TITLE THE SYNTHESIS OF 3-SUBSTITUTED-2-(NITROMETHYLENE)-PIPERIDINES

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THE SYNTHESIS OF

3-SUBSTITUTED-2-(NITROMETHYLENE)-PIPERIDINES

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This thesis is submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Warwick.

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DECLARATION

The observations described in this thesis are those of the author, except where acknowledgement has been made to results and ideas previously published. The work was undertaken at the Department of Chemistry, University of Warwick, between January 1991 and December 1993 and has not previously been submitted for a degree at any institution.

Summary

The class of insecticides known collectively as the nitromethylene heterocycles (NMHs) were discovered in the late 1970's. The NMHs are a group of compounds that are particularly active against certain insects, exhibit low toxicity to vertebrates and are non-persistent in the environment. Their site of action is on the cholinergic synapse where they act as agonists at the post-synaptic nicotinic acetylcholine receptors.

Research into developing these types of compounds has led to a wide range of analogues being synthesised, resulting in a wide variety of activities. Analogues of 2-(nitromethylene)piperidine with small group substituents at the 3-position (e.g. halogens or small alkyl groups), in general, were found to have increased levels of activity.

The work reported in this thesis is the synthesis of some novel 3-substituted-2-(nitromethylene)piperidines.

Initially a series of 3-substituted-2-piperidones was synthesised via the catalytic decomposition of 3-diazo-2-piperidone. Rhodium(II) acetate and methyl trioxorhenium were found to be particularly efficient catalysts. The 1,3-dipolar cycloaddition of electron deficient olefins to 3-diazo-2-piperidone resulted in a range of 3-substituted pyrazolines being formed. Nitrogen could be eliminated from these pyrazolines to give spirocyclopropanes.

3-Alkoxy-2-(nitromethylene)piperidines were synthesised by the nitromethylenation of 3-alkoxy-2-piperidones. However the nitromethylenation of the 3-spirocyclopropyl derivatives was not successful due to steric effects.

To overcome the problems of steric hindrance, 3-diazo-2-(nitromethylene)piperidine was synthesised via a six step synthesis from 2-piperidone. This was the first compound to be synthesised which contains a 3-diazo-1-nitropropene group. Although this diazo compound acted as a 1,3-dipole with electron deficient olefins to give the corresponding pyrazolines, the rhodium catalysed decomposition was found to form 3-oxo-2-(nitromethylene)piperidine as the major product even in the presence of other carbenoid trapping agents. Further investigation into this reaction has led to a proposed mechanism which is outlined in the thesis.

abbreviations

NMR	nuclear magnetic resonance
δ	chemical shift
ppm	parts per million
J	coupling constant
Hz	hertz
s	singlet
bs	broad singlet
d	doublet
dd	doublet of doublets
t	triplet
q	quartet
m	multiplet
exch	exchangeable with D_2O
arom	aromatic
quat	quaternary
nOe	nuclear Overhauser effect
IR	infra red
UV	ultra violet
MS	mass spectrometry
EI	electron impact
CI	chemical ionisation
FAB	fast atom bombardment
tlc	thin layer chromatography
THF	tetrahydrofuran
DMF	dimethyl formamide
DMSO	dimethyl sulphoxide
IPA	isopropyl alcohol
OAc	acetate
acac	acetylacetonate

Chapter1 Insect Nervous System

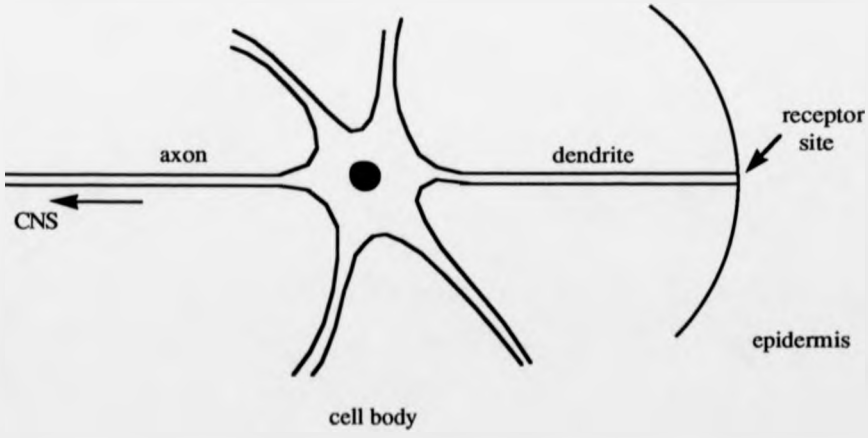
1.1.1 Introduction

A substantial part of the capacity of an insect to regulate its relationships with its internal and external environments depends on its electrically excitable cells. Such cells occur in the sense organs, the nervous system and the muscles. They detect stimuli, process information and coordinate responses by electrical interactions.

The accomplishment of many sexual, reproductive, social and feeding activities of insects depends to a great extent upon the detection and assessment of specific chemical aspects of the environment, which trigger excitation in receptors. These receptors are not chemoselective simply because of their anatomical location or because they are exposed to the environment. They are highly specialised and specific.

Information is transmitted from the external environment to the central nervous system (CNS) by means of discrete electrical impulses. The receptor cell detects a stimulus, converts it into an electrical impulse and

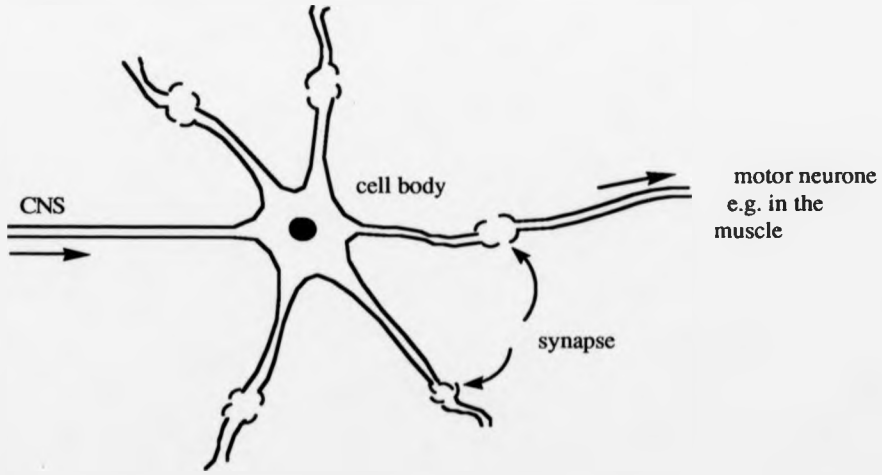
Fig.1: Transmission of electrical impulse from the receptor site to the CNS



transmits this impulse along a short dendrite to a cell body which lies just under the epidermis. This impulse then travels along a long fibre of the neurone (or nerve cell) known as the axon (Fig 1), eventually reaching the CNS, so that the appropriate response can be made to the received stimulus.

The insect responds to a stimulus by passing an electrical impulse along a single long filamentous axon, to a cell body in the region of the body to be affected. The cell body gives off shorter branches, and these are always joined by means of synapses to other neurones (Fig 2)[1].

Fig 2: Transmission of an electrical impulse from the CNS to a motor neurone in response to a stimulus



The process by which neurones respond electrically to stimuli is known as transduction. Neurones utilise the electrical charges carried by ions and the activity of the nervous system ultimately depends on the neurone's capacity to maintain an unequal distribution of sodium (Na) and potassium (K) ions on each side of the cell membrane. The resting potential of most neurones is constant as long as the cell remains

inactive due to lack of stimulation. Under resting conditions there is a high concentration of K^+ and a low concentration of Na^+ inside the membrane. The electrical potential is negative with respect to the outside. Outside the membrane there is a low concentration of K^+, a high concentration of Na^+ and the electrical potential is positive with respect to the inside. Changes in the permeability of the membrane of excitable cells to K^+ and Na^+ ions lead to changes in the potential difference across the membrane and the formation of action potentials in, and the propagation of nerve impulse along, the axon. When this occurs Na^+ ions are actively transported into the cell while K^+ ions are transported out of the cell. This lasts for about a millisecond, then the original equilibrium is reestablished through rapid transport of Na^+ ions out of the cell, and the electrical impulse passes on down the neurone.[2]
In most sensory systems, the magnitude of the action potential is proportional to the log of the stimulus intensity. This enables the receptor to respond to a wide range of stimulus intensities.

Each neurone is almost completely ensheathed by one or more glial cells for protection, but at the synapses the glial sheath is absent.

1.1.2 Synaptic Transmission

Propagation of action potentials is interrupted at synapses, the points where one neurone contacts another neurone or contacts a muscle cell. Transmission across a synapse is normally dependent on the diffusion across the synapse of a chemical released from the pre-synaptic cell. This chemical transmitter combines with specific receptor sites on the membrane of the post-synaptic cell and initiates a permeability change; the neurotransmitter is inactivated by an enzyme which may occur in the membranes of both cells. In general, more than one pre-synaptic action potential is required to initiate a post-synaptic one.

A number of criteria must be met before a substance can be identified, with confidence, as a synaptic transmitter. It should be possible to identify the presence of the substance at the synapse and to demonstrate at the synaptic endings the presence of an enzyme for its inactivation. The substance should be released on stimulation and should be inhibited by competitive antagonists. It should be possible to mimic the physiological action of the suspected transmitter by applying the chemical artificially in appropriate amounts.

Acetylcholine has been shown to be the predominant neurotransmitter in the CNS of insects.[3] It was detected in the A_6 ganglion of the cockroach. It is enriched in isolated nerve endings and is concentrated in isolated synaptic vesicles. The major elements required for the functioning of the cholinergic synapses have also been detected in the nervous tissue of insects.[4]

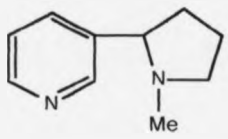
Very high activities of cholineacetyltransferase, the enzyme which synthesises acetylcholine from the precursors choline and acetyl-CoA, are present.[5] The enzyme has been localised in the insect CNS. The inactivating enzyme acetylcholinesterase is also present in the insect CNS, and has been located in the synaptic regions.

Stimulation of the pre-synaptic cell has been shown to result in the accumulation of acetylcholine.

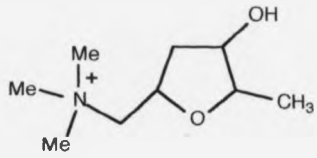
Based on responses to drugs, cholinergic synapses can be classified as one of two types. Either muscarinic (those activated by muscarine [1-2] and blocked by atropine; found in smooth muscle and glands); or nicotinic (those activated by nicotine [1-1] and inhibited by d-tubocurarine; found in voluntary muscles[6,7]). Typically the action of

acetylcholine at nicotinic receptors is quick and short lasting. In contrast, the excitatory action at muscarine receptors is slow and prolonged.

In 1980, Sattelle[8] showed that insects possess three putative receptors,



[1-1]



[1-2]

having nicotinic, muscarinic and mixed (nicotinic/muscarinic) specificity. He also showed that the concentrations of nicotine receptors are over one hundred times those of the muscarinic receptors.

At the post-synaptic cell of a cholinergic synapse, acetylcholine induces changes in membrane permeability resulting in depolarisation of the post-synaptic membrane. The depolarising actions of acetylcholine at this synapse can be mimicked by locally applied acetylcholine and inhibited by d-tubocurarine.

The function of the muscarinic receptors in insects appears to be to regulate the release of acetylcholine from cholinergic pre-synaptic terminals. Experiments involving the application of elevated concentrations of acetylcholine agonists yielded reduced levels of acetylcholine release. This suggests that there is a negative feedback at insect cholinergic synapses.[9]

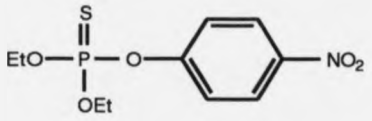
1.2 Insecticides

Most early insecticides were stomach poisons, killing only those species which ingested the treated plant. In those insects which ate the sprayed leaves, free toxins would be liberated within the gut.

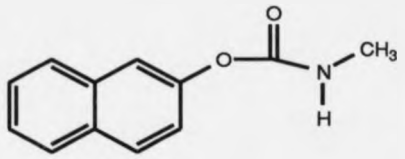
The site of action of most modern insecticides is the insect nervous system, and this approach has several advantages. The nervous system has the characteristic of being vital to the normal functioning of the insect on a short time scale. In contrast to the compounds that affect reproduction or development, neurally active insecticides can provide rapid knockdown. They are used as a residual film deposited on the plant surface. The insecticide can be taken up over the whole surface of the insect or by oral ingestion. To be effective by surface penetration, the insecticides must be sufficiently lipophilic to be absorbed through the cuticular waxes or the epicuticular lining of the tracheal system. The first insecticides to act in this way were the organochlorines, such as dichlorodiphenyltrichloroethane (DDT), aldrin and benzenehexachloride (BHC). These compounds are potent insecticides with apparently little toxicity to man. Unfortunately, the factors that make the inexpensive chlorinated hydrocarbons so desirable as insecticides also make them undesirable on biological grounds. Their great persistence and fat-solubility causes them to accumulate in the ecosystem, and to be stored in the fat of animals and birds towards the end of the food chain. For this reason they are environmentally unacceptable.

The organochlorines were replaced by organophosphates (e.g. parathion [1-3]) and carbamates (e.g. carbaryl [1-4]). They are generally biodegradable by hydrolysis, and hence they do not present the problems of undue persistence associated with the chlorinated hydrocarbons.

Unfortunately many of these insecticides are also highly toxic to mammals.

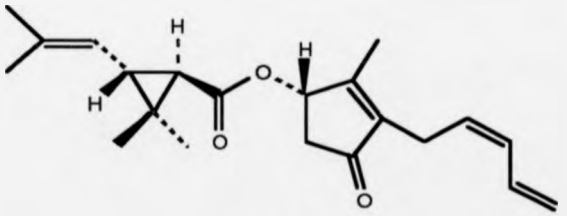


[1-3]



[1-4]

A number of natural products obtained from plant extracts have shown insecticidal activity. Nicotine and rotenone are two early examples. However, their use declined with the introduction of DDT. In recent years, the pyrethroids (e.g. pyrethrin I [1-5]) have been commercially exploited. Their distinct advantage is their low persistence and low mammalian toxicity (although they are very toxic to fish).



[1-5]

1.2.1 Modes of action

DDT appears to bind to the axon membrane and to interfere with the flow of ions into and out of the axon. The effect of these permeability changes is that DDT causes repetitive production of action potentials. In the poisoned insect, this results in hyperexcitability and muscular spasms, followed by paralysis and death.

Organophosphorus and carbamate insecticides inhibit the action of acetylcholinesterase. The enzyme combines with the insecticide, causing a build up of acetylcholine at the synapses. Because the enzyme/insecticide complex has a long life time this results in death.

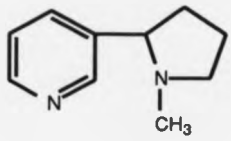
The pyrethroids have the same site of action as DDT. Insects which have grown resistance to DDT are not affected by the pyrethroids. However, non-resistant strains of the same insect show rapid knockdown when treated with the pyrethroids.[10]

1.2.2 Nicotinic acetylcholine receptors as targets for insecticides

Nicotine [1-6] is a non-persistent contact insecticide which occurs naturally in the tobacco plant. However, its use rapidly declined after the introduction of DDT and it has now been replaced by synthetic insecticides, because of its comparatively high mammalian toxicity and its lack of effectiveness in cold weather. Its mode of action is as a potent agonist at the nicotinic receptor sites on the post-synaptic membrane.[11]

Nicotine, and those of its analogues which show insecticidal activity, all show certain structural similarities with acetylcholine [1-10][12]. Nicotine will bind with acetylcholine-receptor protein extracted from house fly heads. There is good correlation between the degree of binding of nicotine and its analogues and their varying toxicity's in the intact insects. Application of a lethal dose produces tremors, convulsions and then paralysis. Death follows within an hour.

In 1930, Smith *et al*[13] showed that the pyridine derivatives anabasine [1-7] and nornicotine [1-8] have comparable activity to nicotine.



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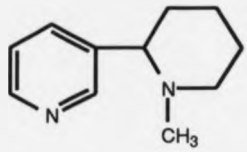

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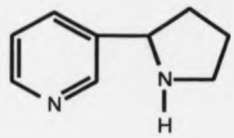
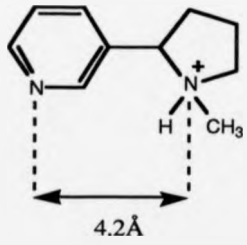
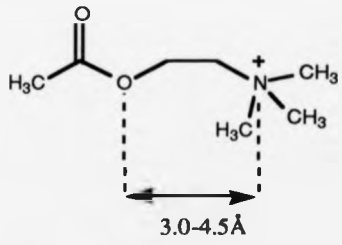


[1-8]

Subsequent examination of a range of nicotine analogues indicated that high insecticidal activity required the presence of a pyridine nucleus joined at its 3-position to the 2-position of a saturated 5- or 6- membered ring. The essential features were the 3-pyridylmethylamine residue with a highly basic side chain nitrogen atom at least 4.2Å away from the pyridine nucleus [1-9]. The pKa of the pyrrolidine nitrogen must be



[1-9]



[1-10]

significantly above 7 to have good insecticidal activity, so that at pH7 at least 90% of the compound will be protonated at the pyrrolidine nitrogen.

The nicotinic cholinergic receptor shows a variation between species and different parts of the nervous system which might provide a basis for species specificity in nicotinic insecticides, thus epitomising the kind of target suited to biorational research.[14]

1.2.3 Nitromethylene heterocycle insecticides

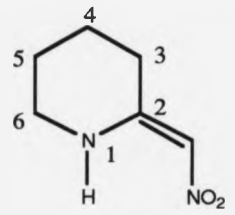
The nitromethylene heterocycles (NMH) are a group of compounds which are particularly active against certain insects by both contact and oral ingestion. They are fast acting, exhibit low toxicity to vertebrates, and are relatively non-persistent in the environment.[15] Insects treated with NMHs showed the following symptoms; lowering of the head, wing flexing, uncontrollable preening, leg tremors, violent body shaking and finally death. The method of application (injection, topical application or ingestion) of the NMH did not significantly alter the intoxication sequence. The symptoms suggested an involvement of the nervous system in the development of the intoxication sequence.

In 1984, Schroeder and Flattum[16] deduced that the major site of action of the NMHs in the cockroach was the cholinergic synapse in the 6th abdominal ganglion. They applied the nitromethylene compounds, as acetone solutions, to a nerve preparation of the 6th abdominal ganglion of the American cockroach which was stimulated through the cercal nerves. This resulted in a brief but intense period of spontaneous giant fibre discharges, followed immediately by a total block to nerve impulse conduction. Acetylcholine and nicotine, known cholinergic agonists, show the same effect as that of NMHs, suggesting that the latter act at the cholinergic synapse. In 1986, this was confirmed by Harris *et al.*[17]

The mode of action of the NMHs is different to that displayed by other major insecticide groups, helping to overcome the problem of resistance. These features combined make the nitromethylenes candidates for a new generation of insect control agents.

In 1987, Soloway[18] and co-workers, in an attempt to exploit this new class of insecticides, synthesised a wide range of 2-(nitromethylene)

heterocycle analogues and discussed the structure-activity relationships of these compounds. His lead compound was 2-(nitromethylene) piperidine [1-11] which showed an activity 1.6 times that of parathion.



[1-11]

The analogues which Soloway and others have synthesised, along with their activities, will be discussed later.

1.2.4 Mammalian versus insect nicotinic receptors

In vertebrates, nicotinic acetylcholine receptors are subdivided into endplate type nicotinic receptors and neuronal type nicotinic receptors. The endplate type receptors are expressed in the muscle, while neuronal type receptors are present in the CNS and in peripheral autonomic ganglia. In general, vertebrate endplate and neuronal type receptors are distinguished pharmocologically by their sensitivities to the snake toxins α-bungarotoxin and κ-bungarotoxin, respectively. Acetylcholine-induced current in mammalian endplate type nicotinic receptors is almost blocked by α-bungarotoxin, but not blocked by κ-bungarotoxin. In neuronal type receptors the current is not affected by α-bungarotoxin but is blocked by κ-bungarotoxin. In both cases there is little or no effect when nitromethylene heterocycles are introduced.

Nicotinic receptors in insects have been identified only in the CNS, and are blocked by α- and κ-bungarotoxin in the cockroach. NMH

compounds show concentration-dependent agonistic effects. NMH compounds are highly toxic to certain insect species, whereas vertebrates appear to be relatively insensitive to these compounds.

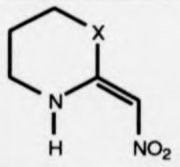
This shows that the three types of nicotinic receptors examined (i.e. vertebrate endplate, vertebrate neuronal and insect nicotinic) differ markedly in their sensitivities to NMHs, offering an explanation for the selective toxicity of NMH insecticides to insects compared to vertebrates.[19]

1.2.5 Insecticidal activity of the nitromethylenes

A structurally diverse range of NMHs have been synthesised and the insecticidal activities of compounds in this class range from zero to highly potent.

The first compound to show activity was 2-(nitromethylene)piperidine (X=CH_2), Table 1, having a relative activity of 160 (compared to 100 for parathion).[18]

Table 1: Relative activity of nitromethylene piperidines containing a second heteroatom.

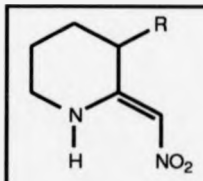


X	relative activity
CH_2	160
O	60
S	1700
N-CH_3	140
parathion	100

The most active compound in this series was 2-nitromethylene-1,3-thiazinane (X=S), but unfortunately this was too photochemically unstable for agrochemical use. N-substitution in all of the above cases led to a dramatic decrease in activity compared to the unsubstituted compound.

It was found that in the 6-membered ring series, when ($X=CH_2$), the greatest activity was when substitution was at the 3-position (Table 2). Compounds with substitution at positions 4,5 and 6 showed very little or no activity.

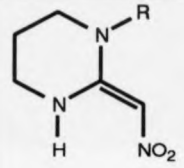
Table 2: Relative activity of 3-substituted-2-(nitromethylene)piperidines.



R	relative activity
CH_3	25
F	70
Cl	70
Br	110
I	35
SCH_3	120
parathion	100

In the hexahydropyrimidine series (Table1,X=NH), simple alkyl derivatives at the 3-position (with the exception of when X=N-Me) show little activity (Table 3). However, this activity is greatly increased when aromatic groups are present (e.g. when R= *p*-chlorophenyl or *p*-chloropyridyl activity is 5-6 times that of parathion). This area is currently undergoing intensive investigation in industry.

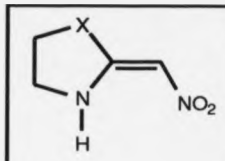
Table 3: Relative activity of substituted hexahydropyrimidines.



R	relative activity
H	5
CH_3	140
C_2H_5	40
$CH_2CH_2CH_3$	0
$CH_2C{\equiv}CH$	60
C_6H_{11}	0
parathion	100

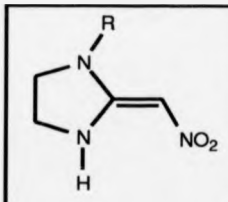
Extensive work has also been carried out on the 5-membered ring series (Table 4). In general, the activity is less than that of the 6-membered ring series, except for the 2-(nitromethylene) imidazolidines (Table 5).

Table 4: Relative activity of nitromethylene pyrrolidines containing a second heteroatom.



X	relative activity
CH_2	90
O	0
S	8
N-CH_3	300
parathion	100

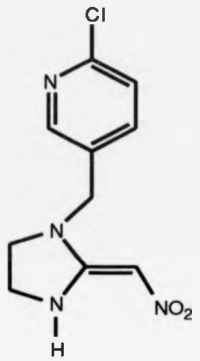
Table 5: Relative activity of substituted 2-(nitromethylene) imidazolidines



R	relative activity
H	12
CH_3	300
C_2H_5	40
$CH_2C{\equiv}H$	140
$CH_2CH{=}CHCl$	200
$CH_2CH{=}CH_2$	90
parathion	100

Later, the introduction of phenyl, benzyl and pyridyl groups led to a large increase in activity, in particular when a *para*-chloro substituent was placed on the aromatic ring.

At present, there is a great deal of research going on to discover new nitromethylene insecticides. However, to date, there is only one commercial product available; imidacloprid (Bayer AG) [1-12].



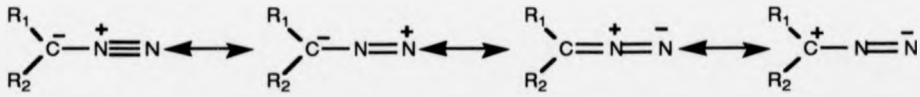
[1-12]

Chapter 2 Diazo Chemistry

2.1 Introduction

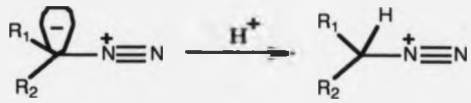
Diazo compounds are molecules of limited stability and readily lose nitrogen to form reactive intermediates. The lowest members of the diazoalkane series are explosive gases, but stability increases with molecular weight and also with the introduction of electron withdrawing groups (e.g. carbonyl of ketone, ester or amide function) next to the diazo carbon, making these especially useful intermediates in organic synthesis.

The electron distribution of the diazo group can be represented by four resonance forms [2-1] to [2-4]. The stability and properties of this group are dependant upon which one of these forms is most predominant. [2-1] and [2-2] dictate the reactivity of the diazo group to acids and electrophiles, whereas [2-4] dictates reactivity to bases and nucleophiles. The diazo group can also behave as a 1,3-dipole ([2-1] and [2-2]) and as an important precursor for the generation of carbenes.



[2-1] [2-2] [2-3] [2-4]

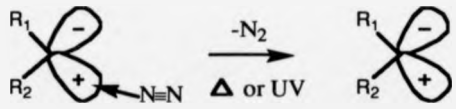
For many reactions, the diazo group can be represented by the ylide [2-1].[20] Unlike many other ylides, diazo compounds are generally stable to air and water. However, the presence of acid causes protonation, leading to a highly reactive diazonium ion [2-5]. As the substituents on the diazo group are made increasingly more electron withdrawing, the ylide becomes less basic and therefore more stable to acid.



[2-1] [2-5]

Reaction of a diazo compound with a transition metal can also often be understood as proceeding via initial donation of electron density by [2-1] to a coordinatively unsaturated metal centre.

Alternatively, the diazo compound can be viewed as a coordination complex [2-6] between a carbene and nitrogen.[20] The coordination is weak, so a small input of energy, either heat or U.V. radiation, can lead to nitrogen loss, the generation of a free carbene [2-7] and a subsequent reaction.



[2-6] [2-7]

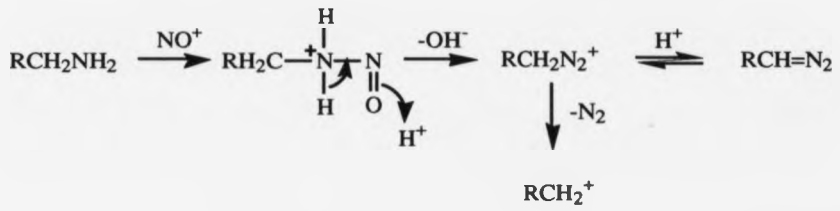
2.2 Synthesis of α-diazocarbonyl compounds

The literature on α-diazoamides is limited. However they can be treated more generally as α-diazocarbonyl compounds.

Several methods are available for the preparation of α-diazoketones. They are easily purified and usually quite stable. Unlike most diazoalkanes they are usually stable to silica gel chromatography.

Diazotisation of primary amines (Scheme 1) is achieved by the direct reaction of a nitrosating reagent with the amine in acid solution. The

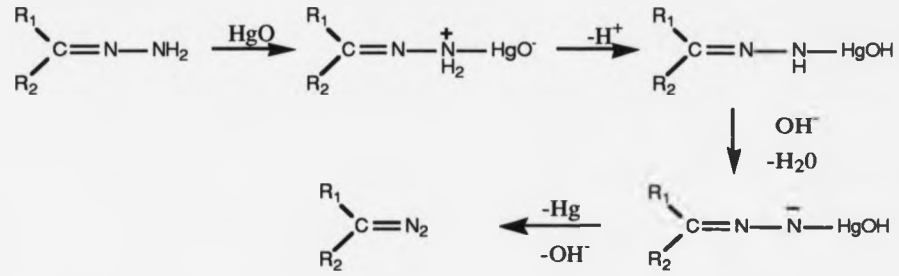
diazonium ion can either a) reversibly deprotonate to give the neutral diazo compound or b) lose nitrogen to form a carbonium ion, and the yield of the diazo compound therefore depends critically on the reaction conditions. Most commonly, sodium nitrite is used in a dilute solution of



Scheme 1

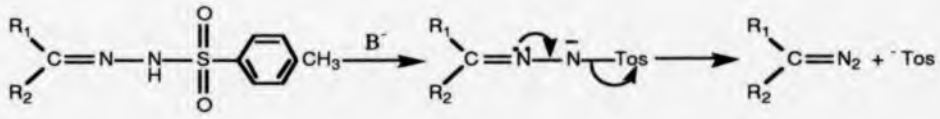
hydrochloric acid,[21] however other dilute acids may be used.[22,23] In most cases the product will precipitate out of solution or can be extracted using a two phase system.[24] Sodium nitrite can also be used in an organic solvent if the diazo compound is too water soluble to be extracted. Takamura *et al* [25] described the use of isopentyl nitrite as a diazotising reagent in chloroform containing a catalytic amount of glacial acetic acid. In this case, the amount of acid and the duration of reaction are crucial as the acid will react with the product.

α-Ketohydrazones are oxidised to diazo compounds (Scheme 2) commonly using HgO[26,27] but also MnO_2[28] or Ag_2O[29] in non-aqueous solvent (usually chloroform, benzene, petroleum ether or diethyl ether). This reaction is catalysed by a base which suggests a mechanism involving electron transfer from the hydrazone anion. Sodium sulphate is used to bind the water produced in the reaction.



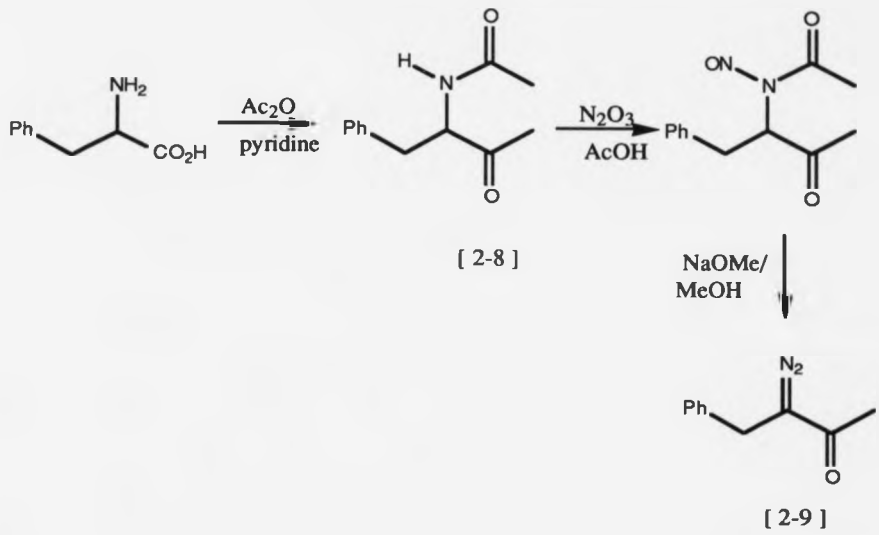
Scheme 2

In addition to the dehydrogenation of hydrazones, which are usually prepared from carbonyl compounds, 1,1-elimination from the sulphonyl hydrazones leads to α-diazocarbonyls.[30-32] This is known as the Bamford-Stevens reaction (Scheme 3), and requires a mild base (e.g. alumina[33]) to remove a proton from the tosyl hydrazone.



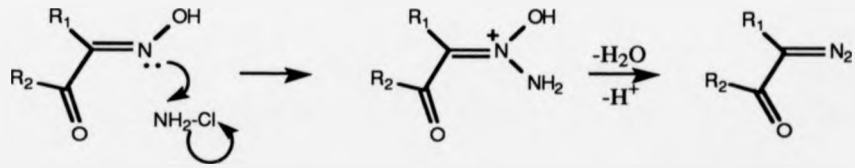
Scheme 3

The synthesis of diazo compounds from N-nitrosamides is used widely in the preparation of diazoalkanes. However, it has attracted very little attention for the preparation of α-diazocarbonyl compounds. The Dakin-West reaction[34] provides a source of N-acyl-α-aminoketones [2-8], which Franzen[35] has exploited for the synthesis of secondary diazoketones (Scheme 4). The ketoamide [2-8] is nitrosated using N_2O_3 in glacial acetic acid and the resulting derivative is separated and then decomposed with sodium methoxide in methanol to give diazoketone [2-9].



Scheme 4

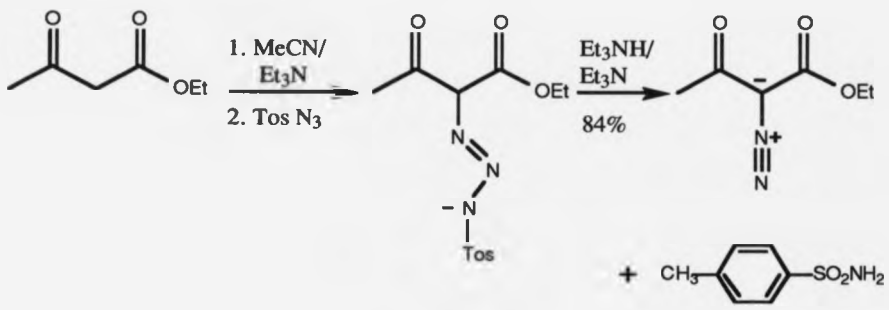
α-Ketoximes can be oxidised with chloramine[36,37] in alkaline solution to give α-diazo carbonyl compounds. This is known as the Forster reaction (Scheme 5).



Scheme 5.

The synthesis of α-diazocarbonyl compounds by the transfer of a diazo group from an organic azide to a suitable substrate containing an active methylene group was studied extensively in the 1960s (Scheme 6). Tosyl azide[38] is the transfer agent of choice because it is stable and easily prepared. The presence of a base is necessary to allow the enolate anion to react with the azide. Commonly used solvent/base pairs are

ethanol/KOH; acetonitrile/triethylamine; methanol/sodium methoxide and methylene chloride/piperidine.



Scheme 6

2.3 Detection of diazo compounds

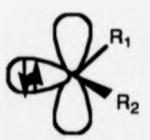
The presence of a diazo compound can be simply detected by the evolution of nitrogen when it is mixed with a strong acid in solution.[39]

The amount of diazo compound present can be calculated by measuring the amount of nitrogen liberated when acid is added.[40,41] This can be useful in determining the yield of a reaction when the diazo compound is difficult to isolate.

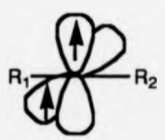
One of the most intense bands in the infra-red spectra of diazo compounds is the stretching vibration of the $C=N_2$ bond. This usually falls in the region between 2000-2100cm^{-1}. In their ^1H NMR spectra, the chemical shifts of the α-protons fall in the range 2.8-6.0δ and they are shifted downfield when the negative charge on the α-carbon can be stabilised by appropriate substituents.[42] In EI-mass spectrometry there is usually a low abundance of the molecular ion, but usually a large peak for the $[M-N_2]^+$ ion. Softer ionisation techniques such as CI may show a larger abundance of the molecular ion.

2.4 Decomposition of diazo compounds

Diazo compounds are used as precursors to carbenes, which are classified as divalent carbon intermediates. More precisely, the carbene carbon is linked to two adjacent groups by covalent bonds, and it possess two non-bonding electrons which may have antiparallel spins (singlet state [2-10]) or parallel spins (triplet state [2-11]). The nature of the ground state depends on the relative energies of the two non-bonding orbitals. If the two orbitals are equivalent, according to Hunds' rules the electrons should be assigned to different orbitals with parallel spins. On the other hand, if the two available orbitals are not degenerate, the two electrons would probably occupy the lower of the two orbitals with consequent spin pairing. Singlet carbenes (not necessarily in the ground state) are expected from most carbene precursors as a consequence of spin conservation.



[2-10]



[2-11]

Skell has suggested two kinds of data to describe the spin states of carbenes.[43,44] The first involves the study of relative reactivities of various olefinic substrates towards carbenes using the competitive method. It was Skell's original notion[43] that triplet carbenes should show selectivity reminiscent of that of typical free radicals. Competitive experiments in the liquid phase showed that dibromomethylene does not select among olefinic substrates in the same way as the tribromomethyl radical. Doering and Henderson,[45] reported similar results with both

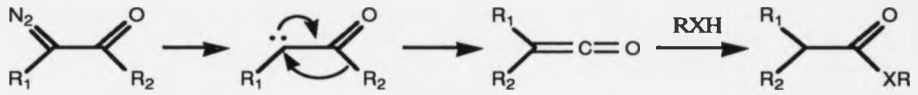
dichloro- and dibromocarbene. Application of the Skell criterion would indicate that the dihalocarbenes react as electron-deficient singlet states.

Skell's second criterion involved the stereospecificity of addition[44]. He reasoned that a singlet carbene might add to a double bond in a single concerted step since such a step could occur with spin conservation. Conversely it was reasoned that addition of a triplet might be expected to involve two adiabatic bond-making processes, with spin inversion being a discrete, intermediate step. Since spin inversion was expected to be 'slow',[46] it was presumed that 'fast' rotation of the intermediate would destroy the steric relationships originally present in the olefin.

Triplet carbenes may be considered as diradicals, although the interaction of two unpaired electrons in orbitals of the same carbon atom gives rise to peculiarities. Singlet carbenes are electron deficient species comparable to carbonium ions; they also posses a non-bonding pair of electrons comparable to carbanions. The electrophilic or nucleophilic character of singlet carbenes therefore depends strongly on the ability of adjacent groups to withdraw electrons from, or supply electrons to, the carbene carbon.

The term carbenoid has been suggested for the description of intermediates which exhibit reactions qualitatively similar to those of carbenes without necessarily being free divalent carbon species.

Direct photolysis of diazo compounds generally produces singlet carbenes and these highly reactive species will then either react with any nucleophiles present or undergo a rearrangement reaction. The most common reaction for an α-keto carbene is to undergo the Wolff rearrangement[47,48] (Scheme 7). They are also prone to react by way of



Scheme 7

an intramolecular [1,2] H-shift to afford α,β-unsaturated ketones [2-12]. [49,50]

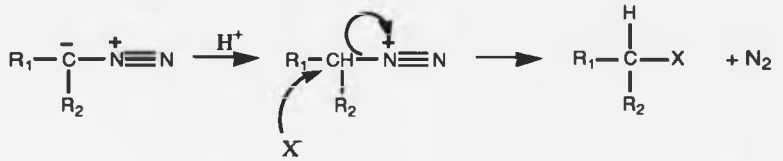
[2-12]

Thermolysis can also lead to the production of carbenes but is not often used since solution temperatures of around 180°C are required.

Transition metal catalysts also cause the loss of nitrogen to produce a carbene. The use of these catalysts lowers the decomposition temperatures and alters the reactivity of the carbene intermediate by forming a complex. Copper, palladium and rhodium salts have been used for this purpose. The intermediate carbenoid is much more stable than the free carbene and as such is less likely to undergo side reactions.

2.5 Non-carbenoid reaction of diazo groups

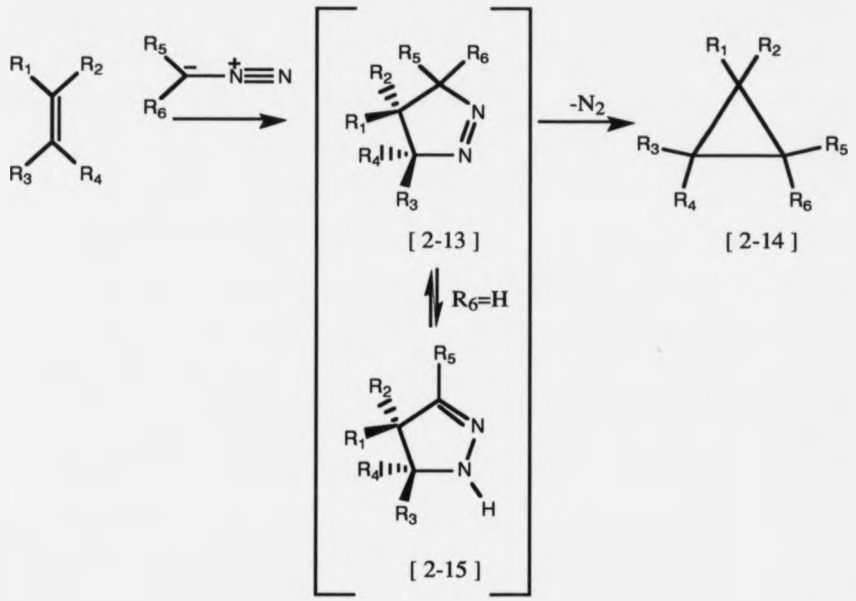
Diazo compounds react rapidly with electrophilic species at the α-carbon. Acids very easily protonate the α-carbon leaving a species which is very reactive towards nucleophiles (Scheme 8). A similar process will occur when the diazo compound is exposed to a halogen, resulting in the formation of a gem dihalide.



Scheme 8

Diazo compounds are 1,3-dipoles and as such can undergo [3+2] cycloaddition reactions with alkenes to form 1-pyrazolines [2-13]. Experimental evidence in favour of a concerted cycloaddition, which is thermally allowed by the Woodward-Hofmann rules, has been summarised.[51] In a separate step nitrogen can be extruded from the pyrazoline to give a cyclopropane [2-14].[52] The extrusion usually occurs under thermal conditions but can also take place photochemically. The initially formed 1-pyrazolines may undergo double bond positional isomerisation to give 2-pyrazolines [2-15], especially when a hydrogen substituent next to nitrogen is reasonably acidic due to the presence of electron-withdrawing groups. In general, electron deficient alkenes will readily form pyrazolines whereas unsubstituted alkenes and those with electron donating substituents will react very slowly if at all.

The initial cycloaddition is generally stereospecific and is considered to be concerted. The regioselectivity of these dipolar additions is not consistently predictable, based upon substitution patterns, unlike other cycloadditions such as Diels-Alder reaction. However, this point is usually of little consequence in the overall transformation leading to cyclopropanes since the two possible regioisomers are converted into the same final product upon loss of nitrogen.



2.6 Rhodium catalysed decomposition of diazo compounds

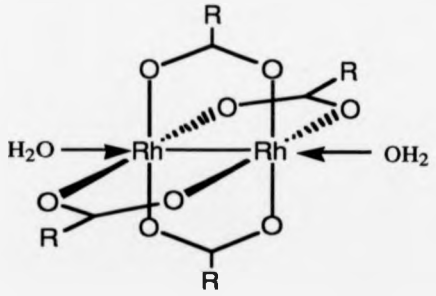
2.6.1 Introduction

The use of metal catalysts for the decomposition of diazo compounds has become increasingly common,[53,54] while the use of thermal and photochemical methods has declined due to the side reactions which occur. Many generalisations have been made to describe several different aspects of the metal-catalysed reactions.

Both heterogeneous and homogeneous catalysts have been used in these reactions. These catalysts have consisted of compounds or complexes of many different metals, but the most common have been copper derivatives[55,56] or metallic copper itself. The development of dimeric rhodium (II) carboxylates [2-16][57-62] as extremely mild catalysts for decomposition of diazo compounds has greatly enhanced the whole field

of carbenoid chemistry and they have quickly become the preferred catalysts. For this reason the rhodium catalysts are reviewed in detail in this section.

Commercially available rhodium (II) acetate , $Rh_2(OAc)_4.2H_2O$ [2-16a], has been the most extensively used catalyst, rhodium (II) pivalate [2-16b] and hexanoate [2-16c] often offer advantages due to their greater solubility. Complexes with electron withdrawing ligands such as trifluoroacetate [2-16d] result in less back-bonding to the carbenoid, producing a more reactive electrophilic carbenoid.[60] Alternatively, the use of rhodium (II) acetamide, $Rh_2(NHCOMe)_4$, generates a carbenoid with greater back-bonding to the metal than in the case of rhodium (II) acetate, resulting in a system with greater selectivity.[63]



	R
a)	Me
b)	tBu
c)	$(CH_2)_4Me$
d)	CF_3

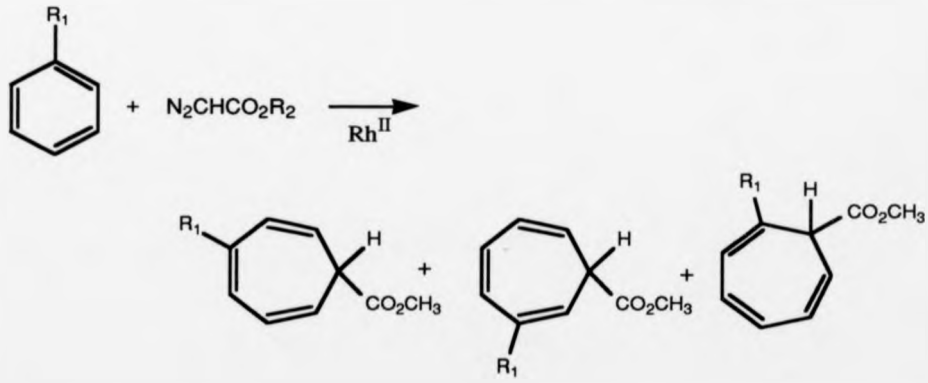
[2-16]

2.6.2 Cyclopropanation

In 1976, Hubert and workers[58] reported that rhodium (II) acetate efficiently catalysed diazo insertion into alkenes to give cyclopropanes. Alkene geometry is retained as would be expected for a concerted process. Almost any kind of alkenes will work with the notable exception of the electron poor olefins, presumably because the latter prefer to undergo 1,3-dipolar cycloaddition reactions.

Intramolecular cyclopropanation reactions can also occur.[64,65] The product obtained will depend on the stability of the cyclopropane formed, and the latter may rearrange to give a ring expansion product.

Ring expansion products result from initial rhodium carbenoid cyclopropanation of aromatic compounds. As an extension to Buchner's classical work on the formation of cycloheptatrienes by cycloaddition of carbenes to aromatic substrates, Hubert and co-workers[59] found that rhodium (II) carboxylates of strong organic acids are highly efficient catalysts. In particular, rhodium (II) trifluoroacetate catalyses the formation of cycloheptatrienes from aromatic compounds and diazo-esters with very high selectivity. In the case of benzene and toluene the yield is almost quantitative (Scheme 9).



R_1	% yield	Distribution of isomers (%)		
H	100		100	
CH_3	95	56	23	17
Cl	72	80	15	5
anisole	73	56	8	0

Scheme 9

2.6.3 Carbenoid insertion into X-H bonds (X= O, S, N)

In 1973, Hubert and co-workers[57] reported the homogeneous rhodium catalysed insertion of ethyl diazoacetate into hydroxylic bonds of alcohols, water and weak acids (Scheme 10).

$$R{-}OH + N_2CH_2CO_2Et \xrightarrow[25^\circ C]{Rh_2(OAc)_4} ROCH_2CO_2Et$$

R	%yield
Et	88
iPr	83
tBu	82
H	80
CH_3CO	93

Scheme 10

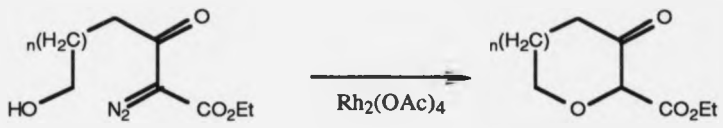
The relative reactivity of O-H bonds towards attack by carbethoxycarbene produced in this catalytic reaction was given: ethanol 2.12; *iso*propanol 1.2; *t*-butanol 1.0. This is also the order of decreasing acidity of the alcohols as well as the order of increasing steric hindrance. In a later paper,[66] Huberts' group subsequently reported that other nucleophiles also underwent an insertion reaction with rhodium carbenoids (Scheme 11).

$$R{-}XH + N_2CH_2CO_2Et \xrightarrow{Rh_2(OAc)_4} RXCH_2CO_2Et$$

R-XH	temp(C)	%yield
phenol	25	90
thiophenol	25	92
aniline	80	70

Scheme 11

More recently Moody *et al*, in a series of papers,[67-69] have reported that the intramolecular rhodium carbenoid insertion into OH bonds leads to cyclic ethers [2-17].



[2-17]

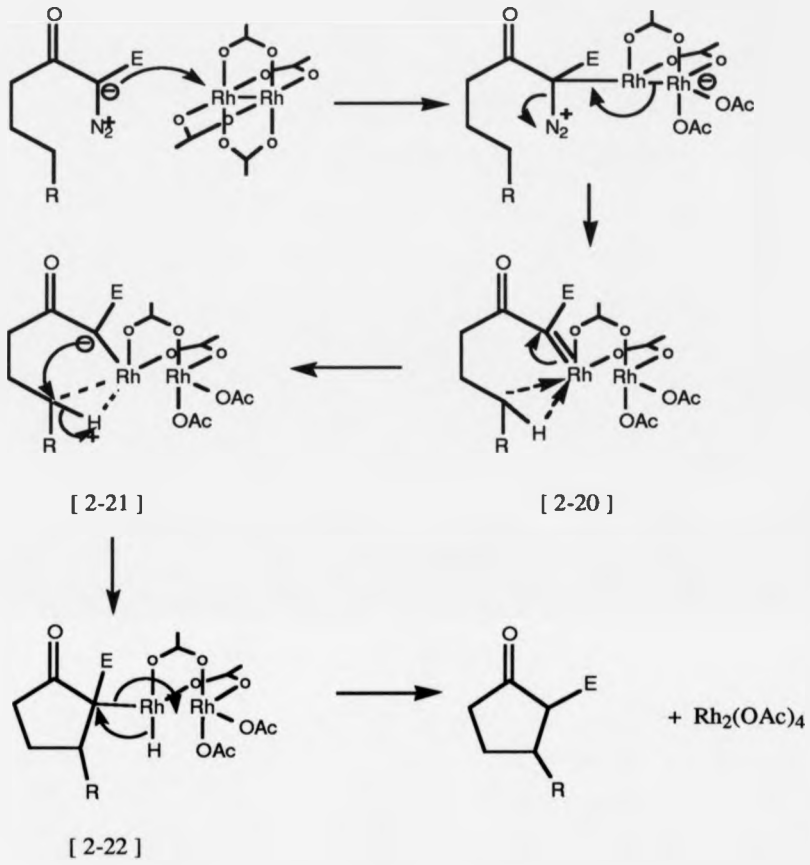
Moody and Taylor[70] also reported that rhodium carbenoids will insert intramolecularly into SH bonds to give cyclic thioethers, via a sulphonium ylide which is quite stable and can sometimes be isolated (see section on ylides).

2.6.4 Insertion into C-H bonds.

The carbenoids generated by rhodium (II) carboxylates from α-diazocarbonyl compounds have been reported to be effective in C-H insertion under extremely mild conditions. α-Diazoketones [2-18] can undergo intramolecular C-H insertion to form the corresponding cyclopentane[71] [2-19].

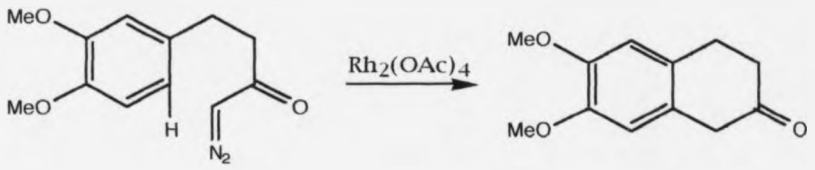
[2-18] [2-19]

Although the mechanism of this reaction is not clear, Taber and Ruckle[72] have offered a hypothesis which accounts for preferential 5-membered ring formation.



The first step requires the formation of a Fischer-type metal-carbene complex [2-20] at a vacant coordination site on rhodium (a well accepted assumption based on the cyclopropanation mechanism). In the next step it is not known whether the C-H insertion is a 3-bond process [2-21]. The role of the carboxylate ligands is also unknown. A hydrogen atom ends up on the rhodium [2-22], followed by a β-hydride transfer from the metal to regenerate the catalyst.

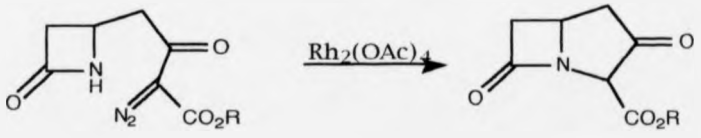
Aromatic C-H insertion is well known[73] (Scheme 12). However, it has not yet been established whether the mechanism is via the Taber route, or via a cyclopropyl intermediate.



Scheme 12

2.6.5 Heteroatom-H insertion

Rhodium (II) mediated heteroatom-H insertion may proceed by initial coordination of the intermediate metal-carbene complex with the non-bonding electrons of the heteroatom. Proton transfer would then give the observed product. This can be an efficient process both for forming C-N bonds[74,75] and C-O bonds.[67,76] A good example of this type of reaction is the key step in the Merck synthesis of carbapenams [2-23].[74,77] The ring closure step is regarded as nucleophilic attack by the lactam N-H on the rhodium carbenoid, rather than insertion into the N-H bond.

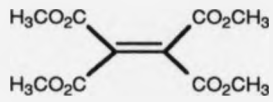


[2-23]

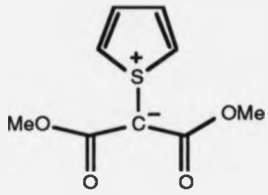
2.6.6 Ylide formation

Thermal and photochemical decomposition of diazoacetic esters in the presence of unsaturated heterocycles such as thiophene, furan and pyrrole[78] give cyclopropanated products. Electrophilic carbenoids can react with sulphur compounds to give sulphonium ylides.[79] If the carbenoid substituents are electron withdrawing enough, the ylides are

stable and can be isolated. A recent review on ylide formation from carbenoids has been written by Padwa and Hornbuckle.[80] Gillespie *et al* [81] showed that rhodium (II) acetate catalysed decomposition of dimethyl malonate in the presence of thiophene under refluxing conditions gave dimer [2-24], but if the reaction is done at room temperature then the sulphonium ylide [2-25] can be isolated as a crystalline solid.

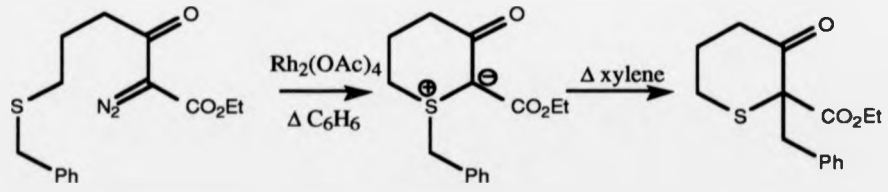


[2-24]



[2-25]

Stable cyclic sulphonium ylides are not as well known in the literature as acyclic sulphonium ylides. However, Moody and Taylor[70] have reported that 1,5 and 1,6-diazo sulphides will undergo rhodium catalysed cyclisation to give sulphonium ylides, some of which can be isolated [2-26], or undergo a 1,2 rearrangement to give the thiane [2-27].



[2-26]

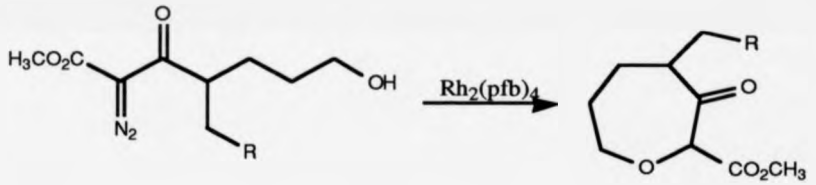
[2-27]

Carbonyl ylides are not stable enough to isolate, but they are used as intermediates, being trapped by undergoing 1,3 dipolar cycloaddition reactions both inter-[82] and intramolecularly.[83,84]

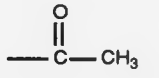
2.6.7 Chemoselectivity

The question of which type of reaction will occur in diazo compounds which contain more than one functional group has recently attracted considerable attention.

Reactions of rhodium carbenoid species with unsaturated alcohols show a preference for O-H insertion over cyclopropanation.[62,85] In the case of diazo compound [2-28], using rhodium perfluorobutyrate as a catalyst, insertion is exclusively into the O-H bond with a yield of 60%. Diazo compound [2-29] gave a mixture of products from which nothing was isolated, but NMR data suggested that both O-H insertion and carbonyl ylide formation had taken place.

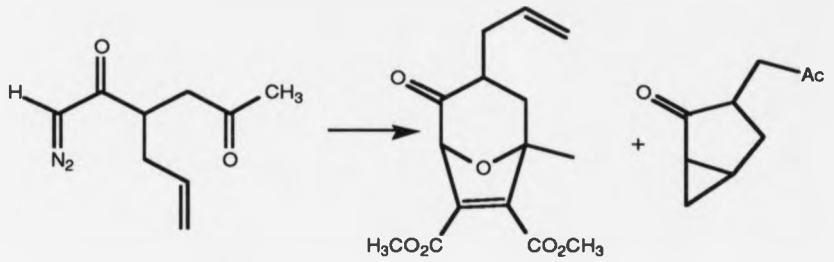


R = $HC{=}CH_2$ [2-28]



[2-29]

Rhodium (II) acetate decomposition of diazo compound [2-30][85] in dimethyl acetylenedicarboxylate (DMAD) gave a mixture of two products: [2-31] which arises from the 1,3-cycloaddition of DMAD to trap the ylide formed from the carbene carbonyl reaction, and [2-32] which is formed by the cyclopropanation of the double bond. The conclusion was drawn that there is a slight preference for carbonyl ylide formation over cyclopropanation.

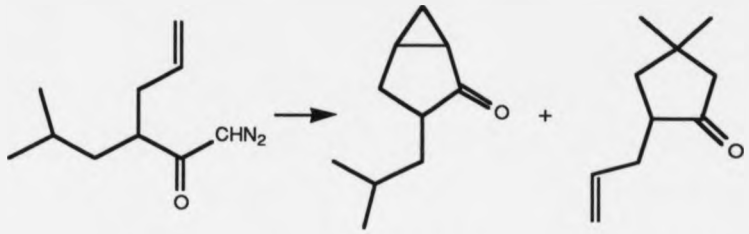


47% 33%

[2-30] [2-31] [2-32]

Padwa *et al* [86] have varied the rhodium ligands to try to favour one reaction over the other. They studied the chemoselectivity of C-H insertion over cyclopropanation, aromatic substitution and aromatic cycloaddition.[87] Rhodium (II) acetate was used as a standard catalyst and its results compared with those of rhodium (II) perfluorobutyrate [$Rh_2(pfb)_4$] and rhodium (II) caprolactamate [$Rh_2(cap)_4$]. Changing ligands on the rhodium causes substantial changes in electron density at the rhodium nucleus relative to that of $Rh_2(OAc)_4$. In the case of $Rh_2(pfb)_4$ the metal carbene formed is highly electrophilic, whereas the metal carbene formed from $Rh_2(cap)_4$ is only weakly electrophilic.

Competition between cyclopropanation and insertion into C-H bonds provides an example of ligand effectiveness in controlling chemoselectivity. Addition of diazoketone [2-33] to $Rh_2(OAc)_4$ in methylene chloride resulted in the formation of the cyclopropane derivative [2-34] and the C-H insertion product [2-35] in roughly equal amounts. When $Rh_2(cap)_4$ was used to catalyse the reaction only formation of cyclopropane [2-34] was observed, whereas catalysis by $Rh_2(pfb)_4$ resulted in the exclusive formation of the insertion product [2-35]



[2-33] [2-34] [2-35]

	relative yield (%)	
$Rh_2(OAc)_4$	44	54
$Rh_2(pfb)_4$	0	100
$Rh_2(cap)_4$	100	0

This selectivity is suprising in view of the order for functional group nucleophilicity which places a C=C bond at a significantly higher level of reactivity than a C-H bond. $Rh_2(pfb)_4$ favours C-H insertion suggesting that a major contributor to this selectivity is the increased electrophilicity at the carbene centre.

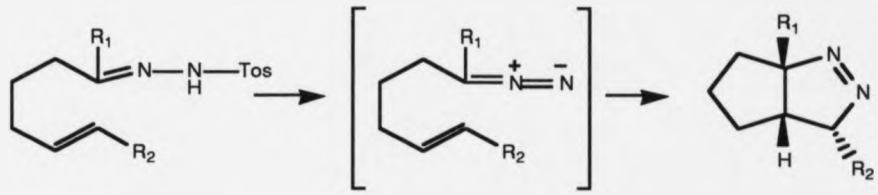
2.7 Diazoalkenes

Some diazoalkenes can be isolated, although many undergo intramolecular cycloadditions at room temperature. The intramolecular cycloaddition of non-activated alkenes also readily occurs. For this reason, diazoalkenes have often been treated as reactive intermediates. Both 1,3-cycloaddition and 1,1-cycloaddition reactions have been observed, depending on the substrate geometry.

2.7.1 Open-chain diazoalkenes

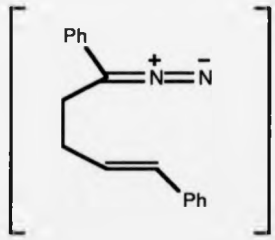
Open-chain diazoalkenes can conceivably cyclise to give either fused or bridged bicyclic products. Only fused products have been reported. Thus when the 1-diazo-alk-5-ene [2-36] is formed from its tosylhydrazone

precursor [2-37] it cyclises to a 5,5-fused bicyclic pyrazoline [2-38] in 69% overall yield.[88]



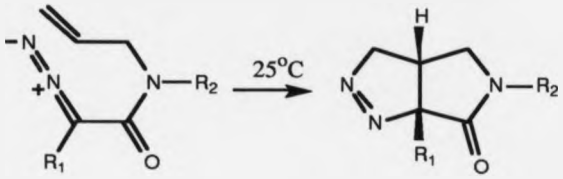
[2-37] [2-36] [2-38]

In contrast, the 1-diazo-alk-4-ene [2-39] did not cyclise at room temperature and was stable unless exposed to air. The 1-diazo-alk-6-ene cyclises only in 16% yield. Longer intervening chains have not been investigated but reduced entropic activation would make these compounds unattractive candidates for high-yield cyclisation.



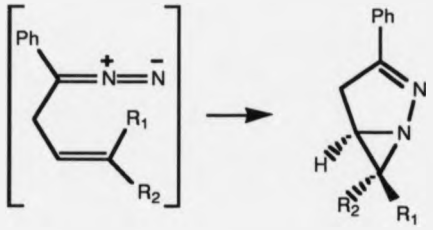
[2-39]

The diazo compound [2-40], prepared from the nitrosamine, cyclised to a pyrrolopyrazoline in 80% yield.[89] The diazo compound [2-41], prepared from diethyl diazomalonate and allylamine, cyclised similarly but at a much more rapid rate. In contrast to the above results, the diazo compounds [2-42] and [2-43] with a one carbon intervening chain undergo exclusive 1,1-cycloaddition.[88] These cyclisations are stereospecific; the alkene stereochemistry is retained.[88,90]



[2-40] R_1=H; R_2=Ph; 80%

[2-41] R_1=CO_2Et; R_2=Me; 90%

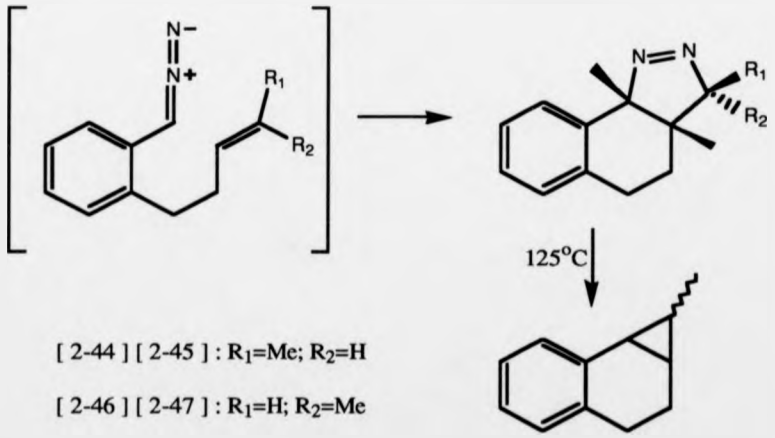


[2-42] R_1=Me; R_2=H; 51%

[2-43] R_1=H; R_2=Me; 46%

2.7.2 Aryl-substituted diazoalkenes

A number of aryl-substituted diazoalkenes have been shown to undergo cyclisation. Thus, diazo compounds [2-44] and [2-46] cyclise to give pyrazolines [2-45] and [2-47] respectively.[91] The alkene stereochemistry was retained in these cyclisations as in the 1,1-cyclisations. The pyrazolines [2-45] and [2-47] both undergo nitrogen extrusion to afford cyclopropanes: this reaction, however, is non-stereospecific.

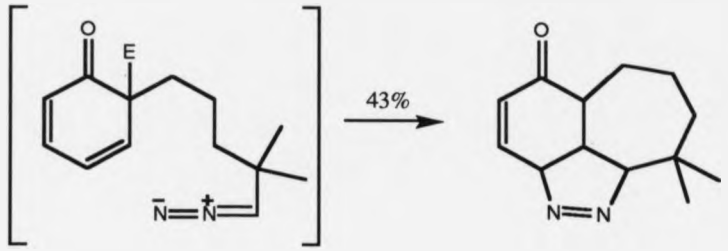


[2-44] [2-45] : R_1=Me; R_2=H

[2-46] [2-47] : R_1=H; R_2=Me

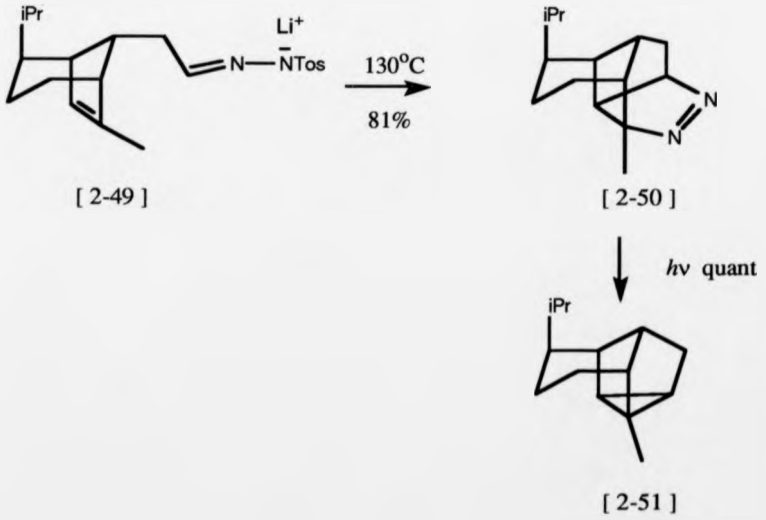
2.7.3 Diazocycloalkenes

A variety of cyclic diazo substrates have been shown to undergo cyclisation. Thus, the diazodiene [2-48] undergoes intramolecular 1,3-cycloaddition in 43% yield.[92]



[2-48] [2-49]

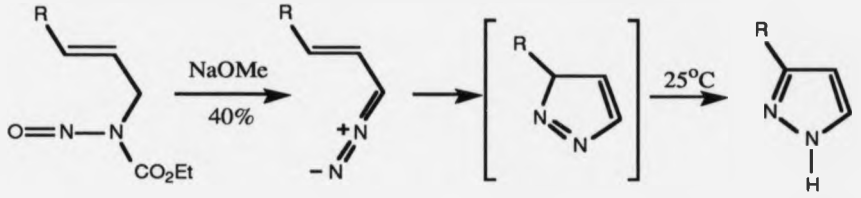
The bicyclic tosylhydrazone salt [2-49] afforded a tetracyclic pyrazoline [2-50] in 81% yield from which nitrogen could be extruded to afford (-)-cyclocopacamphene [2-51].[93]



[2-49] [2-50] [2-51]

2.7.4 Cyclisation of 3-Diazoalkenes

3-Diazoalkenes have been known to cyclise to pyrazoles since 1935.[94,95] This reaction has been rationalised as another variation of intramolecular 1,3-dipolar cycloaddition.[96] The nitrosocarbamates [2-52] were used as precursors of the 3-diazoalkenes [2-53]. The red 3-diazoalkenes were allowed to stand in the dark at room temperature and readily cyclised to pyrazoles [2-54].



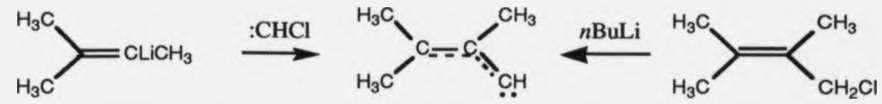
[2-52] [2-53] [2-54]

R	% yield
H	100
CH_3	100
m-NO_2 phenyl	89
p-Cl phenyl	87
phenyl	86

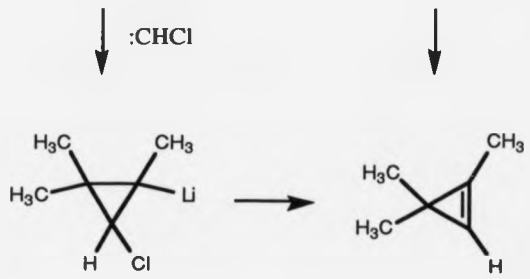
2.7.5 Vinyl Carbenes

In 1961, Closs and Closs[97,98] described the synthesis of cyclopropenes via an alkenyl carbene. Chlorocarbene, generated from methylene chloride, was postulated to add to the π electrons of the alkenyl lithium compound [2-55] to form hypothetical intermediate [2-56], or react with the non-bonding electrons of the incipient carbanion of [2-55] to yield alkenyl carbene [2-57]. Intermediate [2-56] could then give the observed cyclopropene [2-58] by β-elimination of LiCl, while alkenylcarbene [2-

57] can be visualised to cyclise to the same product by rotation of the gem-dimethyl group through 90°.



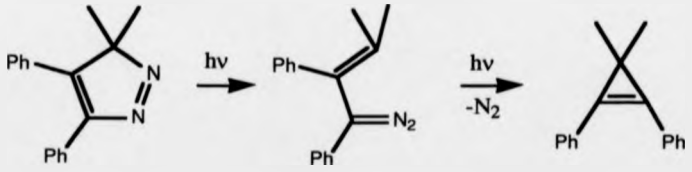
[2-55] [2-57] [2-59]



[2-56] [2-58]

Using a more direct route, *n*-BuLi was added to a solution of 1-chloro-2,3-dimethyl-2-butene [2-59] in THF at -15°C, resulting in the formation of cyclopropene [2-58]. This result is difficult to explain without invoking the alkenylcarbene intermediate [2-57], generated by α-elimination of hydrogen chloride from alkene [2-59].

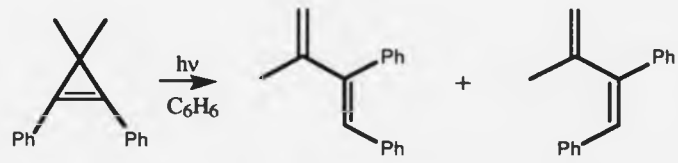
Pincock *et al*, [99] reported the synthesis of the cyclopropene [2-60] from the pyrazole [2-61] using UV radiation. During photolysis the solution turned deep red suggesting the diazo compound [2-62] had been formed as an intermediate. Cyclopropene [2-60] was isolated in high yield.



[2-61] [2-62] [2-60]

The accepted mechanism for the thermal and photochemical decomposition's of diazo compounds is loss of nitrogen to form, in this case, a vinyl carbene. Little is known about the structure and reactivity of such species. They are strongly implicated as intermediates in cyclopropene synthesis,[100] and the pyrolysis of cyclopropenes. [101,102]

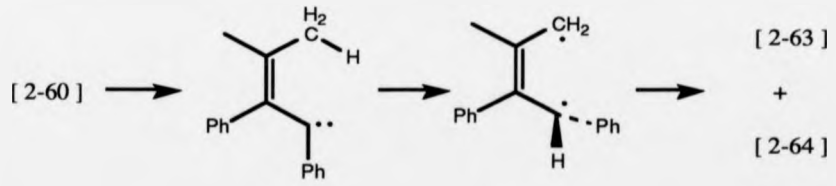
Direct irradiation of [2-60] gave a mixture of alkadienes [2-63] and [2-64].



[2-60] [2-63] [2-64]

Yield=15%. ratio 75% 25%

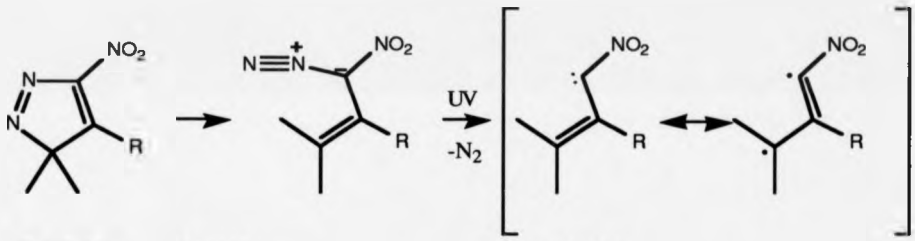
To account for these observations it was proposed[99] that the excited singlet state of the cyclopropene [2-60] opened to give vinyl carbene [2-65]; intramolecular migration of hydrogen gave the diradical [2-66] which rearranges to give alkadienes [2-63] and [2-64].



[2-65] [2-66]

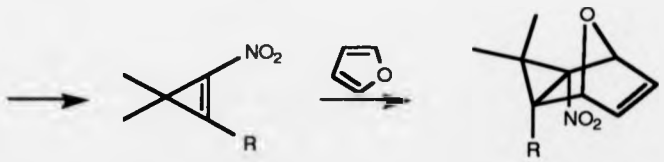
The low product yield and slow rate of disappearance of cyclopropene [2-60] may indicate the return of the vinyl carbene [2-65] to the cyclopropene [2-60] as observed in the thermal decomposition of a cyclopropene.[101]

More recently, Neumann and Miesch [103] have shown that photolysis of both the 3H-pyrazoles [2-67] and [2-68] in a relatively inert solvent such as methylene chloride or ether gave quantitative evolution of nitrogen, but no products could be isolated or characterised from the reaction mixture. However, photolysis in the presence of furan led to the Diels-Alder adduct [2-71] being formed as the major product along with other isomeric mixtures. It appears that the 3H-pyrazole eliminates nitrogen under UV radiation to give a vinyl carbene [2-69] which cyclises to give the nitrocyclopropene [2-70] which is too unstable to be isolated but can be trapped as the Diels-Alder adduct [2-71].



R= C_6H_6 [2-67] [2-69]

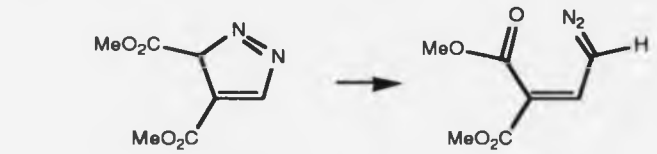
R= CN [2-68]



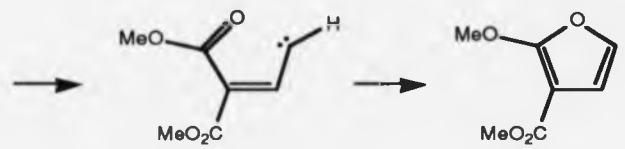
[2-70] [2-71]

In 1991, Nakano *et al* [104] also showed that the 3H-pyrazole [2-72] undergoes photochemical ring opening to the diazoalkene [2-73] followed by decomposition to the vinyl carbene [2-74]. In this case the carbene is trapped by the oxygen of the carbonyl group to give

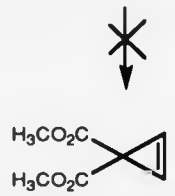
exclusively the furan [2-75]. The formation of the furan is favoured over the formation of the much more highly strained cyclopropene [2-76].



[2-72] [2-73]

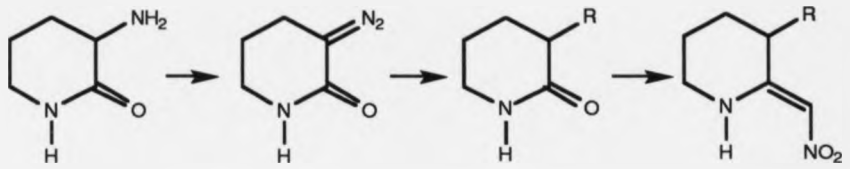


[2-74] [2-75]



[2-76]

Objectives



Initially it was proposed to synthesise 3-diazo-2-piperidone by the diazotisation of 3-amino-2-piperidone which was readily available from ornithine hydrochloride. Catalytic decomposition of 3-diazo-2-piperidone would give a wide range of novel 3-substituted-2-piperidones. Nitromethylenation of these piperidones using methodology described in the literature would allow the synthesis of some novel 3-substituted-2-(nitromethylene)piperidines.

A more direct route to these compounds would be by the catalytic decomposition of 3-diazo-2-(nitromethylene)piperidine. However, compounds containing the 3-diazo-1-nitropropene group are unknown in the literature. If the synthesis of 3-diazo-2-(nitromethylene)piperidine could be achieved and if it proved sufficiently stable to handle, it would provide the opportunity to investigate the behaviour of the first member of a new class of diazo compound. This might have its own unique chemistry and might also provide access to otherwise inaccessible compounds.

Chapter 3 Results and Discussion.

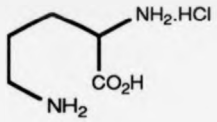
3.1 Synthesis of 3-diazo-2-piperidone.

3-Amino-2-piperidone [3-2] is readily available by the cyclodehydration of L-ornithine hydrochloride [3-1] by various methods.[105-108] In 1978, Pellegata *et al* [105] described the synthesis of 3-amino-2-piperidone as the (S)-isomer, by refluxing L-ornithine hydrochloride in acetonitrile with an excess of hexamethyldisilazane under dry nitrogen for 48hrs. This mixture was then cooled, poured into cold methanol and evaporated to dryness. The residue was taken up in chloroform, filtered through celite and evaporated to give (S)-3-amino-2-piperidone as a white crystalline solid in 91% yield. Our attempts to repeat this method resulted in only 60% yield. This method has the disadvantage of long reaction times and expensive reagents (hexamethyldisilazane) when large quantities are required.

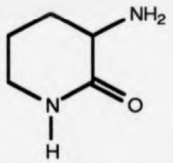
In 1983, Winter *et al* [106] described the cyclodehydration of L-ornithine hydrochloride in methanol. Dry HCl gas was bubbled through the solution until the ornithine had dissolved. The solvent was removed and the residue taken up in water and passed through a Dowex 2 (OH form) column. After evaporation of the water, the residue was dissolved in warm ethyl acetate, filtered and reduced under vacuum to leave (S)-3-amino-2-piperidone as a white crystalline solid in 76% yield. Our attempts to repeat this reaction resulted in a 53% yield.

3-Amino-2-piperidone has also been synthesised in the racemic form by Oklobdzija *et al.*[107] This involved the stirring of L-ornithine hydrochloride with thionyl chloride in methanol for 14hrs. Work up was the same as that used in Winters' method. The yield was 90%. The disadvantages of this method are the long reaction times and a yield of only 48% when we repeated this work.

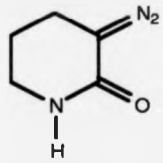
In 1980, Bladé-Font[108] had also described the synthesis of 3-amino-2-piperidone by first dissolving L-ornithine hydrochloride in a minimum amount of water containing one equivalent of sodium hydroxide to free the amine, and then refluxing this solution in toluene for 3hrs over neutral alumina. The excess water and the water produced during the reaction were collected via a Dean-Stark trap. Filtration followed by evaporation of the solvent gave the pure product in 79% yield. Repeating this but refluxing for only 1.5hrs we found that 3-amino-2-piperidone was formed in greater than 90% yield, and that this yield was also obtained in large scale reactions (over 100g). This method also takes the shortest length of time and is the most economical, as the alumina can be reused without purification.



[3-1]



[3-2]



[3-3]

Diazotisation of the amino lactam [3-2] was attempted using a 2-phase system[109], with sodium nitrite and perchloric acid in the aqueous phase and methylene chloride in the organic phase, but without success. The aqueous phase was seen to change colour from very pale yellow to dark yellow indicating the possibility that diazotisation was taking place, but that the product was too water soluble to be extracted into the organic phase.

Takamura *et al* [25] described the diazotisation of α-amino-esters using a slight excess of isopentyl nitrite in chloroform with a catalytic amount of glacial acetic acid. Adopting this method for the present work but using methylene chloride as solvent, 3-amino-2-piperidone [3-2] was

converted to 3-diazo-2-piperidone [3-3] in 35% yield. The product was characterised by a strong band for the diazo group at 2088cm^{-1} in the infra-red spectrum. A series of experiments were then carried out to optimise the yield of this reaction.

Using a slight excess of isopentyl nitrite and 0.2 equivalents of glacial acetic acid, Table 6 shows chloroform to be the most efficient solvent for this reaction.

Table 6: Effect of solvent on the diazotisation of 3-amino-2-piperidone using 1.3eq amyl nitrite + 0.2eq acetic acid

time (min)	methylene chloride	chloroform	benzene
30	30%	48%	9%
60	38%	39%	14%
180	35%	-	10%

The product from this reaction is stable to silica gel chromatography, but very sensitive to exposure to acids. For this reason, the length of time and quantity of acid used in the experiment are crucial. Table 7 shows that the reaction is incomplete if refluxed for less than 15mins, but if left for longer than this, the product will gradually decompose.

Table 7: Effect of time on the diazotisation of 3-amino-2-piperidone using 1.3eq amyl nitrite + 0.2eq acetic acid in chloroform.

time (min)	yield %
60	39
30	48
15	53
10	50

Table 8 shows that the amount of acid used also affects the yield. Too much acid causes rapid decomposition of the product, whilst too little results in incomplete conversion.

Table 8: Effect of acid on the diazotisation of 3-amino-2-piperidone in chloroform using 1.3eq amyl nitrite, refluxing for 15mins.

eq acetic acid	yield %
0.3	36
0.2	53
0.15	60
0.1	51

Overall, the optimum conditions for the synthesis of 3-diazo-2-piperidone are to reflux the corresponding amine in chloroform with 1.3eq isopentyl nitrite and 0.15eq glacial acetic acid. It is important that once the reflux has been stopped, the reaction mixture is immediately quenched with an ice cold saturated solution of sodium hydrogen carbonate to remove the acetic acid present. Rapid work up on a silica column gave a bright yellow solid which was easily recrystallised from cyclohexene. The yellow needles are very stable (except to acids) and can be stored at 0°C for over 12 months without significant decomposition.

3.2 Synthesis of 3-Alkoxy-2-(nitromethylene)piperidines.

3.2.1 Rhodium catalysed insertion of 3-diazo-2-piperidone into O-H bonds of alcohols.

In 1973, Hubert and co-workers[57] described the rhodium-catalysed insertion of carbenoid species into O-H bonds of alcohols. They found that the time required for reaction and the yield were dependent upon the acidity and steric hindrance of the alcohol used.

Table 9 shows the reaction of 3-diazo-2-piperidone with a 2- and 5-fold excess of methanol as the reactant in the presence of rhodium (II) acetate using methylene chloride as a solvent. It can be seen clearly from the table that when a co-solvent is used, longer reaction times are required and a lower yield is produced. Various copper catalysts were used in an attempt to carry out this reaction. The products obtained were in yields typically lower than 10% and very impure. The only exception to this was the copper sulphate catalysed insertion into methanol which proceeded very quickly but with a yield of only 30%.

Table 9: Effect of catalyst and the effect of concentration of reactant upon the reaction of 3-diazo-2-piperidone with methanol

methanol	catalyst	time (hrs)	yield %
neat	$Rh_2(OAc)_4$	1.5	82
5 eq	$Rh_2(OAc)_4$	3.0	69
2 eq	$Rh_2(OAc)_4$	5.0	55
neat	$CuSO_4$	0.5	30
neat	$Cu(acac)_2$	4.0 reflux	10
neat	$Cu(OAc)_2$	5.0 reflux	< 5

3-Diazo-2-piperidone was decomposed with rhodium (II) acetate in the presence of a series of alcohols (Table 10), and the reactions followed by tlc. Infra-red spectroscopy of the products showed the disappearance of the diazo group at 2088cm^{-1} and the retention of the amide carbonyl at 1670cm^{-1}.

In the cases where the alcohols are liquids at room temperature they were used neat as solvents for the reaction. In all other cases, methylene chloride was used as the solvent with a 2-fold excess of the alcohol as reactant. A reaction in THF, with water as the carbenoid trapping agent, was also studied.

Table 10: Reaction of alcohols with 3-diazo-2-piperidone in the presence of rhodium(II) acetate

alcohol	yield %	time (hrs)	temp (°C)
methanol	82	1.5	25
ethanol	81	2.0	25
propan-2-ol	52	4.0	25
t-butanol	52	1.0	83
phenol*	68	5.0	25
benzyl alcohol	53	5.0	45
p-Cl benzyl alcohol*	66	8.0	25
water +	22	10.0	35
* CH_2Cl_2 as solvent		+ THF as solvent	

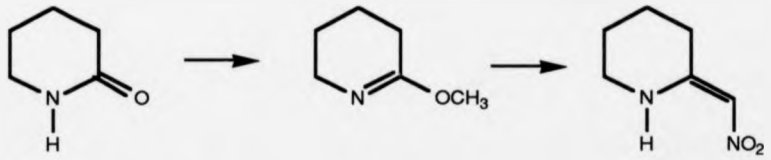
When considering the results in Table 10, the longer reaction times and the lower relative yields for the cases involving phenol and *p*-chloro benzyl alcohol can be explained by the results previously shown in Table 9 where a 2- and 5-fold excess of methanol produced lower yields

and longer reaction times. Otherwise Table 10 shows the expected results. Methanol and ethanol insert into the rhodium carbenoid in high yield with short reaction times. The more sterically hindered propan-2-ol requires a longer reaction time and results in a lower yield. *t*-Butanol reacts very slowly at room temperature: to obtain a reasonable yield the reaction mixture must be heated under reflux.

3.2.2 Nitromethylenation of 3-Alkoxy-2-Piperidones.

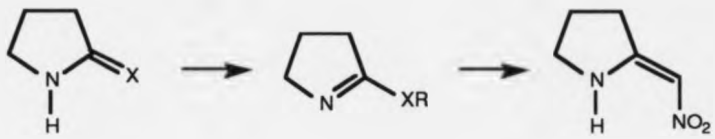
a) Introduction.

Nitromethylenation of 2-piperidone [3-4] can be achieved via a two step process. The first step involves the O-alkylation of the amide to produce iminoether [3-5]. The second step is a condensation reaction with nitromethane to give 2-(nitromethylene)piperidine [3-6].



[3-4] [3-5] [3-6]

Etienne and Correia[110] described the synthesis of 2-(methoxy) pyrrolidine [3-8] from 2-pyrrolidone [3-7] using dimethyl sulphate as the alkylating agent in refluxing benzene giving a yield of 63%. Meerwein *et al* [111] have reported that triethyloxonium tetrafluoroborate (Meerwein reagent) reacts readily with tertiary amides to give O-ethylated species. In 1964, Eschenmoser and co-workers[112] modified this reaction to O-ethylate α-pyrrolidones giving the corresponding iminoethers. In 1969, Oishi *et al* [113] showed that the corresponding 6-membered ring series reacted in the same way to give 2-ethoxy-3,4,5,6-tetrahydropyridines.

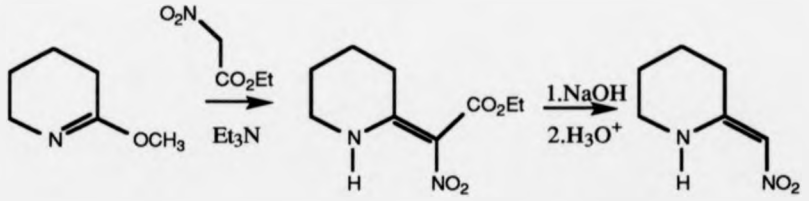


[3-7] X=O [3-8] XR= OMe [3-10]

[3-9] XR= SMe

Nitromethane has been successfully condensed with 2-(methylthio) pyrrolidine [3-9][114] and 2-(methoxy)pyrrolidine [3-8],[114,115] with the elimination of methanthiol and methanol respectively to form the nitromethylene compound [3-10].

Hirai *et al* [116] also described the use of the ethyl nitroacetate anion (Scheme 13) to form the nitromethylene group. Hydrolysis of the ester followed by decarboxylation gave 2-(nitromethylene)piperidine. This reaction may also be catalysed by zinc (II) chloride instead of a base.[116]



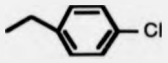
Scheme 13.

b) Nitromethylenation of 3-Alkoxy-2-Piperidones.

Attempts to O-alkylate 3-methoxy-2-piperidone using dimethyl sulphate were not very successful. NMR showed both N- and O-alkylation, but the products could not be isolated from the reaction mixture. However, the use of the more powerful Meerwein reagent proved successful. This also has the advantage of milder reaction conditions (refluxing in methylene chloride as opposed to benzene) and shorter reaction times.

Work up involved the quenching of excess Meerwein reagent with 5M potassium carbonate solution, extraction of the product with methylene chloride and distillation under reduced pressure. The product was isolated in 58% yield and characterised by the absence of signals for an N-H group in both the infra-red and the NMR spectra, and also the presence of an ethoxy group in the NMR. The ethoxy [3-12] and 3-(*p*-chlorobenzyloxy) [3-13] derivatives were produced using the same conditions in 54% and 77% yield respectively.

Petersen and Tietze[117] showed that in iminoethers, the alkyl group has a tendency to migrate from the oxygen to the nitrogen at high temperatures. In our work, we found that distillation of the final product must be carried out at reduced pressure to avoid the formation of the N-alkylated product.

[3-11]	Me	[3-14]
[3-12]	Et	[3-15]
[3-13]		[3-16]

Condensation of 2-ethoxy-3-methoxy-3,4,5,6-tetrahydropyridine [3-11] with a commercial grade of nitromethane gave only a 7% yield of the corresponding nitromethylene compound [3-14]. However, when the nitromethane was dried and freshly distilled from powdered 4A molecular sieves before use, the yield increased to 43%. The introduction of a catalyst (Table 11) had a varied effect on yield, with dry pyridine giving a yield of 52%. The 3-ethoxy [3-15] and 3-(*p*-

chlorobenzyloxy) [3-16] nitromethylene derivatives were produced in yields of 55% and 74% respectively, using pyridine as a catalyst.

All the final products showed a broad singlet at around 10.4δ in the NMR spectrum corresponding to the N-H of the piperidine ring strongly hydrogen bonded to the nitro group, whereas the N-H of the corresponding amides appeared between 6.5 and 7.5δ. The products also showed a singlet at 6.6δ corresponding to the olefinic proton in the nitromethylene group. The infra-red spectrum of the nitromethylene piperidine derivatives showed the disappearance of the C=Nstr at 1680cm^{-1} from the iminoether and the introduction of a strong band at 1605cm^{-1} due to a C=Cstr.

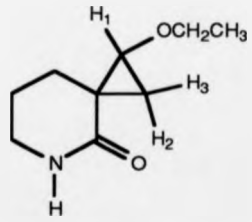
Table 11: Effect of catalyst on yield for the formation of 3-methoxy-2-(nitromethylene)piperidine

catalyst	yield %
control	43
solid K_2CO_3	36
Et_3N	43
dry pyridine	52
$ZnCl_2$	48
DMAP	50

3.3 Reactions of 3-Diazo-2-Piperidone with Alkenes.

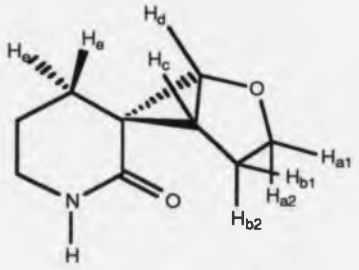
3.3.1 Rhodium (II) acetate cyclopropanation with electron rich olefins.

In the presence of rhodium (II) acetate and ethyl vinyl ether, 3-diazo-2-piperidone underwent smooth and rapid decomposition to give the cyclopropanated product [3-17]. The reaction was followed by tlc, and after the disappearance of the diazo compound (1hr) rapid work up on a silica column gave a white crystalline solid. The infra-red spectrum of this compound showed retention of the amide carbonyl at 1660cm^{-1}, and loss of the diazo group. Proton NMR shows the cyclopropyl protons at 0.7δ and 1.5δ(H_2,H_3) and 3.65δ (H_1) as well as the presence of an ethoxy group at 3.6δ(quartet) and 1.2δ(triplet). The NMR shows the presence of two ethoxy groups indicating that the product is a diastereomeric mixture. It was not possible to separate the two isomers by tlc.

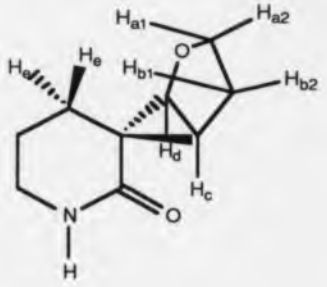


[3-17]

The reaction of dihydrofuran with 3-diazo-2-piperidone was considerably slower (12hr) than that with ethyl vinyl ether. After silica gel chromatography and recrystallisation from diethyl ether/ pentane, a single compound was obtained as a white crystalline solid. There are two possible isomeric products from this reaction, either the fused tetrahydrofuran ring connected *cis* to the amide carbonyl [3-18] or *trans* to the amide carbonyl [3-19].



[3-18]



[3-19]

2D COSY NMR (Table 12) showed that the cyclopropyl proton H(c) couples to protons H(d) and H(b2) but not H(b1). Computer modelling showed that in the case of isomer [3-19], vicinal protons H(c) and H(b1) are at a dihedral angle of approximately 90° to each other, so that a zero coupling constant would be expected from the Karplus equation. This observation suggested that the product isolated was the isomer [3-19].

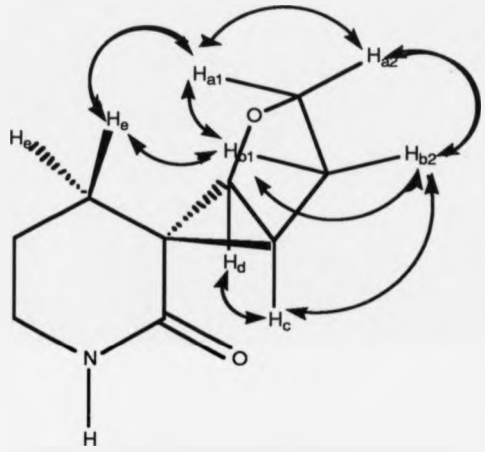
Table 12: 2D COSY NMR of cyclopropyl derivatives

proton	couples to			
a_2	a_1	b_1	b_2	
a_1	a_2	b_1	b_2	
b_1	b_2	a_1	a_2	
b_2	b_1	a_1	a_2	c
c	d	b_2		

A series of nOe difference spectroscopy experiments were carried out, the results of which are shown in Table 13. The cyclopropyl proton H(c) shows no nOe to any of the protons in the amide ring, whereas the protons H(a1) and H(b1) show nOe enhancement to the protons H(e), and as expected the reverse nOe enhancement from protons H(e) to protons H(a1) and H(b1) are also seen. This confirms that the product is

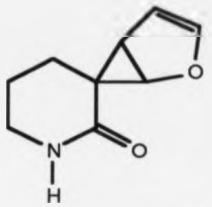
the isomer [3-19] and this is the one whose formation would be most favourable on steric grounds. There was no indication from the NMR of the crude reaction mixture that the isomer [3-18] had been formed.

Table 13: nOe difference spectroscopy for the bicyclic cyclopropyl derivative [3-19]

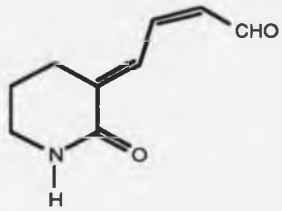


Irradiated proton	nOe observed		
a_1	a_2	e	b_1
b_2	a_2	c	b_1
c	d	b_1	b_2
e	a_1	g	b_1

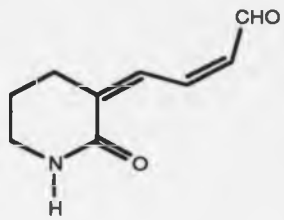
The reaction of 3-diazo-2-piperidone with furan proceeded rapidly in the presence of rhodium (II) acetate forming the cyclopropyl derivative [3-20] which was readily isolated in 60% yield following silica chromatography.



[3-20]



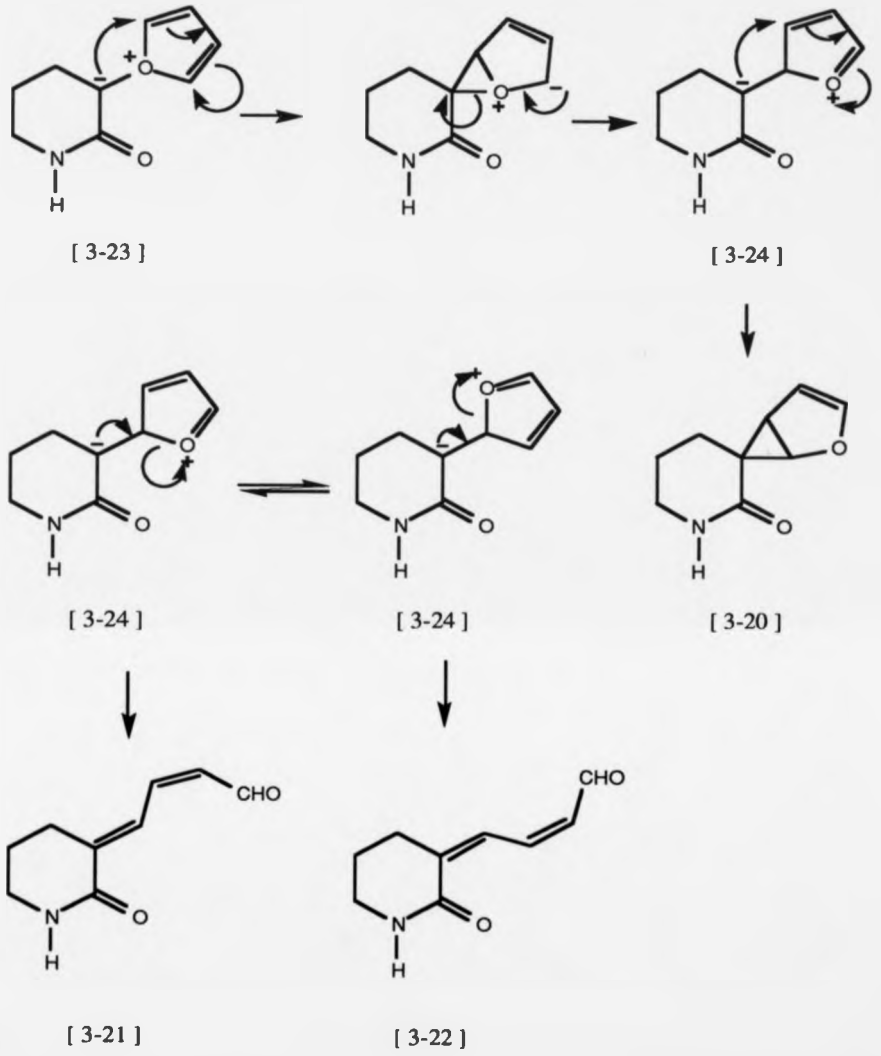
[3-21]



[3-22]

It is well known that furan can also react with diazo compounds in the presence of a rhodium catalyst to form dienals.[118] In this case we would expect to form dienals [3-21] and [3-22]. Evidence for these isomers could be seen in the NMR of the crude sample. Two aldehyde protons could be seen at 9.8 and 10.4δ as doublets as well as the three olefinic protons in the range 6.5-7.5δ. Estimated yields by NMR were 9% for each of the isomers [3-21] and [3-22]. However, attempts to purify either of these isomers by chromatography failed.

The mechanisms for the formation of the products from this reaction are outlined in Scheme 14. The first step is the formation of the oxonium ylide [3-23] from the rhodium carbenoid generated by the action of rhodium (II) acetate on 3-diazo-2-piperidone. This then undergoes a rearrangement to give intermediate [3-24] which can react in one of two ways, either by ring closure to form a cyclopropyl ring [3-20] or by ring opening to give either of the dienals [3-22] or [3-21].



Scheme 14

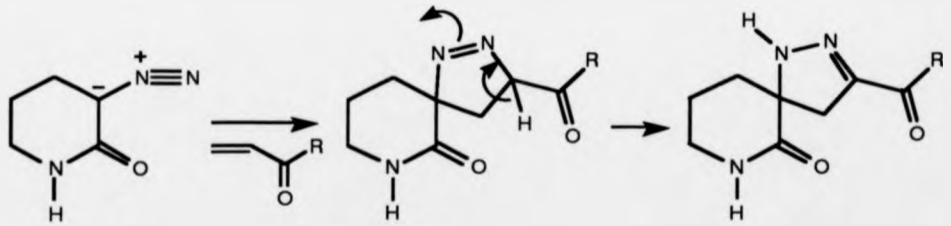
3.3.2 1,3-Dipolar Addition with Electron-Deficient Olefins.

3-Diazo-2-piperidone was found to undergo very fast, high yielding 1,3-dipolar addition to electron deficient olefins (Table 14) resulting in the formation of pyrazolines. This reaction occurred exclusively, even in the presence of rhodium (II) acetate.

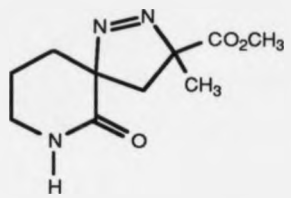
Table 14: 1,3-Dipolar cycloaddition of 3-diazo-2-piperidone with electron deficient olefins

alkene	yield %	time (min)
methyl vinyl ketone	91	30
methyl acrylate	95	30
acrolein	69	20
methyl methacrylate	67	240

The first three alkenes in Table 14 gave the 2–pyrazolines [3-26] which are presumed to be formed via an intermediate [3-25] which undergoes a 1,3 H-transfer. This H-transfer was blocked when methyl methacrylate was used, in this case the 1–pyrazoline [3-27] was obtained.



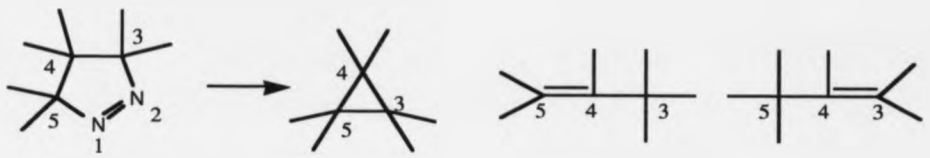
[3-25] [3-26]



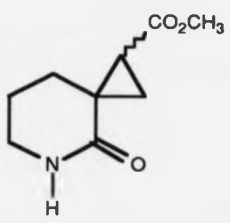
[3-27]

All the pyrazolines were identified by infra-red spectroscopy showing the presence of the amide carbonyl at 1650cm^{-1}, and the presence of a second carbonyl (ester, ketone or aldehyde) depending upon the alkene used. The ^{1}H NMR spectra of the compounds in each case showed a strong geminal coupling (17Hz) at 3.3δ and 2.6δ for the -CH_2- in the pyrazoline ring. The EI-mass spectrum of each of these compounds showed a strong prominent peak for the M-28 ion, indicating the extrusion of nitrogen from the molecular ion.

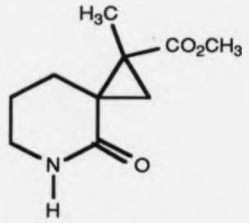
Theoretically, elimination of nitrogen from 1-pyrazolines can give rise to three types of products (Scheme 15), either a cyclopropane or one of two isomeric olefins. The cyclopropane is usually the major product. This was found to be the case when the 1-pyrazoline [3-27] was heated at 110°C in refluxing dioxan, the cyclopropyl derivative [3-29] was isolated in quantitative yield. Proton NMR showed the product to be a geometric isomer mixture, which could not be separated by tlc. Jones and Tai[119,120] have shown that isomeric cyclopropanes are formed upon extrusion of nitrogen from 1-pyrazolines. They also showed that the major products from these type of reactions could not easily be predicted.



Scheme 15.

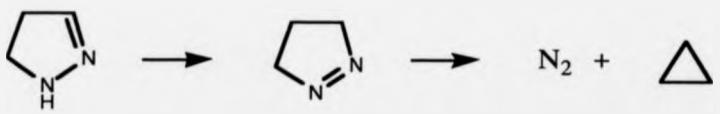


[3-28]



[3-29]

When applied to 2-pyrazolines the reaction is thought to involve prototropic rearrangement followed by loss of nitrogen from the 1-pyrazoline tautomer (Scheme 16).



Scheme 16.

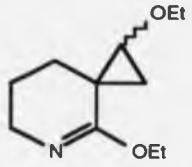
The 2-pyrazoline [3-26], which resulted from the 1,3-dipolar addition of methyl acrylate, extruded nitrogen when heated in solvent at 180°C to form the spirocyclopropane [3-28] which was shown by proton NMR to be a mixture of geometric isomers. The requirement of a higher temperature to extrude nitrogen from the 2-pyrazoline suggests that the rate-determining step of the pyrolysis is the tautomerisation and that subsequent loss of nitrogen is much more rapid than the initial step.

There have been no serious efforts to determine the mechanism of reaction after the loss of nitrogen. The generalised reaction has been viewed as a diradical recombination,[121,122] however, it has never been demonstrated that the reaction can be inhibited by radical scavengers and in one instance[123] such a decomposition has failed to initiate the polymerisation of styrene. For this reason a combined hydride ion shift and dipole recombination has not been ruled out.[124]

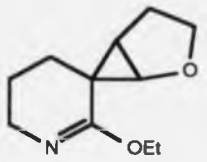
If the transition state is considered to be diradical, the decomposition products and the stereochemical relationships in the derived cyclopropanes can be explained by free radical chemistry. Direct photolysis of pyrazolines leads to cyclopropanes with retention of configuration, whereas thermal conditions give isomeric mixtures. The formation of triplet diradicals (from thermal conditions), having longer lifetimes than their singlet counterparts (from photochemical conditions), would explain the greater extent of stereochemical scrambling in thermal reactions.

3.3.3 Attempted Nitromethylenation of the Cyclopropyl Amides.

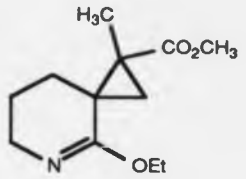
The cyclopropyl derivatives [3-17], [3-19] and [3-29] readily underwent alkylation with the Meerwein reagent to form their respective iminoethers [3-30], [3-31] and [3-32]. Trimethyloxonium tetrafluoroborate was found to give a slightly higher yield than the triethyl derivative (82% as opposed to 73% in the case of cyclopropyl derivative [3-17]).



[3-30]



[3-31]

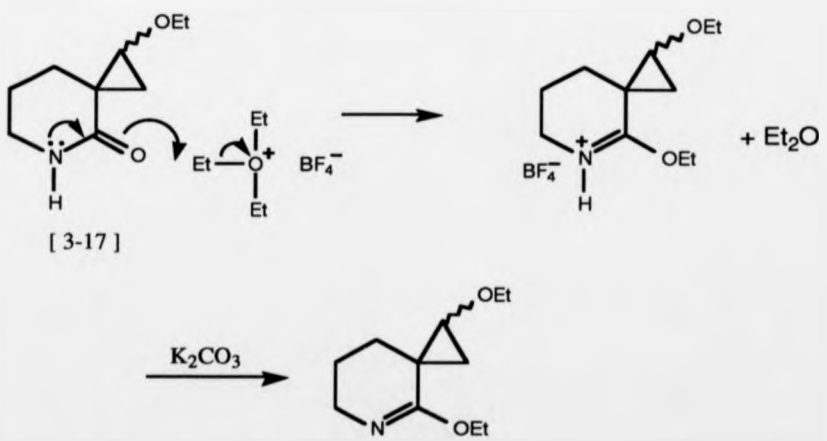


[3-32]

However, condensation of the above iminoethers with nitromethane was unsuccessful. Various bases were used in an attempt to catalyse this reaction as well as higher reaction temperatures and pressures, all with no success. Acid catalysis with zinc chloride also failed, as did attempts to react with the ethyl nitroacetate anion.

To explain why this reaction was not successful we must consider the mechanism of formation of the nitromethylene group.

O-Alkylation of the lactam [3-17] proceeds via the mechanism outlined in Scheme 17 to give the iminoether [3-30].

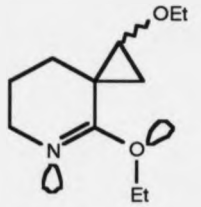


[3-17]

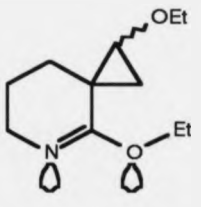
[3-30]

Scheme 17.

Open chain iminoethers can theoretically adopt one of 4 conformations, but as iminoether [3-30] is a cyclic structure there are only 2 conformations available [3-33] and [3-34]. Meese *et al*, [125] have shown that the most stable conformation would be that of conformer [3-33].

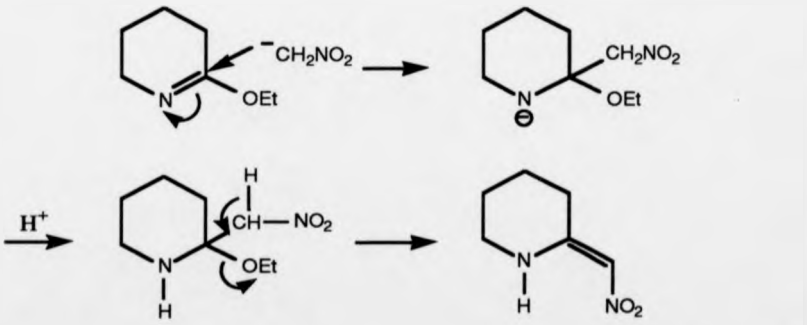


[3-33]



[3-34]

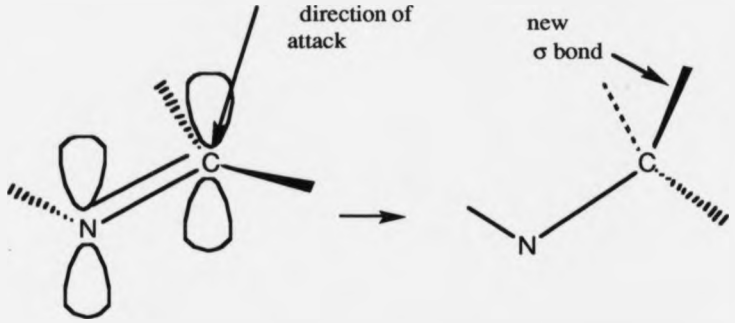
Condensation of iminoethers with nitromethane proceeds via a two stage process (Scheme 18). The first stage is nucleophilic addition of the nitromethane anion to the double bond, forcing the π electrons to become centred on the nitrogen. The nitrogen is then protonated, and this is followed by elimination of ethanol to give the corresponding nitroalkene.



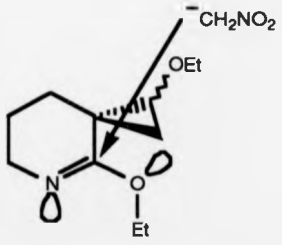
Scheme 18.

In the case of the cyclopropyl iminoethers [3-30], [3-31] and [3-32] the action of the nitromethane anion on the C=N bond can be viewed as nucleophilic attack on the positive carbon centre. The direction of attack

is from above the plane of the C=N bond and at approximately 110° to the N-C axis to give the correct position for the newly formed σ bond (Scheme 19). It can be seen from the diagram [3-35] that the attack of the nitromethane anion is sterically blocked by the position of the cyclopropyl group.



Scheme 19.



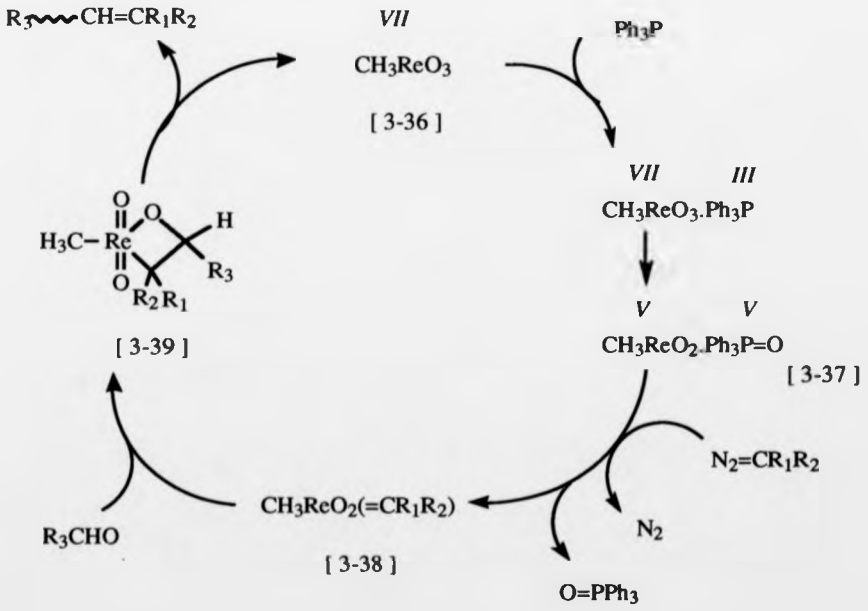
[3-35]

3.4 Aldehyde Olefination using Methyl Trioxorhenium Catalyst.

3.4.1 Introduction.

In 1991, Herrmann and Wang[126] described the use of methyl trioxorhenium (MTO) [3-36] as a catalyst for the coupling of aldehydes with diazo acetates and diazo malonates to produce a carbon carbon double bond. The reaction was carried out at room temperature with 5 mol% of catalyst, and 1 mol equivalent of triphenyl phosphine which acts as a reducing agent.

A mechanism has been proposed[126] for the reaction in which methyl trioxorhenium first generates the adduct [3-37] with triphenyl phosphite. This can be isolated and reacts with diazoalkanes to form a metal stabilised carbene [3-38], which adds to the carbonyl group of an aldehyde to form intermediate [3-39]. The oxo rhenium group is regenerated with the expulsion of the olefin.



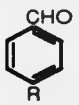
The reaction is not stereospecific with both (Z) and (E) isomers being formed in different ratios depending upon the aldehyde used.

3.4.2 Reaction of 3-diazo-2-piperidone with aldehydes in the presence of methyl trioxorhenium.

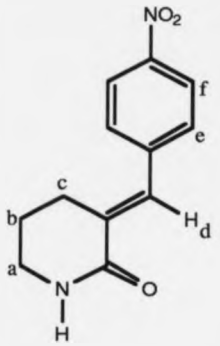
MTO was synthesised by refluxing rhenium (VII) oxide with tetramethyltin for 4hrs in THF.[127] It is important that the solvent was dried before use and that the reaction was carried out under a nitrogen atmosphere. Removal of the solvent left a brown solid from which the MTO could easily be sublimed as white needles.

3-Diazo-2-piperidone was found to react readily with aromatic aldehydes in the presence of MTO and triphenyl phosphine. However, reaction with aliphatic aldehydes produced very low yields and the products were difficult to purify. The reaction times for the aromatic aldehydes were quite long and the yields not very high (Table 15).

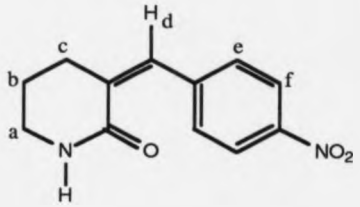
Table 15: Reaction of 3-diazo-2-piperidone with aromatic aldehydes in the presence of MTO

	time (hrs)	yield %
H	12	34
NO_2	7	62
Cl	10	38

The ^1H NMR spectrum of the product of the reaction between *p*-nitrobenzaldehyde and 3-diazo-2-piperidone showed the presence of two isomers, which were separated by column chromatography.



[3-40]



[3-41]

The least polar of the two showed the olefinic proton H(d) at 6.7δ, with the more polar isomer having its olefinic proton H(d) at 7.8δ. Applying the Tobey-Simon rules,[128] the predicted chemical shifts for these protons were calculated (Table 16) to be 7.3δ for the (E)-isomer [3-40] and 6.9δ for the (Z)-isomer [3-41]. The values are only approximate because of the limited number of substituents available in the reference tables. Nevertheless from these results it can be concluded that the least polar fraction is the (Z) isomer [3-41] and the more polar the (E) isomer [3-40] formed in a ratio of approximately 3:1.

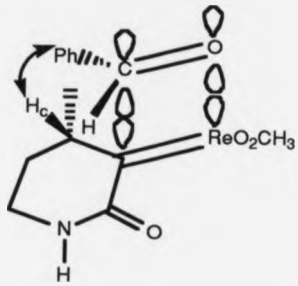
Table 16: Predicted values for the chemical shifts of the olefinic protons for the olefins [3-40] and [3-41]

	E isomer	Z isomer
gem: aromatic	+1.38	+1.38
trans: alkyl	-0.28	-
cis: alkyl	-	-0.22
cis: amide	+0.98	-
trans: amide	-	+0.46
calculated δ	7.36	6.90

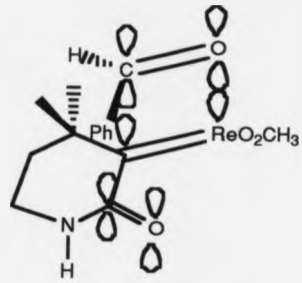
The benzaldehyde derivative had its olefinic protons masked by the aromatic protons and was not separable into isomers by tlc. The *p*-chlorobenzaldehyde derivative formed two isomers, as shown by ^1H NMR, but these could not be separated by tlc. Using the Tobey-Simon rules showed the (Z)-isomer to have its olefinic proton at 7.2δ and the (E)-isomer its olefinic proton at 7.6δ. They were formed in a ratio of 2.5 to 1 in favour of the (Z)-isomer.

At first sight it would be expected that the (E)-isomer would be the favoured product sterically, but closer examination of the rhenium intermediate can help explain why the (Z)-isomer is preferred.

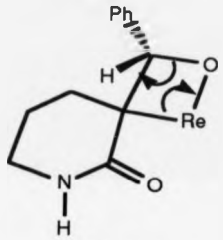
The rhenium carbenoid intermediate can be represented by [3-42] and [3-43]. The aldehyde attacks from above to form a four membered ring [3-44], [3-45] from which the MTO catalyst is eliminated to form the alkene. If, when the aldehyde attacks the rhenium complex, the phenyl ring points away from the amide [3-42], H(c) on the amide ring will hinder the approach of the aldehyde destabilising the formation of intermediate [3-44]. However, if the aldehyde attacks with the phenyl ring towards the amide carbonyl [3-43], secondary orbital overlap between the π electrons of the phenyl ring and the π electrons of the carbonyl group will cause the stabilisation of intermediate [3-45], which will eliminate the MTO catalyst forming the (Z)-isomer [3-41]. This stabilisation of the formation of intermediate [3-45] causes the (Z)-isomer [3-41] to be the preferred product.



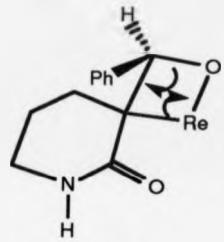
[3-42]



[3-43]



[3-44]



[3-45]

[3-40]

[3-41]

3.5 Synthesis of 3-Diazo-2-(nitromethylene)piperidine.

3.5.1 Introduction.

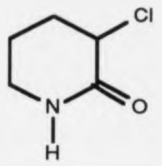
As it was not possible to condense the cyclopropyl derivatives of the lactam series with nitromethane a new approach was needed. An intriguing possibility was the question of whether or not 3-diazo-2-(nitromethylene)piperidine could be synthesised and if it could, whether it would be sufficiently stable to be of synthetic value.

3.5.2 Unsuccessful routes.

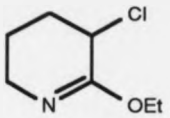
Attempts to form the iminoether of 3-diazo-2-piperidone by alkylation with the Meerwein reagent or dimethyl sulphate were unsuccessful. These reagents are acidic and as such readily caused the loss of the diazo group.

Synthesis of 3-chloro-2-(nitromethylene)piperidine [3-48] would allow the displacement with a nitrogen nucleophile (e.g. azide) of the chloride group. Reduction of the resulting compound would give the amine which could be diazotised to give the desired product.

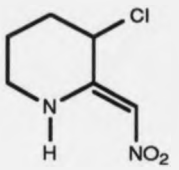
3-Chloro-2-piperidone [3-46] was found to be readily synthesised by the addition of 3-diazo-2-piperidone to a solution of HCl dissolved in dioxan. Removal of the solvent followed by recrystallisation from diethyl ether gave the pure product. Alkylation of chloro compound [3-46] with triethyloxonium tetrafluoroborate proceeded smoothly to give the iminoether [3-47]. However, attempts to condense this product with nitromethane afforded 3-chloro-2-(nitromethylene)piperidine [3-48] only in very low yield (typically between 5-10%).



[3-46]



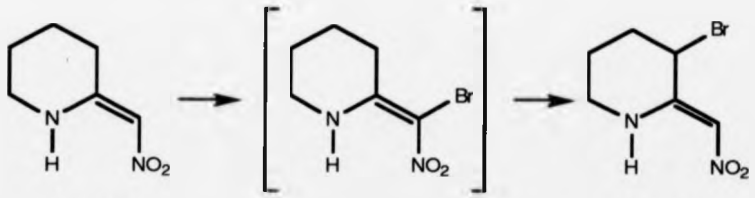
[3-47]



[3-48]

3.5.3 A new approach

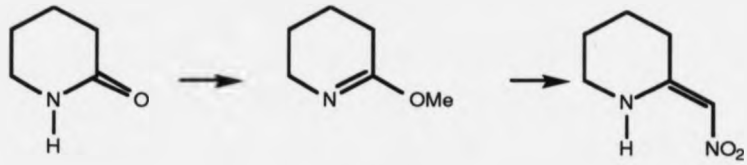
In the late 1970's researchers at Shell[129] discovered that 3-bromo-2-(nitromethylene)piperidine [3-51] could be synthesised by the action of N-bromosuccinimide (NBS) on 2-(nitromethylene)piperidine [3-49]. The reaction proceeds via initial bromination of the methine carbon to give intermediate [3-50] followed by a 1,3 bromine transfer. This information gave us a route to a 3-halogeno-2-(nitromethylene) piperidine which could be used for a displacement reaction with a nitrogen nucleophile.



[3-49] [3-50] [3-51]

The nitroalkene [3-49] was synthesised in two steps from 2-piperidone [3-52], the first involved alkylation with dimethyl sulphate to form the iminoether [3-53]. In the literature, this reaction was carried out using refluxing benzene as the solvent.[110] As we wanted to carry out this reaction on a large scale, it would be easier if the amount of solvent present was kept to a minimum. It was noted that the reaction was normally carried out at 60°C and that at this temperature the lactam [3-52] was a liquid, so we anticipated that it should be possible to add the

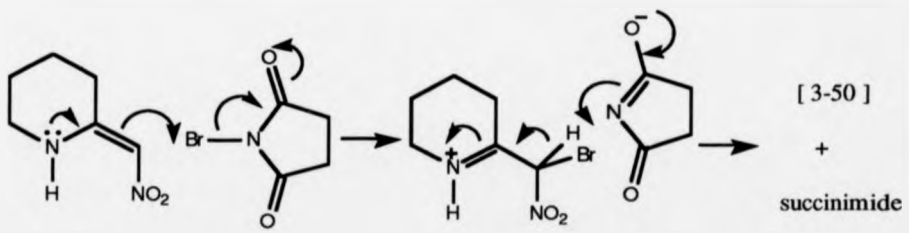
dimethyl sulphate dropwise to the molten 2-piperidone at 60°C with vigorous stirring. Using this method and then quenching the reaction with an ice cold saturated solution of potassium carbonate followed by extraction of the product with diethyl ether, the iminoether [3-53] was obtained in 88% yield, which was a substantial improvement on the 63% yield obtained by refluxing in benzene.



[3-52] [3-53] [3-49]

Condensation of iminoether [3-53] with nitromethane freshly distilled from 4A molecular sieve initially gave quite low yields (30-40%). This was consistent with similar reactions in the literature. The introduction of pyridine as a catalyst had no effect upon this yield. The reaction was carried out in refluxing nitromethane at 101°C. However, it was found that when working on larger scales the production of methanol as a by-product of the reaction was lowering the refluxing temperature to below 85°C after only 1hr. To counteract this, the methanol was slowly distilled out of the reaction mixture together with nitromethane at a rate of 5ml hr^{-1} and replaced by an equal amount of fresh nitromethane via a dropping funnel. This had the effect of maintaining the temperature of the reaction at 101°C. Removal of the solvent after 18hrs of refluxing gave a red solid which was triturated with diethyl ether to give a pale yellow crystalline solid. The yield for this reaction was 68%, again a great improvement on previous attempts and literature methods.

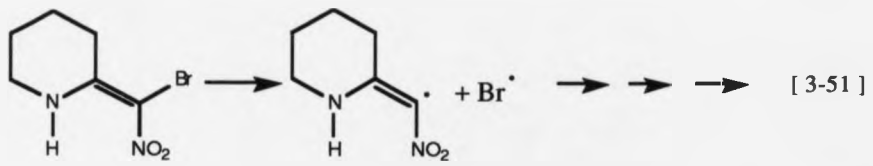
The bromination of nitroalkene [3-49] with an equimolar amount of NBS was carried out by stirring in carbon tetrachloride overnight at room temperature. Tlc showed consumption of the starting 2-(nitromethylene)piperidine and the appearance of a slightly less polar compound. The reaction mixture was then heated under reflux for 1 hr, after which most of the solid material had dissolved. Tlc showed the disappearance of the intermediate with the appearance of a still less polar product. The insoluble brown solid was filtered from the hot solution and the filtrate cooled to -10°C. The bright yellow crystals formed were identified as 3-bromo-2-(nitromethylene)piperidine [3-51] and characterised in the ^{1}H NMR spectrum by the strongly hydrogen bonded N-H at 10.1δ and the olefinic hydrogen at 6.65δ. The mass spectrum showed the molecular ion at 222 and 220 (1:1 relative intensities) indicating the presence of a bromine atom. A second crop of crystals could be obtained by dissolving the brown solid (which had been filtered off) in hot ethyl acetate, treating with decolourising charcoal and washing with water to remove the succinimide present.



Scheme 20.

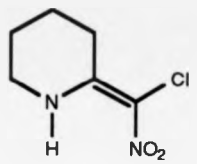
Although the overall mechanism of this reaction is unclear, the first step is outlined in Scheme 20. The second step must involve the formation of radicals upon heating (Scheme 21) followed by a series of radical steps resulting in the formation of the allylic bromide [3-51]. The formation of radicals is further supported by an analogous reaction using N-

chlorosuccinimide instead of NBS. Upon heating in carbon tetrachloride there is no transfer of the chlorine atom, the product isolated being identified as the chlorinated nitroalkene [3-54]. This is consistent with the fact that a C-Cl bond is stronger than a C-Br bond and therefore requires a larger input of energy to cause it to dissociate.



[3-51]

Scheme 21.

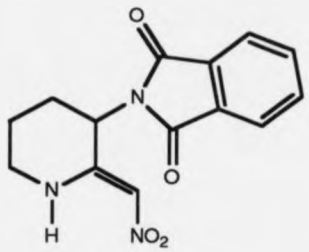


[3-54]

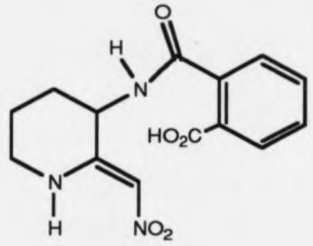
Attempts to displace the bromine in the allylic bromide [3-51] with sodium azide, both in ethanol and in a two phase system (CH_2Cl_2/H_2O), were not very successful. In the latter case, infra-red spectroscopy showed a strong azide band at 2105cm^{-1}, but ^1H NMR showed there to be still some of the starting material present. All attempts to purify the azide failed and a search was therefore made for other nitrogen nucleophiles.

It is well known in the Gabriel synthesis of amines[130] that potassium phthalimide will effect the displacement of a halogen. It has also been reported that this reaction will occur more efficiently in polar solvents such as DMF.[131] Following this approach, a 2-fold excess of potassium phthalimide was added to a solution of 3-bromo-2-(nitromethylene)

piperidine in DMF. After 12 hrs at room temperature the reaction was worked up by pouring into water and extracting with methylene chloride. The resulting red oil was purified on a silica column to give the required product [3-55]. ^{1}H NMR showed the characteristic peaks for the H-bonded N-H at 10.7δ and the olefinic proton at 6.4δ as well as an AA'BB' system for the aromatic protons of the phthalimide group.



[3-55]



[3-56]

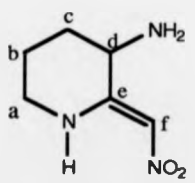
The classical method for the removal of the phthaloyl protecting group to give the free amine is to treat the phthalimide derivative with hydrazine hydrate in either ethanol or methanol.[132] followed by refluxing with dilute hydrochloric acid.

Phthalimide [3-55] was dissolved in hot ethanol together with 2 equivalents of hydrazine hydrate. A white precipitate was formed after 1 hr and was filtered off. ^{1}H NMR showed that the aromatic protons were still present, but instead of the symmetrical AA'BB' system it was now a much more complex second-order spectrum. The infra-red spectrum showed the presence of both a carboxylic acid carbonyl stretch at 1693cm^{-1} and an amide carbonyl at 1665cm^{-1}. From this data, it was concluded that the partially deprotected amide [3-56] had been formed in quantitative yield. All attempts to hydrolyse the amide [3-56] to free the amine with both acid and base catalysis failed. The only product identified from this reaction was phthalic acid. This indicated that the

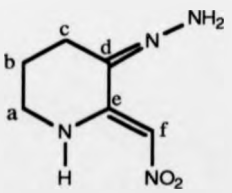
required amine must have been formed during the reaction but was unstable under the reaction conditions.

In 1949, King and Kidd[133] used the milder reaction conditions of two equivalents of hydrazine hydrate in 1M sodium carbonate solution, the reaction being much slower (typically two days).

When the phthalimide derivative [3-55] was stirred at room temperature for two days in 1M sodium carbonate solution with four equivalents of hydrazine hydrate, a bright yellow solid was isolated from the reaction mixture. ^{1}H NMR showed the characteristic N-H, H-bonded to the nitro group at 10.6δ along with the olefinic proton at 7.0δ. However, a clean triplet at 2.3δ indicated that the protons H(c) must have a carbon C(d) with no protons attached. This ruled out the amine [3-57]. Carbon-13 NMR showed 3 sp^2 hybridised carbons, and along with a band at 1658cm^{-1} in the infra-red spectrum, indicated that the carbon at position C(d) was attached to a nitrogen via a double bond. The structure of the product was deduced to be that of the hydrazone derivative [3-58], which fitted with the CI-mass spectrum 171(M+1) as well as the elemental analysis.



[3-57]

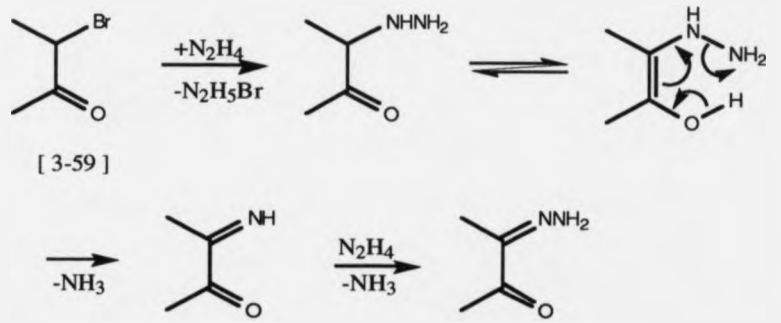


[3-58]

Phthalic acid was again isolated from this reaction, indicating that the amine derivative [3-57] had been formed, and under the milder

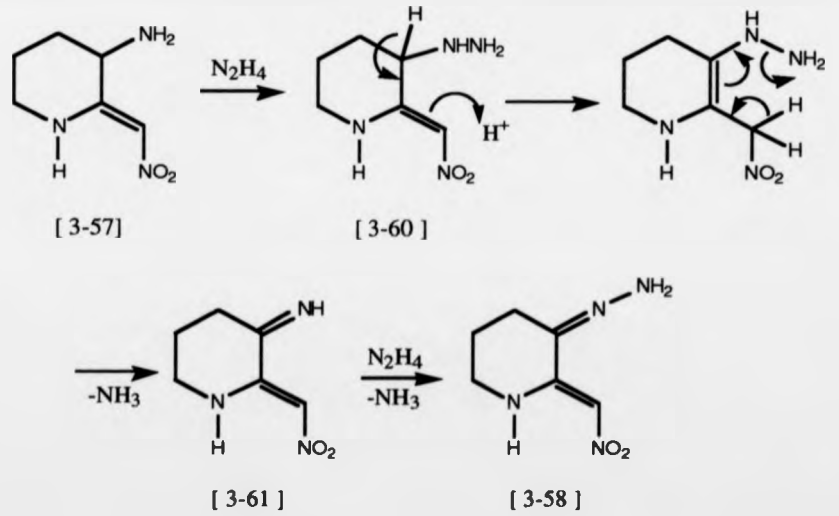
conditions had undergone a further transformation to give the hydrazone [3-58].

In 1965, Hauptmann *et al* [134] described the synthesis of α-diazoketones from the corresponding hydrazone which was derived from the α-bromoketone [3-59] via the mechanism outlined in Scheme 22.



Scheme 22.

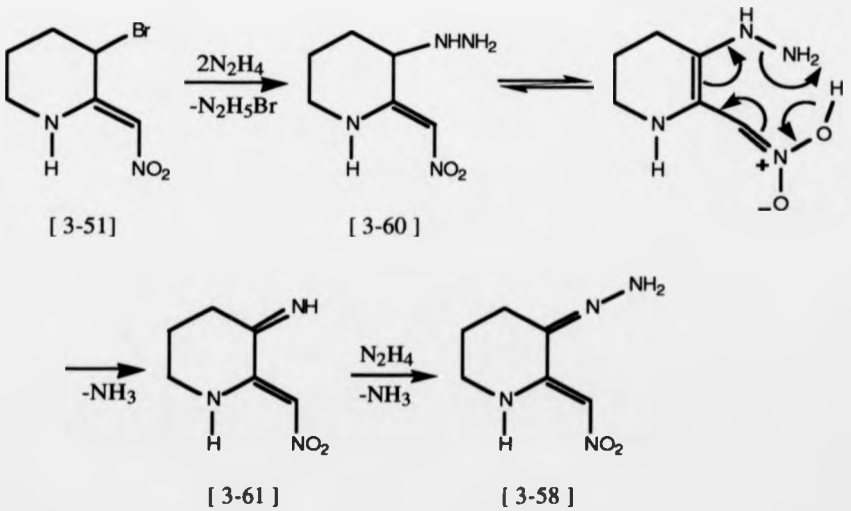
This mechanism helps to explain the formation of hydrazone [3-58]. The fact that phthalic acid was always isolated as a by-product suggests that the amine [3-57] had been produced. Nucleophilic attack of another molecule of hydrazine on amine [3-57] caused displacement of NH_3 to



give intermediate [3-60] which undergoes rearrangement and elimination of another molecule of NH_3 to form imine [3-61]. Nucleophilic attack of a further molecule of hydrazine on this imine and elimination of NH_3 results in the formation of hydrazone [3-58].

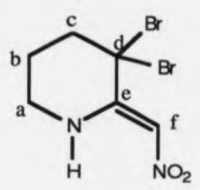
The formation of the hydrazone [3-58] was unexpected, but was an exciting bonus as it gave the possibility of a one step reaction to the desired diazo compound. Considerable effort was put into trying to improve the yield of this reaction (< 10%) with little success. Varying the temperature of reaction and concentration of hydrazine had no effect on overall yield.

Taking our 3-bromo-2-(nitromethylene)piperidine [3-51] and treating with three equivalents of hydrazine hydrate we can envisage a similar reaction occurring to that of Hauptmann's to give the desired hydrazone (Scheme 23). Unfortunately using this method the hydrazone was only produced in 10% yield.

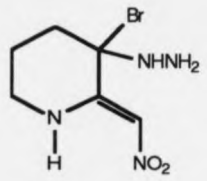


Scheme 23.

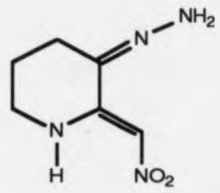
A second bromination of the bromo nitromethylene [3-51] with NBS would allow us to form intermediate [3-62] after the displacement of one of the bromine atoms by hydrazine (Scheme 24). This intermediate could then eliminate hydrogen bromide to give the desired hydrazone [3-58].



[3-63]



[3-62]

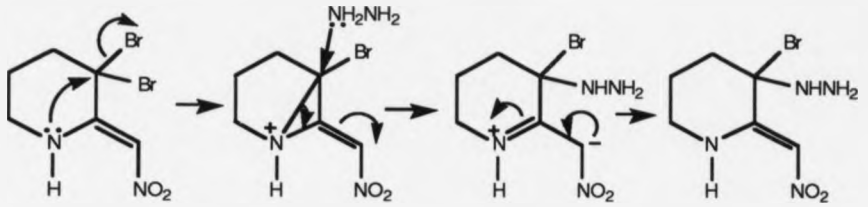


[3-58]

The second bromination was carried out using the same method as the first bromination in 71% yield. The product [3-63] was identified by the disappearance of the signal at 4.7δ for the proton on C(d). The CI-mass spectrum of the product showed the addition of a second bromine (relative intensities of the molecular ion in a ratio 1:2:1).

The dibromo compound [3-63] was dissolved in warm ethanol and 4 equivalents of hydrazine hydrate were added with stirring. The hydrazone [3-58] was isolated after column chromatography in 37% yield. Ethanol was found to be the best solvent for this reaction. Varying the temperature changed the rate at which the product was formed but did not effect the yield. Similarly, base catalysis of the reaction increased the rate of reaction; but not the overall yield. It is unlikely that the mechanism is a straight forward SN2 substitution of hydrazine to give the intermediate [3-62] because of the steric hindrance around C(d). It is believed that the displacement of the first bromine is carried out intramolecularly to give the intermediate [3-64], followed by nucleophilic attack of hydrazine to give a second intermediate [3-65]

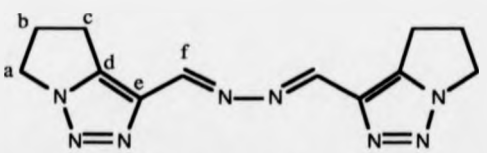
which will rearrange to form the monobromide [3-62]. Elimination of HBr from this intermediate gives the hydrazone [3-58].



[3-63] [3-64] [3-65] [3-62]

Scheme 24.

A second, less polar fraction, was also isolated from this reaction in 15% yield after column chromatography. The EI-mass spectrum of this compound gave a molecular ion of 270, and showed that both of the bromine atoms had been lost during the reaction. From this information it was deduced that the product formed must be a dimer. The 250MHz ^1H NMR spectrum is shown in Fig. 3, from this it can be seen that the dimer formed must be symmetrical. It also shows the absence of a broad N-H group, and this was confirmed by infra-red spectroscopy. ^{13}C NMR showed $3sp^2$ hybridised carbons along with $3sp^3$ hybridised carbons, again confirming that the dimer must be symmetrical. Combining this data with the microanalytical data, the molecular formula was deduced to be $C_{12}H_{14}N_8$. The compound's structure was identified by X-ray crystallography and was found to be the dimer [3-66]. The X-ray crystal structure is shown in Fig. 4. The mechanism for the formation of this compound is at the moment unclear.



[3-66]

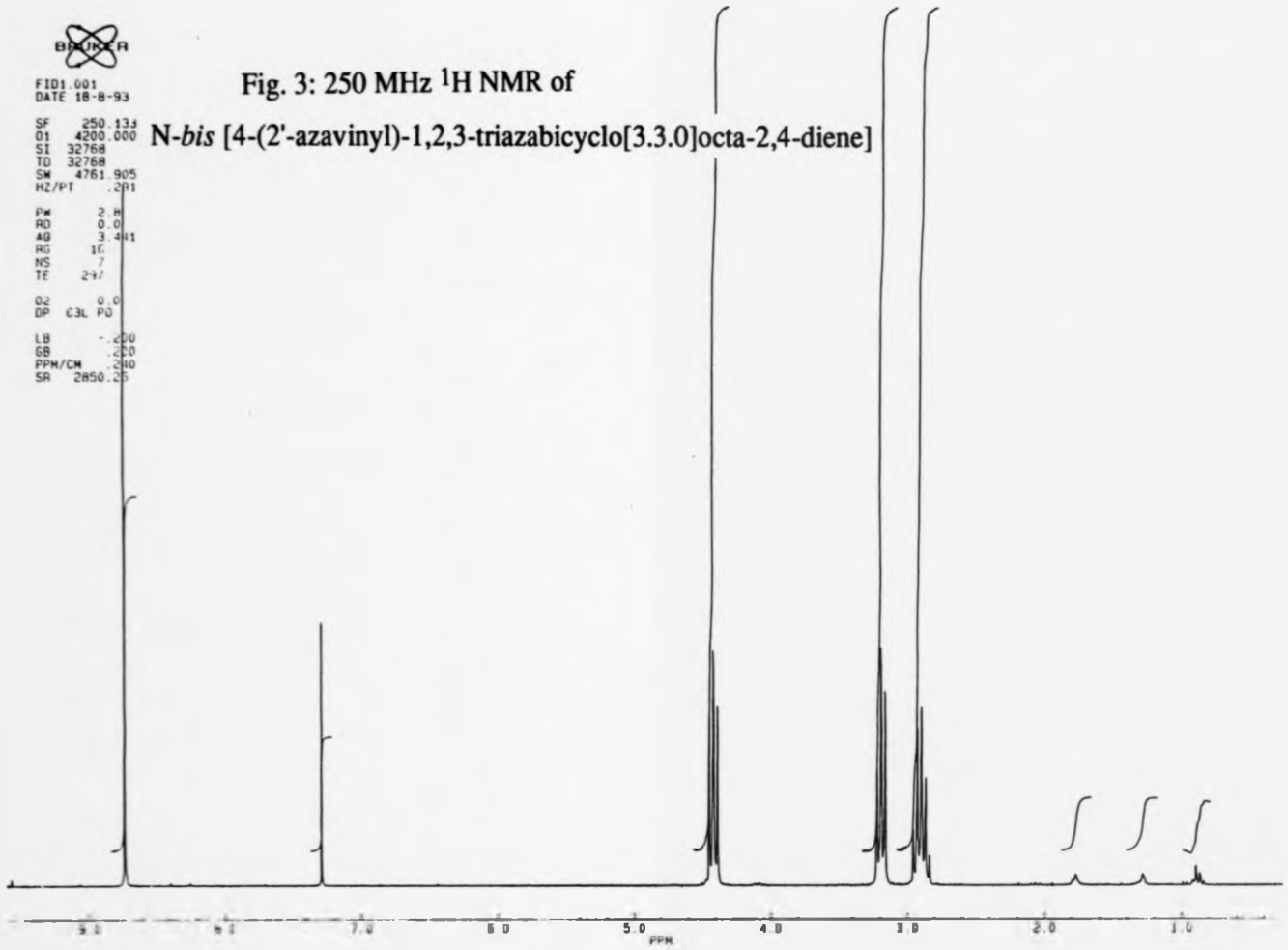


Fig. 3: 250 MHz ^{1}H NMR of

N-*bis* [4-(2'-azavinyl)-1,2,3-triazabicyclo[3.3.0]octa-2,4-diene]

Fig. 4: X-ray crystal structure of

N-*bis* [4-(2'-azavinyl)-1,2,3-triazabicyclo[3.3.0]octa-2,4-diene]

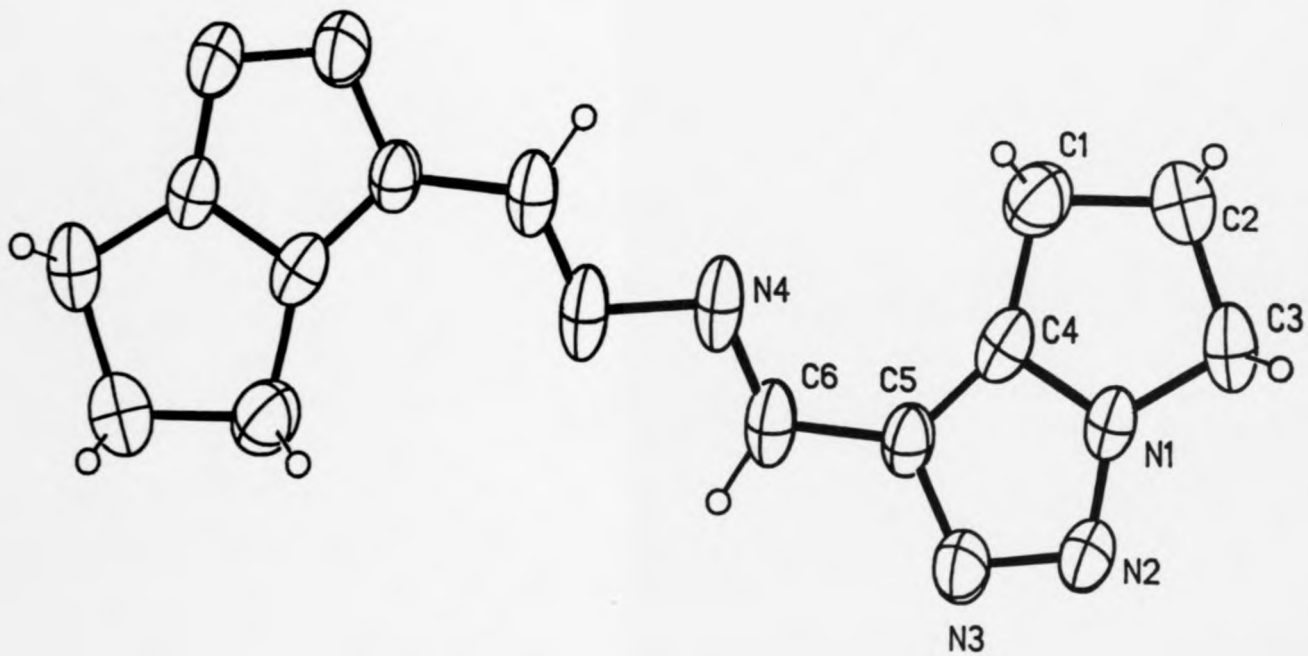
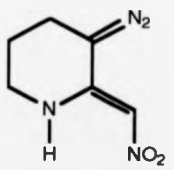


Table 17: Bond lengths and bond angles for dimer [3-66]

bond angles [deg]		bond lengths [Å]	
Cl(1)-C(7)-Cl(2)	111.0(7)	C(7)-Cl(1)	1.730(7)
Cl(1)-C(7)-Cl(3)	109.3(6)	C(7)-Cl(2)	1.730(7)
Cl(2)-C(7)-Cl(3)	112.5(7)	C(7)-Cl(3)	1.730(7)
Cl(4)-C(7')-Cl(5)	109.5(8)	C(7')-Cl(4)	1.739(8)
Cl(4)-C(7')-Cl(6)	110.4(8)	C(7')-Cl(5)	1.739(8)
Cl(5)-C(7')-Cl(6)	109.0(8)	C(7')-Cl(6)	1.739(8)
N(2)-N(1)-C(4)	113.3(3)	N(1)-N(2)	1.323(4)
N(2)-N(1)-C(3)	131.1(3)	N(1)-C(4)	1.335(4)
C(4)-N(1)-C(3)	115.6(3)	N(1)-C(3)	1.452(5)
N(3)-N(2)-N(1)	105.8(3)	N(2)-N(3)	1.319(4)
N(2)-N(3)-C(5)	109.1(3)	N(3)-C(5)	1.362(5)
C(6)-N(4)-N(4)#1	110.8(4)	N(4)-C(6)	1.266(5)
C(4)-C(1)-C(2)	103.5(3)	N(4)-N(4)#1	1.422(6)
C(3)-C(2)-C(1)	109.7(4)	C(1)-C(4)	1.466(6)
N(1)-C(3)-C(2)	101.6(3)	C(1)-C(2)	1.517(6)
N(1)-C(4)-C(5)	103.6(3)	C(2)-C(3)	1.486(6)
N(1)-C(4)-C(1)	109.6(3)	C(4)-C(5)	1.367(5)
C(5)-C(4)-C(1)	146.8(3)	C(5)-C(6)	1.436(5)
N(3)-C(5)-C(4)	108.2(3)		
N(1)-C(3)-C(6)	120.5(3)		
C(4)-C(5)-C(6)	131.3(4)		
N(4)-C(6)-C(5)	121.0(4)		

The hydrazone [3-58] was oxidised to the corresponding diazo compound in 74% yield using yellow mercuric oxide in chloroform in the presence of a catalytic amount of a saturated methanolic solution of potassium hydroxide. The reaction was very rapid at room temperature (approximately 2 mins), but the ^{1}H NMR spectrum showed a mixture of two products. When the reaction was carried out at -5°C, for 15mins followed by rapid work up on a silica column, the pure 3-diazo-2-(nitromethylene) piperidine [3-67] was produced. This was characterised by infra-red spectroscopy, which showed a strong diazo band at 2070 cm^{-1}. The CI-mass spectrum showed a strong peak at 169(M+1) as well as 141(M-28).

The diazo compound [3-67] is the first compound ever synthesised which contains a 3-diazo-1-nitropropene group and as such may have its own unique type of chemistry.



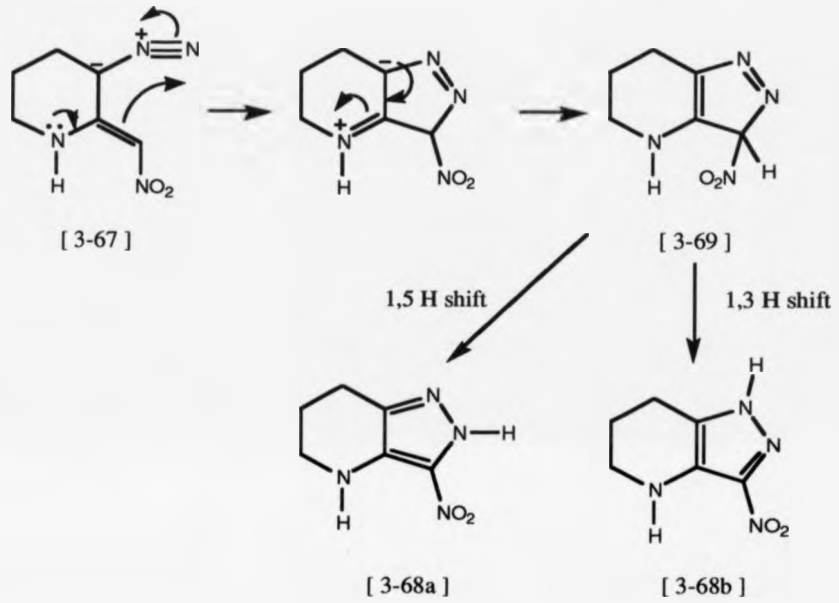
[3-67]

3.6 Chemistry of 3-Diazo-2-(nitromethylene)piperidine

3.6.1 Intramolecular cyclisation of 3-diazo-2-(nitromethylene)piperidine

Oxidation of 3-hydrazono-2-(nitromethylene)piperidine [3-58] in the presence of yellow mercuric oxide but in the absence of a catalyst was very slow and did not give the corresponding diazo compound [3-67]. It was also observed that when the reaction was carried out at room temperature in chloroform in the presence of a catalytic amount of a saturated methanolic solution of potassium hydroxide a mixture of two products was produced. One of the products was identified as the diazo compound [3-67], the other was the same as that produced when no catalyst was used. Upon standing, in solution, the diazo compound gradually disappeared whilst the second product became more prominent, until after a period of 36hrs, when all the diazo compound had disappeared. From this information, it was clear that the diazo compound [3-67] had undergone a rearrangement. This was confirmed by spectral data. Infra-red spectroscopy showed the absence of the diazo band at 2070cm^{-1}. ^{1}H NMR showed that the N-H peak was not strongly H-bonded to the nitro group and had moved upfield to 5.0δ. It also showed the absence of the olefinic proton at 6.6δ. CI-mass spectrometry gave the same molecular ion (169) as that of the diazo compound [3-67], however, in this case there was no peak at m/z 141 which would indicate the loss of nitrogen. On closer examination of the ^{1}H NMR ($CDCl_3$) there was a very broad singlet which covered the region 11.5-14.0δ. Combining this data it was concluded that the diazo compound had undergone an intramolecular cyclisation to give one of the bicyclic products [3-68a] or [3-68b] via the mechanism outlined in Scheme 25.

Once the intermediate [3-69] has been formed it can either undergo a 1,3-H shift to give the isomer [3-68b] or a 1,5-H shift to give the isomer [3-68a].



Scheme 25.

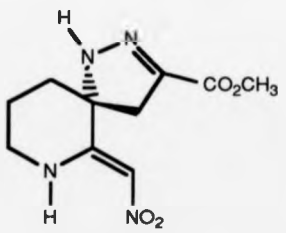
The structure of the isomer which had been formed was not immediately clear from the spectral data available. However, when the ^1H NMR was run in $DMSO_{d6}$, as opposed to $CDCl_3$, the very broad N-H peaks at 5.0δ and 11.5-14.0δ became much sharper and each appeared as two broad singlets of equal intensities. The intermolecular H-bonding between the bicyclic product and the solvent showed that neither one of the isomers [3-68a] or [3-68b] exists alone, but rather they exist in equilibrium. This was confirmed by running the ^1H NMR at a higher temperature (80°C) where the two sets of N-H peaks coalesce.

The cyclisation reaction was quite slow (after 5hrs in solution at 25°C there was still 80% of the diazo compound [3-67] present). Therefore,

3-diazo-2-(nitromethylene)piperidine should be a useful intermediate for reactions which happen rapidly. However, reactions which occurred at a slower rate (> 7hrs) were found to yield the bicyclic cyclisation adduct [3-68] as the major product.

3.6.2 1,3-Dipolar cycloaddition to electron deficient olefins

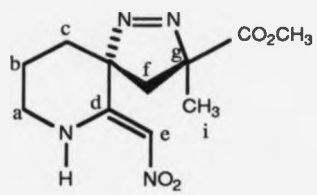
3-Diazo-2-(nitromethylene)piperidine [3-67] was found to undergo smooth 1,3-dipolar cycloaddition to methyl acrylate at room temperature to give the 2-pyrazoline [3-70] in 60% yield. The product was characterised by ^{1}H NMR which showed the N-H at 10.5δ strongly H-bonded to the nitro group as well as the olefinic proton at 6.4δ. Infra-red spectroscopy showed a strong C=O band at 1720cm^{-1} indicating the presence of an ester as well as a band at 1607cm^{-1} which showed the presence of a C=C. CI-mass spectroscopy showed the molecular ion at 255(M+1) as well as a large intensity at 227(M-28).



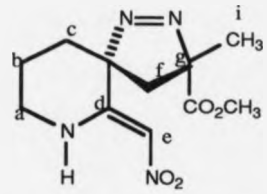
[3-70]

The reaction of 3-diazo-2-(nitromethylene)piperidine [3-67] with methyl methacrylate was substantially slower (12hrs) than that of methyl acrylate (5hrs), presumably due to the steric hindrance of the extra methyl group. As a consequence the bicyclic compound [3-68] was isolated in 36% yield after column chromatography. The 1-pyrazoline was produced in 39% yield as a diastereomeric mixture of the isomers [3-71] and [3-72] which were separated by column chromatography. The

slower running fraction was the major product of the two, produced in a ratio of approximately 2:1.



[3-71]

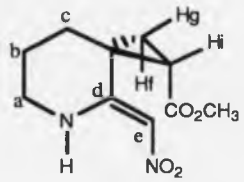


[3-72]

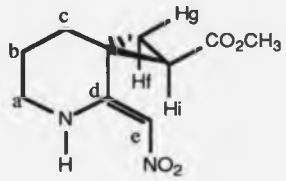
Both of the isomers showed an nOe between the olefinic proton H(e) and one of the geminal protons H(f). The slower running fraction also showed a very small nOe between the olefinic proton H(e) and the methyl protons H(i). This nOe was absent in the faster fraction. From this information it could be concluded that the slower running fraction was the isomer [3-71] which was the major product and that the faster running fraction was the isomer [3-72]. The isomer [3-71] would be expected to be produced in a larger yield as its formation is less sterically hindered.

3.6.3 Extrusion of nitrogen from 1,2,7-triaza-3-methoxycarbonyl-6-(nitromethylene)spiro[4.5]dec-2-ene

The 2-pyrazoline [3-70] was found to extrude nitrogen when heated in 1,2-dichlorobenzene at 180°C for 15mins to give a mixture of the two spirocyclopropyl isomers [3-73] and [3-74]. These isomers were separated by column chromatography. The faster fraction was the major product, produced in a ratio 3:1.



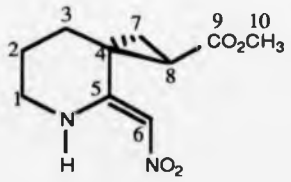
[3-73]



[3-74]

It would be expected that the formation of the isomer [3-74] would be more favourable on steric grounds, because the ester group points away from the nitromethylene group. If this was the case then the faster fraction would be the isomer [3-74]. The 300MHz ^1H NMR, for this fraction, is shown in Fig 5 between 1.0-4.0δ. The singlet at 3.7δ(3H) corresponds to the methoxy group and the multiplet at 3.5δ(2H) to H(a).

Table 18: ^{13}C NMR data for cyclopropyl derivative [3-74]



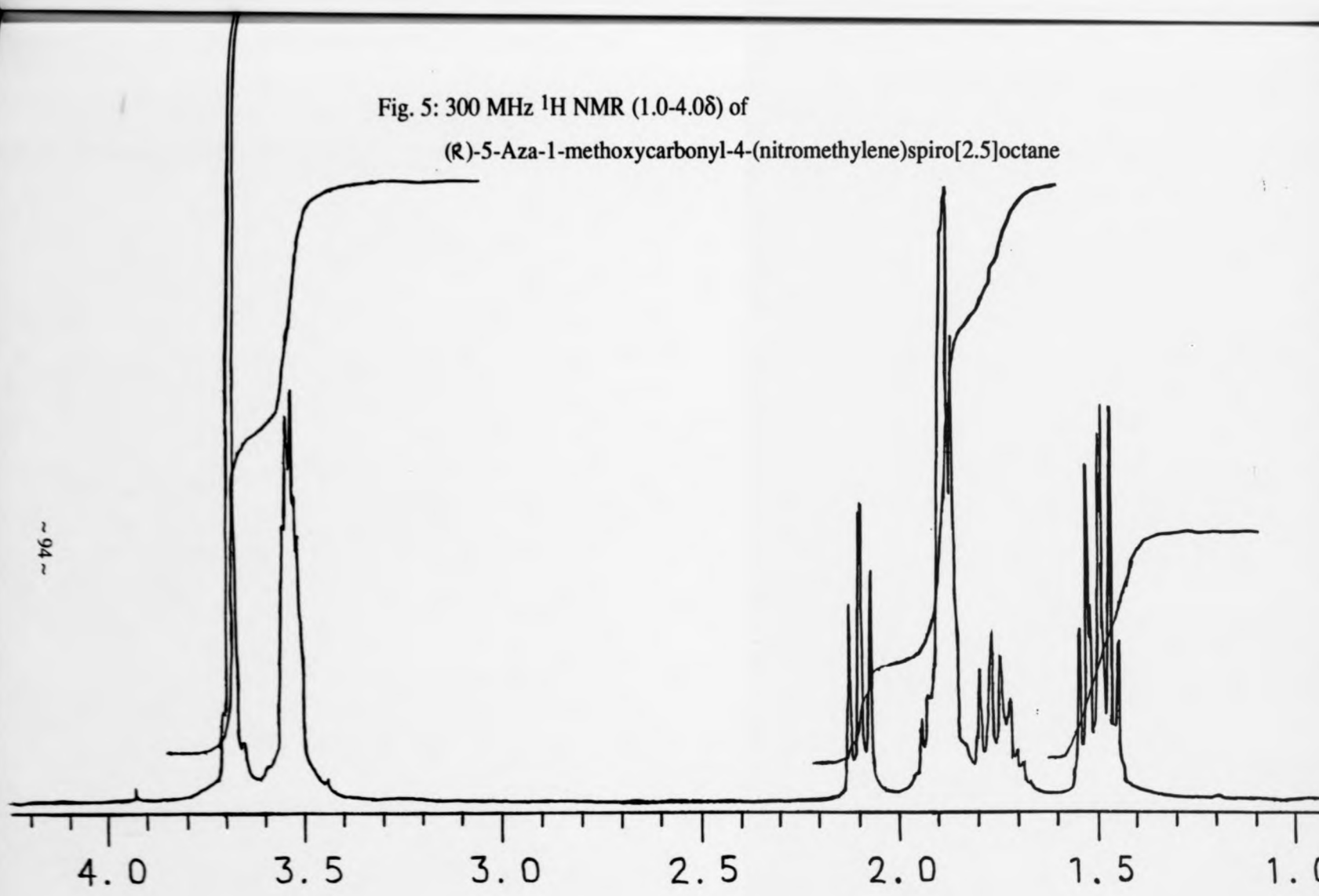
[3-74]

carbon	ppm
1	42
2	20
3	24
4	26
5	163
6	110
7	21
8	30
9	170
10	52

The carbon-13 spectrum (Table 18) was interpreted with the help of a ^{13}C-dept spectrum which showed C(8) to be at 30ppm. C-H correlation showed the proton on C(8) corresponded with the doublet of doublets at 2.1δ in the ^1H NMR. From the same spectrum, the two protons on C(3) appear at 1.9δ, with both the cyclopropyl protons on C(7) at 1.5δ. nOe difference spectroscopy showed that when H(e) was irradiated there was

Fig. 5: 300 MHz ^{1}H NMR (1.0-4.0δ) of

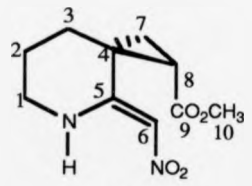
(R)-5-Aza-1-methoxycarbonyl-4-(nitromethylene)spiro[2.5]octane



an enhancement at both H(f) and H(i). Irradiation of H(i) causes an enhancement of H(e) and a small enhancement of H(f). These results confirmed that the faster fraction was the isomer [3-74] which was the major product.

The 300MHz ^{1}H NMR for the slower fraction is shown in Fig 6. The singlet at 3.6δ(3H) corresponds to the methoxy group of the ester and the multiplet at 3.5δ to H(a). The pattern in the region 1.2-2.2δ is different to that of the isomer [3-74] (Fig.5).

Table 19: ^{13}C NMR data for cyclopropyl derivative [3-73]



[3-73]

carbon	ppm
1	40
2	21
3	30
4	28
5	158
6	110
7	16
8	31
9	169
10	52

The carbon-13 spectral data for the slower fraction (Table 19) showed C(8) to appear at 31ppm (this was confirmed using ^{13}C-dept spectroscopy). The C-H correlation spectrum showed the proton on C(8) to be that at 1.95δ in the ^{1}H NMR. The cyclopropyl protons on C(7) appear at 1.75δ H(f) and 1.25δ H(g).

nOe difference spectroscopy showed that when H(e) was irradiated there was an enhancement of H(f) and also at the methyl group of the ester. Irradiation of H(f) showed enhancement of H(e) and H(g) as well as a

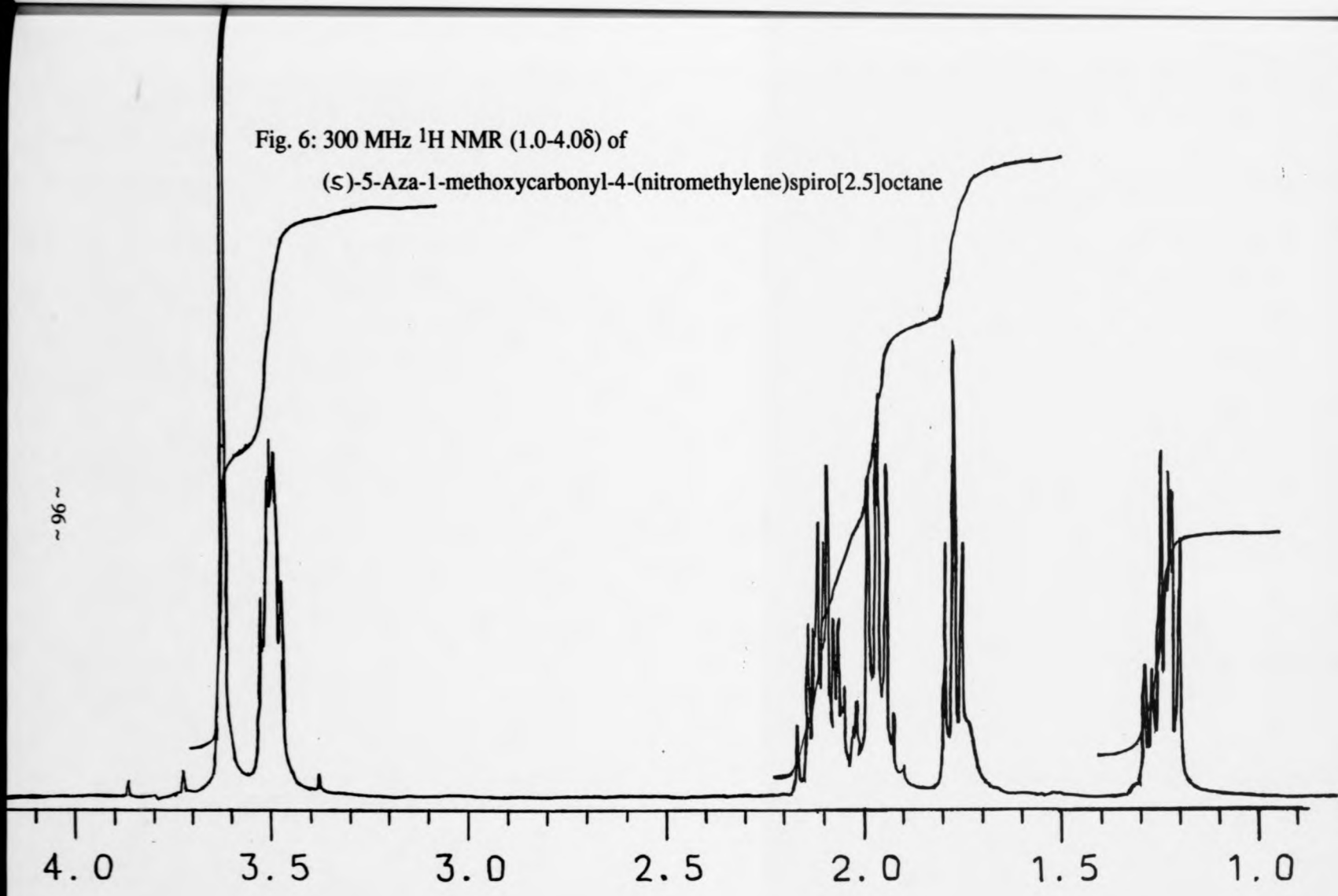
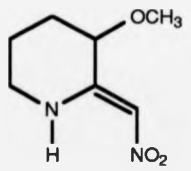


Fig. 6: 300 MHz ^{1}H NMR (1.0-4.0δ) of
(≤)-5-Aza-1-methoxycarbonyl-4-(nitromethylene)spiro[2.5]octane

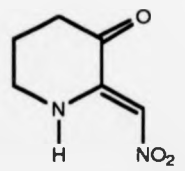
small enhancement of the methyl group of the ester. These results confirmed that the slower fraction (minor product) was that of the isomer [3-73], and that as expected the major product was the one whose formation would be the least sterically hindered.

3.6.4 Rhodium catalysed Reactions of 3-diazo-2-(nitromethylene) piperidine

The rhodium (II) acetate decomposition of 3-diazo-2-(nitromethylene) piperidine in methanol gave the expected O-H insertion product 3-methoxy-2-(nitromethylene)piperidine [3-14] in only 15% yield. Intriguingly the major product of this reaction was identified as being the ketone [3-75] which was formed in 30% yield. This product was characterised by infra-red spectroscopy which showed the presence of a C=Ostr for a ketone at 1735cm^{-1}. ^{1}H NMR showed that the N-H was strongly H-bonded to the nitro group at 9.85δ. The olefinic proton of the nitromethylene group was at 7.1δ.



[3-14]



[3-75]

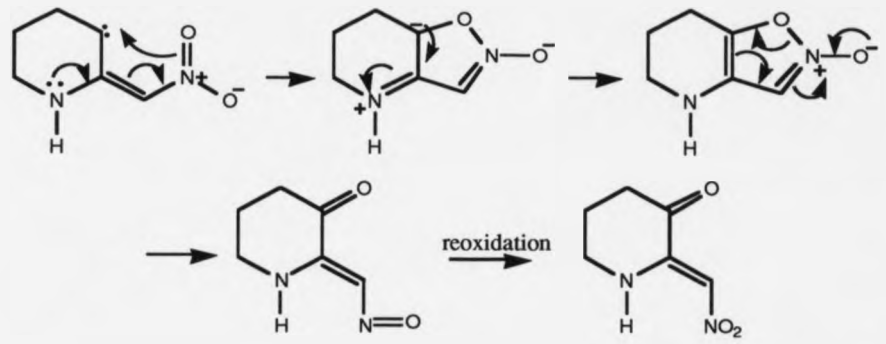
The reaction was repeated using dry methanol under a nitrogen atmosphere. The same products were produced and the yields were identical to those above. This ruled out the possibility of oxidation by molecular oxygen at the carbene centre.

It was thought that the reaction must proceed via oxygen transfer from the nitro group, either inter- or intramolecularly. The effect of concentration of the solution was studied and the results shown in Table 20. In each case 100mg of the diazo compound and 7mg rhodium (II) acetate were used.

Table 20: Effect of concentration of solution of 3-diazo-2-(nitromethylene)piperidine on the yield of ketone [3-75]

volume methanol (ml)	yield %	
	methyl ether [3-14]	ketone [3-75]
10	14	28
50	15	30
100	14	30
200	14	29

The yield of the ketone [3-75] is the actual yield isolated after chromatography, whereas the yields for the methoxy derivative [3-14] are those calculated from the ^1H NMR spectra of the crude samples based on the yield of the ketone. From these results it could clearly be seen that concentration had no effect on this reaction. This would tend to suggest that the reaction proceeded via intramolecular oxygen transfer from the nitro group followed by reoxidation of the resulting nitroso compound by a nitro group of another molecule (Scheme 26), and this would explain why a yield of over 50% could not be achieved.



Scheme 26.

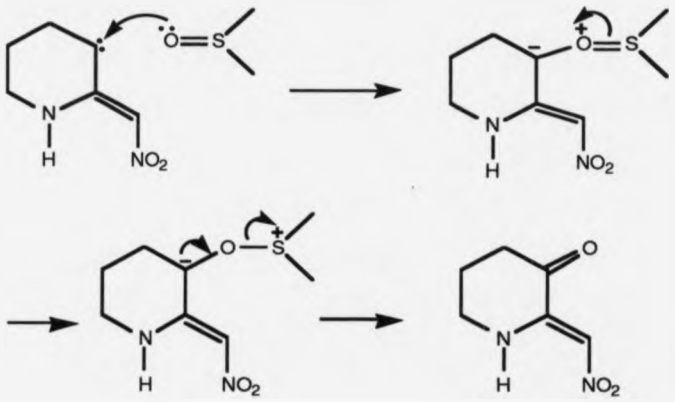
Reaction of 3-diazo-2-(nitromethylene)piperidine with rhodium (II) acetate in dry chloroform under nitrogen again gave the ketone [3-75] in only 30% yield. Table 21 shows the effect of adding an external source of oxygen transfer agent to the reaction mixture in an attempt to increase the yield. Typically two equivalents of the oxygen donor were used with chloroform as a solvent.

Table 21: Effect of the addition of an external oxygen donor on the yield of ketone [3-75]

oxygen transfer agent	% yield ketone
3,4-dinitrotoluene	54
nitrobenzene	62
DMSO	68
5eq DMSO	70
MoO_5.HMPA †	59
acetone *	61
* acetone solvent	† THF solvent

In all cases the yields of the ketone [3-75] were significantly increased. However, it is still unclear as to whether the reaction proceeds via the

mechanism outlined in Scheme 26 (with the reoxidation of the nitroso compound being carried out by the external oxygen transfer agent) or whether the external oxygen transfer agent directly attacks the rhodium carbenoid species (Scheme 27).



Scheme 27.

Reaction of 3-diazo-2-(nitromethylene)piperidine with ethyl vinyl ether in the presence of rhodium(II) acetate again gave only the ketone [3-75] in 30% yield. Two other rhodium catalysts, namely the trifluoroacetate and the pivalate derivatives, were used in an attempt to change the electron density of the rhodium carbenoid species, however the results were the same as that of rhodium(II) acetate. Copper catalysts [$Cu(OAc)_2$, $Cu(acac)_2$, $CuSO_4$] were found to be unable to form a carbenoid species with the diazo piperidine [3-67], the bicyclic cyclisation product [3-68] being produced in quantitative yield. The use of palladium (II) acetate to catalyse the reaction resulted in the rapid evolution of nitrogen. The ketone [3-75] was isolated in only 10% yield. The ^1H NMR of the crude product showed the possibility that the cyclopropyl derivative had been formed, but attempts to isolate it by chromatography were unsuccessful.

3.6.5 Conclusion

The synthesis of 3-diazo-2-(nitromethylene)piperidine has allowed the study of a new class of diazo compound. 3-Diazoalkenes are known to readily cyclise to pyrazoles and for this reason are used as reactive intermediates. In the case of the diazo nitromethylene [3-67] the introduction of a strong electron withdrawing group (nitro group) helps to stabilise the diazo compound enough so that it can be isolated. The rhodium carbenoid intermediate from this diazo compound suprisingly gave the corresponding ketone as the major product irrespective of the carbenoid trapping agent used. In the work described only a limited number of rhodium catalysts were used, however, a wide range of rhodium (II) catalysts are available for the decomposition of diazo compounds. Changing the ligands on the rhodium metal will result in the formation of either a more electropositive or a less electropositive carbenoid (with respect to rhodium (II) acetate) which could be used to further investigate the above reaction. This may result in other nucleophiles being able to trap the carbenoid formed. The use of ^{18}O-labelled DMSO as an oxygen transfer agent in the reaction of 3-diazo-2-(nitromethylene)piperidine with $Rh_2(OAc)_4$ would confirm the mechanism for the formation of the ketone.

Experimental

^{1}H NMR spectra were recorded at 250MHz using a Bruker ACF250 spectrometer or at 400MHz using a Bruker WH400 spectrometer. ^{13}C NMR spectra were recorded at 61.42MHz using a Bruker ACF250 spectrometer. Mass spectra were recorded on a Kratos MS80 spectrometer. Chemical ionisation (CI) mass spectra used ammonia or methane as reagent gas. Infra red were recorded on a Perkin-Elmer 1720X Fourier transform spectrometer. Melting points were recorded on a Gallenkamp apparatus and are uncorrected. Microanalysis quoted to two decimal places were obtained from Medac Laboratories, Brunel University; those quoted to one decimal place were obtained from Shell Research Centre, Sittingbourne. All solvents used were of technical grade and used undried unless otherwise stated. Methylene chloride was dried over and distilled from calcium hydride. THF was dried over and distilled from sodium. Tlc was performed on aluminium backed, precoated silica gel 60 F_{254} from Merck, with a thickness of 0.2mm. Preparative tlc was performed on silica gel 60 PF_{254} from Merck, at a thickness of 2mm. Column chromatography was performed using silica gel 60 (mesh 230-400) from Merck. All products from chromatography were detected using either UV light (254nm) or by staining with iodine.

3-Amino-2-piperidone [3-2]

L-Ornithine hydrochloride [3-1] (100g, 0.59mol) was added to a stirred solution of sodium hydroxide pellets (23.8g, 0.59mol) in water (100ml) at 25°C. After 15mins this solution was added to a stirred mixture of alumina (300g) and toluene (1L) and heated under reflux for 1.5hrs. The water produced during the reaction was collected via a Dean-Stark trap. The reaction mixture was allowed to cool and the alumina was filtered

off and washed with 10% MeOH/CH_2Cl_2 (300ml). The filtrate and washings were combined and the solvent removed under vacuum to leave 3-amino-2-piperidone as a white crystalline solid. Yield=61.1g (90%). m.pt. 35-37°C (lit[106] mpt 35-38°C). I.R.(nujol,cm^{-1}) 3340,3261,3197(N-H), 1646(C=O), 1491, 1377, 1349, 1303, 999, 940. ^1H NMR (400MHz, $CDCl_3$) 7.0δ (1H,bs,N-H,exch), 3.2(2H,m,CH_2N), 3.2 (1H,dd,J=3.8Hz,J=3.9Hz,CH-NH_2), 1.5-2.1(4H,m,CH_2CH_2), 1.75 (2H,bs,NH_2,exch). FAB-MS: m/z(int) 115(M+1,100), 99(10), 70(96), 58(30), 42(42). Found C 52.51, H 8.66, N 24.25. ($C_5H_{10}N_2O$ requires C 52.63% H 8.77% N 24.56%).

3-Diazo-2-piperidone[3-3]

3-Amino-2-piperidone [3-2] (1.6g, 14mmol) was dissolved in chloroform (30ml). Isoamyl nitrite (2.31g, 18mmol) and glacial acetic acid (0.126g, 2.1mmol) were added with vigorous stirring. The resulting solution was refluxed for 15mins, cooled in ice and washed with an ice cold saturated solution of $NaHCO_3$ (10ml). The organic layer was separated off, dried over anhydrous $NaSO_4$ and the solvent removed under vacuum. The red solid was purified by column chromatography (SiO_2: 20%MeOH/CH_2Cl_2) to produce a bright orange solid which was recrystallised from cyclohexene to give 1.07g (60%) of 3-diazo-2-piperidone as bright orange needles. m.pt. 117-120°C. I.R.(nujol,cm^{-1}) 3268,3172(N-H), 2088(C=N_2), 1635(C=O), 1378, 1354, 1320. ^1H NMR (250MHz, $CDCl_3$) 6.5δ(1H,bs,N-H,exch), 3.25(2H,m,CH_2N), 2.7(2H,t,J=6.3Hz,CH_2), 1.9(2H,m,CH_2). ^{13}C NMR ($CDCl_3$,ppm) 167(C=O), 53(C=N_2), 41(CH_2N), 21(CH_2), 20(CH_2). EI-MS: m/z(int) 125(85), 96(12), 68(90), 53(41), 41(100). CI-MS: 126(M+1). Found C 47.96, H 5.66, N 33.28. ($C_5H_7N_3O$ requires C 48.00% H 5.60% N 33.60%).

3-Methoxy-2-piperidone (Table 10)

Rhodium(II)acetate (10mg) was added to a stirred solution of 3-diazo-2-piperidone [3-3] (0.222g, 1.78mmol) in methanol (15ml) at 25°C and the mixture left to stand for 1.5hrs. When the evolution of nitrogen had ceased, tlc showed the disappearance of the 3-diazo-2-piperidone. The solvent was removed under vacuum and the residue dissolved in CCl_4 (20ml). The rhodium catalyst was filtered from solution, and the solvent was removed from the filtrate to leave 3-methoxy-2-piperidone as a colourless waxy solid. Yield=0.159g (82%). m.pt. 35-37°C. I.R. (nujol,cm^{-1}) 3272(N-H), 1670(C=O), 1335, 1204, 1102. ^1H NMR (220MHz,$CDCl_3$,TMS) 7.7δ(1H,bs,N-H,exch), 3.75 (2H,dd,J=7.3Hz, J=4.9Hz,OCH), 3.6(3H,s,OCH_3), 3.35(2H,m,CH_2N), 1.7-2.2 (4H,m,CH_2CH_2). EI-MS: m/z(int) 99(100), 70(61), 58(57), 43(46), 41(53). CI-MS: 130(M+1). Found C 55.89, H 8.74, N 10.64.($C_6H_{11}NO_2$ requires C 55.81% H 8.53% N 10.85%).

3-Ethoxy-2-piperidone (Table 10)

Rhodium(II)acetate (8mg) was added to a stirred solution of 3-diazo-2-piperidone [3-3] (0.245g, 1.96mmol) in ethanol (15ml) at 25°C. After 2hrs the solvent was removed under vacuum and the residue dissolved in CCl_4 (20ml). The rhodium catalyst was removed by filtration, and the solvent evaporated to give 3-ethoxy-2-piperidone as a white solid which was recrystallised from diethyl ether. Yield=0.65g (81%). m.pt. 57-59°C. I.R.(nujol,cm^{-1}) 3198,3083(N-H), 1680(C=O), 1336, 1312, 1116. ^1H NMR (250MHz, $CDCl_3$) 6.2δ(1H,bs,N-H,exch), 3.8(1H,dd,J=4.8Hz, J=7.2Hz,OCH), 3.65(2H,q, J=7Hz,OCH_2), 3.3(2H,m,CH_2N), 1.7-2.1(4H,m,CH_2CH_2), 1.2(3H,t,J=7Hz,CH_3). EI-MS: m/z(int) 99(100), 98(72), 84(13), 70(57), 57(21), 43(18), 41(13). CI-MS: 144(M+1).

Found C 58.74, H 9.32, N 9.17. ($C_7H_{13}NO_2$ requires C 58.74% H 9.09% N 9.79%).

3-*Iso*proxy-2-piperidone (Table 10)

Rhodium(II)acetate (7mg) was added to a stirred solution of 3-diazo-2-piperidone [3-3] (0.244g, 1.95mmol) in propan-2-ol (15ml). The reaction was left to stand at 25°C for 4hrs and the solvent removed under vacuum. The green residue was dissolved in CCl_4 (20ml), filtered and the filtrate reduced to leave 3-isoproxy-2-piperidone as a pale yellow waxy solid. Yield=0.18g(52%). m.pt. 46-49°C. I.R.(nujol,cm^{-1}) 3202,3079(N-H), 1669(C=O), 1495, 1375, 1322, 1312, 1268, 1146, 1089. ^1H NMR (220MHz, $CDCl_3$, TMS) 7.1δ(1H,bs,N-Hexc), 4.1(1H,septet,J=7.8Hz,$\underline{CH}(CH_3)_2$), 3.9(1H,dd,J=6.8Hz,J=4.4Hz,OCH), 3.35(2H,m,CH_2N), 1.7-2.1(4H,m,CH_2CH_2), 1.25(6H,d,J=7.8Hz, $(CH_3)_2$). EI-MS: m/z(int) 99(62), 98(27), 70(30), 55(35), 43(100), 41(35). CI-MS: 158(M+1). Found C 61.54, H 9.64, N 8.53. ($C_8H_{15}NO_2$ requires C 61.15%, H 9.55%, N 8.92%).

3-*Tert*-butoxy-2-piperidone (Table 10)

Rhodium(II)acetate (13mg) was added to a solution of 3-diazo-2-piperidone [3-3] (0.267g, 2.14mmol) in *tert*-butanol (15ml). The reaction was refluxed for 1hr and then the solvent was removed under vacuum. The residue was subjected to column chromatography (SiO_2: 10% MeOH/CH_2Cl_2). The fastest running fraction was 3-*tert*-butoxy-2-piperidone and was isolated as a white crystalline solid. Yield=0.19g (52%). m.pt. 105-110°C. I.R.(nujol, cm^{-1}) 3202,3085(N-H), 1675(C=O), 1366, 1328, 1178, 1108, 1025. ^1H NMR (220MHz, $CDCl_3$, TMS) 6.7δ(1H,bs,N-H,exch), 3.95(1H,dd,J=6.3Hz,J=5.9Hz,OCH), 3.3(2H,m, CH_2N), 1.6-2.0(4H,m,CH_2CH_2), 1.25(9H,s,$C(CH_3)_3$). EI-MS: m/z(int)

156(30), 143(19), 116(100), 98(40), 71(42), 57(90), 41(32). CI-MS:172(M+1). Found C 63.41, H 9.96, N 8.02. ($C_9H_{17}NO_2$ requires C 63.16% H 9.94% N 8.19%.

The slowest running fraction was 3-hydroxy-2-piperidone and was obtained as white crystalline needles. Yield= 32mg(9%). m.pt. 134-136°C. I.R.(nujol,cm^{-1}) 3308(O-H), 3206(N-H), 1652(C=O), 1456, 1319, 1261, 1118, 1096. ^1H NMR (250MHz,$CDCl_3$) 6.7δ(1H,bs,N-H,exch), 4.1(1H,dd,J=6.3Hz,J=9.3Hz,OCH), 4.0(1H,bs,O-H,exch), 3.3(2H,m,CH_2N), 1.6-2.3(4H,m,CH_2CH_2). EI-MS: m/z(int) 99(7), 87(17), 57(43), 55(26), 44(100), 43(62), 41(60). CI-MS: 116(M+1). Found C 52.6, H 8.1, N 12.6. ($C_5H_9NO_2$ requires C 52.17% H 7.83% N 12.17%).

3-Phenoxy-2-piperidone (Table 10)

Rhodium(II)acetate (10mg) was added to a stirred solution of 3-diazo-2-piperidone [3-3] (0.24g, 1.92mmol) and phenol (1g, 10.6mmol) in methylene chloride (15ml). This solution was stirred at 25°C for 5hrs. The reaction mixture was introduced to a column packed with silica and eluted with CH_2Cl_2 until all the excess phenol had been removed. The product was then isolated by elution with 50% MeCN/CH_2Cl_2. The residue was recrystallised from acetone to give 3-phenoxy-2-piperidone as white needles. Yield=0.25g (68%). m.pt. 156-158°C. I.R.(nujol, cm^{-1}) 3286(N-H), 1665(C=O), 1635, 1334, 1318, 1237, 1202, 1072. ^1H NMR(400MHz,$CDCl_3$) 7.3δ(2H,dd,J=7.3Hz,J=8.7Hz,arom), 7.1(1H,bs, N-H,exch), 7.0(2H,dd,J=8.7Hz,J=1Hz,arom), 6.95(1H,t, J=7.3Hz,arom), 4.7(1H,dd,J=5.3Hz,J=7.5Hz,OCH), 3.25-3.4(2H,m,CH_2 N), 1.8-2.2(4H,m,CH_2CH_2). EI-MS: m/z(int) 191(17), 98(28), 94(67), 77(40), 70(100), 55(61), 51(37), 43(78), 41(62). CI-MS: 192(M+1). Found C

69.40, H 6.83, N 7.02. ($C_{11}H_{13}NO_2$ requires C 69.11% H 6.81% N 7.33%).

3-Benzyloxy-2-piperidone (Table 10)

Rhodium(II)acetate (10mg) was added to a stirred solution of 3-diazo-2-piperidone [3-3] (0.23g, 1.84mmol) in benzyl alcohol (5ml). The reaction was left for 5hrs at 25°C. Most of the benzyl alcohol was removed under vacuum (3mmHg) at 80°C, and the remaining oil was subjected to prep tlc (10% MeOH/CH_2Cl_2). The second band contained 3-benzyloxy-2-piperidone which was recrystallised from diethyl ether to give 0.2g (53%) of white needles. m.pt. 88-91°C. I.R.(nujol, cm^{-1}) 3272(N-H), 1661(C=O), 1496, 1454, 1334, 1102, 1028. ^1H NMR (400MHz,$CDCl_3$) 7.2-7.4δ(5H,m,arom), 6.9(1H,bs,N-H,exch), 4.8(2H, 2 x d,J=11.8Hz,OCH_2), 3.8(1H,t,J=6.5Hz,OCH), 3.2-3.35(2H,m,CH_2N), 1.7-2.0(4H,m,CH_2CH_2). EI-MS: m/z(int) 99(100), 91(97), 84(11), 71(11), 51(14), 43(36), 41(32). CI-MS: 206(M+1). Found C 70.51, H 7.38, N 6.42. ($C_{12}H_{15}NO_2$ requires C 70.24% H 7.32% N 6.83%).

3-(*p*-Chlorobenzyloxy)-2-piperidone (Table 10)

Rhodium(II)acetate (10mg) was added to a stirred solution of 3-diazo-2-piperidone [3-3] (0.5g, 4mmol) and *p*-chlorobenzyl alcohol (1.14g, 8mmol) in methylene chloride (15ml). The resulting solution was stirred at 25°C for 8hrs, then introduced to a column packed with silica and eluted with CH_2Cl_2 until the excess alcohol had been removed. The product was eluted using 20% MeCN/CH_2Cl_2, and the solvent removed under vacuum to give 3-(*p*-chlorobenzyloxy)-2-piperidone as white crystals. Yield=0.63g(66%). m.pt. 104-106°C. I.R.(nujol, cm^{-1}) 3191(N-H), 1674(C=O), 1467, 1377, 1309, 1183, 1109(C-Clstr), 810. ^1H NMR (250MHz,$CDCl_3$) 7.3δ(4H,m,arom), 6.0(1H,bs,N-H,exch), 4.8(2H,2 x

d,J=12.1Hz,OCH_2), 3.8(1H,dd,J=6.7Hz,J=5.0Hz,OCH), 3.3(2H,m, CH_2N), 1.9-2.1(4H,m,CH_2CH_2). ^{13}C NMR($CDCl_3$,ppm) 172(C=O), 138(C_{quat}), 133(C-Cl), 129(C_{arom}), 128(C_{arom}), 74(CH), 72(CH_2O), 42(CH_2N), 28(CH_2), 19(CH_2). EI-MS: m/z(int) 125(65), 99(100), 98(70), 89(26), 84(16), 71(12), 43(29), 41(19). CI-MS: 240(M+1). Found C 60.48, H 5.69, N 5.73. ($C_{12}H_{14}NO_2Cl$ requires C 60.25% H 5.86% N 5.86%).

2-Ethoxy-3-methoxy-3,4,5,6-tetrahydropyridine [3-11]

3-Methoxy-2-piperidone (1g, 7.75mmol) was added to a solution of triethyloxonium tetrafluoroborate (2.9g, 15.4mmol) in dry methylene chloride (40ml). The resulting solution was heated under reflux for 5hrs and then cooled in ice. 5M K_2CO_3 (30ml) was added and the mixture shaken for 1hr. The organic layer was removed and the aqueous layer extracted with methylene chloride (2 x 20ml). The organic layer and the combined extracts were dried over anhydrous potassium carbonate and the solvent removed under vacuum to leave an orange oil. Microdistillation of this oil under reduced pressure gave 2-ethoxy-3-methoxy-3,4,5,6-tetrahydropyridine as a colourless liquid. Yield=0.7g (58%). b.pt. 75°C(5mmHg). I.R.(cm^{-1}) 1677(C=N), 1339, 1223, 1202, 1102, 1036. ^1H NMR (250MHz,$CDCl_3$) 4.0δ(2H,q,J=7.0Hz,OCH_2), 3.6(2H,m,CH_2N), 3.5(3H,s,OCH_3), 3.3-3.4(1H,m,OCH), 1.5-2.0(4H,m, CH_2CH_2), 1.3(3H,t,J=7.0Hz,CH_3). EI-MS: m/z(int) 157(26), 142(28), 127(29), 114(39), 99(100), 85(91), 70(75), 58(85), 55(89), 43(40), 41(63). CI-MS: 158(M+1). Found C 61.58, H 9.68, N 8.33. ($C_8H_{15}NO_2$ requires C 61.15% H 9.55% N 8.92%).

2,3-Diethoxy-3,4,5,6-tetrahydropyridine [3-12]

3-Ethoxy-2-piperidone (0.86g, 6mmol) was added to a solution of triethyloxonium tetrafluoroborate (2.3g, 1.22mmol) in dry methylene chloride (30ml). This solution was refluxed for 6hrs and then cooled in ice. 5M K_2CO_3 (50ml) was added and the mixture shaken for 30mins. The organic layer was separated off and the aqueous layer extracted with methylene chloride (2 x 20ml). The organic layer and the extracts were combined, dried over anhydrous potassium carbonate and the solvent removed under vacuum to leave an orange oil. Microdistillation of this oil, under reduced pressure, gave 2,3-diethoxy-3,4,5,6-tetrahydropyridine as a colourless liquid with a pungent odour. Yield=0.55g(54%). b.pt. 80°C (5mmHg). I.R.(cm^{-1}) 1680(C=N), 1445, 1337, 1272, 1221, 1104, 1037. ^1H NMR (250MHz,$CDCl_3$) 4.0δ(2H,q,J=7.0Hz,OCH_2), 3.4(2H,q,J=7.1Hz,OCH_2), 3.35(1H,dd, J=7.0Hz,J=4.6Hz,OCH), 3.3(2H,m,CH_2N), 1.5-2.0(4H,m,CH_2CH_2), 1.3(3Ht,J=7.1Hz,CH_3), 1.25(3H,t,J=7.0Hz,CH_3). ^{13}C NMR ($CDCl_3$, ppm) 161(C=N), 70(OCH_2), 66(OCH), 60(OCH_2), 46(CH_2N), 27(CH_2), 19(CH_2), 15(CH_3), 14(CH_3). EI-MS: m/z(int) 172(30), 142(15), 127(31), 114(37), 99(100), 83(22), 71(58), 55(24), 43(51), 41(34). CI-MS: 172(M+1). Found C 63.48, H 10.06, N 8.01. ($C_9H_{17}NO_2$ requires C 63.16% H 9.94% N 8.14%).

2-Ethoxy-3-(*p*-chlorobenzyloxy)-3,4,5,6-tetrahydropyridine [3-13]

3-(*p*-Chlorobenzyloxy)-2-piperidone (1.25g, 5.23mmol) was added to a solution of triethyloxonium tetrafluoroborate (2g, 10.64mmol) in dry methylene chloride (40ml). The resulting solution was refluxed for 12hrs then cooled in ice. 5M K_2CO_3 (30ml) was added and after 30mins shaking the organic layer was removed. The aqueous layer was extracted with methylene chloride (2 x 20ml). The extracts and the organic layer

were combined, dried over anhydrous potassium carbonate and the solvent removed under vacuum to give a red oil. Microdistillation of this oil, under reduced pressure, gave 2-Ethoxy-3-(*p*-chlorobenzyloxy)-3,4,5,6-tetrahydropyridine as a colourless liquid with a pungent odour. Yield=1.07g(77%). b.pt. 170°C (10mmHg). I.R.(cm^{-1}) 1677(C=N), 1493, 1337, 1221, 1189, 1090(C-Cl), 807. ^1H NMR(250MHz,$CDCl_3$) 7.3δ(4H,m,arom), 4.7(2H,2 x d,J=12.1Hz,OCH_2), 4.0(2H,q,J=7.0Hz, OCH_2), 3.7(1H,t,J=4.7Hz,OCH), 3.2-3.4(2H,m,CH_2N), 1.4-2.0(4H,m, CH_2CH_2), 1.25(3H,t,J=7.0Hz,CH_3). ^{13}C NMR($CDCl_3$,ppm) 161(C=N), 137(C_{quat}), 133(C-Cl), 129(C_{arom}), 128(C_{arom}), 71(OCH_2), 70(OCH_2), 60(OCH), 47(CH_2N), 27(CH_2), 19(CH_2), 14(CH_3). EI-MS: m/z(int) 142(8), 125(75), 99(100), 71(16), 43(14), 41(12). CI-MS: 268(M+1). Found C 63.03, H 7.00, N 4.87. ($C_{14}H_{18}NO_2Cl$ requires C 62.80% H 6.73% N 5.23%).

3-Methoxy-2-(nitromethylene)piperidine [3-14]

2-Ethoxy-3-methoxy-3,4,5,6-tetrahydropyridine [3-11] (0.21g,1.34 mmol) was dissolved in dry, redistilled nitromethane (15ml). A catalytic amount of pyridine (1 drop) was added and the mixture refluxed for 36hrs. The nitromethane was removed under vacuum and the residue sujected to column chromatography (SiO_2: 25% Hexane/THF) to give 3-methoxy-2-(nitromethylene)piperidine as a pale yellow waxy solid. Yield=0.12g (52%). m.pt. 38-40°C. I.R.(nujol,cm^{-1}) 3216(N-H), 1615(C=C), 1495, 1327, 1236, 1179, 1095. ^1H NMR (250MHz,$CDCl_3$) 10.0δ(1H,bs,N-H,exch), 6.7(1H,s,C=CH), 3.8(1H,t,J=5.1Hz,CH) 3.4-3.5(2H,m,CH_2N), 3.4(3H,s,OCH_3), 1.8-2.1(4H,m,CH_2CH_2). EI-MS: m/z(int) 172(18), 142(26), 125(18), 96(100), 85(17), 71(40), 58(81), 55(50), 43(37), 41(73). CI-MS: 173(M+1). Found C 48.75, H 6.98, N 15.91. ($C_7H_{12}N_2O_3$ requires C 48.84% H 7.98% N 16.28%).

3-Ethoxy-2-(nitromethylene)piperidine [3-15]

2,3-Diethoxy-3,4,5,6-tetrahydropyridine [3-12] (0.3g, 1.75mmol) was dissolved in dry, redistilled nitromethane (25ml). A catalytic amount of pyridine (2 drops) were added and the mixture refluxed for 30hrs. The nitromethane was removed under vacuum and the residue sujected to column chromatography (SiO_2: MeCN) to give 3-ethoxy-2-(nitromethylene)piperidine as a yellow crystalline solid. Yield=0.211g (55%). m.pt. 50-55°C. I.R.(nujol,cm^{-1}) 3142,3048(N-H), 1604(C=C), 1455, 1324, 1228, 1094. ^1H NMR (250MHz,$CDCl_3$) 10.1δ(1H,bs,N-H,exch), 6.8(1H,s,C=CH), 3.9(1H,dd,J=4.6Hz,J=6.7Hz,CH) 3.6(2H,q, J=7Hz,OCH_2) 3.4-3.5(2H,m,CH_2N), 1.8-2.1(4H,m,CH_2CH_2), 1.2(3H,t, J=7Hz,CH_3). ^{13}C ($CDCl_3$,ppm) 158(C=CH), 109(C=CH), 72(OCH), 65(OCH_2), 41(CH_2N), 25(CH_2), 18(CH_2), 15(CH_3). EI-MS: m/z(int) 142(21), 96(100), 83(37), 72(14), 55(19), 41(33). CI-MS: 187(M+1). Found C 51.40, H 7.58, N 14.69. ($C_8H_{14}N_2O_3$ requires C 51.61% H 7.53% N 15.05%).

3-(*p*-Chlorobenzyloxy)-2-(nitromethylene) piperidine [3-16]

3-(*p*-Chlorobenzyloxy)-2-ethoxy-3,4,5,6-tetrahydropyridine [3-13] (0.9g, 3.37mmol) was dissolved in dry, redistilled nitromethane (30ml). A catalytic amount of pyridine (2 drops) was added and the mixture refluxed for 40hrs. The solvent was removed under vacuum and the residue subjected to column chromatography (SiO_2: MeCN). The product was recrystallised from THF/Hexane to give 0.7g (74%) of 3-(*p*-chlorobenzyloxy)-2-(nitromethylene) piperidine as pale yellow needles. m.pt. 120-123°C. I.R.(nujol,cm^{-1}) 3172,3149(N-H), 1605(C=C), 1486, 1383, 1323, 1310, 1225, 1096(C-Clstr). ^1H NMR (250MHz,$CDCl_3$) 10.1δ(1H,bs,N-H,exch), 7.3(4H,m,arom), 6.7(1H,s,C=CH), 4.5(2H,s, OCH_2), 4.0(1H,t,J=5.3Hz,CH), 3.2-3.6(2H,m,CH_2N), 1.8-2.2(4H,m,

CH_2CH_2), ^{13}C NMR ($CDCl_3$,ppm) 156(C=CH), 134(C_{quat}), 132(C-Cl), 127(C_{arom}), 127(C_{arom}), 108(C=CH), 70(OCH), 69(OCH_2), 39(CH_2N), 23(CH_2), 16(CH_2). EI-MS: m/z(int) 142(47), 125(77), 96(100), 77(17), 71(34), 55(19), 43(26), 41(24). CI-MS: 283(M+1). Found C 55.28, H 5.37, N 9.78, Cl 12.37. ($C_{13}H_{15}N_2O_3Cl$ requires C 55.22% H 5.31% N 9.91% Cl 12.57%.

5-Aza-1-ethoxy-4-oxo-spiro [2.5] octane [3-17]

Rhodium(II)acetate (10mg) was added to a solution of 3-diazo-2-piperidone [3-3] (0.2g, 1.6mmol) in ethyl vinyl ether (20ml). The reaction was stirred at 25°C for 1hr, then the was solvent removed under vacuum. The residue was purified by column chromatography (SiO_2:MeCN) to give 5-aza-1-ethoxy-4-oxo-spiro [2.5] octane as a white crystalline solid. Yield=0.18g (66%). m.pt. 106-108°C. I.R.(nujol,cm^{-1}) 3182(N-H), 1660(C=O), 1435, 1336, 1194, 1129, 1082, 821. ^1H NMR (250MHz, $CDCl_3$) 6.8δ(1H,bs,N-H,exch), 3.65(1H,dd,J=4.4Hz, J=7Hz,H_1), 3.6(2H,q,J=7Hz,OCH_2), 3.4(2H,m,CH_2N), 1.8-2.0(4H,m, CH_2CH_2), 1.5(1H,t,J=7Hz,H_3), 1.2(3H,t,J=7Hz,CH_3), 0.7(1H,t, J=4.4Hz,H_2). ^{13}C NMR ($CDCl_3$,ppm) 174(C=O), 67(OCH_2), 64(OCH), 42(CH_2N), 25(C_{spiro}), 24(CH_2), 23(CH_2), 21(CH_2), 15(CH_3). EI-MS: m/z(int) 169(8), 140(100), 112(72), 84(16), 77(9), 69(31), 55(19), 41(56). CI-MS: 170(M+1). Found C 64.1;H 9.0;N 8.3. ($C_9H_{15}NO_2$ requires C 63.9% H 8.9% N 8.3%).

5-Aza-1,4-diethoxy-spiro [2.5] octa-4-ene [3-30]

5-Aza-1-ethoxy-4-oxo-spiro [2.5] octane [3-17] (0.47g, 2.78mmol) was dissolved in dry methylene chloride (20ml) and added to a solution of triethyloxonium tetrafluoroborate (1g, 5.32mmol) in dry methylene chloride (20ml). The resulting solution was refluxed for 4hrs, then

cooled in ice. 5M K_2CO_3 (30ml) was added and the reaction mixture shaken for 30mins. The organic layer was removed and the aqueous layer extracted with methylene chloride (2 x 20ml). The organic layer and the extracts were combined, dried over anhydrous potassium carbonate and the solvent removed under vacuum to leave an orange oil which was distilled under reduced pressure to give 5-aza-1,4-diethoxy-spiro [2.5] octa-4-ene as a colourless liquid. Yield=0.4g(73%). bpt 115°C (10mmHg). I.R.(thin film, cm^{-1}) 1663(C=N), 1374, 1314, 1202, 1190, 1071, 734. ^1H NMR (250MHz, $CDCl_3$) 3.95δ(2H,q,J=7.1Hz, OCH_2), 3.65(1H,dd,J=6.95Hz,J=4.2Hz,OCH), 3.6(2H,q,J=7.0Hz, OCH_2), 3.5(2H,m,CH_2N), 1.6-2.0(4H,m,CH_2CH_2), 1.4(1H,dd, J=6.95Hz,J=5.2Hz,CH), 1.2(3H,t,J=7.0Hz,CH_3), 1.1(3H,t,J=7.1Hz, CH_3), 0.6(1H,dd,J=4.2Hz,CH). ^{13}C NMR ($CDCl_3$,ppm) 163(C=N), 66(OCH_2), 62(OCH), 60(OCH_2), 47(CH_2N), 24(CH_2), 23(CH_2), 22(C_{spiro}), 20(CH_2), 15(CH_3), 14(CH_3). EI-MS: m/z(int) 197(63), 168(36), 138(52), 123(100), 95(83), 67(38), 55(39), 43(41), 41(83). CI-MS: 198(M+1). Found C 67.41, H 9.84, N 7.21. ($C_{11}H_{19}NO_2$ requires C 67.00% H 9.65% N 7.11%).

5-Aza-1-ethoxy-4-methoxy-spiro [2.5] octa-4-ene

5-Aza-1-ethoxy-4-oxo-spiro [2.5] octane [3-17] (0.45g, 2.66mmol) was dissolved in dry methylene chloride (20ml), added to a solution of trimethyloxonium tetrafluoroborate (0.8g, 5.48mmol) in dry methylene chloride (20ml) and heated under reflux for 3hrs. After cooling in ice, 5M K_2CO_3 (20ml) was added and the reaction mixture shaken for 20mins. The organic layer was removed and the aqueous layer extracted with methylene chloride (2 x 20ml). The organic layer and the extracts were combined, dried over anhydrous potassium carbonate and the solvent removed under vacuum to leave an orange oil which was

distilled under reduced pressure to give 5-aza-1-ethoxy-4-methoxy-spiro [2.5] octa-4-ene as a very pale yellow liquid. Yield=0.41g(82%). bpt 110°C (10mmHg). I.R.(thin film, cm^{-1}) 1669(C=N), 1441, 1352, 1319, 1205, 1072, 818. ^1H NMR (250MHz, $CDCl_3$) 3.6(1H,t,J=4.2Hz,OCH), 3.5(2H,q,J=7Hz,OCH_2), 3.45(2H,m,CH_2N), 3.45(3H,s,OCH_3), 1.6-1.9(4H,m,CH_2CH_2), 1.65(1H,t,J=5.9Hz,CH), 1.2(3H,t,J=7.0Hz,CH_3), 0.55(1H,dd,J=4.3Hz,J=5.9Hz,CH). ^{13}C NMR ($CDCl_3$,ppm) 164(C=N), 67(OCH_2), 62(OCH), 53(OCH_3), 47(CH_2N), 24(CH_2), 22(CH_2), 21(C_{spiro}), 20(CH_2), 16(CH_3). EI-MS: m/z(int) 183(55), 151(55), 123(100), 111(90), 95(93), 67(84), 55(42), 41(81). CI-MS: 184(M+1). Found C 65.89, H 9.17, N 7.30. ($C_{10}H_{17}NO_2$ requires C 65.57% H 9.24% N 7.61%).

3'-Aza-2-oxa-2'-oxo-spiro[bicyclo[3.1.0]hexane-6,1'-cyclohexane] [3-19]
Rhodium(II)acetate (10mg) was added to a solution of 3-diazo-2-piperidone [3-3] (0.25g, 2mmol) in dihydrofuran (10ml), and the reaction was stirred for 12hrs at 25°C. The solvent was then removed under vacuum, and the residue subjected to column chromatography (SiO_2: 5%Hexane/THF). The second fraction gave a white solid which was recrystallised from diethyl ether/pentane to give 3'-aza-2-oxa-2'-oxo-spiro[bicyclo[3.1.0]hexane-6,1'-cyclohexane] as a white crystalline solid. Yield=0.15g(45%). m.pt. 135-140°C. I.R.(nujol,cm^{-1}) 3228,3187(N-H), 1651(C=O), 1485, 1417, 1366, 1335, 1253, 1148, 1122, 1096, 1048, 820. ^1H NMR (400MHz,$CDCl_3$) 6.0δ(1H,bs,N-H,exch), 4.2(1H,dd,J=8.4Hz,J=18Hz,H_{a2}), 4.1(1H,d,J=6Hz,H_d), 3.9(1H, dt,J=8.9Hz,J=4.4Hz,H_{a1}), 3.35(2H,m,CH_2N), 2.45(1H,dd,J=1.24Hz, J=7.3Hz,H_c), 2.25(1H,m,H_{b1}), 1.8-2.0(3H,m,CH_2,H_{b2}), 1.65(2H,m,H_e). ^{13}C ($CDCl_3$,ppm) 172(C=O), 75(OCH_2), 69(OCH), 42(CH_2N), 30(C_{spiro}), 29(CH), 24(CH_2), 22(CH_2), 19(CH_2). EI-MS: m/z(int)

167(47), 152(14), 138(28), 124(19), 110(42), 83(100), 67(28), 41(35). CI-MS: 168(M+1). Found C 64.22, H 7.93, N 8.14. ($C_9H_{13}NO_2$ requires C 64.67% H 7.78% N 8.38%).

3'-Aza-2'-ethoxy-2-oxaspiro[bicyclo[3.1.0]hexane-6,1'-cyclohex-2'-ene] [3-31]

3'-Aza-2-oxa-2'-oxo-spiro[bicyclo[3.1.0]hexane-6,1'-cyclohexane] [3-19] (0.3g, 1.8mmol) was dissolved in dry methylene chloride (30ml) and added to a solution of triethyloxonium tetrafluoroborate (0.9g, 4.78mmol) in dry methylene chloride (20ml). The resulting solution was heated under reflux for 12hrs, then cooled in ice. 5M K_2CO_3 (50ml) was added and the reaction mixture shaken for 1hr. The resulting solution was filtered through a glass sinta funnel, the organic layer was removed, dried over anhydrous potassium carbonate and evaporated to leave an orange oil which was distilled under reduced pressure to give 3'-aza-2'-ethoxy-2-oxaspiro[bicyclo[3.1.0]hexane-6,1'-cyclohex-2'-ene] as a colourless liquid. Yield=0.29g(83%). b.pt. 95°C (10mmHg). I.R.(thin film,cm^{-1}) 1661(C=N), 1443, 1367, 1312, 1231, 1202, 1180, 1113, 1047, 972. ^1H NMR (250MHz,$CDCl_3$) 4.18δ(1H,m,OCH_2), 4.15(1H,d, J=5.6Hz,OCH), 3.91(2H,q,J=7.1Hz,OCH_2), 3.87(1H,m,OCH_2), 3.5(2H,m,CH_2N), 2.1-2.4(2H,m,CH,CH_2), 1.5-2.0(5H,m,CH_2,CH_2,CH), 1.15(3H,t,J=7.1Hz,CH_3). ^{13}C ($CDCl_3$,ppm) 161(C=N), 75(OCH_2), 66(OCH), 60(OCH_2), 47(CH_2N), 29(C_{spiro}), 27(CH), 24(CH_2), 22(CH_2), 19(CH_2), 14(CH_3). EI-MS: m/z(int) 195(29), 166(37), 138(26), 121(100), 97(20), 81(16), 67(24). CI-MS: 196(M+1). Found C 67.93, H 8.83, N 6.78. ($C_{11}H_{17}NO_2$ requires: C 67.69% H 8.72% N7.18%).

3'-Aza-2-oxa-2'-oxo-spiro[bicyclo[3.1.0]hexane-6.1'-cyclohex-3-ene] [3-20]

Rhodium (II) acetate (15mg) was added to a solution of 3-diazo-2-piperidone [3-3] (0.27g,mmol) in furan (25ml). The reaction mixture was stirred at 25°C for 40mins and then the solvent removed under vacuum. The residue was subjected to column chromatography (SiO_2: 5% IPA/ MeCN) The fastest fraction gave the title compound as an orange crystalline solid. Yield=0.25g(60%). m.pt. 132°C dec. I.R.(nujol, cm^{-1}) 3183,3037(N-H), 1643(C=O), 1594(C=C), 1488, 1421, 1332, 1257, 1146, 960. ^1H NMR (250MHz, $CDCl_3$) 6.9δ(1H,bs,N-H), 6.4(1H,d,J=2.5Hz,OCH), 5.2(1H,t,J=2.6Hz,CH), 4.8(1H,d,J=5.7Hz, OCH), 3.35(2H,m,CH_2N), 2.9(1H,dd,J=5.7Hz,J=2.7Hz,CH), 1.8(2H, m,CH_2), 1.4(2H,m,CH_2). ^{13}C ($CDCl_3$,ppm) 174(C=O), 148(OCH), 102(C=CH), 71(OCH), 42(CH_2N), 36(CH), 22(CH_2), 17(CH_2), 16(C_{spiro}). CI-MS: 166(M+1). Found C 65.6, H 6.6, N 8.2. ($C_9H_{11}NO_2$ requires C 65.5%, H 6.7%, N 8.5%).

1,2,7-triaza-3-methoxycarbonyl-6-oxo-spiro [4.5] dec-2-ene {[3-26] R=OCH_3}

3-Diazo-2-piperidone [3-3] (1g, 8mmol) was dissolved in methyl acrylate (50ml) and stirred at 25°C for 30 mins. The 1,2,7-triaza-3-methoxycarbonyl-6-oxo-spiro [4.5] dec-2-ene was filtered off as a white crystalline solid and washed with chloroform (15ml). Yield=1.6g(95%). m.pt. 160-161°C. I.R.(nujol, cm^{-1}) 3212,3046(N-H), 1730(C=O, ester), 1644(C=O, amide), 1581, 1493, 1342, 1328, 1285, 1261, 1138, 1099, 789. ^1H NMR (250MHz, $DMSO_{d6}$) 8.8δ(1H,bs,N-H,exch), 7.7(1H,bs,N-H,exch, amide), 3.7(3H,s,OCH_3), 3.3(1H,d,J=16.8Hz,CH_2), 3.2(2H,m, CH_2N), 2.65(1H,d,J=16.8Hz,CH_2), 1.6-1.9(4H,m,CH_2CH_2). ^{13}C NMR ($DMSO_{d6}$,ppm) 171(C=O, amide), 163(C=O, ester), 136(C=N), 68(C_{spiro}), 51(OCH_3), 41(CH_2N), 41(CH_2), 34(CH_2), 19(CH_2). EI-MS:

m/z(int) 183(M-28, 34), 153(100), 140(78), 121(92), 108(78), 96(35), 81(32), 43(42). CI-MS: 212(M+1). Found C 51.00, H 6.24, N 19.72. ($C_9H_{13}N_3O_3$ requires C 51.18% H 6.20% N 19.89%).

5-Aza-1-methoxycarbonyl-4-oxo-spiro [2.5] octane [3-28]

1,2,7-triaza-3-methoxycarbonyl-6-oxo-spiro [4.5] dec-2-ene {[3-26] R=OCH_3} (0.2g, 0.95mmol) was suspended in dichlorobenzene (5ml) and heated under reflux for 20 mins. Most of the solvent was removed under vacuum and the remaining oil subjected to column chromatography (SiO_2: 25%MeOH/CCl_4). The second fraction was isolated and identified as 5-aza-1-methoxycarbonyl-4-oxo-spiro [2.5] octane, an off-white solid. Yield=0.13g(75%). m.pt. 70-72°C. I.R.(nujol, cm^{-1}) 3191,3050(N-H), 1737(C=O, ester), 1657(C=O, amide), 1493, 1381, 1356, 1335, 1203, 1177, 953. ^1H NMR (250MHz, $CDCl_3$) 6.7δ(1H,bs,N-H,exch), 3.7(3H,s,OCH_3), 3.35(2H,m,CH_2N), 2.4(1H,dd, J=6.7Hz,J=8.7Hz,CH), 1.8-2.0(4H,m,CH_2CH_2), 1.6(1H,dd,J=3.8Hz, J=8.7Hz,CH_2), 1.2(1H,dd,J=3.8Hz,J=6.7Hz,CH_2) ^{13}C NMR ($CDCl_3$, ppm) 171(C=O), 171(C=O), 52(OCH_3), 43(CH_2N), 29(C_{spiro}), 27(CH), 25(CH_2), 22(CH_2), 21(CH_2). EI-MS: m/z(int) 183(18), 151(36), 123(100), 96(25), 83(44), 67(16), 41(25). CI-MS: 184(M+1). Found C 59.41, H 7.20, N7.51. ($C_9H_{13}NO_3$ requires C 59.02% H 7.10% N 7.65%).

1,2,7-triaza-3-methylcarbonyl-6-oxo-spiro [4.5] dec-2-ene {[3-26] R=CH_3}

3-Diazo-2-piperidone [3-3] (0.11g, 0.88mmol) was dissolved in methylene chloride (2ml) and added, with stirring, to methyl vinyl ketone (10ml) at 25°C. After 30mins the 1,2,7-triaza-3-methylcarbonyl-6-oxo-spiro [4.5] dec-2-ene formed was filtered off as white crystals and washed with methylene chloride (5ml). Yield=0.157g(91%). m.pt. 200-

201°C. I.R.(nujol, cm^{-1}) 3227(N-H), 1659(C=O, amide), 1634(C=O, ketone), 1557, 1429, 1385, 1342, 1286, 1256, 1103, 996, 632. ^{1}H NMR (250MHz, $DMSO_{d6}$) 9.1δ(1H,bs,N-H,exch), 7.7(1H,bs,N-H,exch, amide), 3.2(2H,m,CH_2N), 3.18(1H,d,J=16.7Hz,CH_2), 2.55(1H,d, J=16.7Hz,CH_2), 2.25(3H,s,CH_3), 1.75-1.9(4H,m,CH_2CH_2). ^{13}C NMR ($DMSO_{d6}$,ppm) 193(C=O, ketone), 171(C=O, amide), 145(C=N), 68(C_{spiro}), 41(CH_2N), 40(CH_2), 32(CH_2), 25(CH_3), 19(CH_2). EI-MS: m/z(int) 137(82), 124(65), 78(82), 63(100), 43(49). CI-MS: 196(M+1). Found C 55.35, H 6.64, N 21.48. ($C_9H_{13}N_3O_2$ requires C 55.38% H 6.67% N 21.54%).

1,2,7-triaza-3-formyl-6-oxo-spiro [4.5] dec-2-ene {[3-26] R=H}

3-Diazo-2-piperidone [3-3] (0.19g, 1.52mmol) was dissolved in acrolein (10ml) and stirred for 20 mins at 25°C. The 1,2,7-triaza-3-formyl-6-oxo-spiro [4.5] dec-2-ene formed was filtered off as a white crystalline solid and washed with chloroform (5ml). Yield=0.19g(69%). m.pt. 178-182°C. I.R.(nujol, cm^{-1}) 3164(N-H), 1668(C=O), 1550, 1491, 1343, 1284, 1246, 1127, 1114, 1003, 850. ^{1}H NMR (250MHz, $DMSO_{d6}$) 9.8δ(1H,bs,N-H,exch), 9.5(1H,s,CHO) 7.8(1H,bs,N-H,exch,amide), 3.2(2H,m,CH_2N), 3.15(1H,d,J=16.7Hz,CH_2), 2.65(1H,d,J=16.7Hz, CH_2), 1.6-1.9(4H,m,CH_2CH_2). ^{13}C NMR ($DMSO_{d6}$,ppm) 185(C=O, aldehyde), 170(C=O, amide), 146(C=N), 69(C_{spiro}), 41(CH_2N), 38(CH_2), 34(CH_2), 19(CH_2). FAB-MS: m/z(int) 182 (M+1,94), 154(20), 93(100), 75(41), 44(36). Found C 52.89, H 6.15, N 22.98. ($C_8H_{11}N_3O_2$ requires C 53.04% H 6.08% N 23.20%).

1,2,7-triaza-3-methoxycarbonyl-3-methyl-6-oxo-spiro [4.5] dec-1-ene [3-27]

3-Diazo-2-piperidone [3-3] (1.9g, 15.2mmol) was dissolved in methyl methacrylate (20ml) and stirred for 4 hrs at 25°C. When the yellow solution had turned colourless the solvent was removed under vacuum and the residue recrystallised from diethyl ether / pentane to give 1,2,7-triaza-3-methoxycarbonyl-3-methyl-6-oxo-spiro [4.5] dec-1-ene as white needles. Yield=2.3g(67%). m.pt. 94-97°C. I.R.(nujol, cm^{-1}) 3198,3058(N-H), 1733(C=O, ester), 1658(C=O, amide), 1445, 1373, 1346, 1302, 1274, 1170, 1143, 840. ^1H NMR (250MHz,$CDCl_3$) 7.0δ(1H,bs,N-H,exch), 3.8(3H,s,OCH_3), 3.3-3.5(2H,m,CH_2N), 1.8-2.2(4H,m,CH_2CH_2), 2.05(1H,d,J=12.9Hz,CH_2), 1.9(1H,d,J=12.9Hz, CH_2), 1.5(3H,s,CH_3). ^{13}C NMR ($CDCl_3$,ppm) 171(C=O, amide), 169(C=O, ester), 98(C_{quat}), 98(C_{spiro}), 53(OCH_3), 43(CH_2N), 38(CH_2), 33(CH_2), 23(CH_3), 20(CH_2). EI-MS: m/z(int) 197(M-28,31), 165(46), 137(100), 109(24), 79(16), 67(20), 41(20). CI-MS: 198(M-28+1). Found C 53.39, H 6.75, N 18.46. ($C_{10}H_{15}N_3O_3$ requires C 53.33% H 6.66% N 18.67%).

5-Aza-1-methoxycarbonyl-1-methyl-4-oxo-spiro [2.5] octane [3-29]

1,2,7-triaza-3-methoxycarbonyl-3-methyl-6-oxo-spiro [4.5] dec-1-ene [3-27] (2.25g, 0.01mol) was dissolved in dioxan (70ml) and heated under reflux for 20 mins. The solvent was removed under vacuum and the residue recrystallised from diethyl ether / pentane to give 5-aza-1-methoxycarbonyl-1-methyl-4-oxo-spiro [2.5] octane as white needles. Yield= 1.95g(99%) . m.pt. 112-113°C. I.R.(nujol,cm^{-1}) 3193,3077(N-H), 1715(C=O, ester), 1669(C=O, amide), 1457, 1445, 1315, 1298, 1148, 848. ^1H NMR (250MHz, $CDCl_3$) 7.2δ(1H,bs,N-H,exch), 3.7(3H,s,OCH_3), 3.35(2H,m,CH_2N), 1.7-2.0(4H,m,CH_2CH_2),

1.6(1H,d,J=4.8Hz,CH_2), 1.45(1H,d,J=4.8Hz,CH_2), 1.4(3H,s,CH_3). ^{13}C NMR ($CDCl_3$,ppm) 173(C=O, amide), 171(C=O, ester), 52(OCH_3), 41(CH_2N), 33(C_{spiro}), 32(C_{quat}), 26(CH_2), 22(CH_2), 20(CH_2), 15(CH_3). EI-MS: m/z(int) 197(24), 165(38), 137(84), 98(18), 79(18), 57(36), 41(29). CI-MS: 198(M+1). Found C 60.80, H 7.60, N 6.95. ($C_{10}H_{15}NO_3$ requires C 60.91% H 7.61% N 7.11%).

5-Aza-4-ethoxy-1-methoxycarbonyl-1-methyl-spiro [2.5] octa-4-ene [3-32]

5-Aza-1-methoxycarbonyl-1-methyl-4-oxo-spiro [2.5] octane [3-29] (1.1g, 5.58mmol) was dissolved in dry methylene chloride (20ml) and added to a solution of triethyloxonium tetrafluoroborate (2.5g, 13.3mmol) in dry methylene chloride (20ml). The resulting solution was refluxed for 8hrs, then cooled in ice. 5M K_2CO_3 (20ml) was added and the reaction mixture shaken for 20mins. The organic layer was removed and the aqueous layer extracted with methylene chloride (2 x 20ml). The organic layer and the extracts were combined, dried over anhydrous potassium carbonate and the solvent removed under vacuum to leave an orange oil which was distilled under reduced pressure to give 5-aza-4-ethoxy-1-methoxycarbonyl-1-methyl-spiro [2.5] octa-4-ene as a colourless liquid. Yield=0.75g(60%). bpt 150°C (10mmHg). I.R.(thin film, cm^{-1}) 1728(C=O), 1664(C=N), 1461, 1334, 1279, 1200, 1153, 1038, 781. ^1H NMR (250MHz, $CDCl_3$) 4.0δ(2H,q,J=7.1Hz,OCH_2), 3.7(3H,s,OCH_3), 3.55(2H,m,CH_2N), 1.5-1.7(4H,m,CH_2CH_2), 1.6(1H,d, J=5Hz,CH_2), 1.45(1H,d,J=5Hz,CH_2), 1.4(3H,s,CH_3), 1.2(3H,t,J=7.1Hz, CH_3). ^{13}C NMR ($CDCl_3$,ppm) 173(C=O), 161(C=N), 60(OCH_2), 52(CH_3O), 47(CH_2N), 31(C_{quat}), 30(C_{spiro}), 26(CH_2), 23(CH_2), 21(CH_2), 16(CH_3), 14(CH_3). EI-MS: m/z(int): 225(51), 197(26),

165(41), 137(100), 96(16), 41(50). Accurate mass: Found 225.1359. ($C_{12}H_{19}NO_3$ requires 225.1365).

3-[(*p*-nitrophenyl) methylene]-2-piperidone [3-40] and [3-41]

3-Diazo-2-piperidone [3-3] (0.25g, 2mmol) was dissolved in THF (15ml) and added dropwise to a solution of *p*-nitrobenzaldehyde (0.3g, 2mmol); triphenylphosphine (0.52g, 2mmol) and methyl trioxorhenium (18mg, 3.6mol%) in THF (20ml). The reaction mixture was stirred at room temperature for 7hrs and the solvent removed under vacuum. The residue was subjected to column chromatography (SiO_2: 50% $MeCN/CH_2Cl_2$). The second fraction gave the (Z)-isomer of the title compound [3-41] as a pale yellow crystalline solid. Yield= 0.215g (46%). mpt 120-122°C. I.R.(nujol,cm^{-1}) 3199(N-H), 1669(C=O), 1632(C=C), 1513(NO_2), 1463, 1421, 1343(NO_2), 1312, 1107. ^1H NMR (250MHz,$CDCl_3$) 8.1δ(2H,d,J=8.6Hz,H_f), 7.55(2H,d,J=8.6Hz,H_e), 6.7(1H,s,H_d), 6.4(1H,bs,N-H,exch), 3.4(2H,t,J=5.95Hz,H_a), 2.65(2H,t, J=6.3Hz,H_c), 2.0(2H,m,H_b). ^{13}C ($CDCl_3$,ppm) 165(C=O), 146(C-NO_2), 143(C_{arom}), 134(C_d), 133(C_{quat}), 129(CH), 122(CH), 42(C_a), 32(C_b), 23(C_c). EI-MS: m/z(int) 232(52), 231(98), 185(27), 128(17), 97(25), 85(46), 71(57), 57(100), 43(69). CI-MS: 233(M+1). Found C 61.90, H 5.33, N 11.89. ($C_{12}H_{12}N_2O_3$ requires: C 62.06%, H 5.21%, N 12.06%). The third fraction gave the (E)-isomer of the title compound [3-40] as a pale yellow solid. Yield= 0.072g (15.5%). mpt 125-126°C. I.R.(nujol,cm^{-1}) 3382,3190(N-H), 1668(C=O), 1622(C=C), 1510(NO_2), 1421, 1340, 1107, 993. ^1H NMR (250MHz, $CDCl_3$) 8.2δ(2H,d,J=8.55Hz,H_e), 7.8(1H,s,H_d), 7.5(2H,d,J=8.55Hz,H_f), 6.3(1H,bs,N-H,exch), 3.4(2H, m,H_a), 2.8(2H,m,H_c), 1.9(2H,m,H_b). EI-MS: m/z(int) 232(40), 231(80), 202(19), 185(23), 97(30), 71(62),

43(81). CI-MS: 233(M+1). Found C 61.72, H 5.20, N 11.82. ($C_{12}H_{12}N_2O_3$ requires: C 62.06%, H 5.21%, N 12.06%).

3-(Phenylmethylene)-2-piperidone

3-Diazo-2-piperidone [3-3] (0.25g, 2mmol) was dissolved in THF (15ml) and added dropwise to a solution of benzaldehyde (0.212g, 2mmol); triphenylphosphine (0.52g, 2mmol) and methyl trioxorhenium (15mg, 3mol%) in THF (20ml). The reaction mixture was stirred at room temperature for 12hrs and the solvent removed under vacuum. The residue was subjected to prep tlc (SiO_2: 50% MeCN/$CHCl_3$). The middle fraction gave the title compound as a pale yellow waxy solid. Yield= 0.13g (34%). mpt 71-75°C. I.R.(nujol,cm^{-1}) 3270,3182(N-H), 1668(C=O), 1635(C=C), 1461, 1414, 1321, 1109, 909. ^1H NMR (250MHz,$CDCl_3$) 7.2-7.8δ(6H,m,$5H_{arom}$,CH), 6.3(1H,bs,N-H,exch), 3.2(2H,m,CH_2N), 2.72(2H,t,J=6.4Hz,CH_2), 1.85(2H,m,CH_2). EI-MS: m/z(int) 187(13), 97(54), 83(46), 68(83), 41(89). CI-MS: 188(M+1). Found C 77.30, H 6.87, N 7.00. ($C_{12}H_{13}NO$ requires: C 77.01%, H 6.95%, N 7.49%).

3-[(*p*-Chlorophenyl) methylene]-2-piperidone

3-Diazo-2-piperidone [3-3] (0.25g, 2mmol) was dissolved in THF (15ml) and added dropwise to a solution of *p*-chlorobenzaldehyde (0.3g, 2mmol); triphenylphosphine (0.52g, 2mmol) and methyl trioxorhenium (25mg, 5mol%) in THF (20ml). The reaction mixture was stirred at room temperature for 10hrs and the solvent removed under vacuum. The residue was subjected to prep tlc (SiO_2: 20% $CHCl_3$/MeCN). The middle fraction gave the title compound as a pale yellow waxy solid. Yield= 0.17g (38%). mpt 58-60°C. I.R.(nujol,cm^{-1}) 3185(N-H), 1670(C=O), 1630(C=C), 1481, 1439, 1321, 1222, 1109, 910. ^1H NMR

(250MHz,$CDCl_3$) 7.7δ(2H,d,J=8.5Hz,H_{arom}), 7.5(2H,d,J=8.5Hz,H_{arom}), 7.2(1H,s,CH), 6.3(1H,bs,N-H,exch), 3.3(2H,m,CH_2N), 2.6(2H,t, J=6.2Hz,CH_2), 1.9(2H,m,CH_2). EI-MS: m/z(int) 222(12), 186(15), 158(11), 125(82), 97(68), 68(15), 43(9). CI-MS: 223(M+1). Found C 65.61, H 5.42, N 5.92. ($C_{12}H_{12}NOCl$ requires: C 65.01%, H 5.12%, N 6.32%).

3-Chloro-2-piperidone [3-46]

3-Diazo-2-piperidone [3-3] (2g, 0.016mol) was dissolved in dry dioxan (5ml) and added dropwise with vigorous stirring to a solution of 4M HCl in dioxan (50ml). The yellow colour of the diazo compound faded and after 1hr the solvent was removed under vacuum to leave a pale yellow solid which was recrystallised from diethyl ether to give 3-chloro-2-piperidone as a white crystalline solid. Yield= 1.45g (68%). m.pt. 116-118°C. I.R.(nujol,cm^{-1}) 3255(N-H), 1648(C=O), 1378, 1327, 1177, 812(C-Cl). ^1H NMR (250MHz, $CDCl_3$) 8.0δ(1H,bs,N-H), 4.4(1h,t,J=4.95Hz,CH), 3.4(2H,m,CH_2N), 1.9-2.2(4H,m,CH_2CH_2). EI-MS: m/z(int) 135(23), 133(65), 97(43), 84(68), 82(100), 68(42), 62(69), 58(68), 55(89), 43(34), 41(45). CI-MS: 134(M+1). Found C 44.87, H 6.11, N 10.38, Cl 26.86. (C_5H_8NOCl requires C44.94% H 5.99% N 10.49% Cl 26.69%).

3-Chloro-2-ethoxy-3,4,5,6-tetrahydropyridine [3-47]

3-Chloro-2-piperidone [3-46] (1.45g, 0.011mol) was dissolved in dry methylene chloride (30ml) and added to a solution of triethyloxonium tetrafluoroborate (2.75g, 0.0146mol) in dry methylene chloride (15ml). The resulting solution was heated under reflux for 8hrs, then cooled in ice. 5M K_2CO_3 (30ml) was added and the reaction mixture stirred for 1hr at 25°C. The organic layer was removed and the aqueous layer

extracted with methylene chloride (2 x 20ml). The organic layer and the extracts were combined, dried over anhydrous potassium carbonate and the solvent removed under vacuum to give an orange oil which was distilled under reduced pressure to give 3-chloro-2-ethoxy-3,4,5,6-tetrahydropyridine as a colourless liquid. Yield=1.06g(60%). b.pt. 70°C (10mmHg). I.R.(thin film,cm^{-1}) 1674(C=N), 1370, 1330, 1244, 1208, 1035, 872(C-Cl). ^1H NMR (250MHz, $CDCl_3$) 4.2δ(1H,t,J=3.75Hz,CH), 4.0(2H,q,J=7Hz,OCH_2), 3.4-3.6(2H,m,CH_2N), 1.5-2.1(4H,m,CH_2CH_2), 1.3(3H,t,J=7Hz,CH_3). ^{13}C ($CDCl_3$,ppm) 159(C=N), 61(OCH_2), 49(C-Cl), 46(CH_2N), 30(CH_2), 17(CH_2), 14(CH_3). EI-MS: m/z(int) 163(21), 161(57), 116(49), 98(91), 82(33), 69(37), 55(100), 43(54), 41(74). CI-MS: 162(M+1). Found C 52.43, H 7.46, N 8.41. ($C_7H_{12}NOCl$ requires C 52.17% H 7.45% N 8.70%).

2-Methoxy-3,4,5,6-tetrahydropyridine [3-53]

Dimethyl sulphate (133g, 1.06mol) was added dropwise with stirring over a 2hr period to 2-piperidone [3-52] (100g, 1.01mol) at 45°C. The temperature of the reaction was then raised to 55°C and left for 20hrs. The resulting solution was cooled in ice, and a saturated solution of K_2CO_3 (500ml) was added. The mixture was stirred for a further 2hrs at 25°C, and then diluted with water (200ml). The product was extracted with diethyl ether (4 x 200ml), dried over anhydrous potassium carbonate and the solvent removed under vacuum to give 2-methoxy-3,4,5,6-tetrahydropyridine as a clear colourless liquid with a pungent odour. Yield= 100.6g(88%). b.pt. 70°C (7mmHg). I.R.(thin film,cm^{-1}) 1673(C=N), 1487, 1462, 1387, 1251, 1199, 1005, 832. ^1H NMR (220MHz,$CDCl_3$,TMS) 3.65δ(3H,s,OCH_3), 3.5(2H,t,J=6.5Hz,CH_2N), 2.2(2H,t,J=6.2Hz,CH_2), 1.5-1.9(4H,m,CH_2CH_2). ^{13}C ($CDCl_3$, ppm) 162(C=N), 51(OCH_3), 46(CH_2N), 25(CH_2), 20(CH_2), 22(CH_2). EI-MS:

m/z(int) 113(48), 98(50), 82(61), 70(38), 55(100), 41(66). Found C 63.98, H 9.81, N 11.96. ($C_6H_{11}NO$ requires C 63.72% H 9.73% N 12.39%).

2-(Nitromethylene)piperidine [3-49]

2-Methoxy-3,4,5,6-tetrahydropyridine [3-53] (100g, 0.885mol) was dissolved in nitromethane (200ml) and stirred under reflux for 18hrs. The methanol produced during the reaction was distilled out at a rate of 5ml hr^{-1} along with nitromethane, and fresh nitromethane was added to the reaction mixture at the same rate to maintain the temperature at 102°C. The solvent was then removed under vacuum to leave a red/orange solid which was triturated with diethyl ether to give 2-(nitromethylene)piperidine as a pale yellow crystalline solid. Yield=62g(57%). m.pt. 75-78°C. I.R. (nujol,cm^{-1}) 3189(N-H), 1636(C=C), 1505(NO_2,anti), 1461, 1381(NO_2, sym), 1348, 1328, 1246, 1060, 826. ^1H NMR (220MHz,$CDCl_3$,TMS) 10.6δ(1H,bs,N-H,exch), 6.6(1H,s,C=CH), 3.55(2H,m,CH_2N), 2.45(2H,t,J=5.7Hz,CH_2), 1.8-2.0(4H,m,CH_2CH_2). ^{13}C NMR ($CDCl_3$, ppm) 160(C=CH), 108(C=CH), 41(CH_2N), 26(CH_2), 21(CH_2), 18(CH_2). EI-MS: m/z(int) 142(70), 112(52), 98(30), 83(48), 80(75), 55(94), 41(97). CI-MS: 143(M+1). Found C 50.5, H 7.0, N 19.8. ($C_6H_{10}N_2O_2$ requires C 50.7% H 7.0% N 19.7%).

3-Bromo-2-(nitromethylene)piperidine [3-51]

N-Bromosuccinimide (37.6g, 0.211mol) was added to a suspension of 2-(nitromethylene)piperidine [3-49] (30g, 0.211mol) in carbon tetrachloride (900ml). The resulting mixture was stirred for 15hrs at 25°C, then refluxed for a further 1hr. The reaction mixture was filtered hot, the filtrate cooled to -10°C and the yellow crystals of 3-bromo-2-

(nitromethylene)piperidine were collected by filtration. Yield=28.5g. The insoluble brown solid which was filtered off was dissolved in hot ethyl acetate (300ml) and decolourising charcoal was added. After 10mins the charcoal was filtered off and the filtrate washed with water (5 x 75ml) followed by 5M K_2CO_3 (1 x 50ml), dried over anhydrous sodium sulphate and the solvent removed under vacuum to give a further 9.5g of 3-bromo-2-(nitromethylene)piperidine. Total yield=38g(81%). m.pt.110-115°C. I.R.(nujol,cm^{-1}) 3170,3128(N-H), 1605(C=C), 1507(NO_2,anti), 1391(NO_2,sym), 1336, 1293, 1257, 1182, 711, 570. ^1H NMR(300MHz,$CDCl_3$) 10.1δ(1H,bs,N-H,exch), 6.65(1H,s, C=CH), 4.7(1H,t,J=3.4Hz,CH-Br), 3.4-3.7(2H,m,CH_2N), 1.9-2.4(4H,m, CH_2CH_2). ^{13}C ($CDCl_3$,ppm) 157(C_{quat}), 111(CH=C), 41(CH_2N), 40(C-Br), 28(CH_2), 17(CH_2). EI-MS: m/z(int) 222(38), 220(42), 174(35), 141(53), 94(61), 79(73), 68(70), 55(98), 41(100). CI-MS: 223, 221(M+1). Found C 32.7, H 4.2, N 12.7. ($C_6H_9N_2O_2Br$ requires C 32.6% H 4.1% N 12.7%).

(E)-2-(Chloro-nitromethylene)piperidine [3-54]

2-(Nitromethylene)piperidine [3-49] (5g, 0.035mol) and N-chloro succinimide (4.7g, 0.035mol) were suspended in carbon tetrachloride (100ml) and stirred for 15hrs at 25°C. The reaction mixture was then heated under reflux for a further 2hrs, filtered hot and then cooled in ice. The white needles formed were filtered off and identified as (E)-2-(chloro-nitromethylene)piperidine. Yield=4.8g (78%). mpt 114-117°C. I.R.(nujol,cm^{-1}) 1613(C=C), 1462, 1377, 1338, 1210, 1185, 1046, 805, 736. ^1H NMR (300MHz, $CDCl_3$) 11.4d(1H,bs,N-H), 3.5(2H,m,CH_2N), 2.6(2H,m,CH_2), 1.8(4H,m,CH_2CH_2). ^{13}C ($CDCl_3$,ppm) 160(C=CH), 121(C-Cl), 42(CH_2N), 28(CH_2), 20(CH_2), 18(CH_2). CI-MS: m/z(int)

179(32), 177(M+1,100), 161(17), 143(21), 132(60), 125(79). Found C 41.2, H 5.1, N 16.2. ($C_6H_9N_2O_2Cl$ requires: C 40.9% H 5.1% N 15.9%).

3-Phthalimido-2-(nitromethylene)piperidine [3-55]

Potassium phthalimide (0.84g, 4.54mmol) was added to a solution of 3-bromo-2-(nitromethylene)piperidine [3-51] (0.5g, 2.26mmol) in DMF (20ml). The mixture was stirred for 12hrs at 25°C, then poured into water (30ml) and extracted with methylene chloride (4 x 30ml). The extracts were combined, dried over anhydrous sodium sulphate and the solvent removed under vacuum. The resulting red oil was purified by column chromatography (SiO_2; 5% EtOH/CH_2Cl_2) to give a pale yellow solid which was recrystallised from acetone/petrol 100-120°C to give 3-phthalimido-2-(nitromethylene)piperidine as a pale cream crystalline solid. Yield= 0.36g(55%). m.pt. 200-202°C. I.R. (nujol,cm^{-1}) 3181(N-H), 1775, 1714(C=O), 1618(C=C), 1492, 1388, 1324, 1247, 1097, 1026, 718. ^1H NMR (250MHz,$CDCl_3$) 10.7δ(1H,bs,N-H,exch), 7.8-8.0(4H,m,Harom), 6.4(1H,s,C=CH), 5.0(1H,dd,J=6.3Hz,J=10.8Hz,CH), 3.6(2H,m,CH_2N) 1.9-2.4(4H,m,CH_2CH_2). ^{13}C ($CDCl_3$,ppm) 167(C=O), 157(C=CH), 135(CH_{arom}), 131(C_{arom}), 124(CH_{arom}), 108(C=CH), 45(CH), 42(CH_2N), 24(CH_2), 21(CH_2). EI-MS: m/z(int) 255(20), 241(44), 186(24), 173(42), 104(49), 94(36), 82(100), 76(61), 43(26). CI-MS: 288(M+1). Found C 58.51, H 4.57, N 14.40. ($C_{14}H_{13}N_3O_4$ requires C 58.54% H 4.53% N 14.63%).

3,3-Dibromo-2-(nitromethylene)piperidine [3-63]

N-Bromosuccinimide (0.25g, 1.4mmol) was added to a stirred solution of 3-bromo-2-(nitromethylene)piperidine [3-51] (0.31g, 1.4mmol) in carbon tetrachloride (10ml). The reaction was stirred for 2hrs at 25°C, then heated under reflux for a further 1hr. The insoluble succinimide

was filtered off and the filtrate cooled to -10°C in a water/ice/salt bath to afford 3,3-dibromo-2-(nitromethylene)piperidine as bright yellow crystals. Yield=0.3g(71%). m.pt. 92-96°C. I.R.(nujol,cm^{-1}) 3128(N-H), 1615(C=C), 1489, 1376, 1327, 1234, 1114, 1086, 757(C-Br_2). ^1H NMR (300MHz,$CDCl_3$) 10.5δ(1H,bs,N-H), 7.4(1H,s,H_f), 3.6(2H,m,H_a), 2.9(2H,m,H_c), 2.1(2H,m,H_b). ^{13}C ($CDCl_3$, ppm) 159(C_e), 114(C_f), 51(C_d), 45(C_c), 41(C_a), 21(C_b). CI-MS (CH_4): m/z(int) 301[M+1,(61)], 255(24), 221(86), 205(31), 174(100), 143(80). Found C 24.5, H 3.0, N 9.3. ($C_6H_8N_2O_2Br_2$ requires C 24.0% H 2.7% N 9.3%).

3-Hydrazono-2-(nitromethylene)piperidine [3-58]

3,3-Dibromo-2-(nitromethylene)piperidine [3-63] (3.8g, 0.0127mol) was dissolved in warm ethanol (120ml) and allowed to cool to 25°C. Hydrazine hydrate (3.8g, 0.059mol) was added and the resulting solution stirred for 20hrs at 25°C. The ethanol was removed under vacuum and the residue subjected to column chromatography (SiO_2; 10% MeOH/$CHCl_3$). The first fraction was recrystallised from chloroform/ cyclohexane to give colourless crystals which were identified as N*bis* [4-(2'-azavinyl)-1,2,3-triazabicyclo[3.3.0]octa-2,4-diene [3-66]. Yield= 0.5g (15%). m.pt. 230-235°C. I.R.(nujol, cm^{-1}) 1639(C=N), 1574, 1462, 1316, 1171, 952, 871. ^1H NMR (250MHz,$CDCl_3$) 8.7δ(2H,s,H_f), 4.4(2H,t,J=7.6Hz,H_a), 3.1(2H,t, J=7.3Hz,H_c), 2.9(2H,m,H_b). ^{13}C ($CDCl_3$,ppm) 155(C_f), 143(C_e), 136(C_d), 47(C_a), 28(C_c), 22(C_b). EI-MS: m/z(int) 270(16), 230(16), 149(26), 93(49), 65(81), 43(100). CI-MS: 270 (M+1). Acc. Mass= 270.1348, $C_{12}H_{14}N_8$ requires: 270.1336. Found C 53.80, H 5.25, N 40.95. ($C_{12}H_{14}N_8$ requires: C 53.33%, H 5.19%, N 41.48%). The second fraction gave 3-hydrazono-2-(nitromethylene) piperidine as a bright yellow crystalline solid. Yield= 0.8g(37%). m.pt. 153-156°C. I.R. (nujol,cm^{-1}) 3178(N-H), 1658(C=N),

1601(C=C), 1485, 1383, 1347, 1233, 1186, 1144, 884, 767. ^{1}H NMR (300MHz, $DMSO_{d6}$) 10.6δ(1H,bs,N-H,exch), 7.95(2H,bs,NH_2,exch), 7.0(1H,s,H_f), 3.35 (2H,m,H_a), 2.3(2H,t,J=6.9Hz,H_c), 1.7-1.8(2H,m,H_b). ^{13}C ($DMSO_{d6}$,ppm) 154(C_e), 130(C_d), 103(C_f), 40(C_a), 21(C_c), 19(C_b). EI-MS: m/z(int) 84(85), 66(100), 47(20), 46(31). CI-MS: 171(M+1). Found C 42.2, H 5.9, N 32.2. ($C_6H_{10}N_4O_2$ requires C 42.4% H 5.9% N 32.9%).

3-Diazo-2-(nitromethylene)piperidine [3-67]

3-Hydrazono-2-(nitromethylene)piperidine [3-58] (0.22g, 1.29mmol) was dissolved in chloroform (50ml) and cooled to -5°C in a water/ice/salt bath. The resulting solution was stirred vigorously and sodium sulphate (0.36g, 2.53mmol) and yellow mercuric oxide (0.56g, 2.58mmol) were added. After 10sec, 3 drops of a saturated solution of KOH/MeOH were added. The reaction mixture turned from bright orange to black. After 10mins the mercury was removed by filtration and the filtrate passed through a short bed of silica. Removal of the solvent under reduced pressure gave 3-diazo-2-(nitromethylene) piperidine as an orange/red crystalline solid. Yield=0.16g(74%). m.pt. 105-107°C. I.R. ($CHCl_3$,cm^{-1}) 3200,3140(N-H), 2070(C=N_2), 1580 (C=C), 1390, 1365, 1166, 1094, 970, 880. ^{1}H NMR (300MHz,$CDCl_3$) 10.4δ(1H,bs,N-Hexc), 6.6(1H,s,CH), 3.4(2H,m,CH_2N), 2.75(2H,t, J=6.3Hz,CH_2), 2.0(2H,m,CH_2). CI-MS (NH_3): 186(M+18), 169(20), 158(21), 141(21), 124(23). Found C 42.98, H 4.79, N 32.95. ($C_6H_8N_4O_2$ requires C 42.86% H 4.76% N 33.33%).

2,3,6-Triaza-4-nitrobicyclo[4,3,0] non-1,4-diene [3-68]

3-Diazo-2-(nitromethylene)piperidine [3-67] (0.4g, 2.4mmol) was dissolved in chloroform (30ml) and allowed to stand at 25°C for 36hrs. The solvent was removed under vacuum and the residue recrystallised from THF/Hexane to give 2,3,6-triaza-4-nitrobicyclo[4.3.0] non-1,4-diene as a red powder. Yield= 0.4g (100%). mpt 142-146°C dec. I.R.(nujol,cm^{-1}) 3182,3095(N-H), 1609(C=C), 1495, 1456, 1375, 1337, 1321, 1230, 1186. ^1H NMR (300MHz,$CDCl_3$) 11.5-14.0δ(1H,bs,N-H), 4.8-5.2(1H,bs,N-H), 3.38(2H,t,J=5.48Hz,CH_2N), 2.9(2H,t,J=6.43Hz, CH_2), 2.0(2H,m,CH_2). CI-MS: m/z(int) 169(M+1,100), 153(7), 137(8), 121(4). Found C 42.99, H 4.85, N 33.52. ($C_6H_8N_4O_2$ requries: C 42.86%, H 4.76%, N 33.33%).

1,2,7-Triaza-3-methoxycarbonyl-6-(nitromethylene)spiro[4.5]dec-2-ene [3-70]

3-Diazo-2-(nitromethylene)piperidine [3-67] (0.82g, 4.9mmol) was dissolved in methyl acrylate (100ml) and stirred for 5hrs at 25°C. The solvent was removed under vacuum and the residue subjected to column chromatography (SiO_2: 20%MeCN/CH_2Cl_2). The first product isolated was a red powder which was identified as the intramolecular cycloaddition adduct 2,3,6-triaza-4-nitrobicyclo[4.3.0] non-1,4-diene. Yield= 0.2g(25%). The second fraction was isolated as a pale yellow solid and identified as 1,2,7-triaza-3-methoxycarbonyl-6-(nitromethylene)spiro[4.5]dec-2-ene. Yield= 0.75g (60%). mpt 178-180°C. I.R.(nujol,cm^{-1}) 3332,3155(N-H), 1720(C=O), 1607(C=C), 1567, 1455, 1310, 1242, 1192, 1099, 976. ^1H NMR (300MHz,$DMSO_{d6}$) 10.5δ(1H,bs,N-H,exch), 8.75(1H,bs,N-H,exch), 6.4(1H,s,CH), 3.6(3H,s, OCH_3), 3.3(2H,m,CH_2N), 3.05(1H,d,J=16.5Hz,CH_2), 3.0(1H,d, J=16.5Hz,CH_2), 1.7-1.9(4H,m,CH_2CH_2). ^{13}C ($DMSO_{d6}$, ppm) 163(C=O), 162(C=CH), 136(C=N), 107(CH=C), 66(OCH_3), 52(CH_2),

45(C_{spiro}), 41(CH_2N), 30(CH_2), 18(CH_2). CI-MS: m/z(int) 255 (M+1,100), 227(M-28,52), 210(14), 180(74), 135(8). Found C 47.5, H 5.6, N 22.0. ($C_{10}H_{14}N_4O_4$ requires: C 47.25%, H 5.5%, N22.0%).

5-Aza-1-methoxycarbonyl-4-(nitromethylene)spiro[2.5]octane [3-73] and [3-74]

1,2,7-triaza-3-methoxycarbonyl-6-(nitromethylene)spiro[4.5]dec-2-ene [3-70] (0.5g, 1.97mmol) was suspended in 1,2-dichlorobenzene (5ml) and heated under reflux at 180°C for 15mins. The resulting solution was introduced to a silica column and eluted with methylene chloride until all of the dichlorobenzene had been removed. The mobile phase was then changed (10%MeCN/CCl_4). The first fraction gave a pale yellow crystalline solid which was identified as (R)-5-aza-1-methoxycarbonyl-4-(nitromethylene)spiro[2.5]octane [3-74]. Yield=0.21g(47%). mpt 140-142°C. I.R.(nujol,cm^{-1}) 3274,3141(N-H), 1713(C=O), 1592, 1435, 1321, 1161. ^1H NMR (400MHz,$CDCl_3$) 10.9δ(1H,bs,N-H), 6.2(1H,s,H_e), 3.65(3H,s,OCH_3), 3.5(2H,m,H_a), 2.1(1H,dd,J=7Hz, J=8.56Hz,H_i), 1.7-1.9(4H,m,H_b,H_c), 1.5(1H,dd,J=5.92Hz,J=8.56Hz,H_f), 1.45(1H,t,J=7Hz,H_g). ^{13}C ($CDCl_3$,ppm) 170(C9), 163(C5), 105(C6), 52(C10), 41(C1), 30(C8), 26(C4), 24(C3), 21(C7), 20(C2). CI-MS: m/z(int) 227(M+1,100), 211(16), 180(10). Found C 52.9, H 6.2, N 12.4. ($C_{10}H_{14}N_2O_4$ requires: C 53.1%, H 6.2%, N 12.4%). The second fraction was an off-white solid which was identified as (S)-5-aza-1-methoxycarbonyl-4-(nitromethylene) spiro[2.5]octane [3-73]. Yield= 0.07g(16%). m.pt. 148-149°C. I.R.(nujol, cm^{-1}) 3270,3143(N-H), 1720(C=O), 1591, 1345, 1245, 1161, 1081. ^1H NMR (400MHz,$CDCl_3$) 10.3δ(1H,bs,N-H), 6.5(1H,s,H_e), 3.6(3H,s,OCH_3), 3.5(2H,m,H_a), 1.9-2.1(3H,m,H_b,H_c), 1.95(1H,dd,J=6.16Hz,J=8.12Hz,H_i), 1.75(1H,t, J=6.16Hz,H_f), 1.27(1H,m,H_c), 1.20(1H,dd,J=6.16Hz,J=8.12Hz,H_g). ^{13}C ($CDCl_3$,ppm) 169(C9), 158(C5), 110(C6), 52(C10), 40(C1), 31(C8),

30(C3), 28(C4), 21(C2), 16(C7). CI-MS: m/z(int) 227(M+1). Found C 53.0, H 6.2, N 12.4. ($C_{10}H_{14}N_2O_4$ requires: C 53.1%, H 6.2%, N 12.4%).

1,2,7-Triaza-3-methoxycarbonyl-3-methyl-6-(nitromethylene)spiro[4.5] dec-1-ene [3-71] and [3-72]

3-Diazo-2-(nitromethylene)piperidine [3-67] (0.11g, 0.65mmol) was dissolved in methyl methacrylate (50ml) and stirred for 12hrs at 25°C. The solvent was removed under vacuum and the residue subjected to column chromatography (SiO_2: 30%THF/diethyl ether). The first fraction isolated was a red powder which was identified as the bicyclic cycloaddition product [3-68]. Yield=40mg(36%). The second fraction was recrystallised from diethyl ether and gave (S)-1,2,7-triaza-3-methoxycarbonyl-3-methyl-6-(nitromethylene)spiro[4.5] dec-1-ene [3-72] as a pale yellow crystalline solid. Yield=0.021g(12%). mpt 113-115°C. I.R.(nujol,cm^{-1}) 3223,3186(N-H), 1740(C=O), 1610(C=C), 1493, 1378, 1237, 1023, 986. ^1H NMR (250MHz,$CDCl_3$) 10.6δ(1H,bs,N-H), 6.1(1H,s,H_e), 3.85(3H,s,OCH_3), 3.6(2H,m,H_a), 2.4(1H,d,J=13.5Hz,H_f), 1.7-2.3(4H,m,H_b,H_c), 1.7(1H,d,J=13.5Hz,H_f), 1.6(3H,s,CH_3). ^{13}C ($CDCl_3$,ppm) 170(C=O), 157(C_d), 109(C_e), 97(C_g), 93(C_{spiro}), 53(OCH_3), 42(C_a), 41(C_f), 31(C_c), 23(CH_3), 19(C_b). EI-MS: m/z(int) 240(M-28,47), 194(82), 162(55), 134(100), 94(60), 77(37), 53(35), 41(62). CI-MS: 241([M-28]+1). Found C 49.77, H 6.15, N 20.09. ($C_{11}H_{16}N_4O_4$ requires: C 49.25%, H 5.97%, N 20.89%). The third fraction was recrystallised from diethyl ether and gave (R)-1,2,7-triaza-3-methoxycarbonyl-3-methyl-6-(nitromethylene)spiro[4.5] dec-1-ene [3-71] as a yellow crystalline solid. Yield=0.048g(27%). mpt 114-117°C. I.R.(nujol,cm^{-1}) 3220,3185(N-H), 1727(C=O), 1610(C=C), 1455, 1325, 1230, 1123, 796. ^1H NMR (250MHz,$CDCl_3$) 10.5δ(1H,bs,N-H), 5.9(1H,s,H_e), 3.8(3H,s,OCH_3), 3.6(2H,m,H_a),

2.45(1H,d,J=13.65Hz,H_f), 1.8-2.3(4H,m,H_b,H_c), 1.78(3H,s,CH_3) 1.65(1H,d,J=13.65Hz,H_f),. ^{13}C ($CDCl_3$,ppm) 171(C=O), 158(C_d), 109(C_e), 97(C_g), 94(C_{spiro}), 53(OCH_3), 41(C_a), 41(C_f), 29(C_c), 23(CH_3), 19(C_b). EI-MS: m/z(int) 240(M-28,12), 194(77), 162(28), 134(97), 94(53), 77(27), 57(31), 41(54). CI-MS: 241((M-28)+1). Found C 49.55, H 5.90, N 21.03. ($C_{11}H_{16}N_4O_4$ requires: C 49.25%, H 5.97%, N 20.89%).

3-Oxo-2-(nitromethylene)piperidine [3-75]

3-Diazo-2-(nitromethylene)piperidine [3-67] (0.2g, 1.2mmol) was dissolved in dry chloroform (5ml) and added dropwise to a solution of rhodium (II) acetate (10mg) and DMSO (0.19g, 2.4mmol) in chloroform (50ml). After 30mins the solvent was removed under vacuum and the residue subjected to column chromatography (SiO_2: 5%MeCN/CH_2Cl_2). The second fraction gave 3-oxo-2-(nitromethylene)piperidine as a yellow crystalline solid. Yield=0.127g (68%). mpt. 122-125°C. I.R(nujol,cm^{-1}) 3275(N-H), 1735(C=O), 1615(C=C), 1480, 1380, 1340, 1280, 1170, 1009. ^1H NMR (300MHz,$CDCl_3$) 9.85δ(1H,bs,N-H,exch), 7.1(1H,s,CH), 3.65(2H,m,CH_2N), 2.75(2H,t,J=5.14Hz,CH_2), 2.25(2H,m,CH_2). CI-MS: m/z(int) 157(M+1,100), 151(4), 139(48), 125(26). Found C 46.27, H 5.01, N 17.64. ($C_6H_8N_2O_3$ requires: C 46.25%, H 5.13%, N 17.95%).

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