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Less Familiar Reactions of Oximes

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I. Introduction

Certain reactions of oximes are well known and have been textbook material for years. Among these are hydrolysis to ketones, reduction to amines or hydroxylamines, oxidation to nitro compounds, and the Beckmann and Neber rearrangements. In addition aldoximes undergo some special reactions such as dehydration to nitriles.

In this review we shall concentrate on some less well-known but nevertheless rather general reactions of oximes which have considerable synthetic significance. The reactions discussed are nitrosation, amination to produce diazo compounds, aziridine formation, and a variety of oxidative processes which lead to compounds other than nitro compounds. The effort here has not been to provide exhaustive tabular coverage of all the reactions but to lead the reader to the significant publications in the field. The scope and limitation of each reaction will be indicated.

Many other scattered but less general reactions could have been included but were not. For more extensive coverage the reader is encouraged to examine the several source books cited throughout this review.

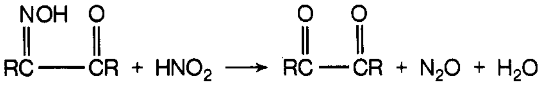
II. Nitrosation Reactions

Oximes react with nitrosating agents in a rather wide variety of ways which depend upon the structure of the oxime, the nature of the nitrosating agent, and the reaction conditions. Some of these reactions have been of considerable synthetic importance for many years. Oximes contain three potentially reactive sites, but in their reactions with nitrosating agents (in which attack presumably is by either the nitrosyl cation, NO^+, or its progenitors, or by the nitrogen dioxide radical, NO_2) attack occurs predominantly at carbon or nitrogen. No oxime nitrites, $R_2C{=}NONO$, have been characterized although this structure has been considered in the literature. The possibility that such species may be intermediates will be considered.

A. N-Nitrosation

1. Deoximation

In 1889 Claisen and Manasse reported that α-oximino ketones were converted to α-diketones by nitrous acid.[1] Since that time this reaction has been used on many occasions for the conversion of oximes to ketones.[2]



$$\mathrm{R}\overset{\mathrm{NOH}}{\overset{\|}{\mathrm{C}}}-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{R} + \mathrm{HNO_2} \longrightarrow \mathrm{R}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{R} + \mathrm{N_2O} + \mathrm{H_2O}$$

Recently, with the advent of the Barton nitrite photolysis reaction[3] and its utility in forming oximes directly from hydrocarbons, the importance of deoximation reactions has increased.

The mechanism of this reaction is of interest because of its relationship to that of reactions to be discussed in more detail.[4] Most investigators have suggested N-nitrosation as the first step, but the subsequent events are still obscure. Thus intermediate **1** could rearrange intra-

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(1) L. Claisen and O. Manasse, *Ber.*, **22**, 530 (1889).

(2) D. T. Manning and H. A. Stansbury, *J. Amer. Chem. Soc.*, **81**, 4885 (1959); C. Djerassi, "Steroid Reactions," Holden-Day, San Francisco, Calif., 1963, pp 61, 343, 345.

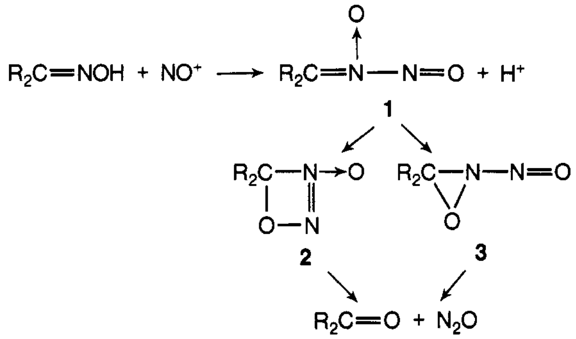
(3) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechel, *J. Amer. Chem. Soc.*, **83**, 4076, 4083 (1961).

(4) The stoichiometry of the reaction is not well defined. There have been occasional reports of nitrogen rather than nitrous oxide as the gaseous product,[2] and in some cases mixtures of the two gases.[5] The main attention here is devoted to the N_2O-forming reaction, but others have suggested mechanisms for both processes.[2,6]

(5) G. Kainz and H. Huber, *Mikrochim. Acta*, **3**, 337 (1959).

(6) J. M. Kliegman and R. K. Barnes, *J. Org. Chem.*, **37**, 4223 (1972).

molecularly either through formation of a four-membered ring **2** or a three-membered ring **3**. [The former process is analogous to that proposed for the intramolecular decomposition of nitrosimines to ketones and nitrogen.[7] The latter would be analogous to the isomerization of nitrones to oxaziridines, a known photochemical process,[8] followed by a cleavage observed in the conversion of ethylenimines to olefins and nitrous oxide.[9]]



Alternatively, it has been suggested that intermediate **1** rearranges to a nitrimine **4** which undergoes subsequent hydrolysis.

$$\mathbf{1} \longrightarrow \underset{\mathbf{4}}{R_2C{=}NNO_2} \xrightarrow{H_2O} R_2C{=}O + [NH_2NO_2] \longrightarrow N_2O + H_2O$$

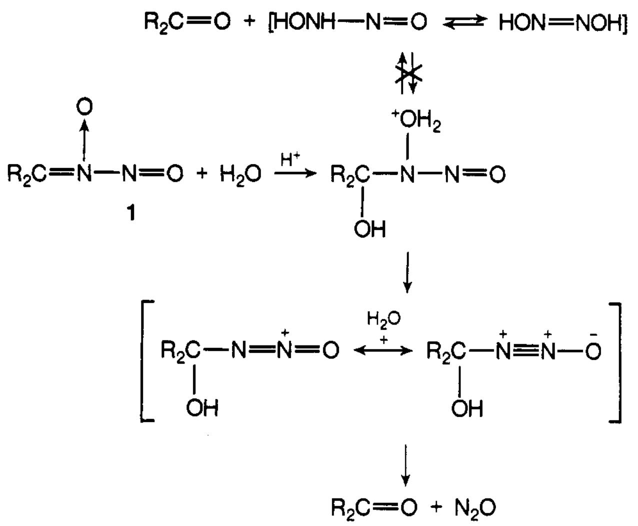
Wieland and Grimm attempted to settle the question by tagging the nitroso oxygen with O^{18} and determining that approximately 90% of the label appeared in the nitrous oxide.[10] This experiment rules out intermediates **2** (0% O^{18} in N_2O) and **4** (50% O^{18} in N_2O), and as a result these authors claimed that **3** must be involved.

However, there are two observations that are not consistent with this proposal. Firstly, as will be developed below, many oximes, particularly those in which the oxime double bond is sterically protected, do not undergo deoximation under these conditions but rather are converted to nitrimines **4**. It is not clear how the bulky group would favor oxygen migration over ring closure. On the basis of the Thorpe-Ingold effect,[11] one might have anticipated such oximes to deoximate even more easily if small ring formation were a critical step.

Secondly, it is known that semicarbazones are converted to ketones with nitrous acid.[12] Since there is no oxygen atom in these derivatives similar to that necessary to form an intermediate such as **3**, there must exist another route to obtain the ketone from an *N*-nitroso intermediate.

We would like to suggest that a mechanism which involves hydrolysis of intermediate **1** can accommodate all the known facts. The crucial point is to avoid any intermediate in which the N-oxygen atoms lose their identity. The reactions might occur as shown in Scheme I. The important step here is the facile loss of the hydroxyl group followed by nitrous oxide from the nitrosohydroxylamine intermediate rather than loss of nitrosohydroxylamine in which the oxygen would be scrambled.[13] The former process finds precedent in the rapid decomposition of *O*-acylhydroxylamines upon nitrosation,[14] a reaction which is thought to involve ionization of the acyloxy group.

SCHEME I



Some analogous reactions (C=N → C=O) have been reported. The semicarbazone cleavage[12] has been cited. Some anils are converted to carbonyl compounds and diazonium salts.[15] Other reagents, such as perchloryl fluoride,[16] lead tetraacetate,[17] and chromous acetate[18] have been used to convert oximes to ketones. It is probable that these reactions proceed by way of *O*-acyl oxime intermediates that rearrange to carbon-oxygen intermediates (see section V).

$$R_2C{=}N{-}Ar + NO^+ \longrightarrow R_2C{=}O + ArN_2^+$$

2. *Formation of Nitrimines (Pernitroso Compounds)*

A number of oximes, particularly in the terpene series, react with nitrosating agents to produce nitrimines **4** (*N*-nitroimines), formerly called pernitroso compounds.[19] All of these oximes are characterized by the presence of a quaternary carbon adjacent to the oxime function. Nitrimines can also be prepared by the action of nitrosyl fluoride on steroid 4- and 5-enes.[20] In this reaction the intermediate olefin adduct, the fluoronitroso compound, tautomerizes to the fluoro oxime which is further nitrosated to yield the fluoronitrimine. In these compounds one of the positions on the adjacent quaternary carbon is occupied by a fluorine atom.

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(7) C. J. Thomas and I. M. Hunsberger, *J. Org. Chem.*, **33**, 2852 (1968).

(8) J. Splitter and M. Calvin, *J. Org. Chem.*, **23**, 651 (1958).

(9) C. L. Bumgardner, K. S. McCallum, and J. P. Freeman, *J. Amer. Chem. Soc.*, **83**, 4417 (1961).

(10) T. Wieland and D. Grimm, *Chem. Ber.*, **96**, 275 (1963).

(11) G. S. Hammond in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 468.

(12) St. Goldschmidt and D. L. C. Veer, *Recl. Trav. Chim. Pays-Bas*, **65**, 796 (1940); **66**, 238 (1947); M. L. Wolfrom, *ibid.*, **66**, 238 (1947).

(13) A very similar mechanism based upon ^{15}N tracer studies has recently been proposed.[6] That work actually bears more on the origin of nitrogen and nitric oxide from some deoximation reactions since all mechanisms proposed show one nitrogen in the nitrous oxide coming from oxime and one from nitrous acid.

(14) J. P. Freeman and L. D. Lillwitz, *J. Org. Chem.*, **35**, 3107 (1970).

(15) (a) J. Turcan, *Bull. Soc. Chim. Fr.*, [5] **2**, 627 (1935); (b) M. P. Doyle, W. Wierenga, and M. A. Zaleta, *J. Org. Chem.*, **37**, 1597 (1972).

(16) J. P. Freeman, *J. Amer. Chem. Soc.*, **82**, 3869 (1960).

(17) Y. Yukawa, M. Sakai, and S. Suzuki, *Bull. Chem. Soc. Jap.*, **39**, 2266 (1966).

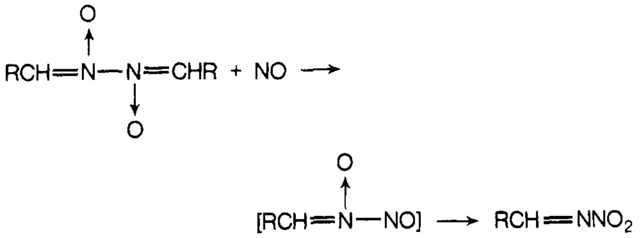
(18) E. J. Corey and J. E. Richman, *J. Amer. Chem. Soc.*, **92**, 5276 (1970).

(19) J. P. Freeman, *J. Org. Chem.*, **26**, 4190 (1961).

(20) G. A. Boswell, Jr., *J. Org. Chem.*, **33**, 3699 (1968).

There is at least one report of an α-ketonitrimine prepared by the action of a nitrite ester on a ketone in the presence of excess base, a reaction in which the derived α-oximino ketone undergoes further nitrosation.[21]

A somewhat different but possibly related route to nitrimines is from the reaction of azine bis(oxides) with nitric oxide.[22] While this appears at first glance to be a free-radical reaction, little is known about the mechanism. Presumably an *N*-nitrosonitrone is the first-formed intermediate.



$$RCH{=}\overset{O\uparrow}{N}{-}\underset{\downarrow O}{N}{=}CHR + NO \longrightarrow [RCH{=}\overset{O\uparrow}{N}{-}NO] \longrightarrow RCH{=}NNO_2$$

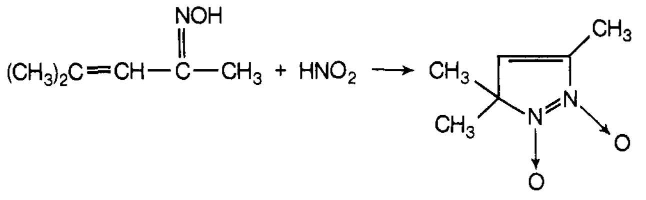
The structure of these compounds was a matter of some controversy for many years but appears finally to have been settled as involving a nitrimino group.[19] This assignment is based upon their spectral properties and facile reduction to nitramines. The hydrolysis of these compounds to ketones and nitrous oxide, a known decomposition product of nitramide, is also consistent with this formulation as is the formation of furfural nitrimine from the reaction of furfural with nitramide.[23]

What is the relationship between deoximation and nitrimine formation? It seems reasonable to assume that the first step in both reactions is formation of a nitrogen-nitrogen bond by nitrosation of the oxime nitrogen. The fact that the oximes that are converted to nitrimines contain a quaternary carbon adjacent to the C-N double bond suggests that attack of water at that bond is hindered in those compounds, allowing the nitrosonitrone function to survive and ultimately to rearrange (possibly by intramolecular disproportionation[19]) to the nitrimine, which can in turn be hydrolyzed under more forcing conditions. A particularly striking example of the effect of steric hindrance on nitrimine stability has been reported by Barton.[24] However, easily hydrolyzed nitrimines have been isolated when nonhydrolytic reactions or conditions were employed.[20,22]

3. *Formation of Heterocycles*

α,β-Unsaturated oximes are converted to a series of novel heterocycles upon treatment with nitrosating agents. These compounds were discovered when it was recognized that the nitrosation of mesityl oxide oxime did not yield the ordinary nitrimine[25] nor an *N*-nitrosonitrone as subsequently proposed[26] but rather a pyrazolenine dioxide derivative, **5**.[27]

Examination of the literature indicated that other α,β-unsaturated oximes had yielded nitrosation products of uncertain structure. It has now been established that all of these are related to the mesityl oxide product **5** with further elaboration of individual molecules dependent upon structure. The results may be summarized as shown in Scheme II.



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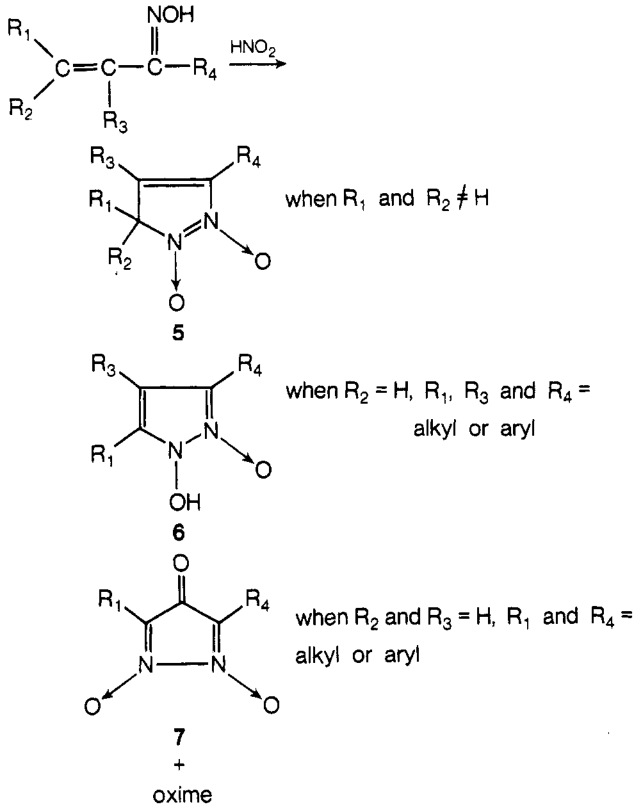
SCHEME II



5 when R_1 and $R_2 \neq H$

6 when $R_2 = H$, R_1, R_3 and R_4 = alkyl or aryl

7 + oxime when R_2 and $R_3 = H$, R_1 and R_4 = alkyl or aryl

Compounds of type **6**, *N*-hydroxypyrazole *N'*-oxides, are tautomers of the mesityl oxide type product, **5**. These unique compounds are relatively strong organic acids, form complexes with metal ions, and undergo electrophilic substitution reactions at the 4 position of the pyrazole ring.[28]

The reactivity of the 4 position may explain the formation of the 3,4-diazacyclopentadienone derivatives, **7**. That is, when R_3 = H, further nitrosation there to produce the oxime or oxidation to form the ketone may occur.[29] A scheme which rationalized the formation of compounds **5**, **6** and **7** has been proposed (Scheme III).

A compound of structure **8** has never been isolated from these reactions. In an effort to obtain such a compound the nitrosation of benzalacetophenone oxime was carried out using isoamyl nitrite in a neutral medium.[30] From this reaction a white solid with properties similar to those of the *N*-hydroxy *N'*-oxides was isolated in 50% yield. However, the structure of this compound was shown not to be **8**, but rather a dimeric structure **9**. (The mass spectrum of compound **9** showed several high

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(21) T. Matsumoto and S. Yasuda, *Tetrahedron Lett.*, 5311 (1968).

(22) L. Horner, L. Hockenberger, and W. Kirmse, *Chem. Ber.*, **94**, 290 (1961).

(23) J. W. Suggett, G. S. Myers, and G. F. Wright, *J. Org. Chem.*, **12**, 373 (1947).

(24) D. H. R. Barton, P. G. Sammes, and M. Silva, *Tetrahedron, Suppl.*, 57 (1966).

(25) R. Scholl, *Ber.*, **21**, 506 (1888).

(26) R. Fusco and G. Trisoglio, *Atti Accad. Lincei, Rend., Cl. Sci. Fis., Mat. Natur.*, [7] **2**, 618, 751 (1941).

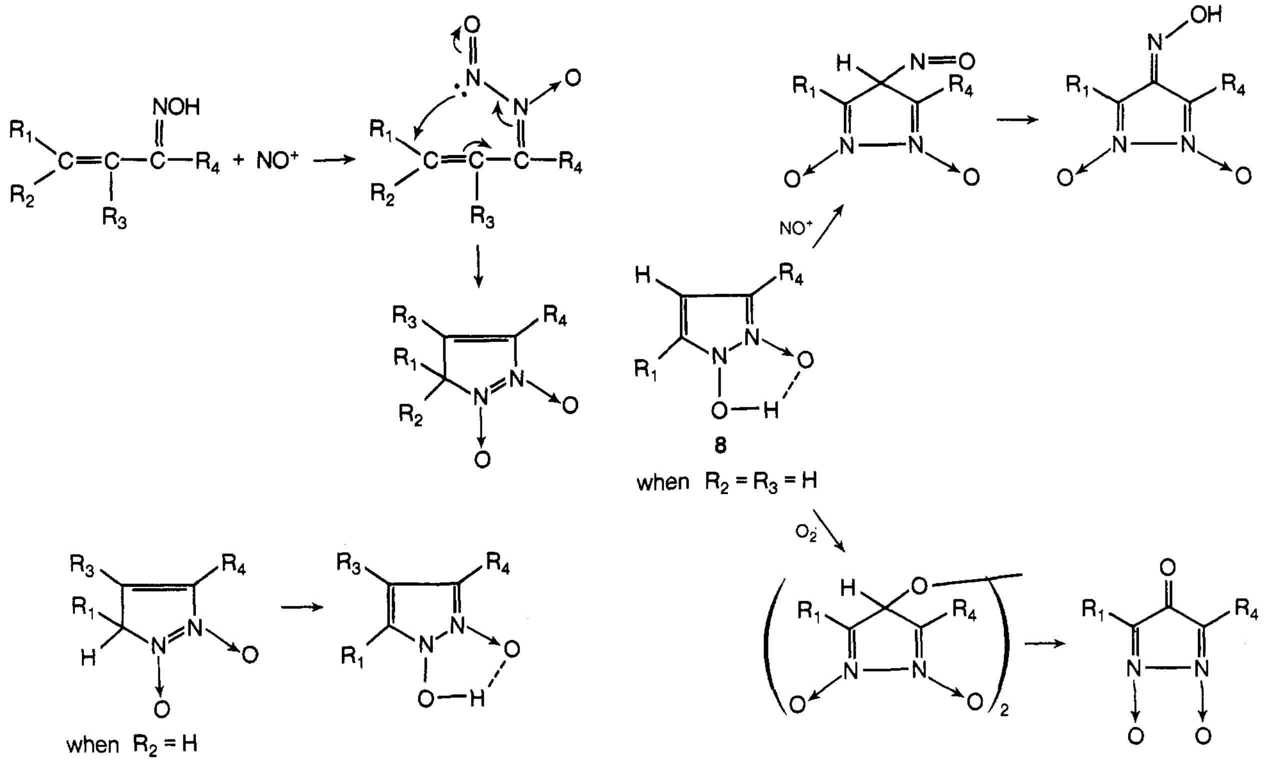
(27) J. P. Freeman, *J. Org. Chem.*, **27**, 1369 (1962).

(28) J. P. Freeman and J. J. Gannon, *J. Org. Chem.*, **34**, 194 (1969).

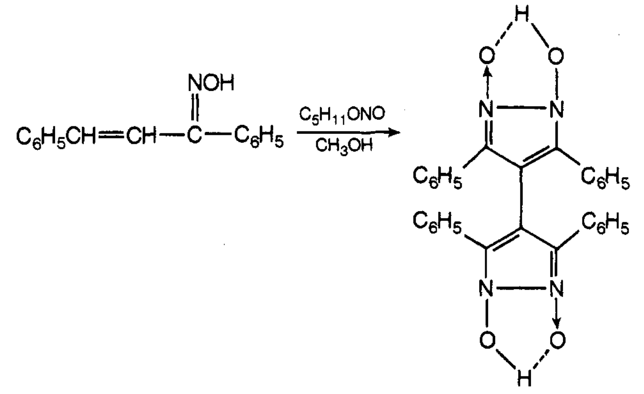
(29) J. P. Freeman, D. L. Surbey, and J. J. Gannon, *J. Org. Chem.*, **34**, 187 (1969).

(30) J. P. Freeman and J. F. Hansen, *J. Chem. Soc., Chem. Commun.*, 961 (1972).

SCHEME III



mass fragments including a molecular ion of very low abundance at *m/e* 502.) Compound **9** was readily oxidized by a variety of oxidizing agents but most conveniently with iodine to a shiny reddish solid, assigned structure **10**. Compound **10** cannot be a planar molecule, however, because of the interference of the four "ortho" phenyl groups. Some preliminary esr experiments suggest possible biradical character for this compound, but details about its structure await further investigation.



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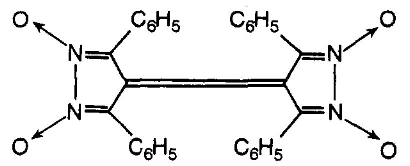

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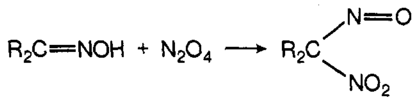
B. C-Nitrosation

1. Pseudonitrole Formation

Many aliphatic ketoximes upon treatment with dinitrogen tetroxide (N_2O_4) in ether form *gem*-nitronitroso compounds, commonly called pseudonitroles, **11**. The early literature on this reaction has been reviewed.[31] This reaction is not of much synthetic utility, but its mechanism may be of some interest because the reaction seems related to those involving halogenation and acetoxylation of oximes[32] (see section V.B).



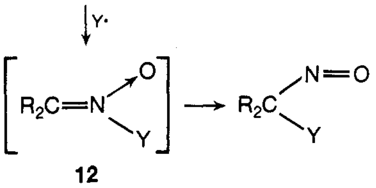
$$R_2C{=}NOH + N_2O_4 \longrightarrow R_2C(N{=}O)(NO_2)$$

11

A number of mechanisms have been postulated for these reactions, but a most reasonable one[33] involves a one-electron transfer from the oxime to an electrophilic radical, coupling of the iminoxy radical[34] with any available radical, and finally rearrangement to the observed product (Scheme IV). Some support for this scheme is found in the fact that acetylation of nitronate anions leads to ketones by way of α-acetoxynitroso compounds,[32] indicating that an intermediate like **12** does in fact rear-

SCHEME IV

$$R_2C{=}NOH + X\cdot \longrightarrow R_2C{=}N\dot{-}O + X^- + H^+$$



12

X = Cl, Br, NO_2, CH_3CO_2

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(31) J. L. Riebsomer, *Chem. Rev.*, **36**, 157 (1945).

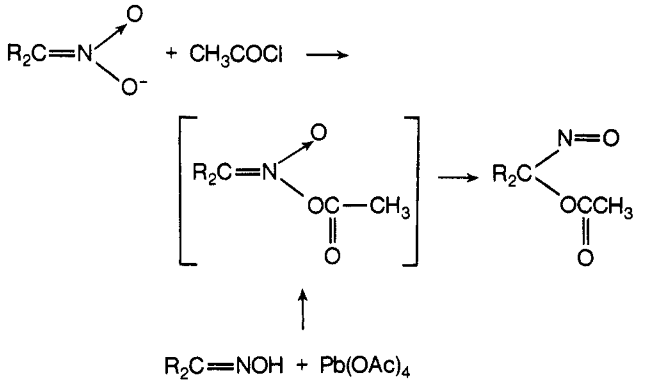
(32) J. H. Boyer in "The Chemistry of the Nitro and Nitroso Group" H. Feuer, Ed., Interscience, New York, N. Y., 1969, p 235.

(33) M. M. Frojmovic and G. Just, *Can. J. Chem.*, **46**, 3719 (1968).

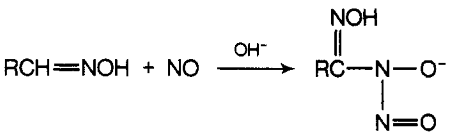
(34) B. C. Gilbert and R. O. C. Norman, *J. Chem. Soc. B*, 86 (1966). It is important to note that iminoxy radicals are of the σ type and that reso-

range to a nitroso compound (Scheme V). This mechanism suggests a common intermediate for the nitrosation of nitronate ions and the reaction of oximes with N_2O_4, reactions which both lead to α-nitronitroso compounds.

SCHEME V



It also suggests that radicals which are not readily reduced to stable anions will not react in the same way. In fact, nitric oxide reacts with oximes like an acylating agent to produce eventually nitrosohydroxylamine derivatives.[35]



$$RCH{=}NOH + NO \xrightarrow{OH^-} RC({=}NOH){-}N(N{=}O){-}O^-$$

However, when an iminoxy radical is generated in the presence of nitric oxide, coupling occurs at nitrogen as illustrated above to yield finally nitrimines.[36]

2. Dinitroalkane Formation

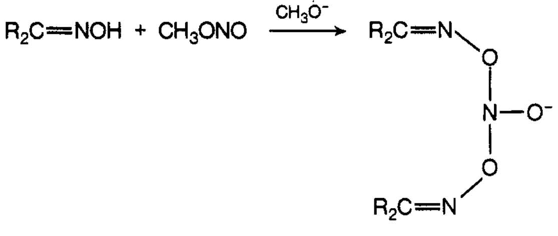
In some cases *gem*-dinitroalkanes are obtained instead of pseudonitroles.[37] It is highly likely that these compounds are derived by oxidation of the first-formed pseudonitrole although other paths have been suggested.[33] Although this reaction is of limited scope, it provides one of the few routes to *gem*-dinitroalkanes.

The contrast between nitrosation of an oxime with aqueous nitrous acid or a nitrite ester and that with N_2O_4 in inert solvents (ether, chloroform) is indicated by the results reported for benzalacetone oxime.[29] Only the heterocyclic derivatives of type **7** were obtained from aqueous nitrous acid while di- and trinitro compounds were obtained when N_2O_4 in ether was used.

C. O-Nitrosation

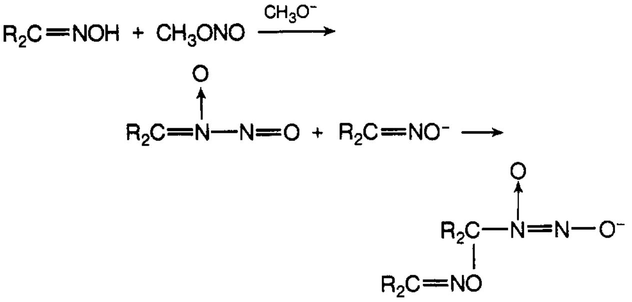
It might have been anticipated that nitrosation would occur easily on oxygen to produce oxime nitrites, but so far no such compounds have been characterized. They had been suggested as the structure for pernitroso compounds, but this has been subsequently excluded. It is possible, based upon the known hydrolytic reactivity of nitrite esters, that they form rapidly but are destroyed under the hydrolytic conditions generally employed.

Recently Förster, *et al.*,[38] proposed that treatment of ketoximes with methyl nitrite in the presence of methoxide ion produced a novel O-nitrosation product, **13**. The



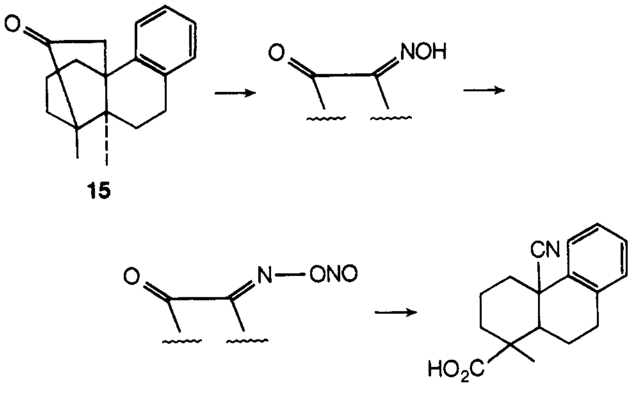
13

structure of this product was certainly not established unequivocally, and an alternative structure more analogous to that from other reactions of this type would be **14**, formed possibly as shown below. The products of hydrolysis of this compound, ketone, oxime, and nitrous oxide, are in fact better rationalized in terms of structure **14** than they are with the Förster structure **13**.



14

Since acylating agents generally cause Beckmann rearrangements, it might have been anticipated that products of this reaction would be encountered in oxime nitrosations. There is, however, only one suggestion in the literature of such a reaction.[21] In the base-catalyzed nitrosation of ketone **15**, a small amount of the nitrile acid **16** was obtained when a large excess of base was used (see below). It was postulated that this reaction is an example of a base-catalyzed Beckmann fragmentation involving the oxime nitrite ester.



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D. Summary

Oximes are either deoximated, converted to nitrimines, or oxidized by nitrosating agents. Their ultimate fate depends upon their structure. α,β-Unsaturated oximes produce novel heterocycles of the pyrazole oxide family.

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nance structures involving radical character at carbon[6] are invalid representations. Whether, in fact, α-nitrosoalkyl radicals exist and are intermediates in chemical reactions has neither been established nor ruled out as yet.

(35) M. J. Danzig, R. F. Martel, and S. R. Riccitello, *J. Org. Chem.*, **26**, 3327 (1961).

(36) O. L. Chapman and D. C. Heckert, *Chem. Commun.*, 242 (1966).

(37) (a) P. A. S. Smith, "Open Chain Nitrogen Compounds," Vol. 2, W. A. Benjamin, New York, N. Y., 1966, p 57; (b) for some recent work in this field, see L. I. Khmel'nitskii, S. S. Novikov, and O. V. Lebedev, *Izv. Akad. Nauk SSSR, Otd., Khim. Nauk*, 477 (1961); *Chem. Abstr.*, **55**, 23389e (1961).

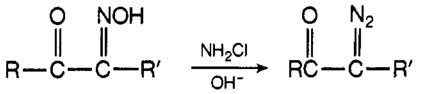
(38) Ch. Förster, W. Kiessling, M. Lubing, W. Pritzkow, and P. Radloff, *J. Prakt. Chem.*, **311**, 370 (1969).

TABLE I. Conversion of Oximes to Diazo Compounds

Oxime	Diazo compd	Yield, %	Ref
Formaldoxime	Diazomethane	70–75	42
Benzaldoxime	Phenyldiazomethane		41
Fluorenone oxime	9-Diazofluorene		41
3-Oximinocamphor	3-Diazocamphor	70	39
Benzil monoxime	Azibenzil		39
2-Oximino-1-tetralone	2-Diazo-1-tetralone	57	43
α-Oximinoisofenchone	α-Diazoisofenchone		44
α-Oximinonopinone	α-Diazonopinone	85	45
2-Oximino-3,3-diphenylindanone	2-Diazo-3,3-diphenylindanone	65	46

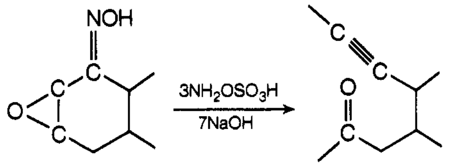
III. Forster Reaction

The conversion of oximes to diazoalkanes by the action of aminating agents such as chloramine or hydroxylamine-O-sulfonic acid in alkaline solution is known as the Forster reaction.[39] First discovered in 1915, it has received renewed attention in recent years because of an interest in the chemistry of diazo ketones.[40] While it is for the synthesis of α-diazo ketones that this reaction has been most extensively used, it is clearly not limited to α-oximino ketones as starting materials. Aryldiazoalkanes[41] and diazomethane[42] itself have been prepared by this reaction (Table I[39,41-46]).



$$R-\overset{O}{\overset{\|}{C}}-\overset{NOH}{\overset{\|}{C}}-R' \xrightarrow[OH^-]{NH_2Cl} R\overset{O}{\overset{\|}{C}}-\overset{N_2}{\overset{\|}{C}}-R'$$

A novel application of this reaction to α,β-epoxy ketoximes provides a route to alkynones.[47]



This route represents one of several ways to convert α,β-epoxy ketones to acetylenic ketones.[48]

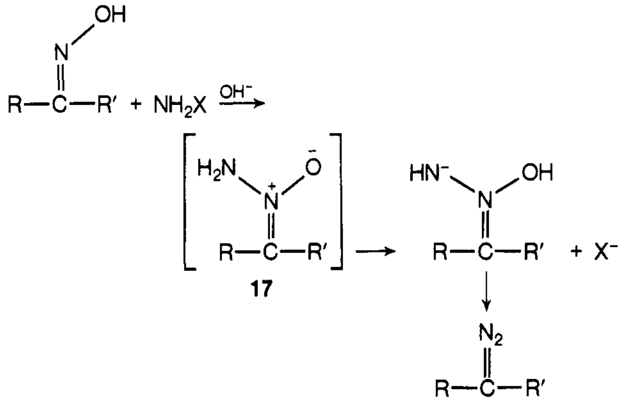
The Forster reaction appears to be mechanistically related to oxime nitrosation; at least, the mechanistic proposals find their counterparts in the two reactions. Scheme VI has been suggested for the Forster reaction.[41] This mechanistic thinking suggested to Meinwald, *et al.*,[41] that the Forster reaction ought to be a general reaction of oximes rather than a special reaction of α-oximino ketones. That this reaction has had limited application to simple aliphatic oximes may be related to the analogous inability to prepare simple nitrimines by the nitrosation of aliphatic oximes: hydrolysis of intermediate 17 may destroy it before processes leading to diazo formation can occur. (Note the formal similarity between intermediate 17, nitrosonitrone 1, and the protonated oxime, the intermediate in acid-catalyzed hydrolysis of oximes.) This suggestion is completely speculative, however, since ketonic by-products have not been explicitly reported, but it might encourage investigators to try mild conditions and nonprotonic media when applying this reaction to easily hydrolyzed carbonyl compounds.

TABLE II. Aziridines from Oximes and Grignard Reagents

Oximes[a]	Grignard reagent	Aziridine	Yield, %	Ref
Hydratropaldehyde	Methyl	*cis*-2,3-Dimethyl-2-phenyl	20	55
Acetophenone	Ethyl	2-Phenyl-2-ethyl	37	50c
Acetophenone	*n*-Propyl	2-Phenyl-2-propyl	23–35	50c
Propiophenone	Methyl	*trans*-2,3-Dimethyl-2-phenyl	41	55
Propiophenone	Methyl	2,2-Diphenyl-3-methyl	43	50b
Propiophenone	Ethyl	2-Phenyl-2-ethyl-3-methyl	50	50c
Desoxybenzoin	Methyl	*cis*-2,3-Diphenyl-2-methyl	49	55
2-Phenylpropiophenone	Methyl	*cis,cis*-2,3-Diphenyl-2,3-dimethyl	23	55
Phenylacetone (*anti*-benzyl)	Phenyl	2-Phenyl-2-benzyl	22	55

[a] In most instances mixtures of syn and anti isomers were employed.

SCHEME VI



IV. Synthesis of Aziridines

A. Oximes and Grignard Reagents

Some years ago Hoch[49] in France and Campbell[50] in the United States reported that many ketoximes yielded aziridines in low to moderate yields when treated with Grignard reagents (see Table II). This reaction bears close resemblance to the Neber rearrangement,[51] and its interpretation is related to that of the Neber reaction. In strictly formal terms this may be represented as shown in Scheme VII. (The aziridine often undergoes ring opening upon hydrolysis to produce amino alcohols also.[50a])

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(39) M. O. Förster, *J. Chem. Soc.*, **107**, 260 (1915).

(40) B. Eistert, M. Regitz, G. Heck, and H. Schwall in "Methoden der Organischen Chemie," Vol. 10, No. 4, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, 1968, p 582.

(41) J. Meinwald, P. G. Gassman, and E. G. Miller, *J. Amer. Chem. Soc.*, **81**, 4751 (1959).

(42) W. Rundel, *Angew. Chem.*, **74**, 469 (1962).

(43) L. Horner, W. Kirmse, and K. Muth, *Chem. Ber.*, **91**, 430 (1958).

(44) P. Yates and S. Danishefsky, *J. Amer. Chem. Soc.*, **84**, 879 (1962).

(45) J. Meinwald and P. G. Gassman, *J. Amer. Chem. Soc.*, **82**, 2857 (1960).

(46) M. P. Cava, R. L. Litle, and D. B. Napier, *J. Amer. Chem. Soc.*, **80**, 2257 (1958).

(47) P. Wieland, H. Kaufmann, and A. Eschenmoser, *Helv. Chim. Acta*, **50**, 2108 (1967).

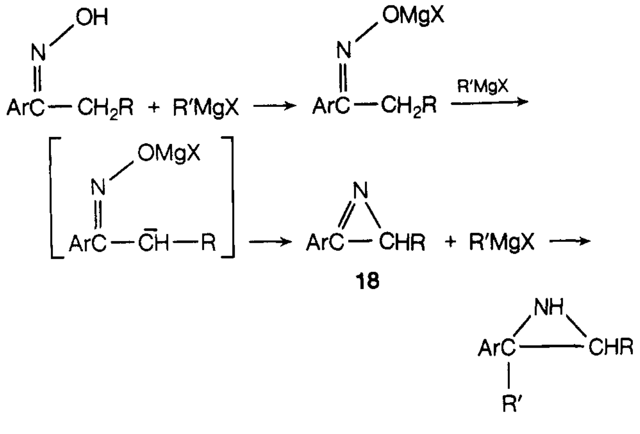
(48) D. Felix, R. K. Müller, U. Horn, R. Joos, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **55**, 1276 (1972).

(49) J. Hoch, *C. R. Acad. Sci.*, **198**, 1865 (1934).

(50) (a) K. N. Campbell and J. F. McKenna, *J. Org. Chem.*, **4**, 198 (1939); (b) K. N. Campbell, B. K. Campbell, J. F. McKenna, and E. P. Chaput, *ibid.*, **8**, 103 (1943); (c) K. N. Campbell, B. K. Campbell, L. G. Hess, and D. J. Schaffner, *ibid.*, **9**, 184 (1944).

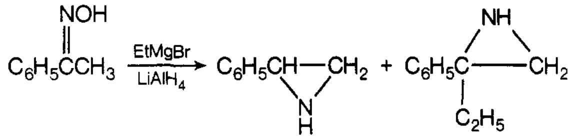
(51) For a review, see C. O'Brien, *Chem. Rev.*, **64**, 81 (1964).

SCHEME VII



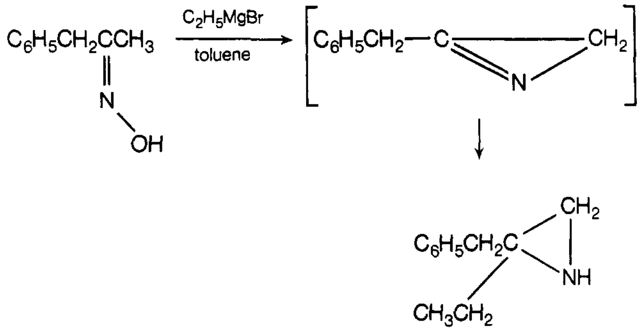
Three features of this reaction have received attention in recent years: (1) the establishment of azirines (**18**) as true intermediates; (2) the effect of oxime stereochemistry on direction of azirine formation; and (3) the stereochemistry of the Grignard addition to the azirine. There has been some speculation about the details of azirine formation along the same lines as have been followed in discussions of the Neber rearrangement. As we shall see, there are some significant differences in the details of the two reactions, but these may be due to differences in reaction conditions rather than to fundamental differences in mechanism.

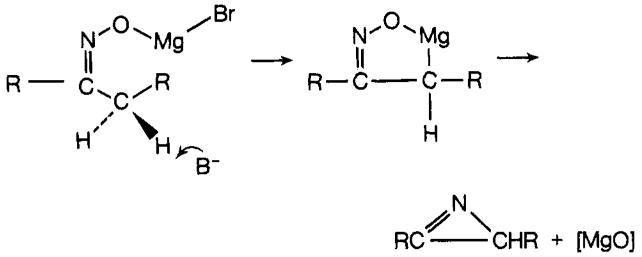
The nature of the intermediates in this reaction, a matter of speculation for many years, was revived principally by renewed interest in the Neber reaction and the proposal of an azirine intermediate in that reaction. In 1963 Eguchi and Ishii[52] found strong suggestive evidence for an azirine intermediate when they found styrenimine among the products of the reaction of acetophenone oxime with a mixture of ethylmagnesium bromide and lithium aluminum hydride in toluene. Since these workers found no imine from the reaction of this oxime with LiAlH$_4$ alone in the same solvent, they reasoned that the oxime was first converted to the azirine by reaction with the Grignard reagent and that the azirine was in turn reduced by the hydride. Interestingly enough, treatment of acetophenone oxime with LiAlH$_4$ in ether yields a mixture of α-phenethylamine (expected product) and *N*-ethylaniline (reduced Beckmann rearrangement product),[53] while later, Kitahonoki and his coworkers[54] showed that, when the reduction was carried out with an excess of LiAlH$_4$ in boiling tetrahydrofuran, styrenimine was indeed formed. Since these reactions seem to be very sensitive to the nature of the medium,[55] one must view the absolute significance of the Eguchi-Ishii experiment cautiously, but it still seems reasonable to believe that azirines are in fact true intermediates and probably that their formation is rate-determining in these reactions.



That azirines are intermediates in both this reaction and the Neber reaction does not establish whether the formation of this intermediate comes about in the same way in the two reactions. Alvernhe and Laurent[55] have shown that azirine formation is stereospecific *in toluene solution, ring formation occurring with the group syn to the oxime hydroxyl group* (Scheme VIII). However, the solvent is critical since substitution of tetrahydrofuran led to a mixture of the two possible products. These authors do not attempt to rationalize this strong stereochemical preference which would appear to involve an unusual front-side displacement. One possible mechanism involves the electrophilic assistance of the magnesium atom in the proton abstraction from the methylene group.

SCHEME VIII





This mechanism suggests that the configurational changes of the methylene carbon might shed some light on the nature of the transition state.

The final stage of this reaction, the addition of Grignard reagent to azirine, also shows a strong stereochemical preference. It can be generally stated that that imine will be produced which arises by approach of the Grignard reagent from the less hindered side of the ring.[55] Hassner and Fowler[56] have shown that the substituents on the sp^3 carbon of the azirine are separated by a wider-than-normal bond angle and thus expect an unusual steric shielding of the ring. Thus the incoming group invariably becomes attached trans to the larger substituent at that carbon. For example, addition of methylmagnesium bromide to propiophenone oxime yields 98% of the trans 1,2-dimethyl isomer and only 2% of the cis isomer.[55] This stereochemistry is consistent with the relatively high energy content of the azirine: the addition reaction is relatively exothermic and product stability is not the controlling factor.

There is one report of a remarkable transformation of oximes employing the Grignard reagent which bears some resgmblance to the foregoing reactions. Treatment of 2-(1-phenylcyclohexyl)cyclohexanone oxime (**19**) with either phenyl- or *p*-tolylmagnesium bromide produced the 1-benzobicyclononenone derivative **20**, R = H.[57] The authors propose that this reaction proceeds through an azir-

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(52) S. Eguchi and Y. Ishii, *Bull. Chem. Soc. Jap.*, **36**, 1434 (1963).

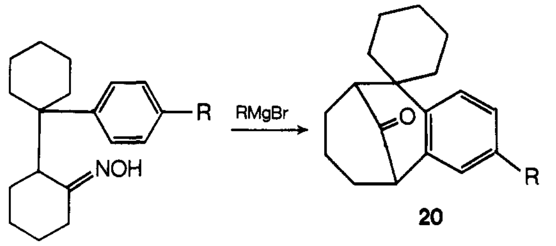
(53) D. R. Smith, M. Marientha, and J. Tipton, *J. Org. Chem.*, **17**, 294 (1952).

(54) For a review of this work, see K. Kotera and K. Kitahonoki, *Org. Prep. Proced.*, **1**, 305 (1969).

(55) G. Alvernhe and A. Laurent, *Bull. Soc. Chim. Fr.*, 3304 (1970).

(56) A. Hassner and F. W. Fowler. *J. Amer. Chem. Soc.*, **90**, 2869 (1968).

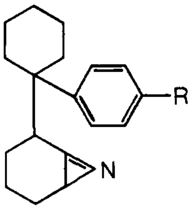
(57) T. Taguchi, K. Miyano, Y. Shimizu, and Y. Kawagoe, *Tetrahedron Lett.*, 4105 (1968).



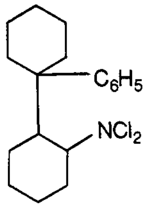
19 **20**

R = H, CH_3, CH_3O, Cl

ine intermediate, presumably **21**. (The exact structure is not definitely assigned in this paper.) The intermediacy of azirine **21** is supported by the fact that 2-(1-phenylcyclohexyl)-*N*,*N*-dichlorocyclohexylamine (**22**) was converted to ketone **20** when successively treated with sodium methoxide and then the Grignard reagent. Treatment of *N*,*N*-dichloramines with base is a known route to azirines.[58]



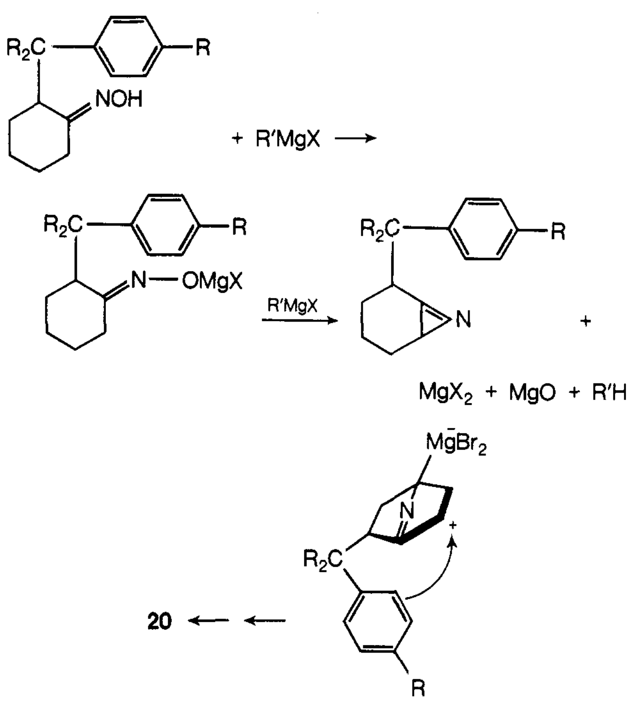
21



22

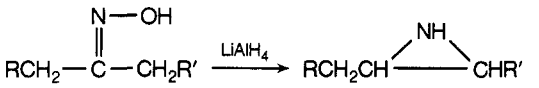
However, the conversion of the azirine to the bicyclic ketone is more obscure. It was suggested that the Grignard reagent undergoes an exchange reaction with the aromatic ring present in the azirine and that this metalated ring then attacks the azirine in a ring-opening process to yield ketimine which, after hydrolysis, gives ketone **20**. Such an exchange process seems highly unlikely, and there is no precedent for the ring-opening process involving nucleophilic attack. On the other hand, acid-catalyzed azirine ring openings to produce α-imino carbonium ion intermediates are known,[59] and such a process, catalyzed by magnesium salts and possibly involving aromatic participation, would account for the products. Presumably, this reaction proceeds because the normal aziridine-forming reaction is sterically inhibited by the tertiary group at the alpha carbon of the azirine ring. In summary the mechanism might be viewed as shown in Scheme IX.

SCHEME IX



B. Oximes and Lithium Aluminum Hydride

Kitahonoki and coworkers have developed a useful synthesis of aziridines based upon the reaction of lithium aluminum hydride with oximes.[54] Since they have recently written a brief review of their work, only the highlights will be emphasized here.



$$\mathrm{RCH_2{-}\overset{\overset{N{-}OH}{\|}}{C}{-}CH_2R' \xrightarrow{LiAlH_4} RCH_2CH\overset{NH}{\frown}CHR'}$$

The reaction bears a very strong resemblance to that of oximes with Grignard reagents (section IV.A). In both azirines seem to be involved, in both the azirines are formed preferentially by syn eliminations, and in both the final addition reaction occurs by approach to the less hindered side of the azirine. The differences that have been noted can be attributed to the greater steric bulk of the Grignard reagent and to the subtle solvent effects noted in the previous discussion. Thus the hydride reduction in tetrahydrofuran is less stereospecific with respect to oxime configuration,[54] but it has been established that the Grignard reaction is also less stereospecific if run in tetrahydrofuran.[55] Apparently the elimination reaction is always stereospecific, but oxime isomerization is occurring in the more polar solvent.

V. Oxidation Reactions

In section II.B the conversion of oximes to pseudonitroles and dinitroalkanes was discussed. Although all the reactions in section II can be considered oxidations, they were treated as nitrosation reactions. In this section several reactions mechanistically similar to those nitrosation reactions will be discussed.

A. Conversion of Oximes to Ketones

It has often been observed that direct hydrolysis of oximes to ketones does not proceed in high yields or, because it is an equilibrium process affected by steric factors, is very slow and subject to side reactions. Alternative methods have been sought among oxidation reactions. One of these methods has already been described —the deoximation caused by nitrous acid (section II).[60] Other reagents that have been useful are perchloryl fluoride,[61] potassium permanganate,[62] potassium dichromate,[62] and ozone.[63] Recently ceric(IV) salts[64] and lead tetraacetate[17] have also been employed.

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[58] H. E. Baumgarten and F. A. Bowen, *J. Amer. Chem. Soc.*, **76**, 4561 (1954).

[59] N. J. Leonard and B. Zwanenburg, *J. Amer. Chem. Soc.*, **89**, 4456 (1967).

[60] For some early examples of this and related oxidative deoximations, see L. Bouveault and R. Locquin, *Bull. Soc. Chim. Fr.*, [3] **31**, 1142 (1904).

[61] J. P. Freeman, *J. Amer. Chem. Soc.*, **82**, 3869 (1960).

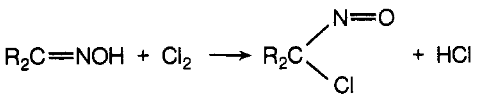
[62] German Patent 1,978,570; *Chem. Abstr.*, **55**, 25808e (1961).

[63] R. E. Erickson, P. J. Andrulis, Jr., J. C. Collins, M. L. Lungle, and G. D. Mercer, *J. Org. Chem.*, **34**, 2961 (1969).

[64] J. W. Bird and D. G. M. Diaper, *Can. J. Chem.*, **47**, 145 (1969).

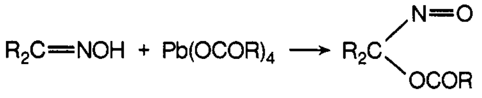
B. Halogenation and Acetoxylation of Ketoximes

Ketoximes are converted to α-chloronitroso compounds by nitrosyl chloride,[65] chlorine[32,65] and hypochlorites,[66] and to α-bromonitroso compounds with bromine.[67]



$$R_2C{=}NOH + Cl_2 \longrightarrow R_2C(N{=}O)(Cl) + HCl$$

The conversion of ketoximes to α-acyloxynitroso compounds (**23**) by the action of lead tetracarboxylates was first reported by Iffland and Criner[67] and later amplified by Kropf and Lambeck[68] and Just and coworkers.[33]



$$R_2C{=}NOH + Pb(OCOR)_4 \longrightarrow R_2C(N{=}O)(OCOR)$$

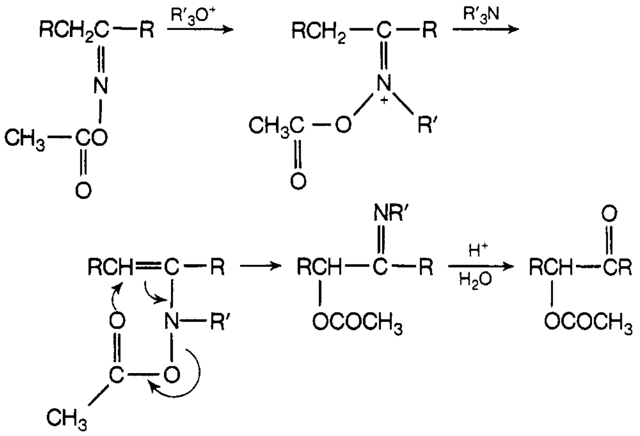
23

These compounds may be intermediates in the oxidation of oximes to ketones.[17] However, the mechanistic interpretation of these reactions is not very clear at the present, and proposals of concerted cyclic processes,[68] ionic processes,[68] and free-radical processes[33] have been made. These reactions may be quite sensitive to reaction conditions as far as mechanism is concerned (see section II.B).

There is an extensive literature on the oxidation of oximes to nitroxyl radicals which will not be reviewed here because of treatments elsewhere.[69]

An unusual oxidation reaction has been reported wherein ketoxime acetates are converted to α-acetoxy ketones (Scheme X).[70]

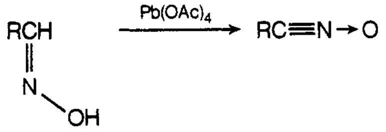
SCHEME X



C. Oxidation of Aldoximes

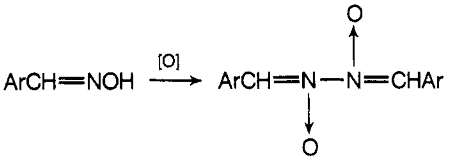
Aldoximes undergo many of the same oxidation reactions as do ketoximes[32,65] but, because of the oxidative lability of the aldoxime C–H bond, they also may be converted to rather different products.

Lead tetraacetate oxidation at −78° of syn aldoximes furnishes a good route to nitrile oxides.[71] The anti isomers are converted to α-acetoxynitroso compounds.



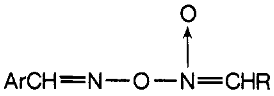
$$RCH{=}N{-}OH \xrightarrow{Pb(OAc)_4} RC{\equiv}N{\rightarrow}O$$

The structure of the products from the oxidation of aromatic aldoximes has been a matter of conjecture for many years.[32,37a] The matter appeared to be settled by the work of Horner[22] who proposed the aldazine bisoxide structure **24**. This structure has been widely accepted but an older, alternative formulation, **25**, has been revived recently.[72] The chemical evidence available persuades this reviewer that structure **24** is the correct one, but possibly more definitive information will be forthcoming.



$$ArCH{=}NOH \xrightarrow{[O]} ArCH{=}\overset{O\uparrow}{N}{-}\underset{\downarrow O}{N}{=}CHAr$$

24



$$ArCH{=}N{-}O{-}\overset{O\uparrow}{N}{=}CHR$$

25

VI. Miscellaneous

A. Reductive Deoximation

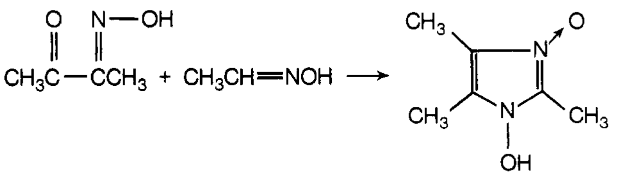
Some reductive methods for converting oximes to ketones have also been developed. Two of the more recent employ iron pentacarbonyl and boron trifluoride[73] and chromous acetate.[18] References to other methods are summarized in this latter article.

B. Unusual Heterocyclic Syntheses

While oximes are often used as starting materials for the synthesis of heterocycles, the reactions involved are straightforward reactions involving addition to the double bond. There are a few unusual reactions which caught the attention of this reviewer and are included to titillate the imagination of the reader. In no way is exhaustive coverage claimed.

1. Imidazole, Pyrrole, and Pyrazole Oxides

N-Hydroxyimidazole *N'*-oxides (**26**) are produced by the condensation of α-keto oximes with aldoximes.[74]



26

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(65) For a comprehensive review of these reactions, see H. Metzger and H. Meier in ref 40, No. 1, p 943.

(66) H. Diekmann and W. Lüttke, *Angew. Chem., Int. Ed. Engl.*, **7**, 387, 388 (1968).

(67) D. C. Iffland and G. X. Criner, *Chem. Ind. (London)*, 176 (1956).

(68) H. Kropf and R. Lambeck, *Justus Liebigs Ann. Chem.*, **700**, 1 (1966).

(69) For example, R. O. C. Norman, *Chem. Soc., Spec. Publ.*, **No. 24**, 140 (1970).

(70) H. O. House and F. A. Richey, Jr., *J. Org. Chem.*, **34**, 1430 (1969).

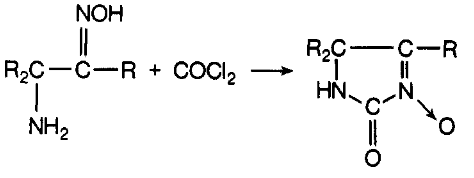
(71) G. Just and K. Dahl, *Tetrahedron*, **24**, 5251 (1968).

(72) H. Kropf and R. Lambeck, *Justus Liebigs Ann. Chem.*, **700**, 18 (1966).

(73) H. Alper and J. T. Edward, *J. Org. Chem.*, **32**, 2938 (1967).

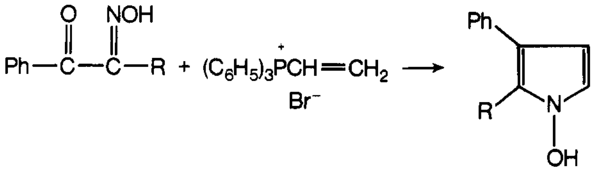
(74) J. B. Wright, *J. Org. Chem.*, **29**, 1620 (1964); F. J. Allan and G. G. Allan, *Chem Ind. (London)*, 1837 (1964).

Recently, the conversion of α-amino ketoximes to 2-oxo-Δ^3-imidazoline 3-oxides (**27**) by the action of phosgene has been reported.[75] Because of the conflicting data in this paper and that previously reported,[76] it is likely that confirmatory investigations will be made before this result is accepted.

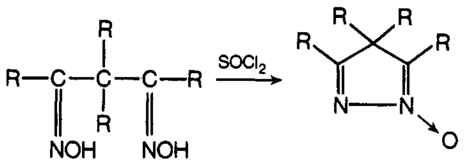


27

N-Hydroxypyrroles have been obtained by condensation of vinyltriphenylphosphonium bromide with α-keto oximes.[77]

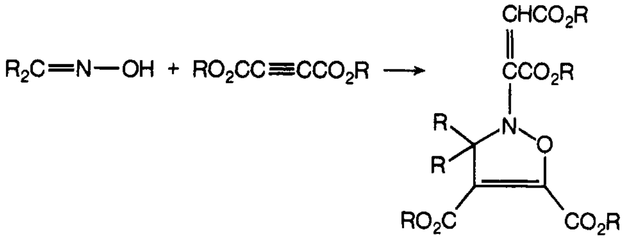


Pyrazole N-oxides are obtained by the action of thionyl chloride on 1,3-dioximes.[78] 4-Ketopyrazole N,N-dioxides have been obtained by oxidation of 1,3-dioximino ketones.[29] Reaction of 1,2-dioximes with sulfur dichloride yields thiadiazole N-oxides.[79]



2. Cycloaddition Reactions

There have been scattered efforts to use the oxime function as a 1,3-dipole in cycloaddition reactions. In general the products resemble those from nitrones which has suggested to some authors that reaction occurs through the nitrone tautomers. Isoxazolidines have been obtained from ketoximes[80] and formaldoxime.[81] With acetylenic dipolarophiles some interesting heterocycles have been reported.[82]



Acknowledgment. We are indebted to National Institutes of Health, National Cancer Institute for a research grant (CA 10742) which, in part, helped to support research for this review.

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(75) H. Gnichtel, R. Walentowski, and K.-E. Schuster, *Chem. Ber.*, **105**, 1701 (1972).

(76) A. Dornow and H.-H. Marquardt, *Chem. Ber.*, **97**, 2163 (1964).

(77) E. E. Schweizer and C. M. Kopay, *J. Org. Chem.*, **37**, 1561 (1972).

(78) H. Gnichtel and H.-J. Schönherr, *Chem. Ber.*, **99**, 618 (1966).

(79) K. Pilgrim, *J. Org. Chem.*, **35**, 1165 (1970).

(80) A. LaBlache-Combier and M. L. Villaume, *Tetrahedron*, **24**, 6951 (1968).

(81) M. Ochiai, M. Obayashi, and K. Morita, *Tetrahedron*, **23**, 2641 (1967).

(82) E. Winterfeldt and W. Krohn, *Angew. Chem., Int. Ed. Engl.*,**6**, 709 (1967).