SYNTHETIC APPROACHES TO DERIVATIVES OF TROPANE

BY

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STATEMENT

The accompanying thesis submitted for the degree of Ph.D entitled "Synthetic Approaches To Derivatives Of Tropane" is based on work conducted by the author in the Department of Chemistry at the University of Leicester between the period October 1987 to September 1990.

All the work recorded in this thesis is original unless otherwise acknowledged in the text or by references. None of the work has been submitted for another degree in this or any other university.

Signed........................................ Date..................
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ABSTRACT

SYNTHETIC APPROACHES TO DERIVATIVES OF TROPANE
BY NICOLA HOWARTH

This thesis is a continuation of the work by Bathate, which had shown that intramolecular cyclisation of trans-1-(benzylamino)-4-chlorocycloheptane and hept-2-ene gave the corresponding nortropane and nortrop-6-ene derivatives. Problems were experienced in the reproducibility of Bathgate's route. Therefore, the intramolecular cyclisation step warranted further development. The best yields of cyclised products were attained when the solvent was changed to acetone. Other approaches to nortropane were sought. Reasonable yields of the cyclised material were only obtained when the nitrogen function was protected with a benzyl or p-methoxybenzyl group. 4-Benzyl aminocycloheptanone was successfully synthesised and its monocyclic amino-ketone and bicyclic amino-alcohol tautomers were found to be in equilibrium.

Selected attempts to dealkylate/debenzylate tertiary amines, in view of obtaining nortrop-6-ene, gave variable results with expectations from the literature not always being fulfilled. It was decided to investigate the dealkylation/debenzylation of tertiary amines in a systematic way. Debenzylation of simple piperidine models was achieved using most of the procedures attempted but debenzylation of N-benzylnortropane and N-benzylnortrop-6-ene was unsuccessful. Removal of the p-methoxybenzyl group from N-p-methoxybenzylnortrop-6-ene was partly accomplished using α-chloroethylchloroformate to afford nortrop-6-ene.

Application of the intramolecular cyclisation route to substituted 1,3-cycloheptadienes was explored. The two dienes chosen for this purpose were 1,3-cycloheptadien-6-ol and 1,3-cycloheptadien-6-one. Both can be prepared from tropone. No difficulties were encountered with the initial nitroso cycloaddition but problems arose later in the pathway using 1,3-cycloheptadien-6-ol due to complications with the hydroxyl protecting group. However, synthesis of N-benzylnortropan-3-one and N-benzylnortrop-6-en-3-one ethylene acetal was achieved from 1,3-cycloheptadien-6-one ethylene acetal.

The epoxidation of azabicyclic alkenes with m-chloroperoxy benzoic acid was examined. Both N-carbethoxy-1,4-dihydro naphthalen-1,4-imine and N-carbethoxy-1,4-dihydroanthracen-1,4-imine gave stereospecifically the corresponding exo- epoxides. Epoxidation of N-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene, though was non-stereospecific. Treatment of N-benzyl-2-azabicyclo[2.2.1]hept-5-ene, 5,8-dimethoxy-1,4-dihydronaphthalen-1,4-imine and 9-methyl-5,8-dimethoxy-1,4-dihydronaphthalen-1,4-imine with m-chloro peroxybenzoic acid resulted in failure, even after protonation to avoid N-oxide formation.
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Chapter One

Introduction
1.1 INTRODUCTION.

In recent years, 7-azabicyclo[2.2.1]heptyl derivatives have been the subject of significant interest as these systems are unique amongst relatively unstrained azacycles in possessing anomalously high nitrogen inversion barriers. The stereochemical consequences of reactions at nitrogen, other than quaternisation of tertiary amines, can rarely be investigated due to rapid pyramidal inversion in the products. However, the configurational stability at nitrogen in these systems, at moderately low temperatures, has facilitated the study of invertomer preferences\(^1\) and heterolysis reactions\(^2\) at nitrogen.

The unusual nature of the bridging nitrogen in the 7-azabicyclo[2.2.1]heptane systems has generated interest in homologous systems, particularly the 8-azabicyclo[3.2.1]octyl derivatives which share the same azabicyclic skeleton as the class of natural products known as tropane alkaloids.

1.2 TROPANE ALKALOIDS.

The tropane alkaloids are found in the higher plant families of Convolvulaceae, Erythroxylaceae, Euphorbiaceae, Proteaceae, Rhizophoraceae and Solanaceae. They are esters derived from relatively simple organic carboxylic acids (atropic, benzoic, cinnamic, iso-valeric, 2- and 3-methylbutyric, tiglic, tropic, truxillic, vanillic and veratic acids) and azabicyclic alkaloids which are all hydroxylated derivatives of tropane (8-methyl-8-azabicyclo
[3.2.1]octane) or nortropane (8-azabicyclo[3.2.1]octane) (Figure 1.1).

![Figure 1.1](image)

The vast majority of tropane alkaloids have been known for a long time and very few new alkaloid structures have been isolated in the last twenty-five years. The main chemical endeavour in this area has therefore concentrated on stereochemical aspects, biogenesis and synthesis. In particular much synthetic work has been performed due to the high physiological activity of certain tropane derivatives, which makes them useful as drugs.

In 1833, the first tropane alkaloids, atropine and 1-hyoscyamine, were isolated. Their names were derived from the plant sources from which they were extracted, *Atropa belladonna* L. (deadly nightshade) and *Hyoscyamus niger* L. (henbane) respectively. They are both members of the Solanaceae family and it is from the former that the name tropane originates. Atropine is the racemic form of hyoscyamine which is a tropic acid ester of tropan-3α-ol (Figure 1.2).
These alkaloids have a long and important history in medicine. Hyoscyamine was mentioned in the Ebers papyrus (ca. 1550 B.C.) as a treatment for abdominal distress and to expel "magic of the belly". Belladonna extract is still widely used as an antispasmodic, antisecretory and sedative in the treatment of functional gastrointestinal disorders. Atropine and L-hyoscyamine also display mydriatic properties.

Cocaine was first isolated in 1862 from the leaves of Erythroxylon Coca Lam,\textsuperscript{5} indigenous to the higher elevations of Peru. The leaves have long been recognised as containing a central nervous system stimulant and the isolation of cocaine was important historically in the pioneering development of local anaesthesia. However, owing to its unpredictability, toxicity and addictive nature, its medicinal use today has been limited to topical application, primarily in ophthalmology. Cocaine is a diester of tropan-3β-ol-2β-carboxylic acid (Figure 1.3).
The other important medicinal alkaloid, hyoscine, was isolated much later, in 1881, by Ladenburg and again independently by Schmidt in 1892, under the name of scopolamine. Scopolamine is the tropic acid ester of 6,7β-epoxytropan-3α-ol (Figure 1.4) and it has been found to stimulate the central nervous system. It has also been claimed to be effective against nerve-paralysing gases.

A selection of non-natural derivatives, mostly esters of the natural tropane alcohols and a number of carboxylic acids which do not occur usually in the plant tissue, have been synthesised and tested pharmacologically. Quaternisation of the same esters gives rise to fundamental
changes in the pharmaceutical activities leading to new
ganglion blocking and central nervous system stimulating
drugs.

Therefore both the chemical and pharmaceutical aspects of
the tropanes secure them a place amongst the most important
alkaloids.

1.3 BIOSYNTHESIS OF HYOSCYAMINE AND SCOPOLAMINE.

1.3.1 THE TROPANE MOIETY.

Substantial evidence has been accumulated to support
scheme 1.1 as the route for the biosynthesis of
hyoscyamine, which is the primary alkaloid formed in the
plant tissue.

Extensive tracer experiments over more than three decades
have established that ornithine (1), a precursor of
hyoscyamine, is incorporated asymmetrically into the
pyrrolidine ring of the tropane moiety in Datura species and
Atropa Belladonna. [2-\(^{14}\text{C}\)] ornithine leads to hyoscyamine
which is labelled at the C-1 bridgehead carbon only (having
the (R) configuration).\(^{3e,9,10}\)

By analogy with the asymmetrical incorporation of
ornithine it was proposed\(^{3e,11,12}\) that to avoid the formation
of putrescine, which is a symmetrical intermediate and which
would lead to equal labelling of the C-1 and C-5 bridgehead
carbons, ornithine (1) should first be methylated to form
\(8-N\)-methylornithine (2). This has been shown to be a direct
precursor of hyoscyamine in Datura Stramonium and Atropa
Belladonna.\(^{11,12}\) Radioactive \(8-N\)-methylornithine (2) has
also been isolated after feeding of \([5-^{14}\text{C}]\) or \([5-^{3}\text{H}]\)
Scheme 1.1
ornithine to *Atropa Belladonna*, and has thereby been shown to be a natural plant constituent. Atropine decarboxylation of δ-N-methylornithine (2) affords δ-N-methylputrescine (3), which is an asymmetric intermediate and an established precursor of the tropane nucleus of hyoscyamine. N-Methyl putrescine (3) is oxidised to 4-methylaminobutanal (4), which has been detected in *Datura* plants fed with [2-14C] ornithine. Condensation of the N-methyl-Δ-pyrrolinium salt (5), which is the cyclised form of 4-methylaminobutanal (4), with acetoacetyl co-enzyme A leads to the co-enzyme A ester of hygrine 1'-carboxylic acid (6). Hydrolysis to (7) followed by another decarboxylation yields hygrine (8). Hygrine (8) has been demonstrated to be a precursor of tropinone (10), which is probably formed through dehydrohygrine (9).

1.3.2 TROPIC ACID MOIETY.

Feeding experiments using variously labelled phenylalanines have shown that all the carbon atoms are incorporated into tropic acid, and that the carboxyl group migrates intramolecularly from C-2 to C-3 in the process. However the biosynthetic pathway from phenylalanine to tropic acid is not clear.
Another route for the biosynthesis of tropic acid has also been proposed, starting from tryptophan (11) as outlined in scheme 1.2.20

Scheme 1.2
Recently, (benzene ring-$^{14}$C)tryptophan and (2-indolyl-$^{14}$C)tryptophan were converted to tropic acid by *Datura Innoxia* roots. The bulk of the benzene ring labelling appeared in the phenyl ring of tropic acid and the 2-indolyl-$^{14}$C label appeared at C-3 in tropic acid, thus substantiating this earlier hypothesis.

**1.3.3 INTERCONVERSION OF THE TROPANES.**

Although hyoscyamine and scopolamine accompany one another in most tropane-producing plants, they are formed during different periods of metabolism.

When hyoscyamine (18) was fed to so-called alkaloid-free plants (*Datura Ferox* branches which had been grafted onto a *Cyphomandra* or tomato root), these plants were able to oxidise it to scopolamine (19). Feeding the alkaloid-free plants with 6,7-dehydrohyoscyamine (20) also led to the formation of scopolamine (119).

Improvement of these investigations was achieved using very young *Datura Stramonium* seedlings and feeding them with (14C-methyl)hyoscyamine (18); 27.5% of the radiocarbon introduced with the hyoscyamine was found in the form of (14C-methyl)scopolamine (19) and 8 to 9% in the form of labelled 6-hydroxyhyoscyamine (21). When 6-hydroxy-(14C-methyl)hyoscyamine (21) was fed to the same seedlings, radioactive scopolamine was also formed.

Thus, hyoscyamine (18) is oxidised by an enzyme into 6-hydroxyhyoscyamine (21) and this in turn is converted into scopolamine (19). Furthermore, 6,7-dehydrohyoscyamine (20)
has been shown recently to be an intermediate in this last stage\(^2\) (Scheme 1.3).

\[ \text{Tr} = \text{-COCH(CH}_2\text{OH)}\text{Ph} \]

1.4 ESTABLISHED SYNTHETIC ROUTES TO THE TROPANE SKELETON.

As mentioned previously, a large amount of synthetic work has been performed in this area due to the interesting pharmacological activity of tropane alkaloids. Therefore, the following review will only outline the general synthetic methods available for the construction of the tropane ring.

In 1917, Robinson\(^2\) discovered, what is now a classical synthesis of one of the simplest tropane alkaloids, tropinone. It involves a Mannich reaction between succindialdehyde, methylamine and acetone (Figure 1.6).
This method was improved later by Schöpf and Lehmann. Acetone was replaced with the calcium salt of acetone dicarboxylic acid and the pH and temperature were modified (pH 11 at 20°C) so as to maximise the yield of tropinone. Since this synthesis is simple, direct and efficient, it has become the industrial basis for the manufacture of tropinone.

Stoll et al. adapted Robinson's route such that furan derivatives were used as the source of the dialdehyde. 2,5-Diethoxy-2,5-dihydrofuran (22), on treatment with hypobromous acid, was converted into the 3-hydroxy-4-bromo derivative (23). Subsequent hydrogenation over Raney nickel, during the addition of methanolic potassium hydroxide, resulted in the formation of 3-hydroxy-2,5-diethoxytetrahydrofuran (24). Cleavage of the ring with hot dilute hydrochloric acid afforded the desired malic dialdehyde (25). At pH 4, this dialdehyde with methylamine hydrochloride and acetone dicarboxylic acid gave rise to 6β-hydroxytropan-3-one (26) in yields ranging from 35% to 55% (Scheme 1.4).
Scheme 1.4

The success of this method has resulted in the formation of a wide range of substituted tropanes and it has failed only once, when using 2,3-epoxysuccindialdehyde\(^{29}\) in an attempt to prepare the alkamine scopinone, which is a direct precursor to scopolamine.

In 1922, Willstätter and Pfannenstiel\(^{30}\) showed that tropinone (10) could also be synthesised from pyrrolidines (Scheme 1.5). This synthetic pathway involved the formation of diethyl 1-methylpyrrole-2,5-diacetate (27) via the intermediate pyrrolidine (28).\(^{31}\) The pyrrole (27) was subsequently reduced and cyclised by a Dieckmann ester condensation to give 2-carbethoxy tropinone (29).
Hydrolysis and decarboxylation of (29) yielded tropinone (10).

Parker et al.\textsuperscript{32} described an alternative route to the intermediate pyrrolidine (28). It involved the condensation of the diacetylenic diester (30) with methylvamine (Figure 1.7).
Willstätter's route has been modified in order to synthesise unnatural analogues of tropane. For example, the synthesis of 3-phenyltropane-3-carboxylic acid\(^{33}\) began with cis-2,5-dicarbethoxypyrrolidine (31), which on tosylation, yielded cis-N-tosyl-2,5-dicarbethoxypyrrolidine (32). This was reduced with lithium aluminium hydride, and treated with thionyl chloride, to give cis-N-tosyl-2,5-bis-(chloromethyl)pyrrolidine (33). On condensing this product with phenylacetonitrile and sodium amide, only one (34) of the two possible isomeric products was isolated. The isomer (34) was ultimately converted into the corresponding 3-phenyltropane-3-carboxylic acid (35) (Scheme 1.6).
It has been found more recently that condensation of the corresponding cis-N-benzyl-2,5-bis-(chloromethyl) pyrrolidine with phenylacetonitrile, in the presence of sodium hydride and dimethylformamide, allowed for the isolation of both tropane isomers (Figure 1.8). The endo-nitrile predominated threefold over the exo-nitrile.
The generality of Willstätter's method seems to be limited only by the availability of active methylene compounds. A further adaptation of this route involves the production of nortropinone (36) from 1-pyrroline-5-carboxylic acid (37), via the intermediate pyrrolidine (38) and pyrroline (39) derivatives (Scheme 1.7).

\[ \text{HO}_2\text{C} \text{N} \rightarrow \text{MeCOCH}_2\text{CO}_2\text{Et} \rightarrow \text{HO}_2\text{C} \text{N} \]

\[ (37) \quad (38) \]

\[ \text{NaOCl} \quad \text{Aqueous buffer} \]

\[ \text{+H} \rightarrow \text{O} \rightarrow \text{N} \]

\[ (39) \quad (36) \]

Scheme 1.7

In 1961, Horak and Zumen described a synthesis of tropinone based on treatment of a mixture of cycloheptadienones, obtained from tropinone methiodide with a large excess of methylamine. Bottini and Gal elaborated this idea and showed that condensation of 2,6-cycloheptadienone, prepared in four steps from cycloheptanone according to the method developed by Garbisch, with methanolic methylamine gave tropinone in 64% yield (Figure 1.9).
The same reaction occurred with ethylamine and benzylamine, leading to N-ethyl and N-benzylnortropinones respectively. This route is limited only by the availability of the cycloheptadienone component.

The reaction of 2,6-cycloheptadienone with amines has been studied further.\textsuperscript{39} 2,6-Cycloheptadienone was subjected to reaction with a variety of arylamines (p-MeOC\textsubscript{6}H\textsubscript{4}NH\textsubscript{2}; C\textsubscript{6}H\textsubscript{5}NH\textsubscript{2}; p-MeC\textsubscript{6}H\textsubscript{4}NH\textsubscript{2}; p-ClC\textsubscript{6}H\textsubscript{4}NH\textsubscript{2}; p-NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}NH\textsubscript{2}) and the corresponding N-arylnortropinones were obtained in yields ranging from 45 to 93\%. The lowest yield was obtained with p-nitroaniline. However, when treated with even one equivalent of morpholine, 2,6-cycloheptadienone gave a 2:1 adduct, whose structure was shown to be (40) (Figure 1.10).
Another investigation of the addition of amines to 2,6-cycloheptadienone was directed towards the preparation of optically active compounds, as in figure 1.11, suitable for circular dichroism experiments. In this way, the synthesis of a large number of N-substituted tropane derivatives (alkyl, aryl, cycloalkyl and carboalkyl) was developed.

![Figure 1.11](image)

This method was extended further by studying the reaction of 2,6-cycloheptadienone with 1,1- and 1,2- disubstituted hydrazines, hydroxylamines, N-alkylhydroxyl amines and carbohydrazides, (Scheme 1.8).
5-Aminocycloheptene (41) was the starting material for another tropane synthesis developed by Nagata et al.\textsuperscript{42} Lead tetraacetate converted this olefin into a bridged aziridine (42) in approximately 90\% yield. This corresponds to the hypothetical aziridinium salt (43) proposed by Archer et al.\textsuperscript{43} to interpret the ready racimisation of d-2-tropanol acetate (44) (Figure 1.12).
Reaction of the bridged aziridine (42) with diethyl-pyrocarbonate followed by reduction produced dl-tropan-2α-ol (45). Quaternisation of (42) produced (46) which reacted
with sodium dimethylmalonate to form the tropanylmalonic ester (47) (Scheme 1.9).

In another transformation of aziridines into tropanes, ethyl-8-azabicyclo[5.1.0]oct-3-ene-8-carboxylate (48) rearranged into N-carbethoxynortropidine (49) in the presence of dichlorobis-(benzonitrile) palladium. The reaction appears to involve four steps (Scheme 1.10).

![Scheme 1.10](image)

In 1972, Bapat et al. discovered that during a Cope rearrangement on 5-allyl-3,3,5-trimethyl-1-pyrrolidine-1-oxide (50) in boiling toluene, the expected product (51) partially cyclised to form isoxazolidine (52) (Scheme 1.11).
The isolated nitrone (51) was also slowly converted to the cycloadduct (52) in boiling xylene. Reduction of the isoxazolidine (52), with lithium aluminium hydride or hydrogen over platinum, afforded 1,6,6-trimethylnortropan-3β-ol (Figure 1.13).

A similar nitrone-induced cycloaddition was reported shortly thereafter by Tufariello et al.\textsuperscript{46} 4-Nitrobut-1-ene, upon reaction with acrolein in methanol containing sodium methoxide followed by acidification with dry hydrogen chloride, yielded the nitro-acetal (53). This nitro-acetal (53) was converted into the nitrone (54) by zinc in aqueous
ammonium chloride solution followed by acidification with hydrochloric acid. The latter was cyclised by heat into the isoxazolidine (55). Quaternisation of the cycloadduct (55) with methyl iodide followed by reduction with lithium aluminium hydride, gave tropan-3β-ol (56) (Scheme 1.12).

This synthetic route was extended to the formation of dl-cocaine.

Although many other synthetic approaches to tropane alkaloids have been investigated, most of the routes reported so far have only been able to produce certain derivatives containing a substituent on the bridging nitrogen atom, functionality within the seven membered ring and, more importantly, a saturated ethano bridge. Now, in order to synthesise tropane alkaloids like scopolamine, the presence of an unsubstituted etheno bridge is required for subsequent epoxidation.

A few synthetic methods for the production of nortrop-6-ene derivatives have been investigated and they all involve
the formation of oxallyl intermediates. In 1968, Turro and Edelson showed that treatment of 2,2-dimethylcyclopropanone with purified N-methylpyrrole produced 2,2-dimethyltrop-6-en-3-one in a 50% yield (Figure 1.14).

Figure 1.14

Hofmann et al. reported a route to trop-6-en-3-one derivatives, involving the reductive halogenation of α,α′-dibromoketones in the presence of sodium iodide, copper and a variety of pyrroles. Once again, this reaction proceeded via the formation of an oxallyl intermediate (Figure 1.15).

Figure 1.15

Although this route has been used to produce a variety of 6,7-dehydrotropinones, it has been found that this reaction only gives high yields when substitution is present and so the compounds produced are not of great practical value.

A simultaneous investigation by Noyori et al. involved the formation of oxallyl intermediates of the type (57), which were generated from α,α′-dibromo ketones (58) and iron
carbonyls. These intermediates could be trapped with either N-carbomethoxypyrrole (59) or N-acetylpyrrole (60), to afford the corresponding substituted nortrop-6-en-3-ones (61) (Scheme 1.13). This method was limited, however, in that dibromoacetone could not be used to produce trop-6-en-3-ones without substituents at C-2 or C-4.

\[
\text{(58)} \quad \text{Fe}_2(\text{CO})_9 \xrightarrow{\text{Fe(II)L}} \text{Fe}(\text{II})L_n
\]

\[
\text{(57)} \quad L_n = \text{Br, CO or solvent}
\]

\[
\text{R-N} \xrightarrow{\text{Fe(II)L}} \text{R'N}
\]

\[
\text{(59) } R = \text{CH}_3\text{OCO} \quad \text{(60) } R = \text{CH}_3\text{CO}
\]

\[
\text{(61)}
\]

Scheme 1.13

A modified synthesis by the same investigators allowed for more flexibility. It was found that \(\alpha,\alpha',\alpha',\alpha'-\text{tetrabromoacetone} \) could be used to give a 2,4-dibromo-nortrop-6-en-3-one (62). Debromination, with a zinc-copper couple in methanol containing 5% ammonium chloride, was accomplished essentially quantitatively to give N-carbomethoxynortrop-6-en-3-one (63) in 60% yield, based on N-carbomethoxypyrrole (Scheme 1.14).
Harpp et al.\textsuperscript{51} showed that an oxallyl equivalent can be produced on treating the silylated epoxide (64) with fluoride. An allene oxide-cyclopropane system (65) is presumed to be formed. Trapping this intermediate with N-carbomethoxypyrrole afforded N-carbomethoxy-2-phenylnortrop-6-en-3-one (66) in 49\% yield (Scheme 1.15).
However, all these synthetic approaches to nortrop-6-ene derivatives result in the production of compounds which contain a tertiary bridging nitrogen and an oxygen function at C-3.

1.5 RECENT DEVELOPMENTS IN THE ELABORATION OF THE TROPANE RING.

In section 1.4 it was seen, from the syntheses outlined, that general and efficient methods for the preparation of the tropane skeleton were limited. They were only able to produce certain analogues.

With this in mind, Kibayashi sought an alternative and more universal pathway, and in 1984 he described a facile route for the elaboration of the tropane ring system which utilised a Diels-Alder cycloaddition of nitroso compounds.
with 1,3-cycloheptadiene. A synthesis of N-benzoylnortropane (74) was proposed, in which the construction of the tropane ring based on a [4+2] nitroso cycloaddition was established (Scheme 1.16).
This route involved a Diels-Alder reaction between 1,3-cycloheptadiene (67) and the acyl nitroso compound (68), generated in situ, to afford the [4+2] cycloadduct (69). Reductive cleavage of the N-O bond, followed by hydrogenation, gave the saturated cis-1,4-amido alcohol (71). Subsequently, a portion of (71) was treated with thionyl chloride and triethylamine to yield the trans-chloride (72) whilst the remainder was converted into the mesylate (73). However cyclisation of (73) to give the tropane skeleton, using a variety of strong bases, failed but N-benzoylnortropane (74) was obtained when the trans-chloride (72) was treated with potassium t-butoxide in a 1:1 hexamethylphosphoric triamide (HMPA) -benzene solution. This ultimate step is thought to involve an internal $S_N2$ process, and so cyclisation will occur in (72) rather than in (73), since only in (72) is the benzoylamino group correctly placed for backside displacement of the anionic leaving group. Attempts to form nortropane (75) and tropane (76), using hydrolysis to remove the benzoyl group from (74), were unsuccessful.

Nevertheless, the synthesis of tropane (76) was accomplished by an alternative nitroso Diels-Alder reaction$^{52}$ (Scheme 1.17).
Thus, 1,3-cycloheptadiene (67) was reacted with 1-chloro-1-nitrosocyclohexane (77), and the cycloadduct (78) was obtained. Reductive treatment, involving N-O bond fission to give (79), was followed by amine protection using either ethyl or benzyl chloroformate to afford (80) and (81) respectively. Reaction with thionyl chloride, in the presence of triethylamine, yielded the corresponding trans-chlorides, (82) and (83), which were converted to N-carbethoxynortropane (84) and N-carbobenzoxyxnortropane (85) when subjected to base-induced intramolecular cyclisation.
Synthesis of tropane (76) was finally achieved by reduction of (84) and (85) with lithium aluminium hydride.

This synthetic approach is an improvement on previous methods because it has the potential for allowing for the introduction of flexibility, and therefore the preparation of both natural and non-natural tropane alkaloids. Synthetic flexibility is one of the keys to achieving effective drug design because skeletal modification of natural products often increases or improves the specific physiological properties.

Work performed here at Leicester by Bathgate\(^5^3\) retained the advantages of the nitroso-cycloaddition developed by Kibayashi,\(^5^2\) but showed that with an appropriately nucleophilic nitrogen, intramolecular cyclisation of trans-1-benzylaminocycloheptane and hept-2-ene could be achieved to afford the corresponding nortropane and nortrop-6-ene derivatives. Subsequent removal of the benzyl group from N-benzylnortropane by hydrogenation, gave rise to nortropane (75), the synthesis of which had previously eluded Kibayashi. This approach will be described in more detail in chapter 2, since the work covered in this thesis is a continuation of this idea.

Recently, Bäckvall\(^5^4\) has reported a closely related synthesis for the transformation of 1,3-cycloheptadiene (67) to tropane alkaloid derivatives. It involves a palladium-catalysed 1,4-chloroacetoxylation of 1,3-cycloheptadiene (67), followed by allylic substitution of the chloro group by an amide function with either retention or inversion of configuration. Cyclisation of the resulting amido acetates
(88 and 91) leads to the nortropane system (89) (Scheme 1.18).

However, attempts to cyclise the unsaturated substrate (90) by palladium catalysis, in order to obtain the corresponding nortrop-6-ene analogues, failed.

Bäckvall also showed\textsuperscript{54} that by using this methodology, it was possible to introduce a nitrogen into a 6-oxy-substituted 1,3-cycloheptadiene so that both the exo- and the endo- isomers of tropane derivatives were obtained (Scheme 1.19).
Scheme 1.19
Chapter Two

Intramolecular Cyclisation Strategies to Nortropane, Nortrop-6-ene and Derivatives
2.1 INTRODUCTION.

This chapter is concerned with the development of the intramolecular cyclisation of seven-membered rings based on earlier work by Kibayashi\(^2\) (see section 1.5) and Bathgate\(^3\) to afford the corresponding tropane derivatives. Variation of conditions, including the base and the leaving group used, will be dealt with in more detail in context.

In 1987, Bathgate\(^3\) reported an improvement of Kibayashi's route\(^2\) which allowed for the formation of both N-benzylnortropane (101) and N-benzylnortrop-6-ene (104) by intramolecular cyclisation of the corresponding trans-1,4-chloroamines. This synthesis retained the advantages of the nitroso-cycloaddition methodology but the nitrogen substituent was subsequently modified. A benzoyl group allowed for an effective nitroso-cycloaddition\(^2\) and N-O bond cleavage to produce the \textit{cis}-1,4-amido alcohol (70). However, reduction to a benzyl group converted the amido-nitrogen to an amino-nitrogen, and thus increased the nucleophilic character of the nitrogen to facilitate the subsequent intramolecular nucleophilic displacement to give the azabicyclic skeleton. It was also a potentially removable substituent for completion of the synthesis. This approach is summarised in Scheme 2.1.
Thus, a Diels-Alder reaction involving 1,3-cycloheptadiene (67) and the acyl nitroso compound (68), generated in situ from benzo hydroxamic acid and tetramethylammonium periodate, yielded the [4+2] cycloadduct (69). Reductive cleavage of the N-O bond, followed by reduction of the C-O and C-C
double bonds, gave the cis-1,4-amino alcohol (99). This was subsequently converted cleanly and efficiently into the hydrochloride salt of the trans-1,4-chloroamine (100), on addition of a molar equivalent of thionyl chloride. Previously, in Kibayashi’s synthesis, an organic base had been added along with the thionyl chloride. However, this was not necessary here as the amino alcohol (99) contained a reactive secondary amine, which acted as an effective intramolecular base and mopped up the hydrogen chloride formed in the reaction. This also ensured that the chloride ion proceeded to attack with inversion of configuration. On basification with anhydrous pyridine, the salt (100) gave rise to the free amine, which cyclised at room temperature to afford N-benzylnortropane (101). Debenzylation was ultimately achieved by hydrogenation, to yield nortropane (75). Thus, the benzylamino group improved the production of the chloro-compound, the cyclisation step and constituted a removable nitrogen protecting group.

The same approach gave the unsaturated analogue, N-benzylnortrop-6-ene (104), from cis-4-(benzoylamino)-2-cycloheptenol (70) via a hydride reduction to cis-4-(benzylamino)-2-cycloheptenol (102), as shown in Scheme 2.2.
The use of thionyl chloride with lithium chloride in chloroform followed by addition of the heterogeneous base, potassium carbonate, under the influence of ultrasound led to the isolation of the desired 1,4-cyclisation product (104) in a 65% yield, accompanied by a 10% yield of the aziridine (105) which arose from 1,2-cyclisation. However, preliminary studies on the removal of the benzyl group from N-benzylnortrop-6-ene (104), to afford the parent molecule nortrop-6-ene, resulted unexpectedly in failure. The previous use of hydrogenation for N-benzylnortropane (101) to produce nortropane (75) obviously could not be used here due to the presence of a double bond. Nevertheless, this was the first synthesis of a simple derivative of nortrop-6-ene which had been achieved in significant yield and it demonstrated the viability of the intramolecular displacement approach given an appropriately nucleophilic nitrogen.
This approach therefore warranted further exploration. Firstly, a study on the modification of the substituents at nitrogen, at a late or early stage in the pathway, required additional investigation so that other nortropane and nortrop-6-ene derivatives might be obtained. It also became necessary to examine all the dealkylation and debenzylation procedures available for tertiary amines, in order to make the parent nortrop-6-ene system. Finally, the versatility of this route using substituted 1,3-cycloheptadienes (for example, 6-oxy substituted 1,3-cycloheptadienes) was worthy of assessment, so that functionality at other positions might be introduced into the bicyclic system.

2.2 DEVELOPMENT OF THE INTRAMOLECULAR CYCLISATION STEP.

We experienced problems in the reproducibility of Bathgate’s route. We consistently only achieved a 38% yield of N-benzylnortropane (101) rather than the reported 88% yield. Numerous difficulties were also encountered in work with the unsaturated compound (102) when using thionyl chloride in the presence of lithium chloride followed by the heterogeneous base, potassium carbonate. Thus, the intramolecular cyclisation step required further development.

We decided to examine the use of a polymer-supported base in this cyclisation step since it would be easy to remove from the mixture at the end of the reaction. The polymer-supported base selected for this purpose was 1,5,7-triazabicyclo[4.4.0]dec-5-ene on polystyrene cross-linked with 2% DVB (TABD). Hence thionyl chloride was added to a
solution of cis-4-(benzylamino)cycloheptanol (99) in deuterated chloroform and the decomposition of the initial product of the reaction, the alkylchlorosulphite, to the desired trans-1,4-chloroamine (100) was monitored by proton (90MHz) n.m.r. (Figure 2.1).

Following completion of this decomposition, the reaction mixture was treated with TABD. Chromatographic purification of the crude material obtained from this reaction, gave N-benzynortropane (101) in a 41% yield. On applying the same procedure to cis-4-(benzylamino)-2-cycloheptenol (102), N-benzynortrop-6-ene (104) was obtained in 33% yield along with an 18% yield of the aziridine (105) (Figure 2.2).
However, although this polymer-supported base allowed for the formation of both N-benzynortropane (101) and N-benzynortrop-6-ene (104), the yield for the saturated analogue was not a great improvement on that obtained by Bathgate’s route.53

Danheiser et al.56 reported an intramolecular cyclisation which led to the bicyclic amine (107). This reaction benefitted by having a bromide ion as a better leaving group (Figure 2.3).
Thus, it was decided to investigate thionyl bromide in this cyclisation step, to generate an intermediate trans-1,4-bromoamine rather than a trans-1,4-chloroamine. It was also thought that the use of 2,2,6,6-tetramethylpiperidine (TMP) might be preferable to pyridine in the cyclisation step, since it was a much stronger non-nucleophilic base. Consequently, a solution of cis-4- (benzylamino)-2-cycloheptenol (102) in deuterated chloroform was treated with thionyl bromide. The decomposition of the initial product, the alkyl bromosulphite, to the trans-1,4-bromoamine hydrobromide (108) was again monitored by proton (90MHz) n.m.r. When this decomposition had been accomplished, anhydrous TMP was added to the reaction mixture and the resulting solution was heated at 45°C to encourage the cyclisation to occur more rapidly and minimise losses due to side reactions. On purifying the crude mixture obtained, N-benzylnortrop-6-ene (104) was isolated in 31% yield (Figure 2.4).
Unfortunately, the yield of N-benzylnortrop-6-ene (104) obtained from this experiment was similar to that obtained using the heterogeneous polymer supported base, TABD.

Finally, it was decided to look at the effect of changing the solvent used in the cyclisation step from deuterated chloroform to a more polar solvent, like acetone, since the cyclisation to form the bicyclic system is known to occur by an internal $S_N$2 mechanism (Figure 2.5).

Now this type of reaction, where the transition state becomes charged, is aided by more polar solvents which are able to stabilise the transition state better and hence promote the reaction.
Thus, thionyl bromide was added to a solution of cis-4-(benzylamino)-2-cycloheptenol (102) in deuterated chloroform and formation of the trans-1,4-bromoamine (108) was monitored by proton (90MHz) n.m.r as before. Following production of this intermediate, the solvent was removed under reduced pressure and replaced with acetone. Anhydrous TMP was then added to this solution and the resulting mixture was heated at 50°C. Purification of the crude product afforded N-benzylnortrop-6-ene (104) in 58% yield and the aziridine (105) in 24% yield (Figure 2.6).

\[
\text{HO} \quad \text{(102)} \quad \xrightarrow{\text{SOBr}_2} \quad \text{NH}_2\text{CH}_2\text{Ph} \quad \xrightarrow{\text{CDCl}_3} \quad \text{Br}^+ \quad \text{NH}_2\text{CH}_2\text{Ph} \quad \text{Br}^- \quad \text{(108)}
\]

\[
\text{PhCH}_2 \quad \text{(104) 58% yield} \quad + \quad \text{NCH}_2\text{Ph} \quad \text{(105) 24% yield}
\]

Therefore, the best yields of cyclised products were attained when thionyl bromide in deuterated chloroform was used, followed by anhydrous TMP in acetone.

2.3 DIRECT APPROACHES TO NORTROPANE AND NORTROP-6-ENE.

Having confirmed the initial difficulties experienced by Bathgate\textsuperscript{55} concerning the debenzylation of N-benzylnortrop-
6-ene (104), other simple, direct and efficient approaches to nortropane (75) and nortrop-6-ene (109) were sought. It was decided to examine the cyclisation of cis-4-aminocycloheptanol (114) and cis-4-amino-2-cycloheptenol (113), previously prepared by Kibayashi and Bathgate respectively, since cyclisation of these compounds would give rise to nortropane (75) and nortrop-6-ene (109) directly.

Cis-4-aminocycloheptanol (114) and cis-4-amino-2-cycloheptenol (113) were prepared by adapting the initial nitroso cycloaddition and subsequent steps, as outlined in Scheme 2.3.

![Scheme 2.3](image)

Reaction of benzyl nitrosoformate (110), generated *in situ* from benzyl N-hydroxycarbamate and tetramethylammonium periodate, with 1,3-cycloheptadiene (67) afforded the Diels-Alder adduct (111) in 87% yield.
Subsequent cleavage of the carboxenyl protecting group using hydrogen bromide in glacial acetic acid,\textsuperscript{60} gave \(8\)-oxa-9-azabicyclo[3.2.2]non-6-ene (112).\textsuperscript{55} The yield was improved from 72\%\textsuperscript{55} to 90\% by further extraction of the product from the aqueous layer using dichloromethane. The N-O bond was cleaved cleanly using zinc in glacial acetic acid\textsuperscript{61} to give (113)\textsuperscript{55} in a 62\% yield. This product was found to be quite soluble in the aqueous medium, and so repeated extractions followed by a continuous extraction, were performed in order to achieve an acceptable recovery. Hydrogenation over palladium on charcoal\textsuperscript{52} gave the corresponding saturated alcohol (114) in 90\% yield.

Attention was primarily directed at the cyclisation of (114) to form nortropane (75) since this process could be investigated without the possible interference of a double bond. Once the optimum conditions required for the cyclisation of (114) had been determined, they could subsequently be applied to (113). Hence, cyclisation of (114) was attempted by adding thionyl chloride to a solution of (114) in deuterated chloroform, in order to form the intermediate trans-1,4-chloroamine, followed by anhydrous TMP. The desired compound (75) appeared to have been formed by comparison with the spectral data recorded by Bathgate\textsuperscript{55} for nortropane (75) but separation of the amine used to induce cyclisation from the bicyclic amine produced proved to be impossible by chromatographic means. It was therefore necessary to use a heterogeneous base for the cyclisation since it could be removed more easily from the mixture at the end of the reaction. On treating a solution of (114) in
deuterated chloroform with thionyl chloride followed by the heterogeneous polymer-supported base, TABD, cyclisation occurred to give (75) as shown by proton (300MHz) n.m.r. By using an internal standard, it was possible to estimate that it had been formed in 26% yield (Figure 2.7). This yield was low but, nevertheless, some cyclisation had been achieved.

![Diagram](image)

**Figure 2.7**

The crude product was not purified further as nortropane (75) is a well documented compound and the unsaturated analogue, nortrop-6-ene (109) was of more interest to us.

Having established the conditions required for cyclisation in (114), the method was applied to the unsaturated cis-1,4-amino alcohol (113). However, on adding thionyl chloride, with an excess of lithium chloride, to a solution of (113) in deuterated chloroform followed by TABD, the desired compound (109) was only produced in 2.3% yield, as estimated by proton (300MHz) n.m.r. (Figure 2.8). Other attempts to cyclise (113) using thionyl chloride, followed by anhydrous potassium carbonate and ultrasound were totally unsuccessful.
Therefore a direct approach to nortropane (75) and, in particular, nortrop-6-ene (109) did not seem feasible.

2.4 PRODUCTION OF NORTROPANES HAVING A POTENTIALLY REMOVABLE NITROGEN PROTECTING GROUP.

In the light of the results described above, it was decided to develop this synthetic pathway to the production of nortropane and nortrop-6-ene derivatives having a nitrogen protecting group which was potentially easier to remove. Thus, routes to N-p-methoxybenzylnortropane and tropane, along with their respective unsaturated analogues, were sought since the removal of both p-methoxybenzyl groups and methyl groups from tertiary amines have literature precedents.

2.4.1 A SUBSTITUTED BENZYL PROTECTING GROUP.

The initial nitroso cycloaddition and subsequent steps were modified to form cis-4-((p-methoxybenzyl)amino)cycloheptanol (120) and cis-4-((p-methoxybenzyl)amino)-2-cycloheptenol (119), precursors to N-p-methoxybenzylnortropane (121) and its unsaturated analogue (122), as shown in Scheme 2.4.
A Diels-Alder addition to 1,3-cycloheptadiene (67) of the acyl nitroso compound (115), generated in situ from p-methoxybenzohydroxamic acid and tetramethylammonium periodate,\textsuperscript{59} afforded the [4+2] cycloadduct (116) in quantitative yield. The p-methoxybenzohydroxamic acid was prepared according to the method described by Hauser et al.\textsuperscript{62} for the formation of benzohydroxamic acid. Subsequent reductive cleavage of the N-O bond was achieved most
efficiently using aluminium amalgam in aqueous tetrahydrofuran.\textsuperscript{63} This gave \textit{cis}-4-((p-methoxybenzoyl)amino)-2-cycloheptenol (117) in 65\% yield. Other methods for the cleavage of the N-O bond were explored, including the use of 5\% sodium amalgam in ethanol\textsuperscript{52} and zinc in glacial acetic acid,\textsuperscript{61} but the best yields of (117) in these cases were 32\% and 35\% respectively. Treatment of (117) with lithium aluminium hydride\textsuperscript{53} gave \textit{cis}-4-((p-methoxybenzyl)amino)-2-cycloheptenol (119) in 85\% yield. However, hydrogenation of (117) over palladium on charcoal\textsuperscript{52} produced \textit{cis}-4-((p-methoxybenzoyl) amino) cycloheptanol (118) quantitatively and this was followed by reduction with lithium aluminium hydride\textsuperscript{53} to give the corresponding saturated alcohol (120) in 81\% yield.

Once again, the cyclisation of the simpler saturated compound (120) was explored first. Initial problems were experienced with this cyclisation step. Numerous attempts to cyclise (120) using thionyl chloride in deuterated chloroform to form the intermediate \textit{trans}-1,4-chloroamine hydrochloride, followed by treatment with anhydrous pyridine or anhydrous potassium carbonate and ultrasound, all resulted in failure giving only unidentifiable products. Nevertheless, these problems were eventually overcome by adding thionyl bromide to a solution of (120) in deuterated chloroform to generate an intermediate \textit{trans}-1,4-bromoamine. On completion the solvent was removed under reduced pressure and replaced by acetone. Subsequently, anhydrous TMP was added to this solution and the resulting mixture was heated
at 50°C. Purification of the crude product afforded N-p-methoxybenzynortropane (121) in 33% yield (Figure 2.9).

![Diagram of compound 120 and reaction pathways](image)

**Figure 2.9**

Having identified the conditions needed to induce cyclisation of (120), the method was applied to the unsaturated alcohol (119). On treating a solution of (119) in deuterated chloroform with thionyl bromide followed by replacement of the solvent with acetone and addition of anhydrous TMP, the desired product, N-p-methoxybenzyl nortrop-6-ene (122), was obtained in 48% yield accompanied by a 12% yield of the aziridine (123) (Figure 2.10).
An attempt to produce the parent secondary amine (109) by deprotection of (122) is discussed in chapter 3.

2.4.2 A METHYL PROTECTING GROUP.

Two routes were examined for the preparation of cis-4-(methylamino)cycloheptanol (125) and cis-4-(methylamino)-2-cycloheptenol (124), potential precursors to the bicyclic amines tropane (76) and trop-6-ene (127). The first approach involved the use of cis-4-amino-2-cycloheptenol (113) (Scheme 2.5), prepared as described in section 2.3.
The cis-1,4-amino alcohol (113) was protected by treatment with sodium hydride and benzyl chloroformate, to give cis-4-((benzoyloxy carbonyl)amino)-2-cycloheptenol (81) in 93% yield. Subsequent reduction of (81) with lithium aluminium hydride afforded (124) in 66% yield and hydrogenation over palladium on charcoal gave the saturated alcohol (125) in 90% yield. However, as this route was fairly long, another pathway was explored.

The second approach involved the reduction of N-(benzoyloxycarbonyl)-8-oxa-9-azabicyclo[3.2.2]non-6-ene (111), as described in Scheme 2.6.
The cycloadduct (111) was made as discussed previously (see section 2.3) and on treatment with lithium aluminium hydride\(^*\) was converted into N-methyl-8-oxa-9-aza-bicyclo[3.2.2]non-6-ene (126) in 67% yield. The N-O bond was cleaved effectively using zinc in glacial acetic acid\(^*\) affording (124) in 87% yield. The saturated alcohol (125) was obtained as in scheme 2.5. Since this pathway was simpler and more efficient than the first, it became the preferred route.

As before, attention was primarily directed towards the cyclisation of (125) but many problems were encountered with this reaction. Attempted cyclisation of (125) using thionyl chloride in deuterated chloroform, to produce the intermediate trans-1,4-chloroamine followed by treatment with anhydrous pyridine resulted in failure. It appeared that pyridine was not a strong enough base to initiate cyclisation. The stronger non-nucleophilic base

\[ \text{Scheme 2.6} \]
diisopropylamine (DIPA) was used instead, and it appeared to cause cyclisation as shown by proton \((90\text{MHz})\) n.m.r, on comparison with the data reported for tropane by Kibayashi.\(^{52}\) Unfortunately separation of the amine used to induce cyclisation from the bicyclic amine formed was impossible by chromatography. Therefore, as in the case of nortropane (section 2.3), a heterogeneous base was employed for cyclisation. Surprisingly, treatment of a solution of (125) in deuterated chloroform with thionyl chloride followed by anhydrous potassium carbonate and ultrasound was unsuccessful. Cyclisation was eventually achieved using the TABD and chromatographic purification of the crude residue obtained, afforded tropane (76) in 34% yield (Figure 2.11).

![Figure 2.11](image)

This approach was applied to the unsaturated alcohol (124). Treatment of a solution of (124) in deuterated chloroform containing an excess of lithium chloride with thionyl chloride followed by TABD resulted in the formation of trop-6-ene (127) in a yield of only 14%. A similar amount of the aziridine (128) was produced (Figure 2.12).
Demethylation of these azabicyclic compounds is covered in chapter 3.

2.5 TAUTOMERISM IN 4-AMINOCYCLOHEPTANONE DERIVATIVES.

2.5.1 INTRODUCTION.

Physoperuvine is the major alkaloid found in the roots of Physalis peruviana Linne which is a member of the Solanaceae plant family. In 1976, it was formulated as 3-methylamino cycloheptanone (Figure 2.13) by Ray et al., on the basis of chemical and physical evidence.

However, the need for a revision of its structure became apparent when analysis of its infrared spectrum showed no carbonyl absorption band and the carbon-13 n.m.r spectrum showed the lack of a carbonyl carbon in the molecule.

Thus, in order for an unambiguous elucidation of the structure of physoperuvine, Ray et al. subjected it to X-ray crystallographic analysis and it was surprisingly found
to be the hydrochloride salt of a bicyclic molecule (Figure 2.14).

![Figure 2.14](image)

Dependence of the structure of physoperuvine on pH was also studied. It was determined that while the salt remained exclusively in the bicyclic form (as shown in Figure 2.14), the free base was an equilibrium mixture of the bicyclic amino-alcohol (130) and the monocyclic amino-ketone (129), the equilibrium being shifted towards the former. From circular dichroism measurements, the ratio of the amino-ketone (129) to the amino-alcohol (130) was found to be 1:45 (Figure 2.15).

![Figure 2.15](image)

Comparable work has been performed by Smith at Leicester University, on the higher homologue 4-aminocyclooctanone. From variable-temperature carbon-13 n.m.r. and infrared data, it was possible to determine that
at room temperature this compound was undergoing a rapid tautomerism between the amino-ketone (131) and the amino-alcohol (132) forms (Figure 2.16). However, at the lower temperature of -50°C, the tautomerism was slowed sufficiently compared to the n.m.r. time scale, to identify the presence of the amino-alcohol form (132).

![Figure 2.16](image)

As a result of these observations, we decided that it would be interesting to examine the tautomerism in another 4-aminocycloheptanone derivative, 4-benzylaminocycloheptanone.

2.5.2 SYNTHESIS AND TAUTOMERISM OF 4-BENZYLAMINOCYCLOHEPTANONE.

4-Benzylaminocycloheptanone (136) was prepared from cis-4-benzoylaminocycloheptanol (71) as outlined in Scheme 2.7.
The cis-1,4-amido alcohol (71) was synthesised from 1,3-cycloheptadiene, as shown earlier in section 2.1. Oxidation of (71) was accomplished using Jones' reagent, to give 4-benzoylamino cycloheptanone (133) in a 70% yield. The carbonyl group was subsequently protected as the acetal (134) in a 78% yield. Reduction of (134) with lithium aluminium hydride produced (135) (62% yield); deprotection of the carbonyl group using one molar aqueous hydrochloric acid in tetrahydrofuran gave (136) in a 94% yield.

An infrared spectrum of 4-benzylaminocycloheptanone (136) at room temperature showed a strong absorption band at 1690 cm$^{-1}$ corresponding to a carbonyl moiety. This implied...
that a substantial portion of the amino-ketone form (136) existed. However, the broadness of both the proton and the carbon-13 n.m.r. spectra recorded for this compound at room temperature suggested that there was a rapid interconversion of the amino-ketone (136) and the amino-alcohol (137) forms (Figure 2.17) as expected.

\[
\begin{align*}
\text{(136)} & \quad \text{NHCH}_2\text{Ph} \\
\text{(137)} & \quad \text{NCH}_2\text{Ph} \\
\end{align*}
\]

Figure 2.17

At the lower temperatures (-50°C and -60°C) it was possible to slow down the tautomerism sufficiently to see the bicyclic form (137) by carbon-13 n.m.r. A peak at 888.9 became apparent at these low temperatures, and this was assigned to C-1 which was bonded to both nitrogen and oxygen.

These observations were entirely in accord with the results previously obtained for physoperuvine\textsuperscript{66} and 4-aminocyclo-octanone.\textsuperscript{67}

2.6 CONCLUSION.

From the results discussed in sections 2.2, 2.3 and 2.4, it can be concluded that the best yields of the cyclised products are obtained when the nitrogen function is protected with either a benzyl or p-methoxybenzyl group. Cyclisation of \textit{cis}-4-methylaminocycloheptanol (125) and its corresponding unsaturated alcohol (124) proceeded in much
lower yields. Cyclisation of cis-4-aminocycloheptanol (114) and cis-4-amino-2-cycloheptenol (113) to produce nortropane (75) and nortrop-6-ene (109) directly did not occur efficiently. It therefore seemed that the best nitrogen protecting group was a benzyl group. In light of this, it was decided that a thorough investigation of all the known debenzylation procedures for tertiary amines was necessary in order to obtain the desired parent molecule, nortrop-6-ene (109).

Finally, in section 2.5 it was shown that 4-benzylaminocycloheptanone (136) could be synthesised successfully; the monocyclic amino-ketone and the bicyclic amino-alcohol tautomers were shown to be in equilibrium.
Chapter Three

Dealkylation and Debenzylation of Tertiary Amines
3.1 INTRODUCTION.

As discussed in chapter two, debenzylation of N-benzyl-nortropane (101) to afford nortropane (75) could be achieved easily and efficiently by hydrogenation over palladium on charcoal.\textsuperscript{53} Nevertheless, this method could not be applied to the unsaturated analogue, N-benzyl-nortrop-6-ene (104), due to the presence of the double bond. An initial exploration into the debenzylation of N-benzyl-nortrop-6-ene (104) by Bathgate,\textsuperscript{55} included treatment with alkali metals (lithium, sodium and potassium) in liquid ammonia, phenyl chloroformate, vinyl chloroformate and hydrogenation in the presence of sodium nitrate and resulted, unexpectedly, in failure. Subsequent confirmation of these difficulties during the present work was nevertheless coupled with the finding that the best yields of azabicyclic products from the synthetic pathways outlined in chapter two were obtained when the nitrogen moiety was protected by either a benzyl or a p-methoxybenzyl group. A thorough investigation into dealkylation and debenzylation procedures available for tertiary amines was clearly of the utmost importance.

N-Dealkylation reactions and, more specifically, N-demethylation reactions are important in both organic synthesis and structural determinations. In 1900, von Braun\textsuperscript{71} discovered one of the first dealkylation methods for tertiary amines. It involved the use of cyanogen bromide to yield a disubstituted cyanamide (Figure 3.1).
This reaction proceeds through a quaternary ammonium bromide intermediate, which may react further by either nucleophilic attack of the bromide ion on the alkyl group ($S_N2$) or loss of the alkyl group as a carbocation ($S_N1$) to form the products (Figure 3.2).

The tertiary amine can be either cyclic or acyclic and the operative mechanism for the second step is dependent upon the nature of the substituents.

However, the use of cyanogen bromide to perform dealkylations of tertiary amines has been largely replaced with chloroformate reagents, which have proved to be more selective and produce cleaner reaction products. The generally accepted reaction sequence for these reagents is outlined in Scheme 3.1.\textsuperscript{72}
The 1:1 complex formed has two possible fates: nucleophilic attack of the chloride ion on the O-alkyl component, which results in no net effect on the amine (path b), or nucleophilic attack of the chloride ion on one of the substituents on the nitrogen atom (path a) to give the carbamate ester, which in turn can be hydrolysed to afford the secondary amine.

Several different chloroformates have been reported in the literature, each one claimed as an improvement on the last. These improvements include better yields, increased availability of the reagents, cheaper reagents and more importantly, easier conversion of the carbamate esters into the desired secondary amines. In 1967, Hobson and McCluskey\textsuperscript{72} declared that phenyl chloroformate surpassed its methyl and ethyl analogues in the cleavage of tertiary amines. They showed that dimethylanaline (138) could be converted into phenyl-N-methylcarbanilate (139) in 80% yield and quinuclidine (140) into phenyl 4-(2-chloroethyl)
piperidine-N-carboxylate (141) in 88% yield when using this reagent (Figure 3.3).

![Chemical structure](image1)

Figure 3.3

The conversion of 21-deoxyajmaline (142) into phenyl 21-deoxydihydro 21-iodochanoajmaline-N-carboxylate (143), through reaction with phenyl chloroformate in the presence of lithium iodide, was also reported (Figure 3.4).

![Chemical structure](image2)

Figure 3.4

The major drawback in the use of phenyl chloroformate, however, is the hydrolysis of the resultant phenyl carbamate since the use of strong acid or base hydrolysis is often necessary for long periods of time.
To avoid this problem, Montzka et al.\textsuperscript{73} used 2,2,2-trichloroethyl chloroformate instead. The intermediate carbamate derivatives were reported to be highly crystalline and easily purified. The attractive advantage of this reagent was that these trichloroethyl carbamate derivatives were readily converted into the desired secondary amines in high yields by treatment with zinc in either methanol or 90% acetic acid. In this way, 3α-acetoxytropane (144) was demethylated to 3α-acetoxy nortropane (145) in an overall yield of 75\%, as was morphine (146) to normorphine (147) (Figure 3.5).

Rice\textsuperscript{74} used this reagent to attempt the demethylation of 2'-hydroxy-2,5-dimethyl-9α-propyl-6,7-benzomorphan (148),
but the corresponding N-nor derivative could only be obtained in yields of 40% or less (Figure 3.6).

\[ \text{(148)} \]

Figure 3.6

Therefore, he decided to re-examine the use of phenylchloroformate and he showed that by using a known procedure involving hydrazine\(^7\) to cleave the resulting amides, the hydrolysis problems experienced previously with this reagent could be overcome. Thus morphine (146) and codeine (149) (Figure 3.7) were demethylated in 84 and 89% yields respectively.

\[ \text{(149)} \]

Figure 3.7

In 1977, Olofson et al.\(^7\) introduced vinyl chloroformate. Its selectivity and ease of removal (usually accompanied by gentle heating) caused it to become the reagent of choice.
for these transformations. This method was compared to the previously known procedures through a series of reactions with N-ethyl piperidine (Scheme 3.2).

The increased yields found with this reagent were attributed to the enhanced electrophilicity of the acyl carbon attached to an electron-withdrawing \(-\text{OCH}=\text{CH}_2\) moiety. To illustrate the use of vinyl chloroformate, noroxymorphone (151) was prepared from oxymorphone (150) in 98% yield, as opposed to a previous procedure for making this intermediate in the oxymorphine synthesis which utilised the von Braun cyanogen bromide reaction and only achieved an overall yield of 20% (Figure 3.8).
However, the best method found in the literature to date for the dealkylation of tertiary amines involves the use of the inexpensive reagent, $\alpha$-chloroethyl chloroformate. With this reagent dealkylation of N-ethylpiperidine was effected in a 99% yield (Figure 3.9). The high yield is related to the fact that the $\alpha$-chloroethyl group in the intermediate quaternary salt is sterically hindered to $S_N2$ attack by the chloride ion and the cation which would be produced by $S_N1$ cleavage is unstable. The cleavage of the

\[
\begin{align*}
\text{N-Et} & \quad \text{ClOOCOCHCICH}_3 \\
\rightarrow & \quad \begin{cases} \\
\text{Et} & \quad \text{N-COOCHCICH}_3 \\
\text{Cl} & \quad \text{+} \\
\end{cases} \\
\text{MeOH/heat} & \quad \text{N-COOCHCICH}_3 \\
\end{align*}
\]

99% yield
α-chloroethyl carbamate ester was accomplished by simply heating in methanol.

From selected attempts to dealkylate/debenzylate tertiary amines, we gradually realised that the results obtained were very variable, and expectations from the literature procedures were not always fulfilled. It also became apparent that there was a difference between monocyclic and bicyclic amines. In view of this, we decided to investigate the dealkylation/debenzylation of tertiary amines in a systematic way.

3.2 SYNTHESIS OF TERTIARY AMINES REQUIRED FOR DEALKYLATION/DEBENZYLATION RESEARCH.

In order to explore the dealkylation/debenzylation procedures, reported in the literature over a range of tertiary amines, a number of monocyclic and bicyclic amines were prepared. The monocyclic amines produced for this purpose were N-benzylpyrrolidine (154ax), N-benzylpiperidine (154bx), N-p-methoxybenzylpiperidine (154by) and N-3,4-dimethoxybenzyl piperidine (154bz). They were synthesised as outlined in Scheme 3.3.
Scheme 3.3

Reaction of the acyl compounds \((x,y,z)\) with the monocyclic amines \((152a,b)\) in the presence of an aqueous solution of sodium hydroxide,\(^{81}\) afforded the corresponding amides \((153ax, bx, by, bz)\). Subsequent reduction with lithium aluminium hydride gave the desired N-aryl tertiary amines \((154ax, bx, by, bz)\).

The bicyclic amines which were made for this investigation were \(N\)-benzyl-2-azabicyclo[2.2.1]hept-5-ene\(^{82}\) \((158a)\) and \(N\)-benzyl-2-azabicyclo[2.2.2]oct-5-ene\(^{82}\) \((158b)\). They were produced by an aza Diels-Alder reaction involving a simple iminium salt, generated under Mannich-like conditions, and 1,3-cyclopentadiene \((157a)\) or 1,3-cyclohexadiene \((157b)\) as shown in Scheme 3.4.
Thus, addition of the diene (157a,b) to an aqueous solution of benzylamine hydrochloride (155) and formaldehyde afforded the cycloadducts (158a,b) in yields of 91% and 30% respectively.

These compounds together with N-benzylnortropane (101), N-benzylnortrop-6-ene (104), N-p-methoxybenzylnortrop-6-ene (122), prepared as described in chapter two, and the commercially available N-ethylpiperidine and tropan-3α-ol now allowed for an extensive study of this dealkylation/debenzylation area.

3.3 INVESTIGATION OF DEALKYLATION/DEBENZYLATION METHODS.

3.3.1 CHLOROFORMATES.

It was decided to examine the dealkylation/debenzylation of a range of tertiary amines using vinyl chloroformate (VOCCl)\textsuperscript{76} and α-chloroethyl chloroformate (ACECl).\textsuperscript{80} For the investigation with VOCCl, the substrate was treated with VOCCl in dichloromethane and the resulting solution was heated at reflux. Subsequently, gaseous hydrogen chloride
was bubbled through the reaction mixture and, following solvent evaporation, the residue was warmed in methanol. For the exploration involving ACECl, the substrate was treated with ACECl in 1,2-dichloroethane, except for N-p-methoxybenzynortrop-6-ene (122) where the solvent used was dichloromethane. After heating, the solvent was removed and the residue was warmed in methanol. The results are summarised in Table 3.1.
<table>
<thead>
<tr>
<th>Substrate</th>
<th>VOCCI</th>
<th>ACECI</th>
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* = Literature substrate

Table 3.1
From the results obtained, it can be seen that all the analogues of the simple monocyclic amine, piperidine, readily underwent dealkylation/debenzylation with either VOCCl or ACECl. Piperidine hydrochloride was isolated in yields ranging from 77 to 88%. However, although demethylation of the literature substrate, tropan-3α-ol, could be accomplished with ACECl to give nortropan-3α-ol hydrochloride in 67% yield, all the azabicyclic benzyl analogues failed to produce their corresponding "nor" derivatives with either VOCCl or ACECl. Only the hydrochloride salts of the unreacted starting material were recovered.

Nevertheless, removal of the p-methoxybenzyl group from N-p-methoxybenzynortrop-6-ene (122) can be partly achieved using ACECl, but the reaction never goes to completion and so some unreacted starting material is always recovered as well. From proton (300MHz) n.m.r. spectra, it was possible to estimate that nortrop-6-ene (109) had been produced in 50% yield. Unfortunately, the majority of (109) was lost during an attempted chromatographic separation and the compound was isolated in only 5% yield. Nortrop-6-ene (109) was recognisable due to the simplicity of the proton n.m.r. (300MHz) spectrum which consisted of a series of multiplets between δ1.44 and δ2.22 for the protons in the three methylene groups, a broad singlet at δ4.30 for the two bridgehead protons and a singlet at δ6.09 for the two olefinic protons. The carbon-13 n.m.r. (75MHz) spectrum for (109) was also fairly simple consisting of only four peaks; two triplets at δ22.4 and δ29.7 for the carbon atoms in the
methylene groups, a doublet at δ58.7 for the two bridgehead carbons and a doublet at δ129.0 for the two olefinic carbons. Thus, the spectroscopic analysis was entirely in accord with that expected for nortrop-6-ene (109).

3.3.2 CONCENTRATED SULPHURIC ACID IN TRIFLUOROACETIC ACID.

It has been reported that p-methoxybenzyl\textsuperscript{183} and 3,4-dimethoxybenzyl\textsuperscript{184} groups can be removed from tertiary amines on treatment with a 5% solution of concentrated sulphuric acid in anhydrous trifluoroacetic acid in the presence of an excess of anisole, to trap the resulting carbocation. This approach was therefore applied to the simple, monocyclic amines N-p-methoxybenzyl piperidine (154by) and N-3,4-dimethoxybenzyl piperidine (154bz) (Figure 3.10).

![Diagram](https://via.placeholder.com/150)

**Figure 3.10**

However, in both cases only starting material was recovered and so this method was not developed further to the azabicyclic systems.
3.3.3 PHOTOLYTIC CLEAVAGE.

In 1988, Pandey and Rani announced a mild method for N-debenzylation which involved a photosensitized single electron transfer using 9,10-dicyanoanthracene (9,10-DCA) as the electron acceptor in a neutral medium. In this way, an iminium cation is produced, which on subsequent hydrolysis liberates the corresponding debenzylated amine (Scheme 3.5).

\[
\text{N} \text{hv} \xrightarrow{9,10-\text{DCA}} \left[ \begin{array}{c} \text{N}^+ \text{Ph} \\ \text{Ph} \\ 1. \text{-H}^+ \\ 2. \text{-e}^- \end{array} \right] \xrightarrow{\text{H}_2\text{O}} \text{N}^+ + \text{PhCHO}
\]

Scheme 3.5

It was decided to explore this reaction using the simple, monocyclic benzyl amines N-benzylpyrrolidine (154ax) and N-benzylpiperidine (154bx).

The electron acceptor, 9,10-DCA (162), was prepared by reaction of sodium cyanide (160) with 9-cyanoanthracene (159) in the presence of sodium 9,10-anthraquinone-\(\alpha\)-sulphonate (\(\alpha\)-SAS) (161) (Figure 3.11); it was isolated in a 90% yield.
The α-SAS (161), required for this reaction, was produced by treating anthraquinone (163) with oleum (164) and mercury(II) oxide followed by addition of an aqueous solution of sodium chloride (Scheme 3.6). This gave α-SAS (161) in 70% yield.
However, on irradiating a solution of the benzyl amine (154 ax,bx) in acetonitrile/water with 9,10-DCA in a Rayonet reactor fitted with 3500A lamps (Figure 3.12), no reaction was found to occur, even after ten hours. Only unreacted starting material was isolated. Irradiation at shorter wavelengths also failed to induce any N-debenzylation.
Since our attempts at N-debenzylation using this methodology were unsuccessful even when applied to the literature substrate (154ax), we did not consider it worthwhile to extend this idea any further.

3.3.4 IRON (II)-CATALYSED REACTION OF AMINE OXIDES.

A simple, one-pot method for the dealkylation of tertiary amines, under mild and virtually neutral reaction conditions, has been reported.\textsuperscript{88} It is based on an iron(II)-catalysed rearrangement of amine oxides as illustrated in Scheme 3.7.
This approach was therefore applied to the simple monocyclic amine N-benzylpiperidine (154bx) and to the bicyclic amine, N-benzyl-9-azabicyclo[4.2.1]oct-7-ene (166), prepared at Leicester.67 Thus, m-chloroperoxybenzoic acid was added to a solution of the amine (154bx, 166) in dichloromethane. Subsequently, a catalytic amount of iron(II) chloride, as a

Figure 3.13
molar aqueous solution, was added with stirring and the reaction was monitored by t.l.c. The results obtained are detailed in Figure 3.13.

The method worked effectively with the monocyclic N-benzyl piperidine and on acidification of the reaction mixture with gaseous hydrogen chloride, piperidine hydrochloride was afforded in 65% yield. No reaction occurred with the bicyclic amine; in this case only unreacted starting material was isolated.

3.3.5. 2,3-DICHLORO-5,6-DICYANO-1,4-BENZOQUINONE (DDQ).

This reagent has been shown to remove p-methoxybenzyl protecting groups from oxygen functions. It was therefore considered worthwhile to investigate use of this same methodology on the simple piperidine model, N-p-methoxybenzyl piperidine (154by). A solution of the amine (154by) in dichloromethane was treated with a solution of DDQ followed by a separate addition of water. However, even after forty-eight hours, only starting material was present in the reaction mixture (Figure 3.14).
3.3.6 QUATERNISATION AND SELECTIVE DEBENZYLATION.

Since there is literature precedent to demonstrate that the cleavage of benzyl groups occurs more readily than that of methyl groups in quaternary ammonium salts, it was decided to prepare the corresponding methiodide of N-benzynortrop-6-ene (104). This was achieved by heating (104) in a large excess of methyl iodide with an equivalent volume of acetone, as suggested by McKenna et al. The ammonium salt (167) was isolated in a 74\% yield (Figure 3.15).

\[
\begin{align*}
\text{CH}_2\text{Ph} & \quad \text{N} \\
\text{Mel/acetone} & \quad \text{heat} \\
(104) & \quad (167)
\end{align*}
\]

Figure 3.15

By proton (300MHz) n.m.r., (167) was found to exist as a pair of diastereoisomers which were present in a ratio of 2:1 in favour of the diastereoisomer formed by equatorial attack (Figure 3.16). The singlet attributed to the methyl protons in the major diastereoisomer occurred at significantly higher field (δ3.14) than the corresponding signal in the minor diastereoisomer (δ3.41), indicating that it must lie within the shielding cone of the double bond. Similarly, the singlet assigned to the benzylic methylene protons in the major diastereoisomer arises at lower field (δ5.29) than the same signal in the minor diastereoisomer.
In the minor diastereoisomer it is this group which lay within the shielding cone of the double bond.

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_2\text{Ph} \\
\text{PhCH}_2 & \quad \text{CH}_3
\end{align*}
\]

Equatorial attack

Axial attack

\[
\begin{array}{c}
2 \\
1
\end{array}
\]

Figure 3.16

It had been anticipated that the major diastereoisomer formed would be the one from equatorial attack based on a review by Bottini,\(^9\) which described many examples of preferred equatorial attack during quaternisation of tropanes.

The first selective debenzylation reaction of (167) attempted was Emde's reduction.\(^9\) Thus an aqueous solution of (167) was heated to reflux and sodium amalgam was added in portions whilst heating was continued. However, the major product of this reaction was the unreacted quaternary ammonium salt and none of the desired product trop-6-ene (127) was isolated (Figure 3.17).
The second attempted selective debenzylation reaction tried involved the use of thiophenol. The ammonium salt (167) was heated with thiophenol in a 20% aqueous solution of sodium hydroxide. However, a proton (90MHz) n.m.r. spectrum recorded for the crude reaction mixture showed no indication of the desired compound, trop-6-ene (127); the only identifiable material was unreacted starting material (Figure 3.18).

The dealkylation/debenzylation approach could have been extended to the use of benzeneselenol, which has been claimed to achieve dealkylation of tertiary amines to afford the corresponding secondary amine. However, since the use of this reagent to cleave N-benzyl groups in tertiary amines had not been demonstrated, it was decided to end this exploration here.

3.4 CONCLUSION.

From this investigation, it is possible to conclude that debenzylation of the simple, monocyclic piperidine models could be achieved readily and efficiently using most of the procedures attempted. In contrast, debenzylation of the azabicyclic systems resulted in many unexpected problems. In fact none of the methods tried were able to remove the
benzyl protecting group from either N-benzynortropane (101) or N-benzynortrop-6-ene (104).

However, removal of the p-methoxybenzyl group from N-p-methoxy benzynortrop-6-ene (122) could be partly accomplished using ACECl to yield the desired parent system, nortrop-6-ene (109). This may therefore be a valid route to the production of this compound but better purification techniques need to be found for the crude reaction mixture, in order that it may be isolated without loss.

The reason why N-p-methoxybenzyl nortrop-6-ene (122) underwent partial débenzylation with ACECl whereas N-benzynortropane (101) did not may lie in the mechanism for this reaction. From section 3.1, it is known that dealkylation/debenzylation of tertiary amines with either VOCCl or ACECl proceeds through a quaternary ammonium chloride intermediate, which may react further by either nucleophilic attack of the chloride ion on the alkyl group (SN2) or the loss of the alkyl group as a carbocation (SN1) to form the products. Now, the only occasion in which partial debenzylation was achieved in an azabicyclic system is when a p-methoxy substituent was present on the benzyl group, thus causing the reaction to be more SN1-like in character since the p-methoxy function would enhance the stability of the carbocation formed. This suggests that in azabicycles debenzylation may prefer to proceed in a SN1 fashion rather than in an SN2 way, as nucleophilic attack of the chloride ion on the benzyl group in the quaternary ammonium chloride intermediate may be sterically hindered.
If this is an important factor, then N-2,4-dimethoxybenzyl nortrop-6-ene may be completely debenzylated under the same conditions, since the two methoxy functions should provide even more stability for the resulting carbocation. Thus, another pathway to nortrop-6-ene (109) may be via the formation of N-2,4-dimethoxybenzynortrop-6-ene (Figure 3.19).

The behaviour of the bridging nitrogen in azabicycles may also be different, thus contributing to these difficulties experienced with debenzylation. Davies encountered unexpected problems with cleavage of a N-benzyl group in a 7-azabicyclo[2.2.1]heptadiene system (Figure 3.20) by hydrogenation. In order to accomplish total debenzylation, a solution of this compound in glacial acetic acid needed to be hydrogenated at 1 atmosphere in the presence of 10% palladium on charcoal for forty-eight hours.
It was shown in chapter 2 that it was possible to synthesise both tropane (76) and trop-6-ene (127) although they were not obtained in as good a yield as their N-benzyl analogues. These N-methyl compounds must be seen as an alternative for the preparation of nortrop-6-ene (109) and its analogues, due to the unexpected difficulties encountered with N-debenzylation. There is already literature precedent for demethylation in these systems using either VOCCl\textsuperscript{76} or ACECl\textsuperscript{80} as discussed in section 3.3.1.

However, in order to examine the general development of this route to substituted 1,3-cycloheptadienes (see chapter four), it was decided to continue the use of the benzyl nitrogen protecting group in view of the experience gained earlier and the ready availability of large quantities of the required starting materials. Also there is no problem with the removal of the benzyl protecting group from the saturated azabicyclic compounds, as this can be achieved by hydrogenation\textsuperscript{53} It is only in the unsaturated analogues that difficulties arise. Nevertheless, once the important targets have been established, it will be possible to extend the synthesis to the N-p-methoxybenzyl, N-2,4-dimethoxybenzyl or N-methyl analogues so that the respective "nor" compounds may eventually be obtained.
Chapter Four

Functionalised Azabicyclic Systems
From 1,3-Cycloheptadien-6-ol Derivatives
4.1 INTRODUCTION.

4.1.1 OVERALL STRATEGY.

Section 2.2 described our development of the Bathgate\textsuperscript{53} route to N-benzylnortropane (101) and N-benzylnortrop-6-ene (104) from 1,3-cycloheptadiene. Extension of this approach to oxygenated derivatives warranted further investigation in view of the occurrence in nature of a wide selection of tropane alkaloids bearing oxygen substituents.

Previously, Kibayashi\textsuperscript{52} had reported that numerous attempts to induce a cycloaddition between 6-benzoyloxy-1,3-cycloheptadiene (168) and the acyl nitroso compound (68), generated \textit{in situ}, had resulted in failure despite the use of conditions which had proved successful in the formation

\[
\begin{align*}
\text{OOCPh} & \quad \text{PhCONO} \quad \rightarrow \\
\text{(168)} & \quad \text{(68)} & \quad \text{(169)}
\end{align*}
\]

Figure 4.1
of N-benzyl-8-oxa-9-azabicyclo[3.2.2]non-6-ene (69) (Figure 4.1).

He had therefore resorted to using the alternative dienophile 1-chloro-1-nitrosocyclohexane (77) (Figure 4.2).

\[
\begin{align*}
\text{OOOCPh} & \quad \text{Cl} & \quad \text{NO} \\
(168) & \quad (77) & \quad (170)
\end{align*}
\]

Figure 4.2

Nevertheless, an investigation into the use of substituted 1,3-cycloheptadienes with the acyl nitroso compound (68), was still considered worthwhile since it might be possible to overcome these difficulties.

By developing the approach in chapter 2 to substituted 1,3-cycloheptadienes it was hoped that a route to both the exo- and endo-isomers of nortropan-3-ol and nortrop-6-en-3-ol derivatives would eventually be achieved (Figure 4.3). This would make this synthesis comparable to Bäckvall's work\textsuperscript{52}, but with the possibility that the corresponding unsaturated analogues might also be accessible; Bäckvall's attempts to produce the unsaturated analogues had been unsuccessful.
4.1.2 ROUTES TO OXYGENATED SUBSTRATES.

Due to the dearth of readily-available substituted 1,3-cycloheptadienes in the literature, the two dienes which were selected for this exploration were suitably protected forms of 1,3-cycloheptadien-6-ol (172) and 1,3-cycloheptadien-6-one (173). Both these dienes can be prepared from tropone (171) (Figure 4.4).
In order to synthesise tropone (171), tropylium tetrafluoroborate (176)\textsuperscript{96} is required. This can be made from cycloheptatriene (174) by a two-step process, as outlined in Scheme 4.1.

\begin{center}
\begin{align*}
\text{2} & \quad \text{+ 3PCI}_5 & \quad \text{CCl}_4 & \quad \left[ \begin{array}{c} \text{Cl}^- \\ \text{PCl}_6^+ \\ \text{BF}_4^- \end{array} \right] \\
(174) & \quad \text{(175)} \quad \text{(176)}
\end{align*}
\end{center}

\textbf{Scheme 4.1}

Treatment of cycloheptatriene (174) with phosphorous pentachloride affords the tropylium hexachlorophosphate-tropylium chloride double salt (175). This is then immediately reacted with aqueous fluoroboric acid, to give tropylium tetrafluoroborate (176) in 78% yield.

A few synthetic approaches to the preparation of tropone (171) from tropylium tetrafluoroborate (176) have been described in the literature. At first sight, the best method appeared to be one involving the oxidation of the tropylium salt (176) with dimethyl sulfoxide (DMSO)\textsuperscript{97} (Figure 4.5).
Figure 4.5

It was claimed that this reaction proceeded via the intermediate (177) to afford tropone (171) in 58% yield. However, on repeating this work, we consistently achieved only a 10% yield. Therefore, alternative routes to tropone (171) were sought as this low yield was not acceptable for the first step in a synthetic pathway.

In 1972, McCullagh and Wolfmann\textsuperscript{98} reported that the tropylium salt (176) could be converted to tropone (171), via the formation of tropylium azide (178) (Scheme 4.2).
Thus, tropylium tetrafluoroborate (176) was treated with sodium azide in water and the resulting tropyl azide (178) extracted into benzene. After drying, this solution was subjected to a simple air oxidation in the presence of a benzene slurry of basic alumina resulting in the formation of tropone (171) in a reported 42% yield. However, the best yield of tropone (171) which we obtained from this procedure, was 20% yield. We also discovered that this route was unpredictable since on repetition using the same conditions no tropone (171) was isolated.

Finally, on the verge of abandoning the synthesis of tropone (171), another method for its preparation from tropylium tetrafluoroborate (176) was uncovered. This new approach had been developed by Reingold et al., who had previously reported the synthesis of tropone (171) from tropylium tetrafluoroborate (176) by oxidation with DMSO. \(^97\)
Following complaints of widespread difficulty with repetition of this work and in view of difficulties in reproducing his own yields, he had decided to reinvestigate this reaction.

Subsequently, it was found that on heating tropylium tetrafluoroborate (176) in DMSO, a 1:1 mixture of tropone (171) and cycloheptatriene (174) was produced. Thus, the previously-proposed intermediate for this reaction (177), could not be correct as it did not account for the generation of cycloheptatriene (174) along with tropone (171). Furthermore, it was shown that addition of anhydrous solid sodium carbonate markedly accelerated the reaction and that the sodium carbonate catalysed reaction worked equally well in dimethylformamide and, with heating, in acetone, tetraglyme or acetonitrile. On a preparative scale, the best results were obtained when tropylium tetrafluoroborate (176) was treated with anhydrous sodium carbonate in acetonitrile and the resulting mixture was heated to reflux. In this way, tropone (171) was afforded in a 48% yield (Figure 4.6).

![Diagram](image-url)
The mechanism proposed for this reaction is shown in Figure 4.7.

On repeating this work, we consistently obtained tropone (171) in 33% yield. Although this yield was a little lower than reported, it was more acceptable. The other product of this reaction, cycloheptatriene (174) could, in theory, be reconverted to the tropylium salt (176) and hence eventually provide more tropone (171). This makes this method for the production of tropone (171) more economical.

Tropone (171) can be selectively reduced to either 1,3-cycloheptadien-6-ol (172) or 1,3-cycloheptadien-6-one (173) by varying the hydride reagent, solvent and the method of work-up (Figure 4.8).
4.2 DEVELOPMENT OF THE INTRAMOLECULAR CYCLISATION ROUTE TO NORTROPAN-3-OL/NORTROP-6-EN-3-OL AND THEIR DERIVATIVES.

In order to examine the initial stages of the intramolecular cyclisation route and in particular the Diels-Alder reaction, 1,3-cycloheptadien-6-ol (172) was simply protected with an acetoxy group, according to the method described by Bäckvall $^{101}$ (Figure 4.9). Although this was not an ideal protecting group for the whole synthetic pathway, it was sufficient for an investigation into the preliminary steps.
1,3-Cycloheptadien-6-ol (172) was treated with acetic anhydride in the presence of triethylamine and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) to produce 6-acetoxy-1,3-cycloheptadiene (179) in 64% yield.

Subsequently, (179) was reacted with the acyl nitroso compound (68), generated in situ from benzohydroxamic acid and tetramethylammonium periodate. The same conditions were used as for the formation of N-benzoyl-8-oxa-9-azabicyclo[3.2.2]non-6-ene (69). After five hours at room temperature the desired [4+2] cycloadduct (180) was produced as a mixture of diastereoisomers in an overall yield of 64% (Figure 4.10).
The ratio of the diastereoisomers was 2:1 (as estimated by proton (300MHz) n.m.r.) and the exo- isomer (180a) was favoured over the endo- form (180b). The signal attributed to the 3-endo proton of the major adduct (180a) occurred at a significantly higher field than usual, at δ4.82, indicating that it was lying within the shielding cone of the C₆-C₇ double bond. In contrast, the 3-exo proton in (180b) appeared at δ5.31. In both diastereoisomers the bridgehead protons arose as broad singlets at δ4.71 and δ5.39, and in the major product (180a) the olefinic protons gave a doublet of doublets at δ6.30 and δ6.36 whereas in the minor product (180b) the olefinic protons produced a multiplet peak at δ6.40. These shifts are comparable to those observed for N-benzoyl-8-oxa-9-azabicyclo[3.2.2]non-6-ene (69), where the bridgehead protons had appeared as broad singlets at δ4.70 and δ5.44 and the olefinic protons had produced a broad singlet at δ6.30.

Thus, the problems experienced earlier by Kibayashi, concerning the cycloaddition of a substituted 1,3-cycloheptadiene and the acyl nitroso compound (68) did not seem to be generally applicable since no problems were encountered here.

Having succeeded in preparing the Diels-Alder adduct (180), it was decided to explore the next stages in the synthesis in order to identify any other difficulties which might result from this extra substituent (Scheme 4.3).
Both the reductive cleavage of the N-O bond using aluminium amalgam in aqueous tetrahydrofuran and hydrogenation over palladium on charcoal occurred cleanly and efficiently, to give the saturated cis-1,4-amido alcohol (182) in a quantitative yield.

However, this route was not extended any further, as the next step in this pathway involved reduction with lithium aluminium hydride. This would have resulted in the loss of the acetoxy protecting group along with the reduction of the benzoyl group to afford a product containing two free hydroxyl groups. Although the presence of the second hydroxyl function at C-6 may not have hindered the subsequent cyclisation step (since formation of the desired [3.2.1] azabicycle, comprising a six- and a five-membered ring would have been more favourable than the alternative production of an azabicycle containing a seven- and a four-
membered ring) it was decided that a more suitable hydroxyl protecting group should be used to continue this exploration.

Having established that a substituent on 1,3-cycloheptadiene did not affect the initial nitroso cycloaddition as first feared, it was decided to follow this synthetic pathway through with 6-tert-butyldimethylsiloxy-1,3-cycloheptadiene (183) (Scheme 4.4). A tert-butyldimethylsilyl group was believed to be one of the most stable hydroxyl protecting groups, whose removal at the end of the synthesis (using tetrabutylammonium fluoride in

![Scheme 4.4](image-url)
tetrahydrofuran) could be accomplished without affecting the rest of the molecule.

Thus, 1,3-cycloheptadien-6-ol (172) was treated with tert-butyldimethylsilyl chloride in the presence of imidazole, to give (183) in an 87% yield. Subsequently, (183) was reacted with the acyl nitroso compound (68) to afford the [4+2] cycloadduct (184), as a mixture of diastereoisomers once more, in an overall yield of 64%. In this case, the ratio of the diastereoisomers was 4:1 (as estimated by proton (300MHz) n.m.r.) in favour of the exo-form (184a). The signal assigned to the 3-endo proton of the major adduct (184a) arose at δ3.80, due to the shielding effect created by the C₆-C₇ double bond, whereas the signal for the 3-exo proton appeared at δ4.44. Reductive cleavage of the N-O bond using aluminium amalgam in aqueous tetrahydrofuran occurred effectively and the unsaturated cis-1,4-amido alcohol (185) was produced in 94% yield.

However, problems were encountered with the subsequent hydrogenation step. When (185) was subjected to hydrogenation over palladium on charcoal for sixteen hours it was discovered that saturation of the double bond was accompanied by loss of the silicon protecting group to give (186) in a quantitative yield (Figure 4.11). This was a surprising result since this silicon protecting group is reported to be stable to hydrogenation. Nevertheless, on monitoring the reaction more closely, it was found that saturation of the double bond could be achieved after four hours, with no deprotection of the hydroxyl function, to
afford the desired saturated cis-1,4-amido alcohol (187) in 99% yield.

More severe difficulties were experienced with the next stage, involving the reduction of (187) with lithium aluminium hydride. It was noted that, even on monitoring the reaction very closely, removal of the silicon protecting group competed with reduction of the amide giving (188) rather than the required compound (189) (Scheme 4.5).
Due to the numerous unforeseen problems with the tert-butyldimethylsilyl protecting group, it was decided to use the tert-butyldiphenylsilyl group since it is a much more bulky group and so should be harder to remove. Thus, this synthetic route was repeated with 6-tert-butyldiphenylsiloxy-1,3-cycloheptadiene (190) (Scheme 4.6).
Treatment of 1,3-cycloheptadien-6-ol (172) with tert-butyl diphenylsilyl chloride in the presence of imidazole\textsuperscript{104} gave (190) in 82\% yield. Subsequently, (190) was reacted with the acyl nitroso compound (68) to afford the Diels-Alder adduct (191), again as a mixture of diastereoisomers, in an overall yield of 88\%. The ratio of diastereoisomers produced here was 3:1 (as estimated by proton (300MHz) n.m.r.) in favour of the exo- form (191a). Again the signal attributed to the 3-endo proton in the major adduct (191a) occurred at significantly higher field (δ3.83) than
the 3-exo proton in (191b) (δ4.47), since it was experiencing the shielding effect of the C6-C7 double bond. Reductive cleavage of the N-O bond, using aluminium amalgam in aqueous tetrahydrofuran proved to be more difficult than previously experienced as the reaction proceeded at a much slower rate. Eventually the optimum conditions for this reaction were determined and the unsaturated cis-1,4-amido alcohol (192) was produced in 97% yield. Hydrogenation of (192) over palladium on charcoal gave the corresponding saturated cis-1,4-amido alcohol (193) in quantitative yield.

However, problems were encountered once more with the reduction using lithium aluminium hydride. For both the saturated (193) and unsaturated (192) cis-1,4-amido alcohols only low yields of the desired amino alcohols, (194) and (195) respectively, were obtained (Figure 4.12). Compound (194) was obtained in 28% yield and (195) in 14% yield.
From the proton and carbon-13 n.m.r data acquired for both (194) and (195), it was found that only one of the two possible diastereoisomers was present, which accounted for the low yields. Other compounds isolated from the reduction of (193) were tert-butyldiphenylsilylol, (186) and (188). Thus, it appears that one of the diastereoisomers undergoes
loss of the silicon protecting group faster than the reduction of the benzoyl group. It was proposed that the diastereoisomer which underwent this loss was the one bearing the silicon protected hydroxyl function at C-6 cis to the amido group (Figure 4.13). In this case, the lithium aluminium hydride could co-ordinate to both the carbonyl oxygen in the amide and the oxygen of the protected hydroxyl group, thereby encouraging the silicon protecting group to depart.

![Figure 4.13](image)

Cyclisation of the one diastereoisomer of (194) was attempted in order to form N-benzyl-3-tert-butylidiphenylsiloxy nortropane (196). Thionyl bromide was added to a solution of (194) in deuterated chloroform in order to generate the intermediate trans-1,4-bromoamine hydrobromide. On completion of the bromination, the solvent was removed in vacuo and replaced with acetone. Subsequently, anhydrous TMP was added to the solution and the resulting mixture was heated at 50°C. However, purification of the crude material gave (196) in only 15% yield (Figure 4.14).
The formation of (196) was determined by comparison of the proton n.m.r. (300MHz) spectrum obtained with that recorded for N-benzynortropane (101). Due to the high symmetry in these systems, the proton n.m.r. spectra are reasonably simple. The two bridgehead protons appeared as a broad singlet at δ3.09 and the benzylic methylene group as a singlet at δ3.51, both of which were comparable to that observed for N-benzynortropane (101) where the signal attributed to the two bridgehead protons had arisen at δ3.15 and that for the benzylic methylene group at δ3.52. The signal assigned to the C-3 proton in (196) occurred at δ4.05.

In view of the low overall yield, it was decided to abandon this route and to concentrate on the use of 1,3-cycloheptadien-6-one (173) in the pathway instead due to the unexpected difficulties experienced with the protected hydroxyl group of 1,3-cycloheptadien-6-ol (172) and the subsequent loss of one of the diastereoisomers on formation of the saturated cis-1,4-amino alcohol (194) and its unsaturated analogue (195). This also meant that in order to synthesise both the endo- and the exo- isomers of nortropan-3-ol and nortrop-6-en-3-ol derivatives, the isomer
produced would now have to be oxidised and selectively reduced, according to the methods developed by Beckett\textsuperscript{105} and Noyori et al.\textsuperscript{50} to afford the other stereoisomer (Figure 4.15).

![Figure 4.15](image)

Both nortropan-3-one and nortrop-6-en-3-one derivatives would have to be made if the route involving the use of tert-butyl diphenylsiloxo-1,3-cycloheptadiene (190) was continued and this justified an exploration of the use of 1,3-cycloheptadien-6-one (173) which should provide the bicyclic amino ketones in a more economical fashion.

4.3 DEVELOPMENT OF THE INTRAMOLECULAR CYLISATION ROUTE TO NORTROP-3-ONE/NORTROP-6-EN-3-ONE AND DERIVATIVES.

When 1,3-cycloheptadien-6-one (173) was reacted with the acyl nitroso compound (68) no reaction was found to occur even though the same conditions were used as in the formation of N-benzoyl-8-oxa-9-azabicyclo[3.2.2]non-6-ene (69)\textsuperscript{52} (Figure 4.16).
It was decided to protect the 1,3-cycloheptadien-6-one (173) using ethylene glycol, prior to the initial nitroso cycloaddition (Figure 4.17).

![Figure 4.16](image)

Figure 4.16

The 1,3-cycloheptadiene (173) was treated with ethylene glycol in the presence of a catalytic amount of p-toluene sulphonic acid monohydrate (TsOH.H₂O), to afford 1,3-cycloheptadien-6-one ethylene acetal (197) in 64% yield. Subsequently, (197) was reacted with the acyl nitroso compound (68), and the desired [4+2] cycloadduct (198) was formed in 59% yield (Figure 4.18).
Since the initial problems experienced with the nitroso cycloaddition of the free ketone (173) had been overcome the synthetic pathway was now extended to the preparation of 6-ethylene acetal-cis-4-(benzylamino)-cycloheptanol (202) and its unsaturated analogue (201), as outlined in Scheme 4.7.
Reductive cleavage of the N-O bond was achieved cleanly and efficiently using aluminium amalgam in aqueous tetrahydrofuran,⁶³ to give the unsaturated cis-1,4-amido alcohol (199) in 96% yield. Treatment of (199) with lithium aluminium hydride⁵³ afforded the unsaturated cis-1,4-amino alcohol (201) in 56% yield. Hydrogenation of (199) over palladium on charcoal,⁵² to produce the saturated cis-1,4-
amido alcohol (200) (99%), followed by reduction with lithium aluminium hydride\(^{53}\) gave (202) in 51% yield. All these reactions proceeded smoothly with no complications resulting from the presence of the acetal.

The cyclisation of (202) was attempted first in order to avoid any difficulties which might be encountered when a double bond is present. Thionyl bromide was added to a solution of (202) in deuterated chloroform, to generate an intermediate trans-1,4-bromoamine. The solvent was removed \textit{in vacuo} and replaced by acetone. Subsequently, anhydrous TMP was added to this solution and the resulting mixture was heated at 50°C. On purifying the crude reaction mixture by flash chromatography, it was found that the cyclised material was, in fact, a mixture of two products which had co-eluted. One product (203) still contained a protected ketone function but in the other product (204), the ketone function had been deprotected (Figure 4.19). The overall yield of the cyclised material was 42%.

\begin{figure}[h]
\centering
\includegraphics{figure4.19}
\caption{Figure 4.19}
\end{figure}
The ratio of (203) to (204) in the mixture was 3:2 (as estimated by proton (300MHz) n.m.r.).

Finally, this mixture was subjected to acid hydrolysis in order to obtain N-benzynortropan-3-one (204). The cleavage of the acetal moiety proved to be more difficult than first anticipated. Treatment of the mixture with an 80% aqueous solution of acetic acid followed by heating at 65°C failed to induce any deprotection and only the mixture of (203) and (204) was recovered. When the mixture was dissolved in tetrahydrofuran and a 5% aqueous solution of hydrochloric acid was added, some acetal-protected product (203) was still isolated, even after leaving the reaction for twenty-four hours at room temperature. The acetal protecting group was eventually cleaved by dissolving the mixture in tetrahydrofuran and adding a one molar aqueous solution of hydrochloric acid followed by heating at reflux overnight. This afforded the desired product (204) in quantitative yield (Figure 4.20).
The proton n.m.r. (300MHz) spectrum recorded for (204) was simple due to its high symmetry. It comprised a series of multiplets between δ1.62 and δ2.68 for the protons in the four methylene groups in the azabicyclic ring, a broad multiplet at δ3.48 for the two bridgehead protons, a singlet at δ3.74 for the benzylic methylene group and a multiplet between δ7.24 and δ7.45 for the five phenyl ring protons. The carbon-13 n.m.r. (75MHz) spectrum for (204) was also fairly simple; the carbon atoms in the azabicyclic ring gave two peaks at δ27.8 and δ48.2, the carbon atom in the benzylic methylene group produced a peak at δ55.1, the two bridgehead carbon atoms arose at δ58.5, the phenyl ring carbon atoms gave three peaks at δ127.0, δ128.3 and δ128.4, a peak at δ139.3 and the carbonyl carbon atom appeared at δ210.2. The infra-red spectrum recorded for (204) showed a strong carbonyl absorption at 1700cm⁻¹.

The debenzylation of (204) using hydrogenation⁵³ was not attempted due to the small amount of material synthesised. Subsequently, the cyclisation of the corresponding unsaturated cis-1,4-amino alcohol (201) was investigated. On treating a solution of (201) in deuterated chloroform with thionyl bromide, followed by replacement of the solvent with acetone and addition of anhydrous TMP, the desired 1,4-cyclisation product (205) was isolated in 11% yield (Figure 4.21). In this case, all the cyclised material obtained still contained a protected ketone function. Although the yield of (205) was low it was not accompanied by any of the aziridine side-product which might have been formed by 1,2-
cyclisation. The other products of the reaction were unidentifiable.

![Diagram](image)

**Figure 4.21**

The proton n.m.r (300MHz) spectrum recorded for (205) contained a series of multiplets between δ1.81 and δ2.19 for the two methylene groups in the azabicyclic ring, a broad singlet at δ3.56 assigned to the two bridgehead protons and the benzylic methylene group, two multiplets at δ3.78 and δ3.87 for the four acetal protons, a singlet at δ6.06 for the two olefinic protons and a multiplet between δ7.20 and δ7.40 for the five phenyl ring protons. The infra-red spectrum obtained for (205) showed no carbonyl absorption band.

The deprotection of the ketone function in (205) and its subsequent debenzylation were not tried due to the low yield of cyclised material isolated. It was decided not to repeat the synthesis of (205) in order to examine its deprotection and debenzylation, as from chapter three, it is known that debenzylation of unsaturated azabicycles is very difficult (see chapter 3). However, having established the viability of this route when using the acetal-protected form of 1,3-cycloheptadien-6-one (173), this pathway could now be
extended to the synthesis of the corresponding N-p-methoxybenzyl analogues which, as discussed earlier in section 3.3.1, can be partially debenzylated using α-chloroethyl chloroformate (ACECl). In this way, nortrop-6-en-3-one should ultimately be produced.

4.4 CONCLUSION.

From sections 4.2 and 4.3, it can be seen that the route developed in section 2.2 can be applied to substituted 1,3-cycloheptadienes. The difficulties experienced earlier by Kibayashi,52 concerning a nitroso cycloaddition of a substituted 1,3-cycloheptadiene with the acyl nitroso compound (68), were not encountered here.

The problems discovered in section 4.2 when using protected forms of 1,3-cycloheptadien-6-ol (172), were due mainly to unforseen complications with the loss of these hydroxyl protecting groups. However, when the acetal-protected form of 1,3-cycloheptadien-6-one (173) was used in this pathway instead (section 4.3) no such difficulties were encountered although this route was generally lower yielding than with 1,3-cycloheptadien-6-ol (172).

The yield of N-benzynortrop-6-en-3-one ethylene acetal (205) from this synthetic pathway was low but the cyclisation step has not yet been optimised. Nevertheless, even with this poor yield, this route has an advantage over Bäckvall's synthetic approach52 (section 1.5) since it has the potential of producing nortrop-6-en-3-ol derivatives. The exo- and endo- isomeric alcohols could be produced from the bicyclic amino ketones, as discussed previously, using
the approaches developed by Beckett\textsuperscript{105} and Noyori et al.\textsuperscript{50} 

It has been found that when diisobutylaluminium hydride (DIBAL-H)\textsuperscript{50} is used nortropan-3-one derivatives are reduced almost exclusively to the endo-alcohol. However, when treated with sodium in isobutanol,\textsuperscript{105} the major product of reduction is the exo-alcohol (Figure 4.22).

\begin{center}
\begin{tikzpicture}
% TikZ code for the molecular structures
\end{tikzpicture}
\end{center}

\textbf{Figure 4.22}
Chapter Five

Epoxidation of AzaBicyclic Alkenes
5.1 INTRODUCTION.

In order that the natural tropane alkaloids, like scopolamine, along with non-natural analogues may be eventually prepared from the synthetic approaches described in chapters two and four, it will be necessary to epoxidise the etheno bridge in the nortrop-6-ene derivatives (Figure 5.1).

![Figure 5.1](image)

The main obstacle to be overcome here is that, in the presence of an unprotected tertiary amine, formation of the corresponding N-oxide will compete with epoxidation of the double bond.

In 1959, Fodor reported a stereospecific synthesis of scopolamine from tropane-3α,6β-diol in which epoxidation of one of the intermediates, 3α-acetoxytrop-6-ene (206), was claimed, despite some initial difficulties. Treatment of (206) with monoperoxyphthalic acid had afforded the N-oxide (207) as the major product, whereas an excess of this peroxy acid had given a poor yield of O-acetylscolpine-N-oxide (208). Under acidic conditions no epoxidation had occurred, owing to deactivation of the ethylenic bond by the positively charged tropanium nitrogen atom. However, the required epoxidation was finally accomplished by oxidation of the trifluoroacetate salt of (206) in acetonitrile, with
a solution of trifluoroperoxyacetic acid in dichloromethane\textsuperscript{108} (Figure 5.2).

\textbf{Figure 5.2}

However, the yield of O-acetylscopine (209) obtained from this oxidation was not mentioned and a major disadvantage of this reaction is that it is slow, since it required eight days at 5°C. Fodor also reported here\textsuperscript{108} that a better yield of (209) could be achieved by epoxidation of (206) with formic acid and an 80% solution of hydrogen peroxide. Again no yield was quoted and the reaction was still sluggish as it needed five days at room temperature and an extra addition of hydrogen peroxide during the conversion.

In view of this, it was essential to explore the epoxidation of alkenes with peroxo acids in the presence of nitrogen functionalities. In order to ascertain the conditions required for epoxidation, it was decided first to
examine model compounds containing a nitrogen moiety which had been suitably protected to avoid N-oxide formation. Thus, the three compounds selected for this investigation were N-carbethoxy-1,4-dihydronapthalen-1,4-imine, N-carbethoxy-1,4-dihydroanthracen-1,4-imine and N-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene due to their ready availability. Once the conditions for epoxidation had been assessed, they were applied to N-benzyl-2-azabicyclo[2.2.1]hept-5-ene, 5,8-dimethoxy-1,4-dihydronaphthalen-1,4-imine and 9-methyl-5,8-dimethoxy-1,4-dihydronaphthalen-1,4-imine model compounds with unprotected nitrogen atoms. The peroxo acid chosen for this exploration was m-chloroperbenzoic acid (MCPBA) as it is commercially available, can be used in a wide variety of inert solvents and the resulting epoxides can be isolated easily.

5.2 MODEL STUDIES.

5.2.1 1,4-DIHYDRONAPTHALEN-1,4-IMINE AND 1,4-DIHYDROANTHRACEN-1,4-IMINE DERIVATIVES.

The preparation and investigation of the epoxidation of N-carbethoxy-1,4-dihydronapthalen-1,4-imine (214) was aided by an undergraduate research project.\textsuperscript{112} The substrate (214) was synthesised according to the method developed by Marchand et al.\textsuperscript{64} and Davies et al.\textsuperscript{113} (Scheme 5.1).
Scheme 5.1

Benzynne (212), generated in situ from anthranilic acid (210) and isoamyl nitrite (211), was added to a solution of N-carbethoxypyrrole (213) and the desired Diels-Alder adduct (214) was isolated in a 19% yield. The main difficulty encountered with this preparation was the separation of (214) from the crude mixture at the end of the reaction. In order to purify (214) successfully, a short-path distillation (falling film) was necessary.

The epoxidation of (214) with MCPBA, in the non-coordinating solvent dichloromethane, was studied subsequently (Figure 5.3). The method of epoxidation applied was that used by Dahill et al. for the formation of cis- and trans-1,2-epoxy-4-(exo-5-exo-isocamphyl) cyclohexane.
After ninety hours at room temperature the reaction was complete and the epoxide (215) had been produced in an 86% yield. Subsequently, (215) was examined by proton n.m.r. spectroscopy (300MHz) so that the stereochemistry of the product could be established.

It was found that (215) existed as a pair of rotamers, rotation occurring about the N-CO bond, since there were two overlapping quartets for the ethyl group methylene protons at δ4.17 and the singlet expected for the two bridgehead protons had been split into two signals (δ5.11 and δ5.19).

The rotation about the N-CO bond is sufficiently slow compared to the n.m.r. time scale, due to the partial double bond formation. The rotation is hindered by resonance (limiting structure (A)) in the ground state (Figure 5.4). However a strong contribution of the limiting structure (B) to the resonance helps to reduce the double bond character in the N-CO bond and hence the rotational energy barrier is lower for the urethanes than for amides.
From the proton n.m.r (300MHz) spectrum recorded for (215), it was also determined that the sole product of this reaction was the exo-epoxide of (214) (Figure 5.5).

Two doublets were observed at δ3.43 (J=3.5Hz) and δ3.46 (J=3.5Hz) for the epoxide protons. These protons are not equivalent in this compound since restricted rotation about the N-CO bond makes it unsymmetrical. The coupling constants of 3.5Hz measured for both doublets is comparable to that observed for the two oxirane protons in the pesticide dieldrin, an exo-epoxide (Figure 5.6). In the presence of a chiral lanthanide shift reagent, the coupling constant measured for the oxirane protons in this compound was 3.3Hz.
If the endo-epoxide of (214) had been produced, additional coupling of the two oxirane protons with the bridgehead protons would also have been seen.

The proton n.m.r. (300MHz) spectrum of (215) was more complex than anticipated since it was recorded below the coalescence temperature and hence hindered rotation about the N-CO bond made the compound unsymmetrical. However, it was shown using variable temperature proton n.m.r. that on warming a sample of (215), the two doublets observed at room temperature previously for the oxirane protons (at δ3.43 and δ3.46) broadened and eventually coalesced to give a singlet at δ3.20 with a coalescence temperature of 94.3°C (367.3K). Now the free energy of activation at coalescence, ΔG‡, can be calculated using the equation 5.1.

$$\Delta G^\dagger = RT_c \left[23+\ln\left(\frac{T_c}{\Delta \nu}\right)\right]$$

$$= 8.3 \times 10^{-3} T_c \left[23+2.3 \log_{10}\left(\frac{T_c}{\Delta \nu}\right)\right] \text{ KJmol}^{-1}$$

Equation 5.1

where \(T_c\) is the coalescence temperature, \(R\) is the gas constant and \(\Delta \nu\) is the frequency separation of the initially sharp lines. Consequently, from the results obtained for (215), it was possible to establish that the free energy of activation for the rotation about the N-CO bond in (215) was
Therefore, epoxidation of (214) with MCPBA had afforded only the exo-epoxide of (214) as a pair of rotamers. It was decided to investigate epoxidation in a similar system, N-carbethoxy-1,4-dihydroanthracen-1,4-imine (216) since a sample of (216) had been previously prepared by Durrant\textsuperscript{116} here at Leicester using the route outlined in Scheme 5.2.

![Scheme 5.2](image)

Treatment of (216) with MCPBA\textsuperscript{114} in deuterated chloroform afforded the desired epoxide (217) in 90\% yield after twenty-four hours at room temperature (Figure 5.7).
On examining (217) by proton n.m.r. (300MHz), it was found that it also existed as a pair of rotomers, since there were two overlapping ester methylene protons at δ4.21 and the singlet expected for the two bridgehead protons had again been split into two signals (δ5.25 and δ5.35). It was also established that the sole product of this reaction was the exo-epoxide of (216) with two doublets arising at δ3.47 (J=3.5Hz) and δ3.50 (J=3.5Hz) for the two unequivalent oxirane protons (Figure 5.8).

It had been anticipated that the major product of epoxidation for (214) and (216) would be the exo-epoxide based on reports in the literature for the related bicyclic carbon-bridged system, norbornene. Epoxidation of norbornene with MCPBA had given the exo-epoxide as the sole product in near quantitative yield (Figure 5.9).
The approach of the peroxy acid to the exo face of norbornene is aided by distortion of the olefinic C-H bonds.\textsuperscript{118} From model calculations, it has been shown that the olefinic C-H bonds are bent in the endo-direction (away from C-7 and below the C-1, C-2, C-3, C-4 plane) by 3.4\textdegree. Although these distortions are small, they are not energetically insignificant and they result in the molecule being more open to attack from the exo-face (Figure 5.10).

However, the urethane moiety on the bridging nitrogen atom in (214) and (216) may also be assisting in the approach of the peroxy acid to the exo-face providing it lies over the centre of the \(\pi\)-bond. This stereoelectronic control of epoxidation has been shown to occur with a number of neighbouring groups.

In 1958, Henbest\textsuperscript{119} discovered that oxidation of cyclohex-2-enol (218) with peroxybenzoic acid afforded only the \textit{cis}-epoxide (219) (Figure 5.11). This hydroxyl-directed epoxidation of allylic alcohols has now evolved into a reliable and highly stereoselective method for the construction of vicinal centres.
Henbest attributed the steering effect of the hydroxyl group to hydrogen bonding between itself and O(2) in the peroxy acid\textsuperscript{119} (Figure 5.12). This mechanism has become widely accepted.

Later, Whitham et al.\textsuperscript{120} suggested an alternative hydrogen bonding interaction which involved the carbonyl oxygen \textit{i.e.} O(3). Finally, Sharpless,\textsuperscript{121} after analysis of stereoelectronic effects, formulated that the allylic hydroxyl group is co-ordinated to O(1) in the approaching peroxy acid whose remaining lone pair of electrons then become favourably aligned with the \( \pi \)-system of the double bond (Figure 5.13).
This mechanism can also be used to rationalise the syn epoxidation of allylic amides\textsuperscript{122,123,124} by analogous NH bonding\textsuperscript{125} (Figure 5.14).

However, this mechanism cannot be used to account for any steering of the peroxy acid by the urethane function in (214) and (216), as these compounds cannot offer any free OH or NH groups for hydrogen bonding. This was also the case for compounds (220) and (222), the epoxidation of which was examined by Kocovsky\textsuperscript{125} (Figure 5.15). In both these compounds it was found that the (N,N-dimethylcarbamoyl)oxy group was, nevertheless, capable of controlling the epoxidation in a syn fashion.
From further experimental evidence, Kocovsky\textsuperscript{125} proposed an alternative mechanism to explain this behaviour, in which the hydrogen bonding formulated by Sharpless\textsuperscript{121} was reversed \textit{i.e.} from the peroxy acid to the urethane group of the substrate. He also determined that it was the carbonyl oxygen in the urethane group, rather than the ether oxygen, which acted as the acceptor for hydrogen bonding and it is therefore the carbonyl oxygen which is responsible for the pronounced syn steering in (220) and (222) (Figure 5.16).
This carbonyl steering of the approach of the peroxy acid can also be used to account for the syn epoxidation of the homoallylic urethane \((224)\)\(^{126}\) (Figure 5.17).

Now, this mechanism could be considered for compounds (214) and (216), whereby hydrogen bonding between the peroxy acid molecule and the carbonyl oxygen in the urethane moiety occurs, thus aiding in the attack from the exo-face (Figure 5.18).
As mentioned previously, the distortion of the olefinic C-H bonds in norbornene-type derivatives towards the endo-face encourages exo-attack. However, if the urethane group on the bridging nitrogen atom, also assists in the approach of the peroxo acid to the exo-face, then this steering effect could be of great importance in the epoxidation of nortropane derivatives where there is little norbornene-type distortion.

5.2.2 2-AZABICYCLO[2.2.2]OCT-5-ENE DERIVATIVES.

A sample of N-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (225) had been prepared by Moss here at Leicester, according to the procedure developed by Cava\(^\text{127}\) (Figure 5.19).

This sample was used in the following exploration of epoxidation which was assisted by an undergraduate research participant.\(^\text{128}\) Treatment of (225) with MCPBA\(^\text{114}\) in
dichloromethane afforded the desired epoxide (226) in 64% yield after sixty hours at room temperature (Figure 5.20).

![Figure 5.20](image)

On inspecting the proton n.m.r. (300MHz) spectrum recorded for (226), it was found that the epoxidation of (225) had resulted in the formation of both the endo- and the exo-epoxides of (225) in a ratio of 3:2. This ratio was based on the integration for the C-3 protons in the endo-product; the doublet for the axial proton (δ3.52) was well separated from the doublet for the equatorial proton (δ3.07) due to the presence of the oxirane ring (Figure 5.21). In contrast, the C-3 protons in the exo-product appeared as a multiplet at δ3.43.

![Figure 5.21](image)
The two isomers were successfully separated by flash chromatography and from the proton n.m.r (300MHz) spectra subsequently obtained for each isomer, it was established that each existed as a pair of rotomers, in accordance with earlier observations for (215) and (217) (see section 5.2.1). Thus, the singlet expected for the bridgehead proton at C-1 was split into two signals in each case (δ4.38 and δ4.48 (endo); δ4.40 and δ4.53 (exo)) and two overlapping quartets were obtained for the ethyl group methylene protons (δ4.10 (endo), δ4.14(exo)). This was due to slow rotation about the N-CO bond on the n.m.r. time scale. The two oxirane protons produced a multiplet peak at δ3.32 in both the endo- and the exo-epoxides, whilst the bridgehead proton at C-4 appeared at δ2.36 in the endo- epoxide and at δ2.37 in the exo-epoxide.

The carbon-13 n.m.r. (75MHz) spectrum recorded for each isomer was complex as a result of this hindered rotation about the N-CO bond, and hence the presence of a pair of rotamers. In the exo-epoxide, the peaks at δ28.9 and δ29.1 were assigned to the bridgehead carbon atom C-4, those at δ44.9 and δ45.1 to the C-3 carbon atom, the peaks at δ47.1 and δ47.8 to the bridgehead carbon atom C-1 and those at δ51.1, δ51.4 and δ51.5 to the two oxirane carbons. For the endo-epoxide, the corresponding peaks for the bridgehead carbon atom C-4 arose at δ28.2 and δ28.3, for the C-3 carbon atom at δ46.8 and δ46.9, for the bridgehead carbon atom C-1 at δ44.9 and δ45.3 and for the two oxirane carbon atoms at δ50.7, δ50.8, δ52.1 and δ52.3.
Therefore, it follows that in the case of compound (225) there was little discrimination between the two faces of the double bond on epoxidation, resulting in the production of almost equal amounts of both the exo- and endo-epoxides of (225). In (225), it is unlikely that the neighbouring urethane group would assist in the approach of the peroxy acid to afford the exo-isomer, as postulated earlier for (214) and (216) (see section 5.2.1) since in this compound the carbonyl oxygen is too remote from the double bond.

5.2.3 2-AZABICYCLO[2.2.1]HEPT-5-ENE DERIVATIVES.

Having determined the conditions necessary for the epoxidation of alkenes with MCPBA, they were applied to N-benzyl-2-azabicyclo[2.2.1]hept-5-ene (158a), which was synthesised as described in section 3.2. In order to prevent N-oxide formation, (158a) was converted first into its trifluoroacetate salt (227).

However, treatment of (227) with MCPBA in deuterated chloroform at room temperature resulted in failure; only starting material was recovered even after 72 hours. It was decided to repeat this reaction and heat it at 45°C. Nevertheless, after ninety hours, none of the desired epoxide was isolated (Figure 5.22).
5.2.4. 5,8-DIMETHOXY-1,4-DIHYDRONAPHALEN-1,4-IMINE DERIVATIVES.

Since the epoxidation of (225) with MCPBA, under acidic conditions resulted in failure, it was decided to investigate the epoxidation of other model compounds bearing a free nitrogen function to determine whether the initial problems experienced with (158a) could be overcome. 5,8-Dimethoxy-1,4-dihydroronaphalen-1,4-imine (228) and 9-methyl-5,8-dimethoxy-1,4-dihydroronaphalen-1,4-imine (229) were selected for this purpose, since samples of these compounds had previously been prepared by Durrant\textsuperscript{116} here at Leicester according to the methods outlined in Figure 5.23.
Therefore, solutions of (228) and (229) in deuterated chloroform were treated with trifluoroacetic acid, to convert these amines into their corresponding salts, followed by mCPBA and these two reactions were monitored periodically by proton n.m.r (90MHz). However, even after seven days at room temperature, the only compound observed in each case was unreacted starting material (Figure 5.24).
5.3 CONCLUSION.

From section 5.2 it can be concluded that epoxidation of an alkene with MCPBA can proceed smoothly without any added complications provided that the amino nitrogen is suitably protected, for example as a urethane. Compounds (214) and (216) gave stereospecifically the exo-epoxides (215) and (217) respectively. This is presumably due to the distortion of the olefinic C-H bonds as in norbornene, which creates a greater steric shielding of the endo-face. However an additional probable factor is participation of the carbonyl oxygen in the urethane group which can hydrogen-bond with the approaching peroxyacid molecule. In contrast, epoxidation of (225) was non-stereospecific giving both the endo- and exo-epoxides. Problems arose on epoxidation of alkenes with MCPBA in the presence of a free nitrogen function. Even after protonation to avoid N-oxide
formation, (159a), (228) and (229) failed to yield the desired epoxides. However, as discussed in section 5.1, Fodor\textsuperscript{108} reported that epoxidation could be achieved in systems of this kind and therefore further exploration of epoxidation conditions is justified in the parent nortrop-6-ene derivatives. A lengthy study at this stage though on model compounds was not considered worthwhile.

Nevertheless, providing that the nitrogen protecting group can be removed from the nortrop-6-ene derivatives (synthesised by approaches described in chapters two and four) to give the parent molecule nortrop-6-ene in reasonable yields, the nitrogen could be reprotected as a urethane to enable epoxidation of the unsaturated etheno bridge with MCPBA. Hence compounds similar in structure to scopolamine could ultimately be prepared (Figure 5.25).

![Diagram](image)

Figure 5.25

In this way, it may be possible, by increasing the size of the urethane substituent, to hinder approach from the exo-face and thus produce the non-natural endo-epoxides.

Similarly, it is feasible that the natural exo-epoxides could be obtained from the urethane-protected nortrop-6-ene via formation of the corresponding iodo lactone (Figure 5.26).
It will be difficult to remove the urethane function at the end of the synthesis without affecting the epoxide group. Still, having made the epoxide, a number of other reactions could be studied including reduction with lithium aluminium hydride to give 6-hydroxytropane, which is similar in structure to 6-hydroxyhyoscyamine (one of the compounds isolated in the biosynthetic pathway of scopolamine (see section 1.3)), and treatment with base to afford 6,7-dihydroxynortropane (Figure 5.27).

Other methods for the epoxidation of nortrop-6-ene derivatives could also be considered. In 1982, Iwasaki et al.\textsuperscript{129} demonstrated that alkenes could be epoxidised using a variety of O-alkylperoxycarbonic acids, generated \textit{in situ} in
a biphasic solvent system from alkyloxycarbonyl imidazoles and 35% aqueous hydrogen peroxide (Figure 5.28).

![Figure 5.28]

This method may be appropriate for the epoxidation of protonated amines so eliminating the need to protect the nitrogen atom with a urethane group prior to oxidation.

Epoxides can be prepared as well from chlorohydrins\textsuperscript{130} on treatment with base (Figure 5.29). Chlorohydrins may be formed from reaction of the alkene with hypochlorous acid,\textsuperscript{131} generated \textit{in situ} from water and gaseous chlorine, or from N-chlorosuccinimide in aqueous acid.\textsuperscript{132}

![Figure 5.29]

This approach could therefore be applied to the urethane-protected nortrop-6-ene in the hope that on hydrolysis of the chlorohydrin to give the epoxide, the urethane moiety is also cleaved (Figure 5.30).
Thus, there are still many directions worthy of investigation concerning the epoxidation of nortrop-6-ene derivatives, providing they can be obtained in reasonable yields.
Chapter Six

Experimental
EXPERIMENTAL.

INSTRUMENTATION.

Proton n.m.r. spectra were recorded on Perkin-Elmer EM390 and Jeol JNM-PS100 spectrometers. High field proton n.m.r. (300MHz) spectra were recorded on a Bruker AM300 spectrometer. Chemical shifts were recorded in ppm (δ) downfield from the internal reference tetramethylsilane (TMS). Signal characteristics are described using the following standard abbreviations: s-singlet, d-doublet, t-triplet, q-quartet, quin-quintet, m-multiplet, exch-exchangeable, br-broad and combinations of these.

Infra-red spectra were recorded on a Perkin-Elmer 298 spectrometer using 0.1mm sodium chloride solution cells or sodium chloride plates. Band positions, given in wavenumbers (cm⁻¹) are described by the standard abbreviations: s-strong, m-medium and w-weak.

Routine mass spectra were obtained using a VG Micromass 16B spectrometer. Accurate mass spectra were made at the SERC Mass Spectrometry Centre, University College of Swansea.

Elemental analyses were carried out by Butterworth Laboratories Ltd, Teddington, Middlesex.

Melting points were determined using a Kofler microheating stage and are uncorrected.

TECHNICAL.

Diethyl ether was dried over sodium wire and distilled from lithium aluminium hydride. Dichloromethane and dimethylsulphoxide were distilled from calcium hydride.
Petroleum ether and ethyl acetate were distilled prior to use. Methanol and ethanol were dried and purified with magnesium and iodine as described by Vogel.\textsuperscript{133} Tetrahydrofuran and toluene were distilled from sodium metal in the presence of benzophenone. Triethylamine and pyridine were distilled from potassium hydroxide. All other solvents and reagents were dried and purified as described by Perrin et al.\textsuperscript{134}

Flash chromatography was carried out according to the method of Still et al.\textsuperscript{135} using silica gel manufactured by Merck and Co., Kieselgel 60, 230-400 mesh (ASTM). Thin layer chromatography was conducted on pre-coated aluminium sheets (60-254) with a 0.2mm layer thickness of silica gel, manufactured by Merck and Co.
PREPARATION OF TETRAMETHYLAMMONIUM PERIODATE.  
A solution of periodic acid (12.5g, 0.055 mmol) in water (32.35ml) was added in portions to a 20% solution of tetramethylammonium hydroxide in methanol (25.00g, 0.055 mmol), whilst stirring at 0°C. The precipitated white solid was separated and recrystallised from t-butanol (11.55g, 79%).

PREPARATION OF N-BENZOYL-8-OXA-9-AZABICYCLO[3.2.2]NON-6-ENE (69).  
1,3-cycloheptadiene (2.18g, 20.13 mmol) was added to a suspension of tetramethylammonium periodate (7.45g, 28.11 mmol) in chloroform (280ml). To this mixture a solution of benzohydroxamic acid (3.93g, 28.68 mmol) in dimethyl formamide (20ml) and chloroform (60ml), was added dropwise with stirring at room temperature, over 20 minutes. The resulting mixture was left to stir for a further 3 hours. Subsequently, the chloroform was distilled at reduced pressure. The residue was dissolved in diethyl ether (200ml) and washed with water (4 X 60ml). The organic layer was separated, dried (MgSO₄), and the solvent was removed in vacuo to yield a crude orange gum. This crude material was purified by flash chromatography (1:1 petroleum ether (40-60°C) : diethyl ether) to afford (69) as a pale yellow solid (3.22g, 70%).

Rᶠ 0.3 (1:1 petroleum ether (40-60°C) : diethyl ether).
δ<sub>H</sub> (90MHz, CDCl<sub>3</sub>): 1.45-1.95 (series of m, 6H), 4.70 (brs, 1H), 5.40 (brs, 1H), 6.30 (brt, J=4.5Hz, 2H), 7.30-7.80 (m, 5H).

PREPARATION OF CIS-4-(BENZOYLAMINO)-2-CYCLOHEPTENOL (70).<sup>52, 53</sup>

A solution of (69) (3.22g, 14.05 mmol) in aqueous tetrahydrofuran (THF:H<sub>2</sub>O, 10:1) (81ml) was cooled to 0°C with stirring under nitrogen. Aluminium amalgam prepared by sequential exposure (10-20 s) of small strips of aluminium foil (3.08g, 0.11 mol) to 1M (aq) potassium hydroxide solution, distilled water, mercuric chloride solution (0.5%), distilled water and tetrahydrofuran, was then added to the solution of Diels-Alder adduct. Stirring was continued at 0°C for a further 16h.

The reaction mixture was diluted with tetrahydrofuran (230ml), stirred vigorously for 1.5h, and then filtered through a pad of celite. The filtrate was diluted with toluene and concentrated at reduced pressure to yield (70) as a white crystalline solid (2.99g, 92%).

δ<sub>H</sub> (90MHz, CD<sub>3</sub>OD): 1.45-2.10 (series of m, 6H), 4.37 (brd, J=10.5Hz, 1H), 4.63 (brd, J=10.5Hz, 1H), 5.66 (brd, J=12.0Hz, 1H), 5.80 (brd, J=12.0Hz, 1H), 7.40-7.55(m, 3H), 7.75-7.85(m, 2H).

PREPARATION OF CIS-4-(BENZOYLAMINO)CYCLOHEPTANOL (71).<sup>52</sup>

A solution of (70) (2.18g, 9.45 mmol) in methanol (60ml) was hydrogenated in the presence of 5% palladium on
charcoal. After 16h, the catalyst was filtered off and the solvent removed in vacuo to give (71) as a white crystalline solid (2.18g, 99%).

δH (90MHz, CD3OD): 1.35-2.05 (series of m, 10H), 3.90 (brm, 1H), 4.10 (brm, 1H), 7.35-7.55 (m, 3H), 7.75-7.85 (m, 2H).

PREPARATION OF CIS-4-(BENZYLAMINO)CYCLOHEPTANOL (99) 53

A suspension of (71) (1.07g, 4.59 mmol) in dry diethyl ether (30ml) was added dropwise to a stirred slurry of lithium aluminium hydride (0.76g, 19.94 mmol) in dry diethyl ether (70ml). After refluxing for 10h, decomposition of the excess hydride was effected by addition of a water-saturated solution of diethyl ether. The resulting solution was dried (MgSO4) and the solvent was removed in vacuo. The residue obtained was purified by dissolving it in diethyl ether (30ml) and washing with 2M (aq) hydrochloric acid (2 X 30ml). The combined aqueous layers were subsequently washed with fresh diethyl ether (3 X 30ml) before being basified with 2M (aq) sodium hydroxide. Finally, the aqueous layer was extracted with dichloromethane (6 X 30ml) and the combined organic layers were dried (MgSO4). The solvent was removed in vacuo to yield (99) as a colourless, viscous oil (0.76g, 76%).

δH (90MHz, CDCl3): 1.50-2.00 (series of m, 10H), 2.80 (brs, exch., 1H), 2.98 (m, 1H), 3.74 (brs, 2H), 4.00 (m, 1H), 7.24 (brs, 5H).
PREPARATION OF $\text{CIS-4-}(\text{BENZYLAMINO})-\text{2-CYCLOHEPTENOL (102)}$.\textsuperscript{53}

A solution of (70) (0.08g, 3.46 mmol) in dry tetrahydrofuran (60ml) was added dropwise to a stirred slurry of lithium aluminium hydride (0.53g, 14 mmol) in dry tetrahydrofuran (40ml). After refluxing for 10h, decomposition of the excess hydride was effected by addition of a water-saturated solution of diethyl ether. The resulting solution was dried (MgSO$_4$) and the solvent was removed in vacuo. The product was purified by recrystallisation from petroleum ether (80-100°C), to afford (103) as colourless needles (0.57g, 78%).

$\delta_H$ (90MHz, CDCl$_3$): 1.50-1.88 (series of m, 6H), 3.02 (brs, exch., 1H), 3.24 (brm, 1H), 3.68 (brs, 2H), 4.12 (brm, 1H), 5.84 (dd, $J=12.0$, 6.0Hz, 1H), 6.14 (dd, $J=12.0$, 6.0Hz, 1H), 7.22 (brs, 5H).

CYCISATION OF $\text{CIS-4-}(\text{BENZYLAMINO})\text{CYCLOHEPTANOL (99)}$ TO GIVE $\text{N-BENZYL NORTROPANE (101)}$.\textsuperscript{53}

In the two cyclisation procedures described below, the desired product (101) was isolated by flash chromatography (80:19:1, petroleum ether (40-60°C):diethyl ether:triethylamine).

$R_f$ 0.39 (80:19:1, petroleum ether (40-60°C):diethyl ether:triethylamine).
(i) Thionyl chloride (20.0\mu l, 0.27 mmol) was added dropwise to a solution of (99) (0.055g, 0.25 mmol) in dry deuterated chloroform (1ml) at 0°C. The reaction was allowed to warm to room temperature and it was monitored periodically by 90MHz proton n.m.r. After 0.5h, the proton n.m.r. spectrum recorded contained new signals, which were assigned to the formation of the initial product of the reaction, the alkyl chlorosulphite derivative.

\[ \delta_H \ (90\text{MHz, CDCl}_3): \ 1.18-2.05 \ (\text{series of m, 10H}), \ 3.15 \ (\text{brm, 2H}), \ 3.52 \ (s, 2H), \ 7.20-7.40 \ (m, 5H). \]

After 22h, the proton n.m.r. spectrum showed that the alkyl chlorosulphite derivative had completely decomposed into the hydrochloride salt of the trans-1,4-chloroamine (100).

\[ \delta_H \ (90\text{MHz, CDCl}_3): \ 1.70-2.40 \ (\text{brm, 10H}), \ 2.98 \ (\text{brm, 1H}), \ 4.00 \ (\text{brs, 2H}), \ 5.35 \ (\text{brm, 1H}), \ 7.35 \ (\text{brm, 3H}), \ 7.58 \ (\text{brm, 2H}), \ 9.75 \ (\text{brs, 2H, NH}_2^+). \]

Therefore, after cooling to 0°C, anhydrous pyridine (88.5\mu l) was added and the solution was allowed to warm to room temperature over 1h. The reaction mixture was subsequently poured into 2M (aq) sodium hydroxide solution.
(2ml) and the aqueous layer was extracted with dichloromethane (3 X 2ml). The combined organic layers were dried (MgSO₄) and the solvent was removed in vacuo. Purification afforded (101) as a colourless oil (0.019g, 38%).

(ii) Thionyl chloride (14.0μl, 0.19 mmol) was added dropwise to a solution of (99) (0.0386g, 0.18 mmol) in dry deuterated chloroform (1ml) at 0°C. The reaction mixture was allowed to warm to room temperature and it was monitored periodically by 90MHz proton n.m.r. Following the formation of the hydrochloride salt of the trans-1,4-chloroamine (100), 1,5,7-triazabicyclo[4.4.0]dec-5-ene on polystyrene cross-linked with 2% DVB (TABD) (0.15g) was added and the suspension was rocked for 6h. Subsequently, the polymer-supported base was removed by filtration under nitrogen, and the filtrate was concentrated in vacuo. Purification of the crude residue gave (101) (0.015g, 41%).

**CYCLISATION OF CIS-4-(BENZYLAMINO)-2-CYCLOHEPTENOL (102) TO GIVE N-BENZYNORTROP-6-ENE (104).**

In the three cyclisation procedures described below, the crude mixtures obtained were purified by flash chromatography (89:10:1, petroleum ether (40-60°C):diethyl ether:triethylamine). The first fraction isolated afforded the crystalline side product (105).

Rf 0.23 (89:10:1, petroleum ether (40-60°C):diethyl ether:triethylamine).
\[ \delta_H \ (90 \text{MHz, CDCl}_3): \ 1.50-2.15 \text{ (series of m, 8H), 3.32, 3.74 (AB quartet, } J=14.0\text{Hz, 2H), 5.75 (m, 2H), 7.20-7.38 (m, 5H).} \]

Further elution gave (104)

\[ R_f \ 0.125 \ (89:10:1, \text{petroleum ether (40-60°C):diethyl ether:triethylamine}). \]

\[ \delta_H \ (90 \text{MHz, CDCl}_3): \ 1.06-1.72 \text{ (series of m, 6H), 3.45 (brs, 2H), 3.50 (s, 2H), 5.91 (s, 2H), 7.20-7.38 (m, 5H).} \]

(i) Thionyl chloride (10.78\mu l, 0.15 mmol) was added dropwise to a solution of (102) (0.03g, 0.14 mmol) and anhydrous lithium chloride (0.03g), in dry deuterated chloroform (1ml) at 0°C. The reaction mixture was sonicated for 3h and it was monitored periodically by 90MHz proton n.m.r. From the proton n.m.r spectrum after 3h, it was seen that the hydrochloride salt of the trans-1,4-chloroamine (103) was the only product present. Thus, the heterogeneous, polymer-supported base, TABD, (0.1g) was added and the suspension was rocked for 12h. Subsequently, the polymer-supported base was removed by filtration under nitrogen, and the filtrate was basified with gaseous ammonia. The white precipitate formed was filtered off and the solvent was removed from the filtrate in vacuo. Purification gave rise to (104) (0.009g, 33%) and (105) (0.005g, 18%) as colourless oils.
(ii) Thionyl bromide (21.5μl, 0.28 mmol) was added dropwise to a solution of (102) (0.055g, 0.25 mmol) in dry deuterated chloroform (1ml) at 0°C. The reaction mixture was allowed to warm to room temperature and it was monitored periodically by 90MHz proton n.m.r. After 20min., the proton n.m.r. spectrum recorded contained new signals, which were assigned to the formation of the alkyl bromosulphite derivative.

δH (90MHz, CDCl3): 1.68-2.55 (brm, 6H), 4.14 (brm, 3H), 5.30 (brm, 1H), 6.12 (brm, 2H), 7.38 (brs, 3H), 7.58 (brs, 2H), 9.25 (brs, 2H, NE2+)

After 4h, the proton n.m.r. spectrum showed that the alkyl bromosulphite had been converted entirely into the hydrobromide salt of the trans-1,4-bromoamine (108).

δH (90MHz, CDCl3): 1.80-2.60 (brm, 6H), 4.18 (brm, 3H), 4.85 (brm, 1H), 6.18 (brs, 2H), 7.48 (brs, 3H), 7.70 (brs, 2H), 9.45 (brs, 2H, NH2+)

Therefore, after cooling to 0°C, anhydrous 2,2,6,6-tetramethylpiperidine (TMP) (140.0μl) was added and the solution was allowed to warm to room temperature. Subsequently, the reaction mixture was heated at 45°C for 19h. The solvent was removed in vacuo and the residue was triturated with diethyl ether. The combined ethereal extracts were basified with gaseous ammonia and the white precipitate was filtered off. Solvent evaporation and
purification of the crude material, afforded (104) (0.016g, 31%).

(iii) Thionyl bromide (97.0µl, 1.25 mmol) was added dropwise to a stirred solution of (102) (0.25g, 1.15 mmol) in dry deuterated chloroform (10ml) at 0°C. The reaction mixture was allowed to warm to room temperature and stirring was continued for a further 5h. Subsequently, the solvent was removed in vacuo and replaced with dry acetone (10ml). After cooling to 0°C, anhydrous TMP (650.0µl) was added and the solution was left to warm to room temperature, whereupon it was heated to 50°C for 19h.

The mixture was then filtered, and the filtrate was concentrated under reduced pressure. The residue was triturated with diethyl ether, and the combined ethereal extracts were basified with gaseous ammonia. The white solid was filtered off and the solvent was removed in vacuo. Purification led to the isolation of (104) (0.133g, 58%) and (105) (0.054g, 24%).

**PREPARATION OF BENZYL N-HYDROXYCARBAMATE.**

Benzyl chloroformate (34.0g, 0.2 mol) was added dropwise to a stirred solution of hydroxylamine hydrochloride (15.5g, 0.22 mol) and sodium hydroxide (18.0g, 0.45 mol) in water (250ml) at 0°C. The reaction mixture was allowed to warm to room temperature and stirring was continued for a further 4.5h. Subsequently, the pH was adjusted to 2 using 6M (aq) hydrochloric acid. The yellow oil liberated was extracted from the aqueous solution with diethyl ether (3 X 100ml).
The combined organic layers were washed with water (50ml) and dried (Na₂SO₄). The solvent was removed in vacuo, and the viscous residue obtained was triturated with petroleum ether (40-60°C) until crystalline and recrystallised from 1:1 benzene-petroleum ether (40-60°C) to yield colourless plates (22.58g, 68%), m.p. 69-70°C (lit m.p. 71°C).

**PREPARATION OF N-(BENZOYLOXYCARBONYL)-8-OXA-9- AZABICYCLO[3.2.2]NON-6-ENE (111).**

To a solution of 1,3-cycloheptadiene (2.0g, 21.24 mmol) and benzyl-N-hydroxycarbamate (3.68g, 22.72 mmol) in dry dichloromethane (40ml), was added a suspension of tetramethy lammonium periodate (6.10g, 23.02 mmol) in dry dichloromethane (14ml) over 30min. at 0°C. After stirring at room temperature for 2.5h, the reaction mixture was washed with aqueous sodium metabisulphite (15%, 3 X 20ml), saturated aqueous sodium hydrogen carbonate (2 X 20ml) and brine (20ml) and dried (MgSO₄). The solvent was removed in vacuo and the resulting orange gum was purified by flash chromatography (2:3 diethyl ether:petroleum ether (40-60°C)) to yield (111) as a pale yellow crystalline solid (4.76g, 87%).

**νmax (CH₂Cl₂):** 3040w, 2940m, 1690s, 1550w, 1500w, 1420s, 1355m, 1260s cm⁻¹.

**δH (90MHz, CDCl₃):** 1.22-2.00 (series of m, 6H), 4.80 (brm, 2H), 5.16 (s, 2H), 6.20 (m, 2H), 7.30 (s, 5H).
PREPARATION OF 8-OXA-9-AZABICYCLO[3.2.2]NON-6-ENE (112).\textsuperscript{55}

A solution of hydrogen bromide in glacial acetic acid (45\%, 10.4ml) was added dropwise to (111) (1.73g, 6.70 mmol) at 0°C. The reaction mixture was allowed to warm to room temperature and stirring was continued for a further 2h before it was poured into ice-water (35ml). The aqueous solution was washed with dichloromethane (23.5ml), cooled, and then carefully basified with 2M (aq) sodium hydroxide. The product was extracted into dichloromethane (6 X 25ml) and dried (MgSO\textsubscript{4}). Removal of the solvent in vacuo afforded (112) as a colourless oil (0.75g, 90\%).

\[ \text{V}_{\text{max}} (\text{CH}_2\text{Cl}_2) : 3380w, 3055s, 2985m, 2940w, 1500w, 1420m, 1260s \text{ cm}^{-1}. \]

\[ \delta_{\text{H}} (90MHz, \text{CDCl}_3) : 1.05-1.95 \text{ (series of m, 6H)}, 3.62 \text{ (m, 1H)}, 4.54 \text{ (m, 1H)}, 4.90 \text{ (brs, exch., 1H)}, 6.08 \text{ (brdd, J=9.0, 6.5Hz, 1H)}, 6.46 \text{ (brdd, J=9.0, 6.5Hz, 1H)}. \]

PREPARATION OF CIS-4-AMINO-2-CYCLOHEPTENOL (113).\textsuperscript{55}

Zinc powder (18.12g, 0.28 mol) was added to a solution of (112) (2.26g, 18.08 mmol) in glacial acetic acid (55ml) at 0°C. The reaction mixture was heated at 50-60°C for 4h and then filtered. The residue was washed with glacial acetic acid (70ml) and the filtrate evaporated in vacuo. The residue was cooled, basified with concentrated ammonia solution and the product was extracted into dichloromethane (11 X 40ml). Since this product was found to be soluble in the aqueous medium, a continuous extraction of the aqueous
layer was subsequently performed for 24h, so as to optimise the yield of (113). The combined organic layers were dried \((Na_2SO_4)\) and the solvent was removed in vacuo to give (113) as a pale orange waxy solid (1.43g, 62%).

\[ \delta_H \ (90MHz, CDCl_3): \ 1.50-2.20 \ (series \ of \ m, \ 6H), \ 2.70 \ (brs, \ exch., \ 3H), \ 3.45 \ (m, \ 1H), \ 4.20 \ (m, \ 1H), \ 5.42-5.90 \ (m, \ 2H). \]

**PREPARATION OF CIS-4-AMINOCYCLOHEPTANOL (114).**52

A solution of (113) (0.38g, 3.02 mmol) in methanol (20ml) was hydrogenated in the presence of 5% palladium on charcoal. After 16h, the catalyst was removed by filtration and the solvent was removed in vacuo to afford (114) as a colourless oil (0.39g, 99%).

\[ \nu_{max} \ (CH_2Cl_2): \ 3605w, \ 3200w, \ 2930s, \ 2860m, \ 1580w, \ 1450w \ cm^{-1}. \]

\[ \delta_H \ (300MHz, CD_3OD): \ 1.25-1.99 \ (series \ of \ m, \ 10H), \ 2.88 \ (m, \ 1H), \ 3.78 \ (m, \ 1H). \]

\[ \delta_C \ (75MHz, CD_3OD): \ 21.4(t), \ 31.5(t), \ 33.0(t), \ 38.2(t), \ 38.6(t), \ 53.0(d), \ 72.0(d). \]

**CYCLISATION OF CIS-4-AMINOCYCLOHEPTANOL (114) TO GIVE NORTROPANE (75).**53

Thionyl chloride (21.3\(\mu\)l, 0.29 mmol) was added dropwise to a solution of (114) (0.035g, 0.27 mmol) in dry deuterated chloroform (1ml) at 0°C. The reaction mixture was allowed
to warm to room temperature and its progress was monitored periodically by 90MHz proton n.m.r. After 0.5h, the proton n.m.r. spectrum showed the presence of the alkyl chlorosulphite derivative.

$$\delta_H \text{ (90MHz, CDCl}_3\text{)}: 1.65-2.40 \text{ (brm, 10H), 3.38 (brm, 1H), }$$
$$5.45 \text{ (brm, 1H), 8.22 (brs, 3H, NH}_3^{+})$$

After 20h, the proton n.m.r. spectrum confirmed that the alkyl chlorosulphite derivative had completely decomposed to the hydrochloride salt of the trans-1,4-chloroamine.

$$\delta_H \text{ (90MHz, CDCl}_3\text{)}: 1.58-2.52 \text{ (brm, 10H), 3.32 (brm, 1H), }$$
$$4.15 \text{ (brm, 1H), 8.13 (brs, 3H, NH}_3^{+})$$

Therefore, the heterogeneous polymer-supported base, TABD (0.25g), was added to the reaction mixture and the suspension was rocked for 6h. Subsequently, the polymer-supported base was removed by filtration under nitrogen and proton n.m.r. spectrum of the filtrate showed that (75) had been formed (0.008, 26%).

$$\delta_H \text{ (300MHz, CDCl}_3\text{)}: 1.12-1.90 \text{ (series of m, 10H), 3.00 (brs, exch., 1H), 3.88 (brs, 2H).}$$

This product was not purified any further.
CYCLISATION OF CIS-4-AMINO-2-CYCLOHEPTENOL (113) TO GIVE NORTROP-6-ENE (109).

Thionyl chloride (19.6μl, 0.27 mmol) was added dropwise to a solution of (113) (0.031g, 0.25 mmol) and anhydrous lithium chloride (0.0487g) in dry deuterated chloroform (1ml) at 0°C. The reaction mixture was sonicated for 25h and it was monitored by 90MHz proton n.m.r. After 25h, it was assumed that the hydrochloride salt of the trans-1,4-chloroamine had been formed. Thus, the heterogeneous polymer-supported base, TABD (0.2g), was added and the suspension was rocked for 4h. Subsequently, the polymer-supported base was removed by filtration under nitrogen, and the filtrate was basified with gaseous ammonia. After removal of the white precipitate formed, by filtration, the solution was studied by 300MHz proton n.m.r. It was determined that the desired product (109) had been formed (0.0006g, 2.3%).

δH (300MHz, CDCl₃): 1.42-2.17 (series of m, 6H), 4.28 (brs, 2H), 6.10 (s, 2H).

This product was not purified.

PREPARATION OF p-METHOXYBENZOHYDROXAMIC ACID

A) POTASSIUM p-METHOXYBENZOHYDROXAMATE:

Separate solutions of hydroxylamine hydrochloride (35g, 0.5 mol) in methanol (180ml), and potassium hydroxide (42g, 0.75 mol) in methanol (105ml), were prepared at the boiling
point of the solvent. Both were cooled to 30-40°C, and the solution containing the alkali was added to the hydroxylamine solution whilst stirring. Any excessive rise of temperature incurred during the addition was prevented by occasional cooling in an ice bath. After all the alkali had been added, the mixture was allowed to stand in an ice bath for 5 min. to ensure complete precipitation of potassium chloride. Methyl-p-methoxybenzoate (41.13g, 0.25 mol) was subsequently added with vigorous stirring, so as to ensure thorough mixing. The suspension was then filtered immediately and the residue was washed with methanol, before allowing the filtrate to stand at room temperature. After 24 h the crystals formed were filtered, washed with absolute ethanol and left to dry in the air (29.64g, 58%).

B) p-METHOXYBENZOHYDOXAMIC ACID:

A stirred mixture of the potassium salt (29.64g, 0.15 mol) in 1.25M (aq) acetic acid (116ml) was heated until a clear yellow solution was obtained. The solution was allowed to cool to room temperature and finally chilled in an ice bath. p-Methoxybenzohydroxamic acid separated as crystals, which were filtered and dried (18.27g, 91%), m.p. 156-158°C.

PREPARATION OF N-(p-METHOXYBENZOYL)-8-OXA-9- AZABICYCLO [3.2.2]NON-6-ENE (116).

1,3-Cycloheptadiene (2.0g, 21.24 mmol) was added to a suspension of tetramethylammonium periodate (7.84g, 29.58 mmol) in chloroform (140ml). A solution of p-methoxybenzohydroxamic acid (6.2g, 30.24 mmol) in
dimethylformamide (20ml) and chloroform (60ml) was added dropwise to this mixture, with stirring at room temperature, over 20min. The resulting mixture was left to stir for a further 22h.

Subsequently, the chloroform was removed in vacuo. The residue was dissolved in diethyl ether (400ml) and washed with water (4 X 100ml). The organic layer was separated, dried (MgSO₄), and the solvent was removed in vacuo to yield a crude orange gum. This material was purified by flash chromatography (9:1 diethyl ether:petroleum ether (40-60°C)) to afford (116) as a pale pink waxy solid (5.49g, 100%). An analytical sample was prepared by recrystallisation from petroleum ether (80-100°C), m.p. 62-64°C.

$R_f$ 0.36 (9:1 diethyl ether:petroleum ether (40-60°C)).

$C_{15}H_{17}NO_3$ Requires C 69.48% H 6.61% N 5.40%

Found C 69.26% H 6.42% N 5.25%

$\nu_{\text{max}}$ (CH₂Cl₂): 3020m, 2940s, 2870w, 2840m, 1635s, 1600s, 1570s, 1505s, 1430s, 1375s, 1300s, 1240s, 1215s cm⁻¹.

$\delta_H$ (300MHz, CDCl₃): 1.35-1.90 (series of m, 6H), 3.80 (s, 3H), 4.74 (brs, 1H), 5.40 (brs, 1H), 6.28 (brt, $J=3.7$Hz, 2H), 6.87 (m, 2H), 7.73 (m, 2H).

$\delta_C$ (75MHz, CDCl₃): 18.4(t), 28.4(t), 30.0(t), 55.0(q), 76.1(d), 112.8(d), 126.5(s), 127.5(d), 129.0(d), 130.5(d), 161.0(s).
PREPARATION OF CIS-4-(p-METHOXYBENZOYLAMINO)-2-CYCLOHEPTENOL (117).

A solution of (116) (5.96g, 0.02 mol) in aqueous tetrahydrofuran (THF:H$_2$O, 10:1) (141ml) was cooled to 0°C with stirring under nitrogen. Aluminium amalgam prepared by sequential exposure (10-20s) of small strips of aluminium foil (5.38g, 0.20 mol) to 1M (aq) potassium hydroxide solution, distilled water, aqueous mercuric chloride solution (0.5%), distilled water and tetrahydrofuran, was then added to the solution of Diels-Alder adduct. Stirring was continued at 0°C for 2 days. Subsequently, some fresh aluminium amalgam (aluminium foil (1.8g, 0.07 mol)) was added to the reaction mixture and stirring was continued at 0°C for a further 3 days.

The reaction mixture was diluted with tetrahydrofuran (411ml), stirred vigorously for 1.5h, and then filtered through a pad of celite. The filtrate was diluted with toluene and concentrated in vacuo to give a yellow-white solid. Trituration with diethyl ether, afforded an insoluble white crystalline material, which was found to be (117) (3.92g, 65%). An analytical sample was prepared by recrystallisation from toluene, m.p. 177-178°C.

C$_{15}$H$_{19}$NO$_3$ Requires C 68.94% H 7.33% N 5.36%

Found C 68.74% H 7.32% N 5.28%
$V_{\text{max}}$ (CH$_2$Cl$_2$): 3350w, 3310w, 2915s, 2460s, 2400w, 1620s, 1570m, 1450s, 1435m, 1375m cm$^{-1}$.

$\delta_H$ (300MHz, CD$_3$OD): 1.50-2.07 (series of m, 6H), 3.83 (s, 3H), 4.37 (brd, $J=10.2$Hz, 1H), 4.61 (brd, $J=8.6$Hz, 1H), 5.64 (brdt, $J=12.0$, 3.0Hz, 1H), 5.78 (brdt, $J=12.0$, 2.6Hz, 1H), 6.96 (dt, $J=8.9$, 2.5Hz, 2H), 7.79 (dt, $J=8.9$, 2.5Hz, 2H).

$\delta_C$ (75MHz, CD$_3$OD): 26.4(t), 34.9(t), 37.0(t), 52.3(d), 55.9(q), 72.5(d), 114.6(d), 127.8(s), 130.1(d), 133.7(d), 138.8(d), 163.8(s), 168.7(s).

m/z(%): 261(m$^+$) (1), 243(13), 152(26), 135(100), 107(8), 92(10), 77(13), 32(73).

**PREPARATION OF CIS-4-(p-METHOXYBENZOYLAMINO)CYCLOHEPTANOL (118).**

A solution of (117) (1.0g, 3.83 mmol) in methanol (40ml) was hydrogenated in the presence of 5% palladium on charcoal. After 16h, the catalyst was filtered off and the solvent was removed *in vacuo* to give (118) as a white crystalline solid (1.01g, 100%). An analytical sample was prepared by recrystallisation from toluene, m.p. 98-99°C.

C$_{15}$H$_{21}$NO$_3$ Requires C 68.41% H 8.04% N 5.32%

Found C 68.37% H 7.94% N 5.13%
$v_{\text{max}}$ (CH$_2$Cl$_2$): 3330w, 2940s, 2850s, 1620m, 1600m, 1570w, 1525m, 1500m, 1460s, 1375m, 1250m cm$^{-1}$.

$\delta_H$ (300MHz, CD$_3$OD): 1.25-2.17 (series of m, 1OH), 3.80 (s, 3H), 3.86 (m, 1H), 4.03 (m, 1H), 6.93 (dt, J=6.6, 2.1Hz, 2H), 7.77 (dt, J=6.6, 2.2Hz, 2H).

$\delta_C$ (75MHz, CD$_3$OD): 21.8(t), 29.6(t), 33.8(t), 36.4(t), 38.4(t), 52.1(d), 56.2(q), 72.2(d), 114.9(d), 128.3(s), 130.4(d), 163.9(s), 168.9(s).

m/z(%): 263(m$^+$) (13), 152(16), 135(100), 107(16), 92(23), 77(31), 64(13).

C$_{15}$H$_{22}$NO$_3$ [mH$^+$] Requires 264.1599
Found 264.1600

**PREPARATION OF CIS-4-(p-METHOXYBENZYLAMINO)-2-CYCLOHEPTENOL (119).**

A solution of (117) (0.71g, 2.27 mmol) in dry tetrahydrofuran (23ml) was added dropwise to a stirred slurry of lithium aluminium hydride (0.42g, 11.06 mmol) in dry tetrahydrofuran (49ml). After heating at reflux for 10h, decomposition of excess hydride was effected by addition of a water-saturated solution of diethyl ether. The resulting solution was dried (MgSO$_4$) and the solvent was removed in vacuo, to yield a yellow, glassy solid. Subsequent purification by flash chromatography (95:4:1, diethyl ether:methanol:triethylamine) afforded (119) as a
white crystalline solid (0.57g, 85%). An analytical sample was prepared by recrystallisation from toluene, m.p. 39-40°C.

$R_f$ 0.46 (95:4:1, diethyl ether:methanol:triethylamine).

\[ \text{C}_{15}\text{H}_{21}\text{NO}_2 \] Requires C 72.84% H 8.56% N 5.66%
Found C 72.69% H 8.77% N 5.72%

$\nu_{\text{max}}$ (CH$_2$Cl$_2$): 3595w, 3110w, 3040m, 2980m, 2920m, 1605w, 1510m, 1420m, 1250s cm$^{-1}$.

$\delta_H$ (300MHz, CDCl$_3$): 1.55-1.84 (series of m, 5H), 2.17-2.32 (m, 1H), 3.27 (td, J=6.4, 1.8Hz, 1H), 3.63, 3.73 (AB quartet, J=12.6Hz, 2H), 3.77 (s, 3H), 4.19 (td, J=6.8, 1.6Hz, 1H), 5.86 (dd, J=11.4, 6.2Hz, 1H), 6.15 (dd, J=11.4, 6.3Hz, 1H), 6.85 (dt, J=8.7, 2.5Hz, 2H), 7.21 (dt, J=8.6, 2.5Hz, 2H).

$\delta_C$ (75MHz, CDCl$_3$): 21.2(t), 31.8(t), 34.3(t), 51.0(t), 55.1(d), 55.2(q), 68.2(d), 113.9(d), 129.4(d), 131.6(s), 134.6(d), 139.0(d), 158.8(s).

m/z(%) : 247(m$^+$)(7), 229(8), 122(16), 121(100), 91(13), 77(15), 32(21).
PREPARATION OF CIS-4-(p-METHOXYBENZYLAMINO)-2-CYCLOHEPTANOL (120).

A solution of (118) (0.71g, 2.20 mmol) in dry tetrahydrofuran (22ml) was added dropwise to a stirred slurry of lithium aluminium hydride (0.44g, 11.70 mmol) in dry tetrahydrofuran (52ml). After refluxing for 10h, decomposition of the excess hydride was effected by addition of a water-saturated solution of diethyl ether. The resulting solution was dried (MgSO₄) and the solvent was removed in vacuo, to yield a yellow oil. Subsequent purification by flash chromatography (95:4:1, diethyl ether:methanol:triethylamine) afforded (120) as a colourless oil (0.55g, 81%).

Rf 0.20 (95:4:1, diethyl ether:methanol:triethylamine).

νmax (CH₂Cl₂): 3600w, 3180w, 3040m, 2930m, 2850m, 1610w, 1510m, 1460m, 1240s cm⁻¹.

δH (300MHz, CDCl₃): 1.40-1.98 (series of m, 10H), 2.99 (m, 1H), 3.14 (brs, exch, 1H), 3.63, 3.72 (AB quartet, J=12.6Hz, 2H), 3.78 (s, 3H), 4.02 (m, 1H), 6.86 (m, 2H), 7.24 (m, 2H).

δC (75MHz, CDCl₃): 18.2(t), 28.9(t), 32.7(t), 34.4(t), 35.5(t), 50.9(t), 55.1(d), 55.3(q), 69.1(d), 113.9(d), 129.4(d), 131.7(s), 158.8(s).
m/z (%): 249 (m⁺) (3), 176 (9), 136 (4), 121 (100), 91 (7), 84 (9), 77 (7), 41 (9).

C₁₅H₂₄NO₂ [mH⁺] Requires 250.1807
Found 250.1807

**CYCLISATION OF CIS-4-(p-METHOXYBENZYLAMINO) CYCLOHEPTANOL (120) TO GIVE N-P-METHOXYBENZYL NORTROPANE (121).**

Thionyl chloride (19.45 μL, 0.25 mmol) was added dropwise to a stirred solution of (120) (0.052 g, 0.21 mmol) in dry deuterated chloroform (1 mL) at 0°C. The reaction mixture was allowed to warm to room temperature and stirring was continued for a further 24 h. Subsequently, the solvent was removed *in vacuo* and replaced with dry acetone (1 mL). After cooling to 0°C, anhydrous TMP (120.0 μL) was added and the solution was left to warm to room temperature, whereupon it was heated at 50°C for 5 h.

The solvent was removed *in vacuo* and the solid residue was triturated with diethyl ether. The combined ethereal extracts were basified with gaseous ammonia and the white solid, which formed, was removed by filtration. Solvent evaporation *in vacuo* gave an orange oil. Purification by flash chromatography (80:19:1, petroleum ether (40-60°C): diethyl ether: triethylamine) afforded (120) as a colourless oil (0.016 g, 33%).

Rᶠ 0.21 (80:19:1, petroleum ether (40-60°C): diethyl ether: triethylamine).
\( V_{\text{max}} \) (CH\(_2\)Cl\(_2\)) : 2930s, 2865m, 2830m, 1600w, 1505m, 1230m cm\(^{-1}\).

\( \delta_H \) (300MHz, CDCI\(_3\)) : 1.27-2.05 (series of m, 10H), 3.15 (brt, J=3.2Hz, 2H), 3.45 (s, 2H), 3.79 (s, 3H), 6.84 (m, 2H), 7.29 (m, 2H).

\( \delta_C \) (75MHz, CDCI\(_3\)) : 16.8(t), 26.4(t), 31.4(t), 55.2(q), 56.3(t), 59.3(d), 113.5(d), 129.7(d), 132.2(s), 158.4(s).

m/z(\%): 231(m\(^+\)) (87), 202(11), 188(24), 134(23), 121(97), 110(13), 94(23), 77(26), 55(30), 41(51).

C\(_{15}\)H\(_{21}\)NO [m\(^+\)] Requires 231.1623

Found 231.1623

CYCLISATION OF CJS-4-(p-METHOXYBENZYLAMINO)-2-CYCLOHEPTENOL (119) TO GIVE N-P-METHOXYBENZYLNORTROP-6-ENE (122).

Thionyl bromide (73.85\(\mu\)l, 0.95 mmol) was added dropwise to a stirred solution of (119) (0.20g, 0.79 mmol) in dry deuterated chloroform (4ml) at 0°C. The reaction mixture was allowed to warm to room temperature and stirring was continued for a further 24h. Subsequently, the solvent was removed in vacuo and replaced with dry acetone (4ml). After cooling to 0°C, anhydrous TMP (455.4\(\mu\)l) was added and the solution was left to warm to room temperature, whereupon it was heated at 50°C for 5h.

The solvent was removed under reduced pressure and the solid residue was triturated with diethyl ether. The
combined ethereal extracts were basified with gaseous
ammonia and the white solid produced was removed by
filtration. Solvent evaporation in vacuo yielded a crude
orange oil. Purification was effected by flash
chromatography (70:29:1, petroleum ether (40-60°C):diethyl ether:triethylamine). The first fraction isolated afforded
the aziridine (123) as a colourless oil (0.022g, 12%).

R_f 0.31 (70:21:1, petroleum ether (40-60°C):diethyl ether:triethylamine).

ν_max (CH₂Cl₂): 3000m, 2920s, 2830m, 1605m, 1505s, 1235s cm⁻¹.

δ_H (300MHz, CDCl₃): 1.51-2.27 (series of m, 8H), 3.28 (d, J=13.4Hz, 1H), 3.74 (d, J=8.4Hz, 1H), 3.79 (s, 3H), 5.65 (ddd, J=11.3, 6.4, 3.6Hz, 1H), 5.83 (ddd, J=11.6, 4.1, 2.7Hz, 1H), 6.85 (dt, J=8.7, 2.5Hz, 2H), 7.27 (m, 2H)

δ_C (75MHz, CDCl₃): 23.5(t), 29.8(t), 31.2(t), 42.8(d), 47.5(d), 55.2(q), 64.5(t), 113.6(d), 126.2(d), 128.8(d), 131.8(s), 133.3(d), 158.5(s).

m/z(%): 229(m⁺)(21), 169(10), 121(100), 108(49), 91(37), 81(60), 65(20), 53(36), 41(51).

C₁₅H₁₉NO [m⁺] Requires 229.1467
Found 229.1467
Further elution gave the desired compound (122) as a colourless oil (0.088g, 48%).

Rf 0.20  (70:21:1, petroleum ether (40-60°C):diethyl ether:triethylamine).

$\nu_{\text{max}}$ (CH$_2$Cl$_2$):  2930s, 2830m, 1605w, 1580w, 1505m, 1450w, 1325w, 1235m cm$^{-1}$.

$\delta_H$ (300MHz, CDC$_3$):  1.22-1.75 (series of m, 6H), 3.41 (s, 2H), 3.43 (brd, J=2.6Hz, 2H), 3.77 (s, 3H), 5.89 (s, 2H), 6.83 (dt, J=8.7, 2.4Hz, 2H), 7.26 (dt, J=8.3, 2.4Hz, 2H).

$\delta_C$ (75MHz, CDC$_3$):  16.6(t), 25.6(t), 55.2(q), 57.1(t), 65.1(d), 113.5(d), 129.2(d), 129.8(d), 132.3(s), 158.3(s).

m/z(%):  229(m$^+$) (70), 200(4), 169(6), 149(4), 121(100), 108(13), 94(27), 77(34), 41(36).

C$_{15}$H$_{19}$NO  [m$^+$] Requires  229.1467
   Found  229.1467
PREPARATION OF CIS-4-((BENZOYL OXYCARBONYL)AMINO)-2-CYCLOHEPTENOL (81).55

A solution of (113) (0.13g, 1.02 mmol) in diethyl ether (10ml) was added dropwise to a stirred suspension of sodium hydride (60% dispersion, 0.07g) in dry diethyl ether (40ml). After stirring at room temperature for 2h, the reaction mixture was cooled to 0°C, and benzylchloroformate (0.2ml, 1.4 mmol) was added dropwise. The resulting solution was left to warm to room temperature, stirred for a further 2h, and then poured into water (15ml). The organic layer was separated and the aqueous layer was extracted further with dichloromethane (3 X 20ml). The combined organic layers were dried (MgSO₄) and the solvent was removed in vacuo to yield (81) as a white crystalline solid (0.25g, 93%).

δ₇ (90MHz, CDCl₃): 1.40-2.00 (series of m, 6H), 4.30 (brm, 1H), 4.40 (brm, 1H), 5.00 (brs, exch., 1H), 5.10 (s, 2H), 5.54 (brdd, J=12, 4Hz, 1H), 5.77 (brdd, J=12, 3Hz, 1H), 7.20 (s, 5H).

PREPARATION OF CIS-4-(METHYLAMINO)-2-CYCLOHEPTENOL (124) FROM (81).

A solution of (81) (1.50g, 5.74 mmol) in dry tetrahydrofuran (30ml) was added dropwise to a stirred slurry of lithium aluminium hydride (0.95g, 24.92 mmol) in dry tetrahydrofuran (20ml). After refluxing for 10h, decomposition of the excess hydride was effected by the addition of a water-saturated solution of diethyl ether.
The resulting solution was dried (MgSO₄), and the solvent was removed in vacuo to yield a yellow oil. Purification was achieved by dissolving the crude material in diethyl ether (20ml), and washing with 2M (aq) hydrochloric acid (2 X 25ml). The combined aqueous extracts were subsequently washed with fresh diethyl ether (3 X 25ml) before being basified with 2M (aq) sodium hydroxide. The aqueous solution was extracted with dichloromethane (10 X 20ml) and the combined organic extracts were dried (MgSO₄). The solvent was removed in vacuo to afford (124) as a pale yellow solid (0.54g, 66%). An analytical sample was prepared by recrystallisation from petroleum ether (80-100°C), m.p. 62-64°C.

C₈H₁₅NO  Requires  C 68.04%  H 10.71%  N 9.92%
    Found    C 68.20%  H 10.41%  N 9.73%

ν_max (CH₂Cl₂): 3690w, 3600w, 3050s, 2980s, 2930m, 1600w,
              1545w, 1440m, 1420s, 1260s cm⁻¹.

δ_H (300MHz, CDCl₃): 1.54-1.84 (series of m, 6H), 2.39 (s, 3H), 3.13 (td, J=6.5, 1.8Hz, 1H), 4.18 (td, J=6.8, 1.7Hz, 1H), 5.84 (dd, J=11.4, 6.2Hz, 1H), 6.13 (dd, J=11.4, 6.3Hz, 1H).

δ_C (75MHz, CDCl₃): 21.0(t), 31.5(t), 34.1(q), 34.3(d),
                   57.7(d), 68.2(d), 134.7(d), 138.8(d).
m/z(%): 141(m+) (21), 123(10), 96(60), 94(21), 91(15), 82(16), 81(16), 70(100), 68(19), 57(20), 44(22), 42(29), 41(18), 32(19).

PREPARATION OF CIS-4-(METHYLAMINO)CYCLOHEPTANOL (125).

A solution of (124) (0.32g, 2.25 mmol) in methanol (30ml) was hydrogenated in the presence of 5% palladium on charcoal. After 16h the catalyst was removed by filtration and the solvent was evaporated in vacuo to yield (125) as a pale yellow oil (0.29g, 90%).

\[ \nu_{\text{max}} \text{(CH}_2\text{Cl}_2) : 3690\text{w}, 3600\text{w}, 3050\text{s}, 2980\text{s}, 2940\text{s}, 2860\text{m}, 1660\text{w}, 1600\text{w}, 1540\text{w}, 1460\text{m}, 1440\text{s}, 1420\text{s}, 1265\text{s cm}^{-1}. \]

\[ \delta_H \ (300\text{MHz, CDCl}_3) : 1.35-1.90 \text{ (series of m, 10H), 2.38 (s, 3H), 2.79 (m, 1H), 3.23 (brs, exch., 1H), 3.98 (m, 1H).} \]

\[ \delta_C \ (75\text{MHz, CDCl}_3) : 18.3(t), 28.6(t), 32.6(t), 34.0(q), 34.3(t), 35.7(t), 57.7(d), 69.2(d). \]

m/z(%): 144(mH+) (100), 130(3), 100(3), 70(11), 44(6).

C\textsubscript{8}H\textsubscript{18}NO [mH+] Requires 144.1388

\text{Found} 144.1388
PREPARATION OF N-METHYL-8-OXA-9-AZABICYCLO[3.2.2]NON-6-ENE (126).

A solution of (111) (1.50g, 5.79 mmol) in dry tetrahydrofuran (50ml) was added dropwise to a stirred slurry of lithium aluminium hydride (0.95g, 25.14 mmol) in dry tetrahydrofuran (50ml). After refluxing for 10h, decomposition of excess hydride was effected by the addition of a water-saturated solution of diethyl ether. The resulting solution was dried (MgSO₄) and the solvent was removed in vacuo to yield an orange oil. The crude material was purified by flash chromatography (59:40:1. diethyl ether:petroleum ether (40-60°C):triethylamine) to afford (126) as a colourless oil (0.54g, 67%).

R_f 0.2 (59:40:1. diethyl ether:petroleum ether (40-60°C):triethylamine).

v_max (CH₂Cl₂): 3680w, 3620w, 3020s, 2980m, 2980m, 2935m, 1515w, 1430w, 1255w, 1210s cm⁻¹.

δ_H (300MHz, CDCl₃): 1.18-1.94 (series of m, 6H), 2.58 (s, 3H), 3.47 (m, 1H), 4.44 (m, 1H), 6.13 (brdd, J=9.2, 6.9Hz, 1H), 6.32 (dd, J=9.3, 6.4, 1.5Hz, 1H).

δ_C (75MHz, CDCl₃): 18.5(t), 31.8(t), 45.6(q), 61.0(d), 71.9(d), 126.8(d), 127,9(d).
m/z(%): 139(m+) (14), 110(12), 94(28), 79(64), 77(15), 40(30), 32(100).

C₈H₁₄NO [mH⁺] Requires 140.1075
Found 140.1087

PREPARATION OF CIS-4-(METHYLAMINO)-2-CYCLOHEPTENOL (124)
FROM (126).

Zinc powder (2.97g, 45.44 mmol) was added to a stirred solution of (126) (0.36g, 2.61 mmol) in glacial acetic acid (15ml) at 0°C. The reaction mixture was heated at 50-60°C for 4h and then filtered. The residue was washed with glacial acetic acid (10ml) and the filtrate was evaporated in vacuo. The residue was cooled, basified with concentrated ammonia solution and the product was extracted into dichloromethane (6 X 30ml). The combined organic layers were dried (Na₂SO₄) and the solvent was removed in vacuo to yield a pale yellow solid (0.32g, 87%).

CYCLISATION OF CIS-4-(METHYLAMINO)CYCLOHEPTANOL (125) TO GIVE TROPANE (76).⁵⁰

Thionyl chloride (18.9μl, 0.26 mmol) was added dropwise to a solution of (125) (0.034g, 0.24 mmol) in dry deuterated chloroform (1ml) at 0°C. The reaction mixture was allowed to warm to room temperature and it was monitored periodically by 90MHz proton n.m.r. After 10min., the n.m.r spectrum contained new signals, which were assigned to the formation of the alkyl chlorosulphite derivative.
After 19.5h, the proton n.m.r spectrum showed that the alkyl chlorosulphite derivative had completely decomposed into the hydrochloride salt of the trans-1,4-chloroamine.

Therefore, the heterogeneous polymer-supported base, TABD (0.2g), was added and the suspension was rocked for 12h. Subsequently, the polymer-supported base was removed by filtration under nitrogen, and the filtrate was basified with gaseous ammonia. The white solid produced was removed by another filtration, and on examination of the proton n.m.r. for the crude solution it was found that the desired compound (76) had been formed. Purification was effected by flash chromatography (ammonia saturated solution of diethyl ether) to afford (76) as a pale yellow oil (0.01g, 34%).

\[ R_f \quad 0.22 \quad \text{(ammonia saturated solution of diethyl ether).} \]

\[ \delta_H \quad (300MHz, CDCl_3): \quad 1.31-2.05 \quad \text{(series of m, 10H), 2.68 (s, 3H), 3.09 (brt, J=3.2Hz, 2H).} \]
CYCLISATION OF CIS-4-(METHYLAMINO)-2-CYCLOHEPTENOL (124) TO GIVE TROP-6-ENE (127).

Thionyl chloride (161.1μl, 2.21 mmol) was added dropwise to a solution of (124) (0.29g, 2.03 mmol) and anhydrous lithium chloride (0.40g) in dry deuterated chloroform (8ml) at 0°C. The reaction mixture was sonicated for 3h before being left overnight at room temperature. Subsequently, the heterogeneous polymer-supported base, TABD (1.6g) was added and the resulting suspension was rocked for 12h. The polymer-supported base was removed by filtration under nitrogen, and the filtrate was basified with gaseous ammonia. The white precipitate formed was removed by another filtration and the solvent was evaporated at reduced pressure to give a crude orange oil. This crude material was purified by flash chromatography (9:1, diethyl ether:petroleum ether (40-60°C) saturated with gaseous ammonia). The first fraction isolated afforded the aziridine (128) as a colourless oil (0.034g, 13.5%)

Rf 0.48 (9:1, diethyl ether:petroleum ether (40-60°C) saturated with gaseous ammonia).

δH (300MHz, CDCl3): 1.25-2.06 (series of m, 8H), 2.43 (s, 3H), 5.62 (m, 1H), 6.00 (brdd, J=11.5, 5.7Hz, 1H).

Further elution gave the desired compound (127) as a colourless oil (0.035g, 14%).
R$_f$ 0.34 (9:1, diethyl ether:petroleum ether (40-60°C) saturated with gaseous ammonia).

$\delta_H$ (300MHz, CDCl$_3$): 1.25-2.06 (series of m, 6H), 2.21 (s, 3H), 3.40 (brd, J=2.5Hz, 2H), 5.86 (s, 2H).

m/z(%): 123(m$^+$)(36), 108(14), 94(100), 80(16), 70(21), 57(26)

C$_8$H$_{13}$N [m$^+$] Requires 123.1048
Found 123.1048

PREPARATION OF 4-(BENZOYLAMINO)CYCLOHEPTANONE (133).

A solution of chromic acid was prepared by dissolving chromium trioxide (0.7g, 7.0 mmol) in water (1ml). The resulting solution was cooled in an ice-bath, and concentrated sulphuric acid (0.61ml, 0.011 mol) followed by water (2ml) were cautiously added with manual stirring.$^{68}$ Subsequently, a solution of (71) (0.23g, 1.00 mmol) in HPLC grade acetone (0.6ml) was titrated with the freshly prepared solution of chromic acid, at room temperature. A persistent orange-brown colouration indicated the end point. Ethanol was then added until the solution turned green and the chromium salt had precipitated. Thus, the solution was filtered and the solvent was removed in vacuo. Chloroform (5ml) was added to the residue, and the solution was dried (MgSO$_4$). Evaporation of the solvent in vacuo yielded a beige waxy solid. Purification by recrystallisation from
toluene afforded (133) as a white crystalline solid (0.16g, 70%).

$\nu_{\text{max}}$ (nujol mull): 3320m, 2920s, 2850s, 1690m, 1630m, 1575w, 1525m, 1455m, 1375w, 1320w cm$^{-1}$.

$\delta_H$ (300MHz, CDC$_3$): 1.45-2.62 (series of m, 10H), 4.12 (m, 1H), 6.99 (brd, J=7.6Hz, exch., 1H), 7.36 (brt, J=7.5Hz, 2H), 7.46 (brt, J=7.3Hz, 1H), 7.76 (brd, J=7.2Hz, 2H).

$\delta_C$ (75MHz, CDC$_3$): 20.7(t), 30.0(t), 35.8(t), 39.5(t), 43.2(t), 51.5(d), 126.8(d), 128.1(d), 131.1(d), 134.3(s), 166.4(s), 213.5(s).

m/z(%): 232(mH$^+$)(97), 122(4), 105(7).

C$_{14}$H$_{18}$NO$_2$ [mH$^+$] Requires 232.1337
Found 232.1337

**PREPARATION OF 4-(BENZOYLAMINO)CYCLOHEPTANONE ETHYLENE ACETAL (134).**

A mixture of (133) (0.106g, 0.46 mmol), benzene (2ml), ethylene glycol (28.3µl, 0.51 mmol), and p-toluene sulphonate monohydrate (0.023g) was brought to reflux in a Dean and Stark apparatus. After 4h no more water appeared to be collecting. Thus, the reaction mixture was basified with 2M (aq) sodium hydroxide, and the solid which precipitated from the solution was extracted into dichloromethane (3 X 2ml). The combined organic layers were washed with water (2 X 2ml).
and dried (MgSO₄). Solvent evaporation in vacuo yield a white crystalline product which was purified by flash chromatography (diethyl ether) to afford (134) as a white solid (0.10g, 78%).

R_f 0.58 (diethyl ether).

ν_max (CH₂Cl₂): 3420w, 3380w, 2940m, 2880w, 1650s, 1600w, 1575m, 1510s, 1480m, 1320w cm⁻¹.

δ_H (300MHz, CDCl₃): 1.56-2.05 (series of m, 10H), 3.89 (m, 4H), 4.25 (brdt, J=11.8, 4.0Hz, 1H), 6.71 (brd, J=7.9Hz, 1H), 7.41 (m, 3H), 7.76 (brd, J=7.7Hz, 2H).

δ_C (75MHz, CDCl₃): 19.4(t), 28.5(t), 34.0(t), 35.2(t), 38.2(t), 49.8(d), 63.9(t), 64.0(t), 11.9(s), 126.7(d), 128.2(d), 131.0(d), 134.8(s), 166.2(s).

m/z (%): 276 (mH⁺) (97), 230 (3), 154 (11), 115 (4), 105 (10), 99 (6).

C₁₆H₂₂NO₃ [mH⁺] Requires 276.1599
Found 276.1600

PREPARATION OF 4-(BENZYLAMINO)CYCLOHEPTANONE ETHYLENE ACETAL (136).

Lithium aluminium hydride (0.053g, 1.39 mmol) was carefully added to a stirred solution of (134) (0.088g, 0.32 mmol) in dry tetrahydrofuran (3ml). After refluxing for
10h, decomposition of excess hydride was effected by the addition of a water saturated-solution of diethyl ether. The resulting solution was dried (MgSO₄) and removal of the solvent in vacuo gave a colourless oil. Purification was achieved using flash chromatography (99:1, diethyl ether:triethylamine) to afford (135), as a colourless oil (0.052g, 62%).

Rf 0.45 (99:1, diethyl ether:triethylamine).

v_max (CH₂Cl₂): 3010m, 2930s, 2880s, 1650w, 1600w, 1590w, 1450m, 1370m, 1335w cm⁻¹.

δ_H (300MHz, CDCl₃): 1.30-1.99 (series of m, 10H), 2.73 (m, 1H), 3.77 (d, J=1.6Hz, 2H), 3.89 (m, 4H), 7.20-7.35 (m, 5H).

δ_C (75MHz, CDCl₃): 19.6(t), 28.3(t), 33.7(t), 35.9(t), 3.7(t), 51.4(t), 58.1(d), 64.0(t), 112.4(s), 126.8(d), 128.0(d), 128.3(d), 140.8(s).

m/z(%): 262 (mH⁺) (97), 210 (4), 115 (9), 91 (4).

C₁₆H₂₄NO₂ [mH⁺] Requires 262.1807
          Found   262.1807

PREPARATION OF 4-(BENZYLAMINO)CYCLOHEPTANONE (136).

A 1M (aq) solution of hydrochloric acid (2ml) was added to a solution of (135) (0.046g, 0.177 mmol) in tetrahydrofuran (2ml). The reaction was left to reflux overnight.
Subsequently, the solution was basified with a 2M (aq) solution of sodium hydroxide and extracted with dichloromethane (8 X 2ml). The combined organic layers were dried (MgSO₄). Solvent evaporation in vacuo gave a yellow waxy solid (0.057g), which was purified by flash chromatography (50:49:1, diethyl ether:petroleum ether (40-60°C):triethylamine) to afford (136) as a white, waxy solid (0.036g, 94%).

Rf 0.33 (50:49:1, diethyl ether:petroleum ether (40-60°C):triethylamine).

νmax (CH₂Cl₂)(RT): 3660w, 3570w, 3380w, 3010m, 2940s, 2870s, 1690s, 1600w, 1490m, 1450s, 1360m, 1335m cm⁻¹.

δH (300MHz, CDCl₃)(RT): 1.61-2.36 (br, series of m, 10H), 2.94 (brs, 1H), 3.81 (d, J=1.7Hz, 2H), 7.24-7.37 (m, 5H).

δC (75MHz, CDCl₃)(RT): 19.7(brt), 28.0(brt), 29.7(brt), 38.3(brt), 49.6(brt), 57.1(brd), 128.1(d), 128.3(d), 128.6(d), 140.4(s).

m/z(%): 217(m⁺)(4), 189(3), 174(7), 160(10), 146(30), 133(20), 91(100), 65(13), 55(16), 41(16).

C₁₄H₂₀NO [mH⁺] Requires 218.1545
Found 218.1545
PREPARATION OF N-BENZOYL PYRROLIDINE (153ax).

Benzoyl chloride (4.9ml, 0.042 mol) was carefully added, over the course of 1h, to a stirred mixture of sodium hydroxide (2.2g, 0.055 mol), pyrrolidine (3.52ml, 0.042 mol) and water (17ml). During the addition, the reaction mixture was cooled in a surrounding water bath. Subsequently, it was left to stir at room temperature for a further 1h.

The oily product, which separated, was extracted into dichloromethane (2 X 10ml) and the combined organic extracts were washed with water (10ml) and dried (MgSO₄). Evaporation of the solvent in vacuo afforded (153ax) as a pale yellow oil (7.35g, 99%).

δ_H (90MHz, CDCl₃): 1.88 (brm, 4H), 3.49 (brdt, J=21.0, 6.0Hz, 4H), 7.38 (m, 5H).

PREPARATION OF N-BENZYL PYRROLIDINE (154ax).

A solution of (153ax) (0.79g, 4.50 mmol) in dry diethyl ether (50ml) was added dropwise to a stirred slurry of lithium aluminium hydride (0.74g, 19.53 mmol) in dry diethyl ether (50ml). After refluxing for 10h, decomposition of excess hydride was effected by addition of a water saturated solution of diethyl ether. The resulting solution was dried (MgSO₄) and the solvent was removed in vacuo to yield a yellow oil. Subsequent purification by flash chromatography (70:29:1, diethyl ether:petroleum ether (40-60°C):triethylamine) gave (154ax) as a pale yellow oil (0.56g, 77%).
Rf 0.34 (70:29:1, diethyl ether:petroleum ether (40-60°C):triethylamine).

δ\textsubscript{H} (90MHz, CDCl\textsubscript{3}): 1.79 (m, 4H), 2.50 (m, 4H), 3.60 (s, 2H), 7.26 (brs, 5H).

**PREPARATION OF N-BENZOYLPIPERIDINE (153bx).**

Benzoyl chloride (3.52ml, 0.03 mol) was carefully added, over the course of 1h, to a stirred mixture of sodium hydroxide (1.58, 0.039 mol), piperidine (3.00ml, 0.03 mol) and water (12ml). During the addition, the reaction mixture was cooled in a surrounding water bath. Subsequently, it was left to stir at room temperature for a further 1h.

The oily product, which separated, was extracted into dichloromethane (2 X 10ml) and the combined organic extracts were washed with water (10ml) and dried (MgSO\textsubscript{4}). Evaporation of the solvent *in vacuo* afforded (153bx) as a straw coloured, viscous oil (5.32g, 93%).

δ\textsubscript{H} (90MHz, CDCl\textsubscript{3}): 1.59 (brs, 6H), 3.48 (brs, 4H), 7.30 (s, 5H).

**PREPARATION OF N-BENZYLPIPERIDINE (154bx).**

A solution of (153bx) (0.79g, 4.20 mmol) in dry diethyl ether (20ml), was added dropwise to a stirred slurry of lithium aluminium hydride (0.69g, 18.23 mmol) in dry diethyl ether (30ml). After leaving at reflux temperature for 10h, decomposition of excess hydride was effected by addition of
a water-saturated solution of diethyl ether. The resulting solution was dried (MgSO₄) and the solvent was removed in vacuo to give (154bx) as a colourless oil (0.62g, 85%).

δₓ (90MHz, CDCl₃): 1.41 (brm, 6H), 2.30 (brm, 4H), 3.38 (s, 2H), 7.19 (s, 5H).

PREPARATION OF N-p-METHOXYBENZOYL PIPERIDINE (153by).

p-Methoxybenzoyl chloride (5.52g, 0.032 mol) was carefully added over the course of 1h, to a stirred mixture of sodium hydroxide (1.51g, 0.038 mol), piperidine (2.9ml, 0.029 mol) and water (12ml). During the addition the reaction mixture was cooled in a surrounding water bath. Subsequently, it was left to stir at room temperature for another 1h.

The oily product, which separated, was extracted into dichloromethane (3 x 20ml), and the combined organic extracts were washed with water (20ml) and dried (Na₂SO₄). Evaporation of the solvent in vacuo afforded (153by) as a yellow oil (5.59g, 87%).

δₓ (90MHz, CDCl₃): 1.59 (brs, 6H), 3.48 (brs, 4H), 3.71 (s, 3H), 6.83 (brd, J=9.0Hz, 2H), 7.32 (brd, J=9.0Hz, 2H).

PREPARATION OF N-p-METHOXYBENZYL PIPERIDINE (154by).

A solution of (153by) (1.37g, 6.24 mmol) in dry diethyl ether (50ml) was added dropwise to a stirred slurry of lithium aluminium hydride (1.03g, 27.12 mmol) in dry diethyl ether (30ml). After leaving at reflux for 10h, decomposition of the excess hydride was effected by addition
of a water-saturated solution of diethyl ether. The resulting solution was dried (MgSO₄) and the solvent was removed in vacuo to give (154by) as a colourless oil (1.06g, 83%).

δₜ (90MHz, CDCl₃): 1.35 (brm, 6H), 2.31 (brm, 4H), 3.34 (s, 2H), 3.72 (s, 3H), 6.76 (brd, J=9Hz, 2H), 7.13 (brd, J=9Hz, 2H).

**PREPARATION OF N-3,4-DIMETHOXYBENZOYLPIPERIDINE (153bz).**

3,4-Dimethoxybenzoyl chloride (1.47g, 7.33 mmol) was carefully added, over the course of 1h, to a stirred mixture of sodium hydroxide (0.38g, 9.54 mmol), piperidine (0.73ml, 7.33 mmol) and water (3.83ml). During the addition, the reaction mixture was cooled in a surrounding water bath. Subsequently, it was left to stir at room temperature for a further 3h.

The oily product, which was separated, was extracted into dichloromethane (3 X 4ml) and the combined organic extracts were washed with water (4ml) and dried (MgSO₄). Evaporation of the solvent in vacuo afforded (153bz) as a colourless oil (1.64g, 90%).

δₜ (90MHz, CDCl₃): 1.56 (brs, 6H), 3.44 (brs, 4H), 3.79 (s, 6H), 6.82 (m, 3H).
PREPARATION OF N-3,4-DIMETHOXYBENZYLPiperidine (154bz).

A solution of (153bz) (1.51g, 6.03 mmol) in dry diethyl ether (50ml) was added dropwise to a stirred slurry of lithium aluminium hydride (1.00g, 26.4 mmol) in dry diethyl ether (30ml). After refluxing for 10h, decomposition of the excess hydride was effected by addition of a water-saturated solution of diethyl ether. The resulting solution was dried (MgSO₄) and the solvent was removed in vacuo to yield an orange oil. Subsequent purification by flash chromatography (89:10:1, diethyl ether:petroleum ether (40-60°C):triethylamine) gave (154bz) as a pale yellow oil (1.13g, 79%).

Rᵥ  0.28 (89:10:1, diethyl ether:petroleum ether (40-60°C):triethylamine).

δₜ (300MHz, CDCl₃):  1.43 (brquin, J=5.4Hz, 2H), 1.56 (brquin, J=5.5Hz, 4H), 2.35 (brt, J=4.8Hz, 4H), 3.40 (s, 2H), 3.86 (s, 3H), 3.88 (s, 3H), 6.81 (m, 2H), 6.89 (d, J=1.5Hz, 1H).

δc (75MHz, CDCl₃):  24.4(t), 26.0(t), 54.4(t), 55.9(q), 63.6(t), 110.7(d), 112.3(d), 121.2(d), 131.3(s), 147.9(s), 148.7(s).
PREPARATION OF N-BENZYL-2-AZABICYCLO[2.2.1]HEPT-5-ENE (158a).82

Neat 1,3-cyclopentadiene (3.00g, 0.05 mol) was added dropwise to a stirred mixture containing a 2.5M (aq) solution of benzylamine hydrochloride (0.025 mol) and a 37% aqueous solution of formaldehyde (0.032 mol). Subsequently, the heterogeneous reaction mixture was stirred vigorously for a further 3h at room temperature.

The reaction was then diluted with an equal volume of water and washed with diethyl ether (2 X 20ml). The aqueous layer was basified with solid potassium hydroxide and extracted with diethyl ether (4 X 15ml). The combined organic extracts were dried (MgSO₄) and removal of the solvent in vacuo afforded (158a) as an orange, viscous oil (3.83g, 91%).

δH (90MHz, CDCl₃): 1.55, 1.79 (br AB quartet, J=9.0Hz, 2H), 1.70 (brd, J=2.3Hz, 1H), 3.03 (brs, 1H), 3.30 (dd, J=9, 2.3Hz, 1H), 3.42, 3.72 (AB q, J=13.5Hz, 2H), 3.90 (brs, 1H), 6.18 (m, 1H), 6.46 (m, 1H), 7.38 (s, 5H).

PREPARATION OF N-BENZYL-2-AZABICYCLO[2.2.1]OCT-5-ENE (158b).82

Neat 1,3-cyclohexadiene (1.00g, 0.013 mol) was added dropwise to a stirred mixture containing a 2.5M (aq) solution of benzylamine hydrochloride (0.008 mol) and a 37% aqueous solution of formaldehyde (0.008 mol). Subsequently, the reaction was sealed in a Youngs tube and heated at 55°C.
for 48h. The heterogeneous mixture was stirred vigorously throughout.

The reaction was then diluted with an equal volume of water and washed with diethyl ether (2 X 5ml). The aqueous layer was basified with solid potassium hydroxide and extracted with dichloromethane (9 X 5ml). The combined organic extracts were dried (MgSO₄) and removal of the solvent in vacuo afforded a pink/orange oil (1.3g).

Purification by flash chromatography (40:59:1, diethyl ether:petroleum ether (40-60°C):triethylamine) gave (158b) as a colourless oil (0.48g, 30%).

Rf 0.37 (40:59:1, diethyl ether:petroleum ether (40-60°C):triethylamine).

δᵢ (90MHz, CDCl₃): 1.16-2.08 (series of m, 5H), 2.42 (brs, 1H), 2.99 (dd, J=9.0, 2.3Hz, 1H), 3.26 (brs, 1H), 3.34, 3.56 (AB quartet, J=13.5Hz, 2H), 6.28 (m, 2H), 7.22 (m, 5H).

DEALKYLATION/DEBENZYLATION OF TERTIARY AMINES USING VOCCl.⁷⁶

(1) N-ETHYLPIPERIDINE.⁷⁶

VOCCl (243.9µl, 2.87 mmol) was added to dry dichloromethane (10ml) and the resulting solution was cooled to 0°C. Subsequently, a solution of N-ethyl piperidine (0.25g, 2.21 mmol) in dry dichloromethane (10ml) was added dropwise and the reaction was allowed to warm to room temperature.

After heating at reflux for 4h, a small aliquot of the reaction mixture was removed and the solvent was evaporated
in vacuo. A proton (90MHz) n.m.r. spectrum of the residue showed the presence of the N-VOC derivative.

$\delta_H$ (90MHz, CDCl$_3$): 1.64 (m, 6H), 3.57 (m, 4H), 4.46 (dd, J=6.0, 1.5Hz, 1H), 4.80 (dd, J=13.5, 1.5Hz, 1H), 7.25 (dd, J=13.5, 6.0Hz, 1H).

Therefore, an excess of gaseous hydrogen chloride was bubbled through the reaction mixture and the solvent was removed in vacuo. The residue was dissolved in methanol (30ml) and the solution was heated at 50-60°C for 4.5h. Subsequently, the mixture was concentrated in vacuo to give piperidine hydrochloride as a white solid (0.22g, 83%).

$\delta_H$ (90MHz, CDCl$_3$): 1.91 (brm, 6H), 3.12 (brm, 4H), 9.20 (brs, 2H, NH$_2^+$).

(2) N-BENZYLPIPERIDINE (154bx):

VOCCl (135.5|Il, 1.59 mmol) was added to dry dichloromethane (10ml) and the resulting solution was cooled to 0°C. Subsequently, a solution of (154bx) (0.21g, 1.23 mmol) in dry dichloromethane (15ml) was added dropwise and the reaction was allowed to warm to room temperature.

After refluxing for 4h, the formation of the N-VOC derivative was verified by analysis of a small aliquot of the reaction mixture. Thus, an excess of gaseous hydrogen chloride was bubbled through the reaction mixture and the solvent was removed in vacuo. The residue was dissolved in methanol (30ml) and the solution was heated at 50-60°C for
4.5h. Subsequently, the mixture was concentrated in vacuo to afford a yellow waxy solid, which was purified by trituration with cold diethyl ether, to give piperidine hydrochloride (0.13g, 85%).

(3) N-P-METHOXYBENZYLPIPERIDINE (154by):
VOCl (133.0μl, 1.57 mmol) was added to dry dichloromethane (10ml) and the resulting solution was cooled to 0°C. Subsequently, a solution of (154by) (0.25g, 1.21 mmol) in dry dichloromethane (15ml) was added dropwise and the reaction was allowed to warm to room temperature. After being kept at reflux for 2h, removal of a small aliquot of the reaction mixture showed that the N-VOC derivative had been produced. Hence, an excess of gaseous hydrogen chloride was bubbled through the reaction mixture and the solvent was removed in vacuo. The residue was dissolved in methanol (30ml) and the solution was heated at 50-60°C for 4.5h. Subsequently, the mixture was concentrated at reduced pressure to afford a beige waxy solid, which was purified by trituration with cold diethyl ether to give piperidine hydrochloride (0.13g, 88%).

(4) N-BENZYL-2-AZABICYCLO[2.2.1]HEPT-5-ENE (158a):
VOCl (166.2μl, 1.96 mmol) was added to dry dichloromethane (12.5ml) and the resulting solution was cooled to 0°C. Subsequently, a solution of (158a) (0.28g, 1.50 mmol) in dry dichloromethane (18ml) was added dropwise and the reaction was allowed to warm to room temperature.
After heating at reflux for 4h, an excess of gaseous hydrogen chloride was bubbled through the reaction mixture and the solvent was removed \textit{in vacuo}. The residue was dissolved in methanol (50ml) and the solution was heated at 50-60°C for 4.5h. However, on concentrating this mixture at reduced pressure, only the hydrochloride salt of the starting material was obtained.

(5) \textbf{N-BENZYLNORTROPANE (101)}:

\textit{VOCCl (33.0μl, 0.39 mmol)} was added to dry dichloromethane (1ml) and the resulting solution was cooled to 0°C. Subsequently, a solution of (101) (0.06g, 0.3 mmol) in dry dichloromethane (6ml) was added dropwise and the reaction was allowed to warm to room temperature.

After heating at reflux for 4.5h, an excess of gaseous hydrogen chloride was bubbled through the reaction mixture and the solvent was removed \textit{in vacuo}. The residue was dissolved in methanol (8ml) and the solution was heated at 50-60°C for 4h. However on concentrating this mixture \textit{in vacuo}, only the hydrochloride salt of the starting material was recovered.

(6) \textbf{N-BENZYLNORTROP-6-ENE (104)}:

\textit{VOCCl (28.3μl, 0.33 mmol)} was added to dry dichloromethane (1ml) and the resulting solution was cooled to 0°C. Subsequently, a solution of (104) (0.051g, 0.26 mmol) in dry dichloromethane (5ml) was added dropwise and the reaction was allowed to warm to room temperature.
After heating at reflux for 6h, an excess of gaseous hydrogen chloride was bubbled through the reaction mixture and the solvent was removed in vacuo. The residue was dissolved in methanol (6ml) and the solution was heated at 50-60°C for 4.5h. However, on concentrating this mixture in vacuo, only the hydrochloride salt of the starting material was isolated.

DEALKYLATION/DEBENZYLATION OF TERTIARY AMINES USING ACECl. 

(1) N-ETHYLPIPERIDINE: 

ACECl (291.0μl, 2.7 mmol) was added dropwise to a stirred solution of N-ethyl piperidine (0.23g, 2.07 mmol) in dry 1,2-dichloroethane (10ml) at 0°C over 15min. Subsequently, the mixture was kept at reflux for 3h. The solvent was removed in vacuo and the residue was dissolved in methanol (20ml). The resulting solution was heated at 50°C for 3h. The mixture was then concentrated at reduced pressure to afford a brown, waxy solid, which was purified by recrystallisation from ethanol to give piperidine hydrochloride as a white crystalline solid (0.19g, 77%).

(2) TROPAN-3α-OL: 

ACECl (185.4μl, 1.72 mmol) was added dropwise to a stirred solution of tropan-3α-ol (0.24g, 1.72 mmol) in dry 1,2-dichloroethane (10ml) at 0°C over 15min. Subsequently, the mixture was kept at reflux for 7h. The solvent was removed in vacuo and the residue was dissolved in methanol (10ml). The resulting solution was heated at 50°C for 3h. Removal of the solvent in vacuo gave a pale, yellow solid, which
was purified by recrystallisation from ethanol to give nortropan-3α-ol hydrochloride as fine, white crystals (0.19g, 67%), m.p. 199-201°C (lit m.p. 136 200°C).

δH (90MHz, CD3OD): 1.98-2.67 (series of m, 10H), 3.83 (brm, 1H), 4.04 (brm, 2H).

(3) N-BENZYL-2-AZABICYCLO[2.2.1]HEPT-5-ENE (158a).

ACECl (142.5µl, 1.32 mmol) was added dropwise to a stirred solution of (158a) (0.20g, 1.02 mmol) in dry 1,2-dichloroethane (10ml), at 0°C over 15min. Subsequently, the mixture was kept at reflux for 7h. The solvent was removed in vacuo and the residue was heated at 50°C for 3h. However, removal of the solvent in vacuo only gave the hydrochloride salt of the starting material.

(4) N-BENZYL-2-AZABICYCLO[2.2.2]OCT-5-ENE (158b).

ACECl (101.5µl, 0.94 mmol) was added dropwise to a stirred solution of (158b) (0.14g, 0.72 mmol) in dry 1,2-dichloroethane (5ml) at 0°C over 15min. Subsequently, the mixture was kept at reflux for 10h. The solvent was removed in vacuo and the residue was dissolved in methanol (5ml). The resulting solution was heated at 50°C for 3h. However, evaporation of the solvent in vacuo only afforded the hydrochloride salt of the starting material.
(5) N-BENZYNORTROPANE (101).

ACECl (37.6 µl, 0.35 mmol) was added dropwise to a stirred solution of (101) (0.053 g, 0.27 mmol) in dry 1,2-dichloroethane (2.5 ml) at 0°C over 15 min. Subsequently, the mixture heated at reflux for 12 h. The solvent was removed in vacuo and the residue was dissolved in methanol (2.5 ml). The resulting solution was heated to 50°C for 3 h. However, evaporation of the solvent in vacuo only gave the hydrochloride salt of the starting material.

PREPARATION OF NORTROP-6-ENE (109) FROM N-P-METHOXYBENZYL NORTROP-6-ENE (122) USING ACECl.

ACECl (241.1 µl, 2.23 mmol) was added dropwise to a stirred solution of (122) (0.26 g, 1.12 mmol) in dry dichloromethane (6 ml) at 0°C over 15 min. Subsequently, the reaction mixture was allowed to warm to room temperature before being brought to reflux for 24 h. The solvent was removed in vacuo and the residue was dissolved in dry methanol (6 ml). The resulting solution was heated at 60°C for a further 2 h. Evaporation of the solvent in vacuo afforded a yellow solid. Preliminary purification involved an aqueous work-up in which the solid was dissolved in water (2 ml) and the aqueous solution was washed with diethyl ether (3 x 4 ml). The aqueous layer was basified with 2 M (aq) sodium hydroxide and extracted with dichloromethane (10 x 2 ml). The combined organic extracts were dried (Na₂SO₄) and removal of the solvent in vacuo gave a yellow oil. A proton (90 MHz) n.m.r. spectrum of this crude product showed the presence of
starting material together with a new product (50% yield estimated by n.m.r.). Further purification by flash chromatography (87:12:1, chloroform:methanol:triethylamine) and identification using a PMA stain, gave (109) (0.006g, 5%) as a colourless oil. The low yield is due to the polarity of the compound and difficulties were experienced in identifying the product containing fractions. (109) is not UV active and it does not show on staining with iodine.

\[ R_f \quad 0.19 \quad (87:12:1, \text{chloroform:methanol:triethylamine}). \]

\[ \nu_{\text{max}} \quad (\text{CH}_2\text{Cl}_2): \quad 3660\text{w}, 3450\text{w}, 2960\text{s}, 2930\text{s}, 2860\text{m}, 1660\text{w}, 1610\text{m}, 1590\text{m}, 1510\text{w}, 1450\text{w}, 1395\text{w} \text{ cm}^{-1}. \]

\[ \delta_H \quad (300\text{MHz, CDCI}_3): \quad 1.44-2.22 \quad (\text{series of m, 6H}), \quad 4.30 \quad (\text{brs, 2H}), \quad 5.08 \quad (\text{brs, exch., 1H}), \quad 6.09 \quad (\text{s, 2H}). \]

\[ \delta_C \quad (75\text{MHz, CDCI}_3): \quad 22.4(\text{t}), \quad 29.7(\text{t}), \quad 58.7(\text{d}), \quad 129.0(\text{d}). \]

\[ m/z(\%) \quad (\text{mH}^+) \quad 110(\text{mH}^+)(100), \quad 105(11), \quad 88(56), \quad 80(10), \quad 74(6). \]

\[ \text{C}_7\text{H}_{11}\text{N} \quad [\text{m}^+] \text{ Requires 109.0891} \]

\[ \text{Found 109.0892} \]
ATTEMPTED REMOVAL OF N-P-METHOXYBENZYL$^{83}$ AND N-3,4-DIMETHOXY
BENZYL$^{84}$ GROUPS WITH CONCENTRATED SULPHURIC ACID IN TRI
FLUOROACETIC ACID.

(1) N-p-METHOXYBENZYL PIPERIDINE (154by).

(154by) (0.22g, 1.09 mmol) was added to a 5% solution of
concentrated sulphuric acid in anhydrous trifluoroacetic
acid (10ml) containing an excess of anisole (236.8μl, 2.18
mmol). After heating at reflux for 8h, the trifluoroacetic
acid was removed in vacuo. The residue was dissolved in
water (5ml) and washed with diethyl ether (2 X 5ml). Then
the aqueous layer was basified with a concentrated ammonia
solution and extracted with dichloromethane (6 X 10ml). The
combined organic extracts were dried (MgSO₄). Acidification
of the organic solution with trifluoroacetic acid followed
by solvent evaporation, however, only resulted in the
isolation of the trifluoroacetic acid salt of the starting
material.

(2) N-3,4-DIMETHOXYBENZYLPIPERIDINE (154bz).

(154bz) (0.20g, 0.86 mmol) was added to a 5% solution of
concentrated sulphuric acid in anhydrous trifluoroacetic
acid (10ml) containing an excess of anisole (187.2μl, 1.72
mmol). After heating at reflux for 8h, the trifluoroacetic
acid was removed in vacuo. The residue was dissolved in
water (10ml) and washed with diethyl ether (2 X 5ml).
Basification of the aqueous layer with a 2M (aq) solution of
sodium hydroxide was followed by extraction with
dichloromethane (6 X 5ml). The combined organic extracts
were dried (MgSO₄). However, removal of the solvent in vacuo only afforded starting material.

**PREPARATION OF SODIUM 9,10-ANTHRACINONE α-SULPHONATE (α-SAS) (161).**

A vigorously stirred mixture of yellow mercuric oxide (0.50g, 0.002 mol) and a 20% solution of oleum (60.00g) was heated to 100°C. Subsequently, anthraquinone (50.00g, 0.24 mol) was added and stirring was continued, whilst the mixture was heated at 147-152°C for 1h. The hot acid solution was then poured cautiously into hot water (500ml) with stirring, and the mixture was boiled for a further 5min. The unchanged anthraquinone was removed by filtration and washed with hot water (100ml). The light brown filtrate, together with the water washings, was heated to 90°C and a solution of sodium chloride (12.54g, 0.21 mol) in water (125ml) was added. After cooling to room temperature, the sodium salt (161), which crystallised in the form of golden plates, was collected by filtration, washed with cold water (100ml) and dried in vacuo at 100°C (24.50g, 70%).

**PREPARATION OF 9,10-DICYANOANTHRACENE (9,10-DCA) (162).**

A mixture of 9-cyanoanthracene (159) (0.61g, 30.00 mmol) and (161) (1.51g, 50.00 mmol) in dry dimethyl sulfoxide (80ml) was stirred under dry nitrogen. Subsequently, the reaction mixture was heated to 80°C, and sodium cyanide (160) (0.40g, 80.00 mmol) was added after 1h. Upon this addition an intense magenta colour developed and a yellow crystalline material separated.
After 1.75h, the reaction was quenched with water (10ml), which had been degassed with nitrogen, and the mixture was poured into water (300ml) containing a saturated solution of ammonium chloride (50ml). The aqueous mixture was then filtered, so as to retain the quinone in solution. The yellow solid that was obtained was recrystallised from chloroform, to yield (162) as golden, yellow crystals (0.62g, 90%), m.p. 334-335°C (lit m.p. 335°C).

m/z(%): 228(m+)(98), 201(11), 175(5), 114(7), 100(7), 87(8), 32(29).

**ATTEMPTED N-DEBENZYLATION VIA A PHOTOSENSITISED SINGLE ELECTRON TRANSFER.**

(1) **N-BENZYLpyrroolidine (154ax).**

An acetonitrile:water (7:3) solution (69.5ml) containing (134ax) (0.21g, 1.29 mmol, 1.85x10^{-2}M) and 9,10-DCA (162) (0.001g, 0.006 mmol, 8.3x10^{-5}M) in a pyrex tube, was irradiated in a Rayonet reactor fitted with 3500A lamps. The reaction was monitored periodically by t.l.c.

However, after 10h, a t.l.c. of the reaction mixture showed that only starting material was present. This was verified by removing a small aliquot of the reaction mixture and evaporating the solvent in vacuo after acidification with a 2M (aq) solution of hydrochloric acid. A proton (90MHz) n.m.r spectrum of the residue, was in accordance with that of the hydrochloride salt of the starting material.
**N-BENZYLPIPERIDINE (154bx).**

An acetonitrile: water (7:3) solution (37ml) containing (154bx) (0.12g, 0.69 mmol, 1.85x10^{-2}M) and 9,10-DCA (162) (0.001g, 0.003 mmol, 8.3x10^{-5}M) in a pyrex tube, was irradiated in a Rayonet reactor fitted with 3500A lamps. The reaction was monitored periodically by t.l.c.

However, after 10h, a t.l.c. of the reaction mixture showed that only starting material was present, as did proton n.m.r (90MHz) of a small aliquot. Therefore, the reaction was irradiated at the shorter wavelength of 3000A for a further 24h. Nevertheless, this failed to induce any debenzylation and only unreacted starting material was recovered.

**IRON (II) CATALYSED DEALKYLATION OF TERTIARY AMINES.**

**N-BENZYLPIPERIDINE (154bx).**

A stirred solution of (154bx) (0.097g, 0.557 mmol) in dichloromethane (1.5ml) was cooled to 0°C and treated with m-chloroperoxybenzoic acid (0.12g, 0.557 mmol, 80% purity) in several portions. Subsequently, a 1N (aq) solution of iron(II)chloride (0.223ml) was added and stirring was continued at -10 to 0°C for a further 7h, before being left overnight at room temperature. The mixture was then treated with a 2M (aq) solution of hydrochloric acid (3ml) and the dichloromethane was removed \textit{in vacuo}. The aqueous residue was washed with diethyl ether (2 X 3ml), basified with 2M (aq) sodium hydroxide, and extracted with dichloromethane (6 X 3ml). The combined organic extracts were dried (MgSO₄). Acidification of the organic solution with gaseous hydrogen...
chloride, followed by evaporation of the solvent in vacuo, afforded piperidine hydrochloride as a pale yellow solid (0.04g, 65%).

(2) N-BENZYL-9-AZABICYCLO[4.2.1]NON-7-ENE (166).

A stirred solution of (166) (0.057g, 0.268 mmol) in dichloromethane (0.5ml) was cooled to 0°C and treated with m-chloroperoxybenzoic acid (0.058g, 0.268 mmol, 80% purity) in several portions. Subsequently, a 1N (aq) solution of iron(II)chloride (0.11ml) was added and stirring was continued at -10 to 0°C for a further 7h, before being left overnight at 4°C. The mixture was then treated with a 2M (aq) solution of hydrochloric acid (1.3ml) and the dichloromethane was removed in vacuo. The aqueous residue was washed with diethyl ether (2 X 1.5ml), basified with a 2M (aq) solution of sodium hydroxide, and extracted with dichloromethane (10 X 2ml). The combined organic extracts were dried (MgSO₄). Acidification of the organic solution with gaseous hydrogen chloride, followed by evaporation of the solvent in vacuo afforded a yellow/orange oil, which solidified on standing. Purification of this solid by trituration with cold petroleum ether (40-60°C), gave a white solid which was identified by proton n.m.r. (90MHz) as the hydrochloride salt of the starting material.
ATTEMPTED REMOVAL OF THE N-p-METHOXYBENZYL GROUP FROM N-p-METHOXYBENZYL PIPERIDINE (154by) USING DDQ.

A solution of (154by) (0.20g, 0.98 mmol) in dichloromethane (7ml) was added dropwise to a stirred solution of DDQ (0.44g, 1.95 mmol) in dichloromethane (8ml), followed by a separate addition of water (0.4ml). The resulting mixture was left to stir at room temperature for 48h. Subsequently, the reaction mixture was washed with aqueous sodium metabisulphite (15%, 3 X 15ml) and aqueous sodium bicarbonate (15%, 3 X 15ml), and the organic layer was dried (MgSO₄). However, acidification of the organic solution with gaseous hydrogen chloride followed by solvent evaporation, resulted only in the isolation of the hydrochloride salt of the unreacted starting material.

PREPARATION OF N-METHYL-N-BENZYLNORTROP-6-ENIUM IODIDE (167).

Methyl iodide (400.0μl, 6.43 mmol) was added to a solution of (104) (0.13g, 0.63 mmol) in dry acetone (400.0μl) at 0°C. After heating the reaction at reflux for 3h, the solvent was removed in vacuo to yield an orange solid. Purification of the residue by trituration with cold acetone, afforded (167) as a yellow solid (0.16g, 74%).

νmax (nujol mull) 3050w, 3010w, 2970w, 2960m, 2940m, 1460m, 1450s, 1375m, 1330m, 1265s, 1210w cm⁻¹.
$\delta_H$ (300MHz, CD$_3$OD): major diastereoisomer 1.64-1.92
(series of m, 4H), 2.63 (m, 2H), 3.14 (s, 3H), 4.79 (brs, 2H), 5.29 (s, 2H), 6.29 (s, 2H), 7.46 (m, 5H).
Minor diastereoisomer 1.64-1.92 (series of m, 4H), 2.17 (m, 2H), 3.41 (s, 3H), 4.67 (brs, 2H), 5.00 (s, 2H), 6.42 (s, 2H), 7.71 (m, 5H).

$\delta_C$ (75MHz, CDCl$_3$): major diastereoisomer 13.7(t), 20.5(t), 49.0(q), 66.6(t), 73.2(d), 130.6(d), 130.7(s), 130.9(d), 132.1(d), 134.1(d).
Minor diastereoisomer 13.3(t), 20.8(t), 41.1(q), 59.3(t), 75.1(d), 129.5(s), 130.4(d), 130.8(d), 131.6(d), 132.9(d).

m/z(%): (no m$^+$ found) 214 (m$^+\text{-I}^{-}) (9), 200(97), 145(36), 124(20), 110(11), 44(3).

**ATTEMPTED SELECTIVE DEBENZYLATION OF N-METHYL-N-BENZYLNORTROP-6-ENIUM IODIDE (167) USING EMDES REDUCTION.**

A solution of (167) (0.093g, 0.27 mmol) in water (4ml) was heated to reflux. Subsequently, sodium amalgam (3.00g) was added in portions over 30min. The reaction was kept at reflux for a further 7h. The solution was then decanted from the mercury residue and acidified with a 2M (aq) solution of hydrochloric acid. The solvent was removed in vacuo to yield a yellow/white solid. This solid was triturated with chloroform and the combined organic extracts were dried (MgSO$_4$). Removal of the solvent in vacuo afforded an orange oil. However analysis of this crude
material by proton n.m.r. (90MHz) showed only the presence of unreacted starting material.

ATTEMPTED SELECTIVE DEBENZYLATION OF N-BENZYNORTROP-6-ENIUM IODIDE (167) USING THIOPHENOL. 93

(167) (0.076g, 0.223 mmol) was added to a solution of thiophenol (46.0μl, 0.45 mmol) in a 20% aqueous solution of sodium hydroxide (90.0μl). The reaction mixture was sealed in a reacto-vial and heated at 90°C for 7h.

Subsequently, the aqueous solution was extracted with dichloromethane (6 X 1ml) and the combined organic extracts were dried (MgSO4). Evaporation of the solvent in vacuo, however, afforded only unreacted starting material.

PREPARATION OF TROPYLIUM TETRAFLUOROBORATE (176). 96

Cycloheptadiene (24.20g, 0.26 mol) was added to a suspension of phosphorous pentachloride (100.00g, 0.48 mol) in carbon tetrachloride (800ml). The flask was equipped with a mechanical stirrer and an exit valve, for the hydrogen chloride gas evolved. The mixture was stirred for 3h at room temperature.

Subsequently, the tropylium hexachlorophosphate-tropylium chloride double salt was separated from the reaction mixture by filtration, washed with a small amount of fresh carbon tetrachloride, and added immediately to vigorously stirred absolute ethanol (400ml), which was cooled to 0°C. A 40% aqueous solution of fluoroboric acid (90ml, 0.39 mol) was added to the resulting reddish solution and the dense, white precipitate which formed was separated by filtration, washed
with a little cold ethanol followed by diethyl ether, and air dried at room temperature to afford (176) as a cream coloured solid (33.50g, 78%).

**PREPARATION OF TROPONE (171).**

A mixture of (176) (1.00g, 5.62 mmol), anhydrous sodium carbonate (0.40g, 3.77 mmol) and dry acetonitrile (10ml) was heated to reflux under nitrogen for 1h, cooled and the solvent was removed *in vacuo*. The residue was washed with dichloromethane (6ml), filtered, washed with water (2 x 5ml) and a saturated solution of sodium chloride (5ml), dried (MgSO₄), and concentrated *in vacuo* to give a brown oil. Purification was achieved by flash chromatography (ethyl acetate) to afford (171) as a pale brown oil (0.20g, 33%).

Rf 0.36 (ethyl acetate).

δₓ (90MHz, CDCl₃): 6.94 (m, 6H).

**PREPARATION OF 1,3-CYCLOHEPTADIEN-6-OL (172).**

Sodium borohydride (0.47g, 12.5 mmol) was slowly added to a solution of (172) (0.71g, 6.60 mmol) in methanol (14ml) and distilled water (2ml) with vigorous stirring. Gas evolution occurred immediately. The mixture was stirred vigorously for 2h and any remaining hydride was then decomposed by dropwise addition of glacial acetic acid (2ml). After neutralisation with an aqueous solution of sodium bicarbonate, the mixture was extracted with diethyl ether (3 x 7ml) and the combined ethereal extracts were
dried (MgSO₄). Subsequently, the solvent was removed in vacuo to give (172) as a brown oil (0.72g, 100%).

δₜₜ (90MHz, CDCl₃): 2.40-2.58 (brt, J=3.0Hz, 4H), 2.63 (brs, exch., 1H), 4.18 (quin., J=5.0Hz, 1H), 5.80 (m, 4H).

PREPARATION OF 1,3-CYCLOHEPTADIEN-6-ONE (173). ¹⁰⁰

A solution of (171) (10.00g, 0.094 mol) in anhydrous diethyl ether (200ml) was added dropwise to a suspension of lithium aluminium hydride (2.82g, 0.074 mol) in anhydrous diethyl ether (400ml) with vigorous stirring. The mixture was stirred rapidly at room temperature for 2h and then added to glacial acetic acid (100ml) with stirring. After 10min., the mixture separated into two layers and it was then neutralised with an aqueous solution of sodium bicarbonate. The layers were separated and the organic layer was washed with a 10% aqueous solution of sodium bicarbonate (2 X 200ml), dried (MgSO₄) and concentrated in vacuo to give a brown oil. Purification was achieved by flash chromatography (79:20:1, petroleum ether (40-60°C):diethyl ether:triethylamine) to afford (173) as a yellow oil (4.07g, 40%).

Rₜ 0.63 (79:20:1, petroleum ether (40-60°C):diethyl ether:triethylamine).

δₜₜ (90MHz, CDCl₃): 3.07 (s, 2H), 3.18 (s, 2H), 5.90 (m, 2H), 6.40 (brdt, J=10.5, 2.0Hz, 2H).
PREPARATION OF 6-ACETOXY-1,3-CYCLOHEPTADIENE (179).  

(172) (0.20g, 1.79 mmol) and acetic anhydride (569.0μl) were dissolved in triethylamine (2ml) at room temperature. DMAP (0.05g, 0.44 mmol) was added in portions and the mixture was stirred at room temperature for 3.5h. Methanol (6.5ml) was added, whilst cooling the reaction mixture to 0°C, and the resulting solution was allowed to stir for a further 1.5h at room temperature. The solution was concentrated in vacuo and diethyl ether (10ml) was added. The ethereal solution was washed with a saturated solution of sodium bicarbonate (3 X 4ml) and dried (MgSO₄). Evaporation of the solvent in vacuo gave an orange oil. Purification by flash chromatography (4:1, petroleum ether (40-60°C): diethyl ether) afforded (179) as a light yellow oil (0.18g, 64%).

Rf 0.47 (80:20, petroleum ether (40-60°C): diethyl ether).

δH (90MHz, CDC13): 2.03 (s, 3H), 2.51 (m, 4H), 5.13 (m, 1H), 5.84 (m, 4H).

PREPARATION OF N-BENZOYL-3-ACETOXY-8-OXA-9-AZABICYCLO[3.2.2]NON-6-ENE (180).

(179) (0.18g, 1.15 mmol) was added to a suspension of tetramethylammonium periodate (0.43g, 1.61 mmol) in chloroform (15ml). To this mixture was added dropwise to a solution of benzohydroxamic acid (0.23g, 1.64 mmol) in dimethylformamide (1ml) and chloroform (3ml) with stirring,
at room temperature, over 20 min. The resulting mixture was left to stir for a further 5 h.

Subsequently, the chloroform was removed in vacuo. The residue was dissolved in diethyl ether (15 ml) and washed with water (3 X 4 ml). The organic layer was separated, dried (MgSO₄), and the solvent was evaporated in vacuo to yield an orange/brown gum. This crude material was purified by flash chromatography (3:1, diethyl ether:petroleum ether (40-60°C)) to afford (181) as a pale yellow, viscous oil (0.21 g, 64%).

Rf 0.19 (3:1, diethyl ether:petroleum ether (40-60°C)).

δ₉ (300 MHz, CDCl₃): major diastereoisomer (180a) 2.00 (s, 3H), 2.02 (m, 2H), 2.39 (dt, J=14.6, 6.0 Hz, 2H), 4.71 (brs, 1H), 4.82 (m, 1H), 5.39 (brs, 1H), 6.30 (dd, J=8.4, 1.3 Hz, 1H), 6.36 (dd, J=8.1, 1.5 Hz, 1H), 7.33-7.74 (m, 5H).

Minor diastereoisomer (180b) 1.97 (s, 3H), 2.08 (m, 2H), 2.55 (ddd, J=15.1, 4.9, 4.1 Hz, 2H), 4.71 (brs, 1H), 5.31 (brt, J=5.1 Hz, 1H), 5.39 (brs, 1H), 6.40 (m, 2H), 7.33-7.74 (m, 5H).

δ₁₃C (75 MHz, CDCl₃): major diastereoisomer (180a) 20.8 (q), 33.8 (t), 35.4 (t), 67.9 (d), 68.3 (d), 72.5 (d), 127.4 (d), 128.2 (d), 129.5 (d), 130.2 (d), 131.4 (d), 133.9 (s), 169.8 (s).

Minor diastereoisomer (180b) 20.9 (q), 35.2 (t), 36.7 (t), 67.9 (d), 72.5 (d), 73.3 (d), 127.4 (d), 128.2 (d), 129.5 (d), 130.2 (d), 130.4 (d), 133.9 (s), 169.4 (s).
PREPARATION OF 6-ACETOXY-CIS-4-(BENZOYLAMINO)-2-CYCLOHEPTENOL (181).

A solution of (180) (0.21g, 0.74 mmol) in 4.5ml of aqueous tetrahydrofuran (THF:H₂O, 10:1) was cooled to 0°C with stirring under nitrogen. Aluminium amalgam prepared by sequential exposure (10-20s) of small strips of aluminium foil (0.16g, 6.01 mmol) to a 1M (aq) potassium hydroxide solution, distilled water, 0.5% mercuric chloride solution, distilled water and tetrahydrofuran, was then added to the solution of Diels-Alder adduct. Stirring was continued at 0°C for a further 48h.

The reaction mixture was diluted with tetrahydrofuran (17ml), stirred vigorously for 1.5h, and then filtered through a pad of celite. The filtrate was diluted with toluene and concentrated in vacuo to yield (181) as a white crystalline solid (0.22g, 99%). An analytical sample was prepared by recrystallisation from toluene, m.p. 168-169°C.

C₁₆H₁₉O₄N \text{Requires} \quad \text{C 66.42\% H 6.62\% N 4.84\%}

\text{Found} \quad \text{C 66.17\% H 6.45\% N 4.74\%}

\nu_{\text{max}} \ (\text{CH}_2\text{Cl}_2) \quad 3445\text{s}, 3285\text{s}, 3050\text{m}, 2950\text{m}, 2930\text{m}, 2820\text{w},
1705\text{s}, 1625\text{s}, 1600\text{m}, 1575\text{m}, 1550\text{s}, 1480\text{w}, 1445\text{m}, 1425\text{m},
1375\text{m},1340\text{m}, 1325\text{m}, 1265\text{s} \text{ cm}^{-1}.

\delta_{\text{H}} \ (300MHz, \text{CD}_3\text{OD}): \text{major diastereoisomer} \quad 1.41 \ (s, \ 2\text{H}),
1.70 \ (q, J=11.5\text{Hz}, \ 1\text{H}), 1.79 \ (q, J=11.5\text{Hz}, \ 1\text{H}), 2.02 \ (s, \ 3\text{H}), 4.42 \ (m, \ 1\text{H}), 4.65 \ (m, \ 1\text{H}), 5.10 \ (tt, J=11.2, 3.6\text{Hz},
1H), 5.67 (dt, J=11.8, 2.8Hz, 1H), 5.82 (m, 1H), 7.41-7.55 (m, 3H), 7.79-7.85 (m, 2H).

Minor diastereoisomer 2.07-2.25 (m, 4H), 2.15 (s, 3H), 4.80 (brm, 1H), 5.03 (brm, 1H), 5.32 (sept, J=2.7Hz, 1H), 5.76 (m, 1H), 5.87 (m, 1H), 7.41-7.55 (m, 3H), 7.79-7.85 (m, 2H).

δC (75MHz, CD3OD): major diastereoisomer 21.2(q), 39.7(t), 42.5(t), 47.0(d), 66.7(d), 72.1(d), 128.0(d), 129.1(d), 132.3(d), 132.4(d), 135.1(s), 138.0(d), 171.2(s).

Minor diastereoisomer 21.3(q), 38.2(t), 40.2(t), 45.8(d), 65.9(d), 70.6(d), 125.9(d), 128.0(d), 129.1(d), 133.5(d), 135.1(s), 138.1(d), 168.9(s).

m/z(%): 290 (mH+) (51), 272(100), 230(6), 205(3), 139(11), 122(34), 105(11).

C16H20O4N [mH+] Requires 290.1392
Found 290.1392

PREPARATION OF 6-ACETOXY-CIS-4-(BENZOYLAMINO)CYCLOHEPTANOL (182).

A solution of (181) (0.11g, 0.39 mmol) in methanol (4ml) was hydrogenated in the presence of 5% palladium on charcoal. After 16h, the catalyst was filtered off and the solvent was removed in vacuo to give (182) as a viscous, colourless oil which crystallised on standing (0.11g, 99%).

Vmax (CH2Cl2): 3670w, 3600w, 3440m, 3370w, 2940m, 2860w, 1720s, 1650s, 1600m, 1575m, 1510s, 1480s, 1365m, 1235s cm⁻¹.
δ_H (300MHz, CD3OD): major diastereoisomer 1.40 (s, 2H),
1.75-2.06 (series of m, 6H), 2.00 (s, 3H), 3.95 (brm, 1H),
4.10 (brm, 1H), 4.28 (brm, 1H), 7.38-7.52 (m, 3H), 7.78-7.83 (m, 2H).

Minor diastereoisomer 2.01-2.32 (series of m, 8H), 2.22 (s, 3H),
4.78 (brm, 1H), 4.92 (brm, 1H), 5.22 (brm, 1H), 7.38-7.52 (m, 3H), 7.78-7.83 (m, 2H).

δ_C (75MHz, CD3OD): major diastereoisomer 21.2(q), 29.2(t),
33.3(t), 41.9(t), 44.2(t), 48.5(d), 67.9(d), 70.2(d),
128.2(d), 129.3(d), 132.4(d), 135.7(s), 171.6(s).

Minor diastereoisomer 21.4(q), 29.1(t), 33.4(t), 40.2(t),
42.5(t), 47.0(d), 67.3(d), 69.6(d), 126.0(d), 128.2(d),
129.3(d), 135.7(s), 169.0(s).

m/z (%): 292 (mH+) (100), 276 (50), 244 (16), 230 (19), 219 (16),
139 (20), 122 (31), 105 (9).

C_{16}H_{22}NO_{4} [mH+] Requires 292.1549
Found 292.1549

PREPARATION OF 6-BUTYLDIMETHYL SILOXY-1,3-CYCLOHEPTADIENE (183).

Tert-butyldimethylsilyl chloride (0.91g, 6.05 mmol) was
added to a stirred solution of (172) (0.61g, 5.50 mmol) and
imidazole (0.82g, 12.10 mmol) in dry dichloromethane (5ml).
The mixture was left to stir at room temperature for a
further 4h.
Subsequently, the precipitated imidazole hydrochloride was filtered off and washed with dichloromethane. The filtrate was collected and the solvent was removed in vacuo, to yield a pale orange oil. Purification by flash chromatography (diethyl ether) gave (183) as a yellow oil (1.08g, 87%).

\[ \text{\( \nu_{\text{max}} (\text{CH}_2\text{Cl}_2): \) 3020m, 2960s, 2930s, 2900s, 2860s, 1615w, 1585w, 1470m, 1465m, 1390m, 1380m, 1360m, 1245m cm}^{-1} \]

\[ \delta_H (300MHz, \text{CDCl}_3): \] 0.11 (m, 6H), 0.94 (m, 9H), 2.52 (m, 4H), 4.10 (m, 1H), 5.70 (m, 2H), 5.84, 2H).

\[ \delta_C (75MHz, \text{CDCl}_3): \] -4.8 (q), 25.9 (q), 40.9 (t), 71.4 (d), 126.0 (d), 128.0 (d).

\[ m/z(\%) : \text{(No m}^+\text{ found) } 167 (m^+\text{-tBu}) (29), 149(9), 91(56), 75(100), 57(16), 41(29). \]

\[ \text{C}_{13}\text{H}_{25}\text{OSi } [\text{mH}^+] \text{ Requires 225.1674} \]

\[ \text{Found } 225.1675 \]

**PREPARATION OF N-BENZOYL-3-\text{\textasciitilde}BUTYLDIMETHYLSILOXY-8-OXA-9-AZA-BICYCLO[3.2.2]NON-6-ENE (184).**

(183) (0.79g, 3.51 mmol) was added to a suspension of tetramethyl ammonium periodate (1.3g, 4.90 mmol) in chloroform (46ml). To this mixture a solution of benzohydroxamic acid (0.69g, 5.00mmol.) in dimethylformamide (3ml) and chloroform (10ml) was added dropwise, with
stirring, at room temperature, over 20 min. The resulting mixture was left to stir for a further 4 h. Subsequently, the chloroform was removed in vacuo. The residue was dissolved in diethyl ether (68 ml) and washed with water (3 X 17 ml). The organic layer was separated, dried (MgSO₄) and the solvent was removed in vacuo to yield a brown gum. This crude material was purified by flash chromatography (2:3 petroleum ether (40-60°C): diethyl ether) to afford (184) as a glass (0.80 g, 64%). An analytical sample was prepared by recrystallisation from petroleum ether (80-100°C).

\[ R_f \ 0.22 \quad (2:3 \text{ petroleum ether (40-60°C): diethyl ether}). \]

C₂₀H₂₉NO₃Si Requires C 66.81% H 8.13% N 3.89%

Found C 66.51% H 7.80% N 3.79%

\[ \nu_{\text{max}} \quad (\text{CH}_2\text{Cl}_2): \ 2950 \text{m}, 2920 \text{m}, 2880 \text{w}, 2850 \text{m}, 1635 \text{m}, 1610 \text{s}, 1570 \text{w}, 1445 \text{m}, 1370 \text{m}, 1360 \text{w}, 1300 \text{w}, 1235 \text{w} \ \text{cm}^{-1}. \]

\[ \delta_H \quad (300 \text{MHz, CDCl}_3): \ 	ext{major diastereoisomer (184a)} \ 0.05 \ (s, 3H), 0.06 \ (s, 3H), 0.90 \ (s, 9H), 2.02 \ (\text{ddd, } J=14.3, 10.2, 1.5 \text{Hz}, 2H), 2.29 \ (m, 2H), 3.80 \ (\text{brm, 1H}), 4.70 \ (\text{brs, 1H}), 5.43 \ (\text{brs, 1H}), 6.34 \ (\text{brdd, } J=6.4, 1.5 \text{Hz}, 2H), 7.35-7.75 \ (m, 5H). \]

\[ \text{Minor diastereoisomer (184b)} \ 0.08 \ (s, 3H), 0.09 \ (s, 3H), 0.90 \ (s, 9H), 1.85 \ (\text{brm, 2H}), 2.49 \ (\text{brm, 2H}), 4.44 \ (\text{brs, 1H}), 4.70 \ (\text{brs, 1H}), 5.43 \ (\text{brs, 1H}), 6.43 \ (\text{brdd, } J=5.8, 1.5 \text{Hz}, 2H), 7.35-7.75 \ (m, 5H). \]
$\delta_C$ (75MHz, CDCl$_3$): -4.8(q), 17.9(s), 25.7(q), 38.0(t), 40.5(t), 66.4(d), 68.0(d), 73.2(d), 127.6(d), 128.3(d), 128.5(d), 129.6(d), 130.2(d), 132.2(d).

m/z(%): 359(m$^+$)(3), 302(12), 223(11), 179(10), 105(100), 77(26), 75(22), 72(13).

**PREPARATION OF 6-\textit{BUTYLDIMETHYLSILOXY-CIS-4-(BENZOYL AMINO)-2-CYCLOHEPTENOL (185).**

A solution of (184) (0.15g, 0.43 mmol) in 3ml of aqueous tetrahydrofuran (THF:H$_2$O, 10:1) was cooled to 0°C with stirring under nitrogen. Aluminium amalgam prepared by sequential exposure (10-20s) of small strips of aluminium foil (0.01g, 3.51 mmol) to a 1M (aq) potassium hydroxide solution, distilled water, 0.5% mercuric chloride solution, distilled water and tetrahydrofuran, was then added to the solution of the Diels-Alder adduct. Stirring was continued at 0°C for a further 18h.

The reaction mixture was diluted with tetrahydrofuran (8ml), stirred vigorously for 1.5h, and then filtered through a pad of celite. The filtrate was diluted with toluene and concentrated in vacuo to yield (185) as a glass (0.15g, 94%). An analytical sample was prepared by recrystallisation from toluene, m.p. 54-55°C.

C$_{20}$H$_{31}$O$_3$NSi Requires C 66.44% H 8.64% N 3.87%

Found C 66.70% H 8.79% N 3.71%

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$v_{\text{max}}$ (CH$_2$Cl$_2$): 3620m, 3400s, 2940s, 2850s, 1645s, 1600m, 1575m, 1515s, 1480m, 1445m, 1365m cm$^{-1}$.

$\delta_H$ (300MHz, CDCl$_3$): major diastereoisomer 0.30 (s, 3H), 0.32 (s, 3H), 1.09 (s, 9H), 1.75-2.43 (series of m, 4H), 4.23 (m, 1H), 4.53 (brd, $J=11.1$Hz, 1H), 4.76 (brd, $J=11.1$Hz, 1H), 5.85 (brm, 1H), 5.97 (brm, 1H), 7.59-7.75 (m, 3H), 7.96-8.07 (m, 2H).

Minor diastereoisomer 0.31 (s, 3H), 0.32 (s, 3H), 1.15 (s, 9H), 1.75-2.43 (series of m, 4H), 5.00-5.07 (overlapping with MeOH, 2H), 5.35 (brs, 1H), 5.85 (brm, 1H), 5.97 (brm, 1H), 7.59-7.75 (m, 3H), 7.96-8.07 (m, 2H).

$\delta_C$ (75MHz, CDCl$_3$): major diastereoisomer -4.1(q), 19.2(s), 26.6(q), 44.3(t), 47.3(t), 47.8(d), 67.5(d), 71.7(d), 128.6(d), 129.8(d), 132.8(d), 132.9(d), 135.9(s), 138.8(d), 169.5(s).

Minor diastereoisomer -4.1(q), 19.2(s), 26.7(q), 42.5(t), 44.7(t), 46.2(d), 66.6(d), 69.0(d), 128.5(d), 128.9(d), 133.1(d), 134.6(d), 135.9(s), 139.2(d), 169.5(s).

m/z(%): (no m$^+$ found) 344 (m$^+$/OH) (10), 304 (33), 212 (19), 178 (26), 105 (100), 91 (13), 77 (36), 57 (10), 41 (7).

C$_{20}$H$_{32}$O$_3$NSi [mH$^+$] Requires 362.2151

Found 362.2151
PREPARATION OF 6-5-BUTYLDIMETHYL SILOXY-CIS-4-(BENZOYLAMINO) CYCLOHEPTANOL (187).

A solution of (185) (0.20g, 0.50 mmol) in methanol (6ml) was hydrogenated in the presence of 5% palladium on charcoal. After 4h, the catalyst was filtered off and the solvent was removed in vacuo to afford (187) as a pale yellow, thick gum which crystallised on standing (0.20g, 99%).

V<sub>max</sub> (CH<sub>2</sub>Cl<sub>2</sub>): 3660w, 3600w, 3440m, 3400m, 2930s, 2890m 2860s, 1650s, 1600m, 1575m, 1510s, 1480s, 1360m, 1320m, 1240m cm<sup>-1</sup>.

δ<sub>H</sub> (300MHz, CD<sub>3</sub>OD): major diastereoisomer 0.09 (s, 3H), 0.11 (s, 3H), 0.89 (s, 9H), 1.40-1.94 (series of m, 8H), 3.33 (brm, 1H), 3.89 (brm, 1H), 4.07 (brm, 1H), 7.40-7.53 (m, 3H), 7.76-7.83 (m, 2H).

Minor diastereoisomer 0.09 (s, 3H), 0.11 (s, 3H), 0.92 (s, 9H), 1.70-1.94 (series of m, 4H), 2.10 (brm, 2H), 2.25 (brm, 2H), 3.84 (brm, 1H), 4.24 (brm, 1H), 4.35 (brm, 1H), 7.40-7.53 (m, 3H), 7.76-7.83 (m, 2H).

δ<sub>C</sub> (75MHz, CDCl<sub>3</sub>): major diastereoisomer -4.3(q), 19.2(s), 26.6(q), 30.0(t), 34.2(t), 48.7(d), 48.8(t), 68.6(d), 69.5(d), 128.5(d), 129.7(d), 132.7(d), 136.2(s), 169.4(s).
Minor diastereoisomer -4.3(q), 19.2(s), 26.7(q), 30.2(t), 34.3(t), 43.6(t), 46.2(t), 47.8(d), 67.9(d), 68.8(d), 128.5(d), 129.7(d), 132.6(d), 136.2(s), 169.4(s).

m/z(%): 364(mH+) (100), 348(31), 219(50), 139(57), 122(50).

C_{20}H_{34}NO_3Si [mH+] Requires 364.2308
Found 364.2308

PREPARATION OF 6-tert-BUTYLDIPHENYL SILOXY-1,3-CYCLOHEPTADIENE (190).

Tert-butyldiphenylsilyl chloride (1.82ml, 7.00 mmol) was added to a solution of (172) (0.70g, 6.37 mmol) and imidazole (0.95g, 14.00 mmol) in dry dichloromethane (10ml). The mixture was left to stir at room temperature overnight. Subsequently, the precipitated imidazole hydrochloride was filtered off and washed with dichloromethane. The filtrate was collected and the solvent was removed from the filtrate in vacuo, to yield an orange oil. Purification was achieved by flash chromatography (4:1, petroleum ether (40-60°C):diethyl ether) to afford (190) as a pale yellow oil (1.82g, 82%).

Rf 0.78 (4:1, petroleum ether (40-60°C):diethyl ether).

V_{max} (CH_2Cl_2): 3070w, 3020m, 2960m, 2930s, 2900m, 2860m, 1590w, 1470w, 1425m, 1390w, 1375w, 1360w, 1220w cm^{-1}.
\( \delta_H \) (300MHz, CDCl\(_3\)): 1.06 (s, 9H), 2.44 (brt, \( J=5.5\text{Hz} \), 4H), 4.12 (m, 1H), 5.54 (m, 2H), 5.73 (m, 2H), 7.32-7.45 (m 6H), 7.66 (m, 4H).

\( \delta_C \) (75MHz, CDCl\(_3\)): 19.2 (s), 27.0 (q), 40.3 (t), 72.5 (d), 126.1 (d), 127.5 (d), 128.1 (d), 129.5 (d), 134.4 (s), 135.8 (d).

m/z(%): 349 (mH\(^+\)) (14), 308 (20), 274 (34), 216 (21), 196 (40), 110 (53), 93 (100).

C\(_{23}\)H\(_{29}\)O\(_3\)Si \[mH\(^+\)\] Requires 349.1987

Found 349.1988

PREPARATION OF N-BENZOYL-3-\( \text{\textsuperscript{t}}\)BUTYLDIPHENYLISILOXY-8-OXA-9-AZA
BICYCLO[3.2.2]NON-6-ENE (191).

(190) (7.80 g, 22.4 mmol) was added to a suspension of
tetramethylammonium periodate (8.29 g, 31.3 mmol) in
chloroform (296 ml). To this mixture a solution of
benzohydroxamic acid (4.38 g, 31.93 mmol) in
dimethylformamide (21 ml) and chloroform (63 ml) was added
dropwise, with stirring, at room temperature, over 20 min.
The resulting mixture was left to stir overnight.

Subsequently, the chloroform was removed in vacuo. The
residue was dissolved in diethyl ether (423 ml) and washed
with water (3 \times 106 ml). The organic layer was separated,
dried (MgSO\(_4\)) and the solvent was evaporated in vacuo to
yield an orange gum. This crude material was purified by
flash chromatography (3:2, petroleum ether (40-60\(^\circ\)C):diethyl ether) to afford (192) as a glass (9.51 g, 88\%). An
analytical sample was prepared by recrystallisation from petroleum ether (80-100°C), m.p. 35-36°C.

Rf 0.35 (3:2, petroleum ether (40-60°C):diethyl ether).

C₃₀H₃₄NO₃Si Requires C 74.50% H 6.88% N 2.90%

Found C 74.40% H 7.09% N 2.88%

νₘₐₓ (CH₂Cl₂): 3050w, 2960s, 2930s, 2860m, 1705m, 1610s, 1570w, 1445m, 1425m, 1370m, 1360m, 1300w, 1220w cm⁻¹.

δ_H (300MHz, CDCl₃): major diastereoisomer (191a) 1.10 (brs, 9H), 1.93-2.40 (series of m, 4H), 3.83 (brm, 1H), 4.63 (brs, 1H), 5.37 (brs, 1H), 6.15 (brm, 2H), 7.38-7.51 (m, 9H), 7.65-7.75 (m, 6H).

Minor diastereoisomer (191b) 1.10 (brs, 9H), 1.93-2.40 (series of m, 4H), 4.47 (brs, 1H), 4.70 (brs, 1H), 5.37 (brs, 1H), 6.50 (brm, 2H), 7.38-7.51 (m, 9H), 7.65-7.75 (m, 6H).

δ_C (75MHz, CDCl₃): 19.0(s), 26.9(q), 37.8(t), 40.2(t), 67.3(d), 68.8(d), 73.1(d), 127.5-135.6 (20 carbon atoms, 17(d) and 3(s)).

m/z(%): 484(mH⁺)(100), 468(3), 426(4), 228(4), 196(7), 139(7), 122(19), 105(14).

C₃₀H₃₄NO₃Si [mH⁺] Requires 484.2308

Found 484.2308
PREPARATION OF 6-TERT-BUTYLDIPHENYLSSILoxy-cis-4-(BENZOYLAMINO)-2-CYCLOHEPTENOL (192).

A solution of (191) (3.01g, 6.23 mmol) in 38ml of aqueous tetrahydrofuran (THF:H\textsubscript{2}O, 10:1) was cooled to 0°C with stirring under nitrogen. Aluminium amalgam prepared by sequential exposure (10-20s) of small strips of aluminium foil (1.37g, 0.051 mol) to 1M (aq) potassium hydroxide solution, distilled water, 0.5% mercuric chloride solution, distilled water and terahydrofuran, was then added to the solution of Diels-Alder adduct. Stirring was continued at 0°C for 4 days. Subsequently, fresh aluminium amalgam (0.68g of Al foil, 0.025mol.) was added to the reaction mixture, and the reaction was left to stir at 0°C for another day.

The reaction mixture was diluted with tetrahydrofuran (105ml), stirred vigorously for 1.5h, and then filtered through celite. The filtrate was diluted with toluene and concentrated in vacuo to yield (192) as a white crystalline solid (2.94g, 97%). An analytical sample was prepared by recrystallisation from toluene, m.p. 141-142°C.

C\textsubscript{30}H\textsubscript{35}NO\textsubscript{3}Si Requires C 74.19% H 7.26% N 2.88%

Found C 74.00% H 7.49% N 2.69%

\(\nu_{max}\) (CH\textsubscript{2}Cl\textsubscript{2}): 3600w, 3440w, 3400w, 3070w, 3020w, 2930m, 2890m, 2860s, 1580w, 1510s, 1480m cm\textsuperscript{-1}. 

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$\delta_H$ (300MHz, CDCl$_3$): major diastereoisomer 1.02 (s, 6H), 1.09 (s, 3H), 1.71-2.15 (series of m, 4H), 4.15 (m, 2H), 4.56 (brm, 1H), 5.71 (m, 2H), 7.23-7.75 (series of m, 15H).
Minor diastereoisomer 1.02 (s, 6H), 1.09 (s, 3H), 1.71-2.15 (series of m, 4H), 4.30 (brm, 1H), 4.84 (brm, 1H), 5.25 (brm, 1H), 5.80 (m, 2H), 7.23-7.75 (series of m, 15H).

$\delta_C$ (75MHz, CDCl$_3$): major diastereoisomer 19.1(s), 27.0(q), 40.9(t), 45.4(t), 46.6(d), 66.5(d), 70.3(d), 126.9(d), 127.67(d), 127.7(d), 128.4(d), 129.8(d), 131.36(d), 131.4(d), 133.4(s), 133.5(s), 134.4(s), 135.7(d), 137.1(d), 166.7(s).
Minor diastereoisomer 19.2(s), 27.1(q), 40.9(t), 43.2(t), 44.4(d), 65.4(d), 67.8(d), 126.9(d), 127.55(d), 127.6(d), 128.4(d), 129.7(d), 131.2(d), 133.7(d), 133.81(s), 133.83(s), 134.43(s), 137.1(d), 166.6(s).

m/z(%): 486(mH$^+$) (11), 468(97), 428(7), 408(7), 276(6), 232(10), 212(13), 196(10), 139(9), 122(39), 105(17).

**PREPARATION OF 6-$t$-BUTYLDIPHENYLSILOXY-CIS-4-(BENZOYLAMINO) CYCLOHEPTANOL (193).**

A solution of (192) (1.48g, 3.06 mmol) in methanol (32ml) was hydrogenated in the presence of 5% palladium on charcoal. After 6h, the catalyst was filtered off and the solvent evaporated in vacuo to afford (193) as a white crystalline solid (1.49g, 99%). An analytical sample was prepared by recrystallisation from toluene, m.p. 47-48°C.
C$_{30}$H$_{37}$NO$_3$Si  Requires  C 73.88%  H 7.65%  N 2.87%
    Found  C 73.56%  H 7.83%  N 2.91%

$\nu_{\text{max}}$ (CH$_2$Cl$_2$):  3600w, 3440m, 3400w, 3040w, 2930s, 2890m,
  2860s, 1645s, 1600w, 1575m, 1510s, 1480s, 1415m cm$^{-1}$.

$\delta_H$ (300MHz, CD$_3$OD):  major diastereoisomer  1.24 (s, 6H),
  1.28 (s, 3H),  1.45-2.49 (series of m, 8H),  4.05 (m, 2H),
  4.40 (m, 1H),  7.48-7.77 (series of m, 15H).
Minor diastereoisomer  1.24 (s, 6H),  1.28 (s, 3H),  1.45-2.49
  (series of m, 8H),  3.74 (m, 2H),  4.73 (brm, 1H),  7.48-7.77
  (series of m, 15H).

$\delta_C$ (75MHz, CD$_3$OD):  major diastereoisomer 19.6(s),
  27.4(q), 29.1(t), 33.3(t), 45.3(t), 48.1(d), 48.3(t),
  67.8(d), 69.4(d), 128.0(d), 128.4(d), 128.5(d), 129.1(d),
  130.6(d), 132.1(d), 134.7(s), 135.5(s), 135.7(s), 136.5(d),
  168.6(s).
Minor diastereoisomer  19.8(s), 27.5(q), 30.0(t), 33.9(t),
  42.5(t), 45.1(t), 46.9(d), 68.2(d), 68.5(d), 128.0(d),
  128.4(d), 128.5(d), 129.1(d), 130.5(d), 132.0(d), 134.8(s),
  135.6(s), 136.2(s), 136.6(d), 168.4(s).

m/z(%):  488(mH$^+$) (97), 430(34), 410(66), 352(7), 232(18),
    214(9), 122(24), 105(41).

C$_{30}$H$_{38}$NO$_3$Si  [mH$^+$] Requires  488.2620
          Found  488.2620
REDUCTION OF (193) WITH LITHIUM ALUMINIUM HYDRIDE TO FORM 6-
\(^{1}\)BUTYLDIPHENYLSILOXY-CIS-4-(BENZYLAMINO)CYCLOHEPTANOL (194).

Lithium aluminium hydride (0.14g, 3.80 mmol) was carefully
added to a stirred solution of (193) (0.43g, 0.88 mmol) in
dry tetrahydrofuran (7ml). After heating at reflux for 5h,
decomposition of excess hydride was effected by addition of
a water-saturated solution of diethyl ether. The resulting
solution was dried (MgSO\(_4\)) and the solvent was removed in
vacuo. The crude residue was purified by flash
chromatography (95:4:1, diethyl
ether:methanol:triethylamine) to afford (194) as a viscous,
colourless oil (0.12g, 28%).

R\(_f\) 0.3 (95:4:1, diethyl ether:methanol:triethylamine).

\(\nu_{\text{max}}\) (CH\(_2\)Cl\(_2\)): 3670w, 3590w, 2930s, 2890m, 2850s, 1105s,
1065s cm\(^{-1}\).

\(\delta\)\(_H\) (300MHz, CDC\(_3\)): 1.06 (s, 9H), 1.60-1.90 (series of m,
7H), 2.19 (brm, 1H), 2.89 (m, 1H), 3.26, 3.43 (AB quartet,
J=12.8Hz, 2H), 4.02 (m, 1H), 4.25 (m, 1H), 7.06 (dd, J=7.7,
1.6Hz, 2H), 7.22-7.36 (m, 9H), 7.65-7.71 (m, 4H).

\(\delta\)\(_C\) (75MHz, CDC\(_3\)): 19.1(s), 27.0(q), 28.6(t), 32.3(t),
42.5(t), 44.7(t), 51.2(t), 51.9(d), 66.4(d), 66.7(d),
127.0(d), 127.5(d), 128.1(d), 128.3(d), 129.5(d), 134.0(s),
134.4(s), 135.8(d), 139.3(s).
m/z(%): 474 (mH\(^+\)) (97), 456 (7), 234 (4), 216 (14), 196 (10),
122 (10), 106 (33), 91 (24).

C\(_{30}\)H\(_{40}\)NO\(_3\)Si \(\text{[mH\(^{+}\)]}\) Requires 474.2828
Found 474.2830

Other products isolated from the reaction were:

1) Tert-butyldiphenylsilyl hydroxide.

\(\delta_\text{H} \) (90MHz, CD\(_3\)Cl\(_3\)): 1.10 (s, 6H), 1.52 (s, 3H), 4.61 (s,
1H), 7.21-7.47 (m, 10H), 7.52-7.78 (m, 5H).

(2) 6-Hydroxy-cis-4-(benzoylamino)cycloheptanol (186).

\(\nu_{\text{max}} \) (CH\(_2\)Cl\(_2\)): 3610w, 3400w, 2960s, 2930w, 2860m, 1640s,
1600w, 1580m, 1450m, 1410m cm\(^{-1}\).

\(\delta_\text{H} \) (300MHz, CD\(_3\)OD): 1.72-2.53 (series of m, 8H), 3.97 (tt,
J=10.5, 2.8Hz, 1H), 4.08 (m, 1H), 4.26 (m, 1H), 7.58-7.73
(m, 3H), 7.95-8.03 (m, 2H).

\(\delta_\text{C} \) (75MHz, CD\(_3\)OD): 29.9 (t), 34.0 (t), 45.6 (t), 48.0 (t),
49.0 (d), 67.8 (d), 68.7 (d), 128.5 (d), 129.7 (d), 132.7 (d),
136.2 (s), 169.4 (s).

m/z(%): 250 (mH\(^{+}\)) (100), 232 (17), 216 (6), 146 (4), 122 (7),
105 (10).
C_{14}H_{20}NO_3 \quad [\text{mH}^+] \quad \text{Requires} \quad 250.1443
\text{Found} \quad 250.1447

(3) 6-Hydroxy-cis-4-(benzylamino)cycloheptanol (188).

\nu_{\text{max}} \quad (\text{nujol mull}): \quad 3640\text{w}, \quad 3580\text{w}, \quad 3440\text{s}, \quad 3060\text{m}, \quad 3030\text{m},
\quad 2930\text{s}, \quad 2860\text{s}, \quad 1640\text{w}, \quad 1495\text{w}, \quad 1460\text{m}, \quad 1450\text{m}, \quad 1365\text{m}, \quad 1265\text{s},
\quad 1220\text{s} \; \text{cm}^{-1}.

\delta_H \quad (300\text{MHz, CDCl}_3): \quad 1.55-2.08 \; (\text{series of m, 8H}), \quad 2.76
\quad (\text{brs, exch., 1H}), \quad 3.71 \; (\text{brs, 2H}), \quad 3.64-4.04 \; (\text{br, series of}
\quad \text{m, 3H}), \quad 7.15-7.40 \; (\text{brm, 5H}).

\delta_C \quad (75\text{MHz, CDCl}_3): \quad 28.0(t), \quad 31.9(t), \quad 42.2(t), \quad 45.2(t),
\quad 50.8(t), \quad 53.9(d), \quad 67.7(d), \quad 68.3(d), \quad 126.8(d), \quad 127.9(d),
\quad 128.2(d), \quad 139.3(s).

m/z(\%): \quad 236(\text{mH}^+)\; (60), \quad 220(97), \quad 205(9), \quad 196(46), \quad 146(3),
\quad 108(17), \quad 91(9).

C_{14}H_{22}NO_2 \quad [\text{mH}^+] \quad \text{Requires} \quad 236.1650
\text{Found} \quad 236.1651
REDUCTION OF (192) WITH LITHIUM ALUMINIUM HYDRIDE TO FORM 6-
BUTYLDIPHENYLSILOXY-CIS-4-(BENZYLAMINO)-2-CYCLOHEPTENOL
(195).

Lithium aluminium hydride (0.08g, 2.00 mmol) was carefully
added to a stirred solution of (192) (0.22g, 0.46 mmol) in
dry tetrahydrofuran (4ml). After heating at reflux for 5h,
decomposition of the excess hydride was effected by addition
of a water-saturated solution of diethyl ether. The
resulting solution was dried (MgSO₄) and the solvent was
removed in vacuo. The crude residue was purified by flash
chromatography (99:1, diethyl ether:triethylamine) to afford
(195) as a viscous oil (0.03g, 14%).

\textit{Rf} 0.44 (99:1, diethyl ether:triethylamine).

\(\nu_{\max} (\text{CH}_2\text{Cl}_2): 3600w, 3180w, 3070w, 3020m, 2930s, 2890m,
2860m, 1450m, 1425w \text{ cm}^{-1}.\)

\(\delta_H (300\text{MHz, CDCl}_3): 1.06 (s, 9H), 1.55-1.80 \text{ (series of } m,
3H), 2.19 \text{ (brm, } 1H), 3.30, 3.46 \text{ (AB quartet, } J=12.9\text{Hz, } 2H),
3.35 \text{ (brtd, } J=6.9, 1.7\text{Hz, } 1H), 4.20 \text{ (m, } 2H), 5.83 \text{ (dd,}
J=11.3, 6.3\text{Hz, } 1H), 6.12 \text{ (dd, } J=11.3, 6.3\text{Hz, } 1H), 7.07 \text{ (dd,}
J=7.7, 1.6\text{Hz, } 2H), 7.22-7.40 \text{ (series of } m, 9H), 7.64-7.71
\text{ (series of } m, 4H).\)

\(\delta_C (75\text{MHz, CDCl}_3): 19.2(s), 27.0(q), 40.5(t), 43.1(t),
51.0(d), 51.4(t), 64.6(d), 67.5(d), 127.1(d), 127.6(d),\)
128.1(d), 128.4(d), 129.7(d), 134.0(s), 134.35(s), 134.4(d),
135.8(d), 138.6(d), 139.2(s).

m/z(%) : 472(mH+)(97), 414(2), 274(3), 216(10), 196(10),
108(21), 91(7).

C₃₀H₃₈NO₂Si [mH+] Requires 472.2671
Found 472.2672

**CYCLISATION OF (194) TO GIVE N-BENZYL-3-L-BUTYLDIPHENYL
SILOXY NORTROPANE (196).**

Thionyl bromide (7.0μl, 0.086 mmol) was added to a
solution of (194) (0.037g, 0.08 mmol) in dry deuterated
chloroform (1ml) at 0°C. The reaction mixture was allowed
to warm to room temperature and it was left for 29h.
Subsequently, the solvent was removed *in vacuo* and replaced
with dry acetone (1ml). After cooling to 0°C, anhydrous TMP
(50.0μl) was added and the solution was allowed to warm to
room temperature, whereupon it was heated at 50°C for 4h.

The solvent was removed *in vacuo* and the brown oily
residue was triturated with diethyl ether. The combined
ethereal extracts were basified with gaseous ammonia and the
white solid formed was removed by filtration. Solvent
evaporation of the filtrate *in vacuo* gave an orange oil.
Purification by flash chromatography (80:19:1, petroleum
ether (40-60°C):diethyl ether:triethylamine) afforded (196)
as a pale yellow oil (0.005g, 15%).
Rf 0.5 (80:19:1, petroleum ether (40-60°C):diethyl ether:triethylamine).

ν<sub>max</sub> (CH<sub>2</sub>Cl<sub>2</sub>): 3070 w, 3020 w, 2950 s, 2930 s, 2890 m, 2850 s, 1460 w, 1425 w, 1385 w, 1340 w, 1110 s, 1065 s, 1050 s cm<sup>-1</sup>.

δ<sub>H</sub> (300MHz, CDCl<sub>3</sub>): 1.08 (s, 9H), 1.25-2.37 (series of m, 8H), 3.09 (brs, 2H), 3.51 (s, 2H), 4.05 (brt, J=5.0Hz, 1H), 7.18-7.66 (series of m, 15H).

m/z (%): 456 (mH<sup>+</sup>) (100), 391 (21), 366 (12), 279 (2), 200 (10), 159 (7), 108 (5), 91 (5).

C<sub>30</sub>H<sub>38</sub>NOSi [mH<sup>+</sup>] Requires 456.2722
Found 456.2723

PREPARATION OF 1,3-CYCLOHEPTADIEN-6-ONE ETHYLENE ACETAL (197).

A mixture of (173) (3.98g, 36.81 mmol), benzene (50ml), ethylene glycol (2.26ml, 40.49 mmol) and toluene-4-sulphonic acid monohydrate (0.018g) was brought to reflux in a Dean and Stark apparatus for 2h. The reaction was stopped when no further water appeared to collect. The reaction mixture was cooled, and washed with a 2M (aq) solution of sodium hydroxide (15ml), followed by water (2 x 20ml). The organic layer was separated and dried over anhydrous sodium carbonate. Solvent evaporation in vacuo yielded an orange oil, which was purified by flash chromatography (79:20:1,
petroleum ether (40-60°C): diethyl ether: triethylamine) to give (197) as a yellow oil (3.56g, 64%).

Rf 0.48 (79:20:1, petroleum ether (40-60°C): diethyl ether: triethylamine).

νmax (CH₂Cl₂): 3025m, 2960m, 2885m, 1710w, 1655w, 1585w, 1475w, 1425w, 1370w, 1340m cm⁻¹.

δH (300 MHz, CDCl₃): 2.51 (d, J=5.0Hz, 4H), 3.96 (s, 4H), 5.75 (m 2H), 5.99 (m, 2H).

δC (75 MHz, CDCl₃): 39.9 (t), 64.3 (t), 127.0 (d), 127.3 (d).

m/z (%): 152 (m⁺) (61), 141 (26), 128 (19), 115 (29), 99 (17), 91 (50), 86 (70), 79 (100), 73 (17), 65 (20), 55 (30), 43 (57).

C₉H₁₂O₂ [m⁺] Requires 152.0837
               Found 152.0837

PREPARATION OF N-BENZOYL-8-OXA-9-AZABICYCLO[3.2.2]NON-6-EN-3-ONE ETHYLENE ACETAL (198).

(197) (3.56g, 23.42 mmol) was added to a suspension of tetramethylammonium periodate (8.66g, 32.69 mmol) in chloroform (309ml). To this mixture a solution of benzohydroxamic acid (4.57g, 33.35 mmol) was added dropwise in dimethylformamide (22ml) and chloroform (66ml) with stirring, at room temperature, over 20min. The resulting mixture was left stirring overnight.
Subsequently, the chloroform was removed \textit{in vacuo}. The residue was dissolved in diethyl ether (442 ml) and washed with water (3 X 110 ml). The organic layer was separated, dried (MgSO$_4$) and the solvent was removed \textit{in vacuo} to yield an orange oil. This crude material was purified by flash chromatography (90:9:1, diethyl ether:petroleum ether (40-60°C):triethylamine) to afford (198) as a pale yellow, viscous oil (3.96 g, 59%).

$R_f$ 0.35 (90:9:1, diethyl ether:petroleum ether (40-60°C):triethylamine).

$\nu_{\text{max}}$ (CH$_2$Cl$_2$): 3670 w, 3450 w, 3025 m, 2960 m, 2930 m, 2880 m, 1610 s, 1600 s, 1570 s, 1490 m, 1445 s, 1420 s, 1370 s, 1330 m, 1300 m, 1265 m, 1220 w cm$^{-1}$.

$\delta_H$ (300 MHz, CDCl$_3$): 2.18-2.28 (m, 2H), 2.47 (brd, $J$=15.7 Hz, 1H), 2.56 (brd, $J$=15.0 Hz, 1H), 3.79-3.93 (series of m, 4H), 4.70 (brs, 1H), 5.43 (brs, 1H), 6.40 (brdd, $J$=8.4, 1.2 Hz, 1H), 6.47 (brdd, $J$=8.8, 1.4 Hz, 1H), 7.34-7.46 (series of m, 3H), 7.70 (brd, $J$=6.3 Hz, 2H).

$\delta_C$ (75 MHz, CDCl$_3$): 42.4 (t), 63.7 (t), 64.4 (t), 73.0 (d), 108.1 (s), 127.7 (d), 128.5 (d), 130.0 (d), 130.3 (d), 131.2 (d).

$\text{m/z}$(%): 288 (mH$^+$) (97), 272 (3), 244 (3), 167 (3), 151 (10), 139 (4), 122 (6), 105 (7).
PREPARATION OF 6-ETHYLENE ACETAL-CIS-4-(BENZOYLAMINO)-2-CYCLOHEPTENOL (199).

A solution of (198) (0.92 g, 3.38 mmol) in 19 ml of aqueous terahydrofuran (THF:H₂O, 10:1) was cooled to 0°C with stirring under nitrogen. Aluminium amalgam prepared by sequential exposure (10-20 s) of small strips of aluminium foil (0.74 g, 0.03 mol) to 1 M (aq) potassium hydroxide solution (1 M), distilled water, 0.5% mercuric chloride solution, distilled water and tetrahydrofuran, was then added to the solution of Diels-Alder adduct. Stirring was continued at 0°C for 16 h.

The reaction mixture was diluted with tetrahydrofuran (57 ml), stirred vigorously for 1.5 h, and then filtered through a pad celite. The filtrate was diluted with toluene and concentrated in vacuo to yield (199) a a pale yellow crystalline solid (0.88 g, 96%). An analytical sample was prepared by recrystallisation from toluene, m.p. 166-167°C.

C₁₆H₁₉NO₄ [mH⁺] Requires 288.1236
Found 288.1236

C₁₆H₁₈NO₄ [mH⁺] Requires C 66.42% H 6.62% N 4.84%
Found C 66.14% H 6.75% N 4.59%

vmax (nujol mull): 3320w, 3295w, 2960s, 2920s, 2895s, 2870s, 2850s, 1635m, 1525w, 1460s, 1375m cm⁻¹.
$\delta_H$ (300MHz, CD$_3$OD): 1.75-2.03 (series of m, 4H), 3.96
(brtq, J=6.6, 1.4Hz, 2H), 4.06 (m, 2H), 4.47 (brm, 1H), 4.75
(brm, 1H), 5.68 (m, 1H), 5.83 (m, 1H), 7.40-7.55 (series of
m, 3H), 7.82 (dt, J=6.9, 1.6Hz, 2H).

$\delta_C$ (75MHz, CD$_3$OD): 43.8(t), 46.8(d), 47.0(t), 65.1(t),
65.8(t), 66.8(d), 108.8(s), 128.3(d), 129.4(d), 132.6(d),
133.0(d), 135.6(s), 138.5(d), 169.2(s).

m/z(%): 289(m+)(4), 271(12), 106(11), 105(100), 87(15),
86(9), 78(9), 77(47), 52(13), 43(10), 32(11).

**PREPARATION OF 6-ETHYLENE ACETAL-CIS-4-(BENZOYLAMINO)
CYCLOHEPTANOL (200).**

A solution of (199) (0.31g, 1.09 mmol) in methanol (12ml)
was hydrogenated in the presence of 5% palladium on
charcoal. After 4h, the catalyst was filtered off and the
solvent was evaporated in vacuo to afford (200) as a yellow
gum, which crystallised on standing (0.31g, 99%). An
analytical sample was prepared by recrystallisation from
toluene, m.p. 125-126°C.

$C_{16}H_{21}NO_4\cdot 1/2H_2O$ Requires  C 63.97%  H 7.38%  N 4.66%
Found        C 63.95%  H 7.08%  N 4.52%

$\nu\max$ (CH$_2$Cl$_2$): 3660w, 3600w, 3430m, 2940m, 2890m, 1655s,
1600w, 1575m, 1510s, 1480m cm$^{-1}$.
δ_H (300MHz, CD3OD): 1.78-2.30 (series of m, 8H), 3.88-4.05 (series of m, 5H), 4.22 (brm, 1H), 7.38-7.55 (series of m, 3H), 7.78 (m, 2H).

δ_C (75MHz, CD3OD): 30.0(t), 33.8(t), 44.3(t), 47.4(d), 47.7(t), 64.9(t), 65.8(t), 67.8(d), 109.3(s), 128.2(d), 129.4(d), 132.4(d), 135.9(s), 169.0(s).

m/z(%): 292(mH+) (97), 274(49), 219(7), 171(7), 153(9), 122(9), 115(6), 105(14).

C_{16}H_{22}NO_4 [mH^+] Requires 292.1549
Found 292.1549

PREPARATION OF 6-ETHYLENE ACETAL-CIS-4-(BENZYLAMINO)-2-CYCLOHEPTENOL (201).

A solution of (199) (0.50g, 1.73 mmol) in dry tetrahydrofuran (14ml) was added dropwise to a stirred slurry of lithium aluminium hydride (0.28g, 7.51 mmol) in dry tetrahydrofuran (33ml). After heating the reaction at reflux for 10h, decomposition of the excess hydride was effected by addition of a water-saturated solution of diethyl ether. The resulting solution was dried (MgSO_4) and the solvent was removed in vacuo. The crude residue was purified by flash chromatography (97:2:1, diethyl ether:methanol:triethylamine) to afford (201) as a viscous, colourless oil (0.27g, 56%).

R_f 0.34 (97:2:1, diethyl ether:methanol:triethylamine).
\(\text{V}_{\text{max}} \quad (\text{CH}_2\text{Cl}_2): \ 3660\text{w}, \ 3600\text{m}, \ 3020\text{m}, \ 2950\text{m}, \ 2920\text{m}, \ 2880\text{m}, \ 1600\text{w}, \ 1450\text{m} \ \text{cm}^{-1}.

\(\delta_H \quad (300\text{MHz, CDCI}_3): \ 1.65-1.95 \ (\text{series of m, 4H}), \ 3.39 \ (\text{brd, J=9.0Hz, 1H}), \ 3.70, \ 3.79 \ (\text{AB q, J=12.9Hz, 2H}), \ 3.91 \ (\text{m, 4H}), \ 4.38 \ (\text{brd, J=9.5Hz, 1H}), \ 5.66 \ (\text{brddd, J=11.4, 3.8, 2.1Hz, 1H}), \ 5.82 \ (\text{brd, J=12.6Hz, 1H}), \ 7.20-7.35 \ (\text{m, 5H}).

\(\delta_C \quad (75\text{MHz, CDCI}_3): \ 42.8(\text{t}), \ 45.4(\text{t}), \ 51.2(\text{t}), \ 52.0(\text{d}), \ 63.8(\text{t}), \ 64.2(\text{t}), \ 65.3(\text{d}), \ 108.2(\text{s}), \ 126.8(\text{d}), \ 127.9(\text{d}), \ 128.1(\text{d}), \ 133.3(\text{d}), \ 137.1(\text{d}), \ 139.4(\text{s}).

\(m/z(\%): \ 276(\text{mH}^+)(97), \ 258(10), \ 230(3), \ 159(1), \ 122(1), \ 108(4), \ 91(7).

\(\text{C}_{16}\text{H}_{22}\text{NO}_3 \quad [\text{mH}^+]\) Requires 276.1600

Found 276.1600

**PREPARATION OF 6-ETHYLENE ACETAL-CIS-4-(BENZYLAMINO)CYCLOHEPTANOL (202).**

Lithium aluminium hydride (0.12g, 3.21 mmol) was carefully added to a stirred solution of (200) (0.20g, 0.74 mmol) in dry tetrahydrofuran (6ml). After heating at reflux for 14h, decomposition of the excess hydride was effected by addition of a water-saturated solution of diethyl ether. The resulting solution was dried (MgSO\(_4\)) and the solvent was removed in vacuo. The crude residue was purified by flash chromatography (91:8:1, diethyl ether:methanol:

235
triethylamine) to afford (202) as a colourless gum (0.10g, 51%).

Rf 0.49 (91:8:1, diethyl ether:methanol:triethylamine).

\[ \text{Vmax (CH}_2\text{Cl}_2): 3650\text{w, 3590w, 3410w, 3010w, 2930m, 2880m, 1645w, 1450w cm}^{-1} \]

\[ \delta_H (300MHz, CDCl}_3): 1.77-2.15 \text{ (series of m, 8H), 2.48 (brs, exch., 1H), 2.85 \text{ (brm, 1H), 3.75 (d, J=3.3Hz, 2H), 3.87-3.98 (series of m, 5H), 7.20-7.34 (m, 5H).} \]

\[ \delta_C (75MHz, CDCl}_3): 28.8(t), 33.1(t), 44.1(t), 44.8(t), 51.2(t), 52.7(d), 64.0(t), 64.2(t), 67.0(d), 109.6(s), 126.8(d), 128.0(d), 128.3(d), 140.1(s). \]

\[ m/z(\%): 278(mH^+)\text{ (97), 260(4), 204(3), 188(7), 144(4), 108(7), 88(6).} \]

C\textsubscript{16}H\textsubscript{24}NO\textsubscript{3} [mH\textsuperscript{+}] Requires 278.1756

Found 278.1756

**CYCLISATION OF (202).**

Thionyl bromide (42.8\textmu l, 0.55 mmol) was added dropwise to a stirred solution of (202) (0.13g, 0.47 mmol) in dry deuterated chloroform (2.65ml) at 0\textdegree C. The reaction mixture was allowed to warm to room temperature and stirring was continued for a further 24h. Subsequently, the solvent was removed in vacuo and replaced with dry acetone (2.65ml).
After cooling to 0°C, anhydrous TMP (271.2μl) was added and the solution was allowed to warm to room temperature, whereupon it was heated at 50°C for 4h.

The solvent was removed in vacuo and the solid residue was triturated with diethyl ether. The combined ethereal extracts were basified with gaseous ammonia, and the white precipitate was removed by filtration. Solvent evaporation of the filtrate in vacuo gave an orange/brown oil. Purification by flash chromatography (80:19:1, petroleum ether (40-60°C):diethyl ether:triethylamine) afforded cyclised material (0.05g, 42%), which was found to be a mixture of two products, N-benzyl nortropan-3-one ethylene acetal (203) and N-benzyl nortropane-3-one (204). They had co-eluted on the column.

Rf 0.14 (80:19:1, petroleum ether (40-60°C):diethyl ether:triethylamine).

**N-BENZYNORTROPAN-3-ONE ETHYLENE ACETAL (203).**

\[ \delta_H \] (300MHz, CDCl₃): 1.13 (s, 2H), 1.60-1.70 (m, 2H), 1.85-2.15 (m, 4H), 3.20 (brt, 3.1Hz, 2H), 3.61 (s, 2H), 3.80 (td, J=6.3, 1.0Hz, 2H), 3.94 (td, J=6.3, 1.0Hz, 2H), 7.21-7.44 (m, 5H).

**PREPARATION OF N-BENZYNORTROPAN-3-ONE (204).**

A 1M (aq) solution of hydrochloric acid (2ml) was added to a solution of the mixture of (203) and (204) (0.05g) in tetrahydrofuran (2ml). The reaction was left at reflux.
overnight. Subsequently, the solution was basified with 2M (aq) sodium hydroxide and the aqueous layer was extracted with dichloromethane (8 X 2ml). The combined organic extracts were dried (MgSO\(_4\)). Solvent evaporation in vacuo afforded (204) as a yellow oil (0.04g, 99%).

\[ \text{Vmax (CH}_2\text{Cl}_2): \ 3040\text{s}, 3020\text{s}, 2950\text{s}, 2880\text{s}, 1700\text{s}, 1600\text{w}, 1545\text{w}, 1490\text{m}, 1440\text{s}, 1420\text{s}, 1345\text{s}, 1260\text{s}, 1230\text{s cm}^{-1}. \]

\[ \text{δH (300MHz, CDCl}_3\): \ 1.62 \text{ (d, J=7.9Hz, 2H), 2.11 \text{ (m, 2H),} 2.20 \text{ (dd, J=17.1, 1.5Hz, 2H), 2.68 (brdd, J=16.0, 4.3Hz, 2H), 3.48 (brm, 2H), 3.74 (s, 2H), 7.24-7.45 (m, 5H).} \]

\[ \text{δC (75MHz, CDCl}_3\): \ 27.8\text{ (t), 48.2\text{ (t), 55.1\text{ (t), 58.5\text{ (d), 127.0\text{ (d), 128.3\text{ (d), 128.4\text{ (d), 139.3\text{ (d), 210.2\text{ (s).} \]}

\[ \text{m/z(\%): 215(m\text{+}) (21), 172(8), 157(43), 131(12), 104(24), 91(100), 65(17), 39(17).} \]

\[ \text{C}_{14}\text{H}_{17}\text{NO [m\text{+}] Requires 215.1310 Found 215.1310} \]

**CYCLISATION OF (201) TO GIVE N-BENZYNORTROP-6-EN-3-ONE ETHYLENE ACETAL (205).**

Thionyl bromide (14.1μl, 0.18 mmol) was added dropwise to a stirred solution of (201) (0.042g; 0.15 mmol) in dry deuterated chloroform (1ml) at 0°C. The reaction mixture was allowed to warm to room temperature and stirring was continued for a further 24h. Subsequently, the solvent was
removed in vacuo and replaced with dry acetone (1ml). After cooling to 0°C, anhydrous TMP (87.0μl) was added and the solution was allowed to warm to room temperature, whereupon it was heated at 50°C for 5h.

The solvent was removed in vacuo and the solid residue was triturated with diethyl ether. The combined ethereal extracts were basified with gaseous ammonia, and the white precipitate was removed by filtration. Solvent evaporation from the filtrate in vacuo gave an orange/brown oil. Purification by flash chromatography (80:19:1, petroleum ether (40-60°C):diethyl ether:triethylamine) afforded (205) as a pale yellow oil (0.004g, 11%).

Rf 0.12 (80:19:1, petroleum ether (40-60°C):diethyl ether:triethylamine).

\[ \text{V}_{\text{max}} \text{ (CH}_2\text{Cl}_2): 2950s, 2930s, 2880m, 2850m, 1600w, 1375w, 1325w \text{ cm}^{-1}. \]

\[ \delta_{\text{H}} \text{ (300MHz, CDCl}_3): 1.81 \text{ (dt, J=12.6, 1.7Hz, 2H)}, 2.19 \text{ (dd, J=13.7, 3.6, 2H), 3.56 (brs, 4H), 3.78 (m, 2H), 3.87 (m, 2H), 6.06 (s, 2H), 7.20-7.40 (m, 5H).} \]

m/z(%): 257(m⁺) (14), 170(26), 91(100), 80(12), 65(29), 43(14).

C\textsubscript{16}H\textsubscript{19}NO\textsubscript{2} [m⁺] Requires 257.1416

Found 257.1416
PREPARATION OF N-CARBETHOXY-1,4-DIHYDRO NAPHTHALEN-1,4-IMINE (214).\textsuperscript{64,112,113}

N-carbethoxy pyrrole (12.85g, 0.09 mol) was dissolved in dry tetrahydrofuran (160ml) and the resulting solution was brought to reflux. Isoamyl nitrite (12.34ml, 0.09 mol) and a solution of anthranilic acid (12.60g, 0.09 mol) in dry tetrahydrofuran (40ml) were simultaneously added to the heated solution via separate dropping funnels, over a period of 2h. The mixture was heated at reflux for a further 1.5h.

Subsequently, the reaction was concentrated \textit{in vacuo}, and a volume of dichloromethane (115ml) equal to the volume of tetrahydrofuran removed by distillation was added to the residue. The solution was washed with water, a saturated aqueous solution of sodium bicarbonate and again with water. The organic layer was dried (Na\textsubscript{2}SO\textsubscript{4}) and the solvent was removed \textit{in vacuo} to give a thick black oil. Purification by short path distillation afforded (214) (b.p. 95°C at 5.0 mbar) as a brown crystalline material (3.65g, 19%).

$\delta_H$ (60MHz, CDCl\textsubscript{3}): 1.13 (t, J=7.0Hz, 3H), 4.05 (q, J=7.0Hz, 2H), 5.26 (brm, 2H), 6.85-7.33 (m, 6H).

PREPARATION OF N-CARBETHOXY-EXO-2,3-EPOXY-TETRAHYDRO- NAPHTALEN-1,4-IMINE (215).\textsuperscript{112}

m-Chloroper oxybenzoic acid (80% purity, 1.10g, 6.36 mmol) was added in small portions to a stirred solution of (214) (1.01g, 4.71 mmol) in dry dichloromethane (45ml) at room temperature. Stirring was continued for a further 90h. Subsequently, the mixture was filtered and the filtrate was
concentrated in vacuo. The residue was dissolved in diethyl ether (30ml) and washed with a saturated aqueous solution of sodium bicarbonate (10 X 15ml). The organic layer was dried (MgSO₄) and the solvent removed in vacuo to yield (215) as a pale yellow, waxy solid (0.94g, 86%).

\[ \nu_{\text{max}} \ (\text{CH}_2\text{Cl}_2): 3060\text{w}, 3025\text{w}, 2970\text{m}, 2930\text{m}, 2910\text{w}, 2865\text{w}, 1700\text{s}, 1460\text{m}, 1400\text{s}, 1375\text{s}, 1340\text{s}, 1230\text{s}, 1215\text{s}, 1200\text{m} \ \text{cm}^{-1}. \]

\[ \delta_{\text{H}} \ (300\text{MHz, CDCl}_3): \text{one rotamer, 1.28 (t, J=7.1Hz, 3H), 3.34 (d, J=3.5Hz, 1H), 3.46 (d, J=3.5Hz, 1H), 4.17 (q, J=7.1Hz, 2H), 5.19 (s, 2H), 7.12-7.33 (m, 4H).} \]

\[ \text{Other rotamer, 1.28 (t, J=7.1Hz, 3H), 3.43 (d, J=3.5Hz, 1H), 3.46 (d, J=3.5Hz, 1H), 4.17 (q, J=7.2Hz, 2H), 5.11 (s, 2H), 7.12-7.33 (m, 4H).} \]

\[ \delta_{\text{C}} \ (75\text{MHz, CDCl}_3): 14.4(q), 54.6(d), 55.0(d), 61.5(t), 61.7(d), 62.0(d), 121.4(d), 121.6(d), 126.8(d), 126.9(d), 143.3(s), 143.8(s), 157.4(s). \]

\[ m/z(\%): 232(\text{mH}^+)(3), 202(21), 158(36), 143(33), 128(99), 115(11), 103(17), 94(41), 71(41), 55(21), 43(37). \]

\[ \text{C}_{13}\text{H}_{14}\text{NO}_3 \ [\text{mH}^+] \text{ Requires 232.0974} \]

\[ \text{Found 232.0974} \]
PREPARATION OF N-CARBETHOXY-EXO-2,3-EPOXY-1,2,3,4-TETRAHYDROANTHRACEN-1,4-IMINE (217).

m-Chlorobenzoic acid (80% purity, 0.03g, 0.12 mmol) was added in small portions to a solution of N-carbethoxy-1,4-dihydroanthracen-1,4-imine (0.03g, 0.12 mmol) in dry deuterated chloroform (1ml) at room temperature. Subsequently, the reaction was monitored periodically by proton n.m.r (90Mhz). After 24h, the signal at δ6.90, corresponding to the olefinic protons in the starting material, had disappeared. Thus, the mixture was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in diethyl ether (1ml) and washed with a 2M (aq) solution of sodium hydroxide (3 X 1ml) followed by water (3 X 1ml). The organic layer was dried (MgSO₄) and the solvent removed in vacuo to afford (217) as a pale yellow waxy solid (0.03g, 90%).

V_max (CH₂Cl₂): 2969w, 2930w, 2900w, 1705s, 1400m, 1375s,
1340s, 1245m, 1230m, 1215m cm⁻¹.

δ_H (300MHz, CDCl₃): one rotamer, 1.31 (t, J=7.1Hz, 3H),
3.47 (d, J=3.5Hz, 1H), 3.50 (d, J=3.5Hz, 1H), 4.21 (q, J=7.1Hz, 2H), 5.35 (s, 2H), 7.46-7.82 (m, 6H).
Other rotamer, 1.31 (t, J=7.1Hz, 3H), 3.47 (d, J=3.5Hz, 1H),
3.50 (d, J=3.5Hz, 1H), 4.22 (q, J=7.1Hz, 2H), 5.25 (s, 2H),
7.46-7.82 (m, 6H).
$\delta_C$ (75MHz, CDC13): 14.5(q), 53.6(d), 54.0(d), 61.5(d), 61.6(t), 61.7(d), 120.2(d), 120.5(d), 126.4(d), 128.0(d), 128.1(d), 132.37(s), 132.43(s), 139.9(s), 140.3(s), 157.6(s).

m/z(%): 281(m+)(l), 252 (40), 208 (29), 180 (54), 156(90).

$\text{C}_{17}\text{H}_{15}\text{NO}_3$ [m+] Requires 281.1052

Found 281.1052

PREPARATION OF N-CARBITHOXY-5,6-EPOXY-2-AZABICYCLO[2.2.2]DECANE (226).

m-Chloroperoxybenzoic acid (80% purity, 2.50g, 14.0 mmol) was added in small portions to a stirred solution of N-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (1.52g, 8.4 mmol) in dry dichloromethane (25ml) at room temperature. The mixture was left to stir for 24h, after which a further quantity of m-chloroperoxybenzoic acid (0.82g, 4.70 mmol) was added. Stirring was continued for another 36h. Subsequently, the mixture was dissolved in diethyl ether (50ml) and washed with a 2M (aq) solution of sodium hydroxide (25ml). The aqueous layer was extracted further with diethyl ether (2 X 10ml), and the combined organic extracts were dried (MgSO4). The solvent was removed in vacuo to give (226) as a golden yellow oil (0.32g, 64%). The exo- and endo-isomers were separated by flash chromatography (ethyl acetate).

Exo-epoxide:

$R_f$ 0.63 (ethyl acetate).
δ_H (300MHz, CDCl3): major rotamer, 1.27 (t, J=7.1Hz, 3H), 1.51-1.87 (series of m, 4H), 2.37 (m, 1H), 3.32 (m, 2H), 3.43 (m, 2H), 4.16 (q, J=7.1Hz, 2H), 4.52 (m, 1H).

Minor rotamer, 1.27 (t, J=7.1Hz, 3H), 1.51-1.87 (series of m, 4H), 2.37 (m, 1H), 3.32 (m, 2H), 3.43 (m, 2H), 4.12 (q, J=7.1Hz, 2H).

δ_C (75MHz, CDCl3): major rotamer, 14.7(q), 21.8 (t), 24.5(t), 29.1(d), 44.9(t), 47.1(d), 51.1(d), 51.4(d), 61.1(t).

Minor rotamer, 14.4(q), 21.8 (t), 24.7(t), 28.9(d), 45.1(t), 47.8(d), 51.1(d), 51.5(d), 61.1(t).

m/z (%): 197(m+)(7), 156(22), 139(20), 128(17), 117(12), 111(15), 102(12), 56(22), 41(21), 32(54).

Endo-epoxide:

R_f 0.54 (ethyl acetate).

δ_H (300MHz, CDCl3): major rotamer, 1.24 (t, J=7.1Hz, 3H), 1.64-1.98 (series of m, 4H), 2.36 (brd, J=14.5Hz, 1H), 3.07 (brdd, J=10.6, 1.3Hz, 1H), 3.32 (brm, 2H), 3.52 (brdd, J=10.5, 1.8Hz, 1H), 4.10 (q, J=7.1Hz, 2H), 4.48 (brm, 1H).

Minor rotamer, 1.24 (t, J=7.1Hz, 3H), 1.64-1.98 (series of m, 4H), 2.36 (brd, J=14.5Hz, 1H), 3.07 (brdd, J=10.6, 1.3Hz, 1H), 3.32 (brm, 2H), 3.52 (brdd, J=10.5, 1.8Hz, 1H), 4.11 (q, J=7.1Hz, 2H).
ATTEMPTED EPOXIDATION OF N-BENZYL-2-AZABICYCLO[2.2.1]HEPT-5-ENE (158a) WITH m-CHLOROPEROXYBENZOIC ACID.

(1) Trifluoroacetic acid (14.0µl, 0.18 mmol) was added dropwise to a solution of (158a) (0.034g, 0.18 mmol) in dry deuterated chloroform (1ml). m-Chloroperoxybenzoic acid (80% purity, 0.041g, 0.19 mmol) was added carefully to this solution at room temperature. The reaction was left for 72h. Subsequently the mixture was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in diethyl ether (1ml) and washed with a 2M (aq) solution of sodium hydroxide (2ml) followed by water (2ml). The organic layer was dried (MgSO₄) and evaporation of the solvent in vacuo afforded the unreacted starting material.

(2) Trifluoroacetic acid (15.4µl, 0.20 mmol) was added dropwise to a solution of (158a) (0.037g, 0.20 mmol) in dry deuterated chloroform (1ml). m-Chloroperoxybenzoic acid (80% purity, 0.046g, 0.21 mmol) was added carefully to this solution at room temperature. The reaction mixture was heated at 45°C for 90h. Subsequently the mixture was
filtered and the filtrate was concentrated in vacuo. The residue was dissolved in diethyl ether (1ml) and washed with a 2M (aq) solution of sodium hydroxide (2ml) followed by water (2 X 2ml). The organic layer was dried (MgSO₄) and the solvent evaporated in vacuo to give an orange oil. However, purification by flash chromatography (40:59:1, diethyl ether:petroleum ether (40-60°C):triethylamine) led only to the isolation of unreacted starting material (158a) (95% recovery).
Addendum
ADDENDUM

Since compiling this thesis, Backvall\textsuperscript{137} has reported a stereoselective synthesis for the tropane alkaloids of scopine and pseudoscopine based on the chloroacetoxylation approach which we discussed previously in section 1.5 (see Scheme A.1)

A palladium catalysed 1,4-chloroacetoxylation of the benzyl protected 1,3-cycloheptadien-6-ol (93) afforded the key intermediate (94). Subsequent substitution of the allylic chloride by TsNH\textsuperscript{-} with either retention (Pd(0) catalysis) or inversion (Sn2) of configuration gave (231) and (235) respectively. The epoxy oxygen was introduced syn to the nitrogen function prior to cyclisation by utilisation of the syn-directive effect of the allylic sulfonamido group in the epoxidation. Cyclisation of the epoxides, (233) and (237), followed by replacement of the tosyl group by a methyl group and subsequent debenzylation afforded the desired compounds, scopine and pseudoscopine.
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