LEAD TETRAACETATE OXIDATION OF OXIMES

by

Klaus Dahl

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A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfilment of the requirements for the degree of Doctor of Philosophy

Department of Chemistry,
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To

my parents and Lies

ABSTRACT

The lead tetraacetate oxidation of aldoximes and ketoximes has been studied. Oxidation of aliphatic and aromatic syn aldoximes affords nitrile oxides. Aliphatic anti aldoximes lead to 1-acetoxy-1-nitrosoalkanes and secondary products, notably N-acetoxyhydroxamic acids. Aromatic anti aldoximes afford arylaldazine-bis-N-oxides which decompose on heating to nitrile oxides and aldoximes. Oxidation of sterically hindered ring ketoximes leads via ring cleavage to N-acetoxyhydroxamic acids. For sterically hindered, but not very strained ketoximes, the cleavage proceeds via formation of a nitrile oxide and a carbonium ion. For strained, but not particularly hindered ketoximes, cleavage appears to involve the rearrangement of an intermediate geminal nitrosoacetate. Mechanisms are proposed which require iminoxy radicals as intermediates in the oxidation of anti aldoximes and ketoximes. Oxidation of syn aldoximes appears to proceed by a concerted mechanism. The oxidation products obtained suggest that iminoxy radicals do not participate in radical displacement reactions.[95]

ACKNOWLEDGEMENTS

I sincerely thank Dr. G. Just for timely words of encouragement and constructive criticism which have guided this work to its completion.

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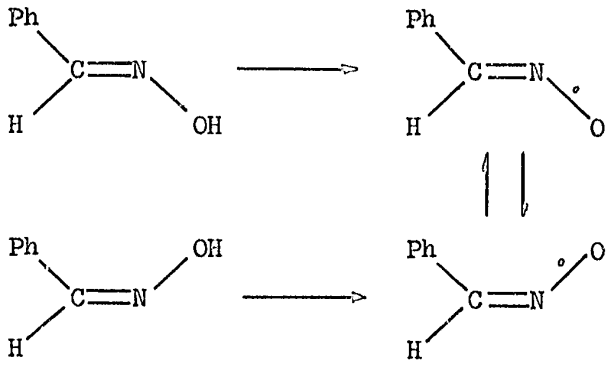
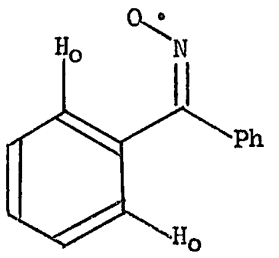
INTRODUCTION

Iminoxy radicals have been detected recently by electron spin resonance techniques (ESR) as transient species in the oxidation of oximes.[1] These radicals, though varying greatly in stability, exhibit three common and interesting features. Firstly, their nitrogen coupling constants are large and characteristic, ranging from 28 to 33 gauss and are thus considerably greater than the coupling constants of nitroxides (10 to 16 gauss), a related class of stable free radicals.[2] Even though a significant portion of the unpaired electron density must reside upon the oxygen atom, the measured coupling constants are comparable to those estimated for unit electron density on nitrogen in azine anion radicals.[3] Calculations[4] based on the data for the radical from dimethylglyoxime[5] indicate that about 45% of the unpaired spin is on nitrogen in an orbital whose p:s ratio is 6.6 : 1 . A second interesting aspect of iminoxy radicals is the detection of cis and trans isomers.[1] For example, oxidation of syn- or anti-benzaldoxime gives

rise to the same 1:1 mixture of two radicals, which indicates isomerization in the oxidation reaction:



Thirdly, coupling occurs to nitrogen and, as was demonstrated for benzophenone iminoxy (1) and fluorenone iminoxy radicals (2),[6] only to the ortho hydrogen atoms (H_o) on the aromatic ring:



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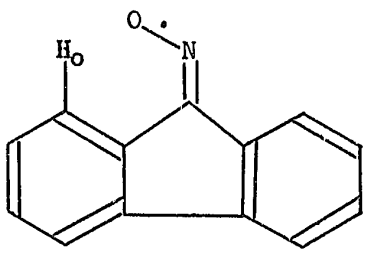
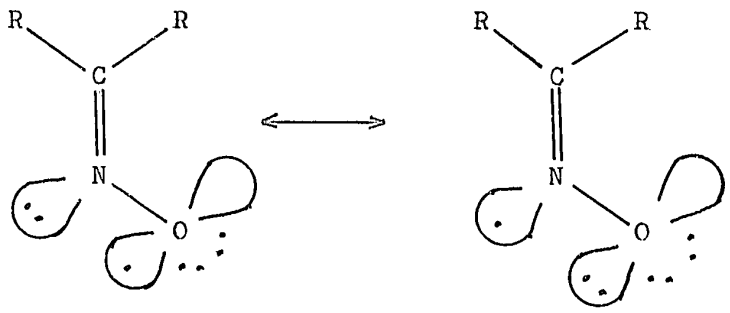


2

This suggests that the unpaired electron is not delocalized over the π-molecular orbital of the aromatic ring, and that the coupling to the ortho hydrogen atoms is probably due to a 1,6-interaction through space.[6]

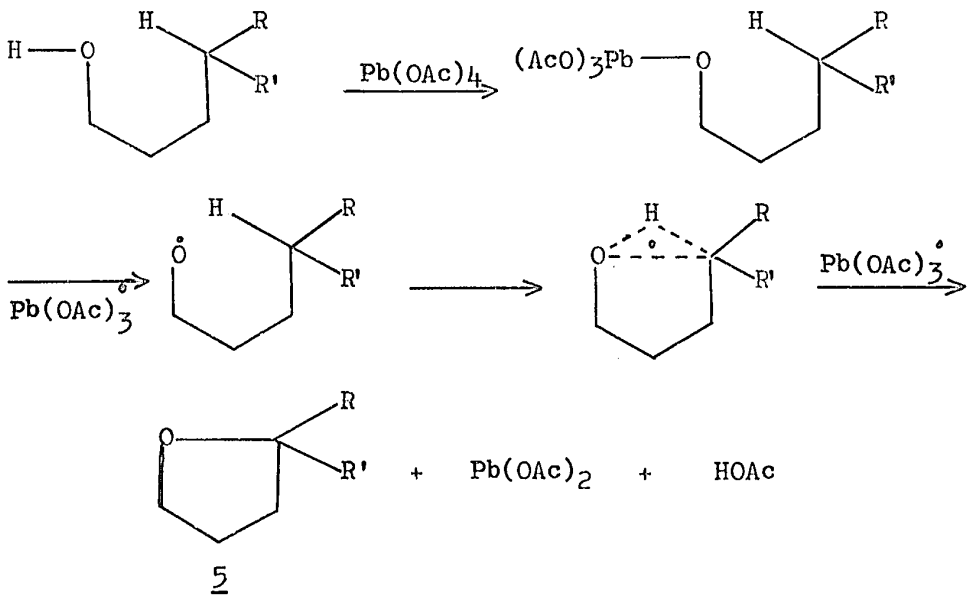
These results are incompatible with the description of iminoxy radicals as π-radicals,[7] and they are best represented as hybrids of structures 3 and 4:



3 4

The unpaired electron is contained in a π-type orbital which is derived from a nitrogen sp^2- and an oxygen p- orbital. This new molecular orbital lies in the nodal plane of the carbon-nitrogen π-bond, so that the radicals are termed σ-radicals.[8] Implicit in this description is the understanding that the unpaired electron cannot be delocalized over the carbon-nitrogen bond, and energy dissipation of this radical would, therefore, most probably occur either by reaction at the nitrogen or at the oxygen atom.

Iminoxy radicals are prepared most conveniently by oxidation of oximes with lead tetraacetate ($Pb(OAc)_4$) in methylene chloride[6] or benzene.[9] Free radicals have also been obtained in the lead tetraacetate oxidation of phenols,[10] and are suggested intermediates[11] in the oxidative cyclization of aliphatic primary and secondary alcohols. The latter reaction leads mainly to tetrahydrofurans (5) and has been formulated as proceeding via alkoxy radicals:



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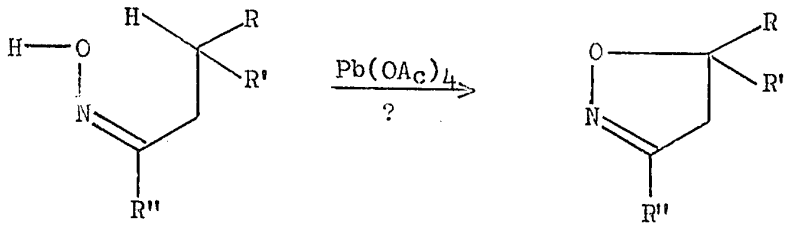
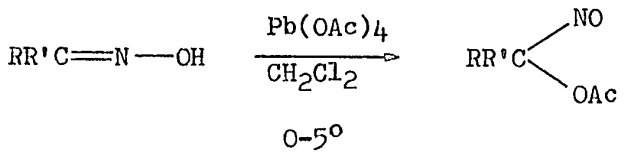
An extension of this reaction to oximes would provide an additional valuable method of functionalizing carbon atoms suitably disposed for an intramolecular free radical displacement reaction. This reaction, however, would afford heterocyclic compounds which contain oxygen and nitrogen. It is the objective of the present investigation to gain some understanding of the chemistry of iminoxy

radicals and in the light of this knowledge, to assess the possibility of an oxidative cyclization of oximes as shown:



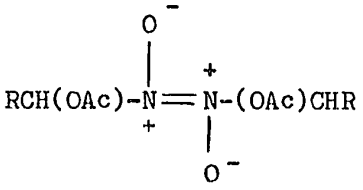
The oxidation of oximes has been the subject of many publications, especially at the turn of this century. Aromatic aldoximes and ketoximes when treated with conventional oxidizing reagents (N_2O_3, $K_3(Fe(CN)_6)$, Na_2CO_3/I_2, etc.) were shown to lead to complex reaction mixtures containing, among other secondary reaction products, furoxans and so-called "oxime peroxides".[12,13] Aliphatic aldoximes were shown to react with peracids to hydroxamic acids in low yield,[14] while aliphatic ketoximes when treated with conventional oxidizing reagents (H_2O_2, $KMnO_4$, CrO_3) afforded mainly the parent ketone.[15] Oxidation of aldoximes and ketoximes with peroxytrifluoroacetic acid was reported to lead to nitro compounds in useful yields.[16]

The lead tetraacetate oxidation of aliphatic ketoximes was shown to afford unstable geminal nitrosoacetates (6):[17]



6

Under comparable conditions, aliphatic aldoximes could be converted to dimeric nitrosoacetates (7), while aromatic aldoximes led to aldoxime anhydride-N-oxides (8).[18] The same compounds have been obtained by different routes and were respectively assigned the structure of oxime peroxides (9),[19] and aldazine-bis-N-oxides (10):[20]



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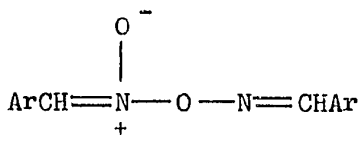

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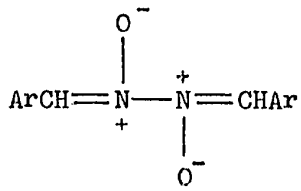

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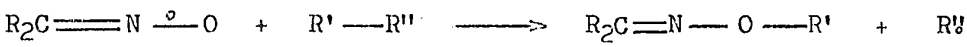
Still other structures have been proposed but appear rather unlikely in the light of modern structural theory.

No information could be found that would give any indications about the ability of iminoxy radicals (which could have been intermediates in the reported oxidation studies) to undergo normal radical displacement reactions:



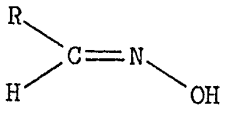
Oxidation of oximes with lead tetraacetate appeared to provide the most promising approach to study the chemistry of iminoxy radicals, because this oxidizing reagent can be used in a variety of solvents over a fairly wide range of temperature; and, if proper precautions are taken, high selectivity in its reactions can be anticipated.[21]

Oxidation of oximes with lead tetraacetate is a rapid reaction even at 0°.[17] This indicates that the conditions used for oxidative cyclization of alcohols (reflux in benzene with lead tetraacetate[11]) are not applicable. To achieve high selectivity and avoid secondary reactions, it appeared advisable to study the lead tetraacetate oxidation of oximes at low temperature. The choice of model compounds was dictated by stereochemical considerations, which should favour a radical displacement reaction. In practice, this narrowed the choice to sterically hindered aldoximes and ketoximes containing methyl groups suitably disposed for a five- or six-membered ring closure.

RESULTS

CHAPTER I. PREPARATION OF OXIMES

Aldoximes and ketoximes were prepared according to standard procedures[22,23] generally from commercially available aldehydes and ketones. In agreement with reported results, unhindered aliphatic aldoximes were obtained as mixtures of their syn and anti isomers:[24,25]



syn ; anti .

Sterically hindered aliphatic aldehydes afforded mainly the syn isomer as was also observed for aromatic aldehydes in general. Aromatic syn aldoximes could be converted to their less stable anti isomers via the oxime hydrochlorides.[23] Reaction of n-heptanal with hydroxylamine hydrochloride and sodium bicarbonate as base, instead of the usual[22,23] sodium hydroxide, afforded anti-n-heptanaldoxime as the sole reaction product; it isomerized readily in carbon tetrachloride solution (1 day, room temperature) to the reported 1:1 mixture of syn-and anti-n-heptanaldoxime.[24] Sterically hindered ketoximes were obtained by reaction of the ketone with hydroxylamine hydrochloride in the presence of sodium acetate in refluxing methanol. Reflux times of up to 48 hours were required for quantitative conversion.

All aldoximes which were prepared are listed in Table 1 (p. 10), and their spectral data are shown (NMR) in Table 2 (p. 11). The ketoximes are given in Table 3 (p. 12), and their spectral data (NMR) in Figure 1 (pp. 13,14).

Configurational assignments for aldoximes are based on the chemical shift position of the "aldehydic" proton,[24,25] for ketoximes on the chemical shift position of the α-substituents (H- or CH_3-).[26, 27] In agreement with reported data, it was noted that the "aldehydic" proton in syn aldoximes absorbs at lower field than the corresponding anti proton ($\delta_s - \delta_a = 0.6$ ppm). Only benzaldoxime constituted an exception in that the "aldehydic" proton of the syn and anti isomer had approximately the same chemical shift. IR[28] and melting point data, however, permitted certain assignment of the respective isomers. The NMR spectra of hindered ketoximes indicated only one isomer, viz., the one with the oxime hydroxy group in the less hindered position.

Table 1

Aliphatic and Aromatic Aldoximes

Aldoxime	m.p. (b.p.) °C found	m.p. (b.p.) °C lit.	% * syn	% * anti	Reference	Remarks
Acetaldoxime	(112-114)	(112-114)	41	59	29	a
Isobutyraldoxime	(141-141.5)	(140)	74	26	30	a
Trimethylacetaldoxime	40-41	41	100	-	31	b
n-Heptanaldoxime	56-57	56-57	-	100	32	c
O-Methylpodocarpinaldoxime	143	-	100	-	33	-
Benzaldoxime (syn)	35	35	100	-	23	-
Benzaldoxime (anti)	130	130	-	100	23	c
Mesitaldoxime	119-121	-	89	11	34	d
p-Methoxybenzaldoxime	45	45	100	-	35	-
p-Nitrobenzaldoxime	126-127	129	100	-	36	e
p-Hydroxybenzaldoxime	115	115-116	100	-	37	e
m-Hydroxybenzaldoxime	90	90	100	-	38	f

a) 760 mm; b) recryst. from pentane at -78°; c) procedure given; d) $m.p._{syn}$: 125°, $m.p._{anti}$: 179°;[34] e) vacuum sublimed, 95°/0.2 mm; f) vacuum sublimed, 80°/0.2 mm.

* NMR estimate.

Table 2

NMR Data of Aldoximes

Aldoxime (RCH'NOH)	N M R Chemical Shift, δ ppm			Solvent
	H'_{syn}	H'_{anti}	OH	
Acetaldoxime	7.30	6.70	9.4	b
Isobutyraldoxime	7.09	6.30	9.5	b
Trimethylacetaldoxime	7.27	-	9.25	a
n-Heptanaldoxime *	-	6.54	10.0	b
O-Methylpodocarpinaldoxime	7.54	-	9.1	-
Benzaldoxime (syn)	8.10 7.94	- -	9.6 11.0	a c
Benzaldoxime (anti) **	-	8.19	8.7	a
Mesitaldoxime	7.81	7.18	10.9	c
p-Methoxybenzaldoxime	8.14	-	9.6	a
p-Nitrobenzaldoxime	7.83	-	11.5	c
p-Hydroxybenzaldoxime	7.87	-	9.5 or 10.6	c
m-Hydroxybenzaldoxime	7.98	-	9.5 or 11.0	c

* Converts on standing (1 day) in CCl_4 solution to a 1:1 syn/anti mixture with signals H'_{syn}: 7.23 H'_{anti}: 6.54 ppm; a) $CDCl_3$; b) CCl_4; c) $(CD_3)_2SO$.

** IR in CS_2 shows bands at 756 and 690 cm^{-1}, typical of anti-benzaldoxime.[28]

Table 3

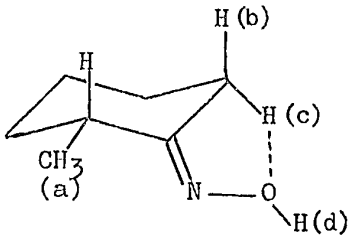
Ketoximes

Ketoxime	m.p. (b.p.) °C found	m.p. (b.p.) °C lit.	Reference	Remarks
Cyclohexanone oxime	90	90	39	-
2-Methylcyclohexanone oxime	44-45	43	40	-
3-Methylcyclohexanone oxime	(115-118)	(115-118)	41	760 mm
2,2,6-Trimethylcyclohexanone oxime	103-104	102.5-103	42	-
2,2,6,6-Tetramethylcyclohexanone oxime	151.5	151	43	a
Camphor oxime	118	118	44	
Fenchone oxime	162	165	45	
Isophorone oxime	100-101	102	46	

a) Procedure given in the experimental section.

Figure 1. NMR Data and Configurational Assignments of Sterically Hindered Ketoximes.[26,47]

2-Methylcyclohexanone oxime



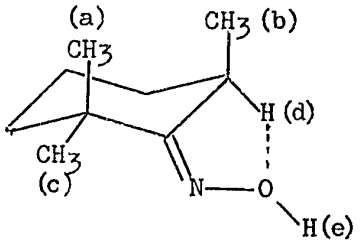
a = 1.09 ppm (D, 3 H, J = 7 cps)

b = 2.16 ppm (M, 1 H)

c = 3.13 ppm (M, 1 H, J_{bc} = 12 cps)

d = 9.9 ppm (S, 1 H)

2,6,6-Trimethylcyclohexanone oxime



a* = 1.12 ppm (S)

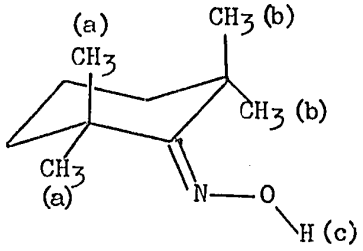
b* = 1.14 ppm (D, J = 7.5 cps)

c* = 1.16 ppm (S)

d = 3.5 ppm (M, 1 H)

e = 9.9 ppm (S, 1 H)

2,2,6,6-Tetramethylcyclohexanone oxime



a = 1.16 ppm (S, 6 H)

b = 1.33 ppm (S, 6 H)

c = 9.6 ppm (S, 1 H)

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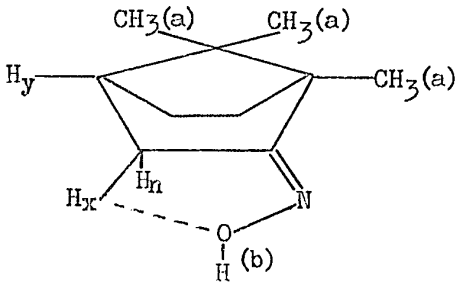
* Total integrated area corresponds to 9 H.

Camphor oxime



a* = 0.79 (S), 0.91 (S), 1.00 (S) ppm

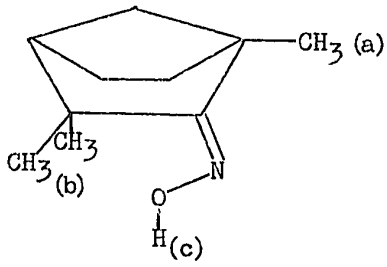
H_n = 2.28 ppm (D, 1 H)

H_x = 2.56 ppm (Q, 1 H)

b = 8.7 ppm (S, 1 H)

J_{yn} = 0 cps ; J_{xn} = 19 cps ; J_{yx} = 3 cps.[48]

Fenchone oxime



a = 1.24 ppm (S, 3 H)

b** = 1.32 (S), 1.35 (S) ppm

c = 8.3 ppm (S, 1 H)

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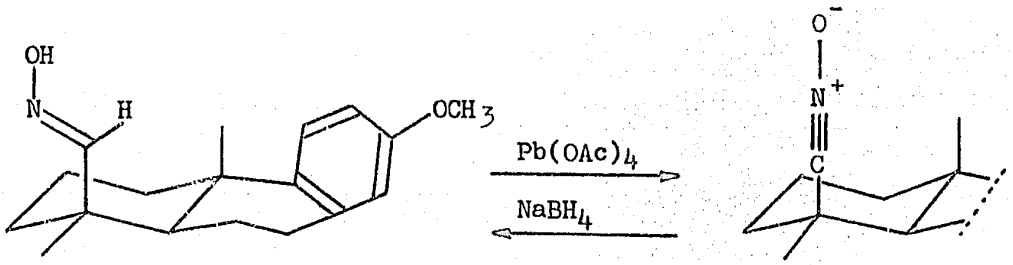
* Total of 9 H ; ** Total of 6 H.

CHAPTER II. OXIDATION OF ALDOXIMES

A. Oxidation of Hindered Syn Aldoximes.

O-Methylpodocarponitrile oxide. As a convenient model for the preliminary study of the lead tetraacetate oxidation of aldoximes, syn-O-methylpodocarpinaldoxime (11) was chosen. Reaction of this compound with lead tetraacetate in methylene chloride (5 min, room temperature) afforded the nitrile oxide 12 in 94% yield:



11 12

The IR spectrum of compound 12 showed an intense band at 2270 cm^{-1} which is typical for nitrile oxides.[49] Moreover, elemental analysis data as well as the NMR spectrum (Figure 2, p. 19) were fully consistent with the assigned structure. Sodium borohydride reduction of 12 afforded a quantitative yield of the starting aldoxime 11. Unlike other known nitrile oxides,[50] O-methylpodocarponitrile oxide is stable at room temperature and thus represents the first example of a stable aliphatic nitrile oxide. Its shelf life at room temperature is well in excess of one year, though heating above its melting point (132°)

converts it slowly to the corresponding isocyanate. Under no conditions can it be made to dimerize to the furoxan .[50] It does, however, react slowly with acetic acid and vinyl acetate in a 1,3-dipolar addition[51,52] to an N-acetoxyhydroxamic acid* and an isoxazoline acetate, respectively.

Reaction of aldoxime 11 with lead tetraacetate in acetic acid (5 min, room temperature) also leads predominantly to the nitrile oxide 12 (80%). As a side product, the N-acetoxy-O-methylpodocarpohydroxamic acid is formed. Conversion to the latter product was also observed when treating the aldoxime in methylene chloride with lead tetraacetate over extended periods of time; formation of the N-acetoxyhydroxamic acid was virtually quantitative after about 2 days.

Mesitonitrile oxide (13). Reaction of 2,4,6-trimethylbenzaldoxime (Mesitaldoxime, 89% syn and 11% anti isomer) with lead tetraacetate in methylene chloride at -78° led to a mixture of two compounds. The major (more soluble) component was isolated (87%) and identified as the 2,4,6-trimethylbenzonitrile oxide (13) (mesitonitrile oxide), while the minor (less soluble) component appeared to be the 2,4,6-trimethylphenylaldazine-bis-N-oxide (14) (identified by IR only, $\bar{\nu}^{CHCl_3}_{max}$: 1580(s), 1450(s), 1380(s), 1340(s), 1090(s), 1072(s), and 915(m) cm^{-1}).[20, 51]

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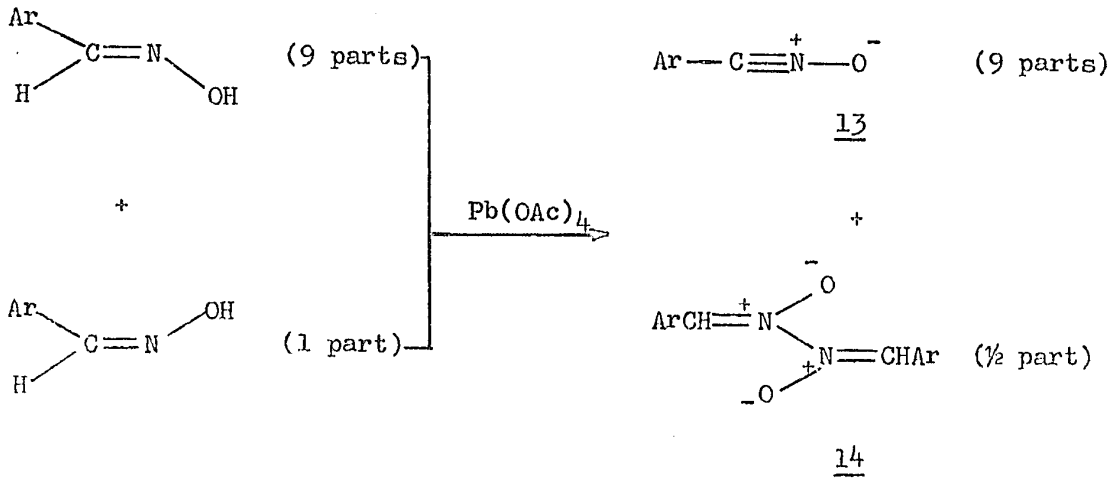
* RCONHOAc. This name has been used in preference to the more correct name, acetylhydroxamate, because it is more descriptive in locating the acetoxy group.

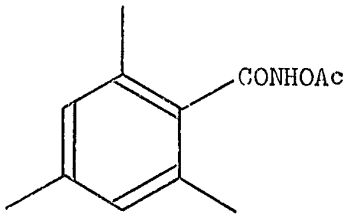


Ar = 2,4,6-trimethylphenyl.

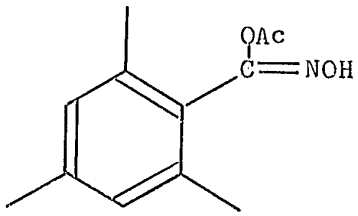
Oxidation of mesitaldoxime at room temperature in methylene chloride also led to nitrile oxide 13 and aldazine-bis-N-oxide 14, but under these conditions more aldazine-bis-N-oxide and less nitrile oxide was formed.

Elemental analysis, IR ($\bar{\nu}_{max}^{CCl_4}$: 2290(s) and 1360(s) cm^{-1}), and NMR data unequivocally established the identity of the oxidation product of syn-mesitaldoxime as mesitonitrile oxide. Purification to constant melting point gave as the highest value 111.5-112° (lit.,[51] 114°). As reported,[51] mesitonitrile oxide does not dimerize to furoxan and appears to have a shelf life well in excess of one year. Contrary to its reported inertness towards pure acetic acid,[51] it was found to react readily with this acid at room temperature to form

the N-acetoxymesitohydroxamic acid (15) (negative ferric chloride test). The reported[51] acid catalyzed (H_2SO_4) addition of acetic acid leading to acetylmesitohydroximic acid (16) (positive ferric chloride test) could not be confirmed.



15



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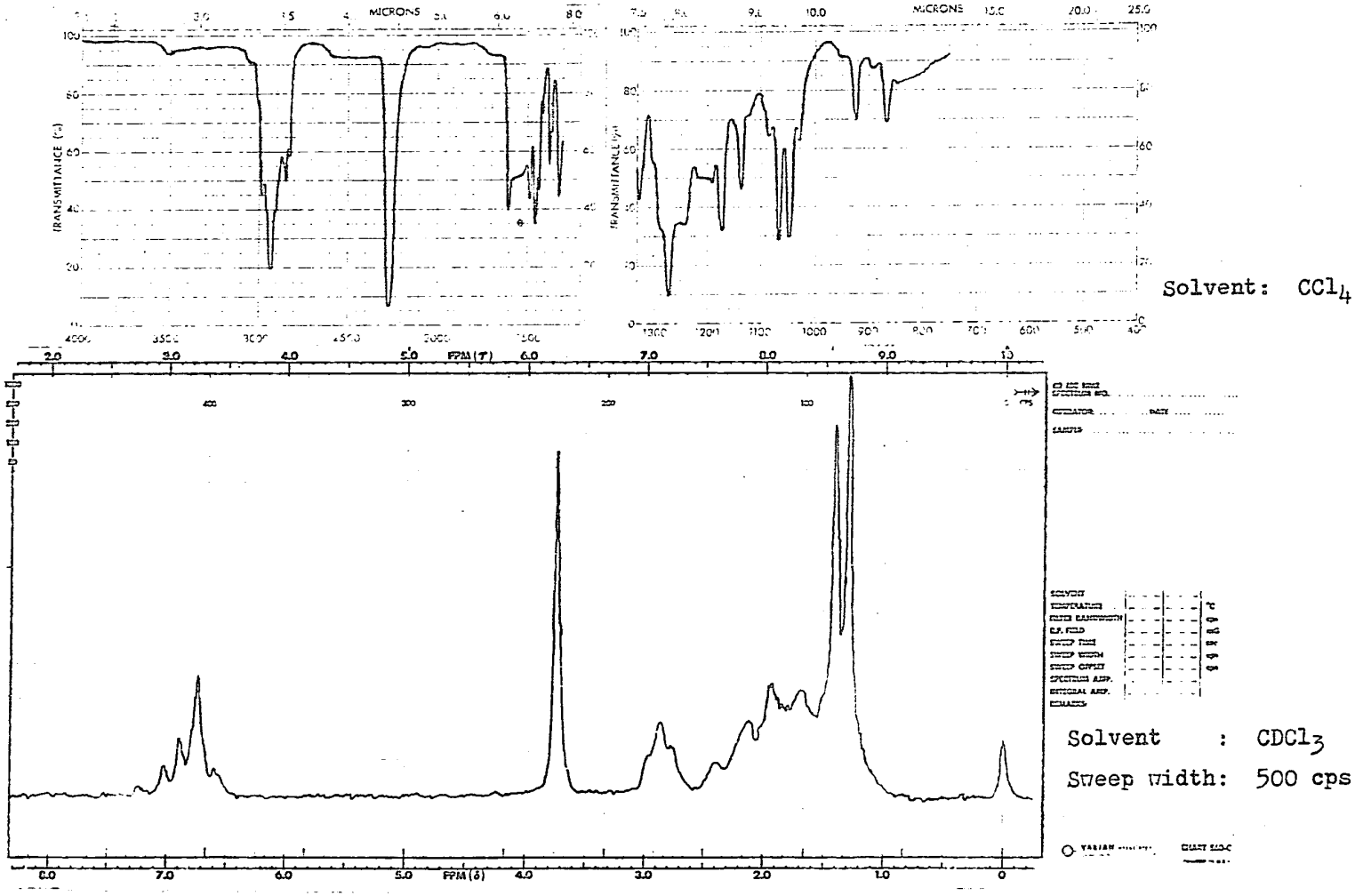
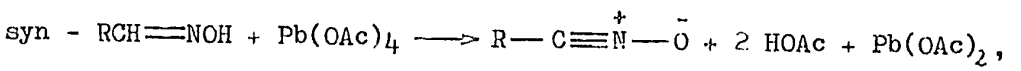


Figure 2. The IR and NMR Spectrum of O-Methylpodocarponitrile Oxide

B. Oxidation of Unhindered Syn Aldoximes.

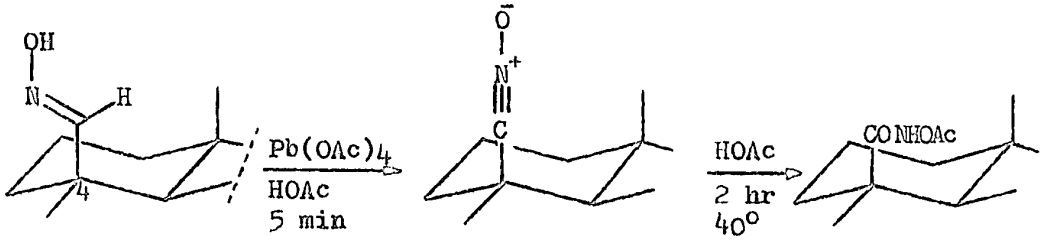
The formation of stable nitrile oxides from sterically hindered syn aldoximes suggested that oxidation of syn aldoximes in general, irrespective of their steric hindrance, might lead to nitrile oxides. By working at very low temperature, it was hoped that the very reactive nitrile oxides[50] could be isolated or trapped. Since the oxidation leads to the formation of two moles of acetic acid per mole nitrile oxide:



reaction between these two components could be reasonably expected to occur. This, in fact was observed. Reaction of a number of aliphatic and aromatic aldoximes with lead tetraacetate in methylene chloride at -78° for 10 to 30 minutes gave N-acetoxyhydroxamic acids (RCONHOAc) in 60 to 100% yield. These compounds do not give a positive colour test for hydroxamic acids immediately upon admixture with a methanolic ferric chloride solution. Prolonged standing at room temperature (hours to days), however, causes slow formation of a mauve colour, thus indicating hydrolysis to free hydroxamic acid.

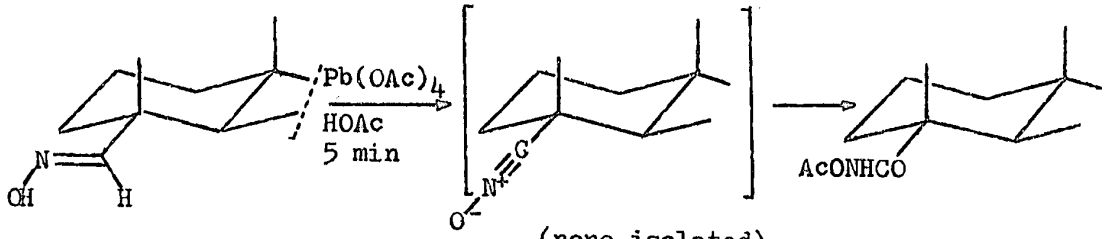
As already pointed out, sterically hindered syn aldoximes reacted at low (-78°) and room temperature to nitrile oxides or their derivatives. In this connection, it is of interest to note that aldoximes epimeric to O-methylpodocarpinaldoxime (11) at

carbon atom 4 did not afford stable nitrile oxides at room temperature, but only the corresponding N-acetoxyhydroxamic acids. Evidently, the equatorially disposed nitrile oxide group, as derived from dehydroabietinaldoxime (17) and abietinaldoxime (18),[53] is sufficiently reactive towards acetic acid at room temperature and leads quantitatively to the N-acetoxyhydroxamic acid.*



11 12

(80% isolated)



17, 18 (none isolated)

The oxidation of syn-trimethylacetaldoxime revealed a second mechanistic path to the formation of N-acetoxyhydroxamic acids. Reaction of this aldoxime with lead tetraacetate in methylene chloride

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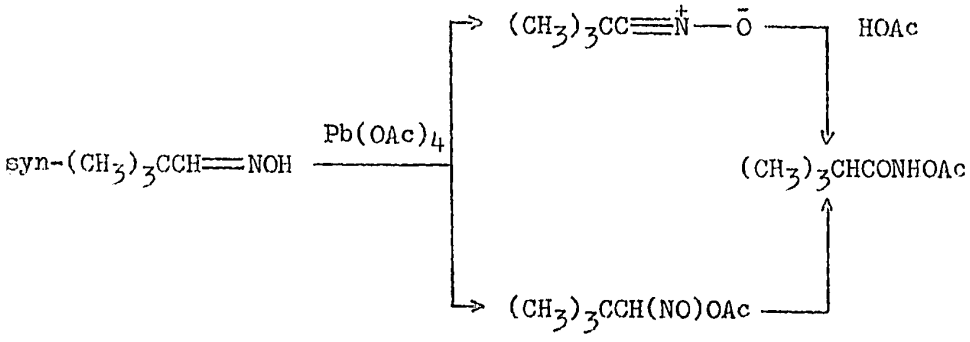
* Partial structures are shown only.

at -20° afforded a mixture of the geminal nitrosoacetate 18 (intensely blue) (25%) and the N-acetoxytrimethylacetohydroxamic acid (75%). The nitrosoacetate 18 was found to rearrange, either on standing in solution, or better by refluxing in ether with a catalytic amount of triethylamine, to N-acetoxytrimethylaceto-hydroxamic acid.



18

This novel rearrangement appears to be general for 1-acetoxy-1-nitrosoalkanes and will be taken up in more detail in the context of the anti aldoxime oxidation (p. 40). Formation of compound 18 could be virtually suppressed by oxidizing syn-trimethylacetaldoxime at -78°, which led in high yield (> 80%) to the N-acetoxyhydroxamic acid; no (blue) nitrosoacetate was detected under these conditions.

Reaction of unhindered aldoximes in acetic acid at room temperature gave rise to product mixtures containing the parent

aldehyde and possibly (IR evidence only) the aldoxime acetate besides nitric oxide, but no N-acetoxyhydroxamic acids (benzaldoxime, isobutyraldoxime and acetaldoxime were tested).

Reaction of aliphatic syn aldoximes in methylene chloride at room temperature afforded blue solutions which have been shown, in an independent investigation,[18] to contain substantial amounts of 1-acetoxy-1-nitrosoalkanes.

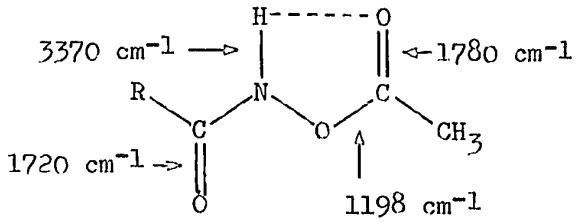
Acetaldoxime (41% syn, 59% anti isomer) when treated with lead tetraacetate in methylene chloride at -78° led to a mixture which contained not more than 30% of N-acetoxyacetohydroxamic acid (IR estimate only). No attempt was made to isolate this compound.

All N-acetoxyhydroxamic acids which were obtained as analytically pure materials are listed in Tables 4 and 5 (pp. 26, 27) together with supporting evidence for their identity (m.p., elemental analysis, IR, and NMR spectral data). In addition, chemical evidence for the identity of N-acetoxytrimethylacetohydroxamic acid was provided by independent synthesis using known procedures:[14]

$$(CH_3)_3CCOOH \xrightarrow[3.\ Ac_2O]{1.\ SOCl_2 \\ 2.\ NH_2OH} (CH_3)_3CCONHOAc \xleftarrow{Pb(OAc)_4} syn\text{-}(CH_3)_3CCH{=}NOH$$

Two of the listed N-acetoxyhydroxamic acids are known (N-acetoxybenzohydroxamic acid[54] and N-acetoxymesitohydroxamic acid[51]) and their melting points were found to be in agreement with those reported.

The IR spectra of N-acetoxyhydroxamic acids show as typical features bands at 3370(m), 1780(s), 1720(s), and 1198(s) cm^{-1}. These bands were assigned to stretching modes of the bonds indicated:[55]



Hydrogen bonding, as shown, was obvious from the absence of a free N-H stretching frequency in the IR spectrum, and was corroborated by the observation that acetylation shifted the N-acetate carbonyl band from 1780 cm^{-1} to 1820 cm^{-1} (formation of a trisubstituted hydroxylamine derivative). Little variation in band position or intensity was observed for the various compounds.

The NMR spectra show as characteristic features two signals, one at 2.2 ppm (singlet, OAc), the other at 9 to 10 ppm (singlet, N-H, exchangeable).

The IR and NMR spectrum of N-acetoxytrimethylacetohydroxamic acid are shown in Figure 3 (p. 25) as a representative example.

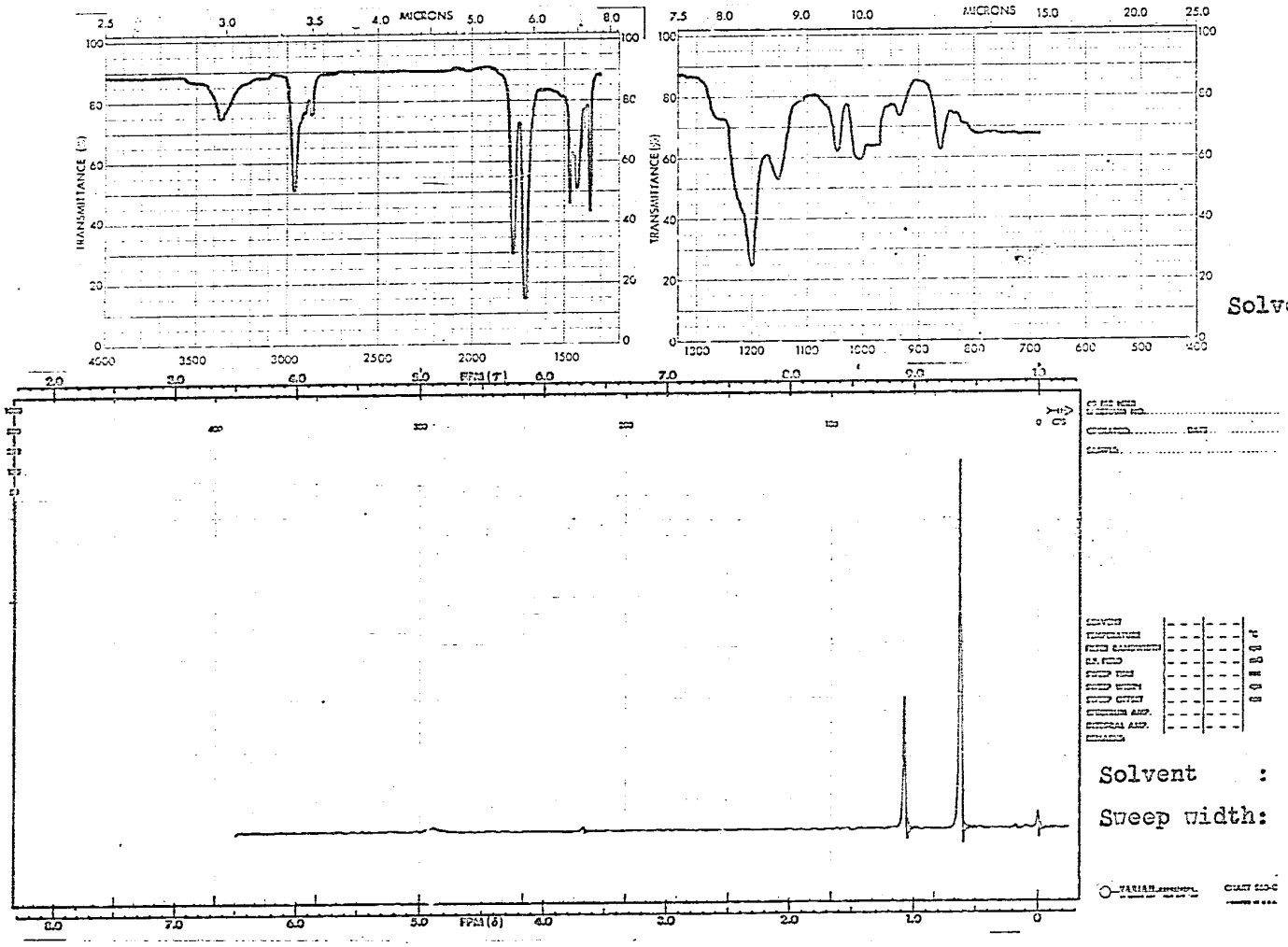


Figure 3. The IR and NMR Spectrum of N-Acetoxytrimethylacetohydroxamic Acid

Table 4

N-Acetoxyhydroxamic Acids Obtained from Aldoximes

RCONHOAc	Yield	m.p.	Anal. %					
			C		H		N	
R	%	°C	calcd.	found	calcd.	found	calcd.	found
$(CH_3)_3C$-	80	116.5	52.81	52.92	8.23	8.23	8.80	8.94
16-Nor-O-methyl-podocarp-4β-yl-	100	150 (dec.)	69.54	69.22	7.88	7.73	4.06	4.28
C_6H_5-	63	126.5 [a]	60.33	60.32	5.06	4.91	7.82	7.76
Mesityl-	100	139.5-140 (dec.) [b]	65.14	65.23	6.83	6.78	6.33	6.26
n-Hexyl-	14	82.5- 83	57.73	57.68	9.15	9.18	7.48	7.38

a) lit.,[54] m.p. 125-126°; b) lit.,[51] m.p. 136-138° (dec.).

Table 5

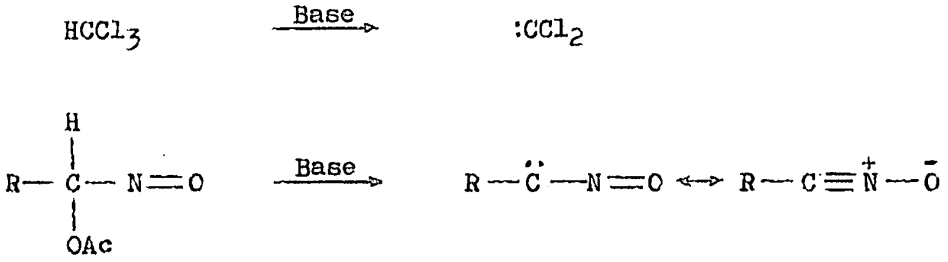
NMR and IR Data for N-Acetoxyhydroxamic Acids
Obtained from Aldoximes

RCONHOAc	NMR Chemical Shift, δ ppm		Solvent	IR $\bar{\nu}_{max}$ cm-1	Solvent
R	N-H	OAc			
$(CH_3)_3C$-	9.8	2.16	c	3370(w-m), 1780(s), 1720(s), 1198(s)	a
16-Nor-O-methyl-podocarp-4β-yl-	9.3	2.18	c	3370(w-m), 1780(s), 1715(s), 1198(s)	a
C_6H_5-	10.4	2.17	c	3360(m), 1790(s), 1705(s)	b [1]
Mesityl-	9.3	2.36 [2]	c	3380(m), 1800(s), 1710(s)	b
n-Hexyl-	9.8	2.18	c	3360(m), 1795(s), 1735(s) 1200(s)	a

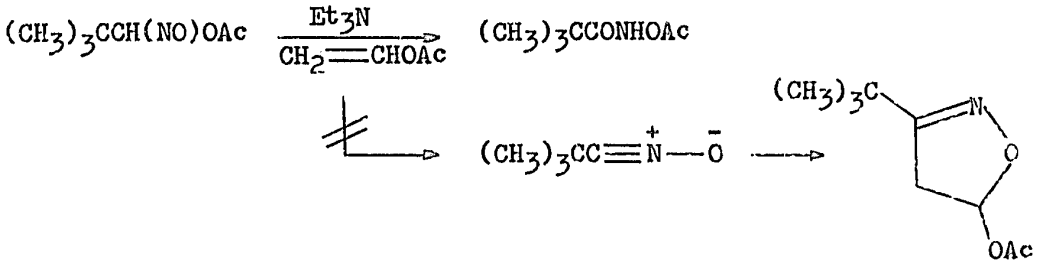
a) CCl_4; b) $CHCl_3$; c) $CDCl_3$; 1) KBr pellet: 3160(m), 1800(s), 1660(s), and 1204(s) cm^{-1};
2) or signal at 2.27 ppm (?).

C. Oxidation of Syn Aldoximes and Trapping of the Intermediate Nitrile Oxides with Vinyl Acetate.

The recognition of two mechanistic pathways for the formation of N-acetoxyhydroxamic acids cast some doubt on the proposed general nature of nitrile oxides as the necessary and only intermediates in the lead tetraacetate oxidation of syn aldoximes. It is conceivable that nitrile oxides are formed by a 1,1-elimination of acetic acid from the geminal nitrosoacetate in analogy to carbene formation:[56]



However, the formation of nitrile oxides by a 1,1-elimination could be excluded on the basis of the following observation. When 1-acetoxy-1-nitroso-2,2-dimethylpropane was treated with triethylamine in a large excess of vinyl acetate only N-acetoxytrimethylacetohydroxamic acid, but no isoxazoline acetate could be isolated:



Nitrile oxides under these conditions are known to give isoxazoline acetates,[52,57] and the formation of such derivatives is therefore diagnostic for nitrile oxides as intermediates.

A general procedure was worked out for high yield conversion of syn aldoximes to isoxazoline derivatives. The aldoxime was dissolved in methylene chloride and a large molar excess (> 100) of vinyl acetate was added. This solution was cooled to -78° and a cold solution of lead tetraacetate in methylene chloride was added over a period of one minute. For high yields efficient cooling was important. After one hour, a solution of triethylamine in methylene chloride was added to neutralize the acetic acid liberated in the oxidation reaction. Depending on the solubility of the aldoxime, oxidation times varied, but one hour was generally found satisfactory. Reaction times of up to two and a half hours still produced the same results. Even when using reasonably large quantities of solvent most aldoximes precipitated to some extent at -78°, yet redissolved as they reacted with lead tetraacetate.

Triethylamine was found to act merely as an acid scavenger since the oxidation in its absence also proceeded to isoxazoline acetates, although in low yields, the main product of the reaction being the N-acetoxyhydroxamic acids. The commonly employed acid scavenger in lead tetraacetate oxidations, calcium carbonate,[58] was found to be ineffective (Na_2HPO_4, $NaHCO_3$, and K_2CO_3 failed similarly).

It could be demonstrated that an anhydrous ethereal solution of acetic acid does not evolve carbon dioxide upon addition of a carbonate ($CaCO_3$, $NaHCO_3$, or K_2CO_3); only after adding a small quantity of water can evolution of a gas (CO_2) be observed.

Triethylamine could be replaced by pyridine. In fact, the oxidation could be carried out in the presence of pyridine. The same products were obtained, yet work-up was more tedious and losses were higher, especially when reacting low molecular weight aldoximes.

The oxidation could also be conducted in methylene chloride alone with subsequent addition of vinyl acetate/triethylamine; this approach gave purer products, but lower yields (40-50%). Further, the reaction could be carried out in the presence of ethanol. The rate of oxidation was higher than in methylene chloride/vinyl acetate as deduced from a sudden temperature rise upon addition of lead tetra-acetate to the aldoxime. This approach also gave lower yields (40-50%).

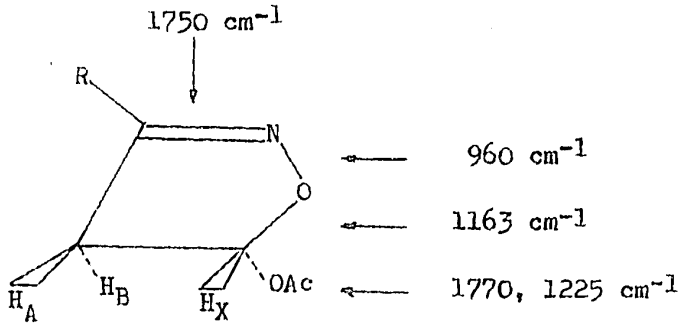
The reaction was found to be limited to syn aldoximes which do not bear a phenolic hydroxy group, and would probably also fail in the presence of aromatic primary and secondary amines. It could be established that phenolic hydroxy groups react faster with lead tetra-acetate than oxime hydroxy groups. For instance, oxidation of para- and meta-hydroxybenzaldoxime (100% syn) afforded tarry products, containing no detectable amounts (IR, NMR) of isoxazoline acetates.

Interception of nitrile oxides by 1,3-dipolar cycloaddition is not limited to vinyl acetate and other dipolarophilic compounds should be equally suitable. The choice of vinyl acetate in this investigation was prompted by the following considerations: 1. vinyl acetate is inexpensive and therefore economical since it has to be used in a large excess; 2. it is volatile and easily removed in the work-up; 3. it leads to highly crystalline derivatives; 4. it is a very reactive olefin which reacts readily with lead tetraacetate at room temperature; it thus served to demonstrate that this reaction can be carried out on oximes bearing reactive double bonds; 5. 5-acetoxy-2-isoxazolines can be readily converted to preparatively useful 2-isoxazoles[59] by simple acetic acid elimination.[60]

The oxidation of acetaldoxime (41% syn and 59% anti isomer) gave a mixture of products which by IR estimate contained not more than 30% of 5-acetoxy-3-methyl-2-isoxazoline. No attempt was made to isolate this compound, since for preparative purposes it can be obtained more conveniently from nitroethane.[57]

All data which were obtained for characterization and identification of the isoxazoline acetates are compiled in Tables 6 and 7 (pp. 35,36). Of the compounds listed only 5-acetoxy-3-phenyl-2-isoxazoline has been described, and its physical properties (m.p., UV absorption) were found to be in satisfactory agreement with literature values.[60,61] The reported divergence in

melting points - 88-89°[61] and 107°[60] - was resolved by showing that recrystallization from hexane/ethanol leads to material melting at 90.5°, and vacuum sublimation affords a material melting at 106°. The two (crystal) forms are interconvertible and arise from the same compound (IR, NMR, Anal., identical). The other isoxazoline acetates were identified by their IR and NMR spectra and elemental analysis data. Characteristic IR features of the isoxazoline acetates are the bands at 1770(s), 1750(shoulder), 1225(s), 1163(s), and 960(s) cm^{-1}, which were assigned to the stretching modes as shown:



Variations in band position for the various substrates (R) were found to be small ($< \pm 7.5$ cm^{-1}). The NMR spectra of the isoxazoline acetates showed in all cases a characteristic set of signals arising from an ABX system of protons. A set of three quartets was observed, respectively centered at (R = alkyl): 2.8 ppm (H_A), 3.3 ppm (H_B), and 6.7 ppm (H_X) with coupling constants J_{AB} = 18 cps, J_{AX} = 6 cps, and J_{BX} = 2 cps. When R = aryl, the signals for H_A and H_B were shifted downfield by ca. 0.4 ppm and for H_X by 0.1 to 0.2 ppm. The nature of

the substituent R had no effect on the coupling constants. Since the signals for protons H_A, H_B, and H_X fell normally well out of the region of proton signals arising from the substituent R, an easy means was provided to estimate relative amounts of isoxazoline acetates in crude reaction mixtures.

As a representative example, the IR and NMR spectrum of 5-acetoxy-3-t-butyl-2-isoxazoline are shown in Figure 4 (p. 34).

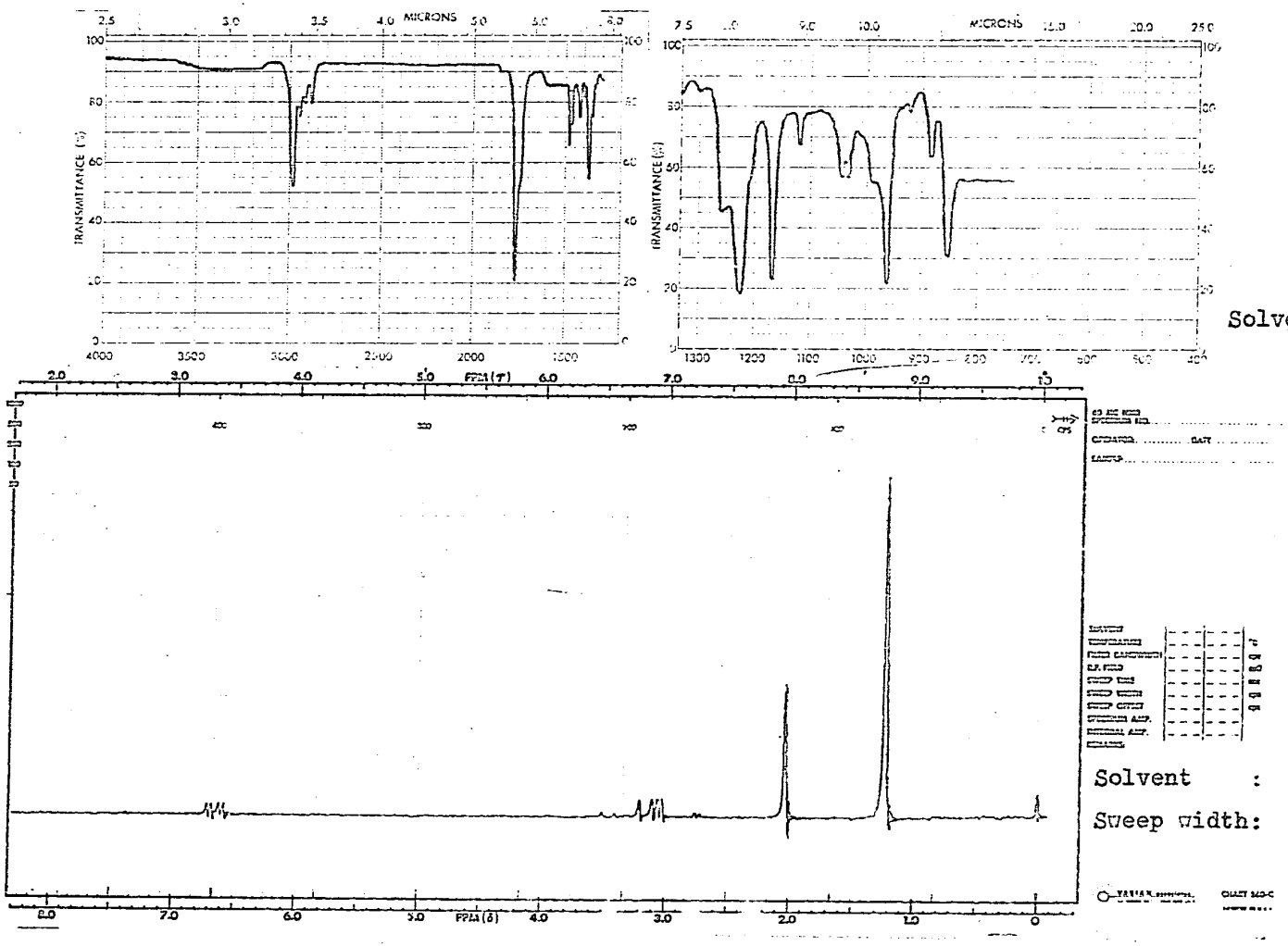
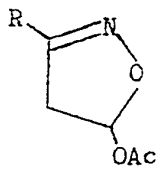


Figure 4. The IR and NMR Spectrum of 5-Acetoxy-3-t-butyl-2-isoxazoline

Table 6

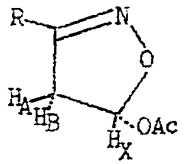
3-Substituted 5-Acetoxy-2-isoxazolines

	Yield	m.p.	Anal. %						Remarks
			C		H		N		
R	%	°C	calcd.	found	calcd.	found	calcd.	found	
$(CH_3)_2CH$-	97	33.5- 34	56.12	56.18	7.65	7.61	8.18	8.19	Recryst., from pentane. Yield based on syn aldoxime.
$(CH_3)_3C$-	78	51.5	58.36	58.45	8.16	8.19	7.56	7.57	
16-Nor-O-methyl-podocarp-4β-yl-	100	52-54	-	-	-	-	-	-	Crude yield.
C_6H_5-	81	90.5 [1)]	64.38	64.39	5.40	5.35	6.83	6.83	m.p. 106°, vac. sublimed.
p-$CH_3OC_6H_4$-	78	140-141	61.27	61.47	5.57	5.81	5.96	6.03	
p-$NO_2C_6H_4$-	86	150	52.80	52.76	4.03	4.31	11.20	11.24	Oxidation time 1½ hr.

1) lit.,[59] m.p. 88-89°.

Table 7

NMR and IR Data for 3-Substituted 5-Acetoxy-2-isoxazolines



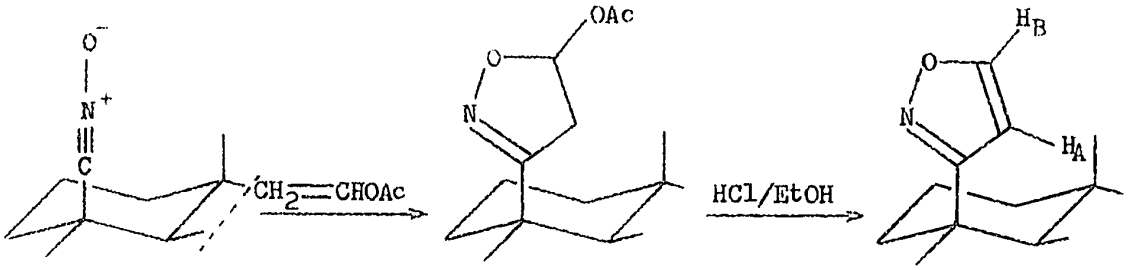
R	NMR Chemical Shift, δ ppm				Solvent	IR $\bar{\nu}_{max}$ cm^{-1}	Solvent
	H_A 1)	H_B 1)	H_X 1)	OAc			
$(CH_3)_2CH$-	2.74	3.23	6.53	2.02	a	1770(s), 1750(m), 1225(s), 1163(s), 960(s)	a
$(CH_3)_3C$-	2.82	3.33	6.78	2.06	b	1770(s), 1755(m), 1225(s), 1168(s), 962(s)	a
16-Nor-O-methyl-podocarp-4β-yl-	2.84	3.32	6.61	1.95 2) 2.02	b	1770(s), 1750(m), 1225(s), 1168(s), 963(s)	a
C_6H_5-	3.28	3.67	6.84	2.04	b	1770(s), 1745(m), 1220(s), 1166(s), 958(s)	a
p-$CH_3OC_6H_4$-	3.31	3.68	6.88	2.08	b	1770(s), 1745(m), 1230(s), 1171(s), 967(s)	a
p-$NO_2C_6H_4$-	3.31	3.72	6.87	2.07	b	1775(s), 1750(m), 1220(s), 1169(s), 958(s)	a

1) Each signal is split into a quartet: J_{AB} = 18 cps, J_{AX} = 6 cps, J_{BX} = 2 cps.

2) 1:1 mixture of diastereomers. a = CCl_4; b = $CDCl_3$.

D. Preparation of 3-Substituted 2-Isoxazoles.

The reaction of O-methylpodocarponitrile oxide (12) with vinyl acetate (reflux in benzene) afforded a 1:1 mixture of the diastereomeric 5-acetoxy-3-(16-nor-O-methylpodocarp-4β-yl)-2-isoxazoline (19) as shown by the NMR spectrum. Separation of the two isomers was not possible as chromatography (TLC*: one spot), crystallization, and vacuum sublimation failed to produce any resolution. The mixture was therefore converted by refluxing in acidic (HCl) ethanol[60] to the corresponding 2-isoxazole (20) (80%, based on nitrile oxide 12):



12 19 20

While the IR spectrum of 2-isoxazole 20 was not particularly informative, the NMR spectrum showed a characteristic set of two doublets at 6.32 and 8.31 ppm, which were respectively assigned to protons H_A and H_B (J_{AB} = 1.7 cps).

---

* Thin Layer Chromatography.

As shown in the preceding section, 3-t-butyl-5-acetoxy-2-isoxazoline can be prepared from trimethylacetaldoxime. When recording an NMR spectrum of this isoxazoline acetate immediately after dissolution in deuterochloroform, a set of signals was obtained consistent with the assigned structure. However, when recording a second spectrum of the same solution after one day, the isoxazoline acetate was converted to about one half to two new compounds (ratio 1:1). Two days later this conversion was complete. Analysis of the spectrum clearly indicated the presence of acetic acid (2.07 ppm, OAc; 11.6 ppm, COOH) and 3-t-butyl-2-isoxazole (1.34 ppm, t-butyl; 6.25 ppm, $H_A-C=C-$; 8.29 ppm, $-C=C-H_B$). Apparently, the acetic acid elimination was catalyzed by hydrochloric acid which is present in chloroform in small quantities.

Under comparable conditions, isoxazoline acetate 19 did not eliminate acetic acid, but required more vigorous conditions. This suggests that the rate determining step is the proton removal by the chloride ion, which probably is much slower in the more hindered isoxazoline acetate 19.

The IR and NMR spectrum of the 1:1 mixture of acetic acid and 3-t-butyl-2-isoxazole are shown in Figure 5 (p. 39).

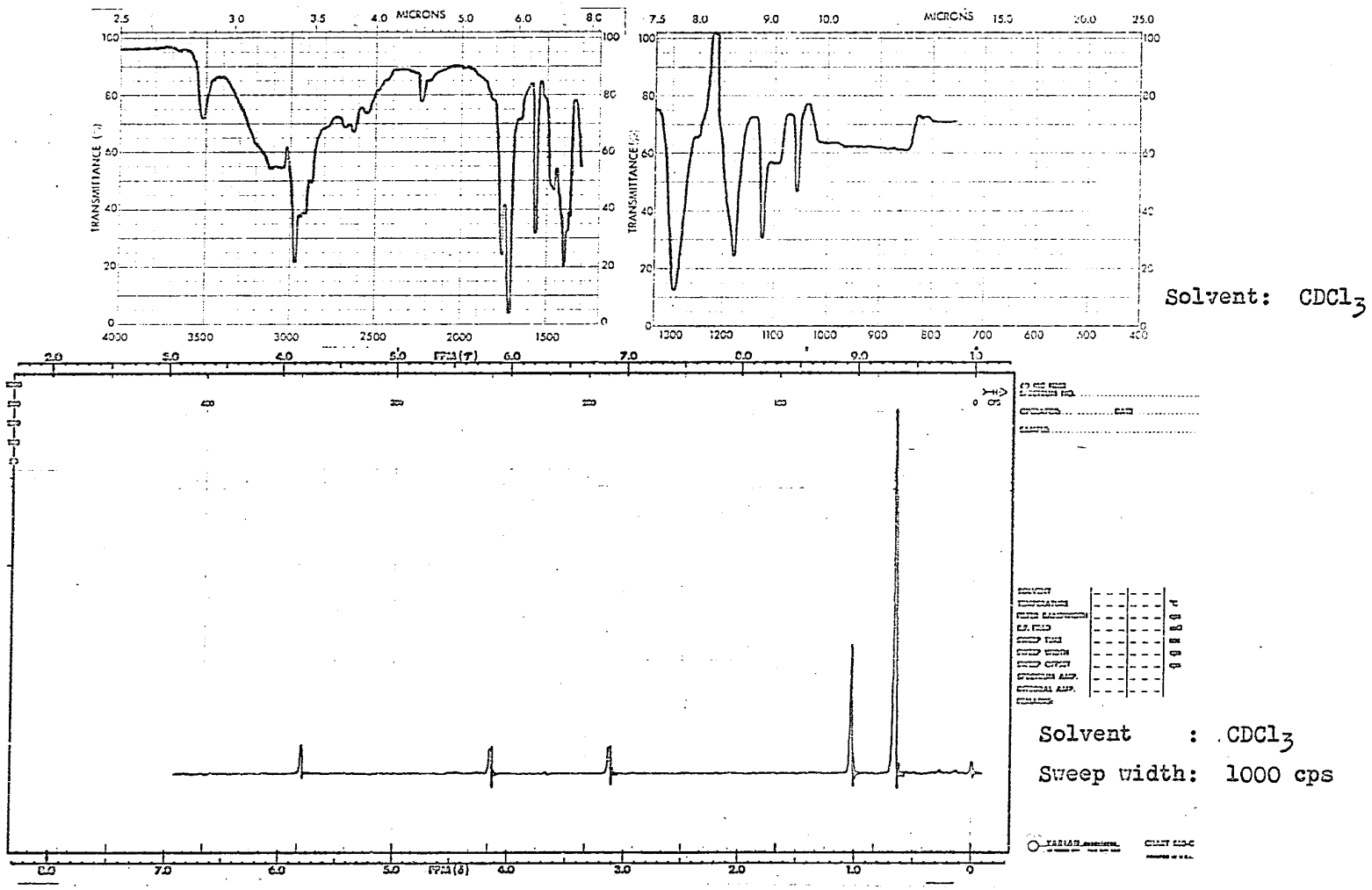


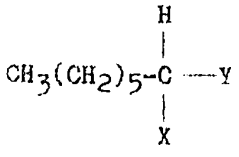
Figure 5. The IR and NMR Spectrum of a 1:1 Mixture of Acetic Acid and 3-t-Butyl-2-isoxazole

E. Oxidation of Anti-n-Heptanaldoxime.

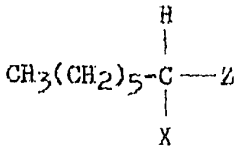
In the oxidation of syn aldoximes it became apparent that the reaction has sterochemical requirements, for oxidation of syn/anti aldoxime mixtures led to much lower yields of nitrile oxides. The yields obtained corresponded approximately to the amount of syn isomer in the aldoxime mixture indicating that anti aldoximes react differently. To further substantiate this point, pure anti-n-heptanaldoxime was treated with lead tetraacetate in methylene chloride at -78°. A hazy yellow solution resulted which on raising the temperature showed the following changes: at -70° formation of a green colour accompanied by precipitation of lead diacetate; the green colour reached an intensity maximum at -55 to -50°, then slowly faded to a grey/yellow at -25 to -20°. A different green/blue colour began to form at -10° which intensified to a deep green/blue at room temperature. The last colour was reversible: it turned to pale yellow at -78° and reappeared on raising the temperature above -10°. An intermediate green colour in the range of -70 to -25° could not be observed again. The same sequence of colour changes was noted for the oxidation of acetaldoxime (41% syn and 59% anti isomer).

NMR and IR spectral analysis of the crude reaction product from the anti-n-heptanaldoxime oxidation revealed a complex mixture, which contained five or more different components. The NMR spectrum

showed as notable features two, partly overlapping, triplets at 6.60 and 6.65 ppm of approximately the same intensity and coupling constant (J = 5 cps). Comparison of the joint integrated area of the two signals with the area of the terminal methyl group indicated the presence of approximately 38 mole % of a 1:1 mixture of components 21 and 22:



21



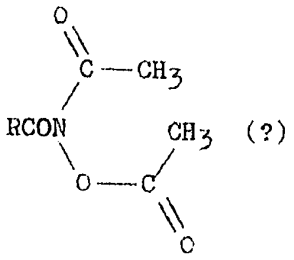
22

Component 21 was later shown to be a geminal nitrosoacetate and 22 appeared to be the corresponding nitroacetate. Further, there were four major singlet signals in the range of 1.8 to 2.2 ppm, suggesting methyl groups attached to fairly electronegative groups ($-\overset{|}{N}-$; $-\overset{|}{C}=O$). Between 2.2 and 6.6 ppm there were no signals. Comparison of the integrated areas between 1.8 to 2.2 and 0 to 1.7 ppm suggested ca. 40 mole % of material which cannot be assigned to compounds bearing a methyl group attached to an electronegative group ($-\overset{|}{N}-CH_3$; $O=\overset{|}{C}-CH_3$). These data are consistent with the spectral characteristics of an aldazine-bis-N-oxide. However, other formulations cannot be excluded at this point.

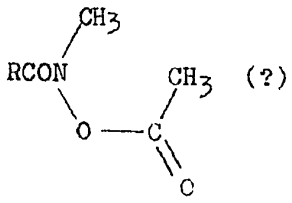
The IR spectrum revealed as notable features bands at 1840(m), 1820(m-s), 1770(s), 1730(m-s), 1295(m-s), 1205(s), and 1128(s) cm^{-1}. Removal of volatile material by pumping at 10° and 0.1 mm Hg permitted collection of a liquid fraction in a cold trap. This fraction was shown to contain acetic anhydride and acetic acid. Reinspection of the crude residue by IR spectroscopy indicated the absence of the bands at 1840, 1730, 1295, and 1128 cm^{-1} which were thus shown to arise from acetic anhydride and acetic acid. It should be noted that the crude oxidation product was washed acid free with sodium bicarbonate solution before the first spectral inspection. Therefore, the acetic acid must have been formed after work-up, i.e., on standing at room temperature.

Low temperature recrystallization (-78°) from pentane permitted isolation of 9 to 14% of 1-acetoxy-1-nitroso-n-heptane. This material accounted for component 21 with a triplet signal in the NMR spectrum at 6.65 ppm. The mother liquor of the recrystallization showed enhanced intensity of the other triplet at 6.60 ppm in addition to other weak and poorly resolved signals in the same region. Interestingly, the IR spectrum of the mother liquor showed now a medium intense band at 1550 cm^{-1} which could be shown not to arise from the nitrosoacetate 21, but rather suggested the presence of a nitro compound (22).

Semi-quantitative IR analysis indicated approximately 10% of acetic anhydride in the crude (not evacuated) oxidation product. The band at 1820 cm^{-1} was shown not to arise from acetyl peroxide,[62] but is most likely due to a trisubstituted hydroxylamine (23 or 24):



23

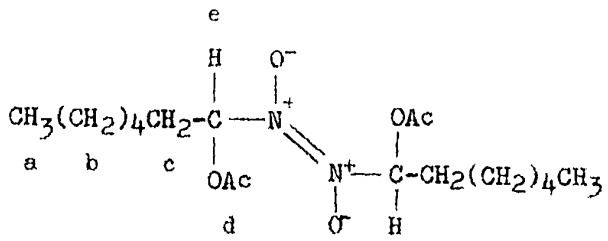


24

In another experiment, it could be shown that the oxidation was not affected by the presence of oxygen. Since free radicals are probable intermediates in this reaction, interaction of these with oxygen could have conceivably led to different products.

The isolated nitrosoacetate 21 is a colourless, crystalline compound which melts at 84 to 85°. When dissolved in chloroform, it gives a blue solution showing only a very weak band in the IR spectrum at 1570 cm^{-1}, which is indicative of monomeric nitrosoacetate.[63] On heating the solution, the blue colour and the band at 1570 cm^{-1} become more intense; on cooling (-78°), a colourless solution results which turns blue again only on raising the temperature above -10°.

These observations in conjunction with the UV spectrum ($\lambda_{max}^{cyclohexane}$ 293 mμ (ε, 3050), trans bis-nitroso configuration[64]) indicate a predominantly dimeric structure for the nitrosoacetate in solution. Confirmation for this conclusion is provided by the solid state IR spectrum (Figure 6, p. 45) which also indicates a trans bis-nitroso configuration[63] ($\bar{\nu}_{max}^{KBr}$: 1660(m) and 1192(s) cm^{-1}) in addition to the presence of an acetate group ($\bar{\nu}_{max}^{KBr}$: 1775(s) and 1220(s) cm^{-1}). This structure proposal is substantiated by the NMR spectrum (Figure 6, p. 45) which permitted to make the following assignments:



a = 0.90 ppm (T, 3 H, J = 5 cps)

b = 1.31 ppm (M, 8 H)

c = 1.84 ppm (M, 2 H)

d = 2.12 ppm (S, 3 H)

e = 6.65 ppm (T, 1 H, J = 5.8 cps)

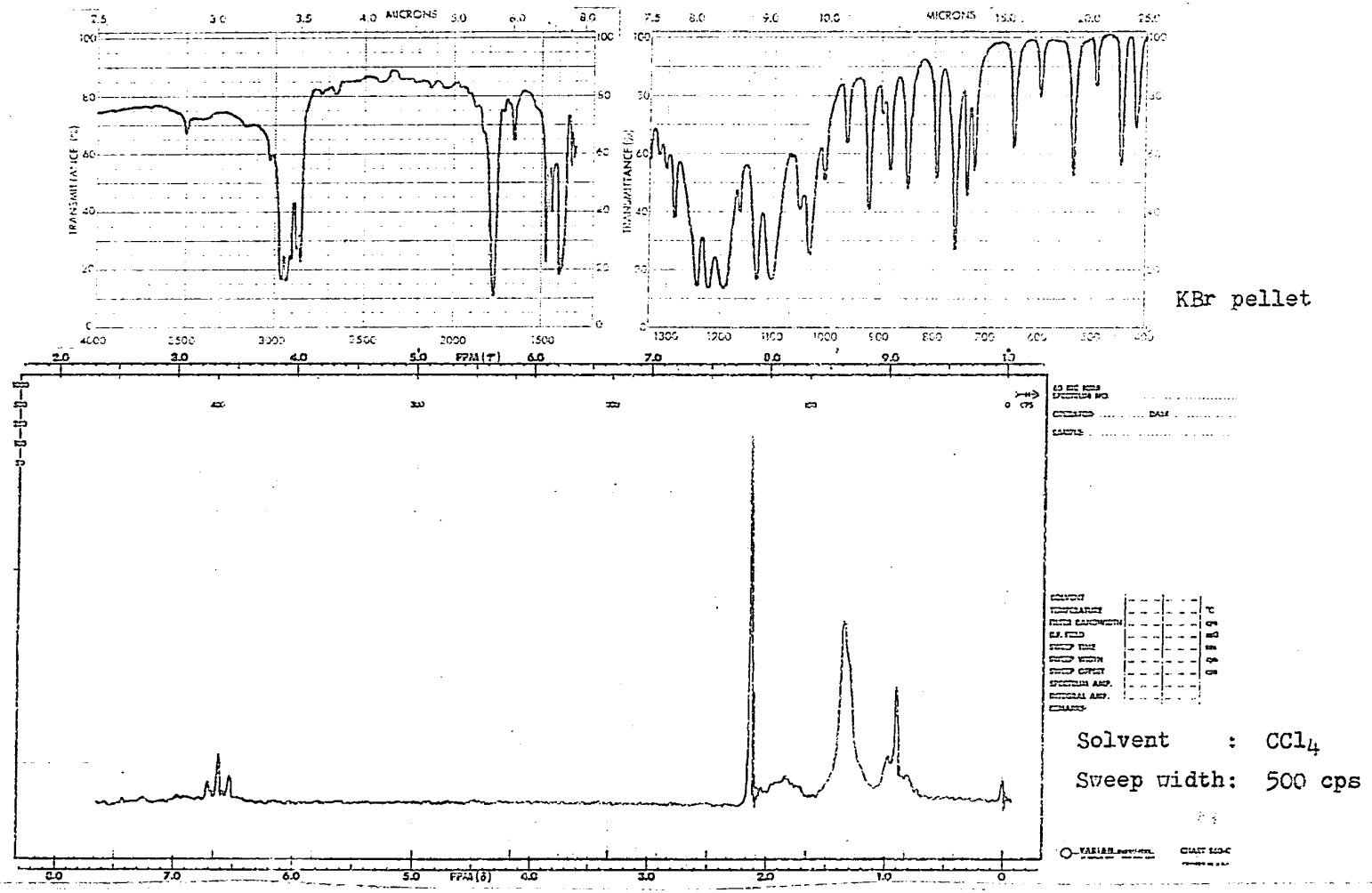
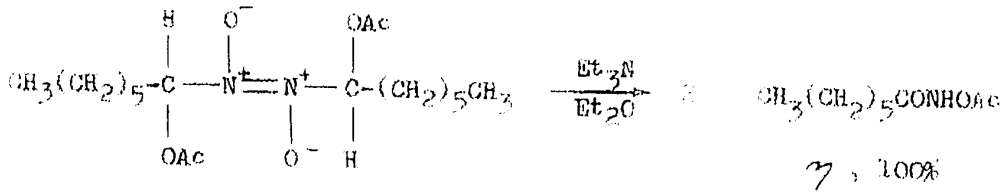


Figure 6. The IR and NMR Spectrum of Dimeric 1-Acetoxy-1-nitroso-n-heptane

F. Rearrangement of 1-Acetoxy-1-nitrosoalkanes.

As pointed out on p. 22, 1-acetoxy-1-nitroso-2,2-dimethylpropane can be easily rearranged to the corresponding N-acetoxyhydroxamic acid, either by prolonged standing in solution or by addition of triethylamine. In an analogous manner, nitrosoacetate 21 was found to rearrange to N-acetoxyheptanohydroxamic acid (25):



21

25, 100%

25

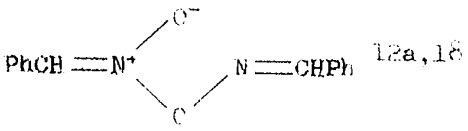
The reaction, therefore, appears to be general for 1-acetoxy-1-nitrosoalkanes. Addition of triethylamine merely accelerates the rearrangement as does gentle heating of the nitrosoacetate as a solid or in solution. Similarly, rearrangement occurs when trying to chromatograph nitrosoacetate solutions on either alumina or silica gel. When storing crystalline nitrosoacetate 21 at -5° in the dark, no changes were observed after two months.

Elemental analysis and spectral data for the N-acetoxyheptanohydroxamic acid are compiled in Tables 4 and 5 (pp. 26, 27).

G. Oxidation of Anti-Benzaldoxime.
(Preparation of Phenylaldazine-bis-N-oxide)

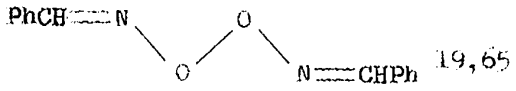
Treatment of anti-benzaldoxime at -78° with an equimolar amount of lead tetraacetate in methylene chloride produced a hazy, yellow solution which turned intensely green on raising the temperature above -70°. The formation of the green colour was accompanied by precipitation of lead diacetate. On further raising the temperature, the green slowly faded to colourless. Work-up at low temperature (-20 to 0°) produced a white crystalline compound which was found to be identical with phenylaldazine-bis-N-oxide (10a).[20] Identity was established by comparison with reported IR spectral data (Figure 7, p. 52) and the melting point (found, 109-110°; reported, 108-109°).[12a, 18] Compound 10a can also be prepared by oxidation of benzaldoxime (syn or anti) with a number of conventional oxidizing agents (N_2O_3,[19] N_2O_4,[12a] Na_2CO_3/I_2,[65] $K_3Fe(CN)_6$,[19] and $Pb(OAc)_4$[18]), as well as by reaction of phenyldiazomethane with nitric oxide.[20] Oxidation of aromatic aldoximes in general leads to this type of compound and both the syn and anti aldoxime give the same product when the reaction is carried out at room temperature.[18,19,65] A number of proposals for the structure have been put forward, and

those most acceptable - in the light of modern theory - are the following:



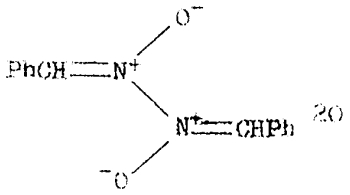
12a,18

5a



19,65

9a

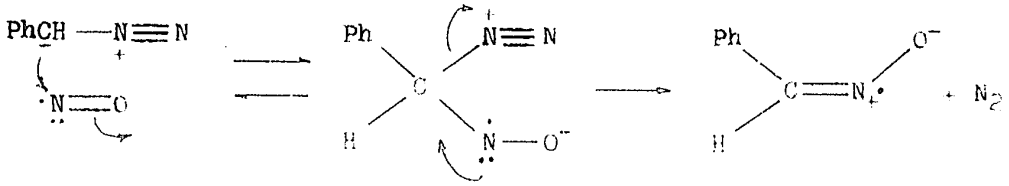


20

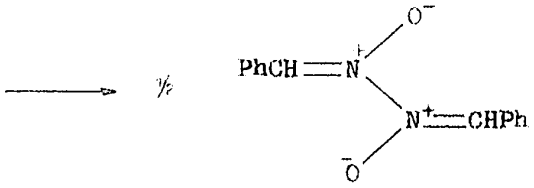
10a

Structure 9a can be excluded because the compound does not behave like a peroxide,[66] i.e., an acidic iodide solution is not oxidized to iodine. The choice between structures 8a and 10a is a more difficult one and is presently debated.[18] Formation of compound 10a

by reaction of phenyldiazomethane with nitric oxide was convincingly rationalized by proposing the following mechanism:[20]

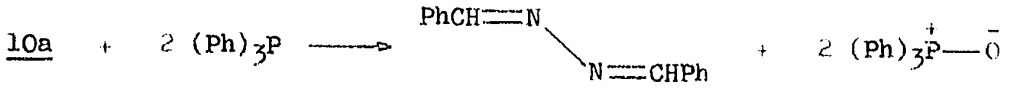


4a



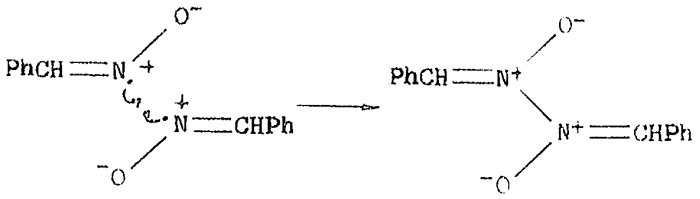
10a

This mechanistic proposal was substantiated by detection of iminoxy radicals 4a (ESR) and measurement of the stoichiometric amount of nitrogen liberated during the reaction. Further, mild reduction of 10a with triphenylphosphine afforded phenylaldazine (26) and triphenylphospine oxide:[20]



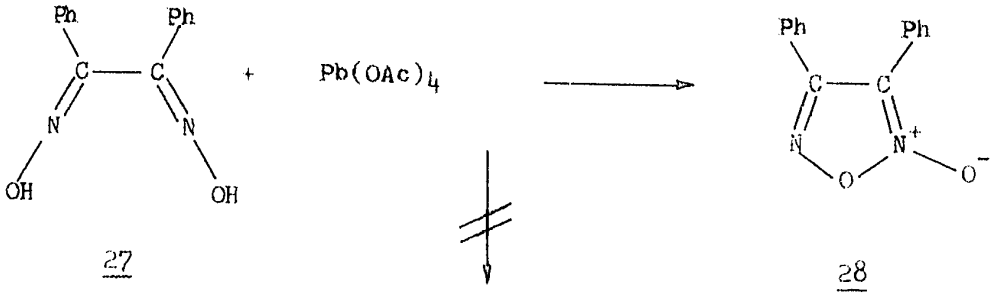
26

Additional evidence for the correctness of structure 10a is provided by the observation of iminoxy radicals 4a in the oxidation of benzaldoxime.[1] These radicals show appreciable spin density at the nitrogen atom,[1,6,9] which would suggest preferential energy dissipation by dimerization at the nitrogen atoms leading to compound 10a:

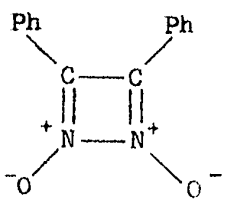


10a

The observation[18] that benzildioxime (27) reacts with lead tetra-acetate to diphenylfuroxan (28) does not invalidate the aldazine-bis-N-oxide structure, because formation of the four-membered ring azine-bis-N-oxide 29 would be highly unfavoured for steric reasons.

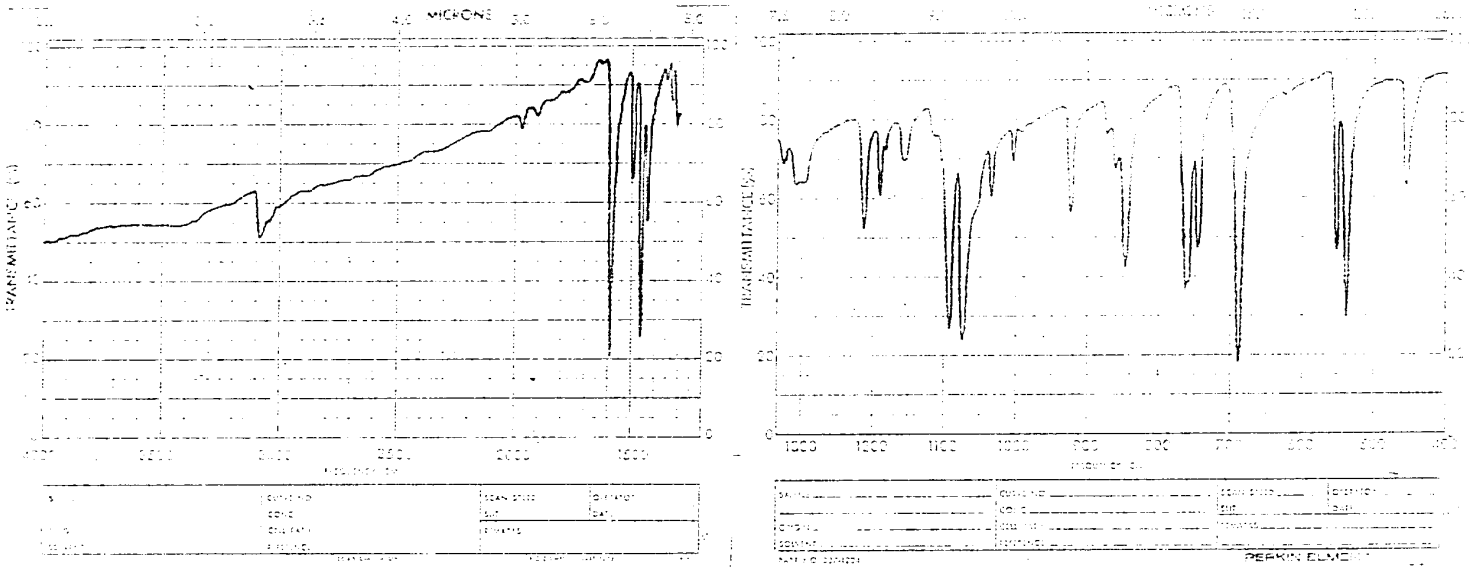


27 28



29

These results suggest strongly that oxidation of aromatic aldoximes leads to aldazine-bis-N-oxides and the product of the low temperature oxidation of anti-benzaldoxime with lead tetraacetate is phenylaldazine-bis-N-oxide (10a).

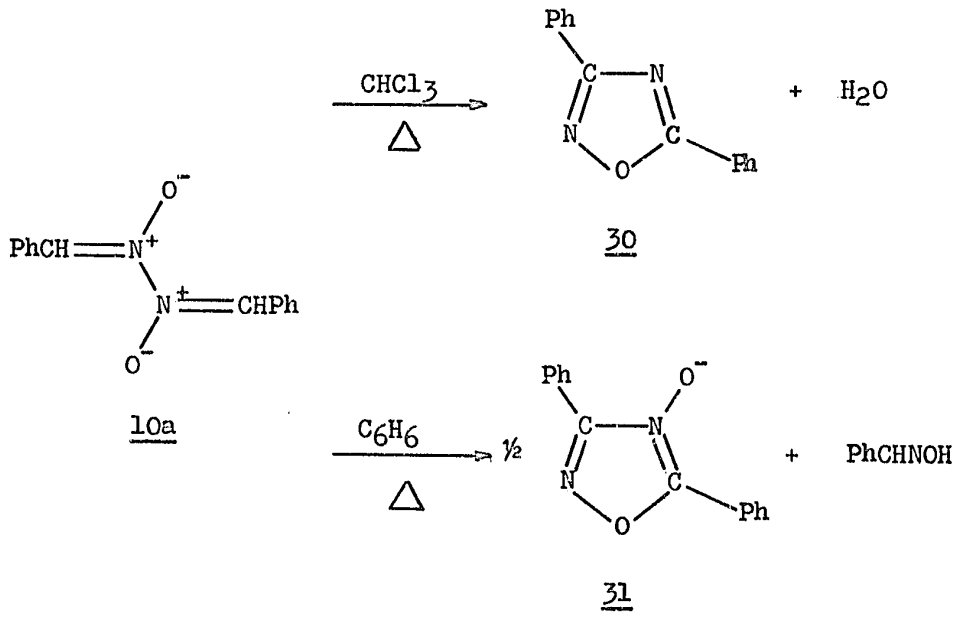


KBr pellet

Figure 7. The IR Spectrum of Phenylaldazine-bis-N-oxide

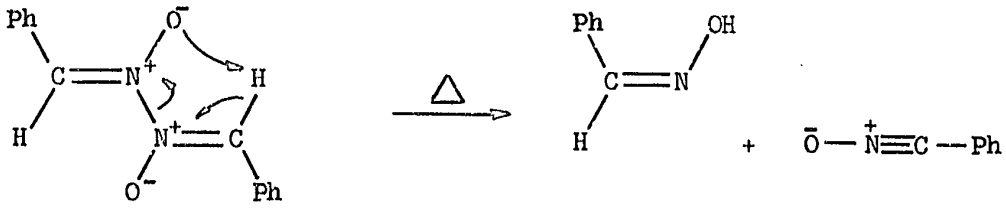
H. Thermal Decomposition of Phenylaldazine-bis-N-oxide.

Aldazine-bis-N-oxides are rather unstable compounds and decompose easily on exposure to light or heat. In particular, heating of phenylaldazine-bis-N-oxide (10a) in chloroform[12a] has been reported to lead to 3,5-diphenyl-2,4-oxadiazole (30) and water, while heating of the same compound in benzene[65] gave predominantly 3,5-diphenyl-2,4-oxadiazole-4-N-oxide (31) and benzaldoxime:



No mechanistic interpretation for the formation of compounds 30 and 31 has been given so far.[12] An attempt to generate and observe (ESR) free radicals in the thermal decomposition of compound 10a led to negative results.[20] It was therefore decided to study the thermal

decomposition by IR spectroscopy in the hope of gaining some understanding about the formation of the oxadiazole derivatives 30 and 31. This approach indeed provided a satisfactory answer. It could be observed that heating of compound 10a in carbon tetrachloride (50°) led to a mixture of benzonitrile oxide and benzaldoxime. In a subsequent reaction all of the benzonitrile oxide and most of the benzaldoxime were consumed. In a second experiment compound 10a was briefly refluxed in vinyl acetate which afforded a semi-crystalline mixture of 5-acetoxy-3-phenyl-2-isoxazoline (1 mole), benzaldoxime (3 moles), and a compound (or compounds) containing only aromatic protons (Ph-?-Ph, 1 mole).* These results clearly indicate that phenylaldazine-bis-N-oxide undergoes thermal decomposition to benzonitrile oxide and benzaldoxime, probably via a transition state as shown:



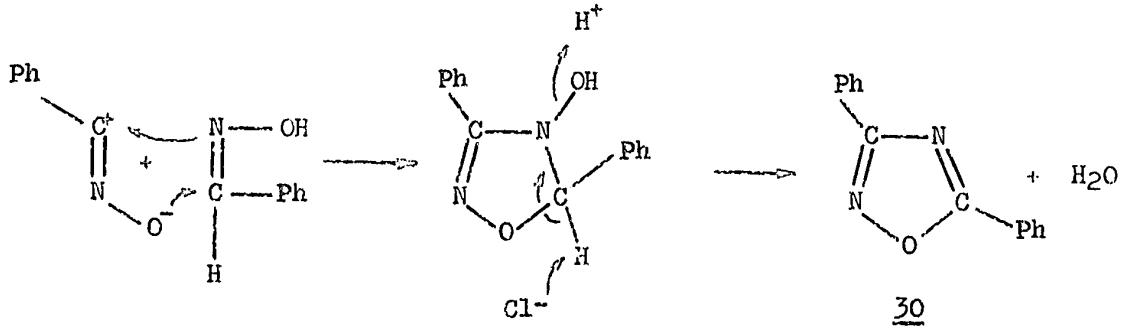
In a subsequent step benzonitrile oxide reacts with any dipolarophile, which is present in solution, to a five-membered ring heterocycle. Thus, reaction of benzonitrile oxide with benzaldoxime would lead to

---

* NMR estimate.

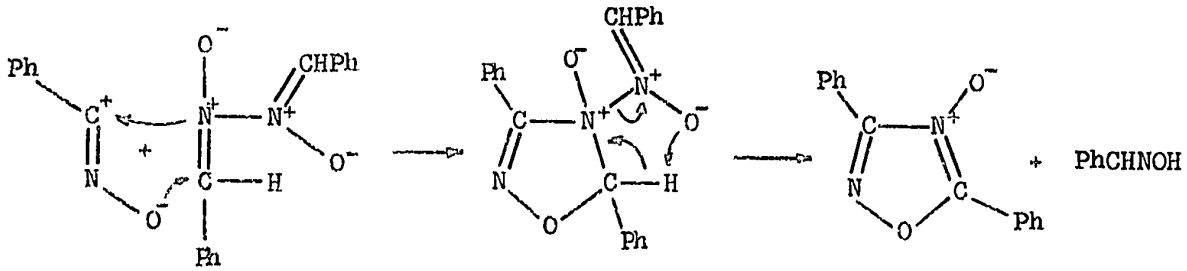
oxadiazole 30 and water (Equation 1), reaction with phenylaldazine-bis-N-oxide to oxadiazole-N-oxide 31 and benzaldoxime (Equation 2), and reaction with vinyl acetate to isoxazoline acetate 32 (Equation 3).

Equation 1:



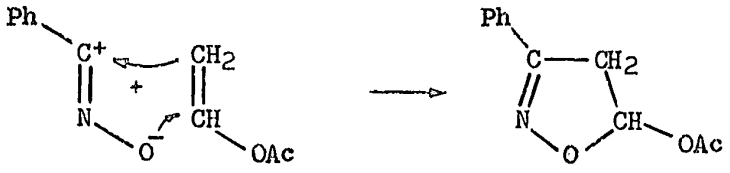
30

Equation 2:



31

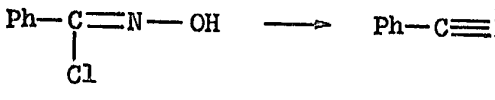
Equation 3:

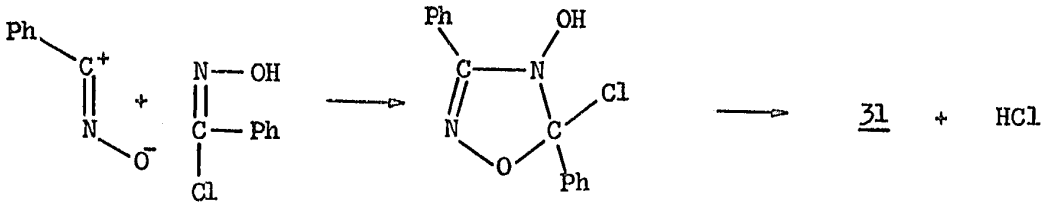


32

The observation that thermal decomposition of compound 10a in chloroform leads predominantly to the oxadiazole 30, suggests that traces of hydrochloric acid - a decomposition product of chloroform - promote fast and complete formation of benzonitrile oxide and benzaldoxime, and may also assist in the indicated (Equation 1) water elimination from the intermediate oxadiazoline. Decomposition in the absence of hydrochloric acid is appreciably slower.* The initially formed nitrile oxide will therefore add to the more reactive dipolarophile - phenylaldazine-bis-N-oxide - leading via an oxadiazoline-N-oxide to oxadiazole-N-oxide 31 and benzaldoxime. Though neither benzaldoxime nor aldazine-N-oxides have been shown to undergo 1,3-dipolar cycloadditions with nitrile oxides, they can be expected to do so on the ground of recent studies on other compounds bearing carbon-nitrogen double bonds (Schiff bases, e.g.).[51,52]

Another example of this type of reaction is found in the formation of the oxadiazole-N-oxide 31 from benzohydroxamic acid chloride:[52,67]





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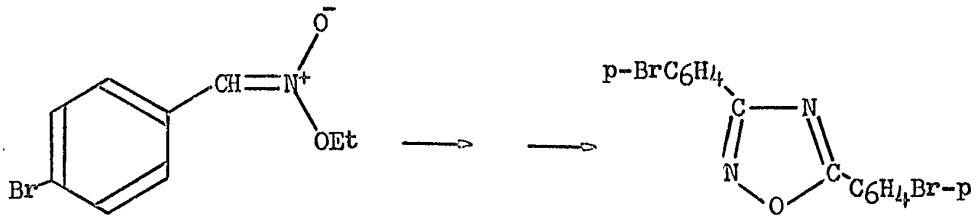
* Catalysis of decomposition by hydrochloric acid has been demonstrated.[18]

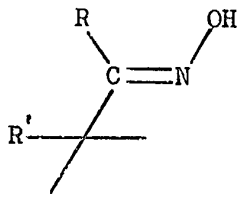
Lastly, the recently[68] discovered conversion of p-bromophenylnitronic acid ester 33 to the oxadiazole 34 finds also a rational explanation by assuming intermediate formation of a nitrile oxide and an aldoxime, followed by a 1,3-dipolar cycloaddition:



33 34

CHAPTER III. OXIDATION OF KETOXIMES

Exploratory experiments with hindered ketoximes of type A:



R, R' = alkyl

A

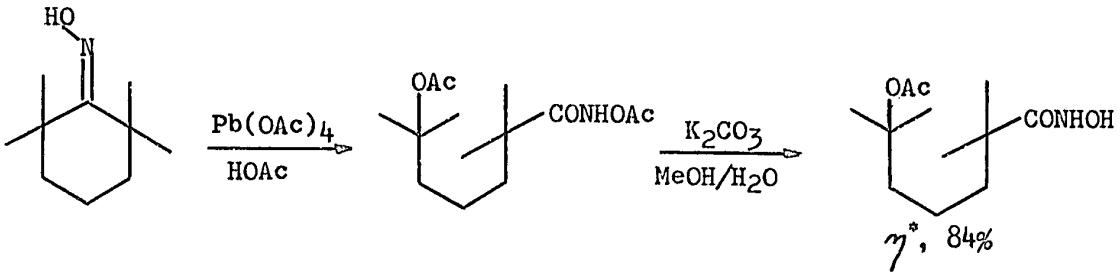
and lead tetraacetate in aprotic solvents, ranging in dielectric constant from one to forty, led to colourless or pale green product mixtures. These mixtures were shown by TLC to consist of two major and eight or more minor components.

Reaction in a protic solvent - acetic acid - however, led to essentially one product (TLC) and was therefore investigated in detail.

A. Oxidative Cleavage of Methylated Cyclohexanone Oximes.

2,2,6,6-Tetramethylcyclohexanone oxime (35). As a first convenient model, 2,2,6,6-tetramethylcyclohexanone oxime was chosen. Its reaction with an equimolar amount of lead tetraacetate in acetic acid at room temperature (10 min) led to a pale green oil.

NMR spectral analysis and titration of the amidohydrogen indicated 90 ± 5% of the hydroxamic acid derivative 36. Compound 36 could not be made to crystallize and chromatographic separation (SiO_2, Al_2O_3) as well as vacuum distillation led to decomposition (isocyanate formation ?). Only molecular distillation at or below 50° gave an oily distillate which was practically pure compound 36. This approach was not used for preparative scale work since mild hydrolysis with methanolic potassium carbonate solution converted the crude product 36 in good yield to the crystalline hydroxamic acid 37:



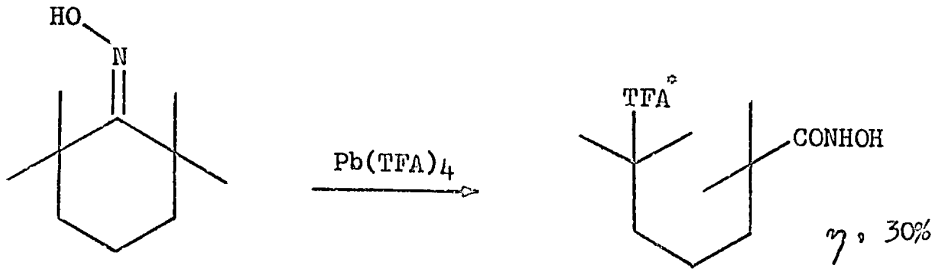
35 36 37

The hydrolysis had to be carried out under carefully controlled conditions to avoid Lossen rearrangement.[69] Compound 37 was fully characterized by elemental analysis and spectral data (Tables 8 and 9, pp. 64, 65, Figure 8, p. 63) and shown to be 6-acetoxy-2,2,6-trimethylheptanohydroxamic acid. The compound gave a strongly positive test for hydroxamic acids with ferric chloride, and it could be titrated furnishing the expected neutralization equivalent.

---

* yield

Reaction of oxime 35 in trifluoroacetic acid with lead tetratrifluoroacetate ($Pb(TFA)_4$) also effected ring cleavage, leading to 6-trifluoroacetoxy-2,2,6-trimethylheptanohydroxamic acid (38).



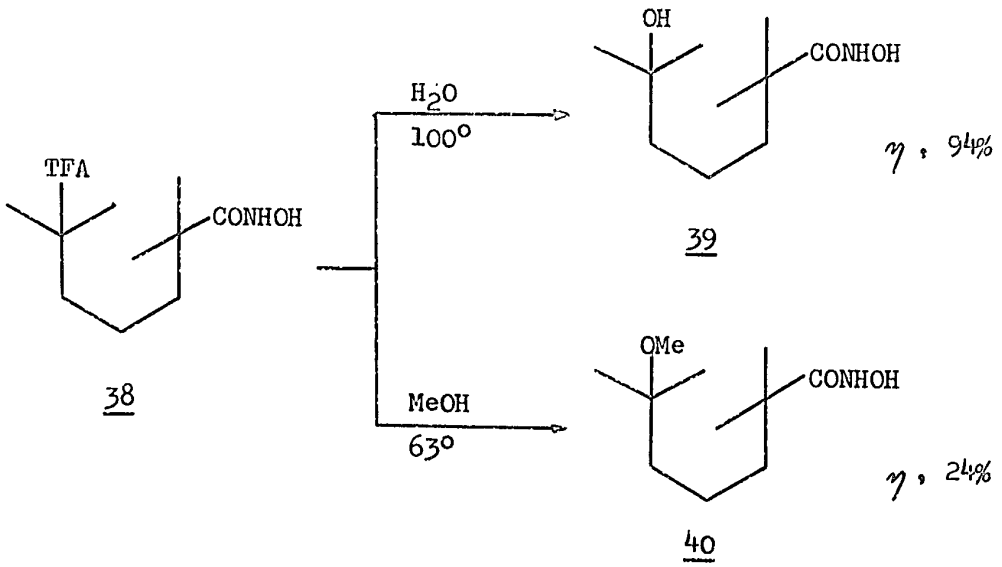
35 38

The probable intermediate corresponding to diacetate 36 could not be isolated as it was hydrolyzed in the work-up. The comparatively low yield of hydroxamic acid 38 can be ascribed to the following reasons: 1. unlike diacetate 36, hydroxamic acid 38 reacts readily with excess oxidizing reagent, probably to carboxylic acid and nitrogen oxides; 2. hydroxamic acid 38 decomposes in trifluoroacetic acid as demonstrated by NMR spectroscopy; 3. hydroxamic acid 38 loses easily the elements of water and trifluoroacetic acid either on heating or mild hydrolysis; 4. isolation of 38 by recrystallization afforded a mother liquor which by spectral inspection still contained substantial amounts of hydroxamic acid 38, yet a second crystal crop could not be obtained. It can thus be safely assumed that cleavage in trifluoroacetic acid is also the predominant reaction, but secondary effects reduce the yield of (isolable) hydroxamic acid 38.

---

* CF_3COO-

As was noted, hydroxamic acid 38 is sensitive to mild hydrolysis, and it was found that brief boiling in water produced the 6-hydroxy-2,2,6-trimethylheptanohydroxamic acid (39). Similarly, methanolysis afforded 6-methoxy-2,2,6-trimethylheptanohydroxamic acid (40) in addition to undefined olefinic hydroxamic acids:



All hydroxamic acids (37, 38, 39, 40) gave a positive test with ferric chloride and showed as common feature in the UV spectrum an $n \rightarrow \pi^*$ transition at 211 mμ (ε, 1500) similar to the one observed for the amide group[70] (cf., appendix for comparative data, p. 151). The IR spectra showed bands at 3450(m), 3250(m), and 1660(s) cm^{-1} which are typical for the hydroxamic acid group, -CONHOH.[71] Further confirmation for the presence of the hydroxamic acid group was obtained from the NMR spectra with two signals, respectively centered at 8.3 ppm (N-H) and 10.3 ppm (N-OH)

in deuterodimethylsulphoxide solution. These assignments were verified by recording spectra of authentic hydroxamic acids (cf., appendix, p. 151).

All data which were used for the characterization of compounds 36, 37, 38, 39, and 40, together with yields in which they were obtained, are compiled in Tables 8 and 9 (pp. 64, 65).

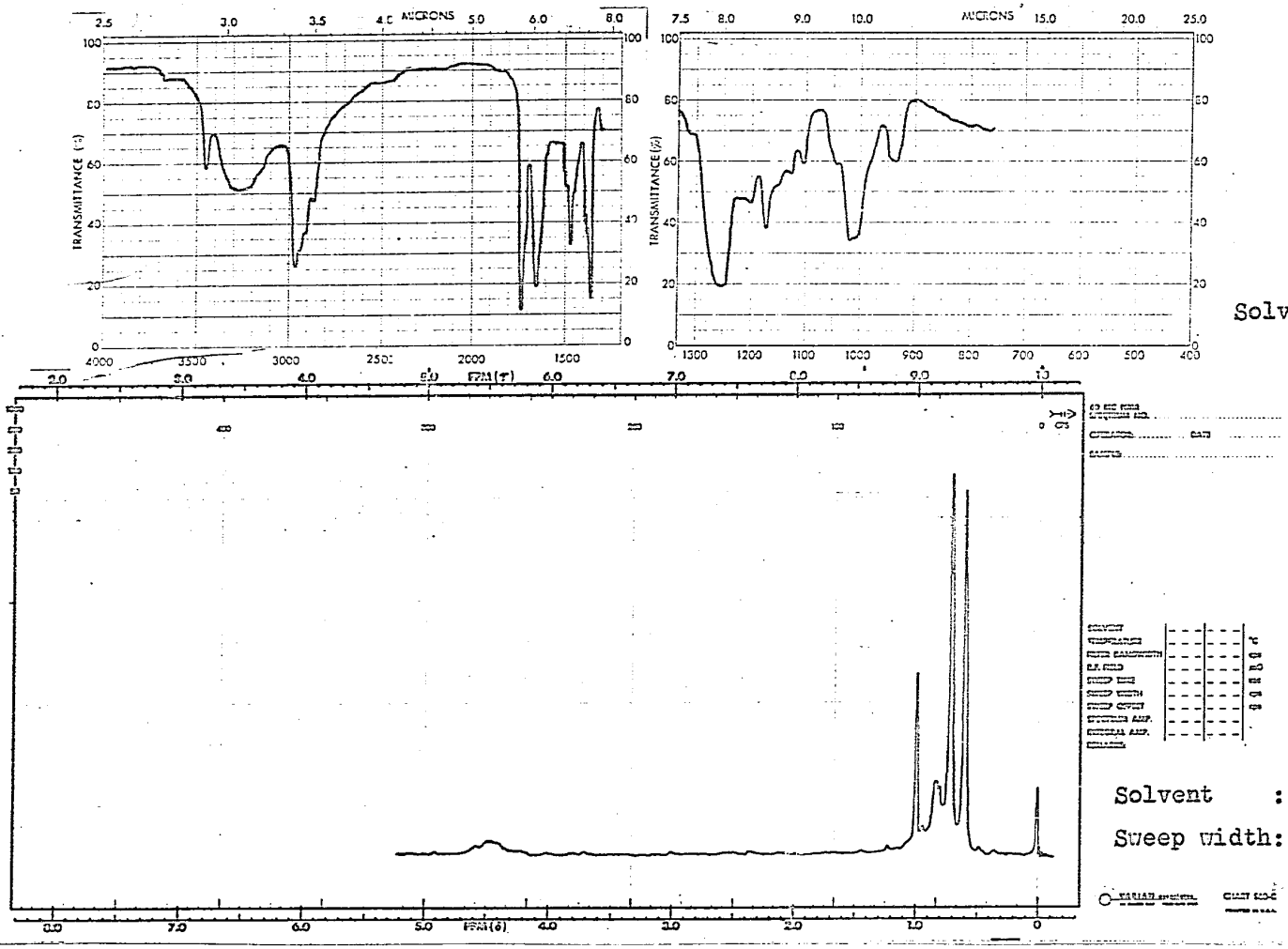
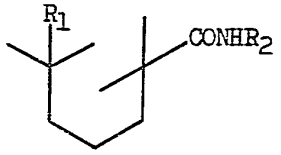


Figure 8. The IR and NMR Spectrum of 6-Acetoxy-2,2,6-trimethylheptanohydroxamic Acid

Table 8

2,2,6-Trimethylheptanohydroxamic Acids and Derivatives

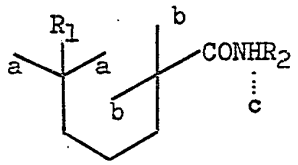


No.	R_1	R_2	Yield %	m.p. °C	Anal. % C calcd.	C found	H calcd.	H found	N calcd.	N found	Remarks
36	OAc	OAc	90	liquid	58.51	60.02	8.77	8.99	4.87	5.45	crude product
37	OAc	OH	84	74-75	58.75	59.07	9.45	9.46	5.71	6.22	
38	TFA	OH	30	81.5-82	48.17	48.57	6.74	6.71	4.68	4.80	% F calcd. 18.90 found 19.25
39	OH	OH	94	112-113	59.08	59.60	10.40	10.51	6.89	6.77	
40	OMe	OH	24	122.5	60.80	61.08	10.67	10.69	6.45	6.01	

Table 9

NMR and IR Data for

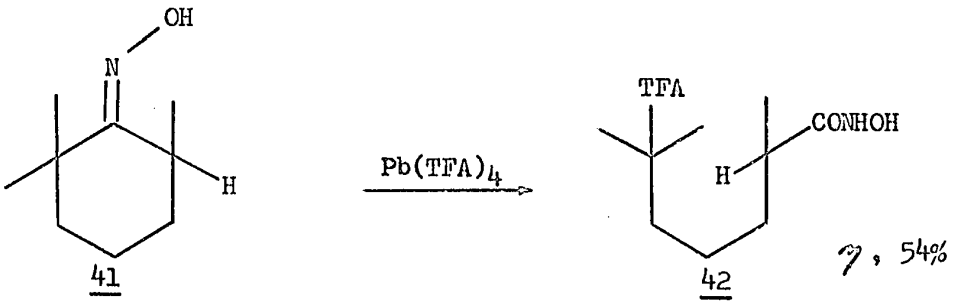
2,2,6-Trimethylheptanohydroxamic Acids and Derivatives



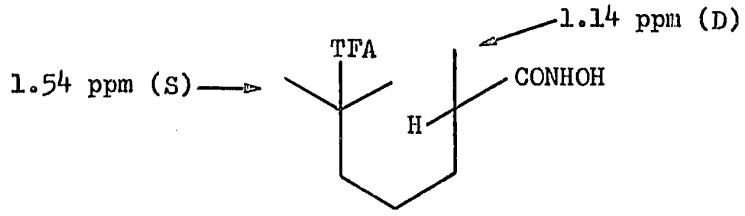
			NMR Chemical Shift, δ ppm					Solvent	IR $\bar{\nu}_{max}$ cm-1	Solvent
No.	R_1	R_2	a	b	c	R_1	R_2			
36	OAc	OAc	1.36	1.20	9.5	1.90	2.17	$CDCl_3$	3350(m), 1790(s), 1740(s), 1720(s), 1248(s), 1198(s)	CCl_4
37	OAc	OH	1.41	1.18	9.0	1.98	9.0	$CDCl_3$	3450(m), 3290(m-s), 1730(s) 1660(s), 1252(s), 1010(m)	CCl_4
38	TFA	OH	1.53	1.18	9.0	-	9.0	$CDCl_3$	3450(m), 3250(m), 1780(s), 1660(s), 1220(s), 1170(s), 1143(s)	CCl_4
39	OH	OH	1.20	1.20	6.3*	6.3	6.3	$CDCl_3$	3605(m-s), 3455(m), 3300(m) 1655(s)	$CHCl_3$
40	OMe	OH	1.17	1.12	9.0	3.18	9.0	$CDCl_3$	3455(m), 3270(m), 2830(m) 1620(s), 1080(s)	CCl_4

* The three-proton peak was resolved in $(CD_3)_2SO$ solution into three signals: 3.95 ppm (tert. OH), 8.43 ppm (N-H), and 10.23 ppm (N-OH); analogous resolution was achieved for the NHOH-group in compounds 37, 38, 39, and 40.

2,2,6-Trimethylcyclohexanone oxime (41). Oxidation of oxime 41 with lead tetraacetate in acetic acid led predominantly to geminal nitrosoacetate, and only very little ring cleavage occurred. Reaction in trifluoroacetic acid, however, afforded 54% of 2,6-dimethyl-6-trifluoroacetoxyheptanohydroxamic acid (42):



Side-products of this reaction were nitric oxide, 2,2,6-trimethylcyclohexanone, and other undefined compounds. As indicated in the above equation, cleavage occurred on the side of the potentially more stable carbonium ion (tertiary carbon). Evidence for this was obtained from the NMR spectrum which showed a doublet (J = 6.7 cps) at 1.14 ppm corresponding to one methyl group, and a singlet at 1.54 ppm corresponding to two methyl groups. This clearly satisfies the following assignment:



Signals arising from the remaining protons were found at the expected positions and are indicated in Figure 9 (p. 67).

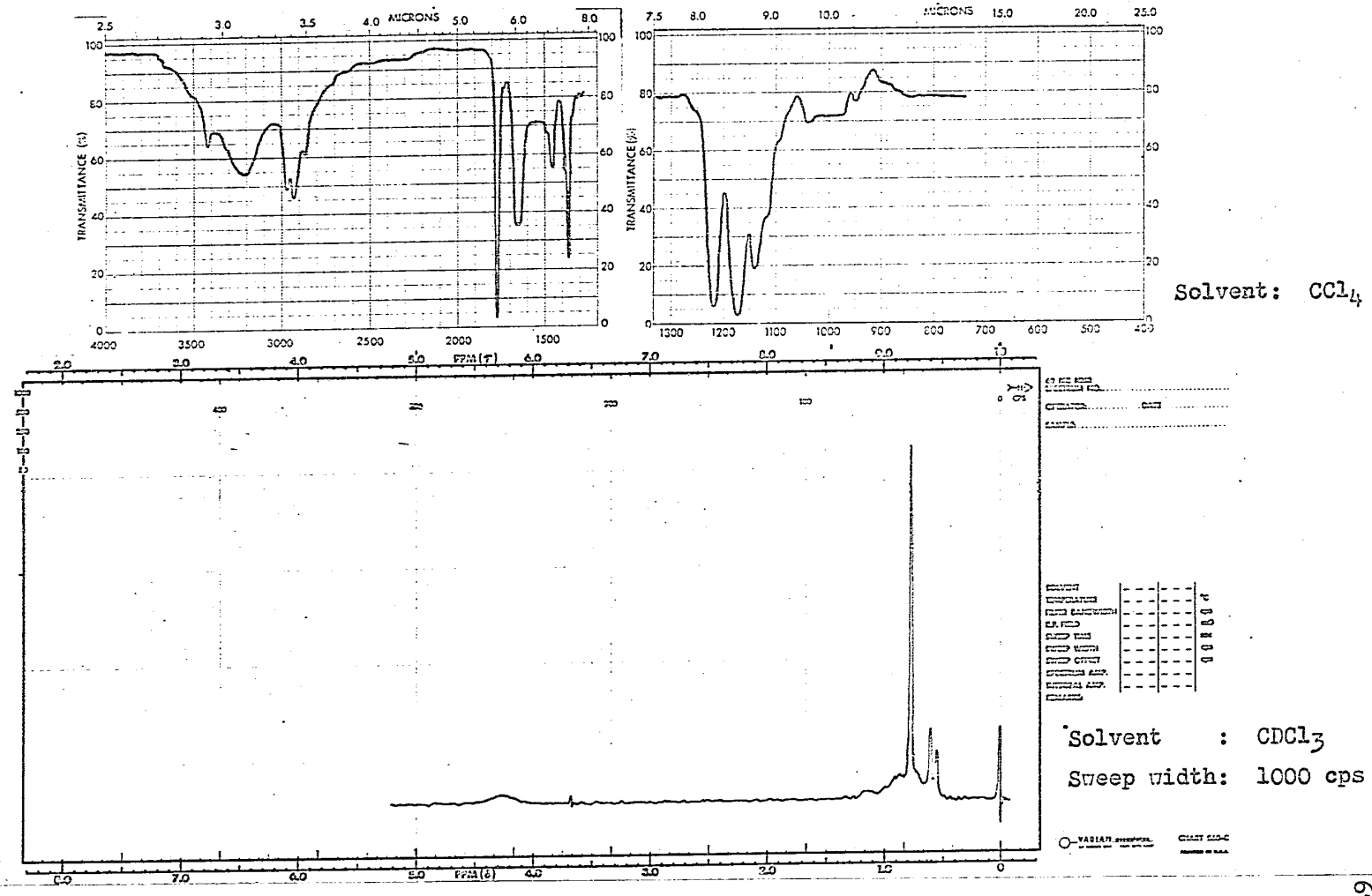
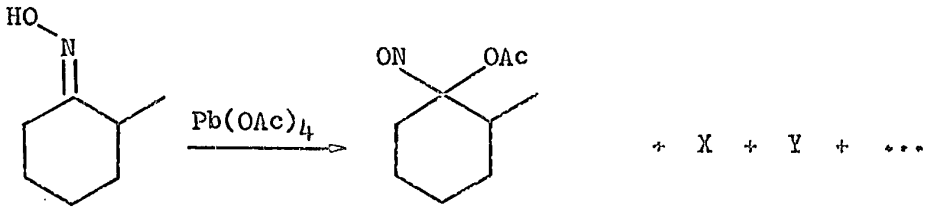


Figure 9. The IR and NMR Spectrum of 2,6-Dimethyl-6-trifluoroacetoxyheptanohydroxamic Acid

2-Methylcyclohexanone oxime (43). Reaction of oxime 43 with lead tetraacetate in acetic acid led to the geminal nitroso-acetate besides other minor products:



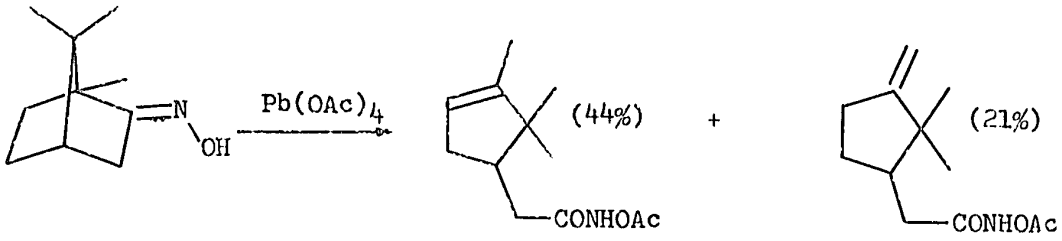
43

This result appears to be general for unhindered ketoximes[72] and has been reported.[17,18]

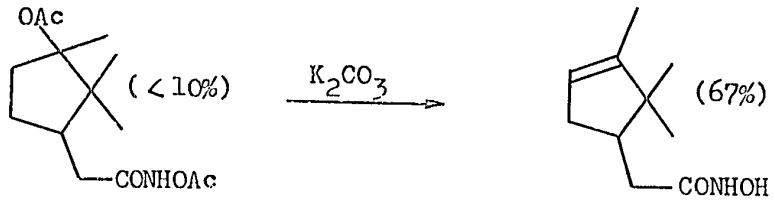
When treating oxime 43 with lead tetratrifluoroacetate in trifluoroacetic acid some ring cleavage occurred, affording approximately 30 to 40% hydroxamic acid (IR estimate, positive ferric chloride test), besides a substantial amount of 2-methylcyclohexanone in addition to other undefined products. Isolation of the hydroxamic acid by crystallization was not possible and chromatographic separation failed because of decomposition. Treatment of the crude oxidation product with 2,4-dinitrophenylhydrazine afforded the hydrazone of 2-methylcyclohexanone, accounting for 60% of the crude product. This result does not necessarily mean that all the hydrazone arose from 2-methylcyclohexanone alone, because geminal nitrosoacetates also convert to hydrazones via hydrolysis to the parent ketone. It can therefore be concluded that ring cleavage occurred to the extent of about 40% or less.

B. Oxidative Cleavage of Camphor Oxime.

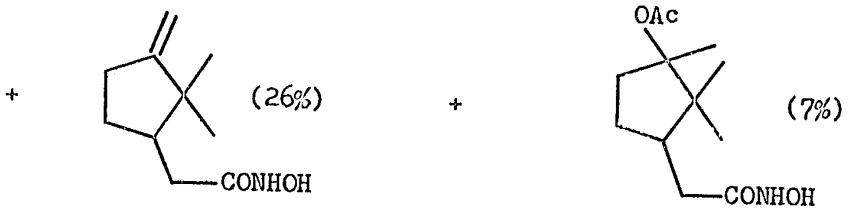
Camphor oxime (44) is a highly strained bicyclic ketoxime and was expected to undergo oxidative cleavage readily. It was found that treatment with lead tetraacetate in acetic acid led first to a blue solution which during work-up turned colourless. The resultant, oily reaction product contained approximately 70% of compounds derivable from a ring cleavage reaction. On the assumption that no rearrangements occurred during this reaction, spectral analysis (NMR, IR) of the mixture suggested the probable presence of the N-acetoxyhydroxamic acids 45, 46, and 47, whose relative amounts were estimated by comparison of suitable signals in the NMR spectrum. Hydrolysis of the crude product with potassium carbonate led to a crystalline mixture (m.p. 84-87°) which probably contains the hydroxamic acids 48, 49, and 50; their relative amounts were again estimated by NMR spectral analysis:



44 45 46



47 48



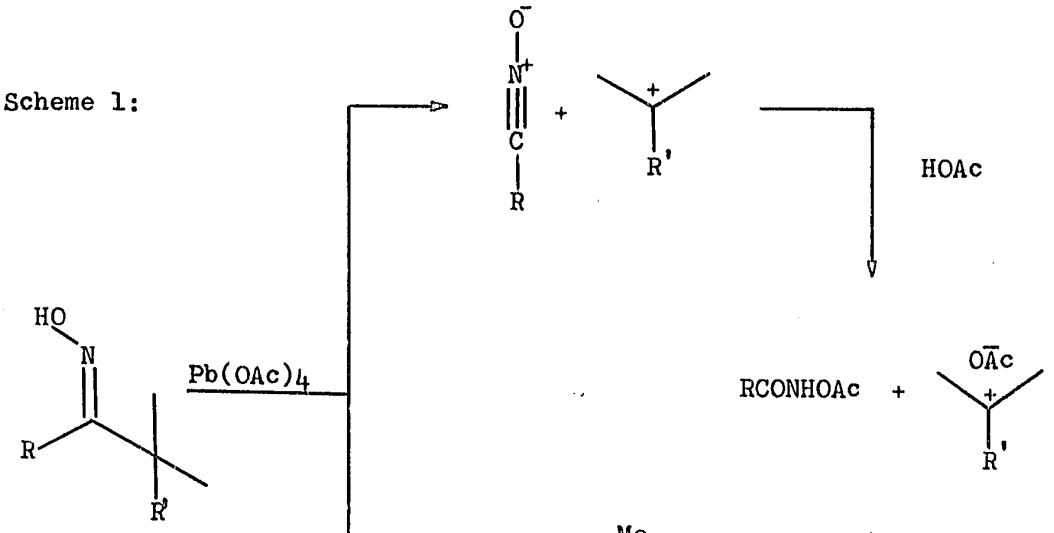
49 50

Recrystallization purified the crude hydrolysis product with respect to non-acidic (non-polar) by-products, but did not effect resolution of the three hydroxamic acids. Separation by paper chromatography was possible, but proved impractical for preparative scale work.

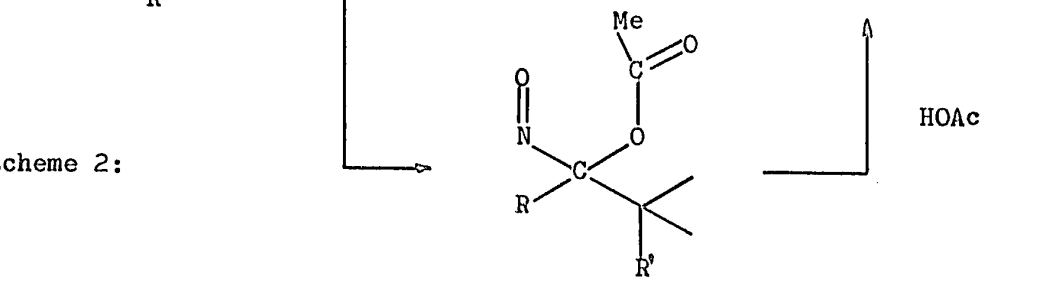
C. Interception of Nitrile Oxides by 1,3-Dipolar Cycloaddition.

The preceding results of the ketoxime oxidation are suggestive of a mechanism proceeding via carbon-carbon bond fission to a nitrile oxide and a stabilized carbonium ion, followed by solvation with acetic acid and product formation (Scheme 1). Yet, the observed rearrangement of 1-acetoxy-1-nitrosoalkanes to N-acetoxyhydroxamic acids (p. 46) indicates the possibility of an alternate mechanistic route. This route would involve formation of a geminal nitrosoacetate which then could undergo rearrangement to an N-acetoxyhydroxamic acid and a carbonium ion. Subsequent solvation of the latter with acetic acid would lead to either acetate or olefin formation (Scheme 2).

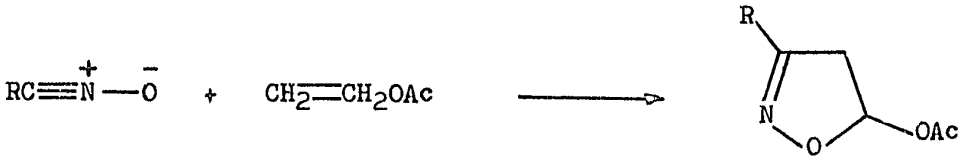
Scheme 1:



Scheme 2:



Both mechanistic proposals are plausible and explain the products obtained. The reaction could conceivably also proceed through both pathways. A decision between these alternatives could be reached, at least in part, by careful observation of colour changes during the reaction, and by interception of the proposed intermediate nitrile oxide with vinyl acetate. Ideally, reaction according to Scheme 1 would involve formation of only one colour, i.e., a green (or blue ?) arising from the intermediate iminoxy radical. If vinyl acetate and a base (to neutralize acetic acid) are present, the nitrile oxide should be diverted in a subsequent step to an isoxazoline acetate:

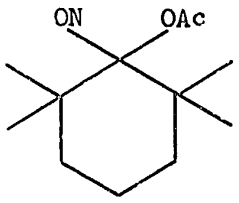


Reaction according to Scheme 2 would require formation of two different colours: a green (or blue ?) arising from the intermediate iminoxy radical and a second, more stable green/blue as the result of nitrosoacetate formation. The latter colour would eventually also fade to colourless indicating final product formation.

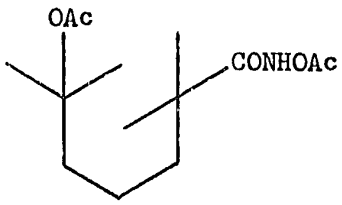
For an experimental test of the above proposals a number of preliminary studies were required. The oxidation of ketoximes is a fast reaction. To follow its various steps by visual observation

requires lowering of the rate of oxidation. This can be done most conveniently by lowering the temperature, but this excludes the use of acetic acid as solvent because it solidifies at 17°. Moreover, acetic acid cannot be used if one hopes to intercept effectively a nitrile oxide by 1,3-dipolar cycloaddition with vinyl acetate. For these reasons, the oxidation was studied in methylene chloride at low temperature (-78° to room temperature) to ascertain whether, and to what extent, cleavage occurs.

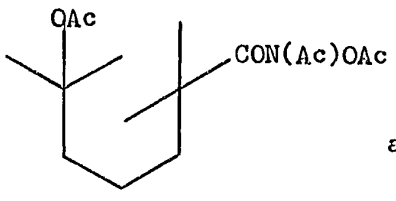
Treatment of 2,2,6,6-tetramethylcyclohexanone oxime (35) with lead tetraacetate in methylene chloride at room temperature produced a green oil. Spectral analysis (IR, NMR) indicated the presence of geminal nitrosoacetate 51 and hydroxamic acid derivative 36 in a ratio of 6:4; other minor components were also present, one possibly being the trisubstituted hydroxylamine 52 and/or 53 (ν(C=O): 1820 cm^{-1}):



51

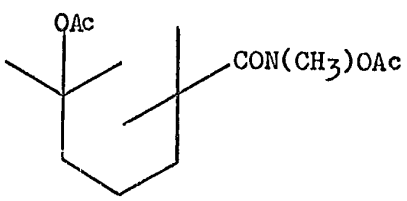


36



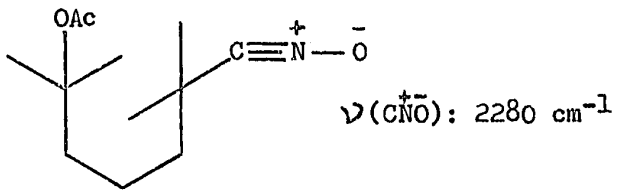
52

and/or



53

When adding lead tetraacetate to oxime 35 at -78°, a yellow, hazy solution resulted which turned green on raising the temperature above -70°. The green colour went through an intensity maximum at about -50° and then faded to a grey/yellow at -30°. A quite different shade of green emerged at -20° and intensified to a blue/green at room temperature. This colour persisted on rechilling to -78°.* At room temperature it persisted for one and a half days, then slowly faded. Work-up at temperatures not exceeding +5° afforded a blue oil which contained by IR estimate nitrosoacetate 51, hydroxamic acid derivative 36, nitrile oxide 54, and 2,2,6,6-tetramethylcyclohexanone in a ratio of 10:1:2:2, besides other products, notably 52 and/or 53.



54

Evidently, lowering of the temperature reduced the yield of cleavage products, but permitted direct observation of the suspected intermediate nitrile oxide 54.

Next the effect of acetic acid was studied. The above low temperature experiment was repeated, but an equimolar amount

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* Because of steric hindrance, dimerization (colourless product) is not favoured.

of acetic acid was added (AcOH:oxime = 1:1). The same colour changes were observed, although the final colour at room temperature was not as intense as in the preceding case. Spectral analysis of the reaction product indicated approximately 40% of compounds derivable from ring cleavage (36, 54). These observations permit the following conclusions: oxidation in methylene chloride gives rise to some ring cleavage, the extent of which depends on temperature and acetic acid concentration. The relative amount of ring cleavage products decreases with decreasing temperature and increases with increasing acid concentration. Ring cleavage leads to an intermediate nitrile oxide.

In subsequent experiments the acetic acid concentration was raised (CH_2Cl_2:HOAc = 8:2, v:v). This led, as anticipated, to still more ring cleavage at the expense of nitrosoacetate formation. The study was then extended to camphor oxime, cyclohexanone oxime, and fenchone oxime. Reaction of camphor oxime gave rise to the following sequence of colour changes: at -78°, pale yellow and hazy; a pale green began to form at -70° which intensified slightly towards -55°, but was much less intense than in the tetramethylcyclohexanone oxime (35) oxidation; at -35° this green faded to a pale yellow which intensified towards -20°, then faded again; at +5°, a blue/green colour emerged which turned fairly intense at room temperature. On cooling to -78°, this colour persisted (no change over four days). When the solution was kept at room temperature, the colour faded to a pale yellow within

three quarters of an hour. On account of the fairly high acetic acid concentration in the reaction solution, no precipitation of lead diacetate occurred during this experiment. Work-up led to a colourless oil which contained about 70% of cleavage products (hydroxamic acid acetates, NMR and IR estimate). A repeat of this experiment, using pure methylene chloride as solvent and conducting work-up below $+5^{\circ}$, yielded a green/blue oil. An IR spectrum of this material showed bands characteristic of nitrosoacetate, acetic anhydride, a trisubstituted hydroxylamine, and N-acetoxy-hydroxamic acids. No nitrile oxide was detectable.

Oxidation of cyclohexanone oxime in methylene chloride/acetic acid (8:2) again showed formation of a green colour upon raising the temperature above -70°. With increasing temperature this colour intensified while slowly changing to a blue/green. No intermediate yellow phase could be observed. The blue/green colour persisted at room temperature for over four days and then noticeably began to fade. At -78° the blue/green colour appeared to be stable (over three weeks no change).

Lastly, fenchone oxime was investigated. This ketoxime is severely strained (bicyclic) as well as providing substantial steric hindrance at the oxime group. Reaction, as before, produced

a green solution at -70°, this colour intensified slightly towards -55°, then faded to a faint yellow. This latter colour persisted up to room temperature. The experiment was repeated with pure methylene chloride as solvent and the same sequence of colour changes was observed. This time, formation of the green colour was accompanied by extensive precipitation of lead diacetate. Work-up at temperatures not exceeding +5° led to a product mixture containing about 50% of nitrile oxide(s) ($\nu(C\equiv\overset{+}{N}-\bar{O})$: 2275 cm^{-1}) and other cleavage products (IR estimate). Addition of acetic acid converted the nitrile oxide(s) at room temperature to N-acetoxyhydroxamic acid(s).

The experiments so far suggest that nitrile oxide formation occurs in situations of severe steric hindrance but little strain (2,2,6,6-tetramethylcyclohexanone oxime), and severe steric hindrance and much strain (fenchone oxime), while a merely strained, but not particularly hindered ketoxime (camphor oxime) prefers ring cleavage via molecular rearrangement of the intermediately formed geminal nitrosoacetate. To confirm further the intermediacy* of nitrile oxides, scavenger experiments with vinyl acetate were conducted.

A solution of 2,2,6,6-tetramethylcyclohexanone oxime (1 equiv.) in methylene chloride/vinyl acetate (50 equiv.)/acetic acid (5 equiv.) was treated with lead tetraacetate at -78°. The reaction mixture was slowly warmed (1 hr) to -10°, then all the acetic acid was neutralized with triethylamine, followed by normal work-up. A product mixture was

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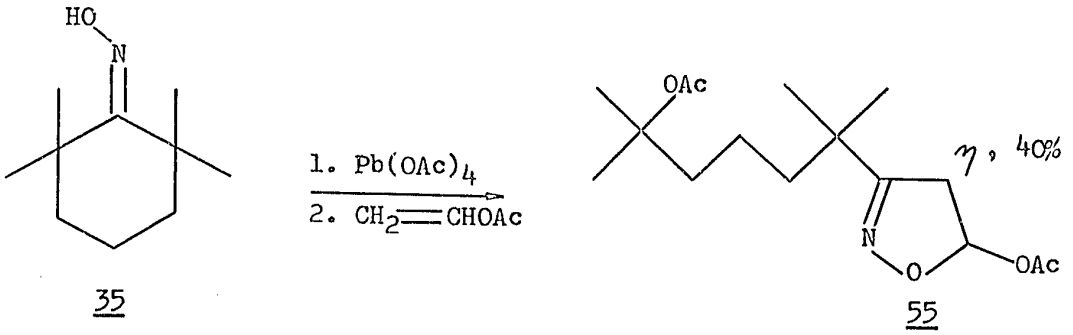
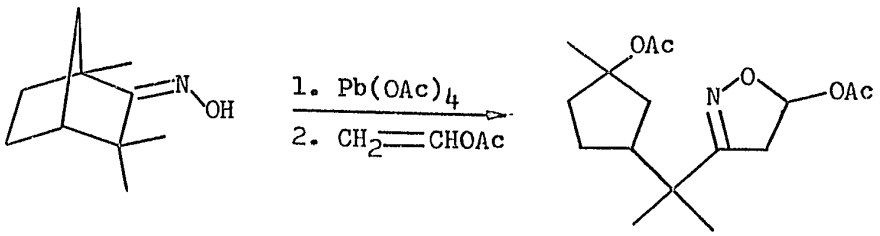
* Intermediate existence of.

obtained which by spectral estimate contained ca. 50% isoxazoline acetate, ca. 20% regenerated ketone, and other products. Vacuum distillation afforded a crystalline residue which was not further purified, but unequivocally shown (NMR) to contain approximately 80% of the expected 3-substituted 5-acetoxy-2-isoxazoline (55):

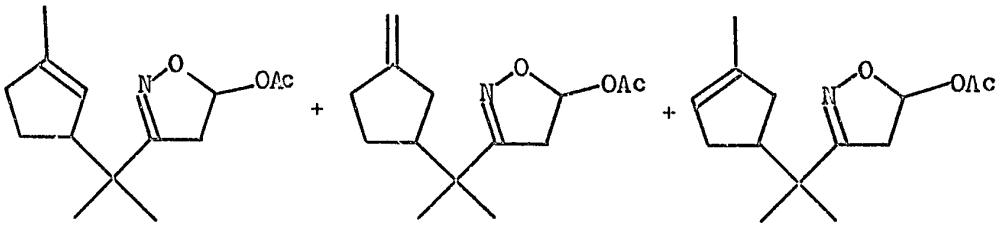


35 55

Analogous interception in the oxidation of fenchone oxime (56) led to a product mixture of four major components (TLC) which were not separated, but spectral analysis of the crude product provided evidence for the presence of isoxazoline derivatives accounting for most of the crude product. The subsequently given structures 57, 58, 59 and 60 appear reasonable on mechanistic grounds, provided no rearrangements occurred, and are in accord with spectral data (NMR, IR) obtained from the mixture.



56 57



58 59 60

On account of extensive overlap of proton signals in the NMR spectrum no quantitative molar ratio for compounds 57 to 60 can be given.

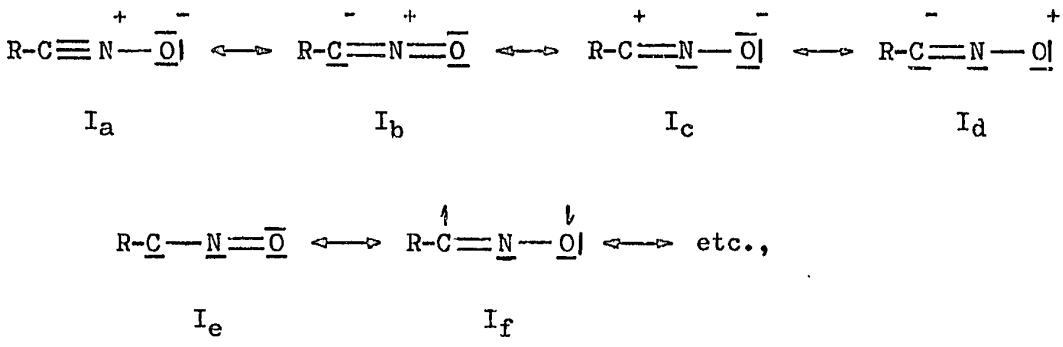
Interception of a nitrile oxide in the camphor oxime oxidation was not possible. A complex reaction mixture was obtained which contained no (or less than 5%) isoxazoline acetate(s) (NMR, IR estimate).

DISCUSSION

CHAPTER II. OXIDATION OF ALDOXIMES

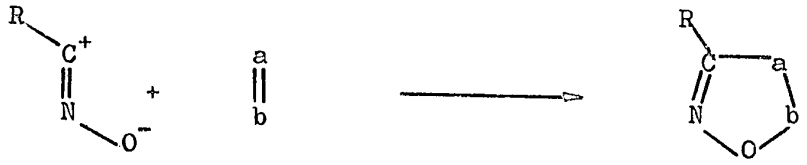
The lead tetraacetate oxidation of oximes involved, in the majority of examples investigated, the intermediacy of nitrile oxides. Before proceeding, therefore, to the actual discussion of the experimental results, a brief review[50] of relevant aspects of nitrile oxide chemistry is appropriate.

The nitrile oxide is a dipolar molecule and can be represented by the following resonance structures:

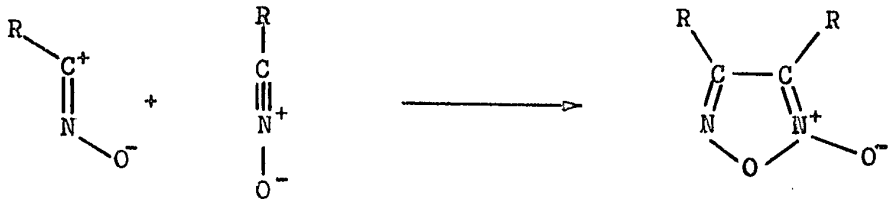


where structures I_a and I_b represent the ground state, structures I_c and I_d the sextet or 1,3-dipolar reactive state, I_e the carbene state, and I_f etc. diradical states. Most of the known chemistry of nitrile oxides is rationalized in terms of canonical contributions I_a to I_d.

As a result of their dipolar nature, nitrile oxides are very reactive compounds and cannot usually be isolated and stored at room temperature. The reaction most typical for nitrile oxides is the 1,3-dipolar addition to a double or triple bond:

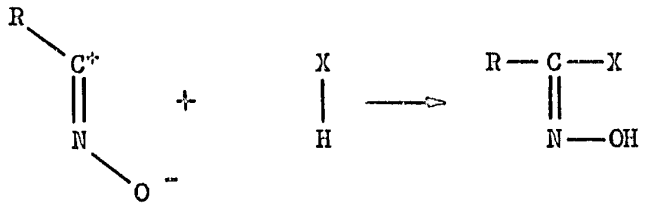


In the absence of a sufficiently reactive dipolarophile (a=b) nitrile oxides dimerize to furoxans:



It is this reaction which limits the lifetime of nitrile oxides at room temperature to a few minutes (aliphatic nitrile oxides) or hours (aromatic nitrile oxide), unless, as could be shown in this and in another recent investigation,[51] the substituent R is made sufficiently bulky to prevent close approach of two nitrile oxide molecules.

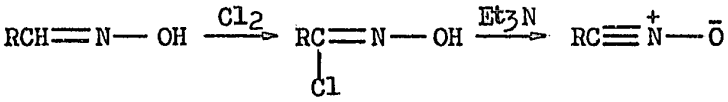
Apart from 1,3-dipolar cycloadditions, nitrile oxides have been shown to react with a great number of nucleophilic reagents leading to derivatives of hydroxamic acids:[51]



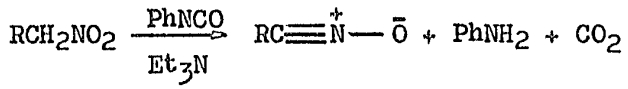
X = Cl-, MeO-, NH_2-, etc.

Nitrile oxides can be prepared by two main routes: one involves the chlorination of aldoximes (syn and/or anti) followed by 1,3-elimination of hydrochloric acid with a base (Equation 1);[51] the other route starts from primary nitroalkanes which are dehydrated with phenylisocyanate in the presence of a base (Equation 2).[57]

Equation 1:



Equation 2:



A recently discovered third route employs bromine in alkaline solution and is closely related to the first method.[51] The oldest and most frequently used preparation is the one depicted in Equation 1. It works well as long as the substituent R does not itself react with chlorine. The bromine reaction is similarly limited, but permits preparation of alkylated benzonitrile oxides.[51] Dehydration of primary nitroalkanes to nitrile oxides[57] presents a mild and efficient mode of preparation. Its application is restricted by the limited availability of primary nitro compounds, especially polyfunctional ones.

The present investigation has shown that the lead tetra-acetate oxidation of syn aldoximes leads in one step to nitrile oxides in high yields (>80%). The limitations of the reaction are few. Starting from readily available aldoximes, the dehydrogenation is effected under extremely mild conditions (-78°). Aromatic and aliphatic aldoximes containing functional groups which would not permit use of conventional preparative methods, can be converted to the corresponding nitrile oxides. Thus, oxidation can be carried out in the presence of olefinic double bonds (vinyl acetate, e.g.) or aliphatic alcohols (ethanol, e.g.). Further, reaction of methoxybenzaldoxime as well as trimethylbenzaldoxime leads in good yields to the respective nitrile oxides.

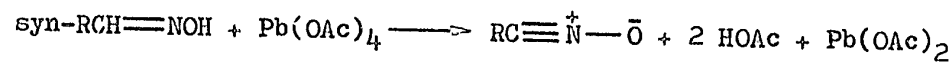
The preparative limitations of the reaction found so far

are not very serious. First, the oxidation has stereochemical requirements, i.e., only syn aldoximes can be dehydrogenated to nitrile oxides, while anti aldoximes afford different products. For aromatic and hindered aliphatic aldoximes this presents no problem, because for these the syn isomer is the more stable, and thus the predominant product in the oximation of the parent aldehydes. Unhindered aliphatic aldoximes are usually obtained as 1:1 mixtures of the syn and anti isomers. However, chromatographic methods are available now[73] which permit separation of these and thus make the pure syn isomers available for conversion to nitrile oxides. Moreover, the isomeric mixture can be converted as such; the nitrile oxide formed (40 to 50%) is intercepted in situ by a suitable reagent leading to the desired product, which can then be isolated by chromatography.

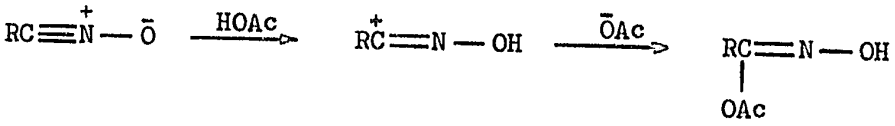
A second limitation arises from the high reactivity of phenolic hydroxy groups. Aldoximes which contain these, afford intractable tarry products upon oxidation with lead tetraacetate at -78°. Evidently, the phenolic hydroxy group reacts faster with lead tetraacetate than the oxime hydroxy group. It can be expected that functional groups of similar reactivity (primary and secondary aromatic amino groups, enolic hydroxy groups), unless suitably protected, would also limit the usefulness of this reaction.

By-products of the lead tetraacetate oxidation of syn

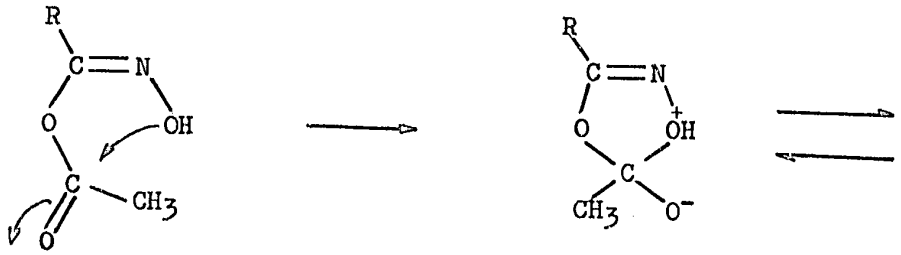
aldoximes are acetic acid and lead diacetate:



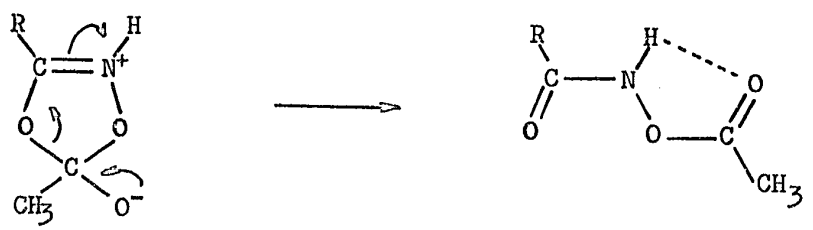
If no special precautions are taken, the nitrile oxide reacts with acetic acid in a subsequent step to an N-acetoxyhydroxamic acid. Formation of this product probably involves the conjugate acid of the nitrile oxide (61). Addition of an acetate ion to 61 would lead to the acetylhydroximic acid (62). In a third step this compound rearranges to the more stable N-acetoxyhydroxamic acid (63).[74] The conversion 62 ⟶ 63 can be rationalized as proceeding through a five-membered ring transition state:



61 62

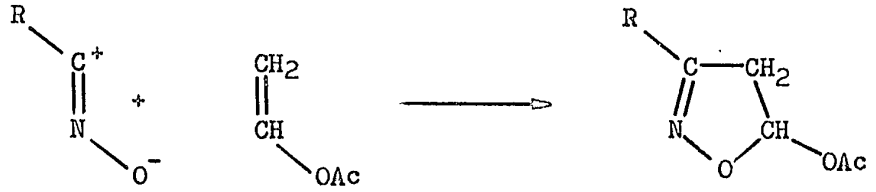


62



63

If the oxidation of syn aldoximes is carried out in the presence of a dipolarophile like vinyl acetate, and followed by neutralization of acetic acid with a base (Et_3N), the intermediately formed nitrile oxide is diverted to a 3-substituted 5-acetoxy-2-isoxazoline (64):

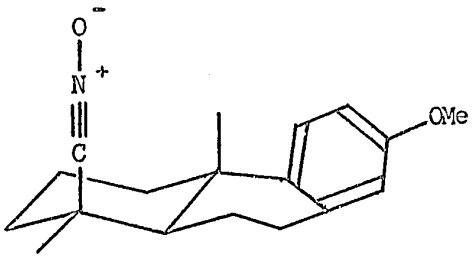


64

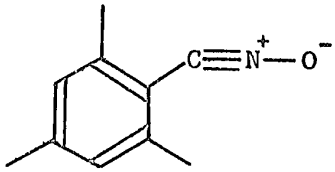
Reaction in vinyl acetate without subsequent neutralization of acetic acid (at -50 to -78°) leads to a mixture of N-acetoxyhydroxamic acid 63 and isoxazoline acetate 64, even when using a large molar excess of vinyl acetate. This clearly indicates that the rate of acetic acid addition is appreciably higher than that of the cycloaddition of vinyl acetate.

Unhindered aldoximes can only be dehydrogenated to nitrile oxides at -78° in high yield. The yields decrease with increasing reaction temperature. At room temperature practically no products derivable from an intermediate nitrile oxide are obtained. This restriction does not apply to severely hindered aldoximes which afford nitrile oxides at low and room temperature in good yields. Provided steric crowding in the vicinity of the nitrile oxide group is great enough to prohibit dimerization to furoxan, the nitrile

oxide is stable and can be stored at room temperature. Two examples of this kind were obtained in the aliphatic O-methylpodocarponitrile oxide (12) and the aromatic mesitonitrile oxide (13).



12



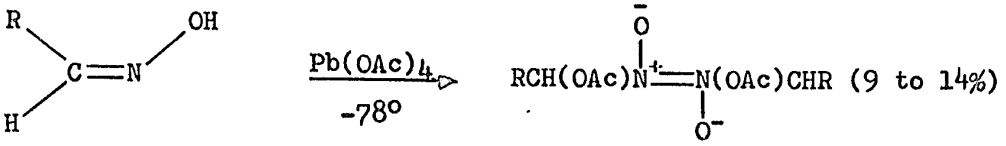
13

Apart from dimerization to furoxans, these nitrile oxides behave like other (unstable) nitrile oxides in undergoing 1,3-dipolar cycloadditions (e.g., isoxazoline and isoxazole formation) and other addition reactions (e.g., N-acetoxyhydroxamic acid formation). They, therefore, provide valuable model compounds for studies of nitrile oxide chemistry which would be difficult or impossible to conduct with nitrile oxides prepared in situ.

Oxidation of aldoximes at or slightly below room temperature (0 to 20°) leads to different products, and syn as well as anti aldoximes give rise to the same results. These results are also obtained when oxidizing anti aldoximes at -78°. Moreover,

the nature of the products depends on whether the aldoxime is aromatic or aliphatic.

Low temperature oxidation of anti-n-heptanaldoxime led to a complex mixture of four or more components. The instability of the products prevented chromatographic separation (TLC or GLC*). Low temperature crystallization and vacuum distillation permitted isolation of nitrosoacetate 21, acetic anhydride, and acetic acid. Spectral analysis of the crude reaction product further suggested the presence of the nitroacetate 22, the trisubstituted hydroxylamine(s) 23 and/or 24, and other undefined products:



R = n-C_6H_{13}

21

+ Ac_2O + AcOH + [$RCH(OAc)NO_2$

22

+ $RCON(Ac)OAc$ and/or $RCON(CH_3)OAc$

23 24

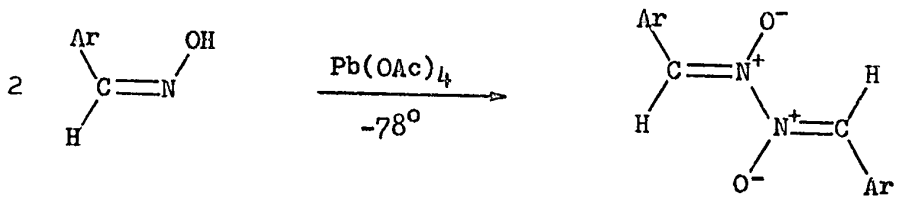
+ X + Y + ...]

---

* Gas Liquid Chromatography.

Similar results were obtained for anti-acetaldoxime, but no product analysis was attempted. An independent, concurrent study has shown that geminal nitrosoacetates of type 21 are generally obtained when oxidizing aliphatic syn and/or anti aldoximes with lead tetraacetate at 0 to 5°. Yields of over 50% have been reported.[18]

Low temperature oxidation of aromatic anti aldoximes leads to essentially one product, the arylaldazine-bis-N-oxides (10):

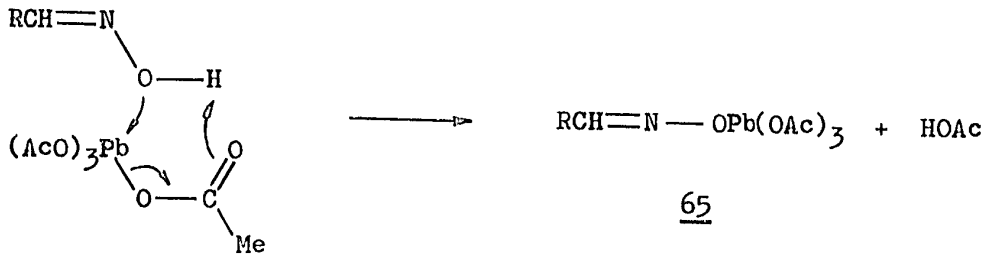


10

These compounds have also been obtained by lead tetraacetate oxidation of syn and/or anti arylaldoximes at 0 to 5°, and an account of this work will be published shortly.[18] In contrast to the low temperature oxidation, where only anti aldoximes convert to aldazine-bis-N-oxides 10 requiring one mole lead tetraacetate per mole aldoxime, oxidation at 0 to 5° of syn and/or anti aldoximes requires only one half mole lead tetraacetate per mole aldoxime to afford aldazine-bis-N-oxides 10. Obviously, this divergent mode of preparation requires different mechanistic explanations.

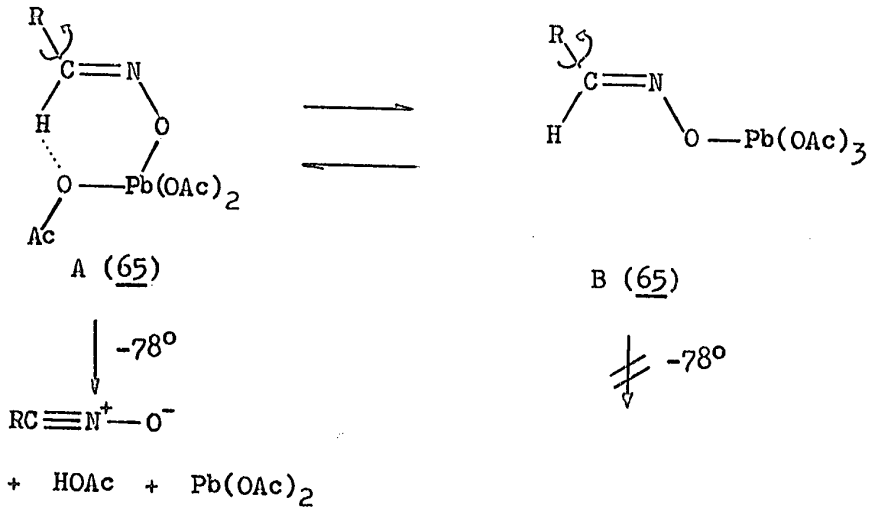
Mechanism of the Aldoxime Oxidation.

The results of the lead tetraacetate oxidation of aldoximes are consistent with the observed intermediacy of iminoxy radicals.[1,6,9] When oxidizing aldoximes at temperatures above -70° a passing intense green colour can be observed; occurrence of this colour was usually accompanied by precipitation of lead diacetate. Though mere observation of a transient green colour is no proof for the presence of iminoxy radicals, it does serve to corroborate the results of recent ESR studies.[1,9] At temperatures below -70° no green colour can be noticed and only in the case of syn aldoximes is substantial precipitation occurring ($Pb(OAc)_2$). This observation seems to indicate that syn aldoximes possess a lower energy barrier to product formation than anti aldoximes. It is proposed that the initial attack of lead tetraacetate on the oxime leads to a lead organic compound in analogy to accepted views for related substrates (alcohols):[21]



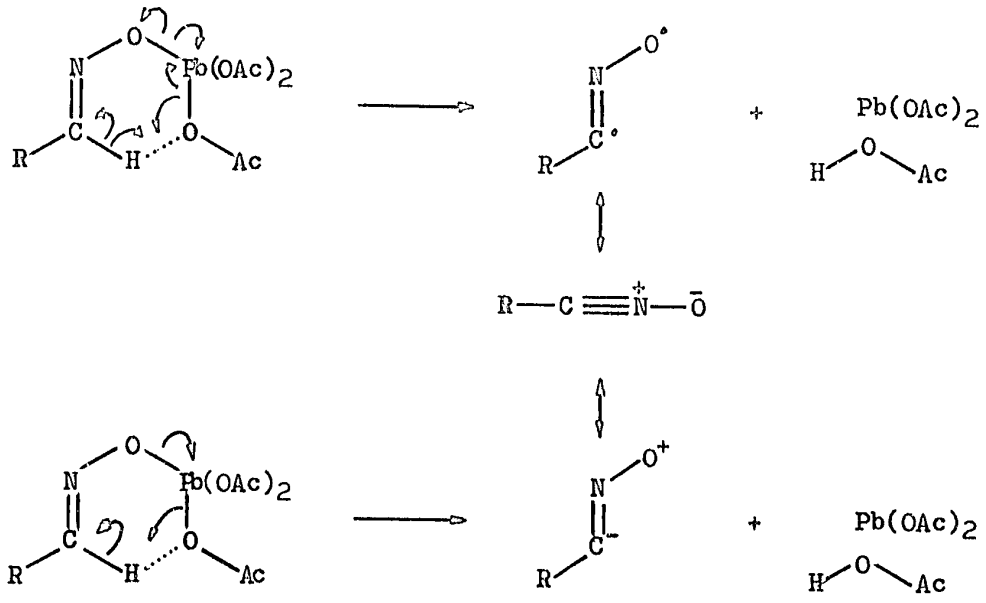
65

The formation of the lead organic compound 65 can be envisaged as proceeding through a six-membered ring transition state. The intermediate 65 is believed to be stable at -78° if derived from an anti aldoxime, but decomposes readily to nitrile oxide, acetic acid, and lead diacetate if formed from a syn aldoxime. In the latter case a conformation A can be written which should provide a low energy path to product formation:



Conformation A represents a high degree of order, and appreciable equilibrium concentration would only be expected if molecular motions, especially rotation about the R↻C bond in intermediate 65, is greatly reduced, either by lowering the temperature (unhindered aldoximes) or increasing the steric requirements of R (hindered aldoximes). The actual collapse of conformer A

can occur either by homolysis or heterolysis of bonds. One mode would produce the nitrile oxide in a diradical, the other in a 1,3-dipolar sextet state:

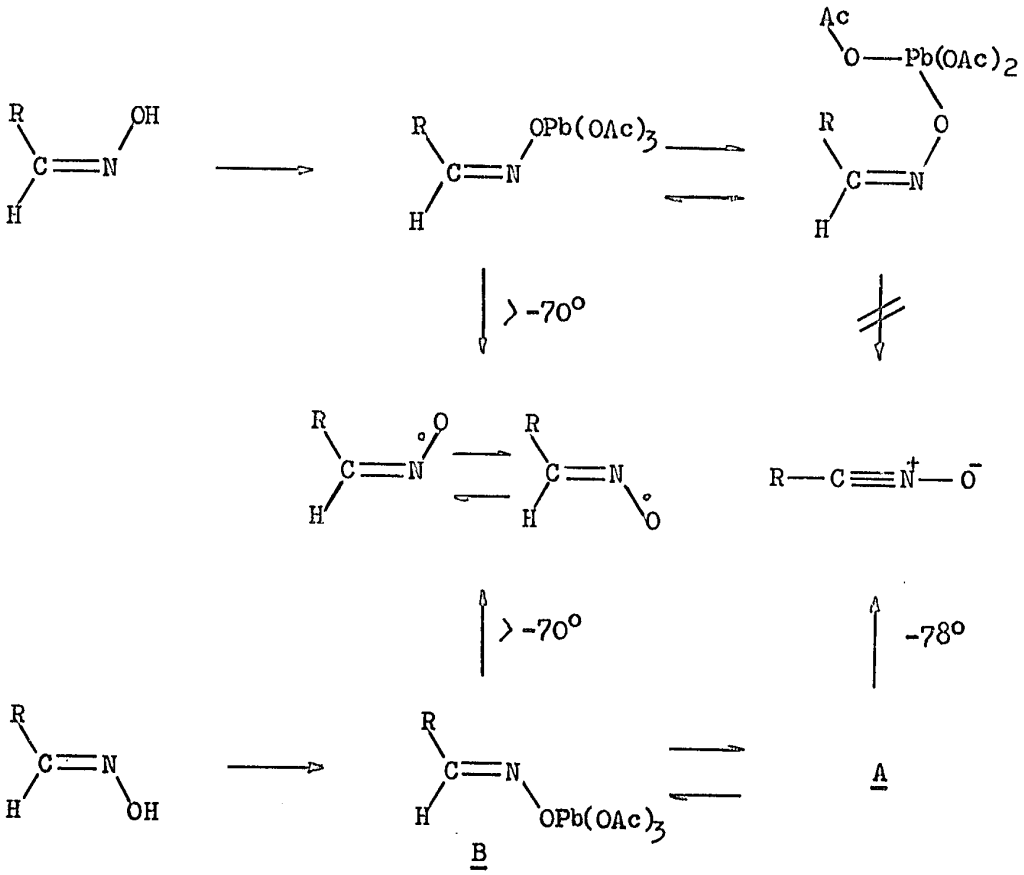


Since bond breakage above -70° leads to (green) iminoxy radicals, it appears reasonable that collapse of conformer A occurs also by homolysis. Little can be said about the timing of this collapse: the electron shift is probably concerted, yet might be initiated at the weakest (?) bond, viz., the bond joining the "oxime-oxygen" and the lead atom.

No product formation will occur through conformer B at a temperature below -70°, but, since B is in equilibrium with conformer A, it will be consumed to the extent as the latter

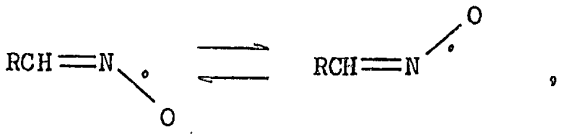
collapses to products. If formation of the lead organic compound 65 takes place at temperatures above -70°, molecular vibration (rotation) appears to be violent enough to effect homolysis of the "oxime-oxygen"/lead bond without assistance from a six-membered ring transition state. This would lead to free iminoxy radicals besides some nitrile oxide. The amount of the latter would be expected to decrease with increasing temperature because of decreasing equilibrium concentration of conformer A.

Anti aldoximes, when treated with lead tetraacetate at -78°, probably also form a lead organic compound of type 65; since no precipitation of lead diacetate can be observed, the compound appears to be stable under these conditions. A conformational equilibrium analogous to the one for the syn isomer does not provide a low energy path to product formation. On raising the temperature above -70°, unassisted homolysis occurs leading to iminoxy radicals, which can also be obtained by homolysis of conformer B.

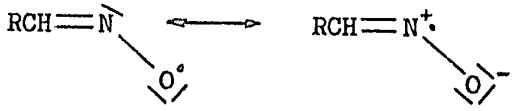


These iminoxy radicals are quite stable at -55° ($\tau_{1/2}$ > 5 min.), but are rapidly consumed at higher temperature. Aromatic iminoxy radicals react to give arylaldazine-bis-N-oxides without formation of any additional intermediate colours. Aliphatic iminoxy radicals appear to dissipate their energy by forming a number of products in the temperature range of -55 to -30°. Further raising of the temperature leads merely (?) to dissociation of dimeric nitrosoacetate (a new blue/green colour emerges). A fully satisfactory explanation for the different behaviour of aliphatic and aromatic iminoxy radicals could not be found although the products formed can be rationalised.

ESR studies have shown that iminoxy radicals exist in a configurational equilibrium at room temperature:[1]

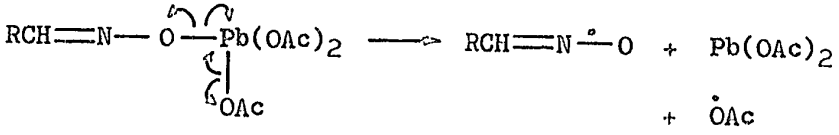


and the results of the present investigation indicate that this equilibrium also exists at low temperature (below -25°), for syn and anti benzaldoxime give the same phenylaldazine-bis-N-oxide, which is therefore probably an isomeric mixture. The large nitrogen coupling constant of iminoxy radicals[1,6,9] indicates substantial unpaired electron density[7] at the nitrogen nucleus. Since the unpaired electron can only be delocalized over the nitrogen and oxygen atom (σ-radical), reactions with low energy requirements can be anticipated to occur either at the oxygen or at the nitrogen, preferentially though at the latter:[2]

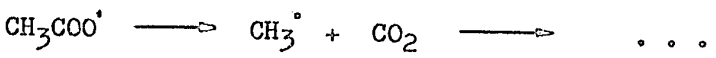


Since radical-radical recombinations require little or no energy of activation,[75] product formation by this process should be preferred over radical displacement reactions, unless the latter are of the intramolecular type (higher probability of interaction).

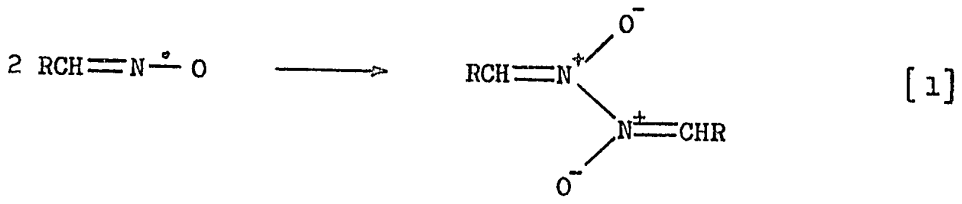
Formation of iminoxy radicals by lead tetraacetate oxidation should also lead to simultaneous production of acetoxy radicals:



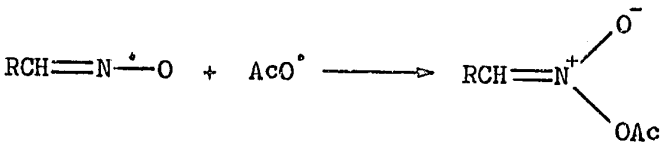
which then decompose to methyl radicals and carbon dioxide, etc.:[76]



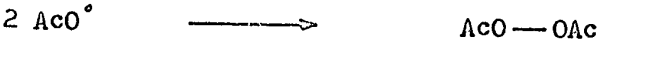
Acetoxy radicals cannot be trapped at room temperature,[77] but it is reasonable to assume that they are sufficiently stable at -55 to -30°, so that recombination with iminoxy radicals can occur. For reasons already mentioned, the following recombinations are most probable:



[1]



[2]



[3]*

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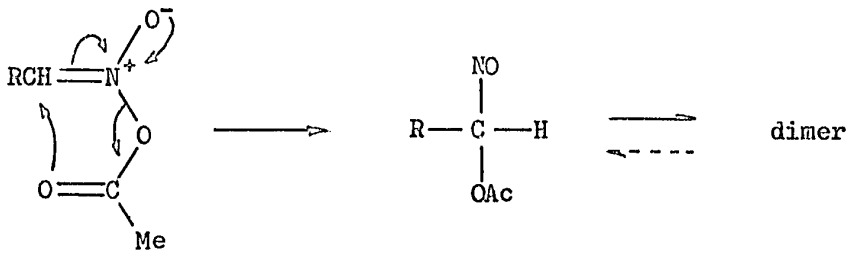
* Evidence for this reaction has been obtained recently.[97]

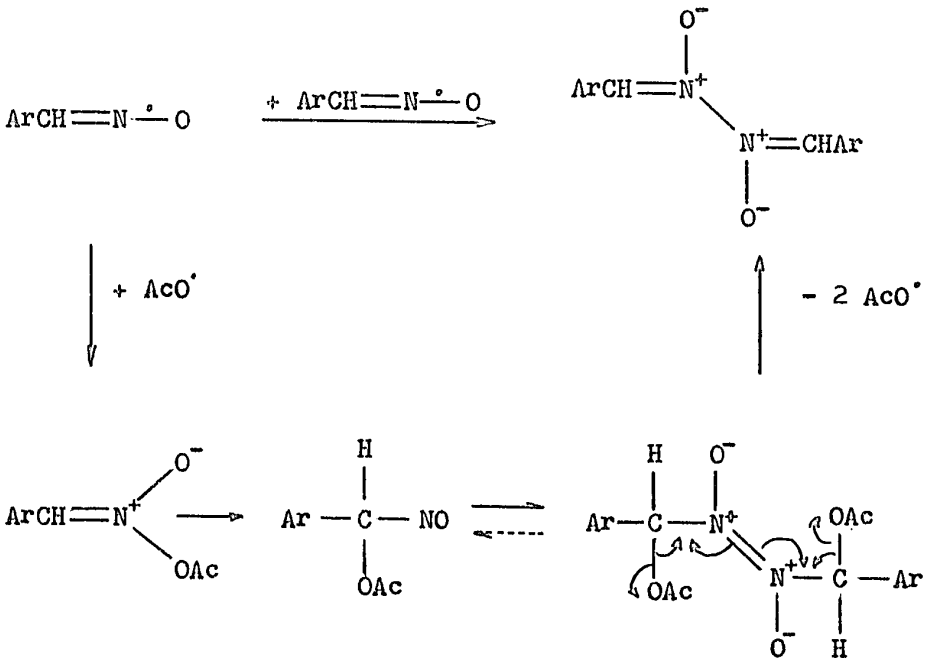
Product analysis gave no evidence for the presence or intermediate participation (in product formation) of acetyl peroxide (equation 3) and its formation, therefore, appears to be unfavoured. Aldazine-bis-N-oxides (equation 1) were the products obtained from aromatic aldoximes, while the unstable mixed nitronic acid anhydride (equation 2) is a likely intermediate in the formation of geminal nitrosoacetates:



Nitronic acids and their derivatives are known to be unstable[68,78] and their isolation is possible only in exceptional cases.[79] Their intermediate existence has been proposed for the formation of nitrile oxides[57] and hydroxamic acid derivatives, the latter forming via nitroso compounds.[80]

Oxidation of aromatic aldoximes does not lead to stable geminal nitrosoacetates as has also been noted elsewhere.[18] Two plausible explanations come to mind to account for this divergent behaviour. Either, aromatic iminoxy radicals dimerize directly to aldazine-bis-N-oxides (equation 1); or, a geminal nitrosoacetate is formed but is too unstable for existence at room temperature.

Such a labile, dimeric nitrosoacetate could conceivably convert to an aldazine-bis-N-oxide by loss of two acetoxy radicals. The driving force for this reaction could be derived from the gain in resonance energy by establishing extended conjugation over two aromatic rings:



Presently available evidence permits exclusion of neither route and possibly both are operating concurrently. A summary of the above suggested mechanisms is outlined in Figure 10 (p. 99).

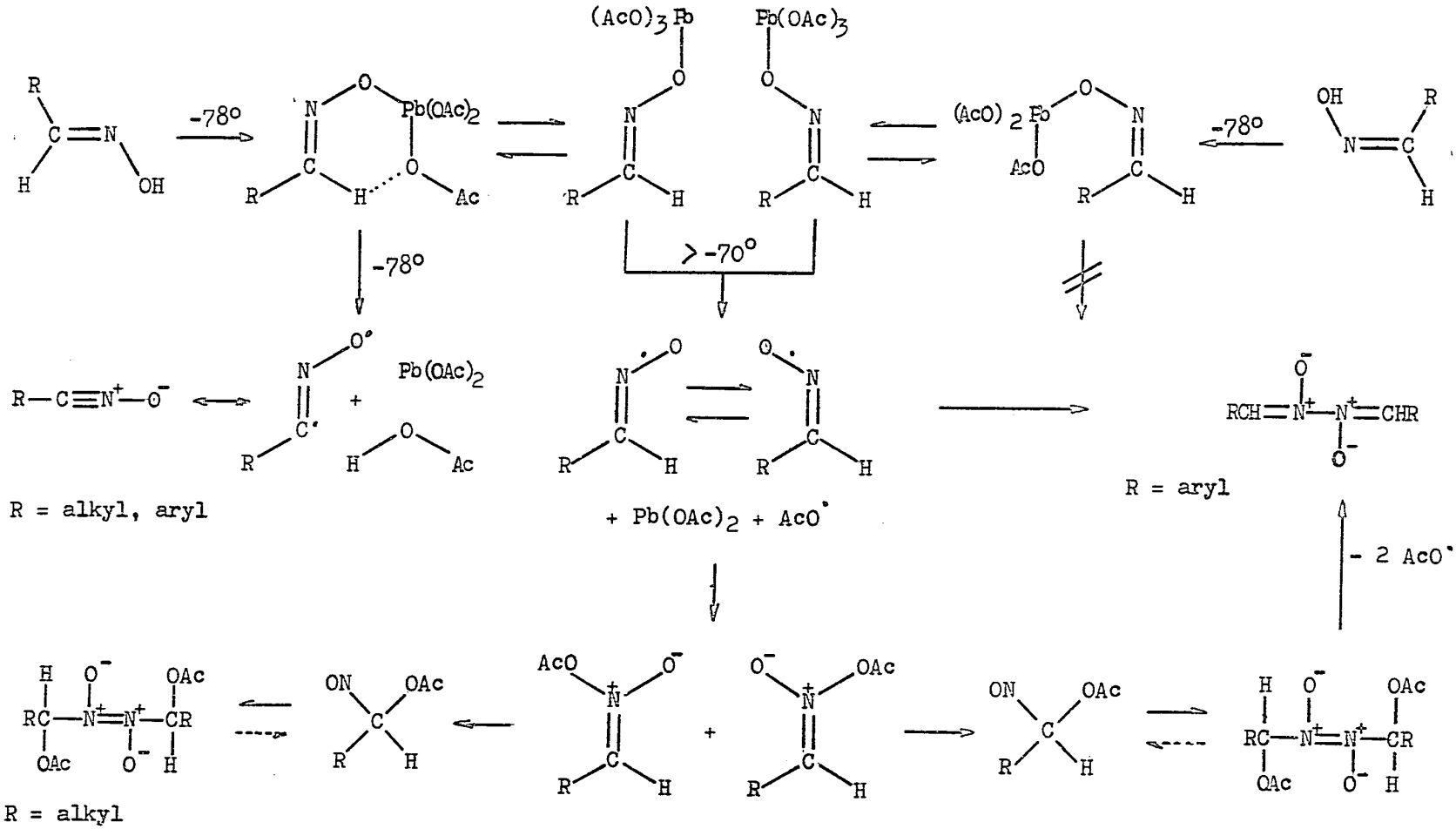
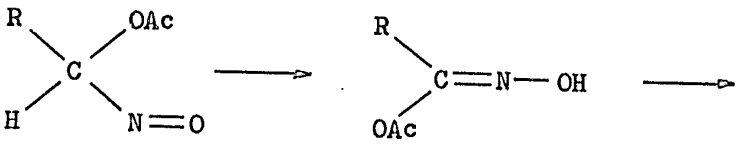


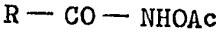
Figure 10. Oxidation Mechanisms for Aldoximes

Aliphatic 1-acetoxy-1-nitrosoalkanes in the solid state are dimeric and stable at room temperature. In solution they are dissociated only to a very small extent and only stable if kept at low temperature ($< -30^{\circ}$). At room temperature rearrangement to N-acetoxyhydroxamic acids occurs. This rearrangement is greatly accelerated by a catalytic amount of triethylamine. Reactions of a related nature involving geminal chloronitroso compounds and leading to hydroxamic acid chlorides are known:[81]

By analogy, the conversion of geminal nitrosoacetates to N-acetoxyhydroxamic acids could proceed first to the acetylhydroximic acid (62), followed by a second rearrangement as discussed for the formation of N-acetoxyhydroxamic acids (63) from nitrile oxides (p. 85).

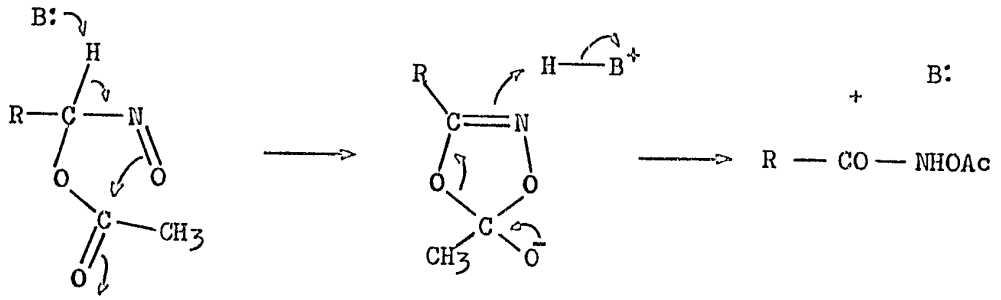


62

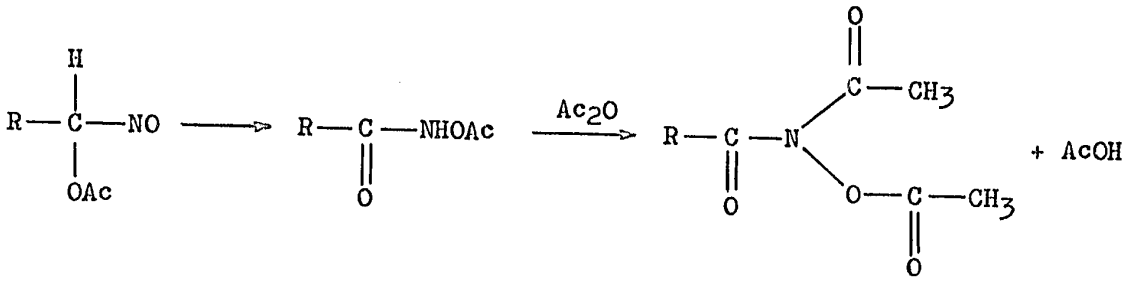


63

Alternatively, a mechanism involving base assisted proton transfer is equally plausible:



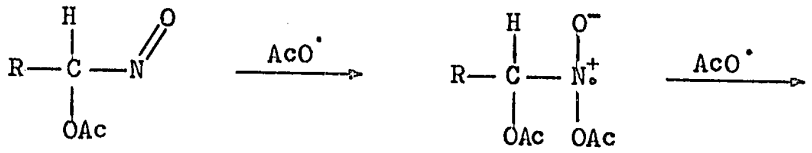
The great ease with which this rearrangement occurs suggests that a nitrosoacetate, initially formed in the oxidation of an aliphatic anti aldoxime, partly rearranges during work-up to an N-acetoxyhydroxamic acid. Since, as was pointed out before, acetic anhydride is a side product of the oxidation, reaction of these two components can lead to the detected trisubstituted hydroxylamine (ν(C=O): 1820 cm^{-1}):



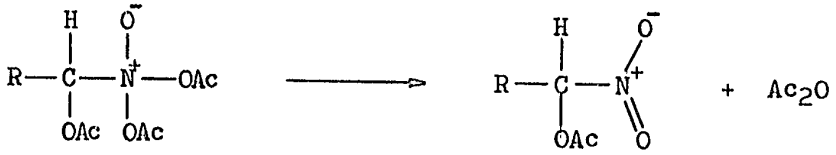
This reaction sequence is partly substantiated by the presence of acetic acid <u>after</u> initial alkaline ($NaHCO_3$-wash) work-up.

The formation of acetic anhydride and the geminal <u>nitro</u>-acetate remains to be explained. The latter type of compound was isolated and characterized in the lead tetraacetate oxidation of pregnenolone-oxime-3-acetate.[82] Its presence in the crude oxidation product of heptanaldoxime was suggested by spectral analysis.

Nitroso compounds are known to be efficient radical traps,[83] and it is conceivable that monomeric nitrosoacetate (p. 97) scavenges still unconsumed acetoxy radicals faster than iminoxy radicals:

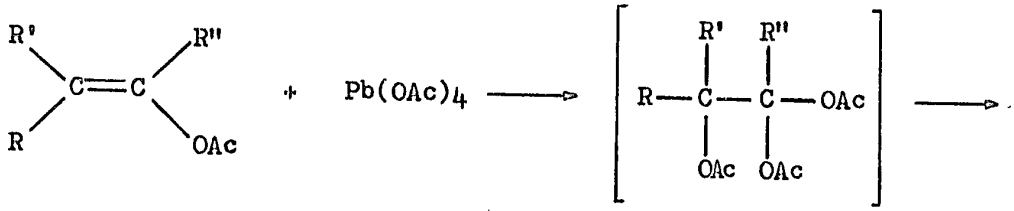


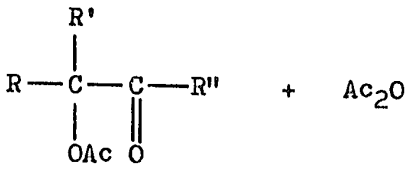
<u>66</u>



<u>67</u> <u>22</u>

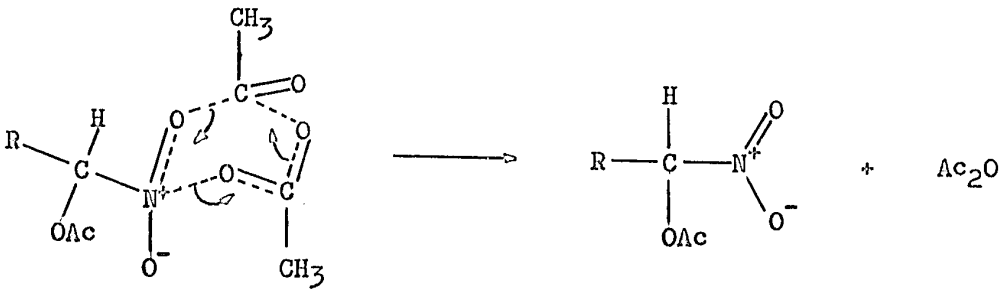
Addition of one acetoxy radical to the geminal nitrosoacetate would lead to a diacetoxynitroxide (66) whose transient presence in the lead tetraacetate oxidation of oximes has been made likely by ESR studies.[84] Recombination with a second acetoxy radical would lead to a triacetoxy compound (67) which can be expected[85] to be unstable, and to convert to geminal nitroacetate 22 and acetic anhydride. The conversion 67—>22 finds an analogy in the lead tetraacetate oxidation of enol-acetates to acetoxyketones and acetic anhydride via an unstable (not isolated) triacetoxy compound:[86]





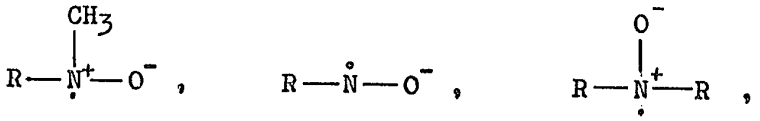
Though the formation of acetic anhydride has as yet not been explained,[86] it can be rationalized by invoking collapse of a

six-membered ring transition state (shown for conversion 67→22):



22

A recent detailed study of secondary radicals in the lead tetraacetate oxidation of oximes indicates the presence of radicals 68, 69, and 70:[87]



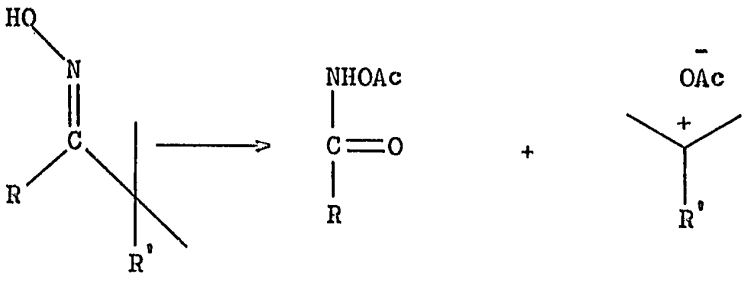
68 69 70

which may be precursors to compounds accounting for undefined material in the oxidation mixture.

CHAPTER III. OXIDATION OF KETOXIMES

The lead tetraacetate oxidation of ketoximes has been the subject of a number of recent publications, and the few product analyses carried out showed the geminal nitrosoacetates to be the only isolable product.[17,18] These results found confirmation in the present investigation for the oxidation of unhindered ketoximes. Sterically hindered ketoximes, however, took a different course of reaction.

Reaction in aprotic solvents led to complex mixtures containing ten or more components. The product distribution apparently was independent of the dielectric constant of the reaction medium. Reaction in a protic solvent, e.g., acetic acid, led mainly to products arising from a carbon-carbon bond cleavage of the ketoxime:



71

These compounds could also be obtained by oxidation in methylene chloride; their respective yields increased with increasing acetic acid concentration and decreased with decreasing temperature. Also, yields were greatly affected by the steric requirements of substituents R and R' as well as by their ability to stabilize an intermediate carbonium ion. The direction of cleavage was a reflection of the stability of the carbonium ion formed. The latter aspect also determined whether intermediate 71 converted to a tertiary acetate and/or olefinic material.

The present study concerned itself with hindered aliphatic ketoximes which contained a cyclohexane ring as the basic structural unit. Thus, methylated cyclohexanone oximes and bicyclic oximes of the camphor series were found to react as outlined above. Since this reaction was found to be restricted to hindered ketoximes, its preparative usefulness is of limited importance. The mechanistic aspects of the carbon-carbon bond cleavage, however, are interesting and warrant a more detailed discussion.

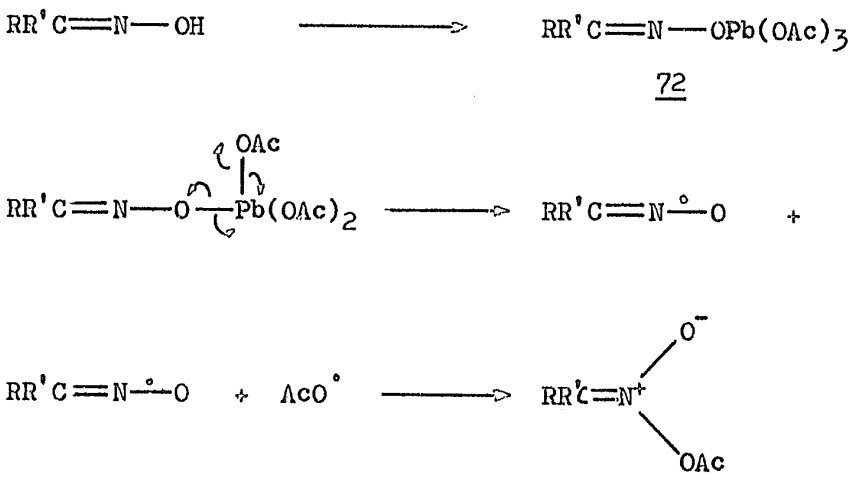
Mechanism of the Ketoxime Oxidation.

The oxidation of ketoximes is a fast reaction, though not as fast as the aldoxime oxidation. When the reaction was initiated at low temperature (-78°) and the progress of product formation was observed with increasing temperature, the same phenomena as in the

anti aldoxime (aliphatic) oxidation were observed: iminoxy radical formation (green), commencing at about -70° with simultaneous precipitation of lead diacetate; fading of the initial green to a nondescript greyish yellow, stable up to about -25° for sterically hindered, but not particularly strained ketoximes (e.g., 2,2,6,6-tetramethylcyclohexanone oxime), and persisting up to +5° for very strained, but not very hindered ketoximes (e.g., camphor oxime). Further raising of the temperature led to a blue/green colour whose intensity was inversely proportional to the steric crowding in the ketoxime, and the acetic acid concentration in the reaction medium. This colour is thought to arise from monomeric geminal nitrosoacetates, and it could be shown that these compounds when derived from ketoximes remain to a large extent monomeric in solution, even at temperatures as low as -78°. By contrast, 1-acetoxy-1-nitrosoalkanes are dimeric (colourless) at -78°.

The above data are suggestive of a mechanism similar to the one proposed for the anti aldoxime oxidation. First, a lead organic compound (72) is formed which subsequently suffers homolysis to an iminoxy radical, an acetoxy radical, and lead diacetate. This is followed by a radical recombination to the nitronic acid mixed anhydride 73. Intermediate 73 can then decompose in two ways, depending on steric crowding in the oxime substrate and proton

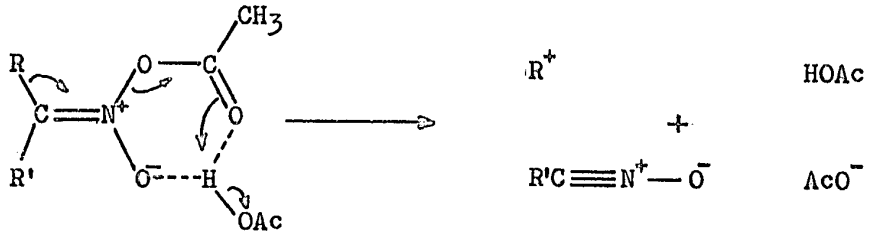
concentration in the reaction medium:



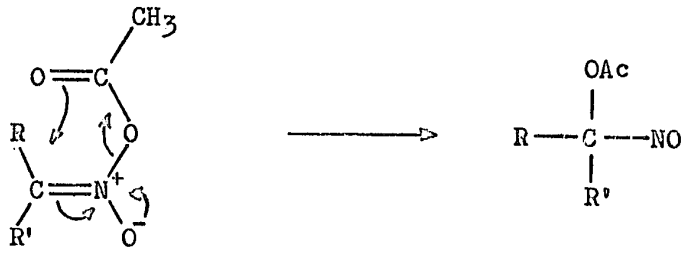
72

73

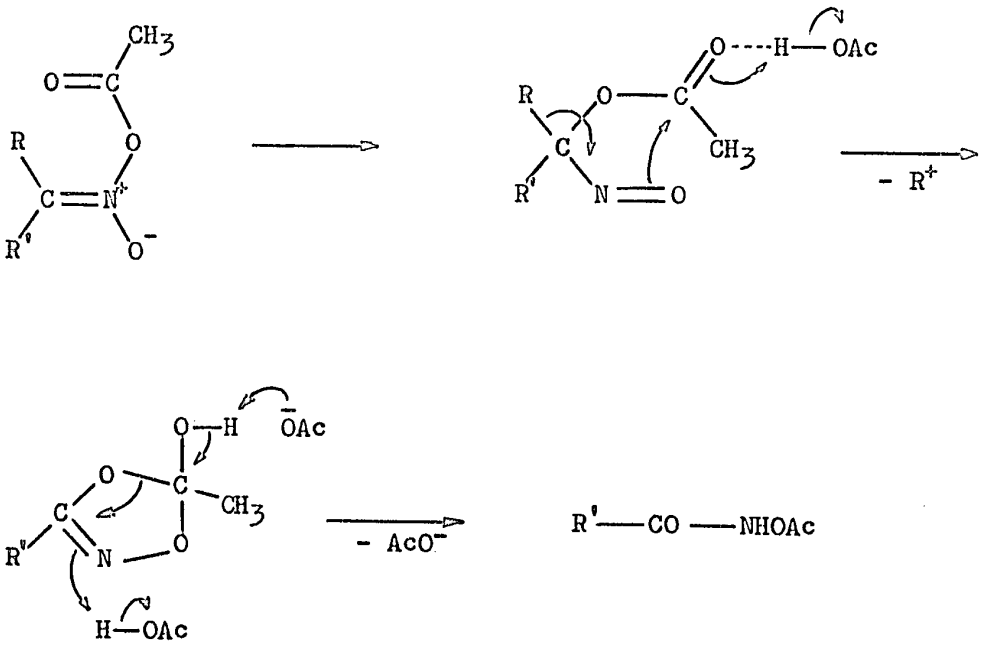
Scheme A: steric requirements of R(R') large; acetic acid concentration important.



Scheme B: steric requirements of R(R') small; acetic acid concentration unimportant.



Scheme C: substituents R(R') constitute a highly strained, but not particularly hindered substrate; acetic acid concentration important:



Mode of cleavage as shown provided R^+ is more stable than R'^+ .

The three possibilities of reaction for nitronic acid mixed anhydride 73 represent formal, limiting cases. Most probably, all three modes of reaction are operating concurrently, but depending on the ketoxime substrate, one or the other is preferred.

For instance, in the oxidation of 2,2,6,6-tetramethylcyclohexanone oxime substantial amounts of nitrile oxide could be trapped by isoxazoline formation with vinyl acetate. This indicates that the nitronic acid anhydride 73 reacts mainly according to Scheme A. Schemes B and C are unfavoured because of steric hindrance for a concerted acetate addition leading to nitrosoacetate. Although this reaction does occur if the acetic acid concentration in the reaction medium is low. Apparently, cleavage according to Scheme A is greatly assisted by a hydrogen-bonded six-membered ring transition state, as shown.

Reaction according to Scheme B is probably general for all unhindered ketoximes affording geminal nitrosoacetates.

A third mechanistic pathway was required to explain the colour changes observed in the camphor oxime oxidation as well as the failure to trap a nitrile oxide. Initially an intensely blue solution was obtained, but this colour did not persist (it faded at room temperature within ¾ hr) and work-up afforded about 70% of cleavage products. This behaviour is best explained by assuming initial nitrosoacetate formation (the camphor substrates should offer little steric resistance to its formation according to Scheme B), followed by an intramolecular rearrangement causing ring cleavage (Scheme C). The driving force for this rearrangement is probably relief of strain in the bicyclic system.

If the substrate is highly strained and hindered (fenchone oxime), no nitrosoacetate is formed and cleavage occurs via free nitrile oxides. The fate of the nitrile oxides has been discussed in the context of the aldoxime oxidation. The fate of the intermediate carbonium ion, however, requires some comment. An open chain tertiary carbonium ion leads to only one compound, a tertiary acetate (e.g., oxidation of 2,2,6,6-tetramethylcyclohexanone oxime). A tertiary carbonium ion which is contained in a five-membered ring affords mainly olefinic material and also some acetate (e.g., oxidation of camphor oxime).

In closing this discussion it should be pointed out that spectral inspection of crude oxidation products (aldoximes and ketoximes), and fractions thereof, gave no indications of compounds which could have possibly arisen from an intramolecular radical displacement reaction, i.e., nitrogen and oxygen containing heterocyclic compounds.

CONCLUSIONS AND CONTRIBUTION TO KNOWLEDGE

Lead tetraacetate oxidation of syn aldoximes provides a mild method of preparation for nitrile oxides which is competitive and in certain respects superior to existing[50] procedures.

Oxidation of anti aldoximes affords products arising from radical-radical recombinations, leading to aldazine-bis-N-oxides for aromatic and geminal nitrosoacetates for aliphatic substrates. In the latter case other products are also formed as a result of secondary reactions.

1-Acetoxy-1-nitrosoalkanes rearrange to N-acetoxyhydroxamic acids. This rearrangement can be catalysed by base.

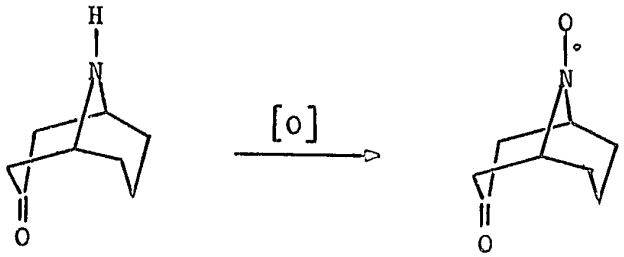
Oxidation of aliphatic, sterically hindered ketoximes leads via carbon-carbon bond cleavage to N-acetoxyhydroxamic acids. In cases of severe steric crowding about the oxime function, nitrile oxides can be detected as intermediates by spectroscopy; trapping them by 1,3 dipolar cycloaddition is also possible. Highly strained, but not very hindered ketoximes apparently form N-acetoxyhydroxamic acids by rearrangement of an intermediate geminal nitrosoacetate.

Oxidation of unhindered ketoximes affords geminal nitrosoacetates as reported.[18,19]

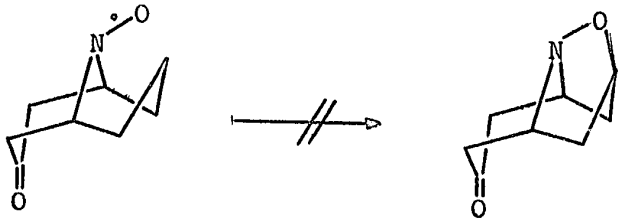
All oxidation reactions can be rationalized by invoking intermediate existence of reported[1,6,9] iminoxy radicals. No evidence for an ionic oxidation mechanism could be obtained.

Intramolecular radical displacement reactions, as projected at the outset of this investigation, were not found to occur. The apparent inability of iminoxy radicals to undergo these reactions, is probably associated with the delocalized nature of the unpaired electron. Energy dissipation of iminoxy radicals occurs preferentially by radical recombination, a process which requires little or no energy of activation. In this respect iminoxy radicals behave like their closest analogues: nitroxides.[2] The observation that iminoxy radicals apparently do not react over the oxygen atom is consistent with the large nitrogen coupling constant (ESR) found, which indicates a substantial concentration of unpaired electron spin density at the nitrogen nucleus.[1] Though nitroxides have appreciably smaller nitrogen coupling constants, they also react preferentially at the nitrogen atom and do not undergo radical displacement reactions. This point is particularly well illustrated by the recent preparation of a stable

nitroxide by oxidation of norpseudopelletierine:[88]



This nitroxide neither dimerizes nor abstracts hydrogen:



EXPERIMENTAL

General. All chemicals used in this study were reagent grade unless otherwise stated in the individual experiments. Melting points were measured in a capillary tube in a sulphuric acid bath, and are corrected to the nearest degree. Analyses were performed by Beller Mikroanalytisches Laboratorium, Göttingen, and Bernhard Mikroanalytisches Laboratorium, Mühlheim, Germany. The NMR spectra were recorded on a Varian A-60 spectrometer, mostly in deuterochloroform, but also in other solvents ($(CD_3)_2SO$, C_6H_6, CCl_4). Tetramethylsilane served as internal standard. IR spectra were recorded on Perkin Elmer "Infracord", "337", and "521" spectrometers in carbon tetrachloride, chloroform, and KBr-pellets as individually noted. Reported band positions were corrected with respect to the polystyrene band at 1946 cm^{-1}. UV spectra were recorded with a Beckmann "DK" spectrophotometer. Solvents used, unless reagent grade, were distilled before use.

Lead tetraacetate. This reagent was purchased in 100 g quantities from Canadian Laboratories Supplies (Matheson, Coleman, and Bell); it contained 4-7% acetic acid as stabilizer and was used as such for all oxidations. Samples recrystallized from acetic acid and washed acid free with petroleum ether gave identical results.

Apparatus. All low temperature oxidations were conveniently carried out in a "Mini-Lab Basic Assembly" (ACE Glass, Inc.), consisting of a reaction vessel fitted with a multineck adapter to accommodate one to three pressure equalization dropping funnels, a low temperature thermometer (pentane), and a connection to a mercury blow-off trap. The reaction mixture could be stirred magnetically, and cooling was provided by a dry-ice/i-propanol bath (-78°).

CHAPTER I. PREPARATION OF OXIMES

The oximes listed in Tables 1, 2, 3 (pp. 10, 11, 13) were prepared according to literature procedures[22] from commercially available aldehydes and ketones (suppliers: Aldrich Chemicals, Fisher Scientific, Canadian Laboratories Supplies). Only those preparations are subsequently given where a modification of existing procedures was desirable, or where no procedures have been described as yet.

Anti-benzaldoxime. The existing procedure[23] does not sufficiently stress the fact that all operations - conversion of syn-benzaldoxime to the hydrochloride, neutralization with base, and solvent removal - have to be carried out fast (< ½ hr), and in the cold (0 to 20°). If this is not observed, very low yields of anti-benzaldoxime are obtained. Recrystallation of the crude product is best carried out with pure hexane; addition of ether promotes isomerization to syn-benzaldoxime.

Anti-n-heptanaldoxime. A sample of practical heptanal was distilled over a short Vigreux column. The fraction distilling at 31°/5 mm* was collected and identified (IR, NMR) as the pure aldehyde.

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* All pressure data refer to mm Hg .

This material (49 g, 0.43 moles) was dissolved in ether (200 ml); hydroxylamine hydrochloride (32 g, 0.46 moles) was added, followed by slow addition of an aqueous saturated solution of sodium bicarbonate (200 ml), then solid sodium bicarbonate was added (25 g, 0.3 moles). The two-phase system was thoroughly stirred at room temperature for 4 hr. The aqueous phase was saturated with sodium chloride and the ether phase was separated. The aqueous phase was extracted with ether (2 x 25 ml), and the combined ether extracts were dried ($MgSO_4$) and freed of solvent (36°/760 mm). Vacuum distillation of the liquid residue afforded a major fraction (30 ml), distilling at 83-84°/5 mm (bath: 120°) which was recrystallized from hexane at -78° (30 g, 0.23 moles, 54%); m.p. 56-57° (lit.,[32] 56-57°). An NMR spectrum of this material, recorded immediately after preparing a carbon tetrachloride solution of it, showed only anti-n-heptanaldoxime; after one day of standing at room temperature this solution contained a 1:1 mixture of syn- and anti-n-heptanaldoxime.

2,2,6,6-Tetramethylcyclohexanone oxime (35). The parent ketone was prepared according to a modified literature procedure.[89,90] 2-Methylcyclohexanone (72 g, 0.64 moles) was dissolved in anhydrous ether (250 ml). Sodamide (80 g, 2.05 moles) was slowly (0.5 hr) added to this solution with stirring and cooling (dry ice/i-propanol bath). When the initial violent reaction had subsided, the mixture was refluxed on the steam bath (1 hr). Then ammonia and most of the

solvent was removed (20°/20 mm); this was followed by slow addition of methyl iodide (290 g, 2.05 moles) in anhydrous ether (100 ml) while stirring and cooling (dry ice/i-propanol bath). Then the reaction mixture was refluxed on the steam bath (1 hr) followed by standing at room temperature over night. Ice water was added, followed by citric acid until the reaction mixture was acidic (pH paper). The iodine liberated was reduced with an aqueous solution of sodium thiosulphate. Subsequently, the reaction mixture was extracted with ether (100 ml, 6 x 25 ml). An aliquot of the combined (and dried) ether extracts was freed of solvent and analysed by IR spectroscopy. A slight asymmetry in the carbonyl band at 1700 cm^{-1} indicated that the methylation was not yet complete. Rather than attempt separation by distillation, the methylation procedure was repeated with the crude product (60 g sodamide, 200 g methyl iodide). The resultant oil (112 g) gave an IR spectrum with a perfectly symmetric carbonyl band, and was also identical in all respects with a spectrum of a sample of 2,2,6,6-tetramethylcyclohexanone obtained previously by methylation to "constant IR spectrum". The crude product contained ca. 88% of the desired ketone as indicated by calculation. This purity was considered satisfactory for direct conversion to the oxime.

The crude 2,2,6,6-tetramethylcyclohexanone (50 g, $\sim$ 0.3 moles) was dissolved in methanol (300 ml) together with hydroxylamine hydrochloride (56 g, 0.8 moles) and anhydrous sodium acetate (72 g 0.9 moles). After refluxing for one day, white lumps floated in

the reaction mixture (oxime ?) which were dissolved by addition of methanol (100 ml). Refluxing was continued for another day (total reflux time: 48 hr). Then, most of the methanol was distilled, water (100 ml) was added, followed by ether extraction (100 ml, 6 x 25 ml). The combined and dried ($MgSO_4$) ether extracts afforded after solvent removal (30°/20 mm) crystalline material (44.5 g, 0.26 moles, 91%, based on 2-methylcyclohexanone). Recrystallization from methanol gave white platelets, melting at 151.5° (21.2 g, 1st crop; 12.4 g, 2nd crop); (lit.,[43] m.p. 151°). Anal. calcd. $C_{10}H_{19}NO$: C, 70.96; H, 11.32; found: C, 70.86; H, 11.37. IR, $\bar{\nu}_{max}^{CCl_4}$: 3590(s), 3300(m), 3240(m), 963(m), 943(s), and 920(m) cm^{-1}. NMR, δ ppm ($CDCl_3$): 1.16 (S, 2 CH_3), 1.33 (S, 2 CH_3), 1.57 (M, 3 CH_2), and 9.64 (S, OH).

CHAPTER II. OXIDATION OF ALDOXIMES

A. Oxidation of Hindered Syn Aldoximes.

O-Methylpodocarponitrile oxide (12). Solid lead tetraacetate (264 mg, 0.59 mmoles) was added to a stirred solution of syn-O-methylpodocarpinaldoxime (11) (146 mg, 0.508 mmoles) in methylene chloride (4 ml). White precipitate formed and the solution turned faintly green. After standing at room temperature for 5 min, the reaction mixture was poured into crushed ice (50 g). The resultant slurry was extracted with ether (5 x 20ml); the combined extracts were washed acid free with saturated sodium bicarbonate solution (2 x 5 ml), then dried ($MgSO_4$) and freed of solvent (30°/20 mm). A white crystalline mass (152 mg) with a slight yellow tinge was obtained, m.p. 123-125°. Recrystallization from methanol gave white crystals (136 mg, 0.478 mmoles, 94%), m.p. 127-128°. A second recrystallization raised the melting point to 131.5-132°. Anal. calcd. for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91; found: C, 75.79; H, 8.39; N, 5.08. IR $\bar{\nu}_{max}^{CCl_4}$: 2270(s) cm^{-1} ($-C\equiv N^+-O^-$). NMR, δ ppm ($CDCl_3$): 1.30 (S, CH_3), 1.42 (S, CH_3), 2.87 (D, J = 6 cps, Ar - CH_2), 3.74 (S, CH_3O), 6.8 (M, 3 aromatic H).

- Sodium borohydride reduction of nitrile oxide 12: sodium borohydride (40 mg, 0.85 mmoles) in anhydrous methanol (5 ml) was

added with stirring to a solution of nitrile oxide 12 (22 mg, 0.077 mmoles) in anhydrous methanol (5 ml). After ½ hr, the reaction mixture was diluted with water (50 ml) and extracted with ether (5 x 20 ml). The combined extracts, after drying ($MgSO_4$) and solvent removal (30°/20 mm), afforded crystalline material (23 mg, ~ 0.077 mmoles, 100%) which showed the same R_f value (SiO_2/airdry), melting point and IR spectrum as aldoxime 11. A mixed melting point was not depressed.

Mesitonitrile oxide (13). A cold solution of lead tetra-acetate (3.456 g, 7.8 mmoles) in methylene chloride (30 ml) was added with stirring to a cold (-78°) solution of mesitaldoxime (1.140 g, 7.00 mmoles, 89% syn, 11% anti isomer) in methylene chloride (30 ml). The cold bath was removed and the reaction mixture was allowed to come to 0°. Then ether (20 ml) was added, followed by stirring (5 min). The resultant suspension was transferred with ether (100 ml) to a separatory funnel and washed with ice-cold water (25 ml), followed by washing with ice-cold saturated sodium bicarbonate solution (4 x 5 ml). The ether extract was dried ($MgSO_4$), and concentrated by evaporation to about 1/3 of its original volume with a stream of dry nitrogen at 0°. A fine precipitate appeared which was collected by filtration (80 mg) and identified by IR as a mixture of mesitylaldazine-bis-N-oxide (14) and nitrile oxide 13 (ratio, 2:1). The filtrate was freed of solvent

with a stream of dry nitrogen at 0°, affording white needles of 13 (978 mg, 6.08 mmoles, 87%; or based on syn aldoxime only, 97%), m.p. 107-109°. Recrystallization from methanol/water gave white needles (1st crop: 900 mg), m.p. 111.5-112°. Repeated crystallizations and vacuum sublimation (35°/0.05 mm) did not raise the melting point (lit.,[51] m.p. 114°). Anal. calcd. for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69; found: C, 74.29; H, 6.65; N, 8.79. IR, $\overline{\nu}^{CCl_4}_{max}$: 2290(s) and 1360(s) cm^{-1} ($-C\equiv\overset{+}{N}-\overset{-}{O}$). NMR, δ ppm ($CDCl_3$): 2.31 (S, CH_3), 2.38 (S, 2 CH_3), and 6.95 (S, 2 aromatic H).

- Modification: Lead tetraacetate oxidation of mesitaldoxime as above but at room temperature gave lower yields of nitrile oxide 13: e.g., 1.372 g of aldoxime (8.42 mmoles) yielded 600 mg of nitrile oxide 13 (3.73 mmoles, 46%). The major side product formed was identified by IR as mesitylaldazine-bis-N-oxide (14): $\overline{\nu}^{CHCl_3}_{max}$: 1580(s), 1450(s), 1380(s), 1340(s), 1090(s), 1072(s), and 915(m) cm^{-1}.

B. Oxidation of Unhindered Syn Aldoximes.

N-Acetoxytrimethylacetohydroxamic acid. Solid lead tetraacetate (5.403 g, 12.1 mmoles) was added at room temperature to a solution of syn-trimethylacetaldoxime (825 mg, 8.20 mmoles) in methylene chloride. The stirred mixture first turned sky-blue, then faded to a light green/blue and white precipitate formed. Stirring

was maintained until the mixture was colourless (9 hr), then ether was added (60 ml), followed by magnesium sulphate (1-2 g). After stirring for 5 hr, the resultant suspension was filtered, washed with ice-cold saturated sodium bicarbonate solution (3 x 5 ml), dried ($MgSO_4$), and most of the solvent was distilled over a short Vigreux column (60°/760 mm). The last 5 to 10 ml of solvent were removed with a stream of dry nitrogen until constant weight was achieved (1.140 g). The crystalline residue, m.p. 112-114°, was redissolved in pentane/ether and stored on dry ice. A crystal crop (1.054 g, 6.61 mmoles, 80%) of white needles resulted, m.p. 115-116°. Repeated crystallization or vacuum sublimation (50°/0.1 mm) raised the melting point to 116-116.5°. The material gave initially a negative ferric chloride test. However, on standing at room temperature (> 4 hr), a deep mauve colour developed. The same observation was made for the subsequently described N-acetoxy-hydroxamic acids.

- Modification: Reaction of syn-trimethylacetaldoxime with lead tetraacetate in methylene chloride at -78° afforded a colourless solution, which on warming to room temperature remained colourless and gave an 80% yield of N-acetoxytrimethylacetohydroxamic acid.

N-Acetoxy-O-methylpodocarpohydroxamic acid. Nitrile oxide 12 (135 mg, 0.474 mmoles) was dissolved in freshly distilled acetic acid (5 ml) and warmed to 40° for 2 hr, then allowed to stand at room temperature over night. Acetic acid was removed (25°/0.2 mm) until constant weight was achieved. The residue consisted of white crystals (163 mg, 0.473 mmoles, 100%) melting at 150° (dec.). Recrystallization from hexane/ether did not raise the melting point.

N-acetoxybenzohydroxamic acid. A cold (-78°) solution of lead tetraacetate (2.694 g, 6.0 mmoles) in methylene chloride (20 ml) was added to a cold (-78°) solution of syn-benzaldoxime (664 mg, 5.49 mmoles) in methylene chloride (20 ml). The resultant hazy, yellow mixture was stirred at -78° for ½ hr, then the cold bath was removed. Ether (60 ml) and magnesium sulphate (1-2 g) were added when the reaction mixture had come to room temperature. The resultant suspension was stirred (20 min), then filtered, washed with ice-cold saturated sodium bicarbonate solution (3 x 10 ml), dried ($MgSO_4$), and freed of solvent with a stream of dry nitrogen. White crystals with a yellow tinge were obtained (714 mg, m.p. 124-125°) which after recrystallization from hexane/ether gave analytically pure material (620 mg, 3.47 mmoles, 63%), m.p. 126.5° (lit.,[54] 125-126°). The material can be sublimed (95°/0.2 mm).

N-acetoxymesitohydroxamic acid (15). Mesitonitrile oxide (13) (161 mg, 1 mmole) was dissolved in freshly distilled acetic acid (0.5 ml, 8.8 mmoles) and anhydrous ether (10 ml) and set aside at room temperature. Crystals began to form after 10 hr. After 48 hr the solvent was removed with a stream of dry nitrogen, followed by evacuation (10°/0.1 mm) until constant weight was achieved (221 mg, 1 mmole, 100%). White platelets resulted, m.p. 139.5-140° (dec.) (lit.,[51] 136-138° (dec.)). Recrystallization from hexane/ether did not raise the melting point. NMR, δ ppm ($CDCl_3$): 2.27 (S, CH_3), 2.36 (S, 3 CH_3), 6.92 (S, 2 aromatic H), and 9.3 (S, NH).

Oxidation of dehydroabietinaldoxime (abietinaldoxime).

- 1. Preparation of dehydroabietinaldoxime (17). A solution of diazomethane at 0° was added to a solution of dehydroabietic acid[91] (230 mg, 0.767 mmoles) in anhydrous ether (15 ml). After normal work-up, the resultant crude methyldehydroabietate was reduced in ethereal solution with lithium aluminium hydride (120 mg) at room temperature (24 hr). Excess reducing agent was destroyed by slow addition of ice water (1 ml) followed by neutralization with ice-cold dilute sulphuric acid (10 ml, 10% H_2SO_4). Ether extraction afforded a pale yellow foam (202 mg, $\sim$ 0.7 mmoles) which by IR and TLC consisted of essentially dehydroabietinol. The total amount

of crude dehydroabietinol was dissolved in freshly distilled acetone (10 ml), cooled to 0°, and a cold solution of Jones reagent (1 ml, CrO_3 in dil. H_2SO_4)[92] in acetone (5 ml) was slowly added with stirring. After 10 min, i-propanol (2.5 ml) was added to destroy excess oxidizing agent. The reaction mixture was diluted with water (15 ml) and extracted with ether (6 x 10 ml). The extract was washed with water (2 x 5 ml), saturated sodium bicarbonate solution (2 x 5 ml), and water (5 ml). Drying ($MgSO_4$) and solvent removal (60°/20 mm) afforded a viscous oil (216 mg), which was shown to consist of dehydroabietinol (< 5%), dehydroabietinal (60-80%), and dehydroabietic acid (20-30%) (by IR and TLC). This crude mixture was treated with hydroxylamine hydrochloride (185 mg, 2.7 mmoles) and sodium acetate x 3 H_2O (506 mg, 3.7 mmoles) in methanol (25 ml) at reflux for 1 hr. Then, the reaction mixture was left to stand over night. Work-up was conducted by first distilling most of the methanol, then diluting with water (30 ml), followed by ether extraction (6 x 10 ml). The combined extracts were washed with 5% sodium carbonate solution (2 x 5 ml) and water (5 ml). Drying ($MgSO_4$) and solvent removal (30°/20 mm) gave a white foam (137 mg), which was shown by IR and TLC to consist of 80-90% of dehydroabietinaldoxime (17). This product was used for the subsequent oxidation experiment.

- 2. Oxidation of aldoxime 17. Solid lead tetraacetate (304 mg) was added to the crude aldoxime 17 (137 mg) in acetic acid (5 ml).

After stirring for ½ hr, the reaction mixture was diluted with ice water (100 ml) and extracted with ether (6 x 10 ml). The combined extracts were washed with water (2 x 10 ml), saturated sodium bicarbonate solution (4 x 5 ml), and water (5 ml), then dried ($MgSO_4$) and freed of solvent (60°/20 mm and 20°/0.2 mm). A yellow foam resulted (151 mg), which by TLC consisted of one major component. The IR spectrum showed all the bands characteristic of an N-acetoxy-hydroxamic acid: $\bar{\nu}_{max}^{CCl_4}$: 3350(m), 1785(s), 1715(s), 1200(s), and 1122(s) cm^{-1}. No nitrile oxide (band at 2270 cm^{-1}) was detectable. O-Methylpodocarpinaldoxime (oxime function axial) gave under identical reaction conditions 80% nitrile oxide.

- 3. Hydrolysis of N-acetoxydehydroabietohydroxamic acid. Hydrolysis of the crude oxidation product of aldoxime 17 (for procedure cf., p. 139) afforded after usual work-up crude, crystalline material, whose IR spectrum indicated hydroxamic acid, $\bar{\nu}_{max}^{CHCl_3}$: 3440(m-s), 3250(m), and 1645(s) cm^{-1}. A ferric chloride test gave an intense mauve colour.

N-acetoxyabietohydroxamic acid. A mixture of resin acids (= techn. abietic acid) was converted to the corresponding aldoximes and oxidized as described above. Again, N-acetoxyhydroxamic acids were obtained. IR, $\bar{\nu}_{max}^{CCl_4}$: 3370(m), 1790(s), 1720(s), 1200(s) and 1122 (m-s) cm^{-1}. No nitrile oxide was detectable.

C. Oxidation of Syn Aldoximes and Trapping of the Intermediate Nitrile Oxides with Vinyl Acetate.

A general procedure was worked out for the low temperature oxidation of unhindered syn aldoximes and trapping of the intermediate nitrile oxide with vinyl acetate. This procedure is illustrated by the oxidation of syn-benzaldoxime. Variations in reaction time and work-up for other aldoximes are noted in Table 6 (p. 35).

A cold (-78°) solution of lead tetraacetate (2.458 g, 5.5 mmoles) in methylene chloride (20 ml) was added during 1 min to a cooled (-78°) and stirred solution of syn-benzaldoxime (569 mg, 4.70 mmoles) in methylene chloride (10 ml) and vinyl acetate (20 ml, freshly distilled, 71-73°/760 mm fraction). While maintaining efficient cooling (-78°), the reaction mixture was stirred for 1 hr. At the end of this period, a pale yellow solution was obtained which contained a substantial amount of white precipitate ($Pb(OAc)_2$). Triethylamine (11 mmoles) in methylene chloride (10 ml) was added for neutralization of acetic acid. The reaction mixture was allowed to come to room temperature, then ether (100 ml) was added, followed by magnesium sulphate (1 to 2 g, to assist precipitation of lead salt), stirring for ½ hr, and filtration. The yellow filtrate was washed with ice-cold saturated sodium bicarbonate solution (5 x 5 ml), which removed remaining lead salts and some of the triethylamine-acetic acid adduct. After drying ($MgSO_4$), the filtrate was

concentrated by distillation over a short Vigreux column (70-75°/760 mm). The concentrate (ca. 20 ml) was freed of remaining solvent with a stream of dry nitrogen, yielding a yellow/brown crystal mass (1.32 g). Recrystallization from hexane/ethanol (95:5, v:v) at -78° afforded white crystals with a faint yellow tinge (781 mg, 3.81 mmoles, 81%), m.p. 87-89°. Spectral analysis (IR, NMR) indicated pure 5-acetoxy-3-phenyl-2-isoxazoline. A second recrystallization raised the melting point to 90.5°. Vacuum sublimation (65°/0.1 mm) gave white crystals of m.p. 106°, which upon recrystallization from hexane/ethanol again melted at 90.5° (lit.,[61] 88-89°). The two (crystal) forms were found to arise from the same compound (IR, NMR, UV, elemental analysis identical). UV, λ_{max}^{EtOH} 254 mμ (ε 24,300) (lit.,[60] 254 mμ (ε 14,300)).

- Modifications: 1. The oxidation could be carried out in methylene chloride alone, followed by addition of vinyl acetate and triethylamine. This approach gave lower yields (ca. 50%). 2. Ethanol was used as solvent instead of methylene chloride. This approach also gave lower yields (40-50%) and the reaction appeared to be more rapid as deduced from a sudden temperature rise (10°) upon admixture of lead tetraacetate and aldoxime. 3. Triethylamine could be replaced by pyridine. In fact, the oxidation could be carried out in the presence of pyridine; however, work-up was more tedious and yields were low. Oxidation without subsequent addition of base led to mixtures of isoxazoline acetates and N-acetoxyhydroxamic acids.

5-Acetoxy-3-(16-nor-O-methylpodocarp-4β-yl)-2-isoxazoline (19). Freshly distilled vinyl acetate (2 ml, 32 mmoles) was added to a solution of nitrile oxide 12 (356 mg, 1.25 mmoles) in benzene (15 ml). The mixture was refluxed for 1 hr when TLC indicated complete conversion to a new product. After solvent removal (30°/20 mm), a white foam was obtained (468 mg, 1.26 mmoles, 100%), m.p. 52-54°. Spectral analysis (IR, NMR) indicated the presence of the isoxazoline acetate 19. The NMR spectrum showed two isomeric compounds in equal proportions. Attempts to separate these by chromatography and fractional crystallization were fruitless. NMR, δ ppm ($CDCl_3$): 1.07 (S, ½ CH_3), 1.18 (S, ½ CH_3), 1.21 (S, ½ CH_3), 1.27 (S, ½ CH_3), 1.95 (S, ½ OAc), 2.02 (S, ½ OAc), 2.84 (M, 2 H), 3.14 (M, 2 H), 3.75 (S, OCH_3), 6.61 (M, 1 H), and signals arising from methylene and aromatic protons.

D. Preparation of 3-Substituted 2-Isoxazoles.

3-(16-nor-O-methylpodocarp-4β-yl)-2-isoxazole (20). A solution of isoxazoline acetate 19 (410 mg, 1.1 mmoles) in ethanol (15 ml), containing hydrochloric acid (1 ml conc. HCl/50 ml EtOH), was refluxed for 2 hr when TLC indicated complete conversion to a new product. Upon solvent removal (40°/20 mm and 20°/0.2 mm), a white semi-crystalline mass was obtained (344 mg) which was recrystallized from acetonitrile/water/ether, affording white

long needles (275 mg, 0.886 mmoles, 80% based on nitrile oxide), m.p. 104°. Anal. calcd. for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.09; N, 4.50; found: C, 76.63; H, 8.21; N, 4.74. IR, no outstanding features can be assigned to isoxazole. NMR, δ ppm ($CDCl_3$): 0.77 (S, CH_3), 1.30 (S, CH_3), 2.87 (M, 2 H), 3.76 (S, OCH_3), 6.32 (D, J = 1.7 cps, 1 H), 6.83 (M, 3 aromatic H), and 8.31 (D, J = 1.7 cps, 1 H), besides signals arising from methylene protons.

3-t-Butyl-2-isoxazole. Adequate description for the preparation of this compound can be found on p. 38 . Its IR spectrum showed bands typical for isoxazoles.[96]

E. Oxidation of Anti-n-Heptanaldoxime.

1-Acetoxy-1-nitroso-n-heptane (21). A cold (-78°) solution of lead tetraacetate (3.755 g, 8.4 mmoles) in methylene chloride (20 ml) was added to a cooled (-78°) and stirred solution of anti-n-heptanaldoxime (951 mg, 7.38 mmoles) in methylene chloride (20 ml). After 3 min at -78°, the mixture was yellow and hazy; on raising the temperature above -70°, a green colour appeared accompanied by white precipitation.* The green colour went through an intensity maximum at -55° to -50°, then slowly faded to a greyish yellow at about -25°.

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* Lead diacetate, verified by: $Pb(OAc)_2 + 2\,KI \longrightarrow PbI_2\downarrow + 2\,KOAc$

A different kind of green/blue appeared at -10° (this temperature point was found to vary somewhat from one experiment to another) and intensified towards room temperature. The formation of the latter colour was reversible: it disappeared on lowering the temperature to -78°, and reappeared on raising it above -10°. To the green/blue reaction solution, ether (60 ml) and magnesium sulphate (1-2 mg) was added with stirring. After 10 min, the resultant suspension was filtered, the filtrate was washed acid free (pH paper) with ice-cold saturated sodium bicarbonate solution (4 x 5 ml), dried ($MgSO_4$) and freed of solvent with a stream of dry nitrogen at 0°. A green oil resulted (1.616 g) which by semi-quantitative IR analysis contained acetic anhydride (10%), acetic acid ($\geq$ 10%), and other products. Extensive pumping (10°/0.2 mm) permitted collection of a volatile fraction in a cold trap. IR analysis of the trap residue indicated acetic anhydride, acetic acid, and some solvent. Upon addition of a drop of dilute sulphuric acid (5%) and brief warming, all acetic anhydride was converted to acetic acid (IR evidence). The oily residue, after pumping (1.15 g), was analysed by NMR and IR (for details cf., p. 40), then dissolved in pentane (10 ml) and stored on dry ice for 3 days. The resultant white crystals (180 mg, 0.481 mmoles, 13.1%*) were filtered and analysed: m.p. 84-85° (not raised upon repeated crystallization).

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* Yields varied from 9 to 14%.

Anal. calcd. for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48; found: C, 57.41; H, 9.16; N, 7.46.

F. Rearrangement of 1-Acetoxy-1-nitrosoalkanes to N-Acetoxyhydroxamic acids.

N-Acetoxyheptanohydroxamic acid. Freshly distilled triethylamine (7.2 mg, 0.07 mmoles) in ethereal solution (2 ml) was added to a solution of 1-acetoxy-1-nitroso-n-heptane (21) (157 mg, 0.42 mmoles) in anhydrous ether (8 ml). The resultant blue mixture was set aside at room temperature. The solution was colourless after 8 hr. Solvent was removed with a stream of dry nitrogen and pumping (0°/0.1 mm, 5 min). A crystalline residue resulted (158 mg, 0.42 mmoles, 100%), m.p. 82.5-83°. Recrystallization from pentane did not raise the melting point. Anal. calcd. for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48; found: C, 57.68; H, 9.18; N, 7.38.

N-Acetoxytrimethylacetohydroxamic acid. Solid lead tetraacetate (1.056 g, 2.38 mmoles) was added to a cold (-20°) solution of syn-trimethylacetaldoxime (217 mg, 2.15 mmoles) in methylene chloride (5 ml). A white precipitate formed and the solution turned slowly blue (5 min). The temperature was raised to 0°, ether was added (30 ml), followed by magnesium sulphate (1 g)

and stirring for 10 min. Then the suspension was filtered; the filtrate (0°) was washed with ice-cold saturated sodium bicarbonate solution (3 x 3 ml) and water (3 ml), dried ($MgSO_4$), and freed of solvent with a stream of dry nitrogen at 0°. A white crystal mass with a blue tinge resulted (262 mg). Analysis by NMR and IR spectroscopy indicated 75% of N-acetoxytrimethylacetohydroxamic acid (for analytical details cf., p. 124) and 25% of 1-acetoxy-1-nitroso-2,2-dimethylpropane (18). Isolation of the latter compound (without extensive rearrangement) could not be achieved, but its spectral data permitted structure assignment and quantitative estimation: IR, $\bar{\nu}_{max}^{CCl_4}$: 1760(s), 1560(s) (verified in $CHCl_3$), 1212(s), 1189(m-s), 1168(m), 1087(s), 1043(m), and 960(m) cm^{-1}. NMR, δ ppm ($CDCl_3$): 1.07 (S, 3 CH_3), 2.16 (S, OAc), and 6.92 (S, 1 H). The yield of nitrosoacetate amounted to 17% (0.403 mmoles, based on trimethylacetaldoxime). Upon dissolving the crystalline mixture in ether and adding a catalytic amount of triethylamine, quantitative conversion to N-acetoxytrimethylacetohydroxamic acid was effected.

- Rearrangement of nitrosoacetate 18 in vinyl acetate.

A mixture of nitrosoacetate 18 (25%) and N-acetoxytrimethylacetohydroxamic acid (75%) (262 mg), prepared from trimethylacetaldoxime as shown above, was dissolved in freshly distilled vinyl acetate (10 ml) containing triethylamine (2.1 mmoles). The solution was heated to 75° and the solvent was distilled over a short Vigreux

column until the volume of the reaction solution was reduced to 1 to 2 ml. Remaining solvent was removed with a stream of dry nitrogen. A crystalline residue resulted (250 mg) which consisted of N-acetoxytrimethylacetohydroxamic acid (> 95%). No isoxazoline acetate could be detected (IR, NMR).

G. Oxidation of Anti-Benzaldoxime.
(Preparation of Phenylaldazine-bis-N-oxide).

A cold (-78°) solution of lead tetraacetate (1.440 g, 3.24 mmoles) in methylene chloride (15 ml) was added to a cold (-78°) solution of anti-benzaldoxime (390 mg, 3.24 mmoles) in methylene chloride (20 ml). After stirring for 1 min, a pale yellow and hazy solution was obtained, which turned green with simultaneous precipitate formation on raising the temperature above -70°. The green colour went through an intensity maximum (at approx. -60°), then gradually faded to a greyish yellow. Ether (100 ml) and ice-cold water (25 ml) were added at room temperature, followed by vigorous stirring for 10 min. The aqueous phase was separated; the ethereal layer was washed with ice-cold saturated sodium bicarbonate solution (3 x 5 ml), and concentrated to a volume of 15 ml by evaporation with a stream of dry nitrogen at -20°. A white crystalline precipitate resulted which was filtered and washed with cold (-50°) ether, then dried over anhydrous calcium

sulphate (22°/0.1 mm). This material (228 mg, 1.05 mmoles, 65%) melted at 109-110° (dec.) and showed the same IR spectrum (KBr pellet, cf., p. 52) as the reported[12a,18] phenylaldazine-bis-N-oxide, m.p. 108-109° (dec.).

H. Thermal Decomposition of Phenylaldazine-bis-N-oxide.

A cold saturated carbon tetrachloride solution of phenylaldazine-bis-N-oxide showed a strong and characteristic band at 1575 cm^{-1} (verified in $CHCl_3$). Upon warming the solution to 50° for 2 min, the 1575 cm^{-1} band became weaker, while new bands appeared at 3590(m), 950(m) (benzaldoxime), and 2290(s) cm^{-1} (benzonitrile oxide). The solution was then set aside at room temperature. After one day, another spectrum was recorded which showed no bands at 2290 and 1575 cm^{-1}, and the oxime bands were appreciably reduced in intensity. This indicated that all of the benzonitrile oxide and phenylaldazine-bis-N-oxide, and most of the benzaldoxime were consumed.

- Interception of nitrile oxide with vinyl acetate.

Phenylaldazine-bis-N-oxide (117 mg, 0.487 mmoles) was refluxed in freshly distilled vinyl acetate (1 ml, 16 mmoles) for 15 min. The resultant, yellow solution was freed of solvent with a stream of dry nitrogen, affording a semi-crystalline residue (148 mg).

Spectral analysis (NMR, IR) indicated the presence of isoxazoline acetate, benzaldoxime, and Ph-?-Ph in a molar ratio of 1:3:2. Compound(s) Ph-?-Ph is(are) probably oxadiazole(s).[65] The same result was obtained when oxidizing anti-benzaldoxime with lead tetraacetate in the presence of vinyl acetate (cf., p. 129). Isolation of the isoxazoline acetate could be achieved by recrystallization from hexane/ethanol.

CHAPTER III. OXIDATION OF KETOXIMES

A. Oxidative Cleavage of Methylated Cyclohexanone Oximes.

Oxidation of 2,2,6,6-tetramethylcyclohexanone oxime (35) in acetic acid. Solid lead tetraacetate (6.036 g, 13.6 mmoles) was added with stirring to a solution of 35 (2.000 g, 11.8 mmoles) in acetic acid (10 ml). After 5 min, acetic acid was removed by vacuum distillation (20°/0.1 mm), affording a pale green oil and lead diacetate. The oil was extracted with chloroform/ether (1:2, v:v). The filtered extract was washed with ice-cold saturated sodium bicarbonate solution (4 x 5 ml), dried ($MgSO_4$) and freed of solvent (40°/20 mm). A pale green oil resulted (3.390 g, 11.8 mmoles). Spectral analysis (NMR) and titration with 0.1 N sodium hydroxide (phenolphthalein) indicated 90 ± 5% of 6-acetoxy-2,2,6-trimethyl-heptanohydroxamic acid N-acetate (36). This material gave a negative ferric chloride test.

Hydrolysis of diacetate 36. A methanolic solution (25 ml) of 36 (341 mg) was neutralized at room temperature with 2 N aqueous potassium carbonate solution (phenolphthalein). After stirring for 24 hr, solvent was removed (20°/0.2 mm) and the residue was dissolved in water (10 ml) and ether (50 ml), then acidified with

a drop of dilute acetic acid. The aqueous phase was separated and extracted with ether (5 x 10 ml). The combined ether extracts were dried (30°/20 mm), affording slightly yellow, crystalline material (320 mg). Recrystallization from hexane gave white crystals (245 mg, 1.0 mmoles, 84%), m.p. 74-75°. Vacuum sublimation (60°/0.1 mm) or repeated recrystallization did not raise the melting point. The material gave a positive ferric chloride test. Analytical data (pp. 64, 65) identified this compound as 6-acetoxy-2,2,6-trimethylheptanohydroxamic acid (37).

Oxidation of oxime 35 in trifluoroacetic acid. Lead tetraacetate (21 g, 47.4 mmoles) was dissolved in trifluoroacetic acid (210 ml) and stirred for 1 hr. This reagent was added in a closed system (exclusion of air moisture) to a solution of oxime 35 (720 g, 42.5 mmoles) in trifluoroacetic acid (35 ml). Addition of each drop of oxidizing reagent caused formation of a transient (5-10 sec), intensely yellow colour. After completing the addition, the reaction mixture was stirred at room temperature for ½ hr, then diluted with ice water (1 000 ml), followed by extraction with ether (2 x 100 ml, 10 x 50 ml). The combined extracts were washed with ice-cold water (2 x 25 ml), ice-cold saturated sodium bicarbonate solution (10 x 50 ml), and water (10 ml), then dried ($MgSO_4$) and freed of solvent (40°/20 mm). A yellow oil resulted (9.386 g), which crystallized to a solid mass on standing. Recrystallization from hexane afforded white crystals

(3.82 g, 12.8 mmoles, 30%), m.p. 79-81°; repeated crystallization or vacuum sublimation (60°/0.1 mm) raised the melting point to 81.5-82°. The material gave a positive ferric chloride test. UV, λ_{max}^{EtOH} 211 mμ (ε, 1550); molecular weight: 299* (mass spectrum), calcd. for $C_{12}H_{20}NO_4F_3$: 299. In conjunction with other analytical data (pp. 64, 65), the compound was identified as 6-trifluoroacetoxy-2,2,6-trimethylheptanohydroxamic acid (38).

Hydrolysis of hydroxamic acid 38. A solution of 38 (36 mg, 0.1204 mmoles) in water (2 ml) was boiled for 10 min, then cooled to room temperature and saturated with ammonium sulphate. Ether extraction afforded white, crystalline material (23 mg, 0.1134 mmoles, 94%), m.p. 111-113°. Recrystallization gave an anlytically pure sample, m.p. 112-113°. UV, λ_{max}^{EtOH} 212 mμ (ε, 1520). The material gave a positive ferric chloride test and its analytical data (pp. 64, 65) identified it as 6-hydroxy-2,2,6-trimethylheptanohydroxamic acid (39).

Methanolysis of hydroxamic acid 38. A methanolic solution of 38 (761 mg, 2.54 mmoles) was refluxed for 24 hr, then all solvent was removed (40°/20 mm), yielding a white crystalline residue (394 mg, m.p. 112-113°). This material was dissolved in water (300 ml), which

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* The parent peak was observed at 167; in the process of measurement CF_3COOH (114) and H_2O (18) was lost (167 + 114 + 18 = 299).

contained 5 ml of methanol, and then extracted with ether (6 x 30 ml). The combined ether extracts were washed with saturated ammonium sulphate solution (2 x 10 ml), dried ($MgSO_4$) and freed of solvent (40°/20 mm). The crystalline residue (206 mg) melted at 105-106°. The wash-waters and the aqueous phase of the ether extraction were combined, saturated with ammonium sulphate, and extracted with a 1:2 mixture (v:v) of chloroform and ether (8 x 15 ml). The combined extracts, after drying ($MgSO_4$) and solvent removal (40°/20 mm), afforded white, crystalline material (130 mg, 0.600 mmoles, 24%), m.p. 121-122°. Repeated crystallizations from hexane or vacuum sublimation (100°/0.5 mm) raised the melting point to 122.5°. UV, λ_{max}^{EtOH} 212 mμ (ε, 1510). The material gave a positive ferric chloride test and was identified (pp. 64, 65) as 6-methoxy-2,2,6-trimethylheptanohydroxamic acid (40). The more ether-soluble crystal fraction, m.p. 105-106°, could not be further purified by recrystallization (hexane) or vacuum sublimation (80°/0.5 mm). Its analytical data indicated a mixture of olefinic and other hydroxamic acids. Elemental analysis, best fit for $C_{10}H_{19}NO_2$, calcd.: C, 64.83; H, 10.34; N, 7.56; found: C, 63.58; H, 10.47; N, 7.64. UV, λ_{max}^{EtOH} 211 mμ (ε, 1800). IR, $\bar{\nu}_{max}^{CCl_4}$: 3460(m), 3260(s), 1660(s), 1080(m), and 890(m) cm^{-1}. NMR, δ ppm ($CDCl_3$): 1.12 (S), 1.17 (S) (no. of H uncertain), 3.16 (S, 1/3 CH_3O), 4.70 (S, 1 H), 5.07 (T (?), J = 6 cps, 0.6 H), and 9.0 (S, 2 H), resolved in $(CD_3)_2SO$: 8.43 (1 H) and 10.25 (1 H)). The material gave a positive ferric chloride test.

Oxidation of 2,2,6-trimethylcyclohexanone oxime (41).

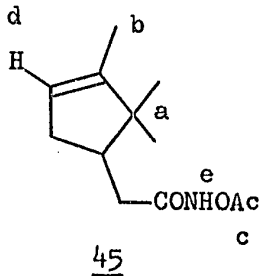
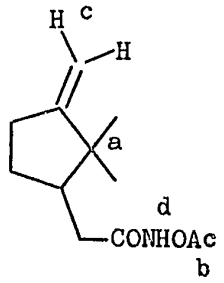
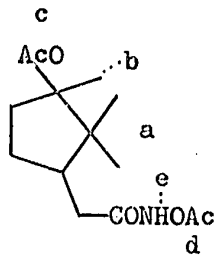
Lead tetraacetate (670 mg, 1.52 mmoles) was dissolved in trifluoroacetic acid (10 ml) and stirred for 1 hr. This reagent was added in a closed system to a solution of oxime 41 (180 mg, 1.16 mmoles) in trifluoroacetic acid (2 ml). In addition to the colour changes observed in the oxidation of oxime 35, the formation of a colourless gas was noticed, which turned brown upon exposure to air (NO_2). After complete addition of oxidizing agent, solvent was removed by vacuum distillation (20°/0.5 mm). Ice-cold saturated sodium bicarbonate solution (10 ml) was added to the oily distillation residue, followed by ether (50 ml). The two-phase system was stirred in an ice bath for 5 min, then the ether layer was separated and the aqueous phase was extracted with ether (5 x 5 ml). The combined ether extracts were washed with ice-cold saturated sodium bicarbonate solution (2 x 5 ml) and water (2 ml), then dried ($MgSO_4$) and freed of solvent (20°/20 mm). An almost colourless oil (247 mg) was obtained which, upon recrystallization from pentane, afforded white crystals (180 mg, 0.631 mmoles, 54%), m.p. 78-80°. Vacuum sublimation (50°/0.05 mm) gave an analytical sample, m.p. 79.5-80.5°. Anal. calcd. for $C_{11}H_{18}F_3NO_4$: C, 46.30; H, 6.36; N, 4.96; found: C, 46.52; H, 6.27; N, 4.92. This material gave a positive ferric chloride test and was identified (pp. 66, 67) as 2,6-dimethyl-6-trifluoroacetoxyheptanohydroxamic acid (42).

Oxidation of 2-methylcyclohexanone oxime (43). A solution of lead tetraacetate (2.643 g, 5.95 mmoles) in trifluoroacetic acid was added to oxime 43 (689 mg, 5.43 mmoles) in trifluoroacetic acid as described in the preceding procedure. Work-up was analogous, affording a yellow oil (641 mg) which by IR spectroscopy contained hydroxamic acid and 2-methylcyclohexanone in a ratio of 4:6, besides other undefined compounds. A ferric chloride test was positive. Isolation of the hydroxamic acid by low temperature crystallization (-78°, pentane) was not possible. A portion (310 mg) of the crude oxidation product was treated with 2,4-dinitrophenylhydrazine[93] which produced the 2,4-dinitrophenylhydrazone of 2-methylcyclohexanone (533 mg, ~ 60% ketone in the crude product), m.p. 135-137° (lit.,[93a] 137°).

B. Oxidative Cleavage of Camphor Oxime (44).

Solid lead tetraacetate (3.450 g, 7.8 mmoles) was added with stirring to a solution of 44 (1.125 g, 6.73 mmoles) in acetic acid (20 ml). The solution turned green/blue. This colour faded with ¾ hr to a pale green. Ice water (200 ml) was added, followed by ether extraction (6 x 20 ml). The combined ether extracts were washed with ice-cold water (4 x 10 ml) and ice-cold saturated sodium bicarbonate solution (4 x 10 ml), then dried ($MgSO_4$) and freed of solvent (30°/20 mm). The oily, pale green residue (1.440 g) was

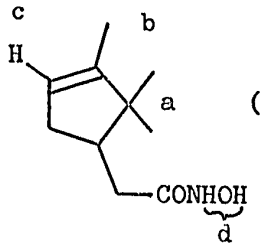
analysed by spectroscopy. IR, $\bar{\nu}_{max}^{CCl_4}$: 3350(w-m), 3040(w), 1790(s), 1735(s), 1650(w), 1190(s), and 882(m) cm^{-1}. The NMR spectrum indicated a mixture of two major and two or more minor components. Chemical shift assignments (and quantitative estimates) could be made for the three components 45, 46, and 47:

Structure		δ ppm ($CDCl_3$):
 45	(44%)	a = 0.83, 1.03 (S) b = 1.65 (S) c = 2.21 (S) d = 5.26 (Q?) e = 9.4 (S)
 46	(21%)	a = 0.87, 1.05 (S) b = 2.21 (S) c = 4.84 (D, J = 2 cps) d = 9.4 (S)
 47	(< 10%)	a = 1.00, 1.23 (S) b = 1.43 (S) c = 2.00 (S) d = 2.21 (S) e = 9.4 (S)

- Hydrolysis of the crude oxidation mixture (45, 46, 47, +).

A methanolic solution (4 ml) of mixture (45, 46, 47, +) (421 mg) was neutralized with 1 N aqueous potassium carbonate (phenolphthalein). The resultant pink solution was stirred at room temperature for 24 hr*, then acidified with a drop of dilute acetic acid and freed of solvent (20°/20 mm). The resultant residue was dissolved in water (10 ml), saturated with ammonium sulphate and extracted with ether (5 x 20 ml). The combined ether extracts were dried ($MgSO_4$) and freed of solvent (30°/20 mm). A faint yellow oil (298 mg) was obtained which crystallized on standing. Recrystallization from pentane/ether afforded white crystals (189 mg), m.p. 84-87°. Repeated crystallization as well as vacuum sublimation (70°/0.02 mm) did not raise the melting point. A ferric chloride test was positive. IR, $\overline{\nu}_{max}^{CHCl_3}$: 3420(m), 3310(m), 1730(m), 1660(s), 1600(w-m), and 880(m) cm^{-1}. The NMR spectrum indicated a mixture of one minor and two major components:

Structure



(67%)

48

δ ppm ($CDCl_3$)

a = 0.75, 0.98 (S)
b = 1.58 (S)
c = 5.18 (M)
d = 9.1 (S)

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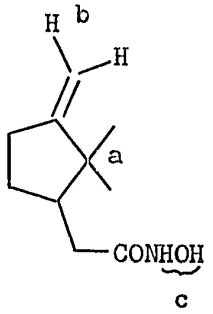
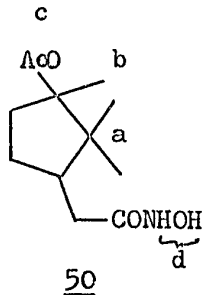
* Work-up immediately after neutralization afforded > 80% starting material.



(26%)

a = 0.82, 1.05 (S)
b = 4.73 (D, J = 1 cps)
c = 9.1 (S)

49



(7%)

a = ? (superimposed)
b = 1.37 (S)
c = 1.97 (S)
d = 9.1 (S)

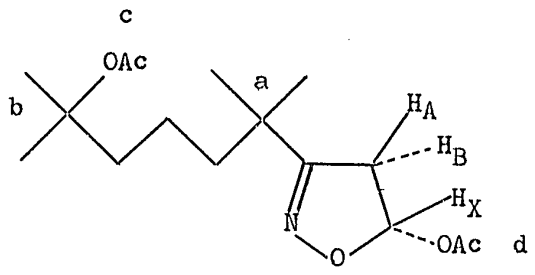
50

C. Interception of Nitrile Oxides by 1,3-Dipolar Cycloaddition.

Preliminary experiments which led to the successful interception of nitrile oxides were discussed in sufficient detail in the RESULTS section (pp. 71-77).

- Interception of nitrile oxide in the oxidation of 2,2,6,6-tetramethylcyclohexanone oxime (35). A cold (-78°) solution of lead tetraacetate (2.201 g, 4.9 mmoles) in methylene chloride (20 ml) and acetic acid (0.5 ml, 8 mmoles) was added to a cold (-78°) solution of oxime 35 (755 mg, 4.46 mmoles) in methylene chloride (15 ml) and freshly distilled vinyl acetate (10 ml), which contained some acetic acid (1 ml, 17 mmoles). The reaction mixture was stirred

at -78° for 20 min, then the temperature was slowly raised (1 hr). At -10° a precooled amount of triethylamine (5 ml, 36 mmoles) was added and the reaction mixture was allowed to come to room temperature. Ether (60 ml) and magnesium sulphate (2 g) were added, followed by stirring for 20 min. The resultant suspension was filtered; the filtrate was washed with ice-cold saturated sodium bicarbonate solution (8 x 5 ml), then dried ($MgSO_4$) and freed of solvent (1. bath: 80°/760 mm, Vigreux column, 2. stream of dry nitrogen). A pale green oil resulted (1.080 g) which by IR and NMR estimate contained approximately 50% isoxazoline acetate 55, and 10-20% 2,2,6,6-tetramethylcyclohexanone, besides geminal nitroso-acetate 51 and other undefined compounds. The crude material was distilled (80°/0.1 mm), affording a pale green/blue oil as distillate (220 mg) and a yellow, crystalline residue (702 mg, ~ 2.25 mmoles, ~ 50%). The distillate was identified as a mixture of geminal nitrosoacetate (major) 51 ($\bar{\nu}^{CCl_4}_{max}$: 1770(s) and 1208(s) cm^{-1}) and 2,2,6,6-tetramethylcyclohexanone (minor) ($\bar{\nu}^{CCl_4}_{max}$: 1705(s) cm^{-1}). The crystalline residue contained ca. 80% of isoxazoline acetate 55. IR, $\bar{\nu}^{CCl_4}_{max}$: 1770(s), 1735(s), 1225(s), 1170(s), and 963(s) cm^{-1}. NMR, δ ppm ($CDCl_3$): 1.25 (S, 2 CH_3, "a"), 1.42 (S, 2 CH_3, "b"), 1.97 (S, OAc, "c"), 2.04 (S, OAc, "d"), 2.84 (Q, 1 H, "H_A"), 3.26 (Q, 1 H, "H_B"), and 6.70 (Q, 1 H, "H_X"); J_{AB} = 18 cps, J_{BX} = 2 cps, J_{AX} = 6 cps.



55

- Attempted interception of nitrile oxide in the oxidation of camphor oxime (44). Oxime 44 was treated as described above in the oxidation of oxime 35. A green oil was obtained which by NMR and IR contained no (or less than 5%) isoxazoline acetate.

- Interception of nitrile oxide in the oxidation of fenchone oxime (56). Oxime 56 (716 mg, 4.29 mmoles) was treated as described in the preceding procedure, but no extra acetic acid was required. The amount of triethylamine needed for neutralization of acetic acid was accordingly reduced. A colourless oil was obtained (917 mg) which consisted of four major components (TLC). No attempt at separating these was made, but spectral inspection clearly indicated the presence of four different isoxazoline acetates (compounds 57, 58, 59, and 60, p. 78). IR, $\overline{\nu}^{CCl_4}_{max}$: 1770(s), 1740(m-s), 1650(w-m), 1630(m), 1225(s), 1168(s), 962(s), and 918(w-m) cm^{-1}.

NMR, δ ppm ($CDCl_3$): 1 to 2 (various singlets), 5-acetoxy-2-isoxazoline: 2.04 (S, OAc), 2.88 (Q, ~ 1 H), 3.27 (Q, ~ 1 H), and 6.71 (Q, ~ 1 H), J_{AB} = 18 cps, J_{BX} = 2 cps, J_{AX} = 6 cps (cf., structure 55); olefinic material: 4.80 (M, exo-methylene), 5.27 (M, endo-methylene).

APPENDIX

UV and NMR Data of Aliphatic Hydroxamic Acids

Aliphatic hydroxamic acids were prepared by standard procedures[14,94] and their UV and NMR spectra were recorded.

Compound	λ_{max}^{EtOH}	ε	δ ppm (CD_3SOCD_3)	
			H_A [1]	H_B [2]
$CH_3CONHOH$	211	1300	9.45 ± 1.54	
$CH_3CH_2CONHOH$	212	1250	8.72	10.39
$CH_3(CH_2)_4CONHOH$	211	1400	8.63	10.32

1) $-CONH_AOH_B$

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