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LEAD TETRAACETATE OXIDATION OF ALDOXIMES

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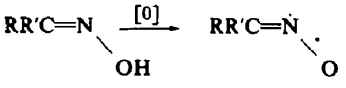
Abstract—The lead tetraacetate oxidation of aldoximes at low temperature has been studied. Oxidation of aliphatic and aromatic *syn*-aldoximes affords nitrile oxides. Aliphatic *anti*-aldoximes lead to dimeric 1-acetoxy-1-nitroso-alkanes and secondary products. Aromatic *anti*-aldoximes afford arylaldazine-*bis*-N-oxides which decompose on heating to nitrile oxides and aldoximes. Mechanisms are proposed which require iminoxy radicals as intermediates in the oxidation of *anti*-aldoximes, while the oxidation of *syn*-aldoximes appears to proceed in a concerted manner.

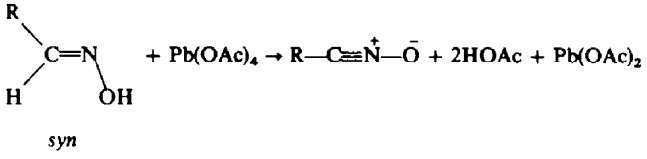
OXIDATION of oximes by reagents such as ceric ammonium nitrate or lead tetraacetate produces iminoxy radicals which are of σ-type.[1] This description implies localization of the unpaired electron in a molecular orbital between the N and O atom and would suggest a fairly reactive species.



The chemistry of iminoxy radicals has received only little attention so far,[2] although a number of oxidation studies have been undertaken, but without recognition or specifically noting the intermediate formation of iminoxy radicals.[3]

We now wish to elaborate on our preliminary account of the lead tetraacetate oxidation of aldoximes.[4] In a separate communication we shall give a detailed account of the lead tetraacetate oxidation of ketoximes.[5]

The observation[4] that *syn*-aldoximes react with lead tetraacetate in methylene chloride at $-78°$ to give nitrile oxides, lead diacetate, and acetic acid has been found to consitute a general reaction

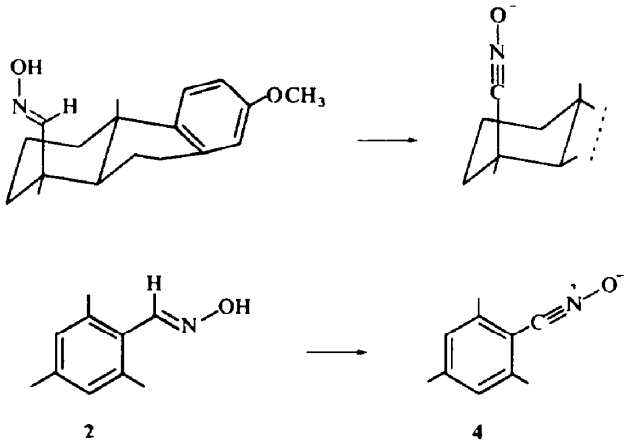


(1)

syn

Yields of nitrile oxides were generally high (over 80%), but decreased rapidly with increasing temperature. Only in cases where the substituent R had large steric requirements could nitrile oxides also be obtained when conducting the oxidation at room temperature. In particular, oxidation of *syn*-O-methyl-podocarpinaldoxime (**1**) and *syn*-mesitaldoxime (**2**) led to the respective nitrile oxides **3** and **4**:*

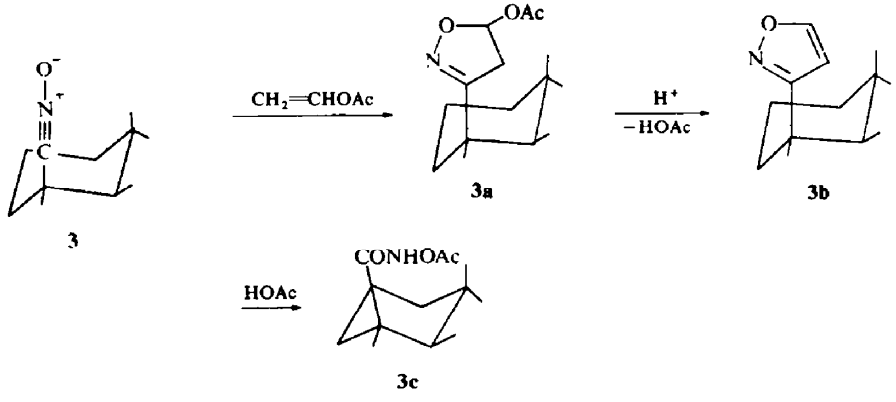
* The preparation of nitrile oxide **4** was best carried out at low ($-78°$) temperature, although it could also be obtained at room temperature, but in lower yield (46%). A major side product in the oxidation at room temperature was mesitylaldazine-*bis*-N-oxide.



2 4

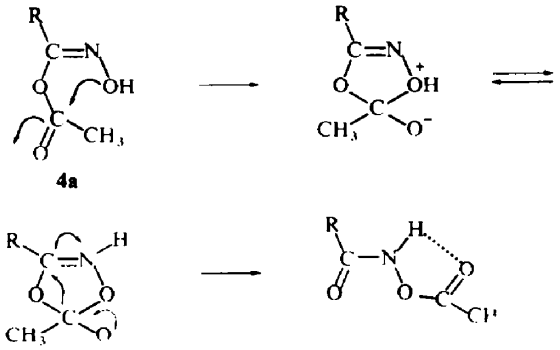
Compound **3** is the first example of a stable aliphatic nitrile oxide while the aromatic nitrile oxide **4**, which is also stable, has been prepared recently by hypobromite oxidation of *syn*- and/or *anti*-mesitaldoxime.[6]

The stability of the two nitrile oxides (**3** and **4**) is due to severe steric hindrance towards dimerization to furoxans. Apart from this reaction, however, other 1,3-dipolar addition reactions[7] with low steric requirements were found to occur readily. Thus, sodium borohydride reduction of nitrile oxide **3** gave a quantitative yield of aldoxime **1**. 1,3-Dipolar cycloaddition with vinyl acetate gave a 1:1 mixture of the diastereomeric isoxazolinyl acetates **3a**; subsequent acetic acid elimination[8] led to the isoxazole **3b** in good yield (80%). Further, the corresponding acetyl hydroxamate



3 3a 3b 3c

(**3c**) was obtained in quantitative yield by addition of acetic acid. Nitrile oxide **4** similarly undergoes 1,3-dipolar cyclo-additions readily,[6] and reacts with acetic acid quantitatively to the acetyl mesitohydroxamate (**4b**) (negative ferric chloride test) rather than to the reported[6] acetylmesitohydroximic acid (**4a**). Most probably the acetylhydroximic acid (**4a**) is formed as an intermediate and rearranges to the more stable acetyl hydroxamate (**4b**). The IR spectra of compounds of type **4b** indicated



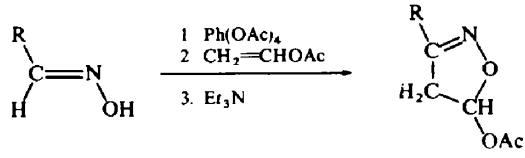
4a

(2)

R = 2,4,6-trimethylphenyl 4b

substantial hydrogen bonding as shown; this observation was substantiated by a shift of the N-acetate carbonyl band from 1780 cm^{-1} to 1820 cm^{-1} upon acetylation.

Since unhindered nitrile oxides are very reactive compounds, their isolation was not practical. In the absence of special precautions they were found to react with acetic acid, a by-product of the oxidation reaction (Eq. 1), to the corresponding acetyl hydroxamates (cf, Table 1). If the oxidation was carried out in the presence of a dipolarophile, like vinyl acetate, and followed by neutralization* of the acetic acid at low temperature, the intermediate nitrile oxides were diverted by 1,3-dipolar cycloaddition to 3-substituted 5-acetoxy-2-isoxazolines (cf. Table 3).



This reaction appears to be widely applicable. Starting from readily available aldoximes, the dehydrogenation is effected in one step under extremely mild conditions (−78°). Aromatic and aliphatic aldoximes containing functional groups which would not permit the use of conventional preparative methods,[7] can be converted to the corresponding nitrile oxides. Thus, oxidation can be carried out in the presence of olefinic double bonds (e.g. vinyl acetate) or aliphatic alcohols (e.g. ethanol). The few limitations of the reaction which have been found so far are the following. Firstly, the oxidation has stereochemical requirements, i.e. only *syn*-aldoximes can be dehydrogenated to nitrile oxides, while *anti*-aldoximes afford different products which will be dealt with later. A second limitation arises from the high reactivity of phenolic OH groups. Aldoximes which contain these, afford intractable tarry products upon oxidation at −78°. Evidently, the phenolic OH group reacts faster with lead tetraacetate than the oxime OH group. It can be expected that functional groups of similar reactivity (primary and secondary aromatic amino groups, enolic OH groups), unless suitably protected, would also limit the usefulness of this reaction.

* The best results were obtained with triethylamine as base; pyridine could also be used, but gave lower yields. Acid scavengers like $CaCO_3$, K_2CO_3, $NaHCO_3$, and NaH_2PO_4 were found to be ineffective.

TABLE 1. ACETYL HYDROXAMATES OBTAINED FROM ALDOXIMES

RCONHOAc	Yield	m.p.	Anal. %					
			C		H		N	
R	%	°C	Calc	Found	Calc	Found	Calc	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	60·33	60·32	5·06	4·91	7·82	7·76
Mesityl-	100	139·5–140 (dec)	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

TABLE 2. NMR AND IR DATA FOR ACETYL HYDROXAMATES OBTAINED FROM ALDOXIMES

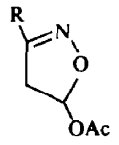
RCONHOAc	NMR Chemical shift, δ ppm		Solvent	IR ν_{max} cm^{-1}	Solvent
R	N—H	OAc			
$(CH_3)_3C$-	9·8	2·16	c	3370 (w-m), 1780 (s), 1720 (s), 1198 (s)	a
16-Nor-O-methyl-podocarp-4β-yl-	9·3	2·18	c	3370 (w-m), 1780 (s), 1715 (s), 1198 (s)	a
C_6H_5-	10·4	2·17	c	3360 (m), 1790 (s), 1705 (s)	b*
Mesityl-	9·3	2·36†	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, $CDCl_3$.

* KBr pellet: 3160 (m), 1800 (s), 1660 (s), and 1204 (s) cm^{-1}.

† Or signal at 2·27 ppm (?).

TABLE 3. 3-SUBSTITUTED 5-ACETOXY-2-ISOXAZOLINES

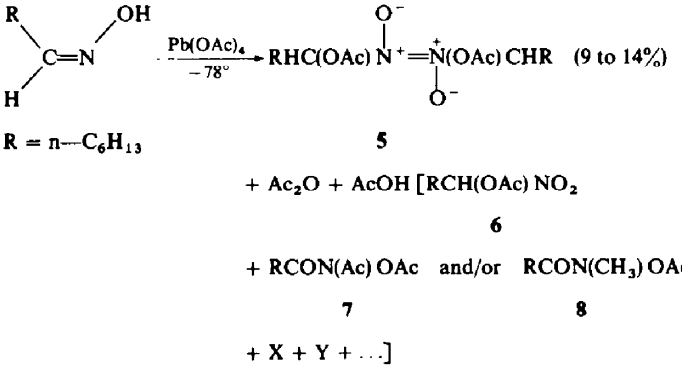


R	Yield %	M.p °C	Anal. % C Calc	C Found	H Calc	H Found	N Calc	N Found	Remarks
Me_2CH-	97	33·5–34	56·12	56·18	7·65	7·61	8·18	8·19	Recryst. from pentane. Yield based on *syn-aldoxime*
Me_3C-	78	51·5	58·36	58·45	8·16	8·19	7·56	7·57	
16-Nor-O-methyl-podocarp-4β-yl-	100	52–54	—	—	—	—	—	—	Crude yield
Ph-	81	90·5	64·38	64·39	5·40	5·35	6·83	6·83	M.p. 106°, vac sublimed
p-$MeOC_6H_4$-	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

Unhindered *syn*-aldoximes can only be dehydrogenated to nitrile oxides at −78° in high yield. At room temperature, the products obtained are identical to those obtained from low or room temperature oxidation of *anti*-aldoximes. The nature of these products depends on whether the aldoxime is aliphatic or aromatic.

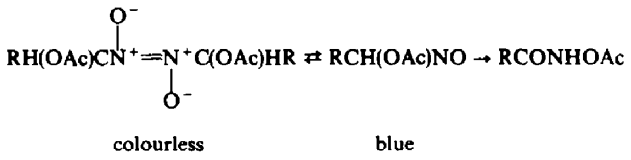
Aliphatic anti-*aldoximes*

Quantitative studies, in conjunction with literature results,[3a] have shown that the oxidation of all aliphatic *anti*-aldoximes follows the same pattern. Therefore, the results of the oxidation of the readily available *anti*-heptanaldoxime will be discussed in greater detail. Reaction of this aldoxime with lead tetraacetate at −78° produced a pale yellow solution, which, unlike in the oxidation of *syn*-aldoximes, contained no precipitate (lead diacetate). On raising the temperature above −70°, the solution turned distinctly green and precipitation of lead diacetate was observed. The green colour reached an intensity maximum at −55 to −50°, then slowly faded to a grey-yellow colour at −25 to −20°. A different green-blue colour emerged at −10° and intensified towards room temperature. This second colour was reversible: it turned to pale yellow at −78° and reappeared on raising the temperature above −10°. The intermediate green colour in the range of −70° to −25° could not be observed again. Spectral analysis (IR, NMR) indicated a complex mixture of four or more components. The instability of the products prevented chromatographic separation. Low temperature crystallization and vacuum distillation permitted isolation of nitrosoacetate **5**, acetic anhydride, and acetic acid. Moreover, inspection of IR and NMR spectra of the crude reaction mixture suggested the presence of nitroacetate **6**,* the tri-substituted hydroxylamine(s) **7** and/or **8**, and other undefined products.

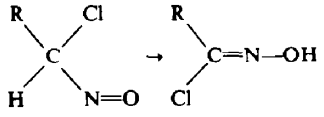


Compounds of type **5** which are in equilibrium with the monomeric form, were found to rearrange easily to the acetyl hydroxamates, either by standing at room temperature dissolved in an inert solvent, or by reflux in ethereal solution with a catalytic amount of triethylamine.

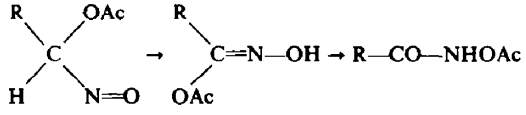
* This type of compound was obtained and fully identified in the lead tetraacetate oxidation of pregnenolone oxime 3-acetate. G. Just and O. Chin, unpublished results.



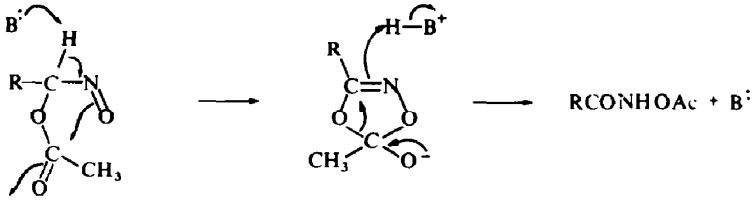
The facile rearrangement of these nitrosoacetates is similar to the known rearrangement of *geminal* chloronitroso compounds, which leads to hydroxamic acid chlorides.[9]



By analogy, the conversion of *geminal* nitrosoacetates could first proceed to the acetylhydroximic acid, followed by a second rearrangement as shown in equation 2.



A mechanism involving base assisted proton transfer is equally plausible.



The great ease with which this rearrangement occurs suggests that a nitrosoacetate, which is initially formed in the oxidation of an aliphatic *anti*-aldoxime, partly rearranges to an acetyl hydroxamate. Since, as was pointed out before, acetic anhydride is a side product of the oxidation, reaction of these two components could lead to a trisubstituted hydroxylamine, whose presence was suggested by the IR spectrum of the crude reaction product (ν(C=O): 1820 cm^{-1}).

$$RCONHOAc + Ac_2O \rightarrow RCON(Ac)OAc + HOAc$$

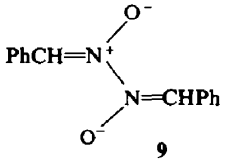
Acetic acid, as required by the above equation, was detected after intial alkaline work-up of the crude oxidation mixture. This indicates that it must have been formed after work-up.

Aromatic anti-*aldoximes*

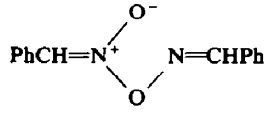
Treatment of *anti*-benzaldoxime, the behaviour of which is characteristic of most aromatic *anti*-aldoximes,[3a] with an equimolar amount of lead tetraacetate in methylene chloride at −78°, produced a hazy, yellow solution which turned intensely green

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 colour slowly faded. Work-up at low temperature (−20 to 0°) produced a colourless compound (65%) which was found to be phenylaldazine-*bis*-N-oxide. Identity was established by comparison with reported IR spectral data and the melting point.[3a, 10]* This compound can be obtained by oxidation of *syn*- and/or *anti*-benzaldoxime at room temperature with a number of other oxidizing agents, [10, *] as well as in the reaction of phenyldiazomethane with nitric oxide.[2c]

A number of proposals for the structure have been put forward, and the two most acceptable are the formulation as aldazine-*bis*-N-oxide (**9**)[2b,c] and aldoxime anhydride-N-oxide (10)[3a].

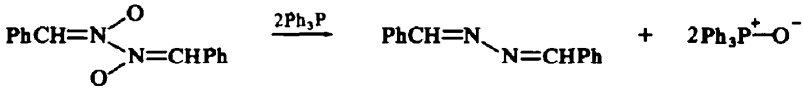


9



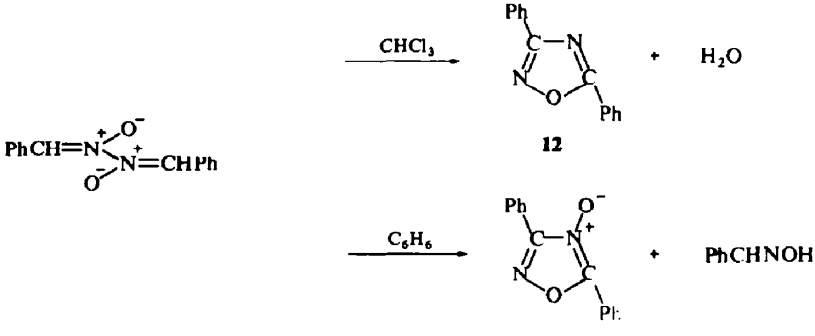
10

Presently available experimental data do not permit rigorous exclusion of either structure, but it appears to us that a formulation as phenylaldazine-*bis*-N-oxide is in better accord with the observed triphenylphosphine reduction to phenylaldazine:[2c]



Moreover, the thermal decomposition of compound **9** finds a more straightforward mechanistic interpretation when assuming the aldazine-*bis*-N-oxide structure.

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 (**9**) in benzene[3d] has been preported to lead to 3,5-diphenyl-2,4-oxadiazole-N-oxide (**11**) and benzaldoxime, while heating the same compound in chloroform[3e, 10] gives predominantly 3,5-diphenyl-2,4-oxadiazole (**12**) and water.



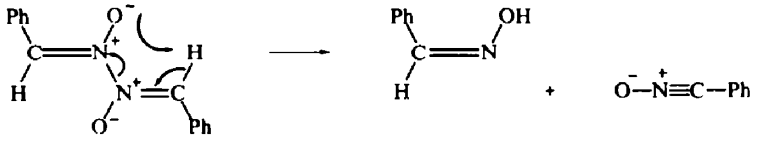
12

11

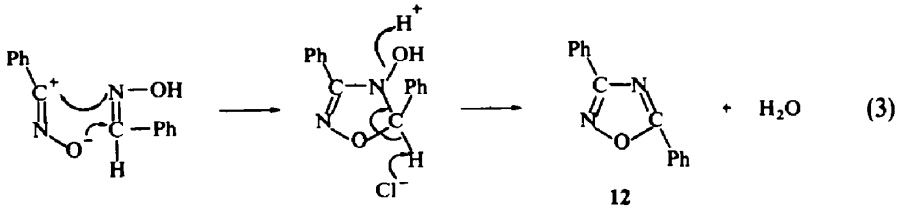
* We gratefully acknowledge receipt of a sample of phenylaldazine-*bis*-N-oxide from Drs. O. Chapman and R. Swindell, Iowa State University of Science and Technology, for purposes of comparison.

No mechanistic interpretation for the formation of compounds **11** and **12** has been given so far.[11]

An attempt to generate and observe free radicals in the thermal decomposition of compound **9** led to negative results.[2c] It was therefore decided to study the thermal decomposition by IR and NMR spectroscopy in the hope of gaining some understanding about the formation of the oxadiazole derivative **11** and **12**. This approach indeed provided a satisfactory answer. When a carbon tetrachloride solution of compound **9** was heated to 50°, an IR spectrum of the warm solution clearly indicated the presence of a nitrile oxide ($\nu(C\equiv\overset{+}{N}—O)$: 2290 cm^{-1}) and an aldoxime (ν(OH): 3590 and δ(N—O): 950 cm^{-1}). After cooling the solution to room temperature and allowing it to stand overnight, another spectrum was recorded which indicated the absence of nitrile oxide and phenylaldazine-*bis*-N-oxide bands and showed the bands of the aldoxime in greatly reduced intensity. In a second experiment, compound **9** 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), besides a small amount of benzaldehyde.* These results clearly indicate that phenylaldazine-*bis*-N-oxide undergoes thermal decomposition to benzonitrile oxide and benzaldoxime, probably via a transition state as shown:

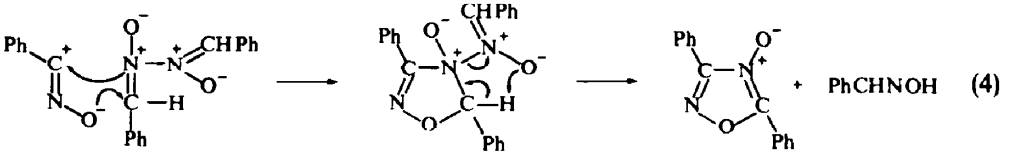


In a subsequent step benzonitrile oxide is consumed by a 1,3-dipolar cycloaddition affording 5-membered heterocyclic compounds. Thus reaction with benzaldoxime could lead to oxadiazole **12** and water (Eq 3), reaction with phenylaldazine-*bis*-N-oxide to oxadiazole-N-oxide **11** and benzaldoxime (Eq 4), and reaction with vinyl acetate to isoxazolinyl acetate **13** (Eq 5)



(3)

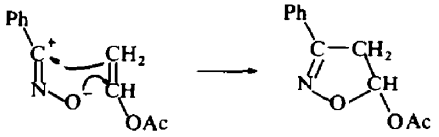
12



(4)

11

* NMR estimate. The isoxazolinyl acetate was isolated by crystallization from hexane.

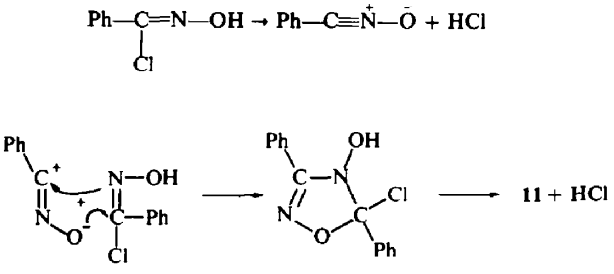


(5)

13

The observation that thermal decomposition in chloroform solution leads predominantly to the oxadiazole **12**, 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 (Eq 3) water elimination from the intermediate oxadiazoline. Decomposition in the absence of hydrochloric acid is appreciably slower.* The initially formed nitrile oxide could therefore add to the more reactive dipolarophile—phenylaldazine-*bis*-N-oxide (?)—leading via an oxadiazoline-N-oxide to oxadiazole-N-oxide **11** and benzaldoxime.

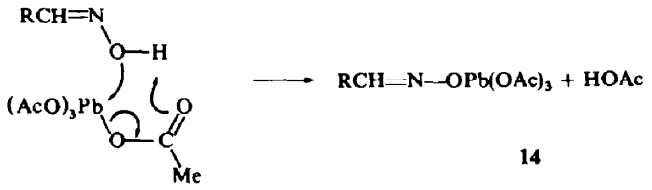
Another example of this type of reaction is found in the formation of oxadiazole-N-oxide **11** from benzohydroxamic acid chloride.[12]



DISCUSSION

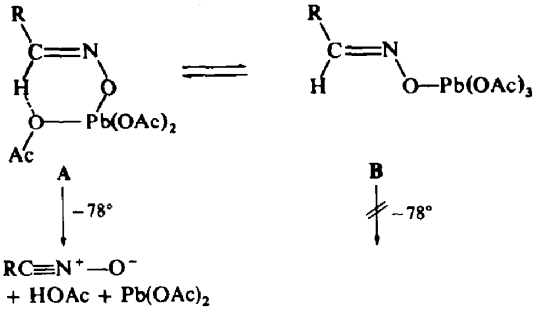
The results of the lead tetraacetate oxidation of aldoximes are consistent with the observed intermediacy of iminoxy radicals.[1,2] When oxidizing aldoximes at temperatures above $-70°$ a passing intense green colour can be observed; occurrence of this colour was usually accompanied by precipitation 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. At temperatures below $-70°$ no green colour can be noticed and only in the case of *syn*-aldoximes can precipitation of lead diacetate be observed. 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):

* Catalysis of decomposition by hydrochloric acid has been demonstrated.[3a]



14

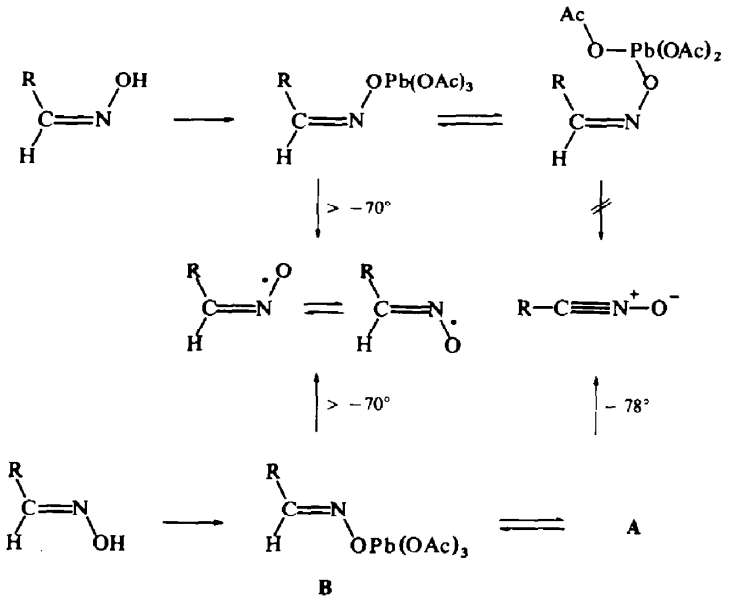
The formation of the lead organic compound **14** can be envisaged as proceeding through a six-membered ring transition state. It is believed to be stable at $-78°$ if derived from an *anti*-aldoxime, but to decompose readily to nitrile oxide, acetic acid, and lead diacetate if formed from a *syn*-aldoxime. 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 at low temperature (unhindered aldoximes) or if the steric requirements of R are large (hindered aldoximes).

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 **14** takes place at temperatures above $-70°$ molecular vibration (rotation) appears to be violent enough to effect breakage of the "oxime-oxygen"/lead bond without assistance from a 6-membered ring transition state. This could 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**.

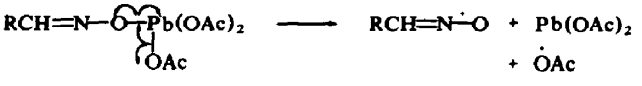
anti-Aldoximes, when treated with lead tetraacetate at $-78°$, probably also form a lead organic compound of type **14**; since no precipitation of lead diacetate can be observed, the compound appears to be stable under these conditions. A conformational equilibrium analogous to the one for the *syn* isomer does not provide a low energy path to product formation. On raising the temperature above $-70°$, unassisted homolysis could occur leading to iminoxy radicals, which can also be obtained by homolysis of conformer **B**.



These iminoxy radicals are quite stable at −55°, 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 has as yet not been found.

ESR studies have shown that iminoxy radicals exist in a configurational equilibrium at room temperature, and the results of the present investigation suggest that this equilibrium also exists at low temperature (−25°), for *syn*- and *anti*-benzaldoxime give the same phenylaldazine-*bis*-N-oxide. The large nitrogen coupling constant of iminoxy radicals[1] indicates substantial unpaired electron density 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.[2b] Since radical-radical recombinations require little or no energy of activation,[14] product formation by this process should be preferred.

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

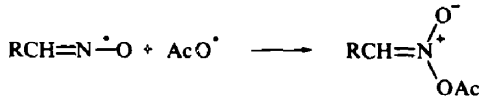


which then decompose to methyl radicals and carbon dioxide, etc.:[15]

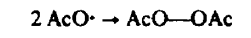
$$CH_3COO\cdot \rightarrow CH_3 + CO_2 \rightarrow \ldots$$

Acetoxy radicals cannot be trapped at room temperature,[16] but it is reasonable to assume that they are sufficiently long lived at -55 to $-30°$, so that recombination with iminoxy radicals can occur. Taking these data into consideration, the following recombinations are most probable:

(6)

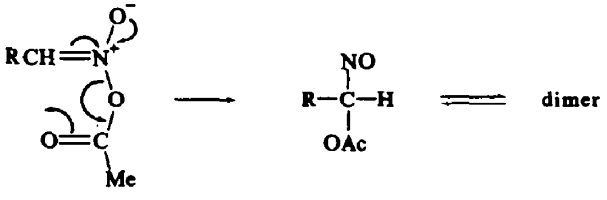


(7)



(8)

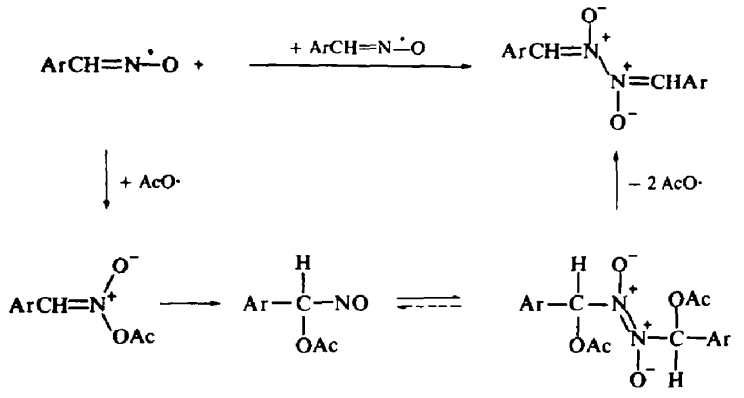
Product analysis gave no evidence for the presence or intermediate participation (in product formation) of acetyl peroxide (Eq 8) and its formation, therefore, appears to be unfavoured.* Aldazine-*bis*-N-oxides (Eq 6) were the products obtained from aromatic aldoximes, while the unstable mixed nitronic acid anhydride (Eq 7) is a likely intermediate in the formation of geminal nitrosoacetates:



Nitronic acids and their derivatives are known to be unstable[18] and their isolation is possible only in exceptional cases.[19] Their intermediate existence has been proposed for the formation of nitrile oxides[20] and hydroxamic acid derivatives, the latter forming via nitroso compounds.[21]

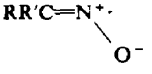
Oxidation of aromatic aldoximes does not lead to stable *geminal* nitrosoacetates as has also been noted elsewhere.[3a] Two explanations come to mind to account for this divergent behaviour. Either, aromatic iminoxy radicals dimerize directly to aldazine-*bis*-N-oxides (Eq 6) or, a *geminal* nitrosoacetate 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:

* A recent study has shown, however, that this reaction does occur under certain circumstances.[17]



Presently available evidence permits exclusion of neither route and possibly both are operating concurrently.

The results of the present investigation suggest that iminoxy radicals dissipate their energy preferentially by radical-radical recombinations. These recombinations appear to occur only at the N atom which is in accord with the high unpaired spin density at this site. No evidence could be obtained for reactions involving radical–radical recombinations at the O or at the "carbonyl carbon" atoms. It is therefore concluded that iminoxy radicals participate in reactions mainly in form of the following resonance hybrid:



This conclusion has also been reached for the lead tetraacetate oxidation of ketoximes,[5] and finds further confirmation in a related concurrent study by Chapman and Heckert on the ceric ammonium nitrate oxidation of aromatic ketoximes.[22]

EXPERIMENTAL

All chemicals used in this study were reagent grade unless otherwise stated in the individual experiments. M.ps were measured in a capillary tube in a sulphuric acid bath, and are corrected. Analysis were performed by Beller Mikroanalytisches Laboratorium, Göttingen, and Bernhard Mikroanalytisches Laboratorium, Mühlheim, Germany. The NMR spectra were recorded on a Varian A-60 spectrometer, with TMS serving as internal standard. IR spectra were recorded on Perkin–Elmer "Infracord", "337", and "521" spectrometers, UV spectra were recorded with a Beckman "DK" spectrophotometer. Solvents used, unless reagent grade, were distilled before use.

Lead tetraacetate (Matheson, Coleman, and Bell) contained 4–7% AcOH as stabilizer and was used as such for all oxidations. Samples recrystallized from AcOH and washed acid free with petrol gave identical results.

Apparatus. All low temp oxidations were conveniently carried out in a "Mini-Lab Basic Assembly" (ACE Glass, Inc.), consisting of a reaction vessel fitted with a multi-neck adapter to accommodate one to 3 pressure equalization dropping funnels, a low temp thermometer (pentane), and a connection to a Hg blow-off trap. The reaction mixture could be stirred magnetically, and cooling was provided by a dry-ice/i-propanol bath (−78°).

Aldoximes. The aldoximes were prepared according to literature procedures[23] from commercially available aldehydes. Unhindered aliphatic aldoximes were obtained as mixtures of their *syn* and *anti*

isomers, the relative proportions of which were determined by NMR spectroscopy.[24] Sterically hindered aliphatic aldoximes were obtained in form of their *syn* isomers only. Similarly, aromatic aldehydes gave predominantly the *syn*-aldoximes. *anti*-Heptanaldoxime was prepared by reaction of heptanaldehyde in ether with hydroxylamine hydrochloride and sodium bicarbonate at room temperature. This compound was stable in the crystalline form, but isomerized to the reported[24a] 1:1 mixture of the *syn* and *anti* isomers on standing in carbon tetrachloride solution for one day.

Oxidation of hindered syn-*aldoximes*

O-*Methylpodocarponitrile oxide* (**3**). Solid lead tetraacetate (264 mg, 0·59 mmoles) was added to a stirred soln of *syn*-O-methylpodocarpinaldoxime (146 mg, 0·508 mmoles) in CH_2Cl_2 (4 ml). Colourless ppt formed and the soln turned faintly green. After standing at room temp for 5 min, the reaction mixture was poured into crushed ice (50 g). The resultant slurry was extracted with ether (5 × 20 ml); the combined extracts were washed acid free with sat $NaHCO_3$ aq (2 × 5 ml), then dried ($MgSO_4$) and freed of solvent (30°/20 mm). A colourless crystalline mass (152 mg) with a slight yellow tinge was obtained, m.p. 123–125°. Recrystallization from MeOH gave colourless crystals (136 mg, 0·478 mmoles, 94%), m.p. 127–128°. A second recrystallization raised the m.p. to 131·5–132°. (Found: C, 75·79; H, 8·39; N, 5·08. $C_{18}H_{23}NO_2$ requires: C, 75·75; H, 8·12; N, 4·91%); IR (CCl_4): 2270 (s) cm^{-1} (—C≡N^+—O^-); NMR, δ ppm ($CDCl_3$): 1·30 (S, Me), 1·42 (S, Me), 2·87 (T, J = 6 c/s, Ar—CH_2), 3·74 (S, MeO), 6·8 (M, 3 aromatic H).

Sodium borohydride reduction of nitrile oxide **3**. $NaBH_4$ (40 mg, 0·85 mmoles) in anhyd MeOH (5 ml) was added with stirring to a soln of **3** (22 mg, 0·077 mmoles) in anhyd MeOH (5 ml). After 0·5 hr, the reaction mixture was diluted with water (50 ml) and extracted with ether (5 × 20 ml). The combined extracts, after drying ($MgSO_4$) and solvent removal (30°/20 mm), afforded crystalline material (23 mg, 100%) which showed the same R_f value (TLC), m.p., and IR spectrum as *syn*-O-methylpodocarpinaldoxime. Mixed m.p.: no depression.

Mesitonitrile oxide **4**. A cold soln of lead tetraacetate (3·456 g, 7·8 mmoles) in CH_2Cl_2 (30 ml) was added with stirring to a cold (−78°) soln of mesitaldoxime (1·140 g, 7·00 mmoles, 89% *syn*, 11% *anti* isomer) in CH_2Cl_2 (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 sat $NaHCO_3$ aq (4 × 5 ml). The ether extract was dried ($MgSO_4$), and concentrated by evaporation to about ½ of its original volume with a stream of dry N_2 at 0°. A fine ppt appeared which was collected by filtration (80 mg) and identified by IR as a mixture of mesitylaldazine-*bis*-N-oxide and **4** (ratio, 2:1). The filtrate was freed of solvent with a stream of dry N_2 at 0°, affording colourless needles of **4** (978 mg, 6·08 mmoles, 87%; or based on *syn*-aldoxime only, 97%), m.p. 107–109°. Recrystallization from MeOH/water gave colourless needles (1st crop: 900 mg), m.p. 111·5–112°. Repeated crystallizations and vacuum sublimation (35°/0·05 mm) did not raise the m.p. (lit.,[6] m.p. 114°). (Found: C, 74·29; H, 6·65; N, 8·79. Calc. for $C_{10}H_{11}NO$: C, 74·51; H, 6·88; N, 8·69%); IR (CCl_4): 2290 (s) and 1360 (s) cm^{-1} (—C≡N^+—O^-). NMR, δ ppm ($CDCl_3$): 2·31 (S, Me), 2·38 (S, 2 Me), and 6·95 (S, 2 aromatic H).

Modification. Lead tetraacetate oxidation of mesitaldoxime as above but at room temp gave lower yields of **4**: e.g., 1·372 g of aldoxime (8·42 mmoles) yielded 600 mg of **4** (3·73 mmoles, 46%). The major side product formed was identified by IR spectroscopy as mesitylaldazine-*bis*-N-oxide: IR ($CHCl_3$): 1580 (s), 1450 (s), 1380 (s), 1340 (s), 1090 (s), 1072 (s), and 915 (m) cm^{-1}.

Oxidation of unhindered syn-*aldoximes*

Acetyl 2,2,2-trimethylhydroxamate. Solid lead tetraacetate (5·403 g, 12·1 mmoles) was added at room temp to a soln of *syn*-trimethylacetaldoxime (825 mg, 8·20 mmoles) in CH_2Cl_2. The stirred mixture first turned sky-blue, then faded to a light green/blue colour and colourless ppt formed. Stirring was maintained until the mixture was colourless (9 hr), then ether was added (60 ml), followed by $MgSO_4$ (1–2 g). After stirring for 5 hr, the resultant suspension was filtered, washed with ice-cold sat $NaHCO_3$ aq (3 × 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 N_2 until constant wt 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 colourless needles resulted, m.p. 115–116°. Repeated crystallization or vacuum sublimation (50°/0·1 mm) raised the m.p. to 116–116·5°. A soln of this material gave initially a negative $FeCl_3$ test. However, on standing at room temp (>4 hr), a deep mauve colour developed. The same observation was made for the subsequently described acetyl hydroxamates.

Modification. Reaction of *syn*-trimethylacetaldoxime with lead tetraacetate in CH_2Cl_2 at $-78°$ afforded a colourless soln, which on warming to room temp remained colourless and gave an 80% yield of acetyl 2,2,2-trimethylacetohydroxamate.

Acetyl O-methylpodocarpohydroxamate. Compound **3** (135 mg, 0·474 mmoles) was dissolved in freshly distilled AcOH (5 ml) and warmed to 40° for 2 hr, then allowed to stand at room temp overnight. AcOH was removed (25°/0·2 mm) until constant wt was achieved. The residue consisted of colourless crystals (163 mg, 100%) m p. 150° (dec). Recrystallization from hexane/ether did not raise the m.p.

Acetyl Benzohydroxamate A cold (−78°) soln of lead tetraacetate (2·694 g, 6·0 mmoles) in CH_2Cl_2 (20 ml) was added to a cold (−78°) soln of *syn*-benzaldoxime (664 mg, 5·49 mmoles) in CH_2Cl_2 (20 ml). The resultant hazy, yellow mixture was stirred at −78° for 0·5 hr, then the cold bath was removed. Ether (60 ml) and $MgSO_4$ (1–2 g) were added when the reaction mixture had come to room temp. The resultant suspension was stirred (20 min), then filtered, washed with ice-cold sat $NaHCO_3$aq (3 × 10 ml), dried ($MgSO_4$), and freed of solvent with a stream of dry N_2. Colourless 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.[25] 125–126°). The material can be sublimed (95°/0·2 mm).

Acetyl Mesitohydroxamate. Compound **4** (161 mg, 1 mmole) was dissolved in freshly distilled AcOH (0·5 ml, 8·8 mmoles) and anhyd ether (10 ml) and set aside at room temp. Crystals began to form after 10 hr. After 48 hr the solvent was removed with a stream of dry N_2, followed by evacuation (10%/0·1 mm) until constant wt was achieved (221 mg, 1 mmole, 100%). Colourless platelets resulted, m.p. 139·5–140° (dec; lit.,[6] 136–138°, dec). Recrystallization from hexane/ether did not raise the m.p. NMR, δ ppm ($CDCl_3$) 2·27 (S, Me), 2·36 (S, 3 Me), 6·92 (S, 2 aromatic H), and 9·3 (S, NH).

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 workup for other aldoximes are noted in Table 3.

A cold (−78°) soln of lead tetraacetate (2·458 g, 5·5 mmoles) in CH_2Cl_2 (20 ml) was added during 1 min to a cooled (−78°) and stirred soln of *syn*-benzaldoxime (569 mg, 4·70 mmoles) in CH_2Cl_2 (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 soln was obtained which contained a substantial amount of colourless ppt ($Pb(OAc)_2$). Triethylamine (11 mmoles) in CH_2Cl_2 (10 ml) was added for neutralization of AcOH. The reaction mixture was allowed to come to room temp, then ether (100 ml) was added, followed by $MgSO_4$ (1 to 2 g, to assist precipitation of lead salt), stirring for 0·5 hr, and filtration. The yellow filtrate was washed with ice-cold sat $NaHCO_3$aq (5 × 5 ml), which removed remaining Pb 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 N_2, yielding a yellow/brown crystal mass (1·32 g). Recrystallization from hexane/EtOH (95:5, v:v) at −78° afforded colourless 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 m.p. to 90·5°. Vacuum sublimation (65°/0·1 mm) gave colourless crystals of m.p. 106°, which upon recrystallization from hexane/EtOH again melted at 90·5° (lit.,[26] 88–89°). UV, λ_{max}^{EtOH} 254 mμ (ε, 24,300) (lit.,[8] 254 mμ (ε, 14,300)).

5-Acetoxy-3-(16-nor-O-methylpodocarp-4β-yl)2-isoxazoline (**3a**). Freshly distilled vinyl acetate (2 ml, 32 mmoles) was added to a soln of **3** (356 mg, 1·25 mmoles) in benzene (15 ml). This mixture was refluxed for 1 hr when TLC indicated complete conversion to one new product. After solvent removal (30°/20 mm), a colourless foam was obtained (468 mg, 1·26 mmoles, 100%), m.p. 52–54°. Spectral analysis (IR, NMR) indicated the presence of **3a**. The NMR spectrum showed two isomeric compounds in equal proportions. Attempts to separate these by chromatography and fractional crystallization were fruitless. NMR, δppm ($CDCl_3$): 1·07 (S, ½ Me), 1·18 (S, ½ Me), 1·21 (S, ½ Me), 1·27 (S, ½ Me), 1·95 (S, ½ OAc), 2·02 (S, ½ OAc), 2·84 (M, 2 H), 3·14 (M, 2 H), 3·75 (S, OMe), 6·61 (M, 1 H), and signals arising from methylene and aromatic protons.

3-(16-Nor-O-methylpodocarp-4β-yl)2-isoxazole (**3b**). A soln of **3a** (410 mg, 1·1 mmoles) in EtOH (15 ml), containing HCl (1 ml conc HCl/50 ml EtOH), was refluxed for 2 hr when TLC indicated complete conversion to one new product. Upon solvent removal (40°/20 mm and 20°/0·2 mm), a colourless semi-crystalline mass was obtained (344 mg) which was recrystallized from acetonitrile/water/ether, affording

colourless long needles (275 mg, 0·886 mmoles, 80% based on nitrile oxide), m.p. 104°. (Found: C, 76·63; H, 8·21; N, 4·74. $C_{20}H_{25}NO_2$ requires: C, 77·13; H, 8·09; N, 4·50%); NMR δ ppm ($CDCl_3$): 0·77 (S, Me), 1·30 (S, Me), 2·87 (M, 2 H), 3·76 (S, Me), 6·32 (D, J = 1·7 c/s, 1 H), 6·83 (M, 3 aromatic H), and 8·31 (D, J = 1·7 c/s, 1 H), besides signals arising from methylene protons.

Oxidation of anti-*heptanaldoxime.*

1-*Acetoxy*-1-*nitrosoheptane* (**5**). A cold (−78°) soln of lead tetraacetate (3·755 g, 8·4 mmoles) in CH_2Cl_2 (20 ml) was added to a cooled (−78°) and stirred soln of *anti*-heptanaldoxime (951 mg, 7·38 mmoles) in CH_2Cl_2 (20 ml). After 3 min at −78°, the mixture was yellow and hazy; on raising the temp above −70°, a green colour appeared accompanied by precipitation of lead diacetate. The green colour went through an intensity maximum at −55° to −50°, then slowly faded to a greyish yellow colour at about −25°. A different kind of green/blue colour appeared at −10° (this temp point was found to vary somewhat from one experiment to another) and intensified towards room temp. The formation of the latter colour was reversible: it disappeared on lowering the temp to −78°, and reappeared on raising it above −10°. To the green/blue reaction soln, ether (60 ml) and $MgSO_4$ (1–2 g) was added with stirring. After 10 min, the resultant suspension was filtered, the filtrate was washed acid free (pH paper) with ice-cold sat $NaHCO_3$ aq (4 × 4 ml), dried ($MgSO_4$) and freed of solvent with a stream of dry N_2 at 0°. A green oil resulted (1·616 g) which by semiquantitative IR analysis contained Ac_2O (10%), AcOH (> 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 Ac_2O, AcOH, and some solvent. The oily residue, after pumping (1·15 g), was analysed by NMR and IR spectroscopy (for details cf., Results Section), then dissolved in pentane (10 ml) and stored on dry ice for 3 days. The resultant colourless crystals (180 mg, 0·481 mmoles, 13·1%)* were filtered and analysed; m.p. 84–85° (not raised upon repeated crystallization). (Found: C, 57·41; H, 9·16; N, 7·46. $C_9H_{17}NO_3$ requires: C, 57·73; H, 9·15; N, 7·48%); UV $\lambda_{max}^{cyclohexane}$: 293 mμ (ε, 3050) (*trans-bis*-nitroso configuration. [27a]). IR, $\nu_{max}^{(KBr)}$: 1775(s) and 1220 (s) cm^{-1} (acetate); 1660 (m) and 1192 (s) cm^{-1} (*trans-bis*-nitroso configuration[27b]). NMR, δ ppm ($CDCl_3$): 0·90 (T, J = 5 c/s, Me), 1·31 (M, 8 H), 1·84 (M, 2 H), 2·12 (S, OAc), and 6·65 (T, J = 5·8 c/s, 1 H).

Rearrangement of 1-*acetoxy*-1-*nitrosoalkanes to acetyl hydroxamates.*

Acetyl heptanohydroxamate. Freshly distilled Et_3N (7·2 mg, 0·07 mmoles) in ethereal soln (2 ml) was added to a soln of **5** (157 mg, 0·42 mmoles) in anhyd ether (8 ml). The resultant blue mixture was set aside at room temp. The soln was colourless after 8 hr. Solvent was removed with a stream of dry N_2 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 m.p.

Acetyl 2,2,2-trimethylacetohydroxamate. Solid lead tetraacetate (1·056 g, 2·38 mmoles) was added to a cold (−20°) soln of *syn*-trimethylacetaldoxime (217 mg, 2·15 mmoles) in CH_2Cl_2 (5 ml). A colourless ppt formed and the soln turned slowly blue (5 min). The temp was raised to 0°, ether was added (30 ml), followed by $MgSO_4$ (1 g) and stirring for 10 min. Then the suspension was filtered; the filtrate (0°) was washed with ice-cold sat $NaHCO_3$ aq (3 × 3 ml) and water (3 ml), dried ($MgSO_4$), and freed of solvent with a stream of dry N_2 at 0°. A colourless crystal mass with a blue tinge resulted (262 mg). Analysis by NMR and IR spectroscopy indicated a product ratio of 75:25 for acetyl 2,2,2-trimethylacetohydroxamate and 1-acetoxy-1-nitroso-2,2-dimethylpropane (**15**). Isolation of the latter compound (without extensive rearrangement) could not be achieved, but its spectral data permitted structure assignment and quantitative estimation: IR, (CCl_4): 1760 (m), 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 Me), 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 Et_3N, quantitative conversion to acetyl 2,2,2-trimethylacetohydroxamate was effected.

Rearrangement of nitrosoacetate **15** *in vinyl acetate.*† A mixture of **15** (25%) and acetyl 2,2,2-trimethylacetohydroxamate (75%; 262 mg) was dissolved in freshly distilled vinyl acetate (10 ml) containing Et_3N (2·1 mmoles). The soln was heated to 75° and the solvent was distilled over a short Vigreux column until the volume of the reaction soln was reduced to 1 to 2 ml. Remaining solvent was removed with a stream of

* Yields varied from 9 to 14%.

† The reason for this experiment was to disprove the following reaction sequence:

$$RCH(OAc)NO \longrightarrow R-\ddot{C}-N=O \longrightarrow R-C\equiv\overset{+}{N}-\bar{O} \longrightarrow RCONHOAc$$

dry N_2. A crystalline residue resulted (250 mg) which consisted of acetyl 2,2,2-trimethylacetohydroxamate (>95%). No isoxazolinyl acetate could be detected (IR, NMR).

Oxidation of anti-*benzaldoxime*

Phenylaldazine-bis-N-*oxide.* A cold (−78°) soln of lead tetraacetate (1·440 g, 3·24 mmoles) in CH_2Cl_2 (15 ml) was added to a cold (−78°) soln of *anti*-benzaldoxime (390 mg, 3·24 mmoles) in CH_2Cl_2 (20 ml). After stirring for 1 min, a pale yellow and hazy soln was obtained which turned green with simultaneous ppt formation on raising the temp above −70°. The green colour went through an intensity max (at approx −60°), then gradually faded to a greyish yellow colour. Ether (100 ml) and ice-cold water (25 ml) were added at room temp, followed by vigorous stirring for 10 min. The aqueous phase was separated; the ethereal layer was washed with ice-cold sat $NaHCO_3$aq (3 × 5 ml), and concentrated to a volume of 15 ml by evaporation with a stream of dry N_2 at −20°. A colourless crystalline ppt resulted which was filtered and washed with cold (−50°) ether, then dried over $CaSO_4$ (22°/0·1 mm). This material (228 mg, 1·05 mmoles, 65%) m.p. 109–110° (dec; lit.,[3a] 108–109°, dec) showed the same IR spectrum as reported for phenylaldazine-*bis*-N-oxide.[3a]

Thermal decomposition of phenylaldazine-bis-N-*oxide.* A cold sat CCl_4 soln of phenylaldazine-*bis*-N-oxide showed a strong and characteristic band at 1575 cm^{-1}. Upon warming the soln 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 soln was then set aside at room temp. 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 soln was freed of solvent with a stream of dry N_2, affording a semi-crystalline residue (148 mg). Spectral analysis (NMR, IR) indicated the presence of isoxazolinyl acetate, benzaldoxime, and Ph-?-Ph in a molar ratio of 1:3:2. Compound(s) Ph-?-Ph is(are) probably oxadiazole(s).[3, 10] The same result was obtained when oxidizing *anti*-benzaldoxime with lead tetraacetate in the presence of vinyl acetate. A minor side product in both experiments was benzaldehyde. Isolation of the isoxazolinyl acetate could be achieved by recrystallization from hexane/EtOH.

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