NITROSOCARBONYL COMPOUNDS IN SYNTHESIS

A thesis presented in part fulfilment of
the requirements for the Degree of Doctor
of Philosophy

by

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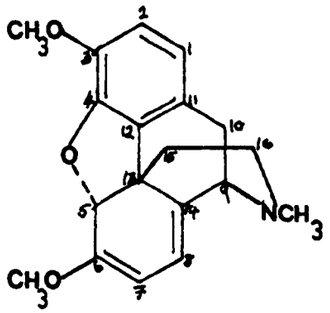
SUMMARY.

Diels-Alder adducts have been prepared by the action of the reactive intermediate, 2,2,2-trichloroethyl nitrosoformate, on a series of simple conjugated dienes, and the reductive de-acylation and cleavage of these adducts have been investigated. The methods developed in this study have been applied to a new preparation of 14β-aminocodeinone *via* the cycloadduct of 2,2,2-trichloroethyl nitrosoformate with thebaine. Nitrosyl hydride, HNO, produced by the periodate oxidation of hydroxylamine, has been trapped by *N*-benzyloxycarbonylnorthebaine and *N*-t-butoxycarbonylnorthebaine to form the corresponding cycloadducts. These thermally labile compounds have been characterised by formation of their *N*-acetyl derivatives.

The intramolecular ene reactions of *C*-nitrosocarbonyl compounds and nitrosoformates have been studied. The cyclisation of 1-nitrosocarbonylhept-4-ene, generated by the thermal cleavage of its adduct with 9,10-dimethylanthracene, did not proceed cleanly. However, five olefinic nitrosoformates, generated by the thermal cleavage of their cyclopentadiene adducts, have been shown to undergo intramolecular ene reactions to give cyclic hydroxamic acids. The nitrosoformates of 3,3-dimethylallyl alcohol, 2-methylprop-2-en-1-ol, 4-methylpent-3-en-1-ol, 3-methylcyclohex-3-en-1-ol, and 4-methylcyclohex-3-en-1-ol, cyclised to give 5,6,6,7, and 6-membered ring compounds respectively. In each case only one mode of cyclisation was observed.



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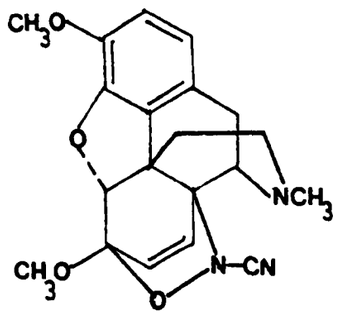

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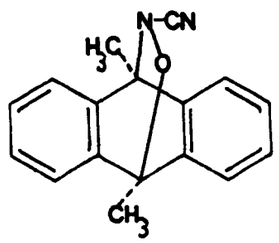

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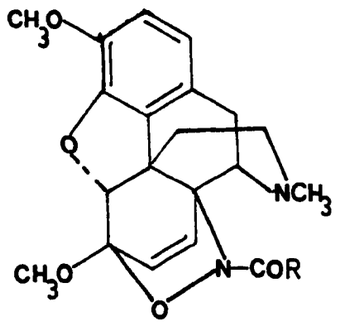
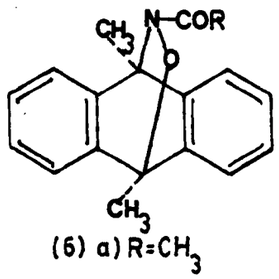


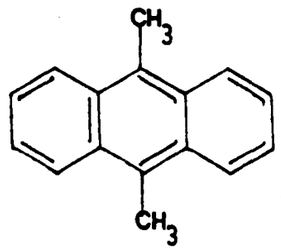
(5) a) R=Ph

b) R=CH_3



(6) a) R=CH_3

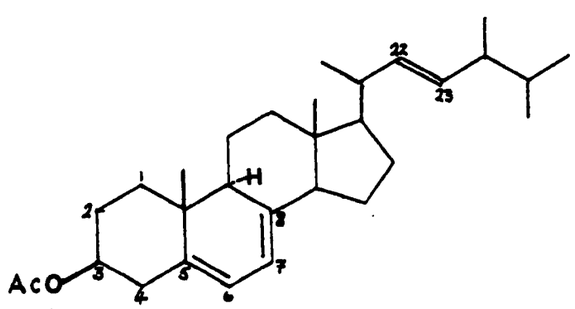
b) R=Ph



(4)

+ RCONO

(Scheme 1)



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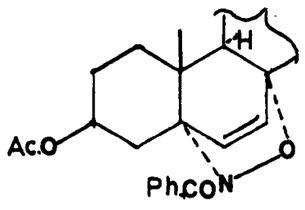
Chapter 1

The Chemistry of Electrophilic C-Nitroso-Compounds.

This discussion contains a survey of the main topics covered by Kirby[1] in his review of electrophilic C-nitroso-compounds, together with a more detailed account of work published since it was written. It has long been known that addition of nitrosoalkanes to conjugated dienes, to form 1,4-cycloadducts, is favoured by electron-withdrawing substituents α to the nitroso-group.[2] If the α-carbon of a C-nitroso-compound is itself part of an electron-withdrawing group it is logical to expect high reactivity. The first known example of a reactive species of this type was nitrosyl cyanide. Formed by the action of silver cyanide on nitrosyl chloride, nitrosyl cyanide was rapidly trapped by thebaine (1) as its cycloadduct (2).[3] The 9,10-dimethyl-anthracene adduct of nitrosyl cyanide (3) first provided evidence for the free existence of the species.[4] When the adduct (3) was heated in benzene with thebaine, the nitrosyl cyanide moiety was transferred rapidly to thebaine although, in the absence of thebaine, no decomposition of (3) was observed. First order kinetics were observed for the formation of the thebaine adduct (2) and the appearance of 9,10-dimethylanthracene (DMA) (4). This is consistent with rate determining dissociation of the adduct (3) followed by rapid capture of nitrosyl cyanide by thebaine. The structure of nitrosyl cyanide was finally elucidated by microwave spectroscopy.[5]

C-Nitrosocarbonyl compounds, RCONO, are also members of this class of activated C-nitroso-compounds. These compounds had been postulated as transient intermediates in the pyrolysis of alkyl nitrites in the presence of aldehydes,[6] and in the oxidation of hydroxamic acids.[7,8,9] Kirby and Sweeny,[10] reasoning that intermediates of this type would be powerfully dienophilic, oxidised benzohydroxamic acid and acetohydroxamic acid with periodate in the presence of thebaine to yield the cycloadducts (5a) and (5b) respectively. The transient nitrosocarbonylalkanes and -arenes were also shown to be effectively trapped by simple conjugated dienes such as butadiene and cyclopentadiene.[11] Unlike nitrosyl cyanide, the structures of C-nitrosocarbonyl compounds have not been established by spectroscopic means, nor have these compounds been detected by any physical method. There is therefore no absolute proof of their existence. There is, however, indirect evidence for the free existence of these species. The DMA adducts of nitrosocarbonylmethane and nitrosocarbonylbenzene,(6a) and (6b), which are stable at room temperature, were decomposed in hot benzene in the presence of thebaine.[10] An intermolecular transfer of the C-nitrosocarbonyl species took place to yield the corresponding thebaine adducts. First order kinetics were observed for the formation of DMA. Again this suggests a slow dissociation of the adducts (Scheme 1), followed by rapid trapping of the nitrosocarbonyl moiety by thebaine.

Nitrosocarbonyl cycloadducts have been shown by Kirby and MacKinnon[12] to undergo a [3,3]sigmatropic rearrangement. Treatment of ergosteryl acetate (7) with nitrosocarbonylbenzene, generated by



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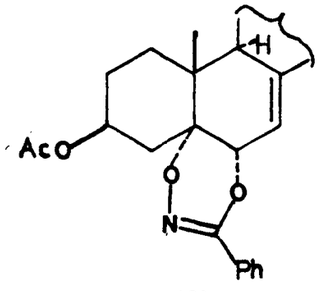

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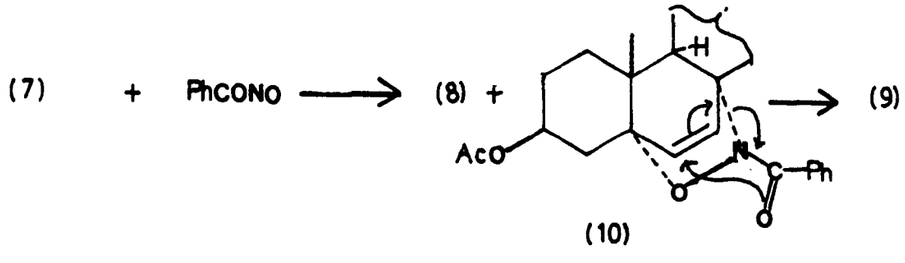
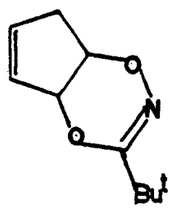


(Scheme 2)



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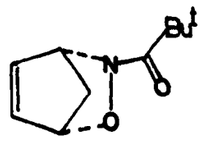

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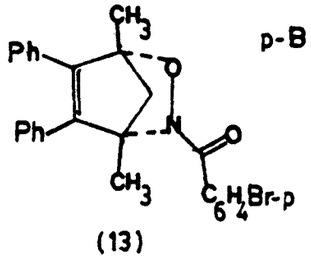

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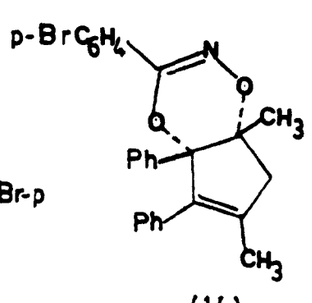

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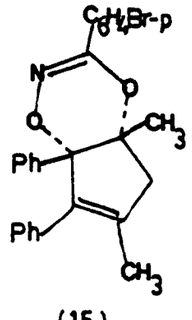
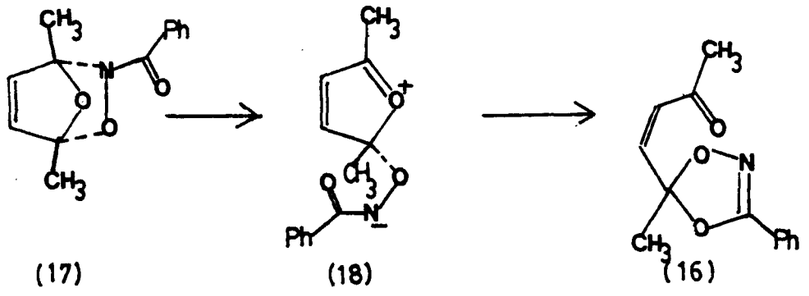


(15)

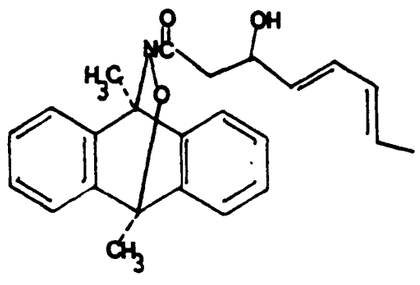
oxidation of benzohydroxamic acid, gave, in addition to the oxazine (8), a new type of adduct (9). Although in principle the dioxazine (9) could have been obtained by a [4+2]cycloaddition, with the nitrosocarbonylbenzene acting as a 4π component, the [3,3] rearrangement shown in Scheme 2 was proposed instead. There was evidence to support this postulated pathway. When the total reaction mixture was observed by n.m.r. spectroscopy after cold evaporation of solvent, signals attributed to the adduct (8) and the isomeric adduct (10) were seen but none of the dioxazine (9). When the reaction mixture was heated to 60°C, however, complete conversion of the adduct (10) to the dioxazine (9) was observed. To disprove the alternative pathway involving a retro-Diels-Alder cleavage of adduct (10) followed by recombination, the mixture of compounds (8) and (10) was heated with triphenyl phosphine, an efficient trap for nitrosocarbonyl compounds. The isomerisation took place as smoothly as before. They proposed that this novel [3,3]sigmatropic rearrangement was facilitated by the relief of the cis-fused B-C ring interactions.

MacKay and Watson[13] also report 5,6-dihydro-1,4,2-dioxazine formation in the reaction of nitrosocarbonyl compounds with conjugated dienes. They identified the dioxazine (11) as a co-product in the synthesis of the adduct (12) via the oxidation of trimethylacetohydroxamic acid in the presence of cyclopentadiene. When the adduct (12) was isolated it was found to be thermally stable. They concluded from this that the dioxazine (11) was formed via a [4+2]cycloaddition with the nitrosocarbonyl acting as the heterodiene rather than the



(17) (18) (16)

(Scheme 3)



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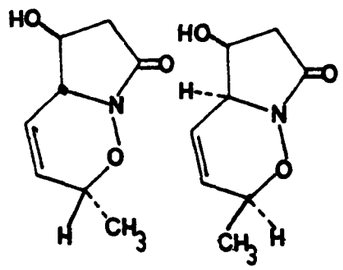
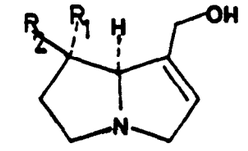
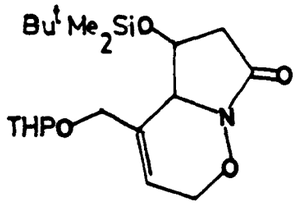


(20 a & b)



(21) a) R_1 = OH, R_2 = H

b) R_1 = H, R_2 = OH



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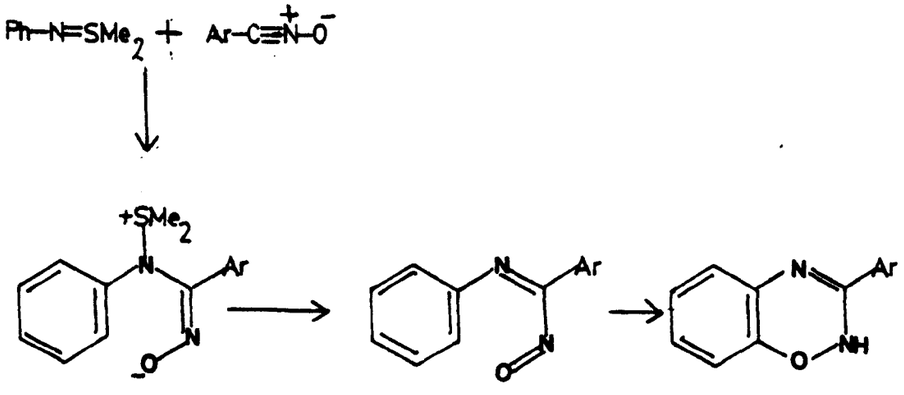
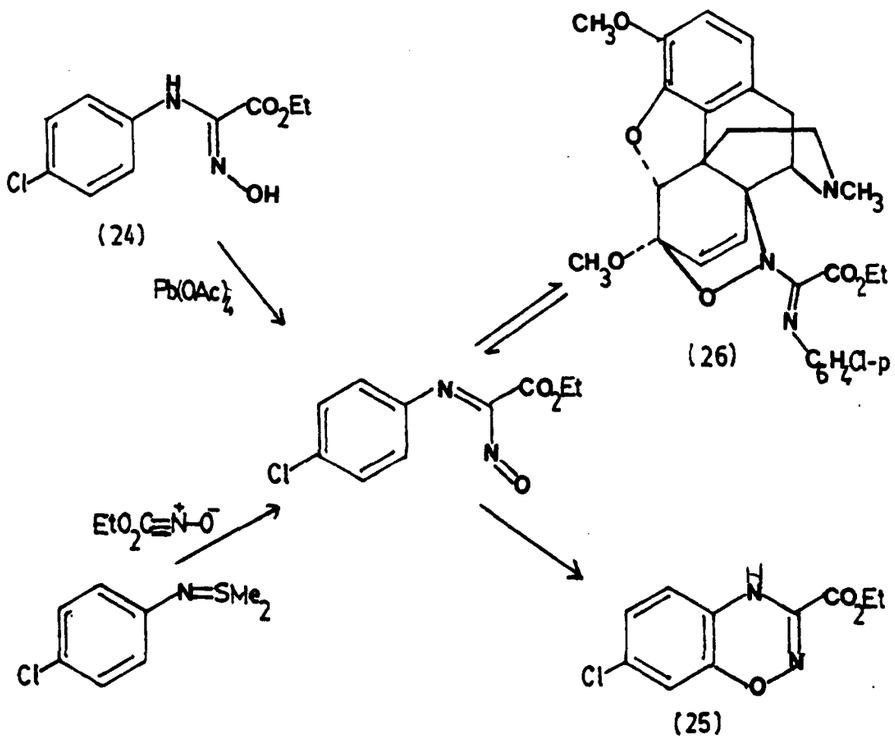


(23)

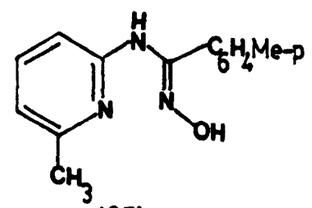
(Scheme 4)

dienophile. In a later communication[14] it was reported that the oxidation of p-bromobenzohydroxamic acid in the presence of 1,4-dimethyl-2,3-diphenylcyclopentadiene, followed by cold work-up, led to the isolation of the usual oxazine-type adduct (13). This compound had a half-life of 9 hours in chloroform at 25°C, isomerising to the dioxazine (14). In the thermal rearrangement of the oxazine (13) both regioisomers (14) and (15) are possible. Only the former can arise as a result of a [3,3]sigmatropic rearrangement of compound (13) but either can be formed by a dissociation-recombination mechanism. X-ray analysis[15] of the crystalline isomerisation product showed that the only product was compound (14). MacKay and co-workers[16] report another heterocyclic system obtainable from dienes and nitrosocarbonyl compounds. Treatment of 2,5-dimethylfuran with nitrosocarbonylbenzene yielded the dioxazole (16). The proposed mechanism for the formation of compound (16) was via the initial formation of the Diels-Alder adduct (17). This either isomerised directly, or via the dipolar structure (18) to the dioxazole (16) (Scheme 3).

Nitrosocarbonyl compounds have been shown to undergo intramolecular cycloadditions.[17] The DMA adduct (19) was obtained by treating the enolate of the DMA adduct of nitrosocarbonylmethane (6a) with 2,4-hexadienal. After the adduct (19) had been heated in refluxing benzene for 5 hours the two intramolecular Diels-Alder adducts (20a) and (20b) were obtained in the ratio 2:1. Keck and Nickell[18] recently used this approach in their synthesis of (±)-heliotridine (21a) and (±)-retronecine (21b). They prepared the intra-



(Scheme 5)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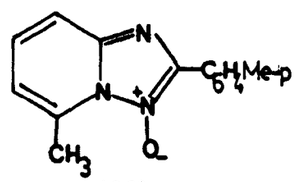
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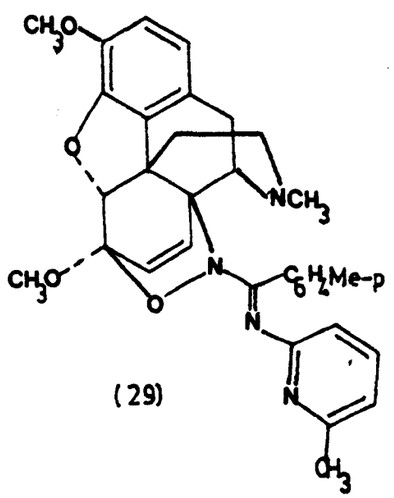
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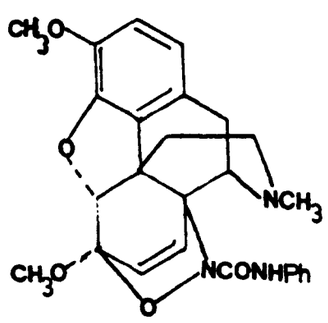
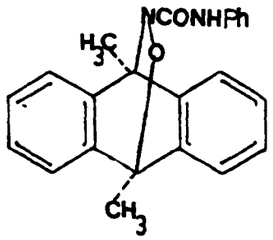

(30)

molecular Diels-Alder adduct (22), as described above, reduced the N-O bond and mesylated the resulting hydroxyl group. Ring closure was achieved by addition of base to give a mixture of bicyclic γ-lactams which were separated and reduced to give (21a) and (21b) after removal of protective groups.

Gilchrist, Harris and Rees[19] proposed another new class of activated C-nitroso-compounds, the C-nitroso-imines, to be intermediates in the preparation of 1,2,4-benzoxadiazines (23) from N-aryl-SS-dimethylsulphimides and nitrile oxides (Scheme 4). In further papers,[20,21] Gilchrist, Rees, and co-workers outlined evidence for this postulate. Oxidation of the amidoxime (24) gave the benzoxadiazine (25) in good yield. When this oxidation was repeated in the presence of thebaine the Diels-Alder cycloadduct (26) was produced in high yield. An identical cycloadduct was isolated from the reaction of N-(4-chlorophenyl)-SS-dimethylsulphimide with ethyl cyanoformate N-oxide and thebaine at low temperatures. From this they reasoned that the nitroso-imine was a common intermediate in the two reactions. When the thebaine adduct (26) was heated in refluxing benzene for 3 hours, a retro-Diels-Alder reaction took place and the transient nitroso-imine cyclised to the benzoxadiazine (25) (Scheme 5). The chemistry of the analogous N-pyridylnitroso-imines was also investigated.[22] When the pyrido-amidoxime (27) was oxidised with lead tetra-acetate, the triazole N-oxide (28) was obtained in good yield. As with N-aryl-amidoximes, repetition of the oxidation in the presence of thebaine at low temperatures caused the intermediate nitroso-imine to be trapped



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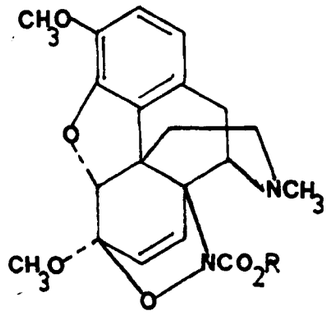
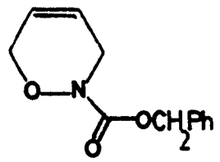


(32) a) R = $PhCH_2$-

b) R = Bu^t-



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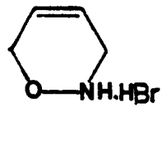

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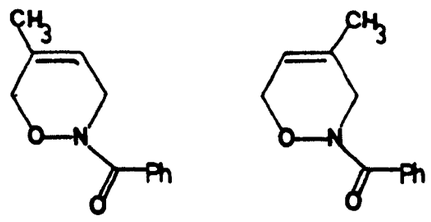
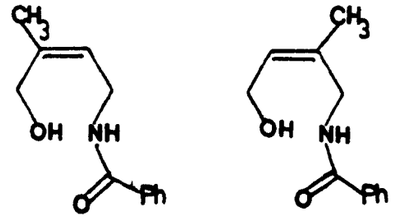


(35a&b)



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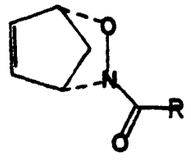


(37) a) R = CH_3

b) R = Ph

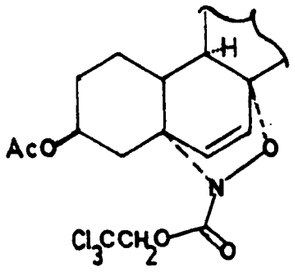
as its cycloadduct (29). The cycloadduct was decomposed in hot benzene to yield the N-oxide (28) and thebaine. In the preparation of triazole N-oxides such as compound (28) by treatment of 2-pyridyl-sulphimides with nitrile oxides, the intermediacy of C-nitroso-imines was also demonstrated by trapping with thebaine.

Little work has been done on the investigation of the C-nitroso-formamides, RR'NCONO. Kirby and MacKinnon[11], to test whether such species might exist, oxidised N-hydroxy-N'-phenylurea in the presence of thebaine to form the thebaine/N-phenylnitrosoformamide adduct (30). The DMA/N-phenylnitrosoformamide adduct (31), prepared in analogous fashion, was found to be unstable.

O-Nitrosocarbonyl compounds or nitrosoformates, ROCONO, are also members of the family of activated nitroso-compounds. They were first proposed by Breslow[23] as intermediates in the thermal decomposition of azidoformates in dimethyl sulphoxide. Bearing in mind the close structural analogy of these putative nitrosoformates to C-nitroso-carbonyl-compounds, Kirby et al.[24] investigated the oxidation of N-hydroxycarbamates, ROCONHOH, in the hope that nitrosoformates would be formed as transient, dienophilic intermediates. N-Benzyloxycarbonyl-hydroxylamine and N-t-butoxycarbonylhydroxylamine were oxidised in the presence of thebaine to yield the adducts (32a) and (32b) respectively. The generality of nitrosoformate adduct formation with simple dienes has since been demonstrated.[11] As with C-nitrosocarbonyl compounds, benzylnitrosoformate was shown to undergo an intramolecular transfer from its DMA adduct to thebaine in hot benzene. The first order rate

constant for the appearance of DMA in this reaction was roughly 10 times greater than for the corresponding transfer of CH_3CONO. The adducts of nitrosoformates and conjugated dienes can be readily de-acylated under a variety of conditions depending upon the choice of the alkoxy group.[11] Thus N-benzyloxycarbonylhydroxylamine was oxidised in the presence of 1,3-butadiene to yield the adduct (33). Treatment of this adduct with hydrogen bromide in acetic acid yielded the parent dihydro-oxazine as its hydrobromide (34). Other examples of de-acylation will be given in the following chapter.

The cycloadducts formed from nitrosocarbonyl compounds and conjugated dienes are potentially valuable for the synthesis of oxazine derivatives and thence, by reductive cleavage of the N-O bond, of 1,4-amino-alcohols. Two major drawbacks to the use of C-nitrosocarbonyl compounds in synthesis were discovered by Kirby and MacKinnon.[11] It was found that the zinc-acetic acid reduction of the isoprene/nitrosocarbonylbenzene adducts, (35a) and (35b), to the amido-alcohols, (36a) and (36b), took several days to go to completion. This inertness is not observed in the zinc reduction of diene/nitrosoarene adducts[2] and was attributed to the presence of the carbonyl group in RCONO adducts. It was also discovered that the amide linkage of nitrosocarbonylalkane and -arene adducts was difficult to hydrolyse thus making the parent dihydro-oxazine hard to obtain. Thus, ethanolysis of the cyclopentadiene/nitrosocarbonylmethane adduct (37a) yielded no product and O-methylation of the cyclopentadiene/nitrosocarbonylbenzene adduct (37b) followed by acid hydrolysis gave only methyl benzoate. An approach which overcomes these problems is described in the following chapter.



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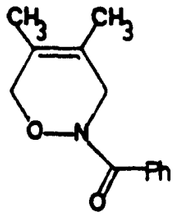

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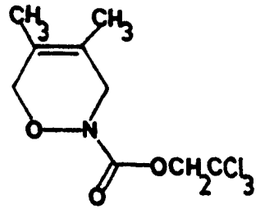


(41)

Chapter 2

Synthetic Applications of 2,2,2-Trichloroethyl Nitrosoformate.

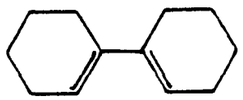
2.1 Formation and Reduction of Diene/2,2,2-Trichloroethyl Nitrosoformate Adducts.

The previously mentioned difficulties encountered in the synthetic use of C-nitrosocarbonyl compounds encouraged us to explore the synthetic applications of a particular nitrosoformate reagent. It is known[2] that the N-O bond in 5,6-dihydro-1,2-oxazines can be cleaved by zinc reduction. Therefore we reasoned that, if cycloadducts were prepared from conjugated dienes and a nitrosoformate bearing a zinc-removable alkoxy group, it should be possible to de-acylate and cleave the N-O bond of such acyl dihydro-oxazines in one operation. Thus a "one-pot" reduction of these cycloadducts tothe corresponding 1,4-amino-alcohols was envisaged. A preliminary study of one such nitrosoformate, 2,2,2-trichloroethyl nitrosoformate, was carried out by MacKinnon.[11] First used by Woodward,[25] the 2,2,2-trichloroethoxy-carbonyl group is now a well known zinc-removable protecting group in amino-acid studies. MacKinnon prepared N-(2,2,2-trichloroethoxy-carbonyl)hydroxylamine (38) in low yield and oxidised it with periodate in the presence of ergosteryl acetate (7) to form the ergosteryl acetate/2,2,2-trichloroethyl nitrosoformate adduct (39). Reduction of the adduct (39) with zinc unexpectedly produced only ergosteryl acetate.

No further work in this area was carried out at that time. Thus we planned to explore the formation of cycloadducts of 2,2,2-trichloroethyl nitrosoformate with simple dienes and to study the reduction of these adducts with zinc. We also intended to re-examine the reduction of the ergosteryl acetate adduct (39).

N-(2,2,2-Trichloroethoxycarbonyl)hydroxylamine (38) was prepared in 75% yield from 2,2,2-trichloroethyl chloroformate by vigorous shaking with aqueous, alkaline hydroxylamine. With an efficient preparation of the alkoxycarbonylhydroxylamine (38) to hand, a series of cycloadducts were prepared from various conjugated dienes. In general, the hydroxamic acid (38) was added to a stirred, ice-cooled, mixture of the diene in ethyl acetate, and sodium periodate in aqueous sodium acetate buffer. The reaction was complete in 1 hour. 2,3-Dimethylbuta-1,3-diene was chosen as the first diene on account of its simplicity and because, unlike buta-1,3-diene, it is a liquid at ambient temperatures. To ensure that this diene acted as an efficient trap for nitrosocarbonyl compounds, benzohydroxamic acid[26] was oxidised in the presence of 2,3-dimethylbuta-1,3-diene and the 2,3-dimethylbuta-1,3-diene/nitrosocarbonylbenzene adduct (40) obtained in high yield as a crystalline solid. Elemental analysis and a mass spectrum confirmed the solid to be a 1:1 adduct of the diene and nitrosocarbonylbenzene. In the proton n.m.r. spectrum of the adduct (40), two singlets at δ 1.75 and 1.60 were assigned to the two vinylic methyl groups. The signals of the four allylic protons adjacent either to oxygen or nitrogen, appeared as a broad singlet at δ 4.16, and no olefinic proton

resonances were observed. Similarly, oxidation of N-(2,2,2-trichloroethoxycarbonyl)hydroxylamine in the presence of the diene produced the 2,3-dimethylbuta-1,3-diene/2,2,2-trichloroethyl nitrosoformate adduct (41) as a colourless oil. Again, analysis and mass spectroscopy proved the compound to be a 1:1 adduct of the nitrosoformate and the diene, and the i.r. spectrum of the oil was consistent with the proposed structure. A broad singlet at δ 1.66 in the proton n.m.r. spectrum of the adduct (41) was assigned to the two vinylic methyl groups. The resonances of the methylene protons of the trichloroethyl group were observed as a singlet at δ 4.88. Two broad singlets at δ 4.34 and 4.08 were attributed to the protons of the two vinylic methylene groups, although it could not be decided which singlet corresponded to the methylene group adjacent to oxygen and which to the methylene group adjacent to nitrogen. Treatment of ergosteryl acetate with 2,2,2-trichloroethyl nitrosoformate generated, as before, by the *in situ* oxidation of the alkoxycarbonylhydroxylamine (38), gave a high yield of the crystalline ergosteryl acetate/2,2,2-trichloroethyl nitrosoformate adduct (39) identical to that prepared by MacKinnon.[11] The orientation of addition of the 2,2,2-trichloroethyl nitrosoformate was assigned by MacKinnon[11] as shown, after inspection of the adduct's proton n.m.r. spectrum. This showed a one-proton doublet of doublets, J 14 Hz and 5 Hz, at δ 3.35, well separated from the rest of the saturated steroid signals. This signal was attributed to the proton 4α-H for the following reasons. The 4α-H proton is deshielded due to the magnetic anisotropy of the amide carbonyl, and the 14 Hz coupling is



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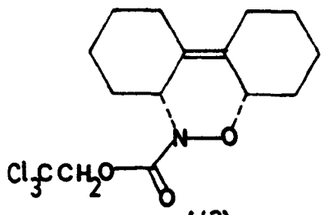

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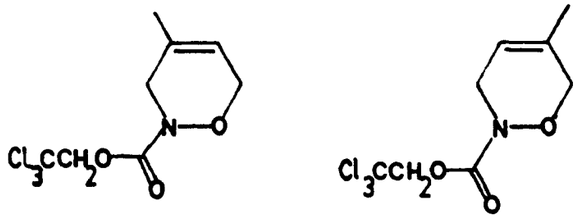
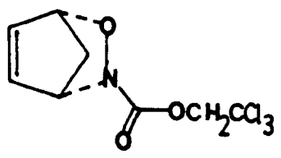


(44 a&b)



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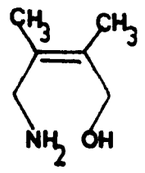
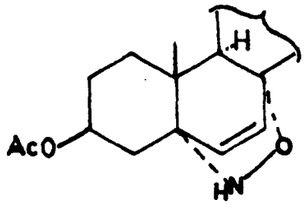


(46)



(47)

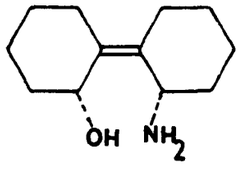
with 4β-H. Decoupling experiments showed that the 5 Hz coupling was with proton 3α-H. The conjugated diene bicyclohexenyl (42) was prepared by treating cyclohexanone with aluminium amalgam[27] and dehydrating the resulting pinacol with phosphorus oxychloride.[28] For confirmation that the oil produced was a conjugated diene it was treated with maleic anhydride. A crystalline solid was isolated which had a melting point in close agreement with that in the literature[29] for the bicyclohexenyl/maleic anhydride adduct. Periodate oxidation of N-(2,2,2-trichloroethoxycarbonyl)hydroxylamine in the presence of bicyclohexenyl produced the bicyclohexenyl/2,2,2-trichloroethyl nitrosoformate adduct (43) as a crystalline solid. In the n.m.r. spectrum of the solid an AB quartet at δ 4.96 and 4.70, J 12 Hz, was assigned to the methylene protons of the 2,2,2-trichloroethyl group, which are non-equivalent as they are adjacent to a chiral centre. A signal at δ 4.15 was attributed to the two methine protons adjacent to either nitrogen or oxygen. Similarly, treatment of isoprene with 2,2,2-trichloroethyl nitrosoformate yielded the isoprene/2,2,2-trichloroethyl nitrosoformate adduct (44). The proton n.m.r. spectrum of the adduct contained two singlets at δ 1.76 and 1.68, with intensities in the ratio 2:1. These signals were attributed to the vinylic methyl protons of two isomers. It could not be discerned whether these signals indicated a mixture of regioisomers (44a) and (44b) or a mixture of amide rotamers of either (44a) or (44b). Freshly distilled cyclopentadiene also efficiently trapped 2,2,2-trichloroethyl nitrosoformate generated in the usual way to give the cyclopentadiene/2,2,2-trichloroethyl nitrosoformate adduct (45) as a crystalline solid in high yield. A multiplet at δ 6.45 in the

proton n.m.r. spectrum of the adduct was assigned to the two olefinic protons in the cyclopentene ring. The signal for the methylene of the 2,2,2-trichloroethyl group was a well defined AB quartet at δ 4.82 and 4.62, J 11 Hz. Another AB quartet at δ 2.05 and 1.80 was attributed to the methylene protons of the cyclopentene ring.

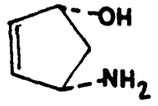
Although the preparation of the cycloadducts had been successfully achieved the results of their zinc reductions were quite disappointing. The 2,3-dimethylbuta-1,3-diene/2,2,2-trichloroethyl nitrosoformate adduct (41) was dissolved in glacial acetic acid and stirred with a large excess of zinc powder. Basification and continuous extraction of the reaction mixture for several days yielded only a very small amount of a brown oil, the i.r. spectrum of which indicated it was possibly the amino-alcohol (46). It was thought that the amino-alcohol (46) was more soluble in water than in organic solvents thus explaining its poor recovery. The zinc reduction of the ergosteryl acetate/2,2,2-trichloroethyl nitrosoformate adduct (39) was then re-examined. The adduct (39) was treated with a 20 fold excess of zinc in acetic acid. The only product isolated was ergosteryl acetate, thus confirming MacKinnon's observation. Since it was possible that an intermediate product was somehow being overreduced, the reduction was carried out using an 8 fold excess of zinc. Most of the starting material was recovered unchanged, and no other product was isolated. Just and Grozinger[30] reported that 2,2,2-trichloroethyl carbamates could be cleaved using zinc dust in a slurry of tetrahydrofuran (THF) and aqueous phosphate buffer. Accordingly the adduct (39) was stirred

in a THF-buffer slurry with a 20 fold excess of zinc. Again only starting adduct (39) was isolated with a high percentage recovery. In a final attempt, the ergosteryl acetate adduct (39) was stirred with an 8 fold excess of zinc-copper couple[31] in glacial acetic acid. The reaction mixture yielded a white solid which proved to be a mixture of ergosteryl acetate and the ergosteryl acetate adduct (39) in the ratio of 2:1 respectively. The isolation of the mixture of adduct (39) and ergosteryl acetate tended to disprove the theory of the overreduction of another, otherwise stable, product. It was concluded that the adduct (39) had been de-acylated to the 'HNO' adduct of ergosteryl acetate (47) which in turn had undergone a retro-Diels-Alder reaction to yield ergosteryl acetate. To prevent this proposed retro-Diels-Alder reaction from occurring, attempts were made to reduce the olefinic linkage of ring B of the ergosteryl acetate/2,2,2-trichloroethyl nitrosoformate adduct. Catalytic hydrogenation of the adduct (39) produced a compound whose n.m.r. spectrum was consistent with tetrahydro-ergosterol. Treatment of the adduct (39) with diimide, produced by the method of Powell et al.[32] had no effect.

It was hoped that better results would be obtained from the zinc reduction of the bicyclohexenyl/2,2,2-trichloroethyl nitrosoformate adduct (43). Being of higher molecular weight, an amino-alcohol produced from its reduction would be less soluble in water than its smaller counterpart (46) from the reduction of the 2,2-dimethylbuta-1,3-diene adduct (41). Treatment of the bicyclohexenyl adduct (43) with a 20 fold excess of zinc in glacial acetic acid yielded an impure



(48)



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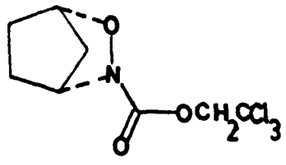
(50)



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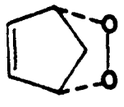

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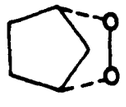


(53)

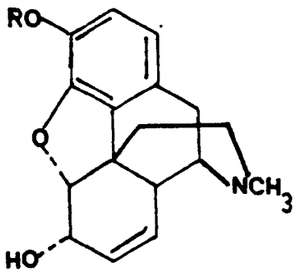
dark brown oil whose i.r. spectrum contained bands corresponding to N-H and O-H stretching vibrations. No carbonyl stretching band was observed. Although it was thought that this compound was the amino-alcohol (48), the oil could not be identified with certainty. In the hope of obtaining a cleaner product, the bicyclohexenyl adduct (43) was stirred in a THF-buffer slurry[30] with a large excess of zinc. Again a dark brown oil was isolated with similar spectral properties to those of the oil obtained previously. This product also could not be purified and therefore could not be characterised.

The zinc-acetic acid reduction of the cyclopentadiene/2,2,2-trichloroethyl nitrosoformate adduct (45) yielded no isolable product at all, even after continuous extraction of the reaction mixture for several days. The reduction was repeated using the zinc-THF-buffer method[30] mentioned above. Again evaporation of the extracts yielded no residue whatsoever. There appeared to be two possible explanations for this occurrence. One was that the amino-alcohol (49) had been formed and was too soluble in water to be extracted. The other explanation was that, as in the case of the ergosteryl acetate adduct's reduction, the adduct (45) had been de-acylated to the 'HNO' adduct (50) and a retro-Diels-Alder reaction had subsequently taken place. The cyclopentadiene formed was thereafter lost on evaporation of solvent. As some of the amino-alcohol (46) derived from the 2,3-dimethylbuta-1,3-diene adduct's reduction had been isolated, and it was unlikely that the amino-alcohol (49) would be more water-soluble, the latter suggestion seemed more probable. To circumvent this

conjectured decomposition of the putative 'HNO' adduct (50) it was planned to reduce the cyclopentadiene adduct (45) to the acyl 2,3-oxazobicyclo[2.2.1]heptane (51). Coughlin and Samolon[33] report that the 2,3-dioxabicyclo[2.2.1]heptene (52) was readily reduced to the saturated system (53) by treatment with diimide. The cyclopentadiene adduct (45) was treated with diimide, made by the method of Powell et al.[32] The impure solid recovered showed no olefinic signals in its n.m.r. spectrum but it could not be purified and characterised fully.

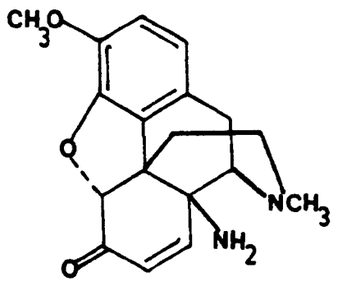
In conclusion, it is clear from the above reduction experiments that the 2,2,2-trichloroethoxycarbonyl groups were being cleaved from the adducts. However, owing to the twin difficulties of the solubility of simple amino-alcohols in water and the supposed instability of 'HNO' adduct intermediates, the desired products could not be obtained. These difficulties were overcome when the method was applied to an actual synthetic problem, the preparation of 14β-aminocodeinone from thebaine. This will be described in Chapter 2.2.

MacKinnon[11] had previously shown that nitrosocarbonylbenzene could be thermally transferred from its cyclopentadiene adduct to thebaine in hot benzene. The corresponding process had not been demonstrated to occur with a cyclopentadiene/nitrosoformate adduct although it was already known[24] that nitrosoformates could be thermally transferred from DMA to other dienes. Accordingly equimolar amounts of the cyclopentadiene/2,2,2-trichloroethyl nitrosoformate adduct (45) and ergosteryl acetate were heated in benzene under reflux. Evap-



(54) a) R=H

b) R=CH_3



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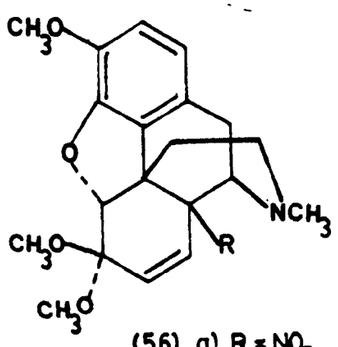
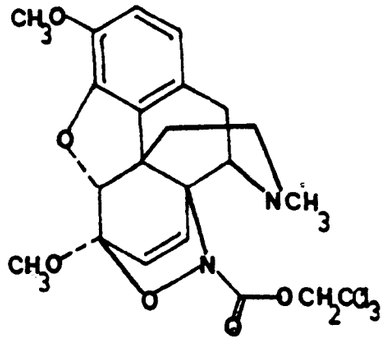


(56) a) R = NO_2

b) R = NH_2



(57)

oration of solvent after 12 hours yielded the ergosteryl acetate/ 2,2,2-trichloroethyl nitrosoformate adduct (39) in quantitative yield. The reaction was found to come to completion more rapidly when benzene was continuously distilled off, the volume of solution being maintained by occasional addition of solvent. One explanation of this phenomenon was that some of the cyclopentadiene released in the retro-Diels-Alder reaction co-distilled with the benzene thus it was unable to compete with the ergosteryl acetate for the free nitrosoformate. The 2,2,2-trichloroethyl notrosoformate was also thermally transferred to bicyclohexenyl giving the bicyclohexenyl adduct (43) in good yield. This reaction took 4 days to go to completion in refluxing toluene, which indicates that bicyclohexenyl is a much inferior nitrosoformate trap than ergosteryl acetate.

2.2 A New Route to 14β-Aminocodeinone from Thebaine.

Opium, the dried latex of the poppy plant Papaver somniferum has been known as a pain reliever for many centuries. The two active, analgesic constituents of opium are morphine (54a) and codeine (54b). However, both alkaloids, though used widely in medicine, produce undesirable side-effects, the most notorious being physical addiction.

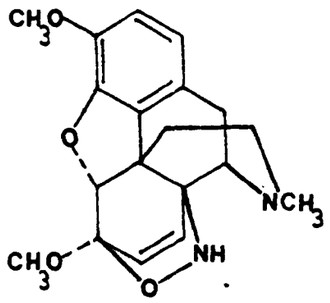
Simple alteration of the basic morphine structure can cause dramatic changes in the drug's effect on man. For instance, change of the N-methyl group of morphine to N-allyl produces an 'antagonist'

drug known as nalorphine. This has little of morphine's opiate action but can block all of morphine's effects. Research is always in progress to produce compounds based on the morphine structure that retain its analgesic properties but are free from undesirable side-effects.

Of particular pharmacological interest to Reckitt and Colman Ltd. were morphinones and codeinones bearing a nitrogen atom at the 14β-position. Pharmacological tests had shown that certain N-acyl and N-alkyl derivatives of these compounds were many thousands of times more potent than morphine in analgesic activity. The parent compound for these substances, 14β-aminocodeinone (55), had previously been synthesised by Kirby et al.[34] In this preparation, thebaine was nitrated in methanol with tetranitromethane. Roughly half of the thebaine precipitated out of solution as its trinitromethane salt, the remainder being converted into 14β-nitrocodeinone dimethyl acetal (56a) The nitrocodeinone (56a) was reduced with zinc to yield 14β-amino-codeinone (55). Recently it has been shown[35] that the yield of the nitration step can be increased by the addition of methanolic ammonia. This prevents formation of the thebaine trinitromethane salt and increases the nitration yield to ca. 60%. The overall yield, based on thebaine, for this reaction sequence is 40-45%. There are disadvantages connected with this route however. Tetranitromethane is a potentially explosive substance, as is the trinitromethane salt of ammonia. Thus large scale application of this method could be hazardous. It would also be advantageous to have a higher yield in

the first step of the sequence. Reckitt and Colman Ltd. were therefore interested in an alternative route to their key compound, 14β-aminocodeinone (55).

Thus, an alternative path to 14β-aminocodeinone was sought. There were certain criteria that had to be fulfilled by any sequence proposed. These were that the reagents had to be inexpensive, the yield at least as good as for the nitration route, and the number of steps no greater. It had already been demonstrated[10] that thebaine was an excellent acceptor of C-nitrosocarbonyl compounds and nitrosoformates. The mode of this cycloaddition is always on the less hindered β-face with nitrogen bonding to C-14. It was thought, therefore, that the thebaine adduct of 2,2,2-trichloroethyl nitrosoformate would be a good starting point for such a pathway to 14β-aminocodeinone. Oxidation of N-(2,2,2-trichloroethoxycarbonyl)hydroxylamine with aqueous sodium periodate in the presence of thebaine, in ethyl acetate, gave the thebaine/2,2,2-trichloroethyl nitrosoformate adduct (57) as a crystalline solid in high yield. In the proton n.m.r. spectrum of the adduct (57) the signals for protons 7-H and 8-H were observed as an AB quartet at δ 6.14 and 6.06 with a coupling of 9 Hz, typical of cis olefinic protons. An AB quartet at δ 4.90 and 4.64, J 11 Hz, was attributed to the methylene protons of the 2,2,2-trichloroethyl group. A singlet at δ 4.59 was assigned to proton 5-H, upfield from its position in thebaine. The signals due to the 3-methoxyl and 6-methoxyl groups were singlets at δ 3.82 and 3.64 respectively. The thebaine adduct (57) was dissolved in refluxing



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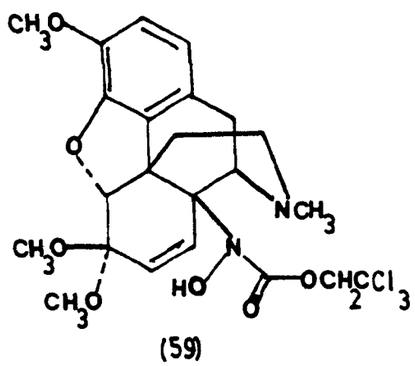

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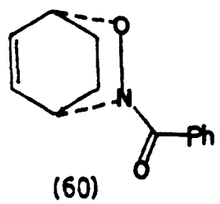

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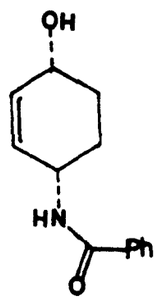
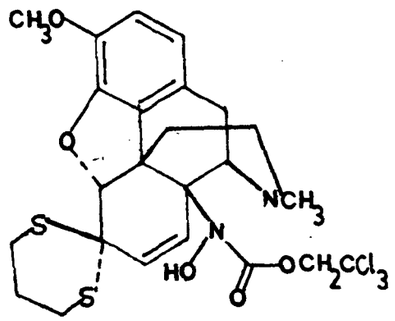


(61)

methanol and treated with zinc and ammonium chloride as in the reduction of 14β-nitrocodeinone dimethyl acetal (56a).[34] It was hoped that the 2,2,2-trichloroethoxycarbonyl group would be removed to leave the thebaine/HNO adduct (58) which would subsequently ring-open in the reaction conditions to give 14β-aminocodeinone dimethyl acetal (56b). This reduction produced many products, however, the major one being thebaine. One explanation for this was that the deprotection had taken place but the resulting thebaine/HNO adduct (58) had then undergone a retro-Diels-Alder reaction. To circumvent this decomposition of the proposed intermediate, the thebaine adduct (57) was stirred in methanolic hydrogen chloride in the hope of forming the corresponding dimethyl acetal (59). However equal amounts of the adduct (57) and the dimethyl acetal (59) were produced as an equilibrium mixture. The two compounds were separated by fractional crystallisation and the dimethyl acetal of the adduct was reduced with zinc and ammonium chloride to give 14β-aminocodeinone dimethyl acetal (56b). Acidic hydrolysis yielded 14β-aminocodeinone (55) in ca. 20% yield from thebaine. Thus it was demonstrated that the desired product could be obtained although in poor yield. The main difficulty was the adduct-acetal equilibrium which had to be overcome for the process to be acceptable. Attempts were made to disturb the equilibrium in favour of the acetal. Lowering the temperature of the reaction mixture increased the proportion of the dimethyl acetal (59) only slightly. Ammonium bromide and ammonium iodide were added to solutions of the adduct (57) in methanolic hydrogen chloride in an

unsuccessful attempt to precipitate the dimethyl acetal (59) preferentially as a salt. The in situ reduction of the mixture was also tried in an attempt to solve this equilibrium problem. It was thought that if the dimethyl acetal (59) was reduced appreciably faster than the thebaine adduct (57) then this would in effect take the reaction to completion by removing the acetal (59) and thus displacing the equilibrium in the desired direction. The thebaine adduct (57) was allowed to come to equilibrium in methanolic hydrogen chloride then zinc dust was added. On work-up, however, many unidentifiable products were obtained. It was observed during this reaction that the zinc was being consumed by reaction with the hydrogen chloride. Accordingly the reaction was repeated using zinc amalgam which is resistant to acid. Thebaine and 14β-aminocodeinone dimethyl acetal (56b) were recovered in almost equal amounts. It seemed that both reductions were taking place at roughly the same rate. Therefore when the equilibrium mixture of acetal and adduct was reduced with zinc amalgam, 14β-aminocodeinone dimethyl acetal and thebaine/HNO adduct (58) were produced, the latter decomposing to thebaine. Keck and Fleming[36] report that the N-O bond of the cyclohexadiene/nitrosocarbonylbenzene adduct (60)was cleaved by aluminium amalgam in tetrahydrofuran (THF) to produce the compound (61). However, when the thebaine adduct (57) was treated with aluminium amalgam in THF, n.m.r. spectroscopy of the product indicated that it had been overreduced, since there were no olefinic signals present in the spectrum.



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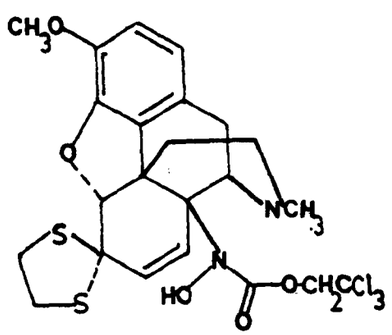

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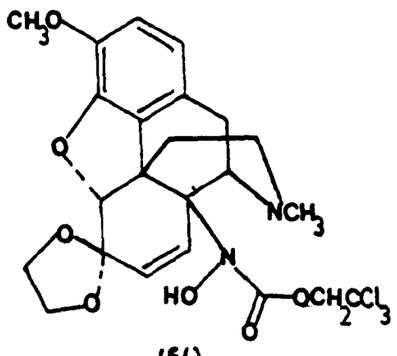

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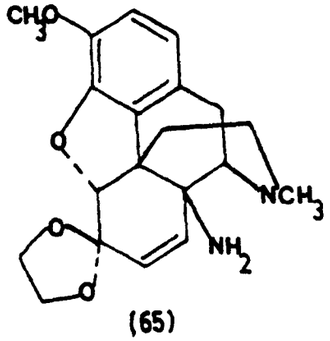
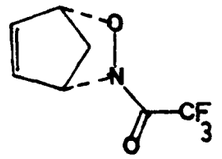


(65)

It is known[37] that cyclic acetals are easier to form than their dialkyl counterparts. Accordingly, the thebaine adduct (57) was treated with propane-1,3-dithiol using boron trifluoride etherate as a catalyst. This time acetal formation went to completion and the adduct's propylene dithioacetal (62) was obtained in good yield. Bands at 3 200 and 1 680 cm^{-1} were observed in the i.r. spectrum of this compound, corresponding to the O-H and carbonyl stretching vibrations respectively. In the proton n.m.r. spectrum of the dithioacetal (62) an AB quartet at δ 6.08 and 5.79, J 8 Hz, was assigned to protons 7-H and 8-H. A singlet at δ 5,20 was attributed to H-5, and the signal for the methylene protons of the 2,2,2-trichloroethyl group was an AB quartet at δ 4.92 and 4.61, J 12 Hz. The n.m.r. signal due to the 3-methoxyl group was a singlet at δ 3.90, and a multiplet in the region δ 3.2-2.7 was attributed to the methylene protons of the propylene dithioacetal group. Unfortunately this compound could not be crystallised and it decomposed on chromatography. Complete purification and characterisation was, therefore, not possible. Treatment of the adduct (57) with ethane dithiol and BF_3. etherate produced an oil which also could not be purified, although there was little doubt (see Experimental Chapter for details) that the dithioacetal (63) had been formed. These results were encouraging. However, as there was some difficulty in purification of the dithioacetals and it was foreseen that their cleavage at a later stage might not be straightforward, it was decided to investigate their oxygen analogues.

Initial attempts to form an acetal from the thebaine adduct using ethylene glycol with toluene-p-sulphonic acid catalysis failed. Nevertheless, bearing in mind how the dimethyl acetal (59) was made, a solution of dry hydrogen chloride in ethylene glycol was prepared. When the thebaine adduct (57) was stirred in this solution the ethylene acetal (64) was formed quantitatively as a crystalline solid. Zinc and ammonium chloride reduction of the ethylene acetal (64) produced 14β-aminocodeinone ethylene acetal (65) in high yield. A band at 3 400 cm^{-1} corresponding to N-H stretching vibrations, was observed in the i.r. spectrum of the acetal (65). In the proton n.m.r. spectrum of the ethylene acetal (65), an AB quartet at δ 5.84 and 5.66, J 9 Hz, was assigned to the cis olefinic protons, 7-H and 8-H. The n.m.r. signal for proton 5-H was a singlet at δ 4.50 and the signal due to the 3-methoxyl group was a singlet at δ 3.83. A broad multiplet at δ 4.02 was attributed to the methylene protons of the ethylene acetal group, and a broad singlet at δ 3.40, exchangeable with D_2O, was assigned to the amino group. This compound (65) was hydrolysed with aqueous acid to give 14β-aminocodeinone (55) in an overall yield of 45-50% from thebaine. The number of steps in this sequence was reduced in the following way. The adduct (57) was converted into the ethylene acetal (64) in glycolic hydrogen chloride as before. The reaction mixture was neutralised directly with ammonium carbonate to generate ammonium chloride in situ. Addition of zinc then effected reduction of (64) to 14β-aminocodeinone ethylene ketal (65). This product was isolated and hydrolysed, without



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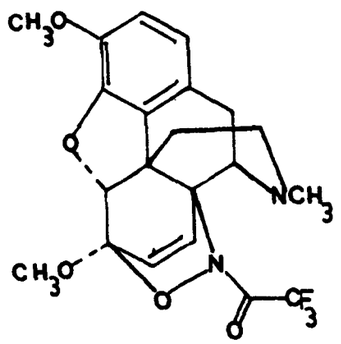


(68)

$CF_3CONHOH$

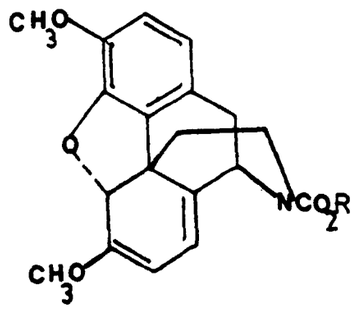
(67)

$Ph_2P(O)NHOH$

(69)

$Ph_2P(O)ONH_2$

(70)



(71) a) R = $PhCH_2$-

b) R = Bu^t-

purification, to give 14β-aminocodeinone.

The foregoing process contains no more operations than that involving nitration of thebaine with tetra-nitromethane. It proceeds in a higher yield and employs inexpensive reagents. Thus all the aforementioned criteria appear to have been met by this pathway.

2.3 Miscellaneous Reactions.

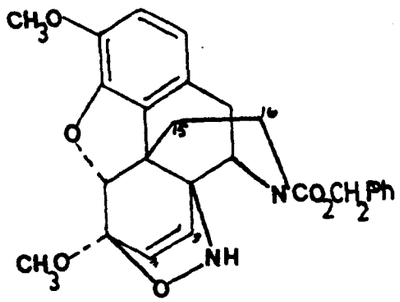
Whilst investigating the preparation of 14β-aminocodeinone (55) some other, unrelated approaches were attempted. The first of these was based on Just and Cutrone's report[38] of the formation of the cyclopentadeine/nitrosocarbonyltrifluoromethane adduct (66) by the oxidation of trifluoroacetohydroxamic acid (67) in the presence of cyclopentadiene. This compound proved to be unstable and decomposed after standing at 40°C for a few minutes. It was hoped that the thebaine adduct of nitrosocarbonyltrifluoromethane (68) would be more stable. If so, this would then form the basis of another route to 14β-aminocodeinone since trifluoroacetamides are easily hydrolysed by base. Treatment of trifluoroacetic anhydride with hydroxylamine hydrochloride after the method of Pomeroy and Craig[39] yielded trifluoroacetohydroxamic acid (67) as crystals with the literature melting point. Periodate oxidation of trifluoroacetohydroxamic acid in methylene chloride containing thebaine led

to the isolation of thebaine alone from the reaction mixture. It was not known whether the reaction failed because the thebaine and the nitrosocarbonyl compound had simply not reacted at all or whether the adduct (68) had indeed been formed only to be cleaved to the 'HNO' adduct (58) which had subsequently decomposed. In an attempt to repeat the literature preparation of the cyclopentadiene adduct (66), cyclopentadiene was treated with nitrosocarbonyltrifluoromethane generated in the usual way. Evaporation of solvent after work-up initially yielded a brown oil which decomposed to an unidentifiable crusty black solid on standing at room temperature for a few minutes. This approach was thus abandoned due to product instability.

It was reported by Harger[40] that the product of the addition of hydroxylamine to diphenylphosphinyl chloride had wrongly been assigned the structure N-(diphenylphosphinyl)hydroxylamine (69) in the literature. He proved that this compound was in fact O-(diphenylphosphinyl)hydroxylamine (70). Inspection of the revised structure led to the idea that this derivative might function as an aminating agent in the manner of O-mesitylenesulphonylhydroxylamine. Electrophilic attack on thebaine, e.g. chlorination and bromination, usually occurs on the diene system at 14-C,[41] therefore it was proposed that treatment of thebaine with O-(diphenylphosphinyl)hydroxylamine in methanol might result in the formation of 14β-aminocodeinone dimethyl acetal (56b) with diphenylphosphinic acid as a co-product. To test this hypothesis, diphenylphosphinyl chloride was added to a solution of hydroxylamine in benzene and O-(diphenylphosphinyl)hydroxylamine (70)

was obtained as white needles with the literature[42] melting point. Thebaine and O-(diphenylphosphinyl)hydroxylamine were heated together in methanol under reflux for 15 hours; however the t.l.c. analysis and an n.m.r. spectrum revealed that no reaction had taken place. The reaction was repeated with N-benzyloxycarbonylnorthebaine (N-CBz-northebaine) (71a). Again after 15 hours in refluxing methanol no reaction had taken place. After these attempts had been made a paper[43] from Bottaro was published which reported that O-p-toluene-sulphonylhydroxylamine formed aziridines with reactive olefins. Thus it would appear that the above attempts had some justification. Possibly a more reactive diarylphosphinylhydroxylamine with p-substituted electron-withdrawing groups would have succeeded. It is also not known whether aziridines would be formed from O-(diphenylphosphinyl) hydroxylamine and reactive olefins.

Having some crystalline, free hydroxylamine remaining from the preparation of O-(diphenylphosphinyl)hydroxylamine we thought it potentially interesting to oxidise this in the presence of thebaine and N-CBz-northebaine. It was not foreseen what one of many possible paths this reaction would take but it was hoped that a transient, electrophilic species from the oxidation of hydroxylamine would attack the electron-rich, diene systems. Addition of tetraethylammonium periodate to a solution of thebaine and an excess of hydroxylamine caused an exothermic reaction accompanied by a vigorous evolution of gas. The solid isolated from the reaction mixture was thebaine, however. The reaction was repeated with N-CBz-northebaine in place of thebaine, and again the oxidation of the hydroxylamine was very



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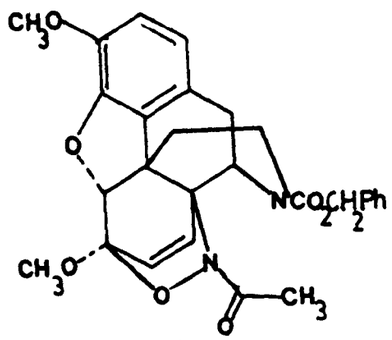

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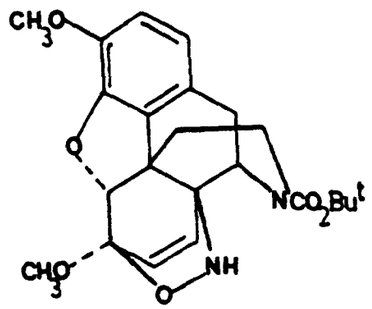

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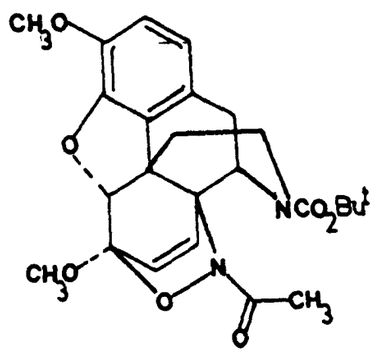
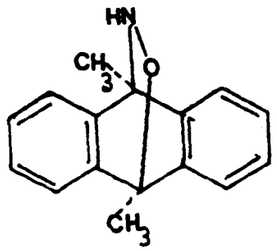


(75)

exothermic. The n.m.r. spectrum of the oil obtained showed no trace of starting material. Signals corresponding to protons 7-H and 8-H were seen as an AB quartet at δ 6.02 and 5.93, J 8 Hz, characteristic of cis olefinic protons, and 5-H gave a singlet at δ 4.58, upfield from its position in N-CBz-northebaine in which it is allylic. The 6-methoxyl group gave a singlet at δ 3.48, upfield from that of N-CBz-northebaine, indicating that 6-C was no longer olefinic. The 3-methoxyl group signal appeared at δ 3.78, roughly the same chemical shift as in N-CBz-northebaine. The multiplet corresponding to 15β-H, recognisable by the 13 Hz couplings to 15α-H and 16β-H, appeared at δ 2.37, ca. 0.3ppm downfield from its position in the starting material due to the proximity of an electron-withdrawing group. Thus it was reasoned that attachments had been made to the diene system at 6-C and 14-C on the β-face. It was proposed that HNO had been formed by the oxidation of free hydroxylamine, just as nitrosocarbonyl compounds, RCONO, are formed by the oxidation of hydroxamic acids. The HNO had then taken part in a Diels-Alder reaction with N-CBz-northebaine to form the N-CBz-northebaine/HNO adduct (72). An identical product was obtained when iodine was used in this reaction as the oxidant, in place of periodate. Attempts to crystallise the HNO adduct (72) failed and after 5 hours in refluxing benzene it reverted to N-CBz-northebaine. It seemed anomalous that the thebaine/HNO adduct (58) should not form at all, therefore an excess of hydroxylamine was again oxidised in the

presence of thebaine. This time, solvent was evaporated in the cold and an n.m.r. spectrum taken immediately. It appeared from the spectrum that roughly two-thirds of the mixture was thebaine, but there were other signals that could be attributed to the thebaine/HNO adduct (58). In most relevant details these signals were very similar to those of the N-CBz-northebaine/HNO adduct (72); 7-H and 8-H protons gave an AB quartet, J 9 Hz, at δ 6.00 and 5.89, a singlet at δ 4.55 was attributed to 5-H, and another singlet at δ 3.50 to the 6-methoxyl group. After standing at room temperature for twenty minutes the mixture gave an n.m.r. spectrum showing signals only for thebaine. Thus, for some unknown reason, the thebaine/HNO adduct (58) was much less thermally stable than the N-CBz-northebaine/HNO adduct (72). In an attempt to find a crystalline derivative, the N-CBz-northebaine/HNO adduct (72) was acetylated with acetyl chloride in pyridine to produce the N-CBz-northebaine/nitrosocarbonylmethane adduct (73) as an oil which would not crystallise. In this compound the cis olefinic protons, 7-H and 8-H, gave signals at δ 6.18 and 6.05 as an AB quartet, J 10 Hz. The 3- and 6-methoxyl group protons gave singlets at δ 3.79 and 3.55 respectively and the acetyl group gave a singlet at δ 1.93. Oxidation of acetohydroxamic acid in the presence of N-CBz-northebaine produced the expected N-CBz-northebaine/nitrosocarbonylmethane adduct (73) with an n.m.r. spectrum identical to that of the one described above. Thus it appeared that the proposed structure of the N-CBz-northebaine/HNO adduct (72) was correct; however, as a crystalline derivative could not be made, it



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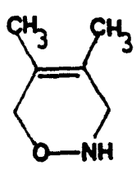

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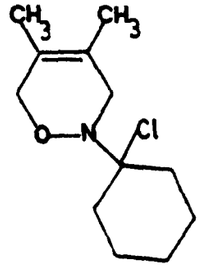

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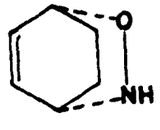


(79)

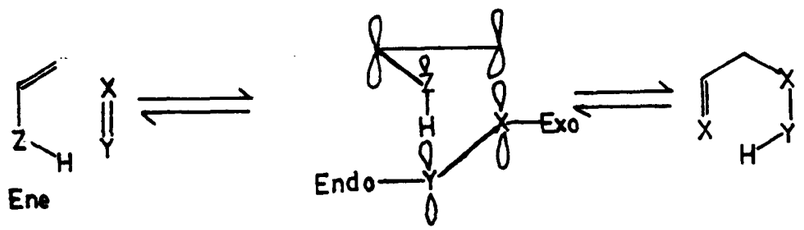
could not be fully characterised. It was known that adducts of N-t-butoxycarbonylnorthebaine (71b) were mostly crystalline solids. Accordingly free hydroxylamine was oxidised in a solution containing N-t-butoxycarbonylnorthebaine (71b) and an oil was isolated which had an n.m.r. spectrum very similar to that of the N-CBz-northebaine/HNO adduct (72) in all relevant areas. This N-t-butoxycarbonylnorthebaine adduct (74) decomposed to N-t-butoxycarbonylnorthebaine after 4 hours in refluxing benzene. Treatment of N-t-butoxycarbonylnorthebaine with nitrosocarbonylmethane generated in the usual way produced the N-t-butoxycarbonylnorthebaine/nitrosocarbonylmethane adduct (75). The adduct (75) crystallised as its hydrate and was fully characterised. Acetylation of the N-t-butoxycarbonylnorthebaine/HNO adduct (74) with acetyl chloride in pyridine produced a crystalline solid giving spectra identical to those of the adduct (75) and having the same melting point. Since the N-t-butoxycarbonylnorthebaine/nitrosocarbonylmethane adduct (75) had been prepared by both routes it was safe to assume that the labile N-t-butoxycarbonylnorthebaine/HNO adduct (74) had indeed been formed.

Nitrosyl hydride, HNO, had previously been generated[44] by the dissociation of the DMA/HNO adduct (76) at 70°C and studied by microwave spectroscopy. Sneed and Brasted[45] postulated it to be an intermediate in the oxidation of hydroxylamine, the final products being N_2O and water. Nevertheless the above examples appear to be the only illustrations of nitrosyl hydride taking part in Diels-Alder reactions to form cycloadducts with conjugated dienes. It

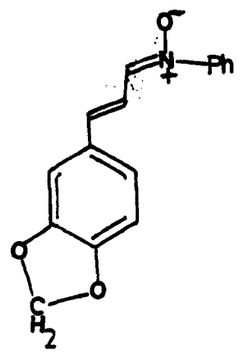
was decided to test whether this was a generally applicable reaction of HNO, by oxidising hydroxylamine in the presence of simple dienes. Many of the potential products of HNO addition to simple dienes are known compounds.[2] The HNO adduct of 2,3-dimethylbuta-1,3-diene, 3,6-dihydro-4,5-dimethyl-1,2-oxazine (77), has been prepared[46] by the addition of 1-chloro-1-nitrosocyclohexane to a solution of the diene in ethanol. The cycloadduct (78) is formed initially and is then solvolysed to give the hydrochloride of the oxazine (77). The same nitroso derivative and 1,3-cyclohexadiene yield the hydrochloride of the 3,6-endoethano-3,6-dihydro-1,2-oxazine (79), i.e. the 'HNO adduct' of 1,3-cyclohexadiene. Periodate oxidation of hydroxylamine in a solution containing 2,3-dimethylbuta-1,3-diene yielded a dark brown oil. T.l.c. analysis showed it to be a mixture of unidentifiable products, none of them starting material and the proton n.m.r. spectrum was very complex. Thus the components had reacted but in an unknown way. Similarly, oxidation of hydroxylamine in the presence of 1,3-cyclohexadiene yielded a dark brown oil. The n.m.r. spectrum of this oil was confusing but a multiplet at δ 6.60 was observed. This is downfield from where the olefinic signals of 1,3-cyclohexadiene appear, possibly indicating that the oxazine (79) was present in the mixture. The oil could not be separated by t.l.c. When the hydroxylamine oxidation was repeated using bicyclohexenyl as the diene component, only the starting diene was obtained after work-up of the reaction mixture. Freshly distilled cyclopentadiene was next dissolved in benzene and hydroxylamine was oxidised in situ.

After work-up and evaporation of solvent, a brown oil was obtained which decomposed to a black insoluble solid on standing at room temperature for a few minutes. It was thought possible that the HNO adduct (50) had formed but had thereafter decomposed. Consequently the reaction was repeated and, after washing, acetic anhydride was added to the solution. This was done in an effort to acetylate and thus stabilise the putative HNO adduct. However, evaporation of solvent again gave a crusty black solid.

From the above evidence it can be seen that adduct formation with conjugated dienes is not a general reaction of nitrosyl hydride. The anomalous stability of the N-alkoxycarbonylnorthebaine/HNO adducts, (72) and (74), cannot be explained at the present time.



(Scheme 6)



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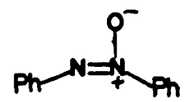

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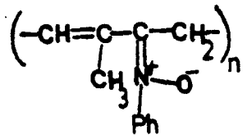

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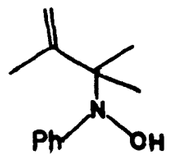

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Chapter Three.

The Inter- and Intramolecular Ene Reaction in Nitroso-Compounds.

3.1 The Intermolecular Ene Reaction.

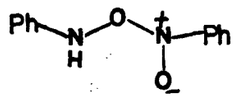
The ene reaction is the addition of a compound with a double or triple bond, the enophile, to an olefin possessing an allylic hydrogen, the ene, and involves an allylic shift of one double bond, transfer of the allylic hydrogen to the enophile and bonding between the two unsaturated termini. Experimental evidence and orbital symmetry considerations[47] are consistent with a concerted pathway involving a supra-suprafacial, endo or exo-oriented interaction (Scheme 6). Fukui and co-workers[47] suggest that the ene process is not an entirely concerted one and that in the transition state A (Scheme 6) the C-X bond is more developed than the H-Y bond. Mechanistic and preparative studies of the intermolecular ene reaction where X,Y, and Z are carbon and/or oxygen have been comprehensively reviewed by Hoffmann.[48]

Molecules with hetero double bonds, such as nitroso groups, also serve as effective enophiles in intermolecular ene reactions. Reactions between aromatic nitroso-compounds and allylic olefins* have been studied for many years. The first account of these was by Allessandri[49] who reported that the reaction of nitroso-benzene and safrole gave the nitrone (80) and azoxybenzene (81). The addition

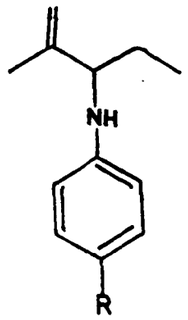
* an allylic olefin shall be taken to mean an olefin possessing an allylic hydrogen.

of nitrosobenzene to natural rubber, cis-1,4-polyisoprene, was also being investigated by Bruni[50] and Pummerer[51] at this time. These authors reported that treatment of a solution of rubber with excess nitrosobenzene produced azoxybenzene (81) and a compound which they named as iso-rubber nitrone (82). They suggested that the azoxybenzene arose from the condensation of an intermediate phenylhydroxylamine and nitrosobenzene.

This field of research lay dormant for many years until Hamer and Macaluso[52] reported that the only products isolated from the additions of p-nitronitrosobenzene and p-bromonitrosobenzene to various allylic olefins were the respective azoxybenzenes. They could not account for the oxygen 'lost' on formation of the azoxycompound as no nitrosobenzene was found to be oxidised to nitrobenzene and the solvent, ethanol, had not been oxidised. The mechanism of such reactions remained obscure for some time. Sullivan[53] was the first to suggest that a possible mechanism was an intermolecular ene process. He studied the reaction of 2,3-dimethylbut-2-ene with nitrosobenzene and proposed that an ene reaction had taken place to yield the unsaturated hydroxylamine derivative (83). He speculated that this proposed intermediate could be oxidised by air or unreacted nitrosobenzene to give the corresponding nitroxide, a species which he detected by e.s.r. spectroscopy. As in previous examples normal work-up of this reaction yielded the azoxybenzene (81). However, when the total reaction mixture was reduced, N-(1,1,2-trimethylprop-2-enyl)aniline was obtained, reinforcing his postulate. Russell[54] pointed out

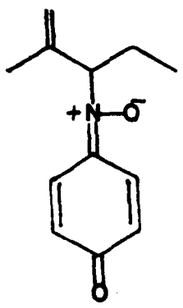


(84)

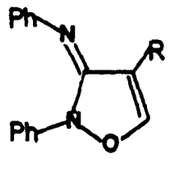


(85) a) R = NMe_2

b) R = OH

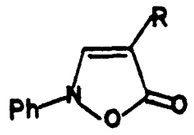


(86)



(87) a) R = Ph

b) R = CO_2CH_3



(88) a) R = Ph

b) R = CO_2CH_3

$$2\ ArN(OH)CH_2R \longrightarrow ArNHCH_2R + Ar\overset{+}{N}(O^-)=CHR + H_2O$$

(Fig.1)

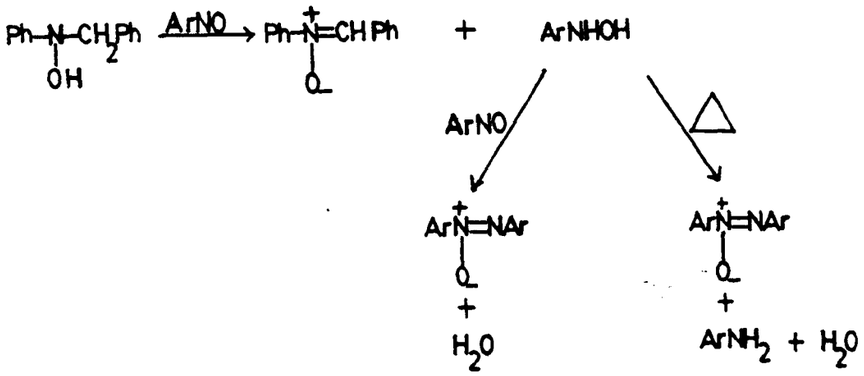
that the e.s.r. spectrum observed by Sullivan was very similar to the spectrum of the adduct (84) from nitrosobenzene and phenyl-nitroxide, and that it was this that he had seen. Sullivan's theory of the intermediate hydroxylamine was supported by Cain et al.[55] They found that treatment of 2-methylpent-2-ene with NN-dimethyl-p-nitrosoaniline gave NN-dimethyl-N'-(1-ethyl-2-methylprop-2-enyl)-p-phenylene diamine (85a) in ca. 50% yield. This reaction was shown to occur with a number of N-alkyl-p-nitrosoanilines and allylic olefins. It was their belief that an ene type process was occurring to give an unstable, intermediate hydroxylamine. However, they were uncertain of the mechanism of the essentially reductive step to the amine. Later, Knight and Pepper[56] investigated the addition of p-nitrosophenol to 2-methylpent-2-ene and isolated not only the p-substituted aniline (85b) but also N-(1-ethyl-2-methylprop-2-enyl)quinoneimine N-oxide (86). They proposed that a bimolecular decomposition of the hypothetical N-alkenyl-N-arylhydroxylamine intermediates would give rise to the observed alkenyl aryl amines (85a)and (85b) and also α-alkenyl-N-arylnitrones. Nitrones are unstable, though, unless they can tautomerise or have an high degree of resonance stability. An example of the former is found in the isolation of the quinoneimine (86).

Knight[57] presented more concrete evidence for the ene nature of these reactions. He added nitrosobenzene to an excess of 2,3-dimethylbut-2-ene in an inert atmosphere, thus avoiding oxidation of

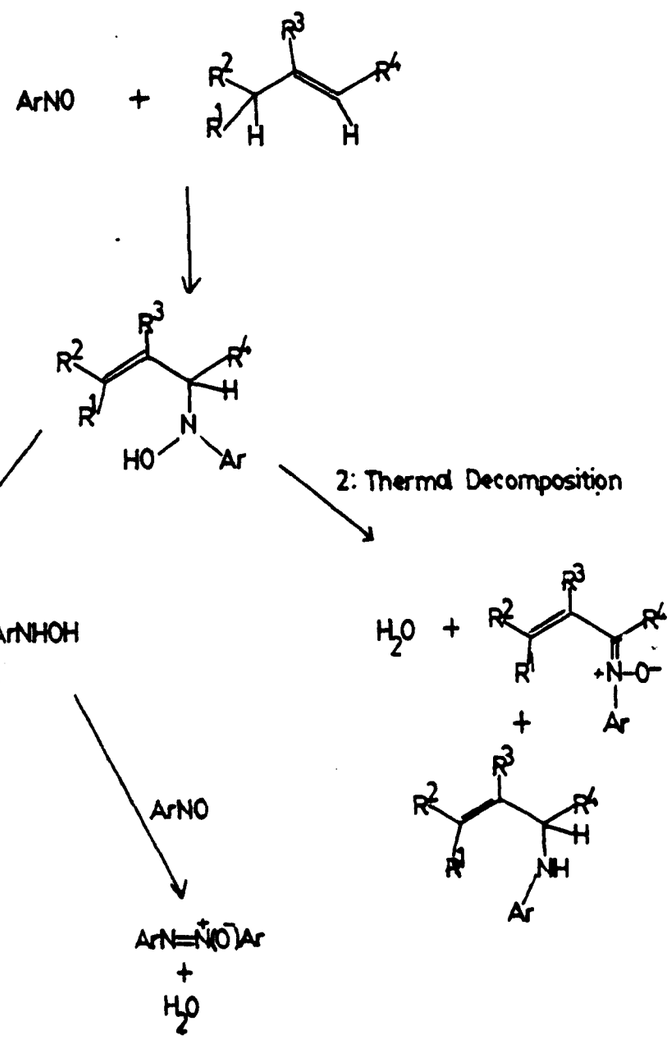
the intermediate, and, by careful work-up, isolated N-phenyl-N-(1,1,2-trimethylprop-2-enyl)hydroxylamine (83). Oxidation of the hydroxylamine gave the corresponding nitroxide which had an e.s.r. spectrum identical to that obtained by Sullivan[53], thus vindicating him. The similarity of the Russell adduct radical (84) thus appears to be coincidental. N-Alkenyl-N-arylhydroxylamines have also been isolated from the reaction of pentafluoronitrosobenzene and various allylic olefins by Haszeldine and co-workers.[58]

Kolak[59] has studied the addition of nitrosobenzene to α-methylstyrene and methyl methacrylate. The products obtained from these reactions were the 4-substuted 3-phenylimino-4-isoxazolines (87a) and (87b) and the 4-substituted 2-phenylisoxazolin-5-ones (88a) and (88b). He proposed that the formation of these products was consistent with a pathway involving oxidation and cyclisation of an initially formed unsaturated hydroxylamine. Further reaction of nitrosobenzene with the cyclised product then produced the final products.

A rationalisation of the diverse reaction products from nitrosoarenes and allylic olefins has been attempted by Knight and Pepper.[60] They made the assumption that in all the above reactions an N-alkenyl-N-arylhydroxylamine was initially formed; therefore the chemistry of N-alkyl-N-arylhydroxylamines would explain how the various final products arose. It was known[61] that N-p-phenyl-substituted N-benzylhydroxylamines decomposed thermally to anilines and nitrones (fig. 1). The rate of decomposition was shown to be second order in the



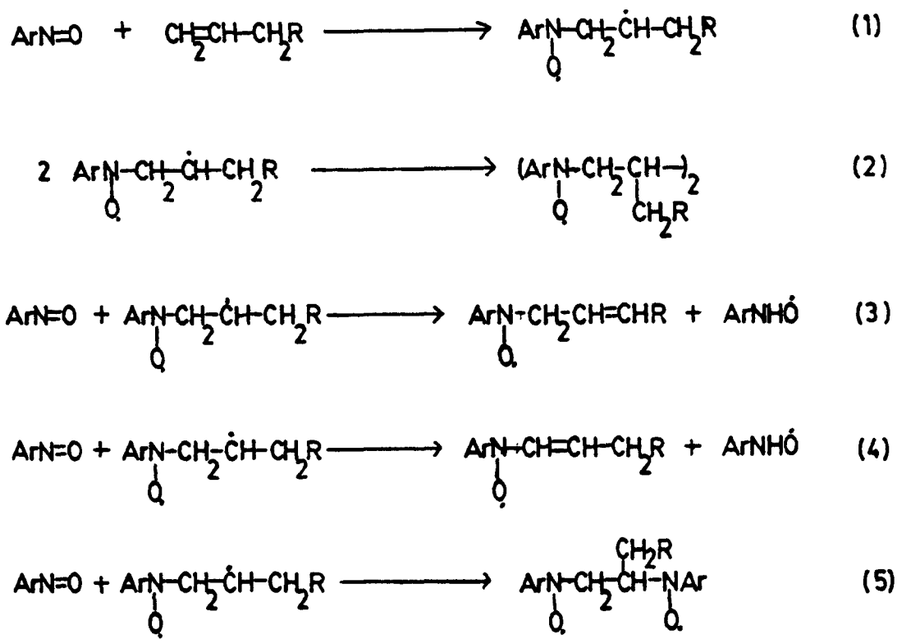
(Scheme 7)



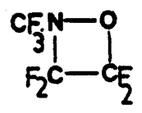
(Scheme 8)

hydroxylamine and to be greatly increased with increasing electron-withdrawing nature of the para substituents. A study[62] had also been made of the oxidation of N-benzyl-N-phenylhydroxylamine with various p-substituted nitrosobenzenes. This had shown that α,N-diphenylnitrone and p-substituted azoxybenzenes were formed quantitatively. However when the nitrosobenzenes had strongly electron-donating substituents the yield of the azoxy compound decreased, primary amines were observed, and the rate of the reaction slowed markedly (Scheme 7). Using these studies as a guide, Knight and Pepper proposed routes by which the initial secondary hydroxylamine can react (Scheme 8). When neutral or electron-withdrawing substituents are present in the aromatic ring of the nitroso-compound, pathway (1) is followed to provide the nitrones and azoxyarenes observed by Allesandri,[49] Bruni,[50] Hamer,[52] and Sullivan.[53] When electron-releasing substituents are present in the aromatic ring, pathway (1) is significantly slowed and the rate of pathway (2) is increased, thus the main products are those of bimolecular decomposition. As observed by Knight,[56] these are N-alkenyl-N-arylamines and nitrones.

Recently Mulvey and Waters[63] offered an alternative reaction scheme to the one proposed above. E.s.r. measurements indicated that the addition of 2,4,6-trichloronitrosobenzene to various allylic olefins occurred by one-electron transfer from the C=C to N=O bonds to give nitroxide radicals. The olefins were present in a very large excess and the reactions were carried out under nitrogen.



(Scheme 9)



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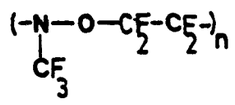

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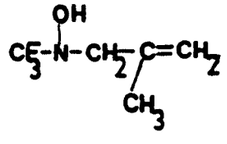
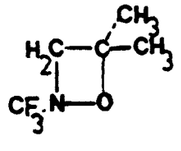


(91)



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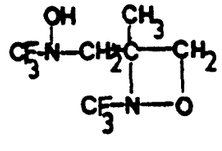
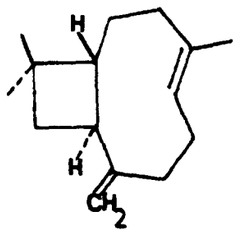


(92)

The e.s.r. spectra usually reached a maximum intensity after ca. 30 minutes and persisted for many hours. For all olefins initial spectra observed were those of the nitroxides $ArN(\dot{O})-CH_2$, i.e. essentially nine-line spectra of the form, 3X(1,2,1). Most olefins also showed secondary six-line spectra of a nitroxide, $ArN(\dot{O})-CHXY$, which gradually appeared and persisted for many hours as the initial nine-line spectra slowly decayed. It was believed that the nitroxide spectra could not be those of biradicals $ArN(\dot{O})CH_2-\dot{C}HR$ containing trivalent carbon as simple aliphatic carbon radicals have lifetimes of milliseconds in liquids at room temperature. Thus they proposed that, following the initial slow addition of the nitrosoarene to the olefin, the tervalent carbon centre must be destroyed by any of the reactions (2)-(5) illustrated in Scheme 9, all of which are well known in free-radical chemistry. Slower decomposition of the nitroxide radicals themselves to give nitrones and hydroxylamine may then follow.

Reaction (3) is effectively the ene reaction sequence proposed previously, whilst reaction (4) may well be a route of preparation of the secondary nitroxide radicals $ArN(\dot{O})CHXY$. Both reactions (3) and (4) may lead to the formation of azoxybenzenes through the dimerisation of ArNHO radicals.[64]

In the aliphatic series most research has been carried out on olefin addition to perfluoronitrosoalkanes, in particular trifluoronitrosomethane. Haszeldine[65] found that trifluoronitrosomethane reacted with tetrafluoroethylene to give a mixture of the



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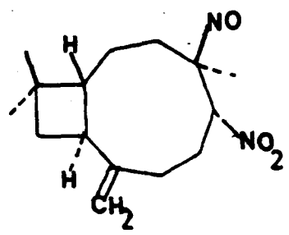

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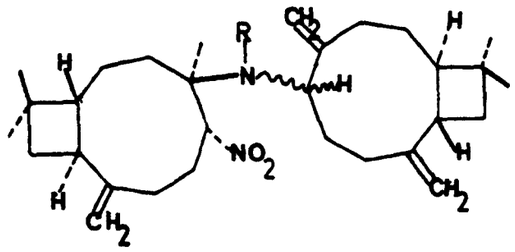
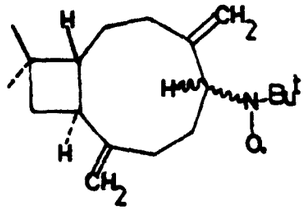


(96) a) R = -O·

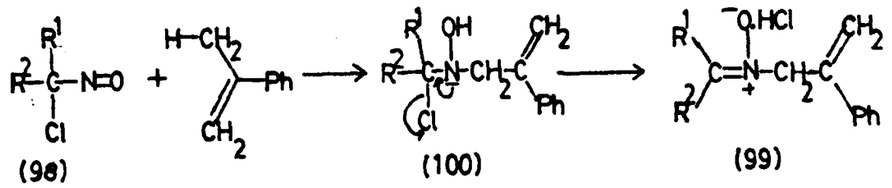
b) R = -OH



(97)

oxazetidine (89) and the copolymer (90). The oxazetidine predominated when the reaction was carried out at 70°C, the copolymer predominated at -45°C. He postulated a radical mechanism to account for the formation of the products. Ginsburg et al.[66] showed by e.s.r. studies that species of the type $CF_3\dot{N}(O)\text{-}R^-$, in which R is the residue of the unsaturated component, were formed in the reactions of perfluorinated olefins and trifluoronitrosomethane. A radical mechanism was advanced for the formation of this anion radical, with radical initiation by the dimerisation of trifluoronitrosomethane. Oxidation of the anion radical, by other radicals for instance, then gives a biradical which cyclises to the corresponding oxazetidine. Olefins with α-methylenic hydrogens react differently with trifluoronitrosomethane. Haszeldine et al.[67] reported that treatment of isobutene with trifluoronitrosomethane at low temperature yielded the allylic hydroxylamine (91) as a crystalline solid which decomposed on warming to room temperature. They visualised the mechanism of this reaction to be a concerted ene process. Ginsburg et al.[68] also investigated the reaction of isobutene with trifluoronitrosomethane and isolated not only the hydroxylamine (91) but also an oxazetidine (92). The mechanism they postulated for this reaction involved initial formation of the unstable oxazetidine (93) which then rearranged to the hydroxylamine (91). Attack on (91) by another molecule of trifluoronitrosomethane gave the stable oxazetidine (92).

There have been very few reports concerning the intermolecular ene reaction of non-fluorinated aliphatic nitroso-compounds.



(98) (100) (99)

98, 99, 100 : a) R^1R^2 = Ad

b) $R^1=R^2=CH_3$

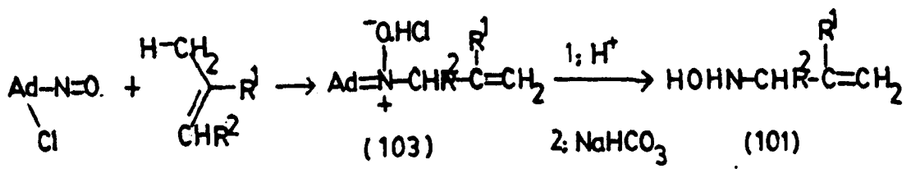
c) $R^1=CH_3$; $R^2=C_2H_5$

d) $R^1=CH_3$; $R^2=C_6H_5CH_2$

e) R^1R^2 = $-(CH_2)_5-$

Ad ≡ 

(Scheme 10)



(102) (103) (101) + Ad=O

101, 102, 103: a) R^1 = Ph; R^2 = H

b) $R^1=CH_3$; $R^2=C_2H_5$

c) $R^1=CH_3$; $R^2=CH_3$

d) $R^1=CH_3$; $R^2=H$

e) R^1 = C_3H_7; $R^2=H$

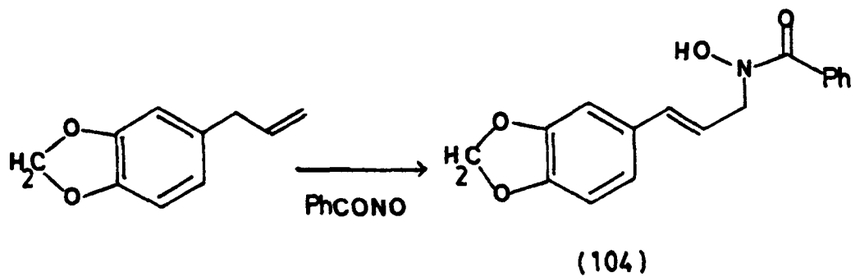
(Scheme 11)

Roberts[69] found that caryophyllene (94), a 9-membered, cyclic olefin containing a reactive, strained, tri-substituted double bond, reacted with caryophyllene nitrosite (95) to produce a stable nitroxide radical (96a). He proposed that the olefin and the nitroso-compound had undergone an ene reaction to produce the hydroxylamine (96b) which had been oxidised *in situ* to the nitroxide. Few examples of nitroxide radicals with β-hydrogens are known. The stability of this compound (96a) was attributed to the steric hindrance to hydrogen abstraction in the bimolecular decomposition needed to give the corresponding nitrone and hydroxylamine. Treatment of caryophyllene (94) with t-nitrosobutane produced the nitroxide (97) which proved to be considerably less stable then (96a).

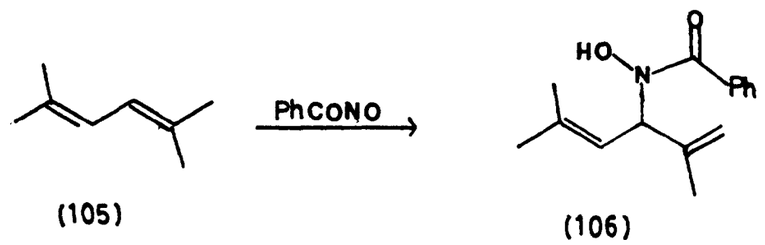
The addition of α-chloronitroso-compounds to allylic olefins has been recently studied by Schenck and De Boer.[70] When α-chloronitrosoadamantane (AdClNO) (98a) was kept in an excess of 2-phenylpropene for 10 days at room temperature the nitrone hydrochloride (99a) precipitated out of solution in high yield as a white solid. It was deduced by them from literature precedents that an *N*-(α-chloroalkyl)-*N*-alkenylhydroxylamine (100a) had been initially formed by an ene reaction between the two components. Heterolytic expulsion of chlorine then brought about the formation of the nitrone hydrochloride (99a) (Scheme 10). They considered that the intermediate hydroxylamine had been protected from the previously mentioned, complex, secondary reactions by the efficient formation of the insoluble salt. The hypothesis of the initial ene reaction was

proved by treating AdClNO with α-trideuteriomethylstyrene The exclusive product from this reaction was the nitrone hydrochloride (99a) with a deuterated vinylidene ,and not methylene, group. This of course does not discriminate between a concerted and a non-concerted path. Hydrolysis of the nitrone hydrochloride (99a) gave adamantanone and the allylic hydroxylamine hydrochloride (101a) which, when heated in refluxing acetone, yielded α,α-dimethyl-N-(2-phenyl)prop-1-en-3-yl nitrone hydrochloride (99b). To establish the scope of this reaction, 2-phenylpropene was treated with a series of α-chloronitroso compounds (98b-e). The corresponding nitrone hydrochlorides (99b-e) were all obtained in good yield. The authors claimed this to be a convenient new route to aliphatic ketonitrones. The reaction of AdClNO with various allylic olefins (102b-e) was also investigated and the adamantylidene nitrone hydrochlorides (103b-e) were obtained after reaction times of up to 20 days. Hydrolysis of the nitrones (103b-e) produced the corresponding allylic hydroxylamines (101b-e) (Scheme 11). 2-Methylpent-2-ene (102b) and 2-methylbut-2-ene (102c) have 2 types of allylic hydrogen and, therefore, 2 isomeric nitrones are possible. It is interesting to note that in both cases only one isomer is formed, the one with the nitrone group attached to the originally least substituted carbon of the double bond.

Kirby and Corrie[71] found that C-nitrosocarbonyl compounds, RCONO, also react with allylic olefins. Nitrosocarbonyl compounds,

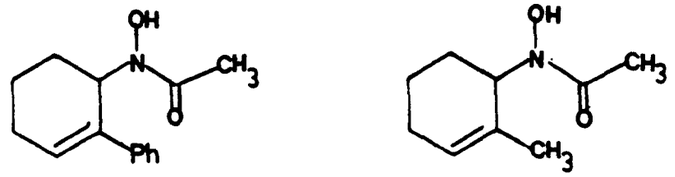


(104)



(105) (106)

(Scheme 12)



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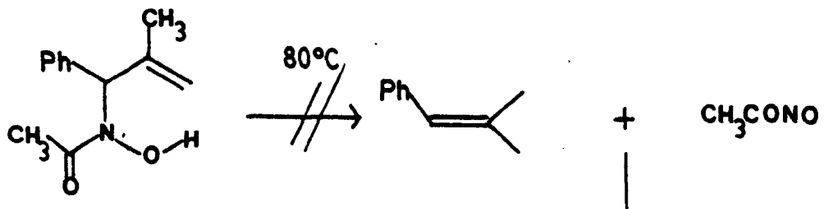
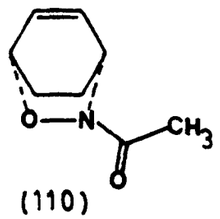
(108)



(109)

(Scheme 13)

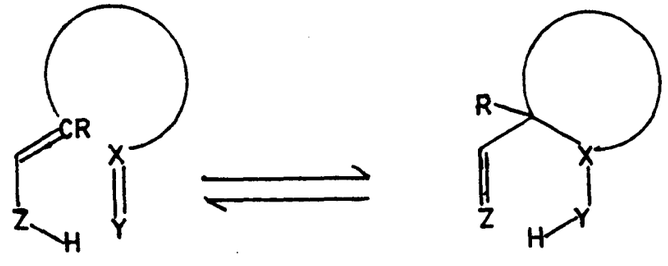


(110)

being transient species, were generated by heating their DMA adducts in solutions of allylic olefins. The nitroso-compound was thus released slowly into the solution. The concentration was thereby kept small thus reducing the possibility of bimolecular decomposition. The sole products obtained were the corresponding N-allylhydroxamic acids, the result of an intermolecular ene reaction. An example of this was the nitrosocarbonyl analogue of Allessandri's[49] reaction of safrole and nitrosobenzene. The DMA/nitrosocarbonylbenzene adduct (6b) was heated in solution with safrole and, after some hours, DMA and the N-allylhydroxamic acid (104) were obtained in good yield (Scheme 12). Thus it appears that N-allylhydroxamic acids are much more stable than the corresponding hydroxylamines. The ene reactions of C-nitrosocarbonyl compounds are very slow compared to their Diels-Alder additions to conjugated dienes, therefore reaction with dienes nearly always produces cycloadducts. This is not the case with 2,5-dimethylhexa-2,4-diene (105) however. As this diene cannot readily adopt a cisoid formation it does not undergo a Diels-Alder reaction, instead it reacted slowly with nitrosocarbonylbenzene to give only the ene product (106) (Scheme 12).

Recently Keck and Yates[72] investigated the reaction of nitrosocarbonylmethane with a series of olefins. The DMA/nitrosocarbonylmethane adduct (6a) was heated in benzene with an excess of the olefins for periods of 24 hours or longer to complete the reactions. As before, N-allylhydroxamic acids were obtained in good yield. They reported that both 1-phenylcyclohexene and 1-methylcyclohexene

TYPE 1



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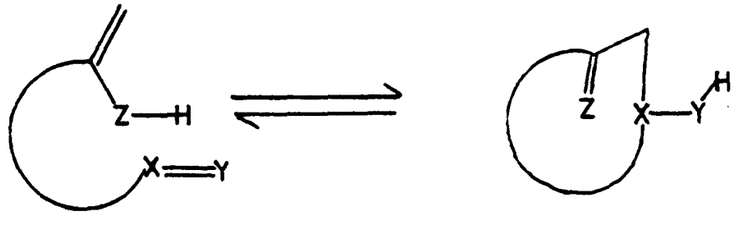

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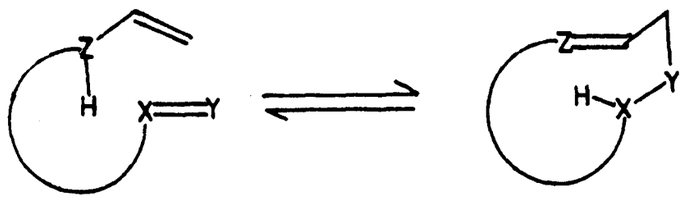
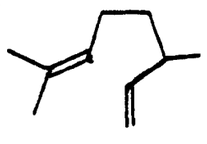


(Scheme 14)



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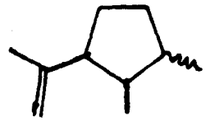
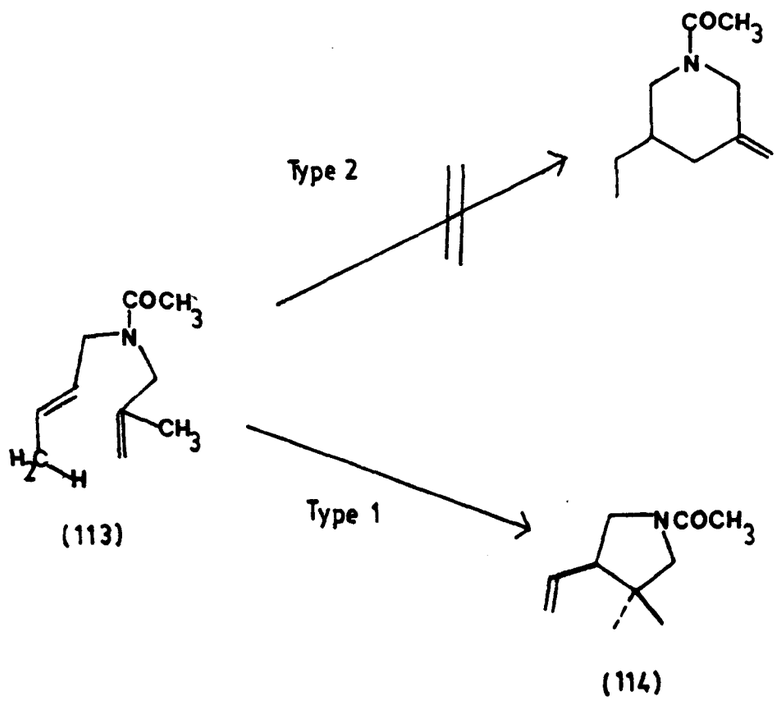


(112)

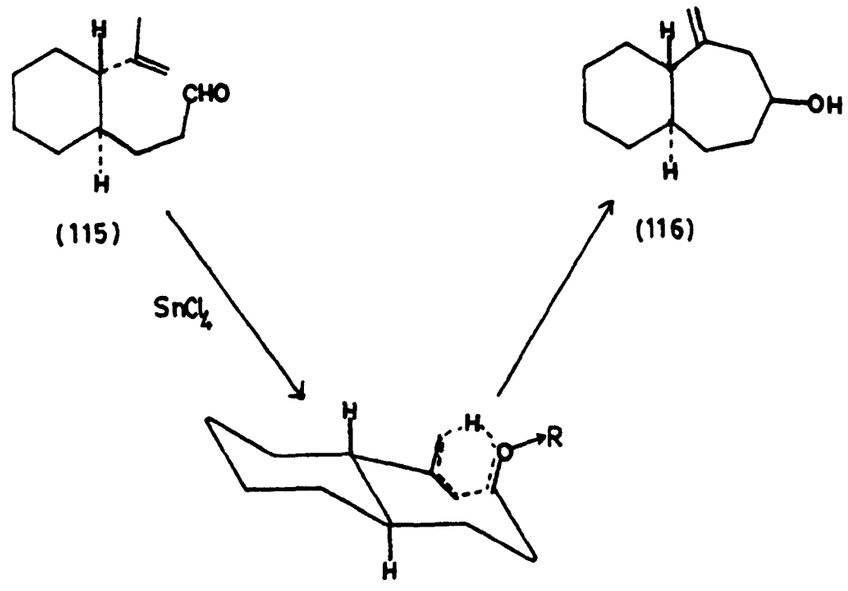
reacted with nitrosocarbonylmethane to give only one of two possible ene products, the N-allylhydroxamic acids (107) and (108) respectively. They speculated that the observed regiospecificity was in agreement with expectation for a two step, or concerted non-synchronous process with formation of the C-N bond first. When the N-allylhydroxamic acid (109) was heated in solution with cyclohexa-1,3-diene for 5 days it was recovered unchanged. As cyclohexa-1,3-diene is an efficient trapping agent for nitrosocarbonyl compounds, and the cyclohexadiene/nitrosocarbonylmethane adduct (110) is stable under the reaction conditions, it was deduced that the observed regiospscificity resulted from kinetic rather than thermo-dynamic control (Scheme 13).

3.2 The Intramolecular Ene Reaction.

Although examples of the intramolecular ene reaction have been known for many years, its synthetic utility has become recognised only relatively recently. The intramolecular ene process has obvious entropic advantages over the intermolecular reaction and shows useful regioselectivity. The scope, limitations, and synthetic utility of the intramolecular process have been extensively reviewed by Oppolzer.[73] He defined three different modes of thermally induced cyclisations. In a Type 1 cyclisation the enophile is initially attached to the olefinic terminal of the ene unit. In a Type 2



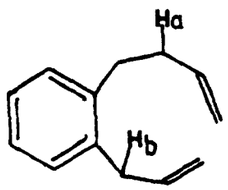
(Scheme 15)



(Scheme 16)

cyclisation attachment is to the central atom of the ene unit and in a Type 3 cyclisation to the allylic terminal of the ene unit (Scheme 14).

The majority of intramolecular ene reactions that have been reported were Type 1 cyclisations, and most of these concerned the thermolysis of 1,6-dienes. Huntsman[74] in his study of this reaction showed that the 1,6-diene (111) cyclised at 450°C to the isopropenylcyclopentane (112) by a non-radical mechanism. This exemplifies the fact that, in the intramolecular ene reactions of 1,6-dienes, C-C bond formation occurs between the closest olefinic termini leading to five-membered rings. In 1,6-dienes the Type 2 cyclisation occurs less readily than the Type 1. An illustration of this is the thermal cyclisation of the N-allyl-N-(but-2-enyl)amide (113) which offers internal competition between Type 1 and Type 2 cyclisation. It was found[75] that the almost exclusive product was the pyrrolidine derivative (114), the product of a Type 1 cyclisation (Scheme 15). The commonest examples of the Type 2 process are the Lewis acid catalysed cyclisations of unsaturated ketones and aldehydes. A good example of this is the stannic chloride catalysed cyclisation of the olefinic aldehyde (115). Anderson et al.[76] found that the only product was an ortho-fused cycloheptanol with an exocyclic double bond. X-Ray studies showed that the sole diastereoisomer (116) formed had an axial (β) hydroxyl group. This product is consistent with a concerted Type 2 ene mechanism (Scheme 16). The few reports of Type 3 cyclisations mainly



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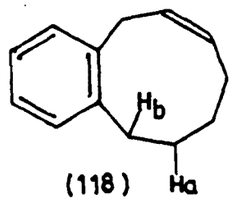

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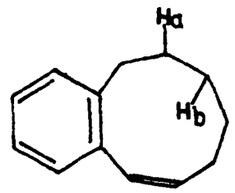

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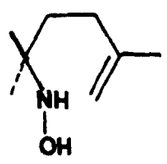

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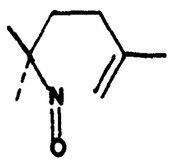

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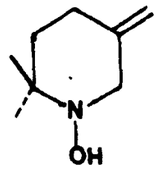

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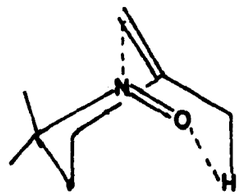
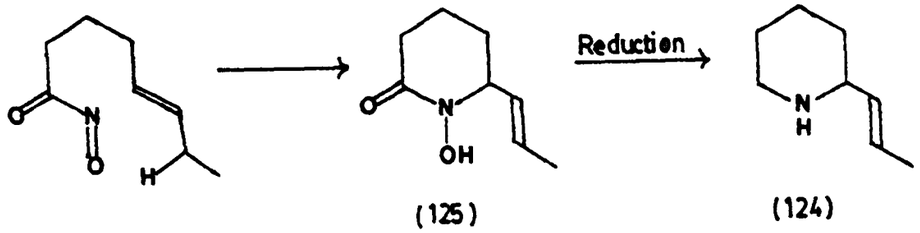


(123)

deal with the thermolysis of α,ω-dienes to cycloalkanes, for example the 1,8-diene (117) gave a mixture of cycloalkanes (118) and (119) when heated at 350°C.[77]

Although there are many examples of their intermolecular ene reactions, the participation of nitroso-groups in intramolecular ene processes has been rarely tested. In one of the few reports Roberts and Motherwell[69] found that the oxidation of the unsaturated hydroxylamine (120) with diethyl azodicarboxylate yielded the nitroso-olefin (121) which rapidly rearranged at room temperature to the new cyclic hydroxylamine (122). They proposed that the ready formation of this compound was achieved by an intramolecular ene reaction via the bicyclo[3.3.1] transition state (123). As can be seen, this is a Type 2 cyclisation as defined by Oppolzer.[73]

While our own work in this field was in progress, two papers of direct relevance were published. The first of these was by Keck and Webb[78] on the intramolecular ene reaction of C-nitrosocarbonyl compounds, and the second by Vedejs and Meier[79] on the intramolecular insertion of acylazocarboxylates. They are discussed fully in the following chapter.



(Scheme 17)

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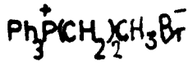

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Chapter 4.

The Intramolecular Ene Reaction in Nitrosocarbonyl Compounds.

4.1 C-Nitrosocarbonyl Compounds.

It was our intention to investigate the intramolecular ene reaction of C-nitrosocarbonyl compounds. On the commencement of our work in this area no examples of this reaction had been reported, although examples of the intermolecular ene reaction occurring in C-nitrosocarbonyl compounds were known.[71, 72.]

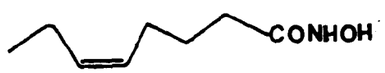
As an illustration of the possible synthetic applications of the intramolecular ene reaction of C-nitrosocarbonyl compounds we planned to synthesise the alkaloid β-coniceine (124). The N-hydroxy-δ-lactam (125) is potentially available from a Type 1 (see Chapter 3) intramolecular ene reaction of 1-nitrosocarbonylhept-4-ene. Reduction of the δ-lactam (125) would then give β-coniceine (124) (Scheme 17). Our first synthetic objective was therefore oct-5-enoic acid (126) (cis- or trans-double bond; see later).

There was a literature preparation[80] of oct-5-enoic acid. In this synthesis but-1-yne was treated with sodamide, and 1-chloro-3-iodopropane was added to the resultant carbanion to give 1-chlorohept-4-yne. Treatment of this compound with sodium cyanide in refluxing acetone gave the corresponding nitrile compound, which was hydrolysed in refluxing aqueous sodium hydroxide to yield oct-5-ynoic acid. Partial catalytic hydrogenation of this acetylene acid gave cis-oct-enoic acid, whereas sodium-liquid ammonia reduction gave trans-oct-5-enoic acid. In our hands, however, this preparation could not be

made to work.

It was planned to prepare oct-5-enoic acid (126) *via* the corresponding alcohol, oct-5-en-1-ol (127). The unsaturated alcohol (127) was obtained from a Wittig reaction between triphenylphosphonium propylide and 5-hydroxypentanal. Bromotriphenylpropylphosphorane (128) was made by heating n-propyl bromide and triphenylphosphine together in a sealed vial at 150°C. The m.p. of the resultant crystalline solid was in agreement with that in the literature.[81] Treatment of a suspension of the phosphonium salt (128) in THF with n-butyl-lithium produced the corresponding ylid, which, on addition of 5-hydroxypentanal, gave oct-5-en-1-ol (127) in high yield, as a mobile liquid. In the n.m.r. spectrum of the alcohol (127), a multiplet at δ 5.32 was assigned to the two olefinic protons and a well defined triplet at δ3.61, J 7 Hz, was attributed to the methylene protons adjacent to the hydroxyl group. The resonances of the two allylic protons adjacent to the methyl group were observed as a broad multiplet at δ1.98. A broad triplet at δ 2.00, J 7 Hz, was attributed to the other two allylic protons and the signal due to the hydroxyl group (exchangeable with D_2O) was a broad singlet. The methyl protons absorbed as a triplet at δ0.90, J 7 Hz. Recently, Schroder and Griffith[82] reported a new method for oxidising alcohols specifically to carboxylic acids in high yield. Following their procedure, a catalytic amount of ruthenium trichloride was added to an aqueous alkaline solution of potassium persulphate. The resulting solution was orange in colour, indicative of the species $[RuO_4]^{2-}$, and upon

addition of oct-5-en-1-ol it turned green. The alcohol was slowly oxidised by the catalytic amount of $[RuO_4]^{2-}$, which in turn was regenerated by the persulphate, functioning as a secondary oxidant. The aqueous solution reverted to an orange colour after one day, indication that the reaction was complete. Acidification and extraction of the solution gave oct-5-enoic acid (126) as an oil in high yield. A broad band at 3 000 cm^{-1} and a band at 1 720 cm^{-1} in the i.r. spectrum of this oil corresponded to the O-H and carbonyl stretching vibrations of the carboxyl group respectively. The proton n.m.r. spectrum of the unsaturated acid (126) contained a broad singlet at δ10.75 which was attributed to the acidic proton (exchangeable with D_2O). Signals for the olefinic protons were observed as a multiplet at δ 5.35, and the methylene protons α to the carboxylgroup gave a triplet at δ 2.32, J 7 Hz. A triplet at δ 0.90, J 7 Hz, was assigned to the methyl protons. The ^{13}C n.m.r. spectrum of the carboxylic acid (126) showed 8 singlets. The signal at δ 180.5 was attributed to the carbonyl carbon and signals at δ 133.0 and 127.7 were assigned to the two olefinic carbons, 6-C and 5-C. There appeared to be only one geometrical isomer of the unsaturated acid (126) present, as only two olefinic carbon signals were observed. From literature precedents the compound obtained from the Wittig reaction was probably the cis-isomer, but either isomer was useful for our purposes. The ethyl ester of oct-5-enoic acid was made by stirring the acid in ethanolic hydrogen chloride. Treatment of ethyl oct-5-enoate with hydroxylamine and sodium ethoxide in ethanol yielded



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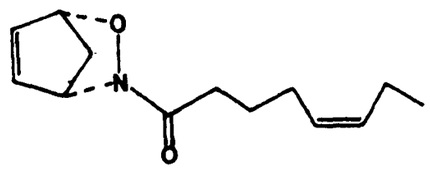

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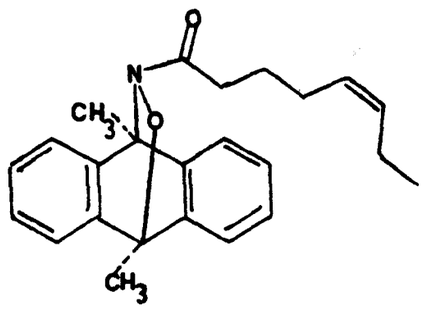

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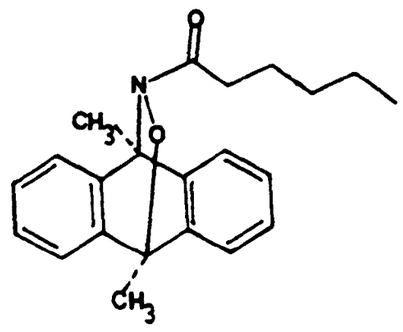


(132)

oct-5-enohydroxamic acid (129) upon acidification and extraction. The i.r. spectrum of the hydroxamic acid (129) showed a broad band at 3 300 cm^{-1} corresponding to N-H and O-H stretching vibrations, and a band at 1 670 cm^{-1} was attributed to the carbonyl stretching vibration. The n.m.r. signal for the N-H and O-H protons (exchangeable with D_2O) appeared as a broad singlet at δ8.52. A multiplet at δ5.35 was assigned to the two olefinic protons. Oct-5-enohydroxamic acid gave a violet colour with ethanolic ferric chloride.

It was hoped that 1-nitroso-carbonylhept-4-ene, generated by the oxidation of oct-5-enohydroxamic acid in solution, would undergo an intramolecular ene reaction. To test this the hydroxamic acid (129) was added to a stirred solution of tetraethylammonium periodate in methylene chloride. The dark brown oil obtained after work-up of the reaction mixture showed many spots on t.l.c. The proton n.m.r. spectrum of this oil was very confused but one of the components was seen to be oct-5-enoic acid. It was thought that one reason for the failure of the above experiment was that the desired product (125), also a hydroxamic acid, might have been oxidised, if formed.

As seen in Chapter 2.1, another method of generating C-nitroso-carbonyl compounds is the thermal dissocation of their cyclopentadiene or DMA adducts. Accordingly oct-5-enohydroxamic acid was oxidised in the presence of cyclopentadiene to give the cyclopentadiene/1-nitroso-carbonylhept-4-ene adduct (130) as an amber oil after chromatography. In the proton n.m.r. spectrum of the adduct (130) a doublet of

multiplets at δ6.45 was attributed to the cis olefinic protons of the cyclopentene ring. A multiplet of relative intensity 4 at δ 5.35 was assigned to the bridgehead methine protons and the side-chain olefinic protons. The cyclopentadiene adduct (130) was then heated in boiling benzene and solvent distilled from the solution, the solution level being maintained by occasional addition of benzene. The idea was that cyclopentadiene released by the thermal dissociation of the adduct (130) would co-distill with the benzene thus pushing the reaction towards completion. The course of the reaction was followed by t.l.c. and judged to be complete after 24 hours when no adduct remained. Evaporation of solvent yielded an intractable brown oil which had a complex n.m.r. spectrum. It seemed possible that this extended period of heating at 80°C might have led to the decomposition of the desired cyclic hydroxamic acid (125), if it had indeed been formed. It was known that the DMA/nitrosocarbonylbenzene adduct (6b) decomposed after ca. 4 hours at 80°C in benzene to DMA and benzoic anhydride, thus it was reasoned that the thermolysis of the DMA adduct of 1-nitrosocarbonylhept-4-ene (131) would come to completion after a similar length of time and thereby the chance of product decomposition would be decreased. Oct-5-enohydroxamic acid (129) was oxidised with tetraethylammonium periodate in the presence of DMA. The proton n.m.r. spectrum of the resultant yellow solid revealed that it was a 1:1 mixture of DMA and the DMA/1-nitrosocarbonylhept-4-ene adduct (131). Among the peaks attributed to the adduct (131) were a

multiplet at δ 5.20 corresponding to the olefinic protons of the alkenyl chain and a triplet at δ 0.90 assigned to the methyl protons. Most significant, however, were the signals attributed to the two methyl groups of the anthracene part of the adduct (131). These signals both appeared as sharp singlets upfield from their position in DMA, the methyl group β to the oxygen atom at δ 2.66 and the methyl group β to the nitrogen atom at δ 2.16. Attempts to separate the mixture by various chromatographic methods all led to the decomposition of the DMA adduct (131)to yield an unidentified, white crystalline solid. The i.r. spectrum of this solid showed no O-H or carbonyl stretching bands, only aromatic and aliphatic C-H stretching bands. The only signals in the proton n.m.r. spectrum of this solid were a multiplet in the aromatic region and a sharp singlet at δ 2.10. The relative intensity of these peaks was 4:3, indicating that the solid was possibly a dimer of DMA. The DMA adduct (131) decomposed to DMA, among other things, on attempts at crystallisation. As it appeared that DMA was an inefficient trap for 1-nitrosocarbonylhept-4-ene and the impure DMA/1-nitrosocarbonylhept-4-ene adduct (131) could not be easily purified, it was planned to synthesise the adduct by another route.

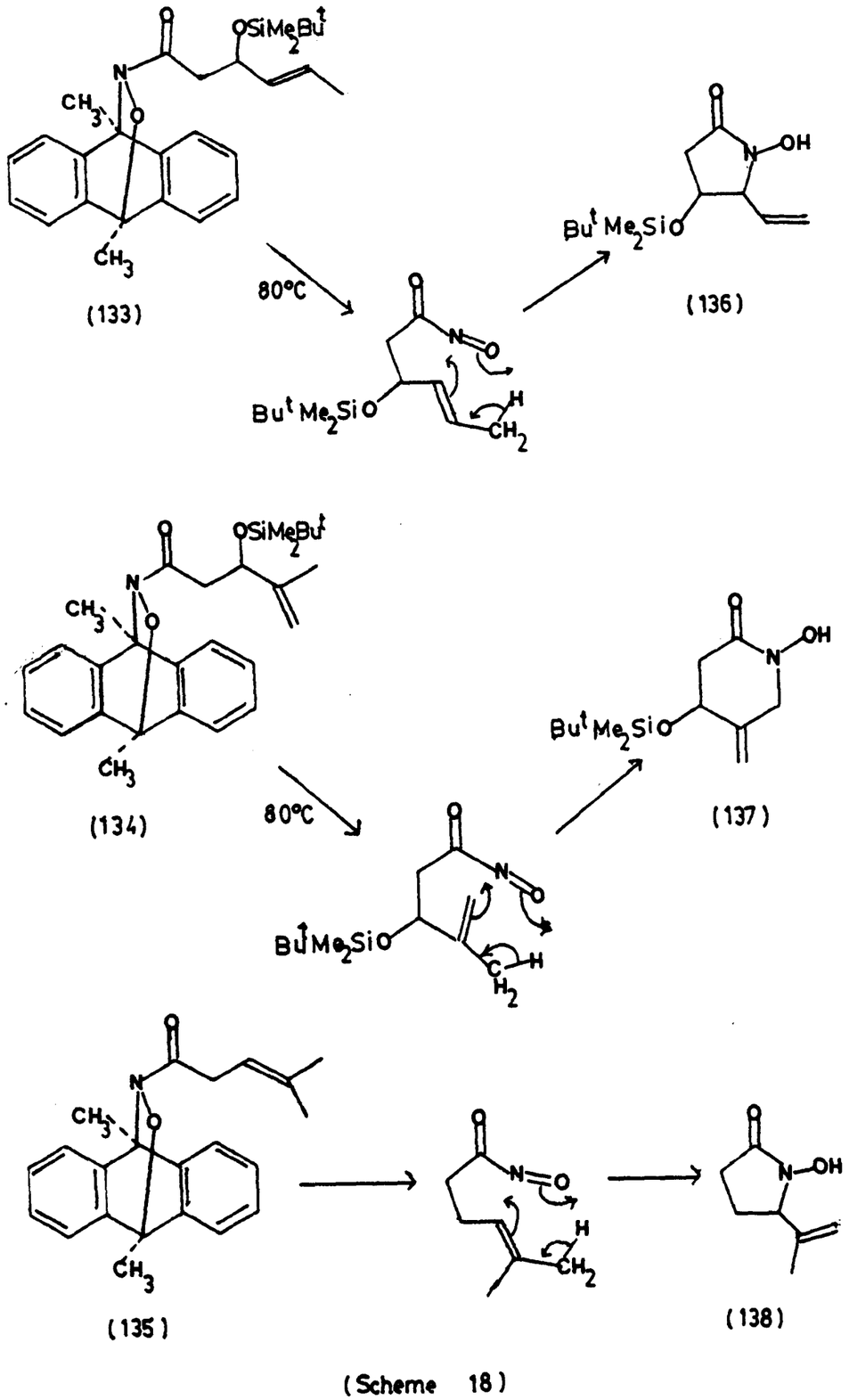
The DMA/HNO adduct (76) was prepared by the reported method[44] which involved de-acylation of the DMA/nitrosocarbonylmethane adduct (6a) with sodium ethoxide. Dilution with diethyl ether and saturation of the solution with hydrogen chloride caused precipitation of the adduct (76) as its hydrochloride. It was thought acylation of

the DMA/HNO adduct with oct-5-enoyl chloride would lead to a more efficient preparation of the DMA/1-nitrosocarbonylhept-4-ene adduct (131). As a test of the feasibility of this reaction, hexanoic acid was heated with thionyl chloride and the resultant acid chloride added to a solution of the hydrochloride of the DMA/HNO adduct in pyridine. The DMA/1-nitrosocarbonylpentane adduct (132) was isolated from the reaction mixture as a yellow solid and crystallised after chromatography. The i.r. spectrum of the adduct showed a carbonyl stretching band at 1 674 cm^{-1}. There was a multiplet in the aromatic region of the adduct's n.m.r. spectrum and two sharp singlets at δ 2.68 and 2.18 attributed to the methyl groups β to the oxygen and nitrogen atoms respectively. Oct-5-enoyl chloride, prepared as above, was likewise added to a pyridine solution of the hydrochloride of the DMA/HNO adduct. The resultant yellow solid was a mixture of DMA and the DMA/1-nitrosocarbonylhept-4-ene adduct in the ratio 1:3 (by ^1H n.m.r. spectroscopy). The DMA adduct (131) was separated as an orange oil by fast elution of the mixture through a florisil column, but could not be fully characterised due to its instability.

The initial 1:1 mixture of DMA and the adduct (131) was heated in benzene at 80°C for 3 hours. Evaporation of solvent yielded a yellow solid that showed 3 spots on t.l.c. analysis corresponding to DMA, oct-5-enoic acid, and a ferric active material. The proton n.m.r. spectrum of the mixture confirmed the presence of DMA and oct-5-enoic acid. It also showed a doublet at δ 1.68 and a multiplet at δ 5.6 attributable to the ferric active material. Elution of the mixture

through a florisil column separated the ferric active material as a brown oil which remains unidentified. The purified DMA/1-nitroso-carbonylhept-4-ene adduct was then thermolysed in hot benzene as above. The n.m.r. spectrum of the solid obtained on evaporation of solvent showed only signals corresponding to DMA and oct-5-enoic acid and t.l.c. analysis showed no ferric active spot.

It seemed possible that the very impure brown oil obtained from the thermolysis of the mixture did contain some of the desired N-hydroxy-δ-lactam (125). The lactam (125) would be a ferric active material, being a hydroxamic acid, and the proton n.m.r. spectrum of this compound would have olefinic signals in the region δ 5-6 and signals at ca. δ 1.6 corresponding to a vinylic methyl group with coupling to the olefinic protons. If the cyclisation had indeed occurred, to a small extent, in the thermolysis of the mixture then a reason had to be found for its non-occurrence in the thermolysis of the purified adduct (131). One possible explanation was that the intramolecular ene reaction of 1-nitrosocarbonylhept-4-ene was a slow process. Thus, when the DMA adduct (131) was heated, an appreciable concentration of the free C-nitrosocarbonyl compound built up. As the concentration of this compound increased so did the rate of its bimolecular decomposition to N_2O and oct-5-enoic anhydride. In the thermolysis of the purified DMA adduct (131), the concentration of the 1-nitrosocarbonylhept-4-ene was of sufficient size that the rate of decomposition exceeded that of cyclisation. When the mixture of the DMA adduct (131) and DMA was heated, the concentration of the free

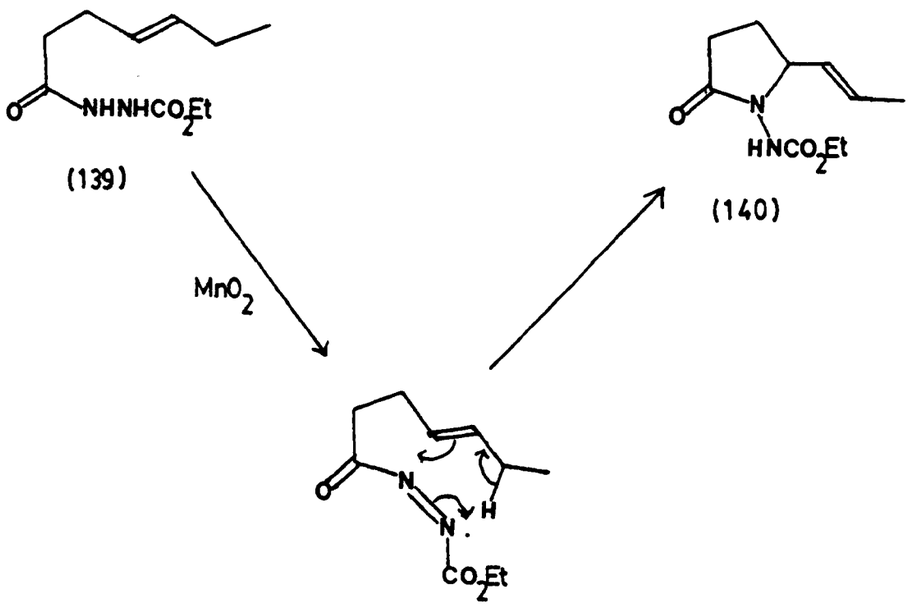


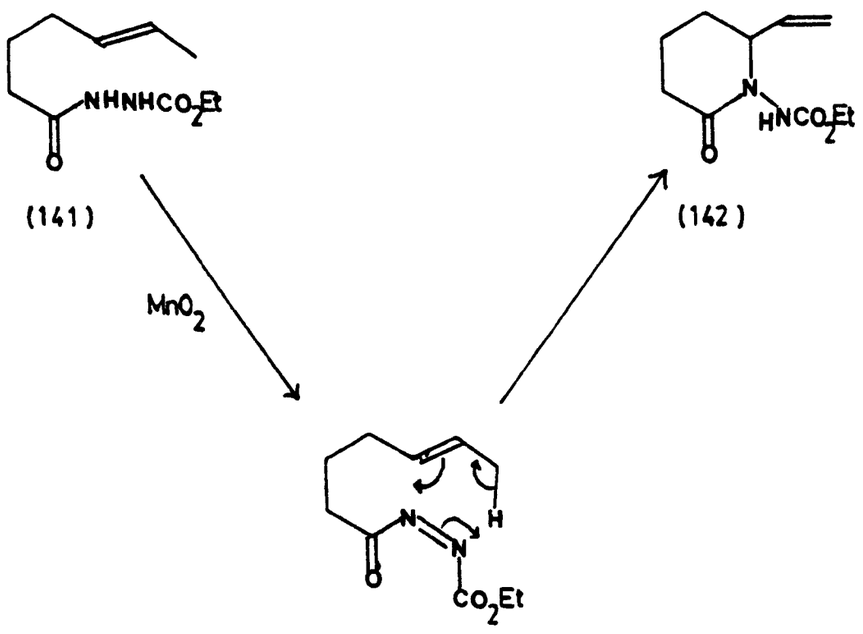
(Scheme 18)

C-nitrosocarbonyl compound was smaller than in the above case at any one time, due to there being more DMA to trap the species. Thus the rate of bimolecular decomposition of 1-nitrosocarbonylhept-4-ene was slightly slower and so some of it managed to cyclise, although most decomposed.

At this point in our work, Keck and Webb[78] reported three examples of the intramolecular ene reaction in C-nitrosocarbonyl compounds. They prepared the DMA adducts (133) and (134) by condensing the enolate of the DMA/nitrosocarbonylmethane adduct with the unsaturated aldehydes methacrolein and crotonaldehyde and silylating the resultant compounds. Similarly, treatment of the enolate with 1-bromo-3-methylbut-2-ene gave the DMA adduct (135). The adducts (133), (134), and (135), when heated in refluxing benzene, slowly underwent retro-Diels-Alder cleavage. The liberated C-nitroso-carbonyl compounds took part in intramolecular ene reactions to give the cyclic hydroxamic acids (136), (137), and (138) in quantitative yield, after 3 hours refluxing (Scheme 18). Inspection of the products showed that compounds (136) and (138) arose from Type 1 intramolecular ene reactions. Compound (137) arose from a Type 2 ene reaction of the corresponding C-nitrosocarbonyl compound (as defined in Chapter 3.2).

A later paper by Vedejs and Meier[79] illustrated the intra-molecular ene reaction of acylazocarboxylates. Oxidation of the hydrazide (139) in methylene chloride with MnO_2 gave a transient orange colour, attributed to the corresponding azo-compound, which





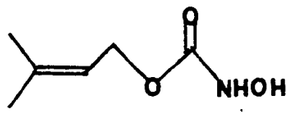
(Scheme 19)

faded after a few minutes. Compound (140), the product of Type 1 intramolecular ene reaction of the intermediate acylazocarboxylate, was isolated in good yield as a crystalline solid. Likewise, MnO_2 oxidation of the hydrazide (141) produced compound (142), also via a Type 1 intramolecular ene reaction of the corresponding intermediate acylazocarboxylate (Scheme 19).

After the publication of the work of Keck and Webb there seemed little point in proceeding with our own, very similar, work in this area. In any case, it appeared that 1-nitrosocarbonylhept-4-ene, was not a good model to illustrate the intramolecular ene reaction in C-nitrosocarbonyl compounds, possibly due to unfavourable geometry in the transition state. We therefore decided to turn our attention to the intramolecular ene reactions of nitrosoformates, ROCONO. It was already known (Chapter 2.1) that the thermal transfer of a nitrosoformate from its cyclopentadiene adduct to another diene was a more facile process than the corresponding transfer of a C-nitrosocarbonyl compound. It was hoped, therefore, that the thermolysis of cyclopentadiene/nitrosoformate adducts would occur at a sufficient rate that the use of DMA adducts would be unnecessary in these studies. This would be advantageous because, as already seen, DMA adducts are more difficult to prepare and purify than cyclopentadiene adducts. DMA is also much more expensive than cyclopentadiene.

4.2 The Intramolecular Ene Reaction in Nitrosoformates.

We planned to study the intramolecular ene reactions of some



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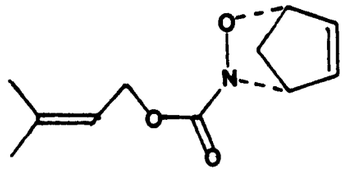

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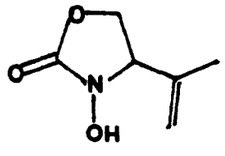

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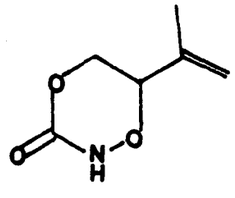
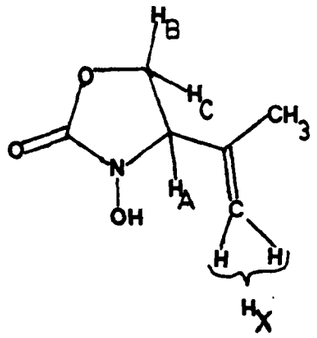


(146)

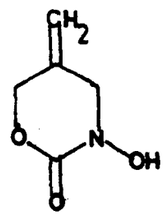
allylic and homoallylic nitrosoformates. It had already been shown by Keck[78] that 1-nitrosocarbonyl-4-methylpent-3-ene underwent a Type 1 intramolecular ene reaction to give the cyclic hydroxamic acid (138), therefore initially we decided to investigate the oxygen analogue of this C-nitrosocarbonyl compound, 3,3-dimethylallyl nitrosoformate. The chloroformate of 3,3-dimethylallyl alcohol was made by stirring the alcohol in a toluene solution containing phosgene at -40°C for 3 hours. The chloroformate solution was then shaken with aqueous, alkaline hydroxylamine. Acidification and extraction of the reaction mixture gave a yellow oil which yielded N-(3,3-dimethylallyloxycarbonyl)hydroxylamine (143) after chromatography. The i.r. spectrum of the hydroxamic acid (143) showed a carbonyl stretching band at 1 715 cm^{-1} and an O-H and N-H stretching band at 3 300 cm^{-1} . The N-H and O-H protons absorbed at δ 7.60 in the n.m.r. spectrum and were exchangeable with D_2O. A triplet of multiplets at δ 5.39, J 8 Hz, was attributed to the olefinic proton, and a doublet at δ 4.61, J 8 Hz, was assigned to the vinylic methylene group. The two vinylic methyl groups absorbed at δ 1.70. Although it was expected that cyclisation would not occur sufficiently rapidly, the hydroxamic acid (143) was oxidised with periodate in methylene chloride. A brown oil was obtained which showed numerous spots on t.l.c. It is possible that the oxidation produced the nitrosoformate in too high a concentration and, instead of cyclising intramolecularly, it decomposed bimolecularly.

As previously stated, it was thought that the retro-Diels-Alder

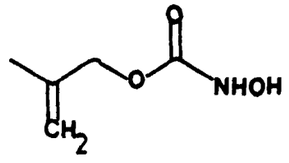
cleavage of cyclopentadiene adducts of unsaturated nitrosoformates would generate the nitrosoformates at a rate slow enough to avoid bimolecular decomposition, and fast enough to minimise thermal decomposition of product. Accordingly the hydroxamic acid (143) was oxidised in the presence of cyclopentadiene to give the cyclopentadiene/3,3-dimethylallyl nitrosoformate adduct (144) as an oil. In the n.m.r. spectrum of the adduct (144) a broad singlet at δ 6.41 was attributed to the olefinic protons of the cyclopentene ring. The olefinic proton of the allyl group gave a triplet of multiplets at δ 5.35, $\underline{J}$ 8 Hz, and a broad doublet at δ 4.62, $\underline{J}$ 8 Hz, was assigned to the two allylic protons. The bridgehead methine protons absorbed as two broad singlets at δ 5.24 and 5.04. A broad doublet at δ 1.99, $\underline{J}$ 9 Hz, was attributed to one of the methylene protons of the cyclopentene ring. The cyclopentadiene adduct (144) was heated in benzene at 80°C under a nitrogen atmosphere and the course of the reaction was followed by t.l.c. After 3 hours, the reaction was judged to be complete as no spot corresponding to the adduct (144) remained. Evaporation of solvent gave a brown oil which crystallised from hexane as white needles. Elemental analysis and mass spectroscopy revealed that the solid had the formula $C_6H_9NO_3$, which was in agreement with the $\underline{N}$-hydroxy-oxazolid-2-one (145) and also with the dioxazinone (146). Both are products of Type 1 intramolecular ene reactions and arise from different modes of attack of the N=O enophile. The oxazolid-2-one (145) was favoured as the structure of the solid because of the previously reported cyclisation of the analogous 1-nitrosocarbonyl-4-



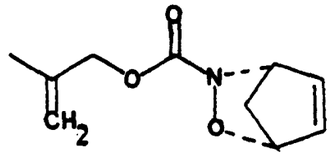
(Fig. 2)



(147)



(148)



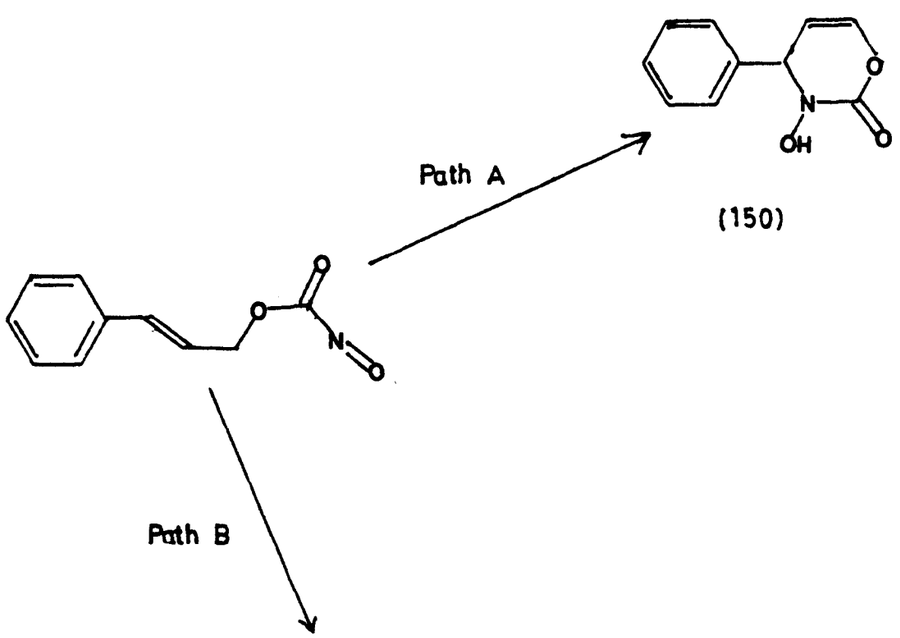
(149)

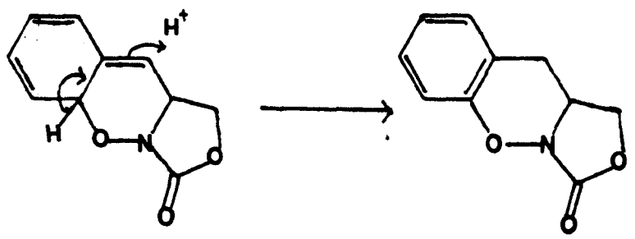
methylpent-3-ene to the 5-membered ring hydroxamic acid (138). The proton n.m.r. spectrum of the compound was very complex and was interpreted by computer simulation of the 100 and 360 MHz spectra. This revealed that the spectra showed an ABCX system and gave values for the coupling constants and chemical shifts of protons A, B, C, and X (Fig. 2). Proton H_A absorbed at δ 4.43 and had couplings J_{AB} 8.5 Hz, J_{AC} 8.6 Hz, and J_{AX} 0.5 Hz. Proton H_B gave a signal at δ4.41, J_{BA} + 8.5 Hz, and J_{BC} -8.7 Hz, and H_C absorbed at δ 4.02, J_{CA} +8.6 Hz and J_{CB} -8.7 Hz. One of the exo-methylene protons (H_x) gave a doublet at δ 5.14, J_{XA} 0.5 Hz. The off-resonance decoupled ^{13}C n.m.r. spectrum showed a singlet at δ 161.1 attributed to the carbonyl carbon, and another singlet at δ 139.1 was assigned to the di-substituted olefinic carbon. The exo-methylene group absorbed as a triplet at δ 117.0 and the vinylic methyl group gave a quartet at δ 29.7 A triplet at δ 65.8 was attributed to the methylene group adjacent to oxygen, but it could not be decided whether the doublet at δ 64.8 corresponded to a methine carbon adjacent to a nitrogen or to an oxygen atom. Thus the carbon-hydrogen backbone of the molecule had been delineated and findings did agree with the oxazolid-2-one (145) structure. However the dioxazinone structure (146) still could not be ruled out as a possibility. The solution i.r. spectrum of the compound showed a band at 3 250 cm^{-1} corresponding to O-H or N-H stretching vibrations. The carbonyl stretching band was at 1 775 cm^{-1}, which is in close agreement to the frequency of the carbonyl stretching vibration of oxazolid-2-one at 1 760 cm^{-1}.[83] Further

arguments in support of structure (145) will be discussed later.

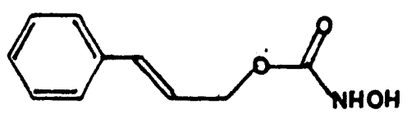
It was thought that the simplest allylic nitrosoformate that could possibly demonstrate the Type 2 intramolecular ene reaction was 2-methylprop-2-enyl nitrosoformate. Inspection of models suggested that a Type 2 process would be favoured. Thus the expected product was the N-hydroxy-oxazin-2-one (147). 2-Methylprop-2-enyl chloroformate was made by stirring 2-methylprop-2-en-1-ol in a solution of phosgene in toluene at 0°C for 3 hours. The chloroformate solution was added to aqueous, alkaline hydroxylamine and shaken for 1 hour. The yellow oil obtained on work-up was chromatographed to give N-(2-methylprop-2-enyloxycarbonyl)hydroxylamine (148) as a colourless oil. The N-H and O-H, and carbonyl stretching vibrations were observed in the i.r. spectrum of the hydroxamic acid at 3 300 and 1 720 cm^{-1} respectively. In the n.m.r. spectrum, the N-H and O-H protons absorbed at δ 7.72 and were exchangeable with D_2O. The olefinic protons gave broad singlets at δ 4.98 and 4.92, and the vinylic methylene group absorbed as a singlet at δ 4.55. A singlet at δ 1.71 was attributed to the vinylic methyl group. Treatment of cyclopentadiene with 2-methylprop-2-enyl nitrosoformate, generated by the *in situ* oxidation of the hydroxamic acid (148), gave the cyclopentadiene/2-methylprop-2-enyl nitrosoformate adduct (149) as an oil, which was purified by distillation. The formula of the adduct (149) was verified by accurate mass measurement. Its n.m.r. spectrum showed a broad singlet at δ 6.42 due to the olefinic protons of the cyclopentene ring. The olefinic protons of the 2-methylprop-2-enyl

group absorbed at δ 4.95 and the bridgehead methine protons gave singlets at δ 5.25 and 5.05. The methylene protons of the cyclopentene ring gave an AB quartet at δ 1.98 and 1.76, J 9 Hz. The downfield doublet was attributed to the proton deshielded by the N-O bond, and was the broader of the two doublets as it had small w-couplings with the olefinic protons of the ring. The adduct (149) was heated in refluxing benzene under a nitrogen atmosphere. After 21 hours, n.m.r. spectroscopy showed that the mixture was still nearly 50% starting adduct. The reaction was judged to be essentially complete after 40 hours. Repetition of the thermolysis in refluxing toluene shortened the reaction time to 9 hours. The oil obtained from both reactions was purified by chromatography and crystallised to give the dihydro-1,3-oxazin-2-one (147) as needles. Elemental analysis and mass spectroscopy were both in agreement with the proposed structure (147). The proton n.m.r. spectrum of the oxazin-2-one (147) showed a broad singlet at δ 7.45 attributed to the O-H group (exchangeable with D_2O). The protons of the exo-methylene group gave a broad singlet at δ 5.24. The methylene group adjacent to oxygen gave a singlet at δ 4.61, and the methylene group adjacent to the nitrogen atom absorbed at δ 4.31 as a broad singlet. The proton-noise decoupled ^{13}C spectrum revealed the exo-methylene carbon's signal at δ 114.4 and the substituted olefinic carbon's signal at δ 133.3. The carbonyl carbon absorbed at δ 156.3 and the methylene carbon adjacent to oxygen at δ 70.1. The methylene carbon adjacent to nitrogen absorbed at δ 54.0. The carbonyl stretching band of the

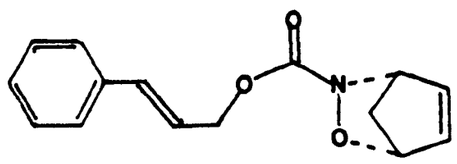




(Scheme 20)



(153)

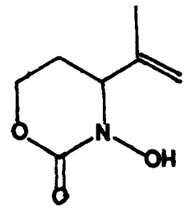


(154)

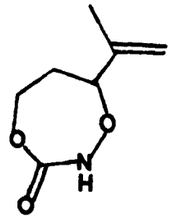
oxazin-2-one (147) appeared at 1 705 cm^{-1} and the O-H group gave a band at 3 220 cm^{-1}. The formation of the oxazin-2-one (147) by the thermolysis of the adduct (149) took considerably longer than the corresponding thermolysis of the adduct (144) to give the oxazolid-2-one (145). It is likely that the rates of dissociation and of recombination for both adducts were similar. Therefore it appears that the transition state required for the formation of compound (147) must be less favourable than the Type 1 transition state for production of the oxazolid-2-one (145). This has a parallel in Oppolzer's[73] observation that in 1,6-dienes and 1,7-dienes and the corresponding enones and dienols containing several allylic hydrogens, preference for hydrogen transfer follows the order Type 1>Type 2 > Type 3.

Cinnamyl nitrosoformate seemed worthy of investigation since there were, in principle, two possible routes for this moiety to react (Scheme 20). Path A involved a Type 3 intramolecular ene reaction, i.e. where the enophile is linked to the allylic terminal of the ene group, and would have resulted in the dihydro-oxazinone (150). The other proposed pathway (B) was an intramolecular Diels-Alder reaction of the nitrosoformate with the aromatic system acting as a diene to give the non-aromatic intermediate (151). It was thought that this would then re-aromatise to give compound (152). Initial attempts to form cinnamyl chloroformate by stirring the alcohol in a toluene solution of phosgene at 0°C led to the formation of cinnamyl chloride. It appeared that the chloroformate was being

formed but was thermally decomposing with loss of CO_2. The reaction was repeated at -78°C and, after 3 hours at this temperature, the reaction mixture was added with shaking to aqueous, alkaline hydroxylamine. N-(Cinnamyloxycarbonyl)hydroxylamine (153) was isolated from the reaction mixture and crystallised after chromatography. The composition of the hydroxamic acid (153) was confirmed by analysis and a mass spectrum. The i.r. spectrum showed N-H and O-H stretching bands at 3 320 cm^{-1} and a carbonyl stretching band at 1 695 cm^{-1}. The N-H and O-H protons, exchangeable with D_2O, gave a broad singlet at δ 7.65, and the aromatic protons absorbed at δ 7.32. The olefinic proton adjacent to the aromatic ring gave a doublet at δ 6.64, J 15 Hz, and the other trans olefinic proton absorbed at δ 6.25 as a doublet of triplets, J 15 Hz and 7 Hz. A doublet at δ 4.77, J 7 Hz, was attributed to the allylic protons. Oxidation of the hydroxamic acid (153) with periodate in the presence of cyclopentadiene produced the cyclopentadiene/cinnamyl nitrosoformate adduct (154) as an oil. This adduct crystallised after chromatography and was fully characterised. The proton n.m.r. spectrum of the adduct showed typical cyclopentadiene adduct features, such as the broad singlet at δ 6.24, attributed to the ring olefinic protons, and the AB quartet at δ 1.98 and 1.72, J 8 Hz, due to the methylene protons of the ring. The cyclopentadiene adduct (154) was dissolved in benzene and heated under reflux for 10 hours. An n.m.r. spectrum of the reaction mixture showed that no reaction had taken place. The adduct was then dissolved in toluene and heated under reflux for 16 hours. The n.m.r. spectrum of the oily black



(155)



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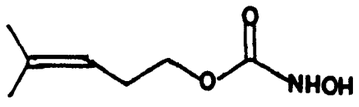
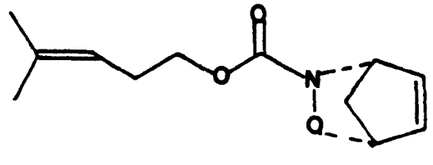


(157)

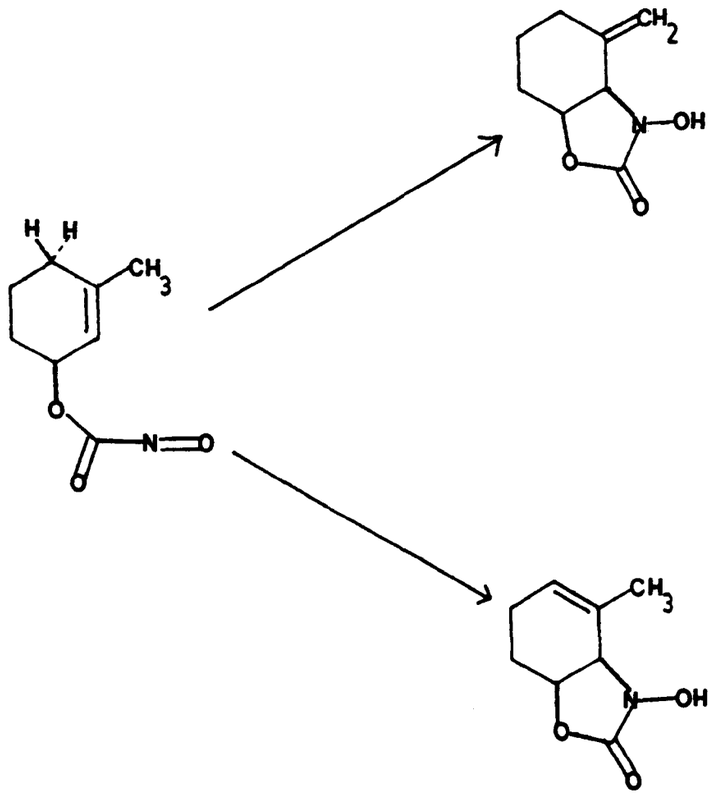


(158)

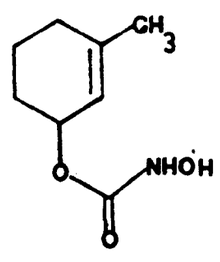
residue obtained on evaporation of solvent was very complex and t.l.c. analysis showed numerous spots. Thus the ene reaction (path A, Scheme 20) had not taken place, probably because the required transition state was too strained. There was a possibility that the nitrosoformate was reacting by path B and there was an equilibrium between the intermediate (151) and the nitrosoformate, but product (152) was not being produced, as the required suprafacial [1,3]sigmatropic proton shift is not a thermally allowed process. If this was the problem it was thought that catalysis by base would solve it. Thus the adduct (154) was heated in refluxing benzene with some NN'-di-t-butylformamidine. The latter was chosen as catalyst since it is a strong base of low nucleophilicity. After 21 hours, n.m.r. spectroscopy revealed that no reaction had taken place.

The homoallylic analogue of 3,3-dimethylallyl nitrosoformate, 4-methylpent-3-enyl nitrosoformate, was the next compound studied in this series. It was expected that this nitrosoformate would undergo a Type 1 intramolecular ene reaction to form the dihydro-oxazin-2-one (155). The alternative mode of cyclisation, with formation of an oxygen-carbon bond, was not considered likely in this case as this would involve formation of a 7-membered ring compound (156). Ethyl 4-methylpent-3-enoate was made by the literature method[84] and was reduced with di-isobutylaluminium hydride in anhydrous diethyl ether to give 4-methylpent-3-en-1-ol. The chloroformate of this alcohol was made by the usual method and treated with aqueous, alkaline hydroxylamine to give the hydroxamic acid (157) as an oil. The i.r. and n.m.r.

spectra of the hydroxamic acid (157) were consistent with expectations. Treatment of cyclopentadiene with 4-methylpent-3-enyl nitrosoformate, generated by the usual method, gave the cyclopentadiene/4-methylpent-3-enyl nitrosoformate adduct (158) as an oil which was purified by chromatography. The n.m.r. spectrum of this compound showed signals typical of cyclopentadiene adducts; a broad singlet at δ 6.42 attributed to the cyclopentene ring olefinic protons, two broad singlets at δ 5.24 and 5.04 due to the bridgehead methine protons, and a broad doublet at δ 1.99, J 9 Hz, assigned to one of the ring methylene protons. The adduct (158) was heated in refluxing benzene and the course of the reaction was followed by n.m.r. spectroscopy. After 3 hours, the reaction was *ca.* 55% complete, and after 8 hours it was essentially finished. Evaporation of solvent yielded the dihydrooxazin-2-one (155) as a brown oil. The oil was purified by chromatography but could not be crystallised. Accurate mass measurement confirmed the formula of the oxazin-2-one (155) and also showed that the major fragment ion corresponded to loss of an oxygen atom. There were bands in the i.r. spectrum of the compound at 3 210 and 1 705 cm^{-1} attributed to the O-H and carbonyl stretching vibrations respectively. The proton n.m.r. spectrum showed a broad singlet at δ 5.30, assigned to the O-H group (exchangeable with D_2O). The *exo*-methylene protons gave a singlet at δ 5.08, and a multiplet of relative intensity 3 at δ4.20 was attributed to the methylene protons adjacent to oxygen and the methine proton adjacent to nitrogen. The methyl group absorbed as a singlet at δ 1.64. The other methylene group gave a multiplet



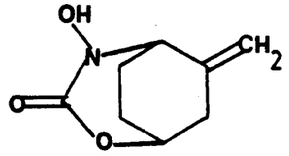
(Scheme 21)



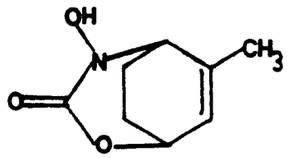
(159)

at δ 2.06, which on irradiation at δ 4.17 collapsed to an AB quartet, J 15 Hz. The off-resonance decoupled ^{13}C n.m.r. spectrum was also in agreement with structure (155). A singlet at δ 155.5 was attributed to the carbonyl carbon and another singlet at δ 141.2 to the fully substituted olefinic carbon. The exo-methylene carbon absorbed as a triplet at δ 114.0 and the methyl group gave a quartet at δ 18.4. An overlapping doublet and triplet at δ 63.7 were attributed to the methine group adjacent to nitrogen and the methylene group adjacent to oxygen. As foreseen, the homoallylic nitroso-formate did undergo a Type 1 intramolecular ene process, and though it did not proceed as fast as the previous Type 1 ene process of the allylic nitrosoformate, the reaction was still faster than the Type 2 ene reaction, as exemplified by 2-methylprop-2-enyl nitrosoformate.

It was believed that unsaturated alicyclic nitrosoformates would show some interesting regiospecificity in their intramolecular ene reactions, from which deductions about the geometrical requirements of the transition states of these reactions could be made. 3-Methyl-cyclohex-2-enyl nitrosoformate can, in theory, give two possible ene products (Scheme 21). As a first step in the generation of this nitrosoformate an attempt was made to prepare the corresponding hydrox-amic acid (159) by the usual method. Unfortunately, all attempts to prepare 3-methylcyclohex-2-enyl chloroformate by treatment of the corresponding alcohol with phosgene led, even at -78°C, to the isolation of a compound thought to be 3-methylcyclohex-2-enyl chloride. There were literature precedents for the extreme instability of this



(160)



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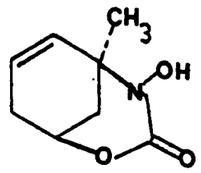
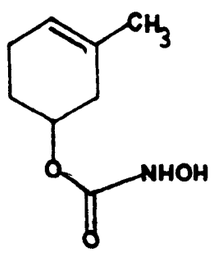
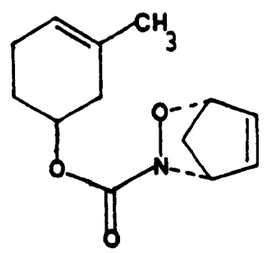


(162)



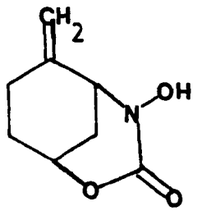
(163)



(164)

chloroformate. Olivier and Young[85] found that α-alkylallyl chloroformates, e.g. α-methylallyl chloroformate, decomposed ca. 40 times faster than benzyl chloroformate at 30°C. A paper[86] was also found which reported that attempts to form the acetate and benzoate of 3-methylcyclohex-2-en-1-ol all met with failure, dehydration being the result. It was decided, therefore, to study the corresponding, homoallylic isomer, 3-methylcyclohex-3-enyl nitrosoformate, which had three feasible intramolecular ene products, the bridged N-hydroxyoxazinones (160), (161), and (162). The sodium-liquid ammonia reduction[87] of 3-methylanisole gave 3-methylcyclohex-3-enone, which was further reduced with lithium aluminium hydride in diethyl ether to give 3-methylcyclohex-3-en-1-ol. The alcohol was stirred for 3 hours in a toluene solution of phosgene at 0°C, and the resulting chloroformate solution was treated with aqueous, alkaline hydroxylamine. The usual work-up of the reaction mixture gave a crystalline solid, the analysis, mass, n.m.r. and i.r. spectra of which were consistent with N-(3-methylcyclohex-3-enyloxycarbonyl)hydroxylamine (163). Oxidation of the hydroxamic acid (163) in the presence of cyclopentadiene gave the cyclopentadiene/3-methylcyclohex-3-enyl nitrosoformate adduct (164) as an oil which was purified by chromatography. The formula of the adduct (164) was confirmed by accurate mass measurement. The proton n.m.r. spectrum of the compound was consistent with expectations for a cyclopentadiene adduct, showing a singlet at δ 6.40 for the cyclopentene olefinic protons, two broad singlets at δ 5.24 and 5.04 for the bridgehead methine protons, and a broad doublet at δ 1.97, J 8 Hz, for one proton of the cyclopentene's

methylene group. The olefinic proton of the cyclohexene ring gave a broad singlet at δ 5.39 and the methyl group absorbed at δ 1.62 as a singlet. The cyclopentadiene adduct (164) was dissolved in benzene and heated under reflux in a nitrogen atmosphere. N.m.r. spectroscopy showed that 40% of the mixture was starting material after 6 hours heating, and after a further 10 hours the reaction was essentially complete. Solvent was evaporated and a brown oil obtained which crystallised from hexane. The analysis and mass spectrum of the solid were in agreement with all of the bridged N-hydroxy-oxazinones (160), (161), and (162). The n.m.r. spectra of the compound, however, proved unquestionably that the sole product was the N-hydroxy-oxazinone (160) bearing the exo-methylene group. The two exo-methylene protons absorbed as singlets at δ 5.18 and 4.98. Multiplets at δ 4.60 and 4.15 were attributed to the methine protons adjacent to oxygen and nitrogen respectively, and the vinylic methylene group gave an AB quartet at δ 2.97 and 2.55, J 18 Hz. In the off-resonance decoupled ^{13}C n.m.r. spectrum of the compound, the carbonyl carbon absorbed at δ156.6 as a singlet and the substituted olefinic carbon gave a singlet at δ 140.4. The exo-methylene carbon absorbed as a triplet at δ 113.8. Doublets at δ 75.8 and 64.1 were attributed to the bridgehead carbons adjacent to oxygen and nitrogen respectively, and a triplet at δ 34.6 was attributed to the vinylic methylene carbon. The other methylene carbons absorbed as triplets at δ 25.8 and 25.4. The intramolecular ene reaction of 3-methylcyclohex-3-enyl nitrosoformate cannot be defined as either a Type 1 or a Type 2 process as the ene unit is



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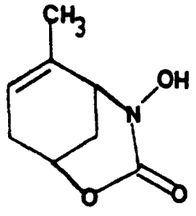

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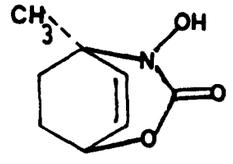

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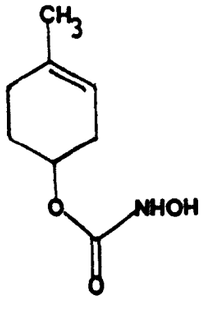

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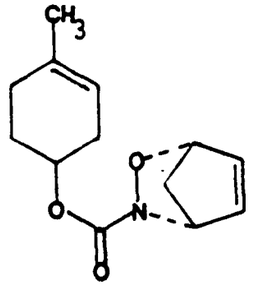


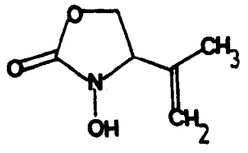
(169)

attached, via the ring, to the enophile by the olefinic terminal and also by the central atom. As there were no signs of the alternative products (161) and (162) in the n.m.r. spectrum of the crude reaction mixture, the ene reaction proceeded with proton transfer exclusively from the methyl group. The rate of this reaction was intermediate between those of the thermolysis of the cyclopentadiene/4-methylpent-3-enyl nitrosoformate adduct (158) and the thermolysis of the cyclopentadiene/2-methylprop-2-enyl nitrosoformate adduct (149).

The final nitrosoformate studied in this series, 4-methylcyclohex-3-enyl nitrosoformate, also had three possible intramolecular ene products, the bridged N-hydroxy-oxazin-2-ones (165), (166), and (167). 4-Methylcyclohex-3-enone was prepared by the sodium-liquid ammonia reduction[87] of 4-methylanisole. Reduction of the enone with lithium aluminium hydride yielded 4-methylcyclohex-3-en-1-ol. Treatment of the alcohol with phosgene followed by aqueous alkaline hydroxylamine produced N-(4-methylcyclohex-3-enyloxycarbonyl)hydroxylamine (168) as a crystalline solid. The compound was fully characterised and the i.r. and n.m.r. spectra were consistent with the hydroxamic acid (168). Oxidation of the hydroxamic acid (168) in the presence of cyclopentadiene yielded the cyclopentadiene/4-methylcyclohex-3-enyl nitrosoformate adduct (169) as a crystalline solid. The formula of the adduct was verified by elemental analysis and mass spectroscopy. The proton n.m.r. spectrum of the adduct showed a broad singlet at δ 6.35, due to the olefinic protons of the cyclopentene ring. A broad singlet of relative intensity 2 at δ 5.20 was

assigned to the cyclohexene's olefinic proton and a methine proton adjacent to nitrogen or oxygen. The other bridgehead proton of the cyclopentene ring absorbed at δ 4.97 and the methine group of the cyclohexene ring gave a singlet at δ 4.90. The adduct (169) was thermolysed in refluxing benzene and the reaction was followed by n.m.r. spectroscopy. After 6 hours heating, one third of the mixture was the adduct (169), and after another 6 hours essentially no adduct remained. The crystalline compound obtained from this reaction was shown by analysis and mass spectroscopy to have the formula $C_8H_{11}NO_3$, consistent with the isomeric bridged N-hydroxy-oxazinones (165), (166), and (167). Only the oxazinone (165) with the exo-methylene group conformed with the n.m.r. spectral details. A singlet at δ4.89 was assigned to the exo-methylene protons and two broad singlets at δ 4.55 and 4.09 were attributed to the methine protons adjacent to oxygen and nitrogen respectively. In the off-resonance decoupled ^{13}C n.m.r. spectrum, the signal due to the carbonyl carbon was a singlet at δ 157.0 and the di-substituted olefinic carbon absorbed as a singlet at δ 145.7. The exo-methylene carbon gave a triplet at δ 112.3, and the methine carbons adjacent to oxygen and nitrogen gave doublets at δ 75.3 and 63.6 respectively. The vinylic methylene group absorbed as a triplet at δ 25.9 and the other two methylene groups of the ring absorbed as coincident triplets at δ 33.5.

As already discussed, there was some doubt over the identity of the ene product of 3,3-dimethylallyl nitrosoformate. N.m.r. spectra had narrowed the possibilities down to two, the oxazolid-



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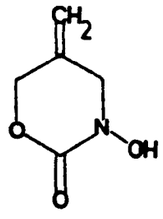

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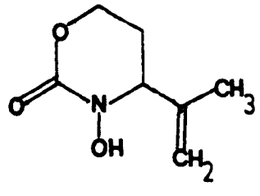

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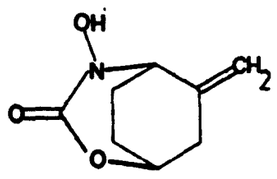

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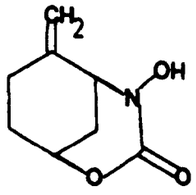

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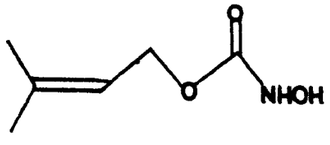

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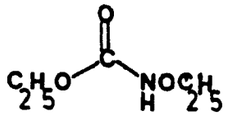


(170)

2-one (145) and the dioxazinone (146). The nitroso group is a polarised enophile and in all literature examples products arise from the formation of a C-N bond; thus the oxazolid-2-one (145) was highly favoured. The dioxazinone (146) was considered as a remote possibility only because the formation of a five-membered ring might have been unfavourable. It came as a surprise, therefore, that this ene product did not give a violet colour when treated with ethanolic ferric chloride, a classical test for hydroxamic acids, whereas similar treatment of the four other ene products (147), (155), (160), and (165) produced violet colours. To investigate this more fully, aliquots of a 5% ethanolic ferric chloride solution (6 mol equiv.) were added to ethanolic solutions of all five intramolecular ene products and the visible spectra of the resulting complexes taken. The spectrum of the ferric complex of N-(3,3-dimethylallyloxycarbonyl)hydroxylamine (143) was also taken. As a model for the dioxazinone (146), N-(ethoxycarbonyl)ethoxyamine (170) was prepared by treating ethyl chloroformate with aqueous, alkaline ethoxyamine.

Table 1 († = corrected for ferric absorbance).

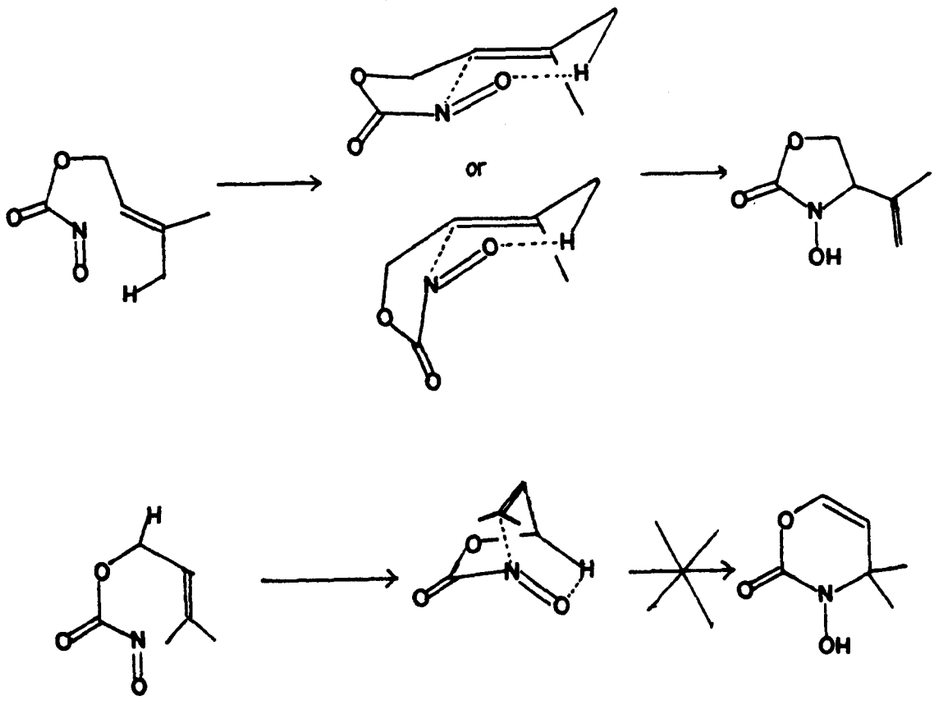
Compd.	Extinction Coefficients $10^{-3}\epsilon$						
	475nm†	500nm†	525nm	550nm	575nm	600nm	625nm
145	1.36	0.55	0.50	0.16	0	0	0
147	1.76	1.85	2.1(λmax)	2.03	1.90	1.70	1.35
155	1.75	1.78	1.85(λmax)	1.78	1.70	1.55	1.20
160	1.94	2.15	2.54	2.79	2.85(λmax)	2.73	2.40
165	1.95	1.71	1.81	1.90(λmax)	1.84	1.71	1.50
143	0.35	0.58	0.78	0.86	0.95(λmax)	0.92	0.80
170	0	0	0	0	0	0	0

Ferric chloride was added to a solution of this compound (170) and the visible spectrum taken as above. Details of these visible spectra are shown in Table 1; it should be noted that the extinction coefficients for all compounds, at 475 and 500 nm, have been corrected for ferric chloride absorption. N-(Ethoxycarbonyl)ethoxyamine (170) showed no absorption at all in the region observed. The complex of the supposed oxazolid-2-one (145) absorbed appreciably at the lower wavelengths but, unlike the complexes of the other hydroxamic acids, did not show an absorption maximum at larger wavelengths. The ferric complexes of the N-hydroxy-oxazinones (147), (155), (160), and (165) also showed appreciable absorption at 475 and 500 nm, unlike that of the acylic N-(3,3-dimethylallyloxycarbonyl)hydroxylamine (143), and, with the exception of the 7-membered ring compound (160), their maxima of absorption occurred at lower wavelengths (Table 1). Thus it is postulated that the behaviour of the five-membered ring oxazolid-2-one (145) is an extreme in a general trend in cyclic N-alkoxycarbonyl-hydroxylamines to form ferric complexes which absorb at lower wavelengths than those of acyclic hydroxamic acids.

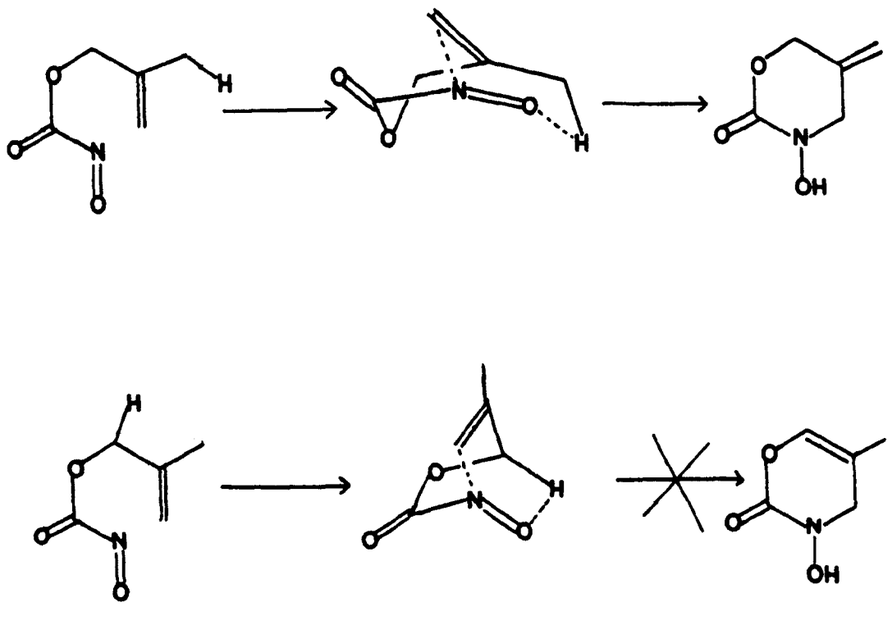
One final piece of evidence for structure (145) came from mass spectroscopy. Major fragment ions in the mass spectra of (147), (155), and (165) correspond to loss of an oxygen atom. This is also a major fragmentation mode in the mass spectrum of the oxazolid-2-one (145).

Summary.

From the five examples of the intramolecular ene reactions of nitrosoformates that we have studied, two empirical rules may be



(Scheme 22)

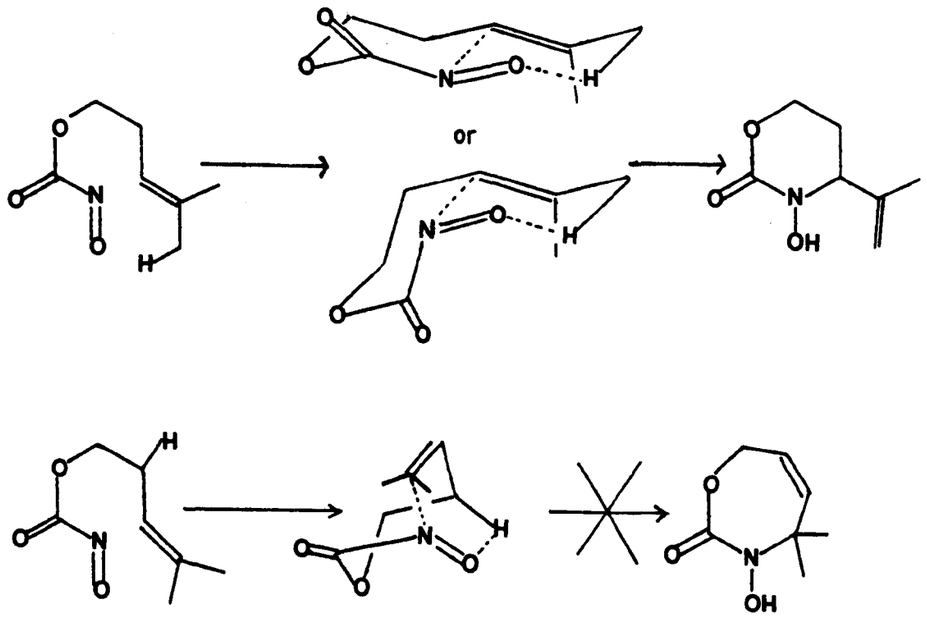


(Scheme 23)

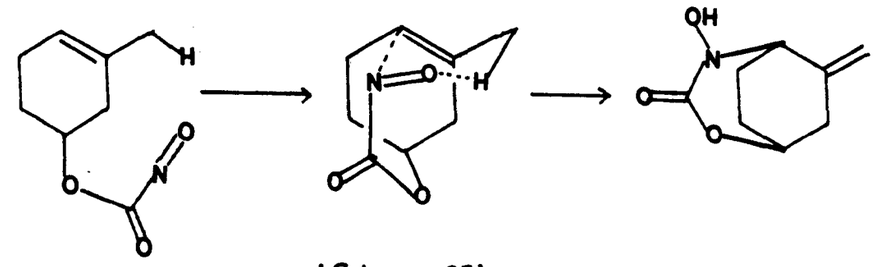
formulated; the nitrogen bonds to the least substituted carbon of the double bond, and proton transfer is always from a methyl group. Of course the generality of these rules has not been tested and, like the classification of each reaction into a Type 1 or Type 2, they do not allow us to explain why some reactions proceed faster than others. It seems that an examination of the transition states that lead to the observed products is more fruitful. In some cases this approach provides possible reasons for the observed regiospecificity of the reactions.

In the following discussion we will assume that the various ene reactions are concerted. There are two possible routes for 3,3-dimethylallyl nitrosoformate to react (Scheme 22) to give cyclic hydroxamic acids. As can be seen, the transition state that the nitrosoformate did not react by is of the bicyclo[2.2.2]-type. A model of this transition state shows that it is impossible for efficient overlap of the π-orbital of the N=O bond, the σ-orbital of the C-H bond, and the π-orbitals of the olefinic linkage. The reaction is therefore disfavoured. The nitrosoformate gives the observed product by reacting through a 5,6-cis or trans-fused transition state, in which the necessary orbital overlaps are more easily achieved.

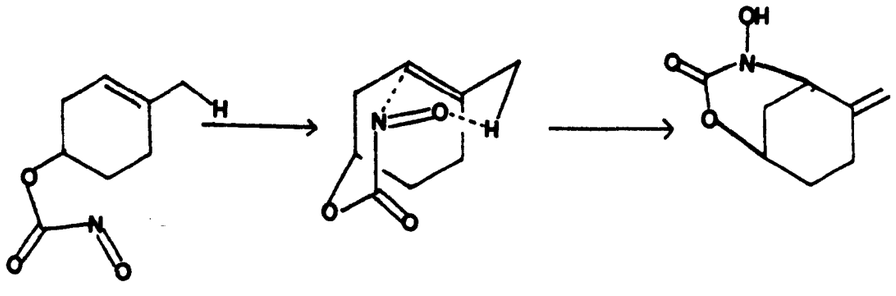
2-Methylprop-2-enyl nitrosoformate also does not react via a bicyclo[2.2.2]-transition state as, again, the orbitals cannot overlap properly for reaction (Scheme 23). Instead the reaction proceeds through a bicyclo[3.3.1]-transition state, in which the geometrical requirements of the ene reaction are better achieved, to give the



(Scheme 24)



(Scheme 25)



(Scheme 26)

N-hydroxy-oxazin-2-one (147).

The high energy of bicyclo[3.2.2]-transition states in intramolecular ene reactions is exemplified by 4-methylpent-3-enyl nitrosoformate. Once more, the nitrosoformate reacts through a cis or trans-fused decalin transition state to give the N-hydroxy-oxazin-2-one (160) (Scheme 24). However, in the example the disfavoured process involves formation of a 7-membered ring.

Of the three acylic nitrosoformates, 2-methylprop-2-enyl nitrosoformate (Scheme 23) reacts slowest. One reason for this may be that the geometrical requirements for the bridged bicyclo[3.3.1]-transition state are much greater than those for the two fused-ring transition states.

The bridged N-hydroxy-oxazinone (160), obtained from the ene reaction of 3-methylcyclohex-3-enyl nitrosoformate, is produced via the tricyclic transition state shown in Scheme 25. It can be seen from models that the transition states required to produce the alternative isomers (161) and (162) are much more strained. The other alicyclic reactant, 4-methylcyclohex-3-enyl nitrosoformate, reacts through the tricyclic transition state as shown in Scheme 26, to give the bridged N-hydroxy-oxazinone (165). Again this transition state looks very favourable in models, whereas the transition states required to give the other isomers, (166) and (167), are not of this cis-fused decalin type, and are much more strained. 4-Methylcyclohex-3-enyl nitrosoformate reacts slightly faster than its 3-methyl isomer probably because the corresponding transition state (Scheme 26) is

less strained than the other (Scheme 25). However they both react slower than 3,3-dimethylallyl nitrosoformate and 4-methylpent-3-enyl nitrosoformate presumably owing to the added geometrical restriction of the cyclohexene ring.

Chapter 5

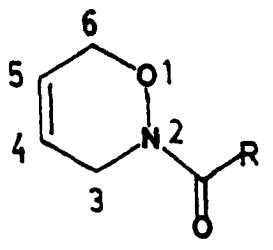
Experimental

General Procedures.

Melting points were measured on a Reichert hot-stage melting point apparatus and are uncorrected. Micro-analyses were done by Mrs. W. Harkness and her staff. Infrared spectra were obtained from Perkin-Elmer 257 or 580 infrared spectrometers by Mrs. F. Lawrie and her staff and only significant absorptions are quoted. Ultraviolet spectra were obtained on a Pye-Unicam SP 800 spectrometer. Mass spectra were recorded on a G.E.C.-A.E.I. MS12 spectrometer by Mr. A. Ritchie and his staff. Accurate mass measurements were made on an A.E.I. (Kratos) MS9 mass spectrometer with a G.E.C.-905 computer system for data capture and processing by Dr. P. Bladon.

Proton nuclear magnetic resonance spectra were recorded on Varian T-60A (60 MHz), Perkin-Elmer R32 (90 MHz), Varian XL-100 (100 MHz), and Bruker WH-360 (360 MHz) spectrometers using tetramethylsilane as the internal standard. ^{13}C nuclear magnetic resonance spectra were recorded on a Varian XL-100 (100 MHz) spectrometer. The following abbreviations are used: s-singlet, d-doublet, t-triplet, q-quartet, m-multiplet, and br-broad.

For convenience, throughout the whole of this work, 2-acyl 3,6-dihydro-2H-1,2-oxazines have been referred to as adducts of conjugated dienes and nitrosocarbonyl derivatives.



Chapter 5

5.2.1 Experimental.

Preparation of N-(2,2,2-Trichloroethoxycarbonyl)hydroxylamine (with J.W.M. MacKinnon).

Hydroxylamine hydrochloride (100 mmol, 6.95 g) and sodium hydroxide (120 mmol, 4.8 g) were dissolved in water (80 ml). 2,2,2-Trichloroethyl chloroformate (20 mmol, 4.23 g) was added with cooling and stirring over ten minutes. The flask containing the mixture was shaken for 1 hour, the contents acidified and extracted with diethyl ether (10 x 80 ml). The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated. Recrystallisation from benzene/light petroleum (b.p. 60-80°) yielded N-(2,2,2-trichloroethoxycarbonyl)hydroxylamine as colourless prisms, m.p. 87-89°C (3.08 g, 75%) (Found: C, 17.5; H, 2.0; N, 7.0; Cl, 50.6. $C_3H_4Cl_3NO_3$ requires C, 17.3; H, 1.9; N, 6.7; Cl, 51.1); ν_{max}(KBr) 3 350, 3 250 (N-H and O-H), 1 715 cm^{-1} (C=O); $\delta(CDCl_3)$ 8,40 (1H, br m, N-H or O-H, exchangeable with D_2O), 6.00 (1H, br m, N-H or O-H, exchangeable with D_2O), and 4.83 (2H, s, $-OCH_2-$).

Preparation of the 2,3-Dimethylbutadiene/Nitrosocarbonylbenzene Adduct (40).

2,3-Dimethylbutadiene (3.65 mmol, 0.3 g) dissolved in ethyl acetate (100 ml) was added to a vigorously stirred solution of

sodium periodate (5.47 mmol, 1.17 g) in 0.5 M aqueous sodium acetate-acetic acid buffer (pH 6, 50 ml) at 0°C. Benzohydroxamic acid (5.47 mmol, 0.75 g) was added over 10 minutes. After an hour stirring at 0°C the mixture was basified (saturated $NaHCO_3$). The organic layer was separated, washed with 0.5 M sodium thiosulphate and brine, dried ($MgSO_4$) and evaporated, yielding the 2,3-dimethylbutadiene/nitrosocarbonylbenzene adduct as an oil. The adduct was crystallised from benzene/light petrol (b.p. 60-80°C) as white prisms (1.93 g, 89%), m.p. 62-5°C. (Found: C, 71.6; H, 6.9; N, 6.8. $C_{13}H_{15}NO_2$ requires C, 71.9; H, 6.9; N, 6.5%); m/e 217; νmax(thin film) 1 640 cm^{-1} (C=O); δ ($CDCl_3$) 7.2-7.8 (5H, m, Ph), 4.16 (4H; br s, O-CH_2 and N-CH_2), 1.75 (3H, br s, methyl), 1.60 (3H, br s, methyl).

Preparation of the 2,3-Dimethylbutadiene/2,2,2-Trichloroethyl Nitrosoformate Adduct (41).

2,3-Dimethylbutadiene (76 mg, 0.95 mmol) dissolved in ethyl acetate (25 ml) was added to a stirred solution of sodium periodate (300 mg, 1.4 mmol) in 0.5 M aqueous sodium acetate-acetic acid buffer (pH 6, 15 ml) at 0°C. N-(2,2,2-Trichloroethoxycarbonyl)hydroxylamine (290 mg, 1.4 mmol) was added over 10 minutes and the solution allowed to stir at 0°C for 1 hour. The mixture was then basified (saturated $NaHCO_3$) and the organic layer was separated, washed with 0.5 M sodium thiosulphate and brine, and dried ($MgSO_4$). Evaporation of solvent yielded the 2,3-dimethylbutadiene/2,2,2-trichloroethyl nitrosoformate adduct as a yellow oil. The adduct was purified by

distillation (b.p. 140°C at 0.2 mm Hg) to give a colourless oil (160 mg, 59%) (Found: C, 37.2; H, 4.3; Cl, 36.8. $C_9H_{12}Cl_3NO_3$ requires C, 37.4; H, 4.2; Cl, 36.9%) ; m/e 287, 289 and 291; ν_{max} (KBr) 1 725 cm^{-1} (C=O); δ ($CDCl_3$) 4.88 (2H, s, $-OCH_2-$), 4.34 and 4.08 (2 x 2H, br s, $-O-CH_2$ and $-N-CH_2$), 1.66 (6H, br s, 2 X methyl).

Preparation of the Ergosteryl Acetate/2,2,2-Trichloroethyl Nitrosoformate Adduct (39). (with J.W.M. MacKinnon).

Ergosteryl acetate (0.33 mmol, 145 mg) was dissolved in ethyl acetate (10 ml) and added to a stirred solution of sodium periodate (0.66 mmol, 140 mg) in 0.5 M aqueous sodium acetate-acetic acid buffer (pH 6, 5 ml) at 0°C. N-(2,2,2-Trichloroethoxycarbonyl) hydroxylamine (0.66 mmol, 137 mg) was added over 10 minutes and the mixture allowed to stir at 0°C for 1 hour. The solution was basified (saturated $NaHCO_3$), and the organic layer was separated, washed with 0.5 M sodium thiosulphate and brine, dried ($MgSO_4$), and evaporated. Recrystallisation from ethyl acetate/light petroleum (b.p. 60-80°C) yielded the ergosteryl acetate/2,2,2-trichloroethyl nitrosoformate adduct as colourless needles (172 mg, 80%), m.p. 157-9°C (Found: C, 61.6; H, 7.6; N, 2.1; Cl, 16.3. $C_{33}H_{48}Cl_3NO_5$ requires C, 61.5; H, 7.5; N, 2.2; Cl, 16.5%) ; ν_{max} (KBr) 1 728 cm^{-1} (C=O); δ ($CDCl_3$) 6.25 (2H, s, 6-H and 7-H), 5.25 (1H, br m, 3-H), 5.12 (2H, m, side chain olefinic H), 4.95 and 4.45 (2H, ABq, J 13 Hz, $-CH_2-O-$), 3.35 (1H, br dd, J 14 Hz, 5 Hz, 4α-H), and 2.10 (3H, s, CH_3-CO).

Preparation of Bicyclohexenyl (42).

Bicyclohexenyl was prepared from cyclohexanone by reduction and coupling with aluminium amalgam[27] and subsequent dehydration of the resulting pinacol by phosphorus oxychloride[28]. The bicyclohexenyl produced was characterised by formation of the maleic anhydride adduct, m.p. 121-3°C (lit.[29] m.p. 122.5-3.5°C).

Preparation of the Bicyclohexenyl/2,2,2-Trichloroethyl Nitrosoformate Adduct (43).

Bicyclohexenyl (1 mmol, 162 mg) was dissolved in ethyl acetate (30 ml) and combined with a solution of sodium periodate (2 mmol, 428 mg) in 0.5 M aqueous sodium acetate-acetic acid buffer (pH 6, 15 ml). The mixture was vigorously stirred at 0°C and N-(2,2,2-trichloroethoxycarbonyl)hydroxylamine (2 mmol, 416 mg) was added over 10 minutes. After an hour stirring at 0°C the mixture was basified (saturated $NaHCO_3$). The organic layer was separated, washed with 0.5 M sodium thiosulphate and brine, dried ($MgSO_4$) and evaporated. The resultant oil was triturated with hexane and recrystallised from benzene/light petrol (b.p. 60-80°C) to yield the bicyclohexenyl/2,2,2-trichloroethyl nitrosoformate adduct as white needles (220 mg, 61%) m.p. 88-90°C (Found: C,48.8, H, 5.6; N, 3.7; Cl, 28.5. $C_{15}H_{20}Cl_3NO_3$ requires C, 48.8; H, 5.6, N, 3.8; Cl, 28.9%); m/e 367, 369 and 371; ν_{max} (KBr) 1 705 cm^{-1} (C=O); δ ($CDCl_3$) 4.96 and 4.70 (2H, ABq, J 12 Hz, $-O-CH_2-$), 4.46 (2H, br m, -N-CH- and -O-CH-), and 3.0 to 1.1 (16H, br m, aliphatic H).

Preparation of the Isoprene/2,2,2-Trichloroethyl Nitrosoformate Adduct (44).

Solutions of redistilled isoprene (0.5 mmol, 34 mg) in ethyl acetate (10 ml) and sodium periodate (0.75 mmol, 160 mg) in 0.5 M aqueous sodium acetate-acetic acid buffer(pH6, 5 ml) were combined and stirred vigorously at 0°C. N-(2,2,2-Trichloroethoxycarbonyl) hydroxylamine was added over 10 minutes and the solution was stirred at 0°C for a further hour. The mixture was then basified (saturated $NaHCO_3$) and the organic layer was separated. The organic layer was then washed with 0.5 M sodium thiosulphate and brine, dried ($MgSO_4$) and evaporated to yield the isoprene/2,2,2-trichloroethyl nitrosoformate adduct as a yellow oil. The oil was distilled to give a mobile colourless liquid, b.p. 135-8°C/0.04 mm Hg, (95 mg 75%) (Found: C, 34.8; H, 3.6; N, 4.8. $C_8H_{10}Cl_3NO_3$ requires C, 35.0; H, 3.6; N, 5.1%) , m/e 273, 275, and 277; ν_{max} (thin film) 1 720 cm^{-1} (C=O); $\delta(CDCl_3)$ 5.57 (1H, br s, olefinic H), 4.82 (2H, s, $-O-CH_2-$), 4.45 (2H, m, $-O-CH_2-$ or $-N-CH_2-$), 4.15 (2H, m, $-O-CH_2-$ or $-N-CH_2-$), 1.76 (ca. 2H, 3, methyl), and 1.68 (ca. 1H, 3, methyl). Irradiation at δ 4.45 caused the singlet at δ1.76 to sharpen and irradiation at δ4.15 caused the singlet at δ1.68 to sharpen.

Preparation of the Cyclopentadiene/2,2,2-Trichloroethyl Nitrosoformate Adduct (45).

Cyclopentadiene was distilled and collected in an ice-cold receiver. Some of this cyclopentadiene (1.5 mmol, 0.13 ml) was

added to a stirred mixture of ethyl acetate (20 ml) and sodium periodate (1.0 mmol, 214 mg) in 0.5 M sodium acetate-acetic acid buffer (pH 6, 10 ml) at 0°C. N-(2,2,2-Trichloroethoxycarbonyl) hydroxylamine (1.0 mmol, 208 mg) was added over 10 minutes and the mixture was stirred in an ice-bath for 1 hour. The mixture was basified (saturated $NaHCO_3$) and the organic layer separated. After washing with brine and 0.5 M sodium thiosulphate, the organic layer was dried ($MgSO_4$) and evaporated yielding the cyclopentadiene/2,2,2-trichloroethyl nitrosoformate adduct as white needles. The compound was recrystallised from ethyl acetate (192 mg, 70%), m.p. 86-7.5°C (Found: C, 34.9; H, 2.8; N, 4.9. $C_8H_8Cl_3NO_3$ requires C, 35.2; H, 2.9; N, 5.1%) m/e 271, 273 and 275: ν_{max} (K Br) 1 710 cm^{-1} (C=O); $\delta(CDCl_3)$ 6.45 (2H, m, olefinic H), 5.36 (1H, br s, -N-CH-), 5.08 (1H, br s, -O-CH-), 4.82 and 4.62 (2H, ABq, J 11 Hz, $-O-CH_2-$), 2.05 (1H, dm, J 11 Hz, methylene H), 1.80 (1H, d, J 11 Hz, methylene H).

Zinc Reduction of the 2,3-Dimethylbutadiene/2,2,2-Trichloroethyl Nitrosoformate Adduct (41).

The adduct (450 mg, 1.6 mmol) was dissolved in glacial acetic acid (3 ml). Activated zinc dust (410 mg, 6.25 mmol) was added and the mixture stirred for 2 hours. Water (10 ml) was added and the mixture basified to pH 10 with 10% aqueous NaOH. A pink precipitate appeared which was filtered off. The aqueous solution was continuously extracted with ethyl acetate for 3 days. The extracts were dried ($MgSO_4$) and evaporated yielding a dark brown residue (13 mg).

This material was not characterised but was thought to be 4-amino-2,3-dimethylbut -2-en-1-ol (46); δ ($CDCl_3$) 4.19 (2H,s, $-CH_2-O-$), 3.9 (2H, br d, $-CH_2-N-$), 1.79 (3H, s, methyl), 1.60 (3H, s, methyl), 6.3 (2H, br s, NH_2, exchangeable with D_2O), 5.1 (1H, br s, OH, exchangeable with D_2O); ν_{max} (CCl_4) 3 500 (s,-OH), 3 450-3 350 cm^{-1} (broad, -OH and NH_2)

Attempted Zinc Reduction of the Ergosteryl Acetate/2,2,2-Trichloroethyl Nitrosoformate Adduct (39)

The adduct (0.33 mmol, 212 mg), in glacial acetic acid (7 ml) was treated with activated zinc dust (6.6 mmol, 430 mg) with stirring for 4 hours. The mixture was filtered free of unreacted zinc, diluted with water (50 ml) and basified (10% aqueous NaOH). A white solid precipitated and was extracted into methylene chloride. The extracts were combined, washed with brine, dried ($MgSO_4$), and evaporated to yield a white crystalline solid which was recrystallised from methanol. The n.m.r. spectrum of the resultant white needles was identical to that of ergosteryl acetate (70 mg, 53%).

The above reaction was repeated using an 8 fold excess of zinc. Zinc dust (2.6 mmol, 169 mg) and the adduct (39) (0.33 mmol, 212 mg) were stirred in glacial acetic acid (7 ml) for four hours and the reaction mixture worked up as above. The starting adduct (39) (131, 62%) was the only product recovered from the reaction mixture.

Attempted Zinc-Phosphate Buffer Reduction[30] of the Ergosteryl Acetate/ 2,2,2-Trichloroethyl Nitrosoformate Adduct (39).

Zinc dust (2.55 mmol, 167 mg) was added to a stirred solution of the adduct (39) (0.17 mmol, 110 mg) in tetrahydrofuran (5 ml) and 1.0 M aqueous potassium dihydrogen phosphate-disodium hydrogen phosphate buffer (pH 4.5, 1 ml). The slurry was stirred at room temperature for 4 hours. Unreacted zinc was filtered off and the filtrate was stirred with H form ion exchange resin (1R 120). The mixture was filtered, the solvent evaporated and the residue dissolved in diethyl ether. The ether was dried ($MgSO_4$) and evaporated to leave a white solid which was spectroscopically identical to the starting adduct (39), (recovered: 95 mg, 85%).

Attempted Zinc-Copper Couple Reduction of the Ergosteryl Acetate/ 2,2,2-Trichloroethyl Nitrosoformate Adduct (39).

Zinc-copper couple was prepared by the method of Smith and Simmons.[31] The adduct (39) (0.17 mmol, 109 mg) was dissolved in glacial acetic acid (5 ml) and zinc-copper couple (1.36 mmol, 174 mg) added with stirring at room temperature. The mixture was stirred at room temperature for 3 hours and was then filtered free of unreacted zinc-copper couple, diluted with water (50 ml) and basified (10% aqueous NaOH). The solution was extracted with methylene chloride and the combined extracts washed with brine, dried ($MgSO_4$), and evaporated. The resultant white solid (60 mg) was shown to be a mixture of ergosteryl acetate and the adduct (39) (in the ratio 2:1 respectively) by n.m.r. spectroscopy.

The Catalytic Hydrogenation of the Ergosteryl Acetate/2,2,2-Trichloroethyl Nitrosoformate Adduct (39).

The ergosteryl acetate/2,2,2-trichloroethyl nitrosoformate adduct (214 mg, 0.33 mmol) was dissolved in ethanol (15 ml) in a 50 ml R.B. flask and 10% Pd-C (20 mg) was added. The mixture was stirred under a hydrogen atmosphere for 24 hours. The solution was filtered and evaporated yielding a white solid which showed 1 spot on t.l.c. [R_F 0.15, silica GF_{254}, eluted with petrol (b.p. 60-80°C) and ethyl acetate in the ratio 3:7]. Proton n.m.r. spectroscopy revealed no signals for olefinic protons, an acetyl group, or a 2,2,2-trichloroethyl group. The product was not further characterised but was thought to be tetrahydro-ergosterol.

Attempted Diimide Reduction[32] of the Ergosteryl Acetate/2,2,2-Trichloroethyl Nitrosoformate Adduct (39)

Dipotassium azodicarboxylate,[88] made from azodicarbonamide, was suspended in a solution of the adduct (39) (0.23 mmol, 148 mg) in methanol (25 ml). A mixture of acetic acid, methanol, and water (1:1:1) (1.5 ml) was added over 1 hour with stirring. When the yellow colour of the dipotassium azodicarboxylate had disappeared, water (25 ml) was added and the reaction mixture extracted with ethyl acetate. The extracts were combined, washed with brine, dried ($MgSO_4$), and evaporated to yield a white solid. The proton n.m.r. and i.r. spectra of the product were identical to those of the ergosteryl acetate/2,2,2-trichloroethyl nitrosoformate adduct (140 mg, 95% recovery of starting material).

Zinc-Glacial Acetic Acid Reduction of the Bicyclohexenyl/2,2,2-Trichloroethyl Nitrosoformate Adduct (43).

The adduct (43) (174 mg, 0.47 mmol) was dissolved in glacial acetic acid (10 ml) and activated zinc dust (770 mg, 11.8 mmol) added with stirring. The mixture was stirred at room temperature for 9 hours, the unreacted zinc was filtered off and the reaction mixture basified (10% aqueous NaOH). The solution was extracted with ethyl acetate, the extracts were combined, washed with brine and dried ($MgSO_4$). Evaporation of solvent yielded a brown oil (60 mg). Proton n.m.r. spectroscopy showed that the product did not contain a 2,2,2-trichloroethyl group and had 2-3 protons exchangeable with D_2O. A solution (CCl_4) i.r. spectrum showed a broad band at 3 425 cm^{-1}, possibly N-H stretching vibration, and a sharper band at 3 605 cm^{-1}, possibly O-H stretching. The product could not be further characterised.

Zinc-Phosphate Buffer Reduction[30] of the Bicyclohexenyl/2,2,2-Trichloroethyl Nitrosoformate Adduct (43).

Zinc dust (9.5 mmol, 620 mg) was added to a stirred solution of the adduct (43) (0.38 mmol, 140 mg) in tetrahydrofuran (12 ml) and 10 M aqueous potassium dihydrogen phosphate-disodium hydrogen phosphate buffer (pH 4.5, 2.4 ml). The slurry was stirred at room temperature for 4 hours. Unreacted zinc was filtered off and the filtrate was stirred with H form ion exchange resin (IR 120). The mixture was filtered, the solvent evaporated and the residue dissolved

in ethyl acetate. The ethyl acetate was washed with brine, dried ($MgSO_4$), and evaporated to leave a brown oil. In the n.m.r. spectrum of the oil there was a broad singlet at δ5.5 for 2-3 protons (exchangeable with D_2O), and there was no signal attributable to the 2,2,2-trichloroethyl group. A solution (CCl_4) i.r. spectrum of the oil showed bands at 3 600 and 3 450 cm^{-1}, possibly attributable to O-H and N-H stretching vibrations.

Attempted Zinc-Glacial Acetic Acid Reduction of the Cyclopentadiene/2,2,2-Trichloroethyl Nitrosoformate Adduct (45).

The cyclopentadiene/2,2,2-trichloroethyl nitrosoformate adduct (136 mg, 0.5 mmol) was dissolved in glacial acetic acid (3 ml) and activated zinc dust was added. The mixture was stirred at room temperature for 4 hours, then filtered free of unreacted zinc, diluted with water (20 ml), and basified (10% aqueous NaOH). The aqueous solution was continuously extracted with ethyl acetate for 4 days. The extracts were combined and dried ($MgSO_4$). Evaporation of solvent left no significant amount of residue.

Attempted Zinc-Phosphate Buffer Reduction[30] of the Cyclopentadiene/2,2,2-Trichloroethyl Nitrosoformate Adduct (45).

The adduct (45) (0.5 mmol, 136 mg) was dissolved in tetrahydrofuran (10 ml) and 1.0 M aqueous potassium dihydrogen phosphate-disodium hydrogen phosphate buffer (pH 4.5, 2 ml). Zinc dust (12 mmol, 780 mg) was added and the mixture was stirred at room

temperature for four hours. The unreacted zinc was filtered off and the filtrate was stirred with H form ion exchange resin. The mixture was filtered, the solvent evaporated, and the residue was extracted with ethyl acetate. The combined extracts were washed with brine and dried ($MgSO_4$). Evaporation of the ethyl acetate left no significant amount of residue.

Attempted Diimide Reduction[32] of the Cyclopentadiene/2,2,2-Trichloroethyl Nitrosoformate Adduct (45).

The adduct (0.26 mmol, 70 mg) was dissolved in methanol (5 ml) and potassium azodicarboxylate[88] (7 mmol, 1.36g) was suspended in this solution. A mixture of water, acetic acid, and methanol (1:1:1) (1.5 ml) was added over 2 hours. The mixture was diluted with water (25 ml), when the yellow colour of the mixture had disappeared, and was extracted with ethyl acetate. The extracts were combined, washed with brine, dried ($MgSO_4$) and evaporated to yield a brown intractable oil (45 mg), giving 5 spots on t.l.c. (silica GF_{254}, eluted with 10% methanol and 90% chloroform), which was not investigated further.

Thermal Transfer of 2,2,2-Trichloroethyl Nitrosoformate from the Cyclopentadiene/2,2,2-Trichloroethyl Nitrosoformate Adduct (45) to Ergosteryl Acetate.

The cyclopentadiene/2,2,2-trichloroethyl nitrosoformate adduct (0.2 mmol, 55 mg) and ergosteryl acetate (0.2 mmol, 88 mg) were dissolved in benzene (10 ml). The solution was placed in a 25 ml

R.B. flask fitted with a condenser set for distillation and an equilibrating dropping funnel filled with benzene. Benzene was distilled over, the volume of solution in the flask being topped up from the dropping funnel. The reaction was followed by t.l.c. and judged to be complete after the spot corresponding to the cyclopentadiene adduct (45) had disappeared [R_F 0.25, silica GF_{254} eluted with 30% ethyl acetate, 70% light petrol (b.p. 60-80°C)] . The reaction was complete in 8 hours. Evaporation of benzene yielded the ergosteryl acetate/2,2,2-trichloroethyl nitrosoformate adduct as a white crystalline solid (123 mg, 96%). Proton n.m.r. and i.r. spectra were identical to those of the adduct made by the 'direct' method; ν_{max} (Nujol mull) 1 730 cm^{-1} (C=O); δ ($CDCl_3$) 6.25 (2H, s, 6-H and 7-H), 5.25 (1H, br m, 3-H), 5.12 (2H, m, side chain olefinic H), 4.95 and 4.55 (2x 1H, doublets, J 13 Hz, $-CH_2-O-$), 3.35 (1H, br dd, J 14 Hz, 5 Hz, 4 H) and 2.10 (3H, s, CH_3-CO).

Thermal Transfer of 2,2,2-Trichloroethyl Nitrosoformate from the Cyclopentadiene/2,2,2-Trichloroethyl Nitrosoformate Adduct (45) to Bicyclohexenyl.

The cyclopentadiene/2,2,2-trichloroethyl nitrosoformate adduct (0.33 mmol, 91 mg) and bicyclohexenyl (0.33 mmol, 54 mg) were dissolved in benzene (20 ml). The solution was placed in a 50 ml R.B. flask fitted with a still-head, a condenser set for distillation, and an equilibrating dropping funnel filled with benzene. Benzene was

distilled over, the volume of the solution in the flask being held roughly constant by addition of benzene from the dropping funnel. The reaction was judged to be complete when, after four days, the reaction mixture showed only one spot by t.l.c. Evaporation of benzene yielded the bicyclohexenyl/2,2,2-trichloroethyl nitrosoformate adduct as a brown oil [R_F 0.5, silica GF_{254}, eluted with 30% ethyl acetate, 70% light petrol (b.p. 60-80°C)]. The adduct crystallised from ethyl acetate/n-pentane as white needles (61 mg, 49%), m.p. 87-90°C. Proton n.m.r. and i.r. spectra of this sample were identical to those of the adduct made by the 'direct' method; ν_{max} (KBr) 1 705 cm^{-1} (C=O); δ ($CDCl_3$) 4.96 and 4.80 (2H, ABq J 12 Hz, $-O-CH_2-$), 4.46 (2H, br m, -N-CH- and -O-CH-) 3.0 to 1.1 (16H, br m, aliphatic H).

The above reaction was repeated using toluene (b.p. 111°C) instead of benzene (b.p. 80°C) as a solvent. The cyclopentadiene/2,2,2-trichloroethyl nitrosoformate adduct (0.33 mmol, 91 mg) and bicyclohexenyl (0.33 mmol, 54 mg) were dissolved in toluene (20 ml) and the toluene was distilled off under nitrogen and topped up as before. The reaction took 4 days to go to completion, as before. Evaporation of toluene and crystallisation of the residual oil from ethyl acetate/n-pentane yielded the bicyclohexenyl adduct (43) as white needles (72 mg, 60%), m.p. 88-90°C.

5.2.2

Preparation of the Thebaine/2,2,2-Trichloroethyl Nitrosoformate Adduct (57).

Thebaine (10 mmol, 3.11 g), in ethyl acetate (100 ml) was added to a vigorously stirred solution of sodium periodate (15 mmol, 3.21 g) in 0.5 M aqueous sodium acetate-acetic acid buffer (pH 6, 50 ml) at 0°C. N-(2,2,2-Trichloroethoxycarbonyl)hydroxylamine (15 mmol, 3.12 g) was added over 15 minutes. After an hour's stirring at 0°C, the mixture was basified (saturated $NaHCO_3$). The organic layer was separated, washed with brine and 0.5 M sodium thiosulphate, dried ($MgSO_4$) and evaporated, yielding the thebaine/2,2,2-trichloroethyl nitrosoformate adduct (57) as an oil. The adduct crystallised from methanol as white needles (82%), m.p. 173-4°C (Found: C, 50.9; H, 4.2; N, 5.6; Cl, 20.8. $C_{22}H_{23}Cl_3N_2O_6$ requires: C, 51.0; H, 4.4; N, 5.5; Cl, 20.8%) ; m/e 520, 518 and 516; ν_{max} (KBr) 1 720 cm^{-1} (C=O); δ ($CDCl_3$) 6.69 and 6.56 (2H, ABq, J 9 Hz, aromatic), 6.14 and 6.06 (2H, ABq, J 9 Hz, 7-H and 8-H), 4.90 and 4.64 (2H, ABq, J 11 Hz, $-O-CH_2-$), 4.59 (1H, s, 5-H), 4.56 (1H, d, J 6 Hz, H-9), 3.82 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 3.40 (1H, d, J 10β 19 Hz, 10α-H), and 2.49 (3H, s, NCH_3).

Attempted Preparation 14β - Aminocodeinone Dimethyl Acetal (56b) by the Zinc Reduction of the Thebaine/2,2,2-Trichloroethyl Nitrosoformate Adduct (57).

The thebaine/2,2,2-trichloroethyl nitrosoformate adduct (0.2 mmol, 103 mg) and ammonium chloride (2 mmol, 107 mg) were dissolved in

methanol (20 ml). Activated zinc dust (3 mmol, 195 mg) was added to the solution and the mixture stirred with heating under reflux for an hour, filtered while hot and the filtrate evaporated to dryness. The residue was portioned between chloroform and water and the chloroform extracts were combined, washed with brine, dried ($MgSO_4$) and evaporated. The resultant brown oil showed 4 spots on t.l.c. (silica GF_{254} , eluted with 90% $CHCl_3$, 10% MeOH), one with the same R_F as thebaine, the other three spots unidentified. Proton n.m.r. spectroscopy revealed that the mixture contained a little thebaine. The mixture was eluted through an alumina (grade III) column with chloroform. Thebaine (25 mg) was isolated from the mixture; the other compounds could not be identified.

Preparation of 14β-*N*-Hydroxy-*N*-(2,2,2-trichloroethoxycarbonyl)amino-codeinone Dimethyl Acetal (59).

The thebaine/2,2,2-trichloroethyl nitrosoformate adduct (0.2 mmol, 103 mg) was dissolved in 0.2 M methanolic hydrogen chloride (4 ml). The mixture was stirred at 0°C for 15 minutes, then basified with solid sodium hydrogen carbonate. The mixture was diluted with water (10 ml), extracted with chloroform, and the extracts were combined and washed with brine. The extract was dried ($MgSO_4$) and evaporated. Proton n.m.r. spectroscopy revealed that the resultant yellow oil was a mixture of required dimethyl acetal and the original adduct in the ratio 45:55. The oil was dissolved in ethyl acetate and 14β-*N*-

hydroxy-N-(2,2,2-trichloroethoxycarbonyl)aminocodeinone dimethyl acetal crystallised out as white plates (33 mg, 30%) m.p. 161-2°C, ν_{max} (KBr) 3 240 cm^{-1} (OH) and 1 695 cm^{-1} (C=O) (Found: C, 50.4; H, 5.1; N, 5.4; Cl, 19.5. $C_{23}H_{27}Cl_3N_2O_7$ required: C, 50.2; H, 4.9; N, 5.1; Cl, 19.4%) m/e 548 (M^+); δ ($CDCl_3$) 6.75 and 6.55 (2H, ABq, J 7 Hz, aromatic), 6.24 and 5.68 (2H, ABq, J 10 Hz, 7-H and 8-H), 5.03 and 4.60 (2H, ABq, J 12 Hz, $-O-CH_2-$), 4.89 (1H, s, 5-H), 3.88 (3H, s, OCH_3), 3.51 (3H, s, OCH_3), 3.25 (3H, s, OCH_3) and 2.40 (3H, s, NCH_3).

The above reaction was repeated twice at lower temperatures:

A The adduct (1.03 g, 2 mmol) was dissolved in 0.2 M methanolic hydrogen chloride (40 ml) and stirred in an ice/salt bath at -15°C for 25 minutes. The mixture was worked up as above. The proton n.m.r. spectrum of the crude product showed a ketal to adduct ratio of 55:45. Recrystallisation from ethyl acetate yielded the acetal as white plates (0.39 g, 38%).

B The adduct (1.03 g, 2 mmol)was dissolved in 0.2 M methanolic hydrogen chloride (40 ml) and stirred at -78°C for three and a half hours. The reaction mixture was worked up as before. The proton n.m.r. spectrum of the crude product showed an acetal: adduct ratio of 60:40. Recrystallisation from ethyl acetate yielded the acetal as white plates (0.40 g, 39%).

Attempt to Improve the Thebaine/2,2,2-Trichloroethyl Nitrosoformate Adduct to Dimethyl Acetal Equilibrium.

The thebaine/2,2,2-trichloroethyl nitrosoformate adduct (103 mg, 0.2 mmol) dissolved in 0.2 M methanolic hydrogen chloride (4 ml), was stirred at 0°C for 15 minutes. A solution of ammonium iodide (230 mg, 1.6 mmol) in methanol (2 ml) was added dropwise over 5 minutes. No precipitate separated out of solution but the reaction mixture went brown. After stirring at 0°C for a further hour the reaction mixture was basified (solid $NaHCO_3$). The mixture was diluted with water (10 ml), extracted with chloroform, and the extracts were combined and washed with brine. The extract was dried ($MgSO_4$) and evaporated. The proton n.m.r. spectrum of the crude product indicated an acetal to adduct ratio of 55:45. Crystallisation of the oil from ethyl acetate yielded 14β-N-hydroxy-N-(2,2,2-trichloroethoxycarbonyl)aminocodeinone dimethyl acetal (identified by ^1H n.m.r. and i.r. spectra) as white plates (35 mg, 32%).

The above reaction was repeated with ammonium bromide (157 mg, 1.6 mmol) in methanol (2 ml) being added to a solution of the thebaine adduct (57) (103 mg, 0.2 mmol) in 0.2 M methanolic hydrogen chloride (4 ml) at 0°C. Again no precipitate formed. The reaction mixture was worked up as above and the crude oil crystallised from ethyl acetate to yield the dimethyl acetal (59) as white plates (29 mg, 30%).

Preparation of 14β-Aminocodeinone Dimethyl Acetal[89] (56b).

14β-*N*-Hydroxy-*N*-(2,2,2-trichloroethoxycarbonyl)aminocodeinone dimethyl acetal (103 mg, 0.2 mmol) and ammonium chloride (107 mg, 2 mmol) were dissolved in methanol (7 ml). Zinc dust (195 mg, 3 mmol) was added with stirring and the mixture heated under reflux for one hour. The zinc was then filtered off and the filtrate evaporated to dryness. The chloroform extracts were combined, washed with brine, dried ($MgSO_4$), and evaporated. The resultant brown oil was eluted through a neutral alumina (grade 3) column with chloroform. Evaporation of solvent yielded 14β-aminocodeinone dimethyl acetal (56b) as a white crystalline solid (61 mg, 85%); ν_{max} (KBr) 3 400 cm^{-1} (NH_2); δ ($CDCl_3$) 6.65 and 6.52 (2H, ABq, *J* 8 Hz, aromatic H), 5.85 and 5.65 (2H, ABq, *J* 10 Hz, 7-H and 8-H), 4.72 (1H, s, 5-H), 3.89 (3H, s, OCH_3), 3.43 (3H, s, OCH_3), 2.50 (2H, br s, NH_2, exchangeable with D_2O), and 2.38 (3H, s, NCH_3). The ^1H n.m.r. and i.r. spectra were identical with those obtained by R.M. Allen.[89]

Preparation of 14β- Aminocodeinone (55).

14β-Aminocodeinone dimethyl acetal (61 mg, 0.17 mmol) was dissolved in methanol (6 ml) and water (2 ml) and 6 M-hydrochloric acid (12 drops) was added. The mixture was refluxed for half an hour, basified with a saturated solution of sodium hydrogen carbonate and extracted with chloroform. The chloroform extracts were combined, washed with brine, dried ($MgSO_4$) and evaporated yielding 14β-aminocodeinone as an oil. This crystallised from methanol as white needles (37 mg 71%), m.p. 189-191°C (lit.[89] 193-4°C); ν_{max} 3 360 and

3 260 (NH_2) and 1 680 cm^{-1} (conjugated C=O); δ ($CDCl_3$) 6.65 and 6.04 (2H, ABq, J 10 Hz, 7-H and 8-H), 6.61 (2H, s, aromatic), 4.69 (1H, s, 5-H), 3.81 (3H, s, 3-OCH_3), 3.22 (1H, d, $J_{10\beta}$ 19 Hz, 10α-H), 2.88 (1H, d, $J_{10\beta}$ 5 Hz, 9-H), 2.38 (3H, s, NCH_3), and 2.18 (2H, s, NH_2 , exchangeable with D_2O); m/e 312 (M^+), 295 and 255 (Found: C, 69.0; H, 6.35; N, 8.9. $C_{18}H_{20}N_2O_3$ requires C, 69.1; H, 6.45; N, 9.0%).

Attempted Preparation of 14β-Aminocodeinone Dimethyl Acetal (56b).

The thebaine/2,2,2-trichloroethyl nitrosoformate adduct (103 mg, 0.2 mmol) was dissolved in 0.2 M methanolic hydrogen chloride (5 ml) and stirred at 0°C for 15 minutes. Activated zinc dust (195 mg, 3 mmol) was added in portions over 20 minutes and the mixture stirred at room temperature for a further hour and a half. The mixture was basified (5% aqueous $NaHCO_3$) then extracted with chloroform. The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated to yield a brown oil (65 mg). Proton n.m.r. spectroscopy and t.l.c. showed that no starting material remained and that the oil was not the desired dimethyl acetal, however the identity of the oil was not discovered.

Zinc Amalgam Reduction of the Thebaine/2,2,2-Trichloroethyl Nitrosoformate Adduct (57).

The thebaine/2,2,2-trichloroethyl nitrosoformate adduct (1.03 g, 2 mmol) was dissolved in 0.7 M methanolic hydrogen chloride (100 ml)

and stirred at 0°C for 15 minutes. Zinc amalgam[90] (2.5 g, 9 mmol) was then added over 20 minutes in portions to the mixture and then the mixture was stirred for a further hour at 0°C. It was then filtered, basified with solid sodium hydrogen carbonate, and extracted with chloroform. The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated to yield a dark brown oil. The proton n.m.r. spectrum of the crude product showed that it contained thebaine and the dimethyl acetal of 14β-aminocodeinone but no starting material. The two components were separated by chromatography (grade 3 neutral alumina column eluted with chloroform). The first fractions were recrystallised from methanol to yield thebaine as plates (500 mg). The following fractions were recrystallised from chloroform/ethanol to yield 14β-aminocodeinone dimethyl acetal as cream plates (260 mg, 41%); δ ($CDCl_3$) 6.65 and 6.52 (2H, ABq, J 8 Hz, aromatic), 5.85 and 5.65 (2H, ABq, J 10 Hz, 7-H and 8-H), 4.72 (1H, s, 5-H), 3.89 (3H, s, OCH_3), 3.43 (3H, s, OCH_3), 3.20 (3H, s, OCH_3), 2.50 (2H, br s, NH_2, exchangeable with D_2O), and 2.38 (3H, s, NCH_3).

The dimethyl acetal was hydrolysed to 14β-aminocodeinone by the procedure given above. The crude solid was recrystallised from methanol to give the product as white needles (161 mg, 23% based on the adduct) m.p. 188-191°C (lit.[89] 193-4°C).

<u>Aluminium Amalgam Reduction[36] of the Thebaine/2,2,2-Trichloroethyl Nitrosoformate Adduct (57).</u>

The thebaine/2,2,2-trichloroethyl nitrosoformate adduct (206 mg,

0.4 mmol) and mercuric chloride (2·18 g, 8 mmol) were dissolved in methanol (25 ml). Aluminium foil (112 mg, 4 mmol), sanded on each side, was added in pieces over 10 minutes. After the mixture had been stirred at room temperature for 3 hours, a grey precipitate had formed which was removed by filtration through celite. The solution was evaporated, the residue extracted with chloroform, and the combined extracts were washed with brine, dried ($MgSO_4$), and evaporated to yield a thick dark brown oil. In the proton n.m.r. spectrum of this product signals for the olefinic protons, 7-H and 8-H, could not be seen, therefore it was assumed that the compound had been over-reduced. The intractable oil could not be characterised.

Preparation of 14β-N-Hydroxy-N-(2,2,2-trichloroethoxycarbonyl)amino-codeinone Propylene Dithioacetal (62).

The thebaine/2,2,2-trichloroethyl nitrosoformate adduct (206 mg, 0.4 mmol) and boron trifluoride etherate (142 mg, 10. mmol) were dissolved in methylene chloride (10 ml) and stirred under a nitrogen atmosphere at room temperature. Propane-1,3-dithiol (0.1 ml 1.0 mmol) was added and the mixture stirred for one and a half hours. The reaction mixture was then washed with 5% aqueous potassium hydroxide, brine, dried ($MgSO_4$) and evaporated. The proton n.m.r. and i.r. spectra of the orange oil obtained showed it to be 14β-N-hydroxy-N-(2,2,2-trichloroethoxycarbonyl)aminocodeinone propylene dithioacetal (181 mg, 73%), with no trace of adduct (57). As the oil defied all attempts at crystallisation and decomposed on chromatography, only

spectral details can be given; ν_{max} (thin film) 3 200 (OH) and 1 680 cm^{-1} (C=O); δ ($CDCl_3$) 6.65 and 6.54 (2H, ABq, J 8 Hz, aromatic H), 6.08 and 5.79 (2H, ABq, J 10 Hz, 7-H and 8-H), 5.20 (1H, s, 5-H), 4.92 and 4.61 (2H, ABq, J 12 Hz, $-O-CH_2-$), 4.18 (1H, s, 9-H), 3.90 ($3H$, s, OCH_3), 3.3-2.7 (6H, br m, $S-(CH_2)_3-S$), and 2.39 ($3H$, s, NCH_3).

Preparation of 14β-N-Hydroxy-N-(2,2,2-trichloroethoxycarbonyl)amino-codeinone Ethylene Dithioacetal (63).

The thebaine adduct (57) (206 mg, 0.4 mmol) and boron trifluoride etherate (0.185 ml, 1.2 mmol) were dissolved in methylene chloride (10 ml) and stirred under a nitrogen atmosphere at 0°C. Ethane-1,2-dithiol (0.66 ml, 1.0 mmol) was added and the solution stirred at 0°C for a further hour. The reaction mixture was washed with 5% aqueous potassium hydroxide and brine, dried ($MgSO_4$) and evaporated to yield a colourless oil. Repeated attempts to crystallise the oil failed and chromatography decomposed the compound. Spectra showed the compound to be 14β-N-hydroxy-N-(2,2,2-trichloroethoxycarbonyl)amino-codeinone ethylene dithioacetal (85%) and that the product contained no starting material; ν_{max} (thin film) 3 300 (OH) and 1 700 cm^{-1} (C=O); $\delta(CDCl_3)$ 6.72 and 6.60 (2H, ABq, J 8 Hz, aromatic), 5.94 and 5.61 (2H, ABq, J 10 Hz, 7-H and 8-H), 5.21 (1H, s, 5-H), 4.80 (2H, s, $-OCH_2-$), 4.10 (1H, s, 9-H), 3.85 ($3H$, s, OCH_3), 3.20 (4H, m, $S-(CH_2)_2-S$), and 2.35 ($3H$, s, NCH_3).

Attempted Preparation of 14β-N-Hydroxy-N-(2,2,2-trichloroethoxycarbonyl)aminocodeinone Ethylene Acetal (64).

The thebaine adduct (57) (103 mg, 0.2 mmol), ethylene glycol (2 ml) and toluene-p-sulphonic acid (35 mg, 0.22 mmol) were dissolved in anhydrous methanol (25 ml) and heated under reflux for one hour. The solvent was evaporated off and the residue extracted with chloroform. The extracts were combined, washed with brine, dried ($MgSO_4$), and evaporated to yield a brown oil. The proton n.m.r. spectrum of the oil was very complex and the product could not be identified.

Preparation of 14β-N-Hydroxy-N-(2,2,2-trichloroethoxycarbonyl)aminocodeinone Ethylene Acetal (64).

Ethylene glycol was distilled at atmospheric pressure and the middle fraction collected. This was dried (Na_2SO_4) and redistilled twice. Dry hydrogen chloride was passed into the glycol to give a stock, concentrated solution. This was diluted as needed. Solutions of glycolic hydrogen chloride were transferred with syringes through rubber seals.

The thebaine/2,2,2-trichloroethyl nitrosoformate adduct (0.517 g, 1.0 mmol) was dissolved in methylene chloride and added to 0.26 M glycolic hydrogen chloride (15 ml). This mixture was stirred at room temperature for 2 hours, then basified with solid sodium hydrogen carbonate. The mixture was diluted with water (20 ml), extracted with chloroform, and the extracts were combined and washed with brine. The extract was dried ($MgSO_4$) and evaporated yielding 14β-N-hydroxy-

N-(2,2,2-trichloroethoxycarbonyl)aminocodeinone ethylene ketal as a clear oil (0.52 g, 95%). This oil crystallised with some difficulty, from methylene chloride/di-isopropyl ether, as white needles, m.p. 137-8°C (Found: C, 50.6; H, 4.5; N, 5.0. $C_{23}H_{25}Cl_3N_2O_7$ requires C, 50.4; H, 4.6; N, 5.1%); m/e 546 (M^+), 533, 531 and 529; ν_{max} (KBr) 3 420 (OH) and 1 720 cm^{-1} (C=O); $\delta(CDCl_3)$ 6.68 and 6.55 (2H, ABq, J 7 Hz, aromatic), 6.10 and 5.68 (2H, ABq, J 10 Hz, 7-H and 8-H), 4.95 and 4.62 (2H, ABq, J 12 Hz, $-O-CH_2-$), 4.78 (1H, s, 5-H), 4.12 (4H, br m, $O-(CH_2)_2-O$), 3.85 (3H, s, OCH_3), 3.19 (1H, d, $J_{10\alpha}$ 19 Hz, 10β-H), and 2.40 (3H, s, NCH_3).

Preparation of 14β-Aminocodeinone Ethylene Acetal (65).

The thebaine/2,2,2-trichloroethyl nitrosoformate adduct (0.517 g, 1 mmol), dissolved in methylene chloride (1 ml), was added to 0.26 M glycolic hydrogen chloride (15 ml) (as above) and stirred at room temperature for 2 hours. Ammonium carbonate (0.192 g, 2 mmol) was then dissolved in the mixture, zinc powder (0.4 g, 6 mmol) added with stirring, and the mixture heated at 70°C for 1 hour. The zinc was then filtered off, the solution basified with saturated sodium hydrogen carbonate and diluted with water (50 ml). The solution was extracted thoroughly with chloroform and the extracts were combined and washed with brine. After drying ($MgSO_4$), the solvent was evaporated yielding 14β-aminocodeinone ethylene acetal as an oil (0.31 g, 87%). This oil was purified by preparative t.l.c. (silica GF 254, eluted with ethyl

acetate, methanol, and diethylamine in proportions 74:25:1), and the band with R_f 0.17 taken. Recrystallisation from diethyl ether yielded the ethylene ketal as white needles, m.p. 203-4°C, ν_{max} (KBr) 3 400 cm^{-1} (NH_2) (Found: C, 67.2; H, 7.0; N, 7.9. $C_{20}H_{24}N_2O_4$ requires C, 67.4; H, 6.7; N, 7.9%); m/e 356 (M^+); δ ($CDCl_3$) 6.62 and 6.50 (2H, ABq, J 8 Hz, aromatic), 5.84 and 5.66 (2H, ABq, J 9 Hz, 7-H and 8-H), 4.50 (1H, s, 5-H), 4.02 (4H, br m, $-O-CH_2-CH_2-O-$), 3.83 (3H, s, OCH_3), 3.40 (2H, br s, NH_2, exchangeable with D_2O), 3.11 (1H, d, $J_{10\beta}$ 19 Hz, 10α-H), 2.92 (1H, d, $J_{10\beta}$ 6 Hz, 9-H), and 2.35 (3H, s, NCH_3).

Preparation of 14β-Aminocodeinone (55).

The thebaine/2,2,2-trichloroethyl nitrosoformate adduct (0.517 g, 1 mmol), dissolved in CH_2Cl_2 (1 ml), was added to a 0.26 M solution of hydrogen chloride in ethylene glycol (15 ml) and stirred for 2 hours at room temperature (as above). Ammonium carbonate (192 mg, 2 mmol) was then dissolved in the mixture, zinc powder (0.4 g, 6 mmol) added with stirring, and the mixture heated at 70°C for one hour. The zinc was filtered off, the filtrate basified with sodium hydrogen carbonate (saturated solution) and further diluted with water (50 ml). This solution was extracted throughly with chloroform and the extracts combined and washed with brine. After drying ($MgSO_4$) the solvent was evaporated yielding crude 14β-aminocodeinone ethylene acetal as an oil.

The ethylene acetal was dissolved in methanol (6 ml) and water

(3 ml) and 6 M-hydrochloric acid (12 drops) was added. The mixture was refluxed for half an hour, basified with a saturated solution of sodium hydrogen carbonate and extracted with chloroform. The chloroform extracts were combined, washed with brine, dried ($MgSO_4$) and evaporated yielding 14β-aminocodeinone as an oil. This crystallised from methanol as white needles (67-70%), m.p. 189-191°C (lit.[89] 193-4°C) (Found: C, 69.0; H, 6.35; N, 8.9. $C_{18}H_{20}N_2O_3$ requires C, 69.1; H, 6.45; N, 9.0%); m/e 312 (M^+), 295 and 255; ν_{max} (KBr) 3 360 and 3 260 (NH_2) and 1 680 cm^{-1} (conjugated C=O); δ($CDCl_3$) 6.65 and 6.04 (2H, ABq, J 10 Hz, 7-H and 8-H), 6.61 (2H, s, aromatic), 4.69 (1H, s, 5-H), 3.81 (3H, s, 3-OCH_3), 3.22 (1H, d, $J_{10\alpha}$ 19 Hz, 10β-H), 2.88 (1H, d, $J_{10\alpha}$ 5 Hz, 9-H), 2.38 (3H, s, NCH_3), and 2.18 (2H, s, NH_2, exchangeable with D_2O).

5.2.3

Preparation of Trifluoroacetohydroxamic Acid (67).

Trifluoroacetohydroxamic acid was prepared by the method of Pomeroy and Craig.[39] Trifluoroacetic anhydride (8.8 g, 42 mmol) and hydroxylamine hydrochloride (1.38 g, 20 mmol) were heated under reflux for 2 hours. Trifluoroacetic acid and trifluoroacetyl chloride were removed *in vacuo*. The product crystallised from methylene chloride as hygroscopic needles (1.6 g, 61%), m.p. 36-9°C (lit.[39] 32-40°C).

Attempted Preparation of the Thebaine/Nitrosocarbonyltrifluoromethane Adduct (68).

Thebaine (311 mg, 1 mmol) and tetraethylammonium periodate[91] (642 mg, 2 mmol) were dissolved in methylene chloride and stirred at 0°C. Trifluoroacetohydroxamic acid (258 mg, 2 mmol) in methylene chloride (5 ml) was added over 10 minutes and the solution was stirred at 0°C for 1 hour. The reaction mixture was washed with saturated aqueous sodium thiosulphate and brine, dried ($MgSO_4$), and evaporated. The proton n.m.r. spectrum of the brown product oil was identical to one of thebaine.

Attempted Preparation of the Cyclopentadiene/Nitrosocarbonyltrifluoromethane Adduct (66).

After the method of Just and Cutrone[38], freshly distilled cyclopentadiene (0.31 ml, 3.75 mmol) and tetraethylammonium periodate

(802 mg, 2.5 mmol) were dissolved in methylene chloride (20 ml) at -78°C. The solution was vigorously stirred and trifluoroaceto-hydroxamic acid (322 mg, 2.5 mmol) added over 10 minutes. The mixture was stirred at - 78°C for 1 hour, then was washed with saturated aqueous sodium thiosulphate and brine, dried ($MgSO_4$), and evaporated. The mobile brown product oil quickly turned into a crusty black intractable solid, after a few minutes standing at room temperature. The solid could not be identified.

Preparation of Hydroxylamine.[92]

Powdered hydroxylamine hydrochloride (11.5g, 0.16 mol) was dissolved in anhydrous ethanol (18 ml) and the solution stirred vigorously at room temperature. A solution of sodium ethoxide (10.9 g 0.16 mol) in ethanol (70 ml) was added dropwise over 2 hours. The mixture was filtered free of sodium chloride and the filtrate was placed in an acetone-dry ice bath. Hydroxylamine crystallised as white needles, m.p. 33°C, and was collected by filtration and washed with diethyl ether.

Preparation of O-(Diphenylphosphinyl)hydroxylamine (70).

After the method of Kreutzkamp and Schlinder,[42] crystalline hydroxylamine (55 mg, 1.6 mmol) was dissolved in anhydrous benzene (20 ml) and stirred at 5°C. Diphenylphosphinyl chloride[93] (200 mg, 0.83 mmol) in benzene (5 ml) was placed in a dropping funnel protected

with a calcium chloride guard tube and added to the solution over 30 minutes. The mixture was allowed to stand for a further hour at 5-15°C. A white precipitate formed which was collected, washed with water and dried *in vacuo*. The precipitate was crystallised from ethanol to yield *O*-(diphenylphosphinyl)hydroxylamine as white needles (100 mg, 50%), m.p. 130-5°C (lit.[42] 131°C).

Attempted Amination of Thebaine.

Thebaine (78 mg, 0.25 mmol) and *O*-(diphenylphosphinyl)hydroxylamine (116 mg, 0.5 mmol) were dissolved in anhydrous methanol (7 ml). The solution was stirred at room temperature and the course of the reaction followed by t.l.c. (silica GF_{254}, eluted with 10% methanol in chloroform). After one day there appeared to be no change in the reactants thus the mixture was heated under reflux for 15 hours. T.l.c. analysis showed no reaction and indeed a proton n.m.r. spectrum of the reaction mixture showed it to contain thebaine plus aromatic signals probably corresponding to *O*-(diphenylphosphinyl)hydroxylamine.

Attempted Amination of *N*-Benzyloxycarbonylnorthebaine. (*N*-CBz-Northebaine) (71a).

O-(Diphenylphosphinyl)hydroxylamine (116 mg, 0.5 mmol) and *N*-CBz-northebaine (104 mg, 0.25 mmol) were dissolved in anhydrous methanol (7 ml) and stirred at room temperature. After 24 hours, t.l.c. analysis (eluting system as above) showed no change in the mixture.

Thus the mixture was heated under reflux for 15 hours. Evaporation of solvent yielded a yellow oil, the proton n.m.r. spectrum of which showed N-CBz-northebaine and other aromatic signals.

Oxidation of Hydroxylamine in the Presence of Thebaine.

A solution of tetraethylammonium periodate (78 mg, 0.38 mmol) in chloroform (5 ml) was added dropwise over 30 minutes to a stirred solution of thebaine (78 mg, 0.25 mmol) and hydroxylamine (82 mg, 2.5 mmol) in chloroform (10 ml) at 0°C. There was an immediate exothermic reaction and gas was vigorously evolved with each drop added. The reaction mixture was then washed with saturated aqueous sodium thiosulphate and brine, dried ($MgSO_4$) and evaporated. A proton n.m.r. spectrum was immediately taken of the residual yellow oil. The spectrum showed mostly thebaine signals but also signals possibly corresponding to the thebaine/HNO adduct (58); δ ($CDCl_3$) 6.00 and 5.89 (2H, ABq, J 9 Hz, 7-H and 8-H), 4.55 (1H, s, 5-H), 3.80 (3H, s, OCH_3), 3.51 (3H, s, OCH_3), and 2.40 (3H, s, NCH_3). After 20 minutes the spectrum was rerun. The above signals had disappeared and the signals corresponding to thebaine were enhanced.

Preparation of the N-CBz-Northebaine/HNO Adduct (72).

N-CBz-Northebaine (0.618 g, 1.5 mmol) and hydroxylamine (0.495 g, 15 mmol) were dissolved in chloroform (25 ml). Tetraethylammonium periodate (0.725 g, 2.25 mmol) in chloroform (5 ml) was added slowly

over 30 minutes with vigorous stirring. During the addition of the oxidant there was a vigorous evolution of gas and the reaction mixture grew warm. The mixture was washed with saturated aqueous sodium thiosulphate and brine, and dried ($MgSO_4$). Evaporation of solvent yielded a yellow oil (600 mg) which was identified as the N-CBz-northebaine/HNO adduct; $\delta(CDCl_3)$ 7.32 (5H, s, aromatic H), 6.64 and 6.54 (2H, ABq, J 9 Hz, aromatic H), 6.02 and 5.93 (2H, ABq, J 8 Hz, 7-H and 8-H), 5.14 (2H, s, Ar-CH_2-) , 4.52 (1H, s, 5-H), 3.78 (3H, s, OCH_3), 3.48 (3H, s, OCH_3), 2.35 (1H, m, $J_{15\alpha}$ 13 Hz, $J_{16\beta}$ 13 Hz, $J_{16\alpha}$ 9 Hz, 15β-H), and 1.71 (1H, br d, $J_{15\beta}$ 13 Hz, 15α-H). All attempts to crystallise the oil were unsuccessful. After being heated at 80°C in benzene for 5 hours the adduct (72) reverted to N-CBz-northebaine.

Preparation of the N-CBz-Northebaine/Nitrosocarbonylmethane Adduct (73).

A N-CBz-Northebaine (103 mg, 0.25 mmol) was dissolved in chloroform (25 ml) with tetraethylammonium periodate (117 mg, 0.375 mmol) and the mixture stirred at 0°C. A solution of acetohydroxamic acid (56 mg, 0.75 mmol) in chloroform (5 ml) was added over 10 minutes and the solution allowed to stir at 0°C for a further hour. The mixture was then washed with saturated aqueous sodium thiosulphate solution, 5% aqueous sodium hydrogen carbonate, and brine, dried ($MgSO_4$), and evaporated. The resultant yellow oil, the N-CBz-northebaine/nitroso-

carbonylmethane adduct (110 mg, 90%), resisted all attempts at crystallisation; δ ($CDCl_3$) 7.32 (5H, br s, aromatic H), 6.78 and 6.54 (2H, ABq, J 8 Hz, aromatic H), 6.18 amd 6.05 (2H, ABq, J 10 Hz, 7-H and 8-H), 5.17 (2H, br s, Ar-CH_2-), 4.58 (1H, s, 5-H), 3.79 (3H, s, OCH_3), 3.55 (3H, s, OCH_3), and 1.93 (3H, s, CH_3-CO).

B The N-CBz-northebaine/HNO adduct (300 mg, 0.66 mmol) was dissolved in pyridine (5 ml). Acetyl chloride (78 mg, 1 mmol) was added dropwise to the stirred ice-cooled solution over 10 minutes. The mixture was stirred at 0°C for a further hour, then was added to ice water. The aqueous mixture was extracted with chloroform. The combined chloroform extracts were washed with 5% HCl and brine, dried ($MgSO_4$), and evaporated to yield the N-CBz-northebaine/nitrosocarbonylmethane adduct as a yellow oil (310 mg, 87%). The oil was spectrally identical to the adduct (73) made by the 'direct' method. Again the oil could not be crystallised.

Preparation of the N-t-Butoxycarbonylnorthebaine/HNO adduct (74).

N-t-Butoxycarbonylnorthebaine (77 mg, 0.2 mmol) and hydroxylamine (1.0 g, 30 mmol) were dissolved in chloroform (10 ml) and stirred at 0°C. A solution of tetraethylammonium periodate (321 mg, 1 mmol) in chloroform (10 ml) was added dropwise over 15 minutes then the mixture was washed with saturated aqueous sodium thiosulphate and brine. After drying ($MgSO_4$) the solvent was evaporated to yield the N-t-butoxycarbonylnorthebaine/HNO adduct as an amber oil (85 mg, 100%);

$\delta(CDCl_3)$ 6.70 and 6.57 (2H, ABq, J 9 Hz, 1-H and 2-H), 6.05 and 5.92 (2H, ABq, J 9 Hz, 7-H and 8-H), 4.52 (1H, s, 5-H), 3.70 (3H, s, OCH_3), 3.50 (3H, s, OCH_3) and 1.45 (9H, s, $-C(CH_3)_3$). The adduct (74) decomposed to N-t-butoxycarbonylnorthebaine after 4 hours in refluxing benzene.

Preparation of the N-t-Butoxycarbonylnorthebaine/Nitrosocarbonylmethane Adduct (75).

A N-t-Butoxycarbonylnorthebaine (109 mg, 0.5 mmol) and tetraethylammonium periodate (240 mg, 0.75 mmol) were dissolved in chloroform (50 ml) and stirred at 0°C. Acetohydroxamic acid (56 mg, 0.75 mmol) was added in portions over 10 minutes and the solution stirred at 0°C for a further hour. The solution was washed with saturated aqueous sodium thiosulphate, 5% aqueous sodium hydrogen carbonate and brine, and dried ($MgSO_4$). Evaporation yielded the N-t-butoxycarbonylnorthebaine/nitrosocarbonylmethane adduct as an amber oil (210 mg, 89%). The oil was crystallised from ethanol/water to give the adduct (75).hydrate as fine white needles (171 mg, 70%), m.p. 162-4°C (Found: C, 61.5; H, 6.6; N, 5.6. $C_{25}H_{30}N_2O_7.H_2O$ requires C, 61.5; H, 6.6; N, 5.7%); m/e 470; ν_{max} ($CDCl_3$) 1 740 and 1 680 cm^{-1} (C=O); $\delta(CDCl_3)$ 6.69 amd 6.56 (2H, ABq, J 8 Hz, 1-H and 2-H), 6.20 and 5.16 (2H, ABq, J 8 Hz, 7-H and 8-H), 4.59 (1H, s, 5-H), 3.81 (3H, s, OCH_3), 3.58 (3H, s, OCH_3), 1.95 (3H, s, CH_3CO), and 1.46 (9H, s, $C(CH_3)_3$).

B The adduct (75) was also made by the acetylation of the N-t-butoxycarbonylnorthebaine/HNO adduct (74). The adduct (74) (83 mg, 0.2 mmol) was dissolved in pyridine (5 ml) and stirred at 0°C. Acetyl chloride (0.22 ml, 0.3 mmol) was added over 10 minutes and the reaction mixture allowed to stand at room temperature for 1 hour before being added to ice-water. The aqueous solution was extracted with chloroform and the combined extracts were washed with 5% dilute HCl, brine, and dried ($MgSO_4$). Evaporation of solvent yielded the N-t-butoxycarbonylnorthebaine/nitrosocarbonylmethane adduct as an oil. The adduct crystallised from ethanol/water (60 mg, 62%), m.p. 160-2°C. The adduct (75) was spectrally identical to the sample made as above.

Oxidation of Hydroxylamine in the Presence of 2,3-Dimethylbuta-1,3-diene.

2,3-Dimethylbuta-1,3-diene (0.13 ml, 1.2 mmol) and crystalline hydroxylamine (500 mg, 15 mmol) were dissolved in chloroform (10 ml) and stirred at 0°C. Tetraethylammonium periodate (1.2 g, 4.0 mmol) in chloroform (5 ml) was added dropwise over 30 minutes. The reaction mixture was washed with saturated aqueous sodium thiosulphate and brine, dried ($MgSO_4$) and evaporated to yield a very dark brown oil. T.l.c. of this oil showed a streak and proton n.m.r. spectroscopy showed no trace of starting material nor any recognisable product.

Oxidation of Hydroxylamine in the Presence of Bicyclohexenyl.

To an ice-cooled solution of bicyclohexenyl (162 mg, 1 mmol) and

hydroxylamine (1 g, 30 mmol) in chloroform (20 ml) was added tetraethylammonium periodate (1,8 g, 6 mmol) in chloroform (10 ml) with stirring. The reaction mixture was washed with saturated aqueous sodium thiosulphate and brine, and dried ($MgSO_4$). The yellow oil obtained on evaporation of solvent was found to be spectrally identical to bicyclohexenyl, the starting diene.

Oxidation of Hydroxylamine in the Presence of Cyclopentadiene.

Freshly distilled cyclopentadiene (1.23 ml, 15 mmol) and hydroxylamine (0.74 g, 22.5 mmol) dissolved in benzene (10 ml) were stirred at 5°C. A benzene solution of iodine (1.9 g, 7.5 mmol) was added over 30 minutes; vigorous gas evolution occurred. The mixture was washed with saturated aqueous sodium thiosulphate and brine, dried ($MgSO_4$) and the solvent was removed by cold evaporation. After standing at room temperature for a few minutes the brown oil obtained turned into a crusty black powder which was insoluble in all organic solvents tried.

The above reaction was repeated using the same amounts of reagents. This time, after washing and drying, the reaction mixture was treated with acetic anhydride (2.04 g, 20 mmol) and pyridine (1 ml) in an effort to acetylate and thus stabilise the putative 'HNO' adduct. The solution was washed with 5% dilute HCl, 5% aqueous $NaHCO_3$ and brine, after standing at room temperature for 30 minutes. The dried

($MgSO_4$), clear solution was evaporated to yield a brown mobile oil which again turned into a crusty black powder on standing.

Oxidation of Hydroxylamine in the Presence of Cyclohexa-1,3-diene.

Cyclohexa-1,3-diene (0.19 ml, 2 mmol) and hydroxylamine (660 mg, 20 mmol) were dissolved in chloroform (15 ml) and stirred at 0°C. A solution of tetraethylammonium periodate (1.3 g, 4 mmol) was added over 15 minutes and gas was vigorously evolved. The solution was washed with water, dried ($MgSO_4$), and the solvent was evaporated to yield a brown viscous oil. T.l.c. analysis of this oil showed a streak. The proton n.m.r. spectrum of the oil showed methylene signals (ca. δ2.2) and an olefinic multiplet at δ6.60, downfield from where the cyclohexa-1,3-diene olefinic signals appear (δ5.80). There appeared to be no cyclohexa-1,3-diene in the mixture, however the product(s) could not be identified.

5.4.1

Preparation of Bromotriphenylpropylphosphorane (128).

Triphenyl phosphine (1.6 g, 6 mmol) and n-propyl bromide (0.74 g, 6 mmol) were heated in a sealed vial at 150°C for 1 hour. This yielded bromotriphenylpropylphosphorane (2.3 g) as a white crystalline powder which was washed with benzene and dried in vacuo, m.p. 213-2°C (lit.[81] m.p. 229-230°C).

Preparation of Oct-5-en-1-ol (127).

Bromotriphenylpropylphosphorane (7.72 g, 20 mmol) was suspended in tetrahydrofuran (200 ml) and stirred at -78°C under a nitrogen atmosphere. A 1.6 M hexane solution of n-butyl-lithium (30 ml, 4.8 mmol) was added over 30 minutes and the solution stirred for a further 30 minutes at -78°C. 5-Hydroxypentanal[94] (2.45 g, 24 mmol) was slowly added to the red mixture and the solution was stirred at room temperature overnight. The mixture, which had gone brown, was then refluxed for one and a half hours, water (1 ml) added, and the solvent evaporated. The residue was extracted with light petrol (b.p. 40-60°C) and the combined extracts were washed with water, dried ($MgSO_4$) and evaporated. The resultant viscous brown oil was distilled to yield oct-5-en-1-ol as a colourless mobile liquid (1.8 g, 70%), b.p. 100°C/25 mm Hg (lit.[95] b.p. 91.5°C at 14 mm Hg); ν_{max} (thin film) 3 340 cm^{-1} (OH); $\delta(CDCl_3)$ 5.32 (2H, m, olefinic H), 3.61 (2H, t, J 7 Hz, $-CH_2-O$), 2.00 (2H, br t, J 7 Hz, allylic H), 1.98 (2H, br m, allylic H), 1.82 (1H, br s, OH, exchangeable with D_2O), 1.48 (4H, br m, methylene H), 0.90 (3H, t, J 7 Hz, $-CH_3$).

Oxidation of Oct-5-en-1-ol to Oct-5-enoic Acid (126).

(Using the method of Schroder and Griffith.[82])

Potassium hydroxide (11.2 g, 200 mmol), potassium persulphate (24.3 g, 90 mmol) and ruthenium trichloride (70 mg, 0.2 mmol) were dissolved in water (800 ml). Oct-5-en-1-ol (1.28 g, 10 mmol) was added to this orange solution which immediately went dark green. The reaction mixture was stirred overnight at room temperature by which time it had turned orange again. The mixture was acidified (5% H_2SO_4), extracted with diethyl ether and the combined extracts were dried ($MgSO_4$) and evaporated to yield a black oil. Oct-5-enoic acid was obtained by distillation as a colourless oil (1.0 g, 71%), b.p. 82-5°C/0.15 mm Hg (lit.[80] b.p. 85-7°C/0.20 mm Hg); ν_{max} (thin film) 3 200-2 500 (OH) and 1 705 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 10.75 (1H, br s, CO_2H, exchangeable with D_2O), 5.35 (2H, m, olefinic H), 2.32 (2H, t, J 7 Hz, $-CH_2-CO$), 2.05 (4H, br m, allylic H), 1.70 (2H, br t, J 7 Hz, methylene H), 0.90 (3H, t, J 7 Hz, $-CH_3$); $\delta_C(CDCl_3)$ 180.5 (C=O), 127.7 (5-C), 133.0(6-C) 33.5 (2-C), 26.4 (3-C), 24.7 (4-C), 20.6 (7-C), and 14.3 (8-C).

Preparation of Ethyl Oct-5-enoate.

A solution of oct-5-enoic acid (1.78 g, 12.5 mmol) in 0.25 M ethanolic hydrogen chloride (25 ml) was stirred for 15 hours at room temperature. The solvent was removed and the residue was dissolved in ether. The ethereal solution was washed with water and a 5% aqueous solution of sodium carbonate, dried ($MgSO_4$), and evaporated to yield a yellow oil. The oil was distilled to give ethyl oct-5-enoate as a colourless oil

(1.53 g, 72%), b.p. 70°C/10 mm Hg; ν_{max} 1 730 cm^{-1} (C=O); δ ($CDCl_3$) 5.35 (2H, m, olefinic H), 4.12 (2H, q, J 8 Hz, $-O-CH_2-$), 2.30 (2H, t, J 7 Hz, $-CH_2CO$), 2.05 (4H, m, allylic H), 1.70 (2H, br t, J 7 Hz, methylene H), 1.20 (3H, t, J 8 Hz, $-O-C-CH_3$), and 0.90 (3H, t, J 7 Hz, $-CH_3$).

Preparation of Oct-5-enohydroxamic Acid (129).

Sodium (0.38 g, 16.5 mmol) was dissolved in ethanol (9 ml). Half of this solution was added to a solution of hydroxylamine hydrochloride (0.69 g, 9.9 mmol) in ethanol (14 ml). This hydroxylamine solution was added with stirring to ethyl oct-5-enoate (1.13 g, 6.6 mmol) in ethanol (3 ml) at 0°C. After 4 hours stirring at 0°C the remainder of the ethoxide solution was added and the mixture left to stand at room temperature for a further 2 hours. The solvent was evaporated, the residue dissolved in water (5 ml), acidified (5% dilute HCl), and extracted with chloroform. The chloroform extracts were combined, dried ($MgSO_4$), and evaporated to yield oct-5-enohydroxamic acid as an amber oil (0.82 g, 80%). The oil was purified by column chromatography (florisil, eluted with 10% methanol in chloroform) but could not be persuaded to crystallise; m/e 157 (M^+); ν_{max} (thin film) 3 300 (N-H and O-H) and 1 670 cm^{-1} (C=O); δ ($CDCl_3$) 8.52 (2H, br s, NH and OH, exchangeable with D_2O), 5.35 (2H, m, olefinic H), 2.30 (2H, t, J 7 Hz, $-CH_2-CO$), 2.05 (4H, br m, methylene H), 1.62 (2H, br t, J 7Hz, methylene H), and 0.90 (3H, t, J 7Hz, $-CH_3$).

Periodate Oxidation of Oct-5-enohydroxamic Acid (129).

Oct-5-enohydroxamic acid (100 mg, 0.64 mmol) in methylene chloride (15 ml) was added dropwise to a stirred solution of tetraethylammonium periodate (320 mg, 1 mmol) at 0°C. The mixture was stirred at 0°C for 1 hour and was then washed with a saturated solution of sodium thiosulphate and brine, dried ($MgSO_4$) and evaporated. The resultant dark bown oil (115 mg) showed numerous spots on t.l.c. [silica GF_{254}, eluted with 20% light petrol (b.p. 40-60°C) in ethyl acetate]. Proton n.m.r. spectroscopy showed that the product contained, among other things, oct-5-enoic acid, but it could not be characterised further.

Preparation of the Cyclopentadiene/1-Nitrosocarbonylhept-4-ene Adduct (130).

A solution of oct-5-enohydroxamic acid (100 mg, 0.64 mmol) in methylene chloride (5 ml) was added dropwise to a stirred solution of tetraethylammonium periodate (320 mg, 1 mmol) and freshly distilled cyclopentadiene (0.08 ml, 1 mmol) in methylene chloride (15 ml) at 0°C. The mixture was stirred for 1 hour at 0°C and was then washed with saturated aqueous sodium thiosulphate, 5% aqueous sodium hydrogen carbonate, and brine. The solution was dried ($MgSO_4$) and evaporated to yield the crude cyclopentadiene/1-nitrosocarbonylhept-4-ene adduct as an oil (136 mg, 95%). This oil was purified by preparative t.l.c. [R_F 0.4, silica GF_{254} eluted with ethyl acetate and light petrol (b.p. 40-60°C) in the ratio 4:1].

The resultant amber oil (90 mg, 65%) could not be persuaded to crystallise; m/e 221 (M^+), 155, and 139: ν_{max} (thin film) 1 725 and 1 680 cm^{-1} (C=O); δ ($CDCl_3$) 6.45 (2H, d m, ring olefinic H), 5.35 (4H, m, methine H and chain olefinic H), 2.14-1.5 (10H, br m, methylene H), and 0.90 (3H, t, $-CH_3$).

Thermolysis of the Cyclopentadiene/1-Nitrosocarbonylhept-4-ene Adduct (130).

The adduct (130) (100 mg, 0.45 mmol) was dissolved in anhydrous benzene (20 ml) in a 50 ml R.B. flask fitted with a condenser set for distillation and an equilibrating dropping funnel filled with benzene. Benzene was distilled off and the solvent level topped up from the dropping funnel. The course of the reaction was followed by t.l.c. [silica GF_{254}, eluted with ethyl acetate and light petrol (b.p. 40-60°C) in the ratio 4:1]. After 24 hours the reaction seemed to be over as the adduct spot (R_F 0.4) had disappeared, although a dark streak at the baseline and a ferric chloride positive spot had appeared. Evaporation of solvent revealed a dark brown viscous oil which proved to be intractable.

Attempted Preparation of the 9,10-Dimethylanthracene (DMA)/1-Nitrosocarbonylhept-4-ene Adduct (131).

Tetraethylammonium periodate (193 mg, 0.6 mmol) and DMA (103 mg, 0.5 mmol) were dissolved in methylene chloride (10 ml) and vigorously stirred at 0°C. A solution of oct-5-enohydroxamic acid

(94 mg, 0.6 mmol) in methylene chloride (2 ml) was added dropwise over 10 minutes and the mixture stirred at 0°C for a further hour. The solution was washed with saturated aqueous sodium thiosulphate, 5% aqueous sodium hydrogen carbonate, and brine, dried ($MgSO_4$) and evaporated to yield a yellow solid. The proton n.m.r. spectrum revealed that the solid was a 1:1 mixture of the DMA adduct (131) and DMA. Attempts to recrystallise the DMA adduct caused it to decompose to DMA.

The two component mixture was subjected to preparative t.l.c. [silica GF_{254}, eluted with 75% ethyl acetate, 25% light petrol (b.p. 40-60°C)]. DMA was easily separated as a bright yellow band (R_F 0.8). A band at R_F 0.6 yielded a white crystalline material which was recrystallised from benzene/light petrol (b.p. 40-60°C) as white needles, m.p. 198-202°C; δ ($CDCl_3$) 7.30 (8H, br m, aromatic H) and 2.10 (6H, s, methyl H), m/e 266, 206 (no molecular ion). The i.r. spectrum of this compound showed no O-H or carbonyl stretching bands. It was thought to be a decomposition product of the DMA adduct (131), catalysed in some manner by the silica. The third band was a 1:1 mixture of the decomposition product and the DMA adduct (131).

The mixture of DMA and DMA adduct (131) was eluted through a neutral alumina column with 20% light petrol (b.p. 40-60°C) and 80% ethyl acetate. Again DMA was easily separated as a bright yellow fraction, however other fractions were mixtures of the DMA adduct (131) and the decomposition product, in varying proportions.

Preparation of the DMA/1-nitrosocarbonylpentane Adduct (132) via Acylation of the DMA/HNO Adduct[44] (76).

Hexanoic acid (88 mg, 0.75 mmol) was heated at 80°C with thionyl chloride (120 mg, 1 mmol) for one and a half hours. This crude acid chloride was then added with stirring at 0°C to a solution of DMA/HNO.HCl[44] (76) (137 mg, 0.5 mmol) in pyridine (5 ml) at 0°C. The mixture was stirred at 0°C for 1 hour and was then added to ice water and extracted with chloroform. The combined chloroform extracts were washed with 5% aqueous HCl, and brine, dried ($MgSO_4$) and evaporated to yield the DMA/1-nitrosocarbonylpentane adduct (132) as a yellow crystalline solid (160 mg). This solid was chromatographed (florisil column eluted with 30% chloroform and 70% carbon tetrachloride) and the white crystalline DMA adduct (132) was recrystallised from ethyl acetate/light petrol (b.p. 60-80°C) as white needles (85 mg), m.p. 112.5-114°C; ν_{max} (KBr) 1 684 cm^{-1} (C=O); δ ($CDCl_3$) 7.30 (8H, br m, aromatic H), 2.68 (3H, s, -O-C-CH_3) 2.18 (3H, s, -N-C-CH_3), 2.10 (2H, t, J 7 Hz, -CH_2CO), 1.4-0.9 (6H, br m, methylene H), and 0.72 (3H, t, methyl).

Preparation of the DMA/1-Nitrosocarbonylhept-4-ene Adduct (131) via Acylation of the DMA/HNO Adduct (76).

Oct-5-enoic acid (142 mg, 10. mmol) and thionyl chloride (0.09 ml, 1.2 mmol), in benzene (2 ml), were heated under reflux for 1 hour. This acid chloride solution was cooled and added to a

stirred solution of DMA/HNO.HCl (274 mg, 1.0 mmol) in anhydrous pyridine (5 ml) at 0°C. After one and a half hours the solution was added to ice water and the mixture extracted with chloroform. The combined chloroform extracts were washed with 5% aqueous HCl and brine, dried ($MgSO_4$) and evaporated. The yellow oil obtained proved (^1H n.m.r.) to be a mixture of DMA and the DMA adduct (131) in the ratio 25:75 respectively. The mixture (350 mg) was chromatographed (florisil column eluted with 5% chloroform, 95% carbon tetrachloride) and some DMA/1-nitrosocarbonylhept-4-ene adduct separated as an orange oil (100 mg); ν_{max} (thin film) 1 670 cm^{-1} (C=O); $\delta(CDCl_3)$ 7.35 (8H, br m, aromatic H), 5.20 (2H, m, olefinic H), 2.66 (3H, s, $-O-C-CH_3$), 2.16 (3H, s, $-N-C-CH_3$), 2.09 (2H, t, J 7 Hz, $-CH_2-CO$), 2.0-1.2 (6H, br m, methylene H), and 0.90 (3H, t, methyl).

Thermolysis of the DMA/1-Nitrosocarbonylhept-4-ene Adduct (131).

A mixture (250 mg total) of DMA (0.45 mmol) and the DMA adduct (131) (0.45 mmol) was dissolved in benzene (10 ml) and heated under reflux in a nitrogen atmosphere for 3 hours. The solvent was evaporated to yield a yellow solid. The proton n.m.r. spectrum revealed the solid to be mostly DMA with no DMA adduct remaining. There were also signals indicating the presence of oct-5-enoic acid, and a doublet at δ1.68 and a multiplet at δ 5.6 of unknown origin. Analysis of the mixture by t.l.c. [silica GF_{254} , eluted with ethyl acetate, light petrol (b.p. 40-60°C), and acetic acid in the ratio 8: 1.9: 0.1] showed a spot (R_F 0.5) corresponding to DMA, a spot at R_F 0.2 corresponding to oct-5-enoic acid, and a ferric active spot

(R_F 0.1). The mixture was eluted through a florisil column (eluant 10% methanol and 90% chloroform) and the ferric active material separated as a dark brown viscous oil (30 mg) which could not be identified.

The above reaction was repeated using only the DMA/1-nitroso-carbonylhept-4-ene adduct (450 mg) in benzene (30 ml). The solvent was evaporated after the mixture had been heated under reflux for 3 hours. Proton n.m.r. spectroscopy revealed only signals associated with oct-5-enoic acid and DMA. Analysis of the mixture by t.l.c. (system as above) showed the presence of DMA and oct-5-enoic acid, but no ferric active material.

5.4.2

Preparation of N-(3,3-Dimethylallyloxycarbonyl)hydroxylamine (143).

3,3-Dimethylallyl alcohol (1.1 ml, 10 mmol) was added dropwise to a stirred 12.5% solution of phosgene in toluene (17.5 ml, 20 mmol) at -40°C. The reaction mixture was stirred for 3 hours at -40°C and was then slowly added with shaking to an ice-cooled solution of hydroxylamine hydrochloride (3.5 g, 50 mmol) and sodium hydroxide (2.8 g, 70 mmol) in water (50 ml). The mixture was shaken at room temperature for 1 hour then acidified (5% dilute HCl) and extracted with diethyl ether. The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated to yield a yellow oil. Elution of this oil through a florisil column with 5% methanol in chloroform gave N-(3,3-dimethylallyloxycarbonyl)hydroxylamine as a colourless oil (650 mg, 45%); m/e 145 (M^+); ν_{max} (thin film) 3 300 (N-H and O-H) and 1 715 cm^{-1} (C=O); $\delta(CDCl_3)$ 7.60 (2H, br s, NH and OH, exchangeable with D_2O), 5.39 (1H, t m, J 8 Hz and allylic coupling, olefinic H), 4.61 (2H, d, J 8 Hz, $-O-CH_2-$), and 1.70 (6H, br s, methyl H).

Oxidation of N-(3,3-Dimethylallyloxycarbonyl)hydroxylamine (143).

N-(3,3-Dimethylallyloxycarbonyl)hydroxylamine (25 mg, 0.16 mmol) was dissolved in chloroform (5 ml) and stirred at 0°C. A solution of tetraethylammonium periodate (16 mg, 0.05 mmol) was slowly added over 10 minutes and the mixture stirred at 0°C for 1 hour. The reaction mixture was washed with saturated aqueous sodium thiosulphate and

brine, dried ($MgSO_4$) and evaporated to give a dark brown oil. T.l.c. analysis of this oil showed numerous spots and the oil was not further investigated.

The Cyclopentadiene/3,3-Dimethylallyl Nitrosoformate Adduct (144).

A solution of freshly distilled cyclopentadiene (0.33 ml, 4 mmol) in ethyl acetate (70 ml) and a solution of sodium periodate (428 mg, 2 mmol) in 0.5 M sodium acetate-acetic acid buffer (pH 6, 35 ml) were mixed and vigorously stirred at 0°C. N-(3,3-Dimethylallyloxycarbonyl)hydroxylamine (290 mg, 2 mmol) in ethyl acetate (5 ml) was added over 10 minutes and the mixture stirred at 0°C for a further hour. The organic layer was then separated, washed with brine, and dried ($MgSO_4$). Evaporation of solvent gave the cyclopentadiene/3,3-dimethylallyl nitrosoformate adduct as an amber oil. The adduct was purified by preparative t.l.c. (silica GF_{254}, eluted with 5% methanol in chloroform) and obtained as a colourless oil (350 mg, 83%); ν_{max} (CCl_4) 1 750 and 1 705 cm^{-1} (C=O); δ ($CDCl_3$) 6.41 (2H, br s, olefinic H), 5.35 (1H, t m, J 8 Hz, olefinic H), 5.24 (1H, br s, -N-C-H or -O-C-H), 5.04 (1H, br s, -N-C-H or -O-C-H), 4.62 (2H, br d, J 8 Hz, $=C-CH_2-$), 1.99 (1H, d m, J 9 Hz, methylene H), 1.72(3H, br s, $-CH_3$), and 1.68 (3H, s, $-CH_3$).

Thermolysis of the Cyclopentadiene/3,3-Dimethylallyl Nitrosoformate. Adduct (144).

The cyclopentadiene/3,3-dimethylallyl nitrosoformate adduct

(50 mg, 0.24 mmol) was heated under reflux in anhydrous benzene (40 ml) under a nitrogen atmosphere. The reaction was followed by t.l.c. (silica GF_{254}, eluted with 5% methanol in chloroform) and was judged to be complete after 3 hours. Evaporation of solvent yielded N-hydroxy-4-isopropenyl-oxazolid-2-one (145) as a brown oil (33 mg, 98%) which was shown to be substantially pure by proton n.m.r. spectroscopy. The oil was crystallised from hexane, m.p. 74.5-75°C (Found: C, 50.4; H, 6.3; N, 9.7. $C_6H_9NO_3$ requires C, 50.35; H, 6.3: N, 9.8%); m/e 143 (M^+), 127, and 112; ν_{max} (CCl_4 soln.) 3 250 (O-H) and 1 775 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 5.14 (2H, m, J_{XA} 0.5 Hz, $=CH_2$), 4.43 (1H, m, J_{AB} 8.5 Hz, J_{AC} 8.6 Hz, J_{AX} 0.5 Hz, $N-C-H_A$), 4.41 (1H, m, J_{BC} -8.7 Hz, J_{BA} + 8.5 Hz, $O-C-H_B$), 4.02 (1H, m, J_{CB} -8.7 Hz, J_{CA} + 8.6 Hz, $O-C-H_C$), 1.77 (3H, br s, $-CH_3$); δ_C ($CDCl_3$) 161.1 (s, C=O), 139.1 (s, $R_1R_2C=$), 117.0 (t, $=CH_2$), 65.8 (t, $-O-CH_2-$), 6.48 (d, -N-C-H), and 29.7 (q, $-CH_3$). δ and J values for the ^1H ABCX system were obtained by computer simulation of 100 and 360 MHz spectra.

Preparation of N-(2-Methylprop-2-enyloxycarbonyl)hydroxylamine (148).

2-Methylprop-2-en-1-ol (0.84 ml, 10 mmol) in toluene (4 ml) was added to a 12.5% solution of phosgene in toluene (17.6 ml, 20 mmol) at 0°C with stirring. After being stirred at 0°C for 3 hours the mixture was added with shaking to a solution of hydroxylamine hydrochloride (3.5 g, 50 mmol) and sodium hydroxide (2.8 g, 70 mmol) in water (50 ml). The reaction mixture was shaken for 1 hour, then acidified (5% dilute HCl) and extracted with diethyl ether. The combined extracts were

washed with brine, dried ($MgSO_4$) and evaporated to yield a mobile yellow oil. The oil was purified by preparative t.l.c. (silica GF_{254}, eluted with 10% methanol in chloroform) yielding N-(2-methylprop-2-enyloxycarbonyl)hydroxylamine as a colourless oil (0.64 g, 49%); m/e 131 (M^+); ν_{max} (thin film) 3 300 (N-H and O-H) and 1 720 cm^{-1} (C=O); $\delta(CDCl_3)$ 7.72 (2H, br s, NH and OH, exchangeable with D_2O), 4.98 (1H, br s, olefinic H), 4.92 (1H, br s, olefinic H), 4.55 (2H,s, $-CH_2-O-$), and 1.71 (3H, s, $-CH_3$).

The Cyclopentadiene/2-Methylprop-2-enyl Nitrosoformate Adduct (149).

Sodium periodate (492 mg, 2.3 mmol) in 0.5 M sodium acetate-acetic acid buffer (pH 6, 20 ml) and cyclopentadiene (0.33 ml, 4 mmol) in ethyl acetate (40 ml) were stirred together vigorously at 0°C. A solution of N-(2-methylprop-2-enyloxycarbonyl)hydroxylamine (300 mg, 2.3 mmol) in ethyl acetate (5 ml) was added over 10 minutes and the reaction mixture stirred at 0°C for 1 hour. The organic layer was separated, washed with saturated aqueous sodium thiosulphate and brine, and dried ($MgSO_4$). Evaporation of solvent yielded a yellow oil which on distillation (Kugelrohr, 110°C at 0.015 mm Hg) gave the cyclopentadiene/2-methylprop-2-enyl nitrosoformate adduct as a colourless oil (340 mg, 74%); m/e 195 (M^+); ν_{max} (CCl_4 soln.) 1 755 and 1 705 cm^{-1} (C=O); $\delta(CDCl_3)$ 6.42 (2H, br s, olefinic H), 5.25 (1H, br s, -N-C-H or -O-C-H), 5.05 (1H, br s, -N-C-H or -O-C-H), 4.95 (2H, br s, olefinic H), 4.52 (2H, s, $-O-CH_2-$), 1.98 (1H, d m, J 9 Hz, methylene H), 1.76 (1H, d, J 9 Hz, methylene H), and 1.72

(3H, s, $-CH_3$) (Found: M^+ 195.0900. $C_{10}H_{13}NO_3$ requires 195.0895).

Thermolysis of the Cyclopentadiene/2-Methylprop-2-enyl Nitrosoformate Adduct (149).

A benzene solution of the adduct (149) (50 mg, 0.26 mmol) was heated under reflux under a nitrogen atmosphere. After 21 hours n.m.r. spectroscopy showed the mixture still to contain ca. 50% adduct (149). The reaction was judged to be essentially complete after 40 hours. T.l.c.analysis of the reaction mixture showed numerous spots, the major one being ferric active (R_F 0.4). The reaction was repeated using toluene as solvent. The adduct (280 mg, 1.43 mmol) was dissolved in toluene (60 ml) and heated under reflux under nitrogen. After 9 hours no starting material remained. Evaporation of solvent yielded a brown oil which was purified by preparative t.l.c. (silica GF_{254}, eluted with 10% methanol in chloroform). Crystallisation of the resultant solid from di-isopropyl ether gave dihydro-3-hydroxy-5-methylene-3H-1,3-oxazin-2-one (147) as white needles (66 mg, 34%), m.p. 68-9°C (Found: C, 46.5; H, 5.5; N, 10.55. $C_5H_7NO_3$ requires C, 46.5; H, 5.4; N, 10.85%); m/e 129 (M^+), 113, 95; ν_{max} (CCl_4 soln.) 3 220 (O-H) and 1 705 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 7.45 (1H, br s, OH exchangeable with D_2O), 5.24 (2H, m, olefinic H), 4.61 (2H, br s, $-O-CH_2-$), and 4.31 (2H, br s, $-N-CH_2-$); $\delta_C(CDCl_3)$ 156.3 (C=O), 133.3 ($R_1R_2C=$), 114.4 ($=CH_2$), 70.1 ($-O-CH_2$), and 54.0 ($-N-CH_2$).

Preparation of N-(Cinnamyloxycarbonyl)hydroxylamine (153).

A solution of cinnamyl alcohol (1.34 g, 10 mmol) in toluene (5 ml)

was added with stirring to a solution of phosgene in toluene (12.5%; 20 mmol, 17.6 ml) at -78°C. The mixture was stirred at this temperature for 3 hours and was then added slowly with shaking to an ice-cooled aqueous solution (50 ml) of hydroxylamine hydrochloride (3.5 g, 50 mmol) and sodium hydroxide (2.8 g, 70 mmol). The reaction mixture was shaken for one hour, then it was acidified (5% dilute HCl) and washed with brine. Drying ($MgSO_4$) and evaporation gave a brown oil which was eluted through a florisil column (10% methanol in chloroform). This yielded N-(cinnamyloxycarbonyl)hydroxylamine as a colourless oil which crystallised from benzene/hexane as white platelets (0.85 g, 44%), m.p. 92-4°C (Found: C, 62.2; H, 5.5; N, 7.3. $C_{10}H_{11}NO_3$ requires C, 62.2; H, 5.7; N, 7.25%); m/e 193 (M^+); ν_{max} (KBr) 3 320 (N-H and O-H) and 1 695 cm^{-1} (C=O); δ ($CDCl_3$) 7.65 (2H, br s, NH and OH, exchangeable with D_2O), 7.32 (5H, br s, aromatic H), 6.64 (1H, d, J 15 Hz, Ar-CH=), 6.25 (1H, d t, J 15 Hz, J 7 Hz, =CH-C-O), and 4.77 (2H, d, J 7 Hz, $-O-CH_2-$).

The Cyclopentadiene/Cinnamyl Nitrosoformate Adduct (154).

N-(Cinnamyloxycarbonyl)hydroxylamine (410 mg, 2.12 mmol) in chloroform (10 ml) was added with stirring to a solution of cyclopentadiene (0.33 ml, 4 mmol) and tetraethylammonium periodate (642 mg, 2 mmol) in chloroform (40 ml) at 0°C. The mixture was stirred at 0°C for 1 hour, and was then washed with saturated aqueous sodium thiosulphate and brine, dried ($MgSO_4$) and evaporated. The residual brown oil was eluted through a silica column with 5% methanol in chloroform, and the resultant colourless oil crystallised from ethyl

acetate/light petrol (b.p. 40-60°C) to yield the cyclopentadiene/cinnamyl nitrosoformate adduct as white prisms (350 mg, 64%), m.p. 60.5-62°C (Found: C, 70.1; H, 5.6; N, 5.4. $C_{15}H_{15}NO_3$ requires C, 70.0; H, 5.8; N, 5.45%); m/e 257 (M^+) and 241; ν_{max} (KBr) 1 705 cm^{-1} (C=O); δ ($CDCl_3$) 7.32 (5H, br s, aromatic H), 6.65 (1H, d, J 15 Hz, Ar-CH=), 6.42 (2H, br s, olefinic H), 6.25 (1H, d t, J 15 Hz and 7 Hz, =CH-C-O), 5.22 (1H, br s, -N-C-H or -O-C-H), 5.09 (1H, br s, -N-C-H or -O-C-H), 4.78 (2H, d, J 7 Hz, -O-CH_2-), 1.98 (1H, d m, J 8 Hz, methylene H), and 1.72 (1H, d, J 8 Hz, methylene H).

Thermolysis of the Cyclopentadiene/Cinnamyl Nitrosoformate (154).

The cyclopentadiene/cinnamyl nitrosoformate adduct (50 mg, 0.19 mmol) was dissolved in benzene (40 ml) and heated under reflux in a nitrogen atmosphere. The reaction was followed by t.l.c. However after 10 hours there was still no change, a fact confirmed, after evaporation of solvent, by a proton n.m.r. spectrum. The adduct (154) was then dissolved in toluene (40 ml) and refluxed under nitrogen for another 16 hours. Evaporation of solvent gave a black oil which showed numerous spots on t.l.c. and no recognisable signals in its n.m.r. spectrum.

Attempted Cyclisation of Cinnamyl Nitrosoformate with Base Catalysis.

The cyclopentadiene/cinnamyl nitrosoformate adduct (100 mg, 0.38 mmol) and NN^1-di-t-butylformamidine (50 mg) were dissolved in benzene and heated under reflux for 21 hours in a nitrogen atmosphere. Solvent was evaporated to yield a dark brown oil which proved to be a

mixture of the two starting materials by n.m.r. and t.l.c. analysis.

Preparation of 4-Methylpent-3-en-1-ol.

Ethyl 4-methylpent-3-enoate was prepared after the method of Hirai and Matsui.[84] This ester was reduced di-isobutylaluminium hydride in anhydrous diethyl ether to give 4-methylpent-3-en-1-ol, b.p. 155-9°C at atmospheric pressure (lit.[96] 157-8°C/771 mm Hg).

Preparation of N-(4-Methylpent-3-enyloxycarbonyl)hydroxylamine (157).

To a solution of phosgene in toluene (12.5 %; 5.3 ml, 6 mmol) at 0°C was added 4-methylpent-3-en-1-ol (300 mg, 3 mmol) with stirring. The solution was stirred for 3 hours at 0°C and was then added with shaking to a solution of hydroxylamine hydrochloride (1.08 g, 15.5 mmol) and sodium hydroxide (0.84 g, 21 mmol) in water (24 ml). The mixture was shaken for 1 hour, then it was acidified (5% dilute HCl) and extracted with diethyl ether. The combined ether extracts were washed with brine and dried ($MgSO_4$). The amber oil obtained on evaporation of solvent was eluted through a florisil column (5% methanol in chloroform) to yield N-(4-methylpent-3-enyloxycarbonyl)hydroxylamine as a colourless oil (200 mg, 42%) which could not be crystallised; ν_{max} (thin film) 3 300 (N-H and O-H) and 1 720 cm^{-1} (C=O); δ ($CDCl_3$) 7.25 (2H, br s, NH and OH, exchangeable with D_2O), 5.11 (1H, t m, J 8 Hz, olefinic H), 4.22 (2H, t, J 8 Hz, $-O-CH_2-$), 2.33 (2H, br q, J 8 Hz, $=C-CH_2-$), 1.69 (3H, s, $-CH_3$), and 1.60 (3H, s, $-CH_3$).

The Cyclopentadiene/4-Methylpent-3-enyl Nitrosoformate Adduct (158).

A solution of N-(4-methylpent-3-enyloxycarbonyl)hydroxylamine (170 mg, 1.07 mmol) in ethyl acetate (2 ml) was added over 10 minutes to an ice-cooled mixture of cyclopentadiene (0.33 ml, 4 mmol) in ethyl acetate (50 ml) and sodium periodate (230 mg, 1.07 mmol) in 0.5 M sodium acetate-acetic acid buffer (pH6, 25 ml). After being stirred for a further hour at 0°C the mixture was washed with saturated aqueous sodium thiosulphate and brine. Drying ($MgSO_4$) and evaporation of solvent yielded the cyclopentadiene/4-methylpent-3-enyl nitrosoformate adduct as an amber oil. The adduct was obtained as a colourless oil (149 mg, 59%) after chromatography (florisil column eluted with 5% carbon tetrachloride in chloroform) and resisted all crystallisation attempts; ν_{max} (thin film) 1 745 and 1 705 cm^{-1} (C=O); m/e 157 ($M^+-C_5H_6$) no molecular ion; δ ($CDCl_3$) 6.42 (2H, br s, olefinic H), 5.24 (1H, br s, -N-C-H or -O-C-H), 5.09 (1H, m, olefinic H), 5.04 (1H, br s, -N-C-H or -O-C-H), 4.09 (2H, t, J 8 Hz, $-O-CH_2$), 2.33 (2H, br q, J 8Hz, $=C-CH_2-$), 1.99 (1H, d m, J 9 Hz, methylene H), 1.69 (3H, 3, $-CH_3$) and 1.61 (3H, s, $-CH_3$).

Thermolysis of the Cyclopentadiene/4-Methylpent-3-enyl Nitrosoformate Adduct (158).

The adduct (158) (90 mg, 0.4 mmol) was heated in benzene (60 ml) under reflux in a nitrogen atmosphere. The extent of the reaction was determined by proton n.m.r. spectroscopy and was found after 3 hours to be ca. 55% complete. After 7 hours only 10% of the reaction mixture was the adduct (158). The brown oil obtained on evaporation

of solvent was eluted through a florisil column with 5% methanol in chloroform to yield dihydro-3-hydroxy-4-isopropenyl-3H-1,3-oxazin-2-one (155) as a colourless oil (46 mg, 72%). All attempts to crystallise the oil met with failure; ν_{max} (CCl_4 soln.) 3 210 (O-H) and 1 705 cm^{-1} (C=O) (Found: m/e 157.0733. $C_7H_{11}NO_3$ requires 157.0739. Found: m/e 141.0786. $C_7H_{11}NO_2$ (M^+-O) requires 141.0790); $\delta_H(CDCl_3)$ 5.30 (1H, br s, OH, exchangeable with D_2O), 5.08 (2H, br s, $=CH_2$), 4.20 (3H, m, $-O-CH_2-$ and -N-CH-), 2.06 (2H, m, $-C-CH_2-C-$), and 1.64 (3H, s, $-CH_3$). Irradiation of δ 4.17 collapsed the multiplet at δ2.06 to an AB quartet, J 15 Hz. $\delta_C(CDCl_3)$ 155.5 (s, C=O), 141.2 (s, $R_1R_2C=$), 114.0 (t, $=CH_2$), 63.7 (t, $-O-CH_2-$), 63.7 (d, -N-CH-), 26.9 (t, $C-CH_2-C$), and 18.4 (q, $-CH_3$).

Attempted Preparation of N-(3-Methylcyclohex-2-enyloxycarbonyl) hydroxylamine (159).

3-Methylcyclohex-2-en-1-ol (0.13 ml, 1.25 mmol) in toluene (2 ml) was added with stirring to a 12.5% solution of phosgene in toluene (2.2 ml, 2.5 mmol) at -78°C. After 3 hours at -78°C the solution was added to an ice-cooled aqueous solution of hydroxylamine hydrochloride (0.45 g, 6.25 mmol) and sodium hydroxide (0.35 g, 8.5 mmol). The mixture was shaken at room temperature for one hour then acidified (5% dilute HCl) and extracted with diethyl ether. The combined ether extracts were washed with brine, dried ($MgSO_4$), and evaporated to yield a colourless oil. The proton n.m.r. spectrum of the oil showed it to be a mixture of the starting alcohol and another compound

thought possibly to be the corresponding chloride. The i.r. spectrum of the oil showed no carbonyl absorption.

Preparation of 3-Methylcyclohex-3-en-1-ol.

3-Methylcyclohex-3-en-1-one was made after the method of A.J. Birch[87] from 3-methylanisole. This ketone was reduced by lithium aluminium hydride in ether to give 3-methylcyclohex-3-en-1-ol, b.p. 90°C/20 mm Hg (lit.[97] b.p. 80°C/14 mm Hg).

Preparation of N-(3-Methylcyclohex-3-enyloxycarbonyl)hydroxylamine (163).

A toluene solution (5 ml) of 3-methylcyclohex-3-en-1-ol (0.4 ml, 3.75 mmol) was added to a 12.5% solution of phosgene in toluene (6.6 ml, 7.5 mmol) at 0°C. The mixture was stirred at 0°C for 3 hours and was then added to a solution of hydroxylamine hydrochloride (1.35 g, 18.75 mmol) and sodium hydroxide (1.05 g, 25.5 mmol) in water (30 ml). The reaction mixture was shaken at room temperature for one hour, then acidified with 5% dilute HCl. The mixture was extracted with diethyl ether and the combined extracts washed with brine and dried ($MgSO_4$). Evaporation of solvent yielded N-(3-methylcyclohex-3-enyloxycarbonyl)hydroxylamine as a solid. Crystallisation from benzene/light petrol (b.p. 40-60°C) yielded the compound as white platelets (370 mg, 58%), m.p. 92-4°C (Found: C, 56.3; H, 7.4; N, 8.0. $C_8H_{13}NO_3$ requires C, 56.1; H, 7.6; N, 8.2%); m/e 171 (M^+); ν_{max} (KBr) 3 320 (N-H and O-H), and 1 680 cm^{-1} (C=O); δ ($CDCl_3$) 7.50 (2H, br s, NH and OH, exchangeable with D_2O), 5.39 (1H, br s, olefinic H), 5.01 (1H,

m, -O-C-H), 2.10 (4H, br m, =C-CH_2-), 1.80 (2H, d m, J 7 Hz, methylene H), and 1.62 (3H, s, -CH_3).

The Cyclopentadiene/3-Methylcyclohex-3-enyl Nitrosoformate Adduct (164).

N-(3-Methylcyclohex-3-enyloxycarbonyl)hydroxylamine (370 mg, 2.16 mmol) was added to a vigorously stirred mixture of cyclopentadiene (0.33 ml, 4 mmol) in ethyl acetate (70 ml) and sodium periodate (462 mg, 2.16 mmol) in 0.5 M sodium acetate-acetic acid buffer (pH 6, 35 ml) at 0°C. The reaction mixture was stirred at 0°C for one hour then the organic layer was separated and washed with a saturated solution of sodium thiosulphate and brine. The solution was dried ($MgSO_4$) and evaporated to give the cyclopentadiene/3-methylcyclohex-3-enyl nitrosoformate adduct as a light amber oil. The adduct (164) was purified by elution through a florisil column with 25% carbon tetrachloride in chloroform; however attempts to crystallise the colourless oil failed (340 mg, 60%); m/e 235; ν_{max} (thin film) 1 740 and 1 695 cm^{-1} (C=O); δ ($CDCl_3$) 6.40 (2H, s, olefinic H), 5.39 (1H, br s, olefinic H), 5.24 (1H, br s, -N-C-H or -O-C-H), 5.04 (1H, br s, -N-C-H or -O-C-H), 4.99 (1H, m, -O-C-H), 2.10 (4H, br m, allylic H), 1.97 (1H, d m, J 8 Hz, methylene H), 1.75 (3H, m, methylene H), and 1.62 (3H, br s, -CH_3) (Found: M^+ 235.1216. $C_{13}H_{17}NO_3$ requires 235.1208).

Thermolysis of the Cyclopentadiene/3-Methylcyclohex-3-enyl Nitrosoformate Adduct (164).

The adduct (164) (60 mg, 0.26 mmol) was dissolved in benzene

(40 ml) and heated under reflux in a nitrogen atmosphere. After 6 hours solvent was evaporated and a proton n.m.r. spectrum run which showed the reaction mixture to be 40% adduct (164) and 60% supposed cyclised product. The mixture was redissolved in benzene (40 ml) and heated under reflux again. After a further 10 hours the reaction was judged to be complete by t.l.c. analysis, and the solvent evaporated to give a brown oil. Crystallisation of the oil from hexane yielded the bridged N-hydroxyoxazinone (160) as white needles (25 mg, 59%), m.p. 98-9°C (Found: C, 56.5; H, 6.8; N, 8.0. $C_8H_{11}NO_3$ requires C, 56.8; H, 6.5; N, 8.3%); m/e 169 (M^+) and 152; ν_{max} (KBr) 3 200 (O-H) and 1 640 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 7.85 (1H, br s, OH, exchangeable with D_2O), 5.18 (1H, s, =C-H), 4.98 (1H, s, =C-H), 4.60 (1H, m, -O-C-H), 4.15 (1H, m, -N-C-H), 2.97 (1H, d m, J 18 Hz, =C-C-H), 2.55 (1H, d m, J 18 Hz, =C-C-H), and 2.10 (4H, br m, methylene H); $\delta_C(CDCl_3)$ 156.6 (s, C=O), 140.4 (s, $R_1R_2C=$), 113.8 (t, $=CH_2$), 75.8 (d, -O-C-H), 64.1 (d, -N-C-H), 34.6 (t, $=C-CH_2-$), 25.8 (t, $-O-C-CH_2-$), and 25.4 (t, $-O-C-CH_2-$). It was found that the thermolysis of the adduct (164) went slower when it was repeated at higher concentrations. The adduct (180 mg) was refluxed in benzene (50 ml) and the reaction was only 70% complete after 18 hours.

Preparation of 4-Methylcyclohex-3-en-1-ol.

4-Methylcyclohex-3-en-1-one was prepared after the method of A.J. Birch[87] by the reduction of 4-methylanisole in sodium-liquid ammonia. The ketone was reduced with lithium aluminium hydride in diethyl ether to give 4-methylcyclohex-3-en-1-ol, b.p. 90-4°C/20 mm Hg

(lit.[86] b.p. 83°C/18 mm Hg).

Preparation of N-(4-Methylcyclohex-3-enyloxycarbonyl)hydroxylamine (168).

4-Methylcyclohex-3-en-1-ol (0.80 ml, 7.5 mmol) in toluene (5 ml) was added to a stirred 12.5% solution of phosgene in toluene (13.2 ml, 15.0 mmol) at 0°C. The mixture was stirred at 0°C for 3 hours then added to an ice-cooled solution of hydroxylamine hydrochloride (2.7 g, 38 mmol) and sodium hydroxide (2.0 g, 50 mmol) in water (24 ml) with shaking. The reaction mixture was shaken for one hour then acidified (5% dilute HCl) and extracted with diethyl ether. The combined ether extracts were washed with brine, dried ($MgSO_4$), and evaporated to yield N-(4-methylcyclohex-3-enyloxycarbonyl)hydroxylamine as a crystalline solid (1.0 g, 83%). The compound was recrystallised from ethyl acetate/light petrol (b.p. 40-60°C) as colourless platelets (860 mg, 72%), m.p. 129-131°C (Found: C, 56.0; H, 7.8; N, 8.0. $C_8H_{13}NO_3$ requires C, 56.1; H, 7.6; N, 8.2%); ν_{max} (KBr) 3 330 (N-H and O-H) and 1 680 cm^{-1} (C=O); δ ($CDCl_3$) 7.20 (2H, br s, NH and OH, exchangeable with D_2O), 5.30 (1H, br s, olefinic H), 5.00 (1H, m, -O-C-H), 2.02 (6H, br m, methylene H), and 1.63 (3H, br s, $-CH_3$).

The Cyclopentadiene/4-Methylcyclohex-3-enyl Nitrosoformate Adduct (169).

Freshly distilled cyclopentadiene (0.29 ml, 3.5 mmol) was dissolved in ethyl acetate (60 ml) and added to a solution of sodium

periodate (375 mg, 1.75 mmol) in 0.5 M sodium acetate-acetic acid buffer (pH 6, 30 ml). The mixture was vigorously stirred at 0°C and a solution of N-(4-methylcyclohex-3-enyloxycarbonyl)hydroxylamine (300 mg, 1.75 mmol) added slowly. The mixture was stirred at 0°C for one hour then the organic layer was separated, washed with saturated aqueous sodium thiosulphate and brine, and dried ($MgSO_4$). Evaporation of solvent yielded the cyclopentadiene/4-methylcyclohex-3-enyl nitrosoformate adduct as a crystalline solid (350 mg, 85%). The adduct (169) was recrystallised from diethyl ether/light petrol (b.p. 40-60°C) as white needles (300 mg, 71%), m.p. 61-2°C (Found: C, 66.2; H, 7.5; N, 5.9. $C_{13}H_{17}NO_3$ requires C, 66.4; H, 7.3; N, 6.0%); m/e 235 and 142; ν_{max} (KBr) 1 750 cm^{-1} (C=O); δ ($CDCl_3$) 6.35 (2H, br s, olefinic H), 5.20 (2H, br s, olefinic H and either -N-C-H or -O-C-H), 4.97 (1H, br s, -N-C-H or -O-C-H), 4.90 (1H, m, -O-C-H), 1.95 (8H, br m, methylene H), and 1.60 (3H, br s, $-CH_3$).

Thermolysis of the Cyclopentadiene/4-Methylcyclohex-3-enyl Nitrosoformate Adduct (169).

The adduct (169) (50 mg, 0.26 mmol) was dissolved in benzene (40 ml) and heated under reflux in a nitrogen atmosphere. After 6 hours solvent was evaporated and a proton n.m.r. spectrum run which showed the reaction mixture to be one third adduct (169), two thirds cyclised product. The mixture was redissolved in benzene (40 ml) and after a further 6 hours refluxing the reaction was shown to be complete by n.m.r. spectroscopy. Evaporation of solvent yielded the

bridged N-hydroxyoxazinone (165) as a brown crystalline solid (45 mg), which recrystallised from chloroform/light petrol (b.p. 40-60°C) as white platelets (30 mg, 70%), m.p. 190-2°C (Found: C, 56.55; H, 6.5; N, 8.1. $C_8H_{11}NO_3$ requires C, 56.8; H, 6.5; N, 8.3%); m/e 169 (M^+), 153 and 125; ν_{max} (KBr) 3 180 (O-H) and 1 680 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 7.50 (1H, br s, OH, exchangeable with D_2O), 4.89 (2H, s, $=CH_2$), 4.55 (1H, br s, -O-C-H), 4.09 (1H, br s, -N-C-H), and 2.3-1.5 (6H, br m, methylene H); $\delta_C(CD_3OD)$ 157.0 (s, C=O), 145.7 (s, $R_1R_2C=$), 112.3 (t, $=CH_2$), 75.3 (d, -O-C-H), 63.6 (d, -N-C-H), 33.5 (2 t, -O-C-$\underline{C}H_2$- and -N-C-$\underline{C}H_2$-), and 25.9 (t, =C-$\underline{C}H_2$-).

Preparation of N-(Ethoxycarbonyl)ethoxyamine (170).

Ethoxyamine hydrochloride (2.43 g, 25 mmol) and sodium hydroxide (2 g, 50 mmol) were dissolved in water (50 ml). Ethyl chloroformate (2.52 g, 25 mmol) was added dropwise and the mixture shaken for one hour. The mixture was extracted with diethyl ether and the extracts were combined, washed with brine, and dried ($MgSO_4$). Evaporation of solvent yielded N-(ethoxycarbonyl)ethoxyamine as a colourless oil (2.9 g, 85%) with spectral details in agreement with those in the literature[98]; ν_{max} (thin film) 3 400 (N-H), 1 765 and 1 730 cm^{-1} (C=O); δ ($CDCl_3$) 7.72 (1H, br s, NH, exchangeable with D_2O), 4.18 (2H, q, J 8 Hz, $-CH_2$-O-CO), 3.90 (2H, q, J 7 Hz, $-CH_2$-O-N), 1.24 (3H, t, J 8 Hz, $-CH_3$), and 1.19 (3H, t, J 7 Hz, $-CH_3$).

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