The Development of a New Method for the Trapping of Nitric Oxide

A Thesis submitted for the Degree of

Doctor of Philosophy

By

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in the

Faculty of Science

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STATEMENT

The accompanying thesis submitted for the degree of Ph.D. entitled "The Development of a New Method for the Trapping of Nitric Oxide" is based on work conducted by the author in the Department of Chemistry of the University of Leicester mainly during the period between October 1994 – December 1997.

All the work recorded in this thesis is original unless otherwise acknowledged in the text or by references.

None of the work has been submitted for another degree in this or any other University.

Signed: ..... Date: 29.9.98

The Development of a New Method for the Trapping of Nitric Oxide

by
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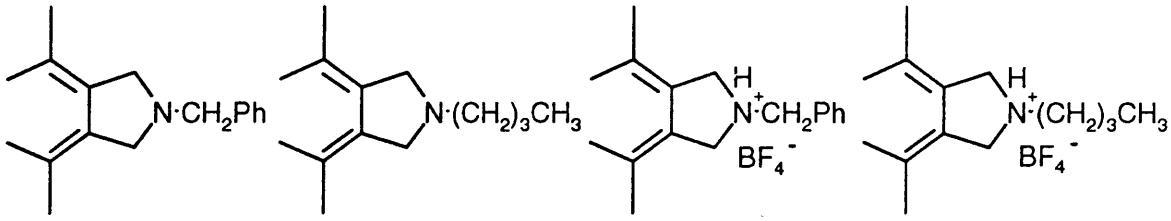
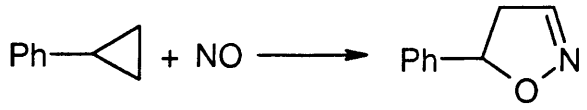
Abstract

Substituted butadienes (1) and (2) were synthesised and their salts prepared, (3) and (4). Compounds (1), (3) and (4) were reacted with nitric oxide (NO), causing the salts to form a material insoluble in deuterated chloroform, and the free amine to undergo an unidentified process after a long reaction time.



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

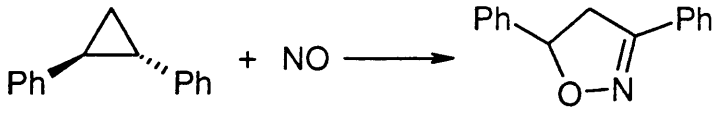
Phenyl cyclopropane (5) reacted with NO to give 5-phenyl-4,5-dihydroisoxazole (6).



(5) (6)

35%

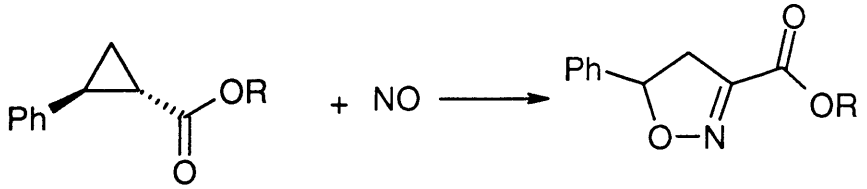
Similarly, racemic *trans*-1,2-diphenylcyclopropane (7) reacted with NO to give 3,5-diphenyl-4,5-dihydroisoxazole (8).



(7) (8)

15%

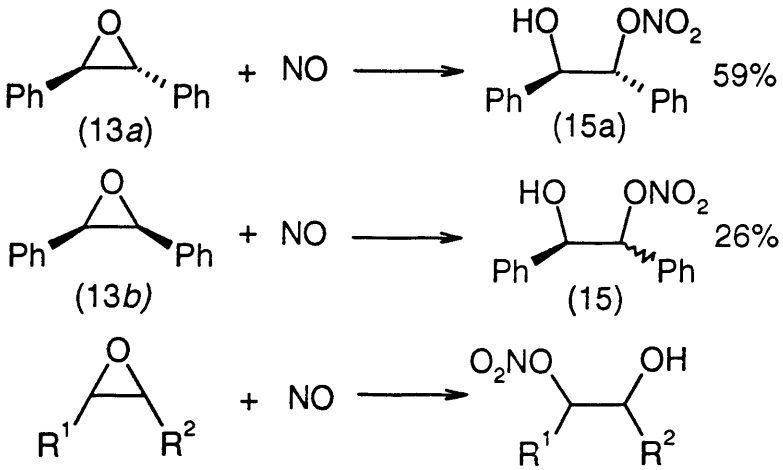
Racemic *trans*-cyclopropane esters (9) and (10) were reacted in a similar way to give the 4,5-dihydroisoxazoles (11) and (12).



(9) R = Et
(10) R = Me

(11) R = Et 26%
(12) R = Me 4%

Epoxides (13) and (14) reacted with NO to give the nitrate esters (15) and (16). The X –ray structure of (15a) was obtained.



(14a) R1 = Ph, R2 = H
(14b) R1 = Ph, R2 = CH_3
(14c) R1 = C_6H_4Cl, R2 = Ph
(14d) R1 = Ph, R2 = COC_6H_5
(14e) R1 = H, R2 = $CH_2OC_6H_4CH_3$

(16a) 37%
(16b) 30%
(16c) 43%
(16d) 44%
(16e) 31%

Epoxides (13) reacted with HNO_3 to give the nitrate (15), providing evidence supporting the suggestion that the reaction with NO proceeds via formation of HNO_3 in solution.

ACKNOWLEDGEMENTS

I would like to thank Prof. Paul Cullis, Dr. Paul Jenkins and Dr Steven Smith (GlaxoWellcome) for their help and supervision, and the E.P.S.R.C and GlaxoWellcome for their funding.

I would also like to thank my fellow postgraduates, past and present, for helping to make the past years enjoyable. Thank you to Mick Lee and Phil Acton for their help, John Fawcett for providing X-ray crystal structure data, and Martin and Dave in stores for their assistance.

Finally I would like my family and friends for their support and encouragement.

ABBREVIATIONS

Å	- ångstrom. 1 Å = 10^{-10}m
DBU	- 1,8-diazabicyclo[5.4.0]undec-7-ene
DCA	- 9,10-dicyanoanthracene
DMAP	- 4-dimethylaminopyridine
DMF	- *N,N*-dimethylformamide
DMSO	- dimethyl sulfoxide (Me_2SO)
GMP	- guanosine monophosphate
GTP	- guanosine triphosphate
NADPH	- nicotinamide adenine dinucleotide phosphate (reduced)
NCS	- *N*-chlorosuccinimide
NO	- nitric oxide
NOS	- nitric oxide synthase
Red-Al®	- sodium bis(2-methoxyethoxy)aluminium hydride $[(CH_3OCH_2CH_2O)_2AlH_2]Na$
SNAP	- *S*-nitroso-*N*-acetylpenicillamine
TEMPO	- 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical
Tf	- triflate (trifluoromethanesulfonate)

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CHAPTER 4 – THE TRAPPING OF NITRIC OXIDE WITH SUBSTITUTED EPOXIDES

CHAPTER 1

Introduction

1.1.1 Nitric Oxide

Nitric oxide is a diatomic free radical that occurs in various ways in the environment. It has long been known to be a reactive by-product of fossil fuel burning and is a pollutant produced by high energy processes like the internal combustion engine and lightning. The aura that surrounds the space shuttle as it orbits is caused by NO. It can contribute to acid rain, and in one case its accidental contamination of cylinders of anaesthetic gas caused a fatality. It might therefore seem surprising that in 1992 *Science* made nitric oxide molecule of the year. However, it is now known that the inorganic molecule is also made by animals, the diversity of the range including barnacles, fruit flies, horseshoe crabs, chickens, trout, and humans. The 'poison' is made throughout the body and plays a vital role in a range of physiological processes.[1] (The primitive horseshoe or limulus crab is included in the list as an item of interest because it has been largely unchanged by evolution for hundreds of millions of years. Its cardiovascular system was found to have the ability to generate nitric oxide like mammalian cells. This suggests that the system goes back in evolution for at least this long). The tissues where it is produced include the vascular endothelium, smooth muscle cells, neurones within the central and peripheral nervous systems and cytotoxic macrophages.

1.1.2 Synthesis of NO

NO is produced by the direct combination of N_2 and O_2 at high temperatures in the internal combustion engine. In industry, nitric oxide

formed by the oxidation of ammonia in the presence of a metal catalyst is an intermediate in the production of nitric acid.

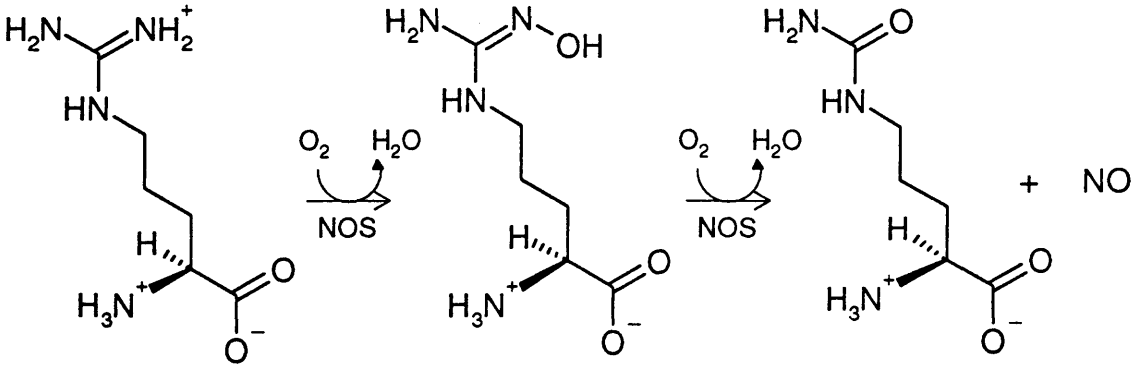
$$4NH_3 + 5O_2 \xrightarrow{\substack{750\text{-}900\,^\circ C \\ Pt/Pt\text{-}Rh\ cat.}} 4NO + 6H_2O$$

$$\underset{\text{nitrogen}}{\text{atmospheric}}\ N_2 \xrightarrow[\substack{\text{Haber} \\ \text{process}}]{H_2} NH_3 \xrightarrow[\substack{\text{Ostwald} \\ \text{process}}]{O_2} NO \xrightarrow{O_2 + H_2O} HNO_3(aq)$$

Lightning, which provides the energy necessary for the combination of nitrogen and oxygen in the atmosphere is the basis of the *arc process* of nitrogen fixation where air is passed through an electric arc to form nitric oxide.[2]

1.1.3 Biosynthesis of NO

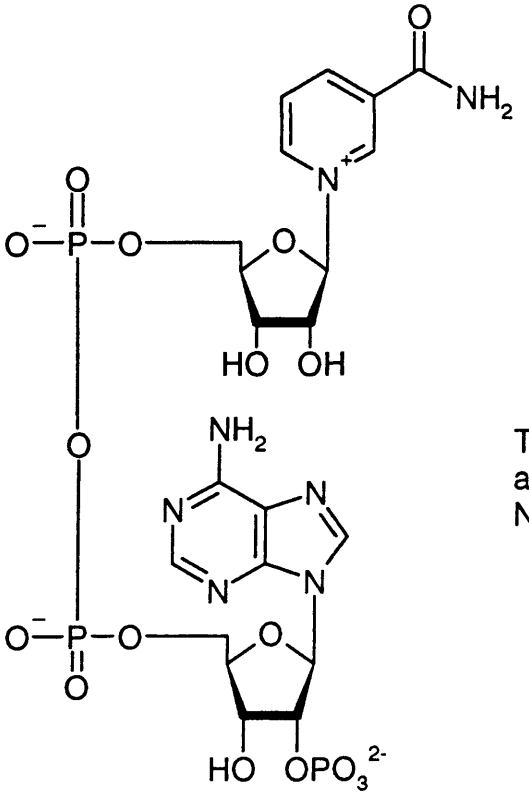
In the body, the enzyme nitric oxide synthase (NOS) is responsible for the biosynthesis of NO. The substrates of NOS are the amino acid L-arginine (1) and molecular oxygen. The first step in the process is the hydroxylation of one of the terminal nitrogens of L-arginine to form the intermediate *N*-hydroxy-L-arginine (2). In the second step, involving oxygen insertion and carbon-nitrogen bond scission, a second and distinct molecule of oxygen is used and L-citrulline (3) and NO are formed. NADPH is present as the electron donor in both oxidations (figure 1).[1a]



L-arginine (1) *N*-hydroxy-L-arginine (2) L-citrulline (3)

Figure 1

(Nicotinamide adenine dinucleotide, $NADP^+$ ($NADPH$ in its reduced form), is a biological electron carrier (figure 2).)[3]



The oxidised form of nicotinamide adenine dinucleotide phosphate $NADP^+$

Figure 2

To understand the reasons for wanting to manipulate nitric oxide in biological systems it is necessary to describe in greater detail some of the functions of NO produced in the body in locations mentioned earlier.

1.1.4 Nitric Oxide as a Vasodilator

Nitric oxide when produced in the vascular endothelium (the layer of cells lining blood vessels) acts as a mediator (figure 3). Several vasoactive substances, including acetylcholine, can bind to receptors on the surface of the endothelial cell membrane.

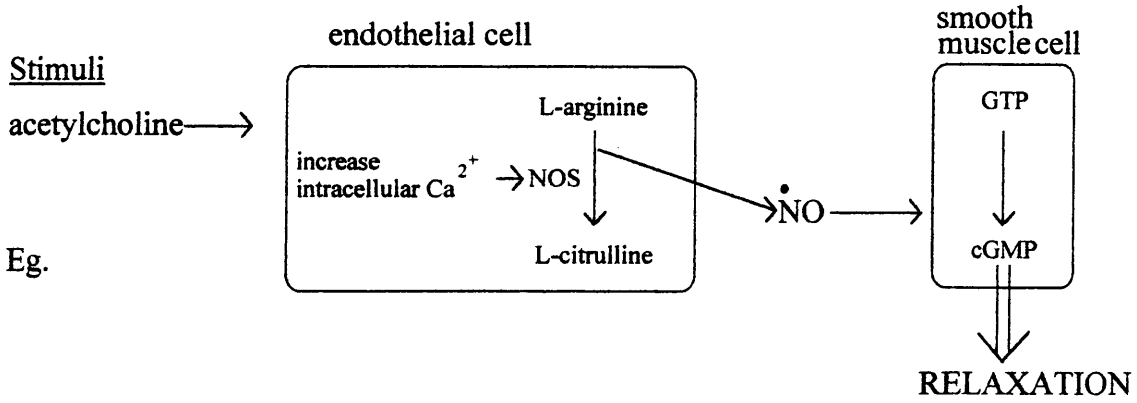
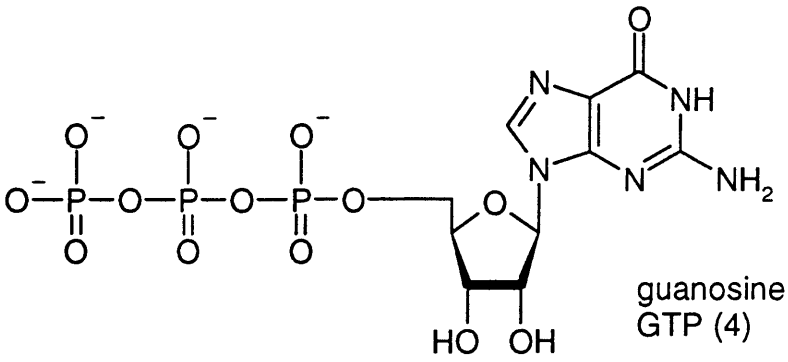


Figure 3

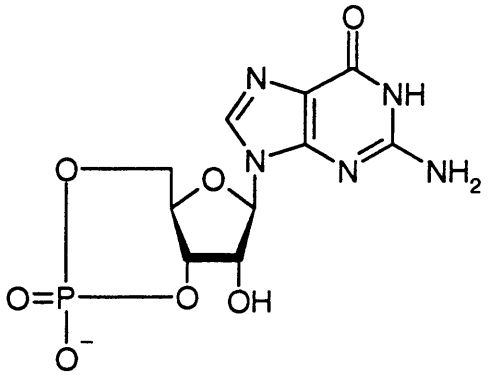
This binding causes calcium ion channels in the membrane to open which allow Ca^{2+} ions into the cells. NOS in endothelial cells is calcium ion dependent, and when Ca^{2+} binds to a calmodulin cofactor the NOS is activated (calmodulin is a calcium binding protein which undergoes a structural change when binding Ca^{2+}, it then binds to the enzyme, modifying its activities). Hence endothelial cells produce nitric oxide which diffuses into adjacent smooth muscle cells. Here it stimulates the conversion of GTP (4) into cyclic GMP (5) by activating the guanylate

cyclase enzyme, resulting in the relaxation of the smooth muscle and consequently vasodilation. [1,3]



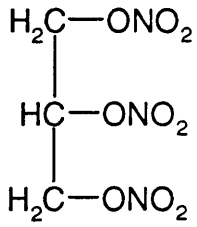
guanosine triphosphate
GTP (4)

guanylate cyclase



cyclic
guanosine monophosphate
cGMP (5)

For many years compounds such as nitroglycerine have been used in the treatment of angina. The pain of angina is caused by constriction of the coronary blood vessels. It is now known that the drugs used to treat the condition work by the release of nitric oxide.[1b]



nitroglycerine

The manipulation of the production of nitric oxide is now seen as a possible approach to the treatment of hypertension. Compounds that would release nitric oxide in the blood vessels could be used to lower blood pressure by vasodilation.

1.1.5 Nitric oxide in the Immune System

Nitric oxide synthase is also present in macrophages, in a form independent of calcium ions. Expression of the enzyme is induced by such agents as lipopolysaccharide (a component of the cell wall of Gram-negative bacteria). Once synthesised, the enzyme will produce NO for as long as substrate is available and the enzyme is active. The NO produced in this way has a cytotoxic function. However, NO synthesis works against the body during the occurrence of septic shock. In the major event of this condition the lipopolysaccharide mentioned above causes the expression of inducible NOS (this form of the enzyme can be found elsewhere in the body, including the vascular endothelial cells and smooth muscle cells, in addition to the macrophage). The resulting overproduction of nitric oxide causes uncontrolled, excessive vasorelaxation and a consequent rapid fall in blood pressure. Insufficient blood supply to the major organs often leads to death.

NOS inhibitors have been used in these cases successfully to restore blood pressure, sometimes to a normal level.[1] An alternative, or additional, approach to this problem might be the trapping of the nitric oxide released in the body. Another reason for wanting to trap nitric oxide

is for analytical purposes. The reactivity and short life of NO make it difficult to detect directly in biological systems. It is necessary to 'fix' it into a longer lived entity.

1.1.6 Properties of Nitric Oxide

At room temperature nitric oxide is a colourless gas with b.p. –151.8°C and m.p. –163.6 °C. It is paramagnetic, containing an odd number of electrons, leaving one electron unpaired in the 2p π^* orbital (figure 4).

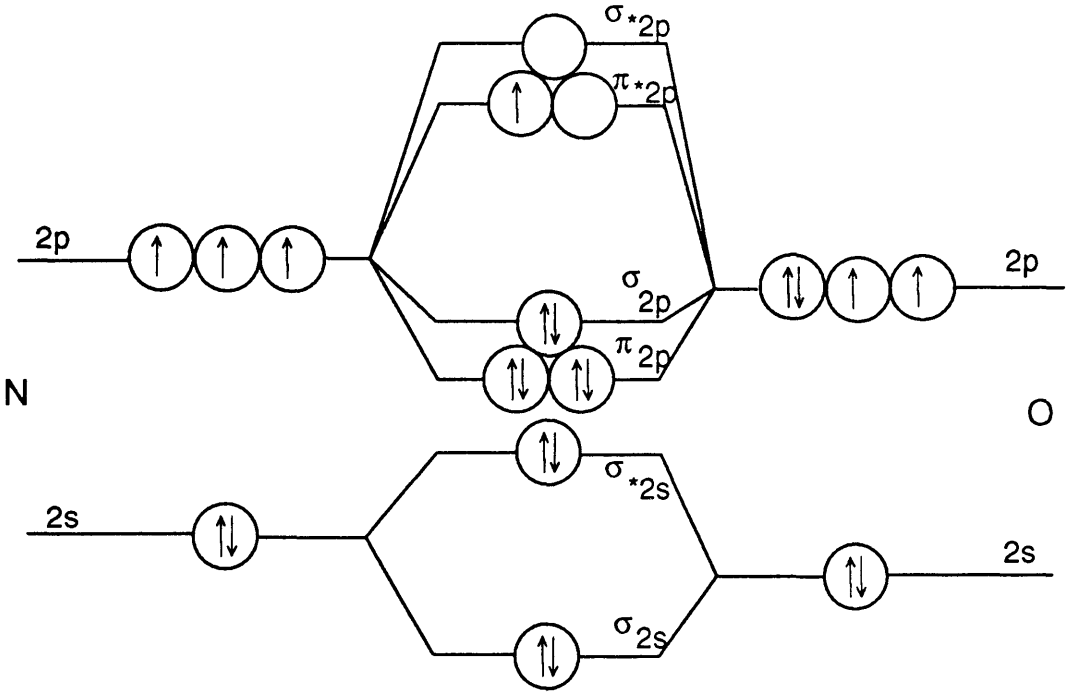


Figure 4. Molecular orbital diagram of nitric oxide (ground state)[14]

Some characteristics of NO, NO^+, NO^-

	$d_{(N-O)}$ [Å]	$\nu_{(NO)}$ [cm^{-1}]	bond order
NO^+	0.95	2300	3
NO	1.15	1840	2.5

NO^-	1.26	1290	2

(Å = Ångstrom. 1 Å = 10^{-10}m)

NO can be represented by several canonical forms.

$$\cdot N^{+}\!\!-\!\!O^{-} \longleftrightarrow \dot{N}\!=\!O \longleftrightarrow N\!\equiv\!O^{+}\cdot \longleftrightarrow N\!\equiv\!O\cdot$$

It can be prepared in the laboratory by the reduction of nitric acid, with Cu for example.

$$8HNO_3 + 3Cu \longrightarrow 3Cu(NO_3)_2 + 4H_2O + 2NO$$

Other ways of producing NO have been mentioned earlier. Nitric oxide reacts instantly with oxygen to give nitrogen dioxide.

$$2NO + O_2 \longrightarrow 2NO_2$$

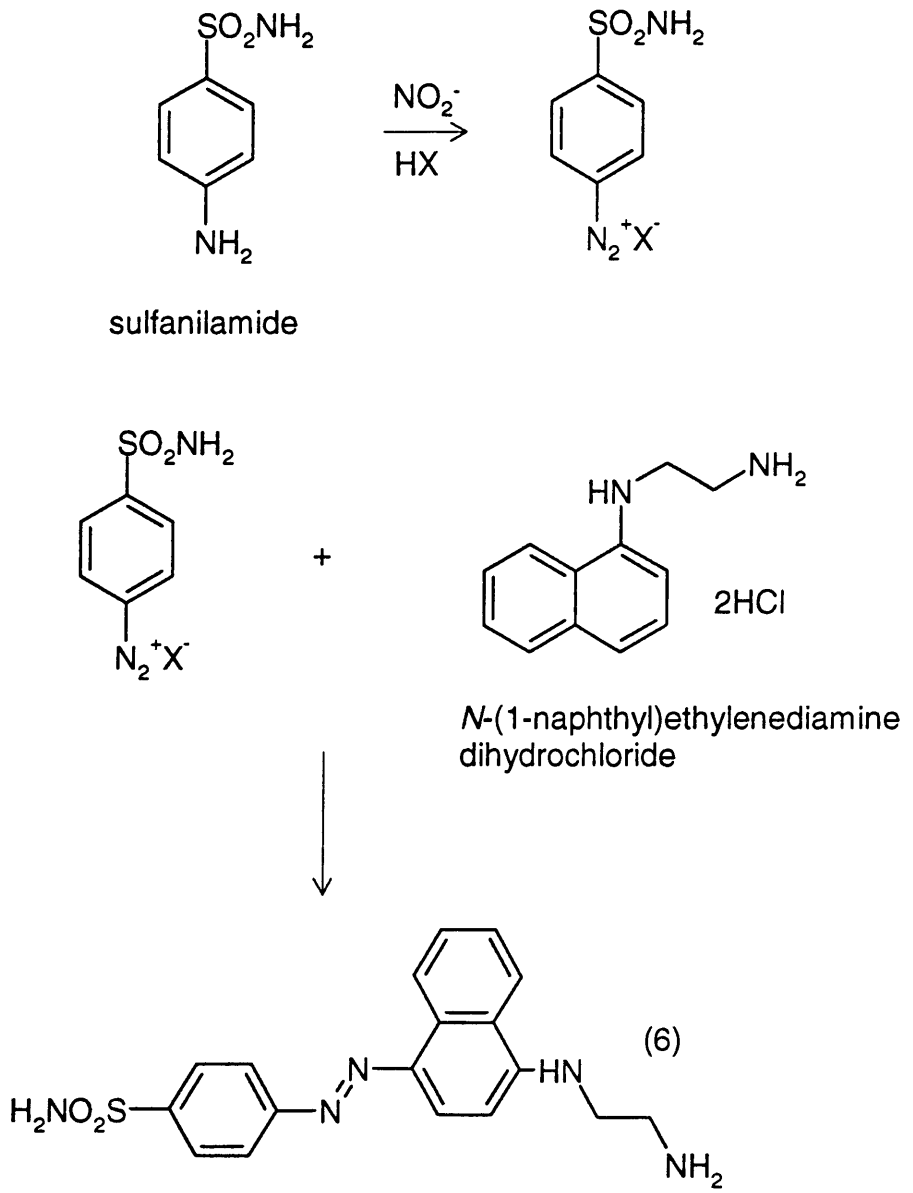
It is thermodynamically unstable and decomposes readily at high pressures in the range 30-50°C.[2,4]

$$3NO \longrightarrow N_2O + NO_2$$

1.1.7 Testing for Nitric Oxide

Quantitative detection of NO in the gas phase can be achieved by chemiluminescence. This is based on the reaction of NO with ozone to produce nitrogen dioxide in its excited state. When this relaxes to its ground state, light is emitted of a characteristic energy which can be detected. Solutions of nitrate and nitrite formed from the oxidation of NO can be assayed using the Griess reaction, as an indirect measurement of NO. After reduction of the nitrate to nitrite, the solution is reacted with

sulfanilamide in acidic *N*-(1-naphthyl)ethylenediamine dihydrochloride solution, which gives rise to the azo derivative, (6) (Scheme 1). The azo derivative can be monitored spectrophotometrically at 548 nm.



Scheme 1

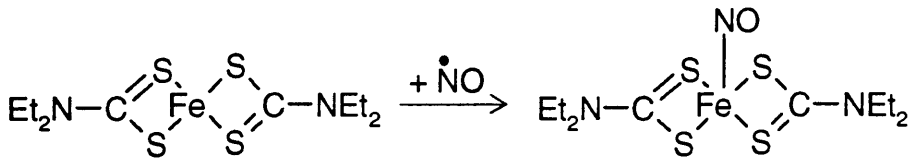
NO can be detected by ESR if it is trapped by a transition metal in a complex, such as Fe(II)-diethyldithiocarbamate (DETC) to give $[NOFe(DETC)_2]$. Since the reaction of NO with oxyhaemoglobin (HbO_2) to form methaemoglobin (Hb^+) and nitrate produces a shift in the absorbance

in the visible spectrum from 415 nm to 405 nm, NO can be quantitatively detected spectrophotometrically in this way.[1a]

$$HbO_2 + NO \longrightarrow Hb^+ + NO_3^-$$
(415nm) (405nm)

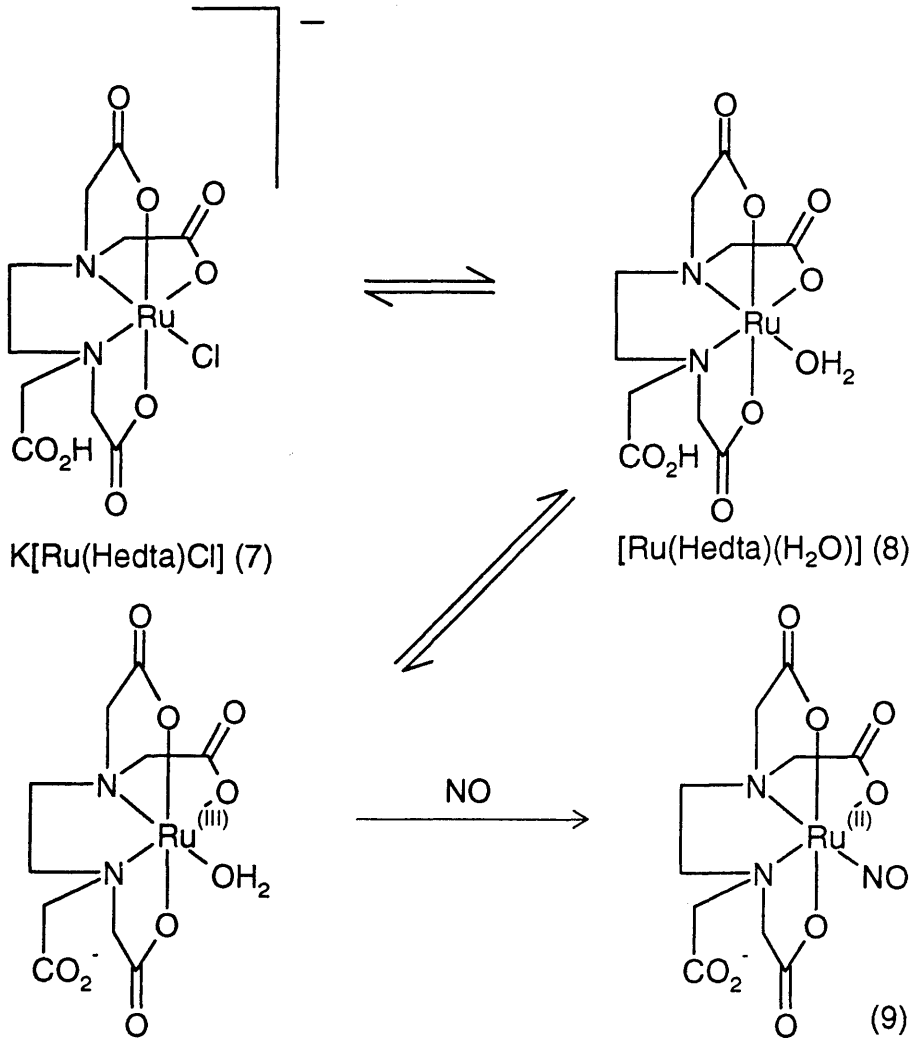
1.1.8 Trapping Nitric Oxide

The iron complex Fe^{2+}-diethyldithiocarbamate has been used to trap NO in a form that is ESR detectable (0.5-10 nmol NO). The mononitrosyl-Fe^{2+}-$(DETC)_2$ complex gave a characteristic ESR signal.[6]



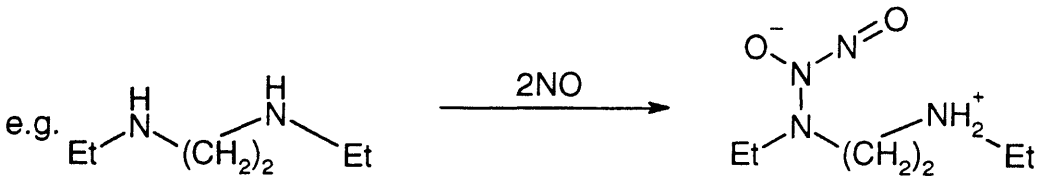
$Fe^{II}(DETC)_2$

In aqueous solution, the ruthenium(III) poly-aminocarboxylate complex, K[Ru(Hedta)Cl (7) reacts with NO via [Ru(Hedta)(H_2O)] (8) to form a ruthenium(II) mononitrosyl complex (9) (scheme 2).[5]



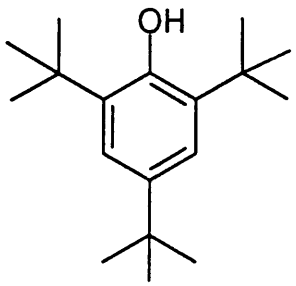
Scheme 2

Polyamines (10) have been found to react with NO to form 'NONOates' (11). These compounds are stable for weeks at room temperature and release NO in acidic solutions.[8]

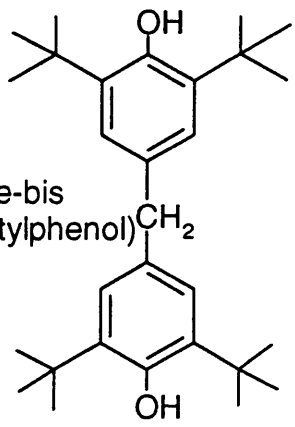


(10) (11)

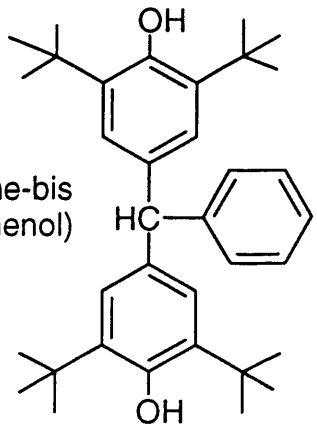
NO was found to react with some substituted phenols (12-14) to produce first a phenoxyl radical (15) which then goes on to react reversibly with more NO (16/17) (Scheme 3).[9]



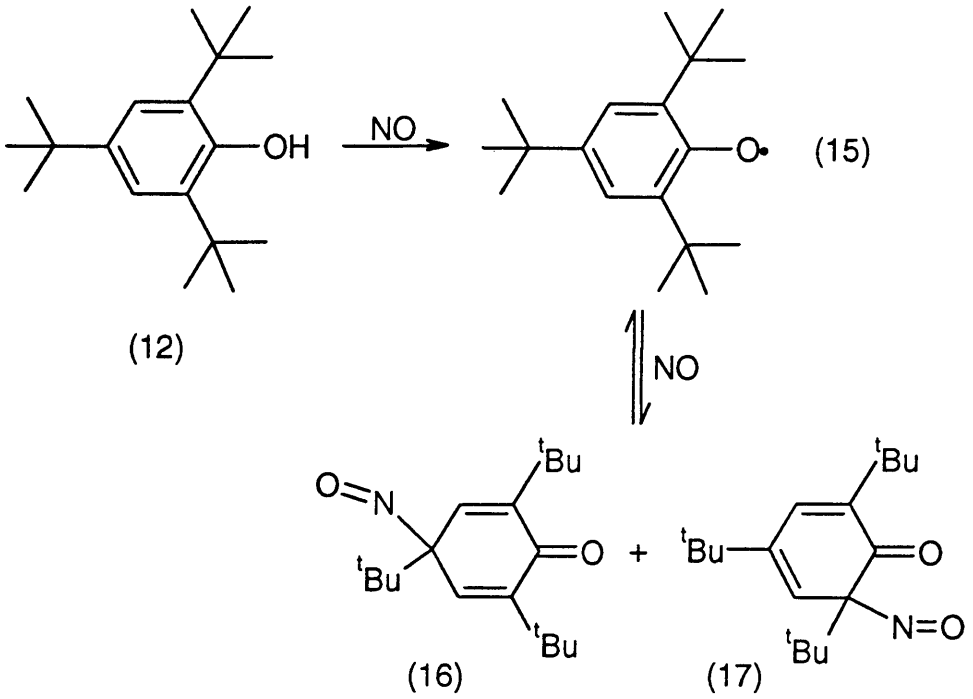
2,4,6-tri-*tert*-butylphenol (12)



4,4'-methylene-bis
(2,6-di-*tert*-butylphenol)
(13)

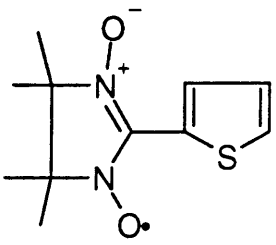


phenyl-4,4'-methine-bis
(2,6-di-*tert*-butylphenol)
(14)

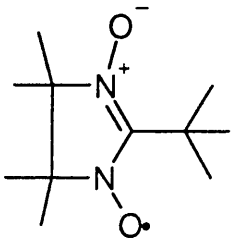


Scheme 3

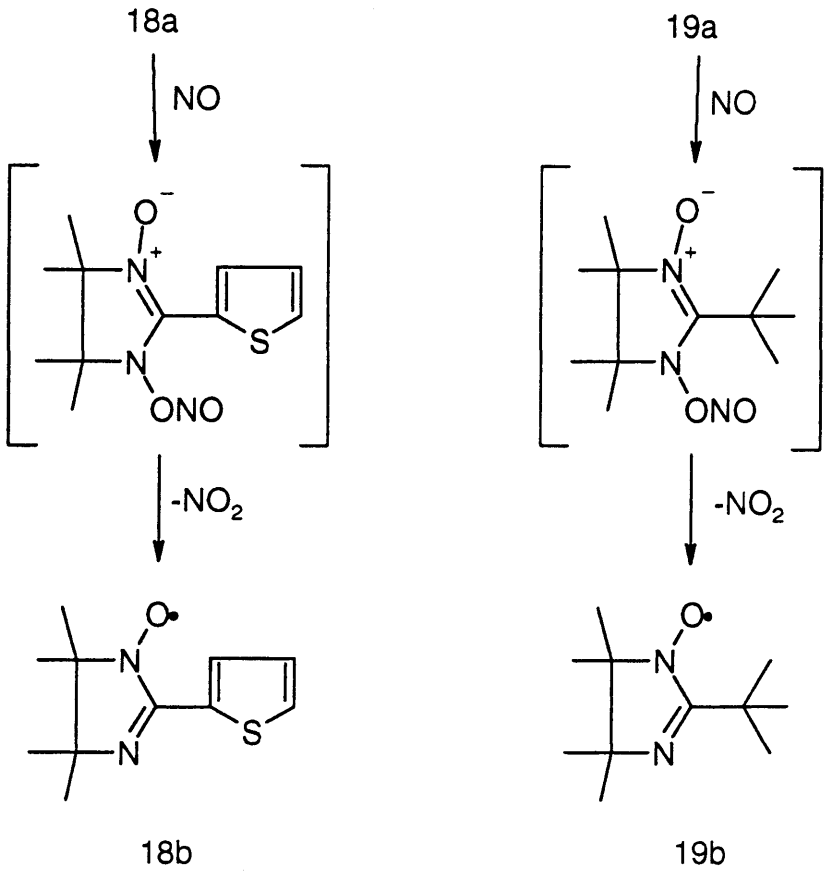
The nitronyl nitroxides (18a) 2,3-didehydro-4,4,5,5-tetramethyl-2-(2'-thienyl)imidazolidine-3-oxide-1-oxyl) and (19a) 2,3-didehydro-4,4,5,5-tetramethyl-2-*tert*-butylimidazolidine-3-oxide-1-oxyl) can react with NO in solution to form the corresponding imino nitroxides (18b and 19b) (scheme 4). The ESR spectra of the two types of compounds are different.[10]



18a



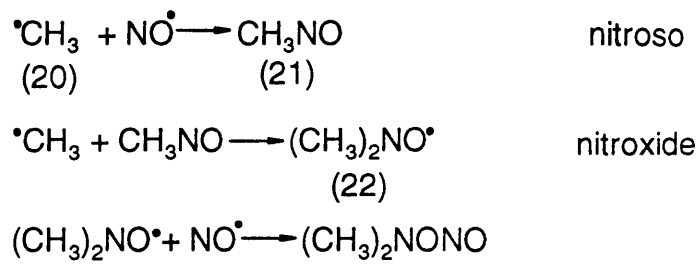
19a



Scheme 4

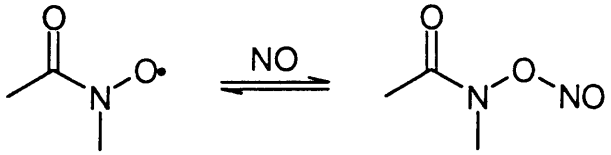
Alkyl (20) radicals have been shown to react with NO, leading to the eventual formation of nitroxides (22). This occurs by the addition of NO to the radical to give a nitroso compound (21), which in turn reacts with another alkyl radical to produce a nitroxide (22) that is detectable by ESR. The longevity of the nitroxide was found to depend on the rate of reaction with any excess NO.[11] (Scheme 5).

E.g.



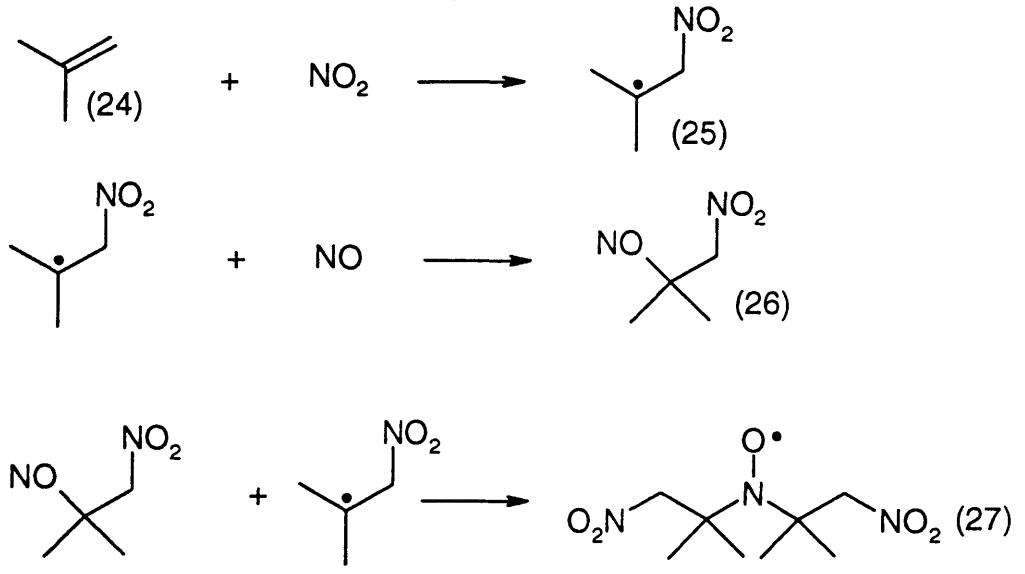
Scheme 5

In similar experiments where oxygen was also present, the dialkyl nitroxide was formed in either a very reduced yield or not seen at all. Instead, acylalkyl nitroxide signals (23) appeared in the ESR. The radical termination reaction of acylalkyl nitroxide with nitric oxide was shown to be reversible.[12] The involvement of NO in the production of alkoxyalkyl nitroxides and new nitrogen centred radicals was also investigated.[13]

e.g. 

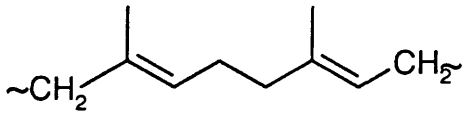
(23)

Nitroxide radicals were observed with nitric oxide and olefins such as isobutylene (24), styrene and α-methyl styrene. These are the result of radical initiation by NO_2, leading to alkyl radicals (25) that react with NO to form a nitroso compound (26). This and a further alkyl radical form the nitroxide (27) (scheme 6).[15]

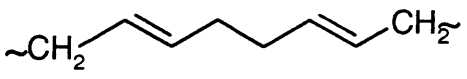


Scheme 6

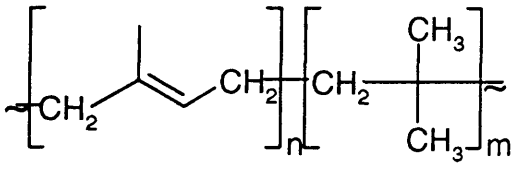
NO reacted with unsaturated polymers (28-31) to produce ESR detectable macromolecular nitroxides (32).[20]



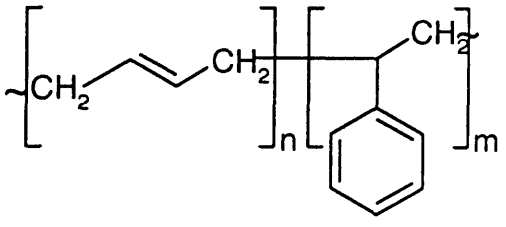
polyisoprene (28)



polybutadiene (29)

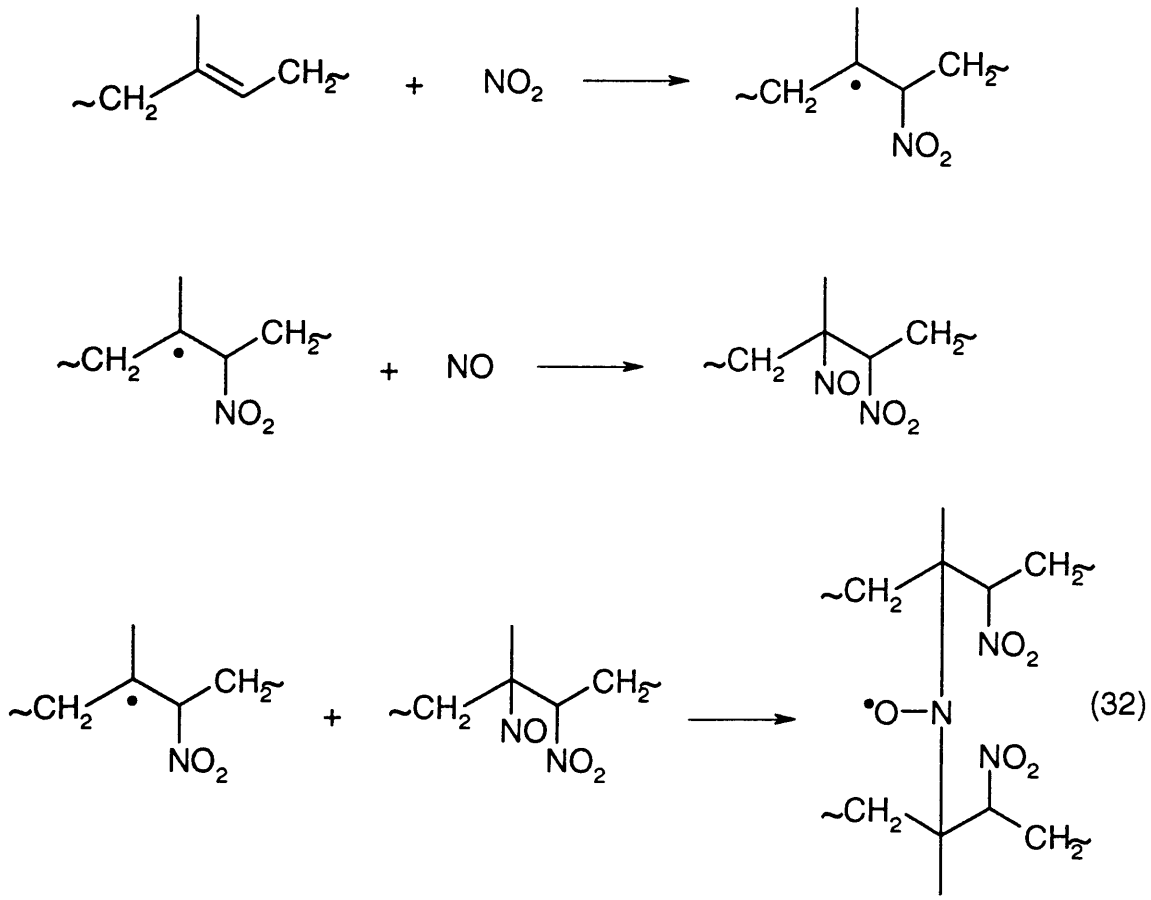


poly(isoprene-co-isobutylene) (30)



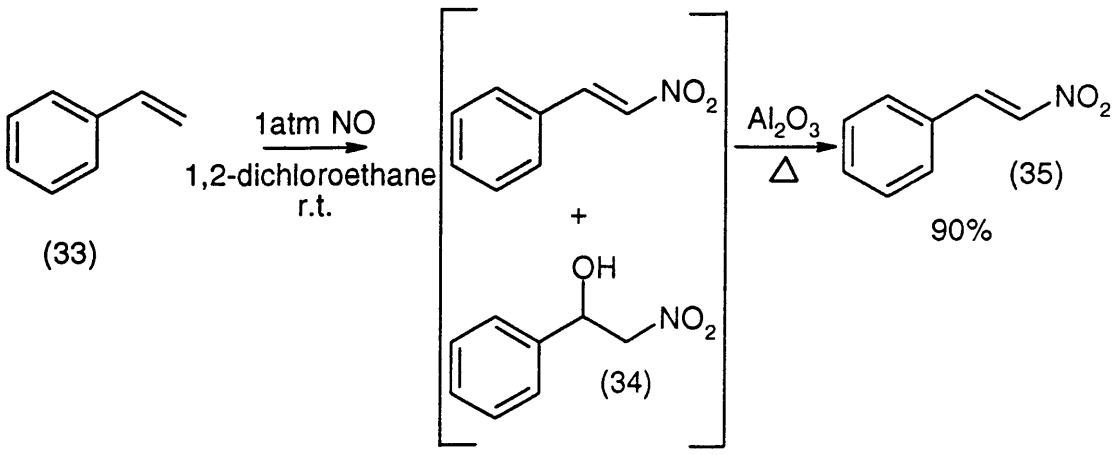
poly(butadiene-co-styrene) (31)

Polymers = synthetic polyisoprene, polybutadiene, poly(isoprene-co-isobutylene), poly(butadiene-co-styrene). These were dissolved in aromatic hydrocarbons and treated with NO (Scheme 7, see also scheme 6. *previous page*)

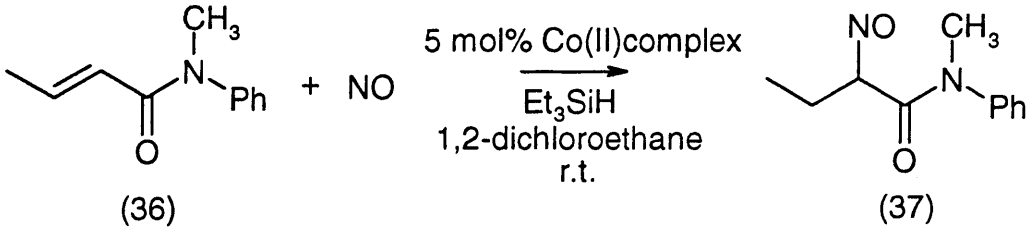


Scheme 7

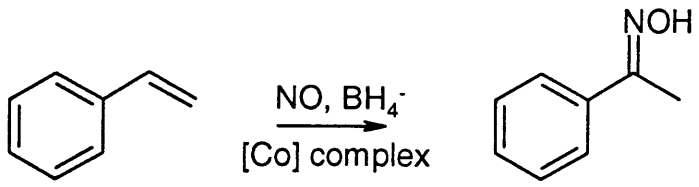
High yields of nitroolefins (35) have been prepared by the treatment of olefins (33) with NO followed by acidic alumina. The alumina is used to dehydrate the nitroalcohol (34) formed in addition to the nitroolefin in the first reaction.[16,17]



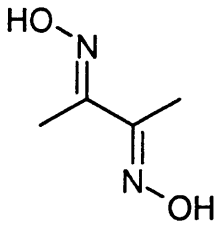
A catalytic amount of a cobalt(II) complex, *N,N'*-bis(2-ethoxycarbonyl-3-oxobutylidene)ethylenediaminatocobalt(II), was used in the conversion of various α,β-unsaturated carboxamides (36) to 2-nitrosocarboxamides (37) by nitric oxide and triethylsilane.[18]



A cobalt catalyst was also used in the reaction of aryl substituted olefins with NO to yield oximes of alkyl aryl ketones (38) in the presence of BH_4^-. The most success was achieved with styrene and its derivatives, and the cobalt catalyst Co(dimethylglyoxime)$_2$(pyridine)Cl.[19]

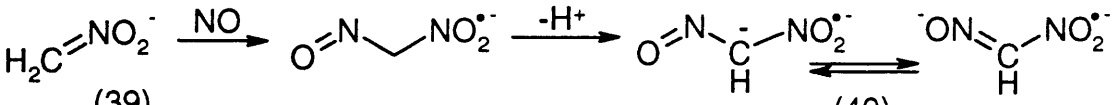


(38)



dimethylglyoxime

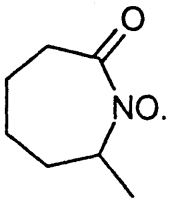
aci-Nitromethane (39), a form of nitromethane present in strongly alkaline conditions, traps NO to give the spin adduct $^{-}ON=CHNO_2^{\bullet -}$ (40).[21]



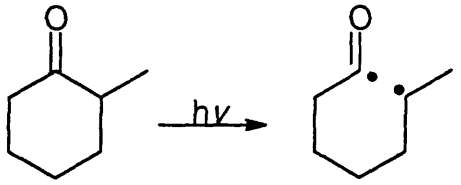
(39)
aci-nitromethane

(40)

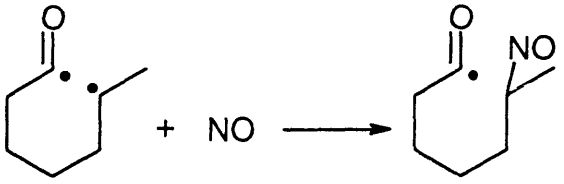
Nitric oxide can trap diradicals formed from the photocleavage of cycloalkanones in solution. For example, if a NO saturated solution of 2-methylcyclohexanone (41) is UV-irradiated, a long lived nitroxide is formed which is believed to be structure (42). This is believed to occur via a stepwise process with the formation of an alkyl nitroso compound (43) followed by the intramolecular trapping of the remaining radical (scheme 8).[22]



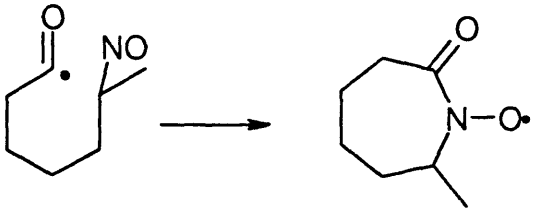
(42)

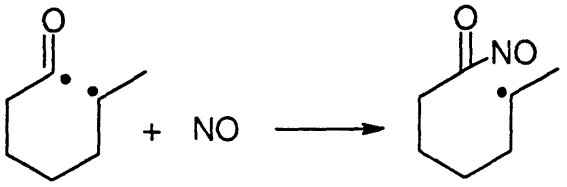


(41)

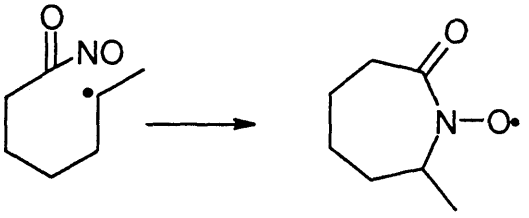


(43a)



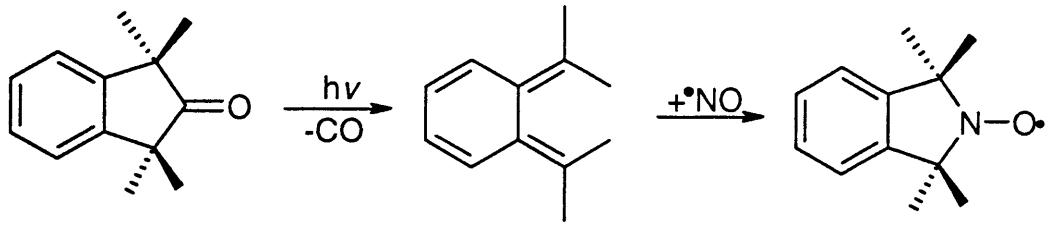


(43b)



Scheme 8

One of the most important examples for this work is by Korth et al. The photodecarbonylation of 1,1,3,3-tetramethyl-2-indanone (44) leads to the formation of the quinodimethane 1,2-bis(isopropylidene)cyclohexa-3,5-diene (45).[23] This short-lived compound ($t_{1/2}$ = 9 min at 20°C) reacts with NO to form a 1,1,3,3-tetramethylisoindolin-2-oxyl radical (46), detectable by ESR (scheme 9).



(44) (45) (46)

Scheme 9

1.1.9 Aims

If a reaction of nitric oxide is to be exploited for medicinal purposes, for example by producing a trap to sequester NO from the biological environment, certain requirements arise that need to be satisfied for the reaction to be useful. The same is true for another example where the purpose of the NO reaction is analytical i.e., to detect NO *in vivo*. Many of the requirements are the same for both.

Synthetic organic chemistry usually requires solubility in a non-aqueous solvent. Most biological reactions, however, take place in aqueous solution. A means of conferring aqueous solubility on participants in the reaction with NO has to be available. Unlike laboratory preparations, physiological temperature and pH are largely beyond control and this may

have to be taken into account in the way it will affect reactions; also in the effect on a compound's stability, or otherwise, of these conditions. The reaction with NO will need to occur with the concentrations of NO that are likely to occur in the body. Once a reaction has taken place, if detection of NO is a requirement, the product must be long enough lived to accommodate the method of detection. (Symons *et al.* envisaged a trap that would allow them to use whole body ESR imaging[24]). It would be helpful if the NO trap did not react much with other substances in the body (or if it did that the product would not confuse detection of the desired reaction). It may be necessary that the trap has the ability to cross cell membranes, whether by diffusion or some active transport mechanism. Conversely, it may be that it is the lack of ability to cross membranes that is a required characteristic. It would be desirable that it is not toxic to the body, that the product is not toxic, and that if either is metabolised the products of this are not toxic (although there may be circumstances where this is of lesser import that the speed or effectiveness of action). Whether the body will metabolise it at all should be considered and how it will be eliminated if not.

The latter considerations are beyond the scope of this investigation. We sought however to address the question of solubility in aqueous systems by preparing compounds which could be formed as salts.

$$R_3N \xrightarrow{HX} R_3\overset{+}{N}HX^-$$

Cyclic butadiene compounds were chosen for their possible reaction with NO to form nitroxides. Many variations are possible.[31] They can be

substituted to allow for aqueous solubility and conformational restraint if required. They can be highly substituted at the possible NO reaction site, and a butadiene was envisaged where the substitution would increase the longevity of the nitroxide product if formed.

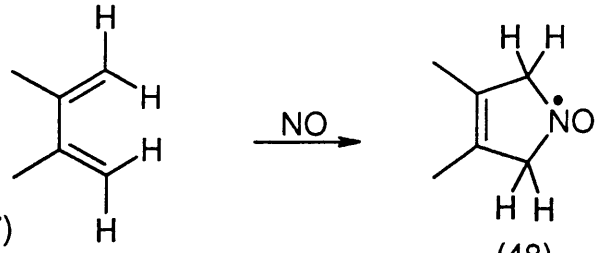
The chemistry of NO was probed further in chapters three and four when substituted cyclopropanes and substituted epoxides were treated with NO. It was known that the nitrosonium cation NO^+ reacted with cyclopropyl benzene to form a five membered heterocycle, a 4,5-dihydroisoxazole, with incorporation of the NO into the cyclopropane ring. A mixture of NO and a photosensitiser, and a mixture of NO and O_2, were both known to react with biaryl cyclopropanes to form 4,5-dihydroisoxazoles. Alkene like in the amount of sp^2 character of the three-membered ring, cyclopropanes were investigated for their reactions with NO. When some successes were found here, substituted expoxides were examined in a similar way, to see if the reaction was applicable to the three-membered heterocycles.

CHAPTER 2

A Study of the Reaction of Nitric Oxide with 1,1,4,4-Tetramethylbutadiene Derivatives

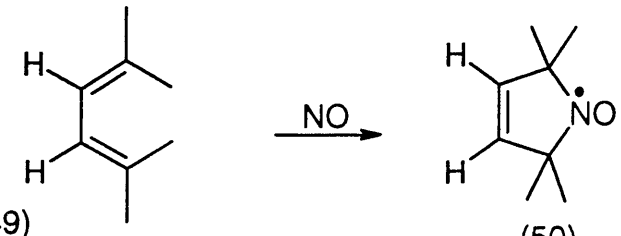
2.1 INTRODUCTION

Symons *et al.* attempted to create an ESR detectable NO trap that could be used under biological conditions, and so be suitable for whole body radio-frequency ESR imaging *in vivo*.[24] A test reaction involved 2,3-dimethyl-1,3-butadiene (47). Whilst the nitroxide produced (48) was not very long-lived, and so not very useful for *in vivo* work, its four equivalent protons produced an ESR signal that 'proved' the reaction occurred. Attention was then turned to 2,5-dimethyl-2,4-hexadiene (49) which reacted to form a longer-lived nitroxide radical (50).



(47) 2,3-dimethyl-1,3-butadiene

(48)



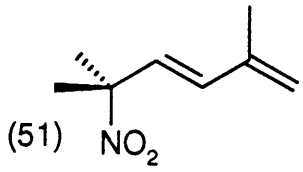
(49) 2,5-dimethyl-2,4-hexadiene

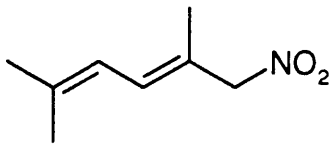
(50)

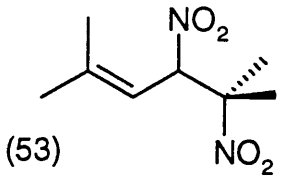
The interpretation of the results was disputed by Rockenbauer and Korecz,[25] who used ESR evidence to support their claim that the reaction had, in common with previous work of their own with nitric oxide and olefins,[15,20] formed a product which was the result of an initial reaction with

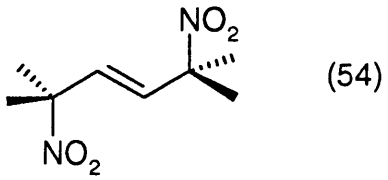
NO_2. This would lead to a long chain nitroxide, instead of the cyclic one shown above.

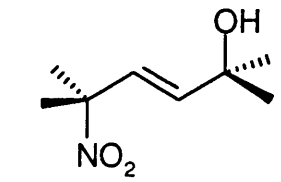
Kelly *et al.* found the reaction of carefully purified NO with 2,5-dimethyl-2,4-hexadiene gave (*E*)-2,5-dimethyl-5-nitro-1,3-hexadiene (51), (*E*)-2,5-dimethyl-6-nitro-2,4-hexadiene (52), (*rac*)-2,5-dimethyl-4,5-dinitro-2-hexene (53), (*E*)-2,5-dimethyl-2,5-dinitro-3-hexene (54) and (*E*)-2,5-dimethyl-5-hydroxy-2-nitro-2-hexene (55).[26]



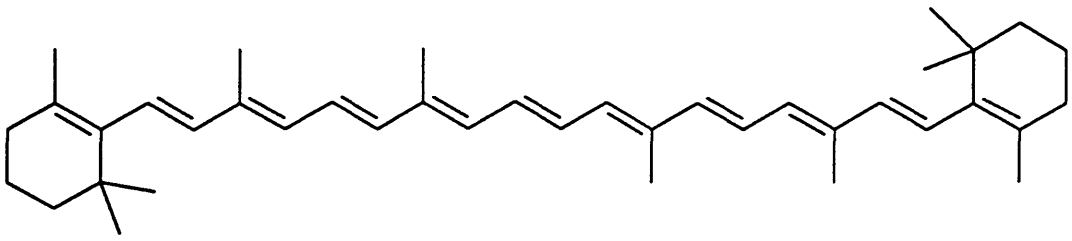






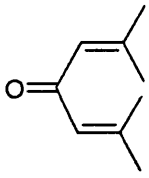


ESR showed that the natural product β-carotene (56) reacted with NO to give a series of nitroxides. The β-carotene molecule shown below contains a number of possible reaction sites; optical spectroscopy suggested a loss of conjugation upon nitroxide formation. The precise structures of the products were not established, but the formation of 5-23 membered rings was suggested.[27]



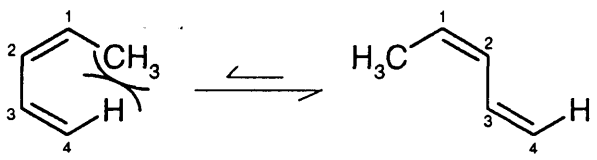
(56)

The fate of substituted butadienes, and phorone (57), with NO has been the subject of further discussion (Gabr and Symons).[28]



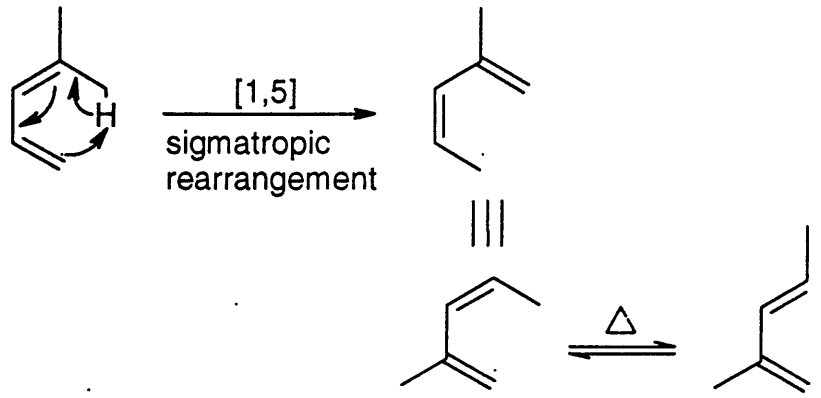
(57)

Conjugated dienes can exist in the *cis* or the *trans* conformations (describing the orientation of the double bonds to each other, sometimes known as cisoid or s-*cis*, and transoid or s-*trans*). For a cheletropic reaction with nitric oxide it would be necessary for the molecule to be in the s-*cis* conformation. However, a methyl group in the C-1 position of the diene (58) disfavours the s-*cis* because of steric interactions with substituents at the C-4 when in this conformation. (This may have been a problem in the reaction described above by Symons.)



(58)

The disubstituted diene, 1,1-dimethylbutadiene, first isomerises to 1,3-dimethylbutadiene before undergoing the Diels-Alder reaction with acrylonitrile.[29]



Butadienes with a *cis*-C-1 methyl perform poorly in Diels-Alder reactions with dienophiles for the reason mentioned above. Jenkins *et al.* showed how the addition of a C-3 methyl group to such a diene allowed a more successful reaction with a dienophile.[30] This is possibly because the steric interactions of the C-1 and C-3 methyls in the trans conformation counter-balance the unfavourable interaction of the C-1 in the cis (figure 5).

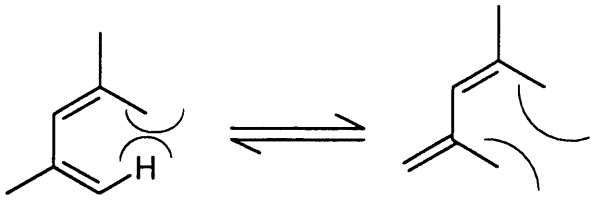
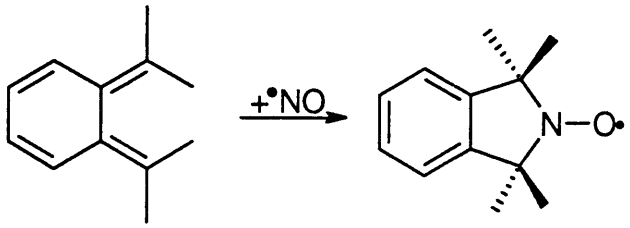


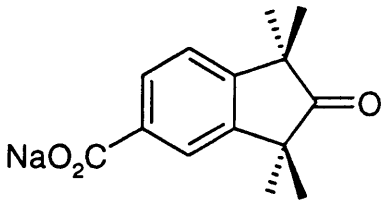
Figure 5

A butadiene 'fixed' in the cis conformation is obviously desirable, tetrasubstituted to increase the longevity of the nitroxide if formed. As mentioned previously, Korth successfully produced a cheletropic NO trap in the form of a quinodimethane (45) formed by the photodecarbonylation of a precursor.[23]

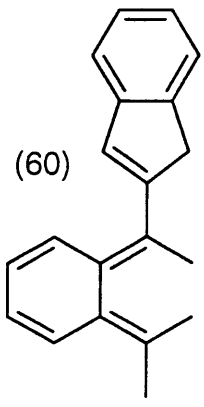


(45) (46)

The insolubility of these compounds in aqueous systems mean that this is unsuitable for NO trapping in biological systems. However, the addition of a carboxylate group was found to give a water-soluble molecule (59) whose ability to react with NO was not impaired, nor was the photodecarbonylation reaction to form the *o*-quinodimethane from the indanone. Korth also sought to improve on the stability of (45), leading to the discovery of (60), which is much more stable and still reacts rapidly with NO.[38]

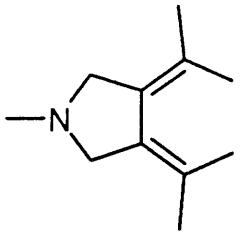


(59)



(60)

The tetra-substituted butadiene (61) below is one of a range prepared by Jelinski and Kiefer.[31]



(61)

The butadiene is fixed in the cis conformation by the five-membered heterocycle in this case. They may also allow the possibility of water-soluble NO trapping systems (figure 6).

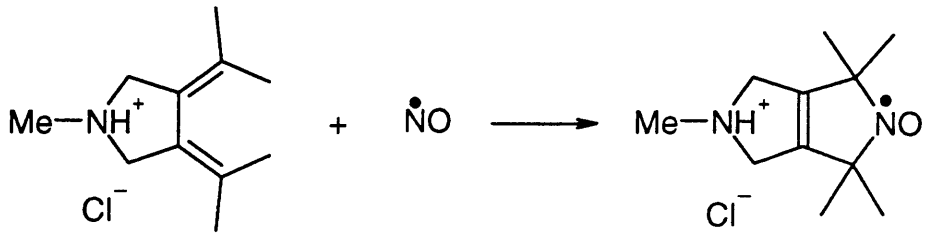
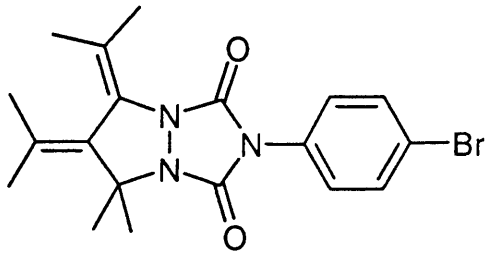


Figure 6

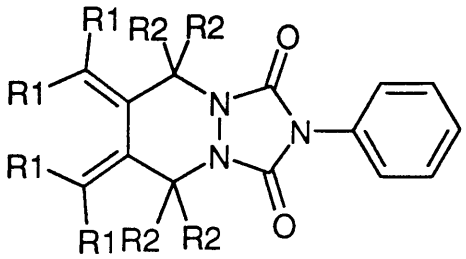
2.1.1 Substituted Butadienes

The two isopropylidene groups on adjacent carbons, in acyclic and cyclic (as above) systems, present a barrier to rotation about the bond between the two carbons, arising from the steric hindrance between the cis methyl groups on the C_1 and C_4. The resulting dienes exist in severely skewed, non-planar chiral conformations.[31] Pasto and Scheidt determined the X-ray structure of (62).[32] The diene is very skewed, they found the dihedral

angle between the two isopropylidene functions to be 52.3°. In a planar conformation the 'inside' carbons of the isopropylidene groups are ~2.1Å apart.

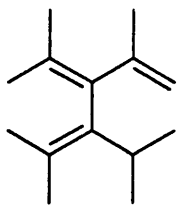
(62) 

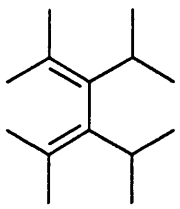
Jelinski and Kiefer used temperature-dependent NMR spectroscopy[31] to calculate the energy barrier to rotation of (61) and a series of compounds related to their original model (63).[33]

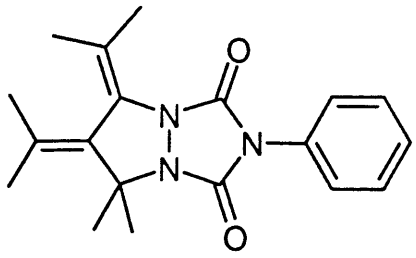
(63) 

a, R1 = Me; R2 = H
b, R1 = H; R2 = Me

Previous examples include the examination of (64) and (65) by Bomse and Morton[34] and (66) by Pasto and Scheidt.[32]

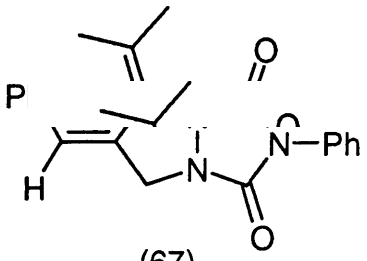
(64) 

 (65)

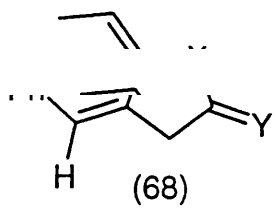


(66)

Cyclic and acyclic examples of this class of compounds have been isolated in optically active form. For example (67) and (68) by Pasto and Borchardt[35] and (69) by Rösner and Köbrich[36].

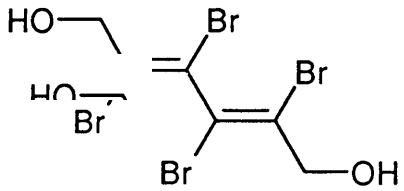


(67)



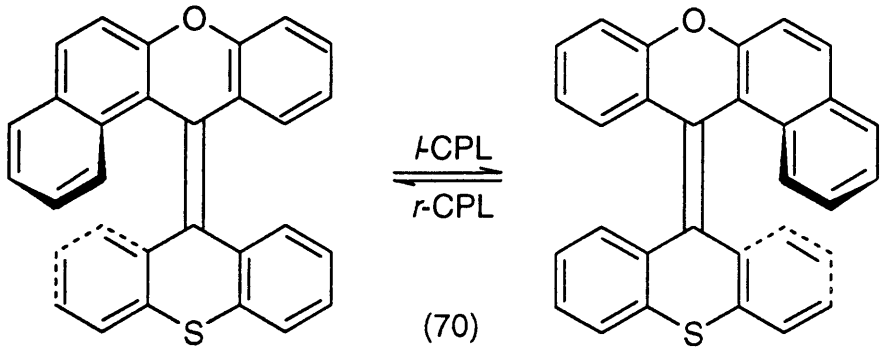
(68)

a, X = NSO_2Cl; Y = O
b, X = O; Y = NSO_2Cl



(69)

Compounds with a chiral axis have been proposed for use as a chiral optical switch in an optical data storage system. The enantiomers of compound (70) can be interconverted by the application of left or right circular polarised light.[37]



(70)

l-CPL = left circular polarised light

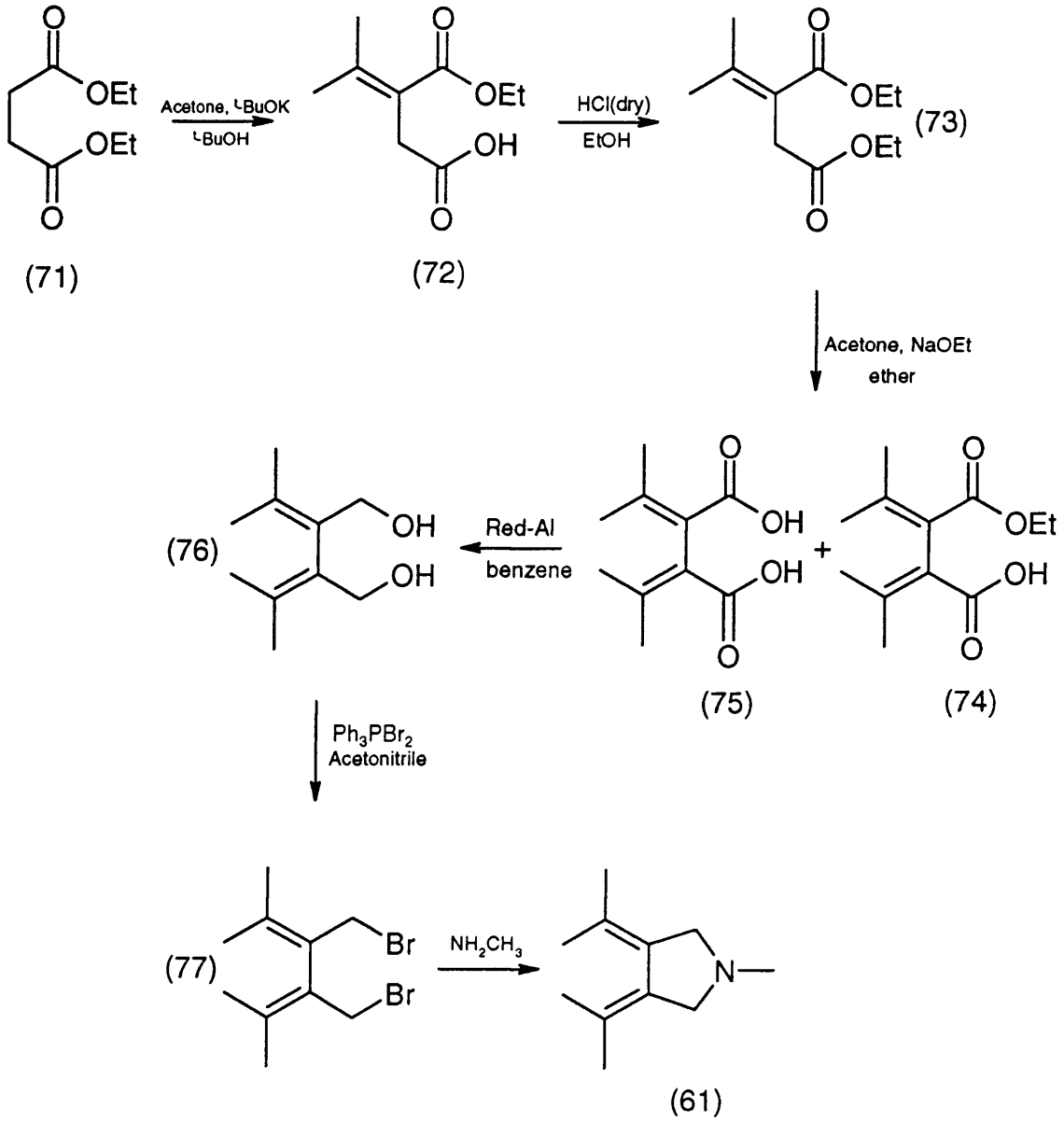
r-CPL = right circular polarised light

2.2 RESULTS AND DISCUSSION

We decided to examine the reaction of amines such as (61) with nitric oxide. The compounds were synthesised from diethyl succinate.

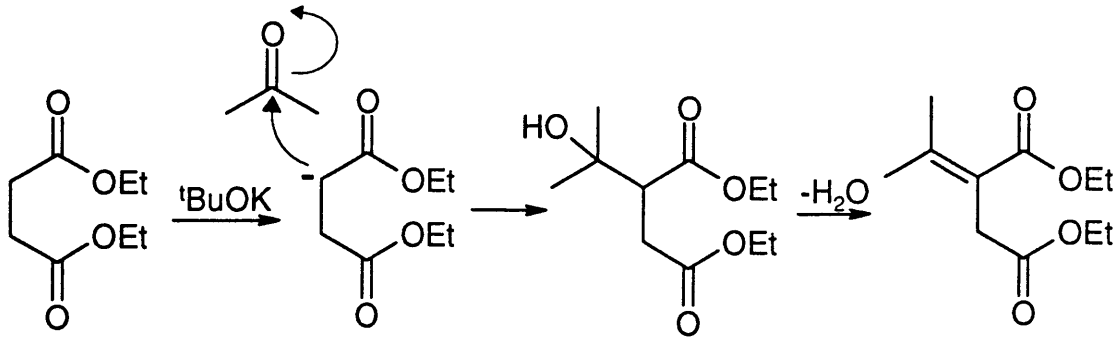
2.2.1 Proposed Reaction Scheme

Jelinski and Kiefer obtained the amine butadiene (61) by the route shown in scheme 10.[31]



Scheme 10

The first two steps are Stobbe condensations[39,40] of acetone and the diesters (71) (diethyl succinate), and (73) (figure 7). Water is released during the formation of the unsaturated product, allowing for at least half of the ester groups to be hydrolysed. Ethanol and dry HCl were used in a re-esterification step to reform the diester (73) of the first product (72).



(71) (73)

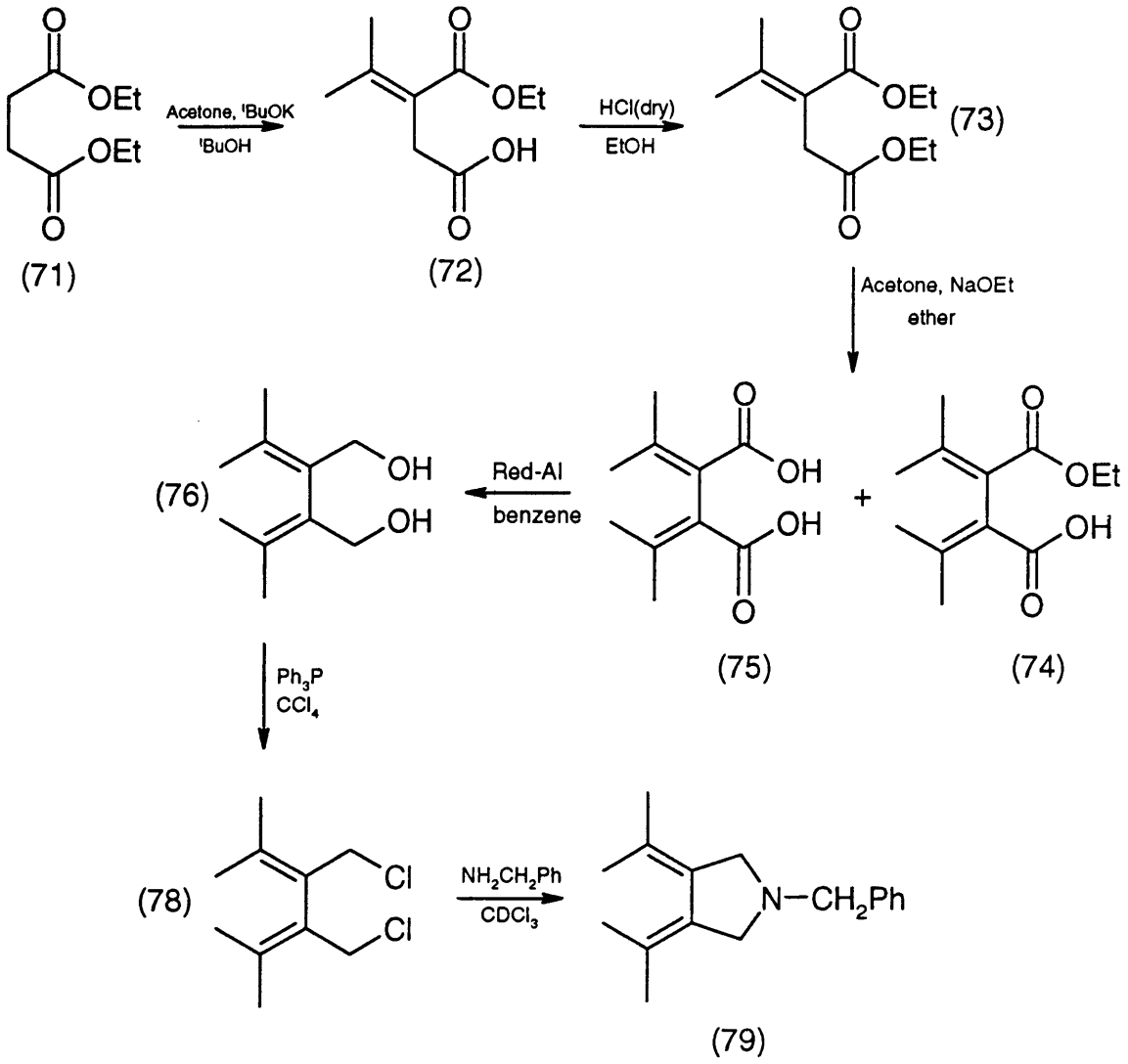
Figure 7

The 'isopropylidene' parts of the molecule then remain unchanged whilst the groups in the C2 and C3 positions (numbering as a butadiene) are modified. Red Al® (sodium bis(2-methoxyethoxy)aluminium hydride) was used as the reducing agent to form the diol, (76). Triphenylphosphine dibromide, formed from the combination of triphenylphosphine and bromine, was the brominating agent in the reaction with the (76).[41] The dibromo compound (77) was reacted with methylamine to give the cyclic amine butadiene (61) (experimental detail here was sparse).

2.2.2 Actual Reaction Scheme (Scheme 11)

As in scheme 10, acetone and diethyl succinate (71) were reacted. The hydrolysed product (72) was not isolated. Purification of the diester (73) proved to be a problem. The ^1H NMR spectrum showed that the signals

arising from the two ester groups of (73) were no longer equivalent as in the symmetrical diethyl succinate.



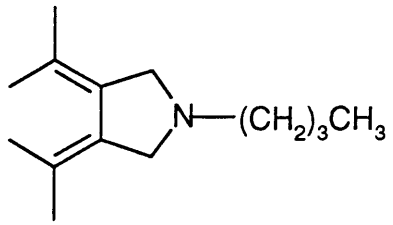
Scheme 11

A second condensation of acetone and the alkene product (73) gave (74) and (75) as before.[39,40] Re-esterification of the mixture of the half-acid/ester and the diacid was not attempted, as the reducing agent, Red-Al ® (which was to be used in the next step), acts upon both carboxylic acid groups and esters.

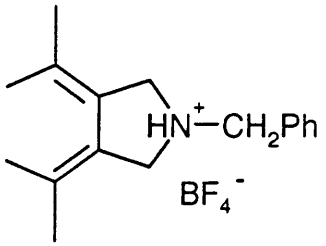
There were problems in the purification of (73) synthesised by the literature method, so LDA was tried as the base in the first Stobbe condensation. LDA (prepared from diisopropylamine and BuLi) was reacted with diethyl succinate and acetone. The result did not appear to be successful and the reaction was not pursued. In order to avoid the use of benzene, an alternative method for the reduction of acids/esters with Red-Al® was sought. Kornet used Red-Al® in the preparation of 1,2-diethyl-4-hydroxymethylpyrazolidine, reducing an ester to an alcohol.[42] This provided the method that was followed to yield the diol (76). The alkene (73), half-acid (74) and diacid (75), and the diol (76) were produced in multi-gram amounts. $LiAlH_4$ was used as the reducing agent in an alternative preparation of diol, (76). The reaction was successful in producing the diol but the yield was less than that of the reaction using Red-Al® to reduce the carboxylic acid/ester groups. Attempts to convert diol (76) to the dibromide (77)[41] had little obvious success. A by-product of the bromination of the diol should be triphenylphosphine oxide. By TLC the reaction mixture appeared to contain triphenylphosphine oxide (low R_f in ether-light petroleum solvent, 1:2 v/v). This was not unreacted triphenylphosphine which runs near to the solvent front in the same solvent. The implication was that the reaction had occurred, but the material which by TLC did not correspond to starting materials or triphenylphosphine oxide could not be isolated, and decomposed during column chromatography.

Finally a chlorination, rather than a bromination, proved successful. A mixture of triphenylphosphine and carbon tetrachloride was stirred at 80°C for 2 hours to produce the dichloride (78).

Given the difficulty of some of the previous reactions, a more readily available and easily handled liquid amine, benzylamine, was used in the final reaction rather than the gaseous methylamine, and benzylamine's relatively simple ^1H NMR signals (aromatic and benzylic protons) did not complicate the ^1H NMR of the product amine. Stirring benzylamine with (78) at 60°C for three hours gave the cyclic amine butadiene (79). The reaction was also repeated successfully with *n*-butylamine (80).

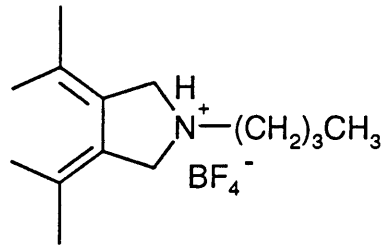
(80) 

The product amines were unstable, and began to decompose within a couple of weeks, even when stored at -20°C. Salts were produced to try and increase the stability (it also being necessary to have the amine in the form of its salt if it is to be water-soluble). The HCl salt of the benzylamine derivative (79) was not formed successfully, but the HBF_4^- salt (81) was readily formed.

(81) 

The HBF_4^- salt of the *n*-butylamine derivative was also produced (82). Both (81) and (82) were formed by the addition of tetrafluoroboric acid-diethyl ether complex ($HBF_4.OEt_2$) to the amine in $CDCl_3$.

(82)

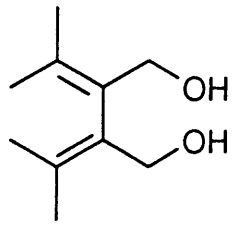


2.2.3 ^1H NMR's of the Substituted Butadienes (76), (78), (79), (80), (81), (82)

The reaction of nitric oxide with the amine-butadienes (79), (81), (82) (section 2.2.5) was carried out in the NMR tube. Described here first are the NMR spectra of the amine-butadienes, as well as those of the diol (76) and dichloride (78).

The ^1H NMR spectra of the diol, (76), might seem initially surprising. The 2-D representation of the molecule, as shown below, suggests a symmetrical structure with the resulting simplification of the NMR spectrum. Singlets produced by the methyl and methylene protons might be expected.

(76)

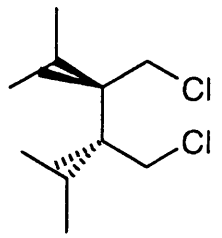


(76) Integration	Multiplicity	Chemical Shift	Assignment
6H	s	1.56	C=C-CH_3
6H	s	1.78	C=C-CH_3
2H	d	3.84	C*H*H-OH
2H	br s	4.02	O*H*
2H	d	4.42	CH*H*-OH

In fact the two methylene protons (R-CH_2-OH) are to be non-equivalent and two (2H) doublets are seen. The isopropylidene groups on adjacent carbons of the diol, as mentioned earlier, are creating a chiral axis in the molecule. The interaction of the methyl groups with each other (if cis) or with the other groups (if trans) make planarity disfavoured as a high-energy state, and force the molecule to adopt a skewed conformation. This is also the case in the dichloride (78).

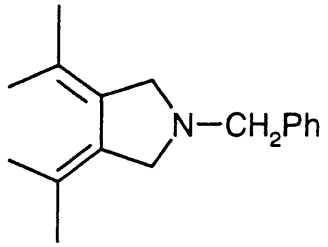
e.g.

(78)



(78) Integration	Multiplicity	Chemical Shift	Assignment
6H	s	1.66	C=C-CH_3
6H	s	1.87	C=C-CH_3
2H	d	4.13	C*H*H-Cl
2H	d	4.31	*C*H*H*-Cl

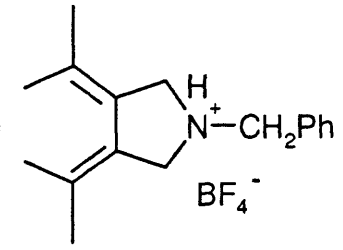
When the 5-membered ring of the tertiary amine (79) is formed, the methylene protons are no longer inequivalent on the NMR timescale and appear as a (4H) singlet.

(79) 

(79) Integration	Multiplicity	Chemical Shift	Assignment
6H	s	1.63	CH_3-C=C
6H	s	1.67	CH_3-C=C
4H	s	3.27	C=C-C*H*$_2$-N x 2
2H	s	3.70	-NC*H*$_2$-Ph
5H		7.21-7.39	aromatic

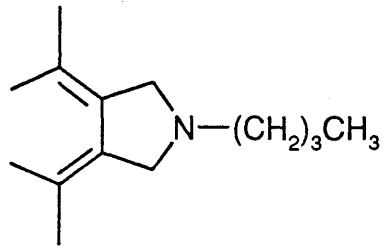
When the amine is acidified to form the salt (81), the methylene protons are inequivalent again. The '$^{+}$NH' is also coupling to these protons, and two doublets of doublets are seen as a result.

(81)



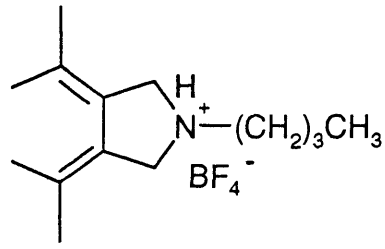
(81) Integration	Multiplicity	Chemical Shift	Assignment
6H	s	1.70	CH_3-=
6H	s	1.73	CH_3-=
2H	v br dd	3.72	=-CH_2-N
2H	br dd	4.15	=-CH_2-N
2H	d	4.28	N-C*H*$_2$-Ph
5H		7.42-7.50	aromatic

In the *n*-butylamine derivative (80), the methylene protons appear as equivalent, as in the benzylamine derivative.

(80) 

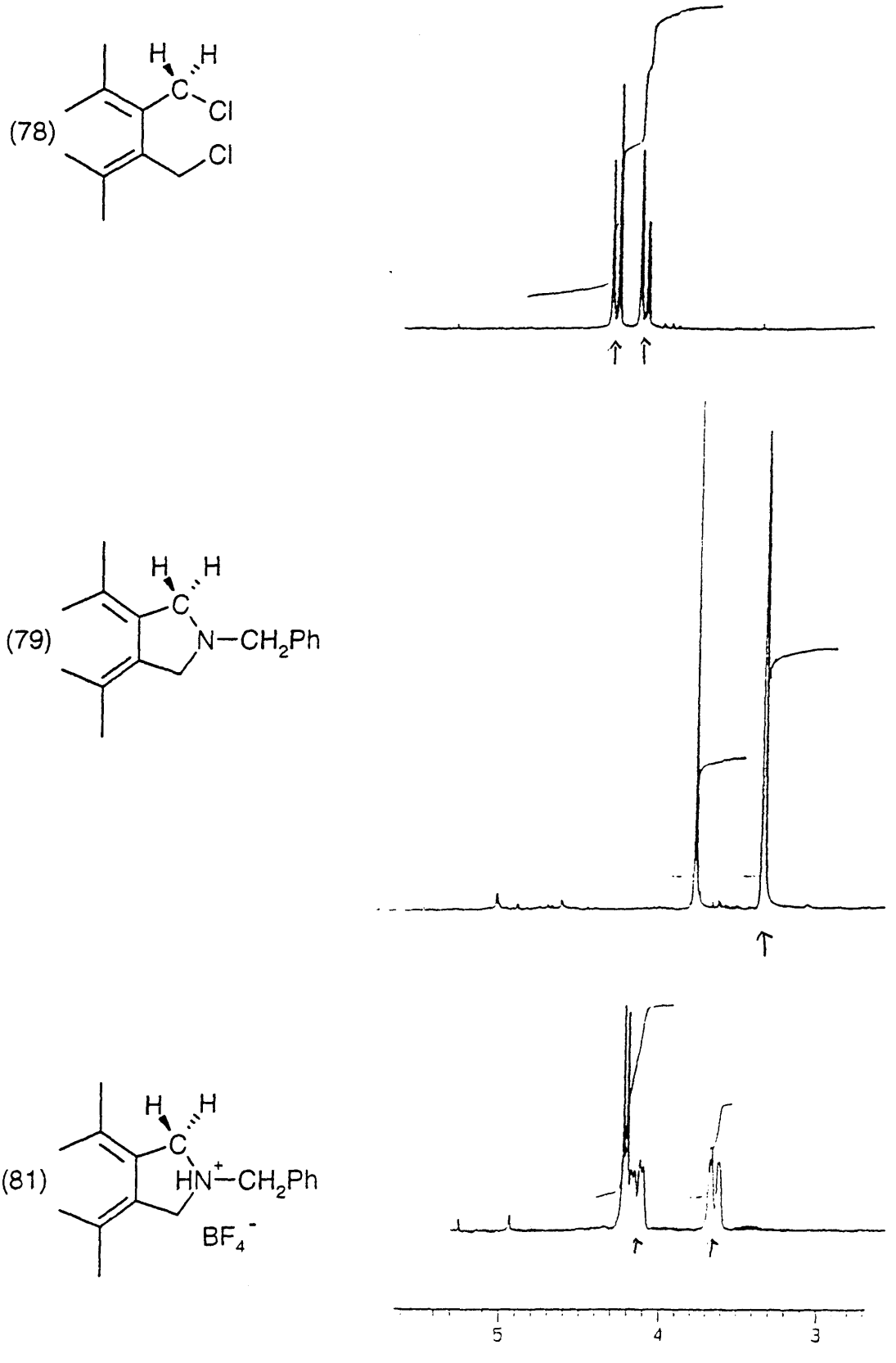
(80) Integration	Multiplicity	Chemical Shift	Assignment
3H	t	0.93	$N(CH_2)_3CH_3$
4H	multiplet CH_2's	1.07-1.57	CH_2CH_2-CH_3
6H	s	1.64	=-CH_3
6H	s	1.71	=-CH_3
2H	br t	2.54	N-CH_2CH_2-
4H	s	3.28	=-CH_2-N x 2

Again, as with the benzylamine derivative, acidification to form the salt (82) of the *n*-butylamine derivative makes the methylene protons appear as inequivalent.

(82) 

(82) Integration	Multiplicity	Chemical Shift	Assignment
3H	t	0.97	N-(CH_2)-C*H*$_3$
4H	multiplet of CH_2's	1.42	$NCH_2(CH_2)_2CH_3$
6H	s	1.71	CH_3-C=C-
6H	s	1.78	CH_3-C=C-
2H	dt	3.16	N*C*H$_2$(CH_2)$_2$$CH_3$
2H		3.63	-C=C-CH_2-N
2H	dd	4.32	-C=C-CH_2-N
1H	br s	10.04	NH

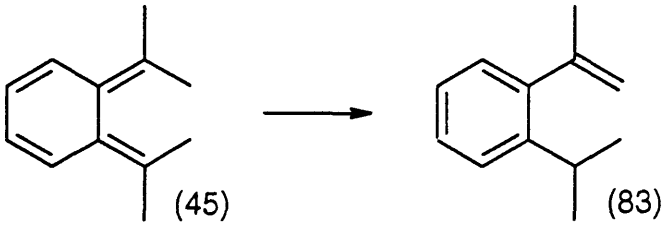
All the above NMR spectra were obtained at room temperature. Jelinski and Kiefer synthesised the range of compounds mentioned earlier, including (72)/(73), (74)/(75), (76), and (70), in order to investigate the barrier to rotation about the single bond linking two isopropylidene (or similar) groups. The restricted rotation caused by the bulky groups was examined using temperature dependent NMR, to find the coalescence temperature, at which free interconversion between enantiomers occurs on the NMR timescale. Their results suggested that seemingly minor changes in the structures studied could produce large changes in the energy barrier to rotation.[31]



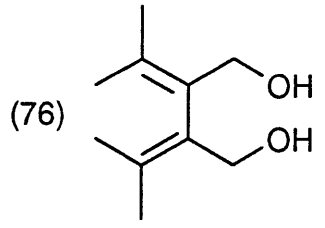
Partial ^1H NMR spectra to show equivalent/inequivalent protons in (78), (79), and (81)

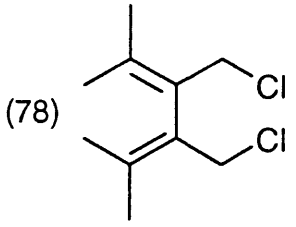
2.2.4 Stabilities of The Substituted Butadienes (76), (78), (79), (81)

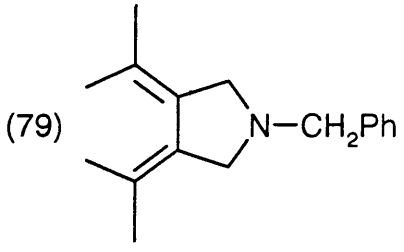
Korth found the half-life of his quinodimethane 1,2-bis(*exo*-isopropylidene)cyclohexa-3,5-diene[23] (45) to be short (140s). This was because of a rapid 1,5-sigmatropic hydrogen shift in the molecule to give *o*-isopropyl-α-methylstyrene (83).

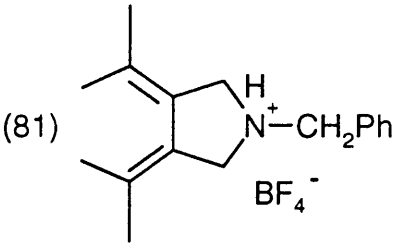


As mentioned before, the cyclic amine butadienes (such as (79)) were unstable and began to decompose within a couple of weeks, even when stored at -20°C; salts of the amines were produced in an attempt to improve their stabilities.

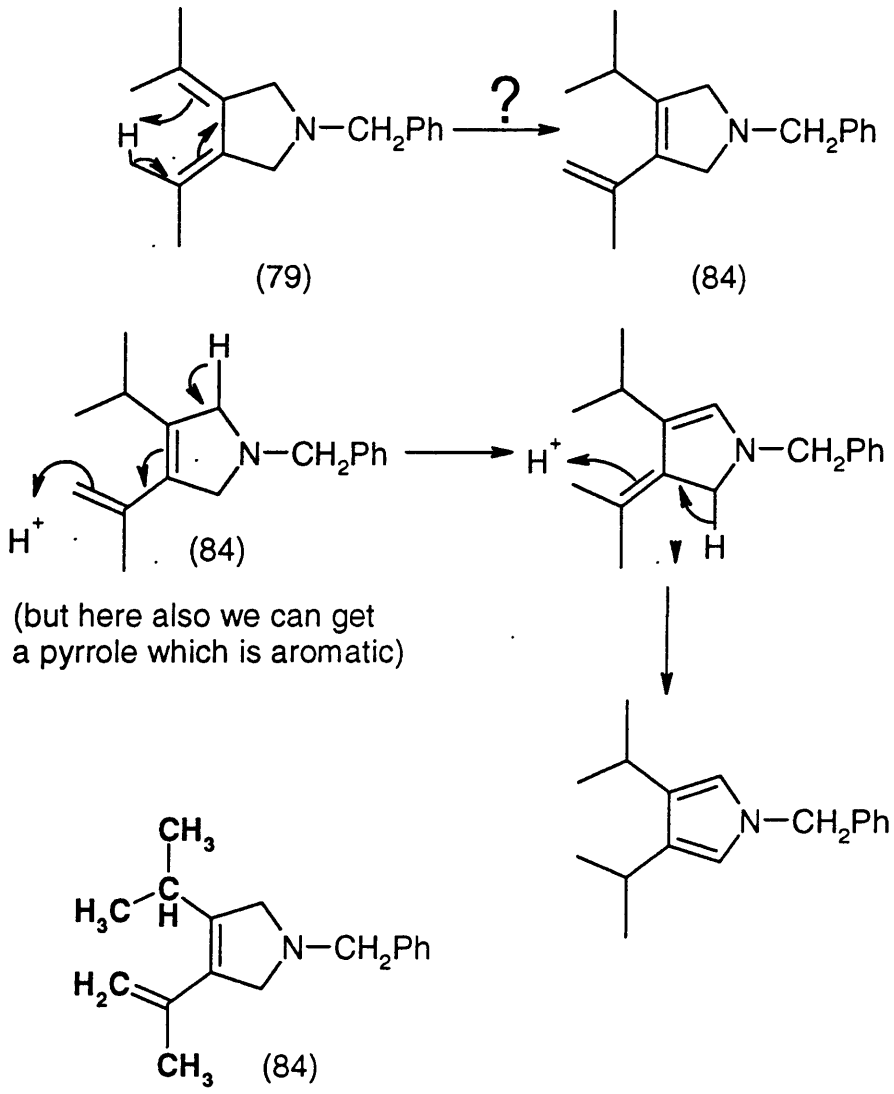






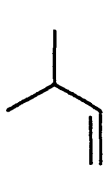


To study its decomposition and investigate whether a 1,5-sigmatropic hydrogen shift was occurring as in the literature[23], a sample of the benzylamine derivative (79) was made into an NMR sample and allowed to stand at room temperature. Similar samples of the diol (76), the dichloride (78) and the benzylamine derivative salt (81) were prepared. The decomposition, or otherwise, of the samples was followed over a period of several months by ^{1}H NMR.

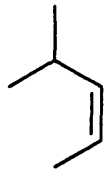


If a 1,5-H migration occurred, a product such as (84) would be formed. To give an idea of the expected chemical shifts of the highlighted protons in

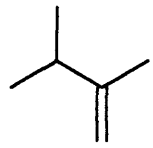
structure (84), known compounds from the Aldrich catalogue were examined (figure 8). See table below.



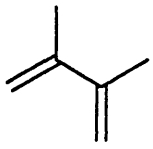
3-methyl-1-butene



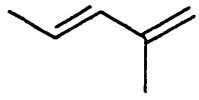
cis-4-methyl-2-pentene



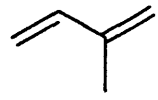
2,3-dimethyl-1-butene



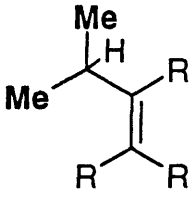
2,3-dimethyl-1,3-butadiene



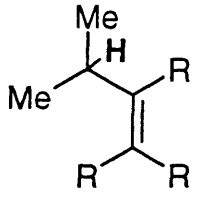
trans-2-methyl-1,3-pentadiene



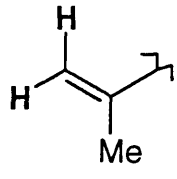
isoprene



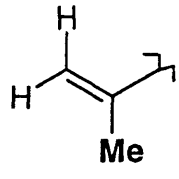
xa



xb



xc



xd

Figure 8

	3-methyl-1-butene	*cis*-4-methyl-2-pentane	2,3-dimethyl-1-butene
xa	1.0	0.95	1.05
xb	2.3	2.6	2.25
	2,3-dimethyl-1,3-butadiene	*trans*-2-methyl-1,3-pentadiene	isoprene
xc	5.0	4.85	5.0
xd	1.9	1.8	1.85

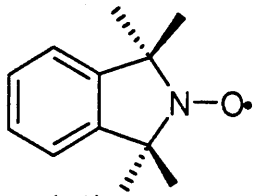
The diol, the dichloride and the benzylamine derivative salt were unchanged, by NMR, over this period, but the free amine had decomposed. Examining the possibility of a 1,5-hydrogen shift occurring

to explain the decomposition, two of the methyl groups, previously isopropylidene, would now be expected to have moved upfield. There are possible signals slightly upfield of the still existing isopropylidene signals (although not upfield to the extent expected from the table.) However, vinylic protons would also be expected to be observed in the δ5.0 (approx.) region and there is little evidence of this, or for an allylic proton from the isopropyl group (approx. δ2.5). Although the amine has clearly decomposed, it is not a single product and it is difficult to say what has occurred.

It is interesting that the amine salt did not decompose in the same period. This would suggest that the lone pair of the nitrogen is involved in the decomposition. The lone pair is not in conjugation to either of the double bonds and so its involvement cannot be explained in this way. It is possible that the induction effect is somehow affecting the decomposition.

2.2.5 NO and the Butadienes

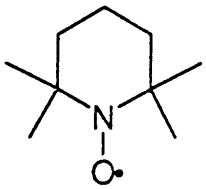
It was hoped that a cyclic nitroxide would be formed by the reaction of NO with the diene part of the molecule, in a way similar to the reactions described by Korth *et. al.*[23,38]



(46)

Symons *et al.* believed that this type of cyclisation had occurred in the reactions of 2,3-dimethyl-1,3-butadiene (47) and 2,5-dimethyl-2,4-hexadiene (49) with NO (see earlier).[24] But as mentioned earlier, Symons's ideas were disputed by Rockenbauer and Korecz,[25] who believed that the product was not a cyclic one, but a long chain nitroxide formed after an initial reaction of NO_2 with one of the double bonds. The alkyl radical resulting from this reaction could then react with NO to form a nitroso compound which could trap another alkyl radical to give a nitroxide containing two original butadiene molecules, which better fit the ESR data obtained. Kelly studied the reaction with 2,5-dimethyl-2,4-hexadiene[26] (49) and he found, as mentioned earlier, a variety of open chain unsaturated nitro compounds resulted. In a continued study of (47) and (49) by Symons and Gabr, results obtained suggested that reactions occurring may include the addition of NO to form allylic radicals, which can cyclise, add more diene and then possibly cyclise, or add more NO to produce nitroso derivatives which can trap another radical to give nitroxides. (Symons's and Kelly's examples were for butadienes which were not 'fixed' in the s-cis conformation.)

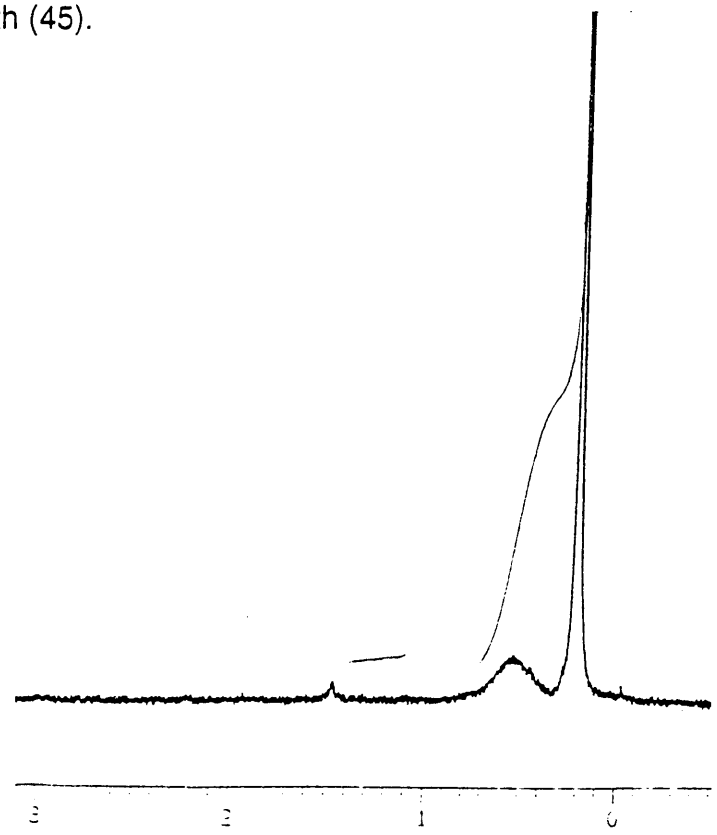
2.2.5.1 TEMPO, a Commercially Available Nitroxide



TEMPO =

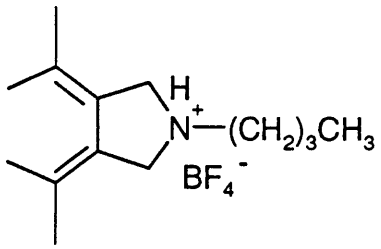
2,2,6,6-tetramethyl-1-piperidinyloxy, free radical

The nitroxide part of the TEMPO molecule is very similar to that which would be expected if any of the butadienes (79), (81), and (82) had formed nitroxides by reacting with NO in a manner similar to Korth's NO trapping reaction with (45).

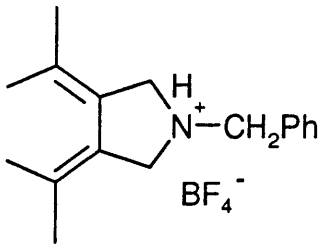


Partial ^{1}H NMR spectrum of a nitroxide – TEMPO

The following butadienes were dissolved in $CDCl_3$ in NMR tubes and bubbled with NO for various lengths of time. The effects were followed by ^{1}H NMR.

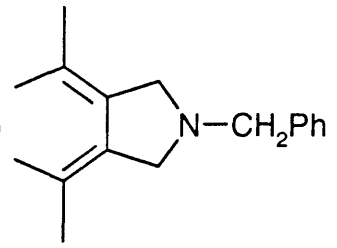
(82) 

The sample of (82) was bubbled for 30 seconds with NO. In the NMR spectrum, the isopropylidene methyls could be seen clearly and other signals existed that might have been the amine but were small and unclear, but mainly ether signals (from the $HBF_4.OEt_2$ complex used to make the salt) were present. After a further minute of NO, only the ether signals were strong (apart from some acetone contamination). When the NMR tube was left overnight at room temperature, the resulting spectrum was similar. A dark orange precipitate had formed out of the yellow solution in $CDCl_3$ during the course of the reaction, and this would seem to be the reason for the disappearance of amine signals from the spectrum.

(81) 

After 2 minutes of NO bubbling into a sample of (81) the amine signals were all present (apart from the 'NH'), but broadened; no coupling was seen to the "$^{+}$NH". After bubbling NO for a further three minutes, the NMR spectrum was similar to the previous one. Another three minutes of NO bubbling and in the NMR the signals due to the amine were greatly reduced. An acetone impurity was the only strong signal, although the

isopropylidene methyls and ether signals (and some signals in the aromatic region) could still be seen (although the various CH_2 signals could not be clearly seen if present, integration of this region showed the presence of protons). After leaving the NMR tube overnight in the freezer, the resulting spectrum was similar. It appears possible (by comparing relative integrations) that the disappearance of the amine signal is caused in part by an increase in the contaminating acetone, leading to the relative intensities of the other components being reduced. However, by comparison (integration) to the ether triplet ($HBF_4.OEt_2$ complex added in approximately 1:1 ratio with the amine) the amine signal is also being reduced. A reason for this loss of amine signal could be that the material was no longer in solution. This would seem to be likely, as a dark solid precipitated out of the orange solution in the NMR tube during these reactions. (A possible explanation for reduced appearance of signals is that the signals are broadening (caused by paramagnetism) and so the ones that were the smallest initially are not seen clearly, and the larger ones are reduced; as previously mentioned, the reduction of signals by the acetone could leave the smallest signals not clearly visible. A combination of these three things might account for the actual spectrum seen.)

(79) 

Bubbling NO through a solution of (79) for five minutes made little difference to the appearance of the NMR spectrum. When the NMR tube was left overnight at room temperature, the resulting spectrum was mostly unchanged, but with slightly more impurities were present. Applying NO for a further five minutes caused the disappearance of the singlet for the four methylene protons. A very broad signal appeared in that region. The 2H singlet for the –N-CH_2Ph was also no longer there. A singlet was present approximately 0.55ppm downfield of the chemical shift of the 2H singlet in the unreacted sample. The isopropylidene methyl singlets and aromatic signal were in the same places. One hour later the spectrum was similar, except for the broad signal was now two broad signals. Another hour later and the spectrum was similar again but the broad signals were broader. By comparing the relative integrations of the acetone impurity present in all the spectra, it would seem that there is some appearance of loss of amine signal because of increase in acetone concentration. Apart from this, the signals due to the isopropylidene methyls are fairly constant in size, they are not decreasing as was the case for the amine salts. There was no precipitation of compound caused by the action of NO on the sample. The effect of NO appears to be mainly on the methylene protons signal – its broadening and apparent split into two.

2.2.6 Conclusion

The main action of NO on the two HBF_4^- amine salts seems to have been to cause the formation of a material insoluble in $CDCl_3$. The free amine

did not react readily with NO and after a long reaction time an unidentified process occurred. The main action appears to be the change in appearance of the methylene protons signal. As mentioned earlier, there are various possibilities for the reaction of NO with a butadiene; a concerted process of addition as Korth[23,38] found and Symons[24] had hoped to find, a reaction involving NO_2 as Rockenbauer and Korecz[25] suggested, reactions that include stepwise additions of NO or NO_2 and the addition of intermediate radicals formed to other intermediates (Symons[28], Kelly[26]). One of the reasons that a tetra-substituted butadiene was chosen was to avoid the disproportionation of the cyclic nitroxide, if formed (figure 9).

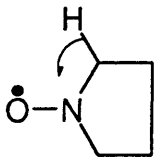


Figure 9

The products formed were probably a mixture and not pure. The NMR spectra are hard to interpret and it is difficult to say which of the possiblities have occurred, if any of them.

CHAPTER 3

The Trapping of Nitric Oxide with Substituted Phenylcyclopropanes

3.1 INTRODUCTION

To investigate further the chemistry of NO, the reactions of the alkene-like cyclopropanes with NO were examined.

3.1.1 Three-membered Rings

The properties of a cyclic compound differ from those of its acylic counterpart.[43] Whilst both will adopt conformations of the lowest energy, minimising non bonding interactions, the cyclic compound will probably not be able to reach as low an energy as the acyclic compound. It will be prevented from doing this by the fact that it does not have the conformational freedom of the acyclic compound and may be strained. Three membered rings have considerable angle strain and this affects their reactivity.

X	Angle CXC in °	C-C in Å	C-X in Å	Strain kcal mol^{-1} (kJ mol^{-1})
CH_2	60	1.510	1.510	27.5 (115)
NH	60	1.481	1.475	27.1 (113)
O	61	1.472	1.436	27.2 (114)
S	48.5	1.492	1.819	19.9 (83)

Some properties of saturated 3-membered rings and their strain energies[43]

Bond angles in three-membered rings are distorted from normal bond angles of 109° for a tetrahedral carbon. As a result of this there are changes in the hybridisation of the ring atoms. The bonds forming the ring have more p character than acyclic sp^3 carbons which allows greater overlap of orbitals 'outside' of the ring (figure 10).

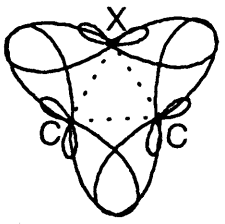
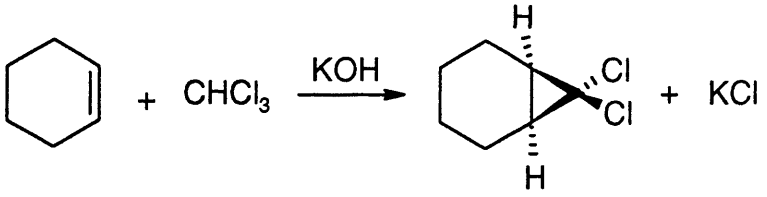


Figure 10

3.1.2 Cyclopropanation

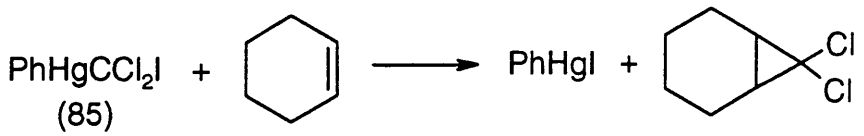
A text-book method for cyclopropane synthesis is by the formation of a halocarbene, from chloroform and a strong base such as potassium hydroxide, in the presence of an alkene.[44]



60%

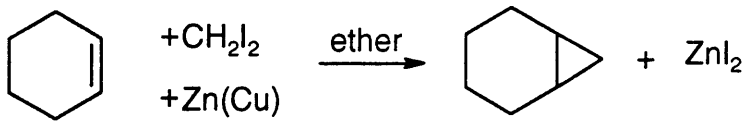
Another way of generating halocarbenes is through organomercurials. For example phenyl(iododichloromethyl)mercury, (85), phenyl(iodobromo-chloromethyl)mercury, and phenyl(iododibromomethyl) mercury, have

been found to react well with carbenophiles (for example, alkenes, which resulted in cyclopropane formation.)[45]



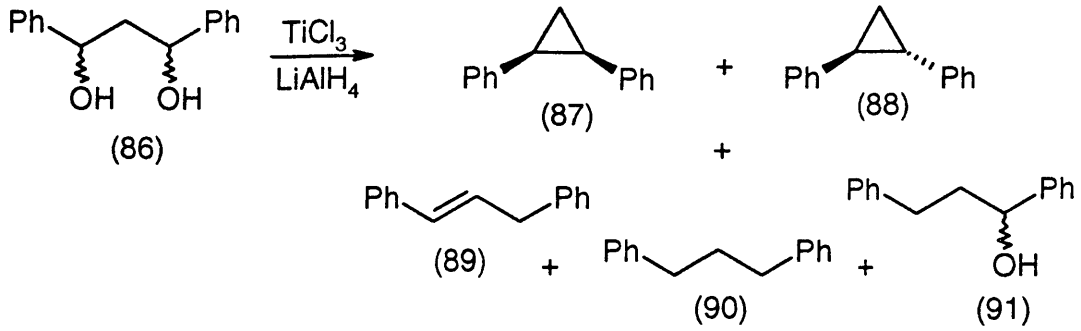
89%

For preparing non-halogenated cyclopropanes, the Simmons-Smith[46] reaction is the text-book method. This involves the treatment of alkenes with diiodomethane and a zinc-copper couple. The reacting species here is not a free carbene but a carbenoid (reagent with carbene-like reactivity) formed from the reaction of the diiodomethane with the Zn-Cu couple.

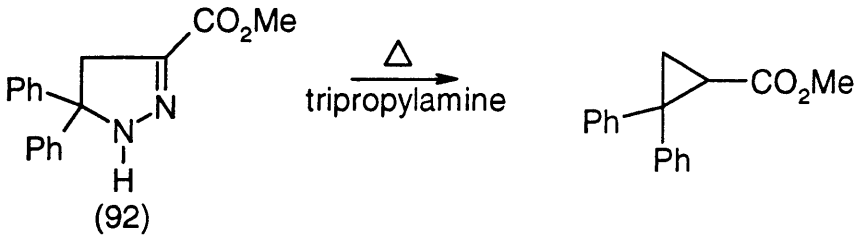


48%

A non carbene-based cyclopropanation involves the *in situ* preparation of low valent Ti species from the reduction of titanium trichloride with lithium aluminium hydride. When these two reagents are reacted with 1,3-diphenyl-1,3-propanediol (86) in THF, *cis*- and *trans*-1,2-diphenylcyclopropanes (87) and (88) are formed (in addition to *trans*-1,3-diphenylpropene (89), 1,3-diphenylpropane (90), and 1,3-diphenyl-1-propanol (91)).[47]



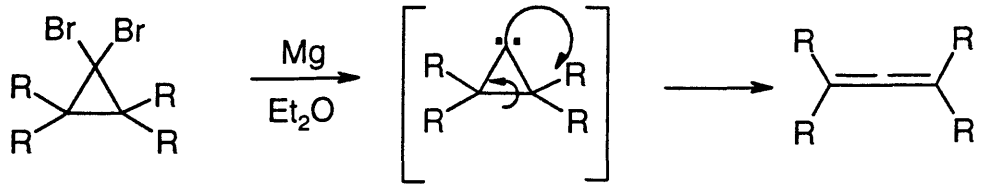
Cyclopropanes can be obtained by the base induced thermal conversion of 5,5-diaryl-3-carboalkoxy-2-pyrazolines (92).[48] The reactions are carried out in hexadecane in the presence of trialkylamines.



3.1.3 Ring Opening Reactions of Cyclopropanes

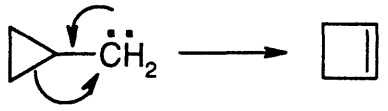
A number of reactions that lead to ring opening are possible for cyclopropanes. These include: rearrangements of cyclopropyl carbene, cyclopropylmethyl carbene and vinyl cyclopropanes, thermal, oxidative and reductive fission, electrophilic and nucleophilic addition, imine- and carbonyl-cyclopropane rearrangement, and free radical fission. This section will concisely review these reactions.[49]

Dibromocyclopropanes such as (93) react readily with magnesium to form carbene (94) which rearranges to allene (95).[50]



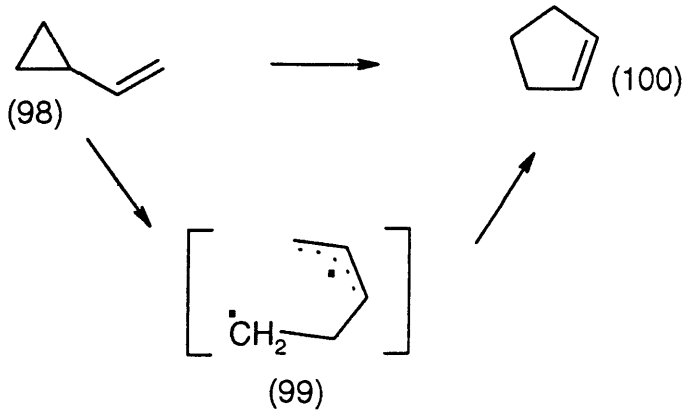
(93) (94) (95)

The cyclopropylmethyl carbene (96) is formed from the corresponding tosyl hydrazone. (96) also undergoes rearrangement to give the cyclobutene (97).[51]



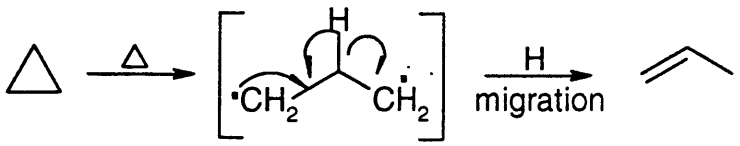
(96) (97)

A vinyl cyclopropane (98) readily undergoes ring opening to form a diradical (99). The diradical is an alkyl radical and an allyl radical. Clearly the stabilised allyl radical is the driving force for this reaction. Ring closure of this diradical forms a cyclopentene (100).[52]



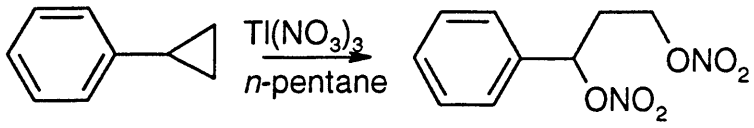
(99)

Thermal ring cleavage of a cyclopropane without the vinyl substitutent is possible in some cases to form a 1,3 diradical (101) which undergoes a 1,2 H-migration to form propene (102).[52]



(101) (102)

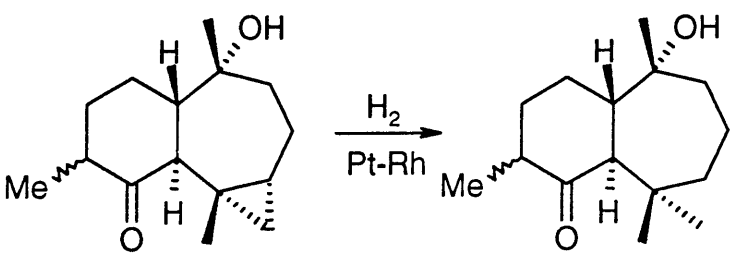
Cyclopropanes can also be cleaved by oxidising agents. For example, the oxidation by thallium (III) nitrate in pentane of cyclopropyl benzene yielded a dinitrate ester (103).[53]



91%

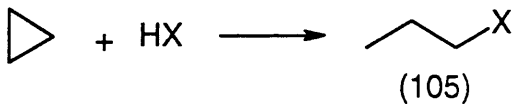
(103)

Reducing agents open appropriately substituted bicyclic cyclopropanes such as (104) to give gem-dimethyl compounds which are of interest in the synthesis of terpenoid derived natural products.[54]

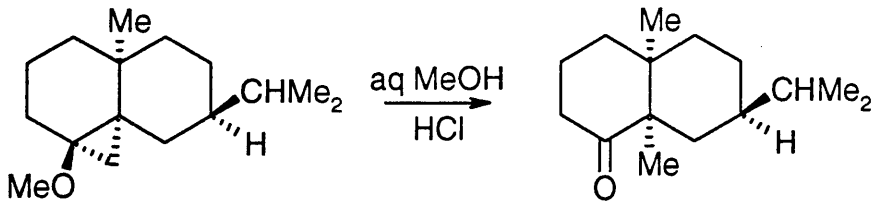


(104) 86%

Cyclopropanes are also opened by electrophilic addition of reagents such as HCl, to produce (105). This reaction is particularly useful in methoxy-substituted bicyclic cyclopropanes e.g., (106) where reaction with methanolic HCl produces a ketone with an α-quarternary centre.[55,56]

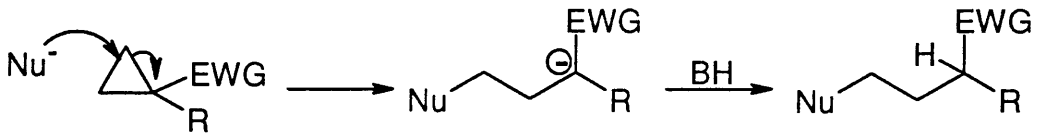


(105)



(106) 100%

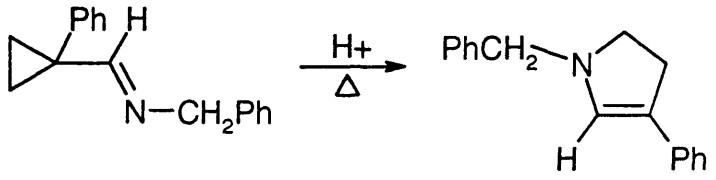
Cyclopropanes substituted by electron withdrawing groups undergo reaction with nucleophilic reagents to produce stabilised anions (107) which are then protonated to give the product.[57]



(107)

Other possibilities exist for the vinyl cyclopropane rearrangement, for example the imine- and the carbonyl-cyclopropane rearrrangements. In these two cases it is less clear that the reaction involves a diradical intermediate as direct ring expansion would seem to be more likely.[58]

This reaction is also possible using an imine. For example, Δ^2-pyrrolines have been reported from the acid catalysed thermal rearrangement of cyclopropyl imines e.g.,(108).[59]



(108)

80%

Cyclopropanes react with radicals to give H-abstraction or ring opening. More reactive radicals such as Cl·, *tert*-BuO·, and imidyl· are usually necessary for H-abstraction. Ring opening is seen with less reactive radicals like I· and Br· (figure 11).[60]

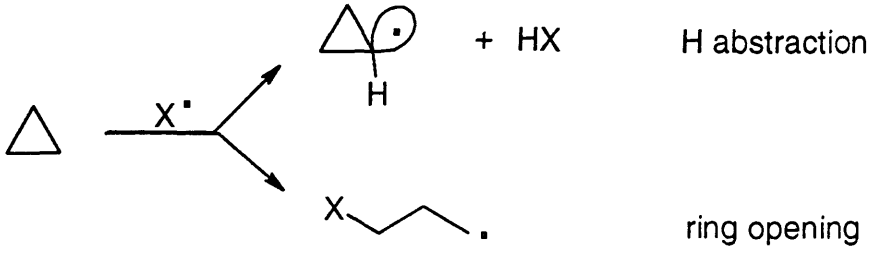
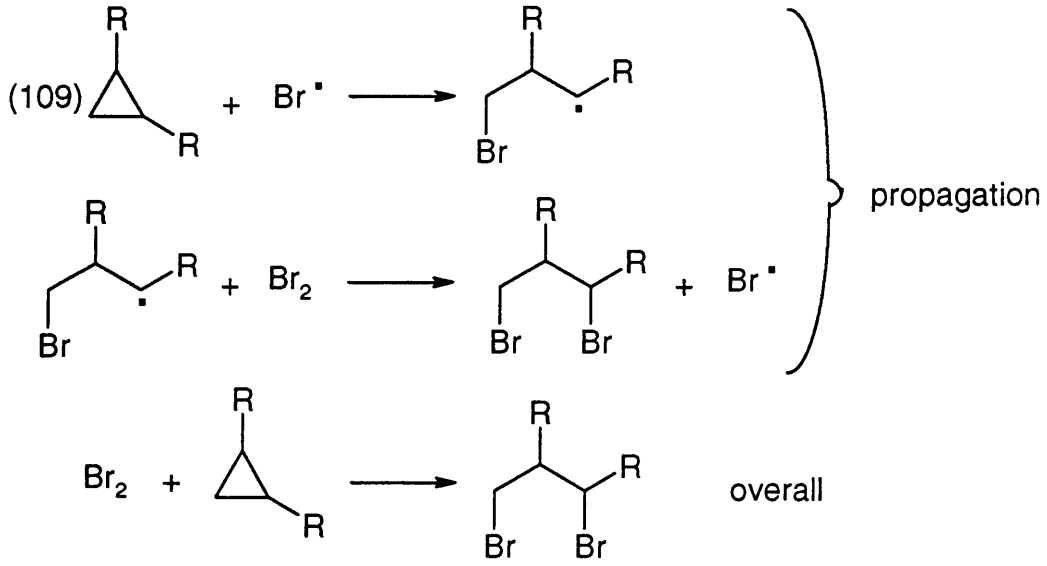


Figure 11

In the 1,3 addition of Br_2 to alkyl cyclopropanes (109), products of H-abstraction were not reported (scheme 12). The attack of Br· on the least

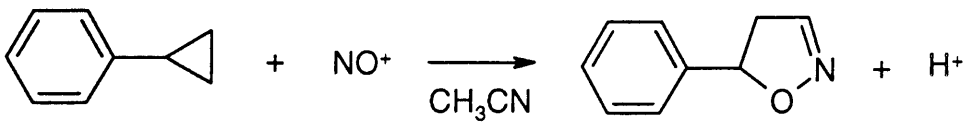
hindered carbon, to yield the most stable radical has been proposed as a mechanism.[61]



Scheme 12

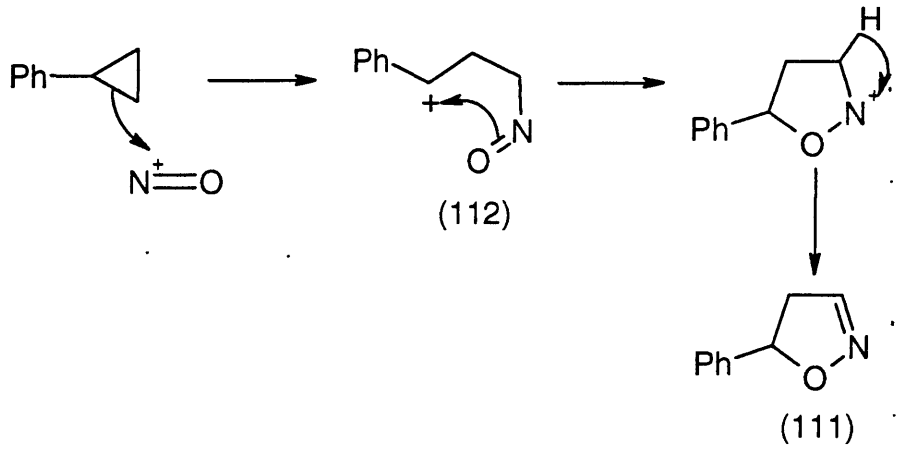
3.1.4 NO and Cyclopropanes

Cyclopropylbenzene (110) reacts with NO^+ in an electrophilic ring opening reaction. Treating (110) with $NO^+BF_4^-$ (a source of NO^+) produced a yellow colour that proved to be 5-phenyl-4,5-dihydroisoxazole (111), after an aqueous work up.[62]



(110) (111)

A possible mechanism for this process involves formation of the benzylically stabilised cation (112), which undergoes cyclisation followed by loss of a proton to give 5-phenyl-4,5-dihydroisoxazole (111).



(112)

(111)

Mizuno *et al.* studied the reaction of 1,2-diarylcyclopropanes (113) with a) NO and a photosensitiser (DCA), b) with $NOBF_4$, and c) with a mixture of NO and O_2. They found that 4,5-dihydroisoxazole deriviatives (114) could be produced from these three reactions.[63]

(DCA = 9,10-dicyanoanthracene)

(113) (114)

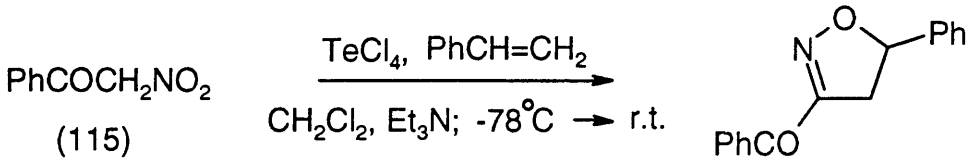
a) X = NO, hν/DCA
b) = $NOBF_4$
c) = NO + O_2

These reactions lead to the idea that a phenylcyclopropane would be an effective trap for nitric oxide. Before describing our results in this area, we

now consider in detail the various methods for the synthesis of 4,5-dihydroisoxazoles (2-isoxazolines).

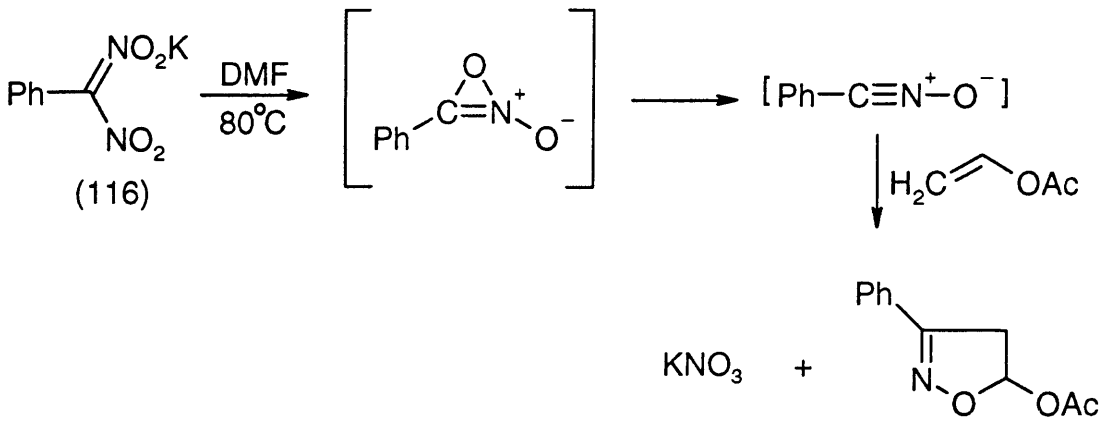
3.1.5 4,5-Dihydroisoxazole Synthesis

β-Keto nitroalkanes e.g.,(115) and olefins can react to form 3-acyl-4,5-dihydroisoxazoles when treated with tellurium tetrachloride and then triethylamine.[64]

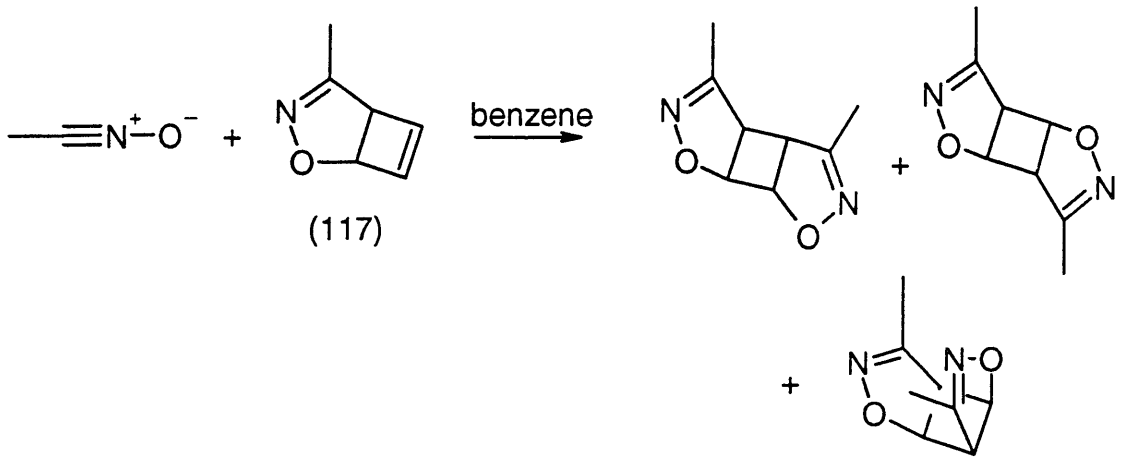


82%

4,5-Dihydroisoxazoles are formed when the potassium salts of the dinitroalkanes phenyldinitromethane (116), 1,1-dinitroethane, and 1,1-dinitropropane are decomposed thermally whilst alkenes are present, in polar solvents such as dimethylformamide (DMF), dimethyl sulfoxide (DMSO, Me_2SO), and dimethoxyethane.[65] A nitrile oxide is believed to be an intermediate in the reaction.

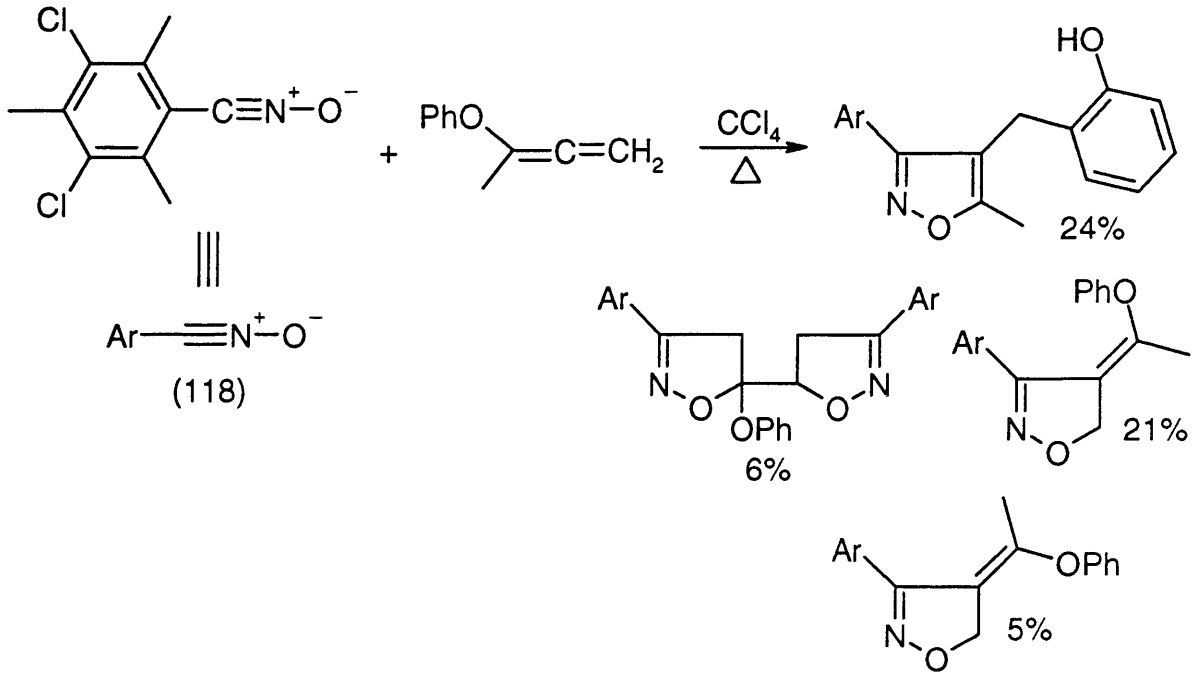


Nitrile oxides generated from chlorohydroximic acids and triethylamine were reacted with alkene-containing 4,5-dihydroisoxazoles e.g., (117), to form a further 4,5-dihydroisoxazole part of the molecule.[66]



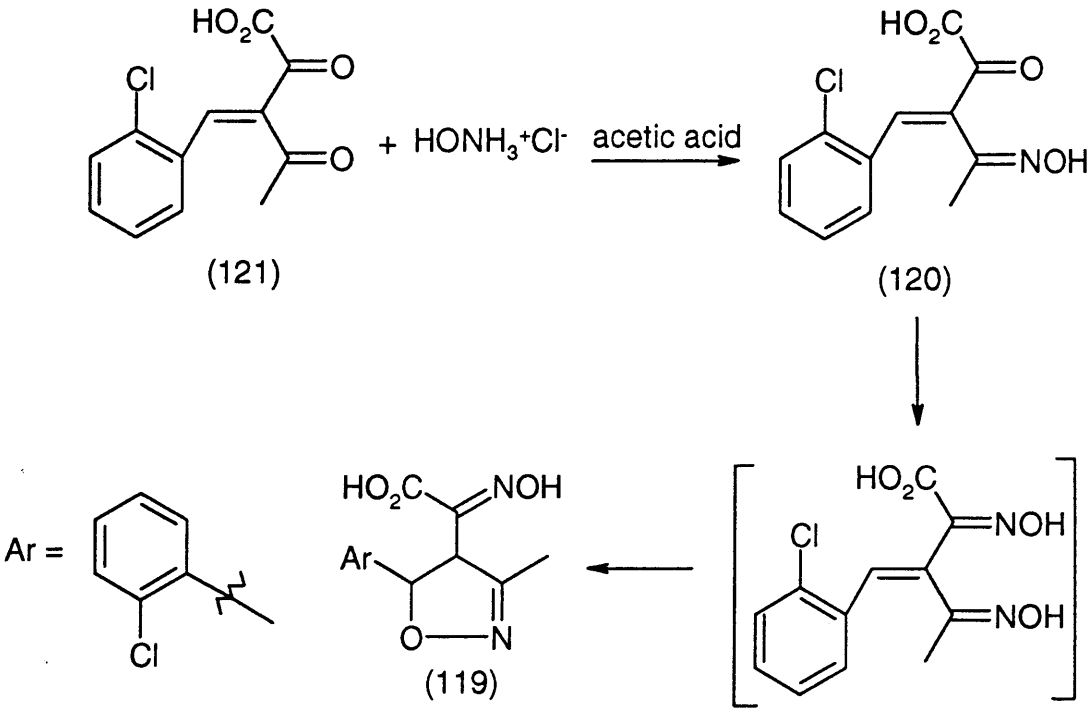
(117)

Reaction of phenoxy–substituted allenes with 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide (118) in refluxing carbon tetrachloride gave a mixture of products, including several 4,5-dihydroisoxazoles.[67]



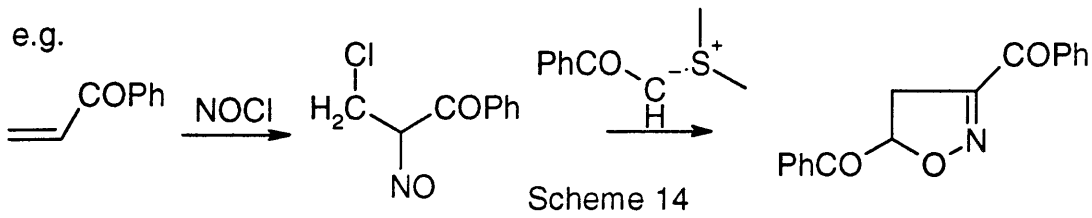
(118)

α,β-Unsaturated ketones can be used in the formation of 4,5-dihydroisoxazoles. 5-(2-Chlorophenyl)-4-(2-hydroxyiminoethanoic acid)-3-methyl-4,5-dihydroisoxazole, (119), and 3-(*o*-chlorobenzylidene)-4-hydroxyimino-2-oxopentanoic acid, (120), were formed as a result of the reaction of 3-(*o*-chlorobenzylidene)-2,4-dioxopentanoic acid, (121), and hydroxylamine hydrochloride in acetic acid. Since (120) gave (119) when treated with hydroxylamine in acetic acid, it is believed that (119) is formed from (121) via (120) (scheme 13).[68]



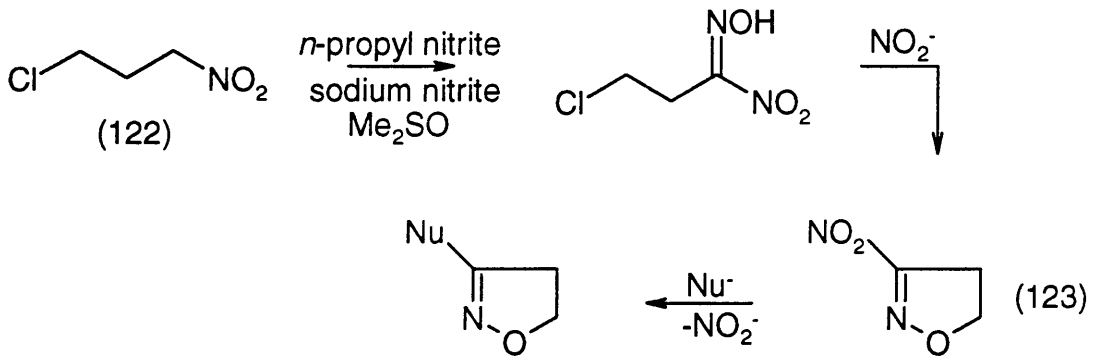
Scheme 13

α-Chlorooximes and nitrosochlorides formed from alkenes react with keto-stabilised sulfonium ylides in THF to give *trans*-5-acyl-4,5-dihydroisoxazoles (scheme 14).[69]



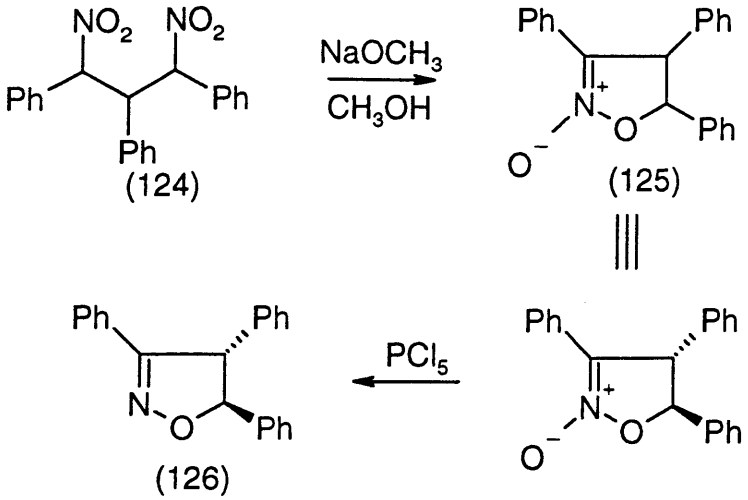
Scheme 14

After nitrosation of 1-chloro-3-nitropropane (122) by a combination of *n*-propyl nitrite and sodium nitrite in DMSO, tautomerisation followed by an intramolecular reaction results in 3-nitro-4,5-dihydroisoxazole (123). (This underwent nucleophilic substitution of the nitro-group by a variety of nucleophiles [$NaSC_6H_5$, $NaO_2SC_6H_5$, NaCN, n-Bu_2Cd, NaN_3]) (scheme 15).[70]



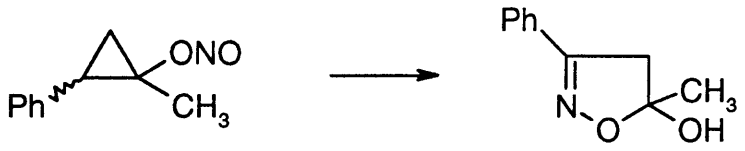
Scheme 15

Heating 1,3-dinitro-1,2,3-triphenylpropane, (124), with sodium methoxide in methanol gives 3,4,5-triphenyl-4,5-dihydroisoxazole-*N*-oxide, (125). (125) was reduced with phosphorus pentachloride to known compound *trans*-3,4,5-triphenyl-4,5-dihydroisoxazole (126) to show the stereochemistry of the phenyl substituents in the racemic (*trans*) (125) (scheme 16).[71]



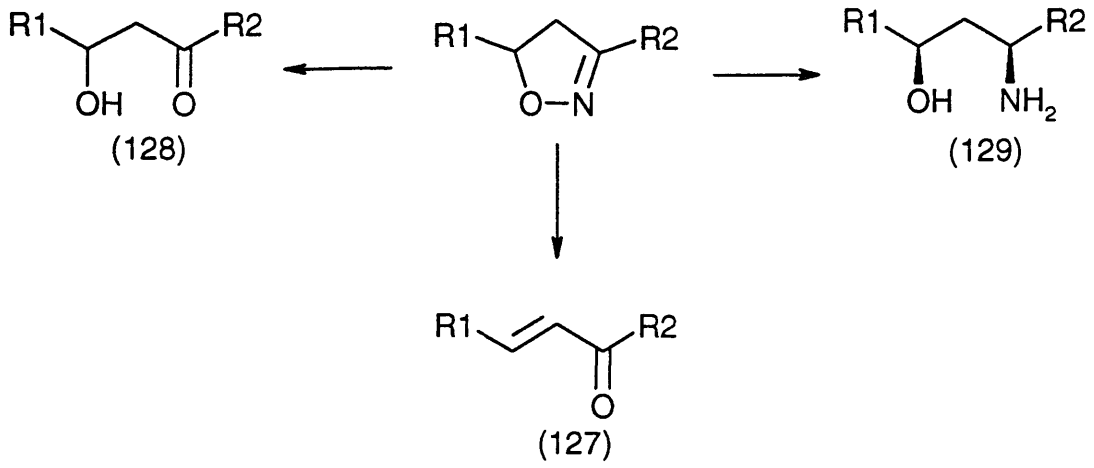
Scheme 16

In a study of the decomposition of cyclopropyl nitrates, ring opened compounds were the usual products. However, 4,5-dihydroisoxazoles were formed in several cases.[72]



3.1.6 Utilisation of Isoxazolines

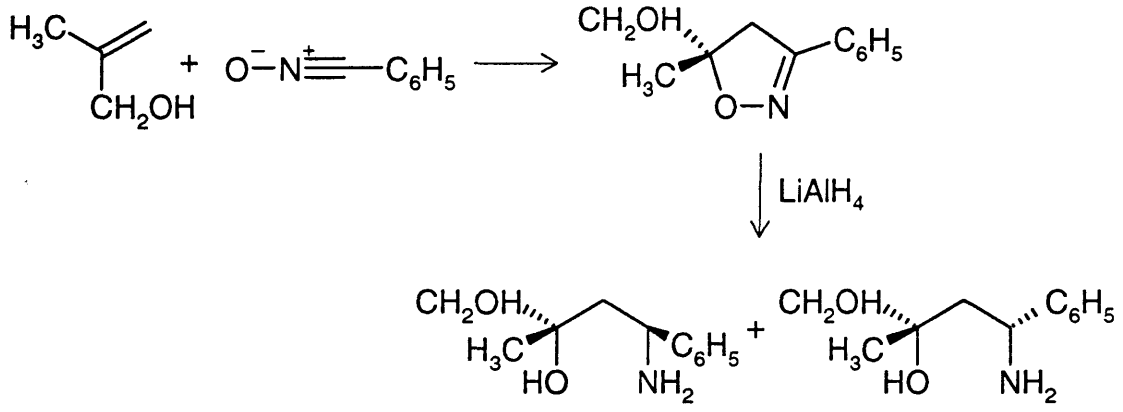
One of the values of 4,5-dihydroisoxazoles is the route they provide (usually stereocontrolled) to a variety of acyclic systems via ring cleavage reactions. Acyclic compounds accessible in this way include α,β-unsaturated ketones (127), β,γ-hydroxyketones (128) and γ-amino alcohols (129) (scheme 17).[73]



Scheme 17

For example, the reaction of alkenes and nitrile oxides, followed by lithium aluminium hydride reduction, gave amino alcohols (Scheme 18).[74]

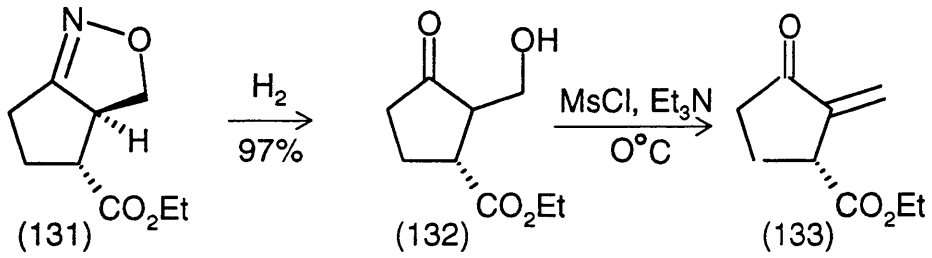
e.g.



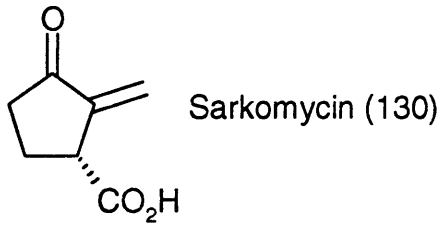
Scheme 18

A 4,5-dihydroisoxazole forms part of a synthesis of the anti-tumour agent sarkomycin (130), an α,β-unsaturated ketone. Dehydration of the β-hydroxyketone (132) (formed by hydrogenation of the 4,5-dihydroisoxazole (131)) gave the cyclopentanone intermediate (133) shown (scheme 19).[75] The 4,5-dihydroisoxazole here was described as a "masked α,β-unsaturated ketone" (acid-catalysed hydrolysis of the ester would

complete the synthesis of sarkomycin[76]). This is a 7-step synthesis which improves upon the original sequence of 10-11 steps to reach sarkomycin.[77]

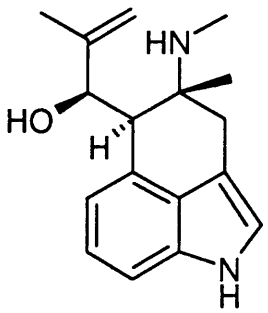


Scheme 19

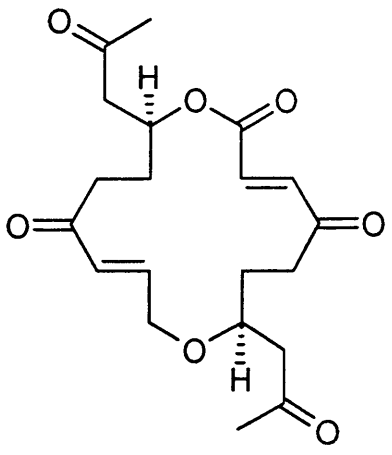


Sarkomycin (130)

4,5-Dihydroisoxazoles have also been used in the synthesis of more complex natural products including the ergot alkaloid (+)-paliclavine (134), and the dilactone antibiotic vermiculine (135).[78]



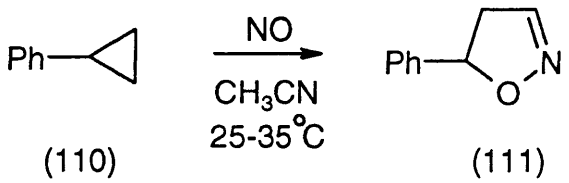
(+)-paliclavine (134)



(-)-vermiculine (135)

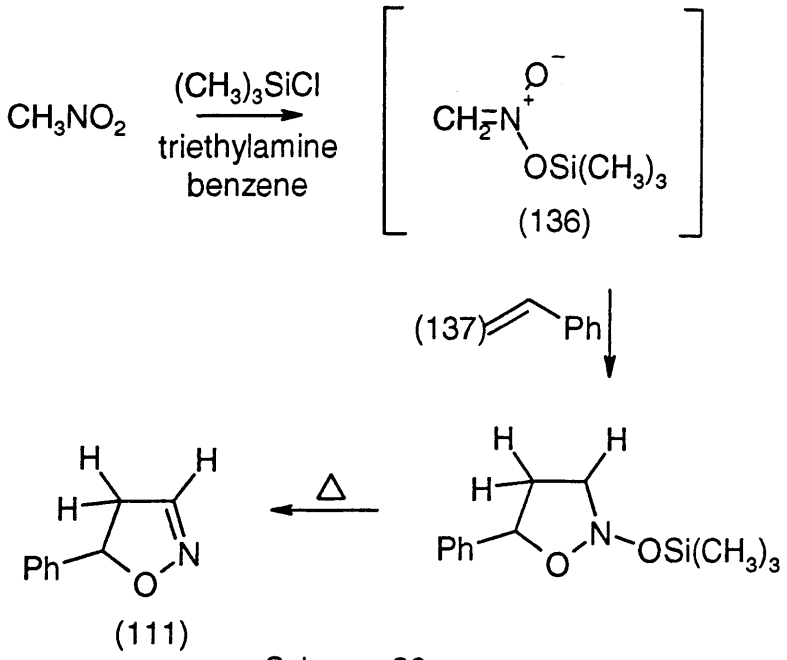
3.2 RESULTS AND DISCUSSION

Phenylcyclopropane (110) dissolved in anhydrous acetonitrile was ice cooled and bubbled with nitrogen for 20 minutes. The temperature was raised to 25-30°C and nitric oxide bubbled briefly (5 seconds). The system was sealed and left to stir under NO. The bubbling of the NO was repeated at intervals for 4 hours, and then the system was sealed under NO overnight at room temperature. After flushing with nitrogen for 20 minutes whilst cooled on ice, the heating and stirring under NO was continued for a further 7 hours and the reaction was sealed overnight at room temperature. Aqueous work-up and column chromatography afforded 5-phenyl-4,5-dihydroisoxazole (111).



(110) (111)

(A reaction under similar conditions, but with dichloromethane as solvent did not yield the 4,5-dihydroisoxazole.) 5-Phenyl-4,5-dihydroisoxazole (111) can be synthesised from a trimethylsilyl nitronate (136) and styrene (137) (scheme 20).[79] A sample prepared by colleagues[80] was used to confirm the identity of the product.

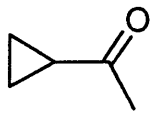


(111)

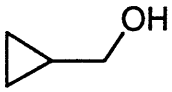
Scheme 20

Other cyclopropanes were tested to see if they reacted in a similar way. Reactions were carried out in acetonitrile, except in cases where the boiling point of the cyclopropane was low (<100°C). In these instances dichloromethane was used as the solvent; this was to try and minimse loss of potential product during removal of solvent by evaporation under reduced pressure. The results are summarised in the table below.

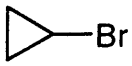
Cyclopropane	Solvent	Results (4,5-dihydroisoxazole)
cyclopropyl methyl ketone	acetonitrile	X
cyclopropylmethanol	acetonitrile	X
bromocyclopropane	dichloromethane	X
cyclopropyl cyanide	acetonitrile	X
α-cyclopropyl benzyl alcohol	acetonitrile	X
cyclopropylamine	dichloromethane	X
(2-phenylcyclopropyl)methanol	dichloromethane	-
cyclopropyldiphenylmethanol	acetonitrile	X
1,2-diphenylcyclopropane	acetonitrile	✓
cyclopropylbenzene	dichloromethane	X
cyclopropyl phenyl sulfide	acetonitrile	X
[(1ethoxycyclopropyl)oxy]trimethylsilane	acetonitrile	X



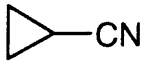
cyclopropyl methyl ketone



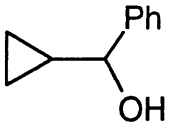
cyclopropylmethanol



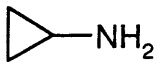
bromocyclopropane



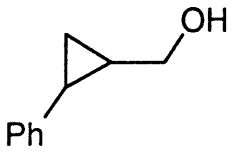
cyclopropyl cyanide



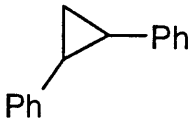
α-cyclopropyl benzyl alcohol



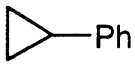
cyclopropylamine



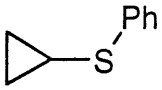
(2-phenylcyclopropyl)methanol



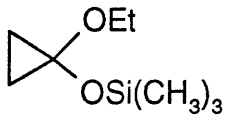
1,2-diphenylcyclopropane



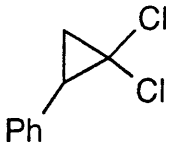
cyclopropylbenzene



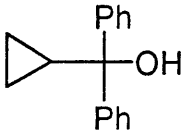
cyclopropyl phenyl sulfide



[(1-ethoxycyclopropyl)oxy]trimethylsilane



(2,2-dichlorocyclopropyl)benzene

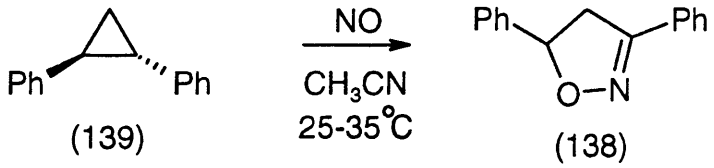


cyclopropyldiphenylmethanol

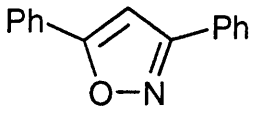
The structures of cyclopropanes listed in table P72

(2,2-dichlorocyclopropyl)benzene acetonitrile -
✓= 4,5-dihydroisoxazole found, X = no 4,5-dihydroisoxazole found, starting material gone,
- = starting material re-isolated

The successful example, where a 4,5-dihydroisoxazole (138) is formed from racemic *trans*-1,2-diphenylcyclopropane (139), is from a cyclopropane similar in structure to the cyclopropyl benzene (also isolated in a reaction with NO in a sealed tube was the isoxazole (140)).

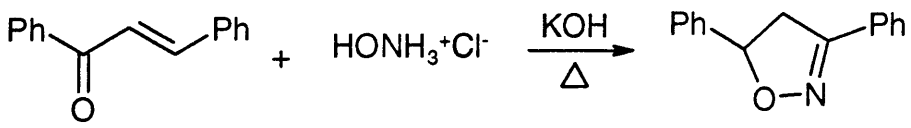


(139) (138)



(140)

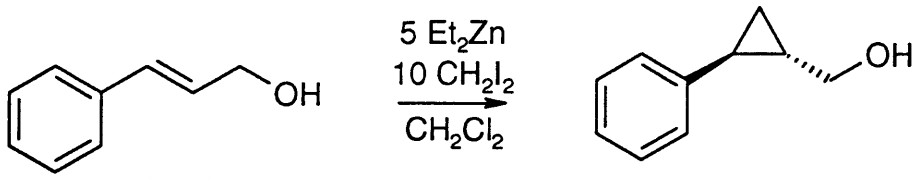
This material was also synthesised by an independent method. The reaction of chalcone (benzylideneacetophenone, 141) and hydroxylamine hydrochloride (142) gave 3,5-diphenyl-4,5-dihydroisoxazole (138).[81] The spectral properties of this compound were identical to those of the NO reaction product, and mixed thin-layer chromatography showed the compounds to be the same.



(141) (142) (138)

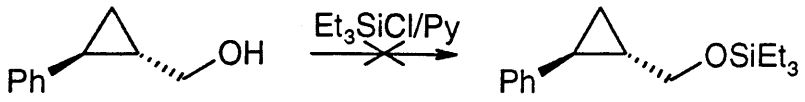
Since the successful examples contained phenyl groups directly attached to the ring, (although this did not appear to guarantee 4,5-dihydroisoxazole formation), this seemed to be a structural feature to investigate further.

Racemic *trans-(*2-phenylcyclopropyl)methanol (143) was one of the cyclopropanes listed earlier. This was the product of a Simmons-Smith cyclopropanation reaction on cinnamyl alcohol (144).



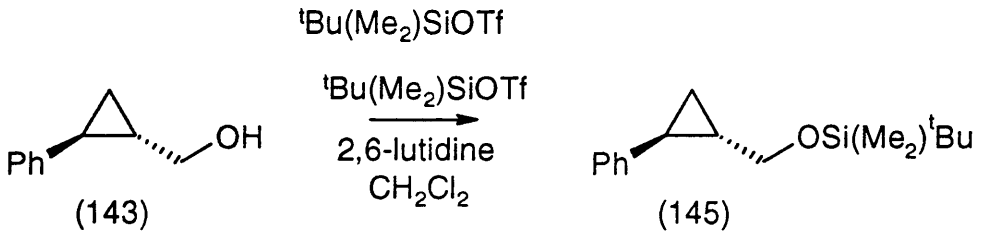
(144) (143)

Since this compound contains a phenyl group directly attached to the cyclopropane ring but this did compound did not react with nitric oxide, it was thought possible that the alcohol functionality could be interfering with the reaction in some way. Seeking to protect this functionality, a silicon protecting reaction was attempted. The reaction of (2-phenylcyclopropyl)methanol (143) with chlorotriethylsilane was followed by TLC until the cyclopropane spot had disappeared. Flash chromatography of the residue afforded what looked like starting material by ^{1}H NMR and mass spectrometry. Since other fractions contained a compound which by ^{1}H NMR and MS could have been the disproportionated silicon protecting group, it seemed that the alcohol was probably successfully protected, but that deprotection had occurred during chromatography.



(143)

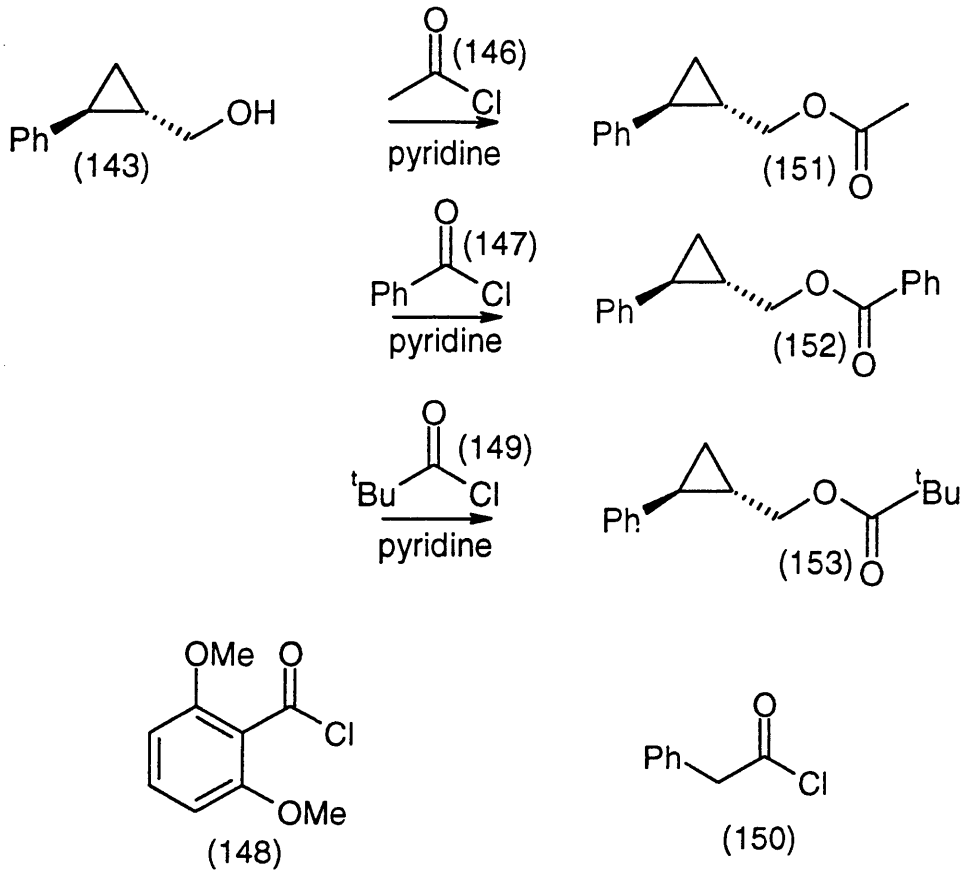
After 48 hours at room temperature, a mixture of (143) and *tert*-butyldimethylsilyl chloride, triethylamine and DMAP in DMF contained mostly unprotected starting material by TLC. *tert*-Butyldimethylsilyltriflate in dichloromethane with 2,6-lutidine was used to sucessfully protect (143) as shown below.



(143) (145)

The compound, (145), was treated with NO in a manner similar to the cyclopropyl benzene, but by TLC the result appeared to be (2-phenylcyclopropyl)methanol.

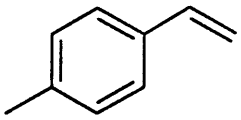
Esterification of the alcohol group was another potential means of protection. Reaction with 5 acid chlorides (acetyl chloride (146), benzoyl chloride (147), 2,6-dimethoxybenzoyl chloride (148), trimethylacetyl chloride (149) and phenylacetyl chloride (150)) was successful in 3 cases. After stirring a mixture of (143) overnight at room temperature with 2,6-dimethoxybenzoyl chloride (148) in pyridine, the starting material was unchanged by TLC. Similarly with phenylacetyl chloride (150), most of the starting material remained by TLC.

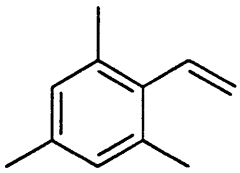


Ester (152) was treated with NO in a similar way to cyclopropyl benzene, but only starting material was seen. When (152) was sealed in a tube with NO and heated to 80°C, with the NO reapplied at intervals, a little starting material remained and faint traces in the NMR of the crude reaction mixture looked like 4,5-dihydroisoxazole signals, but this could not be isolated. (151) was treated with NO in a similar way to the cyclopropyl benzene, some starting material remained but no 4,5-dihydroisoxazole was seen by NMR. (151) was treated with NO in a sealed tube in a similar way to (152), with the temperature raised from 85°C to 95°C after one hour, and the reaction mixture was examined by ^{1}H NMR after a further two hours when traces of 4,5-dihydroisoxazole were seen as well as starting material. After 4 hours at that temperature, it was raised again to

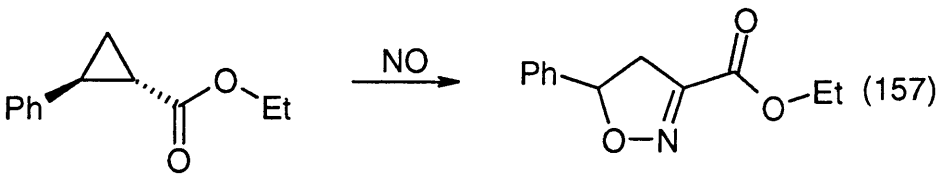
110°C for 3½ hours, and again ^{1}H NMR showed starting material and faint 4,5-dihydroisoxazole signals. After 1½ hours more the temperature was reduced to 95°C for a further 28½ hours, at which point no starting material or 4,5-dihydroisoxazole could be seen by NMR. (153) was treated with NO in a similar way to cyclopropyl benzene for a total of 15 hours, twice being sealed overnight under NO, but only starting material showed by TLC. The sample was then transferred to a sealable tube and treated in a similar way to the (152) for a total of 2¼ hours; some starting material remained but no 4,5-dihydroisoxazole was seen by NMR.

Cyclopropanations of two styrene derivatives (4-methylstyrene (154) and 2,4,6-trimethylstyrene (155)) were attempted to provide phenylcylopropanes, but the reactions with diethyl zinc were not successful and were not pursued.

(154) 

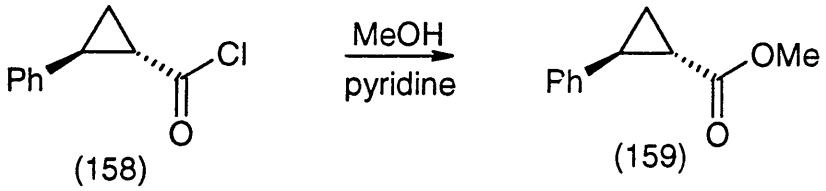
(155) 

A commercially available cyclopropane, racemic ethyl *trans*-2-phenylcyclopropane carboxylate (156), when heated with NO in a sealed tube, did give the corresponding 4,5-dihydroisoxazole, (157).

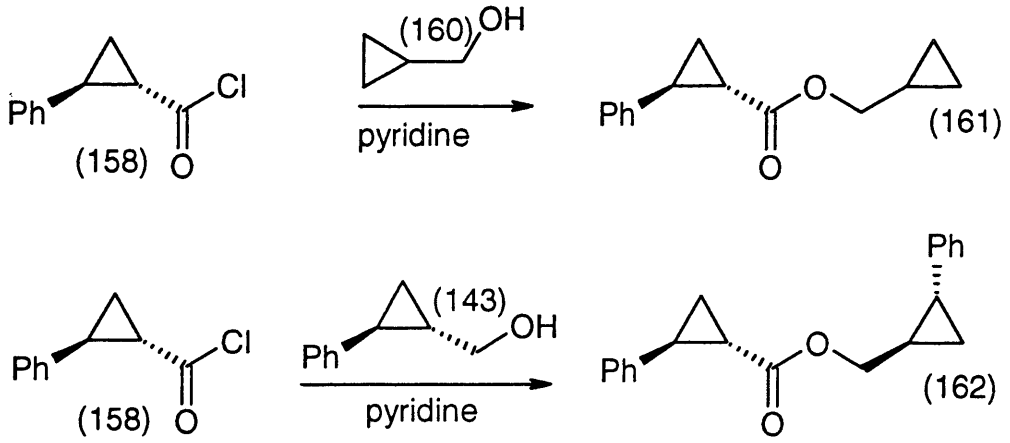


(156) (157)

Racemic *trans*-2-phenyl-1-cyclopropanecarbonyl chloride (158) was esterified to a range of analogues of the ethyl trans-2-phenyl cyclopropane carboxylate (156). The methyl ester (159), formed from (158) and methanol was prepared first.



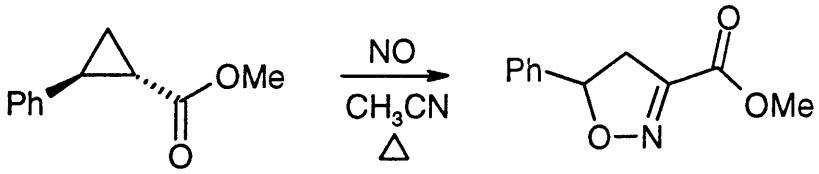
After this, (158) was esterified with cyclopropylmethanol (160) and (2-phenylcyclopropyl)methanol (143).



Compounds (158) and (143) are both *trans* and racemic. In the reaction to give ester (162) only one pair of enantiomers form, as shown by the ^{13}C NMR. We conclude from this that the reaction pathway to form one diastereoisomer is considerably lower in energy that the other. The *trans* acid chloride has the RR and SS configurations with the *trans* alcohol has

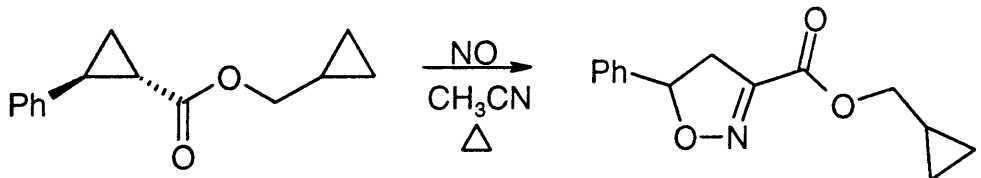
R'R' and S'S', therefore we are seeing one combination of products e.g., RRR'R,' SSS'S' and not the other RRS'S', SSR'R'. Clearly we do not know which combination without an X-ray structure on the product.

A 4,5-dihydroisoxazole (163) was found after the methyl ester (159) was treated with NO in a sealed tube in a similar way to the ethyl ester.



(159) (163)

The cyclopropane ester (161) was treated in a similar way but a very low yield was produced and the resulting product proved very difficult to purify. Spectral data obtained (^{1}H NMR, and high and low resolution mass spectrometry) suggested that the reaction with NO had occurred to form the 4,5-dihydroisoxazole (164), and was consistent with the insertion of NO in the phenyl- and carboxyl- substituted cyclopropane ring.



(161) (164)

Initial studies with the phenylcyclopropane ester, (162), yielded a complicated mixture and the reaction was not pursued.

3.2.1 Regioisomerism of the NO Insertion

3.2.1.1 5-Phenyl-4,5-dihydroisoxazole (111)

The symmetry of phenylcyclopropane (110) means that there are two possible sites for NO insertion and hence three theoretically possible structures for the 4,5-dihydroisoxazole. These are shown below (figure 12), annotated with the expected multiplicity of some the ^{1}HNMR signals that the structure would produce, and an estimation of their expected chemical shift. The actual ^{1}HNMR signals for the 4,5-dihydroisoxazole ring are as follows: 2.98 (1 H, ddd), 3.44 (1 H, ddd), 5.52 (1 H, dd), 7.20 (1 H, br t). It can be seen that only the expected signals of structure (111)1a. are compatible with the actual signals, so it was concluded that this was the regioisomer formed. (This spectral evidence is in addition to the comparison with the compound with the structure (111)1a. from an alternative route, see above.)

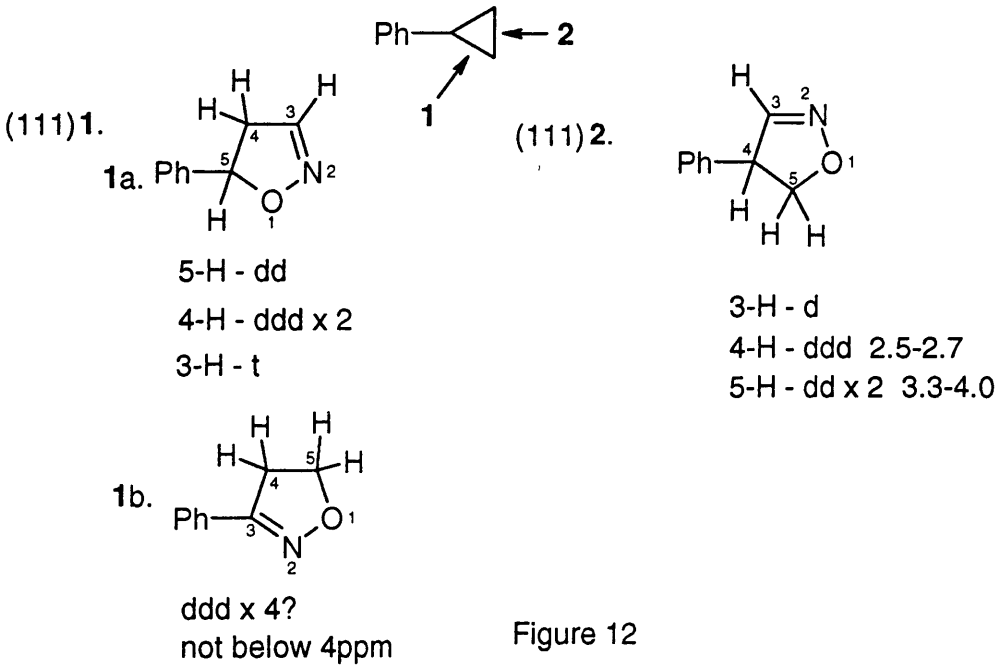
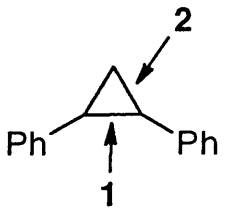


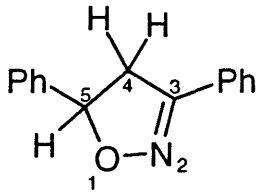
Figure 12

3.2.1.2 3,5-Diphenyl-4,5-dihydroisoxazole (138)

In a similar way to the previous compound, symmetry results in two possible sites on the cyclopropane where NO could insert, and so 3 possible structures for the product (figure 13). The actual ^{1}H NMR signals for the 4,5-dihydroisoxazole ring are as follows: 3.35 and 3.79 (2 H, ddx2), 5.74 (1 H, dd). As with the monophenyl compound (111), there is only one structure with expected signals that are consistent with the actual signals, structure (138)1. (Again this is in addition to confirmation of structure gained by comparison with the spectral data of (138) made by an independent route.)

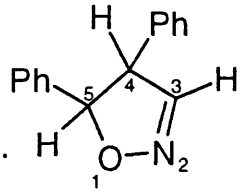


(138)**1**.



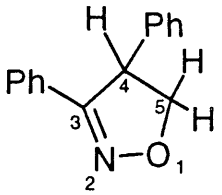
4-H - dd x2
5-H - dd below 4ppm

(138) **2**.



2.a.

3-H - d
4-H - dd 2.5-2.7
5-H - d below 4ppm



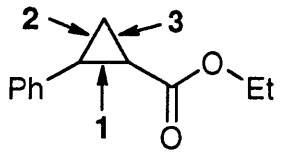
2.b.

4-H - dd 2.5-2.7
5-H - dd x 2 3.3-4.0

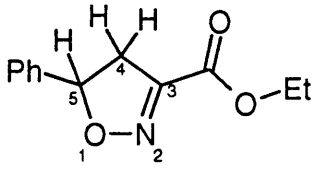
Figure 13

3.2.1.3 3-Ethoxycarbonyl-5-phenyl-4,5-dihydroisoxazole (157)

The lack of symmetry in the starting cyclopropane means that in this case there are 3 sites for NO insertion, and consequently 6 theoretically possible structures (figure 14). The actual ^{1}HNMR signals for the 4,5-dihydroisoxazole ring are: 3.22 and 3.64 (2 H, dd x 2), 5.79 (1 H, dd). Structures (157)1a and (157)1b could be consistent with the actual data, difficulty arises in choosing between the two, and prevents prediction of the structure on ^{1}H NMR data.



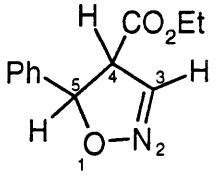
(157)**1**.



1a.

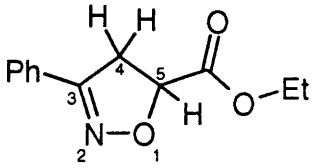
4-H - dd x 2
5-H - dd below 4ppm

(157)**2**.



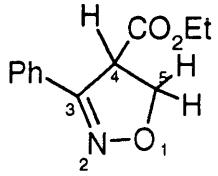
2a.

3-H - d
4-H - dd
5 -H - d below 4ppm



1b.

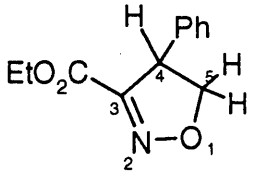
4-H - dd x2
5-H - dd below 4ppm?



2b.

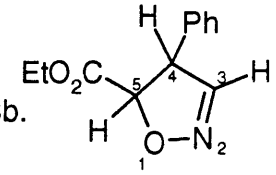
4-H - dd
5-H - dd x 2 3.3-4.0

(157)**3**.



3a.

4-H - dd 2.5-2.7
5-H - dd x2 3.3-4.0

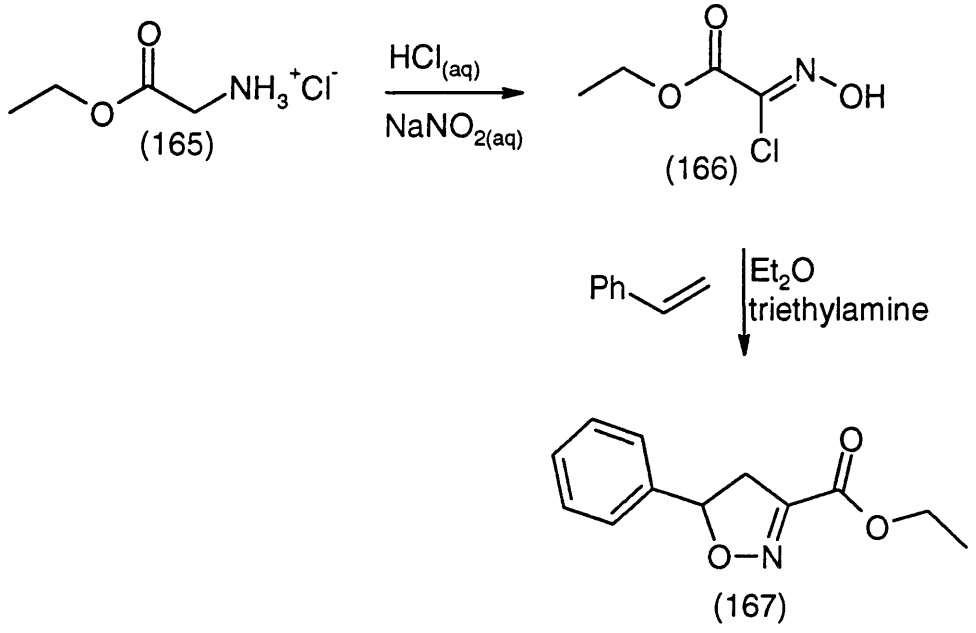


3b.

3-H - d
4-H dd 2.5-2.7
5-H d below 4ppm?

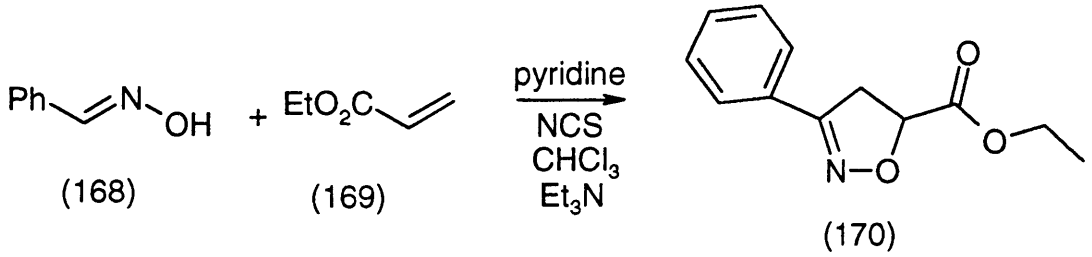
Figure 14

Having narrowed down the options in the way described above, another method of distinguishing between the two structures, (157)1a and (157)1b was necessary. The two 4,5-dihydroisoxazoles were synthesised. Ethyl chlorooximinoacetate (166) and styrene were used to form 3-ethoxycarbonyl-5-phenyl-4,5-dihydroisoxazole (167) (scheme 21).[82] (Ethyl chloro-oximinoacetate was first synthesised from glycine ethyl ester hydrochloride (165).)[83]



Scheme 21

(*E*)-Benzaldehyde oxime (168) and ethyl acrylate (169) were used to give 5-ethoxycarbonyl-3-phenyl-4,5-dihydroisoxazole (170).[84]



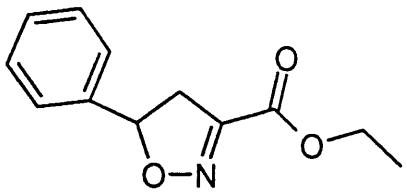
NCS = *N*-chlorosuccinimide

Spectral data from these two compounds was compared with that from the 4,5-dihydroisoxazole (157) formed by the reaction of NO with ethyl *trans*-2-phenylcyclopropane carboxylate.

	(167) 3-ethoxycarbonyl-5-phenyl-4,5-dihydroisoxazole	**(157)**	**(170)** 5-ethoxycarbonyl-3-phenyl-4,5-dihydroisoxazole
^1H	**1.38**(3H, t, J=6.9) **3.21**(1H, dd,J=8.9, 17.8) **3.64**(1H,dd,J=11.5,17.8) **4.36** (2H,q,J=6.9) **5.78**(1H,dd,J=8.9,11.5) **7.29-7.42**(5H,aromatic)	**1.38**(3H, t, J = 7.3) **3.22**(1H,dd,J=8.8,17.8) **3.64**(1H,dd,J=11.6,17.8) **4.37**(2H,q,J=7.3) **5.79**(1H,dd,J=8.8,11.6) **7.31-7.43**(5H, aromatic)	**1.10** (3H, t, J=7.0) **3.42** (1H,d, J=10.0) **3.43** (1H, d, J=8.0) **4.05** (2H,q,J=7.0) **4.95** (1H,dd,J=8.0,10.0) **7.14-7.26**(3H,aromatic) **7.41-7.52**(2H,aromatic)
^{13}C	14.5 (CH_3), 41.8 (CH_2), 62.5 (CH_2), 85.3 (CH), 126.3 (CH x 2), 129.0 (CH), 129.3 (CH x 2), 140.0 (C), 151.6 (C), 161.0 (C)	14.5 (CH_3), 41.9 (CH_2), 62.6 (CH_2), 85.4 (CH), 126.3 (CHx2), 129.1 (CH), 129.3 (CHx2), 139.9 (C), 151.5 (C), 161.0 (C)	14.4 (CH_3), 39.1 (CH_2), 62.2 (CH_2), 78.5 (CH), 127.2 (CHx2), 129.0 (C), 129.1 (CHx2), 130.8 (CH), 156.4 (C), 170.5 (C)
m/z	219 (M^+, 51%), 202 (6), 190 (13), 174 (11), 156 (14), 146 (21), 128 (44), 115 (32), 104 (100), 91 (11), 77 (27), 63 (4), 51 (13);	219 (M^+, 55%), 202 (4), 190 (11), 174 (11), 156 (10), 146 (20), 128 (40), 115 (35), 104 (100), 91 (13), 77 (20), 63 (4), 51 (8)	219 (M^+, 16%), 188 (1), 146 (61), 118 (92), 103 (11), 91 (28), 77 (100), 63 (6), 51 (19)

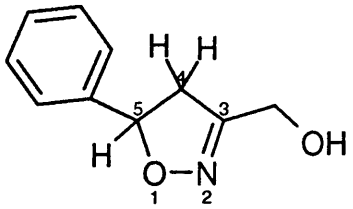
Spectral data for the 4,5-dihydroisoxazoles $C_{12}H_{13}NO_3$

It can be seen that while the multiplicity and integration (^1H NMR) of the compounds (170) and (157) are similar, there is a marked difference in chemical shifts and coupling constants. The ^{13}C NMR spectra are slightly different, and the mass spectra completely so. The data for the compound (167) and (157) are almost identical. From this evidence it was concluded that the 4,5-dihydroisoxazole (157) was the regioisomer 3-ethoxycarbonyl-5-phenyl-**4**,5-dihydroisoxazole, (167) ≡ (157).

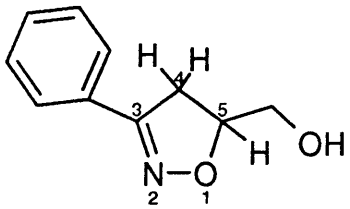


(167)/(157)

Another possible approach to resolve the question about the structure of (157), if the two alternative structures could not be synthesised for some reason, could have been to consider the ^{1}H NMR signals that would have been expected if the carboxylate group were reduced to an alcohol. The structures (157)1a and (157)1b would yield the alcohols shown below.



(157)1a-red



(157)1b-red

The signal for the 5-H would be expected to be significantly different in the two structures. In the (157)1a-red structure it would be likely to have a chemical shift and multiplicity similar to those of analogous protons in the compounds (111), (138) and (157), ie dd, with chemical shift values similar to those shown below.

(111) -: 5.52 (1H, dd, J = 8.2, 11.1, 5-H)

(138) -: 5.74 (1H, dd, J = 8.5, 11.0, 5-H)

(157) -: 5.79 (1H, dd, J = 8.8, 11.6, 5-H)

In the (157)1b-red structure, the extra coupling to the methylene group would increase the complexity of the multiplicity of the 5-H signal and without the close phenyl group, the expected chemical shift would be higher field. Samples of both the ethyl esters (167) and (170) were reduced with sodium borohydride[85] and the above prediction does prove to be the case. Reduction of the ester group would have provided further evidence to the 4,5-dihydroisoxazole's structure if necessary.

5.60 (1H, dd, J = 8.4, 11.0, 5-H) - (157)1a-red

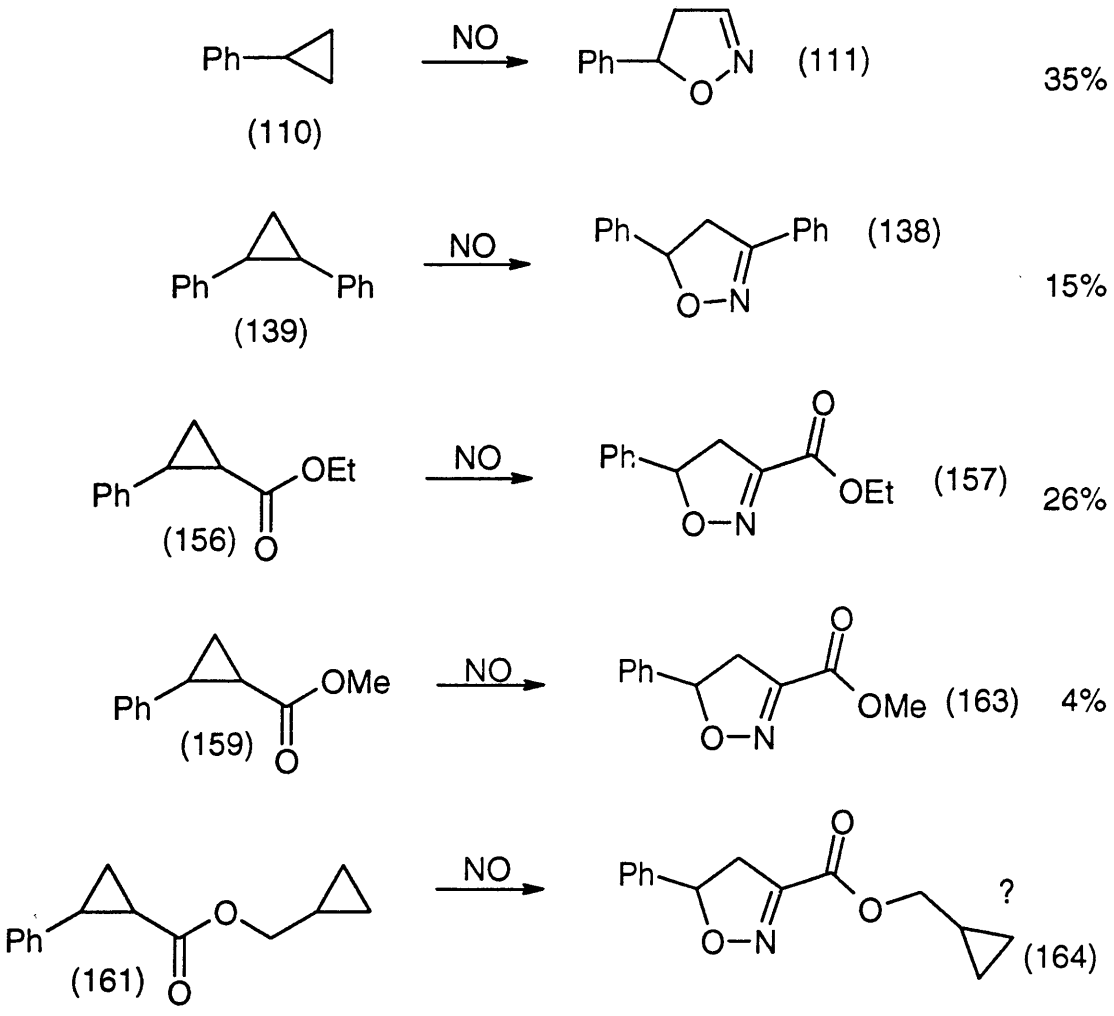
4.84 (1H, m, 5-H) - (157)1b-red

3.2.1.4 3-Methoxycarbonyl-5-phenyl-4,5-dihydroisoxazole (163)

The structure of the 3-methoxycarbonyl-5-phenyl-4,5-dihydroisoxazole was inferred by analogy to the ethyl ester (see ^{1}H chemical shifts below).

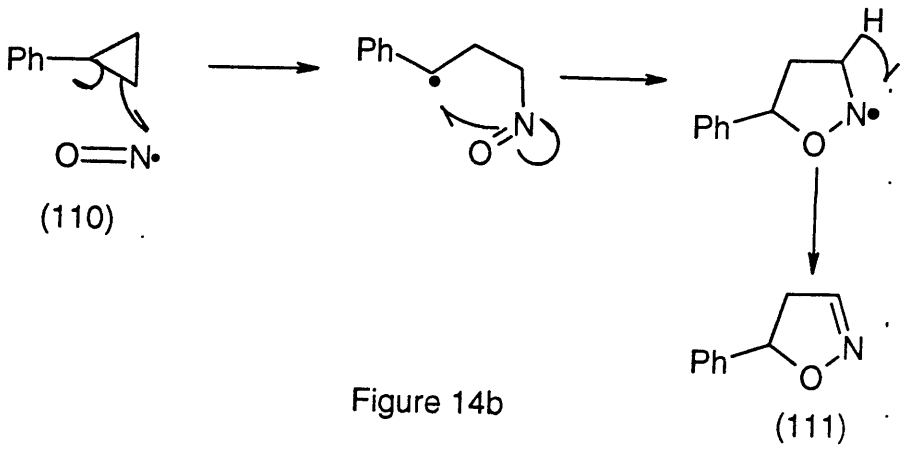
(167)	(163)
1.38(3H, t, J=6.9)	
3.21 & 3.64(2H, ddx2, J=8.9,11.5,17.8)	**3.23 & 3.64** (2H, ddx2,J=8.9, 11.7, 17.8,)
4.36 (2H,q,J=6.9)	**3.91** (3H, s)
5.78(1H,dd,J=8.9,11.5)	**5.79** (1H, dd, J=8.9, 11.7)
7.29-7.42(5H,aromatic)	**7.30-7.43** (5H, aromatic);

3.2.2 Summary of 4,5-Dihydroisoxazoles Formed



3.2.3 Conclusion

The alkene/sp^2 like nature of the cyclopropane ring makes the three-membered ring reactive to ring opening, in this case to a five-membered heterocycle that incorporates NO. 4,5-Dihydroisoxazoles were produced as a result of the treatment of some phenyl-substituted cyclopropanes with NO. The significance of the phenyl group may be that it is stabilising a ring opened radical intermediate in the reaction (figure 14b).



(110)

(111)

Figure 14b

CHAPTER 4

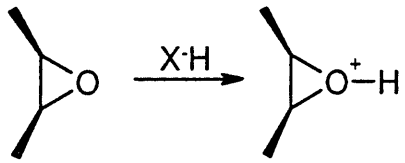
The Trapping of Nitric Oxide with Substituted Epoxides

4.1 INTRODUCTION

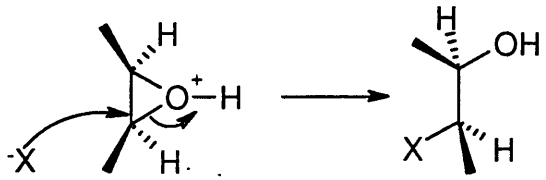
The original work in this chapter is concerned with the reaction of NO with epoxides. The literature relevant to this study is concerned with the acid catalysed opening of epoxides and the formation of nitrate esters. These two areas will be reviewed separately in the introduction.

4.1.1 Acid Catalysed Ring Opening Reactions of Epoxides[86]

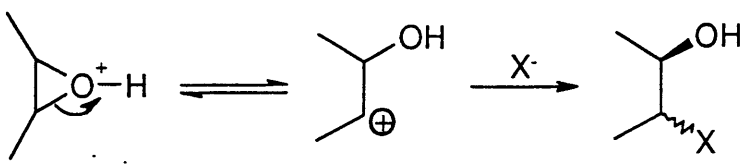
The mechanism of acid catalysed ring opening of epoxides begins with protonation.



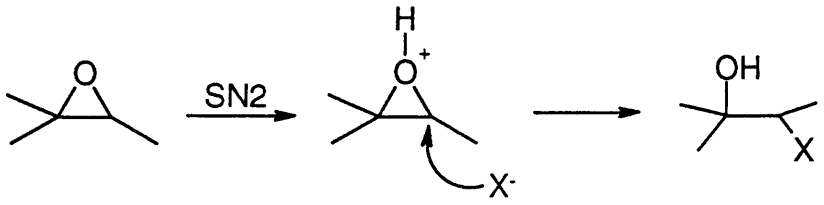
Ring opening from this species can then proceed via S_N1 or S_N2 processes. In the case of an S_N2 opening inversion occurs at the carbon undergoing attack.



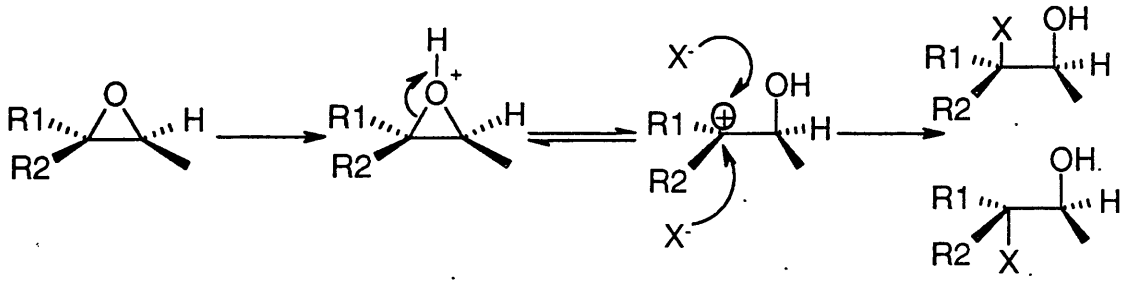
If the attack of the nucleophile is via an S_N1 process, a mixture of diastereoisomers is obtained.



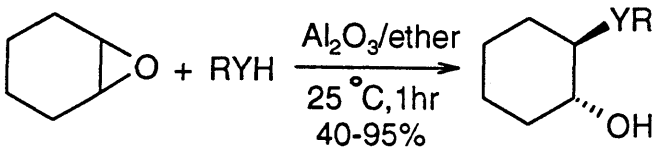
Further substitution leading to unsymmetrical epoxides has regiochemical consequences, with the S_N1 and S_N2 reactions having quite different results. The preferred position of attack in an S_N2 reaction of the epoxide below is the least hindered carbon.

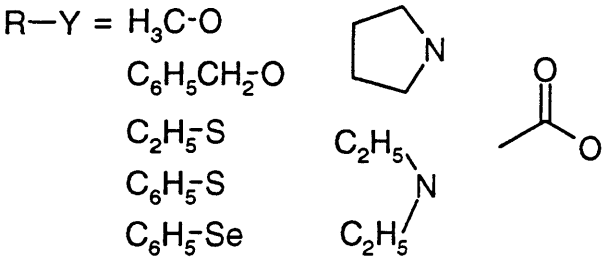


In contrast, the S_N1 reaction favours attack on the most substituted carbon.



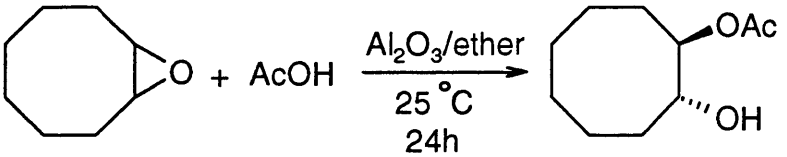
A general method of ring opening involves the use of alumina (Woelm-200 neutral) in addition to the nucleophile, allowing mild conditions and giving good yields with a variety of nucleophiles (scheme 21b).[87]





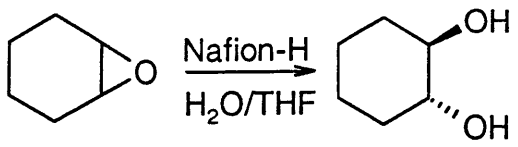
Scheme 21b

The use of alumina increased the yields of ring opened products from epoxides on medium sized rings by reducing side reactions. This increase can be seen in the conversion of *cis*-cyclooctene oxide (171) to *trans*-2-acetoxy cyclooctanol[88] (172) where a yield of 78% was achieved in contrast to 22% previously reported with homogenous reaction conditions.[89]



(171) (172)

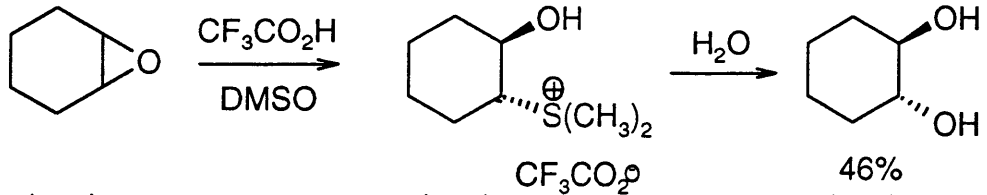
The presence of acid has been used to catalyse the opening of epoxides to diols. *Trans*-cyclohexane-1,2-diol (174) was formed when water and a catalyst, Nafion-H perfluorinated resinsulfonic acid, was used to treat cyclohexene oxide (173). (The methyl ethers of the diol were produced with the use of methanol instead of water.)[90]



73%

(173) (174)

A two-step procedure for diol formation from epoxides reported by Swern begins with reaction of the epoxide with DMSO and an acid. For example, the adduct (176) formed from cyclohexene oxide (175) and DMSO and trifluoroacetic acid is hydrolysed by water to a *trans*-cyclohexane-1,2-diol (177) (scheme 22).[91]

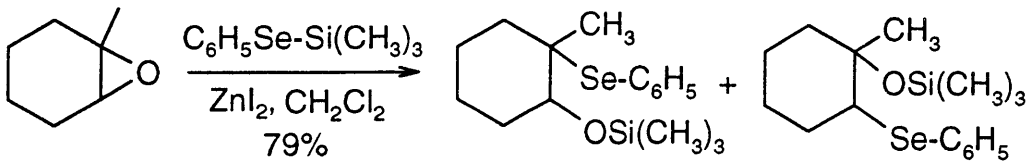


(175) (176) (177)

39% 46%

Scheme 22

A variety of trimethysilyl substituted nucleophiles have been shown to react with epoxides. It is thought that complexation of the epoxides to the silicon of the reagent creates positive charge on the carbon of the bond to be cleaved, explaining the predomination of products which result from the attack of the nucleophile on the more substituted carbon.[92]



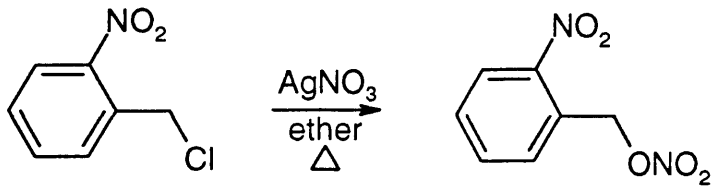
4.1.2 Nitrate Synthesis

The most common methods for the formation of simple nitrates (also known as nitrate esters) are the esterification of alcohols and the reaction of alkyl halides with silver nitrate. Conditions for the alcohol esterification vary, shown here is the synthesis (from 'Organic Syntheses') of methyl nitrate (178) from methanol, using concentrated nitric and sulfuric acid.[93]

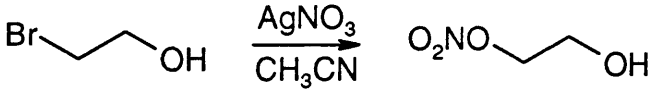
$$CH_3OH + HONO_2 \xrightarrow{(H_2SO_4)} CH_3ONO_2 + H_2O$$
(178)

Other nitric acid variations include the use of anhydrous nitric acid in acetic acid-acetic anhydride.[94]

The reaction of alkyl halides and silver nitrate yields nitrate esters. For example, 2-nitrobenzyl chloride (179) and silver nitrate when refluxed in ether, gave 2-nitrobenzyl nitrate (180).[95] 1-(*O*)-Nitroethanediol (182) was formed from 2-bromoethanol (181) by the action of silver nitrate in acetonitrile.[96]

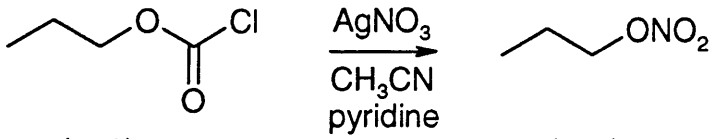


(179) (180)



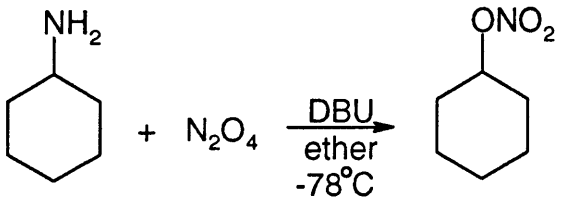
(181) (182)

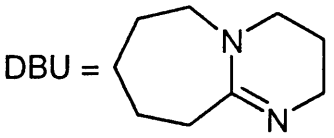
Alkyl chloroformates and silver nitrate in a pyridine catalysed reaction gave alkyl nitrate esters. For example, *n*-propyl chloroformate (183) gave *n*-propyl nitrate (184).[97] Previously, the reaction had been performed without pyridine.[98] Pyridine greatly increased the rate of reaction.



(183) (184)

Primary amines have been nitrosated by dinitrogen tetraoxide at -78°C.[99] However, the presence of a base such as DBU gave improved yields of the nitrate ester product.

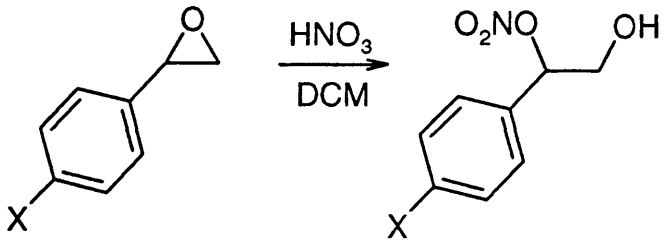




DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

Methods that involve the ring opening of epoxides broaden the choice of available starting materials. Nitric acid was added to a range of epoxides

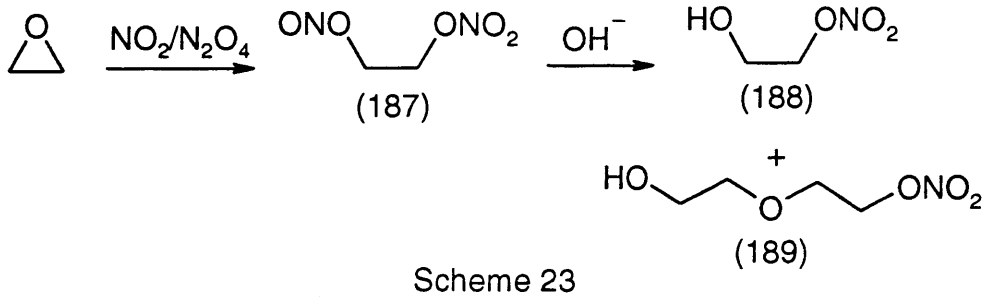
(including ethylene oxide, propylene oxide and methyl glycidyl ether), to give nitro alcohols ($RCH(OH)CH(ONO_2)R$.[100] Two nitration procedures were employed, an aqueous method with ammonium nitrate and water in addition to the acid and epoxide, and a non-aqueous method with the two reagents in chloroform. Styrene oxides (185) were found to react with nitric acid in dichloromethane to form the corresponding nitroethanols (186).[101]



X = NO_2, CF_3, H

(185) (186)

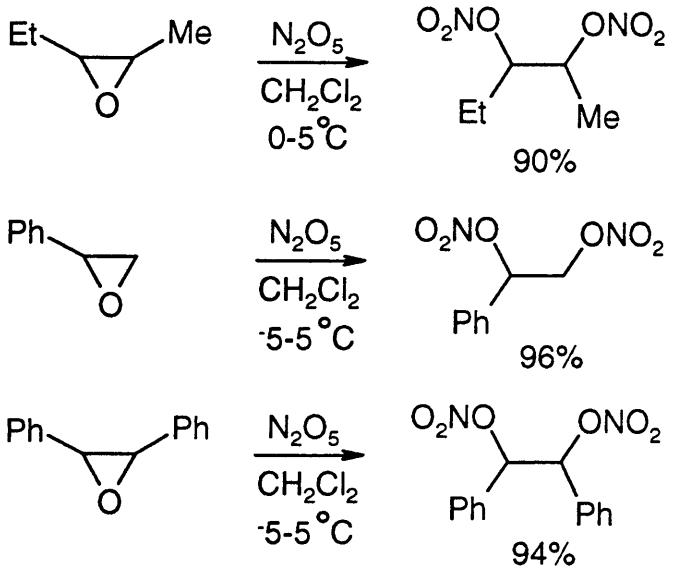
Ethylene oxide was treated with NO_2 to give (187) which was saponified by Na_2CO_2 to (188) and (189) (scheme 23).[102]



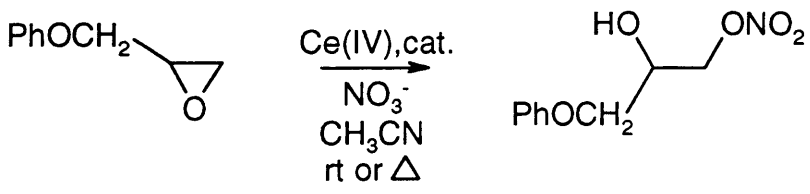
Scheme 23

N_2O_5 (prepared by the ozonolysis of N_2O_4) has been reacted with various epoxides to give dinitrates in good yield. An advantage of the reactions is

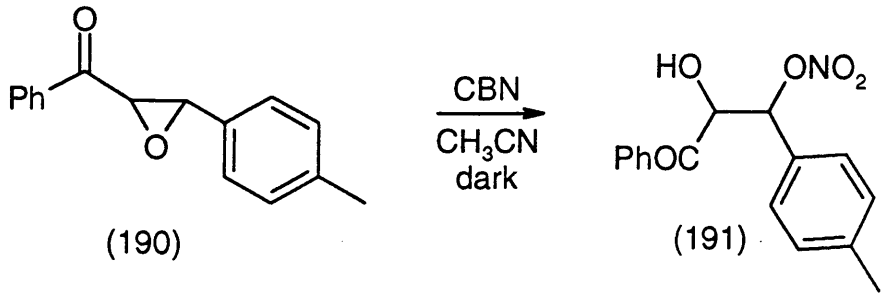
that it involves the complete use of the nitrating agent, so isolation of the product is simplified. Epoxides used include alkyl epoxides, styrene and stilbene oxide, and some polyepoxides.[103]



Nitro alcohols are produced under mild conditions by the action of a catalytic amount of ceric ammonium nitrate (CAN) with or without excess nitrate ions on epoxides.[104] Better yields were obtained when the reaction occurred in the presence of tetra-*n*-butyl ammonium nitrate in dry acetonitrile.

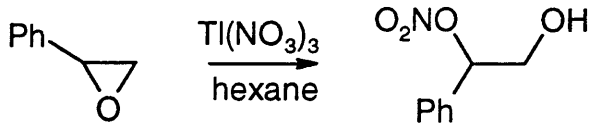


A cerium salt was used again in the formation of a nitrate ester (191), when a chalcone epoxide (190) was treated with $Ce(Bu_4N)_2(NO_3)_6$ (CBN) in acetonitrile.[105]



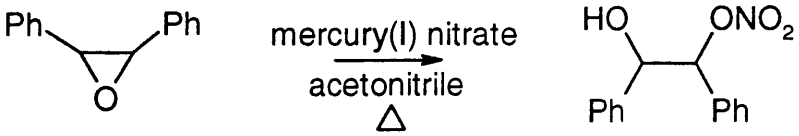
(190) (191)

Epoxides have been converted to α-hydroxy nitrate esters by the use of thallium nitrate, $Tl(NO_3)_3$, in hexane.[106] For example styrene oxide (192) gave 1-(*O*)-nitro-1-phenyl ethanediol (193).



(192) (193)

A refluxed solution of stilbene oxide (194) and mercury(I) nitrate in acetonitrile gave 1-(*O*)-nitro-1,2-diphenyl ethanediol (195).[107]

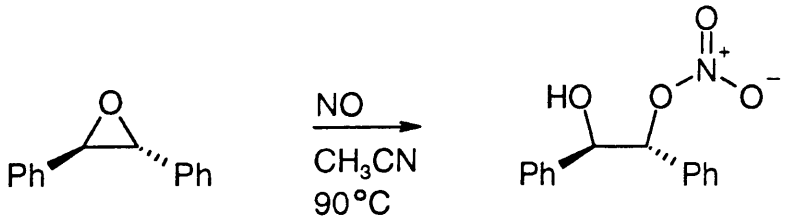


(194) (195)

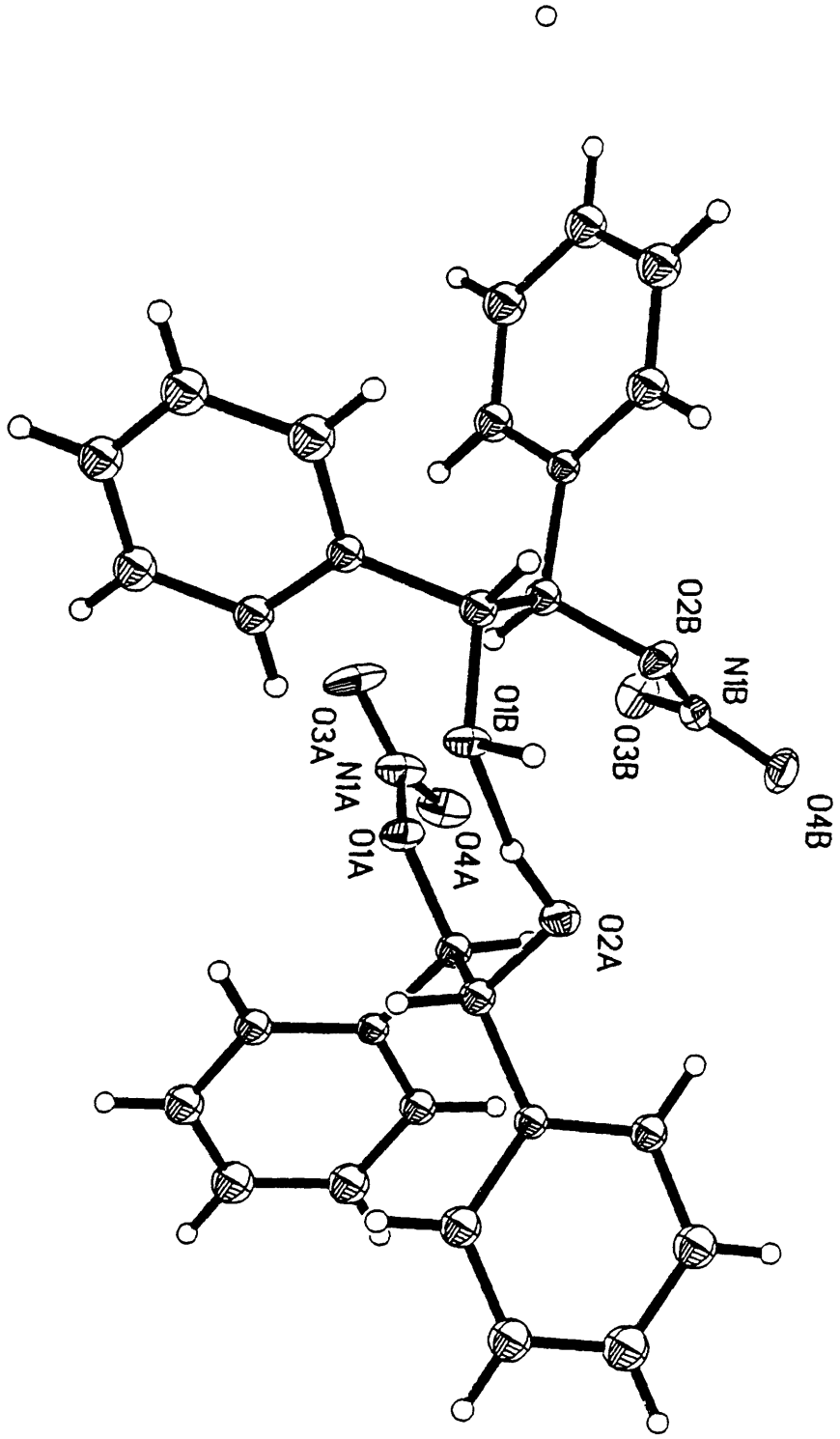
4.2 RESULTS AND DISCUSSION

4.2.1 The Reaction of Stilbene Oxide with Nitric Oxide

Racemic *trans*-Stilbene oxide (194t) was reacted with nitric oxide (NO) in acetonitrile. NO gas was bubbled into the cooled solution, the tube sealed evacuated and refilled with nitric oxide. The sealed tube was heated at 90°C and opened at intervals of a couple of hours to follow the reaction by TLC, the bubbling, sealing etc. repeated after each opening, before resuming heating. T.L.C. showed the appearance of one product spot after approximately 2 hours, reaction was continued until almost all the starting material had disappeared after 6 hours, by which time other products were observed. Evaporation of the reaction mixture followed by column chromatography gave one major product in 59% yield. Mass spectrometry showed this compound to have a molecular weight of 259 and molecular formula of $C_{14}H_{14}NO_4$. Its NMR spectra showed 10 ^{13}C signals, and ^{1}H signals at mainly 2.74, 4.95, and 5.87, along with aromatic signals. After recrystallisation from light petroleum/diethyl ether, final confirmation was obtained from X-ray crystallography showing compound to be a diastereoisomer of 1-(*O*)-nitro-1,2-diphenyl ethanediol (195a).

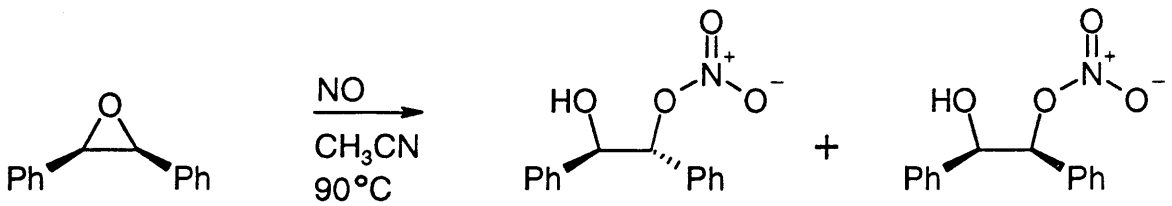


(194t) (195a)



X-Ray Structure of (*RS*, *RS*)-1-(*O*)-Nitro-1,2-diphenyl ethanediol (195a)

When the *cis*-stilbene oxide (194c) was treated in the same way, a similar product was obtained in 26% yield; however, this time a 3b/2a ratio of diastereoisomers resulted. The minor component was the isomer shown above. These have been separated by HPLC.



(194c) (195a) (195b)

We first had to eliminate the possibility that the NO was undergoing air oxidation to HNO_3 and that this was reacting with *cis* and *trans* stilbene oxide. Reaction of *trans*-stilbene oxide with dilute nitric acid produced (195) as a mixture of diastereoisomers (14b:13a), hydrobenzoin (196) as a mixture of diastereoisomers – meso and racemic in 8:21 ratio, and diphenylacetaldehyde (197), arising from acid catalysed rearrangement of epoxide or possibly hydrobenzoin.

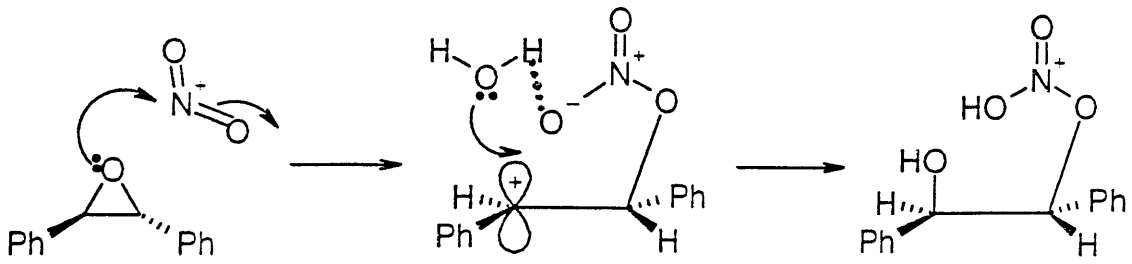
(196) (197)

When *cis*-stilbene oxide was reacted with dilute nitric acid, (195) was produced as a mixture of diastereoisomers (ratio 1b:6a); also isolated was

hydrobenzoin, again as a mixture of meso- and racemic in a similar ratio to that produced from *trans*-stilbene oxide. Diphenylacetaldehyde was also found, along with another aromatic compound with the same R_f, which was not identified. (When *meso*-hydrobenzoin and *racemic* hydrobenzoin were reacted with dilute nitric acid, then diphenylacetaldehyde was not obtained, suggesting that in the reaction of cis- and trans- stilbene oxide, diphenylacetaldehyde is not obtained from the rearrangement of the diol in addition to rearrangement of the epoxide).

The major difference between the NO and the HNO_3 reactions with the *trans*-stilbene oxide (194t) is that the hydroxy nitrate compound (195) was produced in the reaction with NO as a single diastereoisomer which corresponds to opening of the epoxide with retention of configuration.

Since we took no special precautions to remove O_2 from the system we believe that the hydroxy nitro compound (195) is arising from the reaction of the epoxide with nitric acid formed by the oxidation of NO in the presence of traces of water in the system. The retention of configuration in the opening of the *trans*-epoxide may be explained by the epoxide opening by electrophilic attack of NO_2^+ with the cation retaining the trans arrangement of the two phenyl groups and that traces of water attack the carbocation from the same side as the NO_3 group.



(194*t*) (198) (195a)

The reasons for this are twofold; one may be the preference for the trans disposition of the phenyl groups; the other the possible H-bonding of the trace of water with the nitro group.

The *cis*-epoxide (194c), when receiving the same treatment, gives an intermediate carbocation that is less stable due to the cis disposition of the two phenyls, and undergoes rotation to the trans conformer. During this rotation, water is attacking the cation leading to a mixture of products.

We must propose that HNO_3 is formed from NO in the above explanation. It is known that NO reacts instantly with O_2 to form NO_2 (eq.1) and that 3NO give N_20 and NO_2 under high pressures (30-50°C) (eq.2). Whichever process is occurring, some NO_2 is produced. NO_2 reacts with traces of water to form a mixture of nitric acid HNO_3 and nitrous acid HNO_2 (eq.3). Also, nitrous acid decomposes when heated to form HNO_3 and more NO and water (eq.4).

$$2NO + O_2 \longrightarrow 2NO_2 \qquad \text{eq.1}$$

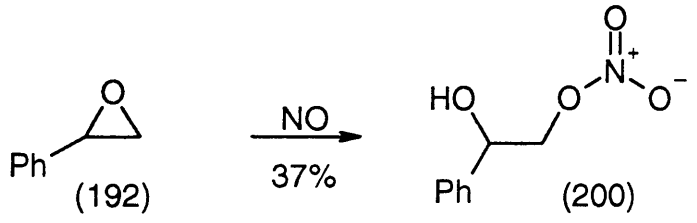
$$3NO \longrightarrow N_2O + NO_2 \qquad \text{eq.2}$$

$$2NO_2 + H_2O \longrightarrow HNO_3 + HNO_2 \qquad \text{eq.3}$$

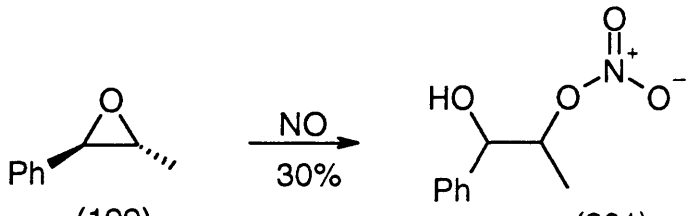
$$3HNO_2 \longrightarrow HNO_3 + 2NO + H_2O \qquad \text{eq.4}$$

4.2.2 The Reaction of NO with other Epoxides

Other epoxides were also reacted with NO in a similar way to *cis*- and *trans*- stilbene epoxide. Mono-substituted styrene oxide (192) and di-substituted (1*R*,2*R*)-(+)-1-phenylpropylene oxide (199) were tested, and produced the corresponding nitrate esters.

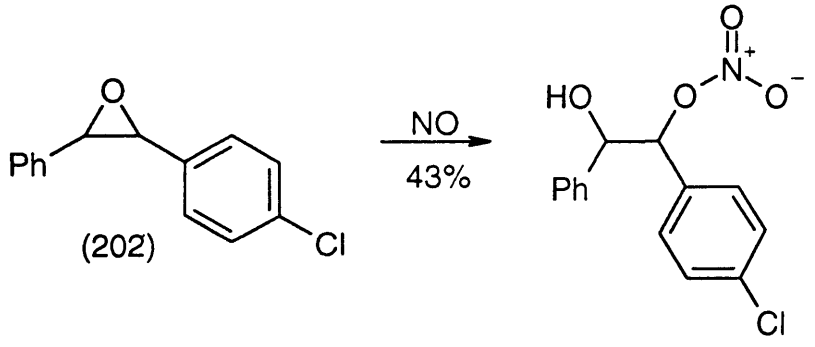


(192) (200)

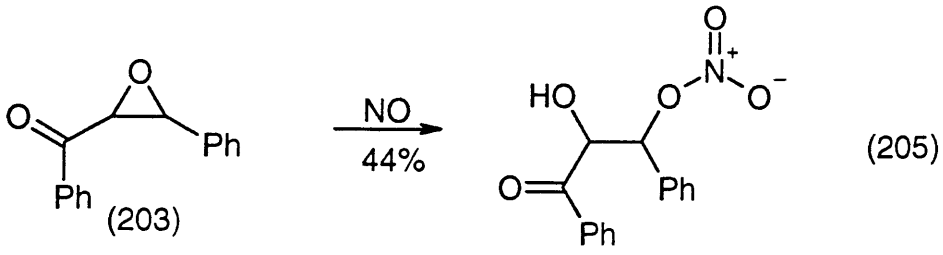


(199) (201)

Racemic *trans*-4-chlorostilbene oxide (202) and racemic *trans*-chalcone-α,β-epoxide (203) gave nitrates (204) and (205).

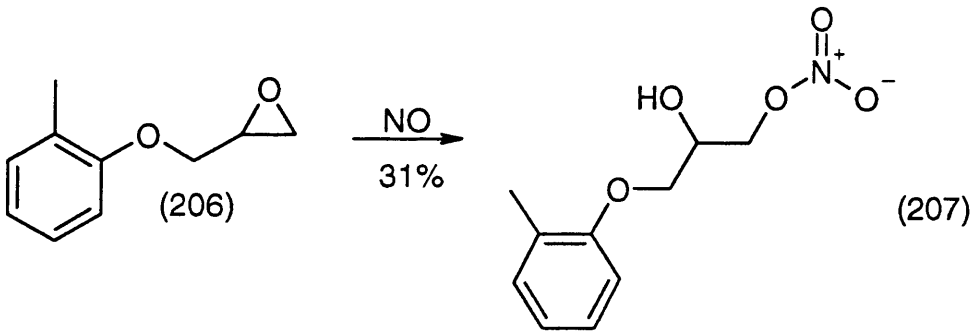


(202) (204)



(205)

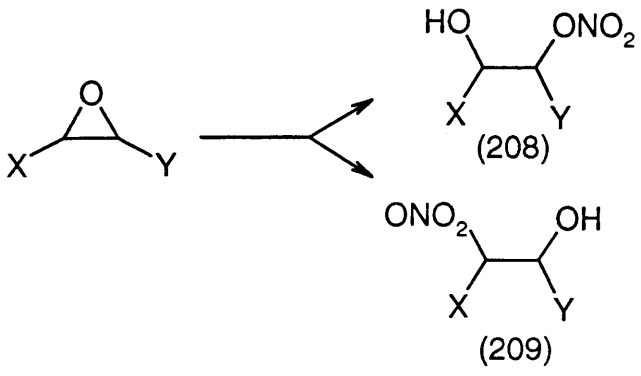
An epoxide which was not phenyl-substituted, glycidyl 2-methylphenyl ether (206) reacted to give the nitrate (207).



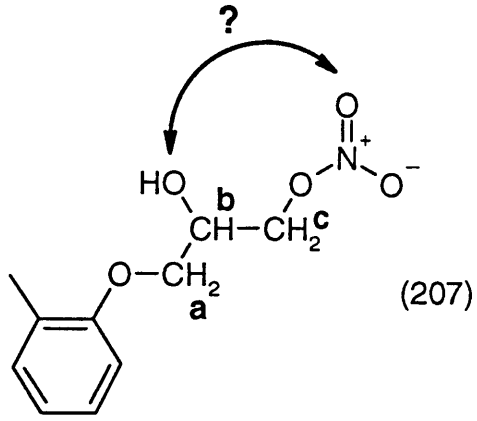
(207)

4.2.3 Regioisomers of the Nitrate Esters

If an unsymmetrical epoxide is ring opened to form a nitrate, two regio-isomers are possible, depending on the positions of nitrate and hydroxyl groups, (208) and (209).



The NMR spectra of the nitrates that have been produced were examined to see if the structure could be determined.

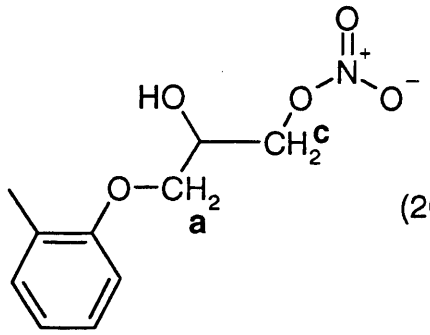


(207)

The ^{1}H NMR of (207) consists of a methyl singlet (2.23δ), an –OH doublet (broadish and too low to be a proton on a carbon attached to an oxygen, and in the H-C correlation, it does not correlate to a carbon signal, 2.62δ), two doublets of doublets integrating for 1H each (~4.05δ), a 1H multiplet (4.33δ), 2 x dd integrating for 1H each (~4.65) and an aromatic region (4H). The three signals in the 4-5δ region correspond to protons a, b and c (not respectively.)

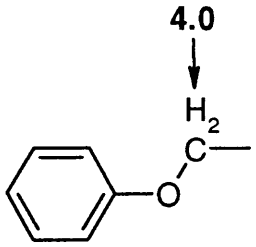
From a COSY spectrum, it can be seen that the 1H multiplet (4.33δ) was coupling to the –OH, so it would seem that this signal corresponds to proton b, and that the –OH group is in fact attached to the carbon with one proton. This means that the –OH and $-ONO_2$ groups are as shown above. (The H_b couples to the dd signals on either side of it in the spectrum, confirming its placement between H_a's and H_c's in the molecule.) Further evidence for this is supplied by the H-C correlation spectrum - the ^{1}H

signal, previously identified as being coupled to the –OH signal, corresponds to a CH carbon, with the other two neighboring signals corresponding to CH_2's.

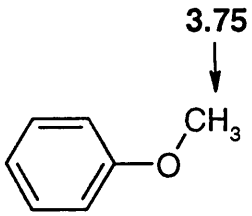


(207)

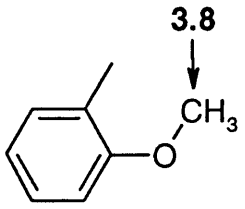
To assign the two pairs of dd's (at ~4.05δ and ~4.65) to protons a and c, spectra of compounds from the Aldrich catalogue were examined (figure 15).



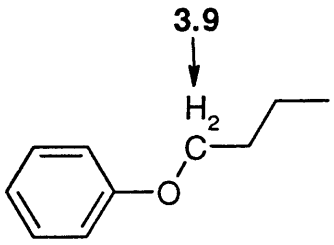
phenetole



anisole



2-methyl anisole



butyl phenyl ether

Figure 15

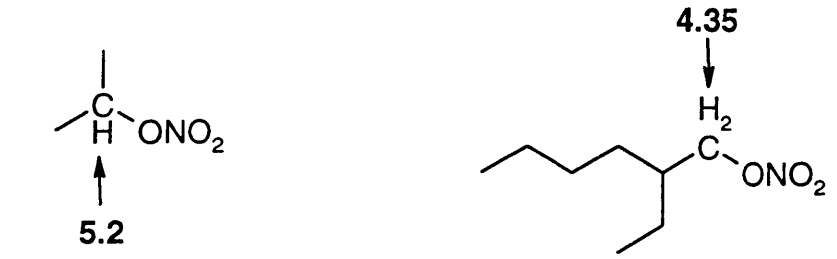
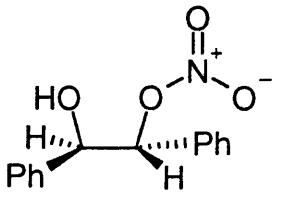


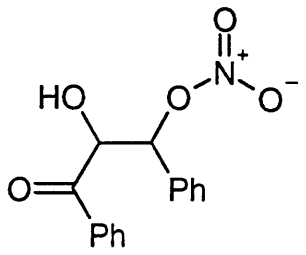
Figure 15 cont.

From these figures it appears more likely that the H_c protons are the lower field signals (~4.65δ). In addition, where it has been possible to distinguish between the *H*C-OH and the *H*C-ONO_2 protons in other nitrates, the *H*C-ONO_2 protons have appeared at a lower field position than the *H*C-OH (see description below - ^{1}H NMR of (195a).)



(195a)

In addition to aromatic protons, the ^{1}H NMR spectrum of (195a) contains three 1H signals, at ~2.7δ, ~5.0δ and ~5.9δ. The signal at 2.7 disappears after a D_2O shake, confirming that the signal belongs to the –OH group, leaving the other two signals to be the *H*C-OH and the *H*C-ONO_2. Before the D_2O shake, the OH doublet is coupling to the dd at 5δ. After the D_2O shake, just a doublet remains at 5δ, showing that the d at 5δ is the *H*C-OH, and so the lower field signal is the *H*C-ONO_2.



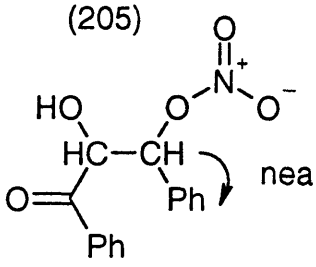
(205)

The ^{1}H NMR spectrum of (205) contains aromatic protons, and signals at ~6.1δ, ~5.4δ, and ~3.9δ. The signal at ~3.9 is on some spectra a doublet, and in others a broad singlet, suggesting that it is the –OH proton (in an H-C correlation spectrum this signal does not correlate to a carbon signal), sometimes coupling to one of the other protons. A COSY spectrum shows the coupling of the signal at 5.4 to the -OH signal and when the –OH signal is a doublet, the signal at 5.4 is a dd, otherwise it is a doublet, whilst the signal at 6.1 is a doublet in both cases, showing that these are the signals for the *H*C-OH and the *H*C-ONO_2 protons respectively.

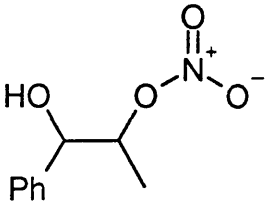
It is difficult to say with certainty the structure of (205). Both the carbons involved carry only one proton, so even with the knowledge of which ^{1}H NMR signal is which, it is not possible to use the H-C correlation to spectrum to resolve the questions in this simple way. However, it can be seen in a TOCSY spectrum that both the nitrate and the hydroxy systems couple to the same signal in the aromatic region. There is no other coupling seen between these two and any other aromatic signal. The size of the coupling is larger for the nitrate. A possible explanation for this is that both the *H*C-OH and the *H*C-ONO_2 protons are unable to couple (within the limits of the TOCSY detection) to the phenyl group which is

separated from them by the carbonyl group, but they are able to couple to the other phenyl group, the larger coupling indicating the group nearest the 'accessible' phenyl group, i.e. (205) has the structure shown below.

(205)



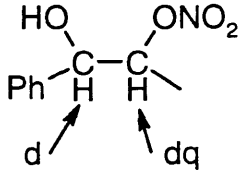
nearer, so coupling larger



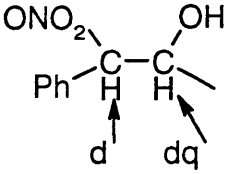
(201)

The structure of (201) was determined by analysis of the ^{1}H NMR spectrum. It consists of a Me doublet at 1.09δ, 1H signals at 2.34δ, 4.14δ and 5.58δ, in addition to an aromatic signal. The doublet at 2.34δ is assigned to the –OH group since this signal is too low to be either the *H*C-OH or the *H*C-ONO_2. The remaining two signals are a multiplet at 4.14δ and a doublet at 5.58δ. The expected multiplicity of the *H*C-OH and the *H*C-ONO_2 can be predicted for the two possible structures.

(201a)



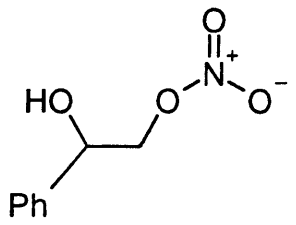
or dd if OH couples



(201b)

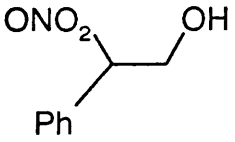
or ddq if OH couples

The –OH signal is a doublet, and so is coupling, hence the options are dd and dq if isomer (a), and d and ddq if isomer (b). Since one of the signals is a doublet, it would seem that structure (b) is the actual structure of (201). This would make the lower field doublet the *H*C-ONO_2 in agreement with the three other examples so far.



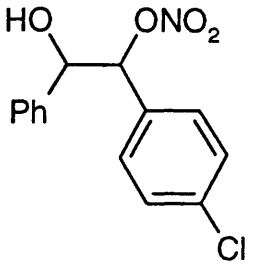
(200)

The ^{1}H NMR spectrum of (200) begins with a broad 1H singlet assigned to the –OH group. This is followed by two 1H doublets of doublets at ~3.9δ, a 1H doublet of doublets at 5.92δ, and an aromatic signal. Since the -OH does not couple in this spectrum, it is not possible to use this to show which of the lower field signals corresponds to the *H*C-OH and the *H*C-ONO_2. However, in previous examples it has been seen that protons next to the nitrate group have a lower chemical shift that protons next to the hydroxyl group, so it would seem reasonable to propose that the dd at 5.92δ corresponded to *H*C-ONO_2, and the dd's at ~3.9δ the two *H*C-OH's. This would mean that the actual structure of (200) is not the one previously shown, but actually as shown below. (figure 16)



(200)
III
(193)

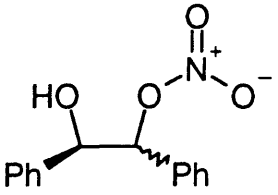
Figure 16



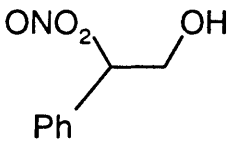
(204)

The structure of (204) was not determined or predicted since the –OH group does not couple and both the –OH and ONO_2 bearing carbons have only one proton attached.

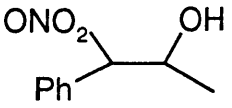
4.2.4 Summary of Nitrates Formed



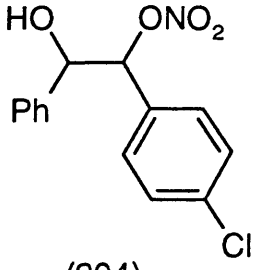
(195)



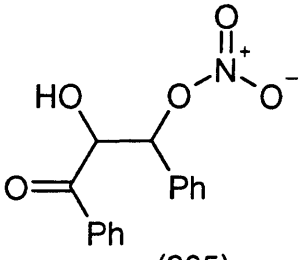
(200/193)



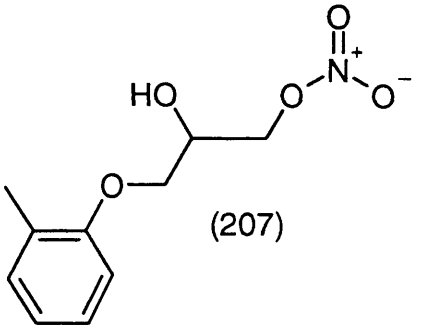
(201)



(204)



(205)



(207)

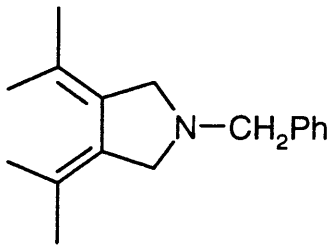
4.2.5 Conclusion

The treatment of some substituted epoxides with nitric oxide resulted in organic nitrate formation, possibly through reaction with nitric acid formed from NO. In comparison with similar treatment of substituted cyclopropanes, generally epoxide reaction times were longer, but the

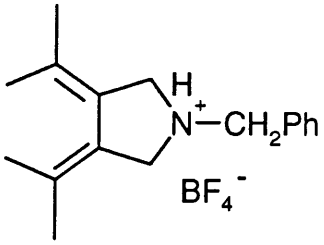
yields better. One epoxide examined reacted as readily without phenyl substituents as those tested did that *were* phenyl-substituted on the three-membered ring.

4.2.6 Overall Conclusions

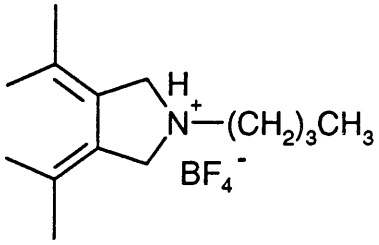
Nitroso compounds, from the reaction of nitric oxide with the substituted butadienes (79), (81), and (82), were not seen, as had been hoped.



(79)

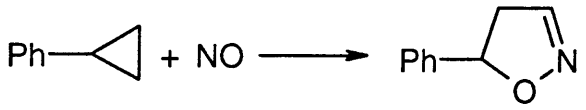


(81)



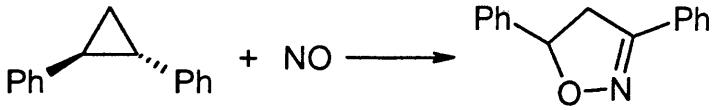
(82)

Some interesting products were seen when phenyl-substituted cyclopropanes were treated with NO.



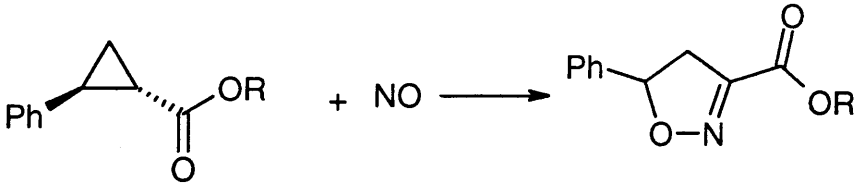
(110) (111)

35%



(139) (138)

15%

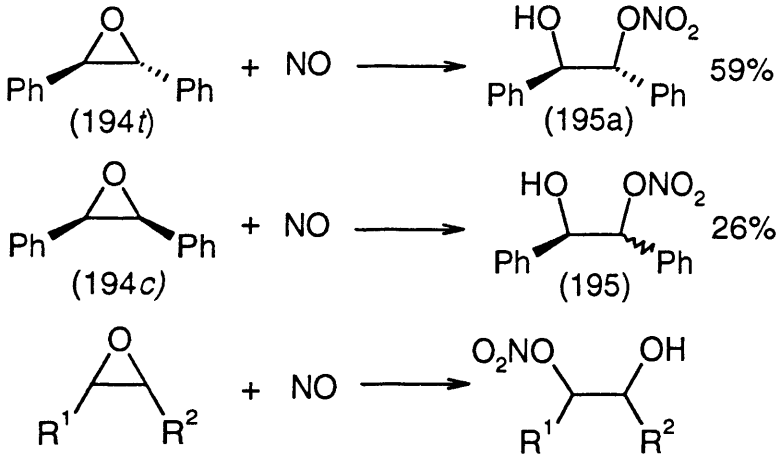


(156) R = Et
(159) R = Me

(157) R = Et 26%
(163) R = Me 4%

High temperatures, and excess nitric oxide, were used in the reaction. This would make the reactions themselves unlikely to be practical in a biological environment with possibly minimal amounts of NO.

Further successful reactions occurred when some epoxides were treated with NO.

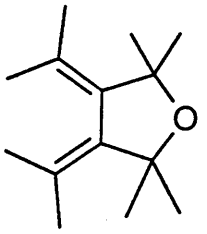


(192) R1 = Ph, R2 = H
(199) R1 = Ph, R2 = CH_3
(202) R1 = C_6H_4Cl, R2 = Ph
(203) R1 = Ph, R2 = COC_6H_5
(206) R1 = H, R2 = $CH_2OC_6H_4CH_3$

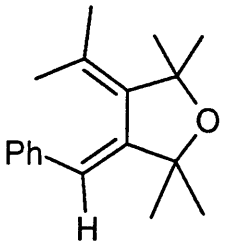
(200) 37%
(201) 30%
(204) 43%
(205) 44%
(207) 31%

Again high temperatures were used, and excess NO. If indeed the reaction occurs by the formation HNO_3 from NO, this would not be very practical in a biological system, either for an NO trap or for NO detection. In addition, some nitrates are known to be explosive, making their synthesis in the body undesirable and this would have to be a consideration.

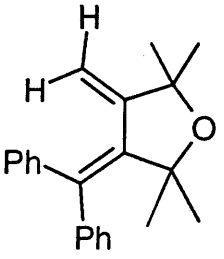
Jelinski and Kiefer synthesised other substituted butadienes, some similar to the cyclic amines in chapter two and some less so.[31] Others are also known[32, 33, 35] and so there are many possibilities for testing with NO that might have more success.



(208)

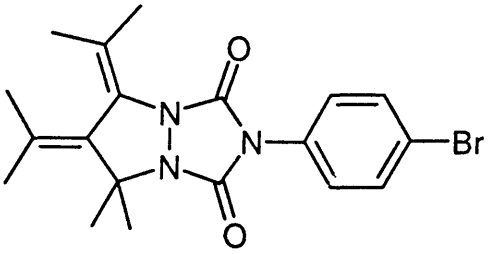


(209)

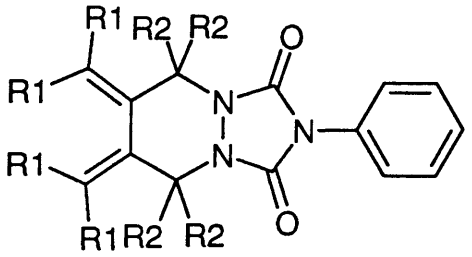


(210)

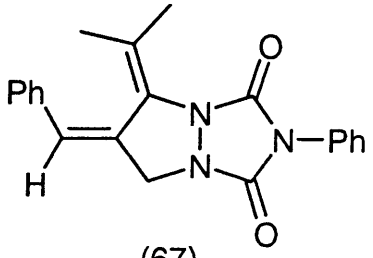
(62)



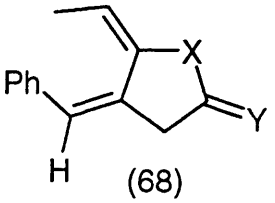
(63)



a, R1 = Me; R2 = H
b, R1 = H; R2 = Me



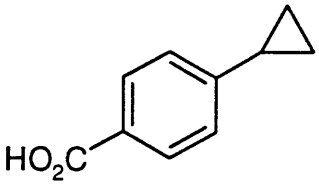
(67)



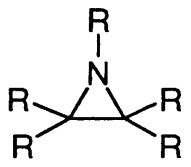
(68)

a, X = NSO_2Cl; Y = O
b, X = O; Y = NSO_2Cl

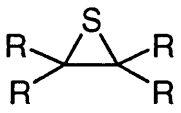
The effect of the phenyl substituents on the cyclopropane reaction with NO could be investigated further. Varying the substituents on the phenyl group would give more information about its participation. For example, a carboxylic acid group *para*- to the cyclopropane should provide further stabilisation of a radical intermediate (with the added benefit of water solubility as the salt).



Greater precautions could be taken with the reaction of the epoxides to exclude oxygen and water, so supporting (or not) the suggestion that these are involved in the reaction with NO. Continuing with three-membered heterocycles, it would be interesting to try the reaction with other heteroatoms in the three-membered ring, such as nitrogen (aziridines) and sulphur (thiiranes). If these proved to be more reactive than the epoxides, they may be better suited to reaction at lower NO concentrations and temperatures.



aziridine



thiirane

This project began the investigation of nitric oxide and substituted butadienes, and provided further insights into the reactions of nitric oxide.

EXPERIMENTAL

Experimental

^{1}H NMR (250 MHz) and ^{13}C NMR (63 MHz) were recorded on a Bruker ARX 250 spectrometer. ^{1}H NMR (400 MHz) and ^{13}C (101 MHz) were recorded on a Bruker DRX 400 spectrometer. Chemical shifts were recorded in ppm (δ) downfield from the internal reference (TMS). Signal characteristics are described using standard abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), br (broad). ^{13}C spectra were recorded using DEPT; C, CH, CH_2, CH_3 are used to indicate quaternary, methine, methylene and methyl carbons respectively.

Nitric oxide was obtained from Merck (BDH), (15l) Minimum Assay 99%, cat. no 6007235.

The IR spectrum was recorded on a PE 298 IR spectrometer. Band intensities are described using standard abbreviations: s (strong), m (medium), w (weak), br (broad), v (very).

Mass spectra were measured on a Kratos Concept H mass spectrometer.

Melting point measurements were made using a Kofler hot stage apparatus and are uncorrected.

HPLC was performed on a Shimadzu LC6A HPLC machine, with Watman Partisilio column, 50cm x 9.4mm ID.

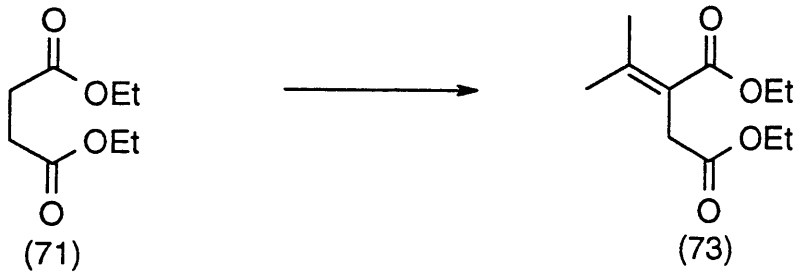
Diethyl ether was distilled from $LiAlH_4$. Dichloromethane and ^{t}butanol were distilled from calcium hydride. Acetonitrile was obtained from Aldrich in a sure-seal bottle. Ethanol was distilled from magnesium and iodine. Tetrahydrofuran (THF) was distilled from sodium metal in the presence of benzophenone. Reagent grade acetone was obtained from May and Baker Ltd. 1,2-Diphenylcyclopropane was obtained from Lancaster. Other chemicals were obtained from Sigma-Aldrich unless otherwise specified.

Flash chromatography was carried out according to the method of Still using Sorbsil 60 silica gel (230-400 mesh) manufactured by Crossfield Chemicals. Thin-layer chromatography was conducted on standard commercial aluminium sheets pre-coated with a 0.2 mm layer of silica gel (Merck 60-254) and plates were visualised using UV light, and solutions of ethanolic vanillin and aqueous potassium permanganate.

'Remove under reduced pressure' refers to the use of a Buchi rotary evaporator with water bath at less than 40°C.

In the NO bubbling experiments, NO entered the solution through a sinter and on exiting the apparatus passed through traps of paraffin, and aqueous iron (II) sulphate solution.

Diethyl 2-(1-methylethylidine)-1,4-butanedioate (73)[39Note1]



(71) (73)

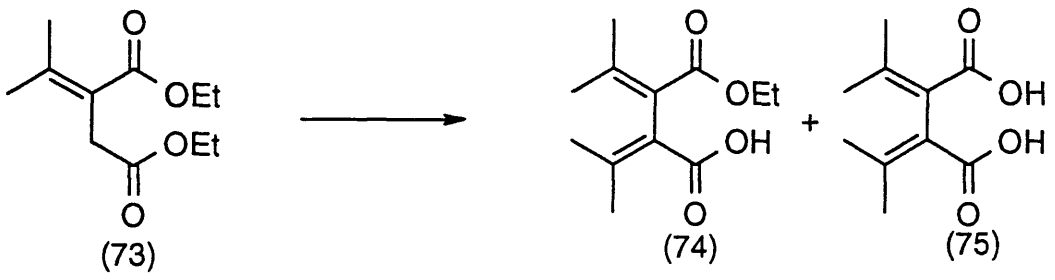
A mixture of diethyl succinate (71) (20.75 g, 119 mmol) and acetone (6.95 g, 120 mmol) was added dropwise to a stirred, refluxing solution of potassium ^{t}butoxide (12.97 g, 116 mmol) in ^{t}butanol (100 cm^3). After refluxing for half an hour, the solvent was removed under reduced pressure, the residue made slightly acidic with dilute HCl, and extracted with diethyl ether (4 x 30 cm^3). The combined ether layers were washed with water and completely extracted with aqueous sodium carbonate (6 x 50 cm^3; 10% w/v). The alkaline solution was made strongly acidic with concentrated HCl, and extracted with diethyl ether (4 x 20 cm^3). These combined ether portions were dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was taken up in ethanol to which acetyl chloride (8.99 g, 115 mmol) was added. After stirring at room temperature for 24 h the alcohol was removed under reduced pressure and the remaining liquid poured into an ice/water mixture. The aqueous solution was extracted with diethyl ether (4 x 30 cm^3), the ether solutions combined, dried ($MgSO_4$) and the ether removed under reduced pressure to give a yellow oil (14.34 g). A sample of this oil (1 g) purified by chromatography on silica gel with diethyl ether-light petroleum (2:3, v/v)

as the eluant gave (73) as a clear, colourless oil (0.6 g, 34%). Note 2; R_f [ether-light petroleum (2:3, v/v)] 0.46; δ_H (250 MHz; $CDCl_3$; Me_4Si) 1.26 (6 H, 2 x t, *J* 7.1, -CH_2CH_3), 1.87 (3 H, s, C=C-CH_3), 2.15 (3 H, s, C=C-CH_3), 3.37 (2 H, s, C=C-CH_2), 4.16 (4 H, 2 x q, *J* 7.1, -CH_2CH_3); δ_C(63MHz; $CDCl_3$; Me_4Si) 14.6 (CH_3), 23.6 (CH_3), 23.6 (CH_3), 35.8 (CH_2), 60.6 (CH_2), 61.0 (CH_2), 121.1 (C), 149.3 (C), 168.2 (C), 171.8 (C); *m/z* (EI^+) 214 (M^+, 6%), 168 (M^+-EtOH, 100), 140 (M^+-$C_3H_6O_2$, 41), 112 (*140*-C_2H_4, 91), 95 (*140*-C_2H_5O, 43), 67 (32).

Note 1 : Made according to the method of Overberger and Roberts.[39]

Note 2 : Purification of (73) proved to be a problem, consequently the crude product was used in the next step of the reaction.

Bis 2,3-(1-methylethylidine)-1,4-butanedioic acid, monoethyl ester (74), and bis 2,3-(1-methylethylidine)-1,4-butanedioic acid (75) [40Note 1]



A mixture of acetone (1.4 g, 24 mmol) and crude yellow oil (73) (4.15 g, 19.4 mmol if pure) in diethyl ether (50 cm^3) was added to a stirred solution of sodium ethoxide (2.0 g, 29 mmol) in diethyl ether (10 cm^3) over 15 minutes whilst cooled by NaCl and ice. After stirring at 5°C for 3 days, the reaction mixture was poured into an ice/ice water mixture. The aqueous solution was washed with diethyl ether, acidified with conc. H_2SO_4 and extracted with diethyl ether (4 x 25 cm^3). The combined ether portions were dried ($MgSO_4$) and the solvent removed under reduced pressure to give an oil (2.39g). The product was a mixture of (74) and (75) which were not isolated[Note 2]; R_f (diethyl ether-light petroleum, 1:1, v/v) 0.03, 0.31; δ_H(250 MHz, $CDCl_3$; Me_4Si) 1.47 (t, *J* 7.1, $-CH_2CH_3$), 2.00 (6 H, s, C=C-CH_3), 2.41 (6 H, s, C=C-CH_3), 4.37 (q, *J* 7.1, $-CH_2CH_3$).

Note 1 : Made according to the method of Stobbe.[40]

Note 2 : (74)/(75) was formed as a mixture of the half acid/half ester and the diacid. These were not isolated as the reducing agent Red-Al used in the next step acts on both carboxylic acids and esters.

Bis 2,3-(1-methylethylidine)-1,4-butanediol (76)[31]

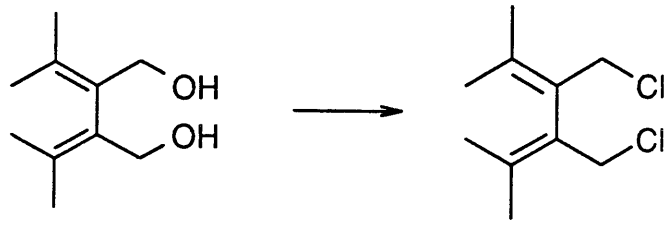
(74) R = H
(75) R = Et

(76)

A solution of (74)/(75) (7.66 g) in THF (70 cm^3) was added dropwise to a stirred solution of Red-Al®[Note 1] (24 cm^3, 65% wt in toluene, 77 mmol) in THF (40 cm^3). After stirring at room temperature for 17 hours, the mixture was added dropwise to a stirred solution of 20% w/v sodium hydroxide (100cm^3), extracted with diethyl ether (4 x 30 cm^3), the combined ether portions dried ($MgSO_4$) and the solvent removed under reduced pressure to give a yellow oil (3.17 g). Chromatography of the residue on silica gel with ether as the eluent gave (76)(1.54 g, 8% from diethyl succinate) as a clear, yellow oil which formed a waxy solid on dissolving in and removal of dichloromethane; m.p.(crude) 45-53°C; R_f (ether) 0.51; $\nu_{max.}$(film/cm-1) 3320v br (OH), 2980w, 2910w, 2860w, 1440w, 1370w, 1000m 910s, 730s; δ_H(250 MHz; $CDCl_3$; Me_4Si) 1.56 (6 H, s, C=C-CH_3), 1.78 (6 H, s, C=C-CH_3), 3.84 (2 H, d, *J* 11.5, C*H*-OH), 4.02 (2 H, br s, O*H*), 4.42 (2 H, d, *J* 11.5, C*H*-OH); δ_C(63 MHz; $CDCl_3$; Me_4Si) 19.7 (CH_3), 21.9 (CH_3), 62.1 (CH_2, 132.0 (C), 133.6 (C); *m/z* (EI) 170 (M^+, 8%), 152 (M^+-H_2O, 71), 137 (93), 119 (43), 109 (100), 91 (39), 81 (54), 67 (44), 55 (34).

Note 1 : Red-Al® = sodium bis(2-methoxyethoxy)aluminium hydride.

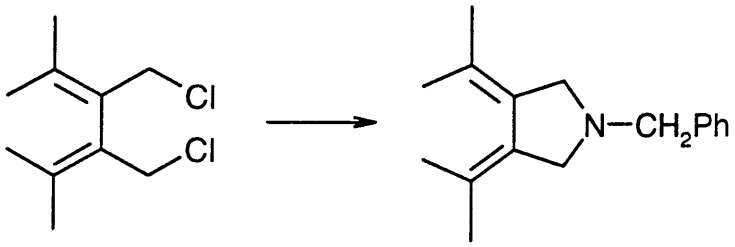
Bis 2,3-(1-methylethylidine)-1,4-butanedichloride (78)



(76) (78)

The diol (76) (0.969 g, 5.7 mmol) was stirred with triphenylphosphine (3.080 g, 11.7 mmol) in carbon tetrachloride (3 cm^3) at 80°C for 2h. Hexane (1 cm^3) was added to the reaction vessel and the reaction mixture stirred for 5 minutes, filtered, and evaporated under reduced pressure. Flash column chromatography of the residue with diethyl ether-light petroleum (1:8, v/v) as eluant gave bis 2,3-(1-methylethylidine)-1,4-butanedichloride (78) as a yellow oil (0.242 g, 21%); R_f (diethyl ether-light petroleum, 1:8, v/v) 0.37; ν_{max} (film)/cm^{-1} 3000s, 2920s, 2840s, 1660w, 1450s, 1380s, 1260s, 1180m, 1020m, 900w, 700s, 620m; δ_H(250 MHz; $CDCl_3$; Me_4Si) 1.66 (6 H, s, CH_3-C=C-), 1.87 (6 H, s, CH_3-C=C-), 4.13 (2 H, d, *J* 11.3, H-C(*H*)Cl), 4.31 (2 H, d, *J* 11.3, *H*-C(H)Cl); δ_C(63 MHz; $CDCl_3$; Me_4Si) 21.0 (CH_3), 23.8 (CH_3), 46.0 (CH_2), 129.8 (C), 139.6 (C); m/z (EI^+) 210 (M^+2Cl^{37}, 6%), 208 ($M^+Cl^{37}Cl^{35}$, 37), 206 (M^+2Cl^{35}, 58), 171 (M^+-Cl^{35}, 24), 157 (M^+-CH_2Cl^{35}, 86), 135 (95), 121 (78), 107 (72), 93 (100), 77 ($C_6H_5^+$, 60), 65 (23), 53 (21); (Found M^+, 206.0629. $C_{10}H_{16}Cl_2^{35}$ requires M, 206.0631).

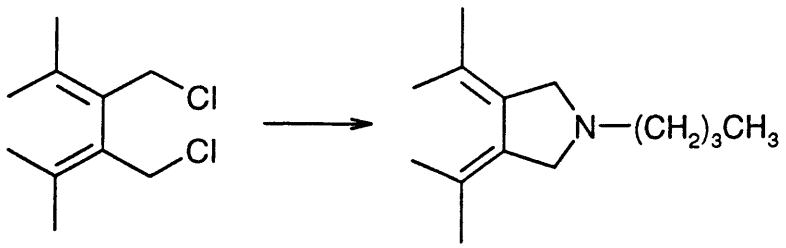
1-Benzyl 3,4-bis(1-methylethylidine) pyrrolidine (79)[31]



(78) (79)

The dichloride (78) (0.086 g, 0.4 mmol) was stirred in $CDCl_3$ (200 µl) with benzylamine (140 µl, 1.2 mmol) at 60°C for 3 h. The solvent was evaporated under reduced pressure. Flash column chromatography of the residue with diethyl ether-light petroleum (1:3, v/v) as eluant gave 1-benzyl 3,4-bis(1-methylethylidine) pyrrolidine (79) as a yellow oil (0.053 g, 53%); R_f (diethyl ether-light petroleum, 1:3 (+ a drop of NH_3), v/v) 0.16; ν_{max} (CH_2Cl_2)/cm^{-1} 2920s, 2860s, 2800m, 1670w, 1500m, 1460s, 1380s, 1340m, 1180m, 1100s, 1030s, 815m, 810m; δ_H(250 MHz; $CDCl_3$; Me_4Si) 1.63 (6 H, s, CH_3-C=C), 1.67 (6 H, s, CH_3-C=C), 3.27 (4 H, s, C=C-C*H*$_2$-N x 2), 3.70 (2 H, s, -NC*H*$_2$-Ph), 7.21-7.39 (5 H, aromatic); δ_C(63 MHz; $CDCl_3$; Me_4Si) 22.0 (CH_3), 23.9 (CH_3), 57.6 (CH_2), 61.4 (CH_2), 124.8 (C), 126.9 (CH), 128.2 (CHx2), 129.0 (CHx2), 131.9 (C), 138.8 (C); m/z (EI^+) 241 (M^+, 26%), 226 (72), 198(10), 134 (13), 91 ($C_7H_7^+$, 100), 84 (70), 51 (20); (Found M^+, 241.1831. $C_{17}H_{23}N$ requires M, 241.1831).

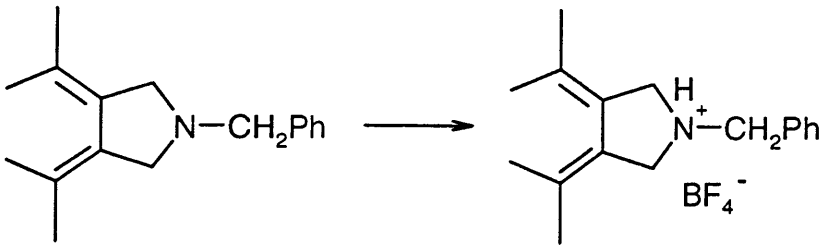
1-*n*-Butyl 3,4-bis(1-methylethylidine) pyrrolidine (80)



(78) (80)

The dichloride (78) (0.045 g, 0.2 mmol) was stirred in $CDCl_3$ (300 µl) with *n*-butylamine (70 µl, 0.64 mmol) at 60°C for 2 h. The solvent was evaporated under reduced pressure. Flash column chromatography of the residue with diethyl ether-light petroleum (1:3-1:1, v/v) as eluant gave 1-*n*-butyl 3,4-bis(1-methylethylidine)pyrrolidine (80) as a yellow oil (0.025 g, 56%); R_f (diethyl ether-light petroleum, 1:1, v/v) 0.25; ν_{max} (film)/cm^{-1} 2920s, 2860s, 2760m, 1730m, 1450m, 1370m, 1260s, 1190m, 1120s, 870w, 790m, 690m; δ_H(250 MHz; $CDCl_3$; Me_4Si) 0.93 (3 H + 2 H impurities, t, *J* 7.4, $N(CH_2)_3CH_3$), 1.07-1.57 (4 H, multiplet CH_2's, $-CH_2CH_2-CH_3$), 1.64 (6 H, s, $=-CH_3$), 1.71 (6 H, s, $=-CH_3$), 2.54 (2 H, br t, *J* 7.4, $N-CH_2CH_2-$), 3.28 (4 H, s, $=-CH_2-N$ x 2), (impurities: 1.26, 4.31, 7.51, 7.69); δ_C(63 MHz; $CDCl_3$; Me_4Si) 14.1 (CH_3), 21.9(CH_3), 23.8 (CH_3), 29.7 (CH_2), 30.4 (CH_2), 57.0 (CH_2), 57.6 (CH_2), 125.0 (C), 131.9 (C), (impurities: 128.4, 128.6, 128.8, 130.9, 131.5, 132.0, 132.2); m/z (EI^+) 207 (M^+, 37%), 192 (58), 164 (100), 135 (15), 107 (13), 83 (15); (Found M^+, 207.1987. $C_{14}H_{25}N$ requires M, 207.1987).

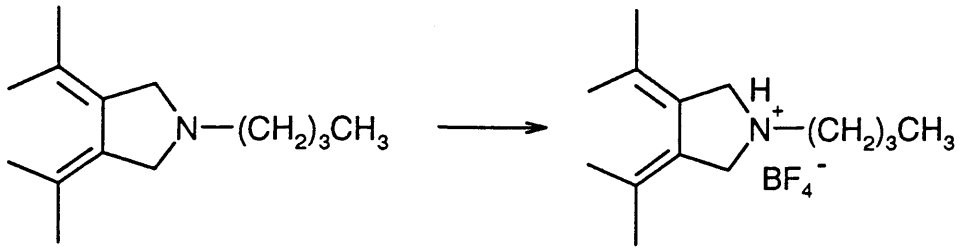
1-Benzyl 3,4-bis(1-methylethylidine) pyrrolidinium tetrafluoroborate (81)



(79) (81)

Tetrafluoroboric acid-diethyl ether complex ($HBF_4.OEt_2$, 85%, 35 µl, 1 eq) was added to an NMR tube containing the amine (79) (0.049g, 0.2 mmol) in $CDCl_3$. The solution was evaporated under reduced pressure to remove excess diethyl ether. ν_{max} (CH_2Cl_2)/cm^{-1} 3140w, 2940m, 1450m, 1260m, 1070s, 1030s, 910m, 690w; δ_H(250 MHz; $CDCl_3$; Me_4Si) 1.70 (6 H, s, CH_3-=), 1.73 (6 H, s, CH_3-=), 3.72 (2 H, v br dd, =-CH-N x 2), 4.15 (2 H, br dd, *J* 5.5, 13.2, =-CH-N x 2), 4.28 (2 H, d, *J* 6.0, N-C*H*$_2$-Ph), 7.42-7.50 (5 H, aromatic); δ_C(63 MHz; $CDCl_3$; Me_4Si) 22.0 (CH_3x2), 23.9 (CH_3x2), 55.8 (CH_2x2), 59.6 (CH_2), 123.0 (Cx2), 129.1 (C), 129.6 (CHx2), 130.3 (CH), 130.4 (CHx2), 133.3 (Cx2); m/z (FAB^+)NBA 571 ([2M-BF_4^-]$^+$, 24%), 475 (9), 394 (9), 242 ([M-BF_4^-]$^+$, 100),198 (12), 136 (78); (Found [2M-BF_4^-]$^+$, 571.3847. $C_{34}H_{48}BF_4N_2$ requires M, 571.3847).

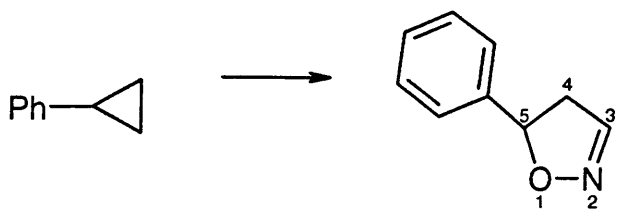
1-*n*-Butyl 3,4-bis(1-methylethylidine) pyrrolidinium tetrafluoroborate (82)



(80) (82)

Tetrafluoroboric acid-diethyl ether complex ($HBF_4.OEt_2$, 85%, 21 µl, 1 eq) was added to an NMR tube containing the amine (80) (0.025g, 0.1 mmol) in $CDCl_3$; ν_{max} (CH_2Cl_2)/cm^{-1} 3140w br, 2940w, 2880w, 1450w br, 1270w, 1065s, 1025s, 910w, 805w, 690w br; δ_H(250 MHz; $CDCl_3$; Me_4Si) 0.97 (3 H, t, *J* 7.2, N-(CH_2)-C*H*$_3$), 1.42 (4 H, multiplet of CH_2's, N-CH_2-(C*H*$_2$)$_2$-CH_3), 1.71 (6 H, s, CH_3-C=C-), 1.78 (6 H, s, CH_3-C=C-), 3.16 (2 H, dt, *J* 6.0, 10.4, N-C*H*$_2$-(CH_2)$_2$-CH_3), 3.63 (2 H + 6 H ether q, -C=C-CH-N x 2), 4.32 (2 H, dd, *J* 5.4, 12.6, -C=C-CH-N x 2), 10.04 (1 H, br s, NH); δ_C(63 MHz; $CDCl_3$; Me_4Si) 13.8 (CH_3), 20.0 (CH_2), 22.0 (CH_3), 24.1 (CH_3), 27.4 (CH_2), 57.1 (CH_2), 123.5 (C), 133.4 (C); m/z (FAB^+)NBA 503 ([2M-BF_4^-]$^+$, 3%), 391 (3), 360 (4), 208 ([M-BF_4^-]$^+$, 100), 192 (5), 149 (25); (Found [2M-BF_4^-]$^+$, 503.4160. $C_{28}H_{52}BF_4N_2$ requires M, 503.4160).

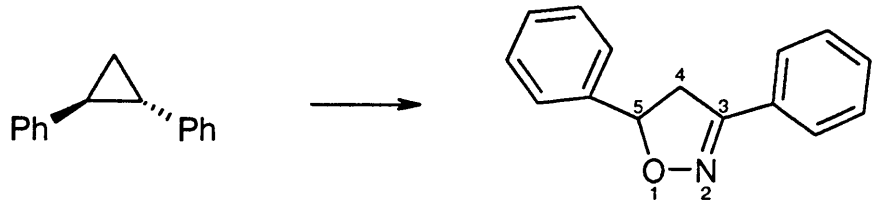
5-Phenyl-4,5-dihydroisoxazole (111)[79]



(110) (111)

Nitrogen was bubbled through a stirred solution of cyclopropyl benzene (110) (0.124 g, 1.0 mmol) in acetonitrile (30 cm^3) for 50 min. The system heated to 25-30°C then nitric oxide bubbled through for 5 sec. , the bubbling repeated at intervals for 4 hours. The system was sealed under NO at room temperature overnight. Nitrogen was bubbled through for 20 minutes, nitric oxide for 5 sec., the temperature was raised to 25-30°C and NO bubbled for 5 sec. at intervals of 7 h. The system was sealed overnight under nitrogen at room temperature. The reaction was poured into sat. $NaHCO_3$ solution (50 cm^3), extracted into diethyl ether (4 x 30 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure. Flash column chromatography of the residue with diethyl ether-light petroleum (1:1, v/v) as eluant gave 5-phenyl-4,5-dihydroisoxazole (111) as a yellow oil (0.054 g, 35%); R_f (diethyl ether-light petroleum, 1:1, v/v) 0.37; δ_H(250 MHz; $CDCl_3$; Me_4Si) 2.98 (1 H, ddd, *J* 1.5, 8.2, 17.8, 4-H), 3.44 (1 H, ddd, *J* 1.5, 11.1, 17.8, 4-H), 5.52 (1 H, dd, *J* 8.2, 11.1, 5-H), 7.20 (1 H, br t, 3-H), 7.27-7.40 (5 H, aromatic); δ_C(63 MHz; $CDCl_3$; Me_4Si) 43.7 (CH_2), 79.9 (CH), 125.7 (CHx2), 128.1 (CH), 128.7 (CHx2), 140.9 (C), 145.5 (CH); m/z (EI^+) 147 (M^+, 16%), 104 (60), 77 ($C_6H_5^+$, 18), 51 (100); (Found M^+, 147.0684. C_9H_9NO requires M, 147.0684).

3,5-Diphenyl-4,5-dihydroisoxazole (138)[63]

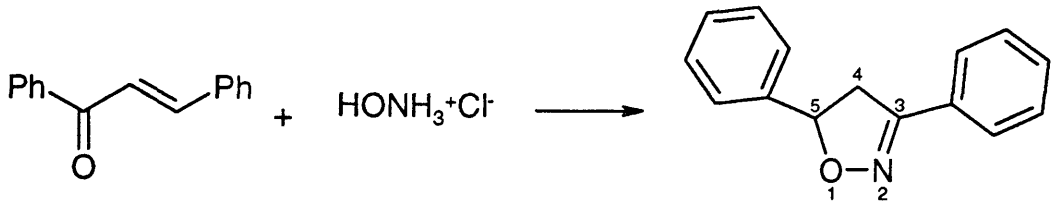


(139) (138)

Racemic *trans*-1,2-diphenylcyclopropane (139) (0.058 g, 0.3 mmol) was dissolved in acetonitrile (40 cm^3) and nitrogen bubbled through the stirred solution for 20 min. The temperature of the system was raised to 25°C and nitric oxide bubbled through the solution for 10 sec. at intervals for 5h. The system was sealed under NO at room temperature overnight. After bubbling with nitrogen for one minute, the system was heated to 30°C and NO bubbled for 10 sec. at intervals for 5 hours. The solvent was removed under reduced pressure. Flash column chromatography of the residue with diethyl ether-hexane (1:3, v/v) as eluant gave 3,5-diphenyl-4,5-dihydroisoxazole (138) as a pale yellow oil (0.01 g, 15%); R_f (diethyl ether-hexane, 1:1, v/v) 0.60; ν_{max} (CH_2Cl_2)/cm^{-1} 3040m, 2920m, 1735m, 1675m, 1640s, 1600m, 1530m, 1495m, 1450s, 1355s, 1320m, 1255s, 1230m, 1040m, 890s, 855s, 690m; δ_H(250 MHz; $CDCl_3$; Me_4Si) 3.35 and 3.79 (2 H, A & B of ABX system, J_{AX} 8.5, J_{BX} 11.0, J_{AB} 16.7, 4-H), 5.74 (1 H, dd, X of ABX system, J_{AX} 8.5, J_{BX} 11.0, 5-H), 7.28-7.75 (10 H + 6 H aromatic impurities, aromatic); δ_C(101 MHz; $CDCl_3$; Me_4Si) 43.6 (CH_2), 83.0 (CH), aromatic: 126.3, 127.2, 128.6, 129.2, 129.2, 129.9, 130.5; 141.4(C), 156.5(C), (impurities present, other peaks observed); m/z (EI^+) 223 (M^+,

53%), 115 (18), 105 (100), 91 (16), 77($C_6H_5^+$, 55), 51 (19); (Found M^+, 223.0997. $C_{15}H_{13}NO$ requires M, 223.0998).

3,5-Diphenyl-4,5-dihydroisoxazole (138)[81Note1]



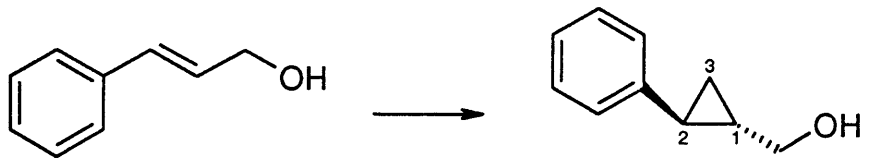
(141) (142) (138)

A solution of *trans*-chalcone (141) (6.02 g, 28.9 mmol), hydroxylamine hydrochloride (142) (4.47 g, 64.2 mmol), and potassium hydroxide (2.37 g, 42.2 mmol) in ethanol (30 cm^3) was heated under reflux for 3 hours. The KCl was filtered off, and the solvent removed under reduced pressure. The residue was dissolved in dichloromethane, poured into water and extracted with dichloromethane (3 x 30 cm^3). The combined dichloromethane layer was washed with water and dried ($MgSO_4$), the solvent removed under reduced pressure. Recrystallisation from ethanol afforded 3,5-diphenyl-4,5-dihydroisoxazole (138) (0.45 g, 7%) as white solid, m.p. 73-74°C; ν_{max} (CH_2Cl_2)/cm^{-1} 3050m, 2960w, 1600m, 1570w, 1500m, 1450m,1430w, 1360s, 1310w, 1260m br, 1095m, 1080m, 1010m br, 900s, 860m, 810m, 770-700m, 690m, 670m; δ_H(250 MHz; $CDCl_3$; Me_4Si) 3.33 and 3.77 (2 H, A and B of ABX system, J_{AX} 8.5, J_{BX} 11.0, J_{AB} 16.7, 4-H), 5.73 (1 H, dd, X of ABX system, J_{AX} 8.5, J_{BX} 11.0, 5-H), 7.30-7.43 (8 H, aromatic), 7.65-7.72 (2 H, aromatic); δ_C(63 MHz; $CDCl_3$; Me_4Si) 43.1 (CH_2), 82.5 (CH), 125.8 (CHx2), 126.7 (CHx2), 128.2 (CH), 128.7

(CHx2), 128.7 (CHx2), 129.5 (C), 130.1 (CH), 140.9 (C), 156.1 (C); m/z (EI^+) 223 (M^+, 100%), 193 (14), 115 (19), 104 (86), 77 ($C_6H_5^+$, 20), 51(8); (Found M^+, 223.0997. $C_{15}H_{13}NO$ requires M, 223.0997).

Note 1 : Made according to the method of Auwers and Muller.

trans-(2-Phenylcyclopropyl)methanol (143)[108]

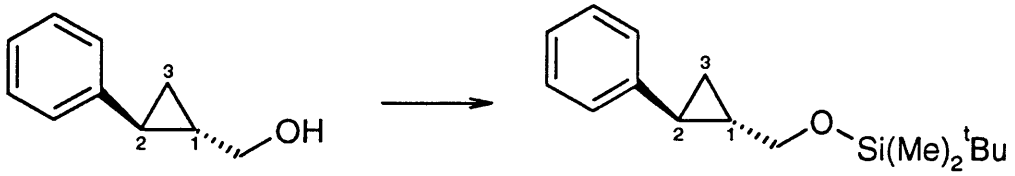


(144) (143)

Cinnamyl alcohol (144) (1.793 g, 13.4 mmol) was dissolved in dichloromethane (50 cm^3) under a nitrogen atmosphere, and cooled to -18°C. Diethyl zinc in hexane (66 cm^3, 5 mol equiv) was added slowly, and the reaction stirred for 30 minutes. Diiodomethane (11 cm^3) was added dropwise, and the reaction mixture stirred for 2 hours. The temperature was allowed to rise to 0°C and the reaction stirred for a further 2 hours. Saturated ammonium chloride solution (50 cm^3) was added to the reaction mixture and the product extracted into diethyl ether (3 x 30 cm^3), washed with brine, dried ($MgSO_4$), and the solvent removed under reduced pressure. Flash column chromatography of the residue with diethyl ether-light petroleum (1:1, v/v) as eluant gave (143) as a yellow oil (1.78 g, 90%); R_f (diethyl ether-light petroleum ether, 1:1, v/v) 0.18; ν_{max} (film)/cm^{-1} 3360brs(OH), 3090m, 3000m, 2930m, 1610m, 1500m, 1460m, 1250w, 1180w, 1090m, 1030s, 1020s, 930w, 880w, 740m, 700s; δ_H(250 MHz;

$CDCl_3$; Me_4Si) 0.91 (2 H, app. ddd, *J* 5.0, 10.0, 13.1 with other coupling, non 1st order, C*H*$_2$ cyclopropane, 3-H), 1.41 (1 H, m, *J* 6.6, 1-H), 1.79 (1 H, app. dt broad, *J* 5.0, 8.5, 2-H), 2.06 (1 H, s, -O*H*), 3.57 (2 H, d, *J* 6.6, C*H*$_2$OH), 7.03-7.27 (5 H, aromatic); δ_C(63 MHz; $CDCl_3$; Me_4Si) 14.3 (CH_2), 21.7 (CH), 25.7 (CH), 66.8 (CH_2), 126.1 (CH), 126.3 (CHx2), 128.8 (CHx2), 142.9 (C); m/z (EI^+) 148 (M^+, 29%), 130 (M^+-H_2O, 22), 117 (M^+-CH_2OH, 100), 104 (42), 91 (34), 78 ($C_6H_6^{+\cdot}$, 11), 77 ($C_6H_5^+$, 11); (Found M^+, 148.0889. $C_{10}H_{12}O$ requires M, 148.0888).

<u>*trans-O-tert*-Butyldimethylsilyl-(2-phenylcyclopropyl)methanol (145)</u>

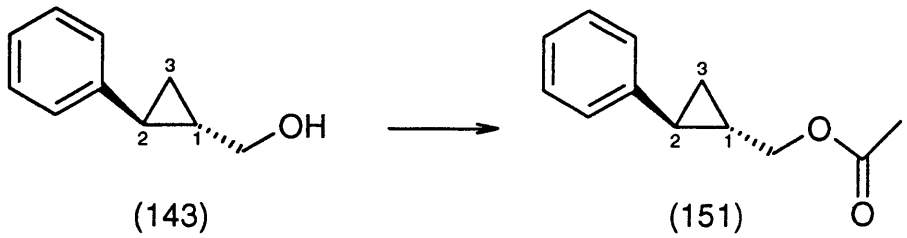


(143) (145)

tert-Butyl trimethysilyltriflate (0.3 cm^3, 1 equiv.) was added dropwise to a stirred solution of (143) (0.182 g,1.2 mmol) and lutidine (0.3 cm^3) in dichloromethane (3 cm^3) at room temperature under an atomosphere of nitrogen. After two hours dichloromethane (10 cm^3) was added, the mixture was poured into water and extracted with dichloromethane (3 x 20 cm^3). The combined dichloromethane layer was washed with water and dried ($MgSO_4$), and the solvent removed under reduced pressure. Flash column chromatography of the residue with diethyl ether-light petroleum (1:1, v/v) as eluant gave *trans-O-tert*-butyldimethylsilyl-(2-

phenylcyclopropyl)methanol (145) as a yellow oil (0.055 g, 17%); R_f (diethyl ether-light petroleum ether, 1:1, v/v) 0.76; δ_H(250 MHz; $CDCl_3$; Me_4Si) 0.04 (6H, s, $(CH_3)_2$-Si), 0.89 (9 H, s, C-$(CH_3)_3$), 0.83-0.95 (2 H, overlapping multiplet, CH_2 cyclopropane), 1.33 (1 H, m, 1-H), 1.77 (1 H, m, 2-H), 3.59 (1 H, dd, *J* 5.9, 10.7, *H*C(H)-O-), 3.69 (1 H, dd, *J* 5.6, 10.7, HC(*H*)-O-), 7.02-7.36 (5 H, aromatic); δ_C(63 MHz; $CDCl_3$; Me_4Si) –7.2 (CH_3), 13.6 (CH_2), 18.4 (C), 20.7 (CH), 25.2 (CH), 26.0 (CH_3x3), 65.8 (CH_2), 125.3 (CH), 125.9 (CHx2), 128.2 (CHX2, 143.1 (C);

<u>*trans*-(2-Phenylcyclopropyl)methyl acetate (151)</u>[109]

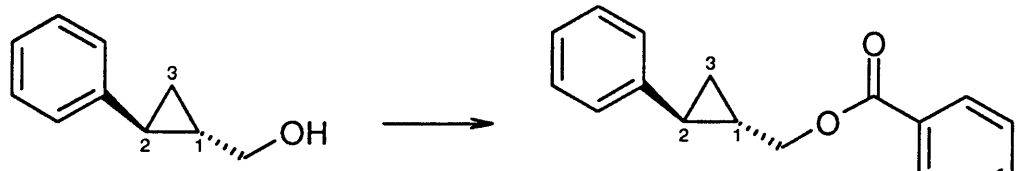


(143) (151)

Acetyl chloride (146) (3 cm^3) was added dropwise to a stirred, ice cooled solution of (143) (0.122 g, 0.8 mmol) and pyridine (2.5 cm^3). After stirring for 3 hours the reaction mixture was poured into water and extracted with diethyl ether (3 x 20 cm^3). The combined ether layer was washed with HCl (2M, 20 cm^3), aqueous sodium bicarbonate (5%wv, 20 cm^3), and then with water (20 cm^3), dried ($MgSO_4$), and the solvent was removed under reduced pressure to give the crude product. Flash chromatography of the residue with diethyl ether-light petroleum (1:1, v/v) as eluant gave *trans*-(2-phenylcyclopropyl)methyl acetate (151) as a colourless oil (0.125 g, 80%);

R_f (diethyl ether-light petroleum, 1:1, v/v) 0.55; δ_H(250 MHz; $CDCl_3$; Me_4Si) 0.97 (2 H, app. ddd, with other coupling, *J* 5.3, 10.6, 13.3, non 1st order, C*H*$_2$ cyclopropane), 1.46 (1 H, m, 1-H), 1.87 (1 H, dt, *J* 5.3, 8.5, 2-H), 1.97(3 H, s, -CC*H*$_3$), 4.01 (1 H, dd, *J* 7.1, 11.4, -C*H*$_2$O-), 4.07 (1 H, dd, *J* 5.0, 11.5, -C*H*$_2$O-), 7.02-7.28 (5 H, aromatic); δ_C(63 MHz; $CDCl_3$; Me_4Si) 14.4 (CH_2), 21.5 (CH), 21.9 (CH), 22.3 (CH_3), 68.4 (CH_2), 126.2 (CH), 126.4 (CHx2), 128.8 (CHx2), 142.4 (C), 171.6 (C); m/z (EI^+) 190 (M^+, 13%), 149 (14), 130 (M^+-CH_3CO_2H, 100), 115 (53), 104 (25), 91 (41), 77 ($C_6H_5^+$, 13), 65 (10), 51 (11); (Found M^+,190.0993. $C_{12}H_{14}O_2$ requires M, 190.0993).

<u>*trans*-(2-Phenylcyclopropyl)methyl benzoate (152)</u>[110]

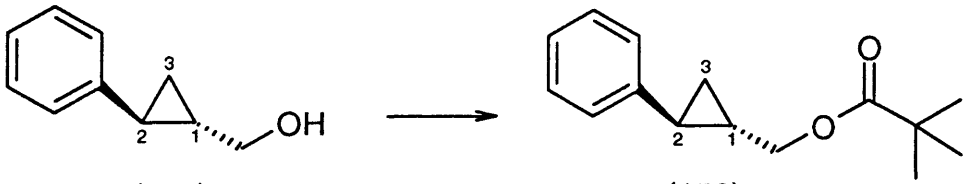


(143) (152)

Benzoyl chloride (147) (0.3 cm^3, 2 equiv.) was added dropwise to a stirred, ice-cooled solution of (143) (0.209 g, 1.4 mmol) in pyridine (3.5 cm^3). After two hours the reaction mixture was poured into water and extracted with ether (3 x 20 cm^3). The combined ether layer was washed with 2M HCl (20 cm^3), aqueous socium carbonate (5% w/v, 20 cm^3) and then water (20 cm^3), dried ($MgSO_4$), and the ether removed under reduced pressure. Flash column chromatography of the residue with diethyl ether-light petroleum (1:2, v/v) as eluant gave *trans*-(2-phenylcyclopropyl)methyl

benzoate (152) as a yellow oil (0.283 g, 78%); R_f (diethyl ether-light petroleum, 1:2, v/v) 0.54; δ_H(250 MHz; $CDCl_3$; Me_4Si)1.02 (2 H, t, J = 6.9, CH_2 cyclopropane), 1.57 (1 H, m , -C*H*-CH_2, cyclopropane), 1.95 (1 H, m, C*H*-Ph, cyclopropane), 4.26 (1 H, dd, *J* 7.0, 11.5, -C*H*$_2$-O-), 4.31 (1 H, dd, *J* 6.8, 11.5, -C*H*$_2$-O-), 7.03-7.27 (5 H, aromatic), 7.34-7.53 (3 H, aromatic), 8.03-8.09 (2 H, aromatic); δ_C(63 MHz; $CDCl_3$; Me_4Si) 14.3 (CH_2), 21.9 (CH), 22.3 (CH), 68.8 (CH_2), 126.3 (CH), 126.5 (CHx2), 128.8 (CHx4), 130.1 (CHx2), 130.8 (C), 133.3 (CH), 142.4 (C), 167.1 (C); m/z (EI^+) 252 (M^+, 23%), 130 (67), 115 (20), 105 (100), 91 (16), 77 (36), 51 (12); (Found M^+, 252.1150. $C_{17}H_{16}O_2$ requires M, 252.1150).

<u>*trans*-(2-Phenylcyclopropyl)methyl 2,2-dimethylpropanoate (153)</u>[111]

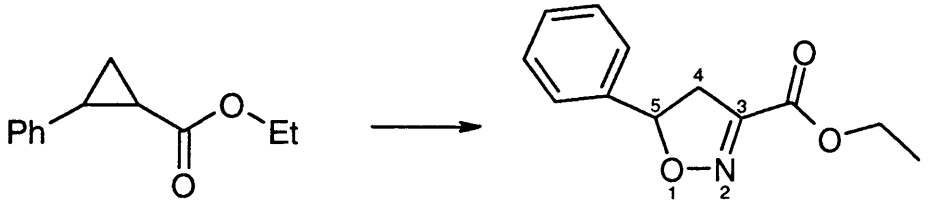


(143) (153)

As for the preparation of (151), trimethyl acetyl chloride (149)(0.2 cm^3) was added dropwise to a stirred, ice-cold solution of (143) (0.16 g, 1.1 mmol) in pyridine (3 cm^3). Flash chromatography of the residue with diethyl ether-light petroleum (1:1, v/v) as eluant gave *trans*-(2-phenylcyclopropyl)methyl 2,2-dimethylpropanoate (153) as a yellow oil (0.110 g, 43%); R_f (diethyl ether-light petroleum, 1:1, v/v) 0.73; ν_{max} (film)/cm^{-1} 3060w, 2980s, 1730s(C=O), 1610m, 1500m, 1460m, 1400m, 1370w, 1288s, 1155s,

1100w, 1030m, 750m, 700s; δ_H(250 MHz; $CDCl_3$; Me_4Si) 0.97 (2 H, m, CH_2 cyclopropane), 1.21 (9 H, s, -C(CH_3)$_3$), 1.45 (1 H, m, 1-H), 1.89 (1 H, dt, *J* 4.8, 8.7, 2-H), 4.03 (1 H, dd, *J* 7.2, 11.5, -CH_2-O-), 4.10 (1 H, dd, *J* 6.8, 11.5, -CH_2-O-), 7.05-7.28 (5 H, aromatic); δ_C(63 MHz; $CDCl_3$; Me_4Si) 13.9 (CH_2), 21.9 (CH), 22.0 (CH), 27.6 (CH_3x3), 68.0 (CH_2), 126.2 (CH), 126.5 (CHx2), 128.7 (CHx2), 142.5 (C), 179.0 (C); m/z (EI$^+$) 232 (M^+, 10%), 130 (M^+-$(CH_3)_3CCO_2H$, 100), 115 (38), 104 (19), 91 (43), 77 ($C_6H_5^+$, 11), 57 ($(CH_3)_3C^+$, 91); (Found M^+, 232.1463. $C_{15}H_{20}O_2$ requires M, 232.1463).

3-Ethoxycarbonyl-5-phenyl-4,5-dihydroisoxazole (157)[82]

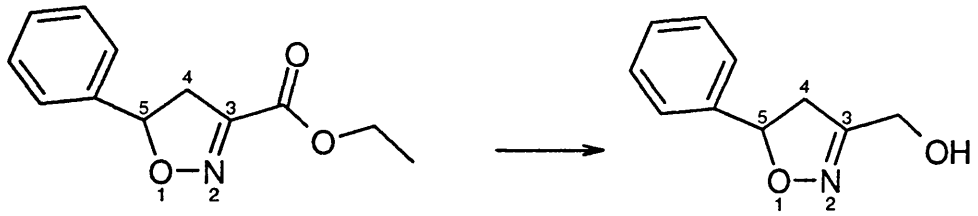


(156) (157)

Ethyl *trans*-2-phenyl cyclopropane carboxylate (156) (0.064 g, 0.3 mmol) was treated according to Method B (see preparation of (200)), the total heating time was 6 h. Flash column chromatography of the residue with diethyl ether-light petroleum (1:2, v/v) as eluant gave 3-ethoxycarbonyl-5-phenyl-4,5-dihydroisoxazole (157) as a yellow oil (0.017 g, 26%); R_f (diethyl ether-light petroleum, 1:2, v/v) 0.31; ν_{max} (CH_2Cl_2)/cm^{-1} 2980w, 1720s, 1590m, 1530w, 1380w, 1350m, 1340w, 1240s, 1120s, 1020m, 930s; δ_H(250 MHz; $CDCl_3$; Me_4Si) 1.38 (3 H, t, *J* 7.3, OCH_2CH_3), 3.22 and 3.64 (2 H, A & B of ABX system, J_{AX} 8.8, J_{BX} 11.6, J_{AB} = 17.8, 4-H), 4.37 (2

H, q, *J* 7.3, OCH_2CH_3), 5.79 (1 H, dd, X of ABX system, *J* 8.8, 11.6, 5-H), 7.31-7.43 (5 H, aromatic); δ_C(63 MHz; $CDCl_3$; Me_4Si) 14.5 (CH_3), 41.9 (CH_2), 62.6 (CH_2), 85.4 (CH), 126.3 (CHx2), 129.1 (CH), 129.3 (CHx2), 139.9 (C), 151.5 (C), 161.0 (C); m/z (EI^+) 219 (M^+, 55%), 190 (M^+-Et, 11), 174 (M^+-OEt, 11), 146 (M^+-CO_2Et, 20), 128 (40), 115 (35), 104 (100), 91 (13), 77 (20); (Found M^+, 219.0895. $C_{12}H_{13}NO_3$ requires M, 219.0896).

3-Hydroxymethyl-5-phenyl-4,5-dihydroisoxazole (157)1a-red)[85Note 1]



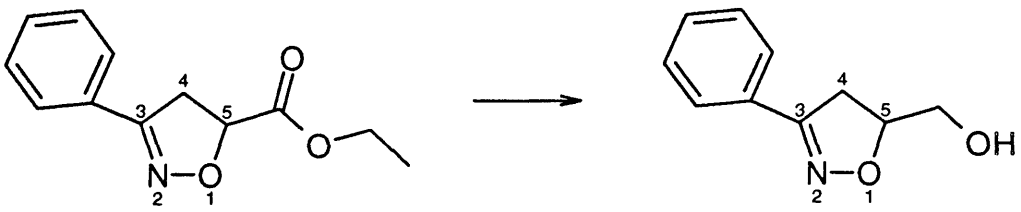
(167) ((157)1a-red)

A solution of $NaBH_4$ (0.23 g, 6.1 mmol) in ethanol (2.5 cm^3) was added to a solution of (167) (0.119 g, 0.5 mmol) in ethanol (2.5 cm^3) and the reaction stirred at room temperature for 3 hours. The ethanol was removed under reduced pressure. Flash column chromatography of the residue with diethyl ether as eluant gave 3-hydroxymethyl-5-phenyl-4,5-dihydroisoxazole (157)1a-red) (0.038 g, 39%) as a white solid, m.p. 68.5-69°C (crude); R_f (diethyl ether) 0.59; ν_{max} (CH_2Cl_2)/cm^{-1} 3600m, 3400br m, 2920m, 2880w, 1610w, 1500m, 1430m, 1330s, 1050s, 1030s, 930m, 880s, 670w; δ_H(250 MHz; $CDCl_3$; Me_4Si) 2.81 (1 H, br.s, -O*H*), 3.02 and 3.47 (2 H, A & B of ABX system, J_{AX} 8.4, J_{BX} 11.0, J_{AB} 17.3, 4-H), 4.42 (2 H, s, CH_2-OH), 5.60 (1 H, dd, X of ABX system, J_{AX} 8.4, J_{BX} 11.0, 5-H),

7.29-7.37(5 H, aromatic); δ_C(63 MHz; $CDCl_3$; Me_4Si) 43.1 (CH_2), 58.1 (CH_2), 82.2 (CH), 125.8 (CHx2), 128.2 (CH), 128.7 (CHx2), 140.6 (C), 158.2 (C); m/z (EI^+) 177 (M^+, 17%), 104 ($C_6H_5C_2H_3^{+\bullet}$, 100), 91 (12), 77 ($C_6H_5^+$, 19), 71 (11); (Found M^+, 177.0790. $C_{10}H_{11}NO_2$ requires M, 177.0790).

Note 1 : Made according to the method of De Micheli, Wade et al.[85]

5-Hydroxymethyl-3-phenyl-4,5-dihydroisoxazole (157)1b-red[112]

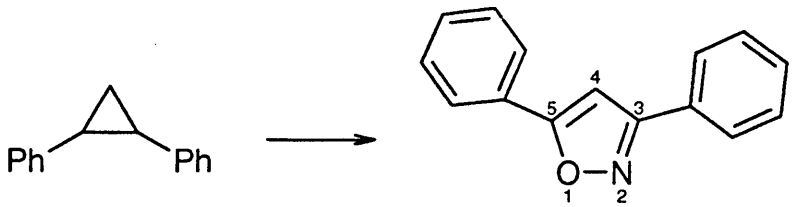


(170) ((157)1b-red)

As for compound ((157)1a-red), (170) (0.118 g, 0.5 mmol) and sodium borohydride (0.234 g, 6.2 mmol) were stirred in ethanol (5 cm^3) at room temperature for 3 hours. Flash column chromatography of the residue with diethyl ether as eluant gave 5-hydroxymethyl-3-phenyl-4,5-dihydroisoxazole ((157)1b-red) (0.056 g, 59%) as a white waxy solid, m.p. 74.5-77°C (crude); R_f (diethyl ether) 0.53; ν_{max} (CH_2Cl_2)/cm^{-1} 3500m, 3440br(OH), 2930m, 2880w, 1600w, 1500m, 1450s, 1435m, 1360s, 1335m, 1300w, 1210w, 1090s, 1080s, 1055s, 1040s, 955m, 920-890s, 810m, 670m; δ_H(250 MHz; $CDCl_3$; Me_4Si) 2.68 (1 H, br s, -OH), 3.26 (1 H, dd, *J* 8.1, 16.7, 4-H), 3.36 (1 H, dd, *J* 10.4, 16.7, 4-H), 3.68 (1 H, dd, *J* 4.6,

12.2, HC*H*-OH), 3.84 (1 H, dd, *J* 3.5, 12.2, *H*CH-OH), 4.84 (1 H, m, 5-H), 7.35-7.42 (3 H, aromatic), 7.60-7.68 (2 H, aromatic); δ_C(63 MHz; $CDCl_3$; Me_4Si) 36.8 (CH_2), 64.0 (CH_2), 81.7 (CH), 127.1 (CHx2), 129.1 (CHx2), 129.7 (C), 130.6 (CH), 157.5 (C); m/z (EI^+) 177 (M^+, 63%), 146 (M^+-CH_2OH, 75), 118 (100), 104 (12), 91 (26), 84 (20), 77 ($C_6H_5^+$, 74), 51 (20); (Found M^+, 177.0790. $C_{10}H_{11}NO_2$ requires M, 177.0790).

3,5-Diphenyl isoxazole (140)[113]

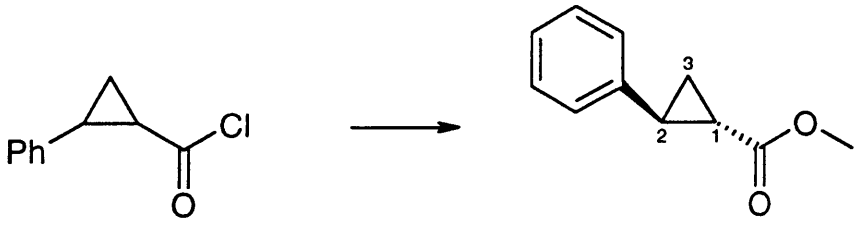


(139) (140)

Racemic *trans*-1,2-diphenylcyclopropane (139) (0.153 g, 0.8 mmol) was treated according to Method B (see preparation of (200)), the total heating time was 20.5 h. Flash column chromatography of the residue with diethyl ether-light petroleum (1:4, v/v) as eluant gave 3,5-diphenyl isoxazole (140) as a white solid (0.025 g, 14%); R_f (diethyl ether-light petroleum, 1:4, v/v) 0.36; ν_{max} (CH_2Cl_2)/cm^{-1} 3050m, 2960m, 2880w, 1725m, 1645s, 1575s, 1495m, 1465s, 1450s, 1400s, 1265s, 1075m, 950m, 855m, 770-680s; δ_H(250 MHz; $CDCl_3$; Me_4Si) 6.83 (1 H, s, 4-H), 7.30-7.95 (10 H + 4H aromatic impurities, aromatic); δ_C(63 MHz; $CDCl_3$; Me_4Si) 97.5 (CH), 125.9 (CHx2), 126.8 (CHx2), 127.5 (C), 128.9 (CHx2), 129.0 (CHx2), 129.2 (C), 130.0 (CH), 130.2 (CH), 163.0 (C), 170.4 (C), impurities present, other peaks observed; m/z (EI^+) 221 (M^+, 85%), 144

(15), 105 (100), 77($C_6H_5^+$, 35); (Found M^+, 221.0841. $C_{15}H_{11}NO$ requires M, 221.0841).

Methyl *trans*-2-phenyl cyclopropyl carboxylate(159)[114]

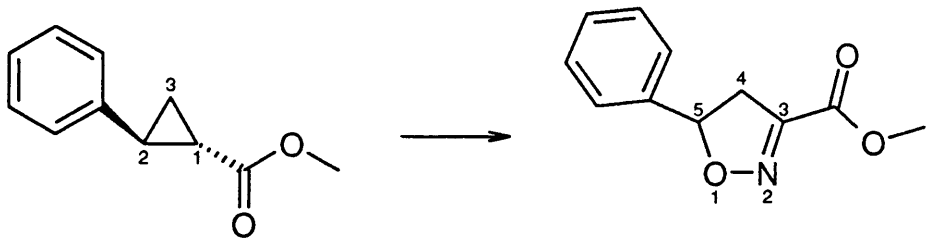


(158) (159)

trans-2-Phenyl-1-cyclopropane carbonyl chloride(158) (0.269 g, 1.5 mmol) was stirred with methanol (0.3 cm^3) in pyridine (2 cm^3) for 1.5 hours at room temperature. The solvent was removed under reduced pressure. Flash chromatography of the residue with diethyl ether-light petroleum ether (1:2, v/v) as eluant gave methyl *trans*-2-phenyl cyclopropyl carboxylate (159) as a yellow oil (0.167 g, 64%); R_f (diethyl ether-light petroleum ether, 1:2, v/v) 0.66; ν_{max} (film)/cm^{-1} 3040w, 2960w, 1730s(C=O), 1610m, 1500m, 1440s, 1400s, 1340s, 1270m, 1200s, 1170s, 1080m, 1040m, 940w, 910m, 840w, 755s, 700s; δ_H(250 MHz; $CDCl_3$; Me_4Si) 1.29 (1 H, ddd, *J* 4.2,6.3, 8.0, 3-H), 1.58 (1 H, dt, *J* 4.5, 9.1, 3-H), 1.89 (1 H, m, 1-H), 2.52 (1 H, ddd, *J* 4.2, 6.3, 9.1, 2-H), 3.69 (3 H, s, -O*CH*$_3$), 7.05-7.28 (5 H, aromatic); δ_C(63 MHz; $CDCl_3$; Me_4Si) 17.4 (CH_2), 24.4 (CH), 26.7 (CH), 52.3 (CH_3), 126.6 (CHx2), 126.9 (CH), 128.9 (CHx2), 140.4 (C), 174.2 (C); m/z (EI^+) 176 (M^+, 30%), 144 (M^+-MeOH,

22), 117 (M^+-CO_2Me, 59), 91 (21), 77 ($C_6H_5^+$, 9), 58 (11), 51 (100); (Found M^+, 176.0838. $C_{11}H_{12}O_2$ requires M, 176.0837).

3-Methoxycarbonyl-5-phenyl-4,5-dihydroisoxazole (163)[115]

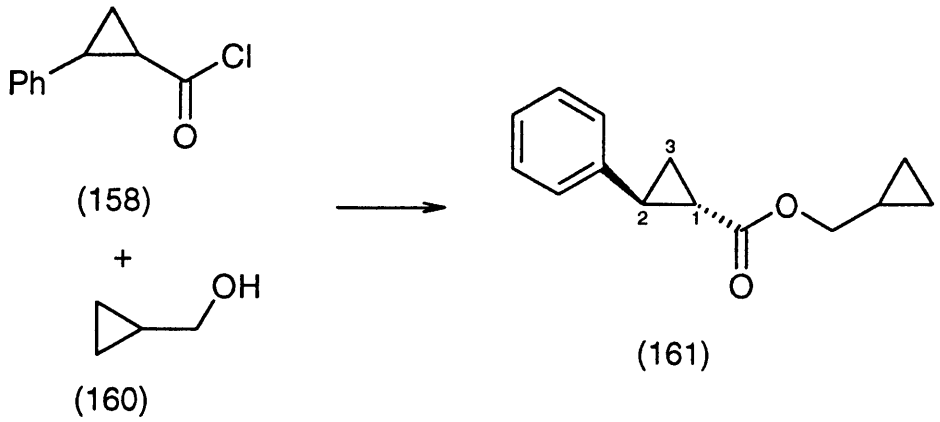


(159) (163)

Methyl *trans*-2-phenyl cyclopropyl carboxylate (159) (0.043 g, 0.2 mmol) was treated according to Method B (see preparation of (200)), the total heating time was 4 h. Flash column chromatography of the residue with diethyl ether-light petroleum (1:2, v/v) as eluant gave 3-methoxycarbonyl-5-phenyl-4,5-dihydroisoxazole (163) as a yellow oil (2 mg, 4%); R_f (diethyl ether-light petroleum, 1:3, v/v) 0.12; ν_{max} (CH_2Cl_2)/cm^{-1} 3690w, 3060w, 2960m, 2920m, 1730m(C=O), 1590w, 1460w, 1410w, 1350w, 1250m, 1200w, 1100s, 1010s, 870w, 810s, 695m; δ_H(250 MHz; $CDCl_3$; Me_4Si) 3.23 and 3.64 (2 H, A&B of ABX system, J_{AX} 8.9, J_{BX} 11.7,J_{AB} 17.8, 4-*H*), 3.91 (3 H, s, CO_2CH_3), 5.79 (1 H, dd, X of ABX system, J_{AX} 8.9, J_{BX} 11.7, 5-H), 7.30-7.43 (5 H, aromatic); δ_C(101 MHz; $CDCl_3$) 41.8 (CH_2), 53.2 (CH_3), 85.5 (CH), 126.3 (CHx2), 129.1 (CH), 129.3 (CHx2), 139.8 (C), 151.3 (C), 161.4 (C); m/z (EI^+) 205 (M^+, 36), 188 (12), 172 (16), 156 (14), 146 (M^+-CO_2Me, 36), 131 (60), 115 (50), 104 ($PhCHCH_2$, 100), 97 (25), 91

(41), 77 ($C_6H_5^+$, 59), 69 (34), 57 (40); (Found M^+, 205.0739. $C_{11}H_{11}NO_3$ requires M, 205.0739).

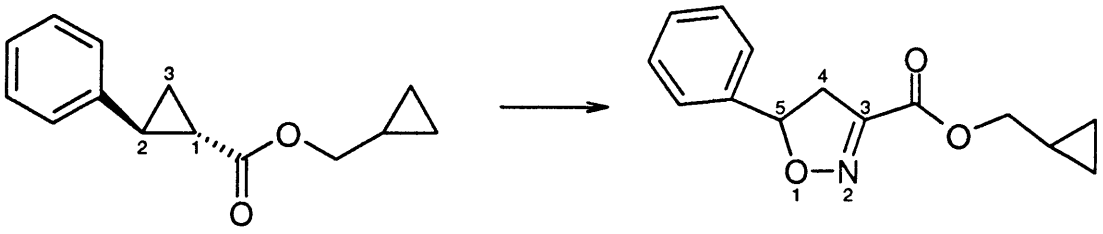
Cyclopropylmethyl *trans*-2-phenyl cyclopropyl carboxylate(161)



A solution of *trans*-2-phenyl-1-cyclopropane carbonyl chloride (158) (0.852 g, 4.7 mmol) and cyclopropylmethanol (160) (0.338 g, 4.7 mmol) in pyridine (4 cm^3) was stirred in an atomosphere of nitrogen for 1.5 hours and left to stand overnight. The reaction mixture was evaporated under reduced pressure. Flash column chromatography of the residue with diethyl ether-light petroleum (1:2, v/v) as eluant gave cyclopropylmethyl *trans*-2-phenyl cyclopropyl carboxylate (161) (0.655 g, 65%) as a white solid, m.p. 42-42.5°C (from light petroleum) (Found: C, 77.5; H, 7.3; $C_{14}H_{16}O_2$ requires C, 77.8; H, 7.4%); R_f (diethyl ether-light petroleum, 1:2, v/v) 0.59; ν_{max} (CH_2Cl_2)/cm^{-1} 3080-3010w, 1720s(C=O), 1610m, 1440m, 1390m, 1320m, 1290-1250m, 1190-1170s, 1080m, 980m, 860w; δ_H(250 MHz; $CDCl_3$; Me_4Si) 0.28 (2 H, m, 2 x CH cyclopropane), 0.57 (2 H, m, 2 x CH cyclopropane), 1.14 (1 H, m, CH_2-C*H* cyclopropane), 1.31 (1 H, ddd, *J*

4.6, 6.4, 8.1, 3-H), 1.60 (1 H, m, 3-H), 1.94 (1 H, m, 1-H), 2.52 (1 H, ddd, *J* 4.1, 6.4, 9.0, 2-H), 3.94 (2 H, d, *J* 7.2, -OCH_2-), 7.08-7.31 (5 H, aromatic); δ_C(63 MHz; $CDCl_3$; Me_4Si) 3.2 (CH_2), 9.8 (CH), 17.2 (CH_2), 24.2 (CH), 26.2 (CH), 69.6 (CH_2), 126.2 (CHx2), 126.5 (CH), 128.5 (CHx2), 140.2 (C), 173.5 (C); m/z (EI^+) 216 (M^+,5%), 145 (M^+-($C_3H_5CH_2O$), 30), 127 (21), 117 (M^+-($C_3H_5CH_2O_2C$), 89), 99 ($C_3H_5CH_2O_2C^+$, 35), 77 ($C_6H_5^+$, 8), 55 (100); (Found M^+, 216.1150. $C_{14}H_{16}O_2$ requires M, 216.1151).

3-Cyclopropylmethoxycarbonyl-5-phenyl-4,5-dihydroisoxazole (164)

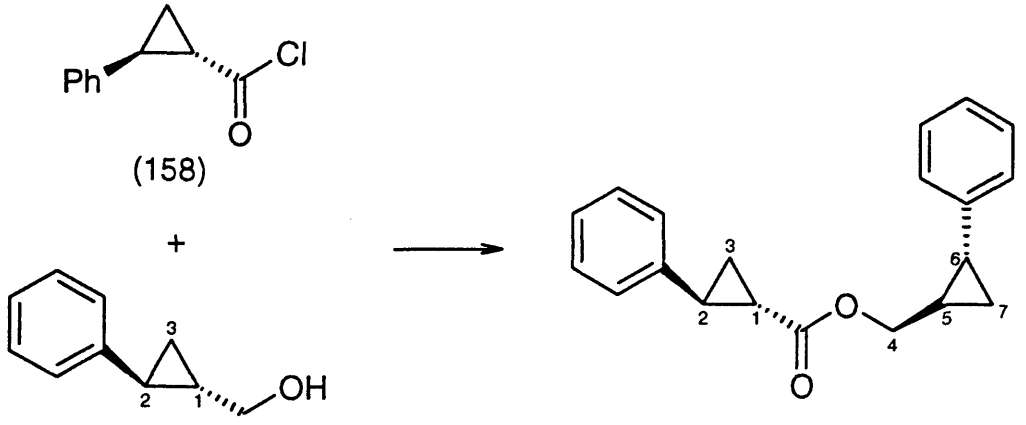


(161) (164)

The cyclopropane derivative (161) (0.080 g, 0.4 mmol) was treated according to Method B (see preparation of (200)), the total heating time was 12.5 h. Flash column chromatography of the residue with diethyl ether-light petroleum (1:5 column followed by 1:2 column, v/v) as eluant gave 3-cyclopropylmethoxycarbonyl-5-phenyl-4,5-dihydroisoxazole (164) as a yellow oil (4 mg); R_f (diethyl ether-light petroleum, 1:2, v/v) 0.32; impure sample - δ_H(250 MHz; $CDCl_3$; Me_4Si) 0.33 (2 H, m, 2 x H-C*H* cyclopropane), 0.61 (2 H, m, 2 x *H*-CH cyclopropane), 1.15 (1 H, m, CH_2-C*H* cyclopropane), 3.23 and 3.65 (2 H, A & B of ABX system, J_{AX} 8.5, J_{BX} 11.7, J_{AB} 17.5, 4-H), 4.13 (2 H, d, *J* 7.2, OCH_2-), 5.79 (1 H, dd, X of ABX

system, J_{AX} 8.5, J_{BX} 11.7, 5-H), 7.25-7.45 (5 H, aromatic); m/z (EI^+) 245 (M^+, 10%), 190 (14), 174 (M^+-$OCH_2C_3H_5$, 5), 146 (M^+-$CO_2CH_2C_3H_5$, 12), 135 (31), 115 (31), 104 (19), 91 (20), 77 ($C_6H_5^+$, 14), 55 (100); (Found M^+, 245.1052. $C_{14}H_{15}NO_3$ requires M, 245.1052).

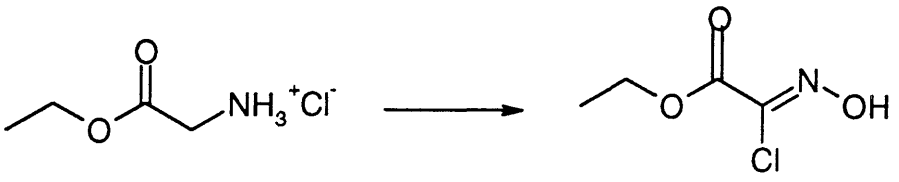
(2-Phenylcyclopropyl)methyl *trans*-2-phenyl cyclopropyl carboxylate (162)



(143) (0.201 g, 1.4 mmol) and trans-2-phenyl cyclopropane carbonyl chloride (158) (0.276 g, 1.5 mmol) were stirred in pyridine (2 cm^3) at room temperature for 25 h. The solvent was removed under reduced pressure. Flash column chromatography of the residue with diethyl ether-light petroleum (1:2, v/v) as eluant gave (2-phenylcyclopropyl)methyl *trans*-2-phenyl cyclopropyl carboxylate (162) as a colourless oil (0.314 g, 80%); R_f (diethyl ether-light petroleum, 1:1, v/v) 0.79; ν_{max} (film)/cm^{-1} 3060w, 3030m, 2950w, 1725s, 1610m, 1500m, 1410s, 1345s, 1265m, 1175s, 1035m, 940m, 760s, 700s; δ_H(250 MHz; $CDCl_3$; Me_4Si) 0.94 (2 H, app. ddd, non 1st order, *J* 5.2, 11.1, 13.3, 7-H), 1.26 (1 H, ddd, *J* 5.4, 6.6, 8.4, 5-H), 1.44 (1 H, m, 1-H), 1.59 (1 H, dt, *J* 4.8, 8.4, 6-H), 1.84 (1 H, dd, *J* 4.8,

9.0, 3-H), 1.92 (1 H, dd, *J* 4.8, 9.0, 3-H), 2.52 (1 H, m, 2-H), 4.06 (1 H, t, *J* 2.4, -OC*H*$_2$-), 4.08 (1 H, t, *J* 2.4, -OC*H*$_2$-), 7.01-7.25 (10 H, aromatic); δ_C(63 MHz; $CDCl_3$; Me_4Si) 14.4 (CH_2), 17.7 (CH_2), 21.9 (CH), 22.3 (CH), 24.7 (CH), 26.8 (CH), 68.7 (CH_2), 126.3 (CH), 126.5 (CHx2), 126.7 (CHx2), 127.0 (CH), 128.8 (CHx2), 129.0 (CHx2), 140.5 (C), 142.4 (C), 173.9 (C); m/z (EI^+) 292 (M^+, 46%), 162 (M^+-$C_{10}H_{10}$, 23), 145 (M^+-$PhC_3H_4CH_2O$, 43) 131 (M^+-$PhC_3H_4CO_2$, 100), 115 (39), 91 (51), 84 (23), 77 ($C_6H_5^+$,6); (Found M^+, 292.1464. $C_{20}H_{20}O_2$ requires M, 292.1463).

Ethyl chlorooximinoacetate (166)[83Note 1]



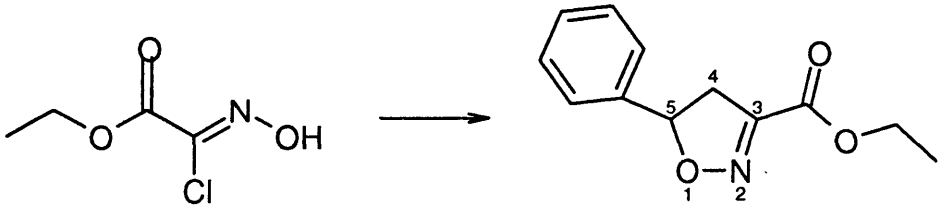
(165) (166)

HCl (conc., 11 cm^3) was added to a stirred, ice cooled solution of glycine ethyl ester hydrochloride (165) (11.996 g, 85.9 mmol) in water (20 cm^3). Salt was added to the water bath and sodium nitrite (0.18 g in 20 cm^3 water), HCl (conc., 10 cm^3), sodium nitrite (0.04g in 20 cm^3 water) were added dropwise, in sucession. The solution was left overnight at room temp. On cooling with dry ice, crystals formed which were collected, dissoved in hot benzene (2 cm^3), filtered, the benzene removed under reduced pressure, heated with light petroleum (b.p. 100-120°C; 4 cm^3) and left to stand overnight. The solution was evaporated under reduced pressure to give ethyl chlorooximinoacetate (166) (2.38 g, 18%) as a white solid, m.p. 75-79°C (from light petroleum b.p.100-120°C)(lit.m.p.

80°C); ν_{max} (CH_2Cl_2)/cm^{-1} 3660w, 3520m, 3340br m, 2990m, 1745s(C=O), 1605m, 1480m, 1380s, 1280-1260s, 1175w, 1070s, 1030s, 860m, 820m, 810m, 770-690m; δ_H(250 MHz; $CDCl_3$; Me_4Si) 1.39 (3 H, t, *J* 7.1, OCH_2CH_3), 4.42 (2 H, q, *J* 7.1, OCH_2CH_3), 10.36 (1 H, br s, N-O*H*); δ_C(63 MHz; $CDCl_3$; Me_4Si) 14.3 (CH_3), 64.3 (CH_2), 133.2 (C), 159.2 (C); m/z (EI^+) 153(M^+ Cl^{37}, 1%), 151 (M^+ Cl^{35}, 2), 134 (25), 123 (100), 106 (M^+ - OEt, 35), 78 (19), 70 (23), 62 (16); $C_4H_6NO_3Cl$ M^+ requires 151.0036, found 151.0036.

Note 1 : Made according to the method of Skinner.[83]

3-Ethoxycarbonyl-5-phenyl-4,5-dihydroisoxazole (167)[82 Note 1]

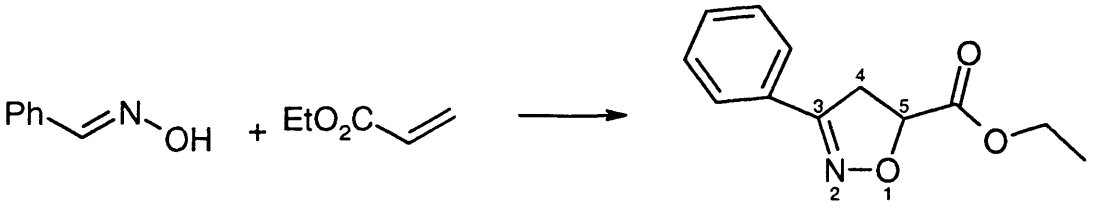


A solution of ethyl chlorooximinoacetate (1.909 g, 12.6 mmol) in diethyl ether (20 cm^3) was added over 30 min to a stirred solution of styrene (3.603 g, 34.6 mmol) and triethylamine (1.3 g) in diethyl ether (20 cm^3) at -5°C. After 24 hours at room temperature, the mixture was filtered and the filtrate evaporated under reduced pressure to yield a yellow oil. Kugelrohr distillation under reduced pressure (162°C, 110 N m^{-2}) gave 3-

ethoxycarbonyl-5-phenyl-4,5-dihydroisoxazole (167) as a yellow oil (0.989 g, 36%); ν_{max} (film)/cm^{-1} 3010w, 2980m, 1720vs, 1630w, 1590s, 1460m, 1380m, 1330m, 1250vs, 1130s, 1020m, 930s, 760s, 700s; δ_H(250 MHz; $CDCl_3$; Me_4Si) 1.38 (3 H, t, *J* 6.9 , OCH_2CH_3), 3.21 and 3.64 (2 H, B & A of ABX system, J_{AX} 8.9, J_{BX} 11.5, J_{AB} 17.8, 4-H), 4.36 (2 H, q, *J* 6.9, OCH_2CH_3), 5.78 (1 H, dd, X of ABX system, J_{AX} 8.9, J_{BX} 11.5, 5-H), 7.29-7.42 (5 H, aromatic); δ_C(63 MHz; $CDCl_3$; Me_4Si) 14.5 (CH_3), 41.8 (CH_2), 62.5 (CH_2), 85.3 (CH), 126.3 (CH x 2), 129.0 (CH), 129.3 (CH x 2), 140.0 (C), 151.6 (C), 161.0 (C); m/z (EI$^+$) 219 (M^+, 51%), 190 (M^+ - C_2H_5, 13), 174 (M^+ - C_2H_5O, 11), 156 (14), 146 (21), 128 (44), 115 (M^+ - $PhCHCH_2$, 32), 104 ($PhCHCH_2^{+\bullet}$, 100), 77 ($C_6H_5^+$, 27), 51 (C_4H_3, 13); (Found M^+, 219.0895. $C_{12}H_{13}NO_3$ requires M, 219.0896).

Note 1 : Made according to the method of King, Magnus and Rzepa.[82]

5-Ethoxycarbonyl-3-phenyl-4,5-dihydroisoxazole (170)[116]

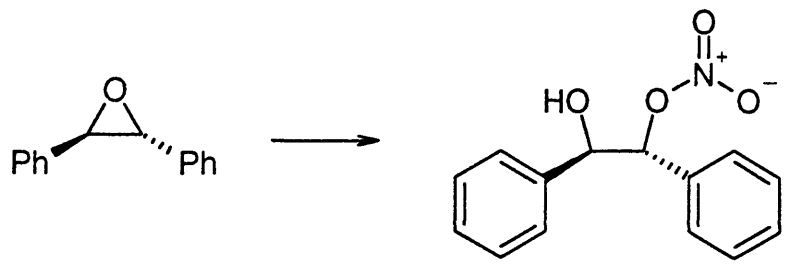


(168) (169) (170)

A solution of syn-benzaldehyde oxime (168) (9.83 g, 81.0 mmol), N-chlorosuccinimide (10.91 g, 81.7 mmol) and pyridine (10 drops) in chloroform (90 cm^3) was heated under reflux for 25 min. The solution was cooled to room temperature and a solution of ethyl acrylate (169) (8.08 g,

80.7 mmol), triethylamine (9.18 g, 90.7 mmol) in chloroform (20 cm^3) was added dropwise. The mixture was heated under reflux for 1 hr and then evaporated under reduced pressure. Flash column chromatography of the residue with diethyl ether-light petroleum (2:1, v/v) as eluant gave 5-ethoxycarbonyl-3-phenyl-4,5-dihydroisoxazole (170) as a yellow oil (2.52 g, 14%)(solidified on standing to a waxy solid, m.p. 39-43°C (crude); R_f (diethyl ether-light petroleum ether, 1:1, v/v) 0.50; ν_{max} (CH_2Cl_2)/cm^{-1} 3680w, 3050w, 2940m, 1740vs (C=O), 1605w, 1450m, 1375m, 1360s, 1260m br, 1210s, 1160m, 1030m, 895s, 870m, 850m, 690m br, 670w; δ_H(400 MHz; Acetone; Me_4Si) 1.29 (3 H, t, *J* 7.13, -OCH_2CH_3), 3.70 and 3.80 (2 H, A and B of ABX system, J_{AX} 7.0, J_{BX} 11.5, J_{AB} 17.0, 4-H), 4.23 (2 H, q, *J* 7.1, -OCH_2CH_3), 5.23 (1 H, dd, X of ABX system, *J* 7.0, 11.5, 5-H), 7.45-7.50 (3 H, aromatic), 7.72-7.77 (2 H, aromatic); δ_C(63 MHz; $CDCl_3$; Me_4Si) 14.4 (CH_3), 39.1 (CH_2), 62.2 (CH_2), 78.5 (CH), 127.2 (CHx2), 129.0 (C), 129.1 (CHx2), 130.8 (CH), 156.4 (C), 170.5 (C); m/z (EI$^+$) 219 (M^+, 16%), 146 (M^+-CO_2Et, 61), 118 (92), 103 (11), 91 (28), 77 ($C_6H_5^+$, 100), 51 (19); (Found M^+, 219.0895. $C_{12}H_{13}NO_3$ requires M, 219.0896).

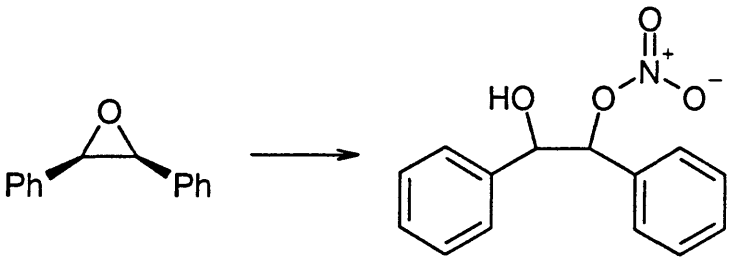
(*RS, RS*)-1-(*O*)-Nitro-1,2-diphenyl ethanediol (195a)[107]



(194t) (195a)

Racemic *trans*-stilbene oxide (194*t*) (0.333 g, 1.7 mmol) was treated according to Method B (see preparation of (200)), the total heating time was 6 h. Flash column chromatography of the residue with diethyl ether-light petroleum (1:8-1:0, v/v) as eluant gave (*RS, RS*)-1-(*O*)-nitro-1,2-diphenyl ethanediol (195a) as a white solid (0.260 g, 59%), m.p. 113-115.5°C (from light petroleum/diethyl ether); (Found: C, 64.9; H, 4.8; N, 5.5; $C_{14}H_{13}NO_4$ requires C, 64.9; H, 5.0; N, 5.4%); R_f (diethyl ether-light petroleum, 1:1, v/v) 0.61; ν_{max} (CH_2Cl_2)/cm^{-1} 3600m, 3050w, 2960w, 2900w, 1640vs, 1495w, 1455m, 1385w, 1265s, 1190m, 1075s, 1035s, 970m, 860s, 770-750w, 700w br; δ_H(250 MHz; $CDCl_3$; Me_4Si) 2.74 (1 H, s, -OH), 4.95 (1 H, d, *J* 8.2, C*H*-OH), 5.87 (1 H, d, *J* 8.2, CH-ONO_2), 7.06-7.14 (4 H, aromatic), 7.22-7.27 (6 H, aromatic); δ_C(63 MHz; $CDCl_3$; Me_4Si) 75.7 (CH), 88.9 (CH), 127.1 (CHx2), 127.3 (CHx2), 128.3 (CHx2), 128.4 (CHx2), 128.5 (CH), 129.1 (CH), 134.4 (C), 137.9 (C); m/z (FAB^+)NBA 260 (MH^+, 9%), 242 (18), 197 (M^+-ONO_2, 41), 180 (10), 167 (68); (Found MH^+, 260.0923. $C_{14}H_{14}NO_4$ requires M, 260.0922).

1-(*O*)-Nitro-1,2-diphenyl ethanediol (195)[107]

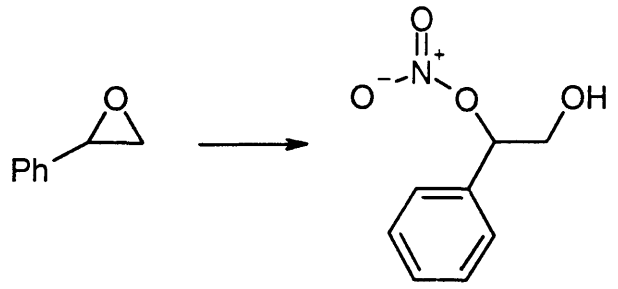


(194*c*) (195)

Cis-stilbene oxide (194*c*) (0.236 g, 1.2 mmol) was treated according to Method B (see preparation of (200)), the total heating time was 11.5 h. Flash column chromatography of the residue with diethyl ether-light petroleum (1:10-1:3, v/v) as eluant gave 1-(*O*)-nitro-1,2-diphenyl ethanediol (195) as a pale yellow oil (0.081 g, 26%, small impurities present. Further chromatography lead to a yield of 0.068 g, 22%); R_f (diethyl ether-light petroleum, 1:3, v/v) 0.20; ν_{max} (CH_2Cl_2)/cm^{-1} 3590m, 3050w, 2920w, 1640vs, 1500w, 1455m, 1310m, 1265s, 1190w, 1100-1000m, 860s, 810m, 695m; δ_H(250 MHz; $CDCl_3$; Me_4Si) diastereoisomer 1: 2.21 (1 H, d, *J* 3.8, -OH), 5.03 (1 H, dd, *J* 3.8, 6.0, C*H*-OH), 5.88 (1 H, d, *J* 6.0, CH-ONO_2). diastereoisomer 2: 2.75 (1 H, d, *J* 2.5, -OH), 4.93 (1 H, dd, *J* 2.5, 8.2, -C*H*-OH), 5.86 (1 H, d, *J* 8.2, -CH- ONO_2). diastereoisomer 1 + diastereoisomer 2: 7.06-7.37 (11 H (1 more than expected), aromatic); δ_C(63 MHz; $CDCl_3$; Me_4Si) diastereoisomer 1: 74.6 (CH), 87.3 (CH), aromatic CH signals – 126.9, 127.1, 127.7, 128.4, 128.5, 129.3, 134.0 (C), 138.6 (C). diastereoisomer 2: 75.7 (CH), 88.9 (CH), aromatic CH signals – 126.6, 127.3, 127.6, 128.4, 128.6, 129.1, 134.4 (C), 137.9 (C); m/z (Cl^+) 232 (11%), 214 (197+NH_3, 100), 197 (M^+-ONO_2, 45), 183 (19), 167 (69),

124 (13), 105 (48), 77 ($C_6H_5^+$, 9); (FAB^+)NBA (Found M^+-ONO_2, 197.0966. $C_{14}H_{13}O$ requires M, 197.0967).

1-(*O*)-Nitro-1-phenyl ethanediol (200)[106]



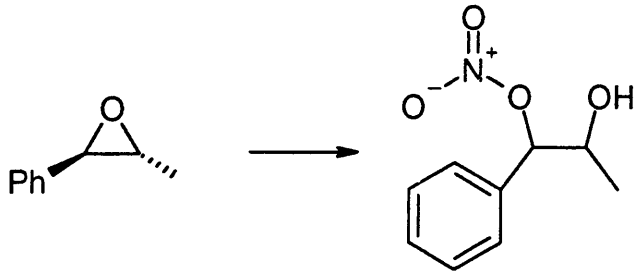
(192) (200)

Method B

Styrene oxide (192) (0.368 g, 3.1 mmol) was dissolved in acetonitrile (4 cm^3) in a Young's tube. Nitric oxide gas was bubbled into the cooled solution, the tube sealed, evacuated and refilled with nitric oxide. The stirred sealed tube was heated at 90°C and opened at intervals to follow the reaction by TLC, the bubbling, sealing and refilling repeated after each opening, before resuming heating. The total heating time was 8 h. The solvent was removed under reduced pressure. Flash column chromatography of the residue with diethyl ether-light petroleum (1:2, v/v) as eluant gave 1-(*O*)-nitro-1-phenyl ethanediol (200) as a yellow oil (0.209 g, 37%); R_f (diethyl ether-light petroleum, 1:2, v/v) 0.29; ν_{max} (film)/cm^{-1} 3570w, 3370m br, 3070w, 2940w, 1725w, 1630s, 1495w, 1455m, 1360w, 1275s, 1190w, 1075m, 1045m, 1030-1000m, 960w, 895m, 860s, 755m, 700s; δ_H(250 MHz; $CDCl_3$; Me_4Si) 2.56 (1 H, s, -OH), 3.82 (1 H, dd, *J* 3.9, 12.9, 2-H), 3.95 (1 H, dd, *J* 8.2, 12.9, 2-H), 5.92 (1 H, dd, *J* 3.9, 8.2, 1-H),

7.32-7.44 (5 H, aromatic); δ_C(63 MHz; $CDCl_3$; Me_4Si) 63.9 (CH_2), 86.0 (CH), 126.7 (CHx2), 129.0 (CHx2), 129.4 (CH), 134.6(C); m/z (EI^+) 183 (M^+, 1%), 121 (M^+-ONO_2, 18), 107 (100), 91 (14), 79 (86), 51 (65); (Found M^+, 183.0532. $C_8H_9NO_4$ requires M, 183.0531).

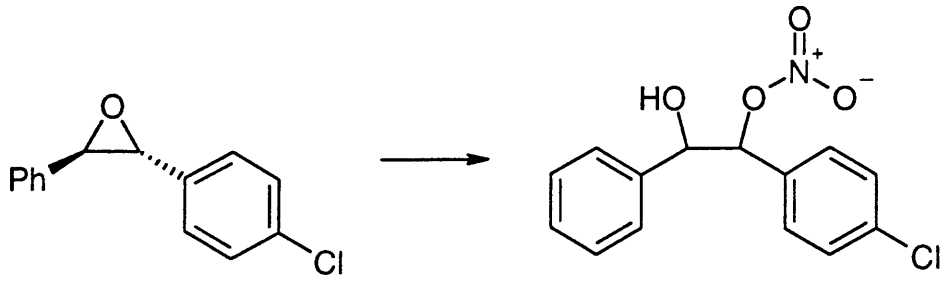
1-(*O*)-Nitro-1-phenyl propane-1,2-diol (201)



(199) (201)

(1R,2R)-(+)-1-phenyl propylene oxide (199) (0.375 g, 2.8 mmol) was treated according to Method B (see preparation of (200)), the total heating time was 17h. Flash column chromatography of the residue with diethyl ether-light petroleum (1:3, v/v) as eluant gave 1-(*O*)-nitro-1-phenyl propane-1,2-diol (201) as a yellow oil (0.165 g, 30%); R_f (diethyl ether-light petroleum, 1:3, v/v) 0.13; ν_{max} (film)/cm^{-1} 3580w, 3400m br, 2980w, 2940-2880w, 1730w, 1630s, 1500w, 1460m, 1380w, 1280s, 1150m, 1090m, 965m, 860s, 755m, 700s, 610s; δ_H(250 MHz; $CDCl_3$; Me_4Si) 1.09 (3 H, d, *J* 6.3, -CH_3), 2.34 (1 H, d, *J* 3.8, -OH), 4.14 (1 H, m, C*H*(OH)), 5.58 (1 H, d, *J* 7.9, -CH(ONO_2)), 7.32-7.44 (5 H, aromatic); δ_C(63 MHz; $CDCl_3$; Me_4Si) 18.8 (CH_3), 68.6 (CH), 89.9 (CH), 127.3 (CHx2), 128.9 (CHx2), 129.4 (CH), 135.1 (C); m/z (EI^+) 178 (2%), 135 (M^+-ONO_2, 11), 107 (100), 79 (63), 51(11); (Found M^+- ONO_2, 135.0810. $C_9H_{11}O$ requires M, 135.0810).

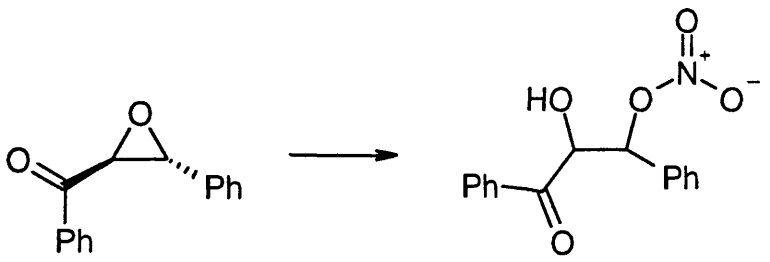
1-*O*-Nitro-1-(4-chlorophenyl)-2-phenyl ethanediol (204)



(202) (204)

Racemic *trans*-4-chlorostilbene oxide (202) (0.415 g, 1.8 mmol) was treated according to Method B (see preparation of (200)), the total heating time was 24.5 h. Flash column chromatography of the residue with diethyl ether-light petroleum (1:13-1:0, v/v) as eluant gave 1-*O*-nitro-1-(4-chlorophenyl)-2-phenyl ethanediol as a yellow oil (204) (0.228 g, 43%); R_f (diethyl ether-light petroleum, 1:1, v/v) 0.28; ν_{max} (film)/cm^{-1} 3400s br, 3040m, 2900m, 1720m, 1640vs, 1490s, 1280vs, 1200s, 1090s, 970s, 860s, 700s; δ_H(250 MHz; $CDCl_3$; Me_4Si) mixture of 2 diastereoisomers 3.00 and 3.07 (1 H, br s, -OH), 4.87 and 4.89 (1 H, d, *J* 8.2, -C*H*(OH)-), 5.79 and 5.84 (1 H, d, *J* 8.2, -CH(ONO_2)-), 6.95-7.40 (11 H (2 more than expected), aromatic); δ_C(63 MHz; $CDCl_3$; Me_4Si) diastereoisomer 1- 75.3 (CH), 89.2 (CH), aromatic CH signals: 127.8, 128.9, 129.1; 134.5 (C), 134.7 (C), 137.0 (C). diastereoisomer 2 - 75.9 (CH), 88.5 (CH), aromatic CH signals: 127.5, 129.0, 129.7; 133.5 (C), 135.4 (C), 138.2 (C); m/z (EI^+) 231 (M^+-ONO_2, 4%), 217 (21), 141 (88), 107 (100), 77 ($C_6H_5^+$, 87), 51 (19); (Found M^+-ONO_2, 231.0577. $C_{14}H_{12}OCl^{35}$ requires M, 231.0576).

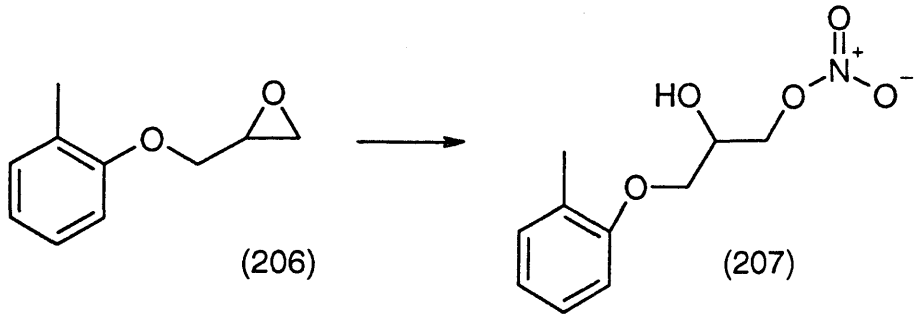
1-O-Nitro-2-benzoyl-1-phenyl ethanediol (205)



(203) (205)

Racemic *trans*-chalcone-α,β-epoxide (203) (0.406 g, 1.8 mmol) was treated according to Method B (see preparation of (200)), the total heating time was 28.5 h. Flash column chromatography of the residue with diethyl ether-light petroleum (1:3, v/v) as eluant gave 1-O-nitro-2-benzoyl-1-phenyl ethanediol (205) as a yellow oil (0.227 g, 44%. Small impurities present, further chromatography lead to 21% yield); R_f (diethyl ether-light petroleum, 1:3, v/v) 0.18; ν_{max} (film)/cm^{-1} 3460s br, 3060m, 2400w, 1690s, 1640s, 1600s, 1510m, 1450s, 1400m, 1280s br, 1120s, 980s, 850s, 760s, 695s; δ_H(250 MHz; $CDCl_3$; Me_4Si) 3.91 (1 H, d, *J* 7.2, -OH), 5.37 (1 H, dd, *J* 3.8, 7.2, -C*H*(OH)-), 6.08 (1 H, d, *J* 3.8, -CH(ONO_2)-), 7.29-7.92 (11 H, 1 more than expected, aromatic); δ_C(63 MHz; $CDCl_3$; Me_4Si) 74.3 (CH), 84.3 (CH), 127.1 (CHx2), 128.6 (CHx2), 128.8 (CHx2), 129.1 (CHx2), 129.4 (CH), 133.7 (C), 134.0 (C), 134.5 (CH), 197.5 (C); m/z (FAB^+)NBA 288 (MH^+, 12%), 154 (62), 136 (100); (Found MH^+, 288.0872. $C_{15}H_{14}NO_5$ requires M, 288.0871).

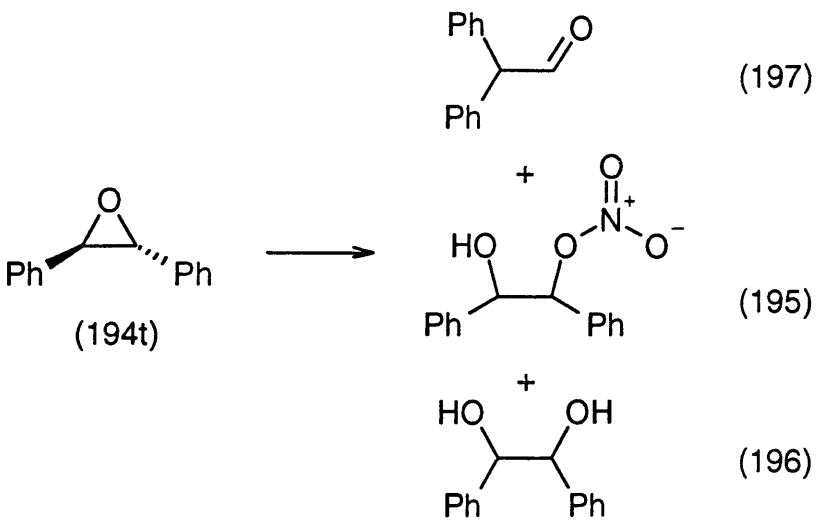
1-*O*-(2-Methylphenyl)-3-*O*-nitro-1,2,3-propanetriol (207)



(206) (207)

Glycidyl 2-methylphenyl ether (206) (0.575 g, 3.5 mmol) was treated according to Method B (see preparation of (200)), heating at 90°C for a total of 15 h, followed by similar treatment at 110°C for 8.5 h, 125°C for a total of 26 h. Flash column chromatography of the residue with diethyl ether-light petroleum (1:1, v/v) as eluant gave 1-*O*-(2-methylphenyl)-3-*O*-nitro-1,2,3-propanetriol (207) as a yellow oil (0.246 g, 31%, a further column produced a more pure sample, 0.154 g, 19%); R_f (diethyl ether-light petroleum, 1:1, v/v) 0.32; ν_{max} (CH_2Cl_2)/cm^{-1} 3600w, 3060w, 2920w, 1640vs, 1495s, 1460m, 1270s, 1240s, 1125m, 1050m, 1000m, 855s, 700w br; δ_H(250 MHz; $CDCl_3$; Me_4Si) 2.23 (3 H, s, -CH_3), 2.62 (1 H, d, *J* 6.0, -OH), 4.04 (1 H, dd, *J* 5.3, 9.5, OC*H*(H)-), 4.08 (1 H, dd, *J* 4.7, 9.5, O-CH(*H*)-), 4.33 (1 H, m, C*H*-OH), 4.64 (1 H, dd, *J* 6.3, 11.6, *H*-C(H)-ONO_2), 4.70 (1 H, dd, *J* 4.7, 11.6, H-C(*H*)-ONO_2), 6.78-6.94 (2 H, aromatic), 7.13-7.19 (2 H, aromatic); δ_C(63 MHz; $CDCl_3$; Me_4Si) 16.5 (CH_3), 67.7 (CH), 68.7 (CH_2), 73.7 (CH_2), 111.6 (CH), 121.8 (CH), 127.2 (C), 127.4 (CH), 131.4 (CH), 156.5 (C); m/z (EI^+) 227 (M^+,42%), 133 (32), 108 (100), 91 ($C_7H_7^+$, 36), 77 ($C_6H_5^+$, 18), 65 (28); (Found M^+, 227.0794. $C_{10}H_{13}NO_5$ requires M, 227.0793).

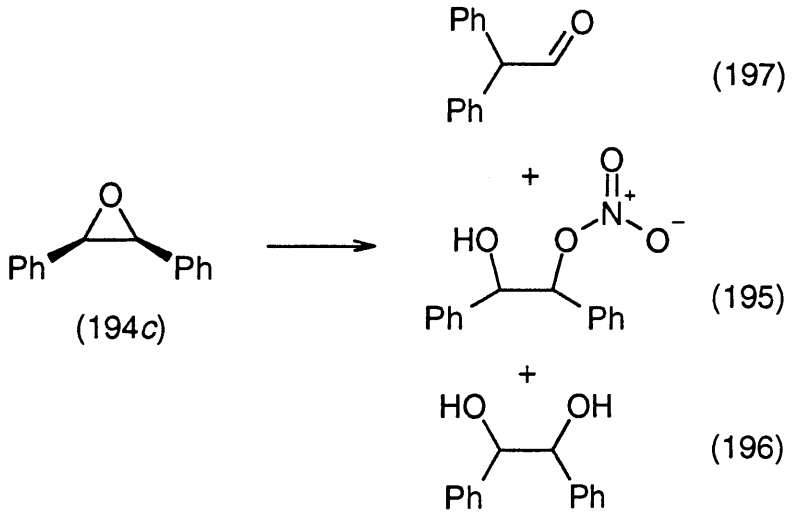
The Reaction of *trans*-Stilbene Oxide with Nitric Acid



Dilute HNO_3 (50 cm^3) was added dropwise to a stirred, ice-cooled solution of *trans*-stilbene oxide (0.528 g, 2.7 mmol) in acetonitrile (30 cm^3). The reaction mixture was extracted with dichloromethane (3 x 30 cm^3). The combined dichloromethane layer was washed with water and dried ($MgSO_4$), and the solvent removed under reduced pressure. Flash column chromatography of the residue with diethyl ether-light petroleum (1:3, v/v) as eluant gave diphenylacetaldehyde (197) as a yellow oil (0.060 g, 11%), 1-(*O*)-nitro-1,2-diphenyl ethanediol (195) as a white waxy solid (0.160 g, 23%), and hydrobenzoin (196) as a white solid (0.248 g, 43%); δ_H(250 MHz; $CDCl_3$; Me_4Si) diphenylacetaldehyde : 4.88 (1 H, d, *J* 2.1, $(Ph)_2$-C-*H*), 7.10-7.84 (10 H + 6 H aromatic impurity, aromatic), 9.94 (1 H, d, *J* 2.1, O=C-*H*); 1-(*O*)-nitro-1,2-diphenyl ethanediol (195) : mixture of diastereoisomers d1- 2.43 (1 H, br s, OH), 4.98 (1 H, d, *J* 5.7, C*H*-OH), d2- 2.96 (1 H, br s, OH), 4.87 (1 H, d, *J* 8.2, C*H*-OH), d1+d2- 5.85 (1 H, m,

C*H*-ONO_2), 7.02-7.36 (10 H, aromatic); hydrobenzoin : mixture of diastereoisomers d1 (m)- 2.79 (2 H, br s, OH x 2), 4.71 (2 H, s, C*H*-OH x 2), d2 ( )- 3.47 (2 H, br s, OH x 2), 4.54 (2 H, s, C*H*-OH x 2), d1+d2- 6.95-7.26 (10 H, aromatic);

The Reaction of *cis*-Stilbene Oxide with Nitric Acid



Dilute HNO_3 (30 cm^3) was added dropwise to a stirred, ice-cooled solution of *cis*-stilbene oxide (0.208 g, 1.1 mmol) in acetonitrile (30 cm^3). The reaction mixture was extracted with dichloromethane (3 x 30 cm^3). The combined dichloromethane layer was washed with water and dried ($MgSO_4$), and the solvent removed under reduced pressure. Flash column chromatography of the residue with diethyl ether-light petroleum (1:3-1:0, v/v) as eluant gave diphenylacetaldehyde (197) as a yellow oil (0.014 g, 6%), 1-(*O*)-nitro-1,2-diphenyl ethanediol (195) as a white solid (0.079 g, 31%), and hydrobenzoin (196) as a white solid (0.099 g, 42%); δ_H(250 MHz; $CDCl_3$; Me_4Si) diphenylacetaldehyde :(impure sample) 4.89 (1 H, d,

J 2.4, $(Ph)_2$-C*H*), 7.20-8.05 (10 H+20 H aromatic impurity, aromatic, 9.95 (1 H, d, *J* 2.4, O=C-*H*); 1-(*O*)-nitro-1,2-diphenyl ethanediol (195) :mixture of diastereoisomers d1- 2.31 (1 H, d, *J* 3.6, OH), 5.02 (1 H, dd, 3.6, 6.0, C*H*-OH), d2- 2.85 (1 H, d, *J* 2.3, OH), 4.92 (1 H, dd, *J* 2.3, 8.1, C*H*-OH), d1+d2- 5.86 (1 H, m, C*H*-ONO_2), 7.04-7.37 (10 H, aromatic); hydrobenzoin :mixture of diastereoisomers d1 (m)- 2.75 (2 H, s, OH x 2), 4.75 (2 H, s, C*H*-OH x 2), d2 ( )- 3.45 (2 H, s, OH x 2), 4.55 (2 H, s, C*H*-OH x 2), d1+d2- 6.95-7.30 (10 H, aromatic);

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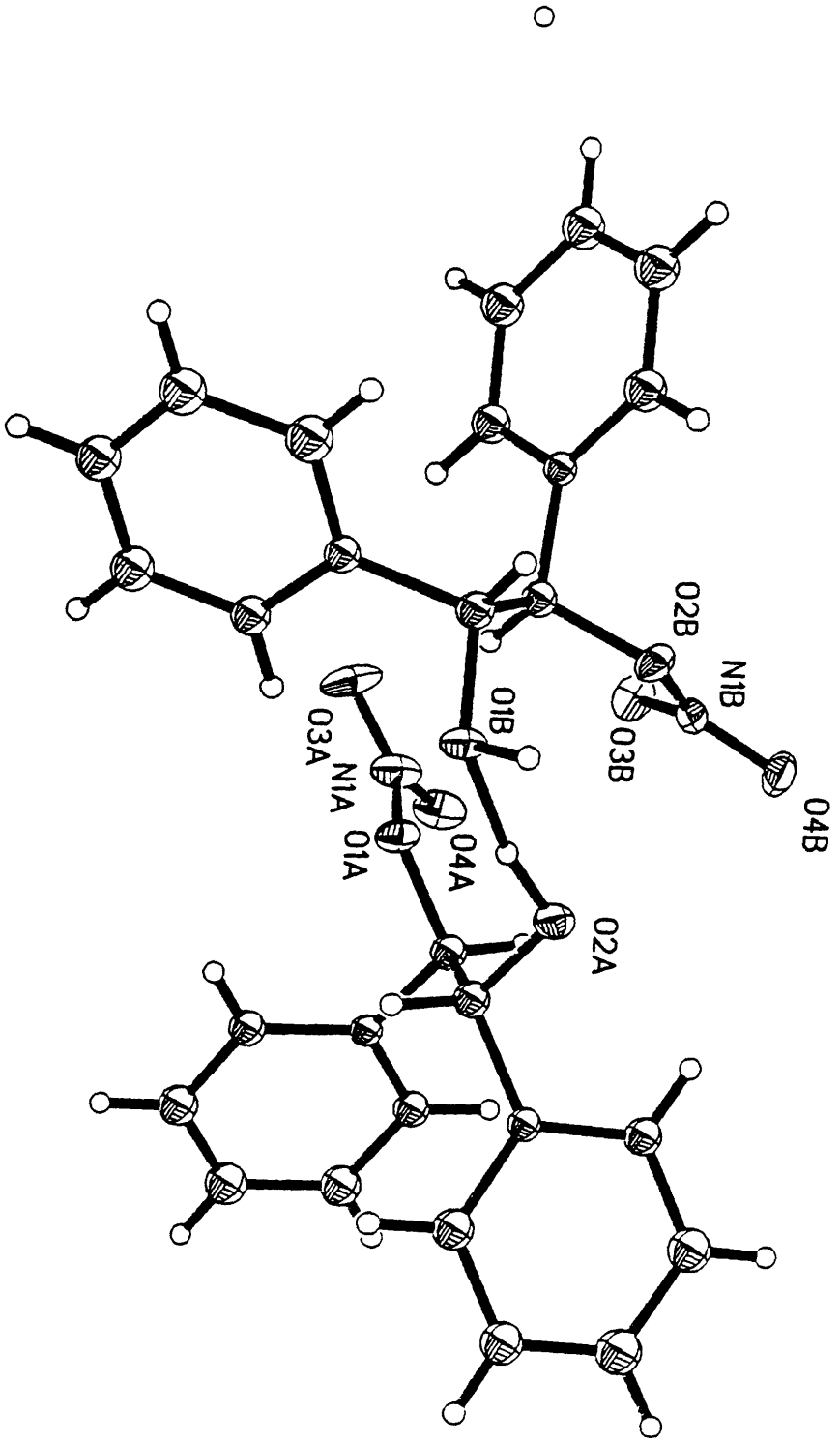
APPENDIX



X-Ray Structure of (*RS*, *RS*)-1-(*O*)-Nitro-1,2-diphenyl ethanediol (195a)

Table 1. Crystal data and structure refinement for 1.

Identification code	9751
Empirical formula	$C_{14}H_{13}NO_4$
Formula weight	259.25
Temperature	170(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 18.42(2) Å alpha = 90° b = 13.715(11) Å beta = 92.36(5)° c = 20.25(2) Å gamma = 90°
Volume, Z	5112(7) $Å^3$, 16
Density (calculated)	1.347 Mg/m^3
Absorption coefficient	0.100 mm^{-1}
F(000)	2176
Crystal size	0.60 x 0.22 x 0.18 mm
θ range for data collection	2.50 to 22.97°
Limiting indices	$0 \le h \le 19$, $-1 \le k \le 15$, $-21 \le l \le 21$
Reflections collected	7548
Independent reflections	6610 (R_{int} = 0.0603)
Absorption correction	Not applied
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6610 / 0 / 525
Goodness-of-fit on F^2	0.955
Final R indices [$I>2\sigma(I)$]	R1 = 0.0731, wR2 = 0.1299
R indices (all data)	R1 = 0.1772, wR2 = 0.1798
Largest diff. peak and hole	0.250 and -0.289 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 1. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1A)	7513(2)	7307(3)	1786(2)	32(1)
O(2A)	7368(2)	5308(3)	1891(2)	30(1)
O(3A)	6600(3)	4207(4)	2193(3)	57(2)
O(4A)	6818(2)	4305(4)	1150(3)	45(1)
N(1A)	6894(3)	4534(4)	1721(3)	37(2)
C(1A)	7756(3)	5698(5)	1334(3)	26(2)
C(2A)	8076(3)	6655(5)	1601(3)	26(2)
C(3A)	8339(3)	5018(5)	1122(3)	22(2)
C(4A)	8744(3)	4481(5)	1580(3)	29(2)
C(5A)	9329(4)	3931(5)	1393(4)	39(2)
C(6A)	9514(4)	3923(6)	738(4)	41(2)
C(7A)	9112(4)	4447(5)	274(3)	37(2)
C(8A)	8522(3)	4976(5)	467(3)	29(2)
C(9A)	8502(3)	7140(5)	1069(3)	24(2)
C(10A)	9257(4)	7084(5)	1084(3)	33(2)
C(11A)	9638(4)	7490(5)	582(4)	38(2)
C(12A)	9277(4)	7933(5)	60(4)	43(2)
C(13A)	8529(4)	7995(5)	35(3)	41(2)
C(14A)	8142(4)	7601(5)	540(3)	30(2)
O(1B)	7194(2)	7402(3)	3083(2)	30(1)
O(2B)	5992(2)	7459(3)	2263(2)	29(1)
O(3B)	5872(3)	6264(4)	1506(2)	37(1)
O(4B)	5964(3)	7790(4)	1220(2)	40(1)
N(1B)	5936(3)	7130(5)	1605(3)	30(2)
C(2B)	6038(3)	6676(5)	2756(3)	26(2)
C(1B)	6504(3)	7087(5)	3323(3)	25(2)
C(3B)	6633(3)	6313(5)	3841(3)	27(2)
C(4B)	6324(4)	6359(5)	4450(3)	40(2)
C(5B)	6477(4)	5647(5)	4926(3)	40(2)
C(6B)	6917(4)	4878(5)	4788(3)	35(2)
C(7B)	7214(4)	4802(5)	4180(3)	38(2)
C(8B)	7074(3)	5507(5)	3710(3)	29(2)
C(9B)	5292(3)	6384(5)	2952(3)	22(2)
C(10B)	5119(4)	5411(5)	3015(3)	34(2)
C(11B)	4450(4)	5114(6)	3251(4)	42(2)
C(12B)	3950(4)	5810(6)	3416(3)	40(2)
C(13B)	4112(4)	6789(6)	3348(3)	40(2)
C(14B)	4784(4)	7074(5)	3123(3)	34(2)
O(1C)	2658(2)	4450(3)	1935(2)	30(1)
O(2C)	2423(2)	6469(3)	1988(2)	34(1)
O(3C)	1737(3)	7324(4)	1258(3)	52(2)
O(4C)	1698(3)	7604(4)	2305(3)	71(2)
N(1C)	1901(3)	7194(5)	1819(4)	47(2)
C(1C)	2775(3)	6034(5)	1417(3)	24(2)
C(2C)	3177(3)	5156(5)	1716(3)	26(2)
C(3C)	3281(3)	6773(5)	1120(3)	24(2)
C(4C)	3342(4)	6793(5)	437(3)	34(2)
C(5C)	3848(4)	7402(6)	165(4)	49(2)
C(6C)	4266(4)	7996(6)	560(5)	54(2)
C(7C)	4213(4)	7976(6)	1241(4)	51(2)
C(8C)	3714(4)	7362(5)	1515(4)	39(2)
C(9C)	3634(3)	4683(5)	1202(3)	23(2)

C(10C)	3301(4)	4206(5)	666(3)	28(2)
C(11C)	3713(4)	3810(5)	182(3)	33(2)
C(12C)	4461(4)	3889(5)	223(3)	34(2)
C(13C)	4795(4)	4349(5)	756(3)	37(2)
C(14C)	4381(3)	4755(5)	1244(3)	30(2)
O(1D)	2275(2)	4356(3)	3211(2)	28(1)
O(2D)	1123(2)	4123(3)	2332(2)	28(1)
O(3D)	1204(3)	3669(4)	1309(2)	48(2)
O(4D)	1040(3)	5210(4)	1503(2)	41(1)
N(1D)	1117(3)	4365(5)	1652(3)	37(2)
C(1D)	1557(3)	4644(5)	3396(3)	25(2)
C(2D)	1117(3)	4965(5)	2774(3)	26(2)
C(3D)	1615(3)	5501(4)	3861(3)	20(2)
C(4D)	1244(3)	5483(5)	4450(3)	32(2)
C(5D)	1273(4)	6267(5)	4873(3)	38(2)
C(6D)	1689(4)	7068(6)	4724(4)	42(2)
C(7D)	2059(4)	7091(5)	4138(3)	35(2)
C(8D)	2018(3)	6313(5)	3718(3)	29(2)
C(9D)	362(3)	5274(5)	2930(3)	25(2)
C(10D)	162(4)	6242(5)	2884(3)	36(2)
C(11D)	-518(4)	6542(6)	3077(3)	44(2)
C(12D)	-1010(4)	5905(7)	3310(4)	47(2)
C(13D)	-817(4)	4925(7)	3339(3)	44(2)
C(14D)	-138(3)	4620(5)	3156(3)	32(2)

Table 3. Bond lengths [Å] and angles [°] for 1.

O(1A)-C(2A)	1.431(7)	O(2A)-N(1A)	1.408(7)
O(2A)-C(1A)	1.463(7)	O(3A)-N(1A)	1.205(7)
O(4A)-N(1A)	1.201(7)	C(1A)-C(3A)	1.498(8)
C(1A)-C(2A)	1.529(8)	C(2A)-C(9A)	1.512(8)
C(3A)-C(4A)	1.380(8)	C(3A)-C(8A)	1.383(8)
C(4A)-C(5A)	1.381(8)	C(5A)-C(6A)	1.383(9)
C(6A)-C(7A)	1.375(9)	C(7A)-C(8A)	1.377(8)
C(9A)-C(14A)	1.388(8)	C(9A)-C(10A)	1.391(8)
C(10A)-C(11A)	1.377(9)	C(11A)-C(12A)	1.369(9)
C(12A)-C(13A)	1.380(10)	C(13A)-C(14A)	1.380(9)
O(1B)-C(1B)	1.446(7)	O(2B)-N(1B)	1.408(6)
O(2B)-C(2B)	1.465(7)	O(3B)-N(1B)	1.210(7)
O(4B)-N(1B)	1.197(7)	C(2B)-C(9B)	1.501(8)
C(2B)-C(1B)	1.514(8)	C(1B)-C(3B)	1.504(8)
C(3B)-C(4B)	1.382(9)	C(3B)-C(8B)	1.403(8)
C(4B)-C(5B)	1.392(9)	C(5B)-C(6B)	1.366(9)
C(6B)-C(7B)	1.373(9)	C(7B)-C(8B)	1.374(9)
C(9B)-C(10B)	1.380(8)	C(9B)-C(14B)	1.383(8)
C(10B)-C(11B)	1.399(9)	C(11B)-C(12B)	1.377(9)
C(12B)-C(13B)	1.384(10)	C(13B)-C(14B)	1.393(9)
O(1C)-C(2C)	1.443(7)	O(2C)-N(1C)	1.416(7)
O(2C)-C(1C)	1.473(7)	O(3C)-N(1C)	1.178(7)
O(4C)-N(1C)	1.207(7)	C(1C)-C(3C)	1.518(8)
C(1C)-C(2C)	1.526(8)	C(2C)-C(9C)	1.513(8)
C(3C)-C(8C)	1.371(9)	C(3C)-C(4C)	1.391(8)
C(4C)-C(5C)	1.384(9)	C(5C)-C(6C)	1.359(11)
C(6C)-C(7C)	1.387(10)	C(7C)-C(8C)	1.379(10)
C(9C)-C(14C)	1.379(8)	C(9C)-C(10C)	1.388(8)
C(10C)-C(11C)	1.377(8)	C(11C)-C(12C)	1.381(9)
C(12C)-C(13C)	1.373(9)	C(13C)-C(14C)	1.390(9)
O(1D)-C(1D)	1.444(7)	O(2D)-N(1D)	1.415(7)
O(2D)-C(2D)	1.463(7)	O(3D)-N(1D)	1.196(7)
O(4D)-N(1D)	1.205(7)	C(1D)-C(3D)	1.508(8)
C(1D)-C(2D)	1.536(8)	C(2D)-C(9D)	1.500(8)
C(3D)-C(8D)	1.375(8)	C(3D)-C(4D)	1.399(8)
C(4D)-C(5D)	1.375(9)	C(5D)-C(6D)	1.380(9)
C(6D)-C(7D)	1.394(9)	C(7D)-C(8D)	1.364(8)
C(9D)-C(14D)	1.378(8)	C(9D)-C(10D)	1.379(9)
C(10D)-C(11D)	1.390(9)	C(11D)-C(12D)	1.357(10)
C(12D)-C(13D)	1.391(11)	C(13D)-C(14D)	1.383(9)

N(1A)-O(2A)-C(1A)	113.8(5)	O(4A)-N(1A)-O(3A)	129.0(6)
O(4A)-N(1A)-O(2A)	118.6(6)	O(3A)-N(1A)-O(2A)	112.4(6)
O(2A)-C(1A)-C(3A)	111.9(5)	O(2A)-C(1A)-C(2A)	103.6(5)
C(3A)-C(1A)-C(2A)	111.4(5)	O(1A)-C(2A)-C(9A)	108.3(5)
O(1A)-C(2A)-C(1A)	110.9(5)	C(9A)-C(2A)-C(1A)	109.3(5)
C(4A)-C(3A)-C(8A)	118.5(6)	C(4A)-C(3A)-C(1A)	120.9(6)
C(8A)-C(3A)-C(1A)	120.4(6)	C(5A)-C(4A)-C(3A)	120.9(6)
C(4A)-C(5A)-C(6A)	119.5(7)	C(7A)-C(6A)-C(5A)	120.3(7)
C(6A)-C(7A)-C(8A)	119.4(7)	C(7A)-C(8A)-C(3A)	121.3(6)
C(14A)-C(9A)-C(10A)	119.1(6)	C(14A)-C(9A)-C(2A)	120.3(6)
C(10A)-C(9A)-C(2A)	120.5(6)	C(11A)-C(10A)-C(9A)	120.1(7)
C(12A)-C(11A)-C(10A)	120.2(7)	C(11A)-C(12A)-C(13A)	120.6(7)
C(12A)-C(13A)-C(14A)	119.6(7)	C(13A)-C(14A)-C(9A)	120.4(7)
N(1B)-O(2B)-C(2B)	114.2(5)	O(4B)-N(1B)-O(3B)	129.9(6)
O(4B)-N(1B)-O(2B)	111.8(6)	O(3B)-N(1B)-O(2B)	118.2(6)
O(2B)-C(2B)-C(9B)	110.4(5)	O(2B)-C(2B)-C(1B)	105.0(5)
C(9B)-C(2B)-C(1B)	113.2(5)	O(1B)-C(1B)-C(3B)	109.2(5)
O(1B)-C(1B)-C(2B)	109.6(5)	C(3B)-C(1B)-C(2B)	109.6(5)

C(4B)-C(3B)-C(8B)	117.8(6)	C(4B)-C(3B)-C(1B)	122.1(6)
C(8B)-C(3B)-C(1B)	120.0(6)	C(3B)-C(4B)-C(5B)	120.5(7)
C(6B)-C(5B)-C(4B)	120.3(7)	C(5B)-C(6B)-C(7B)	120.2(7)
C(8B)-C(7B)-C(6B)	119.8(7)	C(7B)-C(8B)-C(3B)	121.2(6)
C(10B)-C(9B)-C(14B)	118.5(6)	C(10B)-C(9B)-C(2B)	120.0(6)
C(14B)-C(9B)-C(2B)	121.3(6)	C(9B)-C(10B)-C(11B)	121.5(7)
C(12B)-C(11B)-C(10B)	119.2(7)	C(13B)-C(12B)-C(11B)	119.9(7)
C(12B)-C(13B)-C(14B)	120.2(7)	C(9B)-C(14B)-C(13B)	120.6(7)
N(1C)-O(2C)-C(1C)	114.3(5)	O(3C)-N(1C)-O(4C)	129.9(7)
O(3C)-N(1C)-O(2C)	119.0(6)	O(4C)-N(1C)-O(2C)	111.1(6)
O(2C)-C(1C)-C(3C)	109.7(5)	O(2C)-C(1C)-C(2C)	103.3(5)
C(3C)-C(1C)-C(2C)	112.9(5)	O(1C)-C(2C)-C(9C)	108.5(5)
O(1C)-C(2C)-C(1C)	109.6(5)	C(9C)-C(2C)-C(1C)	109.9(5)
C(8C)-C(3C)-C(4C)	120.0(6)	C(8C)-C(3C)-C(1C)	120.9(6)
C(4C)-C(3C)-C(1C)	118.9(6)	C(3C)-C(4C)-C(5C)	119.4(7)
C(6C)-C(5C)-C(4C)	120.2(8)	C(5C)-C(6C)-C(7C)	120.8(8)
C(6C)-C(7C)-C(8C)	119.2(8)	C(3C)-C(8C)-C(7C)	120.4(7)
C(14C)-C(9C)-C(10C)	119.3(6)	C(14C)-C(9C)-C(2C)	120.6(6)
C(10C)-C(9C)-C(2C)	120.0(6)	C(11C)-C(10C)-C(9C)	120.3(6)
C(10C)-C(11C)-C(12C)	120.3(6)	C(13C)-C(12C)-C(11C)	119.8(6)
C(12C)-C(13C)-C(14C)	120.1(6)	C(9C)-C(14C)-C(13C)	120.2(6)
N(1D)-O(2D)-C(2D)	114.2(5)	O(3D)-N(1D)-O(4D)	129.8(6)
O(3D)-N(1D)-O(2D)	112.4(6)	O(4D)-N(1D)-O(2D)	117.8(6)
O(1D)-C(1D)-C(3D)	109.5(5)	O(1D)-C(1D)-C(2D)	108.8(5)
C(3D)-C(1D)-C(2D)	108.1(5)	O(2D)-C(2D)-C(9D)	112.5(5)
O(2D)-C(2D)-C(1D)	105.0(5)	C(9D)-C(2D)-C(1D)	111.7(5)
C(8D)-C(3D)-C(4D)	118.8(6)	C(8D)-C(3D)-C(1D)	121.7(6)
C(4D)-C(3D)-C(1D)	119.5(6)	C(5D)-C(4D)-C(3D)	120.6(7)
C(6D)-C(5D)-C(4D)	119.6(7)	C(5D)-C(6D)-C(7D)	119.9(7)
C(8D)-C(7D)-C(6D)	119.8(7)	C(3D)-C(8D)-C(7D)	121.2(6)
C(14D)-C(9D)-C(10D)	118.0(6)	C(14D)-C(9D)-C(2D)	121.7(6)
C(10D)-C(9D)-C(2D)	120.3(6)	C(9D)-C(10D)-C(11D)	120.4(7)
C(12D)-C(11D)-C(10D)	122.0(8)	C(11D)-C(12D)-C(13D)	117.6(7)
C(12D)-C(13D)-C(14D)	120.9(7)	C(9D)-C(14D)-C(13D)	121.1(7)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2$ x 10^3] for 1.

The anisotropic displacement factor exponent takes the form:

$-2\pi^2$ [$(ha^*)^2 U_{11}$ + ... + $2hka^*b^*U_{12}$]

	U11	U22	U33	U23	U13	U12
O(1A)	38(3)	25(3)	35(3)	0(2)	14(2)	3(2)
O(2A)	32(3)	22(3)	36(3)	-4(2)	10(2)	-8(2)
O(3A)	63(4)	48(4)	62(4)	-3(3)	36(3)	-22(3)
O(4A)	40(3)	44(4)	52(4)	-17(3)	7(3)	-11(3)
N(1A)	35(4)	21(4)	55(5)	-13(4)	19(4)	-3(3)
C(5A)	33(4)	40(5)	44(5)	-1(4)	-4(4)	10(4)
C(6A)	30(4)	45(5)	50(5)	-19(4)	8(4)	-6(4)
C(7A)	44(5)	37(5)	31(4)	-2(4)	5(4)	5(4)
C(11A)	36(5)	29(5)	51(5)	-2(4)	12(4)	-5(4)
C(12A)	61(6)	29(5)	42(5)	-4(4)	31(4)	-5(4)
C(13A)	67(6)	27(5)	29(4)	1(4)	6(4)	-6(4)
O(1B)	29(3)	25(3)	38(3)	-3(2)	10(2)	-7(2)
O(2B)	41(3)	25(3)	21(3)	0(2)	7(2)	1(2)
O(3B)	55(3)	27(3)	29(3)	-9(2)	1(2)	0(3)
O(4B)	53(3)	38(3)	31(3)	14(3)	9(2)	9(3)
N(1B)	26(4)	34(4)	31(4)	4(4)	4(3)	9(3)
C(5B)	60(5)	35(5)	27(4)	2(4)	15(4)	-11(4)
C(6B)	46(5)	30(5)	30(4)	4(4)	-11(4)	1(4)
C(7B)	36(4)	34(5)	44(5)	-6(4)	-2(4)	4(4)
C(11B)	34(5)	31(5)	60(5)	18(4)	11(4)	-4(4)
C(12B)	29(4)	65(6)	27(4)	11(4)	7(3)	3(5)
C(13B)	36(5)	49(6)	36(5)	-4(4)	8(4)	17(4)
O(1C)	34(3)	25(3)	32(3)	5(2)	13(2)	-1(2)
O(2C)	43(3)	29(3)	30(3)	1(2)	15(2)	12(3)
O(3C)	56(4)	61(4)	38(3)	15(3)	9(3)	24(3)
O(4C)	100(5)	61(4)	53(4)	9(3)	36(4)	45(4)
N(1C)	50(4)	40(4)	52(5)	14(4)	19(4)	13(4)
C(5C)	44(5)	48(6)	55(5)	19(5)	19(4)	14(5)
C(6C)	41(5)	28(5)	95(8)	21(5)	28(5)	6(4)
C(7C)	45(5)	36(5)	74(6)	-15(5)	13(5)	-3(4)
C(11C)	43(5)	35(5)	22(4)	2(4)	-4(3)	6(4)
C(12C)	41(5)	29(4)	34(4)	-1(4)	16(4)	10(4)
C(13C)	29(4)	36(5)	47(5)	8(4)	14(4)	-3(4)
O(1D)	28(3)	27(3)	30(3)	0(2)	12(2)	8(2)
O(2D)	38(3)	24(3)	21(3)	-3(2)	9(2)	-3(2)
O(3D)	55(4)	54(4)	35(3)	-28(3)	14(3)	-5(3)
O(4D)	60(4)	43(4)	21(3)	7(3)	-1(2)	-6(3)
N(1D)	28(4)	55(5)	27(4)	-3(4)	9(3)	-6(4)
C(5D)	46(5)	43(5)	25(4)	-7(4)	2(4)	18(4)
C(6D)	56(5)	32(5)	36(5)	-16(4)	-15(4)	11(4)
C(7D)	46(5)	21(4)	37(5)	-11(4)	-3(4)	3(4)
C(11D)	36(5)	47(5)	49(5)	-20(4)	-9(4)	12(4)
C(12D)	24(4)	80(7)	38(5)	-16(5)	2(4)	3(5)
C(13D)	30(5)	68(6)	34(5)	-1(4)	0(4)	-9(5)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

	x	y	z	U(eq)
H(1A)	7442(2)	7236(3)	2236(2)	48
H(1AA)	7413(3)	5829(5)	961(3)	31
H(2AB)	8400(3)	6520(5)	1986(3)	32
H(4AA)	8622(3)	4490(5)	2021(3)	35
H(5AA)	9597(4)	3569(5)	1705(4)	47
H(6AA)	9912(4)	3561(6)	611(4)	50
H(7AA)	9238(4)	4444(5)	-166(3)	45
H(8AA)	8241(3)	5313(5)	150(3)	35
H(10A)	9504(4)	6773(5)	1434(3)	40
H(11A)	10143(4)	7462(5)	598(4)	46
H(12A)	9538(4)	8194(5)	-281(4)	52
H(13A)	8286(4)	8300(5)	-319(3)	49
H(14A)	7638(4)	7644(5)	526(3)	36
H(1B)	7238(2)	8136(3)	3153(2)	45
H(1BB)	6283(3)	6111(5)	2569(3)	32
H(2BA)	6255(3)	7644(5)	3516(3)	30
H(4BA)	6012(4)	6869(5)	4544(3)	48
H(5BA)	6279(4)	5696(5)	5340(3)	49
H(6BA)	7016(4)	4404(5)	5108(3)	42
H(7BA)	7509(4)	4274(5)	4085(3)	45
H(8BA)	7275(3)	5450(5)	3298(3)	34
H(10B)	5454(4)	4941(5)	2898(3)	40
H(11B)	4345(4)	4454(6)	3295(4)	50
H(12B)	3504(4)	5622(6)	3574(3)	48
H(13B)	3771(4)	7258(6)	3452(3)	48
H(14B)	4893(4)	7733(5)	3087(3)	41
H(1C)	2581(2)	4629(3)	2467(2)	45
H(1CA)	2407(3)	5820(5)	1085(3)	29
H(2CB)	3490(3)	5367(5)	2093(3)	31
H(4CA)	3045(4)	6400(5)	167(3)	41
H(5CA)	3903(4)	7405(6)	-289(4)	58
H(6CA)	4592(4)	8421(6)	372(5)	65
H(7CA)	4510(4)	8372(6)	1510(4)	62
H(8CA)	3672(4)	7348(5)	1971(4)	47
H(10C)	2797(4)	4154(5)	634(3)	33
H(11C)	3487(4)	3488(5)	-175(3)	40
H(12C)	4738(4)	3632(5)	-109(3)	41
H(13C)	5299(4)	4388(5)	790(3)	44
H(14C)	4609(3)	5076(5)	1600(3)	36
H(1D)	2383(2)	3678(3)	3333(2)	42
H(1DB)	1314(3)	4098(5)	3608(3)	30
H(2DA)	1366(3)	5511(5)	2568(3)	31
H(4DA)	975(3)	4935(5)	4555(3)	39
H(5DA)	1014(4)	6257(5)	5257(3)	46
H(6DA)	1722(4)	7593(6)	5015(4)	51
H(7DA)	2333(4)	7635(5)	4033(3)	42
H(8DA)	2267(3)	6332(5)	3328(3)	35
H(10D)	485(4)	6697(5)	2724(3)	44
H(11D)	-640(4)	7198(6)	3044(3)	53
H(12D)	-1460(4)	6117(7)	3447(4)	56
H(13D)	-1149(4)	4469(7)	3483(3)	53
H(14D)	-18(3)	3963(5)	3187(3)	39