide has been shown to undergo cyclic addition reactions with Schiff bases. The structure of each of the adducts has been proved and the evidence from substituent effects strongly supports a molecular mechanism. Benzonitrile oxide also forms a cyclic adduct, of proven structure, with thiobenzophenone, but with aci-phenylnitromethane, benzhydroxamic acid, and phenyl isocyanide, the nature of the products indicates a more complex reaction. Tentative mechanisms are proposed.

The reaction of benzonitrile oxide with benzaldoxime has been studied. In neutral solution an adduct is formed but fragmentation occurs in alkaline solution. Ketoximes undergo a less simple reaction with benzonitrile oxide and the structure of the cyclic adduct indicates an indirect reduction has occurred.

Preliminary experiments have been made towards polymer synthesis by cyclic addition reactions.

ACKNOWLEDGEMENTS

The author wishes to express his gratitude for the constant encouragement and guidance of Professor D.H.R. Barton under whose supervision this work was carried out.

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Finally the author thanks the U.S. Rubber Company for the provision of a Fellowship.

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MOLECULAR MECHANISMS

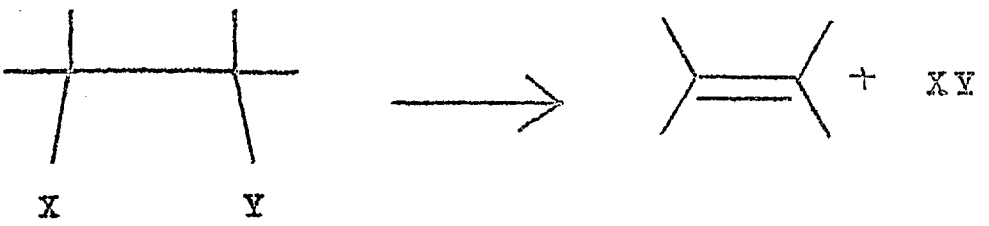
Introduction

Organic chemical reactions can be classified into three main types. The class involving heterolytic cleavage of covalent bonds encompasses all nucleophilic and electrophilic substitution and elimination reactions as well as many reactions of apparently special mechanism all of which however have a common factor in an ionic intermediate.

Ionic reactions rarely occur in the absence of a solvent and are often catalysed by acids and bases. Many ionic reactions are stereospecific.

A free radical reaction involves homolytic cleavage of a covalent bond and although these reactions are fairly insensitive to the nature or absence of a solvent, they are greatly influenced by peroxides, light and the presence of chain inhibitors. They are also usually non-stereospecific.

Molecular reactions can be defined as those in which the bond making and bond breaking processes occur simultaneously by a concerted process without the intervention of ions or radicals. Many are of the four centre type[1].



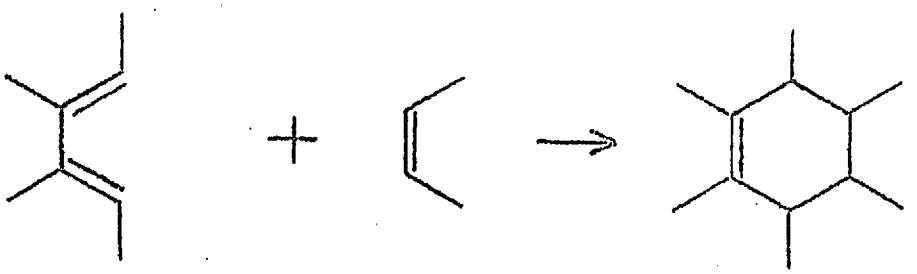
Such a concerted mechanism necessitates a planar cyclic transition state and because of the highly specifically orientated transition state molecular reactions are stereospecific and if intramolecular they satisfy first order kinetics. Other characteristics are insensitivity to free radical inhibitors and initiators, a similar reaction rate in the gaseous phase and in solution, and a non-requirement of acid or base catalysis. When it is realised that in spite of the adverse entropy factor that is often prevalent, many of these reactions proceed under exceedingly mild conditions, it is evident that activation energies must be very low[2]. It is thus manifest that there are elegant possibilities for utilising molecular reactions in degradative or synthetic procedures, the most important advantage over ionic and free radical reactions being that a statistically improbable transition state is demanded resulting in very clean reactions, high

yields, and a lack of rearrangement products.

Few reactions have had their molecular character completely vindicated and there has been acrimony in the recent literature even about reactions where a molecular mechanism had seemed wholly valid. In view of this situation a brief survey of those reactions that are purported to be molecular will be followed by a critical assessment of just to what extent this molecular nature is true. An attempt will be made to demonstrate that a steady graduation from truly molecular to ionic mechanisms can be discerned.

Diels-Alder Reaction

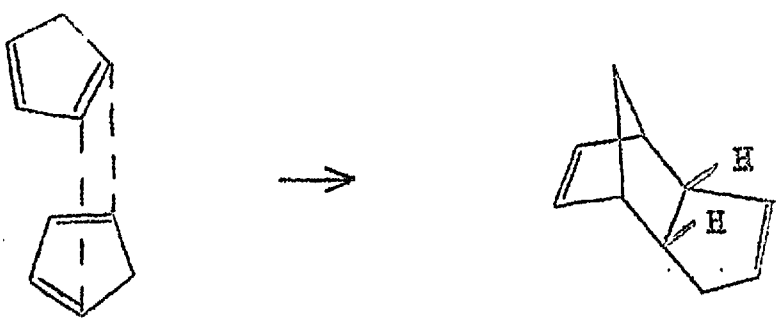
This is the process by which a diene (II) reacts with a dienophile (III) to give an adduct (IV).



II III IV

The prime facts to be accommodated are that the stereochemical relationship of groups attached to the diene and to the olefin are maintained as far as possible in the product, and that if two modes of combination are possible the one favoured is that which results from the maximum accumulation of unsaturated centres in the transition state[3]. Moreover, entropy calculations[4] [5] show that a highly special orientation of reactants is required and it has been calculated[6] that the molar volumes of the transition state and of the adduct are very similar.

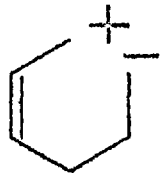
The generally accepted mechanism is that formation of a transition state which is stabilised electrostatically is followed by a reorganisation of electron density[7]. Thus cyclopentadiene gives endo-dicyclopentadiene (V) through the transition state (VI).



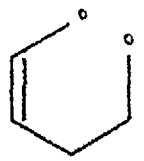
VI V

Support for this one step mechanism is forthcoming from the kinetic and thermodynamic work of Wasserman[8].

The difficulty with two step mechanisms involving intermediates of the type VII and VIII[9] [10] has been to explain the rigid stereochemical results,

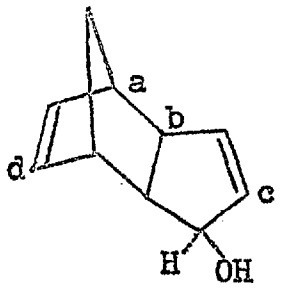


VII

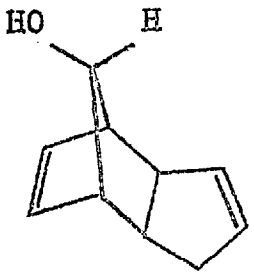


VIII

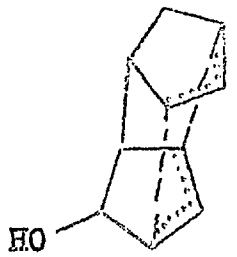
although an ionic mechanism does seem more fitted than molecular mechanism to explain how electron donating substituents in the diene and electron withdrawing substituents in the dienophile both accelerate the reaction. A bi-radical has been shown probably to intervene in the high pressure dimerisation of isoprene[11] but the extension of this result to cyclopentadiene has been shown to be false[6]. Recently Woodward [3] discovered that α-1-hydroxycyclopentadiene (IX) rearranges to the syn-8-isomer (X) at a lower temperature than that at which this system undergoes the reverse Diels-Alder reaction.



IX

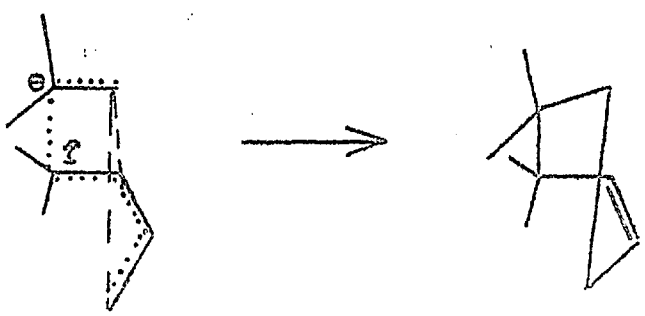


X



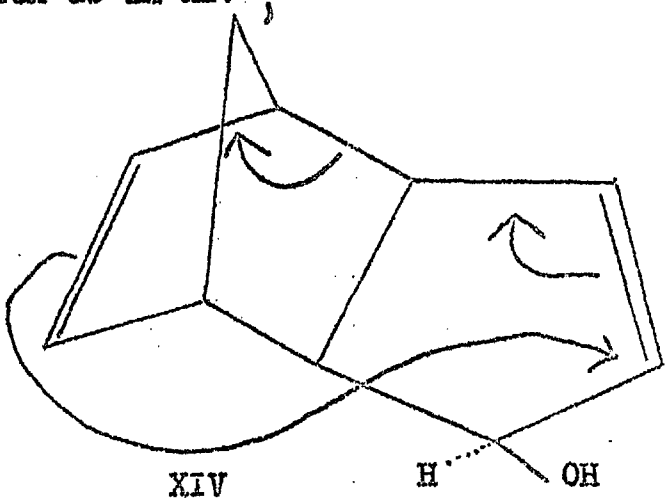
XI

Woodward regards the initial step as scission of bond a-b with subsequent bond formation between d and c and involving the intermediate XI whose stereochemistry is fixed by secondary attractive forces (broken lines). This author extends the theory to the Diels-Alder reaction in general and regards the initial step as first a partial then a full bond formation between e and f (XII) with the secondary attractive forces securing the stereochemistry. The process is completed by formation of the second bond (XII ⟶ XIII)



XII XIII

Dewar[12] criticises this theory on the basis that the mechanism of the rearrangement of IX to X is irrelevant to the mechanism of the Diels-Alder reaction and Woodward's reply[13] is unconvincing. As Woodward himself points out[3] the rearrangement is but a special case of the Cope rearrangement (to be discussed) and although other workers[14] [15] have blithely accepted his hypothesis the conclusion seems inescapable that the rearrangement could be written as in XIV ;



XIV

and the concerted mechanism for the Diels-Alder reaction, although still not rigorously proved, especially as some Diels-Alder reactions are acid catalysed[7], has not been deposed.

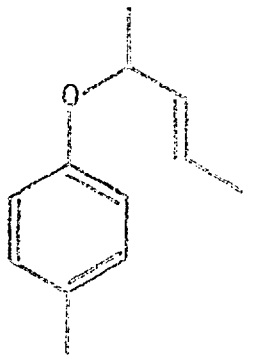
Claisen Rearrangement

The rearrangement of allyl vinyl ethers (XV) and allyl aryl ethers (XVI), conjointly referred to as

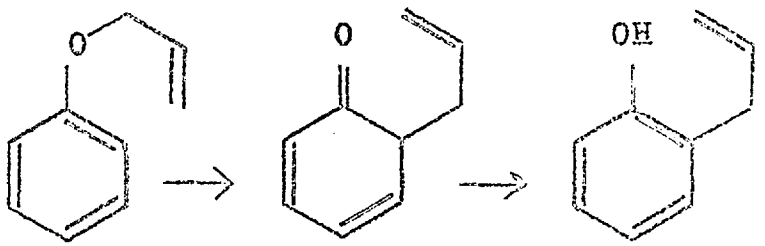
the Claisen rearrangement, has been studied at length.



XV



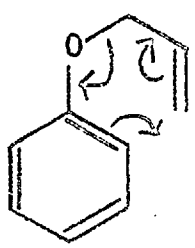
XVIII



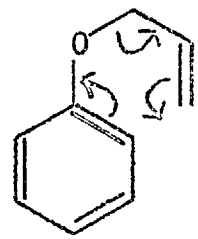
XVI XVII

The aromatic reaction is unimolecular and is unaffected by the addition of acid or base or by the presence of oxygen[16]. It has a high negative entropy of activation[16] [17] indicative of a cyclic transition state and inversion of the allyl group has been proved isotopically[18]. The intramolecular nature of the reaction has been confirmed by rearranging mixtures of allyl phenyl ethers when no cross products are formed[19] and the dienone intermediate XVII has been trapped[22]. Furthermore in the rearrangement of optically active XVIII retention of optical activity is observed in the product[20].

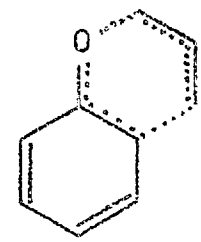
The concerted mechanism of Hurd and Pollack[21] accommodates these facts but a fundamental difficulty arises when depicting this type of mechanism on paper.



XIX



XX

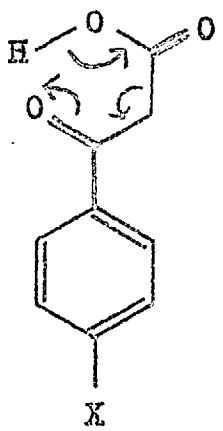


XXI

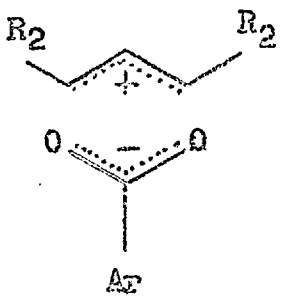
Tarbell and Wilson[21] postulated a directional flow of electrons as in XIX but White[24] states that bond making and bond breaking are not of equal importance in the transition state, the overall electronic change being represented by XX. Goering[26], with the backing of more extensive experimental evidence than White, has shown that solvent and substituent effects are in fact small and there is no need to invoke a somewhat ionic transition state. The cyclic transition state XXI thus most nearly represents the correct mechanism and depicting a directional flow of electrons has very little meaning. Recent work[92] on the decarboxylation of β-keto acids however has shown that in

that case a proton transfer and not a hydride transfer is involved (XXII).

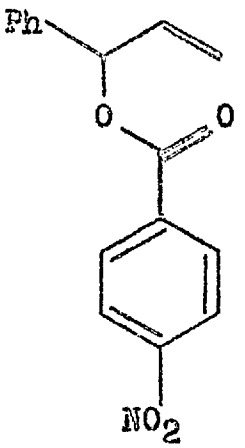
XXII

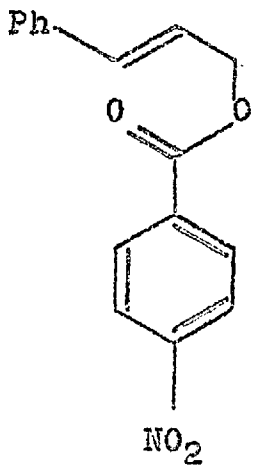


XXIII



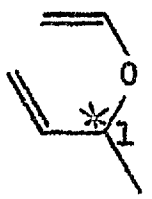
The concerted mechanism contrasts the Claisen rearrangement with the formally similar rearrangement of allyl esters in which an ion pair (XXIII) occurs[25] and demonstrates that the analogous stereochemistry of these two reactions[26][27] is fortuitous. The assertion of Marvel and Stephenson[29] that the two reactions are analogous must therefore be treated with reserve. Further evidence for the concerted nature of the Claisen rearrangement comes from a study of the pyrolysis of allyl vinyl ether[28]. It must be remembered that the rearrangement of α-phenylallyl-p-nitrobenzoate (XXIV) was shown to entail no oxygen exchange[30].





XXIV

and this was construed as evidence for a synchronous mechanism but Winstein[31] demonstrated that this fact was not incompatible with an ion pair intermediate. In the allyl vinyl ether case, which occurs in the gas phase, an ion pair mechanism can reasonably be eliminated and the conclusion[28] that the isotopic results prove a 6-membered cyclic transition state can be accepted. Also the rate of rearrangement of XXV

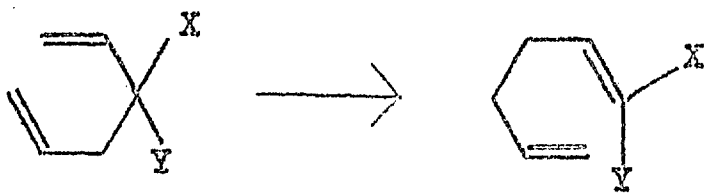


XXV

is equal to the rate of loss of optical activity from C_1, proving that C-O bond breaking cannot be far advanced in time over C-C bond making, again indicating the process is truly concerted.

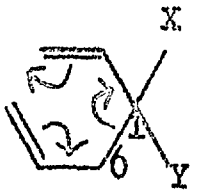
Cope Rearrangement

The rearrangement of allyl vinyl malonates (XXVI) is subject to similar factors to those which govern the Claisen rearrangement(32)

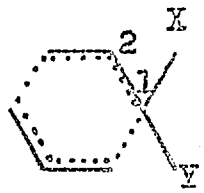


XXVI

Thus the reaction is intramolecular, crotyl groups are inverted, it is first order, and it has a high negative entropy of activation. The facilitation of the reaction by increasing the electron withdrawing power of X and Y is attributed by Cope(32) to their attraction for the electron pair between atoms 1 and 6 resulting in easier cleavage of that bond.



XXVII



XXVIII

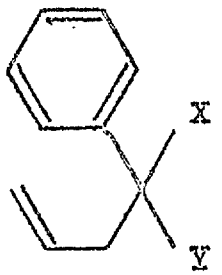
This idea demands the directional flow of electrons depicted in XXVII and perhaps a more reasonable explanation is to draw a Claisen rearrangement type of transition state XXVIII and to regard it as being stabilised by partial conjugation of the 1:2-bond with X and Y. The reaction will proceed in the absence of negative groups[33] and an equilibrium is then established (XXIX $\rightleftharpoons$ XXX).



XXIX XXX

That the driving force for the Cope rearrangement is lower than that for the Claisen rearrangement is indicated by

the stability of XXXI to rearrangement conditions[34].

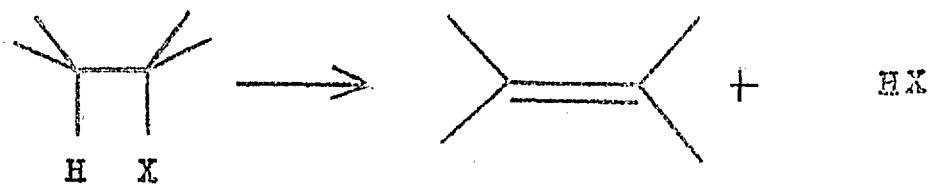


X, Y = Ph, CN, CO_2H

XXXI

Pyrolytic Cis-Eliminations

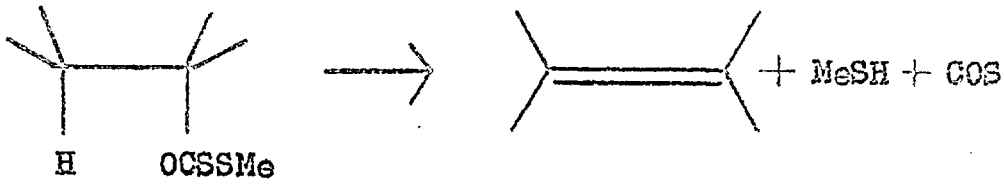
Where X is a suitable group fragmentation in the system XXXII usually occurs on heating.



XXXII

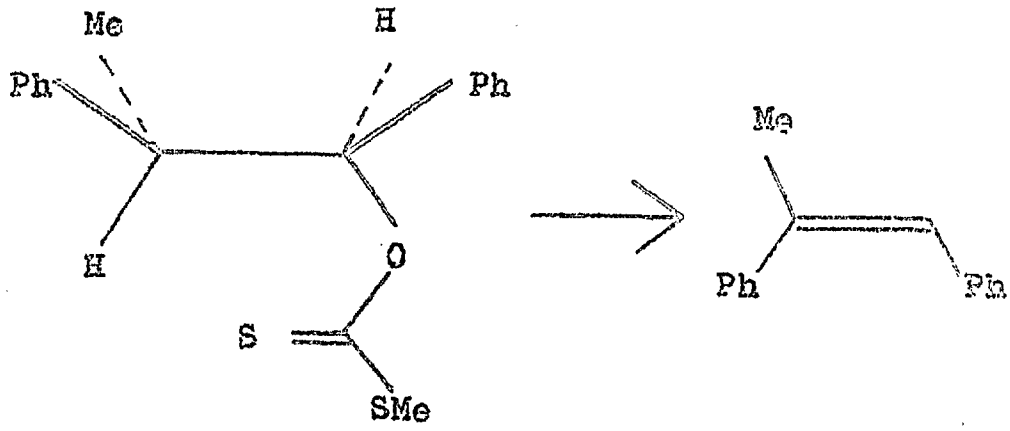
The unique cis-course of the reaction makes this an attractive procedure for the introduction of double bonds under mild conditions.

(a) Chugaev Reaction (XXXIII → XXXIV)



XXXIII XXXIV

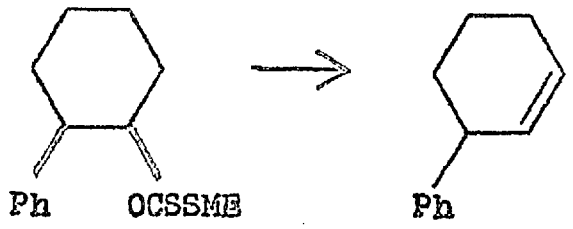
The cis nature of the reaction has been elegantly demonstrated by Cram(35) in converting threo-1:2-diphenyl propan-1-ol xanthate (XXXV) to cis- ∝ -methyl stilbene and the erythro isomer to trans- ∝ -methyl stilbene. The latter reaction is faster than the former reflecting the greater steric hindrance in the threo compound due to the pair of gauche phenyl groups.



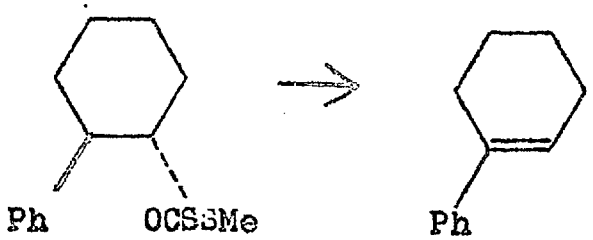
XXXV

Alexander's stereospecific transformations on the phenyl cyclohexyl xanthates (XXXVI and XXXVII)(94) provide independent

evidence of cis elimination.

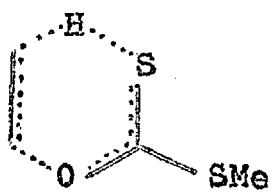


XXXVI

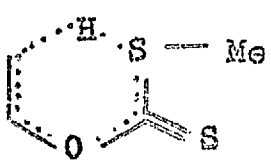


XXXVII

On the basis of first order kinetics, cis elimination, and a high negative entropy of activation a concerted mechanism (XXXVIII) has been proposed[36].



XXXVIII

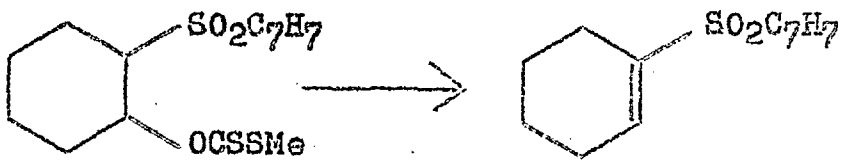


XXXIX

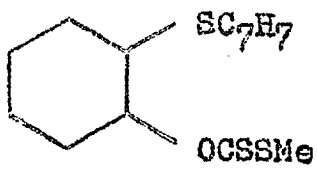
Confirmation for this rather than the alternative transition state XXXIX has been neatly provided by a study of isotope effects[37]. The fact that xanthates pyrolyse at a

relatively low temperature[35] is no doubt partly due to the energetic gain on passing from the system -O-C=S to O=C-S- which yields 20 k cal/mol.[39][40].

Although the Chugaev reaction usually produces some material resulting from trans elimination, Bordwell and Landis[42] have shown that if a strong electron sink is available to activate the β-hydrogen then it is trans elimination that predominates. Thus both cis and trans-2-p-tolylsulphonylcyclohexyl xanthate (XL) give the 1-olefin on pyrolysis whereas the corresponding sulphide (XLI) underwent normal cis elimination in each case.

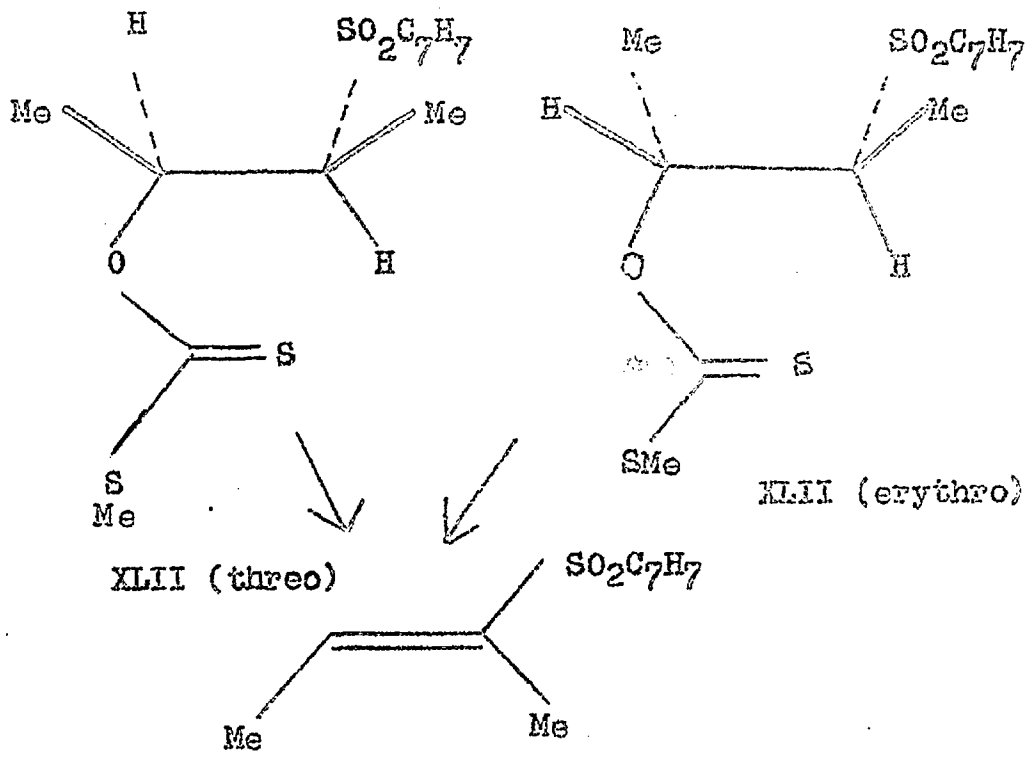


XL (cis or trans)



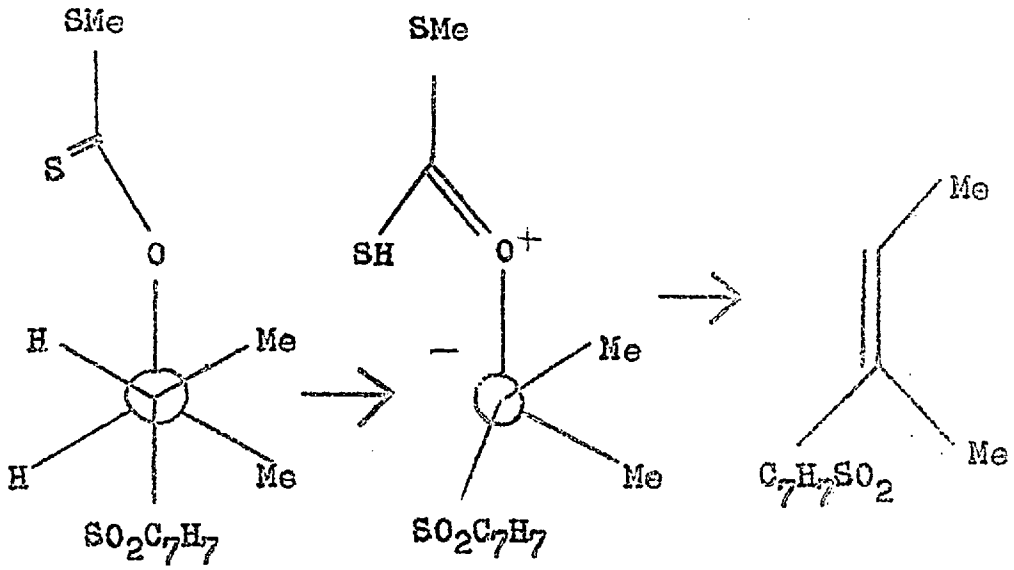
XLI

In the aliphatic series Bordwell and Landis found a similar reaction whereby the S-methyl xanthates of threo and erythro-3-p-tolylsulphonyl butan-2-ol (XLII) yield cis olefin.



Not only does the erythro sulphone undergo overall trans elimination but it does so at a faster rate than the corresponding sulphide and the conclusion is drawn[41] that a dipolar ion is involved rather than a cyclic transition state.

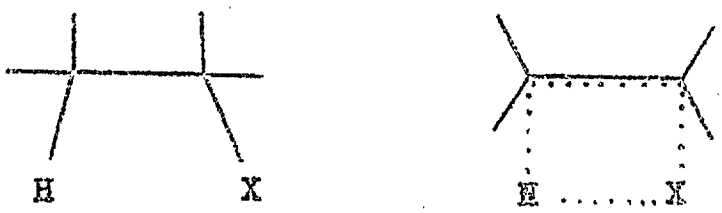
Although the threo-sulphone (XLII) elimination could be concerted these authors prefer a dipolar ion for this reaction too, and point out that if activation is sufficient to produce a dipolar ion then that ion can adopt a staggered conformation thereby overcoming the steric repulsions indigenous to a planar cyclic transition state.



XLII

(b) Halide Pyrolysis

A unimolecular mechanism has been demonstrated for the pyrolysis of several halides[44] and a cyclic transition state (XLIII) is postulated by Barton[43] who has also proved the cis nature of the reaction[45].

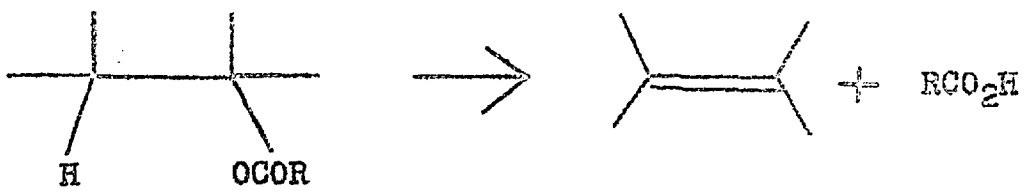


XLIII

β-Alkyl substitution has relatively little effect but

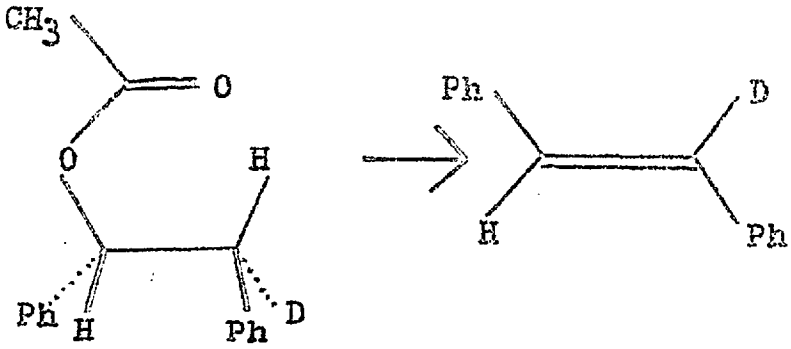
the large increase in rate that is observed with increasing α-substitution led Maccoll[46] to suggest C-X bond stretching was much more important than C-H bond stretching in the transition state. Evidence from the deuterium isotope effect that the C-H bond is as intimately concerned in the transition state as the C-X bond indicates the reaction must be concerted[47].

(c) Ester Pyrolysis (XLIV → XLV)

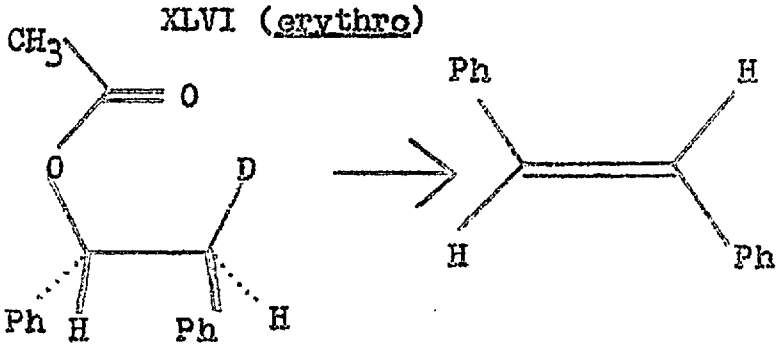


XLIV XLV

The cis nature of the reaction has been elegantly demonstrated[48] by the pyrolysis of the erythro and threo acetates of 2-deutero-1:2-diphenyl ethanol (XLVI and XLVII) which respectively retain and lose deuterium.

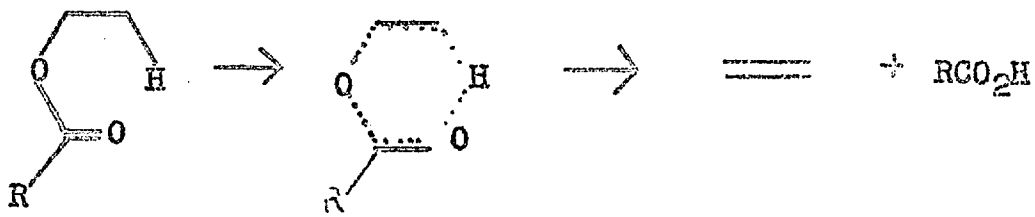


XLVI (erythro)



XLVII (threo)

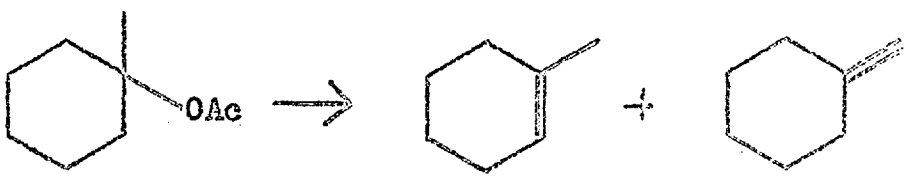
and by the observations of Barton[43] in the steroid field. The concerted mechanism of Hurd[49] (XLVIII) accommodates this evidence



XLVIII

together with the unimolecularity and the negative entropy of activation[38] and it will be shown that this picture of the transition state is compatible with some of the other known characteristics of the reaction.

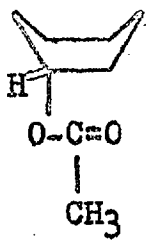
For pyrolysis of aliphatic esters the product distribution can usually be correlated with the number of β-hydrogens that can adopt a cis conformation. Thus in the pyrolysis of sec-butyl acetate but-1-ene is favoured over but-2-ene by a factor of 3:2[50] and the significant conclusion is that steric effects and the stability of the olefin formed make little impression on the course of the reactions. Furthermore this result vitiates against the conclusions of Maccoll[51] concerning mechanism which were based largely upon the erroneous experimentation of Bailey[52] who believed Hofmann elimination was the preferred course. In the alicyclic series the result of the pyrolysis of 1-methylcyclohexyl acetate[50] (XLIX) is instructive.



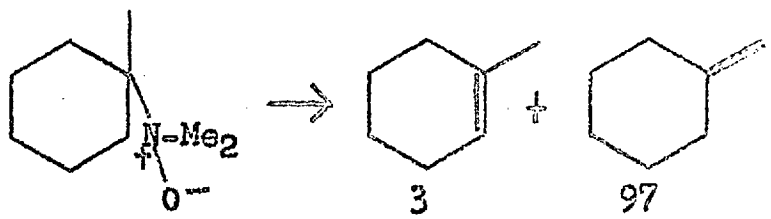
XLIX 75 25

Only in the formation of the exo olefin can a completely eclipsed transition state intervene and the fact that the endo olefin is the major product indicates that either

elimination must occur through the boat form (L) or that an axial hydrogen can eliminate with an equatorial acetoxyl, necessarily through a non-eclipsed conformation. This latter explanation is preferred(50) and confirmation is forthcoming from the pyrolysis of dimethyl (1-methyl cyclohexylamine) oxide (LI) which undergoes elimination in the reverse sense.



L



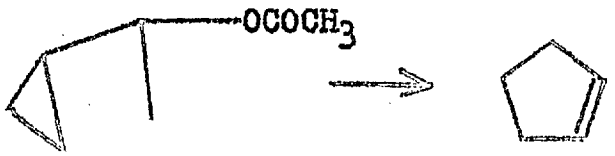
LI

Usually ester and amine oxide pyrolyses give very similar results and it will be subsequently shown that their mechanisms are similar except that amine oxide pyrolysis involves a five membered ring. The low yield of endo isomer in the pyrolysis of LI can be explained by the necessity for a boat form intermediate but with the more flexible six membered ester ring gauche elimination can occur.

Further evidence for the molecular nature of ester pyrolysis is provided by the small effect of α and β

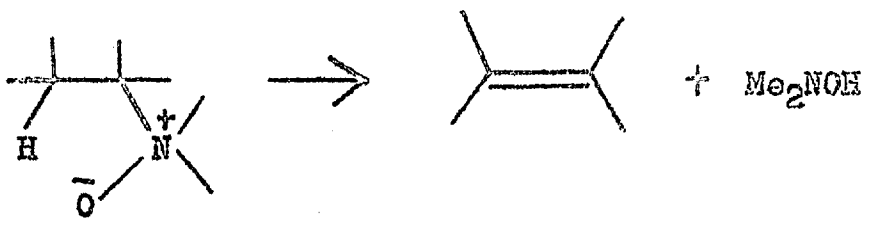
substituents and by the isotopic proof that a large amount of C-H bond breaking occurs in the transition state(39).

Rearrangements are rare in ester pyrolysis as in other reactions discussed in this section and although pyrolysis of 1-cyclopropylethyl acetate (LIII) leads to cyclopentene there is evidence that this may be an artefact from the product of normal pyrolysis, vinyl cyclopropane(54).



LIII

(d) Amine Oxide Pyrolysis (LIV → LV)

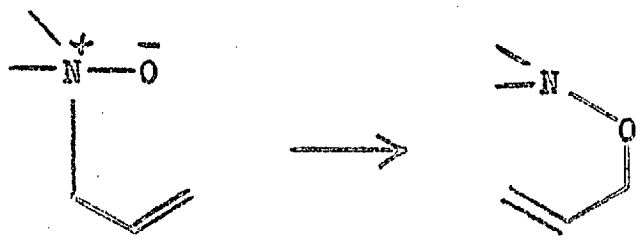


LIV LV

The reaction follows a predominantly cis course as demonstrated by the predominant products in the pyrolysis

of the amine oxides of erythro and threo-2-amino-3-phenyl butane being trans and cis olefins respectively[55]. In spite of the apparent nucleophilic nature of the oxygen function the reaction resembles ester pyrolysis closely especially in the statistical distribution of products where several β-hydrogens of differing acidity are available[39]. The reaction is insensitive to α-substitution but is highly susceptible to β-substitution[56] indicating that C-H bond breaking is of more importance in the transition state than C-N bond breaking. However the evidence as a whole is for a transition state of low ionic character and very like that for ester pyrolysis[39].

Related both to this reaction and to the Claisen rearrangement is the Cope rearrangement (LVI → LVII).

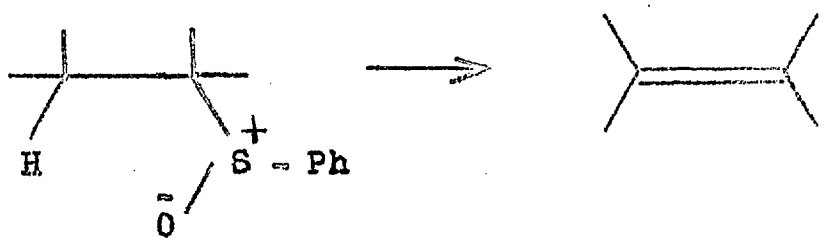


LVI LVII

which is intramolecular and involves crotyl group inversion[57][58]. It is possible for the Cope rearrangement and amine oxide pyrolysis to occur com-

petitively in some systems.

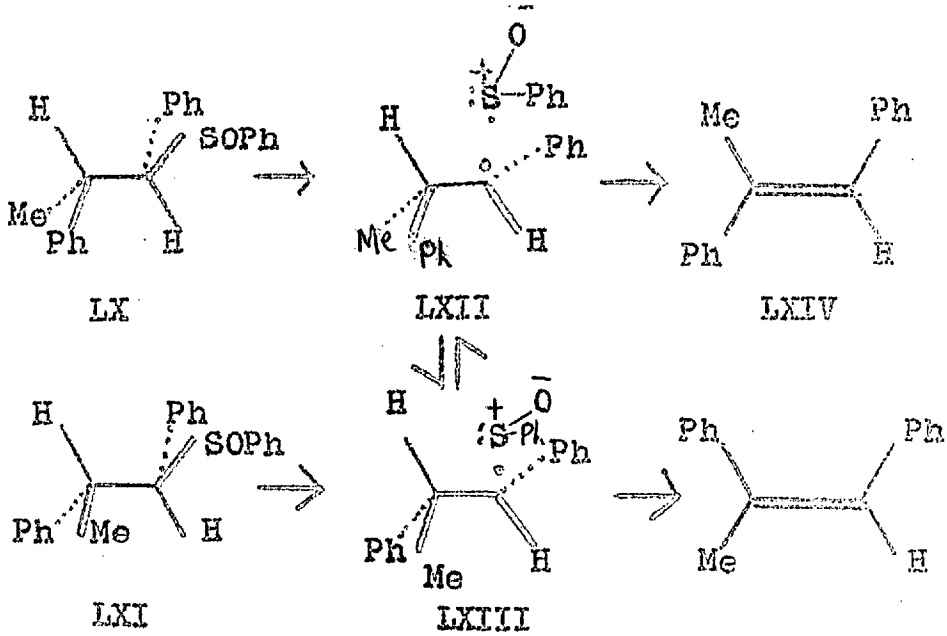
(e) Sulphoxide Pyrolysis (LVIII → LIX)



LVIII LIX

A recent study[59] of this reaction which is formally similar to amine oxide pyrolysis shows that although the temperature required for the elimination is very low the stereospecificity is not high and at elevated temperatures stereospecificity is absent. The activation energy varies with temperature as does the entropy of activation which increases from negative at the lower pyrolytic temperatures to positive at the higher ones. The reaction is insensitive to changes in solvent. On the basis of these facts it is advocated that two mechanisms are operating with that one at the lower temperatures being analogous to the pyrolytic cis eliminations that have already been discussed. The mechanistic scheme proposed for the non-stereospecific part of the reaction is illustrated for the case of

erythro and threo 1:2 diphenyl-1-propylphenyl sulphoxide (LX and LXI respectively).

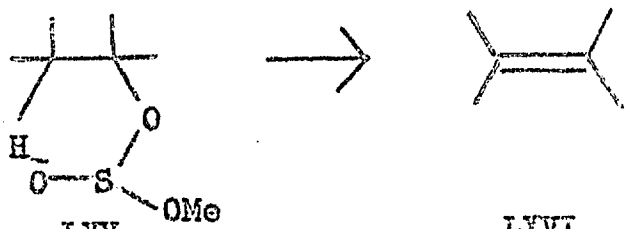


which undergoes homolytic cleavage to radical pairs (LXII and LXIII). At higher temperatures equilibration between LXII and LXIII could well be rapid explaining the predominant formation of that olefin (LXIV) which is derived from the less sterically hindered transition state. At lower temperatures with equilibration between LXII and LXIII inhibited the tendency of the bulky sulphoxide group to be near a proton rather than a larger substituent leads to overall cis elimination in each case. Thus neither the stereochemistry or the kinetics can differentiate between this and a molecular

mechanism but a selection is probably feasible from a consideration of the entropy of activation. The significance of this radical pair mechanism will be considered later.

In a contemporary study[71] of the pyrolysis of di-t-butyl sulphoxide a low reaction temperature and first order kinetics were observed but no further evidence was cited to support the contention[71] that a molecular mechanism similar to that in amine oxide pyrolysis was operating.

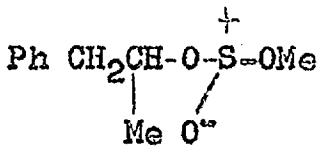
(f) Sulphite Pyrolysis (LXV ⟶ LXVI)



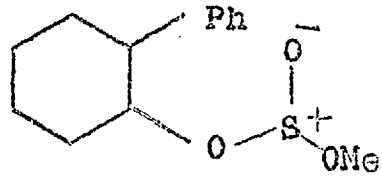
LXV LXVI

In the case of glycol sulphites rearrangements and large substituent effects provide conclusive evidence for an ionic intermediate[60] but the demonstration that the aliphatic sulphite LXVII gave similar amounts of Hofmann and Saytzeff elimination led Price and Berti[61] to the tentative conclusion that a cyclic transition state

was involved.

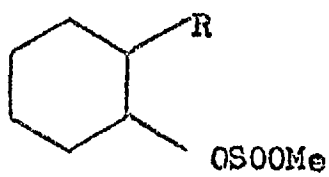


LXVII

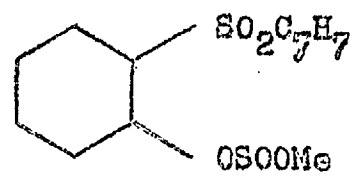


LXVIII

After considering the results of the pyrolysis of cis and trans-2-phenylcyclohexyl methyl sulphite (LXVIII) where both isomers gave conjugated olefin these authors modified their mechanism to an ion pair[62]. Bordwell and Landis[63] demonstrated that the results of this pyrolysis were incorrect and in fact cis-elimination predominated. They showed further that in compounds of type LXIX for corresponding R-substituents the product distribution from both sulphite and xanthate pyrolysis was similar, with cis-elimination prevailing except for cis-2-p-tolyl sulphonyl methyl sulphite (LXX) which underwent trans elimination in a comparable manner to the corresponding xanthate[42].



LXIX

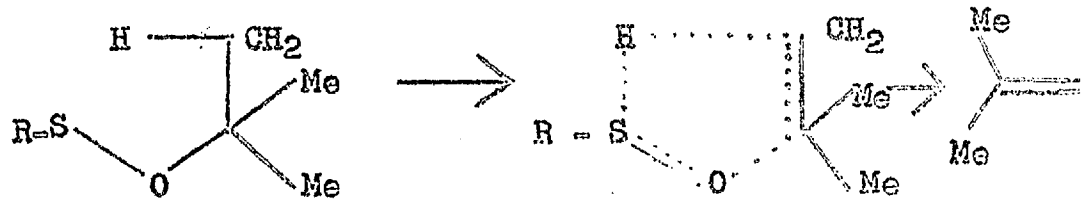


LXX

Although the trans isomer of LXX suffered cis elimination the reaction rate was very similar to that of the cis isomer indicating an ion pair mechanism is operating here also. For the pyrolysis of sulphites not bearing a strongly electron attracting α-substituent Bordwell and Landis prefer a concerted mechanism but seriously consider the possibility of an ion pair intermediate with abstraction by the anion of the nearest proton to give overall cis elimination(63).

(g) Sulphenyl Ester Pyrolysis

In spite of the formal similarity of peroxides, which undergo homolytic fission(64), to sulphenyl esters, the pyrolysis of the latter does not involve free radicals(65) and a cyclic transition state (LXXI) analogous to that for the Chugaev reaction is proposed(65)

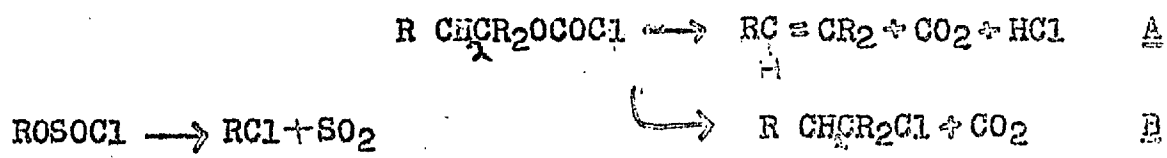


LXXI

but the mechanism has not yet been studied in detail.

(h) Other Pyrolytic Eliminations

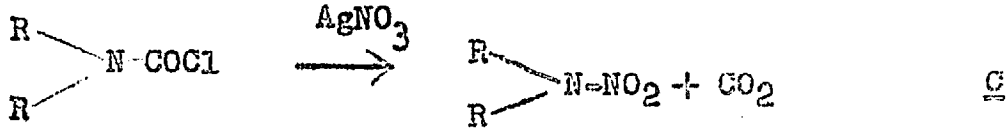
The mechanism of several apparently similar elimination reactions has been elucidated with reasonable probability. Thus the pyrolysis of chlorosulphites (LXXII) is ionic[66] but chloroformates, which



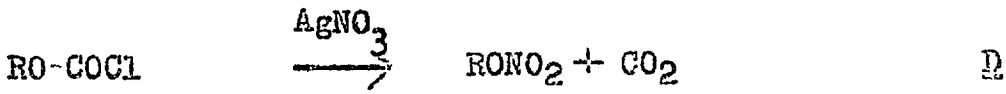
LXXII

undergo two simultaneous pyrolytic reactions, are in a different category. A useful criterion for intermediate carbonium ions in a reaction is the presence of rearrangement products and the fact that some rearrangement does occur in reaction A together with the entropy of activation being about zero is strong evidence for a highly polar transition state[67]. In reaction B however the entropy of activation is negative and complete retention of configuration is observed supporting a molecular process with a cyclic transition state[68].

Related 4-centre reactions (C and D) have been studied[69][70]



C

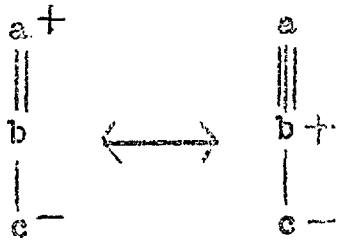


D

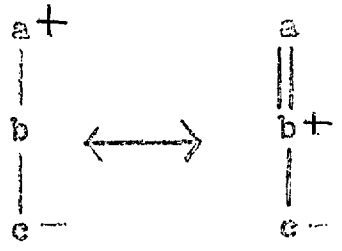
and although first order kinetics and a high degree of retention of configuration occur the evidence appears insufficient to distinguish between an ion pair or a molecular mechanism.

1:3 Cyclo-Additions

1:3 dipolar compounds are of general formula LXXIII and LXXIV both of which can be conveniently written in two resonance forms.

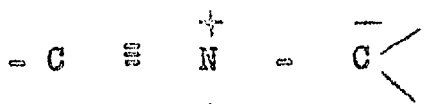


LXXIII



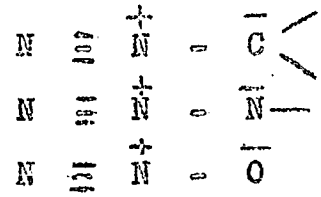
LXXIV

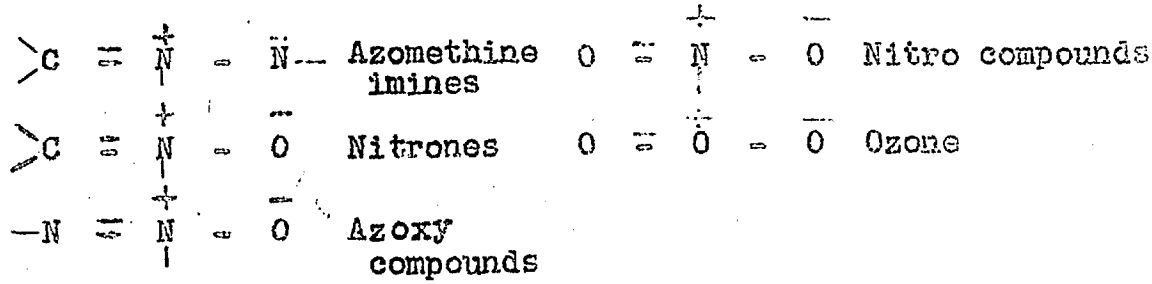
In LXXIII the only possibility for b is nitrogen but in LXXIV b can be either oxygen or nitrogen. As a and c can be carbon, nitrogen, or oxygen, it is seen that a large number of 1:3 dipolar systems could in theory exist but in fact many of these possibilities are unknown. Appended below is a list of molecules of this type which have either been isolated or have been demonstrated to occur as reaction intermediates.



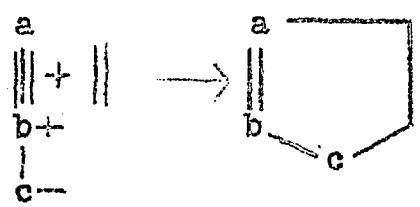




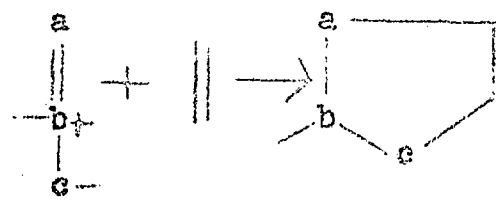




The original reaction associated with 1:3 dipolar compounds is the formation of cyclic adducts (LXXV and LXXVI) with unsaturated molecules.



LXXV



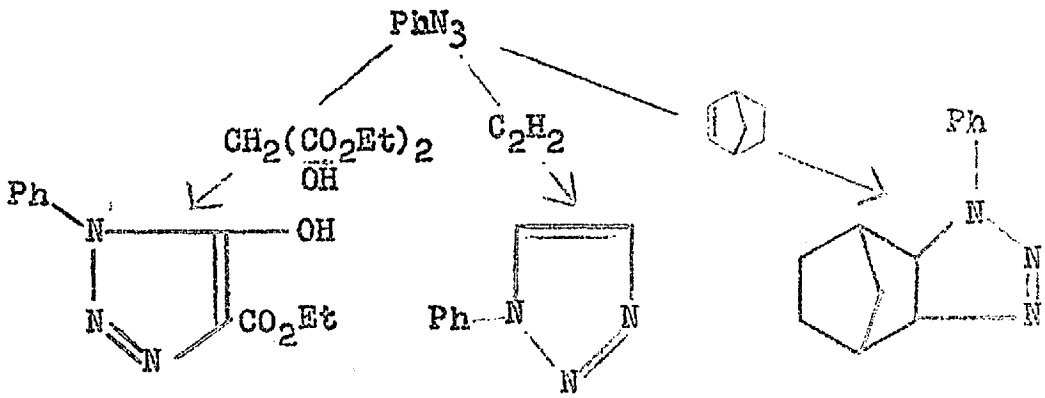
LXXVI

A brief account of the few reactions of this class which were known prior to the work of Quilico on nitrile oxides is followed by a summary both of Quilico's

work and of the thorough general investigation of Huisgen.

Ozone which undergoes ionic reaction with olefins[78] will not be further considered.

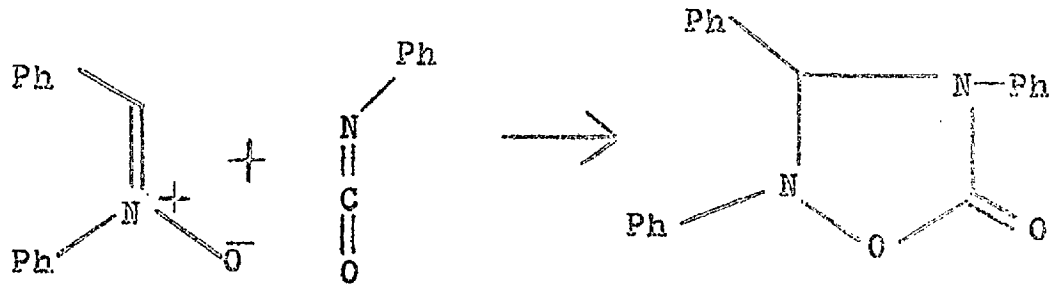
The addition of phenyl azide to activated or strained carbon-carbon double bonds to give adducts of the type LXXVII and LXXVIII and to acetylene yielding LXXIX has long been known[72][73][74]



LXXVIII LXXIX LXVII

and similar reactions are undergone by diazomethane where again activation is usually required to promote addition to an olefin[75][76]. The only recorded 1:3 addition of a nitrone was that of diphenyl nitrone to phenyl isocyanate to yield the adduct LXXX[77], and of the other systems listed above, apart from nitrile oxides which will be dealt with shortly, and nitrous

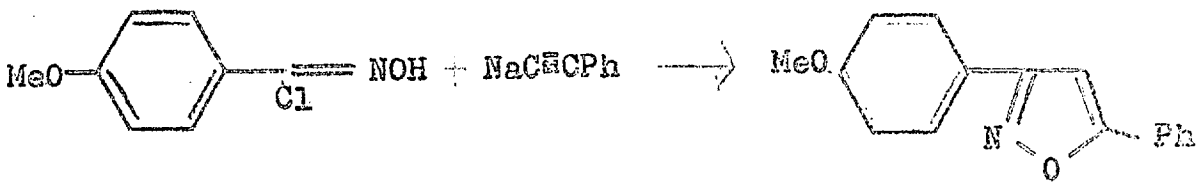
oxide and azoxy compounds which are unreactive, all have been neglected.



LXXX

Nitrile Oxides

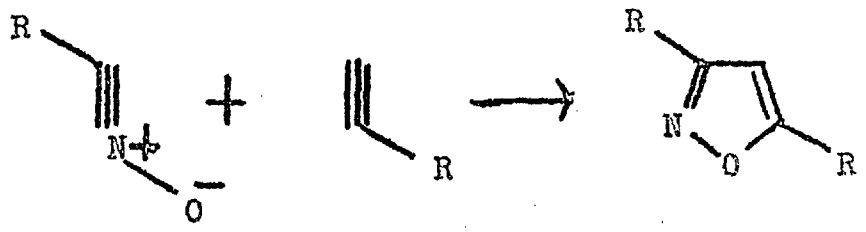
If it is presumed that the hydroxamic chloride LXXXI was the precursor of the corresponding nitrile oxide then the synthesis of LXXXII constituted the first recorded 1:3 addition reaction of that system(79).



LXXXI LXXXII

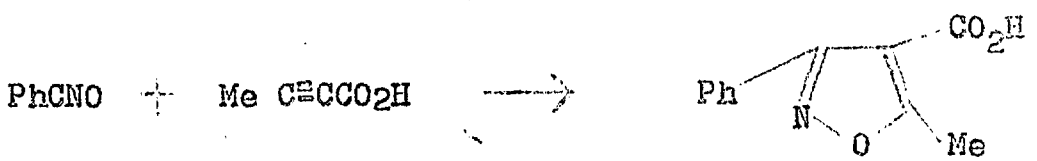
Quilico has been investigating the reaction of benzonitrile oxide and a few other nitrile oxides with

a vast number of olefins and acetylenes for a quarter of a century but the number of significant results that have accrued is singularly few and therefore only a few reactions will be quoted. Reaction of a substituted acetylene with a nitrile oxide leads to a 5-substituted isoxazole[80] (LXXXII).



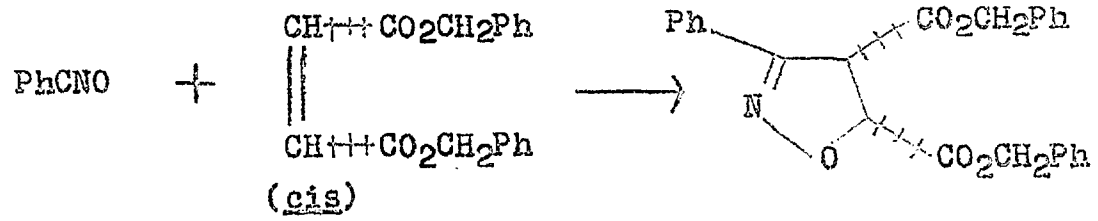
LXXXII

The direction of addition can be inverted by slight substituent effects as exemplified by the reaction of benzonitrile oxide with propiolic acid and with methyl propiolic acid in alkaline solution[81].

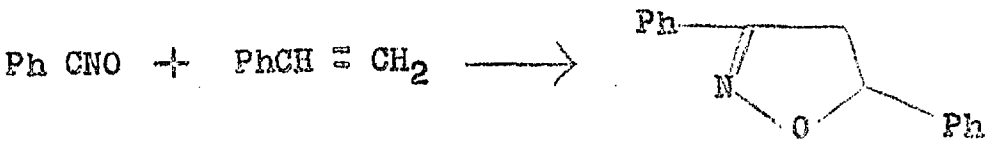


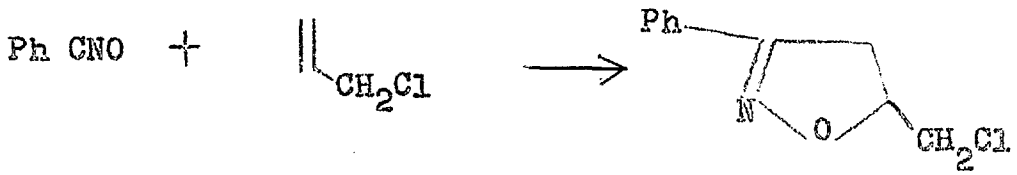


With addition to olefins stereochemistry is preserved with fumarate and maleate esters[82],

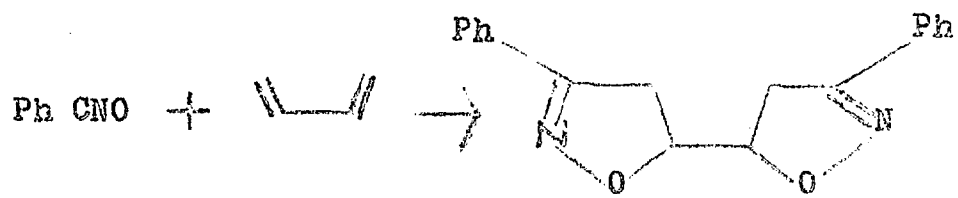


monosubstituted olefins gave 5 -substitution in the product[83],

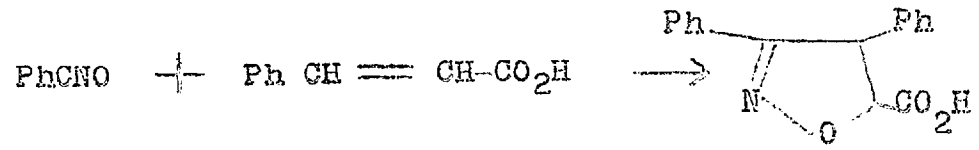




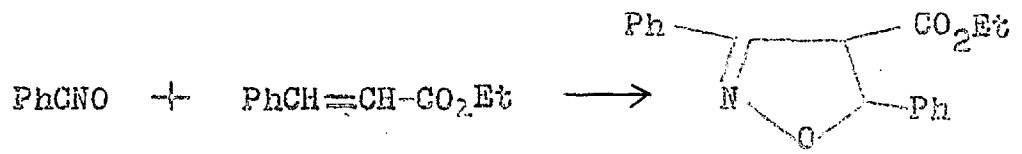
and diolefins simply reacted with two moles of nitrile oxide[84],



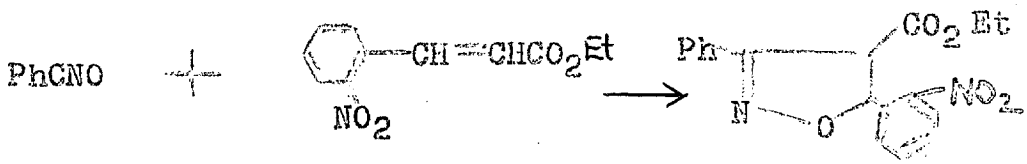
If the olefin contains a free carboxyl group this usually appears in position 5

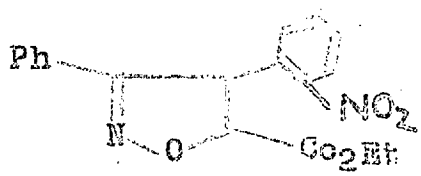


but with the ester the positions are reversed,

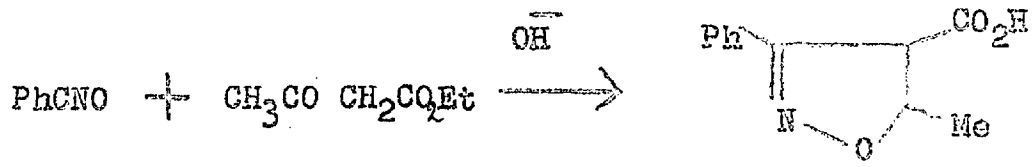


and if the two substituents in the olefin are of a similar nature then both isomers are formed(85).



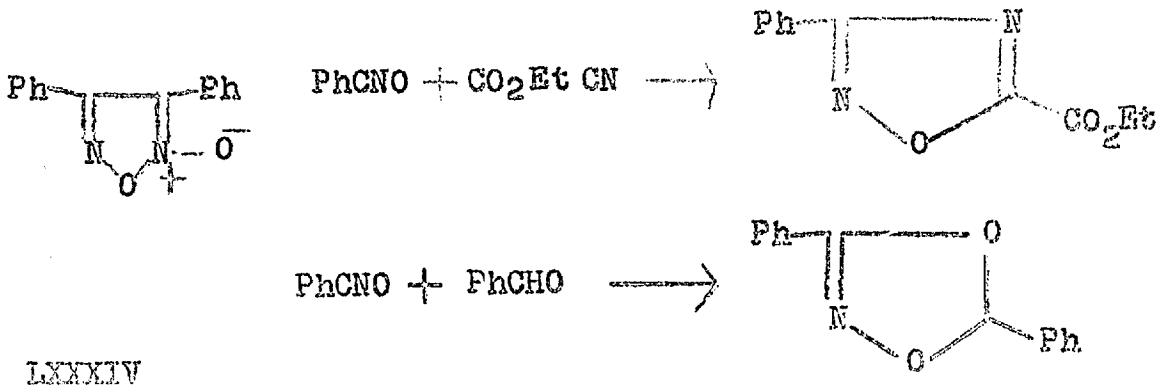


Enols will react with subsequent elimination to the isoxazole(81)



and it has recently been found that although cyclopentenes react easily with benzinitrile oxide a double bond in a six membered ring only reacts if it is conjugated(86).

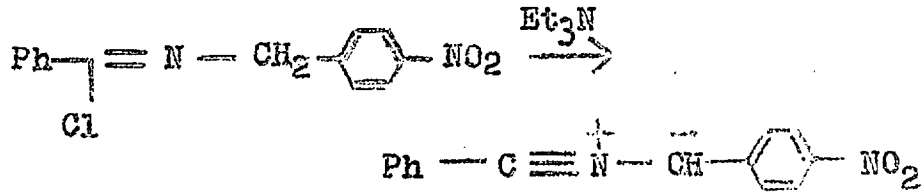
The difficulty in operating with benzanitrile oxide is its great tendency to dimerise and by Quilico's procedure of treating benzhydroximic chloride with aqueous alkali it is not possible to investigate additions to the nitrile oxide where the rate is less than that of the spontaneous dimerisation to furoxan (LXXXIV). Huisgen overcomes this problem by a high dilution method at reduced temperatures and has succeeded in adding benzonitrile oxide to carboxyl and nitrile groups(72)(73).

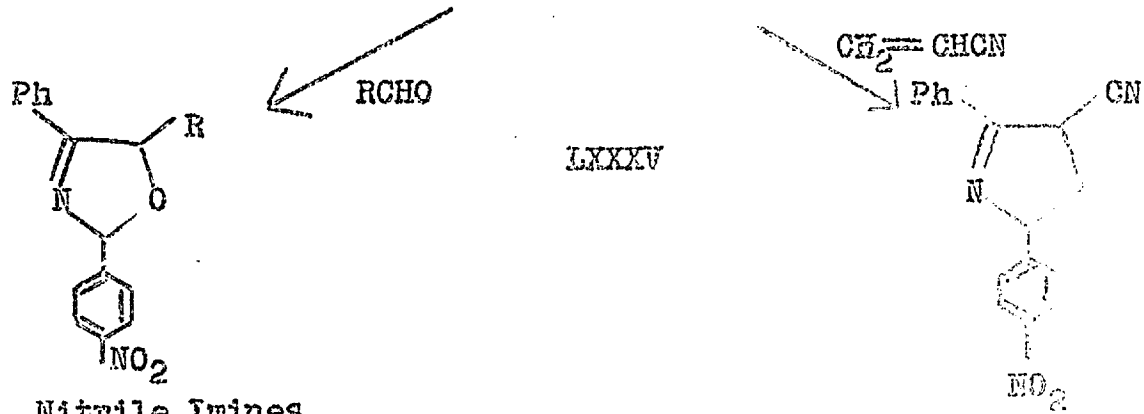


LXXXIV

Nitrile Ylides

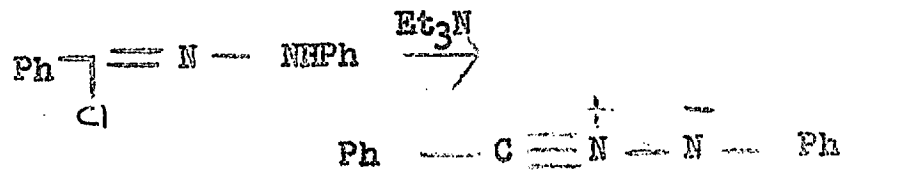
The nitrile ylide LXXXV will again react with nitriles and aldehydes(72)(73)

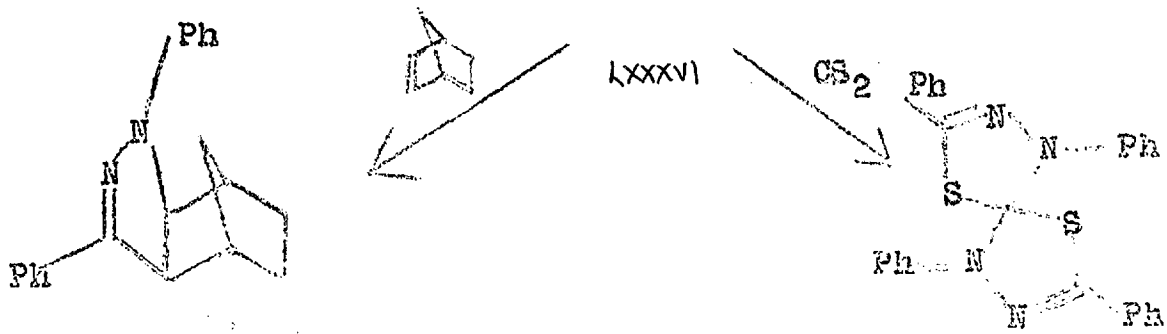




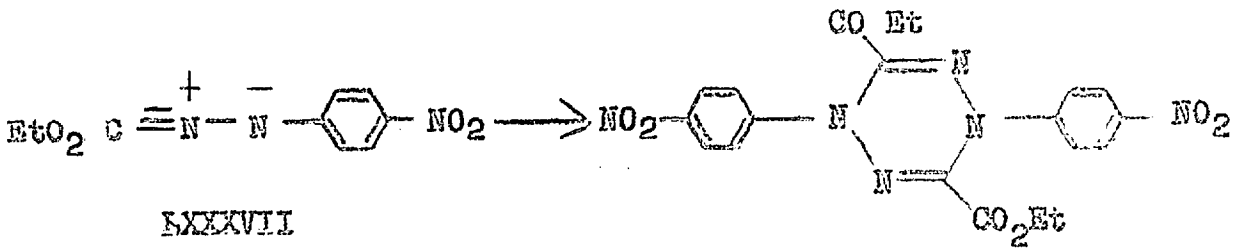
Nitrile Imines

These compounds (LXXXVI) are prepared in a similar way to nitrile oxides and nitrile ylides and undergo analogous addition reactions.





In LXXXVII however stabilisation by the nitro group enables dimerisation to occur

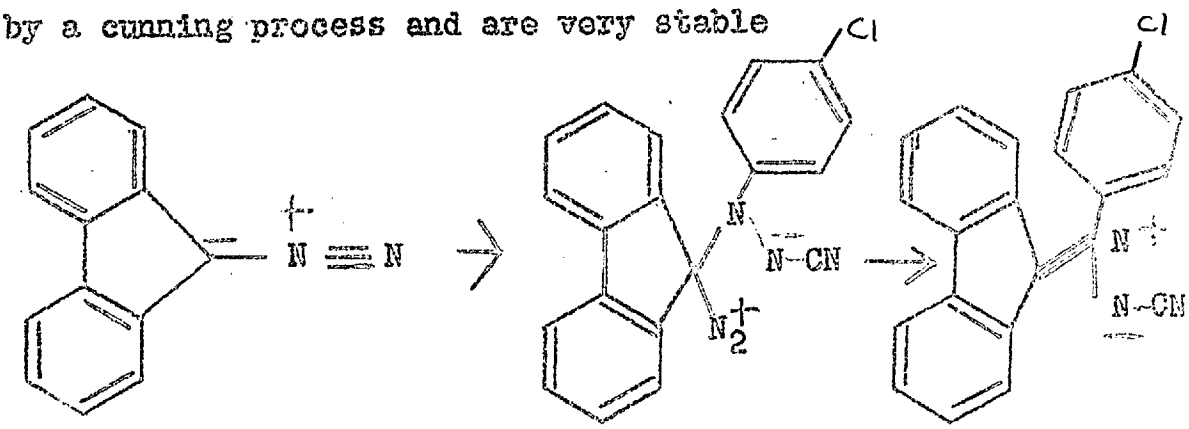


LXXXVII

and Huisgen predicts stereospecific cis addition in a similar manner to the Diels-Alder reaction.

Azomethine Imines

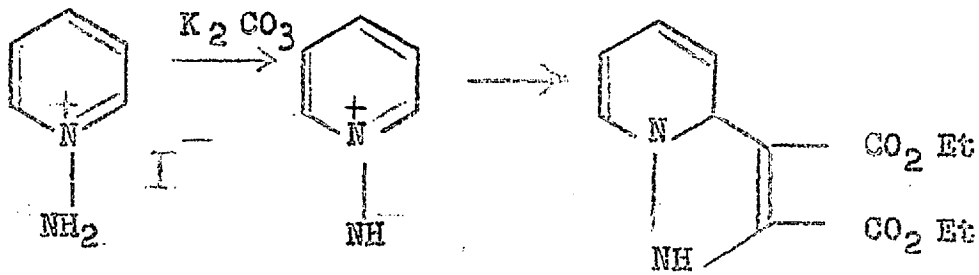
Compounds of the type (LXXXVIII) are prepared by a cunning process and are very stable



LXXXVIII

but reaction does occur with such reactive substrates as

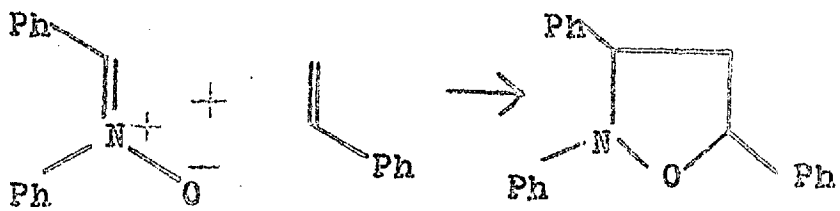
styrene. The remarkable driving force of 1:3 cyclo additions is well illustrated by the reaction of LXXXIX with diethyl acetylene dicaboxylate in which the aromatic resonance of the pyridine nucleus is destroyed.



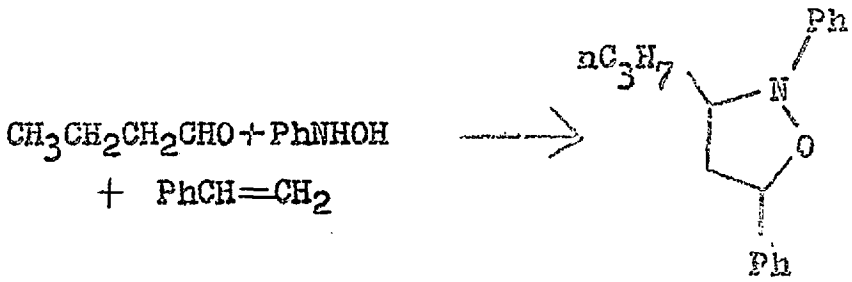
LXXXIX

Nitrones

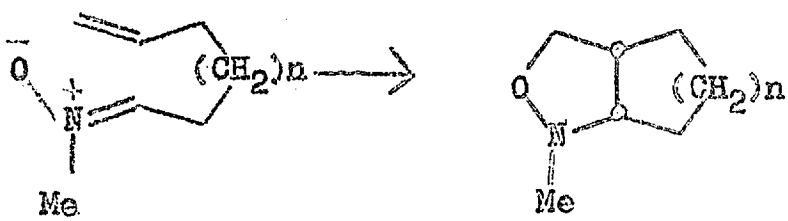
The reactions of nitrones have been found to parallel those of other 1:3 dipolar molecules(72)(73). Diphenyl nitrone is very stable but it does react with styrene



and in the aliphatic series adducts can be obtained by preparing the nitrone in situ in the presence of a substrate.



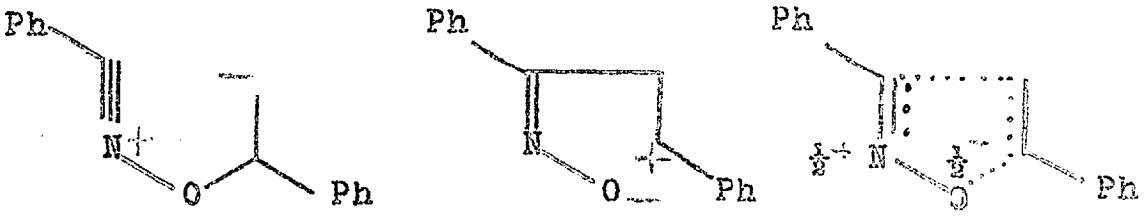
Similar work has been done by Rogers[89] who however neglected to establish the orientation of his products. The results of Delpierre and Lamchen[90] who added ethyl acrylate to a cyclic nitrone are compatible with those of Huisgenand the elegant work of Le Bel and Whang[91] has extended the reaction to an intramolecular case.



n=1 or 2

There is considerable circumstantial evidence for 1:3 cycloadditions being truly molecular but little quantitative work has been done to substantiate this.

It is possible to write three types of intermediate (XC, XCI, XCII) for the reaction of benzonitrile oxide with styrene



XC XCI XCII

but the absence of solvent effects upon rate[72] precludes the first two intermediates. Further evidence for the reaction not being nucleophilic or electrophilic comes from the way in which subtle changes in the structure of the olefin can reverse the mode of addition. The whole question of the mechanisms of nitrile oxide reactions will be discussed at more length when an account of the present work has been given. It should be noted that 1:3 dipolar molecules of the nitrile oxide or azide type are linear but LCAO calculations[72] show bending requires relatively little energy and in fact of all the reactions so far discussed 1:3 cycloadditions occur under the most mild conditions.

Mechanistic Summary

Because inevitably the reactions quoted have been studied from slightly different aspects and with different aims in view it is difficult to extract a unified mechanistic theory from the available evidence. It is generally accepted that a negative entropy of activation, first under kinetics, cis elimination, and a lack of rearrangement are necessary criteria for a molecular mechanism but even then another mechanism could be operating. The facts do however preclude the generalisation[40] that all pyrolytic cis eliminations are molecular.

Ester, xanthates and amine oxide pyrolyses appear to be very similar. Xanthates are pyrolysed in the liquid phase and esters in the gaseous phase but the product distributions are usually nearly identical in spite of this difference and that of temperature[39]. Although in amine oxide pyrolysis a more basic species is involved the similarities to ester pyrolysis are very marked and striking kinetic results are quoted[39] to show just how far the reaction is from being E_2 and thus how little charge separation there must be in the transition state. The smaller stereospecificity

of the Cope reaction as compared with xanthate pyrolysis is attributed to the greater development of double bond character in the transition state for the latter enabling the stability of the olefin to influence the result.

It does appear that the Diels-Alder reaction has great molecular character even though the rearrangement from which Woodward deduced a new mechanism for this reaction has been compared by him to the Cope reaction. The fact that the Diels-Alder reaction can be subject to acid catalysis does suggest the possibility of a polar transition state in some cases.

Probably the nearest approach to pure molecular reactions are cyclic 1:3 additions which proceed smoothly at remarkably low temperatures, in a highly specific manner, often in theoretical yield and are unaffected by solvents(72). It is interesting to consider a 1:3 cyclic addition being analogous to a Diels-Alder reaction with the 1:3 dipolar molecule playing the part of the dienophile and the olefin acting in place of the diene.

The kinetic studies of the Claisen rearrangement(17) although consistent with a concerted mechanism, do indicate some polar character in the transition state. The similarity of sulphite pyrolysis to the Chugaev reaction is striking(63) but the evidence from the

pyrolysis of aliphatic sulphites[60] lend credence to the idea that ion pairs are involved.

It is proposed that there is no abrupt change in mechanism in these reactions and the order in Table I is suggested for decreasing molecular character of the transition state.

T A B L E I

REACTION	NOTES ON MECHANISM
1:3 Cycloaddition	Almost entirely molecular
Diels-Alder	Largely molecular
Amine oxide pyrolysis, Ester and Halide pyrolysis, Chugaev	Largely molecular but with some notable exceptions
Sulphoxide pyrolysis	Molecular/Radical pair simultaneously
Sulphite pyrolysis	Molecular/Ion pair simultaneously
Chloroformate pyrolysis	Largely ion pair but partly molecular
Chlorosulphite pyrolysis	Ion pair

The way in which the characteristics of several of these reactions can be changed by substituent or temperature variation is powerful evidence for the proposed gradual change in mechanism. The trans-Chugaev reaction, the pyrolysis of esters with acidic β-hydrogens, and the small amount of trans elimination invariably associated with ester and xanthate pyrolysis, can all be cited, as can the variation with temperature of the stereospecificity of sulphoxide pyrolysis. Under favourable conditions the pyrolysis of sulphites can be molecular and the same applies under very favourable conditions to the pyrolysis of chloroformates. Furthermore the addition of diazomethane to an olefin is molecular but addition to a ketone involves an ionic intermediate(93).

An investigation of the general validity of Cram's free radical mechanism propounded for sulphoxide pyrolysis would certainly be in order as the only way of distinguishing between this and a molecular mechanism would be by measurement of entropies of activation which in the latter case should be large and negative.

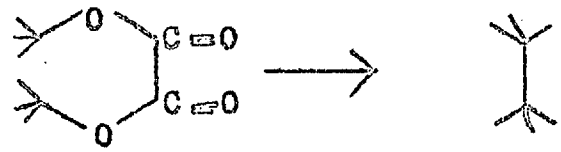
DISCUSSION

INTRODUCTION

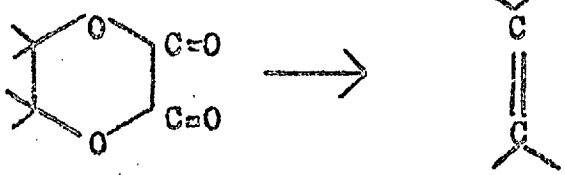
The long term aim of this work was the production of carbon-carbon bonds by synthetic methods which were mild and which proceeded through cyclic transition states. Extension of these molecular mechanistic processes to polymer synthesis was sought. To this end cyclic addition reactions were studied but prior work involved an investigation of other systems where it was predicted that carbon-carbon bond formation by molecular mechanisms might occur.

A. PYROLYTIC EXPERIMENTS

By analogy with carboxylic esters[39], pyrolysis of oxalates should result in carbon-carbon bond formation (i) and (ii).



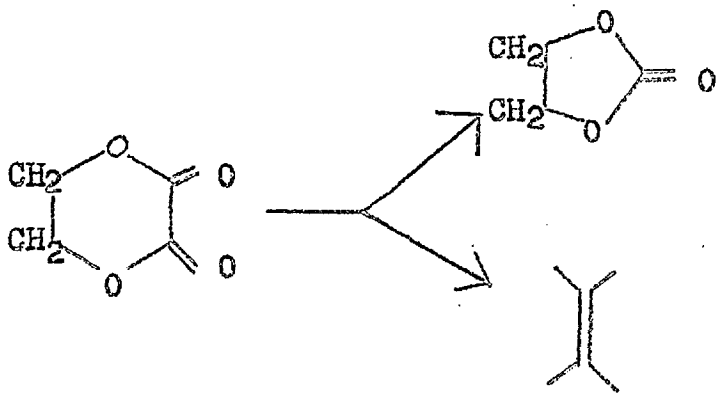
$$+ \quad 2CO_2 \qquad (i)$$



$$+ \quad 2CO_2 \qquad (ii)$$

In the only recorded instance of this reaction[95] degradation to ethylene carbonate and ethylene was in

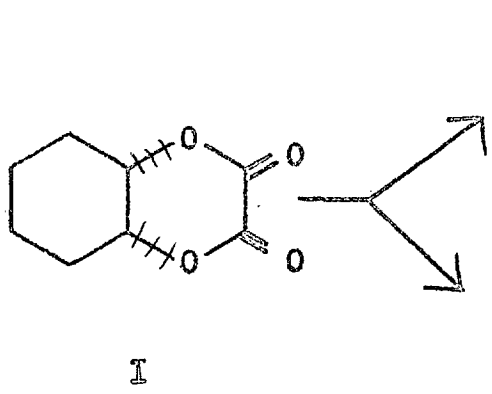
fact observed (iii) and (iv)



+ CO (iii)

+ $2CO_2$ (iv)

and an attempt was made to extend this method. Cis-cyclohexane-1:2-diol[96] did not react with oxalyl chloride but it did undergo a slow ester exchange with dimethyl oxalate in refluxing toluene to furnish cis-1:2-oxalatocyclohexane (I). Pyrolysis led to considerable quantities of carbon dioxide and carbon monoxide (v and vi)



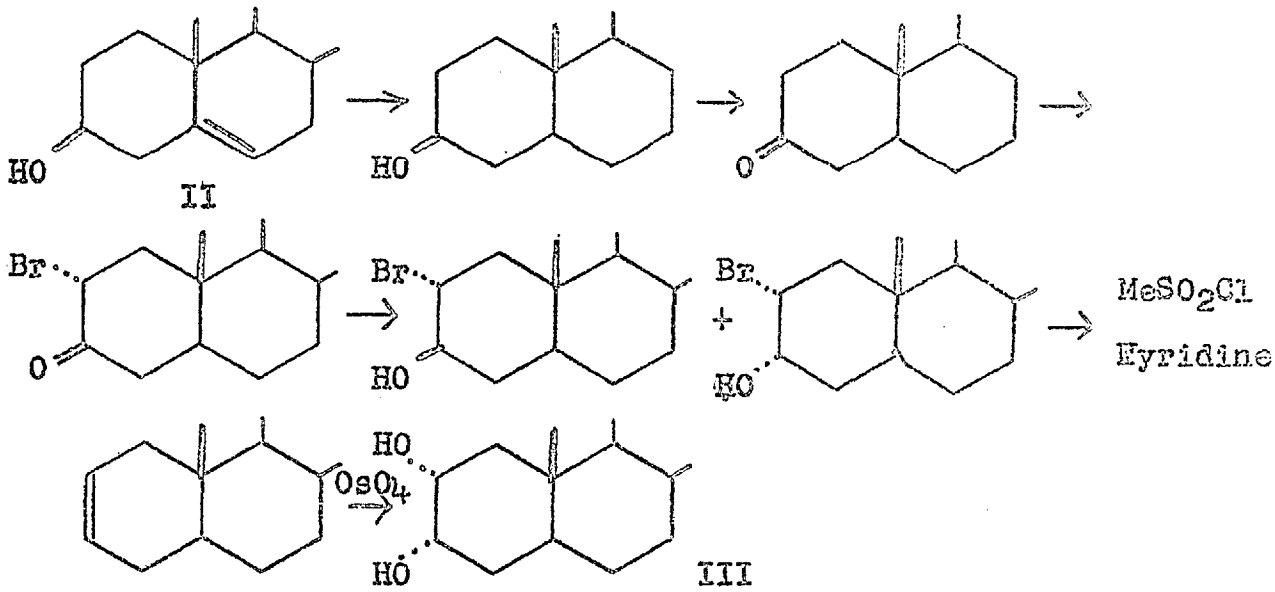
I

+ $2CO_2$ (43%) (v)

+ CO (48%) (vi)

but only minute quantities of cyclohexene were isolated and polymeric material was the major product.

Cholesterol (II) was converted to cholestane-1α :2α -diol (III)(97)(98)(99)



which however did not undergo an exchange with dimethyl oxalate, presumably because of the rigid conformation of ring A of a steroid in comparison with a lone cyclohexane ring.

Dibenzyl oxalate and dicinnamyl oxalate, prepared by the action of oxalyl chloride upon the corresponding alcohols, also underwent estensive polymerisation under pyrolytic conditions.

On the basis of this admittedly limited evidence it would appear that oxalate pyrolysis does not proceed accordingly to a molecular process.

A more promising approach appeared to be via the

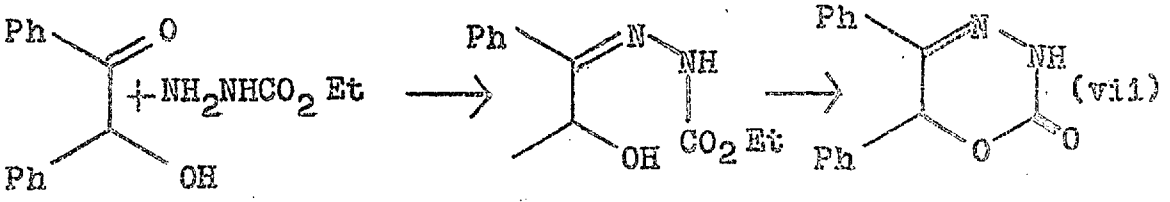
azo ester IV



IV

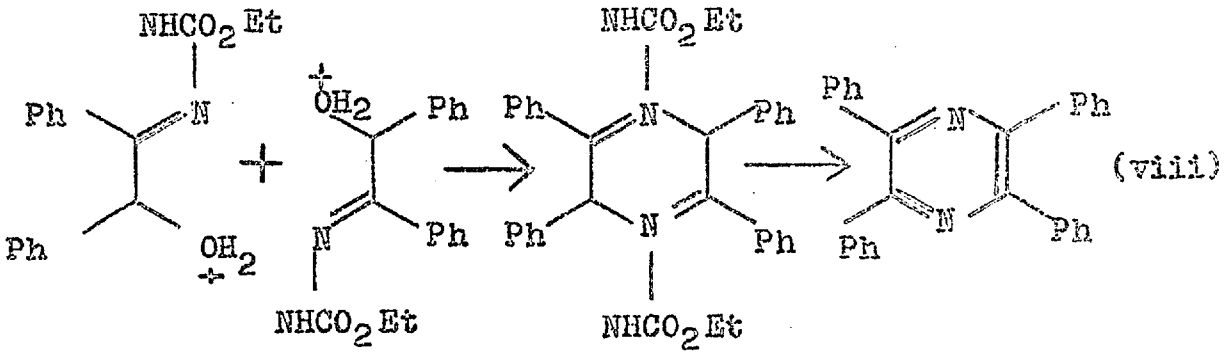
where in comparison with a cyclic oxalate the cis-azo group has introduced considerable strain and a fragmentation might be expected under mild conditions.

Rosenblum and Moltzan[100] have prepared the dihydro-oxadiazin-one V (vii)



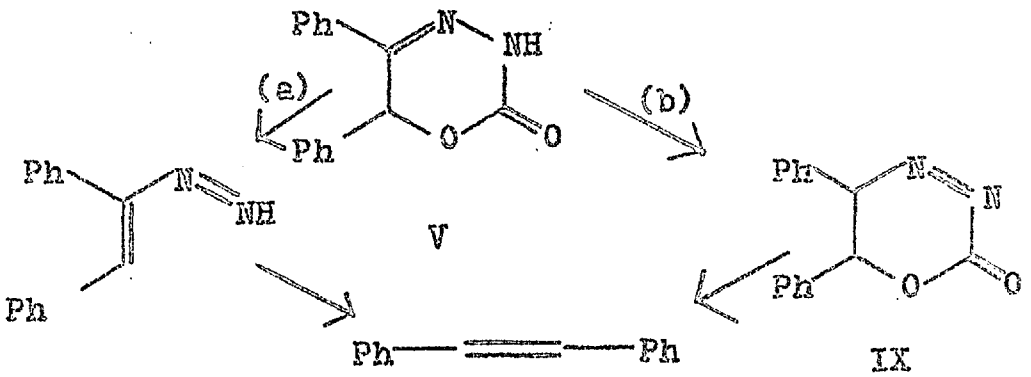
VI V

but only cursory experimental details were given and during experimentation to find satisfactory conditions for the synthesis of VI from benzoin and N-aminourethane it was found that only a trace of acid catalyst is required and if more is used tetraphenyl pyrazine (VII) is formed, presumably by a process such as (viii).



VII

The pyrolysis of the dihydro-oxediazine-one V yields equal amounts of cis and trans-stilbene(100) and so path (b), which involves initial rearrangement to a compound of type IV, is eliminated, as it is highly unlikely that the two possible stereoisomers of the azo-ester IX would be formed in equal quantities.

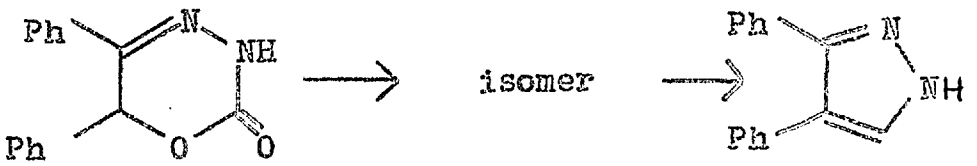


V

IX

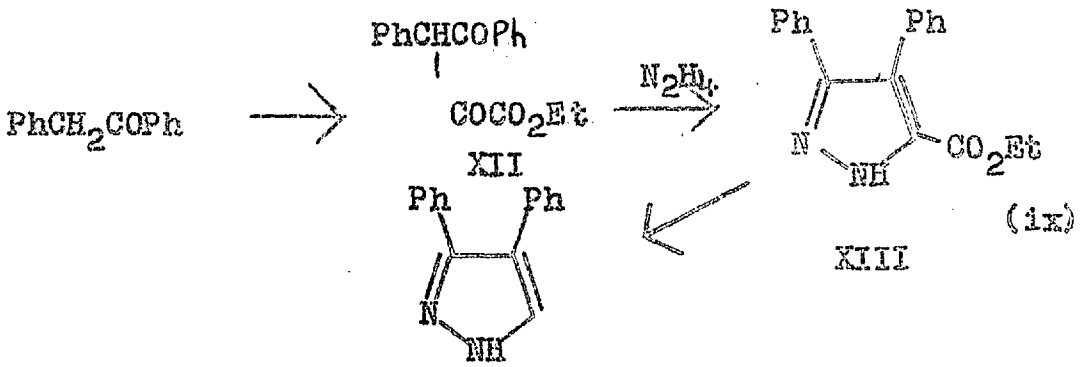
It did, however, appear possible to produce the azo-ester IX either by reduction and dehydrogenation or by base catalysed isomerisation. Of the reagents used to effect the former procedure sodium borohydride, sodium amalgam,

and lithium in ammonia gave no reduction, and catalytic hydrogenation led to hydrogenolysis. Sodium hydride in tetrahydrofuran had no effect, but potassium tert-butoxide in refluxing tert-butanol furnished an isomer (X)



V X XI

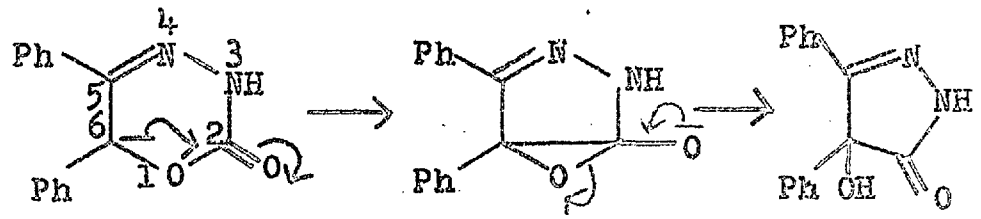
which was evidently not the azo-ester (IX) as it was unaffected by potassium permanganate in acetone, mercuric acetate, concentrated hydrochloric acid, and catalytic hydrogenation. Reduction with lithium aluminium hydride gave 3:4-diphenyl pyrazole (XI) which was independently synthesised[101][124](ix).



When the recommended[124] quantity of hydrazine was reacted with the diketone XII a mediocre yield of the

pyrazole XIII was isolated but the use of one mole of hydrazine resulted in a high yield.

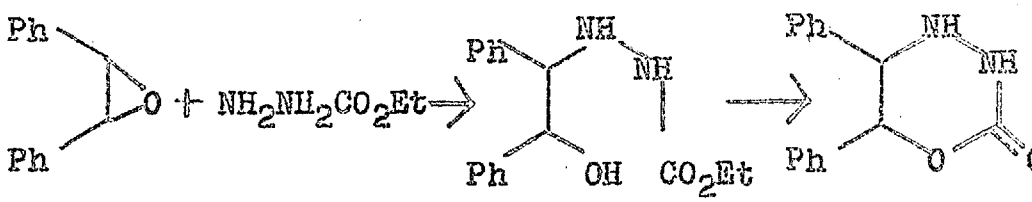
The most reasonable explanation of this rearrangement is that a proton is abstracted from position 6 rather than position 3 in V and a cyclopropanone is formed which rearranges to 3:4-diphenyl-4-hydroxy-1:2-diazole-5-one(x). This then is the structure of the isomer X.



(x)

V X

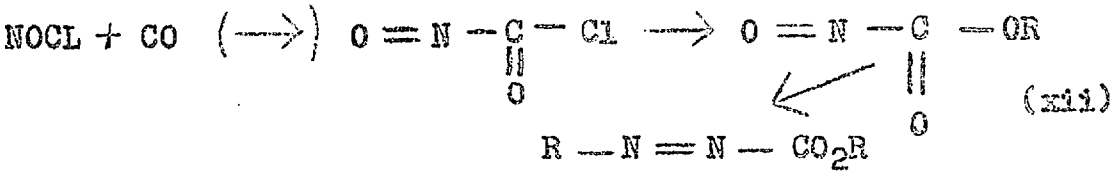
An alternative method was devised for obtaining the reduced azo-ester system (xi),



(xi)

but in practice N-aminourethane did not react with stilbene oxide, prepared by the action of perbenzoic acid on stilbene[102], even under vigorous conditions.

A further process was based on reacting the unknown nitrosocarbonyl chloride (XIV) with an alcohol and then with an amine (xii)



(xii)

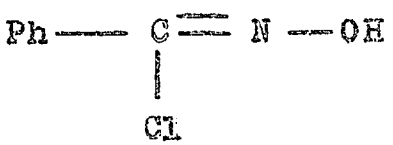
and for this investigation a vacuum line apparatus was built, but under all conditions tried, even in the presence of very active charcoal catalyst, the reaction of carbon monoxide with nitrosyl chloride did not produce the desired reagent.

B. DEGRADATION OF DIPHENYL FUROXAN

An entirely different approach to the problem of carbon-carbon bond formation involved benzonitrile oxide (XV)



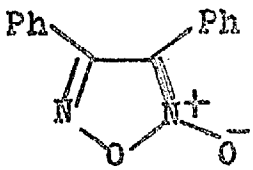
XV



XVI

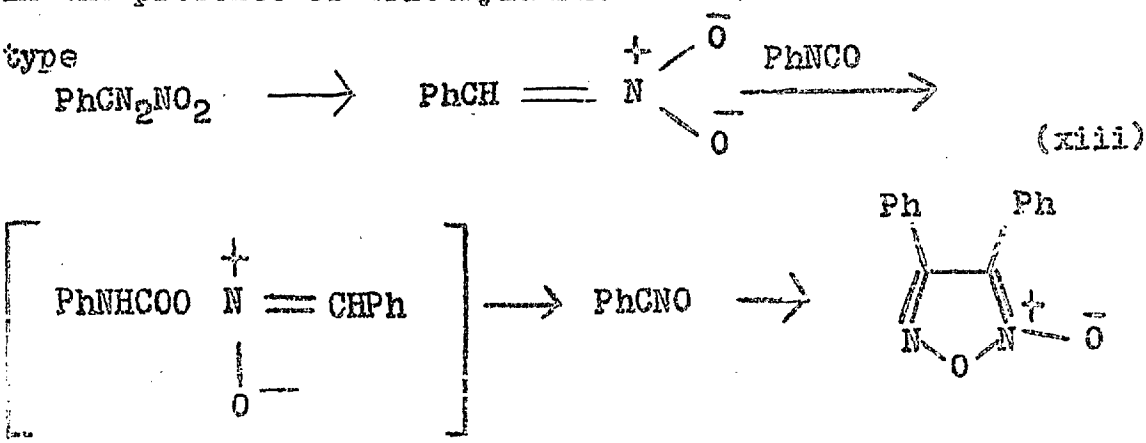
which was first prepared by Wieland[103]. The only method by which benzonitrile oxide has actually been isolated is by the action of base on benzhydroximic chloride (XVI). Quilico[81] invariably used concentrated aqueous sodium hydroxide but it is possible to use sodium carbonate[104] and in the present work triethylamine was utilised as a very rapid and clean reaction results at room temperature.

Several reactions are known in which benzonitrile oxide is formed as an intermediate and usually diphenyl furoxan (XVII) is then isolated.



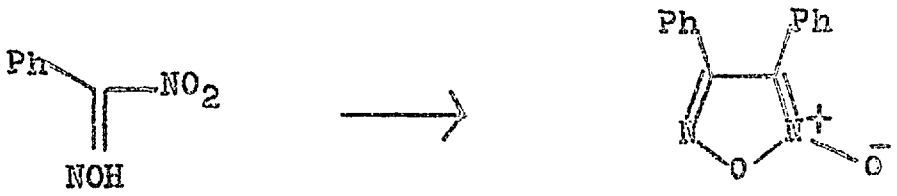
XVIII

The reaction of phenyl isocyanate with phenyl nitromethane in the presence of triethylamine[106] (xiii) is of this type



(xiii)

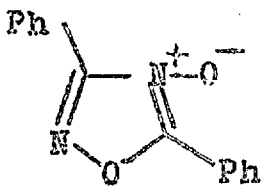
as is the process of warming benzonitrolic acid(107) (XIX).



XIX

The obvious preparative note of treating benzonitrile with peracid was studied but no reaction occurred. A possibility which has not yet received attention is the reaction of nitrous acid and benzamidoxime.

In acid solution benzonitrile oxide dimerises to the oxazoxime (XX)(108)



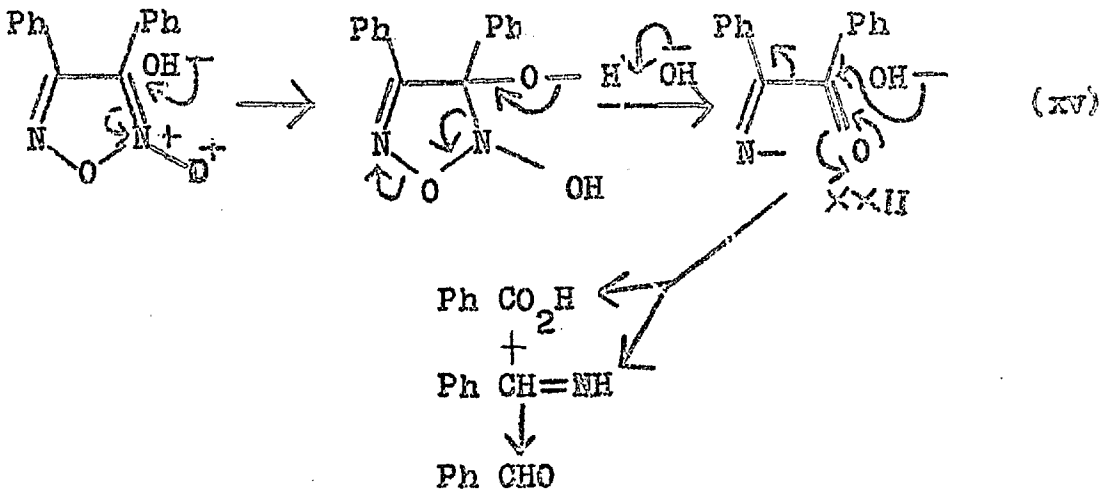
XX

while in neutral solution diphenyl furoxan(104) (XVIII) is formed. The latter 1:3 cyclic addition occurs with particular ease as it is complete in a few hours in dilute ethereal solution at room temperature. If it were possible to cleave the heterocyclic portion of the

furoxan system to leave a hydrocarbon this would effectively constitute a coupling of two aldehyde units (xiv)

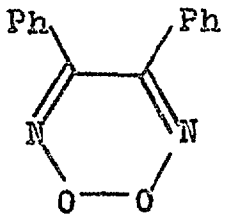
$$2\ RCHO \longrightarrow RCH_2CH_2R \qquad (xiv)$$

and with this aim the reaction of diphenyl furoxan with alkali was studied. Wieland and Semper[107] report that benzoic acid is the product and is formed with difficulty, but when diphenyl furoxan was refluxed with ethylene glycol and potassium hydroxide for a few minutes under nitrogen benzoic acid (45%) and benzaldehyde (46%) were isolated and the solution gave a very strong colour reaction for nitrite. The following mechanistic scheme (xv) is in accord with this evidence



(xv)

and incidentally provides corroboration for the furazan oxide formulation of furoxans (XVIII). According to Kaufmann and Picard[109] even in 1959 the alternative glyoxime peroxide structure (XXI)



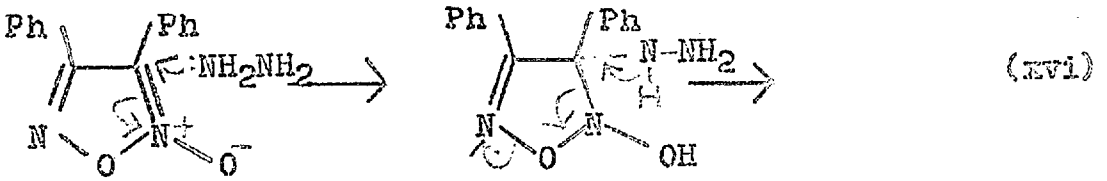
XXI

had not been rigorously excluded.

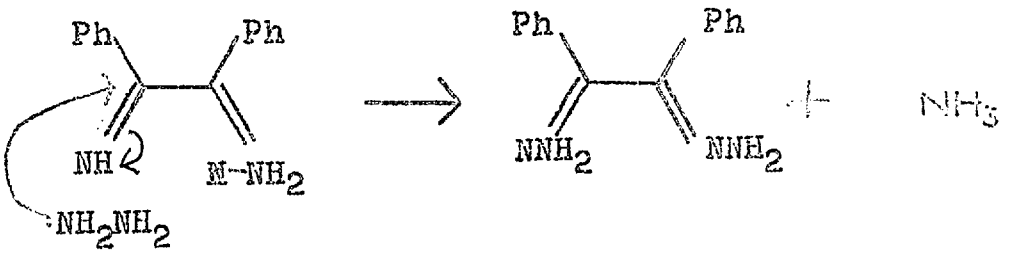
As the treatment of benzil with alkali in a control experiment resulted in the formation of benzilic acid the intervention of benzil in (xv) is precluded and therefore an intermediate of the type XXI must be involved.

The subjection of diphenyl furoxan to Wolff-Kishner reduction with hydrazine hydrate and potassium hydroxide in glycol resulted only in alkaline degradation of the furoxan. When hydrazine hydrate, or preferably hydrazine, was reacted under these conditions with diphenyl furoxan in the absence of alkali the major product was benzil-bis-hydrazone but following the reaction by the changes in the U.V. spectrum showed that several hours were required for completion. This is

in contrast to the rapid alkaline degradation and can best be explained by the marked difference in nucleophilic character of hydrazine and hydroxyl. An analogous mechanism (xvi) is thus implied.

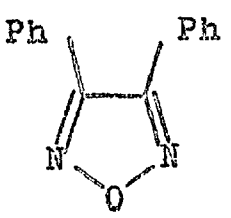


(xvi)

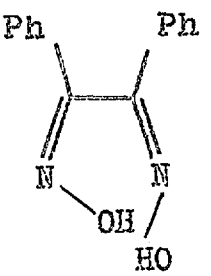


and support was forthcoming from the strong colourimetric indication for ammonia which was obtained by a simple process which separate experiments had shown was satisfactory for detecting ammonia in the presence of hydrazine.

Minor products from the hydrazine-diphenyl furoxan reaction were diphenyl furazan (XXII) and benzil-β-dioxime (XXIII).



XXII



XXIII

These two systems, together with diamines, are reported to be the general products from reduction of furoxans[109] with a variety of reagents. Bis-hydrazone formation has not hitherto been reported from hydrazine reduction.

The reaction of potassium hydroxide with benzil-bis-hydrazone furnished a quantitative yield of dibenzyl (XXIV).



XXIV

Actual isolation of the bis-hydrazone was not required as an equal yield of dibenzyl was obtained by adding alkali to the furozan-hydrazine mixture after that reaction was complete.

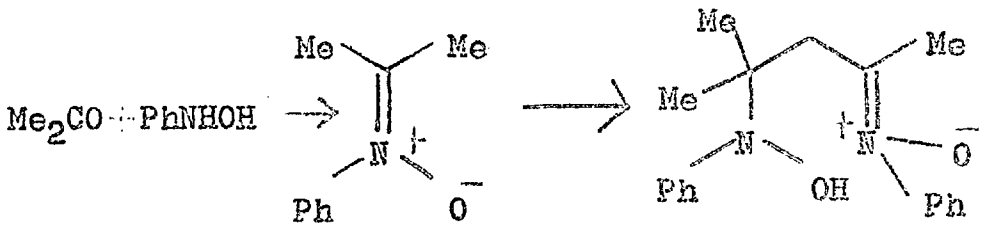
Thus in one case the procedure depicted in (xiv) has been accomplished but as rather brutal reagents and high temperatures were used the method was not extended to other furoxans.

C. CYCLIC ADDITION REACTIONS

1. Nitrones

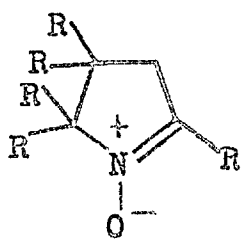
The N-ethers of oximes, or nitrones, which are usually prepared by the condensation of an aldehyde with a hydroxylamine, are formally very similar to nitrile

oxides. They do not however undergo spontaneous 1:3 dimerisation but instead an aldol type of condensation often occurs as exemplified by the reaction of acetone with phenylhydroxylamine[110] (xvii).

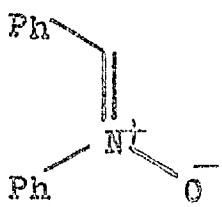


(xvii)

Cyclic nitrones of type XXV are stable in the monomeric form[111] as is diphenyl nitrone (XXVI)

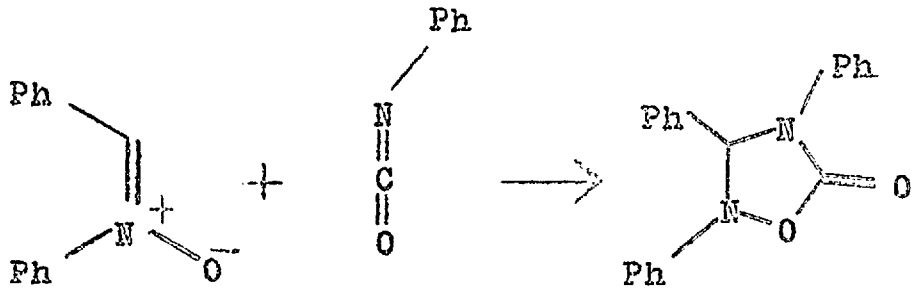


XXV



XXVI

and it was the reaction of the latter with phenyl isocyanate[112] (xviii) that was the only 1:3 cyclic addition reaction of a nitrone known prior to this work.



(xviii)

XXVI

As nitrile oxides react with olefins by a 1:3 cyclic process[84] it was hoped that nitrones would react similarly and then perhaps the adducts could be degraded in a manner akin to that used for diphenyl furoxan. No reaction occurred between diphenyl nitrone and benzonitrile (XXVII), acrylonitrile (XXVIII), cyclohexene (XXIX), benzonitrile oxide (XV), phenyl acetylene (XXXI) or benzylidene aniline (XXXII), even under vigorous conditions, but with styrene in ethanol a slow reaction ensued from which an adduct (XXXIII) was isolated in quantitative yield.

PhCN (XXVII)

CH_2=CH—CN (XXVIII)

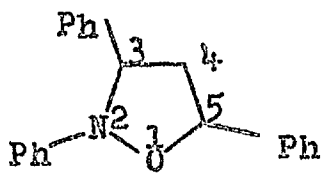


(XXIX)

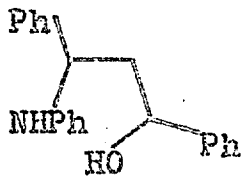
Ph—C≡$\overset{+}{N}$—$\overset{-}{O}$ (XV)

Ph—C≡CH (XXXI)

Ph—CH=N-Ph (XXXII)



XXXIII



XXXIV

The N.M.R. spectrum of the adduct(113) was compatible with structure XXXIII but not with the phenyl substituent being in the 4-position and mild hydrogenolysis led to an amino-alcohol, presumably XXXIV. Huisgen(73) contemoraneously synthesised XXXIII and has proved its structure.

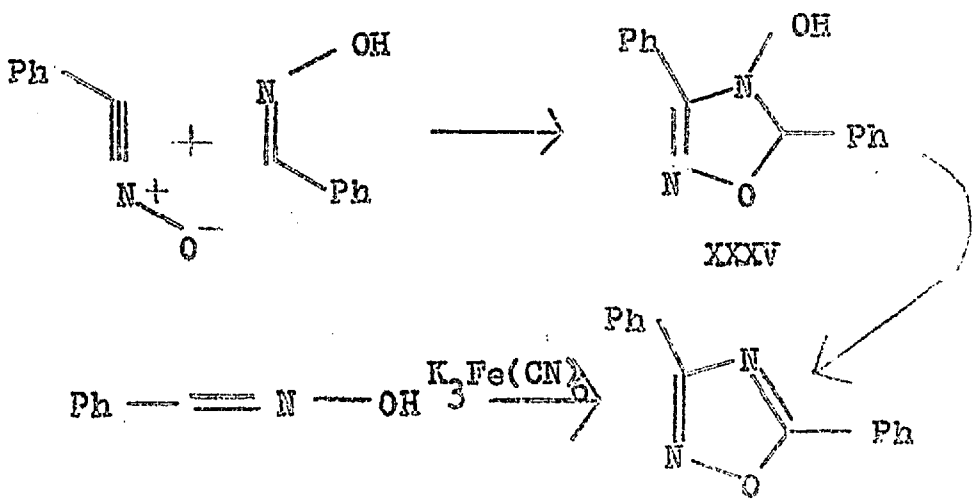
Experiments designed to produce an adduct by generating a more reactive nitrone <u>in situ</u> were unsuccessful. Thus oxidation of diethyl hydroxylamine with mercuric oxide in the presence of benzonitrile and condensation of phenylhydroxylamine with n-butyraldehyde in the presence of benzyl cyanide led in neither case to cyclic addition. At this stage as with furoxans the

study of nitrones was discontinued in view of the lack of a simple procedure for degrading the isoxazolidine (XXXIII) and the reactions of benzonitrile oxide were further considered.

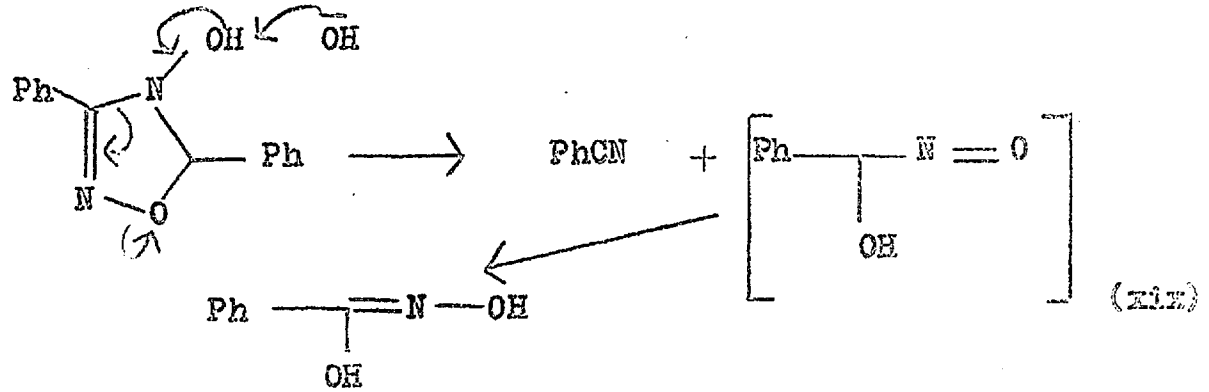
2. Benzonitrile oxide

(a) Benzaldoxime

Benzaldoxime was found to react with benzonitrile oxide in ethereal solution at reflux temperature to give, albeit in low yield, an amorphous adduct (XXXV) which was purified by chromatography since on sublimation dissociation occurred and diphenyl furoxan was isolated. Reprecipitation effected little purification. When treated with acetic anhydride and pyridine under mild conditions the adduct furnished 3-5-diphenyl-1:2:4-oxadiazole (XXXVI), the structure of which was confirmed by synthesis from benzaldoxime[114].

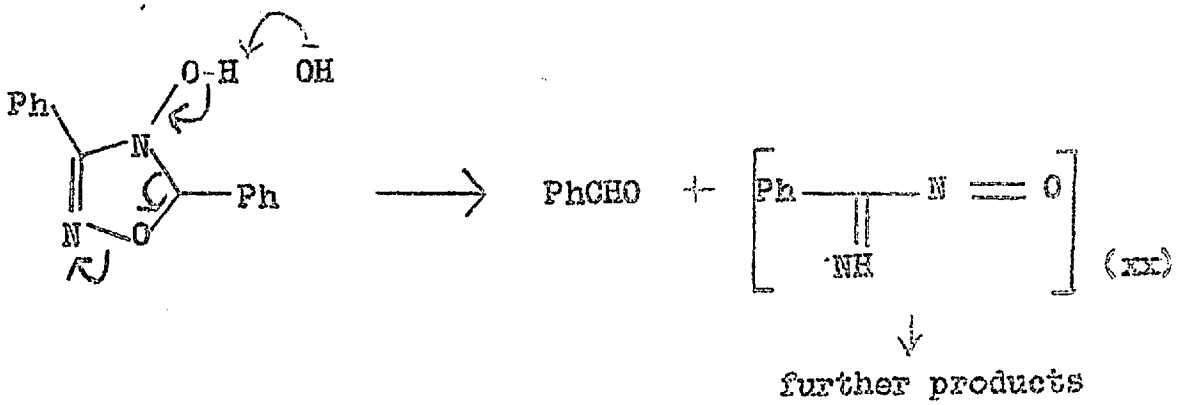


Treatment of the adduct with methanolic sodium hydroxide at room temperature immediately gave a yellow solution from which benzonitrile and benzhydroxamic acid were isolated, providing confirmation of the structure assigned to the adduct, and indicating a concerted alkaline decomposition (xix).



(xix)

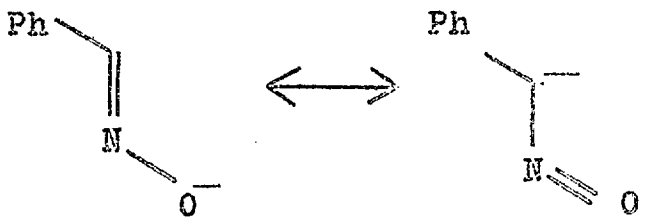
A little benzaldehyde was isolated indicating some decomposition in the reverse sense had occurred (xx).



(xx)

This reaction constituted the first known example of a nitrile oxide undergoing a cyclic addition with a group other than an olefin or an acetylene but the mode

of addition was opposite to that which would form a carbon-carbon bond. A promising idea appeared to be the use of an oxime salt (XXXVII) in which in comparison with an oxime the aldehyde carbon is highly nucleophilic.



XXXVII

As the oxygen of benzonitrile oxide is also nucleophilic this change should inhibit carbon-oxygen bond formation thus increasing the possibility of isolating an adduct resulting from carbon-carbon bond formation if the two processes are competitive. In fact when solutions of benzonitrile oxide and the sodium salt of benzaldoxime were mixed at room temperature a vigorous reaction which was complete within a few minutes ensued. The sodium salt of benzhydroxamic acid was precipitated and the filtrate yielded mainly benzonitrile but also a little benzaldehyde and an unidentified compound, mp. 127°-8°, which had three bands in the OH region in the i.r. Thus the alkaline reaction parallels that in neutral solution except in rate. There are two possible

explanations; firstly, that the initial reaction to form the adduct XXXV has a very low activation energy and is reversible but that the equilibrium is almost completely in favour of the starting reagents. In this case the rapid reaction observed in alkaline solution is due to removal of adduct by fragmentation as soon as it is formed; secondly, the rate of production of the adduct could simply be increased under alkaline conditions. The former explanation can be excluded on the grounds that the adverse entropy factors associated with a cyclic transition state make an instantaneous reaction very unlikely even if the activation energy is zero and that the neutral reaction shows that if the reaction is reversible then a significant amount of adduct is present at equilibrium. Further evidence that the latter explanation is correct will be presented later. Variation of the conditions under which benzaldoxime was reacted with benzonitrile oxide resulted in no fundamental change except that when an excess of alkali was used benzoic acid, rather than benzhydroxamic acid, was isolated.

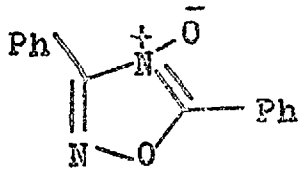
(b) Quaternised Schiff Base

A plan with a similar principle to that of the alkaline oxime reaction was to use a quaternised Schiff

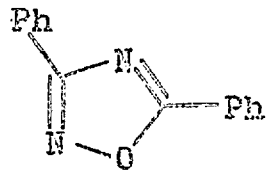
base, but benzylidene methylamine methiodide (XXXVIII)



XXXVIII



XX



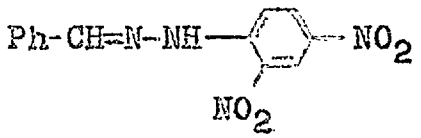
XXXVI

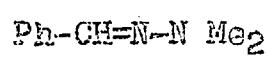
underwent hydrolysis so easily that in practice reaction with benzonitrile oxide gave only the acid dimerisation product of the nitrile oxide (XX) whose structure was confirmed by reduction with phosphorous pentachloride to the corresponding oxadiazole (XXXVI).

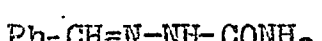
With the object of extending the reaction of nitrile oxides with imines several other systems were studied.

(c) Schiff bases

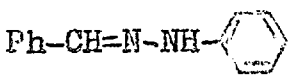
Benzaldehyde-2:4-dinitrophenylhydrazone (XXXIX), semicarbazone (XL), phenylhydrazone (XLI), and dimethylhydrazone (XLII), pyridine-N-oxide (XLIII), and benzaldoxime acetate (XLIV) were all inert.

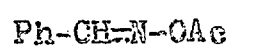

(XXXIX)


(XLII)


(XL)

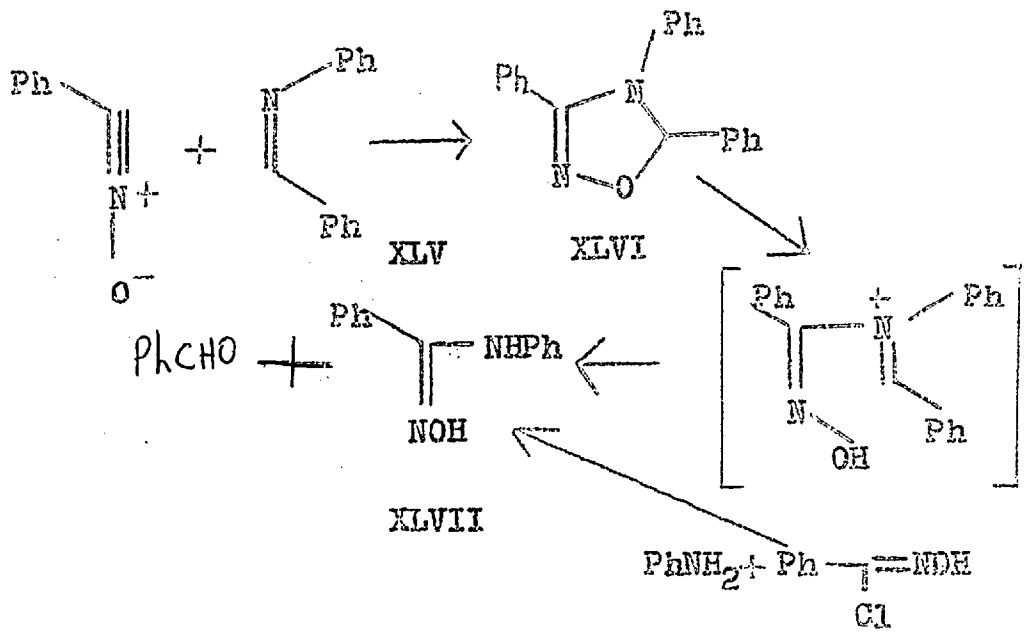

(XLIII)


(XLI)

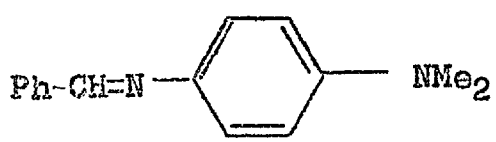

(XLIV)

As a high dilution procedure and generation of the nitrile oxide *in situ* were not followed these negative results may simply reflect the slowness of the reaction compared to the rate of dimerisation of benzonitrile oxide. In each case only diphenyl furoxan and the aldehyde derivative were recovered.

The reaction of benzonitrile oxide with benzylidene aniline (XLV) did lead to an adduct (XLVI) and in 66% yield. The fact that carbon-nitrogen bond formation had occurred was demonstrated by acid degradation which led to benzaldehyde and N-phenyl benzamidoxime (XLVII). The identity of the latter compound was established by synthesis from aniline and benzhydroximic chloride.



Thus addition followed the same sense as in the oxime case but the hope was entertained that by judicious selection of substituents in the Schiff base the direction of addition could be reversed. With this aim p-nitrosodimethylaniline was hydrogenated to p-aminodimethylaniline which was condensed with benzaldehyde to produce the substrate XLVIII. This compound in its fully polarised form has structure IL.

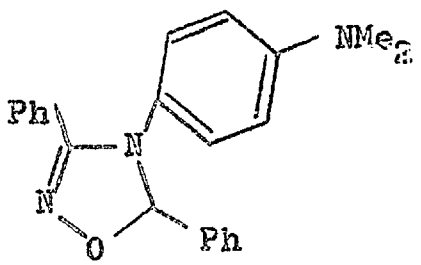


XLVIII

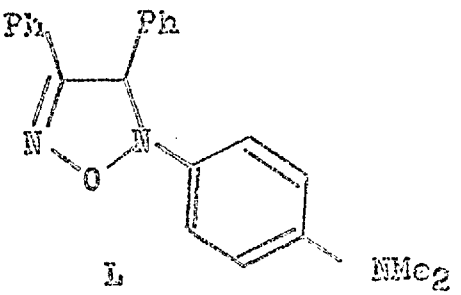


IL

and although the mechanisms of these cyclic 1:3 additions had been considered to be largely molecular in character, at this stage a nucleophilic initiation step for the cyclic process was still favoured. Making the carbon of the Schiff base nucleophilic (IL) should then either retard the reaction with benzonitrile oxide or give the adduct resulting from carbon-carbon bond formation (L).



LI

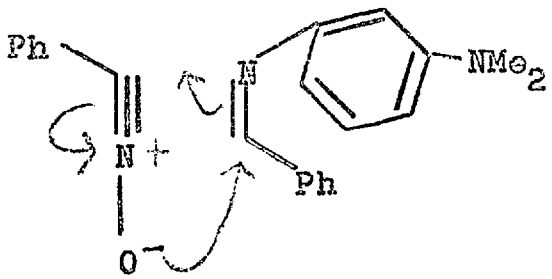


L

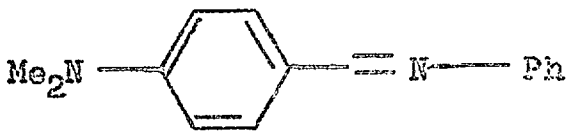
Benzonitrile oxide did react with XLVIII in ethereal solution at room temperature to furnish, in 90% yield, a colourless adduct (LI) which was unaffected by acid but which had an i.r. spectrum extremely similar to that of the benzylidene aniline adduct (XLVI), indicating the two structures were analogous. Proof of this was obtained later. In contrast to expectation the reaction was very fast.

As making the carbon of a Schiff base nucleophilic

(inhibiting (xxi) was fruitless the nitrogen was modified in a similar manner by using LII as a substrate,



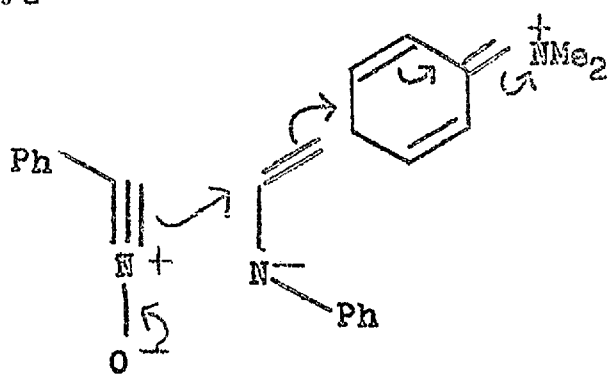
(xxi)



LII

and it was synthesised by the condensation of p-dimethylaminobenzaldehyde[115] with aniline.

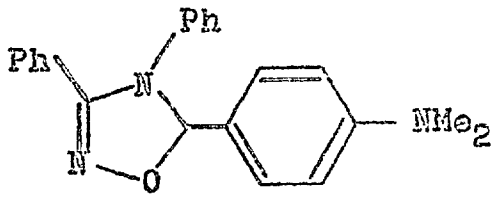
For this variation to succeed in reversing the direction of addition the initial step must be nucleophilic attack from the carbon rather than the oxygen of the nitrile oxide (xxii).



(xxii)

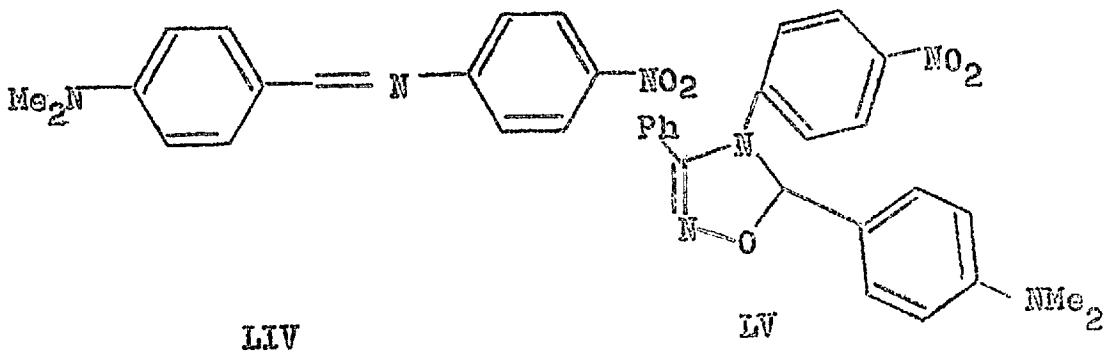
The observed result was than an adduct (LIII) was formed

(78% yield) and again it resulted from carbon-nitrogen bond formation as upon treatment with acid it furnished N-phenyl benzamidoxime.



LIII

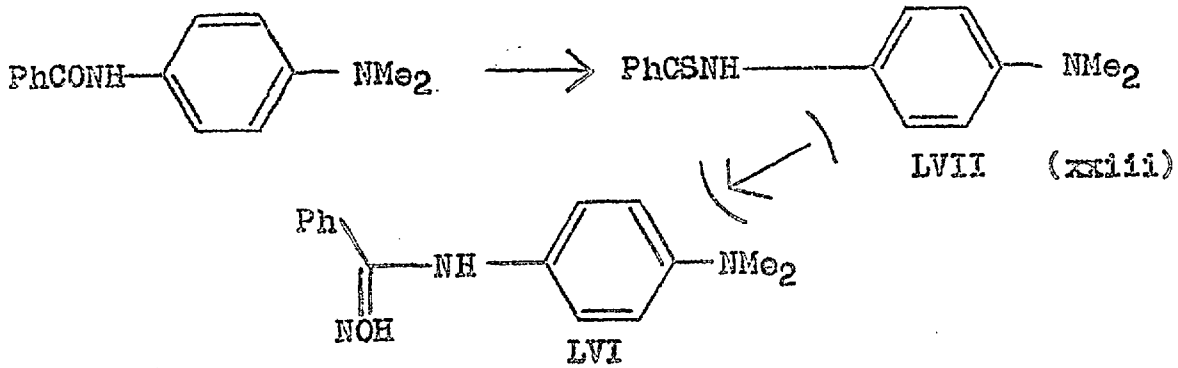
A further analogous cyclic addition reaction was accomplished from the di-substituted Schiff base LIV which, upon reaction with benzonitrile oxide under the usual conditions, led to a red adduct (LV; 80% yield).



LIV LV

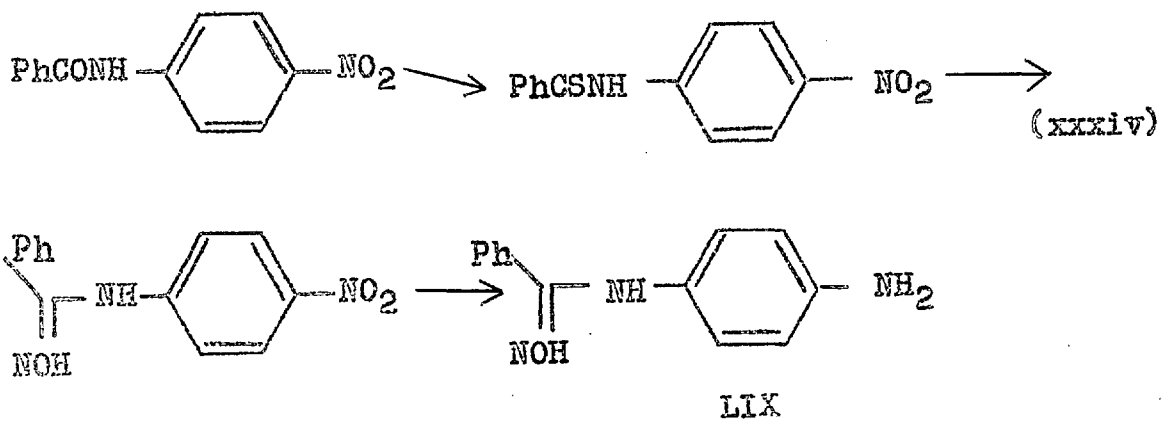
The adduct was unreactive to acid and hydrogenolysis was used for structural proof of both this and the other adduct of unconfirmed orientation (LI). The latter compound absorbed 2.12 moles of hydrogen and furnished a yellow-green compound m.p. 137° which was considered

to be amidoxime LVI and the synthesis of this was accordingly undertaken (xxiii).

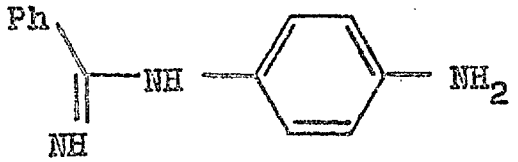


Benzoyl-p-dimethylaminoaniline underwent a smooth reaction with phosphorous pentasulphide to yield the thioamide LVII but attempted oximination of this under various conditions was unsuccessful.

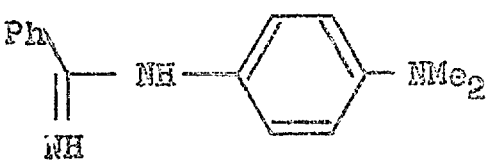
When LV was hydrogenolysed approximately five moles of hydrogen were absorbed indicating that in addition the nitro group had suffered reduction. The expected product was the amidoxime LIX and synthesis of this was accomplished by an analogous route (xxiv) to that which was unsuccessful in the previous case.



Benzoylation of p-nitraniline and treatment of the product with phosphorous pentasulphide furnished the corresponding thioamide which was reacted with hydroxylamine hydrochloride and pyridine under vigorous conditions. Chromotography of the product yielded the nitroamidoxime as an oil which upon hydrogenolysis took up three moles of hydrogen to give the aminoamidoxime LIX whose mp., however, did not correspond with that of the hydrogenolysis product of LV. The i.r. spectra of the two compounds, although extremely similar, were distinctly different in the OH-region and an appraisal of the spectra of the hydrogenolysis products indicated that they were amidines (LX and LXI) and not amidoximes.



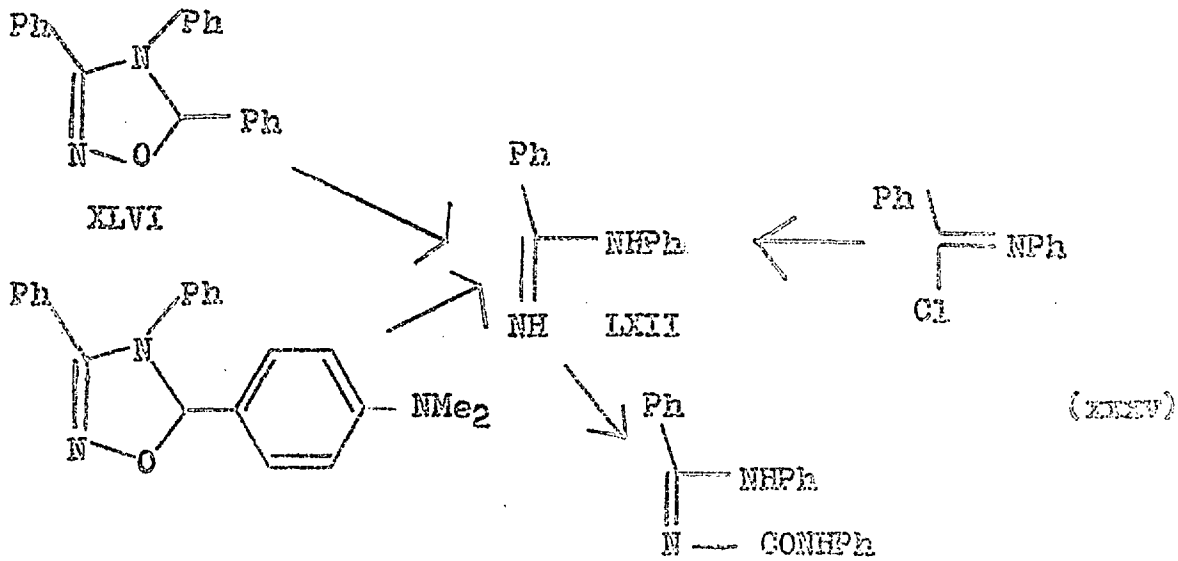
LX



LXI

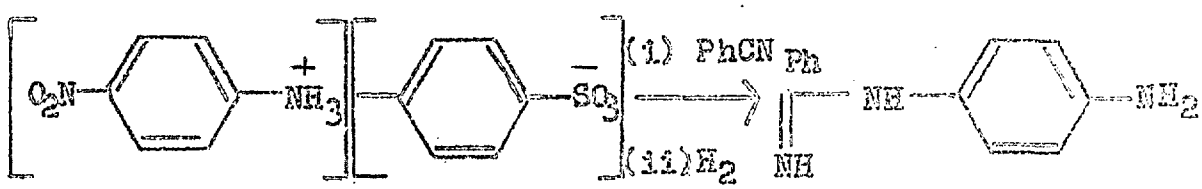
This interpretation was supported by hydrogenolysis of the adducts of proven structure (XLVI and LIII) which in each case led to a compound which was identified as N-phenyl benzamidine (LXII) by formation of a derivative with phenyl isocyanate and by synthesis from

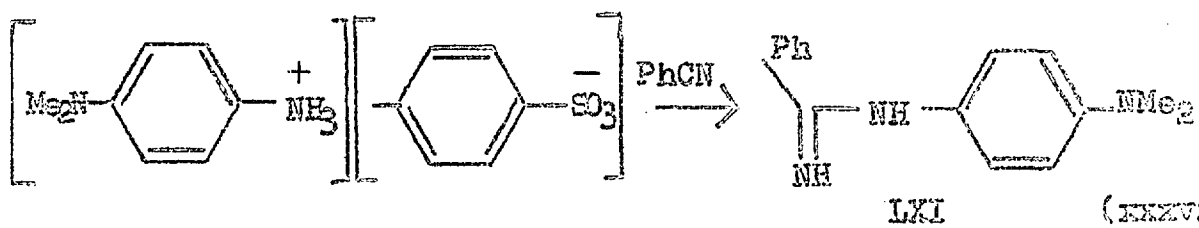
benzimidochloride (xxxv).



(xxxv)

The i.r. spectrum of N-phenylbenzamidine was almost identical with those of the unknown hydrogenolysis products and confirmation of their structure was obtained by synthesis (xxxvi)





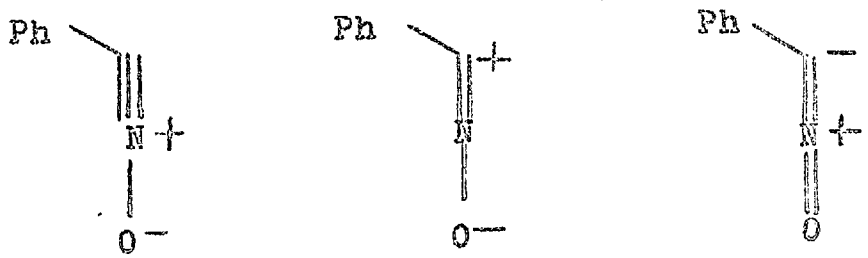
LXI (xxxvi)

in which the appropriate amine-p-toluene sulphonate salt

was heated with benzonitrile.

The most significant feature of the reaction of benzonitrile oxide with this selection of Schiff bases is the way in which the reaction is accelerated by the presence in the Schiff base of electron donating groups, irrespective of their position. These results strongly support the hypothesis that the direction of electron flow in a molecular mechanism is meaningless and that the only effect of dimethylamino substituents is to accelerate the reaction by increasing the electron density available in the C=N bond. This explanation corresponds with the observation (supra) that oximes react with nitrile oxide faster in alkaline than in neutral solution.

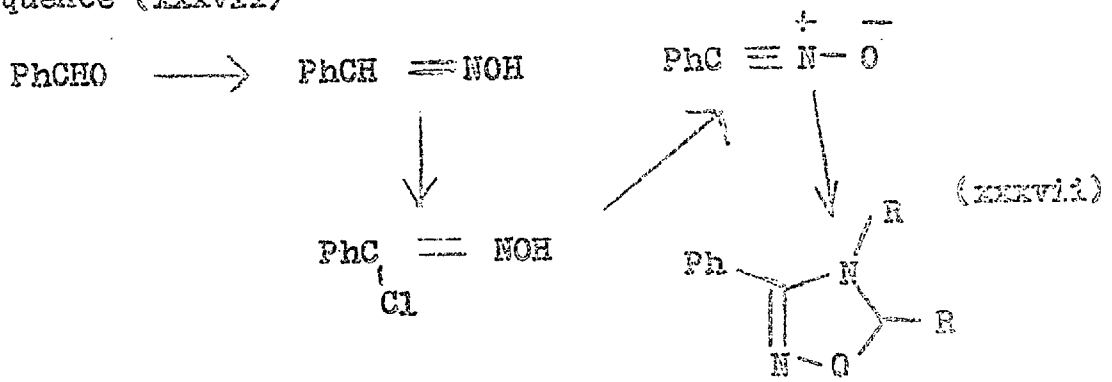
The fact that benzonitrile oxide can be written in three resonance forms (LXII)



LXII

allowing an electrophilic or a nucleophilic attack on the imine to be invoked as convenient also does not support

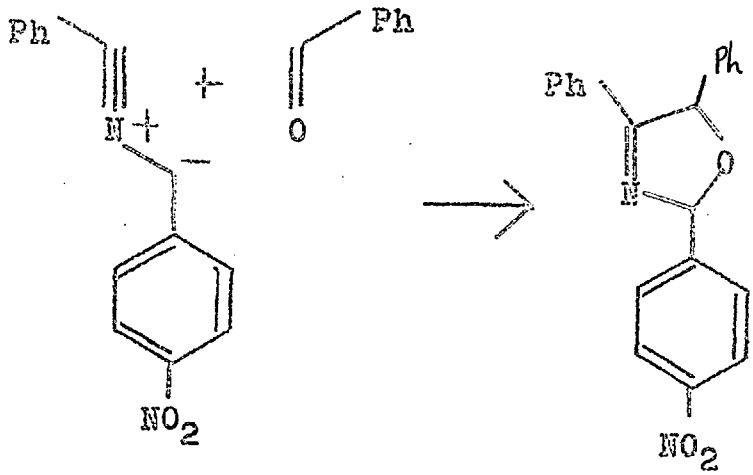
a directional electron flow. If a molecular mechanism is then truly operating a special orientation of the reactants will be required and the great rapidity of the reaction means that the activation energy must be extraordinarily low. It is noteworthy that in the sequence (xxxvii)



(xxxvii)

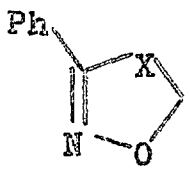
in no case is heating required, the penultimate step is apparently instantaneous, and the last step will proceed rapidly at low temperature.

No explanation can be offered to explain the orientation of the adducts. Huisgen[73] found that nitrile ylides react in the reverse sense (xxxviii) to other 1:3 dipolar reagents.



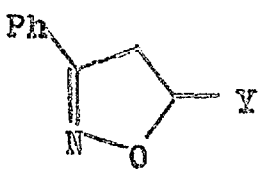
(xxxviii)

but except for furoxan formation he found no case of an addition that involved benzonitrile oxide giving carbon-carbon bond formation and the structure of the adduct could always be depicted by LXIII or LXIV as appropriate.



LXIII

X - hetero atom



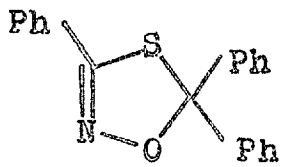
LXIV

Y - negative group

Independently of this work the search was continued for 1:3 dipolar additions that would lead to carbon-carbon bond formation and the reaction of benzonitrile oxide with other molecules was studied.

(d) Thiobenzophenone

Thiobenzophenone appeared to be an interesting substance for study but difficulty was experienced with its preparation. The i.r. spectrum of the product from the action of sodium hydrosulphide on dichlorodiphenylmethane[116] revealed that benzophenone was the major constituent and when reacted with benzonitrile oxide the product gave, albeit rapidly, only a small yield of an adduct. Westheimer[117] also found that this preparative procedure gives impure thiobenzophenone and utilisation of his method[117] whereby benzophenone is reacted with a mixture of hydrogen sulphide and hydrogen chloride under nitrogen gave much purer material. The reaction with benzonitrile oxide was apparently almost instantaneous as on adding a blue ethereal solution of thiobenzophenone to the nitrile oxide at room temperature the colour was immediately discharged. A high yield of a colourless adduct (LXV) was isolated.



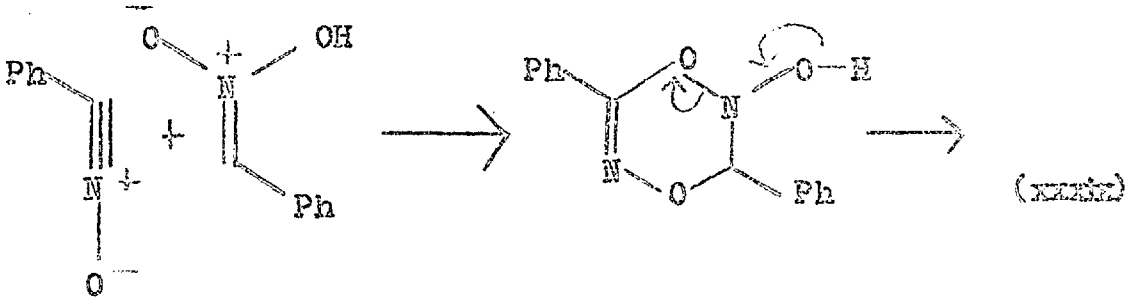
LXV

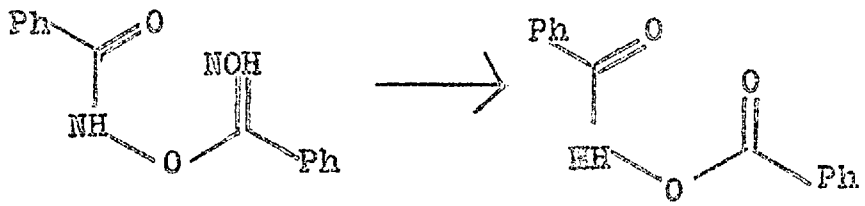
and this upon desulphurisation with Raney Nickel under

vigorous conditions yielded diphenyl methane. Under more mild conditions some diphenyl methane was formed together with a little benzophenone but the major product was benzhydrol indicating that carbon-oxygen bond formation had occurred and that the mode of addition was directly analogous to that of Schiff bases.

(e) Aci-phenylnitromethane and benzhydroxamic acid

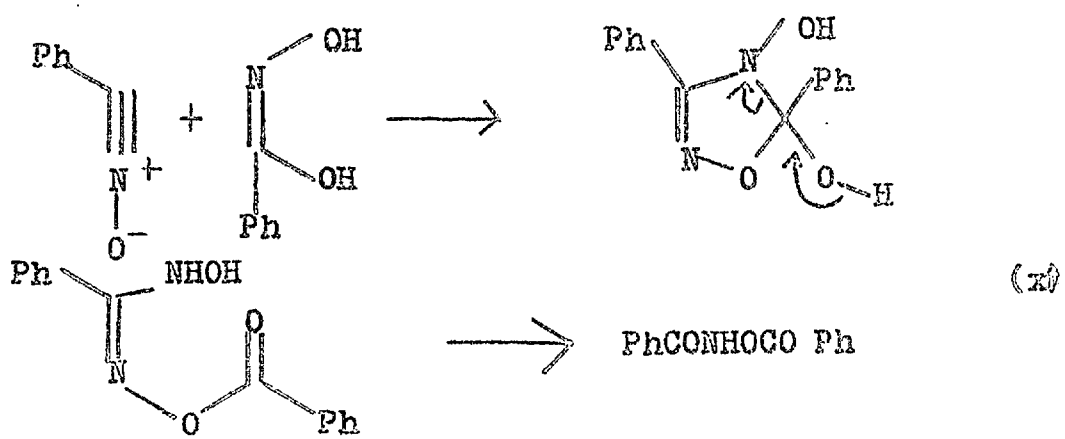
Aci-phenylnitromethane and its O-Methyl ether were then studied as they bear a nitrogen with a formal positive charge and might therefore react with benzonitrile oxide in a similar manner to the dimerisation of the latter. No reaction occurred between aci-phenylnitromethane-O-methyl ether and benzonitrile oxide and when aci-phenylnitromethane itself was treated with benzonitrile oxide at room temperature, as with diphenyl nitrone which contains a similar grouping, little reaction occurred. A small yield of a crystalline product was obtained which was apparently dibenzoyl hydroxylamine (LXVI) and this was proved by an independent synthesis of LXVI from phenylnitromethane, benzoyl chloride, and sodium methoxide[118]. A plausible mechanism for the reaction would be (xxxix)



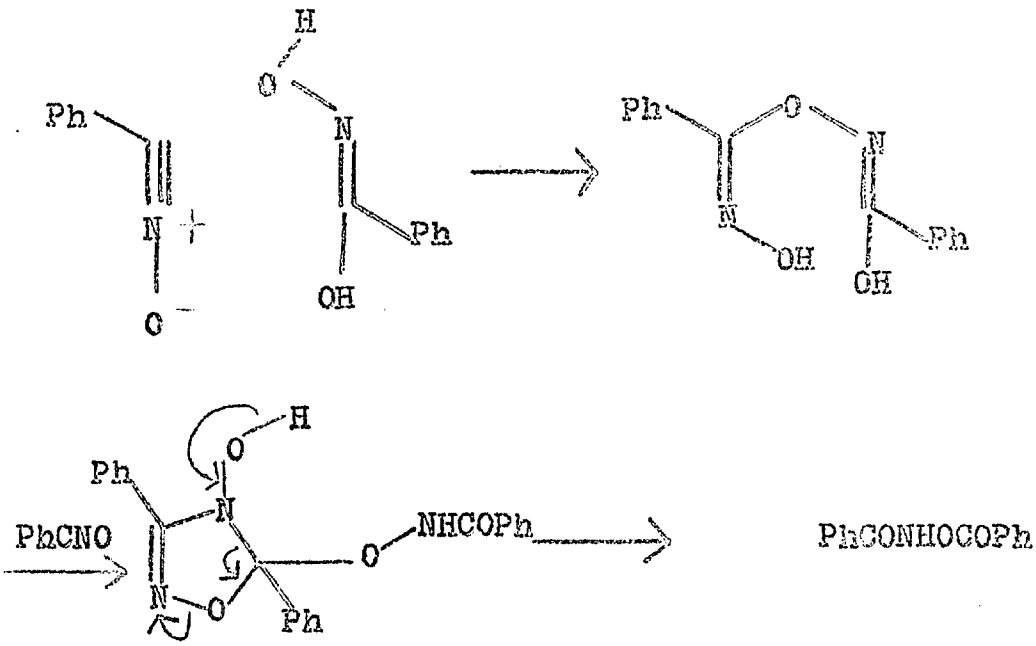


LXVI

in which there is the unusual feature, for reactions of 1:3 dipolar compounds, of a six-membered transition state. A somewhat similar mechanism (xl) can be written for the reaction of benzonitrile oxide with benzhydroxamic acid where again the only product, and in low yield, was dibenzoyl hydroxylamine. An alternative mechanism (xli) utilises nucleophilic attack on the nitrile oxide as the initial step.



(xl)



(xli)

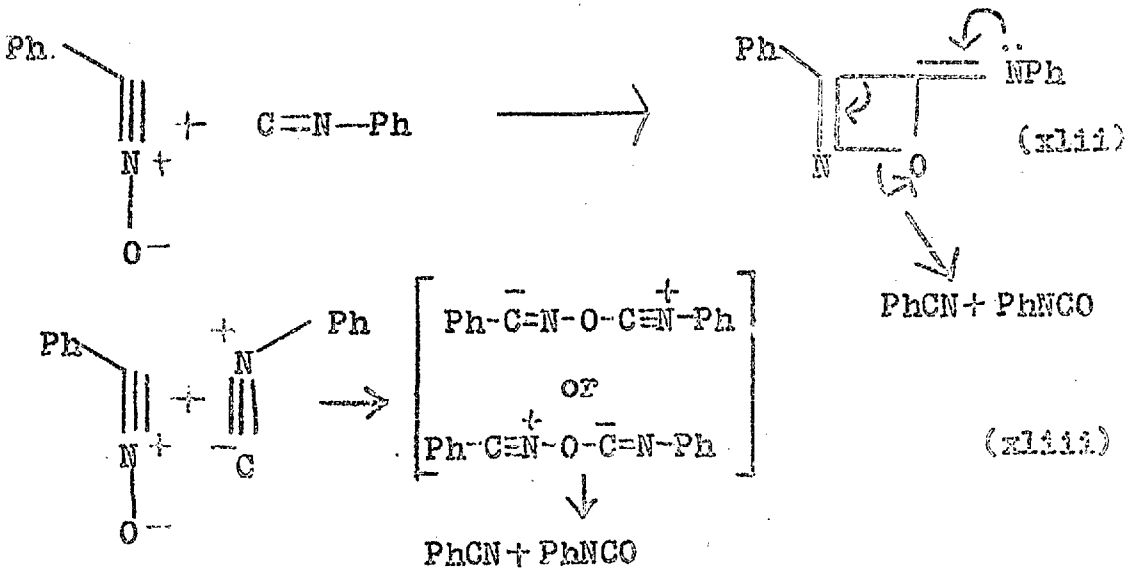
(f) Phenyl isocyanide

A further possibility for carbon-carbon bond formation was based upon the use of an isocyanide and had some theoretical foundation in the work of Quilico[139] who found that the dimerisation product of fulminic acid (LXVII) could be trapped with an acetylene.



LXVII

It seemed possible that carbon-carbon bond formation in the dimerisation of fulminic acid might be paralleled in the reaction of an isocyanide with a nitrile oxide. When phenyl isocyanide, which contained some aniline, was reacted in ethereal solution at room temperature with benzonitrile oxide a vigorous reaction ensued and carbanilide was precipitated, indicating the intermediate formation of phenyl isocyanate. Two types of mechanism can be formulated (xlii and xliii)



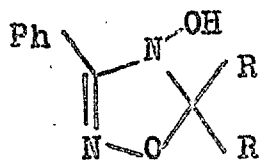
The first treats the isocyanide as a carbene and involves the initial formation of a highly strained system which spontaneously fragmentates. In the second nucleophilic attack by either carbon or oxygen occurs upon an atom bearing some negative charge. Because of the ease of

the reaction the former explanation appears preferable.

As it did thus appear that the cyclic addition reactions of benzonitrile oxide tended to avoid carbon-carbon bond formation if at all possible the study of that reaction which was the most vigorous, that is the interaction of benzonitrile oxide and benzaldoxime in alkaline solution, was extended to obtain more mechanistic information.

(g) Ketoximes

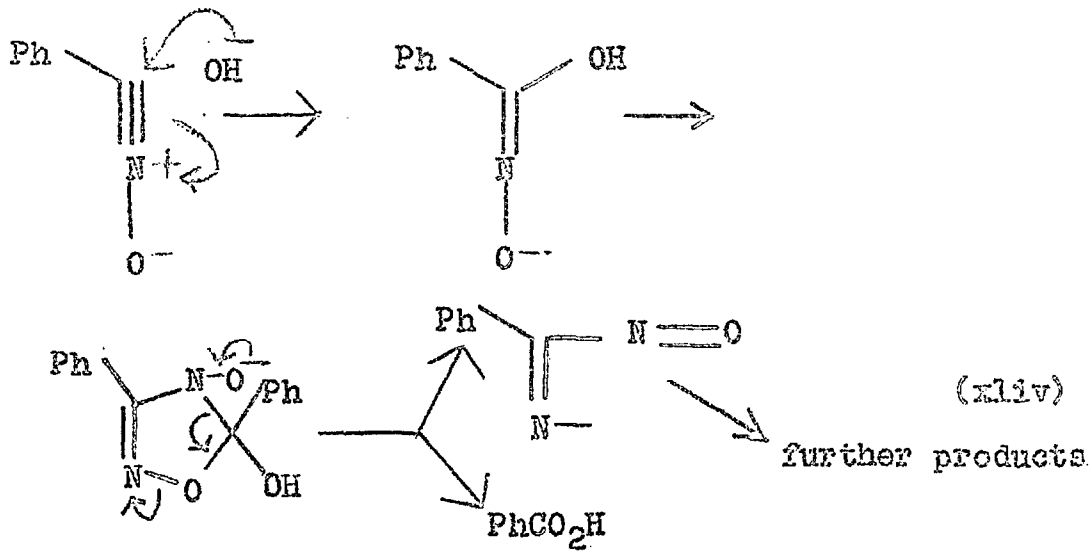
If the reaction of a ketoxime with benzonitrile oxide is to be analogous to that of benzaldoxime then the intermediate adduct would have structure LXVIII



LXVIII

but fragmentation of this could not yield a hydroxamic acid because of the blocking effect of the second R-substituent. When benzonitrile oxide was added to a solution of acetone oxime in ether-methanol at room temperature a vigorous and complex reaction occurred. Initially the solution became red, then a precipitate formed, and finally the colour faded. The precipitate

was benzoic acid and working up the filtrate led to a colourless oil containing a carboxyl group and a compound mp. 135° whose analysis corresponded to that of an adduct with one oxygen removed. Although the reaction was complete in a few minutes the rate appeared to be significantly less than with benzaldoxime and it was believed that the nitrile oxide was itself undergoing alkaline decomposition. This suspicion was strengthened by the low yield that was invariably experienced when benzonitrile oxide was prepared by the method of Quilico[81] which utilised aqueous caustic alkali. In a series of control experiments it was shown that although triethylamine had no effect on benzonitrile oxide a rapid reaction occurred with sodium hydroxide in a variety of solvents. Benzoic acid, and a carboxyl compound, which was the same as that obtained in the acetone oxime reaction, and which gave a positive ester test, were isolated and purified. A large portion of the reaction mixture was unidentified and a likely explanation is that nucleophilic attack on the nitrile oxide to form benzhydroxamic acid is followed by further reaction of this with benzonitrile oxide and an alkaline degradation of the adduct (xliv).



(xliv)

In both the acetone oxime-nitrile oxide reaction and in reactions of this type which will be discussed subsequently nitrile oxide decomposition invariably occurs, but it was found that the process is relatively slow in aqueous acetone and this solvent was used in later runs. The proposal invoking benzhydroxamic acid as an intermediate (xliv) does not invalidate the cyclic mechanism advocated for the benzaldoxime-nitrile oxide reaction as in that case benzhydroxamic acid was proved to arise from the adduct XXXV and therefore it could not be derived from a reaction independent of the benzaldoxime. The isolation of benzoic acid rather then benzhydroxamic acid when excess alkali was used in the latter reaction is further evidence for the scheme depicted in (xliv).

A completely analogous reaction to that of alkaline acetone oxime and benzonitrile oxide occurred when cyclohexanone oxime was subjected to the same conditions. The red compound was slightly less labile and the crystalline product, which analysed similarly, had mp. 161°. Attempted reaction in a solution containing triethylamine as base produced no colour but on concentration, even at reduced temperatures, a spontaneous exothermic reaction resulted, a nitrile and unidentified oils were formed, and diphenyl furoxan was isolated. More information was obtained when methanolic sodium hydroxide was added gradually to a neutral solution of cyclohexanone oxime and benzonitrile oxide when although the red colour was produced initially, upon further addition of alkali it largely faded with effervescence to give a slightly higher yield of the 161° compound.

The reaction of benzophenone oxime with benzonitrile oxide was then studied on the grounds that the red product was likely to be more stable, and this expectation was realised.

In neutral solution no reaction occurred but in a solution that was alkaline due to the presence of triethylamine the reaction exactly paralleled that of

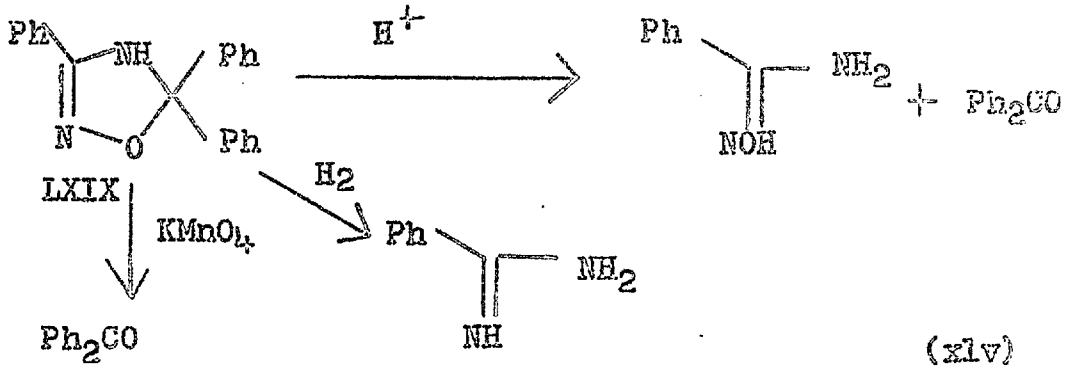
cyclohexanone oxime described above and diphenyl furoxan was the only crystalline product isolated.

Addition of benzonitrile oxide to a solution of benzophenone oxime containing sodium hydroxide resulted in the formation of a red oil with a very strong absorption in the i.r. at 2050 cm^{-1} and a minute quantity of a compound mp. 178° corresponding to the crystalline products from the acetone oxime and cyclohexanone oxime reactions. Initial variation in the reaction conditions produced little significant change. A run with a 2½-fold excess of benzonitrile oxide varied from the equimolar reactions only in forming more of the products resulting from the action of alkali on benzonitrile oxide and only these products were obtained when benzophenone oxime was added to alkaline nitrile oxide.

At -40°, benzonitrile oxide reacted only slowly with alkaline benzophenone oxime and the major portion of the reaction was simply nitrile oxide decomposition. At -10°, however, slow addition of benzonitrile oxide to the alkaline oxime solution did produce the red compound but there was one notable difference to the room temperature reaction. This was that within one hour, and before the reaction mixture had reached

ambient temperature, the red colour had faded with evolution of nitrous oxide, identified by its i.r. spectrum, and with apparently concomitant formation of a considerable amount of the 178° compound. When 2-moles of benzonitrile oxide were used under these conditions the yield of the 178° compound was not further increased.

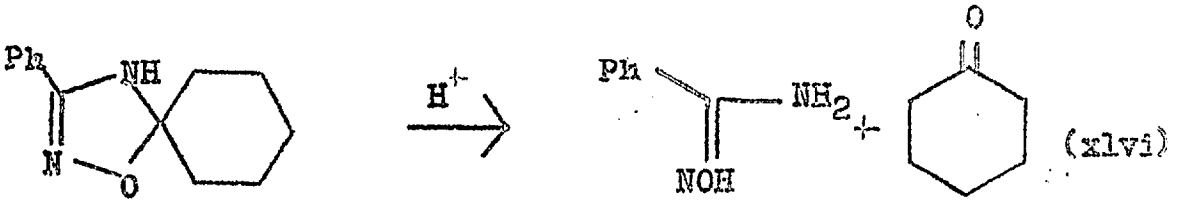
The 178° compound was proved to have the dihydroxadiazole structure LXIX. The i.r. spectrum showed a band at 3300 cm^{-1} and the absence of a carboxyl group. No colour was given with ferric chloride and tosylation and acetylation were ineffective. The compound gave benzophenone on oxidation with hot acid permanganate and acid hydrolysis afforded benzophenone and benzamidoxime. The product isolated from hydrogenolysis was benzamidine (xlv).



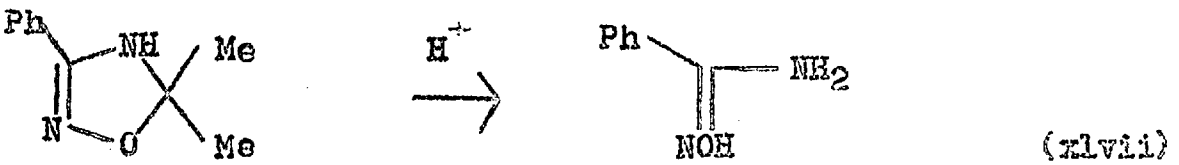
(xlv)

Proof that the compounds from the other oxime-

nitrile oxide reactions were of a similar nature came from their behaviour on acid hydrolysis when LXX (from cyclohexanone oxime) and LXXI (from acetone oxime) both gave benzamidoxime (xlvi and xlvii).

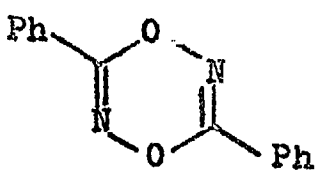


LXX (xlvi)



LXXI (xlvii)

Chromatography of the neutral residue from which LXIX had been isolated in the reaction of benzonitrile oxide with benzophenone oxime gave benzophenone as the major product although a small yield of a compound $C_{14}H_{10}N_2O_2$ was isolated and this is tentatively formulated as LXXII.



LXXII

Irrespective of the actual mechanism by which LXIX was formed an attractive route for its synthesis

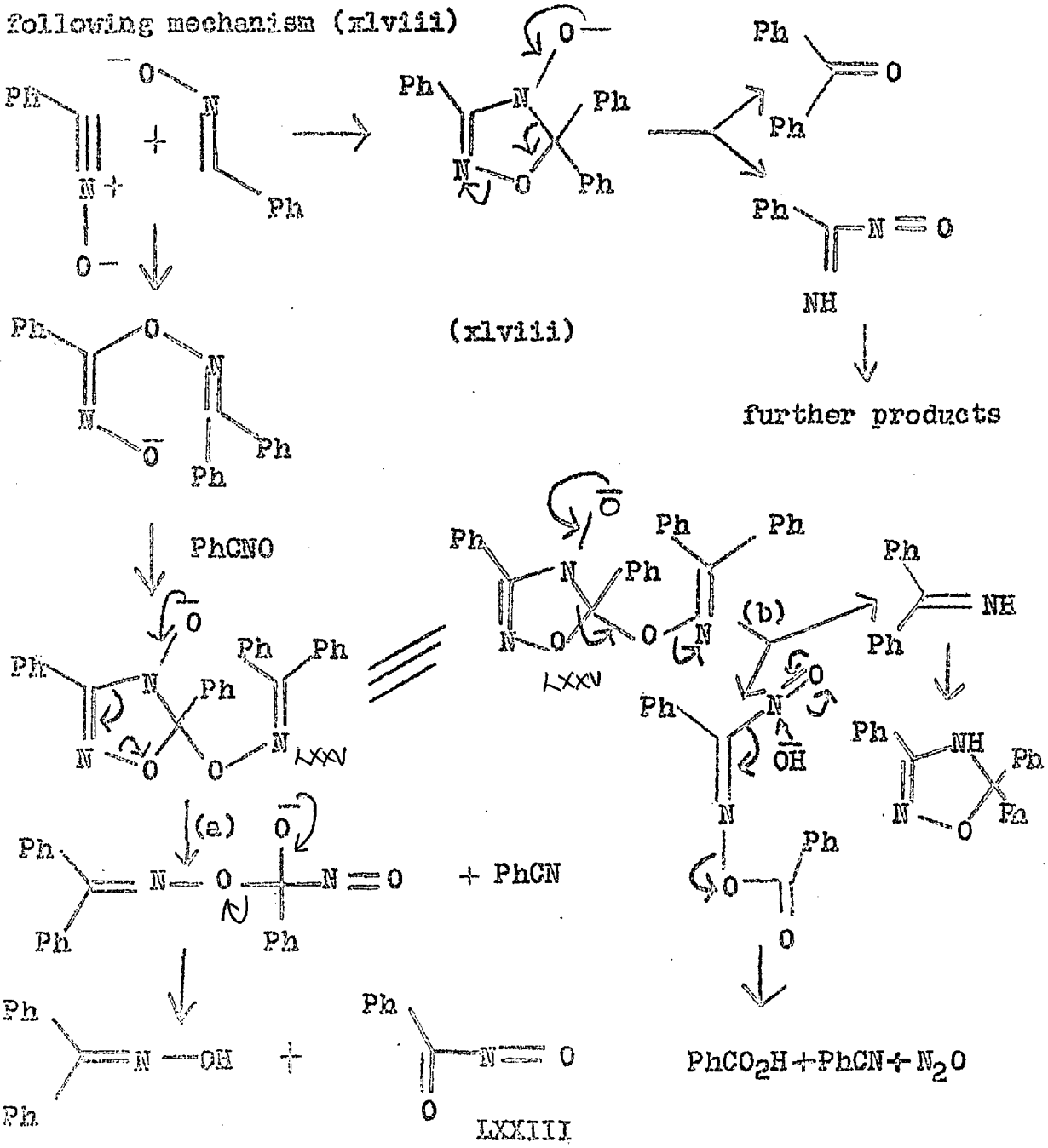
would be the reaction of benzonitrile oxide with benzophenone imine and the latter compound was prepared by pyrolysis of benzophenone oxime and purification through the hydrochloride salt[120]. A rapid and very clean reaction occurred between these two components at room temperature to furnish the adduct LXIX.

For interpetative considerations the benzophenone oxime reaction will be regarded as typical of the three and a collation of the significant features of this reaction that a prospective mechanism has to accommodate will be provided.

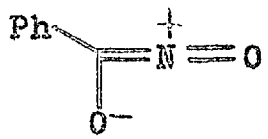
Firstly the fact that the reaction occurs rapidly in alkaline solution completely precludes nucleophilic attack by nitrile oxide on the oxime as benzophenone oxime is unaffected by molten alkali at 350°[121]. Secondly in contrast to the benzaldoxime reaction only traces of nitrile absorption are observed in the product. Thirdly even when an excess of benzonitrile oxide is used some benzophenone oxime is recovered and although this may be due to the nitrile oxide all beingconsumed by alkali the observation may well mean that the oxime is being regenerated in a subsequent reaction. Fourthly in view of the synthesis of LXIX it is very likely that the precursor in this reaction is

benzophenone imine. Also the evolution of nitrous oxide appears to be associated with the disappearance of the red colour and with the formation of LXIX. Fifthly invariably benzophenone is isolated.

Most of these facts can be accommodated by the following mechanism (xlviii)



According to Quilico[84] the group $=CR_2$ is unreactive to benzonitrile oxide although in the present work it was found that benzophenone imine reacted faster than did benzylidene aniline. There remains the possibility, however, that if steric hindrance is operative, a nucleophilic mechanism can be favoured over a molecular mechanism and in (xlviii) both are proposed to be operating simultaneously. The drawbacks of this mechanism are that it predicts the formation of a considerable amount of benzonitrile but in fact little is observed, and it is necessary for the nitroso compound LXXIII to absorb at 2050 cm^{-1}. This could possibly occur through the form LXXIV.



LXXIV

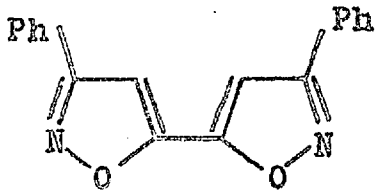
Furthermore when adduct LXXV fragmentates it must do so simultaneously by path (a) and path (b). It is, however, significant that LXXIII has a structure that is independent of the Ketoxime used and this helps to explain the similar colour of the reaction mixture

in the three cases.

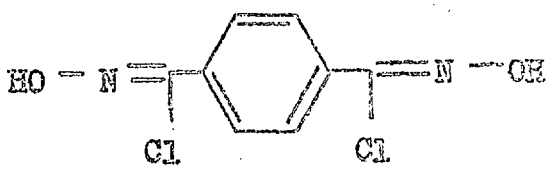
An attempt to characterise the red compound from the benzophenone oxime reaction by titration with 3:5-dinitrobenzoic acid (gas evolution) led to a compound which contained no nitro group and whose analysis indicated a complex structure.

D. POLYMERS

As a model experiment for polymer formation via cyclic addition reactions diacetylene was reacted with benzonitrile oxide. The product, in high yield, was evidently the bis-isoxazole LXXVI, the only evidence for the orientation being analogy with the adduct of butadiene and benzonitrile oxide(84).



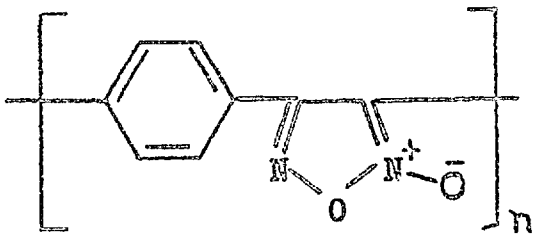
LXXVI



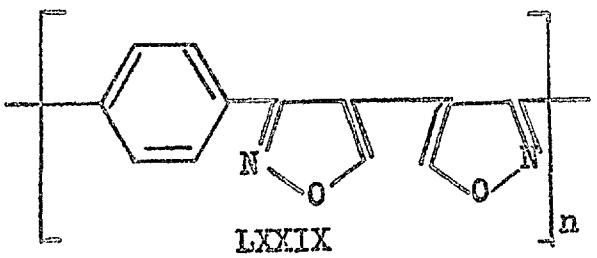
LXXVII

When terephthaldihydroximic acid chloride (LXXVII) was treated with triethylamine in the presence of diacetylene at room temperature a polymer was obtained

which analysed approximately for the polyfuroxan (LXXVIII) but which showed triple bond absorption in the i.r.



LXXVIII



LXXIX

At -25° the polymer produced was free from this absorption bond and analysed approximately for incorporation of diacetylene (LXXIX).

Note on Experimental Section

U.V. Spectra were measured in ethanol.

Light petroleum refers to the fraction b.p. 60°-80°.

EXPERIMENTAL

Dicinnamyl oxalate

Oxalyl chloride (3.9 g.) was added dropwise to redistilled cinnamyl alcohol (8.5 g.). The mixture was diluted with ether and the product was filtered off and recrystallised from ethyl acetate to yield dicinnamyl oxalate, plates, mp. 107-8°, 5.5 g.

Found:	C, 74.52;	H, 5.98
$C_{20}H_{18}O_4$ requires	C, 74.54;	H, 5.63

Pyrolysis of dicinnamyl oxalate

Dicinnamyl oxalate (1.073 g.) was heated at 280° in a stream of nitrogen until evolution of carbon dioxide was very slow (38 min.). Estimation was by absorption in standard baryta and back titration with standard acid and 40.4% of the theoretical quantity of carbon dioxide was obtained. The residue from pyrolysis was chromotographed over alumina (Grade 5) in benzene but no crystalline product was obtained.

Cis-1:2-oxolato-cyclohexane

Cis-cyclohexane-1:2-diol[96] (1.00 g.) and dimethyl oxalate (5.04 g.) were dissolved in toluene and the solution was slowly distilled until there

was no evidence of a hydroxyl band in the i.r. The solvent was distilled off and the residue was distilled under high vacuum and then crystallised from carbon tetrachloride to give cis-1:2-oxalato-cyclohexane, 340 mg., mp. 85°

Found: C, 56.61; H, 6.12

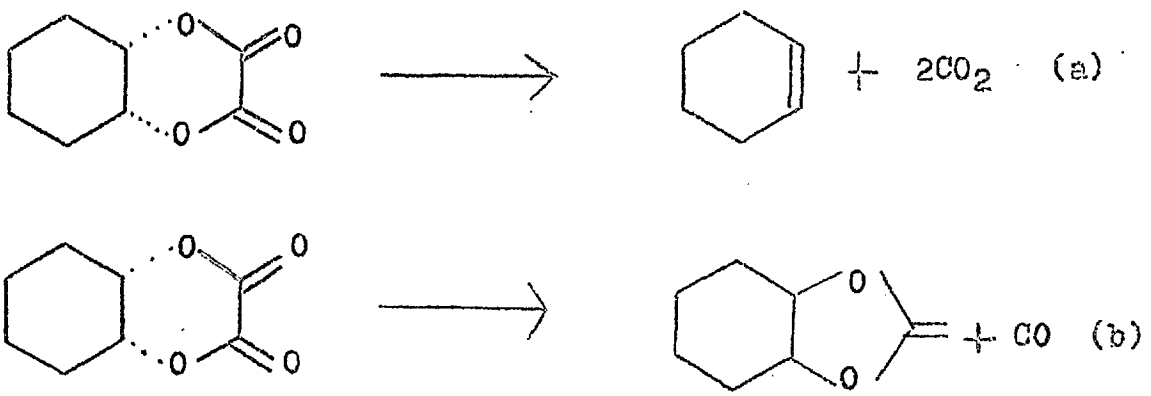
$C_8H_{10}O_4$ requires C, 56.47; H, 5.92

Pyrolysis of cis-1:2-oxalato-cyclohexane

Cis-1:2-oxalato-cyclohexane (698 mg.) was pyrolysed at 300° for 30 hours in a stream of dry nitrogen. The gas stream was passed through a condenser (at -78°) and then over iodine pentoxide and through baryta.

Yield of CO_2 based on (a) = 43%

Yield of CO based on (b) = 48%



A small quantity (~ 100 mg.) of oil was collected in

the cold trap. It was oxidised with nitric acid (d. 1.42) on the steam bath to adipic acid, mp. 150°-1°.

Cholestan-1α:2α-diol

Hydrogenation of cholesterol[26] gave cholestanol mp. 140°-1° (lit.[26] mp. 142°) which was oxidised[38] to cholestanone mp. 129°-30° (lit.[38] mp. 129°-30°). Bromination[53] of this afforded 2α-bromocholestan-3-one mp. 166° (lit.[53] mp. 168°-9°) which was converted[99] to cholest-2-ene mp. 73° (lit.[99] mp. 74°-5°) hydroxylation[98] of which gave cholestan-1α:2α-diol mp. 211°-8° (lit.[98] mp. 212°-4°).

Attempted preparation of Nitrosocarbonyl chloride

A vacuum line was built and pressures were measured with a Bourdon gauge. Carbon monoxide and nitrosyl chloride were mixed at 20°, at 100°, and in the presence of active charcoal (used commercially for phosgene synthesis), but in no case did a change in pressure occur.

N-aminourethane

The condensation of ethyl carbonate and hydrazine hydrate[122] afforded N-aminourethane, b.p. 93°/9 mm., mp. 45°. Lit. mp.[122] 45°.

Benzoin carbethoxyhydrazone

(a) Anomalous reaction

Benzoin (5 g.) and N-aminourethane (2 g.) were dissolved in ethanol (100 ml.) and acetic acid (8 ml.) was added. The solution was refluxed overnight and concentrated to yield tetraphenyl pyrazine, mp. (from acetone-chloroform) 247°, $\lambda\lambda$ max. 233 mμ (ϵ37000), 337 mμ (ϵ22200).

Found: C, 85.17; H, 5.35; N, 7.46; M.Wt., 345

Calc. for $C_{28}H_{20}N_2$: C, 87.42; H, 5.52; N, 7.28; M.Wt., 384

No depression of mp. occurred on admixture with authentic[123] tetraphenyl pyrazine.

(b) Predicted reaction

Benzoin (5 g.) and N-aminourethane (4 g.) were refluxed with acetic acid (4 drops) in ethanol (25 ml.) overnight. After 2 days at 0°, benzoin carbethoxyhydrazone separated, mp. 164°-6° (from ethanol), 3.5 g.; λ max. 279 mμ (ϵ22000). Lit.[100] mp. 170°-1°, λmax. 270 mμ (ϵ22000).

2:3-Dihydro-5:6-diphenyl-1:3:4:6-oxadiazin-2-one (I)

Benzoin carbethoxyhydrazone (1.5 g.) was dissolved in benzene (35 ml.) and potassium carbonate (50 mg.) was

added. The solution was refluxed overnight and cooled to furnish 2:3-dihydro-5:6-diphenyl-1:3:4:6-oxadiazine-2-one, mp. 185°-7°, 1.3 g., λ max 282 mμ (ϵ18200). Lit.(100) mp. 190°-1°, λ max 282 mμ (ϵ14500)

Alkaline isomerisation of I

Potassium (600 mg.) was dissolved in tert. butanol (redistilled from potassium) and I (1.10 g.) was added. The mixture was refluxed until the U.V. maximum had shifted to 300 mμ (30 hrs.). The solution was cooled, acidified with hydrochloric acid, diluted with water, and extracted with ether to yield 3:4-diphenyl-4-hydroxy-5-keto-1:2 diazole, 0.75 g., mp. 211° (from ethanol), λ max 296 mμ (ϵ12900). The analytical specimen was sublimed (160°/10^{-5} mm.), recrystallised from ethyl acetate-light petroleum, and sublimed again, mp. 211°-2°.

Found:	C, 71.40;	H, 4.91;	N, 11.19
$C_{15}H_{12}N_2O_2$ requires:	C, 71.42;	H, 4.80;	N, 11.10

Attempted oxidations of 3:4-diphenyl-4-hydroxy-5-keto-1:2-diazole

(a) The diazole (100 ml.) and mercuric acetate (500 mg.) were dissolved in a mixture of chloroform (3 ml.) and acetic acid (2 ml.). The solution was refluxed for 24 hrs. and cooled. Ether extraction gave

starting material, identified by m.m.p.

(b) The diazole (100 mg.) was added to sulphuric acid (20%; 12 ml.) in the presence of potassium permanganate (300 mg.). The mixture was warmed for 5 min. (steam bath), cooled, and decolourised with sodium bisulphite. After addition of water ethereal extraction yielded benzoic acid, identified by mp. and m.m.p. with an authentic sample.

Reduction of 3:4-diphenyl-4-hydroxy-5-keto-1:2-diazole

The diazole (380 mg.) was dissolved in tetrahydrofuran (redistilled from LAH; 20 ml.). A slurry of lithium aluminium hydride (2.5 g.) in dry tetrahydrofuran (40 ml.) was placed in a three necked flask fitted with stirrer, tap funnel, and a nitrogen inlet. A stream of nitrogen was passed while the diazole solution was added dropwise to the refluxing reducing mixture. After a further 15 hrs. refluxing the excess LAH was destroyed with water and the mixture was acidified with sulphuric acid (20%) and extracted with ether to yield an oil (386 mg.) which largely crystallised. The product was chromatographed over alumina (Grade I) in benzene. Elution with benzene-ether (1:2) gave 3:4-diphenyl pyrazole, 160 mg. mp. 152°-3°

(from benzene-light petroleum), λmax 250 mμ (ϵ10500), identified by comparison of i.r. and U.V. spectra and m.m.p. with authentic material.

Found: C, 81.89; H, 5.39; N, 12.69

Calc. for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49; N, 12.72

3:4-Diphenyl pyrazole

Desoxybenzoin was condensed with ethyl oxalate[124] to yield 3:4-diphenyl-2:4-diketo-1-carbethoxy-propane, mp. 94°-6°. Lit.[124] mp. 106°-7°.

3:4-diphenyl-2:4-diketo-1-carbethoxy-propane (184 mg.) and hydrazine hydrate (31 mg.) were dissolved in methanol (2 ml.). Shaking at room temperature gave a precipitate of 2-carbethoxy-3:4-diphenyl pyrazole mp. 155°-6° (from carbon tetrachloride). Lit.[124] mp. 158°-9°.

2-carbethoxy-3:4-diphenyl pyrazole (66 mg.) was refluxed with a mixture of sodium hydroxide (200 mg.), water (3 ml.) and methanol (3 ml.) for 90 min. The solution was acidified, diluted with water, and extracted with ether to yield 3:4-diphenyl pyrazole-2-oic acid, mp. 252°-8°, 40 mg. Lit.[124] mp. 261°.

3:4-diphenyl pyrazole-2-oic acid was decarboxylated[124] to furnish 3:4-diphenyl pyrazole,

mp. 157°-75°, λ max 250 mμ (ϵ11300). Lit.[124] mp. 154°.

Attempted reaction of Stilbene oxide with N-aminourethane

Stilbene oxide[102] (0.85 g.) was heated with N-aminourethane (1.50 g.) under nitrogen at 130° for 2½ hrs. Only stilbene oxide was recovered.

Diphenyl furoxan[125]

Benzil-α-dioxime (31 g.) was extracted with sodium hydroxide (10%; 200 ml.). Water (400 ml.) was added followed by sodium hypochlorite (270 ml. of 10% solution made up to 600 ml.) in portions with periodic addition of ice to prevent the solution temperature rising above 50°. The product (25 g.) was filtered off and was charcoaled and recrystallised twice from ethanol to yield diphenyl furoxan, mp. 117°, 10.5 g. Lit[125] mp. 118°.

Reaction of diphenyl furoxan with alkali and/or hydrazine hydrate

(a) Diphenyl furoxan + glycol + potassium hydroxide.

Diphenyl furoxan (321 mg.) was refluxed in ethylene glycol (4 ml.) with potassium hydroxide (287 mg.) under nitrogen for 3 min. The red solution was cooled and was diluted with water. Ether extraction gave

benzaldehyde (46%) identified by its smell and the formation of a 2:4-dinitrophenylhydrazone, (119 mg.) mp. 237°. Acidification of the aqueous solution and ether extraction gave benzoic acid (45%), identified by its i.r. spectrum.

(b) Benzil + glycol + potassium hydroxide

Benzil (581 mg.), glycol (8 ml.) and potassium hydroxide (581 mg.) were refluxed under nitrogen for 3 min. The solution was cooled and was extracted with ether to yield benzilic acid, 295 mg., mp. 147°-8°.

(c) Diphenyl furoxan + glycol + hydrazine hydrate.

Diphenyl furoxan (513 mg.), glycol (4 ml.) and hydrazine hydrate (1.5 ml.) were refluxed for 10 hrs. The resulting solution was diluted with water and extracted with ether to yield benzil-bis-hydrazone, mp. 147.5° (from ethanol). Lit.(126) mp. 147°.

(d) Diphenyl furoxan + glycol + hydrazine hydrate. Then potassium hydroxide added.

Diphenyl furoxan (1.06 g.) was refluxed with hydrazine hydrate (4 ml.) and glycol (8 ml.) for 18 hrs. Potassium hydroxide (0.9 g.) was added and the solution was refluxed for 3¾ hrs. (at 145°). Dilution with water and extraction with ether gave an oil (700 mg.) which was separated by chromatography on alumina (Grade 3) in

petroleum ether into dibenzyl, (580 mg.), mp. 51° (lit.(127) mp. 52°), and diphenyl furazan, mp. initially 71°, changing to 94°, but reverting to 71° on sublimation. Both compounds were identified by comparison of their i.r. spectra with those of authentic samples.

(e) Diphenyl furoxan + hydrazine + glycol

Diphenyl furoxan (497 mg.), glycol (4 ml.) and hydrazine (2.5 ml.) were refluxed until absorption at 275 mμ ceased to decrease (3 2/3 hr.). Working up as in (c) yielded benzil-bis-hydrazone, 320 mg., mp. (from ethyl acetate-petrol) 148°-5°, which was identified by m.m.p. and i.r. comparison with an authentic sample.

Reaction of benzil-bis-hydrazone with alkali

Benzil-bis-hydrazone (211 mg.) was refluxed with glycol (2 ml.) and potassium hydroxide (274 mg.) was added. Refluxing was continued until no further change in the U.V. spectrum of an aliquot occurred (15 min.). Dilution with water and ether extraction gave a gum (126 mg.) which was dissolved in petroleum ether and filtered through alumina (Grade 3) to yield dibenzyl mp. 49°-51°, 103 mg. (97%).

Diphenyl furazan

Diphenyl furoxan (0.6 g.), red phosphorous (0.5 g.), and hydriodic acid (3 ml.; d 1.7) were heated

together in a Carius tube at 230° for 3 hrs. After cooling the product was mixed with water, decolourised with thiosulphate, and extracted with ether. The solvent was removed and the residue was dissolved in petroleum ether and filtered through alumina (Grade 5) to yield diphenyl furazan, mp. 93°-4°, 180 mg. Lit.[128] mp. 94°.

Detection of intermediates in cleavage reactions of diphenyl furoxan

(a) Diphenyl furoxan (216 mg.) was refluxed in glycol (5 ml.) with potassium hydroxide (190 mg.). The solution was cooled and a nitrite spot test[129] was strongly positive. On a blank it was negative.

(b) Diphenyl furoxan (525 mg.), glycol (4 ml.) and hydrazine (2.5 ml.) were refluxed together for 1 hr. in a stream of nitrogen which was subsequently passed through water. Sodium hypochlorite (10%) was added to the aqueous solution until evolution of nitrogen ceased and then hydrogen peroxide was added until evolution of oxygen ceased. Addition of Nesslers' solution gave a copious orange-brown precipitate. This procedure had previously been demonstrated to be satisfactory for the detection of ammonia in the presence of hydrazine.

Diphenyl nitrone[131]

Phenyl hydroxylamine (14 g., freshly prepared[130]) was dissolved in ethanol (50 ml.). To the filtered solution was added benzaldehyde (14 g.). Diphenyl nitrone, 7 g., was filtered off after 3 hrs., mp. (from ethanol) 112°, λ max 315 mμ (ϵ20200). Lit.[131] mp. 109°.

4:5-dihydro-3:4-diphenyl-1:2:4-oxadiazole-5-one

Phenyl isocyanate (419 mg.) and diphenyl nitrone (698 mg.) were left at room temperature in benzene (8 ml.) for 3 hrs. and then warmed for 5 min. (steam bath) and cooled to 0° to furnish 4:5-dihydro-3:4-diphenyl-1:2:4-oxadiazole-5-one, 140 mg., mp. 168°-9° (from benzene). Lit.[77] mp. 170°.

1:2:4-triphenyl isoxazolidine

Styrene (500 mg.) and diphenyl nitrone (960 mg.) were refluxed in ethanol (5 ml.) until the U.V. spectrum ceased to change (9 hrs.). The solution was cooled to yield 1:2:4-triphenyl isoxazolidine, 1.2 g., mp. 101° (from petroleum ether-methanol), λ max 240-5 mμ (ϵ12500).

Found: C, 83.70; H, 6.86; N, 4.73

$C_{21}H_{19}N_2O_2$ requires: C, 83.69; H, 6.35; N, 4.65

The yield, corrected for aliquots removed, was 100%.

Degradation of 1:2:4-triphenyl-isoxazolidine

(a) Hydrogenation

The isoxazolidine (78 mg.) was hydrogenated at room temperature over Adams catalyst (27 mg.) until 1.3 mols. had been absorbed. The mixture was filtered and evaporation of the solvent gave a compound mp. 139°-40° (from ethanol-petroleum ether), λmax 248 mμ (ϵ12000), 207 mμ (ϵ31000), i.r. bonds corresponding to NH and OH.

Found: C, 83.41; H, 7.59

$C_{21}H_{21}NO$ requires: C, 83.13; H, 6.98

(b) Acid treatment

The isoxazolidine (273 mg.) was refluxed with methanol (4 ml.) and concentrated hydrochloric acid (1 ml.) for 1 hr. Ether extraction gave a compound mp. 107° (from petroleum ether), 63 mg., $\lambda\lambda$ max 206 mμ (ϵ32000), 254 mμ (ϵ14900).

Benzhydroximic chloride(105)

Benzaldoxime (redistilled, n_D^{22} 1.589; 45 g.) was dissolved in chloroform (100 ml.) in a three-necked flask fitted with a calcium chloride tube, stirrer, and chlorine inlet, and cooled in ice. Chlorine was passed for 5 hrs. and the solution was concentrated in a rotary evaporation to yield benzhydroximic chloride,

40 g., mp. (from petroleum ether), 45°. Lit.(105) mp. 48°.

Benzonitrile oxide

(a) Sodium hydroxide route

A modification of the procedure of Quilico(81) was used. Cold 14% aqueous sodium hydroxide (2 mols.) was added to a suspension of benzhydroximic chloride (1 mol.) in water in portions with shaking. The benzonitrile oxide, which precipitated either as an oil or a colourless solid, was extracted (benzene or ether) and used immediately.

(b) Triethylamine route

Triethylamine (1.1 mol.) was added during a few seconds to a solution of benzhydroximic chloride (1 mol.) in ether or benzene with shaking. The triethylamine hydrochloride was filtered off and the colourless filtrate, which contained the benzonitrile oxide, was used immediately.

Adduct of benzonitrile oxide and maleic anhydride(132)

Benzhydroximic chloride (966 mg.) was converted to benzonitrile oxide (sodium hydroxide route) in ether. Maleic anhydride (400 mg.) was added and the resulting solution was refluxed for 40 min. and cooled to yield

the adduct, mp. 162°-4°, 266 mg., λ max 262 mμ (ϵ12000). Lit.(132) mp. 162°-3°.

Attempted quaternisation of benzylidene-methylamine

Methylamine (30%; 10 ml.) was heated (steam bath) with benzaldehyde (10 g.) for ½ hr. The product was distilled to yield benzylidene-methylamine, b.p. 92°/40 mm. This (6.6 g.) was heated with methyl iodide (13.6 g.) in a Carius tube at 60° for 12 hrs. The product was precipitated three times with ether from methanol, mp. 158°-60°.

The identity of the product as dimethylammonium iodide was shown by comparison of its i.r. spectrum with that of an authentic specimen.

Reaction of dimethylammonium iodide with benzonitrile oxide

Benzonitrile oxide in ether(30 ml.) was prepared (aqueous alkali route) from benzhydroximic chloride (3.3 g.) and was added to a solution of dimethylammonium iodide (895 mg.) in methanol (50 ml.). The mixture was refluxed for 30 min. and extracted with ether to yield 3:5-diphenyl-1:2:4-oxadiazole-4-oxide, mp. 134°-5°. Lit.(103) mp. 134°-5°.

Reduction of 3:5-diphenyl-1:2:4-oxadiazole-4-oxide(133)

The oxide (95 mg.) was mixed with phosphorous pentachloride (160 mg.) and heated on the steam bath for 30 min. The product was cooled, mixed with ice-water, and extracted with petroleum ether. The extract was filtered through alumina (Grade 5) to yield 3:5-Diphenyl-1:2:4-oxadiazole, mp. 102°-4°, whose i.r. spectrum was identical with that of authentic material. Lit.(103) mp. 110°.

3:5-Diphenyl-1:2:4-oxadiazole(114)

Benzaldoxime (1.2 g.) and sodium hydroxide (550 mg.) were dissolved in water(20 ml.). A solution of potassium ferri-cyanide (5 g.) and sodium hydroxide (0.4 g.) in water (100 ml.) was added. Ether extraction gave an oil which was filtered in petroleum ether through alumina (Grade 5) to furnish 3:5-diphenyl-1:2:4-oxadiazole, needles, mp. (from petroleum ether), 106°-8°. Lit.(103) mp. 110°.

Reaction of benzonitrile oxide with benzaldoxime in neutral solution

Benzaldoxime (3.00 g.) was mixed with a solution of benzonitrile oxide (from 7.80 g. benzhydroximic chloride; aqueous alkali route) in ether (20 ml.). The solution was refluxed overnight and the solvent was

removed to leave an oil (7.03 g.) which partially solidified upon the addition of petroleum ether (40°-60°). The adduct, an amorphous solid (4.72 g.) was filtered off and reprecipitation with petroleum ether from benzene solution raised the mp. to 130°-3°. Both sublimation and chromatography over Grade 3 alumina gave diphenyl furoxan, but by chromatography over Grade 5 alumina material of mp. 143°-4° was obtained.

Found:	N, 11.06
$C_{13}H_{12}N_2O$ requires:	N, 13.20

Degradation of the adduct from benzonitrile oxide and benzaldoxime

The adduct (85 mg.) was mixed with acetic anhydride (55 mg.) and pyridine (0.5 ml.) and was warmed for 10 min. (steam bath). The pyridine was evaporated off and the residue was dissolved in petroleum ether-benzene (4:1) and filtered through alumina (Grade 5) to yield 3:5-diphenyl-1:2:4-oxadiazole, mp. 109°-11°, 51 mg., identified by comparison of its i.r. spectrum with that of an authentic sample.

Reaction of benzonitrile oxide with benzaldoxime in alkaline solution

Benzaldoxime (3 g.) was dissolved in a solution of sodium hydroxide (1 g.) in methanol (20 ml.). A

solution of benzonitrile oxide (from 5.8 g. benzhydroximic chloride; aqueous alkali route) in ether (64 ml.) was added to the stirred oxime solution. The solution became yellow, the solvent boiled, and a precipitate appeared. Vigorous stirring was continued for 5 min. and the mixture was then left overnight when the precipitate (2.15 g.) was filtered off. The filtrate was evaporated and the residue was triturated with ether to yield more solid (1.38 g.) and an oil (2.63 g.) which smelt of benzaldehyde. A portion of the oil was analysed by G.L.C. The retention time of the major peak was 15.6 min. compared with 15.8 min. for authentic benzonitrile and the retention time for the minor peak was 11.1 min. compared with 11.1 min. for authentic benzaldehyde. The i.r. spectrum of the oil showed the presence of nitrile and carbonyl and benzaldehyde was confirmed by the formation of a 2:4-dinitrophenylhydrazone, mp. 238°. Upon standing the oil deposited a compound, mp. 127°-8° (from ethyl acetate-light petroleum), i.r. bonds at 3420, 3320, 3100, 1660 cm^{-1}, 224 mg.

A solution of the original solid precipitate (703 mg.) in water was brought to pH 4 with acetic acid.

Continuous ether extraction yielded benzhydroxamic acid, 423 mg., mp. 131°-5° (from ethyl acetate-light petroleum), whose identity was proved by m.m.p. and i.r. comparison with an authentic sample(133)

Action of alkali on benzonitrile oxide-benzaldoxime adduct

The adduct (218 mg.) was dissolved in methanol-ether (1:1; 20 ml.) and a solution of sodium hydroxide (44 mg.) in methanol (5 ml.) was added with swirling. The solution went yellow. Ether (to 25 ml.) was added, the solution was refluxed for 15 min., and the solvent was removed. The residue was extracted with chloroform and this solution showed strong nitrile absorption in the i.r. The solid residue was dissolved in water and was acidified with acetic acid. Ether extractions and crystallisation of the product from ethyl acetate-petroleum ether yielded benzhydroxamic acid, 5 mg., mp. 124°-8°, identified by its i.r. spectrum.

Phenylnitromethane

Phenylnitromethane was prepared from benzyl cyanide(115), b.p. 80°-85°/0.1 mm., n_D^{24}, 1.5318.

Reaction of benzonitrile oxide with aci-Phenylnitromethane

Phenylnitromethane (12 g.) was dissolved in a solution of sodium hydroxide (3.6 g.) in water (50 ml.).

The solution was acidified with 2 N-sulphuric acid and aci-phenylnitromethane was filtered off and dissolved in ether-petroleum ether. This solution was dried (magnesium sulphate) and cooled to yield aci-phenyl-nitromethane, 1.82 g., which was dissolved in dry ether (15 ml.) and mixed with a solution of benzonitrile oxide (from 3.00 g. benzhydroximic chloride; aqueous alkali route) in ether. The resulting solution was left at room temperature overnight and was concentrated to give a mixture of oil and crystals (2.62 g.). The product was crystallised (petroleum ether-ethanol, then benzene) 250 mg., mp. 163.5°-164.5°, i.r. bonds at 3300, 1745, 1695 cm^{-1}.

Found:	C, 69.79;	H, 4.95;	N, 5.75
Calc. for $C_{14}H_{11}NO_3$:	C, 69.70;	H, 4.59;	N, 5.80

The compound was shown to be O:N-dibenzoylhydroxylamine by m.m.p. and i.r. comparison with an authentic sample.

Dibenzoyl hydroxylamine(118)

Phenylnitromethane (2.8 g.) in methanol (20 ml.) was mixed with a solution of sodium (470 mg.) in methanol (10 ml.) and to the warm suspension was slowly added benzoyl chloride (3.0 g.). The mixture boiled and became homogeneous. After heating on the steam bath

for 5 min. it was cooled and filtered. Evaporation of the filtrate and crystallisation of the residue from benzene yielded O:N-dibenzoylhydroxylamine, 0.7 g., mp. 163.5°. Lit.(118) mp. 161°.

Isomerisation of aci-phenylnitromethane

Aci-phenyl nitromethane (1.52 g; supra) was left overnight in dry ether at room temperature. Only phenylnitromethane was recovered.

Reaction of benzonitrile oxide with aci-phenylnitromethane-O-methylether

Aci-phenylnitromethane (1.90 g.) was dissolved in dry ether(35 ml.) and was treated with a solution of diazomethane in ether until evolution of nitrogen ceased(134). Nitrogen was bubbled through the solution to remove excess diazomethane and the solution was then concentrated at room temperature and was immediately added to a solution of benzonitrile oxide (from 2.8 g. benzhydroximic chloride; aqueous alkali route) in ether. Only diphenyl furoxan was isolated on working up.

Reaction of benzonitrile oxide with benzhydroxamic acid

Benzhydroxamic acid (1.18 g.) in methanol (15 ml.) was mixed with a solution of benzonitrile oxide (from 2.2 g. benhydroximic chloride; aqueous alkali route)

in ether (44 ml.). The solution was refluxed for 1 hr., cooled, and concentrated. Recrystallisation of the product (ethanol) yielded benzhydroxamic acid and O:N-dibenzoylhydroxylamine, 60 mg., identified by m.m.p. and i.r. comparison with authentic material.

Thiobenzophenone(117)

Benzophenone (10 g.) in ethanol (95%; 100 ml.) was placed in a three-necked flask fitted with a calcium chloride tube, stirrer, gas inlet, and cooled by ice. A mixture of dry hydrogen sulphide, hydrogen chloride, and nitrogen, was passed for 4½ hrs., then hydrogen sulphide and nitrogen only for 5 hrs. The solution first became blue after 2 hrs. and it was deep violet after 6 hrs. The violet thiobenzophenone 8.7 g., was filtered off under nitrogen and was used immediately.

Reaction of thiobenzophenone with benzonitrile oxide

Crude thiobenzophenone (8.7 g.) was dissolved in dry ether (100 ml.) under nitrogen. Benzonitrile oxide (from 9 g. benzhydroximic chloride; aqueous alkali route) in ether (142 ml.) was gradually run into the thiobenzophenone solution and 65 ml. were required to remove the blue colour. The reaction was apparently instantaneous. The solution was concentrated to yield 3:5:5-triphenyl-1:4:2-oxathiazole, colourless needles, mp. (from ethanol),

112°, 3.90 g. A portion was purified by chromatography on alumina (Grade 3).

Found; C, 75.71; H, 4.84; N, 4.52; S, 10.57

$C_{20}H_{15}NOS$ requires: C, 75.69; H, 4.76; N, 4.41; S, 10.04

Desulphurisation of 3:5:5-triphenyl-1:4:2-oxathiazole

(a) The oxathiazole (1.00 g.) and Raney nickel (3 teaspoonsfuls) in absolute ethanol (25 ml.) were refluxed for 3 hrs. The solution was filtered and concentrated to give an oil (366 mg.). This was filtered through alumina (Grade 3) in petroleum ether to yield an oil (208 mg.) which crystallised on cooling but which was liquid at room temperature. The i.r. spectrum was identical with that of diphenyl methane.

(b) The oxathiazole (600 mg.) and Raney nickel (3 spatulas) were shaken together in absolute ethanol at room temperature for 22 hrs. After filtering and concentrating an oil (380 mg.) was obtained which was crystallised (petroleum ether) to yield benzhydrol, 254 mg., mp. 59°-62°, 77%, identified by comparison of i.r. spectra with an authentic sample. The filtrate yielded benzophenone (38 mg.), identified by its i.r. spectrum and by formation of a 2:4-dinitrophenylhydrazone, mp. 248°-9°.

Reaction of benzonitrile oxide with benzylidene aniline

Benzylidene aniline (2.99 g.) in ether (15 ml.) was mixed with a solution of benzonitrile oxide (from 3.2 g. benzhydroximic chloride; triethylamine route) in ether. The mixture was left overnight and concentrated. Crystallisation of the product (petroleum ether-methanol) gave 4:5-dihydro-3:4:5-triphenyl-1:2:4-oxadiazole, 3.28 g., prisms, mp. 71°-3°. The analytical sample was purified by chromatography in petroleum ether-benzene (10:3) over alumina (Grade 3) and further crystallisation from petroleum ether-ethanol.

Found: C, 79.71; H, 5.71; N, 9.05

$C_{20}H_{16}N_2O$ requires: C, 79.98; H, 5.37; N, 9.33

Action of acid on 4:5-dihydro-3:4:5-triphenyl-1:2:4-oxadiazole

The adduct oxadiazole (1.00 g.) and concentrated hydrochloric acid (2.5 ml.) were left overnight in methanol (20 ml.). The solution was concentrated and then diluted with water. Ether extraction gave an oil which smelt of benzaldehyde, and which formed a 2:4-dinitrophenylhydrazone, mp. 238°-9°, 360 mg. The aqueous solution was basified (sodium hydroxide) and extracted with ether to yield N-phenylbenzamidoxime, mp. 138° (from petroleum ether-ethanol), identified

by i.r. comparison with an authentic specimen. Lit.[136] mp. 138°.

N-phenyl benzamidoxime[137]

Aniline (1.86 g.) in a little ether was added to a solution of benhydroximic chloride (1.56 g.) in ether (25 ml.). The mixture was left for ½ hr. and filtered from aniline hydrochloride. Concentration of the filtrate gave more aniline hydrochloride and N-phenyl benzamidoxime which was difficult to crystallise. It was precipitated with petroleum ether from ethanol and sublimed, mp. 139°.

p-Dimethylaminobenzylidene aniline

p-dimethylaminobenzaldehyde was prepared[115] as yellow-red needles, mp. 65°-68° (Lit.[115] mp. 73°). Aniline and p-dimethylaminobenzaldehyde (3.0 g.) were heated in ethanol (10 ml.) on the steam bath for 10 min. The solution was cooled and the yellow p-dimethylaminobenzylidene aniline was collected, mp. 100° (from ethanol). Lit.[138] mp. 100°.

Reaction of benzonitrile oxide with p-dimethylamino-benzylidene aniline

p-dimethylaminobenzylidene aniline (1.00 g.) was added to a solution of benzonitrile oxide (from 600 mg. benzhydroximic chloride; triethylamine route) in benzene (25 ml.). The clear yellow solution was

left overnight and was concentrated to give an oil (1.51 g.). This was crystallised (ethanol-petroleum ether) to furnish 4:5-dihydro-3:4-diphenyl-5-(p-dimethylaminophenyl)-1:2:4-oxadiazole, 1.02 g., colourless plates, mp. 119°. A portion was chromatographed in petroleum ether-benzene (3:2) over alumina (Grade 3).

Found:	C, 77.03;	H, 5.85;	N, 12.60
$C_{22}H_{21}N_3O$ requires:	C, 76.94;	H, 6.16;	N, 12.24

Acid degradation of 4:5-dihydro-3:4-diphenyl-5-(p-dimethyl aminophenyl)-1:2:4-oxadiazole

The oxadiazole (250 mg.) in methanol (7 ml.) was refluxed with concentrated hydrochloric acid (3 ml.) for 12 hrs. Water (10 ml.) was added and ether extraction yielded a compound 121 mg., which was rejected. The aqueous solution was buffered with sodium acetate and brought to pH 6 with acetic acid. Ether extraction yielded a gum which was crystallised from petroleum ether-benzene to give N-phenylbenzamidoxime, 70 mg., mp. 138°, whose i.r. spectrum was identical with that of an authentic specimen.

N:N-dimethyl-N^1-benzylidene-p-phenylene diamine

p-dimethylaminoaniline (7.0 g.) was dissolved in ethanol and benzaldehyde (5.4 g.) was added slowly with stirring. The solution became warm and N:N-dimethyl-

N^1-benzylidene-p-phenylene diamine separated, mp. 100° (from ethanol), 7.6 g. Lit.(139) mp. 101°.

Reaction of benzonitrile oxide with N:N-dimethyl-N^1-benzylidene-p-phenylene diamine (II)

Benzonitrile oxide (from 3.7 g. benzhydroximic chloride; triethylamine route) in ether (35 ml.) was added to a solution of the Schiff base (II; 3.23 g.) in a mixture of benzene (10 ml.) and ether (7.5 ml.). After two hours the adduct (4.11 g.) was collected and recrystallised (benzene-ethanol) to yield 4:5-dihydro-3:5-diphenyl-4-(p-dimethylaminophenyl)-1:2:4-oxadiazole, colourless needles, mp. 146°, $\lambda\lambda$ max. 230 mμ (ϵ19900), 266 mμ (ϵ19200).

Found:	C, 76.37;	H, 5.95;	N, 12.15
$C_{22}H_{21}N_3O$ requires:	C, 76.94;	H, 6.16;	N, 12.24

Concentrations of the mother liquors afforded a further 0.32 g. of the adduct.

Acid treatment of 4:5-dihydro-3:5-diphenyl-4-(p-dimethylaminophenyl)-1:2:4-oxadiazole

The oxadiazole (307 mg.) was refluxed with acetic anhydride (250 mg.) and toluene-p-sulphonic acid (16 mg.) in benzene (5 ml.) for 5 hrs. Working up yielded starting material, identified by m.m.p.

Hydrogenation of 4:5-dihydro-3:5-dinhenyl-4-(p-dimethylaminophenyl)-1:2:4-oxadiazole

The oxadiazole (1.04 g.) was hydrogenated in ethanol (100 ml.) in the presence of palladium on charcoal (5%; 400 mg.) until absorption (133 ml; 1.8 mols.) was complete. The catalyst was filtered off and the solvent was removed to leave N-(4-dimethyl-aminophenyl)-benzamidine, 520 mg., mp. 135°-137.5° (from petroleum ether-ethanol).

N:N-dimethyl-N^1-benzoyl-p-phenylene diamine (III)

p-nitrosodimethylaniline (7.0 g.) in ethanol (200 ml.) was hydrogenated to completion (2.8 l; 2 mols.) over palladium-charcoal (5%). The catalyst was filtered off and the filtrate was concentrated. 2 N-sodium hydroxide (300 ml.) was added and then benzoyl chloride (7 ml.) in portions with shaking. After 10 min. N:N-dimethyl-N^1-benzoyl-p-phenylene diamine, 3.7 g., was filtered off, mp. 224°-7° (from toluene). Lit.(140) mp. 228°.

Attempted chlorination and oximination of III

Amide III (1.00 g.) was refluxed for 2 hrs. with thionyl chloride (8 ml.) under slight vacuum and protected from moisture. The thionyl chloride was removed (water pump) and benzene was added. This was removed (water pump) and the residue was precipitated

with ether and filtered off. It was dissolved in ethanol and mixed with a solution prepared from sodium (0.39 g.) and hydroxylamine hydrochloride (1.17 g.) in ethanol. Pouring into water gave a product which was not the desired amidoxime.

N:N-dimethyl-N^1-thiobenzoyl-p-phenylene diamine (IV)

N:N-dimethylamino-N^1-benzoyl-p-phenylene diamine (1.11 g.) was dissolved in xylene (25 ml.) and to the boiling solution was added phosphorous pentasulphide (480 mg.) in portions over 4 min. The mixture was refluxed for a further 5 min. and the red solution was decanted from the solid residue and concentrated. The residue was chromatographed in benzene over alumina (Grade 3) to yield N:N-dimethyl-N^1-thiobenzoyl-p-phenylene diamine, yellow needles, mp. 124°-5°, 390 mg.

Attempted oximination of thioamide IV

(a) The thioamide (430 mg.) in ethanol (10 ml.) was refluxed with sodium carbonate (179 mg.) and hydroxylamine hydrochloride (118 mg.) for 18 hrs. The solvent was removed and the residue was chromatographed over alumina (Grade 3) in benzene but no material showing oxime absorption in the i.r. was obtained.

(b) The thioamide (400 mg.) was refluxed with hydroxylamine hydrochloride (0.5 g.) and pyridine (0.5

ml.) in ethanol (5 ml.) for 12 hrs. IV (340 mg.) was recovered.

N-(p-dimethylaminobenzylidene)-4-nitro-aniline (V)

p-dimethylaminobenzaldehyde (5 g.) and p-nitroaniline (4.2 g.) were refluxed in ethanol (20 ml.) for several hours. Cooling produced a low yield of N-(p-dimethylaminobenzylidene)-4-nitro-aniline, mp. 203°, red needles. Lit.(141) mp. 198°-9°.

Reaction of benzonitrile oxide with V

The Schiff base V (1.56 g.) was dissolved in a mixture of benzene (150 ml.) and ethyl acetate (25 ml.) A solution of benzonitrile oxide (from 1.8 g. benzhydroximic chloride; triethylamine route) in ether (56 ml.) was added and the resulting solution was shaken gently for 24 hrs. Starting material V (310 mg.) was collected and the filtrate on concentration yielded 4:5-dihydro-3-phenyl-4-(p-nitrophenyl)-5-(p-dimethylaminophenyl)-1:2:4-oxadiazole, VI), 1.71 g., plates, mp. 137° (from ethanol). The adduct was yellow in solution but the crystals were red.

Found:	C, 68.50;	H, 5.15;	N, 13.71
$C_{22}H_{20}N_4O_3$ requires:	C, 68.03;	H, 5.19;	N, 14.43

Action of acid on VI

The adduct VI (500 mg.) was refluxed in methanol (10 ml.) with concentrated hydrochloric acid (5 ml.) for

2½ hrs. but it was recovered unchanged (m.m.p.).

Hydrogenation of VI

Adduct VI (136 mg.) was hydrogenated in ethanol in the presence of palladium-charcoal (5%; 55 mg.) to completion (39.1 ml.; 4.7 mols.). The catalyst was filtered off and the filtrate was concentrated to yield N-(p-aminophenyl)-benzamidine, mp. 109°-10°(from petroleum ether-ethanol).

(N-benzoyl)-p-nitroaniline

p-nitroaniline (5.0 g.) and pyridine (50 ml.) were mixed with benzoyl chloride (10 ml.). The solution was warmed on the steam bath for 10 min. and poured into water and the resulting suspension was stirred with dilute sulphuric acid. (N-benzoyl)-p-nitroaniline, m.p. 199° (from ethanol) was filtered off Lit.(142) mp. 196°-7°.

(N-thiobenzoyl)-p-nitroaniline

N-benzoyl-p-nitroaniline (2.00 g.) was refluxed with phosphorous pentasulphide (870 mg.) in toluene for 6 hrs. The mixture was chromatographed over alumina (Grade 3) to yield (N-thiobenzoyl)-p-nitroaniline, 337 mg., yellow needles, mp. 148° (from benzene). Lit.(143) mp. 147°.

N-(p-aminophenyl-benzamidoxime

(N-thiobenzoyl)-p-nitroaniline (363 mg.) was refluxed with a solution of hydroxylamine hydrochloride (400 mg.) and pyridine (0.5 ml.) in ethanol (5 ml.) for 13 hrs. The solution was concentrated and extracted with benzene and by chromatography of the extract on alumina (Grade 3) an oil (76 mg.) was isolated. This was hydrogenated in ethanol with palladium-charcoal catalyst (5%; 30 mg.) to completion (26.2 ml.; 3.7 mol.). The catalyst was filtered off and concentration of the colourless filtrate furnished N-(p-aminophenyl)-benzamidoxime, mp. (from ethanol-petroleum ether), 152°, with resolidification and further melting at 175°-7°.

Hydrogenation of 4:5-dihydro-3:4-diphenyl-5-(p-dimethylaminophenyl)-1:2:4-oxadiazole.

The oxadiazole (88 mg.) was hydrogenated (11.8 ml.; 1.8 mol.) over palladium-charcoal (5%) in ethanol to yield N-phenyl benzamidine, 55 mg., mp. (from petroleum ether-benzene), 108°-12°, identified by comparison of its i.r. spectrum with that of an authentic specimen. Lit.(135) mp. 111°-2°.

Hydrogenation of 4:5-dihydro-3:4:5-triphenyl-1:2:4-oxadiazole

The oxadiazole (312 mg.) was hydrogenated in the usual way (uptake 60 ml.; 2.4 mol.) to yield N-phenyl

benzamidine, 230 mg., mp. 117° (from benzene-petroleum ether). To a portion of the product (55 mg.) in benzene (1 ml.) was added phenyl isocyanate (54 mg.). After 10 min. the precipitated adduct was filtered off, mp. (from benzene) 177°-8°.

N-phenylbenzamidine

Benzimidochloride (redistilled) was extracted with petroleum ether. Liquid ammonia (15 ml.) was added to the extract and the resulting precipitate was filtered off and dissolved in chloroform. This solution was washed (water), dried (magnesium sulphate), and evaporated to yield N-phenyl benzamidine, mp. 117°.

N-(p-aminophenyl)-benzamidine[144]

p-nitroaniline (6.9 g.) and toluene-p-sulphonic acid (8.6 g.) were mixed in acetone and the colourless precipitate was filtered off and dried. It (12.5 g.) was mixed with benzonitrile (3.7g.) in a Carius tube which was sealed and heated at 220° for ½ hr. The reaction mixture was basified with ammonia and extracted with chloroform. The extract was dried and concentrated and the residue was chromatographed over alumina (Grade 3) to yield N-(p-nitrophenyl)-benzamidine, yellow prisms, mp. 167°-8° (from benzene). Lit.[144] mp. 167°-8°.

N-(p-nitrophenyl)-benzamidine (68 mg.) was hydrogenated over palladium-charcoal (5%) in ethanol until absorption was complete (20.4 ml.; 3.1 mol.). The catalyst was filtered off and evaporation of the filtrate yielded N-(p-aminophenyl)-benzamidine, mp. 109°-10° (from petroleum ether-ethanol) as colourless needles.

N-(p-dimethylaminophenyl)-benzamidine

A solution of p-Dimethylaminoaniline (1.4 g.) in ethanol-benzene (3:10) was mixed with a solution of toluene-p-sulphonic acid (1.8 g.) in the same solvent. The precipitated salt (2.0 g.) was filtered off, dried, and ground with benzonitrile (700 mg.). The mixture was heated at atmospheric pressure at 200°-220° for 1 hr., cooled, basified with ammonia, and extracted with chloroform. Chromatography over alumina yielded N-(p-dimethylamino-phenyl)-benzamidine, yellow needles, mp. 136°-7°.

Phenyl isocyanide(145)

Aniline was treated with chloroform and potassium hydroxide to furnish phenyl isocyanide, b.p. 72°-76°/30 mm.

Reaction of phenyl isocyanide with benzonitrile oxide

A solution of benzonitrile oxide (from 6.7 g. benzhydroximic chloride; triethylamine route) in ether (50 ml.) was slowly added to a solution of phenyl isocyanide (4.0 g.) in ether (25 ml.). When the addition was approximately half complete a precipitate appeared and ether (25 ml.) was added. The precipitate was collected and combined with a further crop from the mother liquors. Its identity as carbanilide, mp. 243° (from ethanol) was confirmed by a comparison of the i.r. spectrum with that of authentic material.

Found: C, 73.56; H, 5.70; N, 13.20

Calc. for $C_{13}H_{12}N_2O$: C, 73.43; H, 5.86; N, 12.82

The i.r. of the phenyl isocyanide showed clearly the presence of a primary amine. Working up the mother liquors from the reaction afforded diphenyl furoxan, 1.50 g.

Reaction of benzonitrile oxide with acetone oxime

Benzonitrile oxide (from 7.4 g. benzhydroximic chloride; triethylamine route) in ether (150 ml.) was added over 25 min. to a stirred solution of acetone oxime (3.36 g.) in a mixture of methanol (15 ml.) and ether (15 ml.) containing sodium hydroxide (1.84 g.).

Initially the solution became red and towards the end of the addition a precipitate appeared, which, after 2 days, was filtered off and acidified with dilute acetic acid. Ether extraction yielded benzoic acid (340 mg.). The original filtrate was concentrated and diluted with water to give a strongly alkaline solution which was extracted with ether. The extract yielded an oil (3.31 g.) which was separated by chromatography over alumina (Grade 3) into an oxime-containing liquid (663 mg.), a carbonyl-containing liquid (420 mg.) which also contained a little nitrile, and a partially crystalline oil (490 mg.). This latter fraction was recrystallised from petroleum ether-ether to yield 4:5-dihydro-3-phenyl-5:5-dimethyl-1:2:4-oxadiazole, needles, mp. 135°.

Found: C, 68·29; H, 7·15; N, 15·21

$C_{10}H_{12}N_2O$ requires: C, 68.16; H, 6.86; N, 15.90

By further chromatography of the carbonyl-containing oil a colourless liquid absorbing at 1710 cm^{-1} and identical to that formed by the action of alkali alone on benzonitrile oxide was obtained.

Acid hydrolysis of 4:5-dihydro-3-phenyl-5:5-dimethyl-1:2:4-oxadiazole

The oxadiazole (192 mg.) was refluxed with concentrated hydrochloric acid (1 ml.) in methanol (10 ml.)

for 5 hrs. The solution was concentrated, diluted with water, and basified with sodium hydroxide. Ether extraction furnished a gum (103 mg.) to which acetic anhydride (100 mg.) was added. Crystallisation of the product from petroleum ether yielded O-acetyl benzamidoxime, 59 mg., mp. 95°, identified by i.r. comparison with an authentic sample. Lit.(146) mp. 96°.

O-acetyl benzamidoxime

Benzamidoxime was prepared(147), mp. 70°. Acetic anhydride (1 mol.) was added to yield O-acetyl benzamidoxime, mp. 95°-60.

Reaction of benzonitrile oxide with cyclohexanone oxime

(a) Neutral solution

A solution of cyclohexanone oxime (3.00 g.) and benzhydroximic chloride (4.35 g.; 1 mol.) in ether (100 ml.) was stirred while triethylamine (2.81 g.; 1 mol.) in ether (60 ml.) was added over 1 hr. The pink suspension was filtered and evaporated at room temperature but upon removal of the last of the solvent the residue changed from pink to brown exothemically. The i.r. showed nitrile absorption and the only crystalline product isolated was diphenyl furoxan (490 mg.).

(b) Alkaline solution

Cyclohexanone oxime (3.00 g.) and sodium hydroxide (1.11 g.; 1 mol.) were dissolved in a mixture of methanol (40 ml.) and ether (30 ml.) and to this solution was added benzonitrile oxide (from 45 g. benzhydroximic chloride; triethylamine route) in ether (70 ml.) over 2 min. During the addition the solution became deep red and finally cloudiness appeared. The solvent boiled. The mixture was concentrated, diluted with water, and extracted with ether to yield an oil (3.46 g.) from which 4:5-dihydro-3-phenyl-5(spirocyclohexyl)-1:2:4-oxadiazole, 0.73 g., was obtained as needles, mp. 160°-1° (from ethanol-petroleum ether).

Found: C, 71.91; H, 7.48; N, 13.23

$C_{13}H_{16}N_2O$ requires: C, 72.19; H, 7.46; N, 12.95

The mother liquors yielded a red oil (2.64 g.) which was decolourised on alumina and from which no crystalline material was obtained.

Acid degradation of 4:5-dihydro-3-phenyl-5(spiro-cyclohexyl)-1:2:4-oxadiazole

The oxadiazole (200 mg.) was refluxed with concentrated hydrochloric acid (1 ml.) in methanol (10 ml.) for several hours. The solution was concentrated,

diluted with water, and extracted with ether. Evaporation of the ether afforded an oil which gave a 2:4-dinitrophenylhydrazone, mp. 164°-5°. This was identified as cyclohexanone-2:4-dinitrophenyl hydrazone, by m.m.p. and i.r. comparisons with an authentic specimen. The aqueous solution was basified and extracted with ether. Acetylation of the product gave O-acetyl benzamidoxime, mp. 196°-100°, identified by its i.r. spectrum.

Reaction of benzonitrile oxide with alkali

Triethylamine (9 ml.) was added to a solution of benzhydroximic chloride (10.4 g.) in ether (100 ml.) and the filtered solution of benzonitrile oxide was added over 3 min. with stirring to a solution of sodium hydroxide (3.9 g.) in methanol (70 ml.). The mixture became yellow, a precipitate appeared, and the solvent boiled. Water was added and ether extraction gave a yellow oil (3.48 g.) which showed absorption at 1710 cm^{-1} and which was destroyed by chromatography over grade I alumina.

Reaction of benzonitrile oxide with benzophenone oxime

(a) Weakly basic solution

To a stirred solution of benzophenone oxime (400 g.) and triethylamine (8.2 g.) in ether (60 ml.) was

added a solution of benzhydroximic chloride (3.50 g.) in ether (40 ml.) over 15 min. No colour appeared. Stirring was continued for 55 min. when the solution was pale pink. Water was added and the etheral layer was concentrated at room temperature. Initially a red colour appeared and then the product decomposed exothemically to give a brown gum from which diphenyl furoxan (1.25 g.), benzophenone oxime (3.26 g.), and an oil (which contained benzophenone) were isolated.

(b) Alkaline solution at room temperature

Benzonitrile oxide (from 5.2 g. benzhydroximic chloride; triethylamine route) in ether (50 ml.) was added to a stirred solution of benzophenone oxime in methanol (25 ml.) containing sodium hydroxide (1.23 g.; 1 mol.). The solution initially became red and then cloudy. It was stirred for 15 min., concentrated, diluted with water, and extracted with ether to yield a red oil (7.55 g.) which showed strong absorption at 2050 cm^{-1} and 1720 cm^{-1}. By crystallisation from petroleum ether-ethanol the oil afforded benzophenone oxime, 1.16 g., mp. 140°-2°, and concentration of the mother liquors gave 4:5-dihydro-3:5:5-triphenyl-1:2:4-oxadiazole, 170 mg., needles, mp. 178°, $\lambda\lambda$max 238 mμ (ϵ 16400), 311 mμ (ϵ 3700).

Found: C, 79.73; H, 5.56; N, 9.27

$C_{20}H_{16}N_2O$ requires: C, 79.98; H, 5.37; N, 9.33

The residual oil (4.01 g.) was added to a solution of sulphuric acid (2 ml.) in methanol (8 ml.). Vigorous effervescence occurred and the resulting yellow solution was extracted with ether. Removal of the solvent and chromatography of the residue over alumina (Grade 3) in petrol gave a carbonyl-containing oil (420mg.) upon which a hydroxamic acid test for an ester was positive. The oil (390 mg.) was heated with hydrazine hydrate (300 mg.) for 24 hrs. (steam bath). After cooling the product was recrystallised from petroleum ether-ethanol, mp. 111.5°-113°, colourless needles.

(c) Alkaline reaction at low temperature

Benzonitrile oxide (from 19.0 g. benzhydroximic chloride; triethylamine route) in acetone (220 ml.) was added over 10 min. to a stirred solution of benzophenone oxime (18.0 g.) and sodium hydroxide (3.77 g.) in a mixture of acetone (320 ml.) and water (320 ml.) which was in a flask surrounded by a bath at -15°. The temperature of the solution rose from -11° to -4° during the addition and the initially produced red colour had disappeared with gas evolution within 1 hr. and with

concomitant precipitation. Ether extraction yielded 4:5-dihydro-3:5:5-triphenyl-1:2:4-oxadiazole, 4.26 g., mp. 176°-8°, and an oil, 31.3 g. Acidification of the aqueous portion and ether extraction yielded a mixture from which benzoic acid was obtained. The oil (31.3 g.) was extracted with petroleum ether and benzophenone oxime was collected. The extract was chromatographed over alumina (1 kg., Spence grade H deactivated to Grade 3) to furnish benzophenone (3.73 g.), benzophenone oxime (2.33 g.) and a compound, mp. 101°-101.5° (from ethanol), 0.68 g.

Found: C, 70.86; H, 4.96; N, 11.54

$C_{14}H_{10}N_2O_2$ requires: C, 70.58; H, 4.23; N, 11.76

Attempted characterisation of the red oil from benzonitrile oxide and benzophenone oxime

Benzonitrile oxide (from 2.1 g. benzhydroximic chloride; triethylamine route) in acetone (50 ml.) was added to a stirred solution of benzophenone oxime (2.00 g.) and sodium hydroxide (410 mg.) in a mixture of acetone (20 ml.) and water (5 ml.). The solution initially went yellow, then red, and warmed to about 40°. After dilution with water, ether extraction yielded a red oil which was dissolved in ethanol and titrated with 3:5-dinitrobenzoic acid (0.61 g. required; gas evolution) until the colour change of red to yellow was complete.

The solution was cooled and crystallised to yield a yellow compound, 0.51 g., which was purified by chromatography in petroleum ether-benzene (3:1) over alumina (Grade 5). MP. (from ethanol) 130°-130.5°.

Found: C, 84.50; H, 5.61; N, 9.01 (a)
C, 82.56; H, 5.46. (b)
C, 82.81; H, 5.45. (c)
C, 82.39; H, 5.39; N, 8.84 (d)

Analyses (a), (b) and (c) were on the very same sample. Analysis (d) was on a sample prepared subsequently.

Attempted acetylation of 4:5-dihydro-3:5:5-triphenyl-1:2:4-oxadiazole

(a) The oxadiazole (74 mg.) was warmed (steam bath) with acetic anhydride (49 mg; 2 mol.) for 3 hrs. Crystallisation from ethanol yielded starting material, 40 mg., mp. 176°-8°.

(b) The oxadiazole (63 mg.) and acetic anhydride (107 mg.) in pyridine (2 ml.) were left at room temperature for 2 days. Working up yielded starting material, mp. (from benzene) 176°-7°, 56 mg.

Acid hydrolysis of 4:5-dihydro-3:5:5-triphenyl-1:2:4-oxadiazole

The oxadiazole (300 mg.) was refluxed with concentrated hydrochloric acid (1 ml.) in methanol (12 ml.)

for 6 hrs. The solution was concentrated, diluted with water, and extracted with ether to yield benzophenone, 111 mg., characterised by its i.r. spectrum and by the formation of a 2:4-dinitrophenylhydrazone, mp. 240°, 222mg. The aqueous solution, after addition of sodium acetate, was brought to pH 7 with sodium hydroxide. Ether extraction afforded a gum (81 mg.) which was acetylated to give O-acetyl benzamidoxime, 45 mg., mp. 95°-6°, identified by its i.r. spectrum.

Oxidation of 4:5-dihydro-3:5:5-triphenyl-1:2:4-oxadiazole

The oxadiazole (200 mg.) was warmed (steam bath) with a mixture of sulphuric acid (10.; 11 ml.) and potassium permanganate (750 mg.) for 15 min. The mixture was decolourised with sodium bisulphite and was extracted with ether to yield an oil (122 mg.) which upon chromatography over alumina (Grade 3) furnished benzophenone (52 mg.) which was converted to the 2:4-dinitrophenylhydrazine, 62 mg., mp. 239°-41°.

Hydrogenolysis of 4:5-dihydro-3:5:5-triphenyl-1:2:4-oxadiazole

The oxadiazole (400 mg.) was hydrogenated in ethanol over palladium-barium sulphate (10%; 1 g.) until hydrogen absorption was very slow (83.5 ml.; 3.6 mol.). The catalyst was filtered off and concentration yielded

benzamidine, 58 mg., mp. 65°-75°(from ether) which was treated with acetic acid in ether to furnish benzamidine acetic acid salt, mp. 230°-234°d. Lit.(148) mp. 229°d.

Benzophenone imine(120)

Benzophenone oxime (30 g.) was heated with a free flame in an unsealed Carious tube until gas evolution was slow. The product was distilled, b.p. 122°/min., as a yellow green oil. This was dissolved petroleum ether and hydrogen chloride was bubbled through until precipitation of benzophenone imine hydrochloride was complete. The hydrochloride was dissolved in chloroform while ammonia was passed and the ammonium chloride produced was filtered off. Distillation of the filtrate yielded benzophenone imine, 2.81 g., b.p. 108°-16°/6.5 mm. The i.r. showed only very weak absorption in the carbonyl region.

Reaction of benzophenone imine with benzonitrile oxide

Benzophenone imine (2.86 g.) was dissolved in benzene and mixed with a solution of benzonitrile oxide (from 2.71 g. benzhydroximic chloride) in benzene. The resulting solution (90 ml.) was left at room temperature for 1 hr. and 4:5-dihydro-3:5:5-triphenyl-1:2:4-oxadiazole, 3.55 g., mp. 177°-8° (colourless needles)

was filtered off.

1:4- dichloro-but-2-yne

The method of Johnson(149) was used. B.p. 68°-69°/17 mm., n_D^{20}, 1.5072.

Reaction of diacetylene(150) with benzonitrile oxide

Ethanol (45 ml.) and 1:4: dichloro-but-2-yne (10.0 g.) were placed in a three necked flask fitted with a stirrer, condenser connected to a tap funnel, and a condenser fitted with a calcium chloride tube which was connected first to a coiled condenser (at -40°) and then to a liquid air trap. The flask and contents were maintained between 72°and 77° while sodium hydroxide (40%; 46 g.) was added slowly from the tap funnel. Diacetylene solidified in the coiled condenser whose temperature was then allowed to rise until the diacetylene melted and drained into the liquid air trap. A solution of benzonitrile oxide (from 5 g. benzhydroximic chloride; triethylamine route) in ether (80 ml.) was added to the diacetylene and the resulting solution was left overnight. 5:5-bis(-3-phenyl-1:2:4-oxadiazole) was collected as colourless plates, mp. 222°.

Found:	C, 75.15;	H, 5.09;	N, 10.25
$C_{18}H_{12}N_2O_2$ requires:	C, 74.99;	H, 4.20;	N, 9.72

Terephthaldoxime

Terephthaldehyde was prepared(151) m.p. 111°-4°. Lit.(151) m.p. 115°-6°. It was converted to the bis-oxime by a standard procedure, m.p. 219°-20° (from ethanol). Lit.(88) m.p. 201°-2°.

Found:	C, 58.51;	H, 4.90;	N, 17.46
Calc. from $C_8H_8N_2O_2$:	C, 58.53;	H, 4.91;	N, 17.07

Terephthaldihydroximic acid chloride

Terephthaloxime (44 g.) was suspended in a stirred mixture of ether (100 ml.) and chloroform (100 ml.) at 0° and chlorine was passed for 5 hrs. The filtrate yielded terephthaldihydroximic acid chloride, m.p. 181°-4°d (from ethyl acetate) Lit.(87) m.p. 188°d.

Co-Polymer of diacetylene and benzene-1:4-dinitrile oxide

Diacetylene (0.65 g. by assay with benzonitrile oxide) in ether (100 ml.) was stirred (at -28° to -23°) in a three necked flask fitted with a calcium chloride tube, stirrer and droppingfunnel. Terephthaldihydroximic acid chloride (1.28 g.) in ether (20 ml.) was added and this was followed, over 30 min., by a solution of

triethylamine (1.22 g.) in ether (75 ml.) with vigorous stirring. The mixture was left for 2 days at room temperature and the product was filtered off and ground several times with water. It was washed (water, ethanol, ether) and dried, 969 mg.

Found: C, 67.30; H, 3.28; N, 11.48

$C_{12}H_6N_2O_2$ requires: C, 68.57; H, 2.88; N. 13.33

Reaction of benzonitrile oxide with benzophenone oxime. Characterisation of the nitrous oxide

Benzophenone oxime (3.00 g.) and sodium hydroxide (0.61 g.) were dissolved in a mixture of acetone (50 ml.) and water (50 ml.) and the solution was placed in a three necked flask fitted with a stirrer, gas inlet, tap funnel and nitrometer. Carbon dioxide was passed while benzonitrile oxide (from 3.2 g. benzhydroximic chloride; triethylamine route) in acetone (50 ml.) was added to the stirred, cooled (-10°) oxime solution. When addition was complete the reaction mixture was allowed to warm to room temperature and gas evolution associated with the disappearance of the red colour set in. The gas was collected over potassium hydroxide (50%) for 2 hrs. and was transferred via a vacuum line to a gas cell. The i.r. spectrum corresponded to a superimposition of authentic spectra of nitrous oxide and acetone.

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