QUARTERLY REVIEWS

NITRONES

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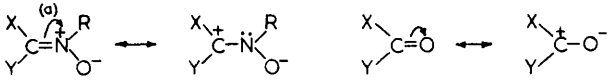
A. Introduction

THE name "nitrone", a contraction for nitrogen ketone, was suggested by Pfeiffer,[1] in 1916, for compounds possessing the group (1), to emphasise their striking similarity with ketones.



(1) (2) (3) (4)

We now recognise that the analogy rests on the mesomeric effects [(1)⟷(2) and (3)⟷(4)] which predominate in both classes of compounds, making the nitrone or azomethine *N*-oxide group (1) behave as an extended carbonyl function.

General usage and Chemical Abstracts have given a certain connotation to the term "nitrone", but the term is in need of a clearer definition. The mere presence of the azomethine *N*-oxide group (>C=N–O) in a molecule does not necessarily endow it with nitrone characteristics any more than the presence of a carbonyl group confers ketonic properties to the wide variety of carbonyl compounds.

The polarisation of the azomethine *N*-oxide group is controlled by the electronic effects of the substituents X, Y, and R. On the one extreme is the isolated system represented by the structure (1; X, Y, and R = alkyl) in which the double bond is fixed and the positive charge is localised between the nitrogen and carbon atoms of the azomethine system. On the other extreme is pyridine *N*-oxide (5), in which a high degree of delocalisation results from its aromatic character. In between these extremes all degrees of delocalisation could exist. The positive charge on the azomethine carbon atom controls most typical nitrone reactions and it must be decided whether any positive charge on the carbon atom, however small, entitles the compound to be included under nitrones, or at what stage delocalisation is too great to warrant inclusion in this class.

The authors prefer to restrict the term "nitrone" to compounds in which the canonical forms (1) and (2) contribute most to the structure and to exclude all azomethine *N*-oxides in which considerable delocalisation

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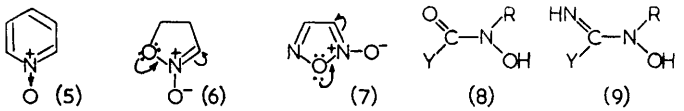
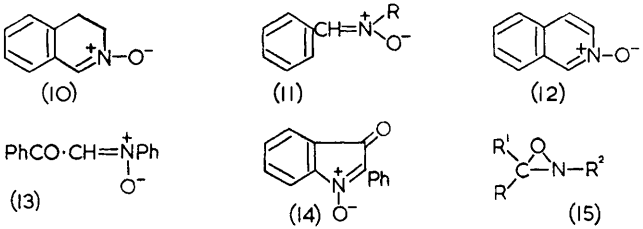
[1] P. Pfeiffer, *Annalen*, 1916, **411**, 72.

of the positive charge occur. We would thus exclude compounds in which the C=N of the azomethine *N*-oxide forms part of an aromatic ring, *e.g.*, pyridine *N*-oxide (5), quinoline *N*-oxide, etc. Compounds in which the nitrogen of group (1) is attached to an atom with unshared electron pairs, *e.g.*, isoxazoline 2-oxide (6) and furoxan (7) are also excluded since the electronic shifts shown will greatly diminish the contribution of the canonical form (2).



If R = H, the group (1) would represent the unstable tautomer of the oximes, and if X or Y were either a hydroxyl group or an amino-group, the structure (1) would be tautomeric with hydroxamic acids (8) or *N*-hydroxyamidines (9).[2] On the other hand the great stability of aromatic systems can be expected to resist loss of aromaticity even when conjugated to group (1) and so should not cause much delocalisation of positive charge. Compounds such as 3,4-dihydroisoquinoline *N*-oxide (10) and *C*-phenyl-*N*-methylnitrone (11, R = Me) are thus considered as nitrones. This viewpoint is strengthened by the fact that the compound (10) undergoes the typical nitrone reaction, 1,3-cycloaddition [see Section D, 4, *c* (*iv*)] 40,000 times faster than the heteroaromatic *N*-oxide (12).[3]



It also follows from this that electron-attracting groups in either X or Y will decrease the electron density on the carbon and its electrophilic properties will be enhanced. This is exemplified by the fact that *C*-benzoyl-*N*-phenylnitrone (13) undergoes 1,3-cycloaddition 110 times faster than *CN*-diphenylnitrone (11, R = Ph).[4] Isatogens, *e.g.*, 2-phenylisatogen (14), similarly show nitrone properties and are considered cyclic *C*-acylnitrones.[4]

Compounds containing the group (1) have been known since the preparation of the first "*N*-alkylated oxime", to which Dittrich[5] assigned the oxaziridine structure (15). During the latter part of the nineteenth century

[2] G. D. Buckley and T. J. Elliot, *J.*, 1947, 1508.
[3] R. Huisgen, *Angew. Chem.* (*Internat. Edn.*), 1963, **2**, 633.
[4] R. Huisgen, *Angew. Chem.* (*Internat. Edn.*), 1963, **2**, 565.
[5] M. Dittrich, *Ber.*, 1890, **28**, 2606.

and the early years of the twentieth century these compounds played an important part in the stereochemical studies of the oximes. The three-membered ring structure (15) was discarded since no real evidence could be offered for its existence and also since stereochemical evidence weighed heavily against it. Thus, Lindeman and Tschang[6] failed to resolve the bromocamphorsulphonate of *N*-methyl-*p*-dimethylaminobenzaldoxime, which, on the basis of the oxaziridine structure, should possess an asymmetric carbon atom. The discovery, and optical resolution, of the true oxaziridines[7] have shown beyond doubt that the so-called "oxime *N*-ethers" were, in fact, true nitrones. Modern methods, notably ultraviolet, infrared, and nuclear magnetic resonance spectroscopy clearly established the structure (1) in nitrones.

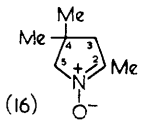
A great number and wide variety of nitrones have been prepared, and the field was reviewed by Smith[8] in 1938, and again by Hamer and Macaluso in 1964.[9] This review will thus not attempt complete coverage of the field, but rather to focus attention on some interesting aspects.

B. Nomenclature

In Chemical Abstracts, the carbon substituents [X and Y in formula (1)] are prefixed by α, and the substituent on nitrogen [R in formula (1)] is prefixed by *N*. In other publications, *e.g. Angewandte Chemie*, the carbon substituents are prefixed by *C* instead of α. I.U.P.A.C. considered nitrones as *N*-alkylated oximes and recommended naming them accordingly. The authors prefer, and have used in this review, the system of naming these compounds as *C*- and *N*-substituted nitrones. Thus, compound (11, R = Me) is named *C*-phenyl-*N*-methylnitrone.

Cyclic nitrones are usually named as the oxides of the parent heterocycle, thus the compound (16) is 2,4,4-trimethyl-l-pyrroline l-oxide, while the structure (17) is 3,4,5,6-tetrahydropyridine 1-oxide (or Δ^1-piperideine *N*-oxide):

Occasionally the terms "aldonitrones" (one *C*-substituent = H) and "ketonitrones" (neither *C*-substituent = H) are used.



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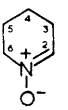


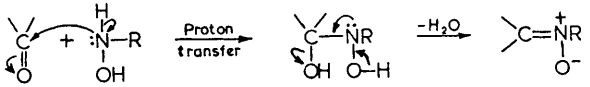
(17)

C. Syntheses

A number of routes to nitrones have been developed; the most important of these are listed as follows.

[6] H. Lindeman and K. T. Tschang, *Ber.*, 1927, **60**, *B*, 1725.
[7] W. D. Emmons, *J. Amer. Chem. Soc.*, 1956, **78**, 6208; 1957, **79**, 5739.
[8] L. I. Smith, *Chem. Rev.*, 1938, **23**, 222.
[9] J. Hamer and A. Macaluso, *Chem. Rev.*, 1964, **64**, 473.

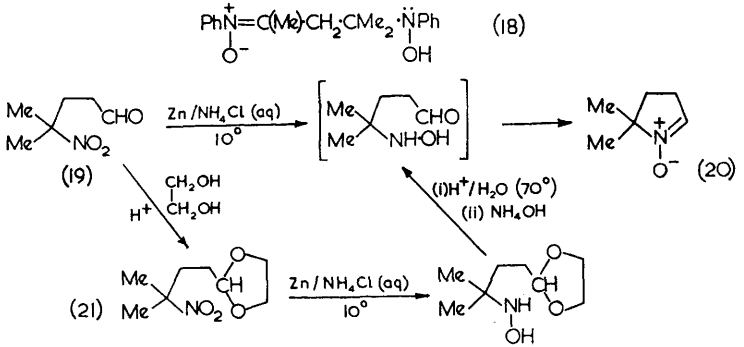
1. From *N*-Substituted Hydroxylamines.—Analogous with the well known formation of oximes from aldehydes and ketones by their reaction with hydroxylamine, reaction with *N*-substituted hydroxylamines gives nitrones.



This method is of fairly general application, and has been used to prepare a wide variety of nitrones, generally in good yields. Many instances are however reported, especially with aliphatic ketones having bulky alkyl groups, where no nitrones are formed. Further, in many cases dimeric products are produced, as in the case of the reaction product of acetone and phenylhydroxylamine for which the structure (18) has been proposed.[10]

Generally speaking, the condensation proceeds more readily with aldehydes than with ketones, though some aldehydes are susceptible to polymerisation reactions under the alkaline conditions usually employed. Often the hydroxylamino-function is generated *in situ*, usually by zinc dust-reduction of a nitro-compound;[2,11] in other cases the aldehyde or ketonic function is liberated *in situ* from the bisulphite complex[12] or from the acetal.[13a]

When the hydroxylamino-group and carbonyl function are suitably placed in the same molecule, condensation to produce cyclic nitrones occurs with great ease. Controlled reduction of γ-nitro-aldehydes or γ-nitro-ketones, generally by the use of zinc dust and aqueous ammonium chloride solution, give γ-hydroxylamino-aldehydes or -ketones, which cyclise to 5-membered cyclic nitrones in good yields.[13b]

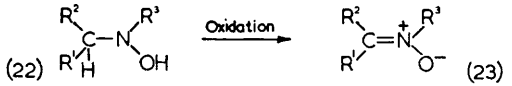


[10] F. H. Banfield and J. Kenyon, *J.*, 1926, 1612.
[11] E. Beckmann, *Annalen*, 1909, **365**, 201; F. C. Brown, V. M. Clark, and Sir Alexander Todd, *Proc. Chem. Soc.*, 1957, 97.
[12] P. Grammaticakis, *Compt. rend.*, 1947, **224**, 1568.
[13] (*a*) R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland, and Sir Alexander Todd, *J.*, 1959, 2094. (*b*) R. F. C. Brown, V. M. Clark, A. Giddey, and Sir Alexander Todd, *J.*, 1959, 2087.

To avoid polymerisation, the nitro-aldehyde (19) can be converted to an acetal, *e.g.* a dioxalan (21) before the alkaline reduction of the nitro-group. Mild acid treatment will then remove the protecting group, and on basification cyclisation occurs.

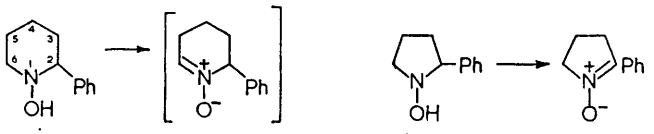
Although the above method is probably the one of choice, availability of the starting material may be limited or steric effects may prevent easy formation of the nitrones. It is thus necessary to study other synthetic methods.

2. From *NN*-Disubstituted Hydroxylamines.—A wide variety of reagents can be used to oxidise both acyclic and cyclic *NN*-disubstituted hydroxylamines to nitrones. This method is only applicable when at least one of the carbon atoms attached to the nitrogen carries a hydrogen atom, [(22) → (23)].



(22) (23)

In some cases it suffices merely to pass oxygen (or air) into an aqueous solution of the hydroxylamine, provided that a suitable catalyst, such as the copper-ammonia complex is present.[13,14] Other oxidising agents which have been used successfully include mercuric oxide,[15] cuperic acetate,[16] hydrogen peroxide,[17] potassium permanganate,[17] potassium ferricyanide,[12] t-butyl hydroperoxide[18] and high-potential quinones.[19] In some cases the course of the oxidation depends on subtle steric effects; thus oxidation with mercuric oxide of 1-hydroxy-2-phenylpiperidine (24) gave the dimer of the nitrone (25), in which the nitrone group is not conjugated with the aromatic ring,[20] whilst the same reagent oxidised 1-hydroxy-2-phenyl-pyrrolidine (26) to the nitrone (27), in which the nitrone group entered into conjugation with the phenyl group.[15,20]

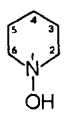


(24) (25) (26) (27)

The unexpected production of the intermediate (25) was explained on conformational grounds;[20] in the most stable form of the piperidine (24)

[14] D. H. Johnson, M. A. T. Rodgers, and G. Trappe, *J.*, 1956, 1093.
[15] J. Thesing and W. Sirrenberg (*a*) *Ber.*, 1959, **92**, 1748; (*b*) 1958, **91**, 1978; (*c*) L Allessandri, *Chem. Abs.*, 1915, **9**, 1045.
[16] H. Rupe and R. Wittwer, *Helv. Chim. Acta*, 1922, **5**, 217.
[17] G. E. Utzinger, *Annalen*, 1944, **556**, 50.
[18] H. E. de la Mare and G. M. Coppinger, *J. Org. Chem.*, 1963, **28**, 1068.
[19] W. D. S. Bowering, V. M. Clark, R. S. Thakur, and Lord Todd, *Annalen*, 1963, **669**, 106.
[20] J. Thesing and H. Meyer, *Annalen*, 1957, **609**, 46.

the phenyl and hydroxyl substituents would be equatorial, and in this form, the hydrogen atom at position-2 is axial and less readily attacked than the equatorial hydrogen at position-6. These distinctions are absent in the pyrrolidine (26). On the other hand no explanations have been offered for the fact that while oxidation of 1-hydroxypiperidine (28) with cupric acetate yields the dimer (30)[21] of the nitrone (29), oxidation with potassium ferricyanide gives a trimer, formulated as (31).[20]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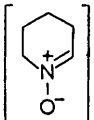
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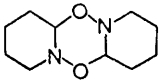
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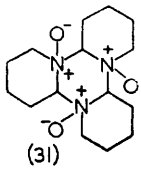
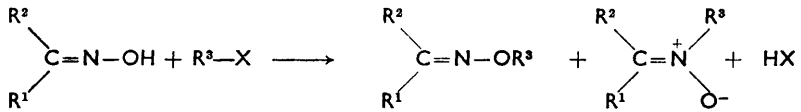

(31)

Whilst the dimer (30) is a typical 1,3-cycloaddition product of the expected nitrone (29), which is thus obviously the intermediate, the trimer (31) would represent a 1,2-addition of this nitrone, and is contrary to reactions normally found for the nitrones. However, the dimer (30), which forms under slightly acid conditions, can be converted to the trimer by acid hydrolysis and addition of excess strong base. It thus appears that the reaction is pH dependent and that the catalyst is not the controlling factor.

3. From Oximes.—The alkylation of oximes usually gives mixtures of the oxime-*O*-ethers (32) and nitrones. The particular isomer formed or its preponderance in the mixture depends on the nature of the oxime, the alkylating agent, and experimental conditions.

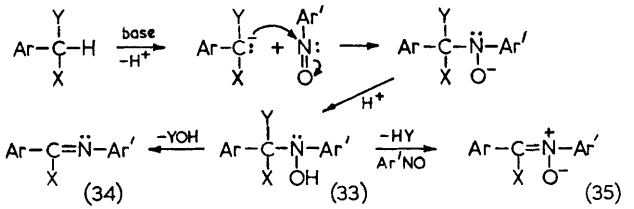

(32)

Thus methyl bromide and benzyl bromide give different ratios, the reagent with the small methyl favouring nitrone formation, whilst the reagent with the larger benzyl favours ether formation. Also the higher the dissociation constant of the oxime, the higher the proportion of *O*-ether produced.[22] As a general method of nitrone synthesis, this method thus suffers from notable shortcomings.

4. From Aromatic Nitroso-compounds.—Aromatic nitroso-compounds react with a variety of reagents to give nitrones and this reaction has proved a fruitful route to many nitrones. The reagents which have been found effective can be divided into the following categories:

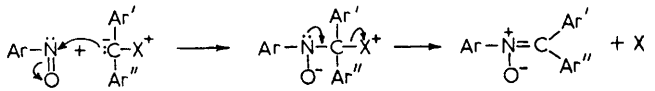
[21] J. Thesing and H. Mayer, *Ber.*, 1956, **89**, 2159.
[22] O. L. Brady and R. F. Goldstein, *J.*, 1926, 2403; O. L. Brady and N. M. Chokshi, *J.*, 1929, 2271.

(a) Reagents containing active methyl, methylene, or methylidene groups. Essentially the reaction involves a base-catalysed addition of the reagent to the nitroso-group, to yield the *NN*-disubstituted hydroxylamine (33). The fate of this product may fall along one or both of two paths: either 1,2-elimination to give the anil (34), or 1,3-elimination to form the nitrone (35).



If Y = H, this elimination is an oxidation, the excess of nitroso-compound acting as oxidising agent. The most notable example of the above reaction is the so-called Kröhnke synthesis,[23] which makes use of pyridinium salts as active methylene reagents (X = H, Y = $N^+C_5H_5$ Cl^-). Other reagents used include *e.g.* 2,4-dinitrotoluene, (X = Y = H);[24] *p*-nitrobenzyl chloride, (X = H, Y = Cl);[25] α-chloro-α-cyanotoluene, (X = CN, Y = Cl);[26] 1,3-diketones, (X = H, Y = CO.R).[27]

(b) Reagents containing an electropositive atom or group which acts as a good leaving group. Generally this reaction can be represented as follows:



Reagents used include diphenyldiazomethane, $[X^+=(\dot{N}\equiv N)]$,[28] sulphonium ylids, $[\dot{X}^+ = (S.Me_2)]$,[29] which gave good yields, and phosphorus ylids, $[X^+ = (\dot{P}.Ph_3)]$,[30] which gave variable amounts of anils as by-products.

Other reagents like alkenes, alkynes, quinones, etc. have been employed but are not generally used, and the mechanisms are obscure.

D. Properties

1. Solubilities.—Nitrones may be either liquids or solids, and due to the polar character of the nitrone group, they tend to be readily soluble in

[23] F. Kröhnke, *Angew. Chem.*, 1953, **65**, 612; 1963, **75**, 181.
[24] J. Tananescu and J. Nanu, *Ber.*, 1942, **75**, 650.
[25] F. Barrow and E. D. Griffiths, *J.*, 1921, 212.
[26] F. Barrow and F. J. Thorneycroft, *J.*, 1939, 773.
[27] A. Schoenberg and R. C. Azzam, *J.*, 1939, 1428.
[28] A. W. Johnson, *J. Org. Chem.*, 1963, **28**, 252.
[29] A. W. Johnson and R. B. La Count, *J. Amer. Chem. Soc.*, 1961, **83**, 417.
[30] S. Trippett, *Quart. Rev.*, 1963, **17**, 406.

water unless hydrophobic substituents, such as aryl groups are present. Extraction from aqueous solution by organic solvents is thus usually only possible after concentration and salting out.

2. Spectral Properties.—(*a*) *Ultraviolet Spectra.* The ultraviolet spectra of a great number of nitrones have been reported. Since much of the work has been carried out on aryl-substituted nitrones, confusion seems to have arisen as to the origin of the absorptions. A strong absorption in the region of 230 mμ which is present in all monomeric unconjugated mono-nitrones, even those with no phenyl substituents, such as the 1-pyrroline 1-oxides, must be due to electronic transitions (*E*-band) in the nitrone group, and cannot be assigned to electronic transitions in the benzene nuclei as suggested by Wheeler and Gore.[31] The position of the absorption maximum may be shifted when the nitrone function is conjugated to phenyl groups, and other *E*- and *K*-bands, due to other chromophores and their combined effects, may occur.[31] In the conjugated dinitrones bathochromic shifts to 331 mμ were observed[32] (see also Section E).

(*b*) *Infrared Spectra.* A strong absorption in the 1600 cm.$^{-1}$ region is characteristic of all nitrones but the exact position of this band varies with different nitrones. In the 1-pyrroline 1-oxides with position-2 unsubstituted, the absorption is usually in the range 1570—1590 cm.$^{-1}$, whilst in the 2-substituted 1-pyrroline 1-oxides the position of the band is somewhat higher and generally lies between 1600 and 1620 cm.$^{-1}$.[13] In acyclic nitrones the position of this band varies over a slightly wider range, depending on the substituents present. The exact origin of this band is not absolutely clear; some authors[15a] attribute it to the C=N stretching mode, others[13a] consider it as due to the C=N$^+$–O$^-$ group as a whole.

Another strong absorption in the region 1170—1280 cm.$^{-1}$ is found in all nitrones, and since a similar band is present in pyridine *N*-oxide and trimethylamine *N*-oxide, it must be considered to be due to the N$^+$–O$^-$ stretching frequencies.

(*c*) *Nuclear Magnetic Resonance.* The nuclear magnetic resonance spectra of a few nitrones are known. Two valuable contributions to the study of nitrones can be derived from them. (i) In the 1-pyrroline 1-oxides the double bond is localised in the Δ^1-position, since no signal in the olefinic proton region was observed for the nitrone (16) and both possible tautomers would have olefinic protons. Similarly, for the nitrone (20) only one proton was found to absorb at low field (proton at C-2); the Δ^2-tautomer would be expected to show two olefinic proton signals.[33] (ii) *gem*-Dimethyl groups at position-5 in nitrone (20) give a singlet at about τ 8·7, which confirms that the adjacent O–N=C< group is planar, and not

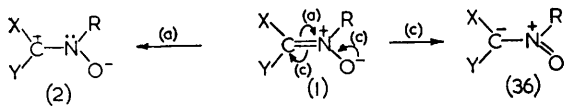
[31] O. H. Wheeler and P. H. Gore, *J. Amer. Chem. Soc.*, 1956, **78**, 3363.
[32] R. F. C. Brown, V. M. Clark, M. Lamchen, and Sir Alexander Todd, *J.*, 1959, 2116.
[33] R. Bonnett and D. E. McGreer, *Canad. J. Chem.*, 1962, **40**, 177.

in the oxaziridine form; the isomeric oxaziridine gives the expected two singlets for the two methyl groups, *cis* and *trans* to the three-membered ring.[33,34,35]

3. Isomerism.—In cyclic nitrones the *syn*-form is dictated by the ring, but in acyclic compounds the double bond in the nitrone group would introduce the possibility of geometrical isomers. However, since resonance imparts a considerable amount of single-bond character to the system one might expect a fairly ready isomerisation between the *syn*- and *anti*-forms. It has been found that heat easily converted α-aryl-α-cyano-*N*-arylnitrones from the *syn*- to the *anti*- form. A number of geometrical isomers of such α-cyano-nitrones have been prepared and their configuration assigned on the basis of dipole measurements.[26] The presence of the polar cyano-group offers an easy way of determining the configuration of the nitrone, for when the cyano-group is on the same side as the polar N^+–O^- bond, high dipole moments result, while the opposite, *anti*-configuration has a lower dipole moment.

At least one attempt has been made to determine the geometry of nitrones by making use of ultraviolet spectroscopy. The nitrone (10) with the phenyl group and the oxygen atom fixed in the *anti*-configuration absorbs at λ_{max} 304, 228, and 211 mμ, while the nitrone (27) absorbing at λ_{max} 288, 221·5, and 205 mμ is rigidly in the *syn*-configuration. On this basis, the geometry of both the nitrones (11, R=Me) with λ_{max} 288, 221·5, and 206 mμ, and (11, R=cyclohexyl) with λ_{max} 291, 223, and 206 mμ, was assigned as *syn*.[15b] The validity of such studies should not necessarily be regarded as having been established.

4. Reactions.—It has been shown (page 329) that the nitrone group could be represented by the resonating system (1)←→(2). A third canonical form (36) could arise from the group (1) by electron shifts (c) which are usually referred to as "back polarisation". The nitrone group is thus a resonance hybrid of the extreme structures (1), (2), and (36).



In most reactions the behaviour of nitrones indicates activation through polarisation scheme (a), but some properties, *e.g.*, geometrical isomerism, indicate a degree of double-bond character (form 1), while some reactions [section D 4, *c* (*iv*)] require (c) as the polarisation step in activation.

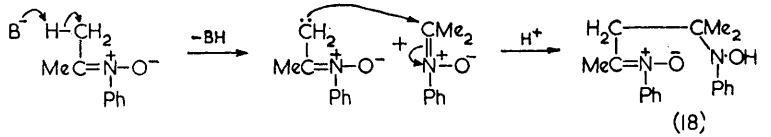
(*a*) *Dimerisation.* (*i*) *Cyclic dimers.* Dimerisation through form (2) will lead to charge neutralisation and may occur in various ways depending

[34] R. Bonnett, V. M. Clark, and Sir Alexander Todd, *J.*, 1959, 2102.
[35] L. Kaminsky and M. Lamchen, *Chem. Comm.*, 1965, 130.

on stability and steric effects. When the dimer is of lower energy than the monomer spontaneous dimerisation will occur. Thus, from 1-hydroxypiperidine, on oxidation with cupric acetate, the cyclic dimer (30) was isolated and not the monomeric nitrone (29).[21] On the other hand 1-hydroxypyrrolidine gives the monomeric 1-pyrroline 1-oxide.[15a] This difference was attributed to a lowering in the Pitzer strain when the six-membered nitrone (29) forms the dimer (30), whilst such a dimerisation of the five-membered nitrone would raise the Pitzer strain.[15a]

The nitrone (10), although being six-membered, is obtained as a monomer. The stability of this monomer has been attributed[20] to deactivation of the nitrone group by conjugation with the aromatic nucleus.

(*ii*) *Acyclic dimers.* The electrophilic character of the carbon atom of the nitrone group activates adjacent methyl and methylene groups, and it is thus not surprising that suitably substituted nitrones, should undergo aldol-type reactions. In some cases the reaction is spontaneous and the aldol dimer is obtained instead of the monomeric nitrone. Thus phenylhydroxylamine and acetone when heated together give the dimer (18), and since no additional basic catalyst is required, either the hydroxylamine or the nitrone intermediate must act as base.[10] Similarly, the nitrone (16) slowly forms the dimer (37) on standing.[36]



(18)

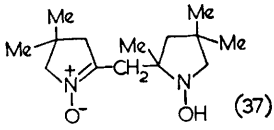
Unless steric effects, or the conditions mentioned above, operate against dimerisation, dimers can be expected to form when nitrones are prepared. Thus, in cases where no reason is obvious, the nitrones reported as monomers could well be re-examined to confirm their monomeric state.

Even the stable monomers can be induced to dimerise under basic conditions, the basic catalyst controlling the product. Thus whilst the nitrone (20) shows little tendency to dimerise when stored at room temperature, it readily dimerises under basic conditions; triphenylmethylsodium produces an aldol-type dimerisation to yield the dimer (38) whilst sodamide in liquid ammonia gives a benzoin-type dimerisation to produce the dimer (39); sodamide in triethylamine produces a mixture of the dimers (38) and (39).[32] No explanation for this is obvious.

(*b*) *Aldol Additions and Condensations.* 2-Methyl-substituted cyclic nitrones do not dimerise under strongly basic conditions, most likely due to repulsion of the anions produced. However, if 2-unsubstituted cyclic nitrones are also present, aldol addition between the two nitrones occurs, thus if the nitrone (16) is treated with triphenylmethylsodium and 4,5,5-trimethyl-1-pyrroline 1-oxide the aldol addition product (40) is formed.[36]

[36] R. F. C. Brown, V. M. Clark, I. O. Sutherland, and Sir Alexander Todd, *J.*, 1959, 2109.

The activation of a methyl group by an adjacent nitrone system is also demonstrated by the aldol-type condensation such nitrones give with aldehydes, *e.g.* the nitrone (16) and benzaldehyde in the presence of potassium hydroxide give the styryl derivative (41).[13a]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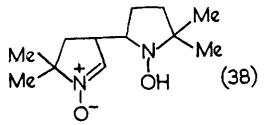
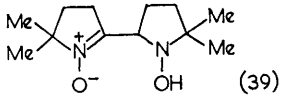
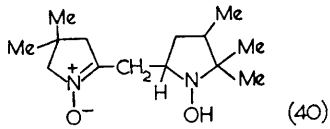

(38)


(39)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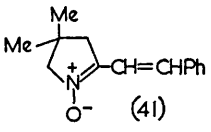
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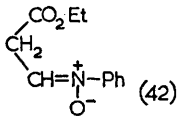
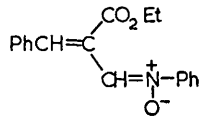

(42)


(43)

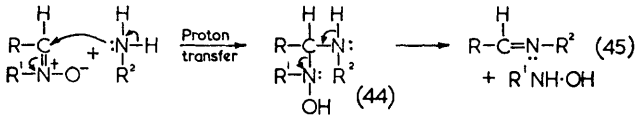
Although aldol-type dimerisation occurs on the methylene group in position-3 of the nitrone (20), [see dimer (38)], no aldol condensations with aldehydes are found with 2-unsubstituted or 2-ethyl-substituted nitrones.[13a] A methylene group activated by being adjacent both to a nitrone and to another electron-attracting group, may, however, condense with aldehydes. Thus the nitrone (42) gave the product (43) with benzaldehyde in the presence of base.[37a]

In the above the nitrones acted as the nucleophiles in the aldol condensations. When the 2-unsubstituted nitrone (20) reacts with nitro-alkanes in the presence of sodium ethoxide, the nitrone reacts as the electrophile, and 1,3-additions to the nitrone, to produce the 2-nitroalkyl-1-hydroxypyrrolidines, occur.

(*c*) *Addition Reactions.* Dimerisation and aldol reactions are specia cases of addition reactions. The polar character of the nitrone group makes it susceptible to a wide variety of 1,3-addition reactions.

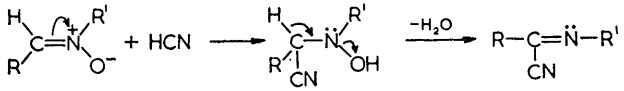
(*i*) *Addition of carbonyl reagents.* Nitrones react with the usual carbonyl reagents to produce derivatives (45) of the parent carbonyl compounds.[37] The mechanism is not certain since no intermediate has been isolated, but a likely route is through the adduct (44), which loses the hydroxylaminoresidue. [See also Section D, 4 (*f*).

[37] (*a*) G. E. Utzinger and F. A. Regenass, *Helv. Chim. Acta*, 1954, **37**, 1892; (*b*) M. Hamana, B. Umezawa, and Y. Goto, *Chem. Abs.*, 1961, **55**, 8405.

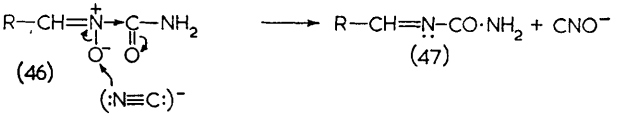


[In (45) R^2 = OH, HN-Ph, HN(2,4-dinitrophenyl), or NH-$CONH_2$ in oximes, phenylhydrazones, 2,4-dinitrophenylhydrazones, and semicarbazones respectively.]

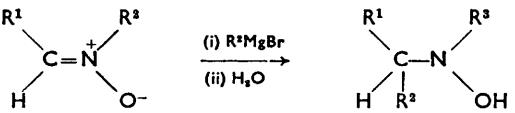
(*ii*) *Addition of hydrogen cyanide.* Hydrogen cyanide adds 1,3 across the nitrone system to give α-hydroxylamino-nitrones. In the presence of base, some of these adducts lose water to form cyano-imines.



The 1-pyrroline 1-oxides react with hydrogen cyanide only when the 2-position is unsubstituted, and these adducts were found to be stable to alkali.[13a] A carbonyl group attached to the carbon of nitrones exerts little effect on the mechanism and cyano-imines are formed. If, however, a carbonyl group is attached to the nitrogen atom, its $-I$ effect influences the nitrone system to lose the oxygen atom; thus potassium cyanide reacts with the nitrone (46) to give the deoxygenated product (47) and potassium cyanate.[38]

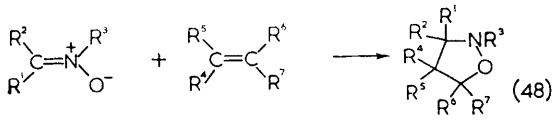


(*iii*) *Addition of Grignard reagents.* Grignard reagents add 1,3 across the nitrone system of aldonitrones and, after hydrolysis of the complex, give hydroxylamines. Ketonitrones may resist such additions and be reduced to imines.[37a] In the 1-pyrroline 1-oxide series normal addition proceeds both with aldo- and keto-nitrones. The reaction is potentially very useful as more highly substituted heterocycles may be produced by this method. Even the dimeric nitrone (30) which is resistant to a number of nitrone reactions, reacts with phenylmagnesium bromide to give the hydroxylamine (24) in excellent yields.[21]



[38] V. Bellavita and N. Cagnoli, *Gazzetta*, 1939, **69**, 583; (*Chem. Abs.*, 1940, **34**, 1638).

(*iv*) 1-3 *Cycloadditions.* Formation of the dimer (30) is a 1,3-cycloaddition between two nitrone systems. The general reaction, cycloaddition of nitrones with unsaturated compounds has been extensively studied in recent years. With olefins, the nitrones react to form isoxazolidines according to the following scheme.

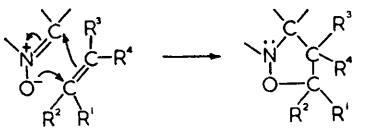


(48)

Unless the addition is stereospecific a stereochemically pure isoxazolidine (48) can only be expected to be formed when $R^1=R^2$ and $R^4=R^5=R^6=R^7$. In all other cases a number of stereoisomeric isoxazolidines may form due to the fact that up to three asymmetric centres could be created, and that with unsymmetrically substituted olefins two orientations of addition are possible. In most of the work reported in this field excellent yields are obtained, but the stereochemistry and substitution pattern of the isoxazolidines have not been determined. The ease with which these adducts are formed and their stability are utilised to trap unstable nitrones or those difficult to purify. In these cases the nitrone is formed *in situ* in the presence of the unsaturated compound and the adduct is isolated.[18,39]

Although cycloaddition to an isolated double bond occurs, conjugation of the olefinic bond with a group which enhances the polarisability of the double bond has a marked effect on the ease of cycloaddition. For example, the rate of addition of *C*-phenyl-*N*-methylnitrone (11, R=Me) to olefins of the type $R-CH=CH_2$, increases fourfold as R changes from alkyl to phenyl and one hundred and fifty fold when $R = CO_2Et$.[3]

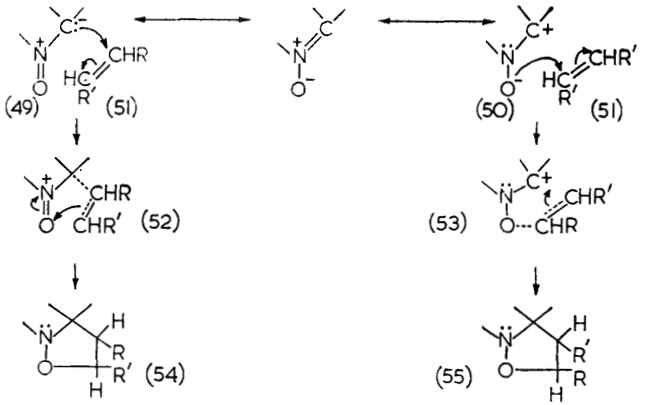
The mechanism of the cycloaddition is not known with certainty, neither is it clear whether it always follows the same pathway. Basically two mechanisms have been considered: (1) A concerted one-step process, *i.e.*, synchronous closure of both bonds as represented below:



In such a process stereospecific *cis*-addition must occur. With unsymmetrical olefins, however, two adducts are possible, depending on the direction of addition, *i.e.*, R^1 and R^2 could be interchanged with R^3 and R^4. Huisgen[3] favoured this mechanism and presented strong arguments for his choice. Unfortunately some of the results on which the argument is based are not yet published and are thus difficult to assess.

[39] R. Grashey, R. Huisgen, and H. Leitermann, *Tetrahedron Letters*, 1960, No. 12, 9.

(2) An alternative mechanism proposed involves a two-step process. The structure of the intermediate will depend on the polarised state or polarisability of the reagents.



The groups R and R′ will determine the polarisation in the addend (51). The mobility of the π electrons in the nitrone system will enable formation of two different activated complexes (52) and (53), through the hypothetical canonical forms (49) and (50) respectively. Stereospecific ring closure of the activated complexes may follow, or, in the absence of steric hindrance, free rotation of the intermediates may result in both *cis*- and *trans*-addition. Either products (54) or (55) may thus be formed, and they may be single products or mixtures of isomers.

The present authors, in their study of cycloaddition of ethyl acrylate to 1-pyrroline 1-oxides favoured this latter mechanism.[40] Thus the nitrone (20) reacts exothermally with ethyl acrylate at room temperature to give a quantitative yield of isomers with partial structure (54; R=H, R′=CO_2Et). This reaction, being fast, would require a low entropy of activation and is thus unlikely to follow a one-step process. If the recognised direction of polarisation of ethyl acrylate is accepted the reaction proceeds through the canonical form (49), the intermediate (52), in this case having the partial structure (56). The adduct could be isomerised to the thermally stable

isomer with partial structure (55; R=H, R′=CO_2Et), which also forms when the nitrone (20) and ethyl acrylate are heated together. In this latter case the reaction was considered to proceed *via* the canonical form (50) and to give the intermediate (57), which ring-closed stereospecifically.

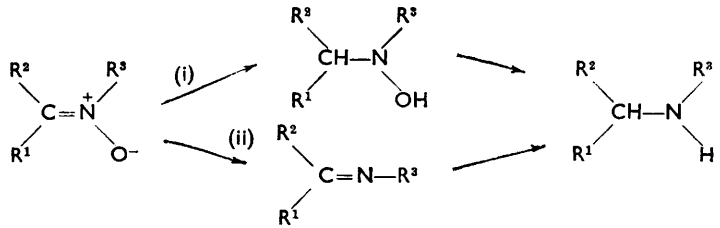
[40] G. R. Delpierre and M. Lamchen, *J.*, 1963, 4693.

This work showed that cycloadditions could be kinetically and thermodynamically controlled, the room temperature reaction having been kinetically controlled whilst the hot reaction submitted to thermodynamic control.

Until more evidence is published, especially a comparison of entropy of activation with overall entropy of the reaction, no decision can be made as to the mechanism of cycloaddition. Under different conditions and with different reagents, different mechanisms may be operative.

1,3-Cycloadditions of nitrones also occur with isocyanates, isothiocyanates, and alkynes.[4] With tetraphenylcyclopentadienone 1,4-addition across the conjugated diene system and 1,2-addition to the nitrone is found.[41]

(*d*) *Reduction.* The nitrogen atom in nitrones is at a high oxidation level and stepwise reduction to secondary amines is possible. Two reduction pathways are possible, each with a different intermediate; (i) addition of hydrogen to form the hydroxylamine and (ii) deoxygenation to the imine.



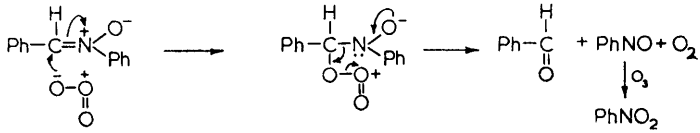
Judicious choice of reducing agent will allow preparation of any of these reduction products. Hydride reagents, *e.g.*, lithium aluminium hydride[40,42] or sodium borohydride,[13a] attack at the electrophilic carbon atom of the nitrone group and, on hydrolysis of the complexes formed, hydroxylamines are obtained in good yields. The reaction stops at the hydroxylamino-stage even when excess of lithium aluminium hydride and fairly vigorous conditions are used.[15a]

Removal of the oxygen atom to form imines can be effected by treatment with a variety of reagents; zinc and acetic acid,[13a] sulphur dioxide,[13a] and triphenylphosphine[43] have proved very successful; other reagents, *e.g.* phosphorus tri- or oxy-chloride have also been used, sometimes with attendant decomposition or side reactions. Generally zinc and mineral acid combinations reduce the nitrone group to the secondary amine.

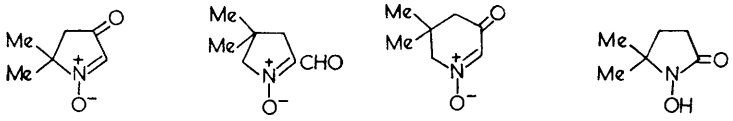
(*e*) *Oxidation.* The oxidation level of the nitrogen atom in nitrones is such that oxidation cannot raise it without disrupting the system and liberating the nitrogen atom as a nitroso- or nitro-group. This happens during the ozonisation of *CN*-diphenylnitrone which gives benzaldehyde

[41] C. W. Brown, K. Marsden, M. A. T. Rogers, C. M. B. Taylor, and R. Wright, *Proc. Chem. Soc.*, 1960, 254.
[42] O. Exner, *Chem. listy*, 1954, **48**, 1543; (*Chem. Abs.*, 1955, **49**, 11603).
[43] F. Angolini and R. Bonnet, *Canad. J. Chem.*, 1962, **40**, 181.

and nitrobenzene.[44] Since oxaziridines are stable to ozone, cleavage of the C=N bond did not occur through a three-membered ring intermediate; the following mechanism best explains this reaction.



Selenium dioxide oxidises the nitrone (20) to give the conjugated keto-nitrone system (58).[45] This is analogous to the oxidation of α-methylene groups in aldehydes and ketones to produce the α-dicarbonyl compounds.[46] When an adjacent methyl group is present, as in 2,4,4-trimethyl-1-pyrroline 1-oxide (16) the reaction is more complex, and in this case the expected aldehyde (59) was not isolated; instead the ring-expanded product (60) was obtained[47]—this is probably an artefact produced by acid treatment of the reaction mixture.



(58) (59) (60) (61)

Attack on the nitrone group of the nitrone (20) has also been observed with iron(III) chloride; the product is the cyclic hydroxamic acid (61).[48]

(*f*) *Hydrolysis.* Acyclic nitrones are generally readily hydrolysed by acids to form aldehydes or ketones and *N*-substituted hydroxylamines. Considerable variation in the stability of nitrones to solvent action is found, and whereas alkyl substituted nitrones are rapidly hydrolysed by aqueous acids and even decomposed by ethanol,[49] the 1-pyrroline 1-oxides are stable in hydroxylic solvents and in dilute aqueous acids. Acyclic aryl nitrones are intermediate between these two extremes in stability.

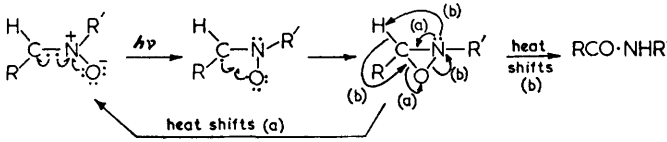
In view of the lability of many nitrones to mildly acidic conditions, some of their reactions with carbonyl reagents [Section D, 4 (*c*) (*i*)] which are usually carried out at low pH, may well proceed through a preliminary hydrolysis and subsequent reaction of the carbonyl compound produced.

[44] A. H. Riebel, R. E. Erickson, C. J. Abshire, and P. S. Bailey, *J. Amer. Chem. Soc.*, 1960, **82**, 1801.
[45] V. M. Clark, B. Sklarz, and Sir Alexander Todd, *J.*, 1959, 2123.
[46] N. Rabjohn, *Org. Reactions*, 1949, **5**, 331.
[47] R. F. C. Brown, V. M. Clark, and Sir Alexander Todd, *J.*, 1959, 2105.
[48] J. F. Elsworth and M. Lamchen, unpublished results.
[49] O. Exner, *Coll. Czech. Chem. Comm.*, 1951, **16**, 258; (*Chem. Abs.*, 1953, **47**, 5884).

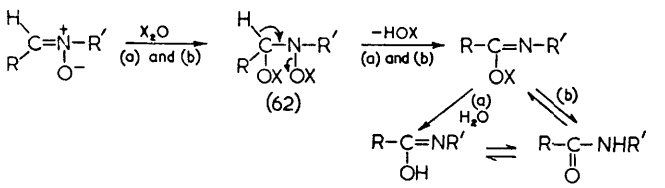
(*g*) *Rearrangements.* The nitrone group is susceptible to a number of rearrangements which reflect both on the reactivity of the nitrones as a class of compounds and the complexity of their chemistry. Such rearrangements may be divided into the following types:—

(*i*) *Photolysis.* Irradiation of nitrones has been shown to produce the isomeric oxaziridines.[34,50] Activation of the π-electrons by light of the appropriate wavelength will be influenced by the substituents on, and adjacent to, the nitrone group, and the isolation of the oxaziridine will also be determined by its stability. Thus whilst 2-unsubstituted 1-pyrroline 1-oxides form oxaziridines readily the 2-substituted isomers have been reported not to give oxaziridines.[34] It has, however, been shown that the 2-substituent does not preclude oxaziridine formation and that 2,5,5-trimethyl-1-pyrroline 1-oxide forms the oxaziridine on irradiation.[35] Oxaziridines may, on heating, either revert to the nitrone or be converted into the isomeric amides. Prolonged irradiation of nitrones may also produce amides.

A radical mechanism is most likely for the oxaziridine formation.



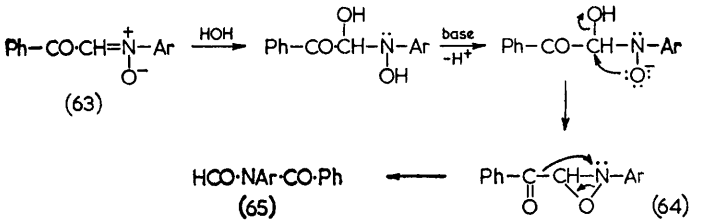
(*ii*) *Amide formation.* In addition to the photolytic rearrangement mentioned above, aldonitrones have been rearranged by a wide variety of chemical reagents. Phosphorus penta-, tri-, and oxy-chlorides, acetyl chloride, acetic anhydride, sulphur dioxide, and even bases in ethanolic solution, have converted nitrones to amides, often in good yields.[51] In most cases the substituents do not migrate as in the case of the classical Beckmann rearrangement, and this would suggest that the mechanism which operates must be different. Kröhnke has suggested two mechanisms to explain the course of the rearrangement.[52] For rearrangements in which no migration of substituents occur, for example by the action of acetic anhydride[51] [scheme (a), X = CH_3CO] or with sodium ethoxide[53] [scheme (b), X = H] the following was suggested.



[50] M. J. Kamlet and L. A. Kaplan, *J. Org. Chem.*, 1957, **22**, 576, J. S. Splitter and M. Calvin, *ibid.*, 1958, **23**, 651.
[51] O. L. Brady and F. P. Dunn, *J.*, 1926, 2411.
[52] F. Kröhnke, *Annalen*, 1957, **604**, 203.
[53] L. Chardonnes and P. Heinrich, *Helv. Chim. Acta*, 1944, **27**, 321.

When X = H, the reaction is merely a hydration of the nitrone group to a nitrone hydrate (62, X = H) which dehydrates to the imidol form of the amide. The existence of such nitrone hydrates has been demonstrated by Kröhnke.[54]

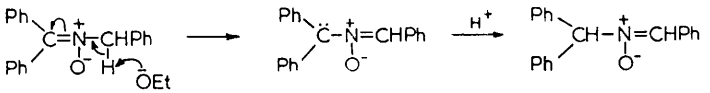
This mechanism cannot however, explain the rearrangements of *C*-benzoyl-*N*-arylnitrones (63) to the formanilides (65) which occur, with migration, under basic conditions. For these rearrangements Kröhnke[52] proposed the following mechanism, which assumes both nitrone hydrates and oxaziridines as intermediates.



(63) (65) (64)

The conversion by heat of an oxaziridine such as (64) into an amide makes this mechanism plausible,[55] but step [(64) to (65)] is probably better represented by the mechanism below.

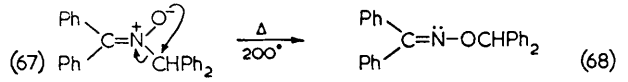
(*iii*) *Ketonitrones to aldonitrones.* Under certain conditions, base-catalysed prototropic shift may occur between the *N*- and *C*-substituents; the net result is the conversion of a ketonitrone into an aldonitrone. The reaction can be explained by the following mechanism.



(66)

(*iv*) *Oxime-O-ether formation.* Heat converts some nitrones into oxime *O*-ethers, but the reaction is not general. Thus whilst the nitrone (66) remained unchanged after prolonged heating at 200°, the nitrone (67) was quantitatively rearranged to the *O*-ether (68) in 1/2 hr. A similar rearrangement can be effected by acid treatment.[56] The following mechanism was suggested.[57]

[54] F. Kröhnke and E. Börner, *Ber.*, 1936, **69**, 2006.
[55] A. Padwa, *Tetrahedron Letters*, 1964, 2001.
[56] M. Martynoff, *Ann. Chim.* (*France*), 1937, **7**, 424.
[57] A. C. Cope and A. C. Haven, jun., *J. Amer. Chem. Soc.*, 1950, **72**, 4897.

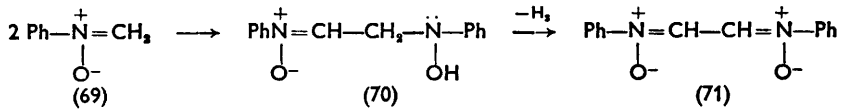


(67) (68)

The above rearrangement may precede acid-catalysed hydrolysis of those nitrones in which the hydroxylamine salt and not the *N*-substituted hydoxylamine salt is produced.

E. Dinitrones

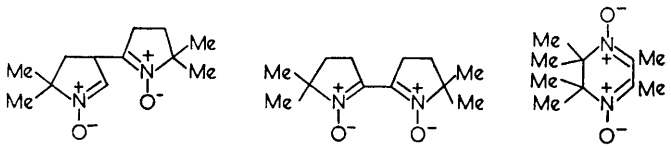
A number of dinitrones have been prepared, usually by oxidation of *NN'*-dihydroxy-compounds, or of *N'*-hydroxynitrones. The dinitrone (71) was considered to be formed by spontaneous dimerisation of the unstable nitrone (69). The dimer (70) must have undergone oxidation during the isolation.[37a]



(69) (70) (71)

Catalytic oxidation of the dimers (38) and (39) gave the dinitrones (72) and (73) respectively.[32]

The properties of these two nitrones were found to be similar to those of the mononitrones, and nitrone (73) gave the normal reaction with phenylmagnesium bromide, adding two moles of the Grignard reagent per mole of dinitrone.



(72) (73) (74)

The nitrone (72) gave two strong absorption bands in the infrared, one at 1570 cm.$^{-1}$, due to a 2-unsubstituted nitrone group and one at 1603 cm.$^{-1}$ due to a 2-substituted nitrone group. In nitrone (73) a pronounced bathochromic shift, due to conjugation of the nitrone systems was observed and absorptions were at 1509 and 1503 cm.$^{-1}$. Similarly, the ultraviolet absorptions at 237 mμ (ϵ16,500) for nitrone (72) and 331 mμ (ϵ18,500) or nitrone (73) showed a bathochromic shift due to the conjugation of the two nitrone systems.[32]

Only one preparation of a monocyclic dinitrone has been reported[58], but later work has shown that the compound produced was not a nitrone[59]. Recently the monocyclic dinitrone (74) was prepared[59] and also showed

[58] J. K. Landquist, *J.*, 1956, 1885.
[59] M. Lamchen and T. Mittag, unpublished results.

the bathochromic shift in both infrared and ultraviolet absorptions, these being at 1545 cm.$^{-1}$ and 347 mμ (ϵ12,300) respectively. This dinitrone, however, did not give the normal nitrone reactions, probably due to the conjugation.

F. Importance and Uses of Nitrones

The peculiar properties and reactivity of the nitrone group has enabled many chemists to make use of these compounds in syntheses. The easy hydrolysis of nitrones to carbonyl compounds has made this an important method for the synthesis of aldehydes and ketones, especially the sensitive or otherwise not easily accessible compounds. This method has been used for aliphatic, aromatic, alicyclic, and heterocyclic compounds, and has been shown to be applicable to saturated as well as unsaturated, mono- as well as di-carbonyl compounds, with or without other functions such as the amino- or carboxyl functions, etc. The nitrones required are usually obtained from the nitroso-compounds by the Kröhnke reaction (p. 335).

The great reactivity of the nitrone group, and the easy removal of the oxygen atom make the nitrones excellent starting materials for a variety of products. Thus Lord Todd and co-workers made use of the reactive nature of the 1-pyrroline 1-oxides to link pyrrole rings together, both directly and through a methylene group,[32] in their attempted synthesis of corrins. A number of new pyrrolines and pyrrolidines were synthesised in this work.[13,32,36,45,47]

The 1,3-cycloadditions also opened up new routes to *N*-bridged heterocyclic compounds and a number of new isoxazolidines have already been prepared by this route.

Through these preparative methods the nitrones have become useful intermediates in many fields of chemistry and with the recent rapid expansion in nitrone research, their usefulness will undoubtedly increase in the near future.

One of us (M.L.) is grateful to his reseach students and colleagues with whom he has had valuable discussion on many aspects of nitrones.