SYNTHETIC APPROACHES TO QUINOLIZIDINE ALKALOIDS

Christa Maria Jungmann

A Dissertation submitted to the Faculty of Science, University of the Witwatersrand, Johannesburg, in fulfillment of the requirements for the Degree of Master of Science.

Department of Chemistry
Johannesburg
June 1992

ABSTRACT

An outline of reported synthetic routes to the Lupine alkaloids, epilamprolobine [2] and lamprolobine [3] and a review of the use of vinylogous amides and urethanes as precursors for the synthesis of alkaloids are presented in Chapter 1. This is followed by a presentation of our strategy for synthesis of the two Lupine alkaloids. Vinylogous cyanamide intermediate 1-(3-hydroxypropyl)-2-cyanomethylenepiperidine [68] plays a key role in this strategy, since exploitation of its ambident nucleophilicity forms the central theme of this project.

The successful route to the intermediate [68] involved the preliminary preparation of the tertiary thiolactam, 1-(2-ethoxycarbonylethyl)piperidine-2-thione [83], by thiation of the secondary lactam 2-piperidinone [72] and conjugate addition at nitrogen with ethyl acrylate in a Michael reaction. Sulphur extrusion of the salt made from [83] and bromoacetonitrile and subsequent reduction of the ester group provided the pivotal vinylogous cyanamide intermediate. A number of alternative routes based on 5-bromopentanoic acid [80], 1-allyl-2-piperidinone [73] and thiolactams [84] and [105] were unsuccessful.

Cyclisation of the intermediate [68] was achieved by an intramolecular α-alkylative ring closure via the corresponding tosylate [116] to form an unsaturated functionalised quinolizidine [69]. Stereoselective carbon-carbon double bond reduction and nitrile reduction resulted in the synthesis of two quinolizidines, lupinamine [11] and epilupinamine [112]. Further transformations led to the formation of the derivatives, N-acetyllupinamine [113] and N-acetylepilupinamine [114], and also to the target alkaloids, epilamprolobine [2] and lamprolobine [3].

DECLARATION

I declare that this dissertation is my own, unaided work. It is being submitted for the Degree of Master of Science in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University.

Christa Maria Jungmann
Christa Maria Jungmann

4th day of June, 1992.

DEDICATION

For my parents, Hans and Ingrid,

my brother, Michael

and

Geoff.

TABLE OF CONTENTS

Page

TABLE OF CONTENTS (continued)

TABLE OF CONTENTS (continued)

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to the following people:

My supervisor, Professor Joseph P. Michael for his constant encouragement and overwhelming enthusiasm throughout the duration of the project.

My family and Geoff, for their unyielding support and help.

Friends and colleagues for their encouragement and ideas.

Mrs. Sigi Heiss for her efficient nmr service, Mrs. M. Maksa (Energy Technology, CSIR) for microanalyses and Dr. L. Fourie (Potchefstroom University) for mass spectral data.

Barry Fairbrother for his helpful and friendly glassblowing service.

CSIR, the University of the Witwatersrand and Professor Joseph P. Michael for their generous financial and moral support.

ABBREVIATIONS

α	*alpha*
β	*beta*
γ	*gamma*
δ	*delta*
υ	*upsilon*
σ	*sigma*
Ac	acetyl
Ar	aromatic
ax	axial
9-BBN	9-borabicyclo[3.3.1]nonane
$BH_3.SMe_2$	borane-methyl sulphide complex
b.p.	boiling point
Bu	butyl
BuLi	butyllithium
ca.	*circa*
cm^{-1}	reciprocal centimetre (wave number)
d	doublet or day(s)
DMF	dimethylformamide
E	*entgegen*
Et	ethyl
et al.	*et alii*
etc.	et cetera
Et_2O	diethyl ether
$Et_3O^+BF_4^-$	triethyloxonium fluoroborate
EtOH	ethanol
eq	equatorial
exp.	experiment
FGI	functional group interconversion
FT	fourier transform
g	gram(s)
gc	gas chromatography
h	hour(s)
HRMS	high resolution mass spectrum
H.T.	hydrolysis time
Hz	hertz

ABBREVIATIONS (continued)

i-Pr	*iso*-propyl
i-Pr$_2$NEt	di*iso*propylethylamine
ir	infrared
J	coupling constant(s)
m	multiplet
ml	millilitre
mm	millimetre
M	molar or Mega
M$^+$	molecular ion
Me	methyl
MeNO$_2$	nitromethane
MeOH	methanol
min	minutes
mol	mole(s)
m.p.	melting point
Ms	methanesulphonyl
m/z	mass-to-charge ratio (ms)
n	*normal*
NEt$_3$	triethylamine
nmr	nuclear magnetic resonance
no.	number
p	*para*
pp.	page(s)
Ph	phenyl
ppm	parts per million
q	quartet
R	*rectus* (="right")
R	alkyl
R.T.	room temperature
s	singlet
S	*sinister* (="left")
S.M.	starting material
S.P.	sodium perborate
t	*tertiary*
t	triplet

ABBREVIATIONS (continued)

temp.	temperature
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
Ts	toluenesulphonyl
w/w	weight-by-weight ratio
Z	*zusammen*
*	antibonding

LIST OF TABLES

TABLE OF FIGURES

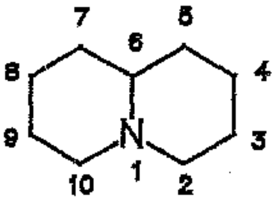
LIST OF FIGURES(continued)

CHAPTER 1

BACKGROUND AND AIMS

1.1 Introduction

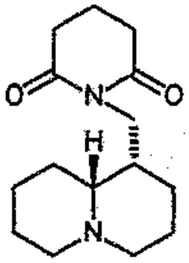
Over 450 alkaloids occur in the plants of the Leguminosae family. Quinolizidine[1-10] (Lupine) alkaloids form the largest single group of legume alkaloids. They are especially prominent in the Papilionaceae[11] subfamily. The quinolizidine backbone [1] is shown below with the azabicyclic numbering system which will be used throughout this project.



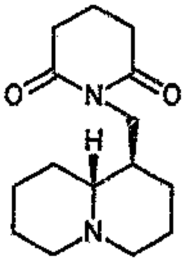
[1]

Some quinolizidine compounds are constituents of poisonous plants and are therefore toxic for humans and livestock, whereas others exhibit potentially useful pharmacological activities. Legume quinolizidine alkaloids are synthesised by plants from the basic amino acid lysine via cadaverine, its decarboxylation product, as toxic defence compounds. They act as natural insecticides and are general feeding deterrents for herbivorous mammals, by rendering the plant unpalatable and toxic. Sheep in particular are susceptible to poisoning, but the effects are fortunately not cumulative. The highest incidence of quinolizidine alkaloid poisoning occurs during autumn. This is the time of year when plants have their seeding stage, and seeds are known to accumulate the highest quantities of alkaloids of all plant parts.

Our target is to synthesise two alkaloids, epilamprolobine [2] and lamprolobine [3], both of which contain the quinolizidine skeleton, for reasons to be made clear later.



[2]



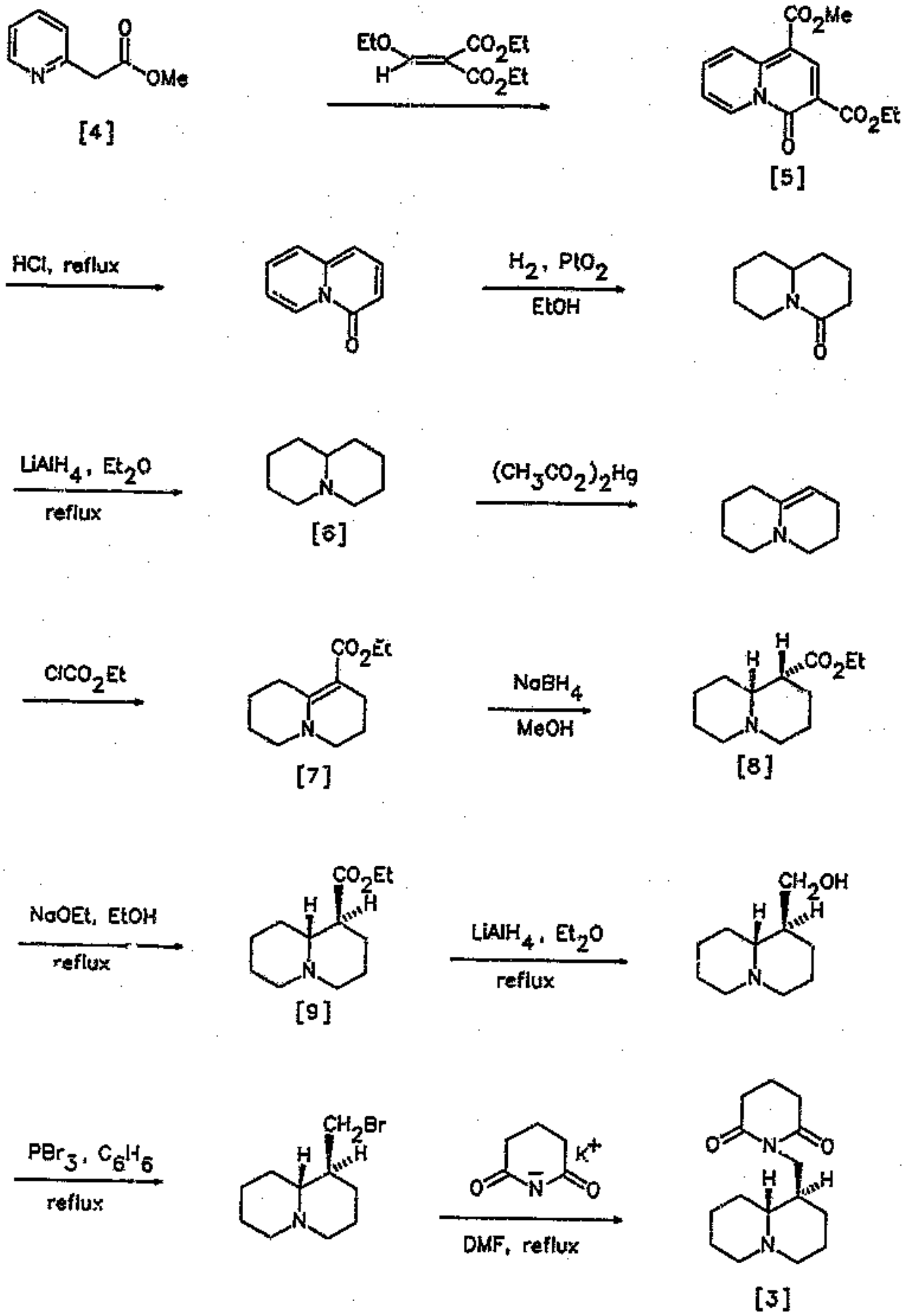
[3]

In the next section, the occurrence of these two Lupine alkaloids will be discussed, together with other reported synthetic approaches. The project will then be put into perspective by a general discussion of the "Wits alkaloids" project. The stereochemistry and conformation of quinolizidine ring systems will be dealt with, followed by an account of the specific aims and strategies of this project, which will conclude the Chapter 1.

1.2 Reported isolation and synthesis of epilamprolobine and lamprolobine

Epilamprolobine has been isolated from the fresh leaves, stems and immature seeds of leguminous plants of *Sophora tomentosa*,[12] which grow in Japan. Lamprolobine has been found to be the major component of the alkaloid fraction extracted and processed from *Lupinus holosericeus*.[13] The apparent close relationship of the latter to *Lupinus caudatus* which is toxic to grazing animals in the Rocky Mountain region of the United States, warranted the investigation of the above-ground parts of the *holosericeus* species. Lamprolobine has also been isolated from the Australian legume *Lamprolobium fruticosum* Benth.,[14,15] a member of the alkaloid-poor Galegeae tribe. Finally, both epilamprolobine and lamprolobine have been isolated from the leaves, stems, seeds and seedlings of *Sophora chrysophylla*,[16] the sole *Sophora* plant native to Hawaii.

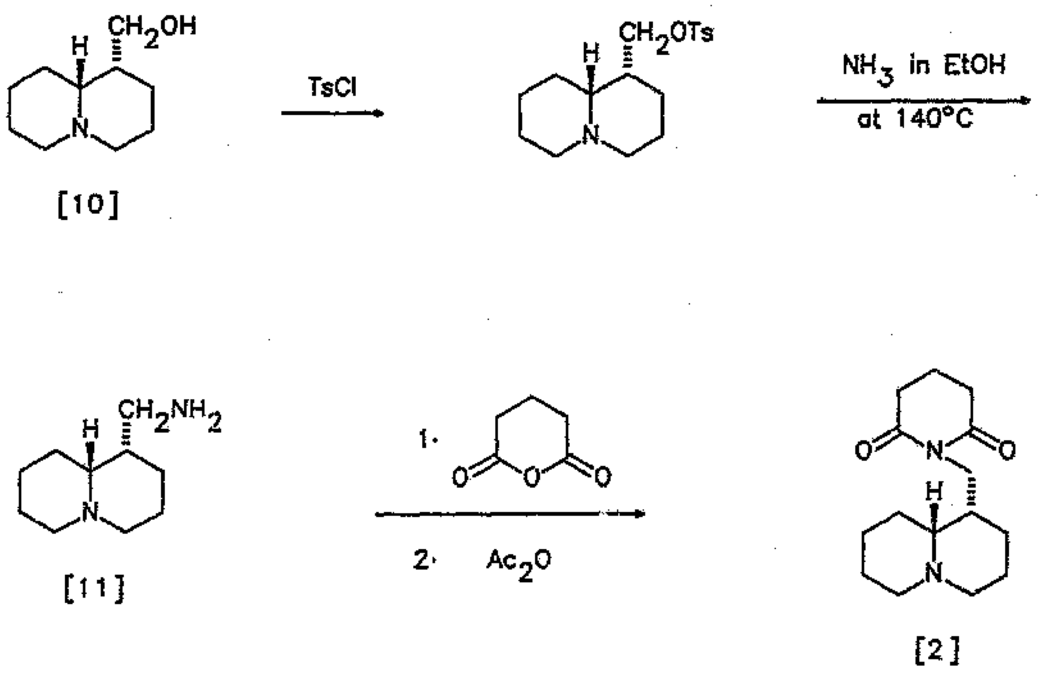
Goldberg and Lipkin[17] reported the synthesis of lamprolobine as illustrated in Scheme 1. A pyridine system functionalised at the α position [4] was the starting material of choice. Condensation with diethyl ethoxymethylenemalonate provided the unsaturated bicyclic backbone with the nitrogen at the bridgehead position [5]. Further manipulation of the ester groups and carbon-carbon double bonds, and later of the amide group, produced quinolizidine [6]. Treatment of the latter with mercuric acetate followed by ethyl chloroformate gave the functionalised unsaturated quinolizidine compound [7], which is a vinylogous urethane (see Section 1.3). Stereospecific reduction of the endocyclic double bond was controlled by using sodium borohydride in the synthesis of the corresponding saturated quinolizidine derivative [8]. The stereochemistry at C-5 and C-6 is opposite to that desired for lamprolobine, and so base-catalysed epimerisation of [8] to [9] was necessary. Ester reduction, functional group conversion and the addition of the glutarimido unit completed the synthesis of lamprolobine.



[4]
OMe
EtO
H
CO_2Et
CO_2Et
CO_2Me
CO_2Et
[5]
HCl, reflux
H_2, PtO_2
EtOH
$LiAlH_4$, Et_2O
reflux
[6]
$(CH_3CO_2)_2Hg$
$ClCO_2Et$
CO_2Et
[7]
$NaBH_4$
MeOH
H
CO_2Et
[8]
NaOEt, EtOH
reflux
CO_2Et
H
[9]
$LiAlH_4$, Et_2O
reflux
CH_2OH
PBr_3, C_6H_6
reflux
CH_2Br
K^+
DMF, reflux
[3]

Scheme 1

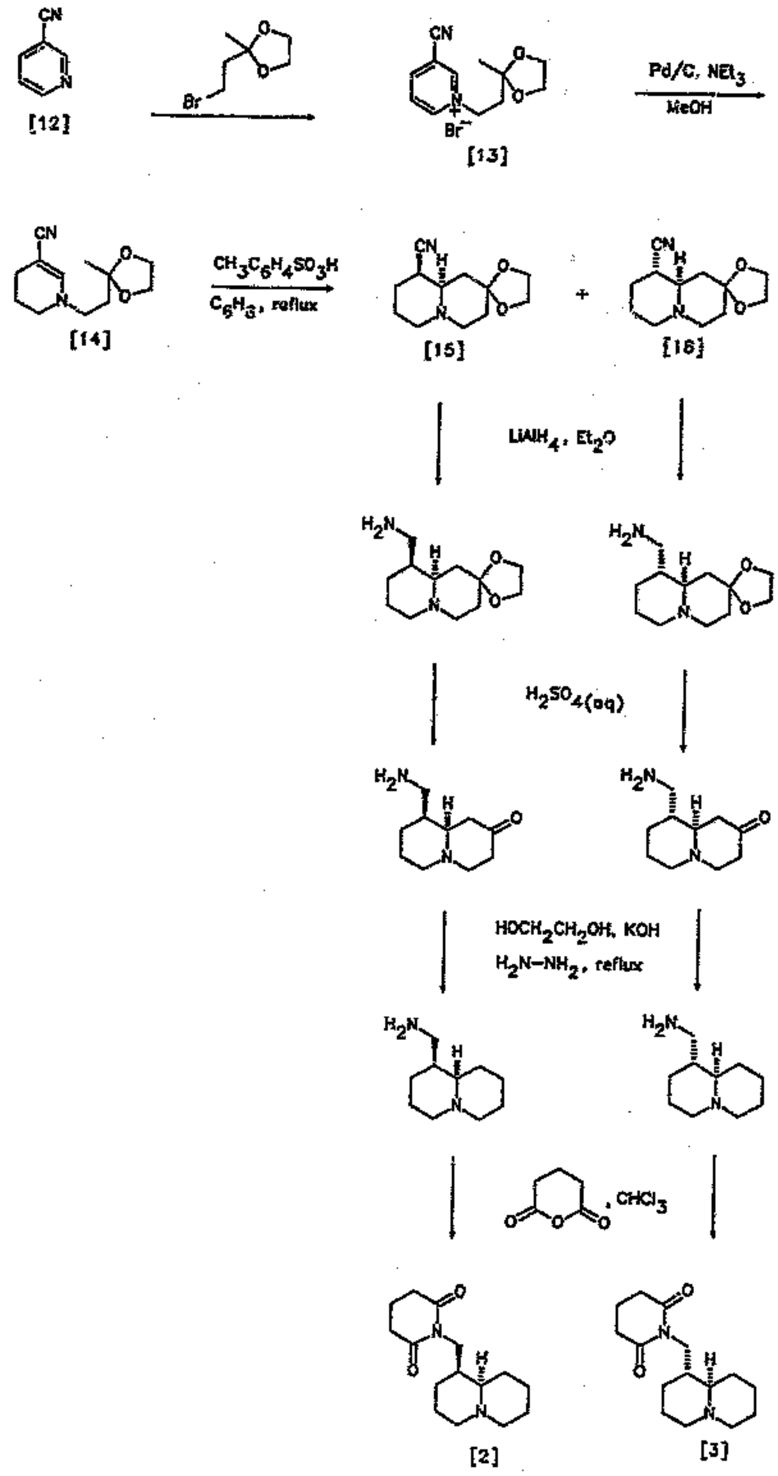
Murakoshi *et al.*[12] synthesised epilamprolobine [2] from naturally occurring lupinine [10] according to the synthetic route outlined in Scheme 2.



Scheme 2

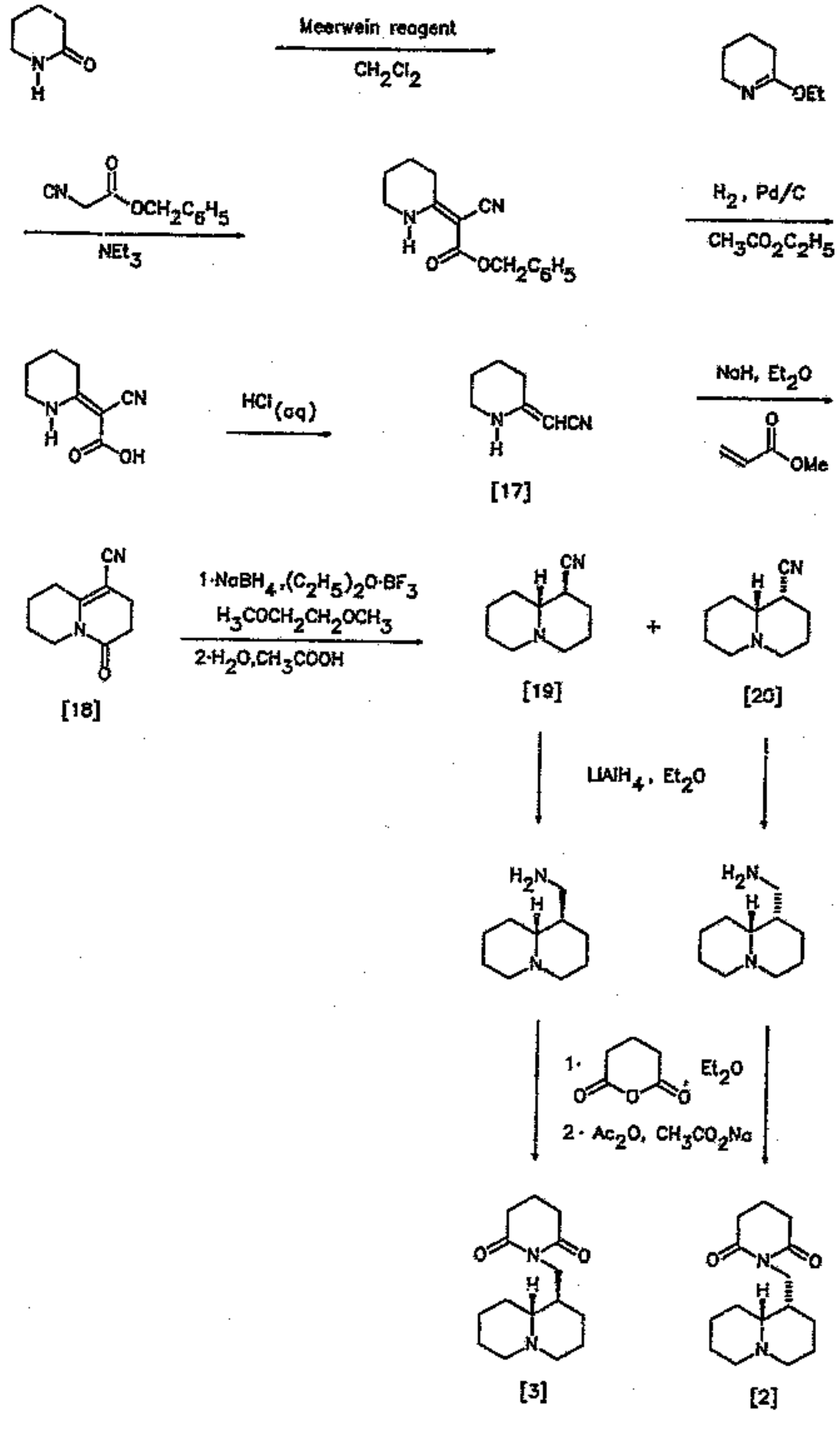
Unlike the previous synthesis, Murakoshi's synthesis has the quinolizidine skeleton established in the starting material. Functional group conversion of the hydroxy group in lupinine to an amine group afforded the precursor [11], needed for the final step in which the glutarimido unit was added.

Wenkert and Jeffcoat[18] reported the synthesis of epilamprolobine and lamprolobine as illustrated in Scheme 3. A pyridine system functionalised at the ß position [12] was the starting material of choice. Alkylation with 4-bromo-2-butanone ethylene ketal yielded the salt [13] which, after undergoing partial hydrogenation, produced an endocyclic vinylogous cyanamide precursor [14] (see Section 1.3). Subsequent acid-catalysed cyclisation produced the isomeric pair [15] and [16]. These two compounds contain the quinolizidine backbone with functionality at C-4 and C-7. Reduction of the nitrile groups to amines provided the correct functionality necessary for later addition of the glutarimido unit. Hydrolysis of the ketals and Wolff-Kishner reduction of the resultant ketones removed the undesired functionality at C-4.


CN
[12]
Br
O
O
CN
N
Br⁻
[13]
Pd/C, NEt3
MeOH
CN
N
[14]
CH3C6H4SO3H
C6H6, reflux
CN
H
N
[15]
+
CN
H
N
[16]
LiAlH4, Et2O
H2N
H2SO4(aq)
HOCH2CH2OH, KOH
H2N–NH2, reflux
CHCl3
[2]
[3]

Scheme 3

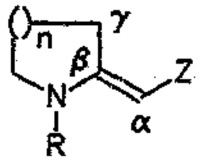
Yamada *et al.*[19] reported the synthesis of epilamprolobine and lamprolobine which is illustrated in Scheme 4. 2-Piperidinone was used as the starting material. After a series of reactions, the exocyclic vinylogous cyanamide [17], which has a secondary ring nitrogen, was afforded. A Michael reaction followed by a cyclisation yielded the functionalised quinolizidine system [18] which itself is a vinylogous cyanamide (see Section 1.3). Reduction of the endocyclic double bond and the amide moiety afforded two isomers [19] and [20] bearing nitrile groups at the C-5 position. Reduction to form the corresponding amines and addition of the glutarimido unit completed the synthesis of epilamprolobine and lamprolobine. This synthesis is of particular significance to us, because the route we have devised (see Chapter 3, Scheme 39) converges with it from compounds [19] and [20] onwards.


Meerwein reagent
CH_2Cl_2
OEt
$OCH_2C_6H_5$
NEt_3
CN
H_2, Pd/C
$CH_3CO_2C_2H_5$
$HCl_{(aq)}$
CHCN
[17]
NaH, Et_2O
OMe
1·$NaBH_4$,$(C_2H_5)_2O·BF_3$
$H_3COCH_2CH_2OCH_3$
2·H_2O,CH_3COOH
[18]
[19]
[20]
$LiAlH_4$, Et_2O
H_2N
1· Et_2O
2· Ac_2O, CH_3CO_2Na
[3]
[2]

Scheme 4

1.3 The "Wits approach" to alkaloids

A long-term project at Wits[20-34] has been exploiting the properties of extended enamines[35-37] conjugated to electron-withdrawing groups. These systems [21] are illustrated in Figure 1.



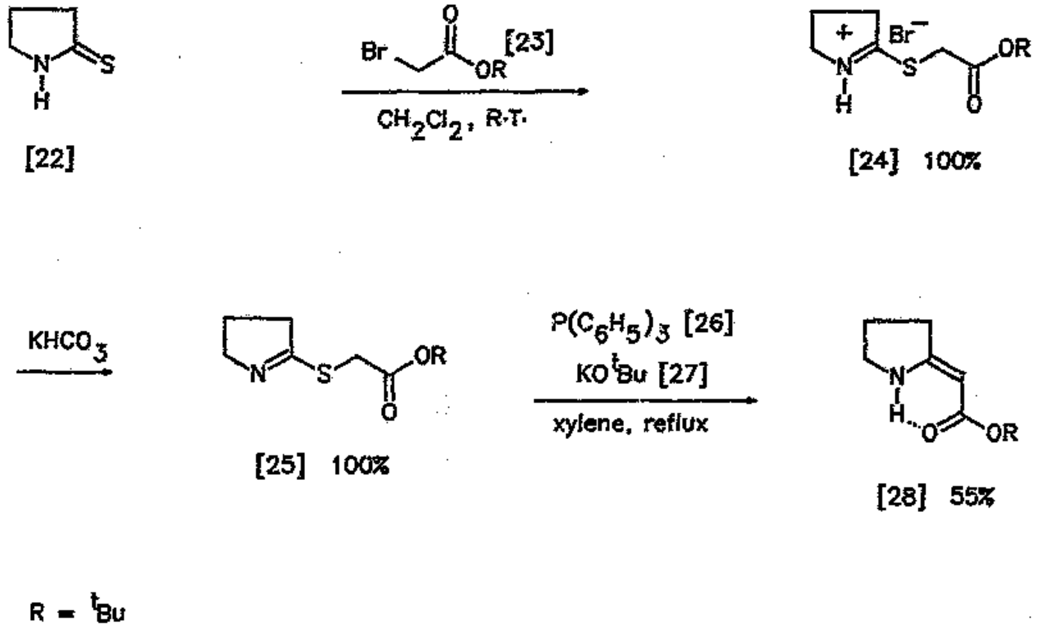
[21]

where n = 1 or 2
Z = CO_2R' (vinylogous urethane)
or Z = COR' (vinylogous amide)
or Z = CN (vinylogous cyanamide)
R = alkyl

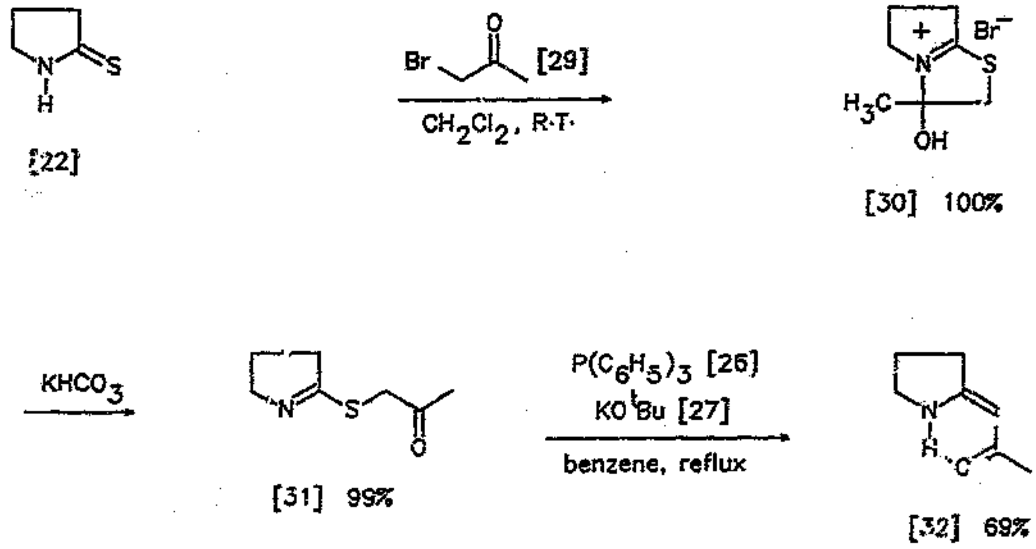
Figure 1

The versatility of exocyclic extended enamines warrants their use as synthetic intermediates. They exhibit ambident nucleophilicity at nitrogen, the α-carbon and the carbonyl oxygen (in the cases of vinylogous urethanes and amides). An anion formed at the γ-carbon position represents another nucleophilic site. Ambident electrophilicity is exhibited at the β-carbon and at the carbonyl carbon.

Despite the existence of other methods,[38-42] the sulphide contraction sequence[43-45] developed by Eschenmoser still remains an excellent synthetic route to exocyclic extended enamines. Although this reaction was initially used as part of his vitamin B_{12} work,[46] its potential has been recognized by us$^{20-34}$ and other workers$^{47-62}$ in the preparation of valuable intermediates for alkaloid syntheses and medically useful compounds. Two reactions representative of Eschenmoser's original work^{43} are illustrated in Schemes 5 and 6. Condensation of the α-halocarbonyl compounds [23] or [29] with the thiolactam [22] (in which the nitrogen is secondary) generated the thioiminoethers [25] or [31], respectively, via the α-thioiminium salts [24] or [30], respectively. Extrusion of sulphur was achieved by using a strong base [27], a sulphur scavenger [26], and heating under reflux in a suitable solvent.

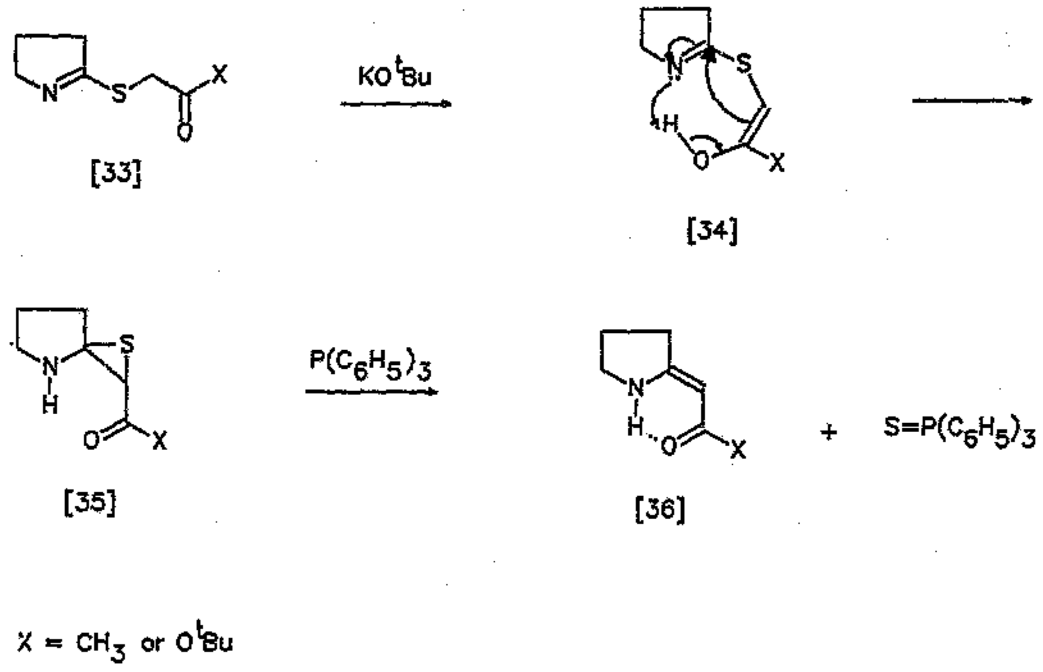


Scheme 5



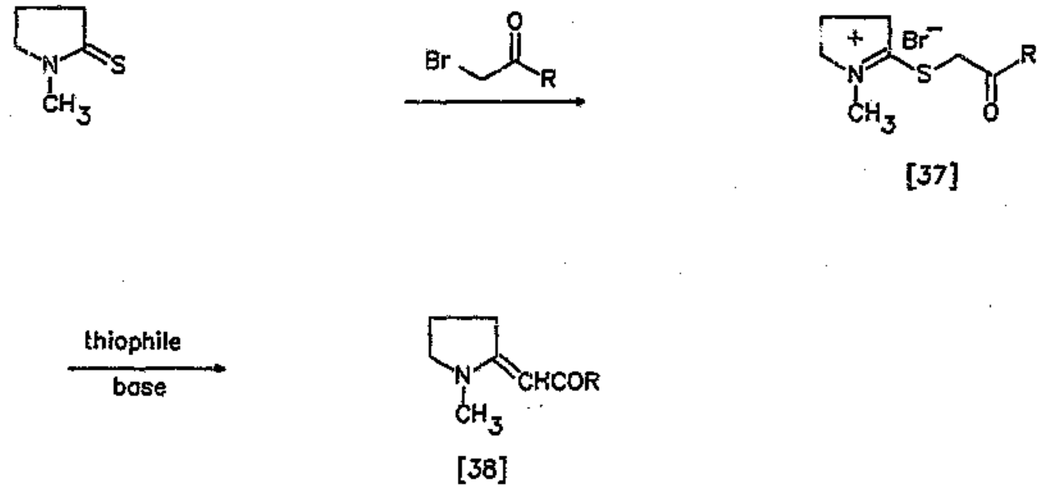
Scheme 6

The proposed mechanism (Scheme 7) of the sulphide contraction reaction assumes the production of an episulphide intermediate [35] formed by an intramolecular attack at the imine carbon of the base-catalysed enol form [34] of the thioiminoether [33]. In both the vinylogous urethane [28] and the vinylogous amide [32] the geometry around the carbon-carbon double bond is *Z*. The formation of the *cis*-s-*cis* structures is favoured by the 6-membered hydrogen-bonded ring.



Scheme 7

Eschenmoser's procedure has been adapted to the contraction of N,N-dialkyl α-thioiminium salts[32] [37] to produce an exocyclic extended enamine [38] in which the nitrogen is tertiary (Scheme 8).

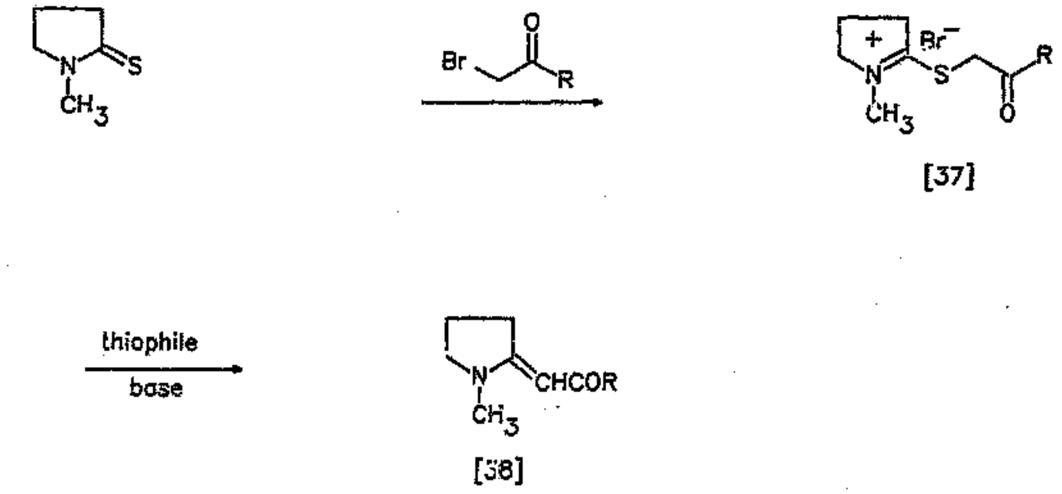


[37]

[38]

Scheme 8

It has been reported[32] that in some cases (e.g. where R = CH_3 in [38]), sulphur extrusion is accomplished in the presence of either a thiophile or a base, but a dramatic increase in yields is achieved by utilisation of both entities. A noteworthy observation is that the sulphide contraction to produce exocyclic extended enamines in which the nitrogen is tertiary, proceeds more rapidly and under milder conditions (weaker base such as triethylamine, room temperature) than its secondary nitrogen analogue.[20] The geometry of a sulphide contracted product bearing a tertiary nitrogen has been found to be *E*, e.g. [39]. This feature prevails in such systems to avoid intramolecular congestion.

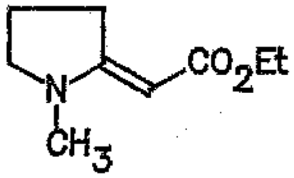


[37]

[38]

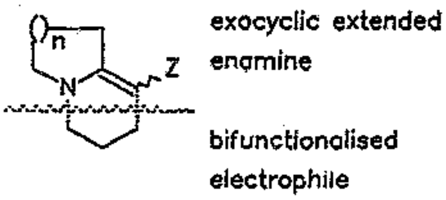
Scheme 8

It has been reported[32] that in some cases (e.g. where R = CH_3 in [38]), sulphur extrusion is accomplished in the presence of either a thiophile or a base, but a dramatic increase in yields is achieved by utilisation of both entities. A noteworthy observation is that the sulphide contraction to produce exocyclic extended enamines in which the nitrogen is tertiary, proceeds more rapidly and under milder conditions (weaker base such as triethylamine, room temperature) than its secondary nitrogen analogue.[20] The geometry of a sulphide contracted product bearing a tertiary nitrogen has been found to be *E*, e.g. [39]. This feature prevails in such systems to avoid intramolecular congestion.



[39]

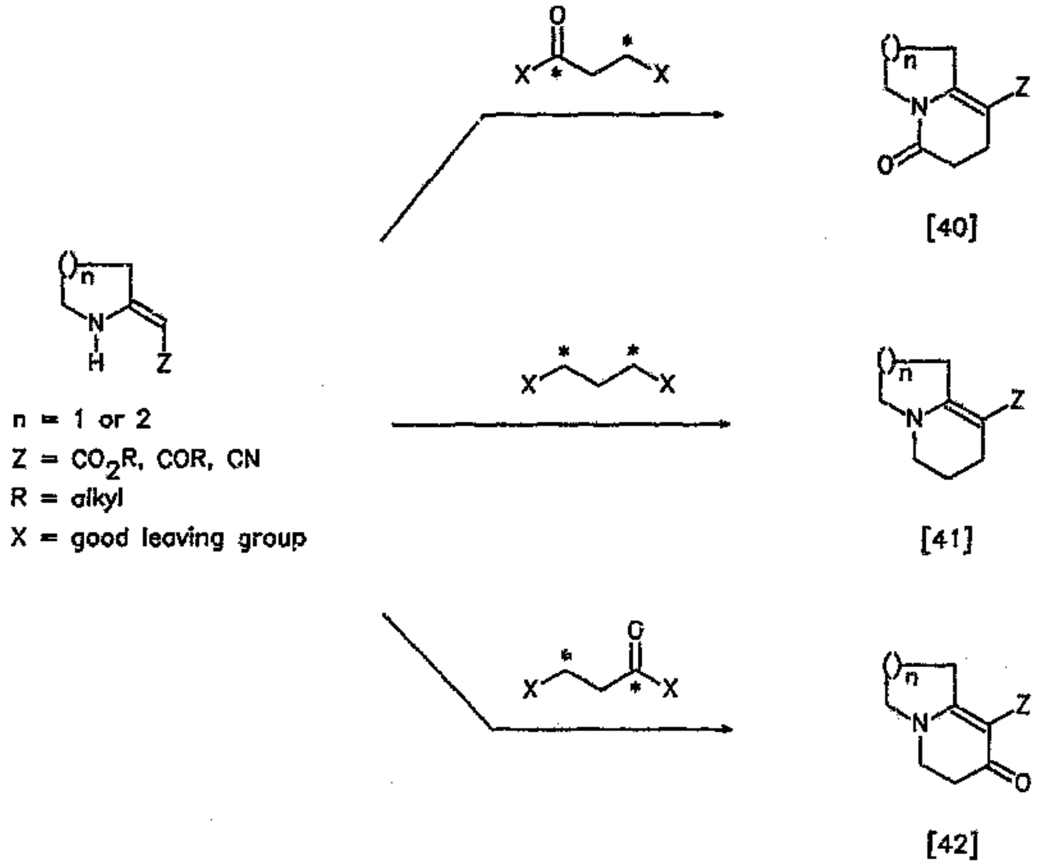
In a continuation of the "Wits approach", a bifunctionalised electrophile may be employed to bridge between any two of the nucleophilic sites present in the exocyclic extended enamine intermediate. In this manner functionalised quinolizidine and indolizidine systems, which comprise the backbone of many complex alkaloids, can be synthesised. This concept, in which the nucleophilic properties of the nitrogen atom and the α-carbon are exploited by the bifunctional electrophile, is pictorially represented in Figure 2. (Syntheses of functionalised quinolizidine,[63] indolizidine[64] and pyrrolizidine[65] systems have been reported using other methods.)



n = 1 (for future indolizidine system)
n = 2 (for future quinolizidine system)
Z = CO_2R', COR', CN
R' = alkyl

Figure 2

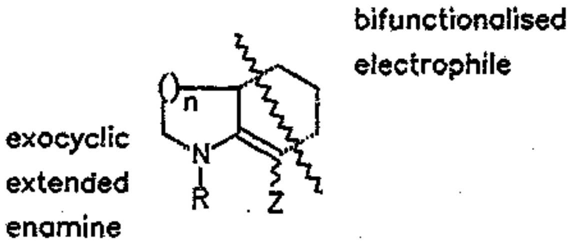
Scheme 9 shows how alkylative and acylative cyclisations may be achieved, depending on the oxidation level of the electrophilic carbon (*).



Scheme 9

Bicyclic system [41] is the product of intramolecular alkylative ring closure while [40] and [42] represent intramolecular acylative ring closures. In all cases, one has the choice of forming the bond to nitrogen before that to the α-carbon, or vice versa.

Figure 3 shows how the "Wits approach" can be involved in the construction of fused bicyclic systems in which the nitrogen is α to the bridgehead position. The nucleophilicity of the anion formed at the γ-carbon position and the α-carbon is used.

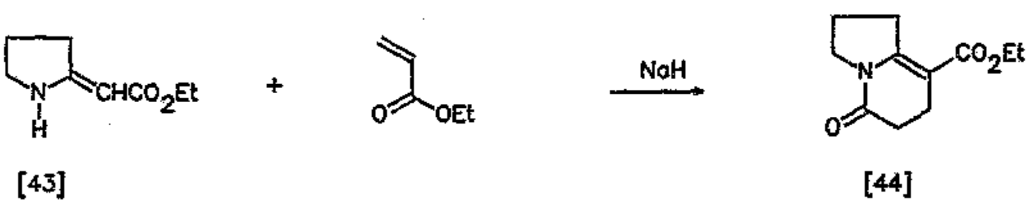


n = 1 or 2
Z = CO_2R; COR; CN
R = alkyl

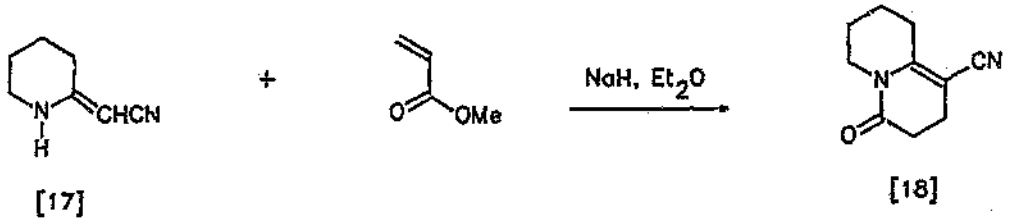
Figure 3

We will now illustrate compounds of the types [40], [41] and [42] that have been synthesised in these laboratories using the "Wits approach".

Two examples of compound [40] where n = 1 and 2 and Z = CO_2Et and CN, respectively, have been prepared by Meerholz[22] ([44]) and Yamada *et al.*[19] ([18]), respectively. Initial α-carbon alkylation of a secondary vinylogous urethane [43] and a secondary vinylogous cyanamide [17], using Michael reagents (ethyl acrylate and methyl acrylate, respectively), followed by intramolecular acylative ring closure afforded [44] and [18], respectively (Schemes 10 and 11).

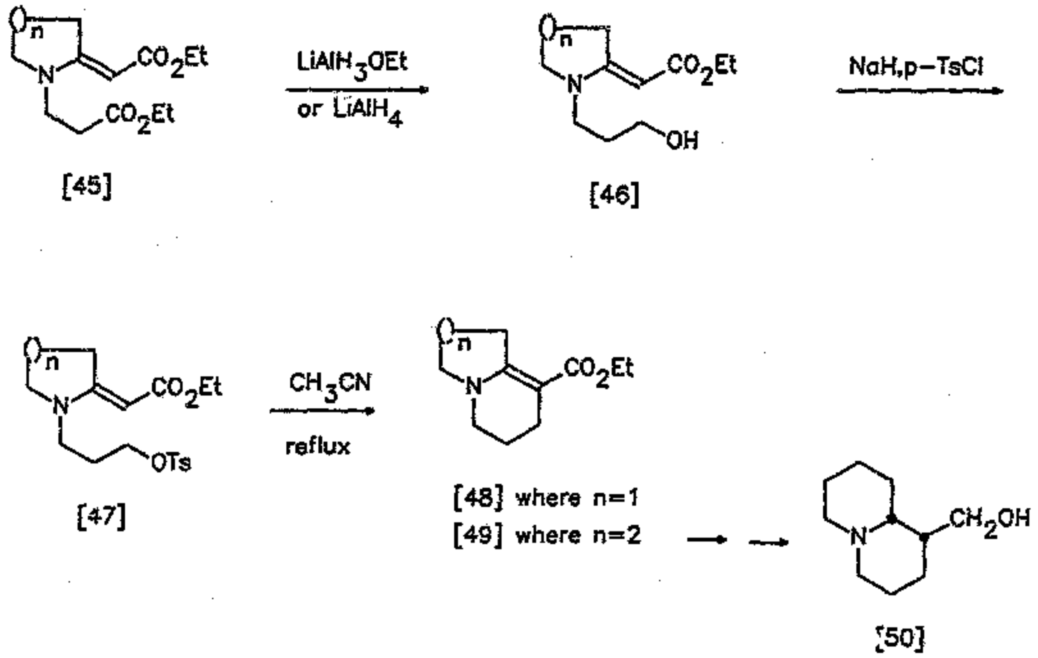


Scheme 10



Scheme 11

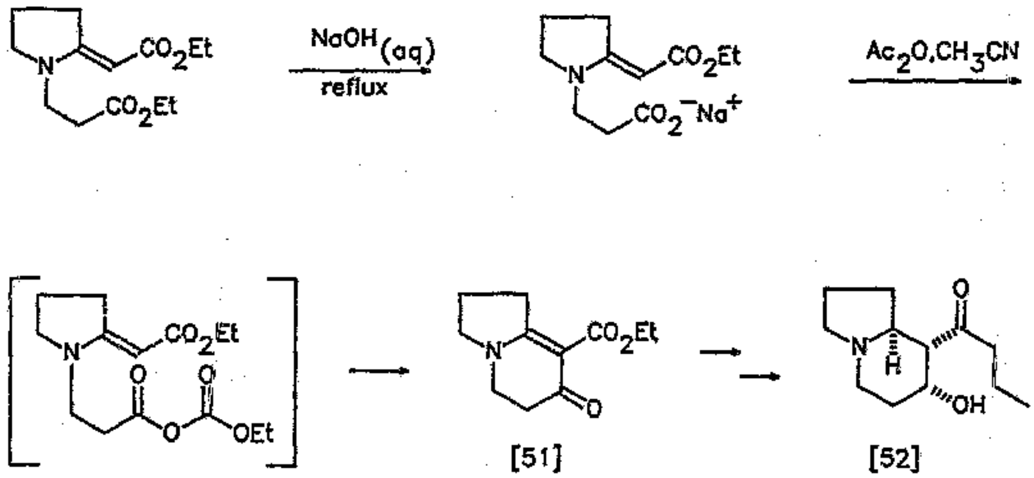
Compounds of type [41], where n = 1 and 2 and Z = CO_2Et have been made by Meerholz[22] [48] and Gerrans *et al.*[28] [49], respectively (Scheme 12). The precursor needed for the formation of [48] and [49] was a tertiary vinylogous urethane [45] with the nitrogen bearing a 3-carbon unit with a terminal functional group. Meerholz[22] and Orlek[21] showed that the vinylogous urethane system does not react intramolecularly with an ester group. In this present case, the ester carbonyl group was chemoselectively reduced to form a primary alcohol [46], leaving the ester of the vinylogous urethane system unperturbed. Conversion of the alcohol to a better leaving group and subsequent cyclisation was achieved by addition of sodium hydride and *p*-toluenesulphonyl chloride and heating under reflux in acetonitrile. The unsaturated functionalised quinolizidine intermediate [49] served as a precursor to (±)-lupinine [50] which is a representative of the Lupine alkaloids.



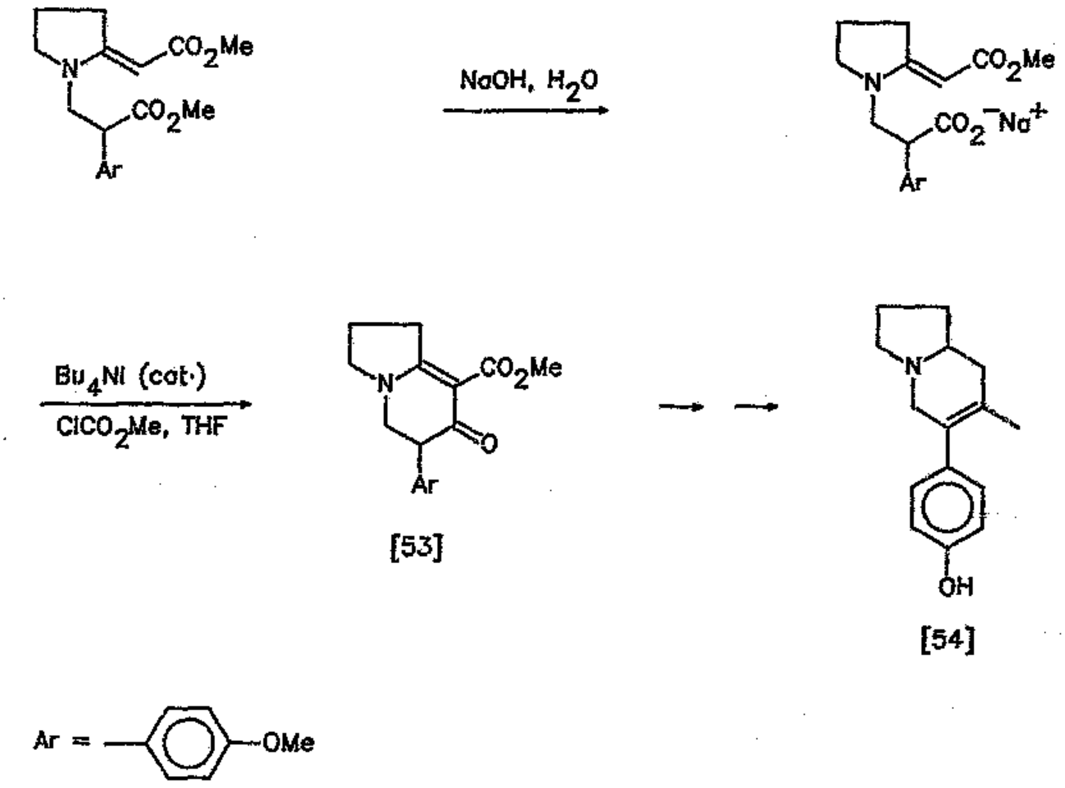
Scheme 12

Two examples of the compound type [42] have been prepared by Howard *et al.*, [51][30] and [53][29]. The problem of failure of the vinylogous urethane system to react intramolecularly with the ester group, presents itself again. However, activation of the ester was achieved by converting it into an anhydride. Contrary to the previous example, the carbonyl group of the ester is retained. This leads to additional functionality being present at the 4-

position of the final product (see Schemes 13 and 14). The unsaturated functionalised indolizidine intermediate [51] served as a precursor to elaeokanine A [52] which is an Elaeocarpus alkaloid. The intermediate [53] was also taken through a series of reactions to afford ipalbidine [54], an alkaloid which has been isolated from *Ipomoea alba* L.



Scheme 13

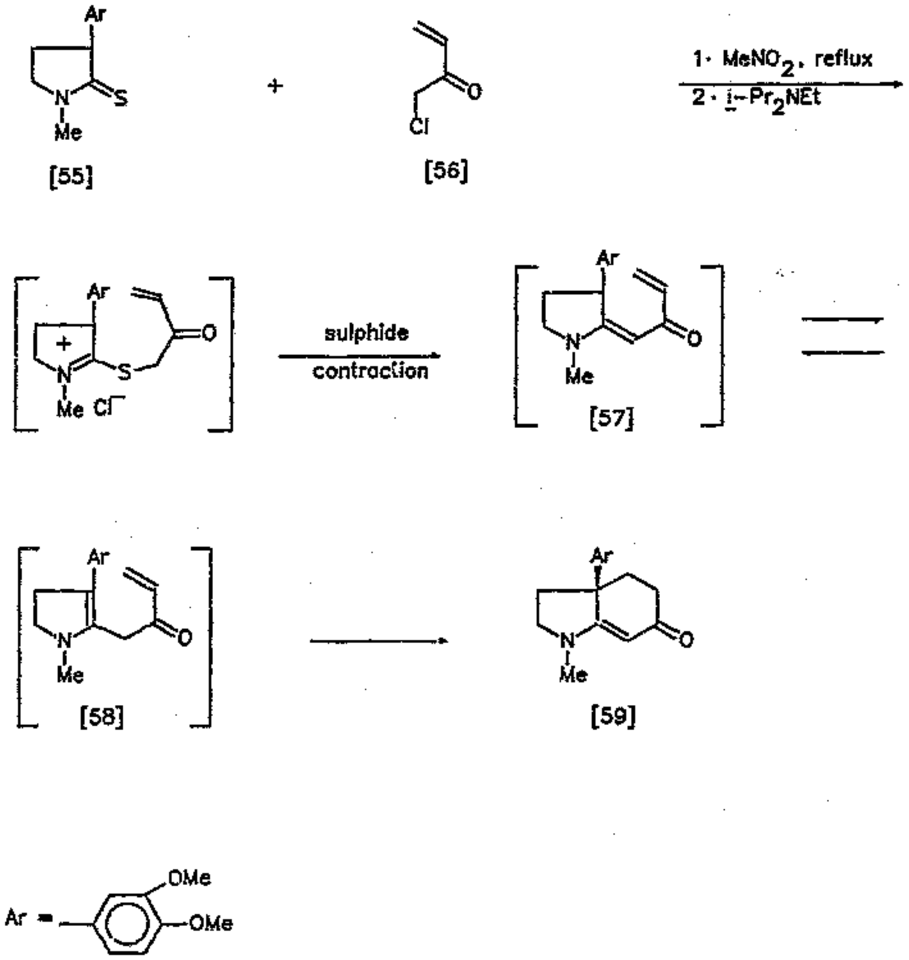


Scheme 14

All the aforegoing examples have been of acylative or alkylative cyclisations to form fused bicyclic systems containing nitrogen at the bridgehead position.

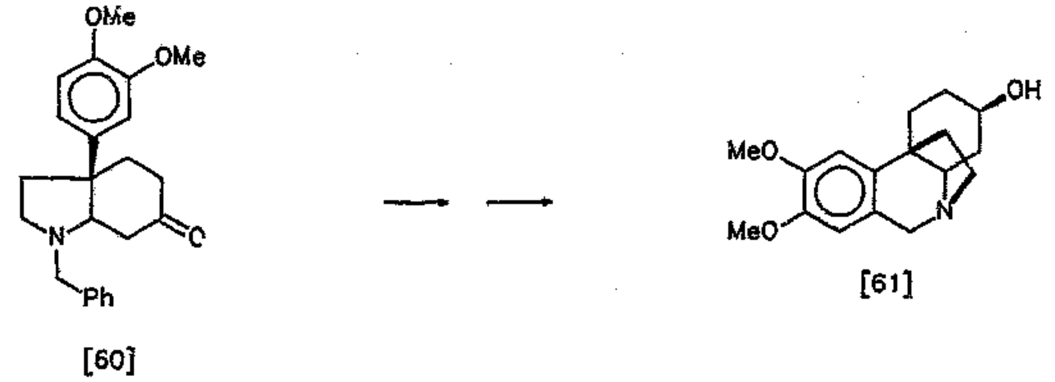
Two examples will now be given of alkylative cyclisations to produce fused bicyclic systems in which the nitrogen is α to the bridgehead position. Howard *et al.*[31] successfully completed the synthesis of Δ^7-mesembrenone [59] (Scheme 15). S-Alkylation of the arylated thiolactam [55] with chloromethyl vinyl ketone [56], followed by sulphur extrusion, afforded a vinylogous enamide intermediate [57].

Spontaneous intramolecular Michael reaction, via an endocyclic enamine tautomer [58], produced the *Sceletium* alkaloid [59].



Scheme 15

Katz[23] synthesised [60] using the same approach (Scheme 16). This served as a precursor to (±)-dihydromaritidine [61] which is an alkaloid of the family Amaryllidaceae.

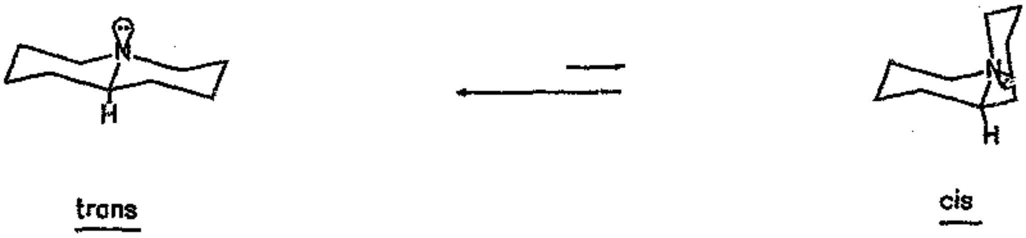


Scheme 16

More recent successes utilising the "Wits approach" have been achieved by Chang,[25] Hosken,[24] Parsons[27] and Zwane.[26] Since their work is not as relevant to the contents of this project as is earlier work by Katz,[23] Meerholz,[22] Orlek,[21] etc., specific examples have not been presented.

1.4 Stereochemistry and conformation of quinolizidine systems

Spectroscopic techniques[66-87] have proved to be of great value in the determination of conformation and the elucidation of stereochemistry of quinolizidine ring systems. Infrared spectroscopy and proton and carbon nuclear magnetic resonance have been used to establish the *cis* or *trans* nature of the fusion between the two rings and have allowed the determination of the *cis* or *trans* relationship of a substituent with respect to the bridgehead hydrogen. The quinolizidine ring system can exist in two possible conformations[66] as shown in Scheme 17.



Scheme 17

The potential to interconvert from one conformer to the other is due to the presence of the conformationally mobile nitrogen atom at the bridgehead position. The thermodynamically more stable is the *trans*-fused ring conformation and this predominates in many alkaloids bearing the quinolizidine skeleton.

1.4.1 Infrared spectroscopy

Bohlmann[84] found that when at least two axial protons on the carbons α to the bridgehead nitrogen were *trans* to the nitrogen lone pair, the resultant *trans*-fused quinolizidine skeleton [62a] exhibited a characteristic series of bands in the infrared spectrum between 2800 and 2700cm^{-1}. These bands were appropriately called "*trans*" or "Bohlmann bands". In contrast, *cis*-fused quinolizidines [62b] contain only one axial proton in a *trans* relation to the nitrogen lone pair and therefore exhibit no *trans* bands (see Figure 4).

[62a]

trans–fused
quinolizidine

[62b]

cis–fused
quinolizidine

Figure 4

Wiewiorowski and Skolik[80] modified the requirements for the occurrence of "*trans* bands". According to their study of Lupine alkaloids, both *trans*- and *cis*-fused quinolizidine skeletons give rise to "*trans* bands". The distinguishing difference lies in the fact that the "*trans* bands" of the latter are present as a stepwise descending set of maxima below 2860cm^{-1} and are lower in intensity whereas the "*trans* bands" of the former are present as well-defined maxima at approximately 2800 - 2750cm^{-1} and are higher in intensity. A less ambiguous description of the occurrence of "*trans* bands" is presented in a later paper by Wiewiorowski *et al.*.[82] They found that the prerequisite for "*trans* bands" was an axial proton on a carbon α to the nitrogen atom and in a *trans* relation to the nitrogen lone pair. The intensity and complexity of the "*trans* bands" increased proportionately as the number of protons so situated increased.

As mentioned previously, infrared spectroscopy is also a powerful tool for determining the stereochemistry of attached substituents. Assignment of configurations of 1-azabicyclo[4.4.0]decan-5-ol[66,83] provides a good example of this method's potential. 1-Azabicyclo[4.4.0]decan-5-ol, in which the hydroxy group is axial [63a] (Figure 5) has the correct spatial orientation to undergo intramolecular hydrogen bonding with the bridgehead nitrogen. An ir-absorption at $3526 cm^{-1}$ is thus present. When the hydroxy group is equatorial [63b] no intramolecular hydrogen bonding opportunity lends itself and thus an absorption at $3618 cm^{-1}$, indicative of a free OH, is observed. Prominent "Bohlmann bands" in both cases predict the existence of only *trans*-fused ring conformations.

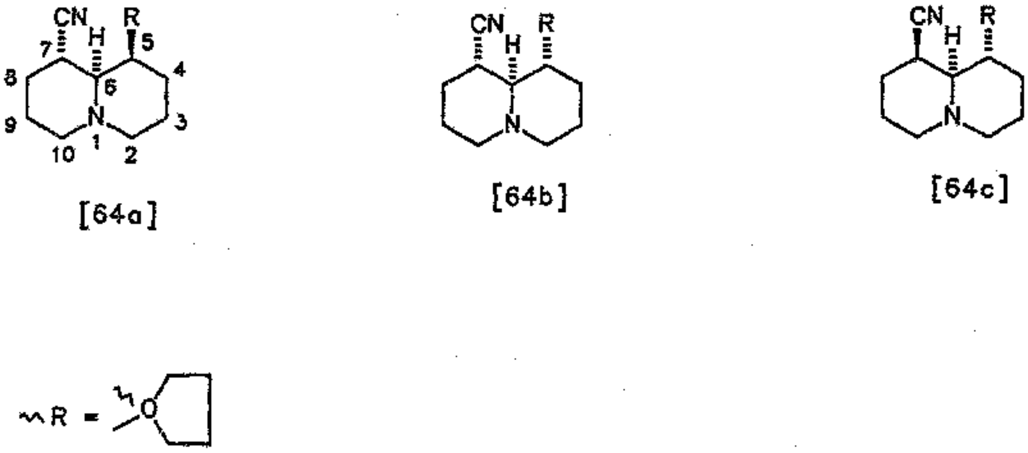
[63a] [63b]

Figure 5

1.4.2 Nuclear magnetic resonance spectroscopy

A study of the proton nmr of quinolizidine revealed that the signals due to the C-2 and C-10 equatorial protons were downfield from those due to the corresponding axial protons.[66,77,84,85] The difference in chemical shift of 0.93ppm between the axial and equatorial methylene protons adjacent to the bridgehead nitrogen can be explained. It is believed that the nitrogen lone pair shields the axial protons by increasing the electron density in their vicinity. This is brought about by the partial participation of the nitrogen lone pair in the σ^* C-H_{ax} orbital on the adjacent methylene carbons. It follows that if the nitrogen lone pair and a methylene proton are both axial and *trans* to each other, the chemical shift difference is the greatest.

Predictions about the conformation and stereochemistry of a quinolizidine-based compound, the ethylene ketal of 1-azabicyclo[4.4.0]decane-5-acetyl-7-carbonitrile[67,70] [64] are discussed hereafter (Figure 6).

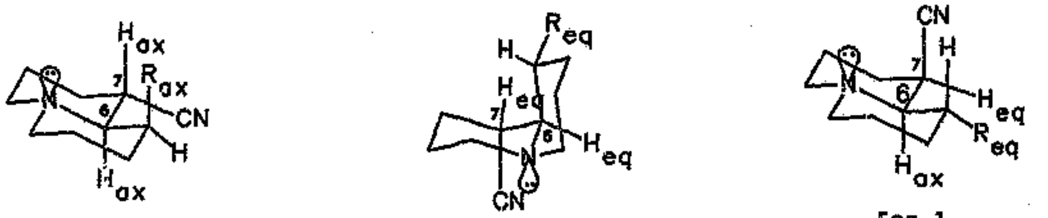


[64a] [64b] [64c]

Figure 6

The configuration and conformation of the three stereoisomers of 1-azabicyclo[4.4.0]decane-5-acetyl-7-carbonitrile were deduced using proton nmr. The characteristic downfield shift of the C-2 and C-10 equatorial protons of [64a] and [64c] to 2.85 and 2.88 ppm, respectively indicated that these two stereoisomers possessed the *trans*-fused quinolizidine system. The bridgehead hydrogen of C-6 is equatorial (with respect to the left hand side ring) in [64b], and thus its nmr signal is shifted downfield to 3.10ppm. The result is therefore a *cis*-fused conformation.

The chemical shift of the methine hydrogen of C-7 provides information about the stereochemistry of the three stereoisomers. In [64a] the upfield shift to 3.03ppm provides evidence for an axially oriented hydrogen and in [64b] and [64c] the relative downfield shift to 3.48 and 3.57ppm, respectively, indicates an equatorial conformation. Coupling constants also aid in the assignment of stereochemistry. Chemical shifts of the methyl group of the ketal unit (R) provide information about the stereochemistry of the latter. An axial orientation of the ketal side chain would result in the methyl protons being deshielded by the bridgehead nitrogen or the nitrile unit to a downfield position. This is indeed found in [64a], where the methyl protons resonate at 1.57ppm. The ketal side chain is equatorial in [64b] and [64c] as the respective chemical shifts of the methyl protons are at normal chemical shifts of 1.26 and 1.25ppm, respectively. Figure 7 illustrates the conclusions drawn from the foregoing discussion.



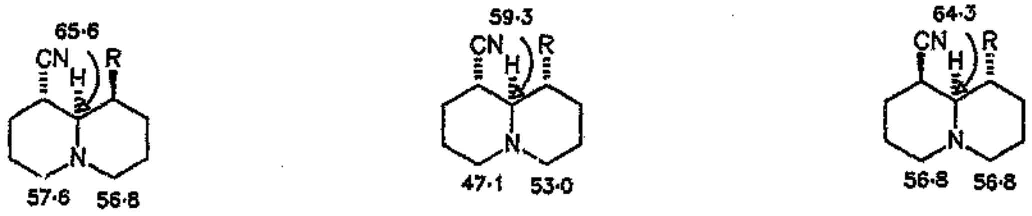
[65a] *trans*-fused

[65b] *cis*-fused

[65c] *trans*-fused

Figure 7

A ^{13}C nmr study of 1-azabicyclo[4.4.0]decane-5-acetyl-7-carbonitrile has provided additional confirmation of the conformation of the three stereoisomers of this compound. Figure 8 shows the important chemical shifts.



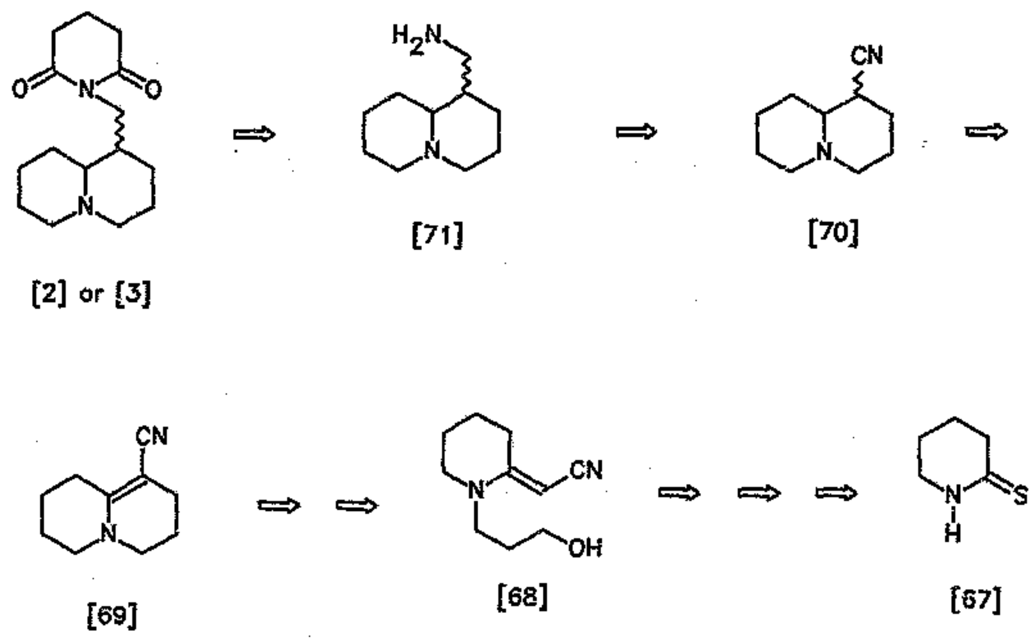
[66a] [66b] [66c]

Figure 8

The occurrence of a *trans*-fused quinolizidine skeleton would render the chemical shifts of C-2 and C-10 identical (or almost identical). Reference to Figure 7 makes this point clearer. This indicates that [65a] and [65c] are *trans*-fused. Stereoisomer [66b] shows a remarkable upfield shift of one aminomethylene carbon, consistent with a *cis*-fused bicyclic system and due to two γ effects exerted by neighbouring ring carbons. The bridgehead carbon provides further evidence of ring fusion, being about 6ppm upfield in [66b] relative to [66a] and [66c].

1.5 The aims and strategies of this project

Our objective is to develop general methods for alkaloid synthesis by exploring the potential of exocyclic extended enamines conjugated to an electron-withdrawing group. The preparation of specific alkaloids is a long-term aim. The current project represents a direct attempt to achieve one of these long-term aims, the synthesis of the Lupine alkaloids, epilamprolobine [2] and lamprolobine [3]. Our intended approach is represented as a retrosynthetic analysis in Scheme 18.

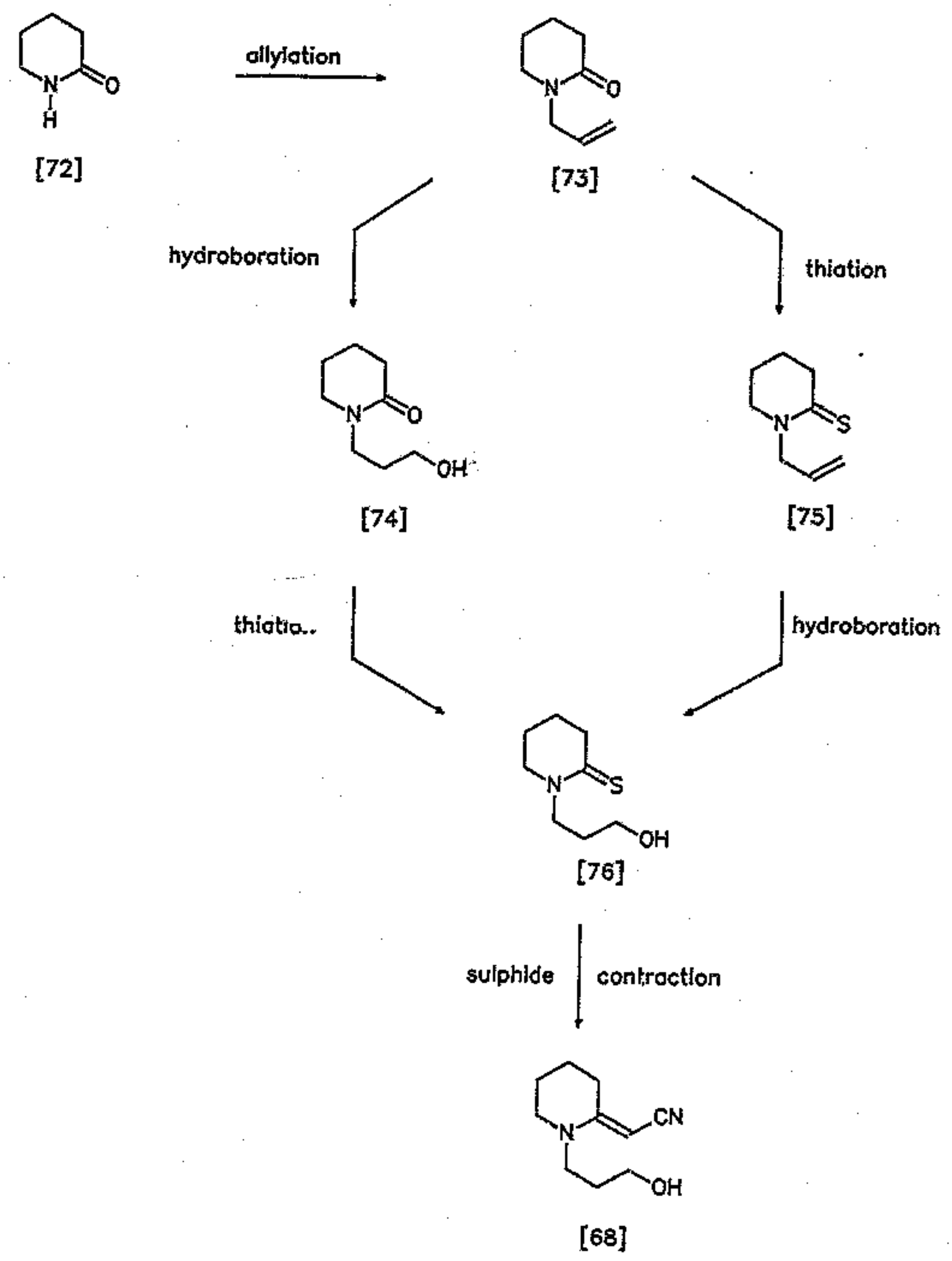


Scheme 18

Our philosophy is to broaden the scope from vinylogous urethane and vinylogous amide precursors (successfully used for the synthesis of alkaloids by workers in these laboratories[28-34]) to vinylogous cyanamide precursors. The availability and diversity of procedures for the preparation of vinylogous cyanamides also make this type of compound an obvious precursor for the proposed synthetic route to epilamprolobine and lamprolobine. Our initial synthetic objective is, therefore, the preparation of 1-(3-hydroxypropyl)-2-cyanomethylenepiperidine [68]. Conversion of the hydroxy group to a suitable leaving group is expected to allow for facile alkylative ring closure (according to the "Wits approach"), producing a functionalised quinclizidine system [69], which itself is a vinylogous cyanamide. This is a potentially useful intermediate for further synthetic work. In the reduction of the endocyclic double bond, utilisation of a stereoselective reducing agent can control the relative stereochemistry at C-5 and C-6. This is necessary in order to establish, at an early stage, the appropriate stereochemical configuration required in the target alkaloids. If necessary, epimerisation of one of the reduced products [70] should allow access to the other. Manipulation of the functional group of each isomeric saturated quinolizidine system [70] should lead to the desired alkaloids.

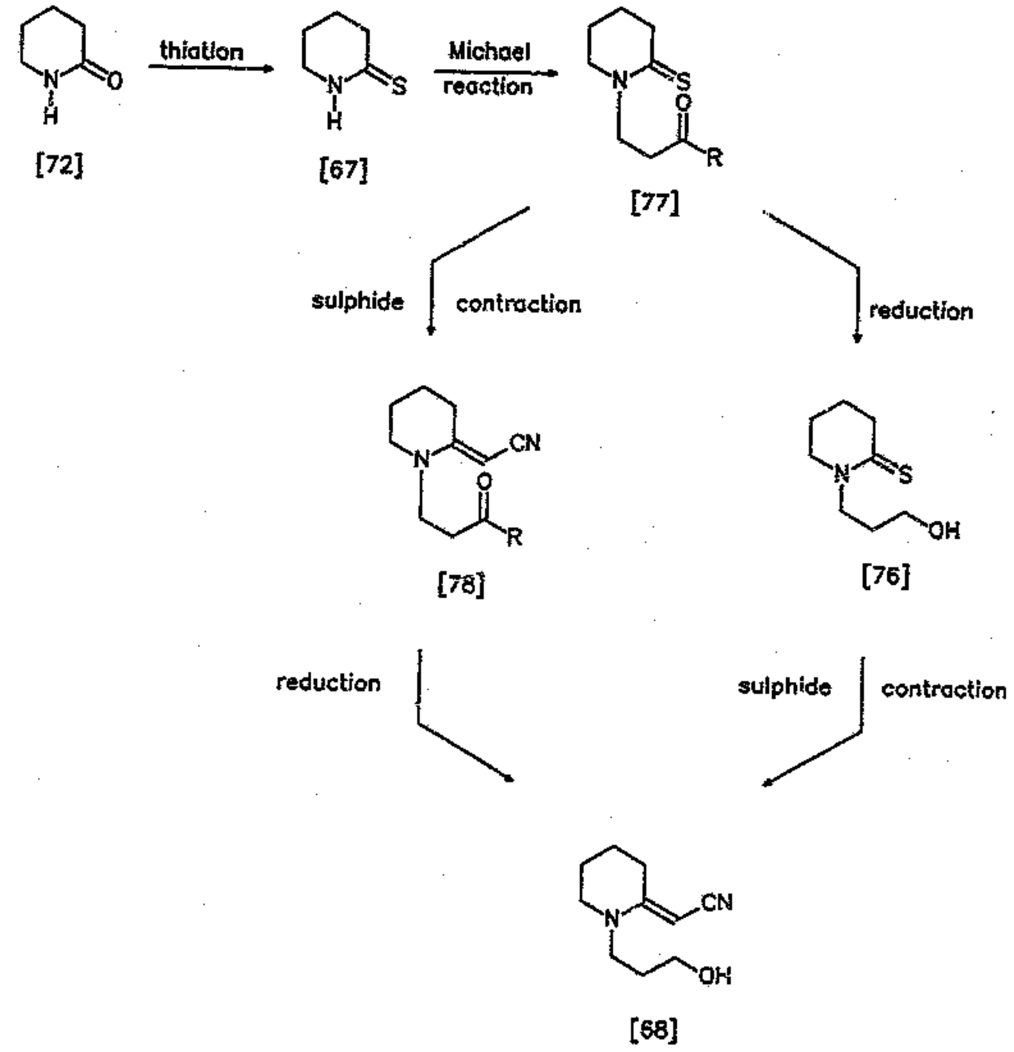
The synthesis of the Lupine alkaloids from [69] should entail a single straightforward route. Scope for variation will, therefore, not be found in different possible synthetic routes, but rather in the use of different reaction parameters. By contrast, there are more options available for preparing the pivotal intermediate [68]. The thiation reaction, the Michael reaction and the sulphide contraction sequence appear to be the three key methods most suited to the construction of [68]. The source of the $CH_2CH_2CH_2OH$ group attached to the ring nitrogen could originate from a) $CH_2CH=CH_2$ or from b) CH_2CH_2COR (where R = OEt, O^tBu, H). Subsequent hydroboration of the former and reduction of the latter is expected to afford the 3-carbon unit bearing the terminal hydroxy group. This is illustrated in Schemes 19 and 20, respectively.

a) **Source**: $CH_2CH{=}CH_2$



Scheme 19

b) <u>Source</u>: CH_2CH_2COR

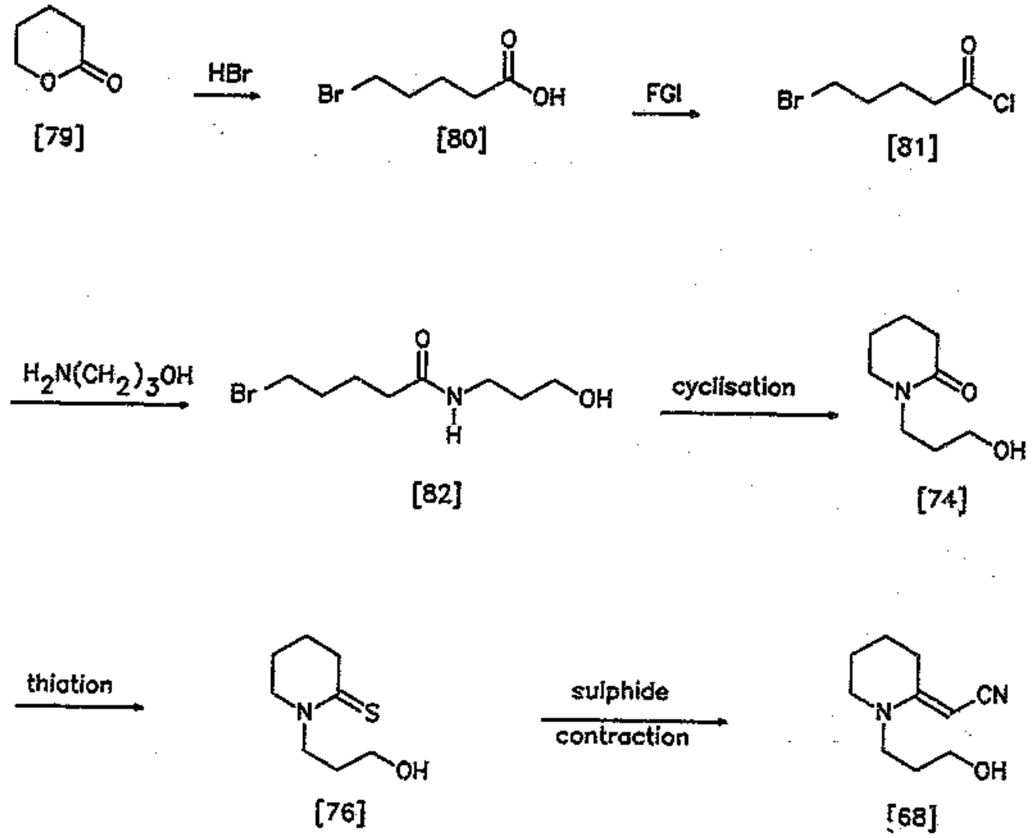


where R = OEt, O^tBu, H

Scheme 20

As illustrated above, there is scope for variation within both synthetic routes. In Scheme 20 the formation of the thiolactam [67] precedes the Michael reaction which is responsible for transforming the secondary nitrogen to a tertiary one. In Scheme 19, the reverse order is employed i.e. allylation before thiation.

A slightly different approach to the synthesis of the key intermediate [68] is shown in Scheme 21.



Scheme 21

Here the 6-membered ring incorporating the nitrogen atom is first synthesised, whereas in Scheme 19 and 20 this ring system is already present in the starting material.

The similarities and differences between our synthetic approach to epilamprolobine and lamprolobine and those reported in the literature will now be discussed.

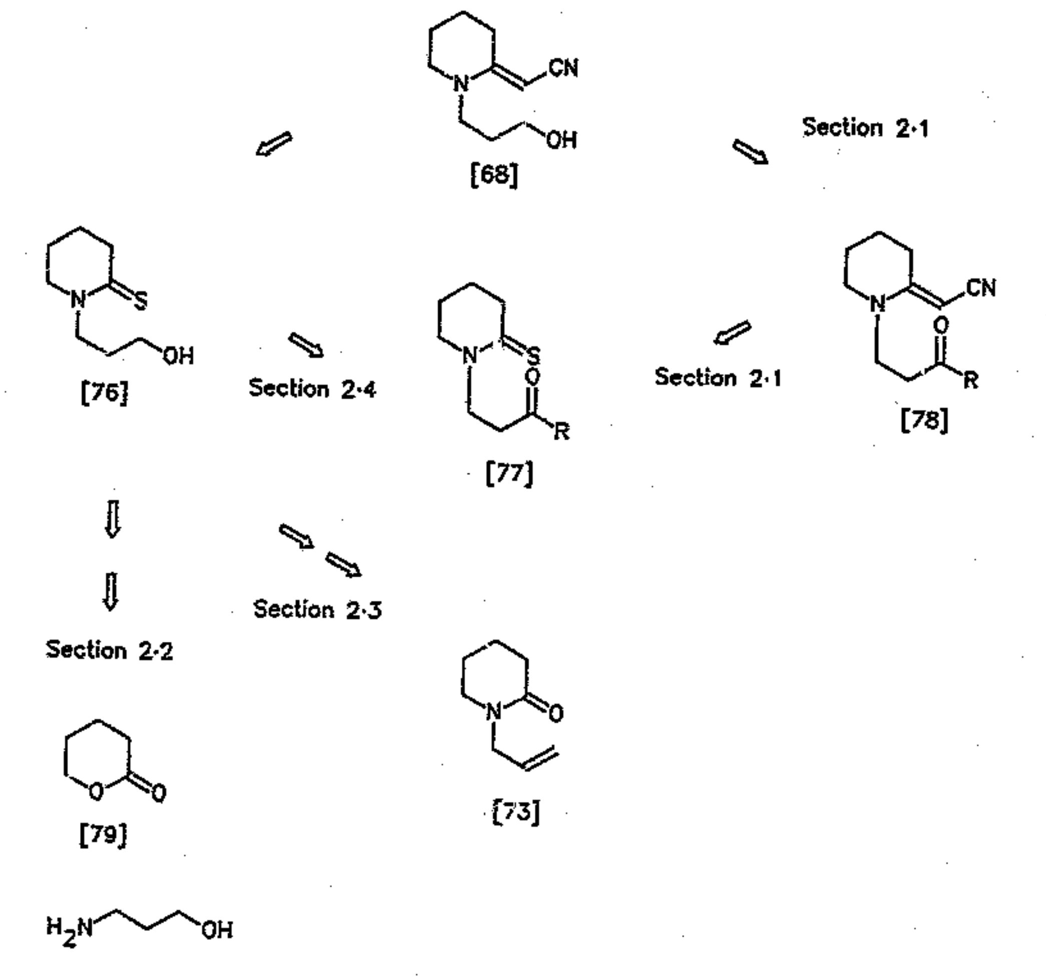
The endocyclic vinylogous cyanamide intermediate [69], which we intend employing in our synthetic route, is very similar to the vinylogous urethane precursor [7] used by Goldberg and Lipkin[17] in their synthesis of lamprolobine (Scheme 1). Both intermediates are extended enamines conjugated to an electron-withdrawing group and are thus expected to exhibit the same properties and chemical reactivity. The preparation of our endocyclic vinylogous cyanamide intermediate will differ dramatically from that described for the similar intermediate by Goldberg and Lipkin. Their synthetic pathway from the vinylogous urethane intermediate to the final target lamprolobine will be similar to our approach except that a functional group conversion will not be necessary in our case.

In our synthesis of epilamprolobine (and lamprolobine) a functionalised quinolizidine system [70] will be prepared from commercially available starting materials. In contrast Murakoshi *et al.*[12] converted the alkaloid lupinine [10] already containing the quinolizidine backbone, in various steps to the alkaloid epilamprolobine.

As described earlier, our synthesis of the saturated functionalised quinolizidine [70] will involve alkylative cyclisation of the exocyclic vinylogous cyanamide intermediate [68], followed by a stereoselective carbon-carbon double bond reduction and epimerisation to afford both isomers of [70]. In comparison, Wenkert and Jeffcoat[18] carried out an acid-catalysed cyclisation of an endocyclic vinylogous cyanamide intermediate [14] to afford a saturated bifunctionalised quinolizidine isomeric pair [15] and [16] (Scheme 3). They needed to reduce the nitrile group, just as we will, but the two additional steps needed to remove the ketal moiety, will not be necessary in our case.

Our synthetic approach to epilamprolobine and lamprolobine is most comparable with that reported by Yamada *et al.*[15] (Scheme 4). Firstly, 2-piperidinone will also be used as the initial starting material and secondly, the nitrile reduction and addition of the glutarimido unit will also comprise the final steps of our syntheses. We intend to cyclise an exocyclic vinylogous cyanamide intermediate ([68]) in which the ring nitrogen is tertiary, whereas Yamada *et al.* utilised an exocyclic vinylogous cyanamide intermediate [17] in which the ring nitrogen was secondary. Our proposed alkylative ring closure entails exploitation of the nucleophilicity of the α-carbon of the vinylogous cyanamide system. In contrast, Yamada *et al.* carried out a Michael reaction at the α-carbon position of the vinylogous cyanamide intermediate [17], followed by an acylative ring closure, which exploited the nucleophilic nature of the ring nitrogen. This synthesis is especially important to us, because the route we have devised (see Chapter 3, Scheme 39) converges with it from compounds [19] and [20] onwards.

Chapter 2 will deal with the attempted and successful syntheses of 1-(3-hydroxypropyl)-2-cyanomethylene-piperidine [68]. The retrosynthesis shown in Scheme 22 serves as a guideline to the organisation of the material in the next chapter.



where $R = OEt, O^tBu, H$

Scheme 22

This will be followed by Chapter 3, which will deal with the synthesis of epilamprolobine and lamprolobine from the vinylogous cyanamide intermediate [68].

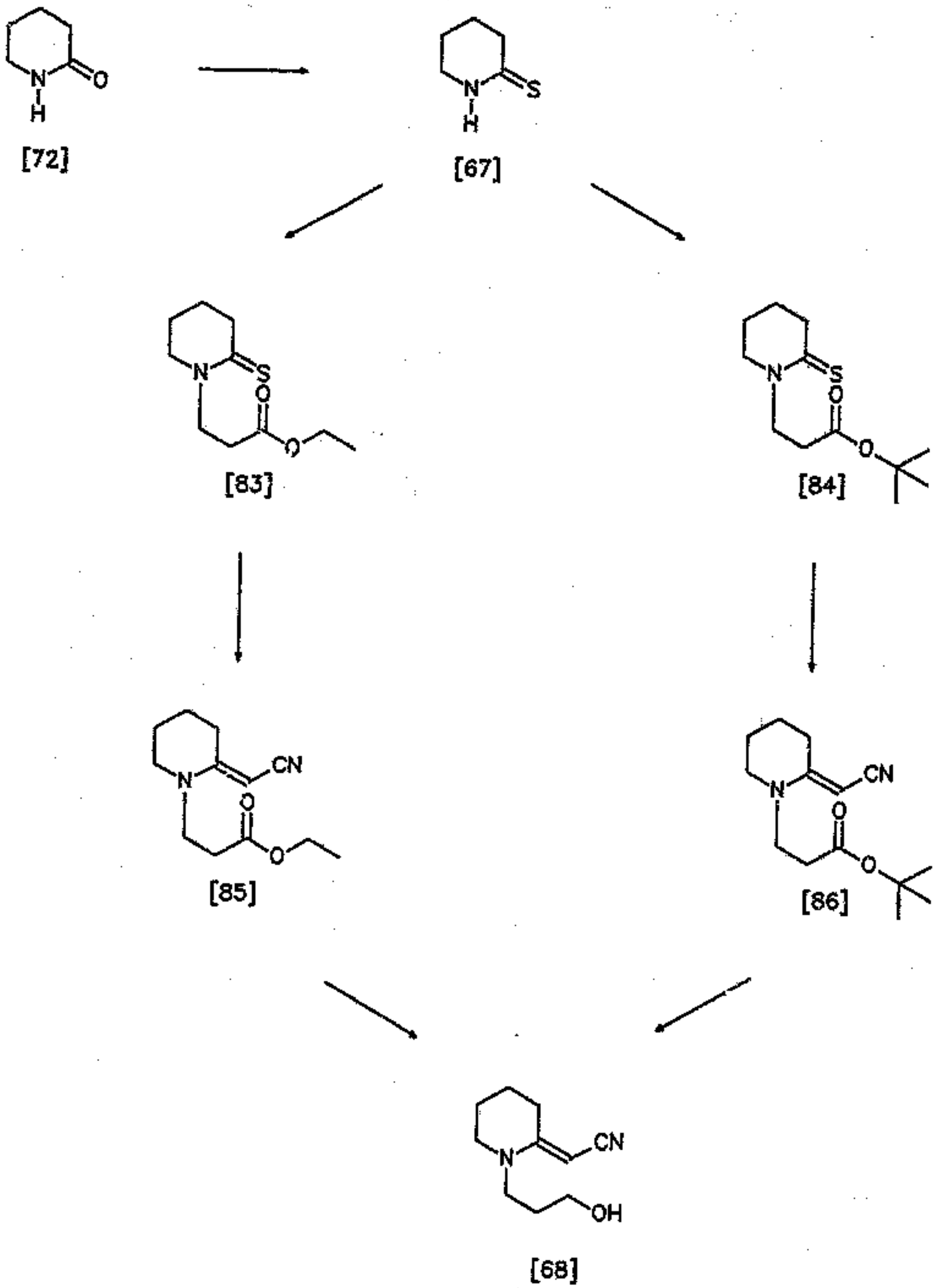
CHAPTER 2

THE SYNTHESIS OF 1-(3-HYDROXYPROPYL)PIPERIDINE DERIVATIVES

This chapter will deal with the synthesis of 1-(3-hydroxypropyl)piperidine derivatives, which are the central intermediates in our approach *en route* to quinolizidine systems and, ultimately, to the target alkaloids. We will begin with a description of the successful approach to the synthesis of 1-(3-hydroxypropyl)-2-cyanomethylenepiperidine [68] (Section 2.1). This will be followed by a brief discussion of some alternative routes to 1-(3-hydroxypropyl)piperidine-2-thione [76] (Sections 2.2, 2.3 and 2.4) that either failed or were abandoned in light of the success obtained in Section 2.1.

2.1 Synthesis of 1-(3-hydroxypropyl)-2-cyanomethylenepiperidine

The synthetic route undertaken for the preparation of the title compound [68] is illustrated in Scheme 23.



Scheme 23

Thiolactams are the precursors needed for the sulphide contraction reaction.[43-45] The process entails S-alkylation of the thiolactam to form a salt, from which sulphur is extruded, to produce an extended enamine system. In our case the desired extended enamine is the exocyclic vinylogous cyanamide, 1-(3-hydroxypropyl)-2-cyanomethylenepiperidine [68]. The thiolactam, piperidine-2-thione [67] can be prepared by thiation of the lactam 2-piperidinone [72]. The former, being a secondary thiolactam would undergo the sulphide contraction reaction under much harsher conditions and in poorer yields than if it were a tertiary thiolactam.[20] Therefore, it would be advantageous to prepare the N-substituted thiolactams 1-(2-ethoxycarbonylethyl)piperidine-2-thione [83] and 1-(2-t-butoxycarbonylethyl)piperidine-2-thione [84] by means of the Michael reaction. Sulphide contraction of these two tertiary thiolactams, followed by chemoselective reduction of the terminal ester group of the contracted products [85] and [86] was expected to produce the pivotal exocyclic vinylogous cyanamide precursor [68] bearing a 3-carbon unit with terminal functionality.

In the sections that follow (2.1.1 - 2.1.4), each of the four reactions, thiation, Michael reaction, sulphide contraction and reduction, will be described.

2.1.1 Synthesis of piperidine-2-thione

A standard method for preparing lactam-2-thiones is by heating the lactam precursor with phosphorus pentasulphide in an inert solvent such as benzene or toluene. In the present work, 2-piperidinone [72] and phosphorus pentasulphide were heated under reflux in benzene to afford the thiated product [67] in 30% yield after column chromatography. The ^{1}H nmr showed the expected downfield shift (to 2.89ppm) of the triplet due to the protons α to the thiocarbonyl group. The protons α to the carbonyl group in the starting material would have resonated at 2.39ppm. The broad singlet due to the N-H proton appeared at 9.90 - 9.40ppm. The ir spectrum provided further evidence in support of the product structure i.e. the C=O stretch at 1650cm^{-1}, the "in plane" N-H deformation at 1465cm^{-1} and the C-N stretch at 1330cm^{-1}, indicative of the lactam were absent. Instead, absorption bands corresponding to a C=S stretch at 1110cm^{-1}, a C-N stretch at 1537cm^{-1} and a N-H deformation at 1350cm^{-1} and 1317cm^{-1} of the thiolactam species were observed. Also, the N-H stretch of [67] was observed at 3360cm^{-1}.

In the search for a better method for the synthesis of piperidine-2-thione [67], Brillon[88] has suggested the preparation of an *in situ* thiating reagent [87], formed by the reaction between phosphorus pentasulphide and sodium carbonate in tetrahydrofuran at 25°C (Scheme 24).

$$P_4S_{10} \quad + \quad Na_2CO_3 \quad \xrightarrow[-CO_2]{THF} \quad (P_4S_{10}O)^{2-}Na_2^{\,2+}$$

[87]

Scheme 24

The merits of this novel approach include the homogeneous solution of [87], the solubility of this ionic species in both tetrahydrofuran and in water, thus permitting an easy workup procedure, and finally the mild conditions (ambient temperature) under which the reaction is performed. Using either a 1:1 or a 5:3 ratio of phosphorus pentasulphide:sodium carbonate, piperidine-2-thione was obtained by Brillon in yields of 85% and 81% respectively.

In this project, piperidine-2-thione was obtained in 88% yield (after column chromatography) when the molar ratio of phosphorus pentasulphide:sodium carbonate:lactam was 1:1:1. In contrast, a very low yield of 12% was afforded when the respective ratio was 3:1.5:1. In the latter case, a white, rubbery solid was formed after the conventional one day reaction period, which was insoluble in all organic solvents at our disposal. Agitation by means of ultrasound did not circumvent this problem.

2.1.2 Conjugate additions with acrylates

Orlek[21] selectively alkylated piperidine-2-thione at nitrogen by using an activated olefin in a Michael reaction. More specifically, he treated piperidine-2-thione [67] with ethyl acrylate in tetrahydrofuran in the presence of a catalytic amount of sodium hydride to afford an excellent yield (94%) of 1-(2-ethoxycarbonylethyl)-piperidine-2-thione [83].

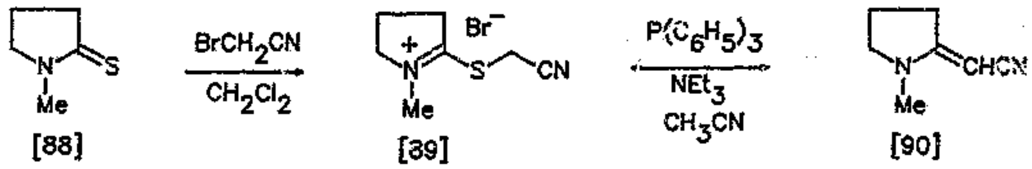
In this project, the same procedure as described by Orlek for the conjugate addition of ethyl acrylate to piperidine-2-thione [67], was followed. An improved yield of 99% of product [83] (purified by distillation and column chromatography) was obtained. The quartet at 4.15ppm and the triplet at 1.27ppm in the ^{1}H nmr spectrum indicated the presence of the ethoxy group. An ester carbonyl signal at 171.6ppm was observed in the ^{13}C nmr spectrum. Further evidence of the Michael product was provided by the ir spectrum, which showed a C=O stretch at 1730cm^{-1}, an asymmetrical C-O stretch at 1185cm^{-1} and a symmetrical C-O stretch at 1160cm^{-1} of the ester group. The high resolution mass spectrum showed a molecular ion at m/z = 215.0980 corresponding to $C_{10}H_{17}NO_2S$.
Possible S-alkylation of piperidine-2-thione by the Michael acceptor to form a thioiminoester was dismissed when a

thiocarbonyl carbon peak at 199.8ppm was observed in the ^{13}C nmr spectrum and the ir-absorption bands characteristic of a thiolactam (i.e. C=S stretch at 1095cm^{-1}, a C-N stretch at 1515cm^{-1} and a N-H deformation at 1350cm^{-1} and 1330cm^{-1}) were present.

The synthetic strategy envisaged in Scheme 23 (Section 2.1) requires the eventual removal of the ester group from the 3-carbon chain on nitrogen, either by hydrolysis or by reduction. For the former process it was thought that a *t*-butyl ester might be more readily cleaved than an ethyl ester. Consequently, a quantity of 1-(2-*t*-butoxycarbonylethyl)piperidine-2-thione [84], a *t*-butyl ester, was prepared in 62% yield (chromatographically pure) by treating piperidine-2-thione [67] with *t*-butyl acrylate in tetrahydrofuran in the presence of a catalytic amount of sodium hydride. The ^{1}H nmr spectrum showed a distinctive singlet at 1.45ppm due to the *t*-butyl protons. The ^{13}C nmr spectrum contained an ester carbonyl carbon signal at 170.8ppm and a thiocarbonyl carbon signal at 199.6ppm. The expected ir-absorption bands of the ester functionality and the thiolactam were present i.e. a C=O stretch at 1710cm^{-1}, an asymmetrical and symmetrical C-O stretch between 1225cm^{-1} and 1200cm^{-1} of the former and a C=S stretch at 1150cm^{-1}, a C-N stretch at 1510cm^{-1} and a N-H deformation at 1345cm^{-1} and 1325cm^{-1} of the latter. Microanalysis confirmed the formula $C_{12}H_{21}NO_2S$.

2.1.3 Sulphide contractions

In a preliminary model study, 1-Methyl-2-cyanomethylenepyrrolidine [90] was prepared according to the sequence illustrated in Scheme 25.



Scheme 25

There were several reasons for the synthesis of this compound. Firstly, the optimisation of the sulphur extrusion technique was desired; secondly, the quality of the bromoacetonitrile reagent in the formation of the salt [89] was tested; and finally, [illegible] wanted to use a thione (1-methylpyrrolidine-2-thione [8[illegible] that would provide a known product [90].[20,23]

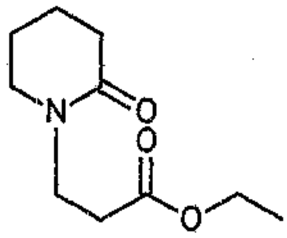
Formation of the salt [89] was accomplished by the addition of bromoacetonitrile to a solution of 1-methylpyrrolidine-2-thione [88] in dichloromethane. Subsequent sulphur extrusion was effected by the sequential addition of triphenylphosphine and triethylamine in acetonitrile. The product was obtained in good yield (71%, chromatographically pure). The ^1H nmr spectrum showed a singlet at 3.58ppm, indicative of the vinyl proton, while the ^{13}C nmr spectrum showed the product's distinguishing nitrile carbon signal at 122.6ppm and vinyl carbon signal at 52.2ppm. There was no doubling up of signals in the ^{13}C nmr spectrum, indicating that only one geometrical isomer had been obtained, which was in contrast to Katz's[23] findings. The ir spectrum of our product contained two absorption bands, indicative of a C=C-C≡N system i.e. a C≡N stretch at 2230cm^{-1} and a C=C stretch at 1630 - 1570cm^{-1}.

Once we had shown that the sulphide contraction worked with a simple model system, 1-(2-ethoxycarbonylethyl)-2-cyanomethylenepiperidine [85] was synthesised by the addition of bromoacetonitrile to neat 1-(2-ethoxycarbonylethyl)piperidine-2-thione [83], followed by sulphur extrusion of the resultant salt with triphenylphosphine and triethylamine. An impressive yield of 85% of the sulphide contracted product was obtained after chromatography. Its structure was substantiated by the ^{1}H nmr spectrum, in which the vinyl proton produced a singlet at 3.76ppm and the quartet at 4.16ppm and triplet at 1.28ppm of the ethoxy ester group were present too. The ^{13}C nmr spectrum showed the distinctive nitrile carbon peak at 122.0ppm, the vinyl carbon peak at 59.9ppm, and the ester carbonyl carbon signal at 171.4ppm. Only one geometrical isomer of 1-(2-ethoxy-carbonylethyl)-2-cyanomethylenepiperidine [85] was obtained. If one considers the strong possibility of intramolecular congestion within the product, one could predict the geometry around the carbon-carbon double bond to be *E*. Confirmation of the existence of a C=C-C≡N system was given by the C≡N stretch and C=C stretch ir-absorption bands at 2175cm^{-1} and 1570cm^{-1}, respectively. Absorption bands due to the ester group were present i.e. the C=O stretch at 1720cm^{-1}, the asymmetrical C-O stretch at 1170cm^{-1} and the symmetrical C-O stretch at 1150cm^{-1}. The high resolution mass spectrum showed a molecular ion peak at m/z = 222.1374, corresponding to $C_{12}H_{18}N_2O_2$.

In a poorer-yielding sulphide contraction reaction, 1-(2-ethoxycarbonylethyl)-2-cyanomethylenepiperidine [85] was prepared in 26% yield (chromatographically pure). It is believed that two contributing factors are responsible for this. Acetone was used as a solvent in the salt formation step and this dilution factor could account for decreased reactivity. A different workup, involving acid-base extraction, was used to try to separate the slightly basic product from the neutral organic material also present.

Product loss to the ether layer during this workup procedure is probable if the assumption of the sulphide contraction product being basic is incorrect.

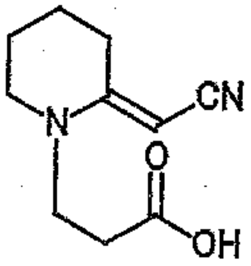
A repetition of the above-mentioned poor-yielding sulphide contraction reaction did not produce the expected sulphide contracted species. Instead, hydrolysis occurred, producing the oxygen analogue of the starting material, 1-(2-ethoxycarbonylethyl)-2-piperidinone [91], in 57% yield (after distillation).



[91]

The vinyl proton peak, which would have been present in 1-(2-ethoxycarbonylethyl)-2-cyanomethylenepiperidine [85], was absent in the ^1H nmr spectrum. Evidence of the ethyl protons of the ethoxy ester group was given by the quartet at 4.14ppm and the triplet at 1.26ppm. The ^{13}C nmr spectrum contained two carbonyl carbon peaks i.e. the lactam carbonyl carbon at 171.8ppm and the ester carbonyl carbon at 169.7ppm. Two ir-absorption bands, an ester C=O stretch at 1725cm^{-1} and a C=O stretch of a 6-ring lactam system at 1625cm^{-1} were present while a C≡N stretch between 2210cm^{-1} and 2185cm^{-1} was absent. Conclusive evidence of the lactam product was provided by the high resolution mass spectrum which showed a molecular ion peak at m/z = 199.1127, corresponding to $C_{10}H_{17}NO_3$.

1-(2-*t*-Butoxycarbonylethyl)-2-cyanomethylenepiperidine [86] was synthesised by the addition of bromoacetonitrile to a solution of 1-(2-*t*-butoxycarbonylethyl)piperidine-2-thione [84] in dichloromethane, followed by sulphur extrusion of the resultant salt with triphenylphosphine and triethylamine. The product [86] was obtained in 10% yield after column chromatography; part of the yield was forfeited by what was believed to be the formation of the carboxylic acid, 1-(2-carboxyethyl)-2-cyanomethylene-piperidine [92], in 26% yield. The ease of hydrolysis of the *t*-butyl group will receive further comment later.



[92]

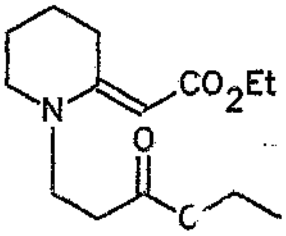
The structure of 1-(2-*t*-butoxycarbonylethyl)-2-cyanomethylenepiperidine [86] was substantiated by ^1H nmr data i.e. the vinyl proton resonated at 3.67ppm and the *t*-butoxy protons produced a singlet at 1.44ppm. Using the same argument as for [85], it is believed that the geometry around the carbon-carbon double bond in [86] is *E*. The ir spectrum showed a C≡N stretch and a C=C stretch of the vinylogous cyanamide system at 2260cm^{-1} and 1612cm^{-1}, respectively and an ester C=O stretch at 1705cm^{-1}.

The ^1H nmr spectrum of the other reaction product [92] did not contain a singlet integrating to nine protons at 1.44ppm, and therefore it was deduced that no *t*-butoxy group was present. Surprisingly, no OH peak was detected and the product was accidentally discarded before an ir spectrum could be obtained to look for absorption bands due to C=O and O-H. Nevertheless, a tentative hypothesis was that the ester functionality of the product [86] was converted to a carboxylic acid group. Despite the low yields, this result is positive from one point of view. 1-(2-*t*-Butoxy-carbonylethyl)-2-cyanomethylenepiperidine [86] was prepared as a precursor to the synthesis of 1-(3-hydroxypropyl)-2-cyanomethylenepiperidine [58] (see Scheme 23) because of the expected ease of hydrolysis of the *t*-butoxy group. In fact the sulphide contracted product [86] was sufficiently unstable that it hydrolysed to a large extent to the carboxylic acid [92] on workup. However, because excellent yields were obtained with the ethyl ester, all further work was carried out with this compound, and work on the *t*-butyl ester was abandoned at this stage.

A point worth mentioning is that it is essential not to delay purification of the sulphide contracted product because oxidation of the phosphorus-containing by-products produced mixtures containing triphenylphosphine oxide that were very difficult to separate.

2.1.4 Ester reduction

Conversion of the ester group of 1-(2-ethoxycarbonylethyl)-2-cyanomethylenepiperidine [85] into a better leaving group was desired with the removal of the carbonyl moiety. The latter was a prerequisite for an alkylative cyclisation further on in the synthetic route. In this way, unwanted functionality at the C-4 position of the quinolizidine system [69] would be avoided. It was important that a chemoselective process was employed that would reduce the ester, but leave the nitrile and carbon-carbon double bond unchanged. Orlek[21,28] reduced the saturated ester of [93], leaving the ester and carbon-carbon double bond of the vinylogous urethane system unperturbed, by using lithium aluminum hydride as the chemoselective reducing agent.



[93]

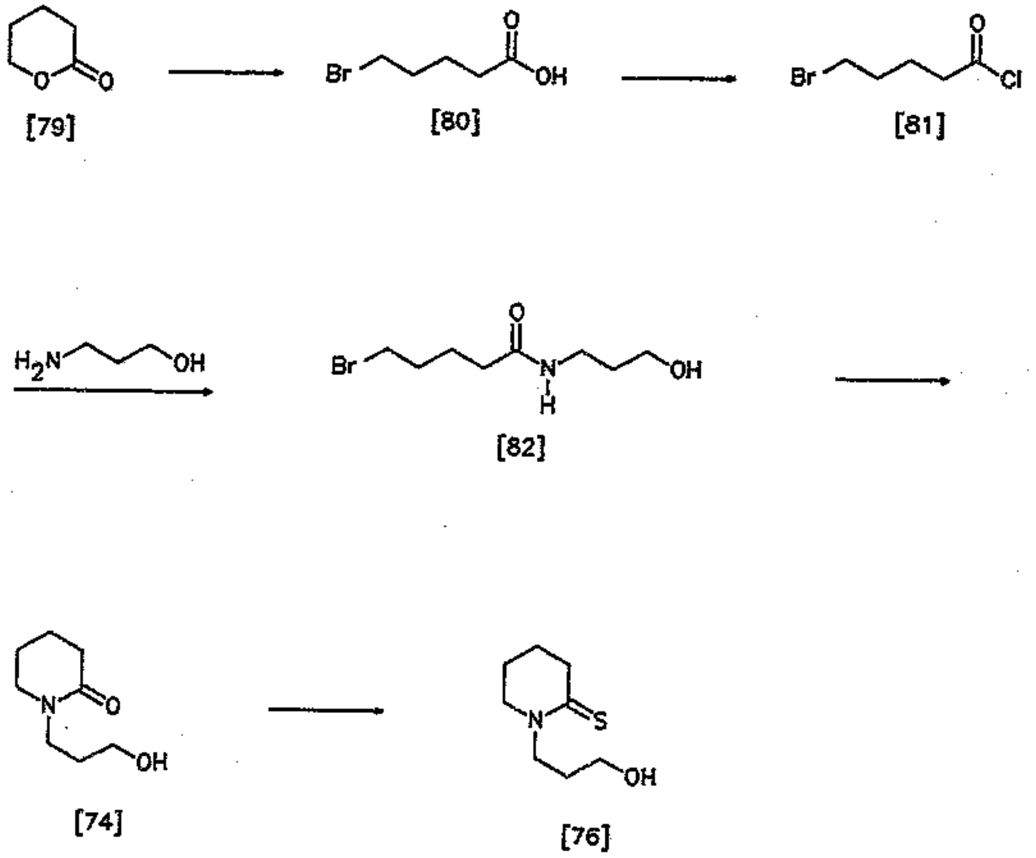
In the light of Orlek's success there was hope for an ester reduction of our similar vinylogous cyanamide system.

1-(3-Hydroxypropyl)-2-cyanomethylenepiperidine [68] was prepared in good yield (74%, chromatographically pure) by heating 1-(2-ethoxycarbonylethyl)-2-cyanomethylenepiperidine [85] and lithium aluminum hydride in tetrahydrofuran. The absence of both a quartet at 4 16ppm and a triplet at 1.28ppm in the ^{1}H nmr spectrum showed that no more starting material was present, while a broad singlet at 3.42 - 3.30ppm of the alcohol product was clearly visible. The vinyl proton singlet at 3.82ppm, together with the nitrile carbon signal at 123.0ppm and the vinyl carbon signal at 57.6ppm provided evidence of the vinylogous cyanamide system present in [68]. No ir-absorption band due to an ester C=O stretch was observed. A broad O-H stretch at 3425cm^{-1}, and a doublet at 1070cm^{-1} and 1050cm^{-1} due to a C-O stretch of the -CH$_2$-OH group indicated that the ester group had indeed been reduced. The presence of the untouched vinylogous cyanamide system was seen by the strong C≡N stretch at 2180cm^{-1} and the equally strong C=C stretch at 1570cm^{-1}. Microanalysis confirmed the formula $C_{10}H_{16}N_2O$.

Further transformations of 1-(3-hydroxypropyl)-2-cyanomethylenepiperidine [68] and its conversion to the target alkaloids epilamprolobine [2] and lamprolobine [3] will be described in Chapter 3. For the remainder of Chapter 2, alternative approaches to 1-(3-hydroxypropyl)piperidine derivatives that either failed or were abandoned, will be discussed.

2.2 Approach based on 5-bromopentanoic acid

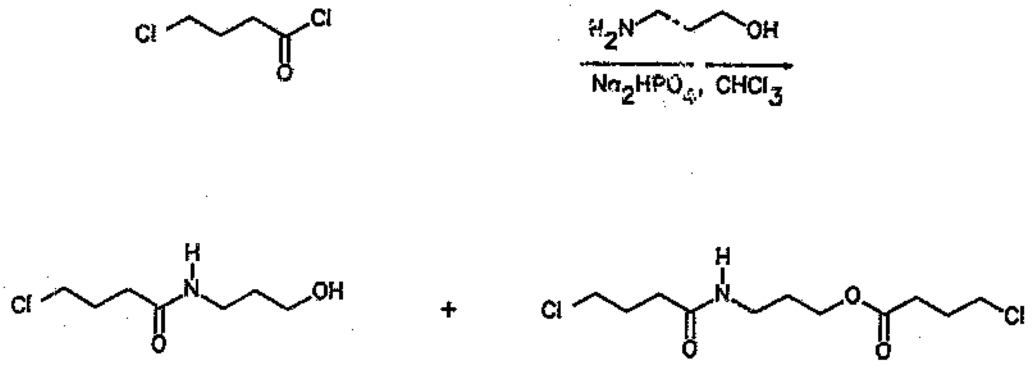
The synthetic route envisaged for the preparation of 1-(3-hydroxypropyl)piperidine-2-thione [76] is illustrated in Scheme 26.



Scheme 26

In this approach we intended to synthesise the 6-membered ring incorporating the nitrogen atom first, unlike the approaches discussed in Sections 2.1, 2.3 and 2.4, where this ring system was already established in the starting material. We were hoping for the thiation of 1-(3-hydroxypropyl)-2-piperidinone [74] to lead to the product [76].

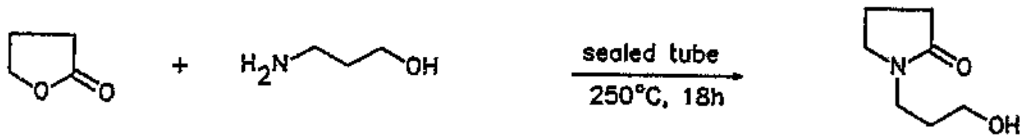
Parsons[27] reported the synthesis of N-(3-hydroxypropyl)-4-chlorobutanamide [94] according to the route outlined in Scheme 27.



24% [94]   55%

Scheme 27

The cyclisation of [94] to form 1-(3-hydroxypropyl)-2-pyrrolidinone [95] (the 5-membered ring analogue of [74] in Scheme 26) was not executed in light of the improved synthesis shown in Scheme 28. Unfortunately, this latter synthetic route is known to fail with δ-valerolactone [79].[122]



81% [95]

Scheme 28

Believing that our 6-membered system might give better results, we attempted nonetheless to synthesise 1-(3-hydroxypropyl)-2-piperidinone [74] according to Scheme 26.

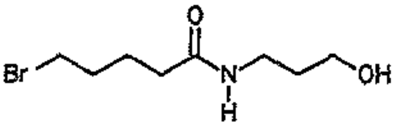
Olah *et al.*[89] prepared 5-bromopentanoic acid [80] in 88% yield by reaction of boron tribromide with δ-valerolactone [79] in dichloromethane at ambient temperature. Bagnall *et al.*[90] also converted [79] to [80] by heating the starting material in hydrobromic acid containing sulphuric acid.

In the present work, the latter procedure was followed to afford 5-bromopentanoic acid [80] in 84% yield without purification. This was not necessary owing to the product's fairly sharp melting point of 36 - 38.5°C (literature 39 - 40°C). Confirmation of the product structure was provided by ^1H and ^{13}C nmr and ir data. A broad singlet at 11.34 - 11.04ppm indicated the presence of the OH proton of the carboxylic acid. The carbonyl carbon chemical shift of 179.7ppm was assigned to that of the carboxylic acid and not to the ester of the starting material, as the latter would have been upfield by about 10ppm.[91] The C=O stretch of the lactone starting material at approximately 1735cm^{-1} was not visible, but instead a COO-H stretch at 3500cm^{-1} and a carboxylic acid C=O stretch at 1705cm^{-1} representative of 5-bromopentanoic acid was observed.

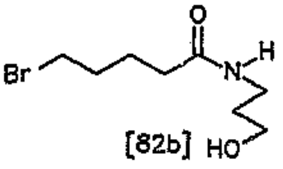
In order to prepare the corresponding acid chloride, 5-bromopentanoic acid and thionyl chloride were heated in chloroform with a trace of dimethylformamide as catalyst. The acid halide, 5-bromopentanoyl chloride [81], was obtained in 81% yield after distillation. Confirmation of its structure was provided by the acid chloride carbonyl carbon signal at 172.8ppm in the ^{13}C nmr spectrum and the strong ir-absorption band at 1790cm^{-1} due to the acid chloride C=O stretch. The ^1H nmr spectrum did not show an

OH proton peak and thus provided evidence that the starting material was no longer present.

The next synthetic step entailed the synthesis of N-(3-hydroxypropyl)-5-bromopentanamide [82]. Addition of a solution of 5-bromopentanoyl chloride [81] to a mixture of disodium hydrogen phosphate and 3-amino-1-propanol in chloroform afforded the product in 30% yield (chromatographically pure). The low yield was attributed to the possible water solubility of [82], which would have led to loss of material during the extraction procedure. The ^{1}H and ^{13}C nmr data substantiated the product structure and indicated that two geometrical isomers of N-(3-hydroxypropyl)-5-bromopentanamide [82a] and [82b] were present in a ratio of approximately 23:7.

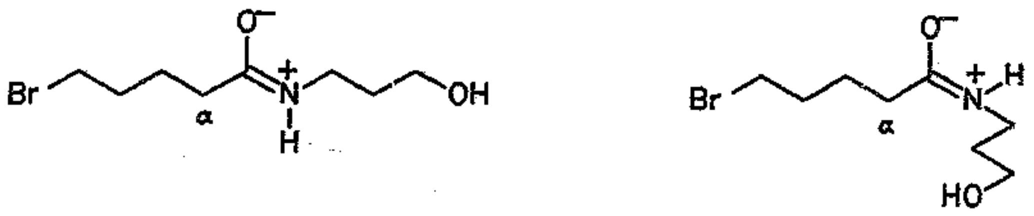


[82a]



[82b]

Two triplets, one for each isomeric NH, were present at 7.59ppm and 4.67ppm in the ^{1}H nmr spectrum. The difference in chemical shifts of the peaks due to the two protons on the α-C to the nitrogen (at 3.37ppm and 3.25ppm) gave further evidence of the two isomers. Verification of the assignment of the broad OH peak at 5.70 - 5.00ppm was given by its disappearance on addition of D_2O. The ^{13}C nmr spectrum contained two upfield signals at 58.2ppm and 44.0ppm due to the carbons α to the alcohol group and α to the nitrogen of the amide group, respectively. Two amide carbonyl peaks at 173.2ppm and 173.1ppm appeared as a consequence of what is believed to be *cis/trans* isomerism about the partial double C-N bond in [82a] and [82b], respectively (shown in Scheme 29). Two signals due to the α carbon to the carbonyl group were also observed (any two values out of 31.2, 31.1 and 31.0ppm - assignment was uncertain).

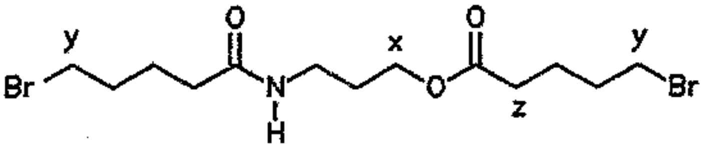


[82a] [82b]

Scheme 29

The ir spectrum of the product [82] showed the following identifying absorption bands: an O-H stretch (3550 - 3250cm^{-1}) and a C-O stretch (1075cm^{-1}) of the -CH_2-OH system, and, a N-H stretch (3550 - 3250cm^{-1}), a C=O stretch (1652cm^{-1}), a N-H deformation and symmetrical N-C=O stretch (1520cm^{-1}) and a C-N stretch (1240cm^{-1}) of the -HNCO- system.

The sequence of addition of reagents is of crucial importance in the synthesis of N-(3-hydroxypropyl)-5-bromopentanamide [82]. Addition of 3-amino-1-propanol to the acid chloride in chloroform containing a suspension of disodium hydrogen phosphate gave the diacylated compound N,O-bis(4-bromobutanoyl)-3-amino-1-propanol [96] in 36% yield (from [80]) after column chromatography.

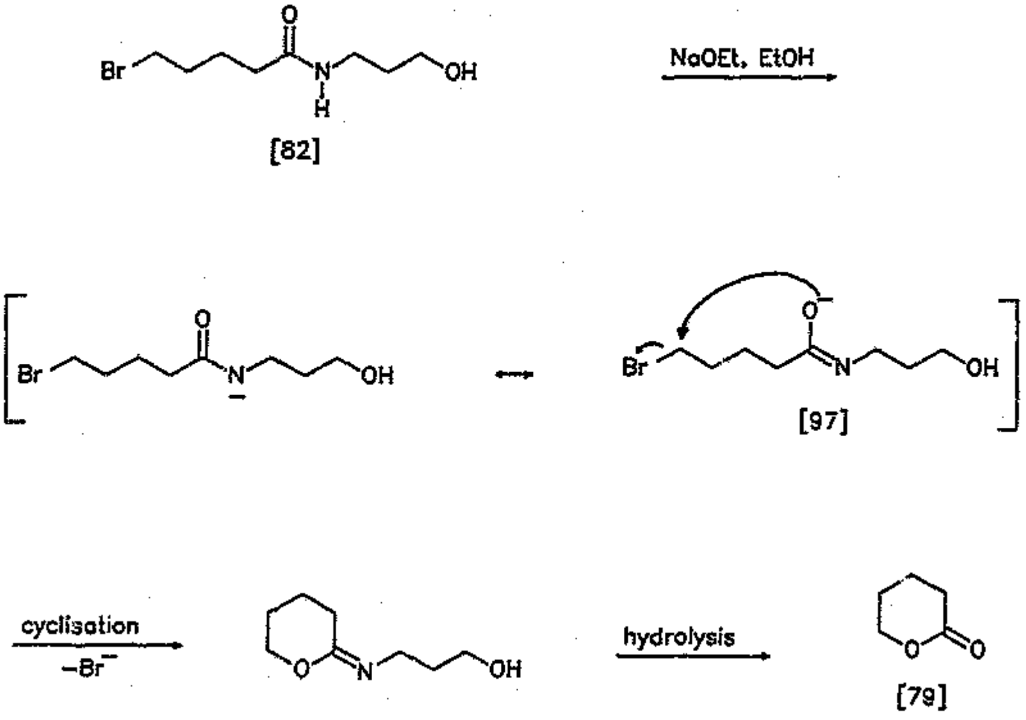


[96]

The ^{1}H and ^{13}C nmr spectra brought certain features to light which led to the conclusion that the diacylated species had been obtained. Firstly, there was no broad OH singlet visible. A triplet at 4.12ppm was due to the protons marked as "x". In the desired product [82], these protons, α to the alcohol oxygen, were more shielded (3.70 - 3.44ppm). A triplet at 3.44ppm due to the protons α to the halogens (marked as "y") integrated to four protons and not two, as would have been expected had [82] been obtained. The appearance of a triplet at 2.36ppm was assigned to the protons marked as "z", which would be absent in the desired product. The ^{13}C nmr spectrum showed thirteen carbon signals, of which one was the amide carbonyl carbon at 172.6ppm and another was the ester carbonyl carbon at 172.5ppm. A noteworthy observation is that the diacylated product was not present as two geometrical isomers.

Although the yield of N-(3-hydroxypropyl)-5-bromopentanamide [82] was poor, we attempted to cyclise it to 1-(3-hydroxypropyl)-2-piperidinone [74] by treatment with sodium ethoxide solution, prepared from sodium metal and absolute ethanol. The ^{1}H and ^{13}C nmr and ir spectra did not give conclusive evidence that the product had been obtained, but starting material was no longer present. This latter statement is substantiated by the absence of the quartet at

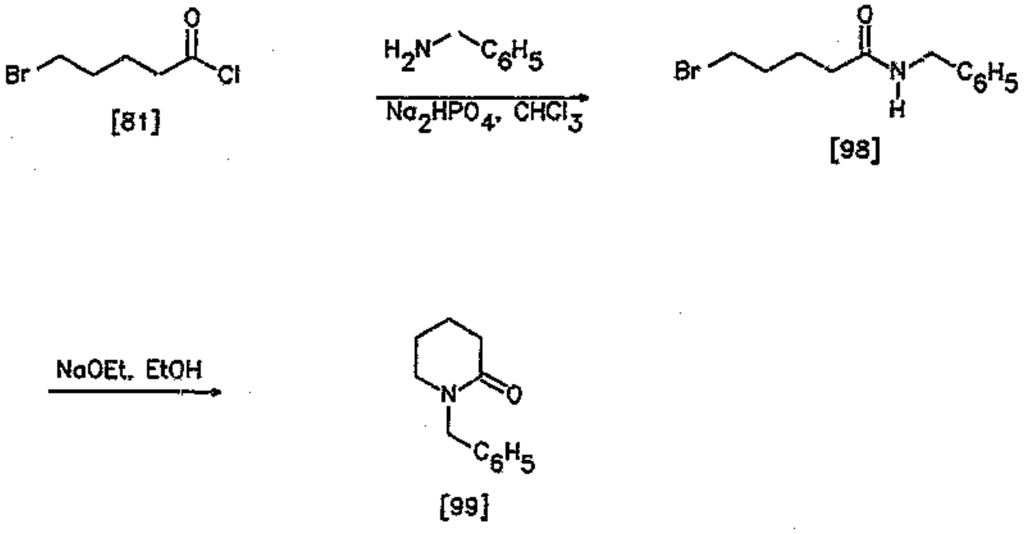
3.25ppm due to the hydrogens α to the nitrogen in the starting material. The free OH of N-(3-hydroxypropyl)-5-bromopentanamide was considered a possible problem contributing to the failure of the cyclisation, in that it could be deprotonated instead of the amide NH proton. Protection of the alcohol would thus be necessary. A second possibility was that cyclisation of the amide anion [97] (being ambident) had occurred through oxygen instead of nitrogen. This would lead to δ-valerolactone being formed after hydrolysis. This idea is illustrated in Scheme 30.



Scheme 30

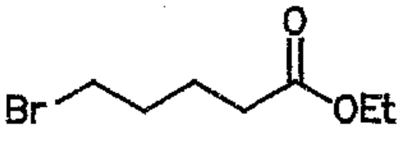
Spectroscopic data[91] confirmed that δ-valerolactone was one of the products that had been obtained. The triplet at 4.12ppm in the ^{1}H nmr spectrum was due to the protons α to the oxygen atom of the ester. The methylene protons α to the carbonyl group resonated at 3.31ppm. The ester carbonyl carbon signal at 172.5ppm appeared slightly upfield from that expected (175.2ppm). The ir spectrum showed absorption bands due to the lactone C=O stretch (at 1720cm^{-1}) and the C-O stretch (at 1195cm^{-1}).

We felt it was worthwhile to check that the acid chloride did in fact react with primary amines, and chose to verify our procedure by using benzylamine, a compound which would not give the possible complications that arose because of the OH group of the 3-amino-1-propanol used previously. Scheme 31 shows the appropriate synthetic route.



Scheme 31

Addition of a solution of 5-bromopentanoyl chloride [81] to a mixture of disodium hydrogen phosphate and benzylamine in chloroform afforded a mixture of N-benzyl-5-bromopentanamide [98] and ethyl 5-bromopentanoate [100] in a ratio of 5:13, respectively.



[100]

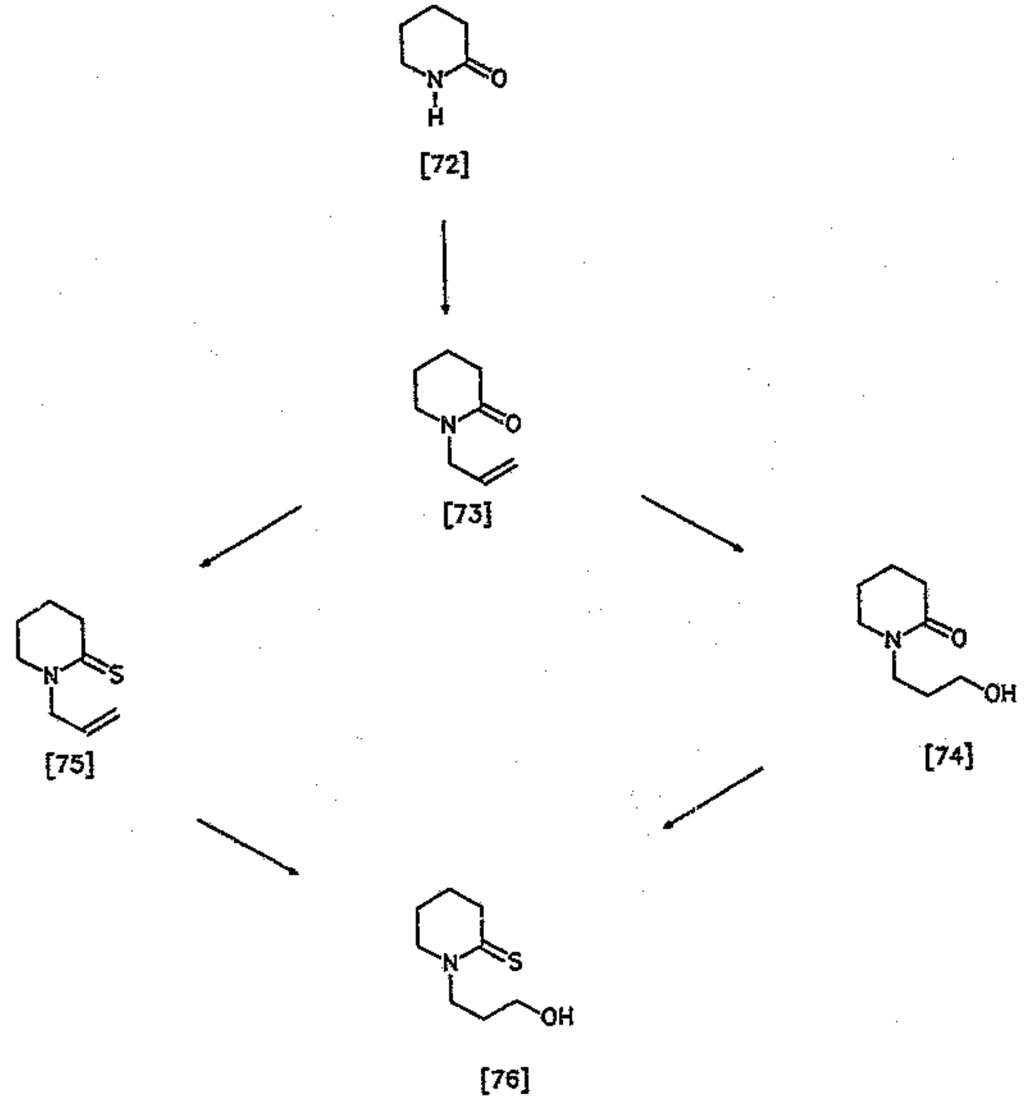
The two products [98] and [100] were obtained in yields of 25% and 66%, respectively. The phenyl protons resonating at 7.40 - 7.06ppm and the doublet at 4.38ppm due to the two protons α to nitrogen in the ^{1}H nmr spectrum provided evidence of the N-benzyl-5-bromopentanamide product. The quartet positioned at 4.10ppm and the triplet at 1.23ppm are indicative of the ethyl 5-bromopentanoate product. The ir spectrum gave further evidence of the mixture. Absorption bands indicative of N-benzyl-5-bromopentanamide included a N-H stretch at 3435cm^{-1}, an amide C=O stretch at 1660cm^{-1}, and a N-H deformation and symmetrical N-C=O stretch at 1505cm^{-1}. The ester C=O stretch at 1720cm^{-1} and the ester C-O stretch at 1250cm^{-1} and 1230cm^{-1} were representative of ethyl 5-bromopentanoate.

The ethoxy group needed for the formation of ethyl 5-bromopentanoate is believed to have originated partly from the ethanol stabiliser in the chloroform solvent, despite prior drying of the solvent using basic alumina. Owing to the large yield of [100] obtained, there must have been an additional source of the ethoxy group besides that from the ethanol stabiliser. Ethyl acetate, a possible provider of OCH_2CH_3 was not used in the workup procedure and so the "supplier" of this group is obscure.

In conclusion, 5-bromopentanoyl chloride [81] did react with benzylamine to produce N-benzyl-5-bromopentanamide [98], however, this product was obtained in unsatisfactory yield together with a large amount of an undesired product, ethyl 5-bromopentanoate [100]. This result did not warrant further cyclisation to produce [99]. The complications encountered in the attempted cyclisation of N-(3-hydroxypropyl)-5-bromopentanamide [82] to 1-(3-hydroxypropyl)-2-piperidinone [74] did not warrant further investigation of this approach.

2.3 Approach based on 1-allyl-2-piperidinones

The synthetic route envisaged for the preparation of 1-(3-hydroxypropyl)piperidine-2-thione [76] is illustrated in Scheme 32.



Scheme 32

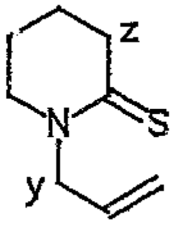
In this approach we intended to convert the secondary lactam, 2-piperidinone [72] into a tertiary lactam, 1-allyl-2-piperidinone [73] by means of an allylation reaction, prior to thiation. This proposed sequence of reaction execution is opposite to that described in Section 2.1, where the thiation of 2-piperidinone [72] was carried out before the addition of the 3-carbon chain to the ring nitrogen by means of a Michael reaction. In this present approach, hydroboration of the carbon-carbon double bond of the allyl group was expected to provide a 3-carbon unit bearing terminal functionality.

2.3.1 Synthesis of 1-allyl-2-piperidinone and -thione

Orlek[21] prepared 1-allyl-2-piperidinone [73] in 87% yield by the addition of 3-bromopropene to a heterogeneous solution of 2-piperidinone [72] and potassium metal in toluene. This was followed by a thiation reaction in which 1-allyl-2-piperidinone and phosphorus pentasulphide were heated in benzene to afford 1-allylpiperidine-2-thione [75] in 77% yield. Tomlinson[92] prepared 1-allyl-2-pyrrolidinone [101] (the 5-membered ring analogue of [73]) by the addition of 3-bromopropene to a heterogeneous solution of 2-pyrrolidinone and sodium hydride in tetrahydrofuran.

In the present work, 1-allyl-2-piperidinone was synthesised in 39% yield (after distillation) by following Orlek's procedure and in a meagre 5% yield (purified) by following Tomlinson's method. The latter low yield was attributable to two factors. Firstly the reaction mixture containing 2-piperidinone and sodium hydride in tetrahydrofuran formed a solid slush which was difficult to stir before and after addition of 3-bromopropene, resulting in a less efficient reaction. Secondly, extensive purification resulted in product loss. The two multiplets at 6.02 - 5.70ppm and 5.43 - 5.02ppm in the ^{1}H nmr spectrum substantiated the existence of the allyl protons. A multiplet at 4.22 - 3.88ppm was due to the protons α to the ring nitrogen and part of the allyl unit. The ^{13}C nmr spectrum contained two carbon signals at 132.0ppm and 116.0ppm due to the internal and terminal carbons of the allyl double bond, respectively. The lactam carbonyl carbon resonated at 168.3ppm, as expected. The ir-absorption bands indicative of the lactam moiety and the allyl group were present. Bands of the former appeared at 1625cm^{-1}, due to the C=O stretch and at 1330cm^{-1}, due to the C-N stretch. Bands of the latter were seen at 3075cm^{-1}, due to the =CH$_2$ stretch and at 995, 985 and 925cm^{-1}, due to the "out of plane" =CH deformation. A C=C stretch absorption band of the allyl group should have been visible between 1650cm^{-1} and 1635cm^{-1}, but perhaps the very strong band due to the lactam C=O stretch overlapped this band.

1-Allylpiperidine-2-thione [75] was prepared in 6% yield (chromatographically pure) by following the thiation procedure of Orlek[21] as mentioned previously. The ^1H nmr spectrum showed two multiplets (at 5.96 - 5.70ppm and 5.28 - 5.08ppm) due to the allyl protons. The downfield shift of the protons marked "y" and "z" to 4.59ppm and 2.96ppm, respectively, clearly showed that the oxygen atom had been substituted by the less electronegative sulphur atom.

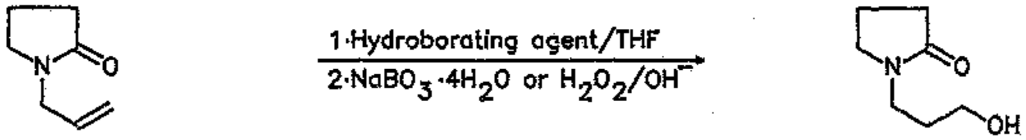


[75]

In the quest to achieve a higher yield of 1-allylpiperidine-2-thione, a solution of 1-allyl-2-piperidinone in tetrahydrofuran was treated with Lawesson's reagent.[93] Despite repeated purification using column chromatography, a more polar impurity remained inseparable from the thiated product. Thin layer chromatography indicated that the product was present in minute quantities.

2.3.2 Hydroboration of a model 1-allyllactam

A plentiful supply of 1-allyl-2-pyrrolidinone [101] was available in the laboratory for another project,[92] so rather than use our precious 1-allyl-2-piperidinone [73], we chose to model the hydroboration reaction with the more abundant compound.
Scheme 33 illustrates the hydroboration reaction.



[101]

[95]

Scheme 33

The results obtained are summarised in Table 1.

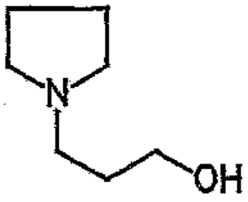
Table 1: Results of attempted hydroboration of [101]

Hydroborating agent	Outcome
0.5M 9-BBN in C_6H_{14} (1.2eq)	[101], [102]
0.5M 9-BBN in C_6H_{14} (1.5eq)	[101], [102]
0.4M 9-BBN in THF (1.5eq)	[101], [102]
0.6M 9-BBN in THF (2.0eq)	[101], [102]
1M BH_3.THF (0.5eq)	[101], impurities
1M BH_3.THF (1.0eq)	[101], impurities
1M BH_3.SMe_2 (1.0eq)	[103] (13%), [104] (1%)
1M BH_3.SMe_2 (1.0eq)*	[101] (21%)

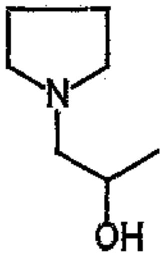
*This reaction was carried out at -27.5°C, whereas all other reactions were carried out at 0°C, and after some time were left to warm up to room temperature.

The bulky 9-borabicyclo[3.3.1]nonane hydroborating agent was unsuccessful in producing 1-(3-hydroxypropyl)-2-pyrrolidinone [95]. ^{1}H nmr data showed the presence of unreacted starting material and the by-product, *cis*-1,5-cyclooctanediol [102] (first 4 entries in Table 1).

From the pentultimate borane-methyl sulphide complex reaction, two unexpected products, 1-(3-hydroxypropyl)pyrrolidine [103] and 1-(2-hydroxypropyl)pyrrolidine [104] were isolated in yields of 13% and 1%, respectively, after column chromatography. The reduction of the lactam carbonyl was indeed a surprising result.



[103]



[104]

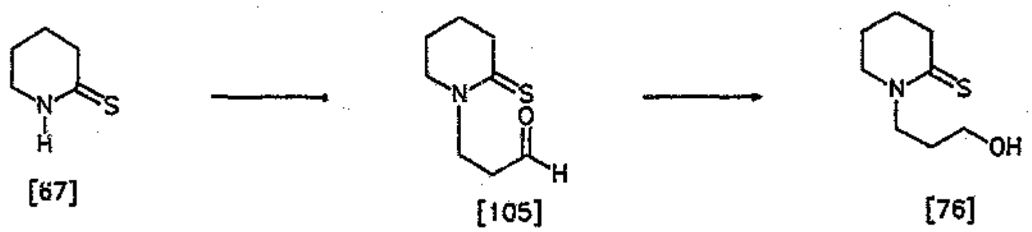
The methylene protons α to the alcohol group in [103] produced a triplet at 3.68ppm. The peak of the terminal alcoholic proton was found as part of a multiplet at 3.40 - 3.07ppm. The two sets of ring methylene protons α to the nitrogen were found to be equivalent and appeared as a multiplet at 2.97 - 2.64ppm. Confirmation of the absence of the amide group was given by the ^{13}C nmr spectrum of [103], which showed no amide carbonyl carbon signal. Instead, two signals, each of double the intensity of the other signals in the spectrum, appeared at 61.3ppm and 22.6ppm. These were assigned to the two equivalent ring carbons α to the nitrogen and to the remaining two equivalent ring carbons, respectively. Reduction of the lactam carbonyl in [104] was proven by the ^{1}H nmr spectrum in which both sets of ring methylene protons α to the nitrogen resonated at 2.97 - 2.60ppm. The OH proton appeared as part of a multiplet at 2.32 - 1.77ppm and the Markovnikov hydration process was substantiated by the doublet at 1.20ppm due to the methyl group.

The ir spectrum of [103] showed absorption bands at 3610cm^{-1} and 1040cm^{-1} of an O-H stretch and a C-O stretch of the $-CH_2OH$ system, respectively. The appearance of an O-H stretch (3575cm^{-1} - 3375cm^{-1}), a C-O stretch of the >CH-OH system (1020cm^{-1}), an asymmetrical CH_3 deformation (1440cm^{-1}) and a symmetrical CH_3 deformation (1392cm^{-1}) of [104] verified the Markovnikov hydration.

In conclusion, we found the hydroboration reaction not to be regioselective and the competing reduction of the lactam carbonyl posed an additional problem. As a result of these findings, there was no point in applying the hydroboration process to 1-allyl-2-piperidinone [73] or 1-allylpiperidine-2-thione [75], and we thus abandoned the route in Section 2.3.

2.4 Alternative attempts to prepare 1-(3-hydroxypropyl)piperidine derivatives

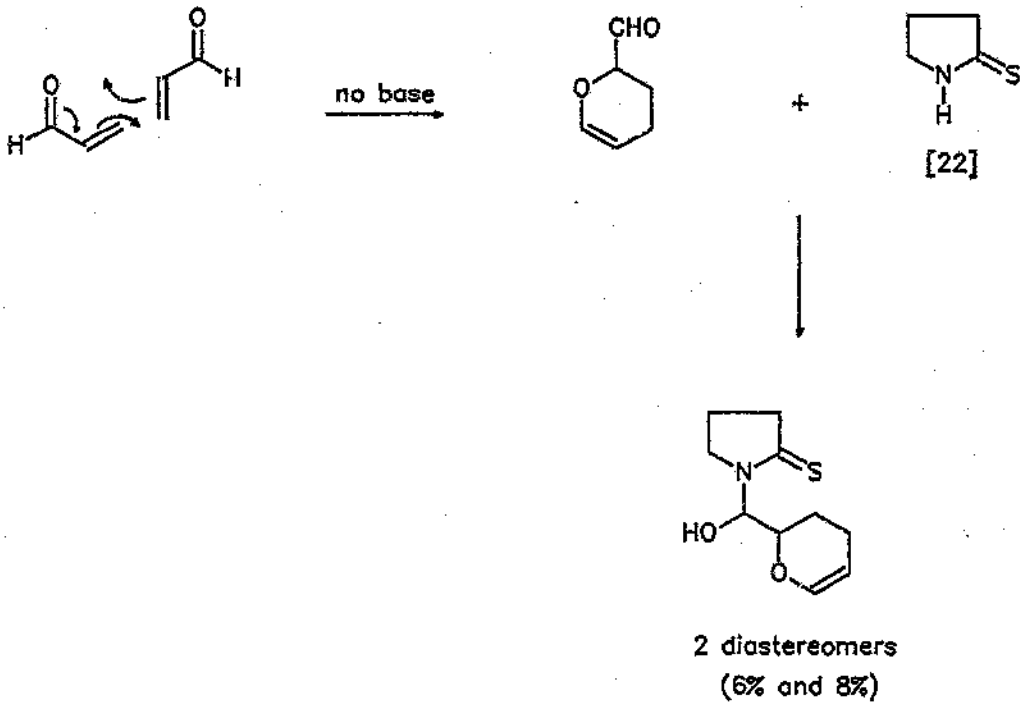
Another synthetic route envisaged for the preparation of 1-(3-hydroxypropyl)piperidine-2-thione [76] is illustrated in Scheme 34.



Scheme 34

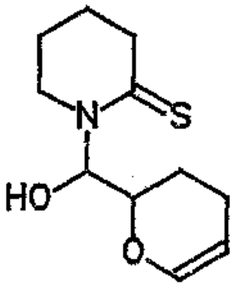
In this approach, we intended to prepare 3-(2-thioxo-1-piperidinyl)propanal [105] by means of a Michael reaction. We hoped that subsequent reduction of this precursor would afford 1-(3-hydroxypropyl)piperidine-2-thione [76]. We chose to investigate this route by virtue of the fact that conjugate additions on the nitrogen of thiolactams are usually ready and reduction of the aldehyde to a primary alcohol should proceed very mildly, without affecting other functional groups.

A solution of piperidine-2-thione [67] in tetrahydrofuran was treated with propenal at room temperature, but only starting thiolactam was recovered in quantitative yield. When the reaction was conducted at an elevated temperature a mixture of unreacted piperidine-2-thione and four other unknown compounds were obtained (as shown by thin layer chromatography). Parsons[27] attempted the conjugate addition of propenal to pyrrolidine-2-thione [22], the 5-membered ring analogue of [6]. It was found that the Michael acceptor dimerised, allowing the chain of events illustrated in Scheme 35 to occur.



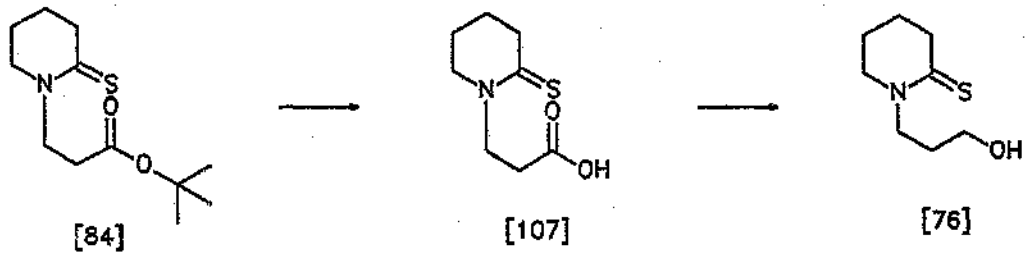
Scheme 35

In the light of these findings it is possible that two of our unknown compounds were diastereomers of [106].



[106]

Another synthetic route for the preparation of 1-(3-hydroxypropyl)piperidine-2-thione [76] is illustrated in Scheme 36.



[84] [107] [76]

Scheme 36

A facile hydrolysis of the *t*-butyl ester of 1-(2-*t*-butoxycarbonylethyl)piperidine-2-thione [84] was expected to achieve a high yield of 3-(2-thioxo-1-piperidinyl)-propanoic acid [107]. This assumption was based on the ready cleavage of the *t*-butyl ester of 1-(2-*t*-butoxycarbonylethyl)-2-cyanomethylenepiperidine [86] in Section 2.1.3. The reduction of the carboxylic acid to a primary alcohol was expected not to present any problems as it is a well-precedented reaction.

A solution of 1-(2-t-butoxycarbonylethyl)piperidine-2-thione [84] in dichloromethane was treated with trifluoroacetic acid to afford the carboxylic acid product [107] in 23% yield. Unreacted starting material was recovered in 6% yield. The singlet at 10.39ppm in the ^{1}H nmr spectrum was clearly indicative of the acidic proton of the product.

The yield was not optimised and further reduction of the acid was not attempted because at this stage the successful alternative discussed in Section 2.1 had been perfected.

The final synthetic route envisaged for the preparation of 1-(3-hydroxypropyl)piperidine derivatives [109] is illustrated in Scheme 37.

[108]

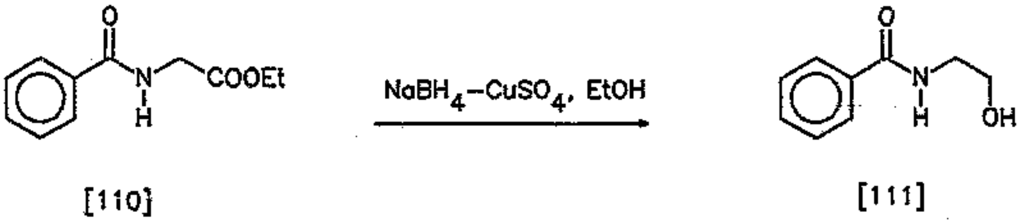
[109]

where X = O or S
R = Et or ^{t}Bu

Scheme 37

Knowing that we could prepare the thiolactams bearing a 3-carbon chain with a terminal ester group on nitrogen (i.e. [108] where X = S and R = Et or ^{t}Bu), we wondered about the possibility of reducing the ester to an alcohol at this early stage - before sulphide contraction rather than after. We also had a small supply of the lactam from the failed sulphide contraction attempt described in Section 2.1.3 (i.e. [108] where X = O and R = Et), which we wanted to reduce. We needed to find reagents that would selectively reduce CO_2R while leaving the C=S or the lactam C=O untouched.

Yoo *et al.*[94] reported the selective reduction of the ester group in [110] by the addition of sodium borohydride to a mixture containing aqueous cupric sulphate and starting material [110] in ethanol. The product [111] was obtained in 82% yield (Scheme 38).



Scheme 38

This unusual reduction procedure utilising a sodium borohydride - cupric sulphate system was carried out unsuccessfully on three compounds, 1-(2-ethoxy-carbonylethyl)piperidine-2-thione [83] (i.e. [108] where X = S, R = Et), 1-(2-*t*-butoxycarbonylethyl)piperidine-2-thione [84] (i.e. [108] where X = S, R = ^{t}Bu) and 1-(2-ethoxy-carbonylethyl)-2-piperidinone [91] (i.e. [108] where X = O, R = Et). In each case starting material was recovered in yields of 14%, 76% and 25%, respectively. Our systems (with the chain containing the ester group on the nitrogen of a lactam or thiolactam) were unexpectedly not reactive towards the reducing agent as compound [110] of similar nature, where the chain with the ester group was attached to an open-chain amide. Perhaps the ester groups of our compounds were sterically inaccessible due to the more bulky lactam ring system or perhaps it was due to lack of N-H participation.

The reduction of 1-(2-ethoxycarbonylethyl)-2-piperidinone [91] was attempted using the well-established reducing agents, lithium aluminum hydride and lithium borohydride. These two reagents, known for their more powerful reducing ability (as compared with $NaBH_4$), were expected to bring about ester reduction. Table 2 summarises the methods used and the outcome.

Table 2: Attempted ester reductions of [91]

Reducing agent	Solvent	Temperature/°C	Result
$LiAlH_4$	THF	0	[91] (89%)
$LiAlH_4$	THF	reflux,25	[91] (81%)
$LiBH_4$	Et_2O	25,reflux	[91] (by TLC)

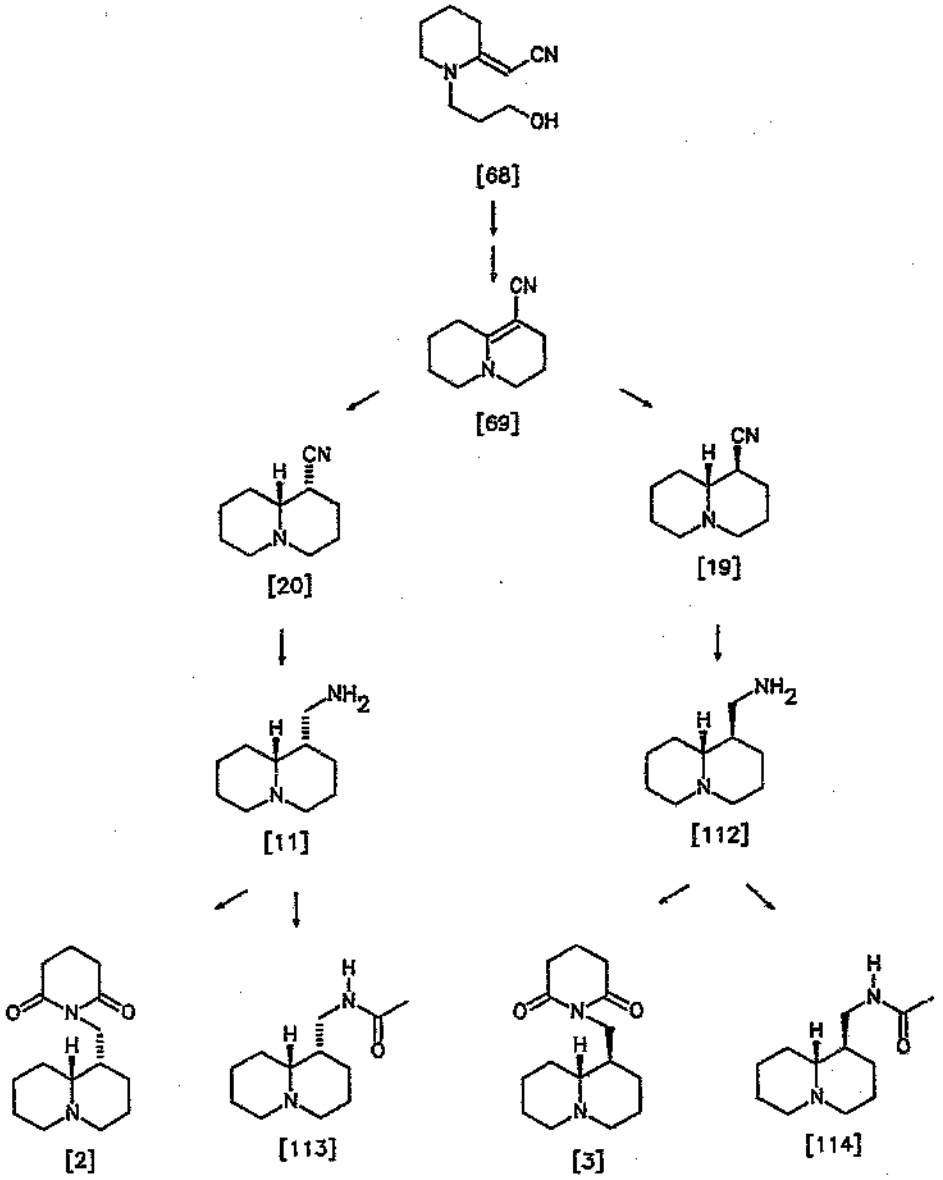
It is believed that the failure of the lithium aluminum hydride reductions may be attributed to the fact that the reducing agent was aged, but in view of the successful reduction reported in Section 2.1.4, the reactions were not repeated with fresh reagents.

It is clear that the strategy described in Section 2.1 has worked best. The following chapter will now pick up the threads at the point where we left off after Section 2.1.4.

CHAPTER 3

THE SYNTHESIS OF EPILAMPROLOBINE AND LAMPROLOBINE

The synthetic route undertaken for the synthesis of the title compounds [2] and [3] (and the derivatives [113] and [114]) is illustrated in Scheme 39.



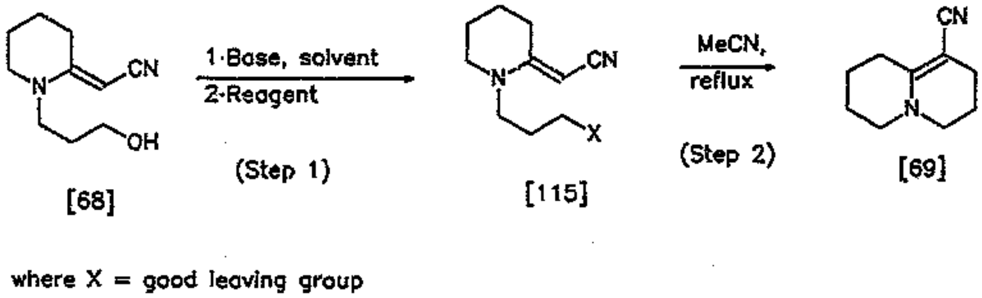
Scheme 39

Conversion of the alcohol group of 1-(3-hydroxypropyl)-2-cyanomethylenepiperidine [68] to a better leaving group has to precede the alkylative cyclisation, which exploits the nucleophilic nature of the α-C of the exocyclic vinylogous cyanamide system. The unsaturated functionalised quinolizidine compound 1-azabicyclo-[4.4.0]dec-5-ene-5-carbonitrile [69] thus produced must then be hydrogenated to form the two isomers, *rel*-5*R*,6*R*-1-azabicyclo[4.4.0]-decane-5-carbonitrile [20] and *rel*-5*R*,6*S*-1-azabicyclo-[4.4.0]decane-5-carbonitrile [19]. Nitrile reduction of each isomer and subsequent addition of a glutarimido unit should produce the target Lupine alkaloids [2] and [3]. We also decided to make the acetyl derivatives of lupinamine [113] and epilupinamine [114] for reasons to be explained later on.

In this chapter each of the synthetic steps outlined in Scheme 39 will be discussed in sequence i.e. cyclisation, hydrogenation, reduction, derivative preparation and final alkaloid synthesis.

3.1 Synthesis of 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile

Scheme 40 illustrates the synthetic route by which the title compound [69] was prepared.

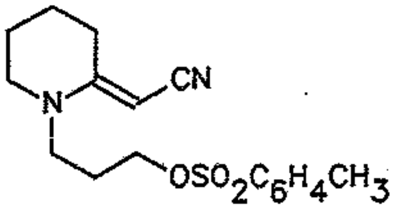


Scheme 40

Firstly, it was essential to activate the alcohol group of [68] to improve its leaving group ability (Step 1). A facile nucleophilic alkylative cyclisation of the appropriate intermediate [115] would then be carried out to produce the product [69] (Step 2).

3.1.1 Tosylate as leaving group

An initial attempt was made to isolate the tosylated intermediate, 1-(3-(4-toluenesulphonyloxy)propyl)-2-cyanomethylenepiperidine [116].



[116]

The sequential addition of sodium hydride (2.2eq) and *p*-toluenesulphonyl chloride (2.2eq) to 1-(3-hydroxypropyl)-2-cyanomethylenepiperidine [68] in refluxing tetrahydrofuran afforded after column chromatography 1-azabicyclo[4.4.0]-dec-5-ene-5-carbonitrile [69] in 3% yield and the intermediate,1-(3-chloropropyl)-2-cyanomethylenepiperidine [117] in 4% yield. (Characterisation of these two compounds will be dealt with at a later stage in this section.) Surprisingly, the desired tosylated intermediate was not obtained.

A more comprehensive series of reactions was then undertaken. Table 3 summarises the results obtained for the cyclisation process (Scheme 40) by altering certain reaction parameters and conditions. The trends observed will be discussed thereafter.

Table 3: Particulars and results of the cyclisation reaction of [68], I

Step 1					Step 2	
Exp. no.	Base	TsCl/eq	Solvent	Reaction temp./°C	Addition of NaI	Result
1	n-BuLi (1.0eq)	1.4	THF	25, reflux	No	[68], [116]
2	NaH (4.0eq)	4.0	dioxane	25, reflux	Yes	[69], impurity
3	NaH (4.0eq)	4.0	THF	25, reflux	Yes	[69], impurity
4	NaH (4.0eq)	4.0	glyme	25	No	[69], impurity
5	NaH (1.8eq)	1.8	glyme	25, reflux	No	[69] (52%)
6	NaH (1.8eq)	1.8	dioxane	25, reflux	No	[69] (53%), [68] (26%)
7	NaH (1.8eq)	1.8	THF	25	Yes	[118] (58%)
8	NaH (2.0eq)	2.0	THF	25	No	[69] (52%), [117] (7%)
9	NaH (2.2eq)	2.2	THF	reflux	No	[69] (41%)
10	NaH (2.0eq)	2.0	THF	25, reflux	No	[69] (70%)

Key: TsCl = $CH_3C_6H_4SO_2Cl$

Effect of using different bases

The potential of the two bases, sodium hydride and *n*-butyllithium, in abstracting the alcoholic proton of 1-(3-hydroxypropyl)-2-cyanomethylenepiperidine [68] was investigated. As Table 3 indicates, sodium hydride is the base of choice. The results of experiment 1 in Table 3 (and experiment 2 in Table 4, for which see Section 3.1.2) highlight the unsuitability of *n*-butyllithium as a base.

Effect of excess reagent

In experiments 2 - 4 (Table 3) too large an excess of sodium hydride and *p*-toluenesulphonyl chloride was used, with the consequence of a less polar (with respect to [69]) solid impurity being formed, which was inseparable from the cyclised product. The impurity was not *p*-toluenesulphonyl chloride, but its identity is obscure. The problem of forming this unknown solid was circumvented by employing a lower percentage excess of reagents e.g. as in experiments 5,6,8 - 10 (Table 3). A 100% excess of both sodium hydride and *p*-toluenesulphonyl chloride proved to be the optimum excess (experiment 10).

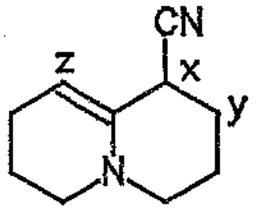
Effect of using different solvents

The promotion of formation of the tosylated intermediate [116] (Step 1) in different solvents was studied. Acetonitrile was the appropriate solvent used to enhance nucleophilic cyclisation (Step 2) and this parameter was kept constant. In this discussion we will compare the results obtained from experiments 5,6 and 7 (Table 3) in which glyme, dioxane and tetrahydrofuran were the respective solvents employed.

In experiment 5, in which glyme acted as the solvent, 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] was obtained in 52% yield after column chromatography. The protons on the electrophilic carbon involved in the cyclisation process produced a triplet at 2.20ppm in the ^1H nmr spectrum of the cyclised product [69]. Further confirmation of the product structure was provided by ^{13}C nmr data which contained signals at 153.9, 122.4 and 69.8ppm due to the quaternary carbon α to the ring nitrogen, the nitrile carbon and the quaternary carbon α to the nitrile group respectively. Important ir-absorption bands included the Bohlmann bands (at 2975, 2930 and 2845cm^{-1}), indicating a *trans*-fused bicyclic structure, a C≡N stretch (at 2155cm^{-1}) and a C=C stretch of a C=C-C≡N system (at 1580cm^{-1}). The high resolution mass spectrum showed a molecular ion peak at m/z = 162.1044 corresponding to $C_{10}H_{14}N_2$.

In experiment 6, in which dioxane acted as the solvent, 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] was obtained in 53% yield and 1-(3-hydroxypropyl)-2-cyanomethylene-piperidine [68] was recovered in 26% yield after column chromatography. This reaction could show more promise if a longer reaction time was allowed. The difference in yields of cyclised product obtained in experiments 5 and 6 is marginal and not worthy of mention.

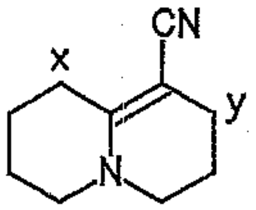
In experiment 7, in which tetrahydrofuran acted as the solvent, an unexpected cyclised compound, believed to be 1-azabicyclo[4.4.0]dec-6-ene-5-carbonitrile [118] (Figure 9), was obtained in 58% yield after column chromatography. The carbon-carbon double bond in the latter compound is less substituted than in the desired product [69] and therefore the result is somewhat surprising.



[118]

Figure 9

A triplet of doublets integrating to one proton appeared at 5.13ppm, a relatively downfield shift as compared with the proton chemical shifts of [69]. This splitting pattern can be explained by the proton marked "x" in Figure 9 coupling with the adjacent methylene protons ("y") and allylic coupling with the vinylic proton ("z"). If the desired cyclised product [69] had been obtained, two distinct triplets at 2.52ppm and 2.20ppm due to the methylene protons marked "x" and "y" in Figure 10 would have been present.



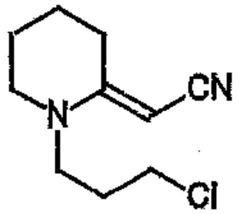
[69]

Figure 10

These triplets were indeed absent, and careful inspection of the structure of [118] indicated no opportunity for triplets to arise from a proton or protons coupling with two equivalent methylene protons. (Methylene protons of C-2 and C-10 resonate as multiplets in both [69] and [118].) The DEPT spectrum of [118] indicated the presence of two methine carbons. These would not be present in [69], which contains only quaternary and secondary carbons. With the aid of a C-H ~~correlated~~ spectrum, the tertiary carbons at 76.6ppm and 53.4ppm were assigned to C-7 and C-5 in Figure 9, respectively. By contrast, C-7 and C-5 of [69] have very different chemical shifts (27.3ppm and 69.8ppm, respectively) from those just quoted for [118]. The ir spectrum of [118] showed two significant peaks at 2170cm^{-1} and 1595cm^{-1} due to a C≡N stretch and a C=C stretch of a C=C-C-C≡N group, respectively. Bohlmann bands, indicative of a *trans*-fused bicyclic structure appeared at 2950, 2930 and 2835cm^{-1}.

It must be mentioned that the anomaly seen in experiment 7 was not representative of the kind of result obtained when tetrahydrofuran was used as the solvent to host intermediate formation. Experiments 8 - 10 support this argument in that 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] was obtained in yields ranging from 41% to 70% (chromatographically pure). 1-Azabicyclo[4.4.0]dec-6-ene-5-carbonitrile [118] was never formed again and no adequate reasoning can be found for its formation in experiment 7.

In experiment 8, the desired cyclised product [69] was obtained in 52% yield and an intermediate, 1-(3-chloropropyl)-2-cyanomethylenepiperidine [117] in 7% yield after column chromatography.



[117]
]

Because of the singlet at 3.79ppm from the vinyl proton of [117], it was believed at first that this compound was the starting material [68]. This possibility was soon dismissed when it was noted that the broad singlet at 3.42 - 3.30ppm due to the alcoholic proton was missing. The triplet at 3.64ppm from the protons α to the alcohol functionality was not present, but instead an upfield shift to 3.57ppm emphasised the presence of another terminal functionality of the 3-carbon unit attached to the ring nitrogen. The ^{13}C nmr spectrum contained carbon signals at 122.3, 59.3 and 42.3ppm due to the nitrile carbon, the vinylic carbon and the α carbon to the chloride atom, respectively. Verification of the intermediate [117] was given by its high resolution mass spectrum which showed a molecular ion at m/z = 198.0928, corresponding to $C_{10}H_{15}N_2Cl$.

Experiment 10 presents the optimum parameters and conditions for the cyclisation reaction. Here 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] was obtained in a good chromatographically pure yield of 70%.

3.1.2 Other leaving groups

Two other reagents capable of converting the alcohol functionality to a better leaving group to facilitate alkylative cyclisation were studied. Table 4 shows the results obtained for the reagents methanesulphonyl chloride and trifluoroacetic anhydride.

Table 4: Particulars and results of the cyclisation reaction of [68], II

Step 1					Step 2	
Exp.no.	Base	Reagent	Solvent	Reaction temp./°C	Addition Of NaI	Result
1a	NaH (1.4eq)	MsCl (1.4eq)	THF	25	No	[69] (26%), [117] (13%)
1b	NaH (1.4eq)	MsCl (1.4eq)	THF	25	Yes	[69] (29%), [117] (6%)
2	n-BuLi (1.0eq)	TFAA (1.1eq)	THF	0,25	No	-

Key: MsCl = CH_3SO_2Cl
TFAA = $CF_3CO_2COCF_3$

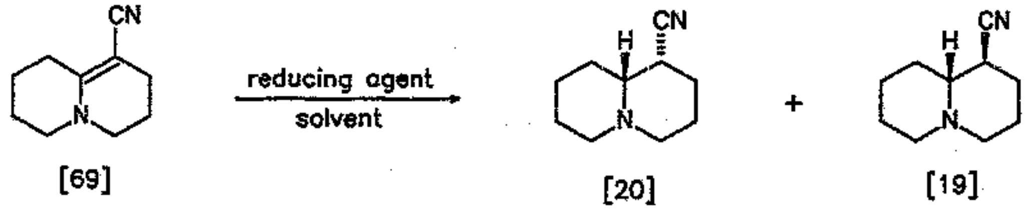
Methanesulphonyl chloride was used in experiment, 1a and 1b to produce the intermediate 1-(3-methanesulphonyloxypropyl)-2-cyanomethylenepiperidine [119]. The cyclisation reaction (experiment 1a) produced 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] in 26% yield, together with the chloro intermediate [117] in 13% yield after column chromatography. The yield of cyclised product was improved (in experiment 1b) to 29% by the addition of sodium iodide. Nucleophilic substitution of Cl^- by I^- afforded a species bearing a better leaving group and cyclisation of this intermediate improved the yield slightly. The structures of [69] and [117] were confirmed by ^1H and ^{13}C nmr data.

Trifluoroacetic anhydride was used in experiment 2 to produce the intermediate 1-(3-trifluoroacetoxypropyl)-2-cyanomethylenepiperidine [120]. After steps 1 and 2 of the cyclisation reaction had been executed, thin layer chromatography revealed what was predicted to be the intermediate [120] and the cyclised product [69]. Unfortunately, these compounds were lost during the purification procedure.

Of all three activators discussed, *p*-toluenesulphonyl chloride is clearly the superior one. As demonstrated in experiments 2 - 6 and 8 - 10 in Table 3, the role of converting the terminal alcohol group to a better leaving group was successfully undertaken by this reagent, which was followed by an alkylative cyclisation.

3.2 Reduction of 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile

Scheme 41 illustrates the type of process which the two isomers, *rel*-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile [20] and *rel*-5*R*,6*S*-1-azabicyclo[4.4.0]decane-5-carbonitrile [19], were expected to be formed.



Scheme 41

The stereoselective reduction of the carbon-carbon double bond of [69] was of utmost importance since access to the two target alkaloids, epilamprolobine and lamprolobine, required that we be able to control the relative stereochemistry at C-5 and C-6. The two isomers [20] and [19] are known compounds for which we have literature precedents (Yamada *et al.*[19]). By preparing these isomers, we reach a point at which we converge with a reported synthesis (see Scheme 4, Section 1.2). Correlation of the data for our products with those in the literature is then possible.

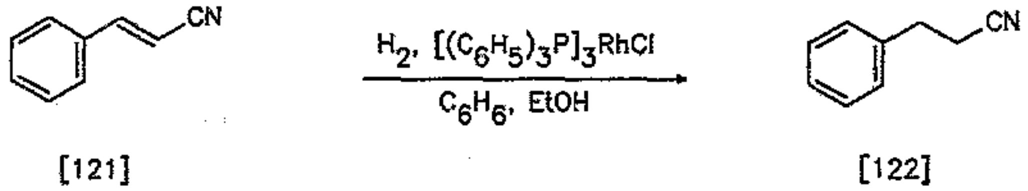
3.2.1 Catalytic hydrogenation

Table 5 summarises various methods that were investigated for the hydrogenation of 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] in the presence of a particular catalyst.

Table 5: Catalytic hydrogenations of [69]

Reducing agent	Solvent	Outcome
$[(C_6H_5)_3P]_3RhCl$, H_2	1:1 C_6H_6:EtOH	[69] (100%)
Ni/Al, NaOH	EtOH	[69] (80%)
5% Pd/C, H_2	EtOH	[69] (95%)
PtO_2, H_2	EtOH	[69] (100%)
PtO_2, H_2	CH_3CO_2H	[20] (82%), [19] (6%)

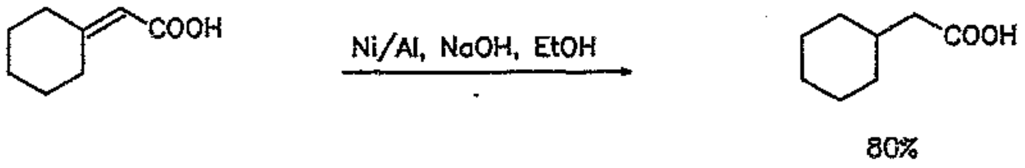
Tris(triphenylphosphine)chlororhodium(I) (Wilkinson's catalyst) has been used as a catalyst for the selective homogeneous hydrogenation of highly substituted internal olefins containing reducible functional groups, amongst which are nitriles. Harmon *et al.*[95] readily reduced relatively unhindered disubstituted olefins like cinnamonitrile [121] to dihydrocinnamonitrile [122] in 86% yield (see Scheme 42).



Scheme 42

Our application of this method (at 500kPa and 60°C) to the reduction of the tetrasubstituted carbon-carbon double bond in [69] was not successful. The vinyl nitrile system [121] is obviously susceptible to reduction, whereas our electronically different vinylogous cyanamide system [69] is not. Steric effects could also have played a role.

The hydrogenation of a wide variety of functional groups by the addition of nickel-aluminum alloy to a reducible material dissolved in a suitable hydroxylic solvent was reviewed by Keefer *et al.*[96] An example of a reduction of a carbon-carbon double bond conjugated to an electron-withdrawing group is illustrated in Scheme 43.

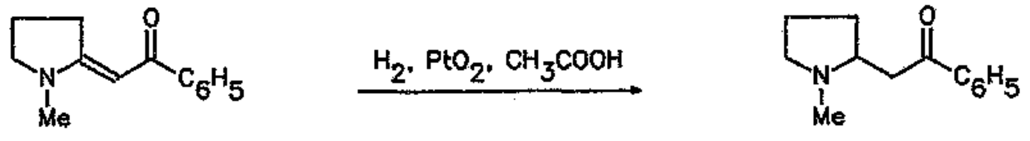


Scheme 43

Application of this method to 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile in which the carbon-carbon double bond is conjugated to a nitrile group (also an electron-withdrawing group) was unsuccessful.

McIntosh *et al.*[97] reported the hydrogenation of 4-cyclopentene-1,3-dione in ethanol using a catalytic amount of 5% palladium on charcoal at room temperature and pressure. Unfortunately only a quantitative recovery of starting material was found when we attempted to hydrogenate [69] under similar conditions.

Michael[20] used platinum dioxide (Adams catalyst) for the hydrogenation of 1-methyl-2-benzoylmethylenepyrrolidine [123] in glacial acetic acid (Scheme 44).

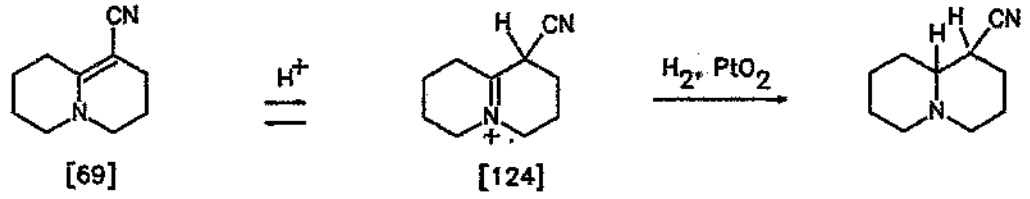


[123]

90%

Scheme 44

The reduction is chemoselective, leaving the carbonyl group of the vinylogous amide system unperturbed. This was also a requirement for our compound, 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile in which competing reduction of the nitrile group was undesired. In the present work, Michael's method of catalytic hydrogenation was employed using different solvents. Comparison of entries 4 and 5 in Table 5 highlights the need for an acidic medium for the successful carbon-carbon double bond reduction. The acidic medium[98] plays a vital role as it is responsible for protonation, so that the functional group to be reduced is probably an iminium system (see Scheme 45). This enables selective reduction by leaving the nitrile functional group untouched. Vinylogous cyanamides are themselves resistant to reduction, as shown by numerous examples in Table 5, 6 and 7 in Sections 3.2.1, 3.2.2 and 3.2.3, respectively. Protonation on carbon, however, generates a salt [124] which is readily reducible. It is of importance to maintain acidic conditions (pH about 4) throughout the reaction in order to promote protonation of the weakly basic conjugated enamine i.e. the vinylogous cyanamide. The envisaged initial protonation step and subsequent reduction step are illustrated in Scheme 45.



Scheme 45

By employing glacial acetic acid as the solvent, *rel*-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile [20] and *rel*-5*R*,6*S*-1-azabicyclo[4.4.0]decane-5-carbonitrile [19] were obtained in respective yields of 82% and 6% after column chromatography. The overall yield of 88% was pleasing, although, a more stereoselective reduction than 14:1 of [20]:[19] would have been welcome. On repeating the reaction, the reaction time was halved and a 65% yield of [20] and 1% yield of [19] were obtained. The lower overall yield was compensated by a higher stereoselectivity of 65:1 of [20]:[19]. The formation of [20] is kinetically controlled, a shorter reaction time favouring its production with respect to [19]. A gas chromatogram of the latter reaction mixture was taken prior to separation of the two isomers by column chromatography to ascertain their respective ratios. A 47.25:1 ratio of [20]:[19] was obtained. It is possible that more of [19] was lost during the purification procedure than [20].

Methods of identification and characterisation of the two isomers included observation of physical state and ^{1}H and ^{13}C nmr, ir, microanalysis and high resolution mass spectroscopy. We will be making a direct comparison of physical properties and spectroscopic data with those reported in the literature by Yamada *et al.*,[19] since we are relying heavily on such comparisons to justify the stereochemistry of our products. *Rel*-5*R*,6*R*-1-azabicyclo-[4.4.0]decane-5-carbonitrile [20] was isolated as a white solid with a melting point of 61°C. Yamada *et al.* described this isomer as being crystalline and melting at 62 - 63°C. The other isomer, *rel*-5*R*,6*S*-1-azabicyclo-[4.4.0]decane-5-carbonitrile [19], was isolated as a pale yellow liquid; Yamada *et al.* reported an oil.

Information drawn from Section 1.4 was used to support the interpretation of ^{1}H and ^{13}C nmr and ir data of the two isomers. The appearance of low-field multiplets at 2.97 - 2.81ppm and 2.91 - 2.71ppm of [20] and [19], respectively is characteristic of the equatorial aminomethylene protons of a *trans*-fused quinolizidine system. Yamada *et al.* found that these equatorial C-2 and C-10 protons resonated at 2.95 - 2.65ppm in [20] and at 2.95 - 2.70ppm in [19]. The triplet of doublets at 2.73ppm of [20] was distinctly downfield with respect to the multiplet at 2.48 -2.28ppm of [19]. Both signals were assigned to the C-5 methine hydrogen by means of C-H correlated spectra and fundamental chemical shift knowledge. The difference in their chemical shifts was attributed to differences in stereochemistry i.e. the C-5 methine hydrogen of [20] possesses an equatorial orientation and is therefore deshielded whereas the same hydrogen of [19] is in a shielded axial position. The C-H correlated spectra of both [20] and [19] identified the bridgehead C-6 proton (in the vicinity of 1.92ppm) to be part of an upfield cluster of signals. It was deduced that these methine protons are both axially orientated and encourage the *trans*-fused bicyclic system. Equatorial methine protons would have resonated at approximately 3.10ppm. Values of 56.3 and 55.9ppm for the C-2 and C-10 methylene carbons of [20] and values of 56.2 and 55.5ppm for the same methylene carbons of [19] were sufficiently low-field and similar in magnitude to deduce a *trans*-fused bicyclic bridge. The chemical shifts of the C-6 bridgehead carbons (62.0ppm for [20] and 63.4ppm for [19]) were as expected from a *trans*-fused conformation. An upfield shift of about 6ppm would have been indicative of a *cis*-fused bicycle. No ^{13}C nmr data were available in the literature and so no comparisons were possible. Complete elucidation of the ^{1}H and ^{13}C nmr of both isomers was not achieved owing to the nonequivalent nature of equatorial and axial protons situated on the same carbon. The differences in chemical environment of the axial and equatorial protons afforded an unresolved upfield multiplet in both ^{1}H nmr spectra. The C-H correlated spectra showed further signs of different resonating abilities of axial and equatorial protons. Definite assignments of the ring methylene carbons, except for C-2 and C-10, were not possible.

Bohlmann bands were present as well-defined maxima (indicating a *trans* conformation) in the 2950cm^{-1} - 2750cm^{-1} region of the ir spectra of both isomers. An ir-absorption band at 2230cm^{-1} for [20] and 2225cm^{-1} for [19] was due to the C≡N stretch. These findings correlated well with Yamada *et al.*, who reported Bohlmann bands at 2900cm^{-1} - 2600cm^{-1} and a C≡N stretch at 2250cm^{-1} for both isomers.

Microanalysis of [20] confirmed the formula $C_{10}H_{16}N_2$. The presence of a molecular ion peak at m/z = 164.1303 in the high resolution mass spectrum of [20] also confirmed the formula. The following mutual peaks (in m/z values) were found in both our mass spectrum and that reported by Yamada *et al.*: 164 (M^+), 111, 110, 97, 83, 55 and 41. The high resolution mass spectrum of [19] showed a molecular ion peak at m/z = 164.1311, corresponding to $C_{10}H_{16}N_2$. Comparison of our mass spectrum with that reported in the literature showed the same mutual peaks as described for [20].

3.2.2 Hydride reducing agents

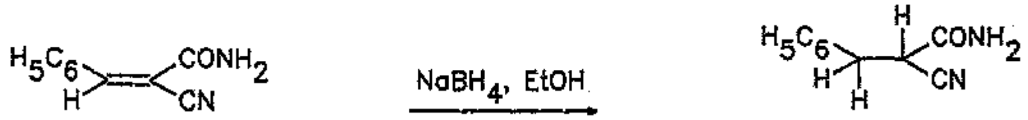
Table 6 summarises our attempts to reduce 1-azabicyclo-[4.4.0]dec-5-ene-5-carbonitrile [69] with various hydrides.

Table 6: Hydride reductions of [69]

Reducing Agent	Solvent	Outcome
$NaBH_4$	EtOH	[69] (91%)[1]
$NaBH_4$	EtOH	[69], 1:1 [20]:[19], impurities[2]
$LiAlH_4$	THF	[69] (93%)
$NaBH_3CN$, H^+	EtOH	[20] (43%), [19] (54%)

Key: 1 = TLC showed a faint spot indicative of the reduced product
2 = according to TLC and gc analysis

The ethylenic linkage of a variety of compounds exhibiting α,β-unsaturation has been selectively reduced by Kadin[99] using sodium borohydride. An example is illustrated in Scheme 46.



[125]

81% [126]

Scheme 46

This method, which promotes preferential reduction of the ethylenic moiety over the nitrile group in a facile manner and within a short time period, seemed well suited to our system [69]. In the first reaction described in Table 6, sodium borohydride was added to 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] in ethanol at room temperature while in the second reaction described in Table 6, a cooled slurry of sodium borohydride in ethanol was treated with a solution of [69]. The presence of large amounts of unreacted starting material persisted in both reactions, meaning that the employment of sodium borohydride for carbon-carbon double bond reduction in this case was not profitable.

Lithium aluminum hydride is a well-established common reducing agent, but as Table 6 shows, was not suited to our purposes.

Sodium cyanoborohydride was used by Hutchins *et al.*[100] in the facile and selective reduction of systems with conjugated double bonds to their saturated analogues i.e. [125] was converted to [126] in 72% yield.
In the present work, a reduction of 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] using sodium cyanoborohydride in acidic ethanol at ambient temperature afforded an overall 97% yield of saturated products after column chromatography, of which 43% was [20] and 54% was [19]. A gas chromatogram of the reaction mixture indicated a 1:1.89 ratio of [20]:[19]. Although this reduction method was higher yielding than the reduction using Adams catalyst under acidic conditions, it was less stereoselective. However, easy separation of [19] and [20] by column chromatography meant that both products could be obtained cleanly and taken through the rest of the synthetic sequence separately.

3.2.3 Transfer hydrogenation attempts

Table 7 summarises various attempted transfer hydrogenation methods of 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69].

Table 7: Attempted transfer hydrogenations of [69]

Reducing agent/s	Solvent	Outcome
K_2CO_3, 5% Pd/C, NaH_2PO_2 in H_2O	THF	[69], 6.4:1 [20]:[19], impurities[1]
10% Pd/C, CH_3CO_2Na, NaH_2PO_2	CH_3CO_2H	[69], [20], [19], impurities[2]
HCOONa, 10% Pd/C	EtOH, H_2O	[69], 9.2:1 [20]:[19], impurities[1]
HCOOH	HCOOH	impurities[2]

Key: 1 = according to TLC and gc analysis
2 = according to TLC only

Boyer *et al.*[101] found sodium hypophosphite to be an effective reagent for the transfer hydrogenation of certain functional groups in the presence of an appropriate catalyst. The reduction of cinnamonitrile [121] to dihydrocinnamonitrile [122] in 87% yield is an example of this method's potential to accomplish the hydrogen transfer reduction of an α,β-unsaturated nitrile to its saturated analogue under mild and inexpensive conditions. It therefore, seemed a convenient alternative to conventional hydrogenation methods. The first two entries in Table 7 show the outcome of the application of this method to our compound, [69]. The results were not satisfactory as a large percentage of starting material was recovered.

A similar, but equally unsuccessful hydrogen transfer method using the method of Wiener *et al.*[102] was carried out using an alkali metal formate salt (sodium formate) as the hydrogen donor and palladium on carbon as the catalyst (third entry in Table 7).

Madsen *et al.*[103] reported a highly stereoselective reduction method of enamines by heating in formic acid. In our present work, after a 20 hour reaction period, thin layer chromatography showed the meagre presence of [20] and [19] and the abundance of unreacted starting material. After 5 days of continued heating, only two polar compounds, possibly lupinamine [11] and epilupinamine [112], were revealed by thin layer chromatography. Formic acid might, therefore, have brought about the reduction of both the carbon-carbon double bond and the nitrile group.

3.2.4 Epimerisation of the products

The conversion of *rel*-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile [20] to *rel*-5*R*,6*S*-1-azabicyclo[4.4.0]decane-5-carbonitrile [19] was desired since a 65:1 stereoselectivity had been achieved in a catalytic hydrogenation (using platinum dioxide under acidic conditions) of 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] (Section 3.2.1). The abundant isomer [20] possessed the appropriate stereochemistry at C-5 and C-6 to act as the precursor for the epilamprolobine [2] target. A sufficient quantity of the other isomer [19], the precursor for the lamprolobine [3] target, was needed. This was supplied by the epimerisation of [20] to [19].

Yamada et al.[19] partially epimerised [20] to [19] by heating rel-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile [20] with a catalytic amount of sodium hydride in benzene.

A 1:4.5 ratio of [20]:[19] was obtained. The epimerisation was expected to proceed in the direction found since the axial nitrile group is ending up in the thermodynamically more favoured equatorial position.

In the present work, this base-catalysed epimerisation was carried out to afford a 1:1.89 ratio of [20]:[19], as determined by gc analysis, prior to separation of the two isomers by column chromatography. Purification yielded 29% of [20] and 55% of [19] i.e. a ratio of 1:1.9, respectively.

The epimerisation of a very similar compound to ours, [8] (see Scheme 1, Section 1.2), was achieved by Célérier *et al.*[38] by the application of heat (200°C).

In this project, *rel*-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile [20] was heated at 149°C and then at 164°C in a Kugelrohr oven. Purification by column chromatography recovered 52% of [20] and afforded a very unexpected 5% of 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69]. No [19] was obtained.

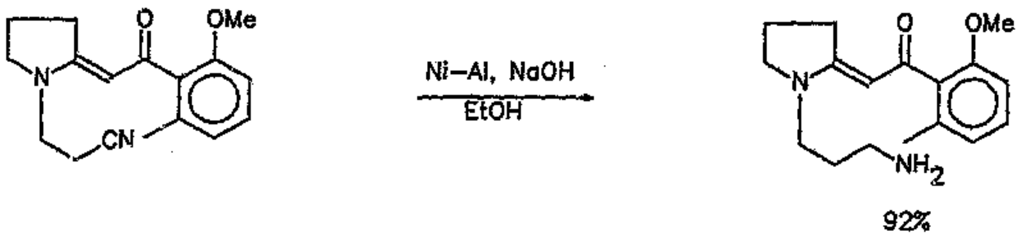
3.3 Synthesis of lupinamine and epilupinamine

Both lupinamine [11] and epilupinamine [112] are known compounds.[104-111] Lupinamine has been utilised as a precursor for the synthesis of the Lupine alkaloid matrine,[112] while both lupinamine[12,18,19] and epilupinamine[17-19] have acted as precursors to epilamprolobine and lamprolobine. Epilupinamine has been formed, together with glutaric acid, on acid hydrolysis of lamprolobine.[2]

Yamada *et al.*[19] achieved the nitrile reduction of *rel*-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile [20] and *rel*-5*R*,6*S*-1-azabicyclo[4.4.0]decane-5-carbonitrile [19] to form lupinamine [11] and epilupinamine [112], respectively, with lithium aluminum hydride. Only the yield for epilupinamine [112] was quoted, which was 99%. However, we were interested in improving the process by using other methods, especially since we found (see later) that lithium aluminum hydride did not give a clean reaction. It was our intention also to supply spectroscopic data for lupinamine and epilupinamine because these are not available in the literature.

3.3.1 Reduction with nickel-aluminum/base

Nickel-aluminum alloy in the presence of base in an alcoholic solvent has provided a means of reducing a nitrile to a primary amine for Michael *et al.*[34] (Scheme 47).



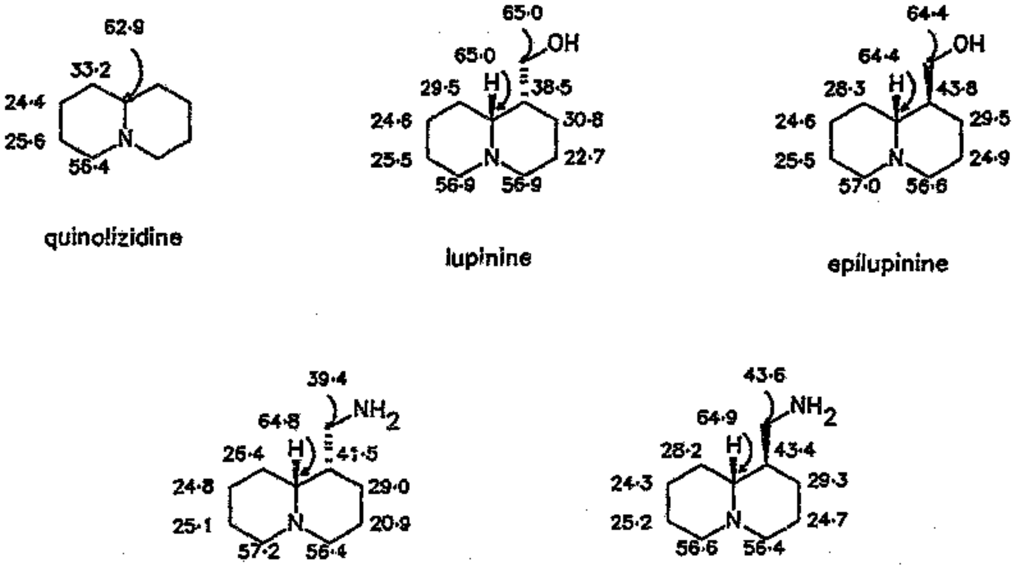
Scheme 47

Under similar reaction conditions, lupinamine and epilupinamine were obtained in excellent yields of 99% and 84% from [20] and [19] respectively. Both amine products were characterised by ^{1}H and ^{13}C nmr and ir spectroscopy.

The ^{1}H nmr spectrum of lupinamine showed a multiplet at 3.01 - 2.62ppm integrating to four protons i.e. C-2 and C-10 equatorial protons and the aminomethylene protons belonging to the side chain at C-5. The triplet of doublets at 2.73ppm corresponding to the C-5 methine proton in the starting material [20] was absent. The ^{13}C nmr spectrum of lupinamine possessed no nitrile carbon peak at 120.5ppm, but instead a signal at 39.4ppm appeared due to the carbon α to the amine group. The ten required carbon signals of the product were upfield from 65ppm.

The ^{1}H nmr spectrum of epilupinamine also contained no C-5 methine proton peak (at 2.48 - 2.28ppm) indicative of the starting material [19]. A multiplet at 3.01 - 2.44ppm was present due to the C-2 and C-10 equatorial protons and the aminomethylene protons of the side chain. The ^{13}C nmr spectrum, which included the signal of the carbon α to the amine group at 43.6ppm, fulfilled our expectations.

A study of the chemical shift assignments[67] for quinolizidine itself and for the alkaloids lupinine and epilupinine together with DEPT spectra and C-H correlated spectra was imperative to the elucidation of the ^{13}C nmr spectra of lupinamine and epilupinamine. Figure 11 shows the chemical shifts of our chosen standards and our deduced values for our amine products.



quinolizidine

lupinine

epilupinine

lupinamine

epilupinamine

Figure 11

The aminomethine, C-6, was expected to be downfield of the other methine, C-5, in both of the amine products. The three aminomethylenes (C-2, C-10 and C-11) were distinct from the other ring methylenes. The aminomethylene of the side chain, C-11, in lupinamine was more shielded than the C-5 methine, whereas in epilupinamine the opposite was true. This was verified by the appropriate DEPT spectra. The assignment of chemical shifts for C-2 and C-10 of epilupinamine were made by comparison with epilupinine. The ^{13}C nmr spectrum of lupinamine showed a remarkable difference in intensity between the C-2 and C-10 peaks. This trait was observed in N-acetyllupinamine [113] and in epilamprolobine [2], both possessing the same conformation (*trans*-fused bridge) and stereochemistry (axial bridgehead methine hydrogen and axial C-5 side chain) as lupinamine. In epilamprolobine (see later in Section 3.5), C-2 and C-10 were distinguished from one another (with the aid of literature data[12]), with C-10 possessing the higher chemical shift. On grounds of chemical shift and intensity of signals, C-2 and C-10 assignments of lupinamine were made. The chemical shifts of C-8 and C-9 of lupinamine and epilupinamine were expected to approach those values of their equivalent sites in quinolizidine. The difference in the C-3 chemical shift between lupinamine and epilupinamine was attributed to the different orientation of the C-5 side chain in space. The axial orientation of the aminomethyl group in lupinamine exerts the γ effect, resulting in an upfield shift of the C-3 signal to 20.9ppm. This effect was absent in epilupinamine because the aminomethyl group is equatorial. This is illustrated in Figure 12.

lupinamine

epilupinamine

Figure 12

The ir spectrum of lupinamine confirmed the *trans*-fused conformation of the quinolizidine skeleton by the presence of Bohlmann bands (well-defined maxima) in the 2930cm^{-1} – 2760cm^{-1} region. A broad band at 3520cm^{-1} - 3170cm^{-1} indicated the NH_2 stretch of the amine and evidence of a NH_2 deformation was given by absorption bands at 1595cm^{-1} and 725cm^{-1}. Similarly, the ir-absorption bands of epilupinamine included the Bohlmann bands (2930cm^{-1} -

2760cm^{-1}), the NH_2 stretch (1600cm^{-1}, 1580cm^{-1}) and the NH_2 deformation (770cm^{-1}). A nominal mass spectrum of both lupinamine and epilupinamine showed no molecular ion peak, but instead a peak due to $M^+ - NH_3$ appeared. Therefore it was not feasible to obtain high resolution mass spectra of the two amine products.

3.3.2 Reduction with hydride reagents

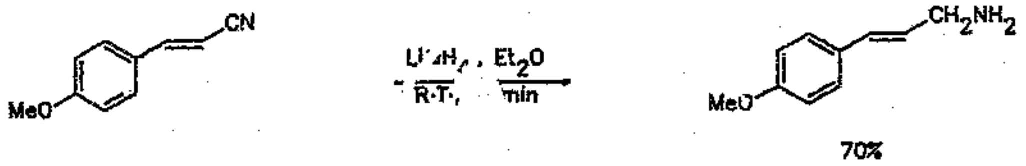
Table 8 summarises successful and unsuccessful reduction attempts of the more abundant isomer, *rel*-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile [20], by using hydride reagents.

Table 8: Attempted hydride reductions of [20]

Reducing agent	Solvent	Outcome
$LiAlH_4$	Et_2O	[11], impurities*
$LiAlH_4$, $AlCl_3$	THF, Et_2O	[20], [11], impurities*
$NaBH_4$, $CoCl_2.6H_2O$	THF, H_2O	[20], (93%)

Key: = * by TLC

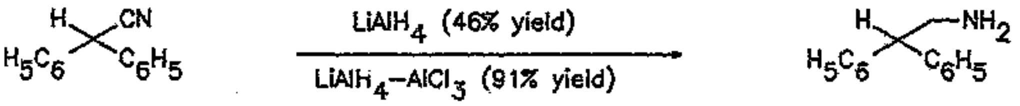
Lithium aluminum hydride, a pre-eminent reducing agent of modern organic chemistry, seemed an appropriate choice, especially in the light of Yamada *et al.*'s[19] achievement of nitrile reduction of *rel*-5*R*,6*R*- and *rel*-5*R*,6*S*-1-azabicyclo[4.4.0]decane-5-carbonitrile. Also, Cimino *et al.*[113] reported a selective reduction of an α,β-unsaturated nitrile system (Scheme 48).



Scheme 48

In the present work, *rel*-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile [20] in ether was added to a suspension of lithium aluminum hydride. This reduction procedure looked promising but was discontinued due to the excellent results obtained in Section 3.3.1.

It is known that the reducing properties of lithium aluminum hydride can be modified by the addition of the Lewis acid, aluminum chloride. Nystrom[114] reported on the improvements of the latter hydridic reagent, with respect to lithium aluminum hydride, on the conversion of nitriles to amines. This is illustrated in Scheme 49.



Scheme 49

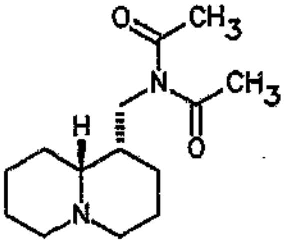
In this project, *rel*-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile in tetrahydrofuran was added to a suspension of lithium aluminum hydride and aluminum chloride in ether to afford starting material, impurities and possibly the lupinamine product. Too little material was obtained to warrant further purification and separation.

The use of transition metal catalysts or coreagents has added new dimensions to the versatility of sodium borohydride reductions. Osby *et al.*[115] have successfully used this transition-metal-assisted hydride reduction method in the transformation of benzonitrile to its corresponding primary amine in an alcoholic solvent at room temperature in 91% yield.
Adaptation of this method to our purposes proved fruitless as the results in Table 8 indicate.

3.4 Synthesis of N-acetyllupinamine and N-acetylepilupinamine

The preparation of these two derivatives, N-acetyllupinamine [113] and N-acetylepilupinamine [114] was necessary to establish the stereochemical configuration[116] of lupinamine [11] and epilupinamine [112], respectively. Both derivatives are known, and in a paper by Wanner *et al.*[117], the most recent account of some physical properties and spectroscopic data is given. Both proton and carbon assignments were reported for N-acetyllupinamine, but only proton assignments were given for N-acetylepilupinamine. A direct spectroscopic comparison of our findings with that reported in the literature would thus enable us to confirm the stereochemistry of lupinamine and epilupinamine while at the same time we could supply the missing data for N-acetylepilupinamine.

Wanner *et al.*[117] obtained N-acetyllupinamine as colourless needles (m.p. 144 - 146°C) in 52% yield by heating lupinamine in acetic anhydride. Following the same procedure, we obtained N-acetyllupinamine [113] as a white solid (m.p. 122.5 - 125°C) in 60% yield and N,N-bis(acetyl)lupinamine [127] in 39% yield after column chromatography.



[127]

A direct comparison of our spectroscopic data with those reported by Wanner *et al.* is made below. In the representation of ^1H nmr and ir data, the literature values will be given at the appropriate places in parentheses.

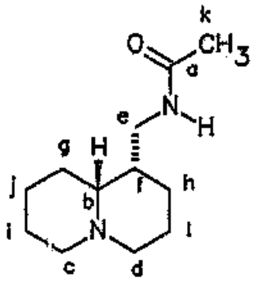
In the ^1H nmr spectrum of N-acetyllupinamine, the NH peak appeared as a broad singlet at 7.87 - 7.60ppm (7.47ppm). The multiplet at 3.10 - 2.62ppm of the lupinamine starting material, due to C-2 and C-10 equatorial protons and C-11 aminomethylene protons, separated out into two multiplets, at 3.60 - 3.24ppm (3.44ppm) due to C-11 protons and at 3.00 - 2.77ppm (2.84ppm) due to C-2 and C-10 equatorial protons in the derivative product. A distinctive singlet due to the methyl group was seen at 1.97ppm (1.96ppm). The remaining 14 protons appeared as a multiplet at 2.29 - 1.06ppm (2.2 - 1.1ppm).

The ^{13}C nmr spectrum provided the correct number of carbon signals. The carbonyl carbon peak at 169.8ppm and the methyl peak at 22.9ppm confirmed the presence of N-acetyllupinamine. No assignments of the ring carbon signals (except for C-2 and C-10) were provided in the literature In this project, δ values were assigned to C-3, C-8 and C-9 of N-acetyllupinamine by comparison with the chemical shifts of the same carbons in lupinamine and epilamprolobine. In the case of the C-4 and C-7 assignments, a simple comparison was not sufficient owing to the fact that in lupinamine C-4 was downfield from C-7, while in epilamprolobine the opposite was true. A definite assignment of C-4 and C-7 in N-acetyllupinamine was possible when we observed the noticeably decreased intensity of the C-7 signal (with respect to all other signals) in both epilamprolobine and N-acetyllupinamine. The presence of a *trans*-fused quinolizidine moiety was apparent from the closeness of the two aminomethylene carbons at the C-2 and C-10 positions.

Table 9 compares carbon chemical shifts given by Wanner et *al.* with our own, together with our assignments (which refer to [113] in Figure 13).

Table 9: Comparison of δ values for [113] with literature values

Literature δ values/ppm	Our δ values/ppm	Our assignments
–	169.84	C-a
64.52	64.09	C-b
57.07	56.68	C-c
56.69	55.77	C-d
41.13	39.73	C-e
35.80	36.28	C-f
29.76	29.27	C-g
26.48	28.11	C-h
25.48	24.71	C-i
24.56	24.26	C-j
23.24	22.90	C-k
21.78	21.21	C-l



[113]

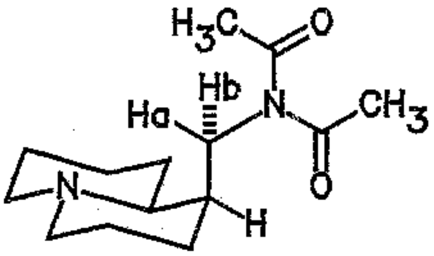
Figure 13

The ir spectrum of N-acetyllupinamine showed characteristic bands of an amide at 3452cm^{-1} (3460cm^{-1}) due to a N-H stretch, at 1659cm^{-1} (1650cm^{-1}) due to an amide C=O stretch and at 1526cm^{-1} (1520cm^{-1}) due to a N-H deformation and a symmetrical N-C=O stretch. The Bohlmann bands at 2944, 2864, 2812 and 2770cm^{-1} (2800, 2760cm^{-1}) attract attention to the *trans*-fused quinolizidine conformation.

A high resolution mass spectrum showed a molecular ion peak at m/z = 210.1733, confirming the formula $C_{12}H_{22}N_2O$.

Our spectroscopic data compared very favourably with those reported in the literature, thereby confirming the stereochemistry at C-5 and C-6 of N-acetyllupinamine and also lupinamine.

N,N-Bis(acetyl)lupinamine [127] was a low-melting (m.p. 39 - 41°C) brown solid. The ^{1}H nmr spectrum showed a singlet at 2.41ppm, which integrated to 6 protons. It was clear that two methyl groups were present. A compound consistent with this finding was indeed the doubly acetylated product. The downfield shift of the C-2 and C-10 equatorial protons to 3.00 - 2.76ppm indicated a *trans*-fused bicyclic system. The two C-11 aminomethylene protons produced two sets of doublet of doublets at 4.14ppm and 3.73ppm. The doublet of doublets at 4.14ppm (J 10.8Hz and 14.5Hz) was due to the proton marked Ha in Figure 14. The doublet of doublets at an upfield position of 3.73ppm (J 3.3Hz and 14.5Hz) was due to the Hb proton, which is *trans* to the C-5 methine proton and close to the ring nitrogen lone pair.



[127]

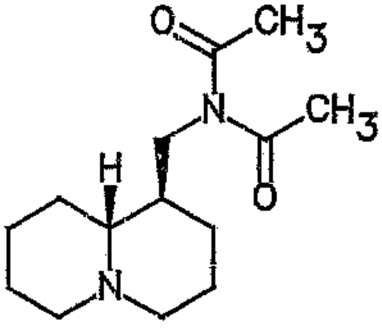
Figure 14

The ^{13}C nmr spectra of both [127] and [113] possessed the same number of carbon signals because the two imide carbonyl peaks and the two methyl peaks in the former are each in the same chemical environment and are thus equivalent. There were marginal differences in chemical shifts between the two products and therefore no distinction could be made between the two by virtue of their ^{13}C nmr spectra.

The ir spectrum of [127] did not show absorption bands due to a N-H stretch or a N-H deformation, indicative of the desired product [113]. An imide C=O stretch appeared at 1700cm^{-1} and Bohlmann bands at 2970, 2885, 2835 and 2790cm^{-1} were present too.

Confirmation of the formula $C_{14}H_{24}N_2O_2$ was provided by the high resolution mass spectrum of [127], which showed a molecular ion peak at m/z = 252.1829.

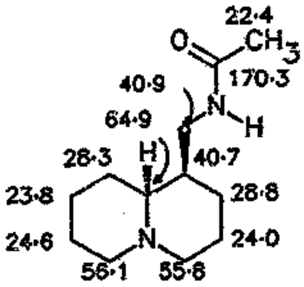
Acetylation of epilupinamine [112] by the procedure described above yielded N-acetylepilupinamine [114] as a white solid (m.p. 128.5 - 131°C) in 75% yield and N,N-bis(acetyl)epilupinamine [128] in 25% yield after column chromatography. Wanner *et al.* isolated N-acetylepilupinamine as an oil in 53% yield. A direct comparison of our ^1H nmr and ir data with those reported by Wanner *et* *al.* is made below. These literature values will be given at the appropriate places in parentheses.



[128]

The NH proton of N-acetylepilupinamine produced a triplet at 7.24ppm (5.56ppm). The C-11 aminomethylene protons appeared as two multiplets at 3.50 - 3.23ppm and 3.21 - 3.00ppm, in contrast to the findings of Wanner *et al.*, where better resolution showed two sets of doublet of doublets of doublets at 3.33 and 3.13ppm, respectively. The C-2 and C-10 equatorial protons produced a triplet at 2.83ppm (a multiplet at 2.79ppm), their position being characteristic of a *trans*-fused quinolizidine skeleton. The methyl singlet appeared at 1.99ppm (1.97ppm). The remaining 14 protons produced a series of multiplets at 2.26 - 0.95ppm (2.2 - 1.0ppm).

The amide carbonyl carbon and methyl carbon signals at 170.3ppm and 22.4ppm, respectively, appeared as expected in the ^{13}C nmr spectrum of N-acetylepilupinamine. Assignments for the ring carbons, C-3, C-4, C-7, C-8 and C-9 were made by drawing comparisons with those values of their equivalent sites in epilupinamine. The closeness in value of the C-2 and C-10 signals again confirmed the conformation of the compound. The DEPT spectrum distinguished the C-5 and C-11 signals. Figure 15 shows the carbon assignments of N-acetylepilupinamine.



[114]

Figure 15

The ir spectrum revealed the appropriate absorption bands: a N-H stretch at 3460cm^{-1} (3450cm^{-1}), an amide C=O stretch at 1660cm^{-1} (1660cm^{-1}), a symmetrical N-C=O stretch at 1510cm^{-1} (1510cm^{-1}) and Bohlmann bands at 2945, 2870, 2817, 2775cm^{-1} (2800, 2760cm^{-1}).

Confirmation of the formula $C_{12}H_{22}N_2O$ was provided by the high resolution mass spectrum of [114], which showed a molecular ion peak at m/z = 210.1728.

Our spectroscopic data compared very favourably with those reported in the literature,[117] thereby confirming the stereochemistry at C-5 and C-6 of N-acetylepilupinamine and epilupinamine. We have also filled a gap in the literature by recording the ^{13}C nmr spectrum of N-acetylepilupinamine.

N,N-Bis(acetyl)epilupinamine [128] was obtained as a yellow liquid. Its ^{1}H nmr spectrum exhibited very similar features as that for [127]. The two sets of doublet of doublets were closer together in terms of δ values (3.82ppm and 3.63ppm) than the corresponding values in the ^{1}H nmr spectrum of [127].

The ^{13}C nmr spectrum of [128] indicated the presence of the imide carbonyl carbon (at 173.4ppm) and methyl carbon (at 26.2ppm) signals. There were marginal differences in chemical shifts between [114] and [128], except for the C-11 signal in [128] which was more deshielded than the C-11 signal in [114] (45.9ppm versus 40.9ppm).

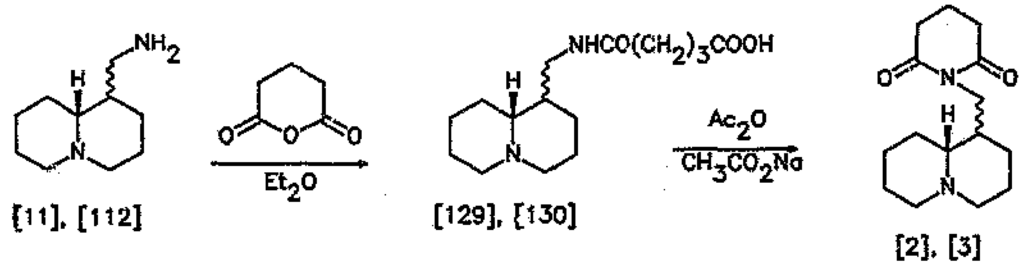
The ir-absorption bands of [128] included an imide C=O stretch at 1698cm^{-1} and Bohlmann bands at 2944, 2864, 2812 and 2768cm^{-1}, but excluded the N-H stretch and N-H deformation of the desired product [114].

A high resolution mass spectrum showed a molecular ion peak at m/z = 252.1841, corresponding to $C_{14}H_{24}N_2O_2$.

3.5 Synthesis of epilamprolobine and lamprolobine

The conversion of lupinamine [11] and epilupinamine [112] to the target alkaloids epilamprolobine [2] and lamprolobine [3], respectively have been reported before[12,18,19] and so they are actually unnecessary, since we have completed formal syntheses of both targets. However, in order to compare reported data and supply missing data for the compounds and also for personal satisfaction, we decided to carry the amines through to the alkaloids.

Scheme 50 illustrates the synthetic pathway by which the glutarimido unit is added to both amine precursors to produce the target alkaloids.

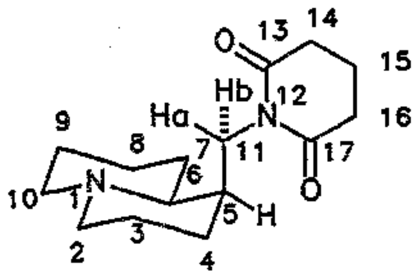


Scheme 50

Yamada *et al.*[19] treated a solution of glutaric anhydride with lupinamine [11] in ether to afford an amide as white crystals. A solution of this amide in acetic anhydride containing sodium acetate was heated to produce epilamprolobine [2] as a solid (m.p. 68 - 68.5°C) in 46% yield (from *rel*-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile [20]). Following the same procedure, we obtained epilamprolobine as a white solid (m.p. 66.5 - 67.5°C) in 54% yield after column chromatography (from [11]). N-Acetyllupinamine [113] was also obtained as a side product in 7% yield.

A direct comparison of our ^1H, ^{13}C nmr and ir data with those reported by Murakoshi *et al.*[12] was made. The correlation was excellent and therefore we will present one set of data (ours) when discussing the characterisation of epilamprolobine.

The ^1H nmr spectrum showed a doublet of doublets (J 10.9Hz and 13.0Hz) at 4.28ppm due to Ha and another doublet of doublets (J 3.5Hz and 13.0Hz) at 3.77ppm due to Hb, in Figure 16. On the basis of these chemical shifts and coupling constants, we deduced the conformation shown in Figure 16. As discussed before for [127] (in Section 3.4), the Ha proton was believed to be in a *trans* relationship with the C-5 proton and was close to the ring nitrogen lone pair. Consequently Ha was deshielded with respect to Hb.



[2]

Figure 16

The ring junction of the quinolizidine moiety was *trans*, as deduced from the characteristic downfield shift of the C-2 and C-10 equatorial protons to 2.94 - 2.78ppm. The triplet at 2.65ppm, integrating to 4 protons, indicated the presence of two sets of equivalent methylene protons at C-14 and C-16. The presence of a symmetric glutarimide moiety in the alkaloid, epilamprolobine, was suggested by three signals at 172.8, 33.1 and 17.2ppm corresponding to two equivalent imide carbonyl carbons (C-13 and C-17), two equivalent methylene carbons α to the carbonyls (C-14 and C-16) and one methylene carbon (C-15), respectively. Signals due to C-2 (57.1ppm) and C-10 (57.6ppm) were very close, indicative of the *trans*-fused bridge. Assignments of peaks in the ^{1}H and ^{13}C nmr spectra were aided by information drawn from DEPT and C-H correlated spectra.

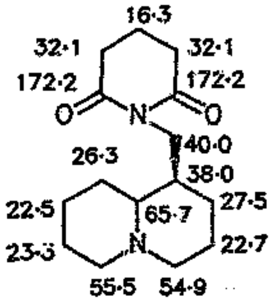
The ir spectrum of epilamprolobine showed the presence of the *trans* quinolizidine conformation by means of the Bohlmann bands at 2925, 2850, 2800 and 2750cm^{-1}. The C=O stretch of the imide group was represented by a medium absorption at 1712cm^{-1} and a strong absorption at 1660cm^{-1}.

Microanalysis confirmed the formula $C_{15}H_{24}N_2O_2$.

Lamprolobine [3] was prepared from epilupinamine [112] according to the same procedure as described for the synthesis of epilamprolobine [2]. Lamprolobine was obtained as a hard, yellow oil in 61% yield after column chromatography (from epilupinamine [112]). N-Acetylepilupinamine [114] was also isolated as a side product in 7% yield. Yamada *et al.*[19] reported a 42% yield (from [19]) of lamprolobine and characterised it by means of ^1H nmr, ir and mass spectroscopy. For purposes of comparison, these literature values will be given at the appropriate places in parentheses. No literature ^{13}C nmr assignments were available.

The multiplet at 3.94 - 3.60ppm (3.80 - 3.65ppm) in the ^1H nmr spectrum of lamprolobine was positively ascribed to the C-11 aminomethylene protons resonating. This assignment was aided by the C-H correlated spectrum and indirectly by the DEPT spectrum. The *trans*-fused quinolizidine system's C-2 and C-10 equatorial protons appeared as a multiplet at 3.25 - 2.92ppm. The triplet due to the two sets of equivalent methylene protons of the glutarimide moiety appeared at 2.70ppm.

As for epilamprolobine, signals were present in the ^{13}C nmr spectrum of lamprolobine which suggested the presence of the symmetric glutarimide moiety i.e. at 172.2ppm (due to C-13 and C-17), at 32.1ppm (due to C-14 and C-16) and at 16.3ppm (due to C-15). Closeness of peaks due to C-2 and C-10 indicated the *trans*-fused conformation. The C-5 and C-11 signals were distinguished with the help of the DEPT spectrum. All ring carbon assignments were made by comparison with the respective values in epilupinamine, N-acetylepilupinamine and N,N-bis(acetyl)epilupinamine [128]. Figure 17 shows the carbon assignments of lamprolobine.



[3]

Figure 17

The relevant ir-absorption bands of lamprolobine included bands at 1727cm^{-1} (1730cm^{-1}) and 1676cm^{-1} (1680cm^{-1}) due to the C=O stretch of the imide group and the usual Bohlmann bands at 2946, 2866, 2812 and 2768cm^{-1} (2900 - 2600cm^{-1}).

The presence of a molecular ion peak at m/z = 264.1875 in the high resolution mass spectrum confirmed the formula $C_{15}H_{24}N_2O_2$. The following mutual peaks (in m/z values) were found in our mass spectrum and that reported by Hart *et al.*[15] with the relative intensities given as percentages in parentheses. (Our relative intensities are quoted first.) 264 (M^+, 21, 50), 222 (9, 17), 152 (60, 60), 150 (19, 22), 138 (100, 100), 136 (21, 20), 124 (17, 17), 111 (41, 37), 110 (50, 45), 98 (28, 24), 97 (53, 44), 96 (27, 22), 84 (19, 13), 83 (80, 54), 82 (20, 14), 56 (14, 1[illegible]), 55 (45, 35), 42 (18, 15) and 41 (33, 22).

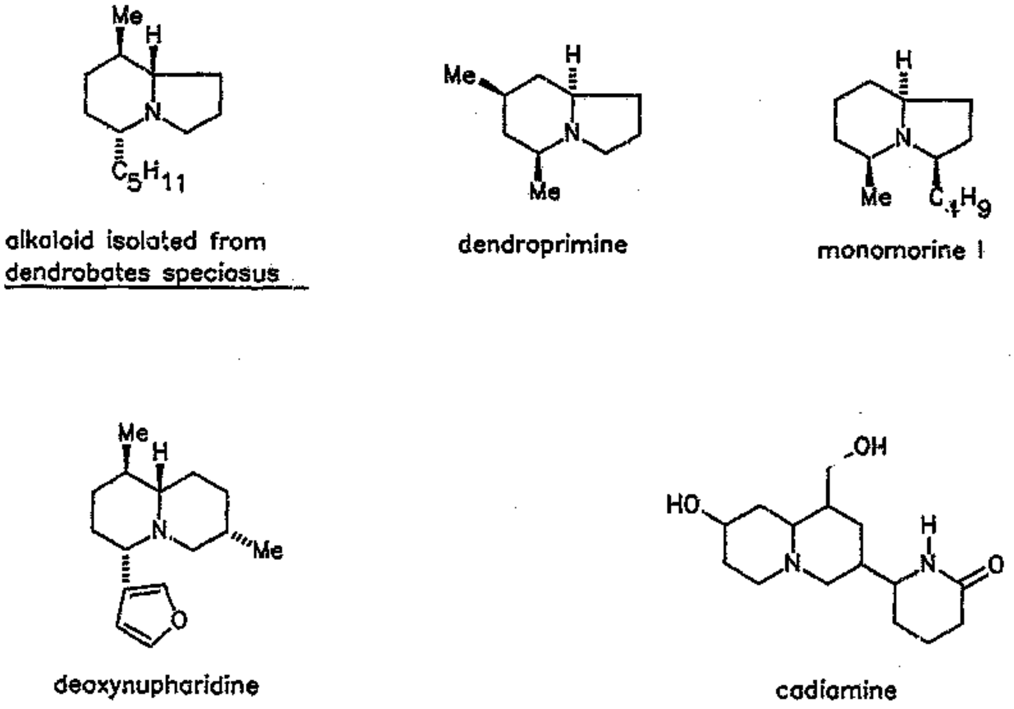
The ultimate aim of synthesising the Lupine alkaloids epilamprolobine and lamprolobine was thus brought to fruition.

CHAPTER 4

CONCLUSION

The Lupine alkaloids epilamprolobine [2] and lamprolobine [3] were synthesised in a novel eight-step synthesis from 2-piperidinone [72] in impressive overall yields of 17% and 11% respectively. In addition two quinolizidine derivatives, N-acetyllupinamine [113] and N-acetylepilupinamine [114], were also prepared in overall yields of 19% and 13% respectively. The vinylogous cyanamide, 1-(3-hydroxypropyl)-2-cyanomethylenepiperidine [68], proved its worth as a suitable precursor in gaining access t quinolizidine alkaloid systems by virtue of its potential to act as an ambident nucleophile. The successful route to this pivotal vinylogous cyanamide precursor involved a four-step reaction sequence. Thiation of the secondary lactam, 2-piperidinone [72] was followed by a Michael reaction in which conjugate addition of a three-carbon unit bearing a terminal ethoxy ester group produced the tertiary thiolactam, 1-(2-ethoxycarbonylethyl)piperidine-2-thione [83]. Sulphide contraction of the salt made from [83] and bromoacetonitrile provided the exocyclic vinylogous cyanamide, 1-(2-ethoxycarbonylethyl)-2-cyanomethylenepiperidine [85]. Chemoselective reduction of the ester functionality to a primary alcohol removed the carbonyl moiety in preparation for the intramolecular α-alkylative ring closure of [68] via the tosylate [116]. This cycloalkylation is only the second of its kind achieved by our group.[28] Other methods of preparing [68] using 5-bromopentanoic acid [80], 1-allyl-2-piperidinone [73] and thiolactams [84] and [105] as starting materials were unsuccessful.

We envisage extending this work by collecting further examples of cycloalkylation in the future. Figure 18 shows possible indolizidine and quinolizidine alkaloid targets[4] in which the second ring might be formed by cycloalkylation. It would be necessary to find even shorter routes to the hydroxypropyl compound, and we need to continue the search for alternative preparations. More importantly, we need a quicker, more reliable method for achieving ring closure. Our conversion of the alcohol group to a reactive sulphonic ester (e.g. tosylate) was slow. Other improved methods for activating the OH might be found in the use of oxonium ions, alkyl perchlorates, tresylates (2,2,2-trifluoro-ethanesulphonates) or triflates.[120]



alkaloid isolated from <u>dendrobates speciosus</u>

dendroprimine

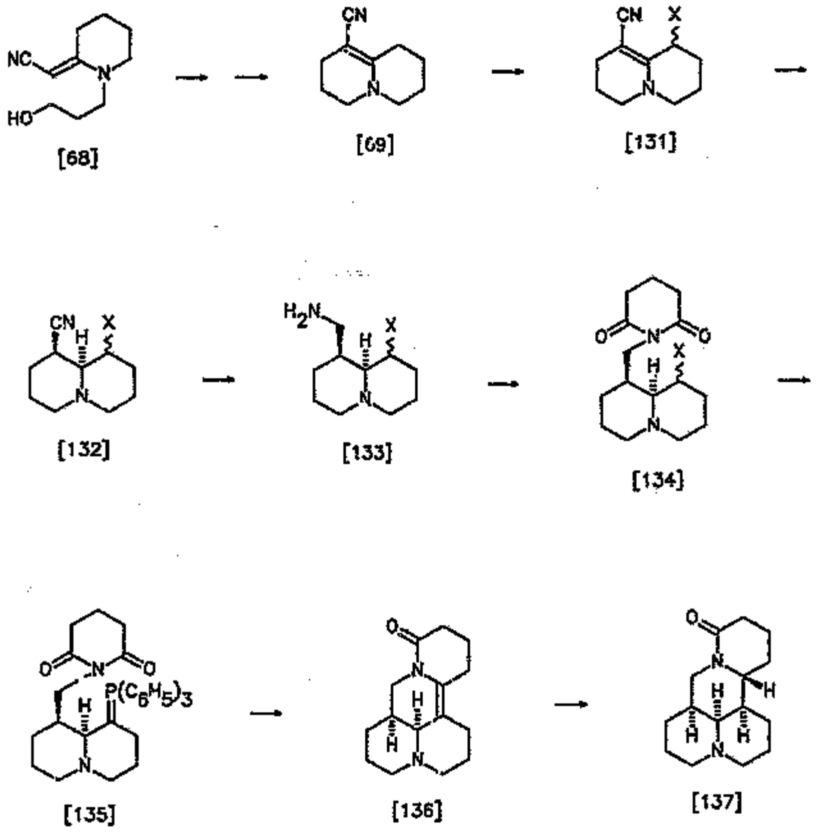
monomorine I

deoxynupharidine

cadiamine

Figure 18

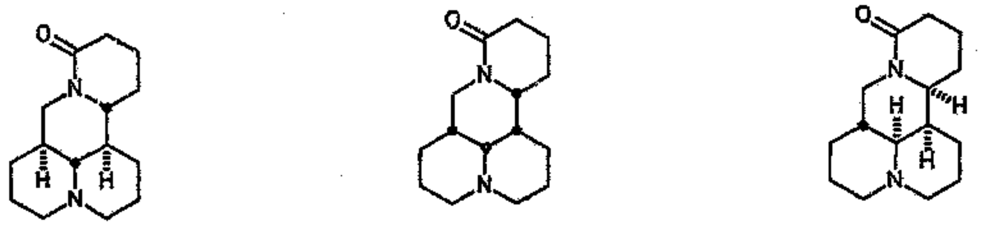
The success of this project should encourage further syntheses of alkaloids using vinylogous cyanamide precursors. A challenging prospect is the utilisation of 1-(3-hydroxypropyl)-2-cyanomethylenepiperidine [68], or very similar compounds, in the synthesis of matrine [137],[2,112,121] a Lupine alkaloid believed to possess pharmacological potential as an antiulcer agent. The proposed synthetic route is shown in Scheme 51.



X = potential leaving group

Scheme 51

Activation of the alcohol group of 1-(3-hydroxypropyl)-2-cyanomethylenepiperidine [68] to enhance its leaving group ability will enable an intramolecular alkylative cyclisation to afford 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69]. This endocyclic vinylogous cyanamide system displays reactivity at the γ-carbon, which is nucleophilic. However, one could also take advantage of its allylic nature to introduce functionality by free-radical substitution, for example bromination with N-bromosuccinimide or allylic oxidation with a range of oxidants. Subsequent stereoselective carbon-carbon double bond reduction of the resulting compound [131] is expected to lead to an intermediate [132] possessing three adjacent stereogenic centres. Stereocontrol at C-5 and C-6 is important in order to establish, at an early stage, the correct stereochemistry needed in the final matrine molecule. The stereochemistry of X is less significant owing to the fact that the later Wittig reaction will produce an sp^2 centre here. The synthetic steps from [132] to [134] will be analogous with those in our syntheses of epilamprolobine [2] and lamprolobine [3], the only difference being that here we will have additional functionality at C-7. A functionality that survives the intermediate steps will therefore need to be chosen. The formation of the phosphorus ylide [135] will be needed for the subsequent intramolecular Wittig reaction to produce [136], an alkaloid called leontalbinine. The final step involves a second stereoselective carbon-carbon double bond reduction. Even in the event of producing the incorrect stereochemistry for matrine, we will inevitably produce diastereomers that in fact are known alkaloids. Examples[2] of these are given in Figure 19.



allomatrine

(5S,6R,7R,11R)

isomatrine

(5S,6R,7S,11R)

darvasamine

(5S,6R,7S,11R)

sophoridine

(5S,6R,7S,11S)

isosophoridine

(5S,6S,7S,11S)

Figure 19

Besides the fact that alkaloids present challenging and exciting synthetic targets, their preparation is often of great use in the medical field, in which they show great pharmacological activity.

CHAPTER 5

EXPERIMENTAL

5.1 General

5.1.1 Solvents, reagents and general procedures

All solvents and most reagents (liquids) were purified before use. All ethers (diethyl ether, THF, glyme, dioxane) were pre-dried over calcium chloride and distilled under nitrogen from sodium-benzophenone. Dichloromethane was distilled from phosphorus pentoxide, toluene from sodium metal and acetonitrile from calcium hydride. Water used as the aqueous phase in extraction procedures was also distilled.

When aqueous solutions were extracted with an organic solvent, the organic phase after separation was dried over anhydrous magnesium sulphate (unless otherwise stated) before removal of the solvent. Evaporation of solvent *in vacuo* refers to the removal of solvent under reduced pressure (*ca.* 25mm Hg) on a rotary evaporator, followed by further drying on an oil pump at below 1mm Hg.

In general, reactions were performed under an atmosphere of nitrogen gas.

For reactions involving moisture-sensitive reagents, all glassware was dried in an oven at 120°C.

5.1.2 Purification of compounds

Products were purified using either distillation or column chromatography. Merck Kieselgel 60 (particle size 0.063 - 0.200mm) was used as the absorbent for conventional preparative column chromatography while Merck Kieselgel 60 (particle size 0.040 - 0.063mm) was used for preparative flash chromatography. On rare occasions, neutral alumina (Hopkin and Williams Ltd., about 100 - 240 mesh, "CAMAG" M.F.C.) was used. All solvents used as eluents were purified by distillation, except for AR methanol. The gradient elution method was used and the eluents quoted in the experimental section refer to those with which the relevant product eluted. The progress of the column chromatography separation, as well as that of the reactions, was monitored using thin layer chromatography (Merck DC-Fertigplatten Kieselgel F-254).

5.1.3 Characterisation of compounds

Most compounds were characterised using ^{1}H nmr, ^{13}C nmr and infrared spectroscopy. In addition, most liquid compounds were characterised by high resolution mass spectrometry and most solid compounds by microanalysis. Isomeric ratios were ascertained by gas chromatographic (gc) techniques.

^{1}H and ^{13}C nmr spectra were recorded on a Bruker AC-200 spectrometer in deuteriochloroform at 200.13 and 50.32MHz, respectively. A few ^{1}H nmr spectra were recorded on a Varian EM-360A spectrometer (60MHz). The peaks in the nmr spectra were assigned with the aid of correlation tables and an additivity rule formula (^{13}C only).[91] The chemical shifts are reported on a δ scale (ppm) relative to tetramethylsilane (TMS).

Infrared spectra of compounds were recorded on a PYE UNICAM 9512 infrared spectrophotometer and on a Jasco FT / IR-5000 infrared spectrophotometer as 10% solutions in chloroform using a cell with a path length of 0.1mm and sodium chloride windows. In some cases, infrared spectra were recorded of neat compounds between sodium chloride plates.

Accurate mass measurements (HRMS) of the molecular ion were obtained using a Varian MAT 212 (CSIR, Pretoria) or a VG 7070E (Potchefstroom University) mass spectrometer. Microanalyses were obtained from Energy Technology, CSIR.

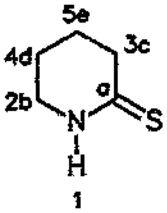
Gas chromatograms were recorded on a Varian 3300 gas chromatograph fitted with a bonded-phase fused silica column supplied by S.G.E. Australia. Column details: length 25m, internal diameter 0.22mm, external diameter 0.33mm, stationary phase BP10, coating of thickness 0.25 microns, temperature tolerance 270°C. Nitrogen (high purity) was used as carrier gas.

5.2 Experimental work relating to Chapter 2

Synthesis of piperidine-2-thione [67]

Piperidine-2-thione was prepared using a slightly modified version of Brillon's thiation procedure.[88]
Phosphorus pentasulphide (4.75g, 2.14 X 10^{-2}mol) was added to dry THF (100ml) followed by anhydrous sodium carbonate (2.26g, 2.13 X 10^{-2}mol). The mixture was stirred vigorously at room temperature for 20min. The resulting slightly opaque yellow solution was treated (dropwise addition) with a solution of 2-piperidinone [72] (2.108g, 2.126 X 10^{-2}mol) in dry THF (20ml). The resulting solution was stirred overnight at room temperature.

An aqueous sodium phosphate solution (10%, 96ml) was added, followed sequentially by ethyl acetate (69ml) and hexane (69ml). After separation, the aqueous phase was extracted with ethyl acetate (55ml X 3). The combined organic extracts were dried, filtered and the solvent was removed *in vacuo*. Purification by column chromatography, eluent: 7:3 hexane:ethyl acetate, afforded piperidine-2-thione [67] (2.163g, 88%) as a white solid, m.p. 94 - 95°C. [R_F (2:1 C_6H_{14}:CH_3COCH_3) 0.24]



[67]

δ_H (200MHz) 9.90 - 9.40 (1H, br s, H-1), 3.50 - 3.20 (2H, m, H-2), 2.89 (2H, t, *J* 6.0Hz, H-3), 2.03 - 1.56 (4H, m, H-4 and H-5);

δ_C (50.32MHz) 201.7 (C-a), 44.3 (C-b), 38.8 (C-c), 20.4 (C-d), 19.8 (C-e), last two assignments are tenuous;

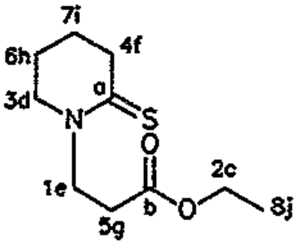
$\nu_{max.}$ ($CHCl_3$) 3360, 2940, 2850, 1570, 1537, 1510, 1450, 1417, 1350, 1317, 1110, 1025, 950cm^{-1}.

Synthesis of 1-(2-ethoxycarbonylethyl)piperidine-2-thione [83]

1-(2-Ethoxycarbonylethyl)piperidine-2-thione was prepared using the procedure reported by Orlek,[21] which was slightly modified during the workup and purification stage.

A solution of piperidine-2-thione [67] (14.919g, 1.295 X 10^{-1}mol) in dry THF (625ml) was treated with a catalytic

amount of sodium hydride (50% suspension in oil, 358mg, 7.47mmol followed by dropwise addition of ethyl acrylate (23.15ml, 21.4g, 2.14 X 10^{-1}mol). The resulting reaction mixture was stirred at 50 - 54°C for 44.5h.
After evaporation of the solvent, the yellow-orange oil was dissolved in dichloromethane (300ml) and washed with water and saturated sodium chloride solution [(100ml + 15ml, respectively) X 3]. The combined aqueous washings were extracted with dichloromethane (50ml). The combined organic extracts were dried, filtered and evaporated *in vacuo*. Two purification techniques were used. Vacuum distillation of half the material afforded 1-(2-ethoxycarbonylethyl)piperidine-2-thione [83] as a yellow liquid, b.p. 160 - 192°C / 21mm Hg. Column chromatography of the remaining material, eluent: 4:1 hexane:ethyl acetate, afforded more product (27.738g in total, 99% overall). [R_F (2:1 C_6H_{14}:CH_3COCH_3) 0.61]



[83]

δ_H (200MHz) 4.19 (2H, t, J 7.0Hz, H-1), 4.15 (2H, q, J 7.1Hz, H-2), 3.54 (2H, t, J 6.1Hz, H-3), 2.97 (2H, t, J 6.5Hz, H-4), 2.85 (2H, t, J 7.0Hz, H-5), 1.98 - 1.81 (2H, m, H-6), 1.81 - 1.65 (2H, m, H-7), 1.27 (3H, t, J 7.1Hz, H-8);

δ_C (50.32Hz) 199.8 (C-a), 171.6 (C-b), 60.6 (C-c), 51.8 (C-d), 50.7 (C-e), 41.6 (C-f), 30.6 (C-g), 22.8 (C-h), 20.2 (C-i), 14.0 (C-j);

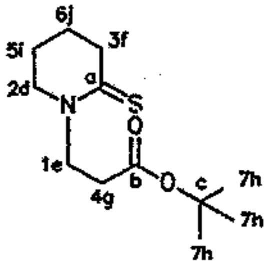
$\nu_{max.}$ ($CHCl_3$) 3000, 2975, 2885, 1730, 1515, 1450, 1415, 1375, 1350, 1330, 1290, 1260, 1185, 1160, 1095, 1050, 1030, 955, 858cm^{-1};

m/z 215 (M^+, 57%), 186 (M^+-29, 95%), 170 (M^+-45, 19%), 142 (M^+-73, 57%), 128 (M^+-87, 15%), 114 (M^+-101, 17%), 91 (100%), 82 (68%), 55 (61%), 44 (74%), 41 (34%), 28 (100%), 27 (38%);

HRMS (Found: M^+ 215.0980. $C_{10}H_{17}NO_2S$ requires M^+, 215.0980).

Synthesis of 1-(2-*t*-butoxycarbonylethyl)piperidine-2-thione [84]

A solution of piperidine-2-thione [67] (1.189g, 1.032 X 10^{-2}mol) in dry THF (15ml) was treated with a catalytic amount of sodium hydride (60% suspension in oil, 25mg, 0.529mmol), followed by dropwise addition of *t*-butyl acrylate (1.80ml, 1.57g, 1.23 X 10^{-2}mol). The resulting reaction mixture was stirred at room temperature for 4.5h, then at 30°C for 16.5h and finally at 55°C for 2.5h.
The solvent was removed *in vacuo*. The remaining red-brown suspension was dissolved in diethyl ether (70ml) and washed with water and saturated sodium chloride solution [(25ml + 10ml, respectively) X 4]. The ethereal extract was dried, filtered and evaporated *in vacuo* to afford 1-(2-*t*-butoxycarbonylethyl)piperidine-2-thione [84] (1.563g, 62%) after column chromatography, eluent: 19:1 hexane:ethyl acetate. [R_F (2:1 C_6H_{14}:CH_3COCH_3) 0.66] The white solid was recrystallised, m.p. 56 - 56.5°C (from hexane).



[84]

δ_H (200MHz) 4.16 (2H, t, J 7.0Hz, H-1), 3.53 (2H, t, J 6.1Hz, H-2), 2.97 (2H, t, J 6.5Hz, H-3), 2.76 (2H, t, J 7.0Hz, H-4), 2.03 - 1.82 (2H, m, H-5), 1.82 - 1.64 (2H, m, H-6), 1.45 (9H, s, 3 X H-7);

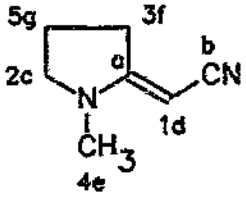
δ_C (50.32MHz) 199.6 (C-a), 170.8 (C-b), 80.7 (C-c), 51.7 (C-d), 50.7 (C-e), 41.6 (C-f), 31.7 (C-g), 27.8 (3 X C-h), 22.7 (C-i), 20.2 (C-j);

$\upsilon_{max.}$ ($CHCl_3$) 2965, 2930, 2855, 1710, 1510, 1440, 1405, 1385, 1365, 1345, 1325, 1285, 1250, 1225 - 1200, 1150, 1090, 1040, 1015, 955, 880, 835cm^{-1};

Found: C, 59.51; H, 8.84; N, 5.76. $C_{12}H_{21}NO_2S$ requires C, 59.23; H, 8.70; N, 5.76%.

Synthesis of 1-methyl-2-cyanomethylenepyrrolidine [90]

1-Methyl-2-cyanomethylenepyrrolidine was prepared previously by Katz[23] and Michael.[20]
In this project, [90] was prepared in 71% yield by treating the α-thioiminium salt of 1-methylpyrrolidine-2-thione [88] (formed by treatment of the thiolactam with bromoacetonitrile in dichloromethane) with triphenylphosphine and triethylamine.



[90]

δ_H (200MHz) 3.58 (1H, s, H-1), 3.47 (2H, t, J 7.0Hz, H-2), 2.84 (2H, t, J 7.8Hz, H-3), 2.79 (3H, s, H-4), 2.00 (2H, quintet, J 7.3Hz, H-5);

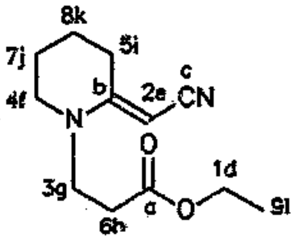
δ_C (50.32MHz) 165.8 (C-a), 122.6 (C-b), 55.0 (C-c), 52.2 (C-d), 32.4 (C-e), 32.0 (C-f), 20.2 (C-g);

$\nu_{max.}$ (CHCl$_3$) 3247, 3055, 2980 - 2875, 2855, 2785, 2700, 2370, 2230, 2175, 1630 - 1570, 1452, 1422, 1405, 1337, 1290, 1235, 1160, 1100, 1067, 1030, 1010, 940, 920, 872, 855, 742, 685, 630cm^{-1}.

Synthesis of 1-(2-ethoxycarbonylethyl)-2-cyanomethylenepiperidine [85]

A sample of 1-(2-ethoxycarbonylethyl)piperidine-2-thione [83] (1.091g, 5.066 X 10^{-3}mol) was cooled to 0°C and treated with bromoacetonitrile (0.39ml, 670mg, 5.6mmol) by dropwise addition. The reaction was left standing at room temperature for 4h, after which a white glue formed. Addition of a solution of triphenylphosphine (1.330g, 5.071 X 10^{-3}mol) in dry dichloromethane (10ml) was followed by triethylamine (0.85ml, 620mg, 6.1mmol). The resulting reaction mixture was stirred at room temperature for 165min.

The solvent and excess bromoacetonitrile was removed *in vacuo*. Diethyl ether was added to the remaining orange solid. This was filtered and the solid ($NEt_3H^+Br^-$) was thoroughly washed with diethyl ether. The combined ethereal washings were evaporated *in vacuo* to afford 1-(2-ethoxycarbonylethyl)-2-cyanomethylenepiperidine [85] (959mg, 85%) as a yellow liquid after column chromatography, eluent: 17:3 to 4:1 hexane:ethyl acetate. [R_F (1:1 C_6H_{14}:$CH_3CO_2C_2H_5$) 0.53]



[85]

δ_H (200MHz) 4.16 (2H, q, J 7.1Hz, H-1), 3.76 (1H, s, H-2), 3.42 (2H, t, J 7.1Hz, H-3), 3.23 (2H, t, J 6.1Hz, H-4), 2.67 (2H, t, J 6.4Hz, H-5), 2.57 (2H, t, J 7.1Hz, H-6), 1.87 - 1.75 (2H, m, H-7), 1.75 - 1.59 (2H, m, H-8), 1.28 (3H, t, J 7.1Hz, H-9);

δ_C (50.32MHz) 171.4 (C-a), 161.1 (C-b), 122.0 (C-c), 60.9 (C-d), 59.9 (C-e), 50.0 (C-f), 47.4 (C-g), 30.3 (C-h), 28.2 (C-i), 23.5 (C-j), 19.6 (C-k), 14.1 (C-l);

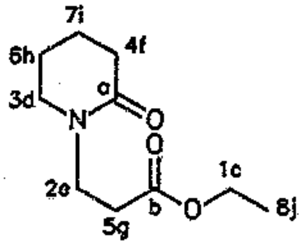
$\nu_{max.}$ ($CHCl_3$) 2940, 2860, 2325, 2175, 1720, 1570, 1440, 1420, 1370, 1345, 1327, 1275, 1260, 1170, 1150, 1095, 1040, 1017, 972, 850, 693cm^{-1};

m/z 222 (M^+, 40%), 177 (M^+-45, 12%), 149 (M^+-73, 94%), 135 (M^+-87, 100%), 122 (64%), 121 (M^+-101, 20%), 97 (84%), 82 (37%), 55 (78%), 41 (36%), 28 (100%), 27 (45%);

HRMS (Found: M^+ 222.1374. $C_{12}H_{18}N_2O_2$ requires M^+, 222.1368).

Attempted synthesis of 1-(2-ethoxycarbonylethyl)-2-cyanomethylenepiperidine [85] and actual synthesis of 1-(2-ethoxycarbonylethyl)-2-piperidinone [91]

Bromoacetonitrile (0.89ml, 1.5g, 1.3 X 10^{-2}mol) was added to a solution of 1-(2-ethoxycarbonylethyl)piperidine-2-thione [83] (2.198g, 1.020 X 10^{-2}mol) in acetone (20ml). The resulting solution was stirred at room temperature for 80min and then at 55°C for 17h. A second addition of bromoacetonitrile (0.36ml, 620mg, 5.2mmol) was made and stirring at 55°C was continued for a further 5.5h. After cooling to room temperature, a solution of triphenylphosphine (2.680g, 1.022 X 10^{-2}mol) in dry dichloromethane (25ml) was added, followed by dry triethylamine (1.71ml, 1.24g, 1.23 X 10^{-2}mol). The reaction mixture was stirred at room temperature for 19h. The solvents and excess bromoacetonitrile were removed *in vacuo*. Diethyl ether (200ml) was added to the remaining orange solid and filtered. The ether filtrate was washed with hydrochloric acid (2M, 45ml X 4). The combined acidic washings were basified with ammonia liquor and extracted with dichloromethane (40ml X 4). The combined organic extracts were dried, filtered and evaporated *in vacuo* to afford 1-(2-ethoxycarbonylethyl)-2-piperidinone [91] (1.151g, 57%) after distillation, b.p. 105 - 140°C / 21mm Hg. [R_F (11:9 C_6H_{14}:CH_3COCH_3) 0.57]



[91]

δ_H (200MHz) 4.14 (2H, q, J 7.1Hz, H-1), 3.61 (2H, t, J 7.2Hz, H-2), 3.35 (2H, br t, J 5.4Hz, H-3), 2.60 (2H, t, J 7.0Hz, H-4), 2.36 (2H, br t, J 7.2Hz, H-5), 1.88 - 1.70 (4H, m, H-6 and H-7), 1.26 (3H, t, J 7.1Hz, H-8);

δ_C (50.32MHz) 171.8 (C-a), 169.7 (C-b), 60.3 (C-c), 48.5 (C-d), 43.5 (C-e), 32.2 (C-f), 32.1 (C-g), 23.1 (C-h), 21.0 (C-i), 13.9 (C-j);

$\upsilon_{max.}$ ($CHCl_3$) 2965, 2935, 2890, 2855, 1725, 1625, 1495, 1465, 1445, 1415, 1375, 1352, 1330, 1315, 1295, 1185, 1172, 1095, 1042, 1020, 967, 855, 825cm^{-1};

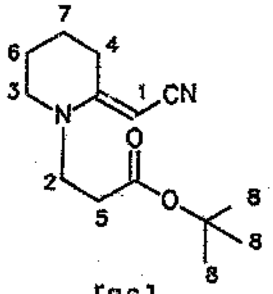
m/z 199 (M^+, 33%), 154 (M^+-45, 37%), 143 (36%), 126 (M^+-73, 37%), 125 (31%), 112 (M^+-87, 72%), 98 (M^+-101, 33%), 84 (100%), 55 (48%), 42 (46%), 29 (31%);

HRMS (Found: M^+ 199.1127. $C_{10}H_{17}NO_3$ requires M^+, 199.1208).

Synthesis of 1-(2-*t*-butoxycarbonylethyl)-2-cyanomethylenepiperidine [86]

A solution of 1-(2-*t*-butoxycarbonylethyl)piperidine-2-thione [84] (181mg, 0.743mmol) in dry dichloromethane (a few drops) was treated with bromoacetonitrile (0.057ml, 98mg, 0.82mmol) at room temperature. The resulting solution was stirred at room temperature for 15min and then heated to 55 - 65°C for 25min. After cooling down to room temperature another addition of bromoacetonitrile (0.057ml, 98mg, 0.82mmol) was made. The reaction contents were again heated to 55 - 65°C for 4.5h. Sequential addition of a solution of triphenylphosphine (196mg, 0.747mmol) in dry dichloromethane (10ml) and dry triethylamine (0.12ml, 87mg, 0.86mmol) followed and the resulting reaction mixture was stirred at room temperature for a further 30min.

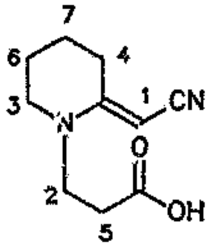
The solvent and excess bromoacetonitrile was removed *in vacuo*. Diethyl ether (10ml) was added to the remaining light orange solid. After filtration, the ether filtrate was evaporated *in vacuo* to afford 1-(2-*t*-butoxycarbonylethyl)-2-cyanomethylenepiperidine [86] (18mg, 10%) as a pale yellow liquid after column chromatography, eluent: 7:3 hexane:ethyl acetate. [R_F (2:1 C_6H_{14}:CH_3COCH_3) 0.38] 1-(2-Carboxyethyl)-2-cyanomethylenepiperidine [92] (24mg, 26%) was also obtained as a colourless liquid after column chromatography, eluent: ethyl acetate. [R_F (2:1 C_6H_{14}:CH_3COCH_3) 0.11]



[86]

δ_H (200MHz) 3.67 (1H, s, H-1), 3.58 (2H, t, J 7.1Hz, H-2), 3.33 (2H, br t, J 5.9Hz, H-3), 2.52 (2H, t, J 7.1Hz, H-4), 2.44 - 1.62 (6H, m, H-5, H-6 and H-7), 1.44 (9H, s, 3 X H-8);

$\nu_{max.}$ (CHCl$_3$) 2985, 2945, 2870, 2260, 1705, 1612, 1480, 1455, 1440, 1385, 1360, 1342, 1315, 1285, 1140, 1022, 990, 835, 680, 635, 535cm^{-1}.



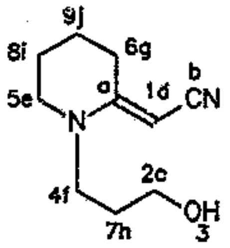
[92]

δ_H (200MHz) 3.69 (1H, s, H-1), 3.65 (2H, t, J 7.1Hz, H-2), 3.32 (2H, br t, J 6.0Hz, H-3), 2.98 (2H, t, J 6.6Hz, H-4), 2.37 (2H, br t, J 5.2Hz, H-5), 1.94 - 1.70 (4H, m, H-6 and H-7).

Synthesis of 1-(3-hydroxypropyl)-2-cyanomethylenepiperidine [68]

A stirred solution of 1-(2-ethoxycarbonylethyl)-2-cyanomethylenepiperidine [85] (1.731g, 7.785 X 10^{-3}mol) in dry THF (125ml) was cooled to 0°C. Lithium aluminum hydride (296mg, 7.81mmol) was added slowly. The reaction mixture was stirred at 0°C for 3h and then at room temperature for a further 62h. The reaction was quenched by the sequential addition of water (0.30ml), sodium hydroxide (15% (w/w), 0.30ml) and water (0.89ml).

The THF solvent was removed *in vacuo*. The remaining yellow solid was dissolved in dichloromethane (250ml) and was washed with saturated sodium chloride solution (50ml X 3) to break the emulsion formed. The organic layer was dried, filtered and the solvent was removed *in vacuo* to afford 1-(3-hydroxypropyl)-2-cyanomethylenepiperidine [68] (1.038g, 74%) as a light pink solid after column chromatography, eluent: 2:3 hexane:ethyl acetate. [R_F (1:1 C_6H_{14}:$CH_3CO_2C_2H_5$) 0.11] Three recrystallisations (from 1:1 hexane:ethyl acetate) afforded a white solid, m.p. 58 - 60°C.



[68]

δ_H (200MHz) 3.82 (1H, s, H-1), 3.64 (2H, t, J 5.9Hz, H-2), 3.42 -3.30 (1H, br s, H-3), 3.30 - 3.16 (4H, m, H-4 and H-5), 2.65 (2H, t, J 6.4Hz, H-6), 1.89 - 1.60 (6H, m, H-7, H-8 and H-9);

δ_C (50.32MHz) 161.6 (C-a), 123.0 (C-b), 59.3 (C-c), 57.6 (C-d), 49.4 (C-e), 48.6 (C-f), 28.0 (C-g), 27.8 (C-h), 23.2 (C-i), 19.4 (C-j);

$\upsilon_{max.}$ ($CHCl_3$) 3612, 3425, 3000, 2950, 2875, 2180, 1720, 1570, 1475, 1445, 1420, 1370, 1345, 1330, 1275, 1260, 1230, 1170, 1150, 1100, 1070, 1050, 975, 945, 915, 690, 645cm^{-1};

Found: C, 66.42; H, 9.20; N, 15.48. $C_{10}H_{16}N_2O$ requires C, 66.64; H, 8.95; N, 15.54%;

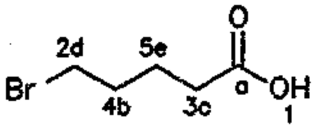
m/z 180 (M^+, 20%), 149 (M^+-31, 43%), 140 (88%), 136 (96%), 135 (M^+-45, 100%), 122 (67%), 121 (M^+-59, 26%), 94 (48%), 82 (39%), 54 (43%), 41 (57%), 31 (47%);

HRMS (Found: M^+ 180.1271. $C_{10}H_{16}N_2O$ requires M^+, 180.1263).

Synthesis of 5-bromopentanoic acid [80][90]

δ-Valerolactone [79] (10.343g, 1.033 X 10^{-1}mol) was heated under reflux in hydrobromic acid solution (48%, 60ml) containing concentrated sulphuric acid (3ml) for 130min, after which it was stirred at room temperature for 41h. Chilled water (*ca.* 20ml) and saturated sodium chloride solution (*ca.* 10ml) were added and extraction with diethyl ether (60 - 80ml X 4) followed. The combined ethereal extracts were dried, filtered and the solvent was removed *in vacuo* to afford 5-bromopentanoic acid [80] (15.641g, 84%) as a white solid, m.p. 36 - 38.5°C. [R_F (CH_3COCH_3)

0.85, yellow when treated with bromocresol green (0.5% solution in ethanol)]



[80]

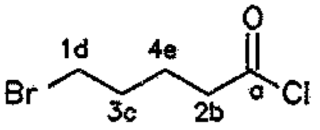
δ_H (200MHz) 11.34 - 11.04 (1H, br s, H-1), 3.43 (2H, t, J 6.4Hz, H-2), 2.41 (2H, t, J 7.1Hz, H-3), 2.10 - 1.60 (4H, m, H-4 and H-5);

δ_C (50.32MHz) 179.7 (C-a), 33.0 (C-b), 32.8 (C-c), 31.7 (C-d), 23.1 (C-e);

$\upsilon_{max.}$ ($CHCl_3$) 3500, 2945, 1705, 1430, 1410, 1280, 1200cm^{-1}.

Synthesis of 5-bromopentanoyl chloride [81]

To a solution of 5-bromopentanoic acid [80] (4.846g, 2.677 X 10^{-2}mol) in dry chloroform (30ml) was introduced dry dimethylformamide (7 drops) followed by thionyl chloride (2.15ml, 3.51g, 2.95 X 10^{-2}mol). The resulting solution was heated under reflux for 132min.
The solvent was distilled off under dry conditions and the remaining solution was purified by distillation to afford 5-bromopentanoyl chloride [81] (4.340g, 81%) as a colourless liquid, b.p. 100 - 120°C / 21mm Hg.



[81]

δ_H (200MHz) 3.44 (2H, t, J 6.2Hz, H-1), 2.99 (2H, t, J 6.8Hz, H-2), 2.04 - 1.70 (4H, m, H-3 and H-4);

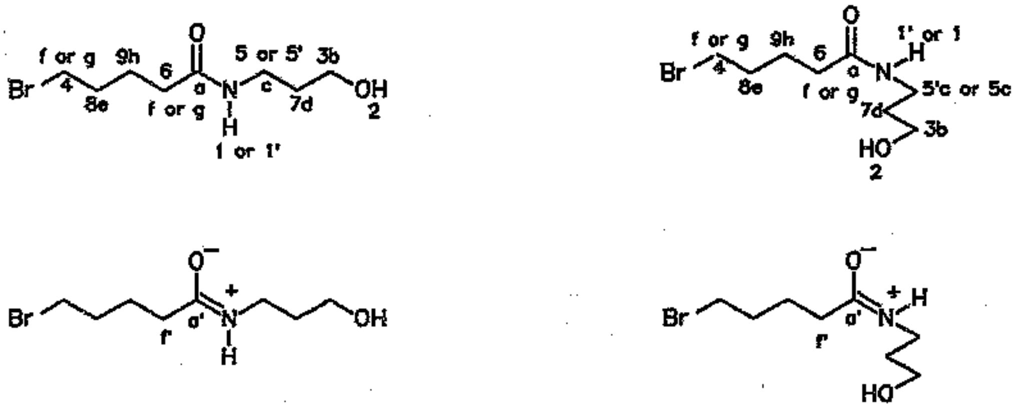
δ_C (50.32MHz) 172.8 (C-a), 45.5 (C-b), 32.5 (C-c), 30.6 (C-d), 23.1 (C-e);

$\nu_{max.}$ (neat) 2965, 2915, 2870, 2850, 1790, 1727, 1697, 1645, 1437, 1390, 1360, 1332, 1272, 1240, 1162, 1130, 1040, 940, 912, 797, 700, 667, 635cm^{-1}.

Synthesis of N-(3-hydroxypropyl)-5-bromopentanamide [82]

3-Amino-1-propanol (0.84ml, 820mg, 11mmol) was added to a suspension of anhydrous disodium hydrogen orthophosphate (4.25g, 2.99 X 10^{-2}mol) in dry chloroform (55ml). Via a dropping funnel equipped with a calcium chloride drying tube, a solution of 5-bromopentanoyl chloride [81] (1.990g, 9.978 X 10^{-3}mol) in chloroform (10ml) was added dropwise at 0°C. The resulting mixture was stirred at room temperature for 45h.

The reaction mixture was washed with hydrochloric acid (2M, 3ml) and water (20ml X 4). After separation of the chloroform layer, the aqueous layer was extracted with ethyl acetate (30ml X 5). The combined organic extracts were dried, filtered and evaporated *in vacuo* to afford N-(3-hydroxypropyl)-5-bromopentanamide [82] (723mg, 30%) after column chromatography, eluent: ethyl acetate. [R_F (1:1 $CH_3CO_2C_2H_5$:CH_3COCH_3) 0.57]



[82]

δ_H (200MHz) 7.59 (1H, t, J 5.5Hz, H-1), 5.70 - 5.00 (2H, br s, 2 X H-2), 4.67 (1H, t, J 5.2Hz, H-1'), 3.70 - 3.44 (8H, m, 2 X H-3 and 2 X H-4), 3.37 (2H, t, J 6.3Hz, H-5), 3.25 (2H, q, J 6.0Hz, H-5'), 2.21 (4H, t, J 6.8Hz, 2 X H-6), 1.95 - 1.40 (12H, m, 2 X H-7, 2 X H-8 and 2 X H-9);

δ_C (50.32MHz) 173.2, 173.1 (2 X C-a, 2 X C-a'), 58.2 (2 X C-b), 43.9 (2 X C-c), 35.4 (2 X C-d), 34.5 (2 X C-e), 31.2, 31.1, 31.0 (2 X C-f, 2 X C-f', 2 X C-g), 22.3 (2 X C-h);

$\upsilon_{max.}$ (CHCl$_3$) 3550 - 3250, 3000, 2960, 2880, 1720, 1652, 1520, 1430, 1275, 1240, 1075cm^{-1}.

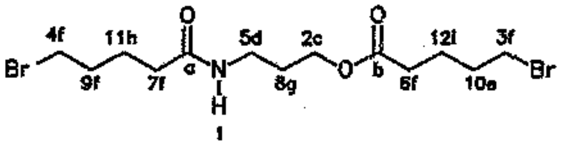
Synthesis of N,O-bis(4-bromobutanoyl)-3-amino-1-propanol [96]

To a solution of 5-bromopentanoic acid [80] (2.037g, 1.125 X 10^{-2}mol) in dry chloroform (15ml) was introduced dry dimethylformamide (7 drops) followed by thionyl chloride

(0.90ml, 1.5g, 1.2 X 10^{-2}mol). The resulting solution was heated under reflux for 147min.

Chloroform (10ml) was added to the reaction vessel followed by anhydrous disodium hydrogen orthophosphate (4.79g, 3.37 X 10^{-2}mol). At 0°C, a solution of 3-amino-1-propanol (0.95ml, 930mg, 12mmol) in dry chloroform (10ml) was dispensed dropwise via a dropping funnel. The mixture was stirred at room temperature for 64h.

The reaction mixture was washed with hydrochloric acid (2M, 30ml) and water (20ml X 4). The chloroform phase was dried, filtered and evaporated *in vacuo* to afford N,O-bis(4-bromobutanoyl)-3-amino-1-propanol [96] (803mg, 18% from [80]) as a yellow liquid after column chromatography, eluent: 2:3 hexane:ethyl acetate. [R_F ($CH_3CO_2C_2H_5$) 0.65 and R_F (1:1 $CH_3CO_2C_2H_5$:CH_3COCH_3) 0.76]



[96]

δ_H (200MHz) 7.02 (1H, br t, J 6.3Hz, H-1), 4.12 (2H, t, J 6.3Hz, H-2), 3.44 (4H, t, J 6.3Hz, H-3 and H-4), 3.30 (2H, q, J 6.3Hz, H-5), 2.36 (2H, t, J 7.0Hz, H-6), 2.26 (2H, t, J 7.1Hz, H-7), 2.19 - 1.62 (10H, m, H-8, H-9, H-10, H-11 and H-12);

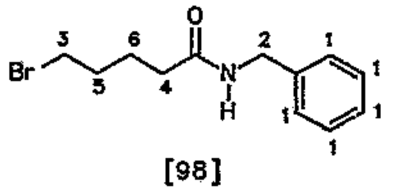
δ_C (50.32MHz) 172.6 (C-a), 172.5 (C-b), 61.5 (C-c), 35.7 (C-d), 34.7 (C-e), 33.0, 32.8, 32.6, 31.5 and 31.3 (5 X C-f), 28.1 (C-g), 23.7 (C-h), 22.9 (C-i).

Attempted synthesis of 1-(3-hydroxypropyl)-2-piperidinone [74]

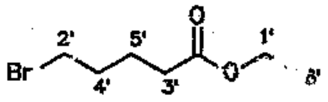
A solution of sodium ethoxide was prepared by adding sodium metal (42mg, 1.8mmol) to absolute ethanol (7ml). This was added to a solution of N-(3-hydroxypropyl)-5-bromopentanamide [82] (335mg, 1.41mmol) in absolute ethanol (9ml) and stirred at room temperature for 76h.
The ethanol solvent was removed *in vacuo* and replaced by ethyl acetate (40ml). This organic layer was washed with water (40ml X 3) and then dried, filtered and the solvent was removed *in vacuo* to afford a mixture (137mg) which contained δ-valerolactone [79], but no desired product [74].

Synthesis of N-benzyl-5-bromopentanamide [98]

An identical procedure as for the synthesis of N-(3-hydroxypropyl)-5-bromopentanamide [82] was followed, but using benzylamine instead of 3-amino-1-propanol. The workup procedure did not involve extraction of the separated aqueous layer with ethyl acetate. The reaction time was shortened from 45h to 2h. N-Benzyl-5-bromopentanamide [98] (25%) and ethyl 5-bromopentanoate [100] (66%) were obtained as yellow liquids. [R_F (1:1 $C_6H_{14}:CH_3CO_2C_2H_5$) 0.76 and 0.49, respectively] The calculated ratio of N-benzyl-5-bromopentanamide:ethyl 5-bromo-pentanoate from nmr data was 5:13, respectively.



[98]



[100]

δ_H (60MHz) 7.40 - 7.06 (5H, m, 5 X H-1), 4.38 (2H, d, J 5.1Hz, H-2), 4.10 (2H, q, J 7.3Hz, H-1′), 3.68 - 3.22 (4H, m, H-2′ and H-3), 2.50 - 2.04 (4H, m, H-3′ and H-4), 2.04 - 1.57 (8H, m, H-4′, H-5′, H-5 and H-6), 1.23 (3H, t, J 7.3Hz, H-6′);

$\nu_{max.}$ ($CHCl_3$) 3435, 3010 - 2860, 1720, 1660, 1505, 1450, 1367, 1250, 1230, 1020cm^{-1}.

Synthesis of 1-allyl-2-piperidinone [73]

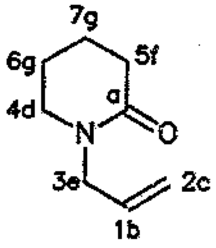
1. Using potassium

1-Allyl-2-piperidinone [73] was prepared in 44% yield by treating the potassium salt of 2-piperidinone [72] (formed from the lactam and potassium metal in refluxing toluene) with allyl bromide according to the procedure used by Orlek.[21] A slight modification of the workup procedure entailed the addition of water (100ml) to the suspension to dissolve the potassium bromide salt. The two phases were separated and the aqueous phase was extracted with diethyl ethyl (50ml X 4). The combined organic extracts were dried, filtered and evaporated *in vacuo*.

2. Using sodium hydride[92]

Sodium hydride (60% suspension in oil, 5.6g, 0.14mol) was introduced to a 250ml two-necked round-bottomed flask equipped with a pressure-equalising dropping funnel with a nitrogen inlet and a calcium chloride drying tube. Dry THF (125ml) was added to the reaction vessel and the calcium chloride drying tube was replaced by a rubber septum. 2-Piperidinone [72] (8.537g, 8.611 X 10^{-2}mol) in THF (5ml) was added to the reaction mixture at 0°C using a syringe.

The mixture was allowed to reach room temperature. A solid slush formed which was difficult to stir. Stirring was, however, continued for 3h after which 3-bromopropene (10.37ml, 14.50g, 1.198 X 10^{-1}mol) was added dropwise at 0°C via the pressure-equalising dropping funnel. The reaction mixture was allowed to attain room temperature. The dropping funnel was substituted for a water-cooled double-surface condenser equipped with a nitrogen inlet. The reaction mixture was heated under reflux for 16.5h.
A mixture of water (25ml), ice, ammonium chloride (0.55g) and hydrochloric acid (enough to make the mixture acidic) was added to the reaction mixture. Extraction with ethyl acetate (75ml X 3) followed. The combined organic layers were dried, filtered and the solvent was removed *in vacuo*. Purification by two successive vacuum distillations provided two fractions collected at 130 - 140°C and 136 - 160°C (at 1mm Hg). TLC of these two fractions revealed the presence of impurities and therefore further purification by means of column chromatography was executed, eluent: 2:1 ethyl acetate:hexane, to afford 1-allyl-2-piperidinone [73] (642mg, 5%) as a pale yellow liquid. [R_F (2:1 $CH_3CO_2C_2H_5$: C_6H_{14}) 0.27]



[73]

δ_H (200MHz) 6.02 - 5.70 (1H, m, H-1), 5.43 - 5.02 (2H, m, H-2), 4.22 - 3.88 (2H, m, H-3), 3.40 - 3.24 (2H, m, H-4), 2.53 - 2.30 (2H, m, H-5), 1.93 - 1.70 (4H, m, H-6 and H-7);

δ_C (50.32MHz) 168.3 (C-a), 132.0 (C-b), 116.0 (C-c), 48.3 (C-d), 46.3 (C-e), 31.4 (C-f), 22.2 and 20.5 (2 X C-g);

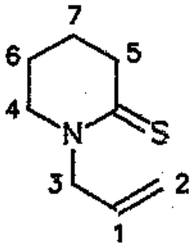
$\upsilon_{max.}$ ($CHCl_3$) 3075, 2975, 2945, 2865, 1625, 1495, 1465, 1447, 1415, 1357, 1330, 1285, 1267, 1175, 1165, 995, 985, 950, 925cm^{-1}.

Synthesis of 1-allylpiperidine-2-thione [75]

1. With phosphorus pentasulphide

1-Allylpiperidine-2-thione was prepared by modifying the procedure of Orlek.[21] Phosphorus pentasulphide (290mg, 1.3mmol) was added over a 5min period to 1-allyl-2-piperidinone [73] (463mg, 3.32mmol) in refluxing benzene (10ml). The reaction mixture was heated under reflux for a further 7h, during which time two more additions of phosphorus pentasulphide [(300mg, 1.4mmol) X 2] were made.

The solvent was removed *in vacuo*. Water (20ml) was added to the remaining residue and basified with potassium carbonate (pH *ca.* 8). The suspension was agitated in an ultrasound bath, and the pH level was maintained by further additions of potassium carbonate, until complete dissolution resulted. The solution was extracted with chloroform (20ml X 3). The combined organic extracts were dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to afford 1-allylpiperidine-2-thione [75] (27mg, 6%) as a yellow liquid after column chromatography, eluent: 9:1 hexane:ethyl acetate. [R_F (9:1 C_6H_{14}:$CH_3CO_2C_2H_5$) 0.22]



[75]

δ_H (200MHz) 5.96 - 5.70 (1H, m, H-1), 5.28 - 5.08 (2H, m, H-2), 4.59 (2H, dt, J 6.0Hz and 1.3Hz, H-3), 3.34 (2H, t, J 6.1Hz, H-4), 2.96 (2H, t, J 6.4Hz, H-5), 1.95 - 1.57 (4H, m, H-6 and H-7).

2. With Lawesson's reagent[93]

A solution of 1-allyl-2-piperidinone [73] (721mg, 5.18mmol) in dry THF (2.5ml) was treated with Lawesson's reagent (1.05g, 2.60 X 10^{-3}mol). The reaction mixture was agitated in an ultrasound bath for 25.5h.

The solvent was removed *in vacuo* to afford a crude product (1.904g). Two successive purification attempts using column chromatography, eluent: 19:1 to 17:3 hexane:ethyl acetate, afforded 1-allylpiperidine-2-thione [75] [R_F (2:1 $CH_3CO_2C_2H_5$:C_6H_{14}) 0.93] together with a more polar impurity [R_F (2:1) $CH_3CO_2C_2H_5$:C_6H_{14}) 0.85].

Attempted synthesis of 1-(3-hydroxypropyl)-2-pyrrolidinone [95]

A general reaction procedure is given and the table which follows provides specific reaction details (Table 10).

A sample of 1-allyl-2-pyrrolidinone [101] was kindly donated by Tomlinson.[92] A solution of 1-allyl-2-pyrrolidinone in dry THF (3 - 4ml) was treated with a hydroborating agent (dropwise addition) at 0°C. The resulting solution was stirred at 0°C and then at room temperature.

One of two workup procedures was used:

a. <u>Using sodium perborate</u>[118,119]

Water (3 - 4ml) was added, followed by sodium perborate at 0°C.

b. <u>Using basic peroxide</u>

A solution of hydrogen peroxide, potassium hydroxide pellets, methanol and water was added at 0°C.

The resulting solution was stirred at room temperature. Water (10ml) was added, followed by diethyl ether (15ml). The two layers were separated and the aqueous layer was extracted with diethyl ether (15ml X 3). The combined organic extracts were washed with saturated sodium chloride solution (20ml), dried, filtered and evaporated *in vacuo*. In case of experiments 7 and 8, extractions were carried out using ethyl acetate as the organic phase while experiment 9 utilised dichloromethane.

Table 10: Reaction details for the attempted hydroboration of [101]

			R.T./min		Workup conditions	
Exp. no.	[101] (mg, mmol)	hydroborating agent (ml, mol)	at 0°C	at 25°C	S.P. (mg, mmol)	H.T. /min
1	(177, 1.41)	0.5M 9-BBN in C_6H_{14} (3.36, 1.68 X 10^{-3})	140	70	(776, 5,04)	120
2	(139, 1.11)	0.5M 9-BBN in C_6H_{14} (3.32, 1.66 X 10^{-3})	480	855	(770, 5.0)	120
3	(135, 1.08)	0.4M 9-BBN in THF (4.5, 1.6 X 10^{-3})	120	900	(770, 5.0)	120
4	(125, 0.998)	0.6M 9-BBN in THF (3.6, 2.0 X 10^{-3})	135	930	(920, 6.0)	120
5	(125, 0.998)	1M BH_3 in THF (0.5, 0.5 X 10^{-3})	120	960	(230, 1.5)	220

Table 10 cont.: Reaction details for the attempted hydroboration of [101]

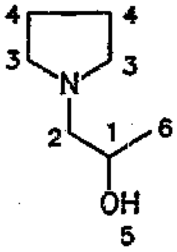
			R.T./min		Workup conditions		
Exp. no.	[101] (mg, mmol)	hydroborating agent (ml, mol)	at 0°C	at 25°C	S.P. (mg, mmol)	H_2O_2 (ml), KOH (mg), MeOH (ml), H_2O (ml)	H.T. /min
6	(131, 1.05)	1M BH_3 in THF (1, 1×10^{-3})	30	1440	discontinued on account of TLC		
7	(128, 1.02)	$BH_3.SMe_2$ (0.1, 1×10^{-3})	120	1140	-	(0.31),(60), (3), (5)	210
8	(253, 2.02)	$BH_3.SMe_2$ (0.19, 2.0×10^{-3})	180	1170	(930, 6.0)	-	1165
9	(40, 0.32)	$BH_3.SMe_2$ (0.03, 3×10^{-4})	*	*	-	(0.099), (20), (1), (1)	120

Key: R.T. = Reaction time S.P. = Sodium perborate H.T. = Hydrolysis time

* Experiment 9 was conducted at -27.5°C, stirred for 320min and quenched at this temperature.

Purification of reaction "products" obtained from experiments 1 → 6 was not feasible since ^{1}H nmr data and thin layer chromatography revealed that the alcohol product had not been obtained.

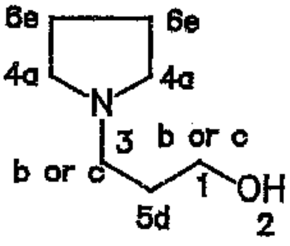
The material obtained from experiments 7 and 8 was combined and purification by column chromatography, eluent: 3:1 hexane:ethyl acetate and 3:2 hexane:ethyl acetate, afforded 1-(2-hydroxypropyl)pyrrolidine [104] (5mg, 1%) and 1-(3-hydroxypropyl)pyrrolidine [103] (50mg, 13%) as colourless liquids, respectively. [Former R_F ($CH_3CO_2C_2H_5$) 0.80 and latter R_F ($CH_3CO_2C_2H_5$) 0.60]



[104]

δ_H (200MHz) 4.51 - 4.32 (1H, m, H-1), 3.38 - 3.22 (2H, m, H-2), 2.97 - 2.60 (4H, m, 2 X H-3), 2.32 - 1.77 (5H, m, 2 X H-4 and H-5), 1.20 (3H, d, J 6.5Hz, H-6);

$\upsilon_{max.}$ ($CHCl_3$) 3575 - 3375, 2975, 2925, 2375 - 2325, 2275, 1620, 1440, 1392, 1310, 1145, 1020, 940, 855cm^{-1}.



[103]

δ_H (200MHz) 3.68 (2H, t, J 6.0Hz, H-1), 3.40 - 3.07 (3H, m, H-2 and H-3), 2.97 - 2.64 (4H, m, 2 X H-4), 2.30 - 1.80 (6H, m, H-5 and 2 X H-6);

δ_C (50.32MHz) 61.3 (2 X C-a), 60.9 (C-b), 60.3 (C-c), 28.2 (C-d), 22.6 (2 X C-e);

$\upsilon_{max.}$ ($CHCl_3$) 3610, 2990, 2955, 2880, 2380, 2260, 1445, 1385, 1315, 1295, 1155, 1040, 860cm^{-1}.

Purification of the mixture produced in experiment 9 by column chromatography, eluent: 4:1 hexane:ethyl acetate, afforded starting material (8mg, 21%). [R_F ($CH_3CO_2C_2H_5$) 0.40]

Attempted synthesis of 3-(2-thioxo-1-piperidinyl)propanal [105]

a) A stirred solution of piperidine-2-thione [67] (201mg, 1.74mmol) in dry THF (7ml) was treated with propenal (0.13ml, 110mg, 1.9mmol). The resulting solution was stirred at room temperature for 4h. A minute sodium hydroxide pellet was added and stirring was continued for 66h.
Removal of propenal and solvent *in vacuo* afforded starting material in quantitative yield. [R_F (2:1 C_6H_{14}:CH_3COCH_3) 0.53]

b) A stirred solution of piperidine-2-thione [67] (163mg, 1.42mmol) in dry THF (7ml) was treated with propenal (0.38ml, 320mg, 5.7mmol). The resulting solution was heated under reflux for 6.5h. TLC showed that unconverted starting material and a mixture of four side products had been obtained.

Attempted synthesis of 1-(3-hydroxypropyl)piperidine-2-thione [76] and 1-(3-hydroxypropyl)-2-piperidinone [74]

These reductions were attempted according to the method of Yoo *et al.*[94] A general reaction procedure is given and the table which follows provides specific reaction details (Table 11).

An aqueous cupric sulphate solution (2M) was added at room temperature to a solution of the thiolactam ([83] or [84]) or lactam ([91]) in ethanol (96%, 5ml). Some cupric sulphate precipitated. The mixture was cooled to 0°C after which sodium borohydride was added portionwise. The reaction mixture was stirred at room temperature and then diluted with ethyl acetate (*ca.* 25ml). The ethyl acetate layer was washed with water (10ml X 4), dried, filtered and concentrated.

Table 11: Reaction details for the attempted reduction of [83], [84] and [91]

Exp.no.	$CuSO_{4(aq)}$ (ml)	Reactant (mg, mmol)	$NaBH_4$ (mg,mmol)	Reaction time/min	Outcome: S.M.(mg,%)
1	(0.069)	[83] (248, 1.15)	(218, 5.77)	20	[83] (35, 14)*
2	(0.0051)	[84] (209, 0.857)	(163, 4.31)	180	[84] (158, 76)
3	(0.026)	[91] (95, 0.48)	(81, 2.1)	20	[91] (24, 25)*

Key: S.M. = starting material
* = starting material was recovered after column chromatography

Attempted synthesis of 1-(3-hydroxypropyl)-2-piperidinone [74]

1. Using lithium aluminum hydride

a) Lithium aluminum hydride (18mg, 0.47mmol) was added to a solution of 1-(2-ethoxycarbonylethyl)-2-piperidinone [91] (203mg, 1.02mmol) in dry THF (10ml) at 0°C. The reaction mixture was stirred at this temperature for 3.5h, after which it was quenched by the sequential addition of water (0.020ml), sodium hydroxide (15% (w/w), 0.020ml) and water (0.053ml).
The reaction mixture was filtered with suction through celite using dichloromethane. The two phases were separated and the aqueous layer was extracted with dichloromethane (2ml X 3). The combined organic extracts were dried, filtered and evaporated *in vacuo* to afford starting material (181mg, 89%).

b) When the reaction was repeated under reflux, starting material (81%) was recovered.

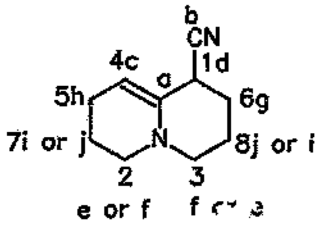
2. Using lithium borohydride

A suspension of lithium borohydride (13mg, 0.61mmol) in dry diethyl ether (8ml) was added to a stirred solution of 1-(2-ethoxycarbonylethyl)-2-piperidinone [91] (253mg, 1.27mmol) in dry diethyl ether (7ml) at room temperature. The reaction mixture was stirred at room temperature for 71.5h and then heated under reflux for 26h.
The reaction was discontinued because only unreacted starting material was present (TLC).

5.3 Experimental work relating to Chapter 3

Synthesis of 1-azabicyclo[4.4.0]dec-6-ene-5-carbonitrile [118]

A solution of 1-(3-hydroxypropyl)-2-cyanomethylenepiperidine [68] (116mg, 0.646mmol) in dry THF (15ml) was treated with sodium hydride (50% suspension in oil, 39mg, 0.81mmol) and stirred at room temperature for 3h. The reaction mixture was cooled to 0°C and *p*-toluenesulphonyl chloride (149mg, 0.780mmol) was added. The reaction mixture was allowed to warm up to room temperature and was stirred for 6h. A further three additions of 20% excess sodium hydride and 20% excess *p*-toluenesulphonyl chloride were made at regular intervals during the next 8d. THF was removed *in vacuo* and was replaced by dry acetonitrile (25ml). The reaction mixture was alternately heated under reflux (5d) and stirred at room temperature (2d) during which time sodium iodide (50mg, 0.33mmol) was added.
The solvent was removed *in vacuo*. The remaining orange-brown solid was dissolved in dichloromethane (50ml) and washed with water (20ml). The two phases were separated and the aqueous layer was extracted with dichloromethane (30ml X 3). The combined organic extracts were dried, filtered and the solvent removed *in vacuo* to afford a product tentatively identified as 1-azabicyclo[4.4.0]dec-6-ene-5-carbonitrile [118] (61mg, 58%) as a brown oil after column chromatography, eluent: 9:1 hexane:ethyl acetate. [R_F (1:1 C_6H_{14}:$CH_3CO_2C_2H_5$) 0.61]



[118]

δ_H (200MHz) 5.13 (1H, td, J 2.9Hz and 1.[illegible]Hz, H-1), 3.29 - 2.90 (4H, m, H-2 and H-3), 2.51 - 2.08 (5H, m, H-4, H-5 and H-6), 2.08 - 1.67 (4H, m, H-7 and H-8);

δ_C (50.32MHz) 153.7 (C-a), 121.2 (C-b), 76.6 (C-c), 53.4 (C-d), 50.2 (C-e), 49.9 (C-f), 29.5 (C-g), 23.7 (C-h), 20.0 (C-i), 17.7 (C-j);

$\upsilon_{max.}$ ($CHCl_3$) 2950, 2930, 2835, 2170, 1595, 1485, 1440, 1370, 1357, 1320, 1180, 1155, 1130, 1070, 980, 885, 640cm^{-1}.

Attempted synthesis of 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69]

n-Butyllithium in hexane (0.054ml, 38mg, 0.59mmol) was introduced to a solution of 1-(3-hydroxypropyl)-2-cyanomethylenepiperidine [66] (107mg, 0.591mmol) in dry THF (10ml) at 0°C. After 30min, the reaction was cooled to -46°C after which trifluoroacetic anhydride (0.090ml, 140mg, 0.65mmol) was added. The reaction contents were allowed to warm up to room temperature, after which they were stirred for 36h. THF was removed *in vacuo* and was replaced by dry acetonitrile (20ml). The reaction mixture was heated under reflux for 6h and then stirred at room temperature overnight.

The solvent was removed *in vacuo*. The remaining yellow-orange oil was dissolved in dichloromethane (40ml) and washed with water (20ml). The two layers were separated and the aqueous phase was extracted with dichloromethane (25ml X 3). The combined organic extracts were dried, filtered and the solvent was removed *in vacuo* to yield a yellow liquid (113mg). No product at all was recovered after column chromatography with hexane-ethyl acetate mixtures.

Synthesis of 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69]

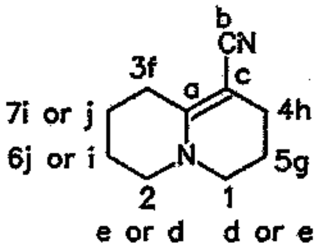
1. With *p*-toluenesulphonyl chloride[21]

The cyclisation procedure utilising the optimum parameters (experiment 10, Table 5) is represented:

A solution of 1-(3-hydroxypropyl)-2-cyanomethylene-piperidine [68] (1.793g, 9.943 X 10^{-3}mol) in dry THF (150ml) was treated with sodium hydride (50% suspension in oil, 956mg, 19.9mmol). The resulting reaction mixture was stirred at room temperature for 72min after which it was cooled to 0°C. An addition of *p*-toluenesulphonyl chloride (3.797g, 1.991 X 10^{-2}mol) followed. The reaction mixture was alternately heated under reflux and stirred at room temperature for a total of 40h and 11d, respectively. THF was removed *in vacuo* and was replaced by dry acetonitrile (150ml). The mixture was heated under reflux for 14h and then stirred at room temperature overnight.

The solvent was removed *in vacuo*. The remaining orange-brown residue was dissolved in dichloromethane (70ml) and washed with water (40ml). The two phases were separated and the aqueous layer was extracted with dichloromethane (40ml X 4). The combined organic extracts were dried, filtered and the solvent was removed *in vacuo* to afford 1-

azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] (1.135g, 70%) as a yellow liquid after column chromatography, eluent: 47:3 to 23:2 hexane:ethyl acetate. [R_F (1:1 C_6H_{14}:$CH_3CO_2C_2H_5$) 0.67]



[69]

δ_H (200MHz) 3.14 - 3.00 (4H, m, H-1 and H-2), 2.52 (2H, t, J 6.3Hz, H-3), 2.20 (2H, t, J 6.2Hz, H-4), 1.89 - 1.71 (4H, m, H-5 and H-6), 1.71 - 1.55 (2H, m, H-7);

δ_C (50.32MHz) 153.9 (C-a), 122.4 (C-b), 69.3 (C-c), 49.6 (C-d), 48.8 (C-e), 27.3 (C-f), 22.73 (C-g), 22.67 (C-h), 19.80 (C-i), 19.76 (C-j);

$\nu_{max.}$ ($CHCl_3$) 2975, 2930, 2845, 2155, 1580, 1485, 1445, 1422, 1360, 1350, 1315, 1255, 1170, 1140, 1110, 1025, 1012, 965, 880, 600cm^{-1};

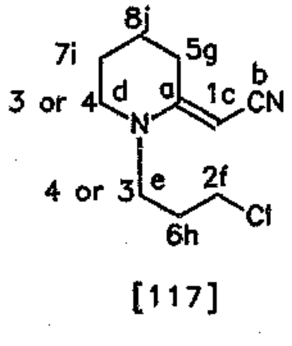
m/z 162 (M^+, 70%), 161 (M^+-1, 100%), 133 (22%), 122 (24%), 106 (10%), 79 (10%), 55 (13%), 41 (16%), 39 (11%), 28 (16%), 27 (11%);

HRMS (Found: M^+ 162.1044. $C_{10}H_{14}N_2$ requires M^+, 162.1157).

2. Alternative reaction with *p*-toluenesulphonyl chloride and formation of 1-(3-chloropropyl)-2-cyanomethylenepiperidine [117]

A solution of 1-(3-hydroxypropyl)-2-cyanomethylenepiperidine [68] (118mg, 0.656mmol) in dry THF (10ml) was treated with sodium hydride (50% suspension in oil, 48mg, 1.0mmol) and was stirred at room temperature for 4h. The reaction mixture was cooled to 0°C and *p*-toluenesulphonyl chloride (176mg, 0.923mmol) was added. The reaction mixture was alternately heated under reflux (33.5h) and stirred at room temperature (108h), during which time a further two additions of 40% excess sodium hydride and 40% excess *p*-toluenesulphonyl chloride were made.

The solvent was removed *in vacuo*. The remaining orange-brown solid was dissolved in chilled dichloromethane (60ml) and was washed with a chilled hydrochloric acid solution (5%, 45ml). The two phases were separated and the aqueous phase was extracted with dichloromethane (40ml X 3). The combined organic extracts were dried, filtered and the solvent was removed *in vacuo* to afford 1-(3-chloropropyl)-2-cyanomethylenepiperidine [117] (5mg, 4%) as a colourless liquid and 1-azabicyclo[4.4 0]dec-5-ene-5-carbonitrile [69] (3mg, 3%) as a yellow liquid after column chromatography, eluent: 91:1 hexane:ethyl acetate. [Former R_F (1:1 C_6H_{14}:$CH_3CO_2C_2H_5$) 0.58 and latter R_F (1:1 C_6H_{14}:$CH_3CO_2C_2H_5$) 0.67]



[117]

δ_H (200MHz) 3.79 (1H, s, H-1), 3.57 (2H, t, J 6.0Hz, H-2), 3.28 (2H, t, J 7.2Hz, H-3), 3.22 (2H, t, J 6.0Hz, H-4), 2.68 (2H, t, J 6.5Hz, H-5), 2.12 - 1.94 (2H, m, H-6), 1.89 - 1.55 (4H, m, H-7 and H-8);

δ_C (50.32MHz) 161.4 (C-a), 122.3 (C-b), 59.3 (C-c), 50.0 (C-d), 48.9 (C-e), 42.3 (C-f), 28.1 (C-g), 27.7 (C-h), 23.4 (C-i), 19.5 (C-j);

m/z 198 (M^+, 11%), 163 (M^+-35, 100%), 149 (M^+-49, 10%), 136 (20%), 135 (M^+-63, 28%), 122 (28%), 121 (M^+-77, 11%), 94 (9%), 67 (11%), 54 (15%), 41 (46%), 32 (51%);

HRMS (Found: M^+ 198.0928. $C_{10}H_{15}N_2Cl$ requires M^+, 198.0924).

3. With methanesulphonyl chloride

When the synthesis of 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] was repeated under the conditions described in "1. With toluenesulphonyl chloride" but with methanesulphonyl chloride instead of toluenesulphonyl chloride, a mixture of 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] and 1-(3-chloropropyl)-2-cyano-methylenepiperidine [117] (2:1, by ^{1}H nmr) was obtained in a yield of about 39%.

The mixture was heated under reflux in acetonitrile with a catalytic amount of sodium iodide in an attempt to cyclise [117] to [69]. Again a mixture of [69] and [117] (*ca.* 5:1, by ^{1}H nmr) was obtained in a yield of about 35%.

Syntheses of *rel*-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile [20] and *rel*-5*R*,6*S*-1-azabicyclo[4.4.0]decane-5-carbonitrile [19]

1. Catalytic hydrogenations

a) Attempted hydrogenation over Wilkinson's catalyst[95]

Tris(triphenylphosphine)chlororhodium(I) (39mg) was added to a solution of 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] (192mg, 1.18mmol) in a benzene-ethanol mixture (1:1, 20ml). The reaction was carried out in an autoclave at a hydrogen pressure of 500kPa and a temperature of 60°C for 8h.

The reaction mixture was filtered with suction through a pad of celite using dichloromethane. The solvent was removed *in vacuo* to afford starting material in quantitative yield.

b) Attempted reduction with a nickel-aluminum alloy[96]

A stirred solution of 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] (85mg, 0.53mmol) in ethanol (96%, 2.13ml) was treated in sequence with nickel-aluminum alloy (130mg) and a sodium hydroxide solution (3M, 2.13ml). The heterogeneous solution was stirred at room temperature for 13.5h.

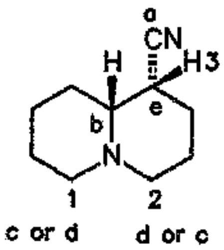
The reaction mixture was filtered with suction through a pad of celite using 96% ethanol. The solvent was removed *in vacuo*. The remaining yellow liquid was diluted with water (20ml), basified with 25% ammonia solution and extracted with dichloromethane (15ml X 4). The combined organic extracts were dried, filtered and the solvent removed *in vacuo* to afford starting material (68mg, 80%).

c) With Adams catalyst in acidic medium[20]

A suspension of platinum dioxide (42mg) in glacial acetic acid (15ml) was prehydrogenated. A time period of 99min elapsed until the hydrogen consumption of the catalyst had ceased. A solution of 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] (393mg, 2.42mmol) in glacial acetic acid (15ml) was added and the resulting heterogeneous solution was stirred at room temperature under a hydrogen atmosphere for 92h.

The reaction mixture was filtered with suction through a pad of celite using dichloromethane. The solvents were removed *in vacuo*. The remaining residue was diluted with water (30ml) and was basified with a sodium hydroxide solution (3M). The basic aqueous phase was extracted with dichloromethane (20ml X 4). The combined organic extracts were dried, filtered and the solvent removed *in vacuo*.

A gc analysis of the mixture showed a ratio of 47.25:1 of [20]:[19] (retention time: 6.25min and 5.41min, respectively). Column chromatography afforded *rel*-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile [20] (327mg, 82%) as a white solid and *rel*-5*R*,6*S*-1-azabicyclo[4.4.0]decane-5-carbonitrile [19] (25mg, 6%) as a pale yellow liquid, eluent: 93:7 hexane:acetone. [Former R_F (2:1 CH_3COCH_3:C_6H_{14}) 0.89 and latter R_F (2:1 CH_3COCH_3:C_6H_{14}) 0.55] Four recrystallisations (from 1:1 hexane:ethyl acetate) of *rel*-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile [20] afforded a white solid, m.p. 61°C. An overall yield of 88% was obtained.



[20]

δ_H (200MHz) 2.97 - 2.81 (2H, m, equatorial H-1 and equatorial H-2), 2.73 (1H, td, J 4.2Hz and 2.5~~Hz, H-3~~), 2.20 - 1.14 (13H, m, remaining H);

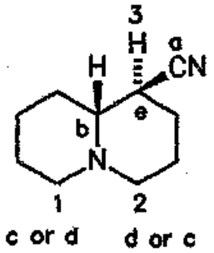
δ_C (50.32MHz) 120.5 (C-a) 62.0 (C-b), 56.3 (C-c), 55.9 (C-d), 34.3 (C-e), 31.4, 27.6, 25.2, 24.0 and 22.1 (remaining ring methylene C);

$\upsilon_{max.}$ ($CHCl_3$) 2945, 2860, 2810, 2760, 2680, 2230, 1585, 1462, 1440, 1395, 1370, 1360, 1347, 1330, 1320, 1305, 1280, 1265, 1180, 1140, 1120, 1110, 1080, 1060, 1020, 997, 985, 955, 890, 867, 850cm^{-1};

Found: C, 73.31; H, 10.07; N, 17.14. $C_{10}H_{16}N_2$ requires C, 73.13; H, 9.82; N, 17.06%;

m/z 164 (M^+, 17%), 111 (23%), 110 (16%), 97 (21%), 83 (100%), 55 (29%), 54 (9%), 41 (14%), 32 (16%), 28 (74%);

HRMS (Found: M^+ 164.1303. $C_{10}H_{16}N_2$ requires M^+, 164.1314).



[19]

δ_H (200MHz) 2.91 - 2.71 (2H, m, equatorial H-1 and equatorial H-2), 2.48 - 2.28 (1H, m, H-3), 2.25 - 1.13 (13H, m, remaining H);

δ_C (50.32MHz) 120.8 (C-a), 63.4 (C-b), 56.2 (C-c), 55.5 (C-d), 34.9 (C-e), 31.3, 28.8, 25.4, 24.2 and 24.0 (remaining ring methylene C);

$\upsilon_{max.}$ ($CHCl_3$) 2930, 2850, 2800, 2755, 2225, 1600, 1455, 1432, 1385, 1360, 1347, 1320, 1290, 1257, 1165, 1120, 1100, 1070, 1055, 1045, 1010, 940, 860, 835cm^{-1};

m/z 164 (M+, 72%), 163 (M^+-1, 17%), 111 (41%), 110 (16%), 97 (22%), 83 (100%), 55 (32%), 54 (10%), 41 (16%), 28 (12%);

HRMS (Found: M^+ 164.1311. $C_{10}H_{16}N_2$ requires M^+, 164.1314).

d) Attempted hydrogenations with Adams catalyst or 5% palladium on carbon in ethanol[97]

In both cases starting material was recovered in quantitative yield.

2. Hydride reductions

a) Attempted reduction with sodium borohydride[99]

A solution of 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] (130mg, 0.801mmol) in absolute ethanol (16ml) was treated with sodium borohydride (112mg, 2.96mmol). The resulting heterogeneous solution was stirred at room temperature for 51h.
Water (20ml) was added and the resulting mixture was neutralised by dropwise addition of a hydrochloric acid solution (20%). After stirring at room temperature for 30min, the reaction mixture was saturated with potassium carbonate and extracted with chloroform (25ml X 3). The combined organic extracts were dried, filtered and the solvent was removed *in vacuo* to afford starting material (119mg, 91%).

A solution of 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] (81mg, 0.50mmol) in ethanol (2ml) was added in portions over an 11min period to a cold (0°C) stirred slurry of sodium borohydride (19mg, 0.51mmol) in ethanol (1ml). The resulting reaction mixture was stirred at 0°C for 131min and then at room temperature for a further 21h. The reaction mixture was diluted with water (50ml) and the resulting cloudy solution was made basic by adding a sodium hydroxide solution (3M). Extraction of the aqueous phase with dichloromethane (15ml X 4) followed. The combined organic extracts were dried, filtered and the solvent removed *in vacuo*.

A gc analysis of the material obtained showed 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] to be the major component and the two reduced (saturated) isomers [20] and [19] (in a ratio of 1:1, respectively) to be minor components. Traces of impurities were also observed. Column chromatography afforded a mixture of 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] and *rel*-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile [20] (70mg), eluent: 47:3 hexane:acetone and *rel*-5*R*,6*S*-1-azabicyclo[4.4.0]decane-5-carbonitrile [19] (1mg, 1%), eluent: 91:9 hexane:acetone.

b) <u>Attempted reduction with lithium aluminum hydride</u>

Lithium aluminum hydride (21mg, 0.56mmol) was introduced portionwise to a stirred solution of 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] (77mg, 0.48mmol) in dry THF (50ml) at 0°C. The heterogeneous solution was stirred at 0°C for 1h after which it was allowed to attain room temperature and was then stirred for a further 36h.

A few drops of water were added to destroy any excess lithium aluminum hydride. The reaction mixture was dried, filtered with suction and the solvent was removed *in vacuo* to afford starting material (72mg, 93%).

c) Reduction with sodium cyanoborohydride[100]

1-Azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] (415mg, 2.56mmol) was dissolved in absolute ethanol (6.40ml) to make up a 0.4M solution. Sodium cyanoborohydride (178mg, 2.83mmol) was added, followed by bromocresol green (0.5% solution in ethanol, 1 drop). Concentrated hydrochloric acid was dispensed when necessary during the course of the reaction to ensure a permanent colour change to yellow (pH *ca.* 4). The reaction mixture was stirred at room temperature for 80min.

Water (36ml) was added to the reaction vessel and the contents were basified with a 25% ammonia solution. The basic aqueous phase was extracted with diethyl ether (45ml x 6). The combined ethereal extracts were dried, filtered and evaporated *in vacuo*.

A gc analysis of the mixture showed a ratio of 1.14:1 of [19]:[20]. Column chromatography afforded *rel*-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile [20] (179mg, 43%) and *rel*-5*R*,6*S*-1-azabicyclo[4.4.0]decane-5-carbonitrile [19] (227mg, 54%), eluent: 93:7 hexane:acetone. An overall yield of 97% was obtained. Characterisation was as previously described.

3. Attempted reduction by hydrogen transfer

a) With sodium hypophosphite[101]

A stirred solution of 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] (79mg, 0.49mmol) in dry THF (5ml) was treated with potassium carbonate (96mg, 0.69mmol) followed by the addition of 5% palladium on carbon (16mg). The resulting reaction mixture was heated to reflux temperature at which point a solution of sodium hypophosphite (77mg, 0.88mmol) in water (1ml) was added dropwise over a 5min period. Heating under reflux was continued for a further 45.5h. A second addition of potassium carbonate (95mg, 0.69mmol) followed by sodium hypophosphite (78mg, 0.89mmol) was made. The reaction mixture was heated under reflux for 48h and then allowed to cool down to room temperature. The solvent was removed *in vacuo*. The remaining residue was filtered with suction through a pad of celite using dichloromethane. The organic filtrate was washed with saturated sodium chloride solution (20ml). After separation of the two phases, the aqueous phase was extracted with dichloromethane (10ml X 4). The combined organic extracts were dried, filtered and the solvent was removed *in vacuo* to yield a mixture (70mg). A gc analysis indicated that a large percentage of starting material had been recovered, besides minor traces of *rel*-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile [20] and *rel*-5*R*,6*S*-1-azabicyclo[4.4.0]decane-5-carbonitrile [19] (in a ratio of 6.4:1, respectively) and impurities.

b) Alternative reaction with sodium hypophosphite[101]

A stirred solution of 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] (111mg, 0.684mmol) in glacial acetic acid (2ml) was treated with 10% palladium on carbon (9mg) followed sequentially by sodium acetate (156mg, 1.90mmol) and sodium hypophosphite (169mg, 1.92mmol). The resulting reaction mixture was heated to 56°C and stirred at this temperature for 4h and then stirred at 65°C for *ca.* 4d during which time a second addition of sodium acetate (155mg, 1.89mmol) and sodium hypophosphite (170mg, 1.95mmol) was made. The reaction mixture was allowed to cool down to room temperature and the solvent was removed *in vacuo*.

The remaining residue was filtered with suction through a pad of celite using dichloromethane. The organic filtrate was washed with water (20ml), the latter having been basified with a sodium hydroxide solution (3M). The two phases were separated and the basic aqueous layer was extracted with dichloromethane (10ml X 3). The combined organic extracts were dried, filtered and the solvent removed *in vacuo* to yield a mixture (65mg). A gc analysis indicated that a large percentage of starting material had been recovered besides minor traces of *rel*-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile [20] and *rel*-5*R*,6*S*-1-azabicyclo[4.4.0]decane-5-carbonitrile [19] and impurities.

c) With sodium formate[102]

Sodium formate was dried at 80°C under vacuum (1mm Hg) for 24h. To a 50ml two-necked round-bottomed flask, equipped with a water-cooled Liebig condenser and a quick-fit thermometer was introduced the following (sequentially): 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] (134mg, 0.823mmol), ethanol (7ml), water (2ml) and sodium formate (168mg, 2.48mmol). The reaction contents were stirred and heated to 70°C, after which 10% palladium on carbon (4mg) was added in one portion. The resulting heterogeneous solution was stirred at 70°C for 20h and then at 60°C for 48h.

The reaction mixture was allowed to cool down to room temperature and the solvent was removed *in vacuo*. The remaining residue was filtered with suction through a pad of celite using dichloromethane. The organic filtrate was washed with water (20ml) which had been basified with a sodium hydroxide solution (3M). The two phases were separated and the basic aqueous layer was extracted with dichloromethane (10ml X 3). The combined organic extracts were dried, filtered and the solvent removed *in vacuo* to yield a mixture (113mg). A gc analysis indicated that a large percentage of starting material had been recovered, besides minor traces of *rel*-5*R*,6*R*-1-azabicyclo-[4.4.0]decane-5-carbonitrile [20] and *rel*-5*R*,6*S*-1-azabicyclo[4.4.0]decane-5-carbonitrile [19] (in a ratio of 9.2:1, respectively) and impurities.

d) With formic acid[103]

1-Azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] (82mg, 0.51mmol) was heated under reflux in 98 - 100% formic acid (1.0ml, 1.2g, 2.6 X 10^{-2}mol) for 19.5h. The solution was allowed to cool to room temperature after which it was made strongly basic by addition of sodium hydroxide (10.5M, 5ml). Extraction using dichloromethane (10ml X 4) followed. The combined organic extracts were dried, filtered and the solvent removed *in vacuo* to afford a mixture (73mg). TLC showed the presence of starting material and traces of the reduced isomers, [20] and [19]. The mixture (73mg) was heated under reflux in 98 - 100% formic acid (2.0ml, 2.4g, 5.3 X 10^{-2}mol) for 120h. The same workup procedure as previously was followed to afford an unidentifiable mixture

Conversion of *rel*-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile [20] to *rel*-5*R*,6*S*-1-azabicyclo[4.4.0]decane-5-carbonitrile [19].

1. Successful epimerisation

Partial epimerisation of [20] to [19] was accomplished by following the procedure of Yamada *et al.*[19] with a few modifications.

Rel-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile [20] (86mg, 0.53mmol) and sodium hydride (50% suspension in oil, 17mg, 0.35mmol) were heated under reflux in benzene (2ml) for 6d. A second addition of sodium hydride (50% suspension in oil, 17mg, 0.35mmol) was made, after which heating under reflux was continued for a further 6h. Water (10ml) was added to the cooled reaction mixture and after separation of the two layers, the aqueous phase was extracted with dichloromethane (10ml X 3). The combined organic phases were dried, filtered and the solvent removed *in vacuo*.
A gc analysis of the mixture showed a ratio of 1.89:1 of [19]:[20]. Column chromatography afforded *rel*-5*R*,6*S*-1-azabicyclo[4.4.0]decane-5-carbonitrile [19] (47mg, 55%) and recovered *rel*-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile [20] (25mg, 29%).

2. Attempted thermal epimerisation[38]

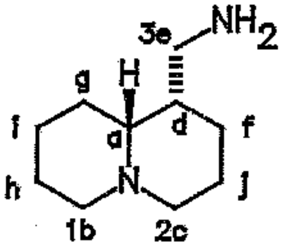
A sample of *rel*-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile [20] (90mg, 0.55mmol) was heated in a Kugelrohr oven at 149°C for 36min and then at 164°C for 160min. Column chromatography afforded 1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69] (5mg, 5%) and recovered *rel*-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile [20] (46mg, 52%), eluent: 93:7 hexane:acetone. No *rel*-5*R*,6*S*-1-azabicyclo-[4.4.0]decane-5-carbonitrile [19] was obtained.

Synthesis of lupinamine [11]

1. With a nickel-aluminum alloy[96]

A solution of *rel*-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile [20] (327mg, 1.99mmol) in ethanol (96%, 8.2ml) was treated in sequence with a nickel-aluminum alloy (492mg) and a sodium hydroxide solution (3M, 8.2ml). Hydrogen gas was expelled on addition of the basic solution. The heterogeneous solution was stirred at room temperature for 9¼h.

The reaction mixture was filtered with suction through a pad of celite using dichloromethane. The solvents, ethanol and dichloromethane, were removed *in vacuo*. The remaining residue was diluted with water (20ml) and basified with a 25% ammonia solution. Extraction using dichloromethane (20ml X 4) followed. The combined organic extracts were dried, filtered and evaporated *in vacuo* to afford lupinamine [11] (333mg, 99%) as a pale yellow liquid. [R_F (9:1 CH_3OH:25% NH_3 solution) 0.50] The product was clean (by TLC and nmr) and so purification was unnecessary.



[11]

δ_H (200MHz) 3.01 - 2.62 (4H, m, equatorial H-1, equatorial H-2 and H-3), 2.13 - 1.06 (16H, m, remaining H);

δ_C (50.32MHz) 64.8 (C-a), 57.2 (C-b), 56.4 (C-c), 41.5 (C-d), 39.4 (C-e), 29.0 (C-f), 26.4 (C-g), 25.1 (C-h), 24.8 (C-i), 20.9 (C-j);

$\nu_{max.}$ ($CHCl_3$) 3520 - 3170, 2930, 2860, 2800, 2760, 2670, 2495, 1647, 1595, 1455, 1435, 1385, 1365, 1352, 1345, 1327, 1297, 1280, 1265, 1170, 1112, 1092, 1080, 1055, 1047, 867, 725, 682, 645cm^{-1}.

2. With lithium aluminum hydride

This reduction was carried out according to the procedure described by Yamada *et al.*[19] A solution of *rel*-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile [20] (95mg, 0.58mmol) in dry diethyl ether (*ca.* 4ml) was added dropwise over a 10min period to a stirred suspension of lithium aluminum hydride (34mg, 0.89mmol) in dry diethyl ether (*ca.* 2ml) at 0°C. The resulting mixture was stirred at 0°C for 37min and then at room temperature for a further 91min. Water (11ml) was added to destroy excess lithium aluminum hydride. After separation of the two layers, the aqueous layer was extracted with diethyl ether (10ml X 4). The combined ethereal extracts were dried, filtered and the solvent was removed *in vacuo*. TLC (2:1 CH_3COCH_3:C_6H_{14}) showed the presence of a baseline spot indicative of lupinamine [11] and traces of minor impurities.

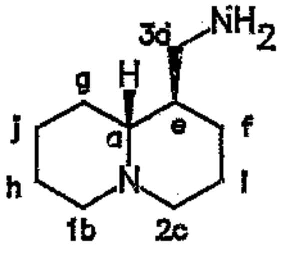
3. Unsuccessful attempts

Employment of lithium aluminum hydride with aluminum chloride[114] for the reduction of *rel*-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile [20] provided unreacted starting material and possibly a trace of lupinamine [11]. An attempted reduction utilising sodium borohydride with a cobalt coreagent[115] afforded starting material (93%).

Synthesis of epilupinamine [112]

A solution of *rel*-5*R*,6*S*-1-azabicyclo[4.4.0]decane-5-carbonitrile [19] (228mg, 1.39mmol) in ethanol (96%, 5.7ml) was treated in sequence with a nickel-aluminum alloy (344mg) and a sodium hydroxide solution (3M, 5.7ml) as described for the reduction of *rel*-5*R*,6*R*-1-azabicyclo-[4.4.0]decane-5-carbonitrile [20]. Epilupinamine [112]

(196mg, 84%) was obtained as a pale yellow liquid. [R_F (9:1 CH_3OH:25% NH_3 solution) 0.66] The product was clean (by TLC and nmr) and so purification was unnecessary.



[112]

δ_H (200MHz) 3.01 - 2.44 (4H, m, equatorial H-1, equatorial H-2 and H-3), 2.20 - 0.75 (16H, m, remaining H);

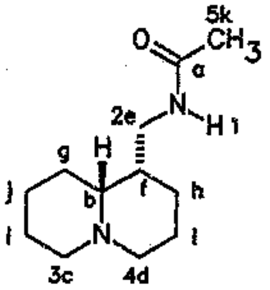
δ_C (50.32MHz) 64.9 (C-a), 56.6 (C-b), 56.4 (C-c), 43.6 (C-d), 43.4 (C-e), 29.3 (C-f), 28.2 (C-g), 25.2 (C-h), 24.7 (C-i), 24.3 (C-j);

$\upsilon_{max.}$ ($CHCl_3$) 3500 - 3200, 2930, 2860, 2805, 2760, 2680, 2495, 1655, 1600, 1580, 1460, 1437, 1390, 1352, 1340, 1310, 1290, 1270, 1250, 1180, 1120, 1110, 1075, 1050, 1015, 965, 855, 815, 770, 650, 605cm^{-1}.

Synthesis of N-acetyllupinamine [113]

This derivative was prepared by following the procedure described by Wanner *et al.*[117] with a few modifications.
Lupinamine [11] (203mg, 1.21mmol) was heated under reflux in acetic anhydride (10ml) for 5h.
The solvent was removed *in vacuo* and the remaining residue dissolved in an ammonia solution (1M, 30ml) and thereafter extracted with dichloromethane (30ml X 4). The combined organic extracts were dried, filtered and the solvent was removed *in vacuo*. Purification by flash column

chromatography using an eluting system of 15% methanol in dichloromethane saturated with concentrated ammonia as suggested by Wanner *et al.*, did not provide optimal separation of the two compounds shown to be present by TLC. The reaction mixture was purified again by flash chromatography, eluent: 19:180:1 methanol:dichloromethane: 25% ammonia solution, to afford N-acetyllupinamine [113] (151mg, 60%) as a white solid and N,N-bis(acetyl)lupinamine [127] (120mg, 39%) as a brown solid, m.p. 39 - 41°C. [Former R_F (9:1 CH_3OH:25% NH_3 solution) 0.57 and latter R_F (9:1 CH_3OH:25% NH_3 solution) 0.71] Four recrystallisations (from methanol) of N-acetyllupinamine afforded a white solid, m.p. 122.5 - 125°C.



[113]

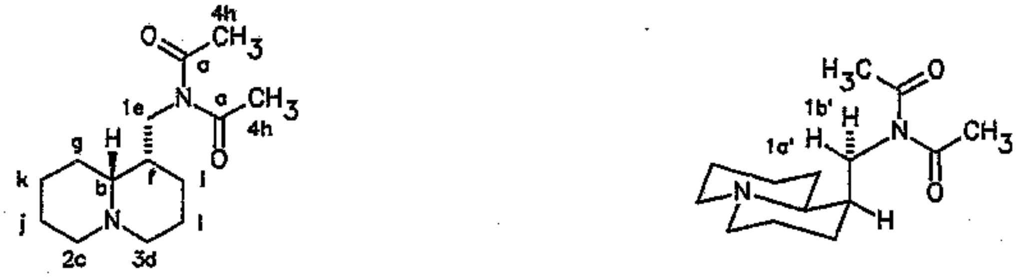
δ_H (200MHz) 7.87 - 7.60 (1H, br s, H-1), 3.60 - 3.24 (2H, m, H-2), 3.00 - 2.77 (2H, m, equatorial H-3 and equatorial H-4), 1.97 (3H, s, H-5), 2.29 - 1.06 (14H, m, remaining H);

δ_C (50.32MHz) 169.8 (C-a), 64.1 (C-b), 56.7 (C-c), 55.8 (C-d), 39.7 (C-e), 36.3 (C-f), 29.3 (C-g), 28.1 (C-h), 24.7 (C-i), 24.3 (C-j), 22.9 (C-k), 21.2 (C-l);

$\upsilon_{max.}$ ($CHCl_3$) 3452, 3224, 3004, 2944, 2864, 2812, 2770, 2684, 2474, 1659, 1526, 1448, 1373, 1352, 1290, 1276, 1214, 1183, 1158, 1129, 1110, 1071, 1058, 870cm^{-1};

m/z 210 (M^+, 8%), 152 (M^+-58, 35%), 138 (M^+-72, 100%), 111 (37%), 110 (39%), 97 (27%), 96 (26%), 83 (95%), 55 (32%), 41 (27%), 32 (27%), 28 (100%);

HRMS (Found: M^+ 210.1733. $C_{12}H_{22}N_2O$ requires M^+, 210.1732).



[127]

δ_H (200MHz) 4.14 (1H, dd, J 14.5Hz and 10.8Hz, H-1a′), 3.73 (1H, dd, J 14.5Hz and 3.3Hz, H-1b′), 3.00 - 2.76 (2H, m, equatorial H-2 and equatorial H-3), 2.41 (6H, s, 2 X H-4), 2.20 - 1.70 (14H, m, remaining H);

δ_C (50.32MHz) 173.5 (2 X C-a), 64.5 (C-b), 57.1 (C-c), 56.3 (C-d), 42.5 (C-e), 38.2 (C-f), 28.7 (C-g), 26.2 (2 X C-h), 25.8 (C-i), 24.9 (C-j), 24.6 (C-k), 20.9 (C-l);

$\nu_{max.}$ ($CHCl_3$) 2970, 2885, 2835, 2790, 1700, 1452, 1425, 1375, 1360, 1340, 1330, 1300, 1267, 1210, 1195, 1185, 1157, 1125, 1107, 1060, 1040, 1010, 975, 955, 895, 860, 845, 690, 612cm^{-1};

m/z 252 (M^+, 8%), 209 (M^+-43, 14%), 152 (M^+-100, 100%), 150 (17%), 138 (M^+-114, 44%), 111 (21%), 110 (19%), 83 (46%), 55 (23%), 43 (M^+-209, 38%), 41 (29%), 28 (73%);

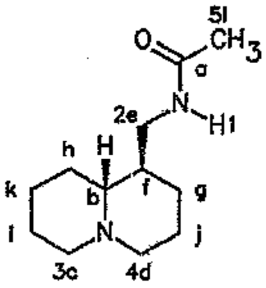
HRMS (Found: M^+ 252.1829. $C_{14}H_{24}N_2O_2$ requires M^+, 252.1838).

Synthesis of N-acetylepilupinamine [114]

This derivative was also prepared by following the procedure described by Wanner *et al.*[117] with a few modifications.

N-Acetylepilupinamine was prepared by heating epilupinamine [112] (196mg, 1.17mmol) under reflux in acetic anhydride (10ml) as described for the preparation of N-acetyl-lupinamine [113].

Flash chromatography afforded N-acetylepilupinamine [114] (184mg, 75%) as a white solid and N,N-bis(acetyl)epi-lupinamine [128] (74mg, 25%) as a yellow liquid, eluent: 19:180:1 methanol:dichloromethane:25% ammonia solution. [Former R_F (9:1 CH_3OH:25% NH_3 solution) 0.66 and latter R_F (9:1 CH_3OH:25% NH_3 solution) 0.78] Four recrystallisations (from methanol) of N-acetylepilupinamine afforded a white solid, m.p. 128.5 - 131°C.



[114]

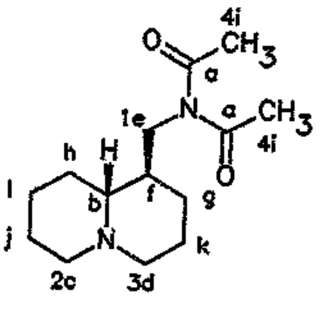
δ_H (200MHz) 7.24 (1H, t, J 5.6Hz, H-1), 3.50 - 3.23 (1H, m, H-2), 3.21 - 3.00 (1H, m, H-2), 2.83 (2H, t, J 10.0Hz, equatorial H-3 and equatorial H-4), 1.99 (3H, s, H-5), 2.26 - 0.95 (14H, m, remaining H);

δ_C (50.32MHz) 170.3 (C-a), 64.9 (C-b), 56.1 (C-c), 55.8 (C-d), 40.9 (C-e), 40.7 (C-f), 28.8 (C-g), 28.3 (C-h), 24.6 (C-i), 24.0 (C-j), 23.8 (C-k), 22.4 (C-l);

$\upsilon_{max.}$ ($CHCl_3$) 3460, 3000, 2945, 2870, 2817, 2775, 2680, 1660, 1510, 1460, 1440, 1365, 1295, 1275, 1180, 1152, 1130, 1110, 1035, 1017, 985, 912, 885, 865, 680, 610cm^{-1};

m/z 210 (M^+, 9%), 209 (M^+-1, 5%), 152 (M^+-58, 29%), 138 (M^+-72, 100%), 111 (36%), 110 (40%), 97 (28%), 96 (23%), 83 (91%), 55 (27%), 41 (21%), 32 (100%), 28 (100%);

HRMS (Found: M^+ 210.1728. $C_{12}H_{22}N_2O$ requires M^+, 210.1732).



[128]

δ_H (200MHz) 3.82 (1H, dd, J 14.3Hz and 10.4Hz, H-1), 3.63 (1H, dd, J 14.4Hz and 4.4Hz, H-1), 2.97 - 2.74 (2H, m, equatorial H-2 and equatorial H-3), 2.41 (6H, s, 2 X H-4) 2.23 - 0.80 (14H, m, remaining H);

δ_C (50.32MHz) 173.4 (2 X C-a), 65.9 (C-b), 56.4 (C-c), 56.1 (C-d), 45.9 (C-e), 41.0 (C-f), 29.2 (C-g), 27.6 (C-h), 26.2 (C-i), 25.0 (C-j), 24.4 (C-k), 24.1 (C-l);

$\upsilon_{max.}$ ($CHCl_3$) 3028, 3018, 2944, 2864, 2812, 2768, 2684, 2498, 2364, 1698, 1580, 1446, 1423, 1373, 1332, 1315, 1290, 1263, 1247, 1214, 1205, 1181, 1154, 1133, 1116, 1071, 1023, 1009, 978, 919, 890, 866, 845, 814cm^{-1};

m/z 252 (M^+, 9%), 209 (M^+-43, 15%), 152 (M^+-100, 100%), 150 (18%), 138 (M^+-114, 48%), 111 (21%), 110 (19%), 83 (42%), 55 (19%), 43 (M^+-209, 27%), 41 (19%), 28 (38%);

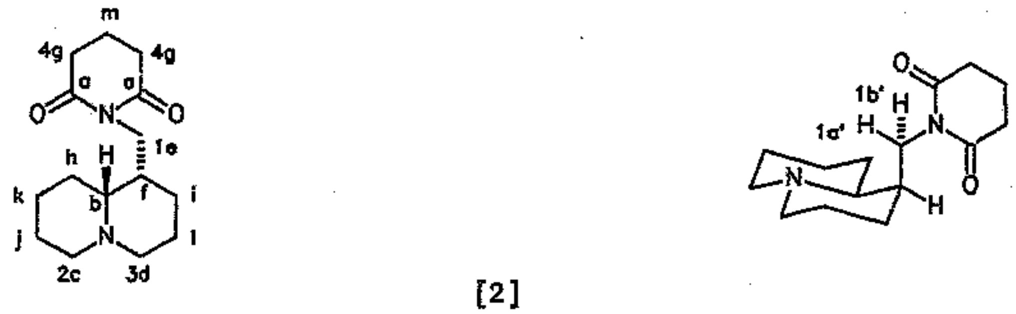
HRMS (Found: M^+ 252.1841. $C_{14}H_{24}N_2O_2$ requires M^+, 252.1838).

Synthesis of epilamprolobine [2]

This alkaloid was prepared by following the reaction procedure described by Yamada *et al.*,[19] with a few modifications.

A solution of lupinamine [11] (165mg, 0.982mmol) in dry diethyl ether (*ca.* 12ml) was added dropwise to a stirred solution of glutaric anhydride (117mg, 1.02mmol) in dry diethyl ether (*ca.* 15ml). White crystals (of the amide [129]) formed immediately. After a reaction time of 45min, the solvent was removed *in vacuo*. The amide was dissolved in acetic anhydride (4.1ml, 4.4g, 4.3 X 10^{-2}mol) with sodium acetate (410mg, 5.00mmol) and the resulting solution was stirred at 80 – 115°C for 70min.

Water (20ml) was added to the cooled reaction and excess acetic anhydride was decomposed and neutralised with sodium carbonate solution. Extraction with chloroform (20ml X 5) followed. The combined organic extracts were dried, filtered and the solvent was removed *in vacuo*. Purification by column chromatography using neutral alumina and benzene as the eluting system, as suggested by Yamada *et al.* proved unsuccessful. Purification by flash chromatography using silica gel, eluent: 40:59:1 methanol:dichloromethane:25% ammonia solution, afforded epilamprolobine [2] (141mg, 54%) and N-acetyllupinamine [113] (14mg, 7%) both as white solids. [Former R_f (9:1 CH_3OH:25% NH_3 solution) 0.82] Four recrystallisations (from 1:1 hexane:ethyl acetate) of epilamprolobine afforded a white solid, m.p. 66.5 – 67.5°C.



[2]

δ_H (200MHz) 4.28 (1H, dd, J 13.0Hz and 10.9Hz, H-1a′), 3.77 (1H, dd, J 13.0Hz and 3.5Hz, H-1b′), 2.94 - 2.78 (2H, m, equatorial H-2 and equatorial H-3), 2.65 (4H, t, J 6.5Hz, 2 X H-4), 2.17 -1.10 (16H, m, remaining H);

δ_C (50.32MHz) 172.8 (2 X C-a), 65.2 (C-b), 57.6 (C-c), 57.1 (C-d), 37.7 (C-e), 37.0 (C-f), 33.1 (2 X C-g), 29.4 (C-h), 26.5 (C-i), 25.5 (C-j), 25.0 (C-k), 21.0 (C-l), 17.2 (C-m);

$\nu_{max.}$ ($CHCl_3$) 2925, 2850, 2800, 2750, 2675, 1712, 1660, 1515, 1455, 1440, 1347, 1280, 1160, 1125, 1115, 1065, 1050, 1032, 1012, 980, 960, 945, 870, 640cm^{-1};

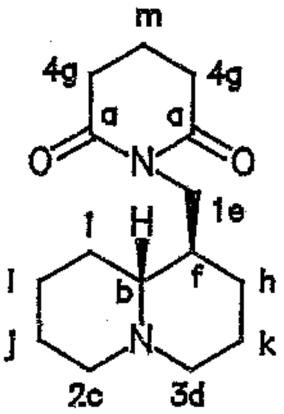
Found: C, 68.54; H, 9.41; N, 10.71. $C_{15}H_{24}N_2O_2$ requires C, 68.15; H, 9.15; N, 10.60%.

Synthesis of lamprolobine [3]

This alkaloid was also prepared by following the reaction procedure described by Yamada *et al.*,[19] with a few modifications.

A solution of epilupinamine [112] (270mg, 1.61mmol) in dry diethyl ether (*ca.* 13ml) was added dropwise to a stirred solution of glutaric anhydride (194mg, 1.70mmol) in dry diethyl ether (*ca.* 20ml). White crystals (of the amide [130]) formed immediately. After a reaction time of 32min, the solvent was removed *in vacuo*. The amide was dissolved in acetic anhydride (6.70ml, 7.25g, 7.10 X 10^{-2}mol) with sodium acetate (671mg, 8.18mmol) and the resulting solution was stirred at 120°C for 40min.

Water (20ml) was added to the cooled reaction and excess acetic anhydride was decomposed and neutralised with sodium carbonate solution. Extraction with chloroform (50ml X 5) followed. The combined organic extracts were dried, filtered and the solvent was removed *in vacuo*. Purification by column chromatography using neutral alumina and an eluting system of 14:5:1 methanol:dichloromethane: 25% ammonia solution proved unsuccessful. Purification by flash chromatography using silica gel, eluent: 40:59:1 methanol:dichloromethane:25% ammonia solution, afforded lamprolobine [3] (261mg, 61%) as a hard yellow oil and N-acetylepilupinamine [114] (24mg, 7%) as a white solid. [Former R_F (9:1 CH_3OH:25% NH_3 solution) 0.79]



[3]

δ_H (200MHz) 3.94 - 3.60 (2H, m, H-1), 3.25 - 2.92 (2H, m, equatorial H-2 and equatorial H-3), 2.70 (4H, t, J 6.5Hz, 2 X H-4), 2.62 - 1.00 (16H, m, remaining H);

δ_c (50.32MHz) 172.2 (2 X C-a), 65.7 (C-b), 55.5 (C-c), 54.9 (C-d), 40.0 (C-e), 38.0 (C-f), 32.1 (2 X C-g), 27.5 (C-h), 26.3 (C-i), 23.3 (C-j), 22.7 (C-k), 22.5 (C-l), 16.3 (C-m);

$\upsilon_{max.}$ ($CHCl_3$) 3028, 3018, 2946, 2866, 2812, 2768, 2436, 1727, 1676, 1464, 1439, 1396, 1354, 1325, 1288, 1247, 1230, 1212, 1172, 1135, 1058, 1019, 994, 940, 909, 690, 671, 665, 611, 565cm^{-1};

m/z 264 (M^+, 21%), 222 (9%), 152 (M^+-112, 60%), 150 (19%), 138 (M^+-126, 100%), 136 (21%), 124 (17%), 111 (41%), 110 (50%), 98 (28%), 97 (53%), 96 (27%), 84 (19%), 83 (80%), 82 (20%), 56 (14%), 55 (45%), 42 (18%), 41 (33%), 32 (42%), 28 (100%);

HRMS (Found: M^+ 264.1875. $C_{15}H_{24}N_2O_2$ requires M^+, 264.1838).

CHAPTER 6

REFERENCES

1. A. D. Kinghorn and M. F. Balandrin, *in* "Alkaloids: Chemical and Biological Perspectives" (S. W. Pelletier, ed.), Vol. 2, pp. 105ff. Wiley (Interscience), New York, 1984.

2. K. A. Aslanov, Y. K. Kushmuradov, and A. S. Sadykov, *in* "The Alkaloids: Chemistry and Pharmacology" (A. Brossi, ed.), Vol. 31, pp. 117ff. Academic Press, London, 1987.

3. M. F. Grundon, *Natural Product Reports (London)* 6, 523 (1989).

4. A. S. Howard and J. P. Michael, *in* "The Alkaloids" (A. Brossi, ed.), Vol. 28, pp. 183ff. Academic Press, London, 1986.

5. F. Bohlmann and D. Schumann, *in* "The Alkaloids" (R. H. F. Manske, ed.), Vol. 9, pp. 176ff. Academic Press, New York, 1967.

6. N. J. Leonard, *in* "The Alkaloids" (R. H. F. Manske and H. L. Holmes, eds.), Vol. 3, pp. 120ff. Academic Press, New York, 1953.

7. N. J. Leonard, *in* "The Alkaloids" (R. H. F. Manske, ed.), Vol. 7, pp. 254ff. Academic Press, New York, 1960.

8. J. A. Lamberton, *Natural Product Reports (London)* 1, 245 (1984).

9. M. F. Grundon, *Natural Product Reports (London)* 1, 349 (1984).

10. S. Okuda, I. Murakoshi, H. Kamata, Y. Kashida, J. Haginiwa, and K. Tsuda, *Chem. Pharm. Bull.* 13, 482 (1965); *Chem. Abstr.* 63, 7060h (1965).

11. M. F. Balandrin, E. F. Robbins, and A. D. Kinghorn, *Biochem. Syst. Ecol.* 10, 307 (1982); *Chem. Abstr.* 98, 86327v (1983).

12. I. Murakoshi, E. Kidoguchi, M. Nakamura, J. Haginiwa, S. Ohmiya, K. Higashiyama, and H. Otomasu, *Phytochemistry* 20, 1725 (1981).

13. W. J. Keller, *Phytochemistry* 19, 2233 (1980).

14. N. K. Hart, S. R. Johns, and J. A. Lamberton, *Chem. Commun.*, 302 (1968).

15. N. K. Hart, S. R. Johns, and J. A. Lamberton, *Aust. J. Chem.* 21, 1619 (1968).

16. I. Murakoshi, M. Ito, J. Haginiwa, S. Ohmiya, H. Otomasu, and R. T. Hirano, *Phytochemistry* 23, 887 (1984).

17. S. I. Goldberg and A. H. Lipkin, *J. Org. Chem.* 35, 242 (1970).

18. E. Wenkert and A. R. Jeffcoat, *J. Org. Chem.* 35, 515 (1970).

19. Y. Yamada, K. Hatano, and M. Matsui, *Agr. Biol. Chem.* 34, 1536 (1970).

20. J. P. Michael, Ph.D. Thesis, University of the Witwatersrand (1975).

21. B. S. Orlek, Ph.D. Thesis, University of the Witwatersrand (1976).

22. C. A. Meerholz, Ph.D. Thesis, University of the Witwatersrand (1977).

23. R. B. Katz, Ph.D. Thesis, University of the Witwatersrand (1983).

24. G. D. Hosken, M.Sc. Dissertation, University of the Witwatersrand (1988).

25. S-F. Chang, Ph.D. Thesis, University of the Witwatersrand (1991).

26. M. I. Zwane, Ph.D. Thesis, University of the Witwatersrand (1991).

27. A. S. Parsons, Ph.D. Thesis, University of the Witwatersrand (1992).

28. G. C. Gerrans, A. S. Howard, and B. S. Orlek, *Tetrahedron Lett.*, 4171 (1975).

29. A. S. Howard, G. C. Gerrans, and J. P. Michael, *J. Org. Chem.* 45, 1713 (1980).

30. A. S. Howard, G. C. Gerrans, and C. A. Meerholz, *Tetrahedron Lett.* 21, 1373 (1980).

31. A. S. Howard, R. B. Katz, and J. P. Michael, *Tetrahedron Lett.* 24, 829 (1983).

32. R. Ghirlando, A. S. Howard, R. B. Katz, and J. P. Michael, *Tetrahedron* 40, 2879 (1984).

33. J. P. Michael, G. D. Hosken, and A. S. Howard, *Tetrahedron* 44, 3025 (1988).

34. J. P. Michael, A. S. Parsons, and R. Hunter, *Tetrahedron Lett.* 30, 4879 (1989).

35. J. V. Greenhill, *Chem. Soc. Rev.* 6, 277 (1977).

36. P. W. Hickmott, *Tetrahedron* 38, 1975 (1982).

37. M. Yoshimoto, N. Ishida, and T. Hiraoka, *Tetrahedron Lett.*, 39 (1973).

38. J. P. Celerier, M. Haddad, C. Saliou, G. Lhommet, H. Dhimane, J. C. Pommelet, and J. Chuche, *Tetrahedron* 45, 6161 (1989).

39. J. P. Celerier, M. G. Richaud, and G. Lhommet, *Synthesis*, 195 (1983).

40. S. I. Goldberg and I. Ragade, *J. Org. Chem.* 32, 1046 (1967).

41. H. W. Pinnick and Y-H. Chang, *Tetrahedron Lett.*, 837 (1979).

42. P. Lorencak, J. C. Pommelet, J. Chuche, and C. Wentrup, *J. Chem. Soc., Chem. Commun.*, 369 (1986).

43. M. Roth, P. Dubs, E. Goetschi, and A. Eschenmoser, *Helv. Chim. Acta* 54, 710 (1971).

44. P. Dubs, E. Goetschi, M. Roth, and A. Eschenmoser, *Chimia* 24, 34 (1970).

45. P. Dubs, Ph.D. Thesis, Eidgenoessischen Technischen Hochschule, Zuerich (1969).

46. A. Eschenmoser, *Quart. Rev.* 24, 366 (1970).

47. H. W. Pinnick and Y-H. Chang, *J. Org. Chem.* 43, 4662 (1978).

48. H. Takahata, T. Suzuki, and T. Yamazaki, *Heterocycles* 24, 1247 (1986).

49. W. Fuhrer, R. Hobi, A. Pfaltz, and P. Schneider, *Helv. Chim. Acta* 57, 1498 (1974).

50. T. Nikiforov, S. Stanchev, B. Milenkov, and V. Dimitrov, *Synth. Commun.* 20, 1977 (1990).

51. H. Bahaji, P. Bastide, J. Bastide, C. Rubat, and P. Tronche, *Eur. J. Med. Chem.* 23, 193 (1988).

52. I. Felner and K. Schenker, *Helv. Chim. Acta* 53, 754 (1970).

53. D. J. Hart, W-P. Hong, and L-Y. Hsu, *J. Org. Chem.* 52, 4665 (1987).

54. R. Fujimoto and Y. Kishi, *Tetrahedron Lett.* 22, 4197 (1981).

55. J. S. Petersen, G. Fels, and H. Rapoport, *J. Am. Chem. Soc.* 106, 4539 (1984).

56. T. Ibuka, G-N. Chu, and F. Yoneda, *J. Chem. Soc., Chem. Commun.*, 597 (1984).

57. D. J. Hart and K. Kanai, *J. Am. Chem. Soc.* 105, 1255 (1983).

58. R. E. Ireland and F. R. Brown Jr., *J. Org. Chem.* 45, 1868 (1980).

59. K. Shiosaki, G. Fels, and H. Rapoport, *J. Org. Chem.* 46, 3230 (1981).

60. A. M. P. Koeskinen and H. Rapoport, *J. Med. Chem.* 28, 1301 (1985).

61. D. J. Hart and W-P. Hong, *J. Org. Chem.* 50, 3670 (1985).

62. R. D. Brunt, F. J. Leeper, I. Grgurina, and A. R. Battersby, *J. Chem. Soc., Chem. Commun.*, 428 (1989).

63. M. L. Bremmer, N. A. Khatri, and S. M. Weinreb, *J. Org. Chem.* 48, 3661 (1983).

64. R. V. Stevens, L. E. DuPree Jr., and P. L. Loewenstein, *J. Org. Chem.* 37, 977 (1972).

65. J-C. Gramain, R. Remuson, and D. Vallee, *J. Org. Chem.* 50, 710 (1985).

66. T. A. Crabb, R. F. Newton, and D. Jackson, *Chem. Rev.* 71, 109 (1971).

67. E. Wenkert, B. Chauncy, K. G. Dave, A. R. Jeffcoat, F. M. Schell, and H. P. Schenk, *J. Am. Chem. Soc.* 95, 8427 (1973).

68. E. Wenkert, J. S. Bindra, C-J. Chang, D. W. Cochran, and F. M. Schell, *Accts. Chem. Res.* 7, 46 (1974).

69. E. Wenkert, C-J. Chang, H. P. S. Chawla, D. W. Cochran, E. W. Hagaman, J. C. King, and K. Orito, *J. Am. Chem. Soc.* 98, 3645 (1976).

70. I. M. Skvortsov, *Russ. Chem. Rev.* 48, 262 (1979).

71. T. A. Crabb, *in* "Annual Reports in NMR Spectroscopy" (E. F. Mooney, ed.), Vol. 6A, pp. 249. Academic Press, London, 1975.

72. J. Skolik, H. Podkowinska, P. Pietrzak, and U. Majchrzak-Kuczynska, *Ser. Chem.*, 171 (1989); *Chem. Abstr.* 114, 24256m (1991).

73. H. Podkowinska and J. Skolik, *Org. Magn. Reson.* 22, 379 (1984); *Chem. Abstr.* 101, 171579d (1984).

74. M. Sugiura and Y. Sasaki, *Chem. Pharm. Bull.* 24, 2988 (1976); *Chem. Abstr.* 86, 105310e (1977).

75. H. Beierbeck and J. K. Saunders, *Can. J. Chem.* 54, 632 (1976); *Chem. Abstr.* 86, 71067p (1977).

76. F. Bohlmann and R. Zeisberg, *Chem. Ber.* 108, 1043 (1975).

77. S. Ohmiya, H. Otomasu, J. Haginiwa and I. Murakoshi, *Chem. Pharm. Bull.* 28, 546 (1980); *Chem. Abstr.* 93, 110532c (1980).

78. D. Tourwe and G. Van Binst, *Heterocycles* 9, 507 (1978); *Chem. Abstr.* 88, 191172g (1978).

79. F. Bohlmann, *Chem. Ber.* 91, 2157 (1958).

80. M. Wiewiorowski and J. Skolik, *Bull Acad. Pol. Sci., Ser. Sci. Chim.* 10, 1 (1962); *Chem. Abstr.* 57, 13313a (1962).

81. J. Skolik, P. J. Krueger, and M. Wiewiorowski, *Tetrahedron* 24, 5439 (1968); *Chem. Abstr.* 69, 59468m (1968).

82. M. Wiewiorowski, O. E. Edwards, and M. D. Bratek-Wiewiorowski, *Can. J. Chem.* 45, 1447 (1967).

83. H. S. Aaron, G. E. Wicks Jr., and C. P. Rader, *J. Org. Chem.* 29, 2248 (1964).

84. F. Bohlmann, D. Schumann, and M. Schulz, *Tetrahedron Lett.*, 173 (1965); *Chem. Abstr.* 62, 9956f (1965).

85. H. P. Hamlow, S. Okuda, and N. Nakagawa, *Tetrahedron Lett.*, 2553 (1964); *Chem. Abstr.* 62, 1223a (1965).

86. G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Topics I and II. Wiley (Interscience), New York, 1972.

87. M. Shamma and D. M. Hindenlang, "Carbon-13 NMR Shift Assignments of Amines and Alkaloids", Plenum Press, New York, 1979.

88. D. Brillon, *Synth. Commun.* 20, 3085 (1990).

89. G. A. Olah, R. Karpeles, and S. C. Narang, *Synthesis*, 963 (1982).

90. W. H. Bagnall, E. P. Goodings, and C. L. Wilson, *J. Am. Soc.* 73, 4794 (1951).

91. E. Pretsch, J. Seibl, W. Simon, and T. Cierc, "Tables of Spectral Data for Structure Determination of Organic Compounds", Springer-Verlag (1983).

92. G. D. Tomlinson, Ph.D. Thesis, University of the Witwatersrand (1991).

93. S. Scheibye, B. S. Pedersen, and S. O. Lawesson, *Bull. Soc. Chim. Belg.* 87, 229 (1978); *Chem. Abstr.* 89, 108050t (1978).

94. S-E. Yoo and S-H. Lee, *Synlett*, 419 (1990).

95. R. E. Harmon, J. L. Parsons, D. W. Cooke, S. K. Gupta, and J. Schoolenberg, *J. Org. Chem.* 34, 3684 (1969).

96. L. K. Keefer and G. Lunn, *Chem. Rev.* 89, 459 (1989).

97. J. M. McIntosh and P. Beaumier, *J. Org. Chem.* 37, 2905 (1972).

98. R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.* 93, 2897 (1971).

99. S. B. Kadin, *J. Org. Chem.* 31, 620 (1966).

100. R. O. Hutchins, D. Rotstein, N. Natale, J. Fanelli, and D. Dimmel, *J. Org. Chem.* 41, 3328 (1976).

101. S. K. Boyer, J. Bach, J. McKenna, and E. Jagdmann Jr., *J. Org. Chem.* 50, 3408 (1985).

102. H. Wiener, J. Blum, and Y. Sasson, *J. Org. Chem.* 56, 4481 (1991).

103. J. O. Madsen and P. E. Iversen, *Tetrahedron* 30, 3493 (1974).

104. V. A. Mnatsakanyan, L. S. Arutyunyan, and E. Y. Agababyan, *Arm. Khim. Zh.* 26, 325 (1973); *Chem. Abstr.* 79, 92448j (1973).

105. V. Boido, C. Boido-Canu, and F. Sparatore, *Studi Sassar., Sez.* 2 57, 811 (1979); *Chem. Abstr.* 93, 220552s (1980).

106. V. Boido, A. Boido, C. Boido-Canu, and F. Sparatore, *Farmaco, Ed. Sci.* 34, 673 (1979); *Chem. Abstr.* 91, 151090j (1979).

107. S. M. Gafurova, A. M. Saiitkulov, A. M. Aslanov, A. A. Abduvakhabov, A. I. Ishbaev, and A. M. Maksudov, *Uzb. Khim. Zh.*, 36 (1978); *Chem. Abstr.* 90, 23351n (1979).

108. F. Sparatore, B. Cappello, and V. Boido, *Boll. Soc. Ital. Biol. Sper.* 53, 803 (1977); *Chem. Abstr.* 88, 120960b (1978).

109. V. Boido and F. Sparatore, *Farmaco, Ed. Sci.* 29, 517 (1974); *Chem. Abstr.* 82, 25966a (1975).

110. F. Sparatore, V. Boido, P. Preziosi, E. Miele, and G. De Natale, *Farmaco, Ed. Sci.* 24, 587 (1969); *Chem. Abstr.* 71, 50294k (1969).

111. S. Okuda, K. Tsuda, and H. Kataoka, *Chem. Ind.*, 1115 (1961); *Chem. Abstr.* 62, 14750b (1965).

112. F. Bohlmann, D. Schumann, U. Friese, and E. Poetsch, *Chem. Ber.* 99, 3358 (1966).

113. G. Cimino, M. Gavagnin, G. Sodano, A. Spinella, G. Strazzullo, F. J. Schmitz, and G. Yalamanchili, *J. Org. Chem.* 52, 2301 (1987).

114. R. F. Nystrom, *J. Am. Chem. Soc.* 77, 2544 (1955).

115. J. O. Osby, S. W. Heinzman, and B. Ganem, *J. Am. Chem. Soc.* 108, 67 (1986).

116. S. Okuda, H. Kataoka, and K. Tsuda, *Chem. Pharm. Bull.* 13, 491 (1965); *Chem. Abstr.* 63, 7059h (1965).

117. M. J. Wanner and G-J. Koomen, *Tetrahedron* 47, 8431 (1991).

118. G. W. Kabalka, T. M. Shoup, and N. M. Goudgaon, *J. Org. Chem.* 54, 5930 (1989).

119. G. W. Kabalka, T. M. Shoup, and N. M. Goudgaon, *Tetrahedron Lett.* 30, 1483 (1989).

120. J. March, *in* "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", third edition, J. Wiley and Sons, Ch. 10, pp. 312 (1985).

121. B. A. Abdusalamov, *Khim. Prir. Soedin.*, 3 (1984); English translation in *Chem. Nat. Compounds*, 1 (1984); *Chem. Abstr.* 100, 188864v (1984).

122. J. P. Michael, private communications.

CHAPTER 7

APPENDIX

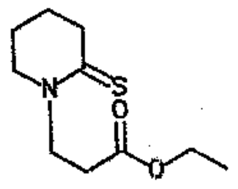
The proton, carbon-13 and ^{13}C-^{1}H correlation spectra of important compounds prepared, are shown in Table 12. Chemical shifts are reported on the δ scale.

Table 12: Spectra of important compounds

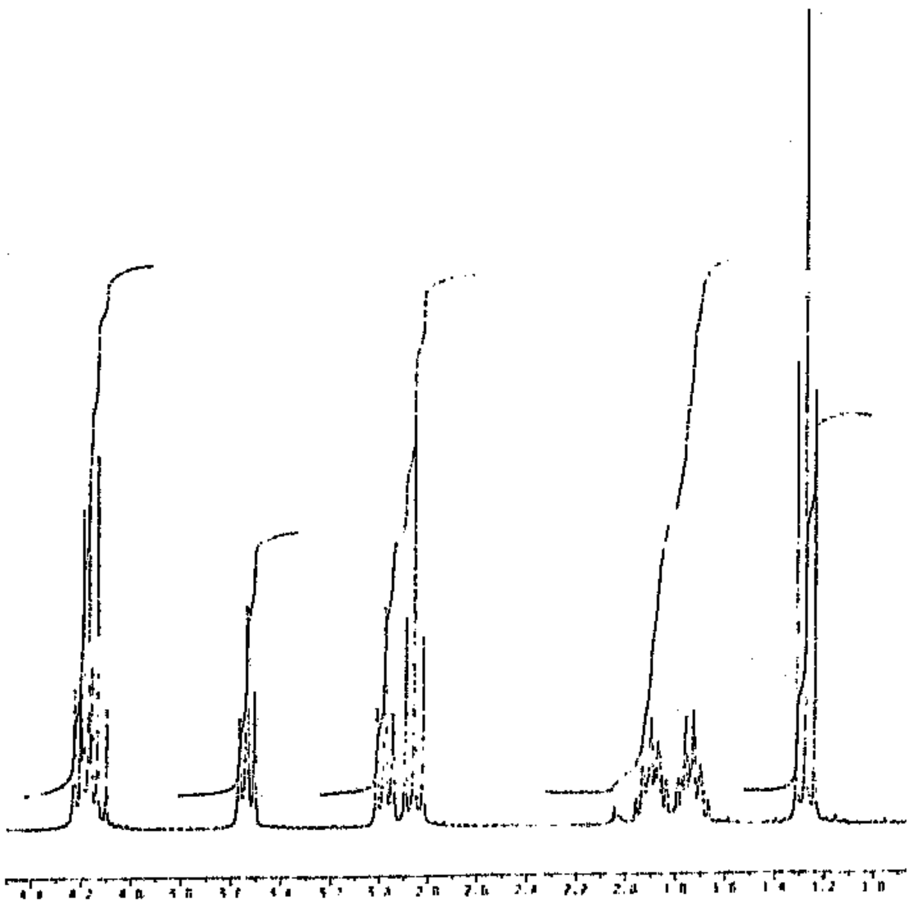
Spectrum	Compound name and number	Page
^{1}H ^{13}C ^{13}C-^{1}H	1-(2-ethoxycarbonylethyl)piperidine-2-thione [83]	191 191 192
^{1}H ^{13}C ^{13}C-^{1}H	1-(2-t-butoxycarbonylethyl)piperidine-2-thione [84]	193 193 194
^{1}H ^{13}C ^{13}C-^{1}H	1-(2-ethoxycarbonylethyl)-2-cyanomethylenepiperidine [85]	195 196 197
^{1}H ^{13}C ^{13}C-^{1}H	1-(3-hydroxypropyl)-2-cyanomethylenepiperidine [68]	198 198 199
^{1}H ^{13}C ^{13}C-^{1}H	1-azabicyclo[4.4.0]dec-5-ene-5-carbonitrile [69]	200 200 201
^{1}H ^{13}C ^{13}C-^{1}H	1-azabicyclo[4.4.0]dec-6-ene-5-carbonitrile [118]	202 202 203
^{1}H	1-(3-chloropropyl)-2-cyanomethylenepiperidine [117]	204

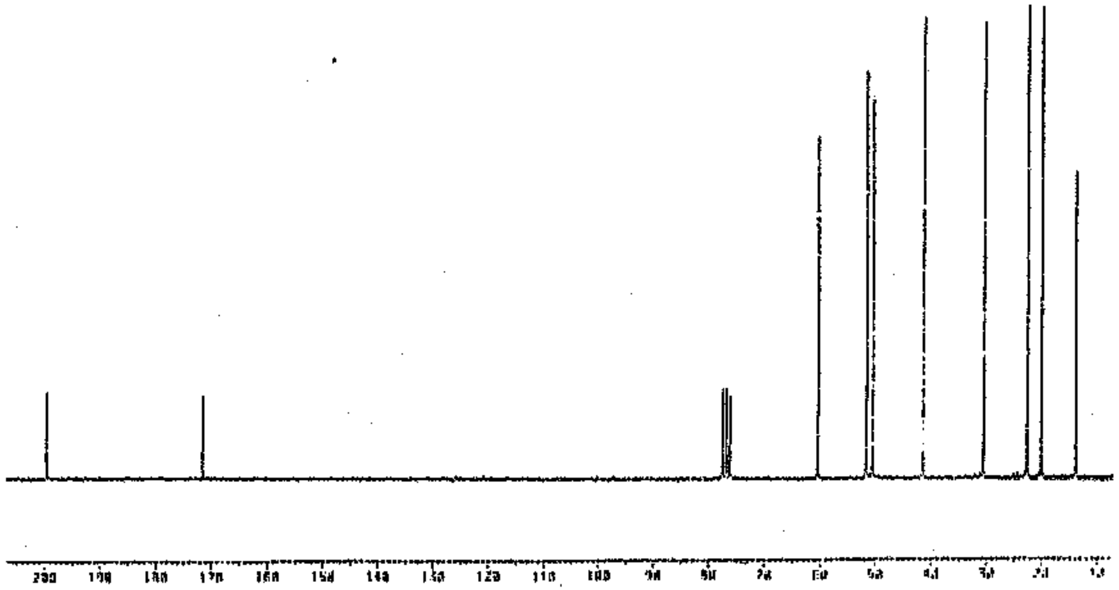
Table 12: Spectra of important compounds (continued)

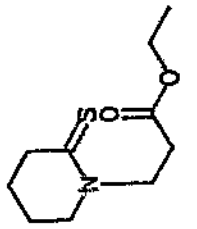
Spectrum	Compound name and number	Page
^{1}H ^{13}C ^{13}C-^{1}H	*rel*-5*R*,6*R*-1-azabicyclo[4.4.0]decane-5-carbonitrile [20]	205 205 206
^{1}H ^{13}C ^{13}C-^{1}H	*rel*-5*R*,6*S*-1-azabicyclo[4.4.0]decane-5-carbonitrile [19]	207 207 208
^{1}H ^{13}C	lupinamine [11]	209 209
^{1}H ^{13}C ^{13}C-^{1}H	epilupinamine [112]	210 210 211
^{1}H ^{13}C	N-acetyllupinamine [113]	212 213
^{1}H ^{13}C	N-acetylepilupinamine [114]	214 215
^{1}H ^{13}C	N,N-bis(acetyl)lupinamine [127]	216 216
^{1}H ^{13}C	N,N-bis(acetyl)epilupinamine [128]	217 217
^{1}H ^{13}C ^{13}C-^{1}H	epilamprolobine [2]	218 218 219
^{1}H ^{13}C ^{13}C-^{1}H	lamprolobine [3]	220 220 221



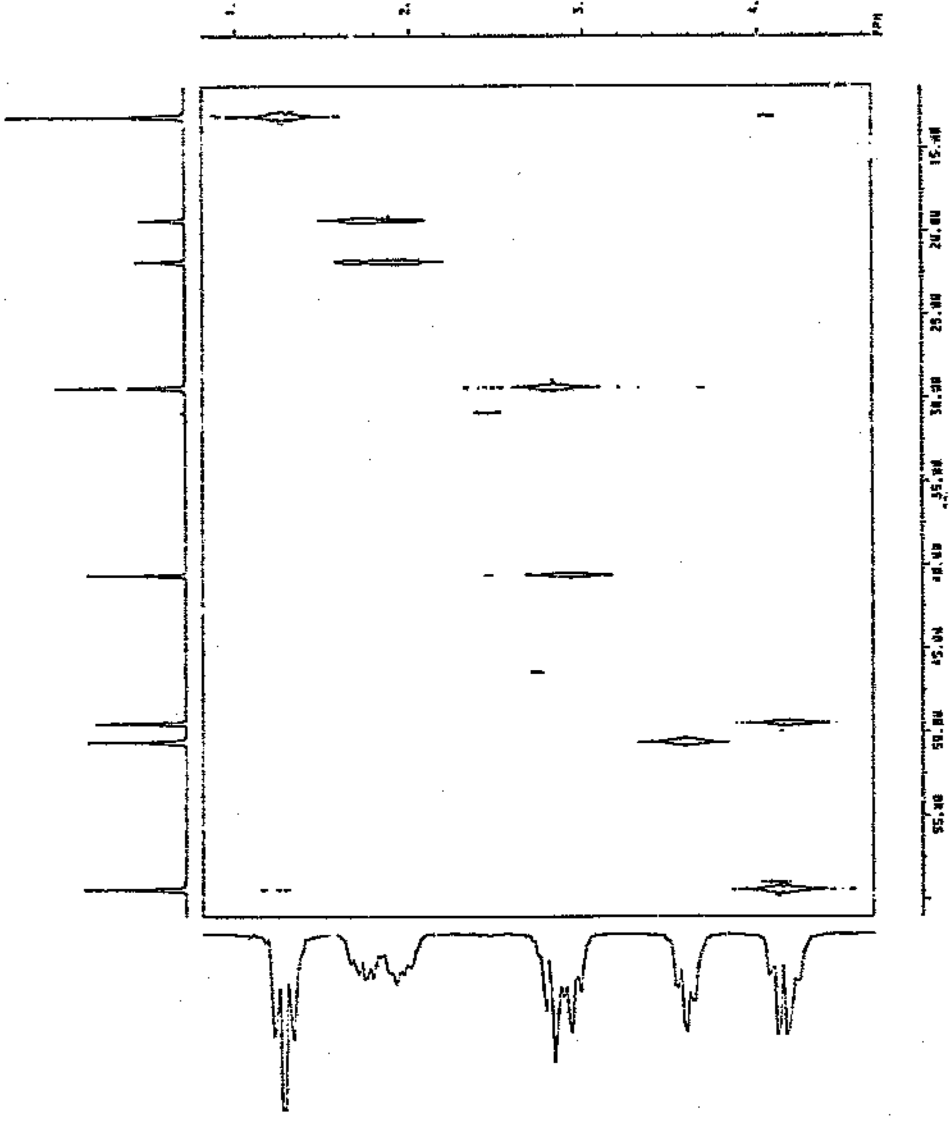
[83]

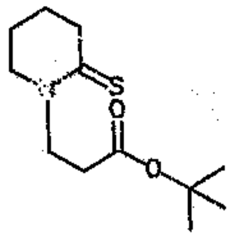




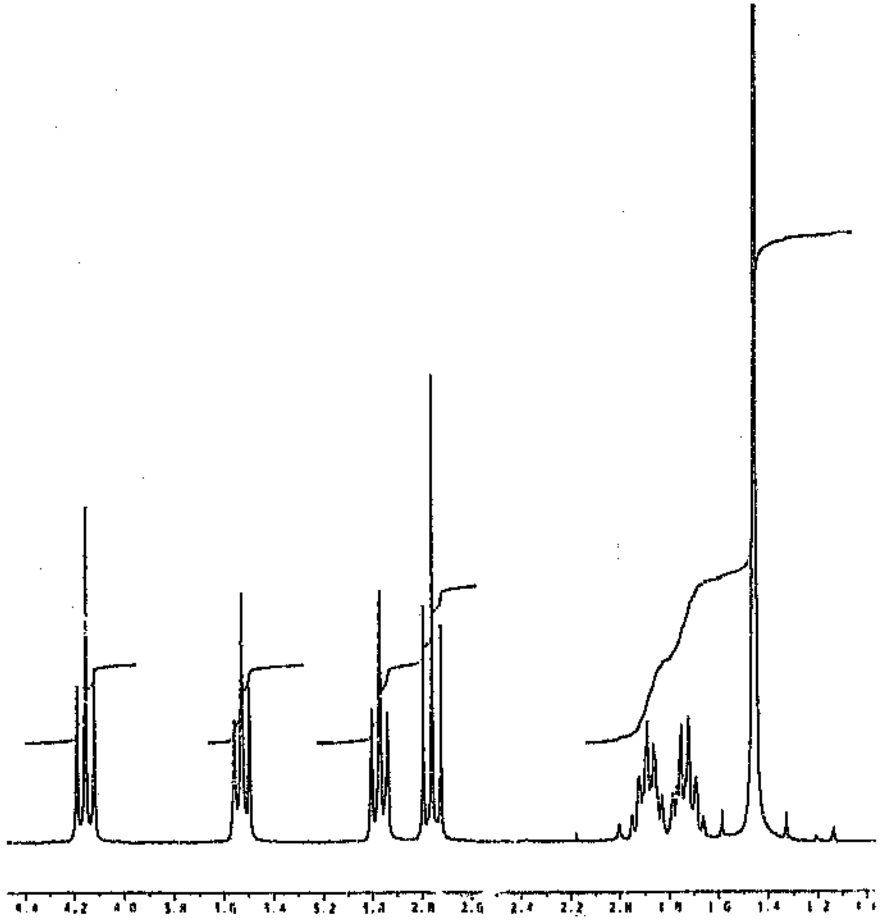


[83]

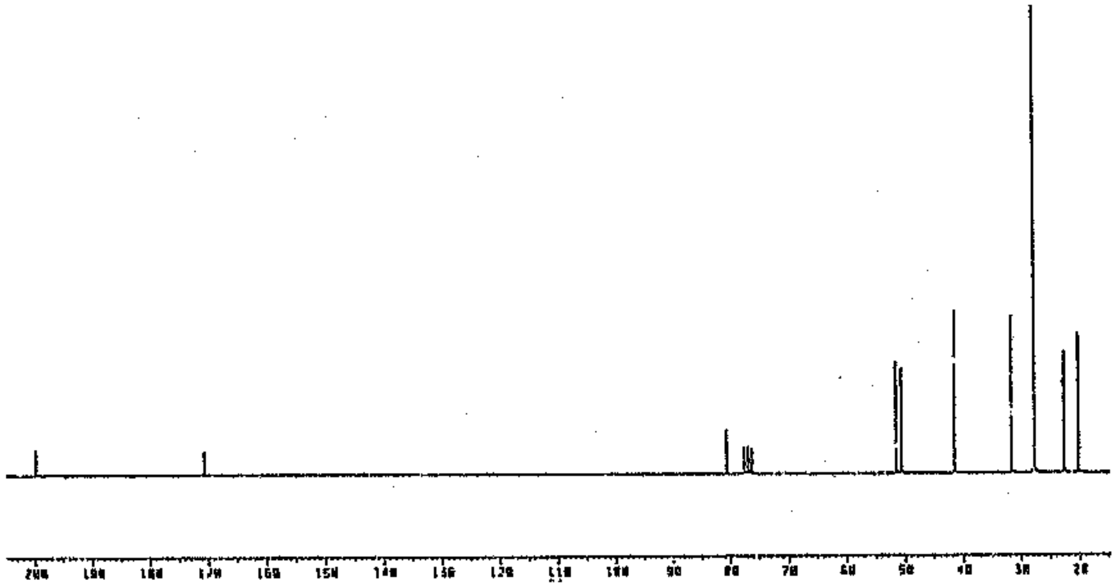

1.00
2.00
3.00
4.00
PPM
15.00
20.00
25.00
30.00
35.00
40.00
45.00
50.00
55.00



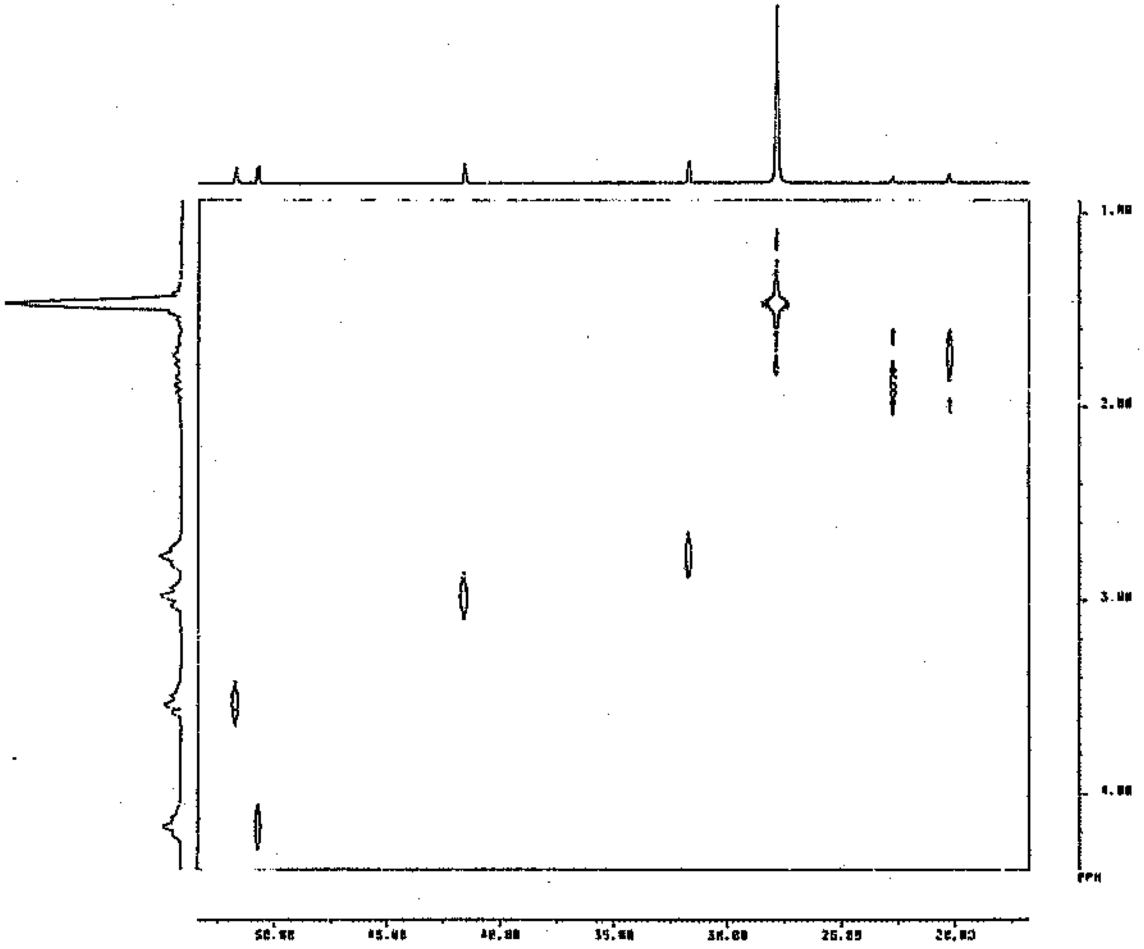
[84]

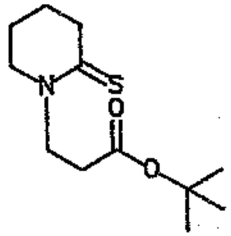


4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2

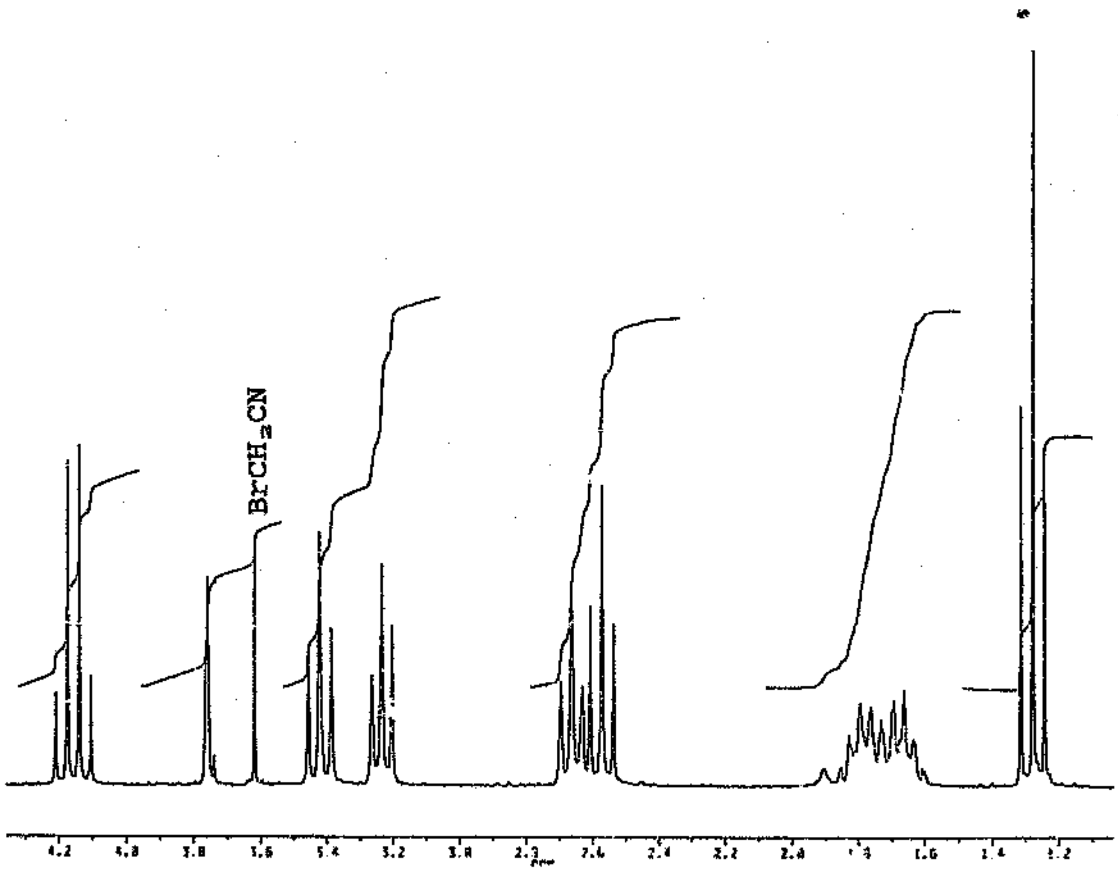


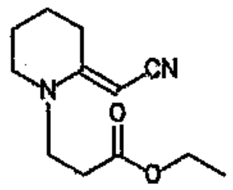
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20



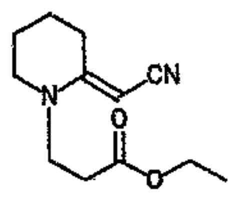


[84]

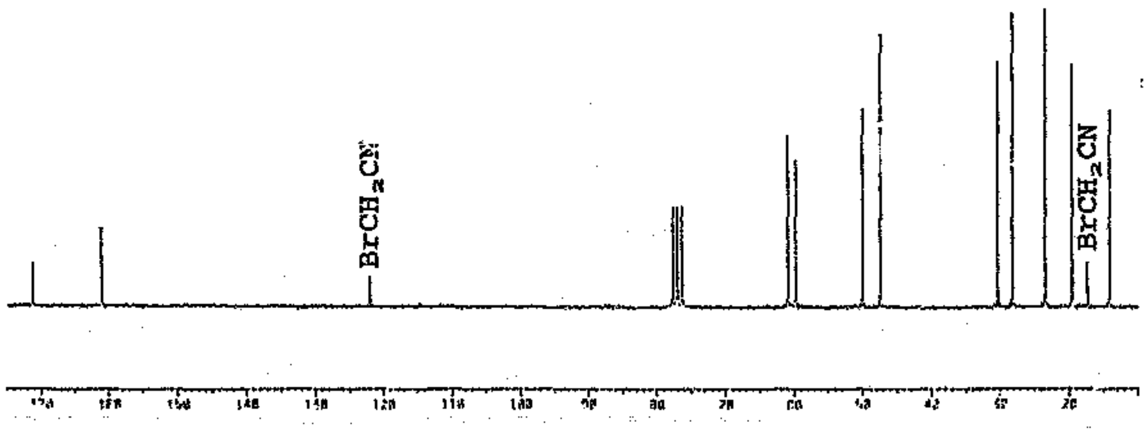


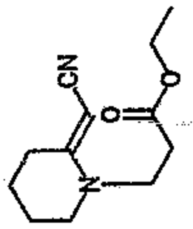


[85]

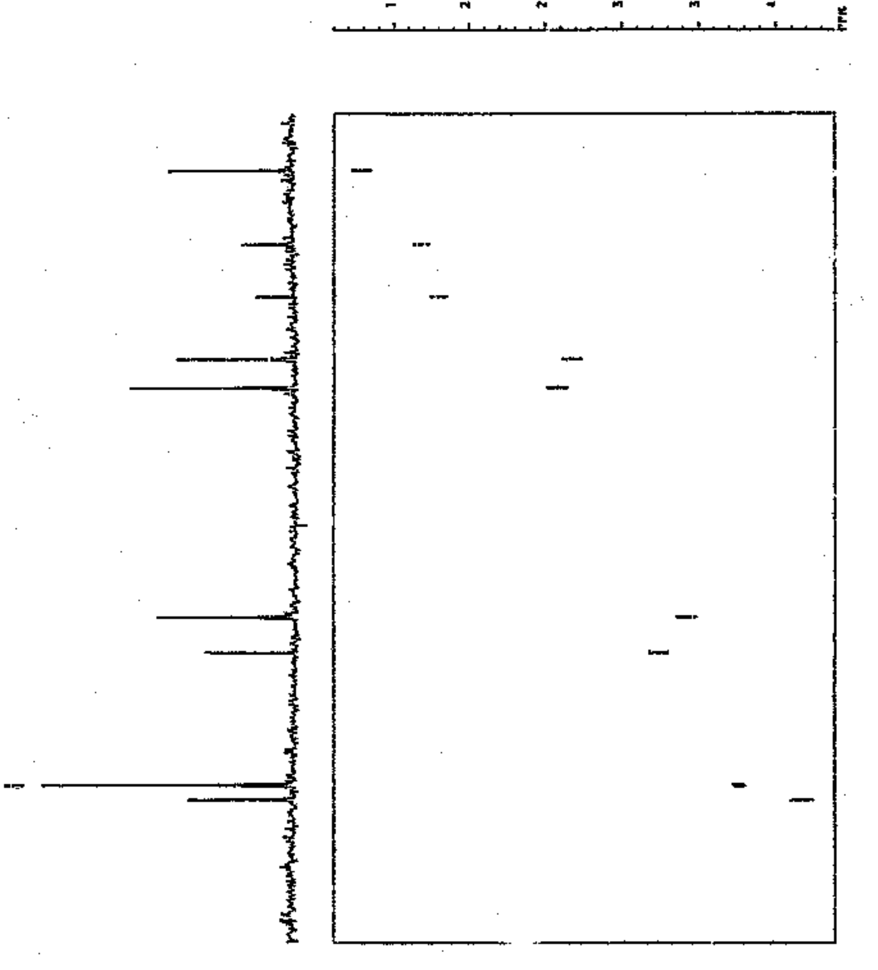


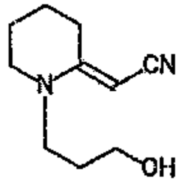
[85]


BrCH$_2$CN
BrCH$_2$CN
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

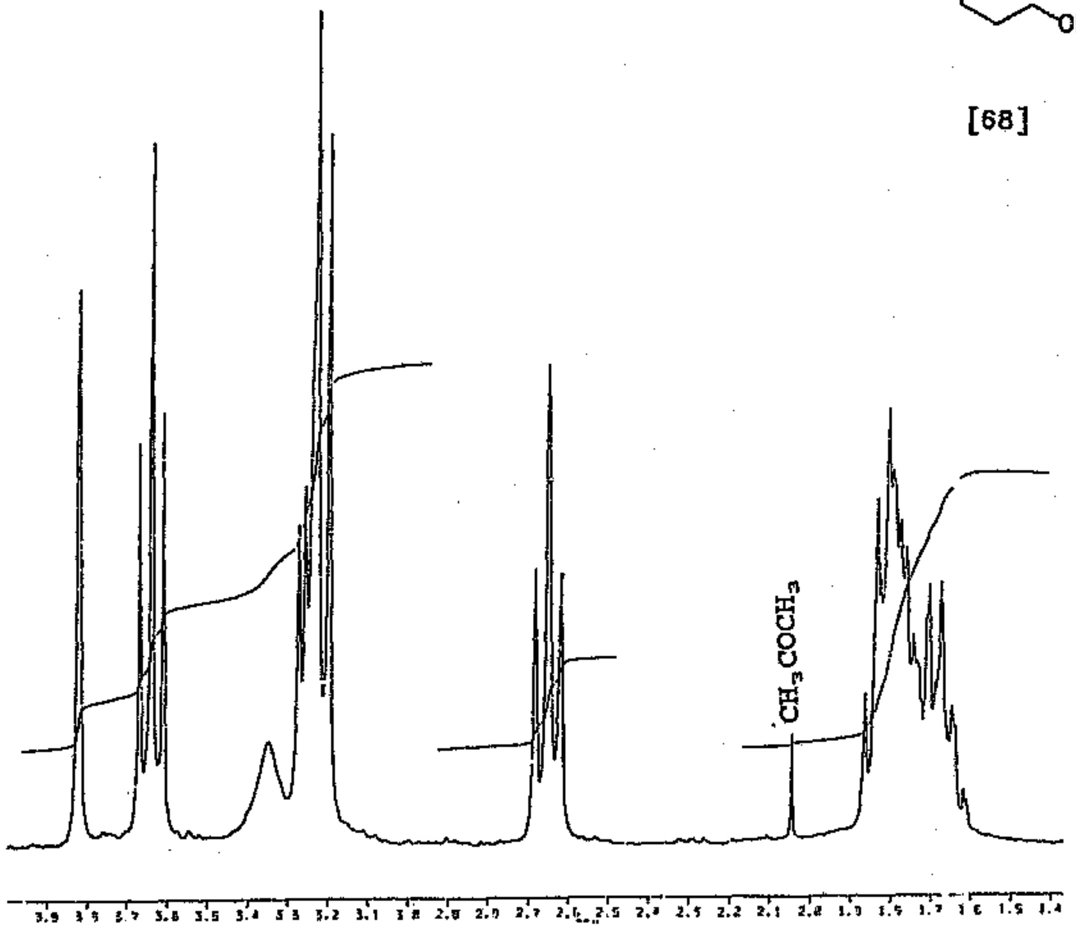

CN
O
O
N

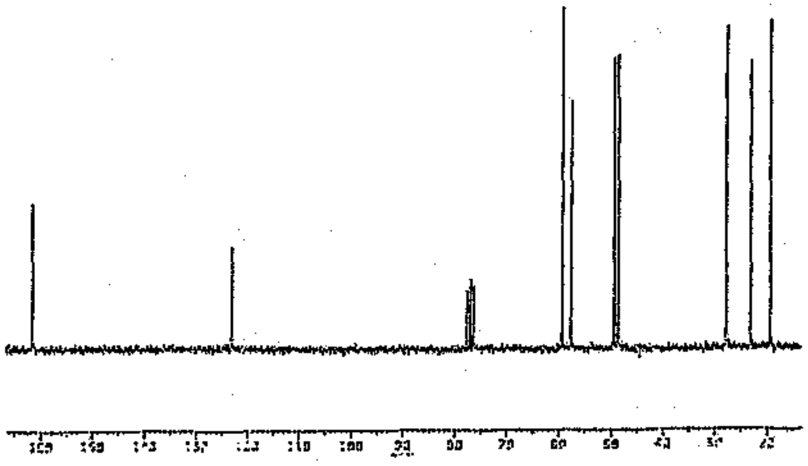
[85]

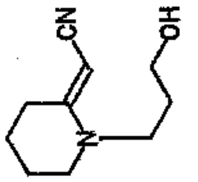

1.5
2.0
2.5
3.0
3.5
4.0
ppm
15.0
20.0
25.0
30.0
35.0
40.0
45.0
50.0
55.0
60.0
65.0
70.0



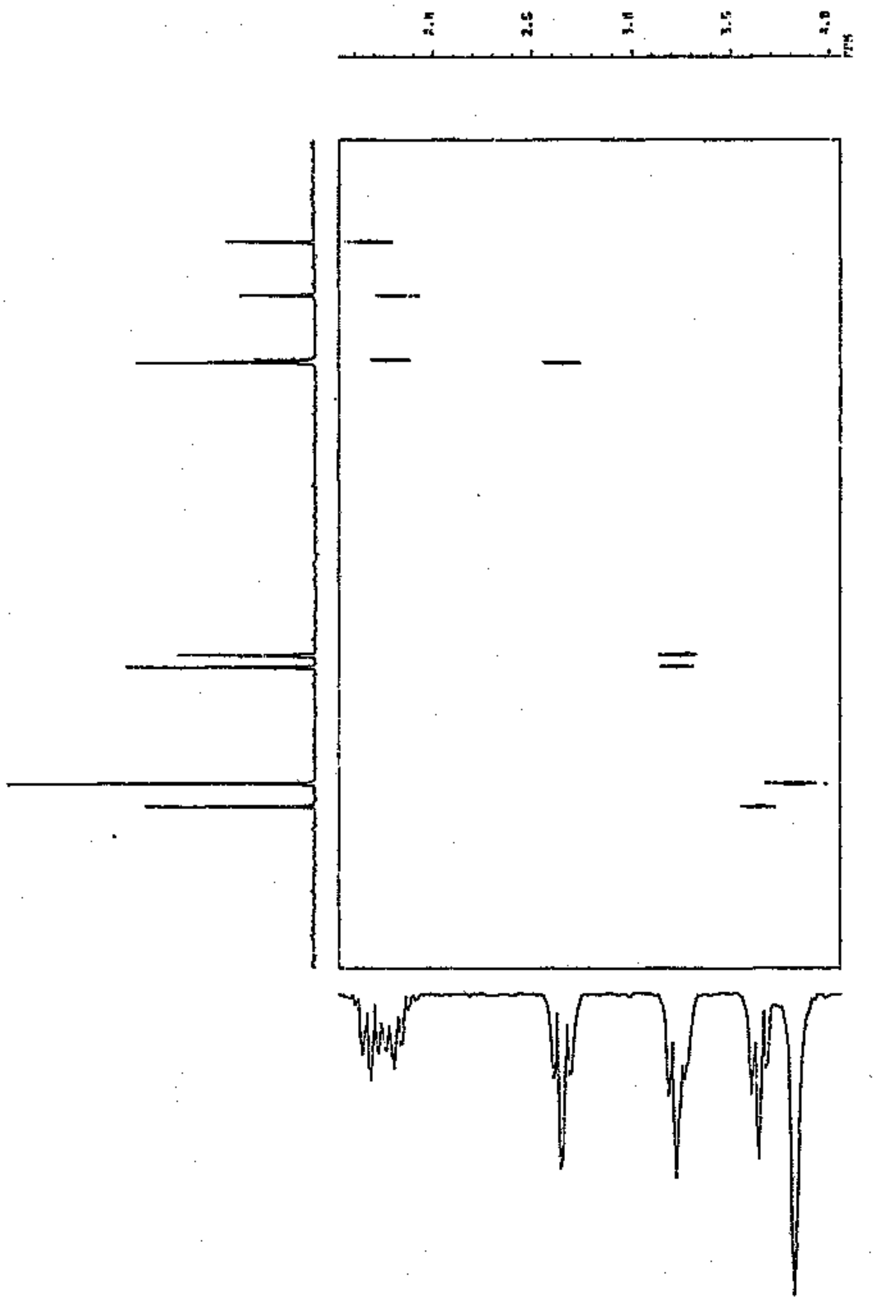
[68]

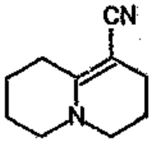

CH$_3$COCH$_3$
3.9
3.8
3.7
3.6
3.5
3.4
3.3
3.2
3.1
3.0
2.9
2.8
2.7
2.6
2.5
2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4


160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

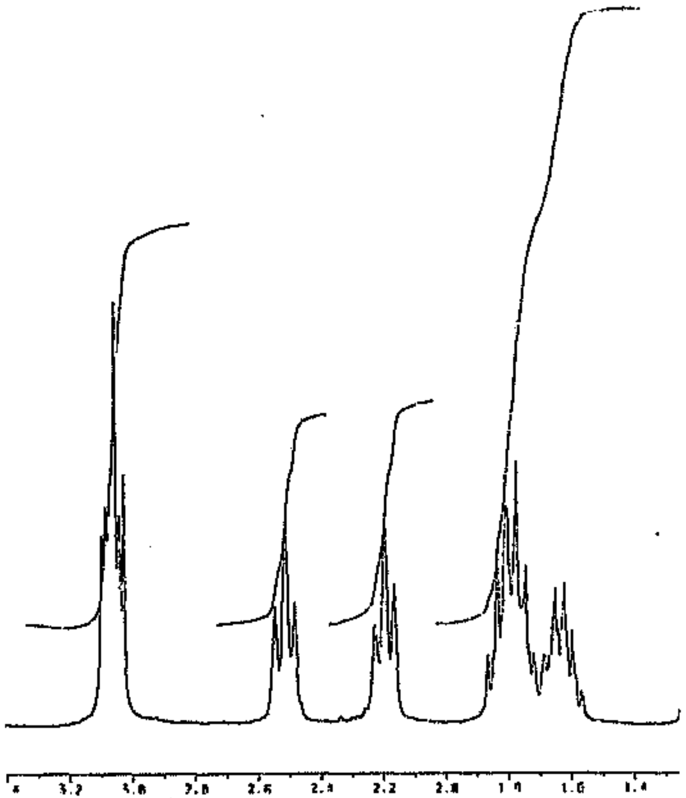

CN
N
OH

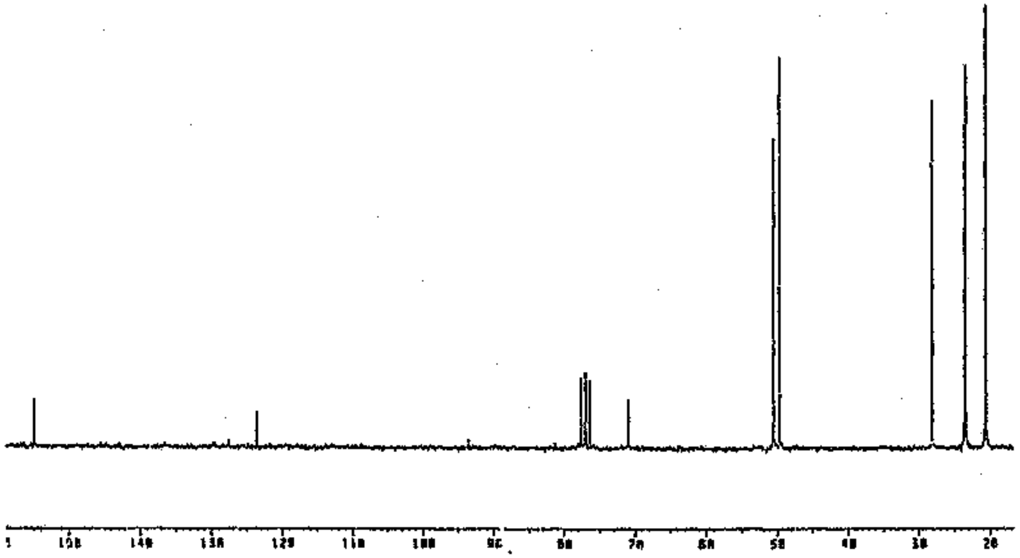
[68]

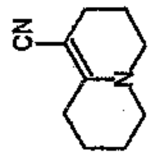

2.0
2.5
3.0
3.5
4.0
PPM
15.0
20.0
25.0
30.0
35.0
40.0
45.0
50.0
55.0
60.0
65.0


CN
N

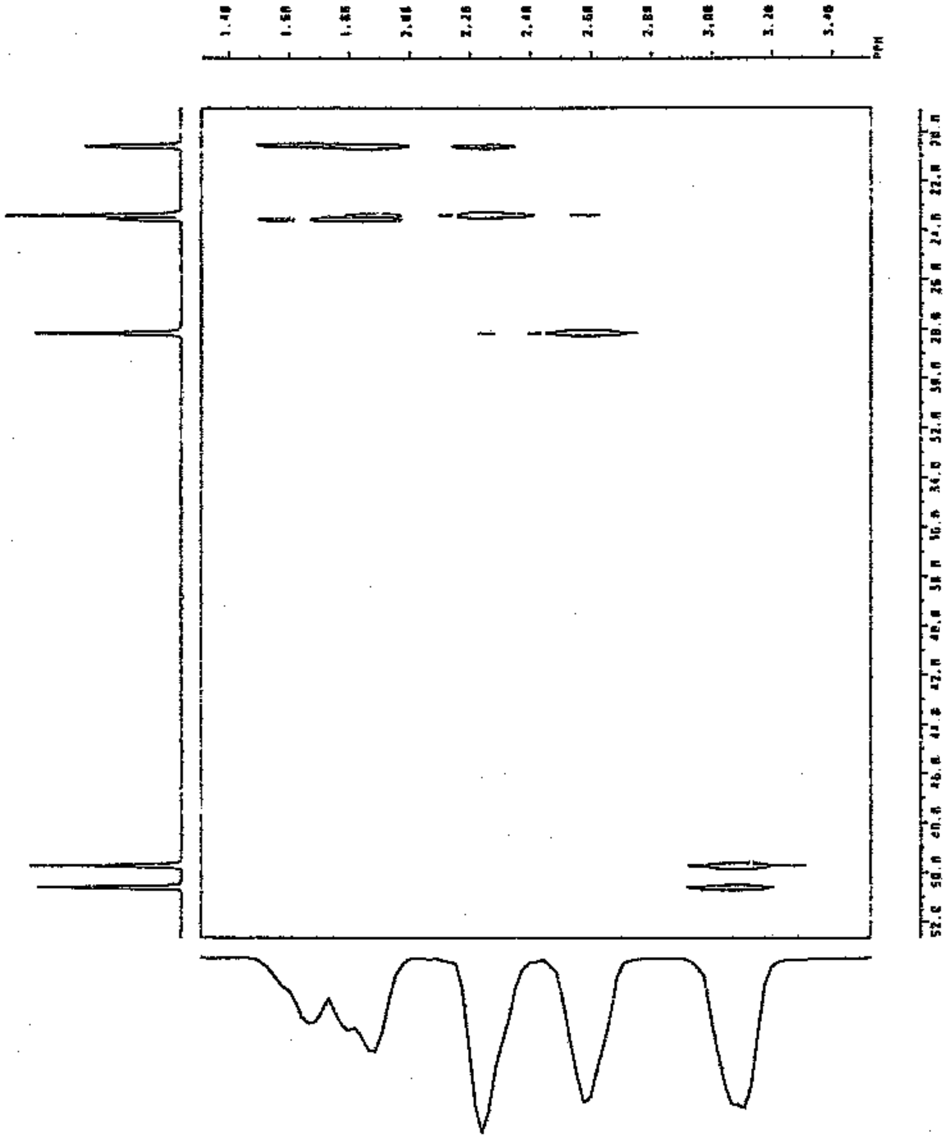
[69]

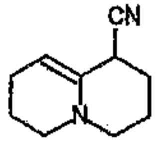

3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4


150
140
130
120
110
100
90
80
70
60
50
40
30
20

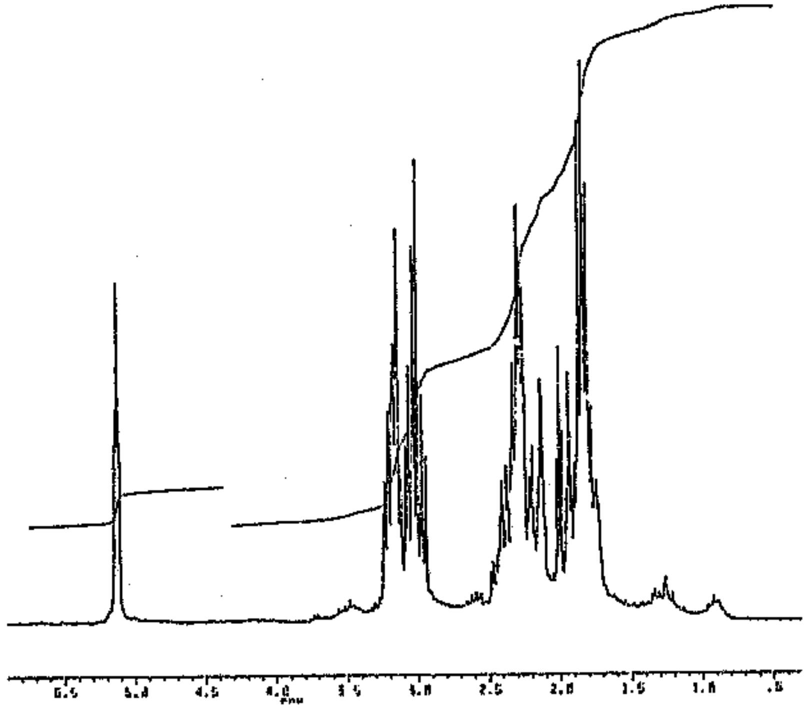

CN
N

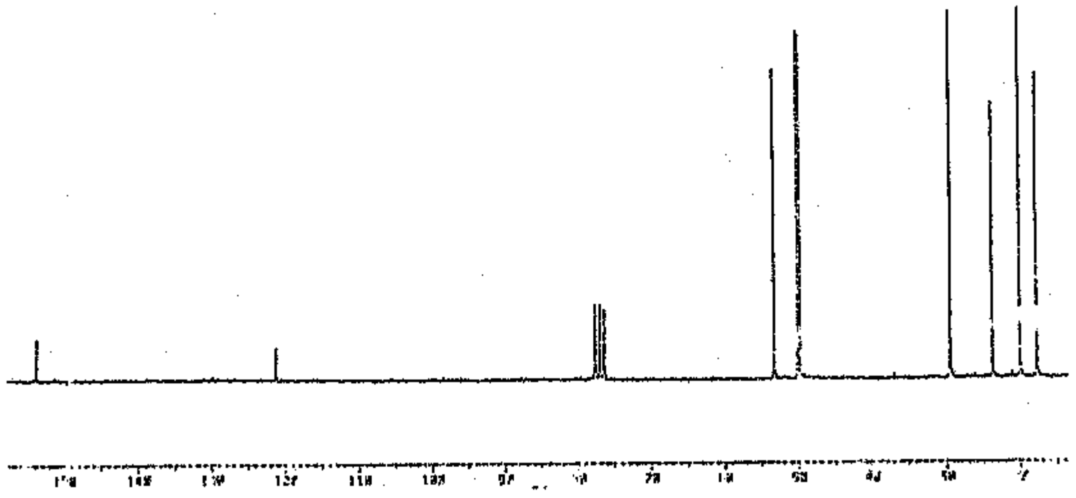
[69]

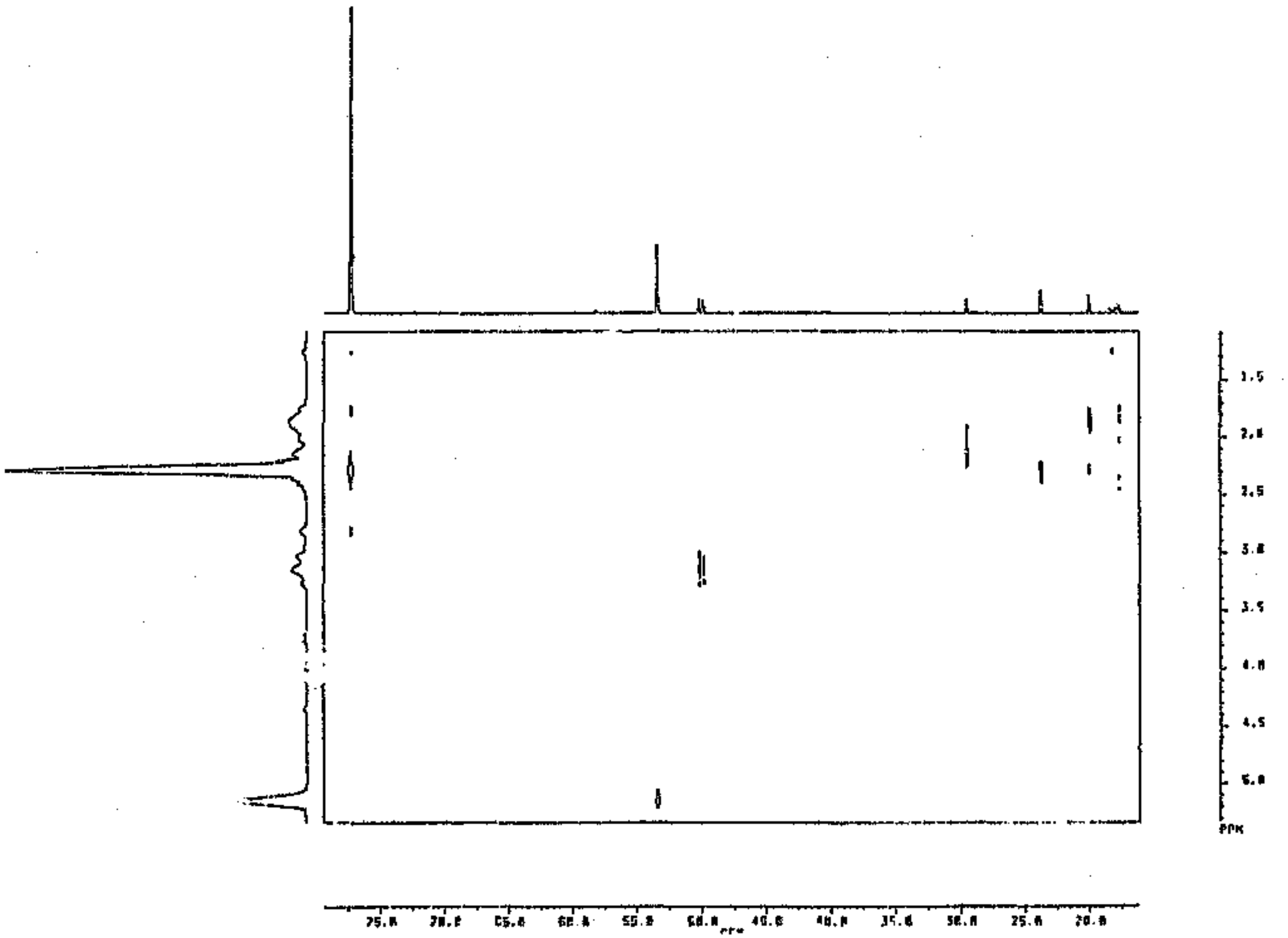

1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00
3.20
3.40
PPM
20.0
22.0
24.0
26.0
28.0
30.0
32.0
34.0
36.0
38.0
40.0
42.0
44.0
46.0
48.0
50.0
52.0

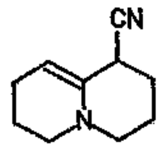


[118]

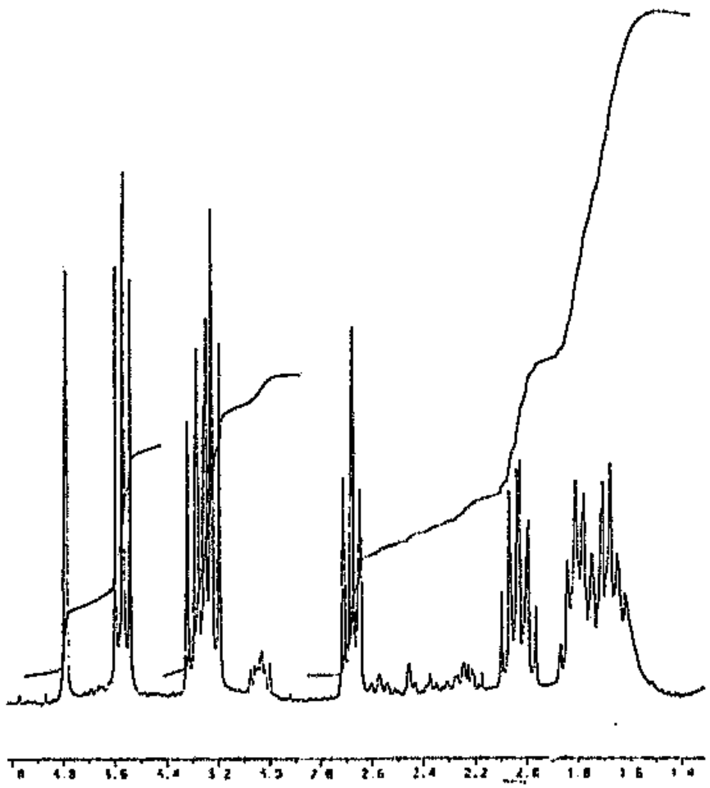


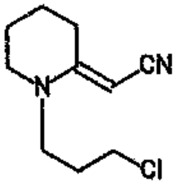



75.0
70.0
65.0
60.0
55.0
50.0
45.0
40.0
35.0
30.0
25.0
20.0
PPM
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
PPM

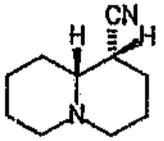

CN
N

[118]

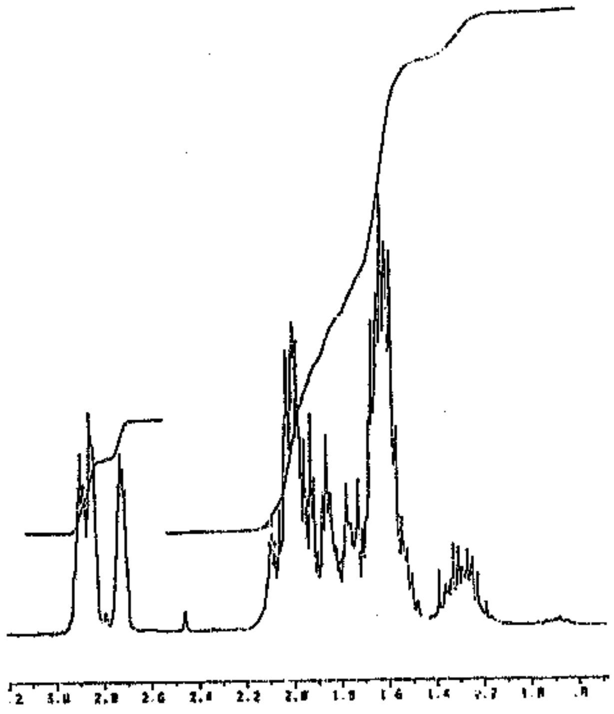


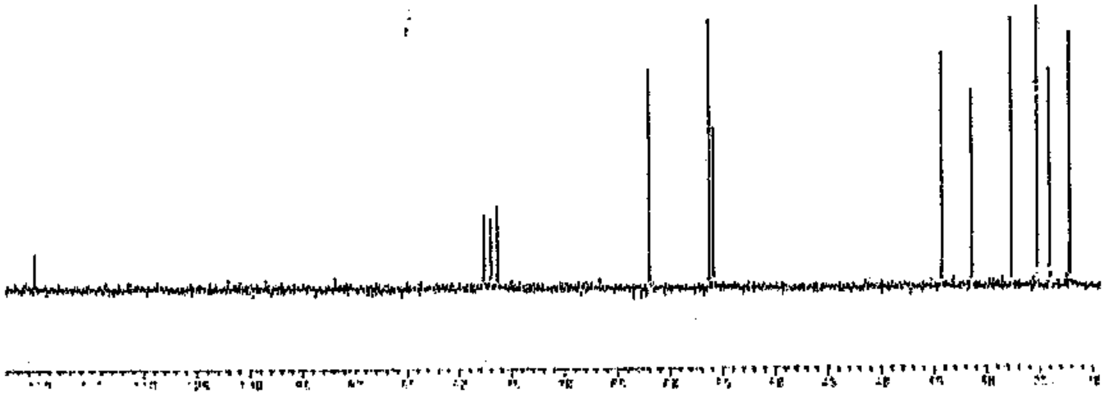


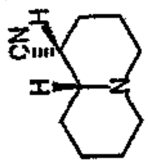
[117]



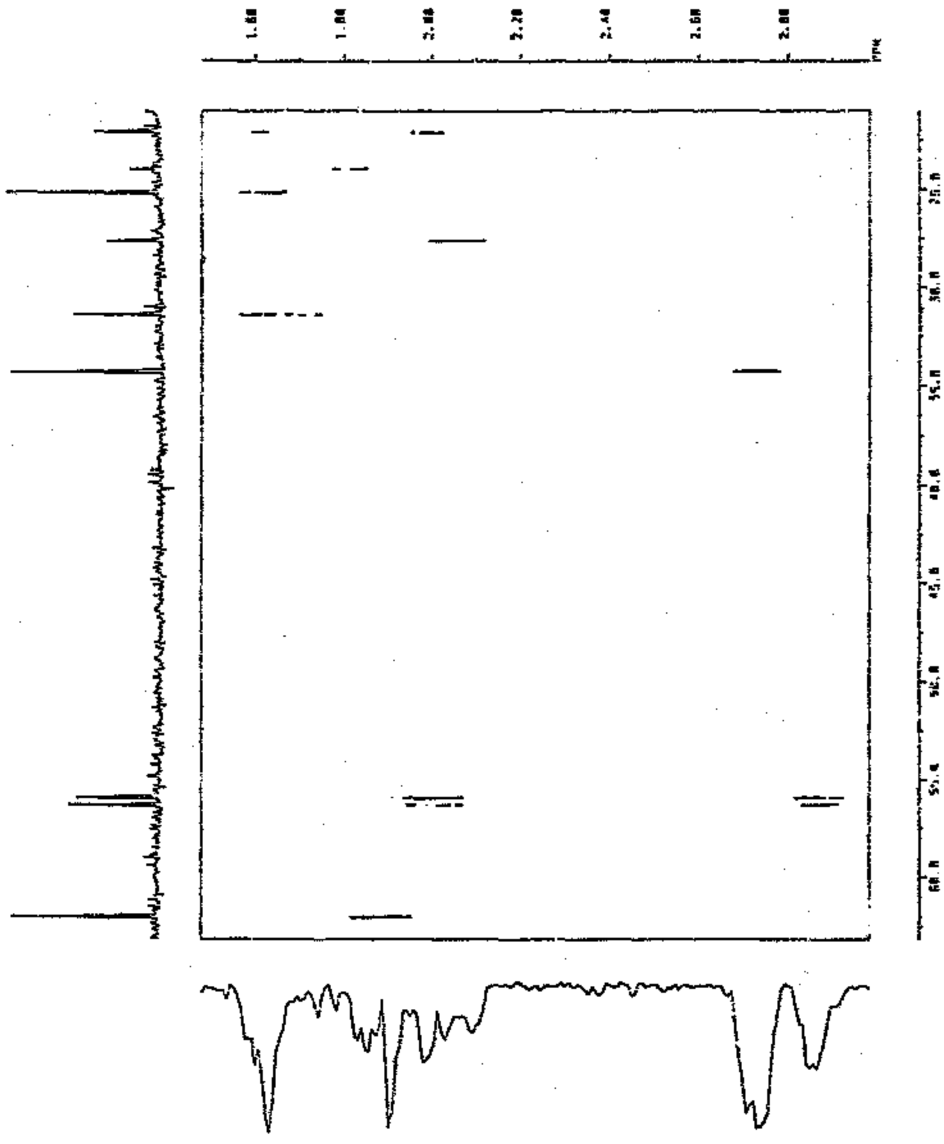
[20]

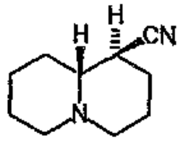




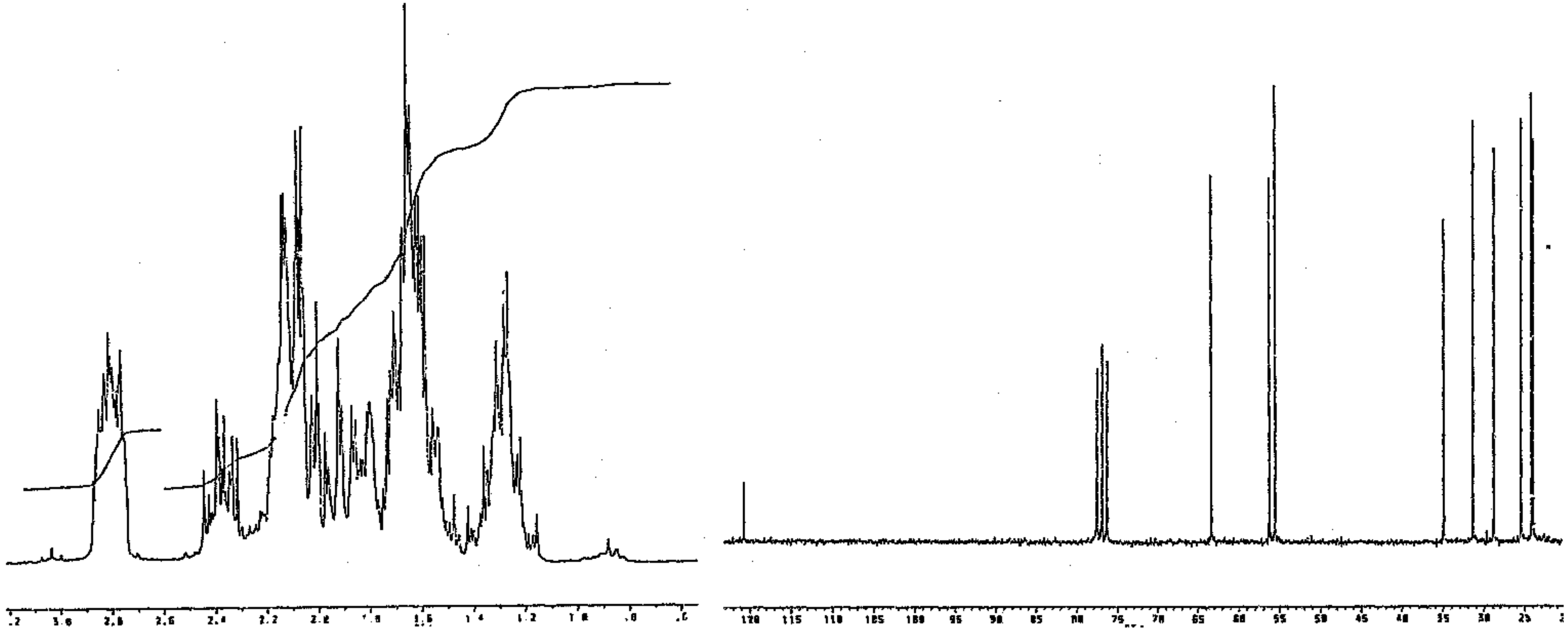

CN
H
H
N

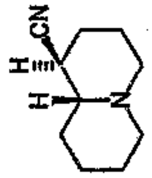
[20]


1.60
1.80
2.00
2.20
2.40
2.60
2.80
PPM
25.0
30.0
35.0
40.0
45.0
50.0
55.0
60.0

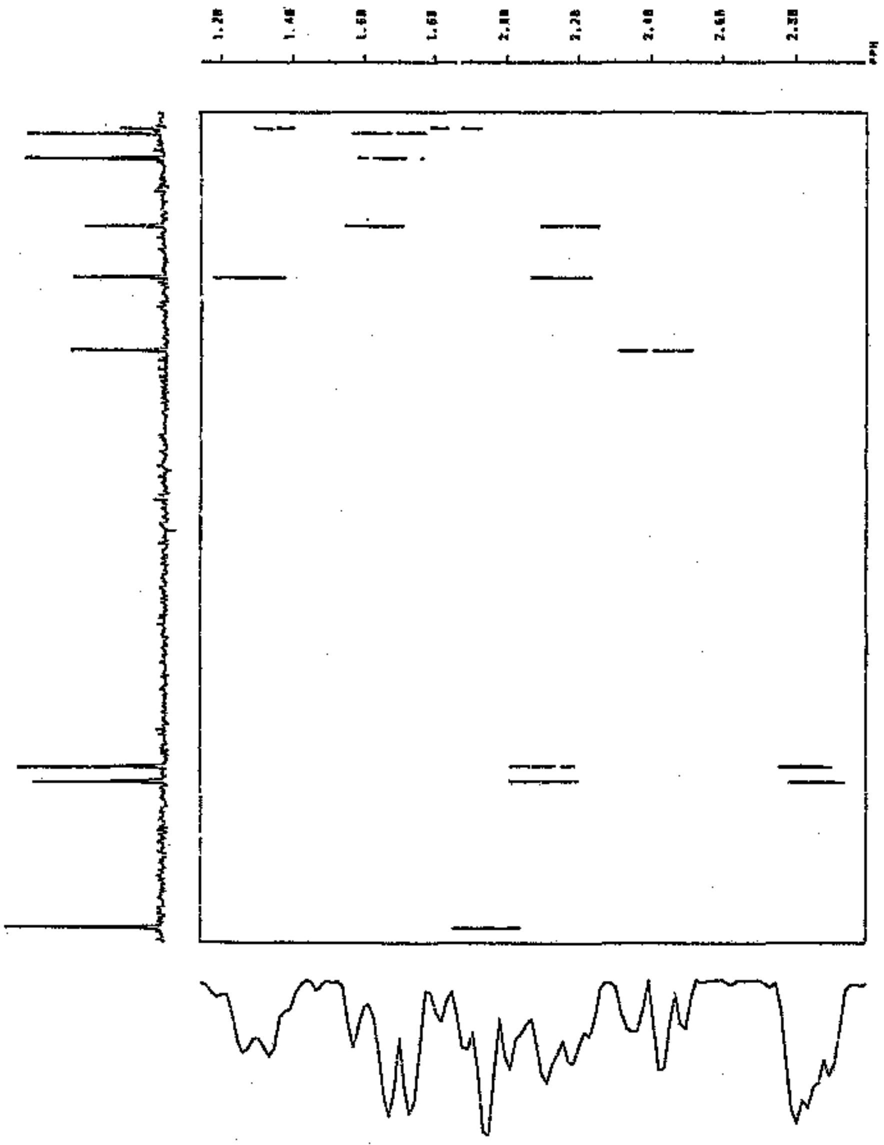


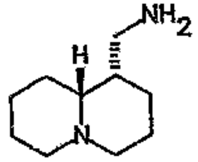
[19]


3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
.8
.6
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25

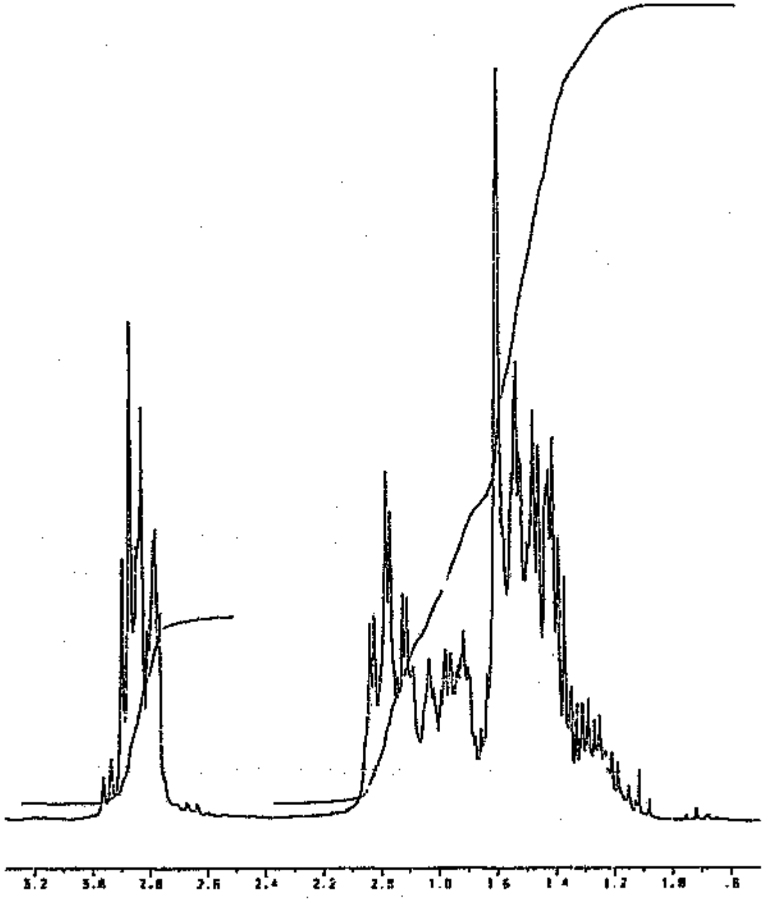

H
H
CN
N

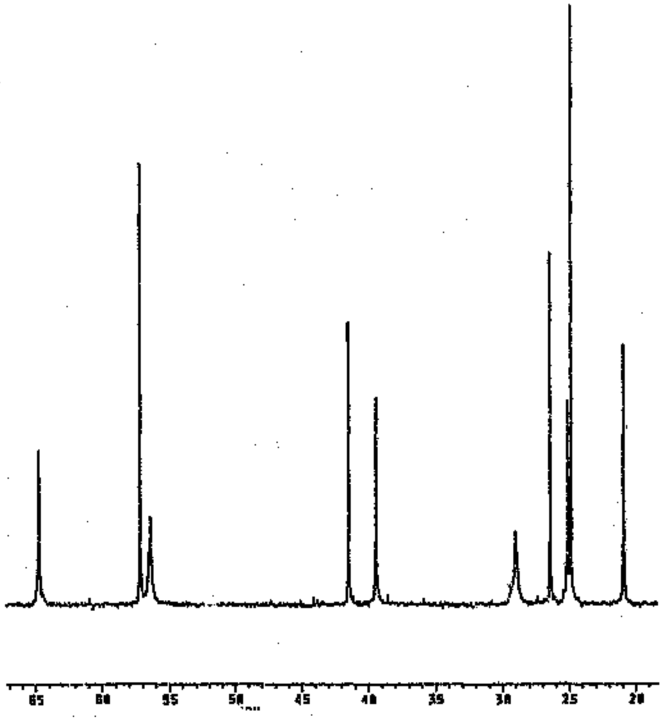
[19]

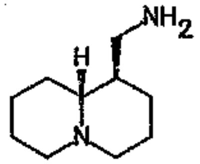

1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
PPM
25.0
30.0
35.0
40.0
45.0
50.0
55.0
60.0
PPM


NH2
H
N

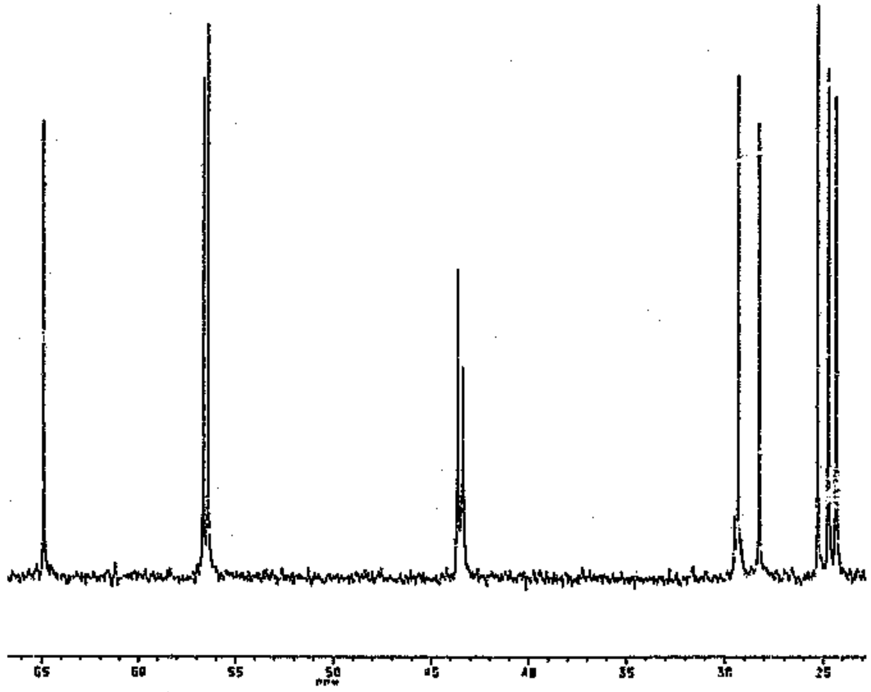
[11]

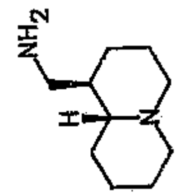

3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
.8


65
60
55
50
45
40
35
30
25
20



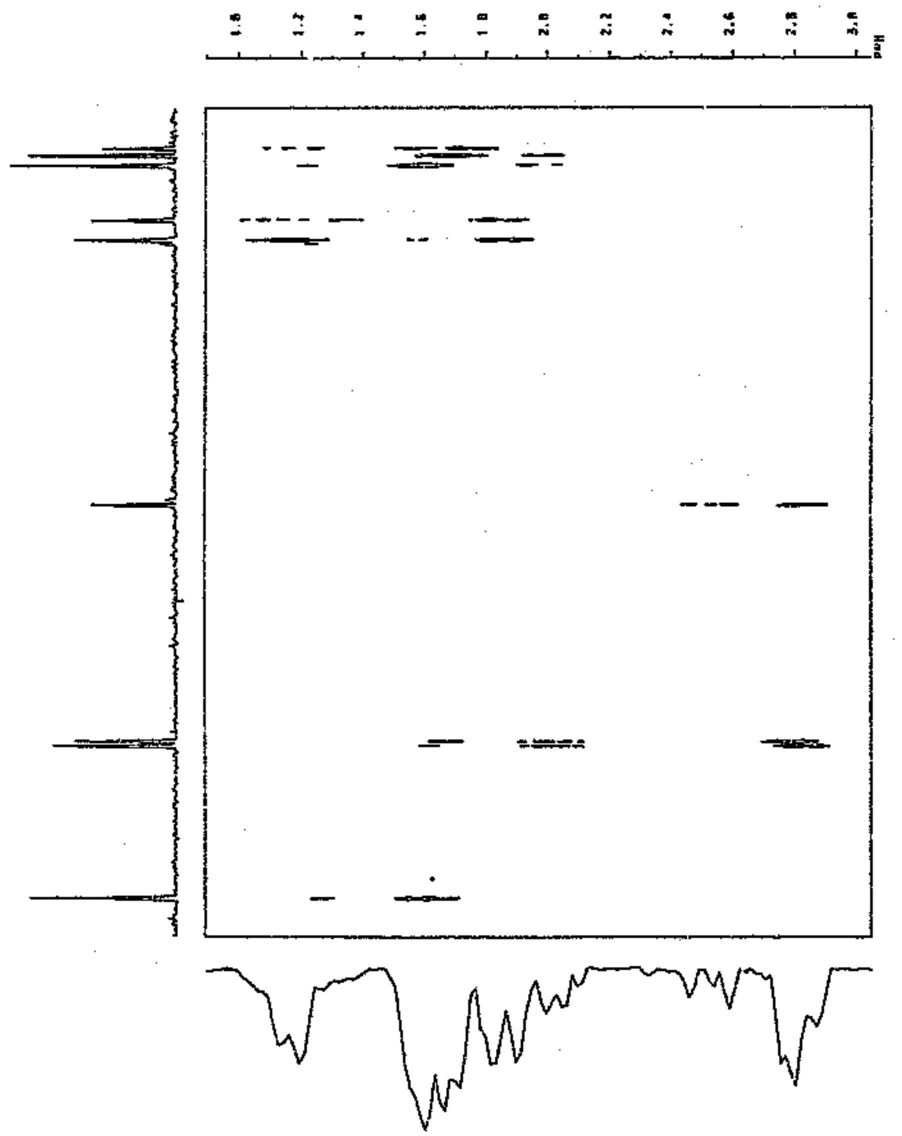
[112]



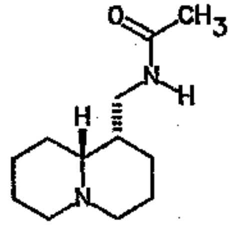


H
N
NH2

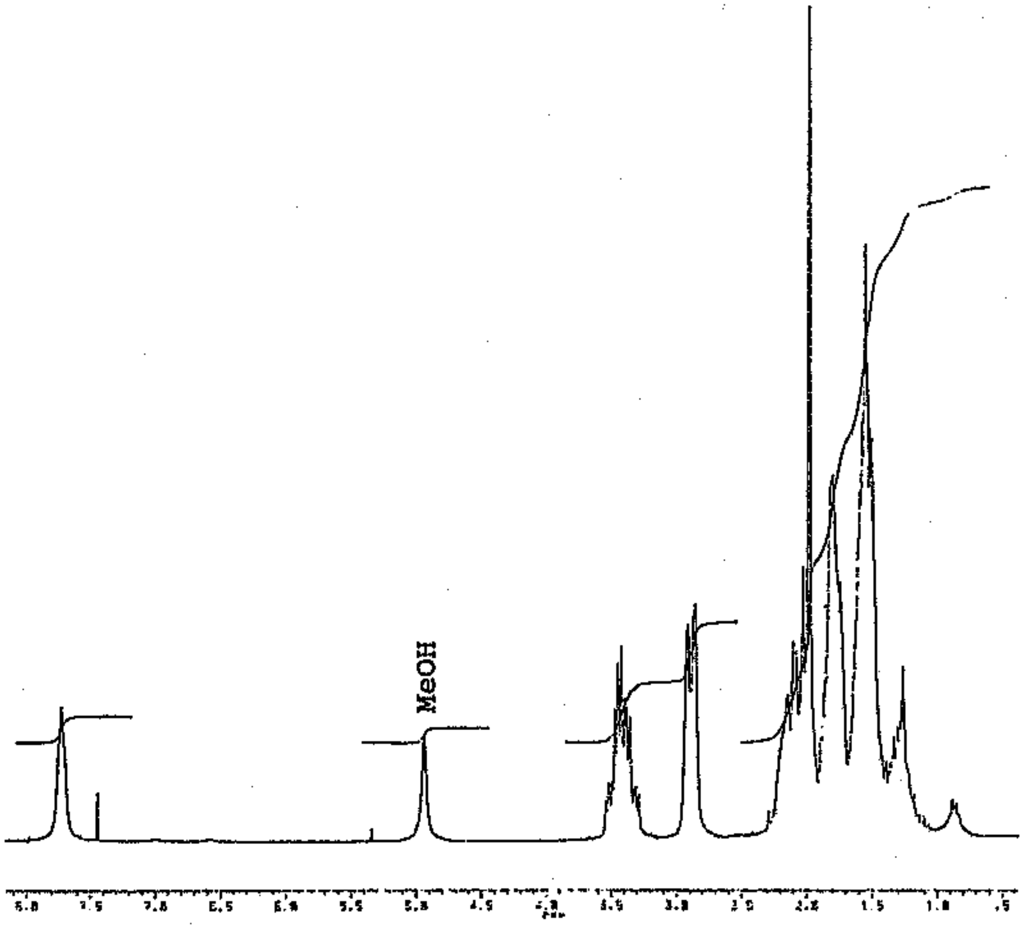
[112]

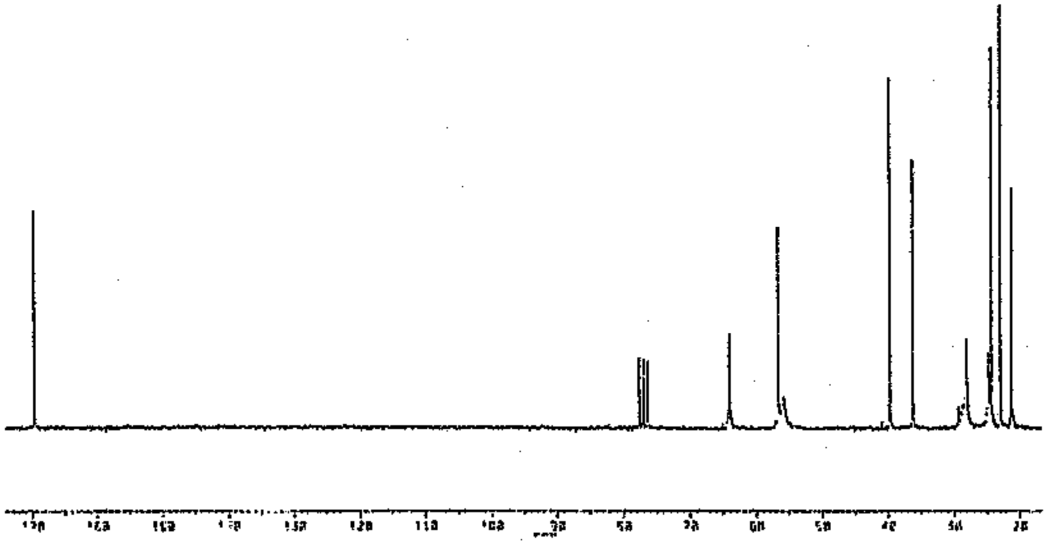


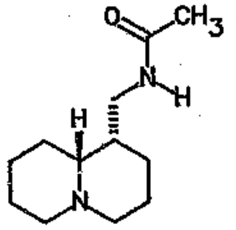
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
ppm
25.0
30.0
35.0
40.0
45.0
50.0
55.0
60.0
65.0



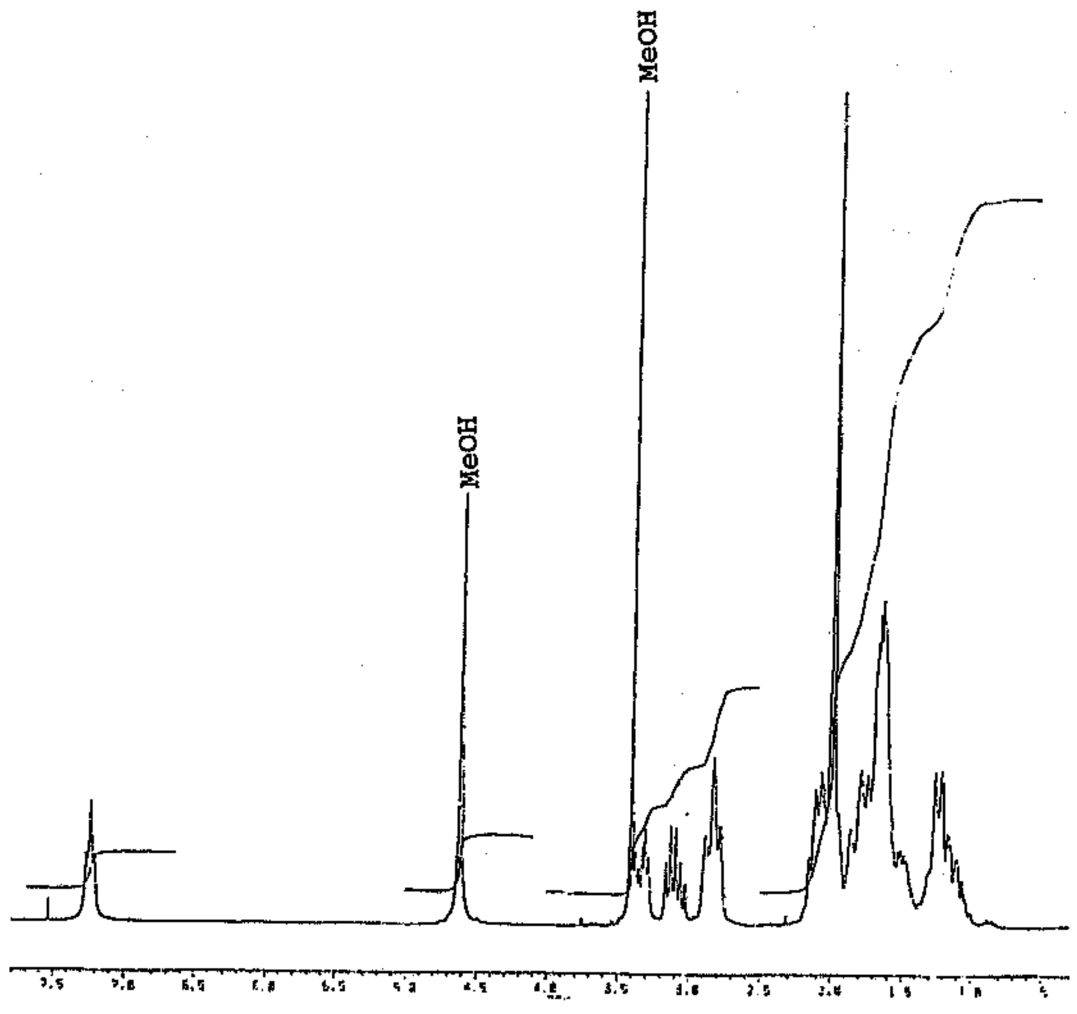
[113]

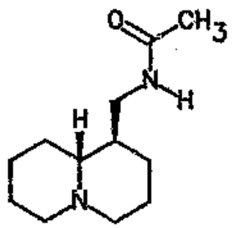




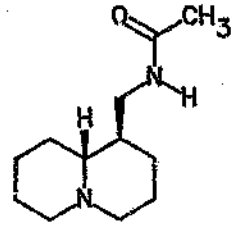


[113]



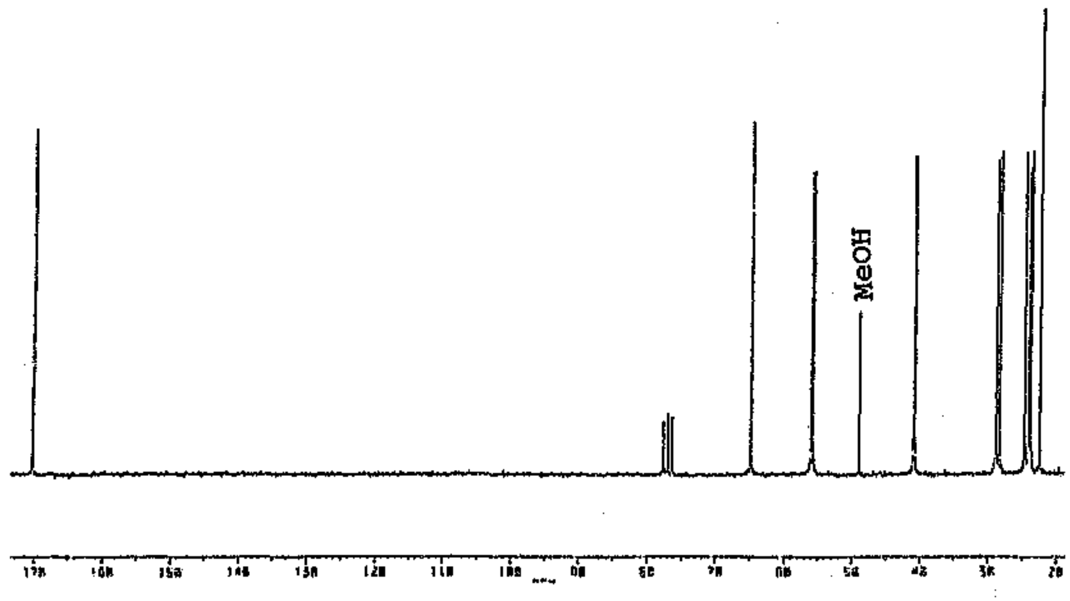


[114]

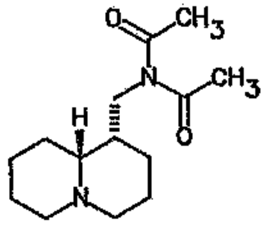


O
CH3
N
H
H
N

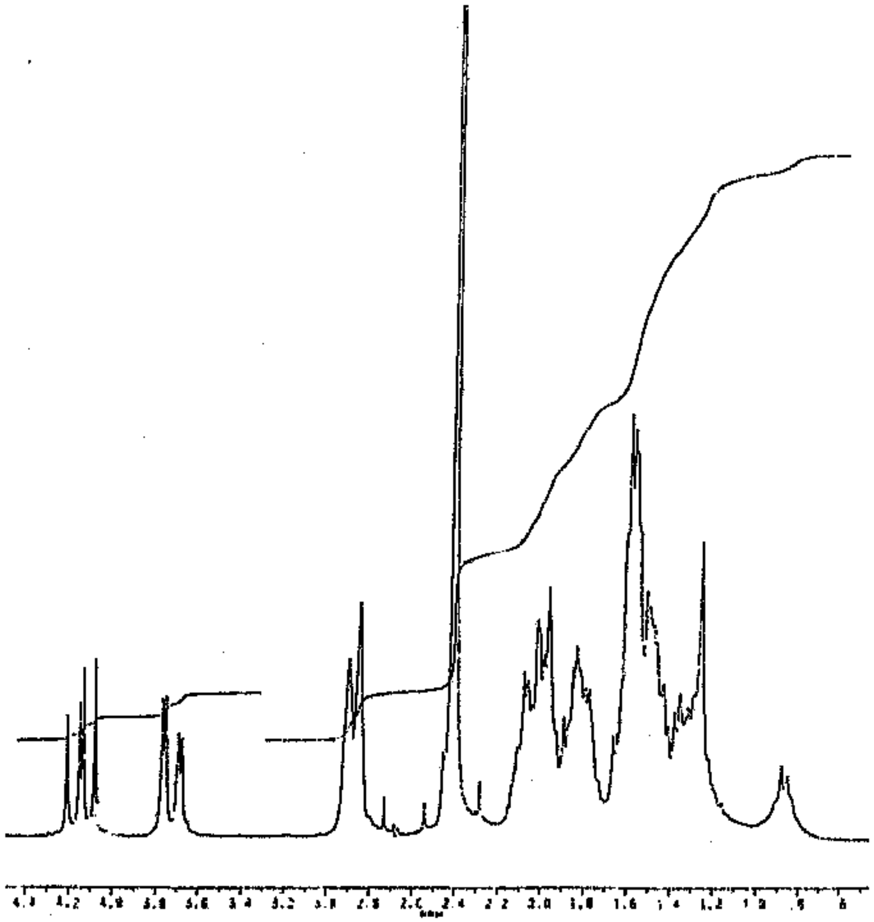
[114]

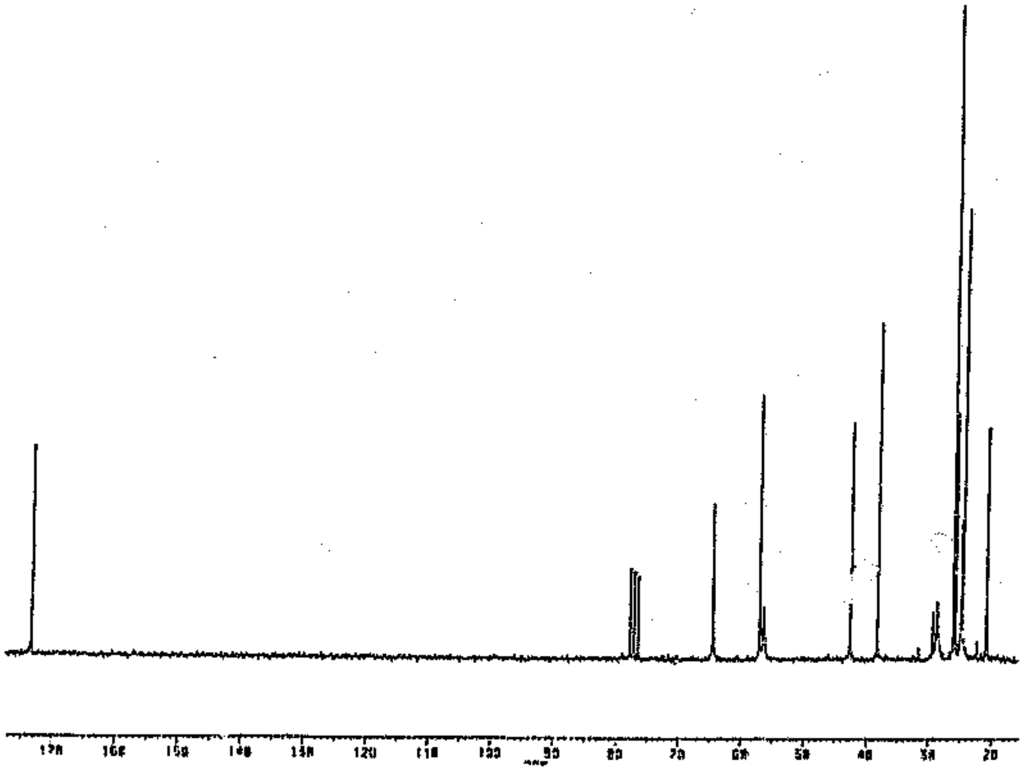


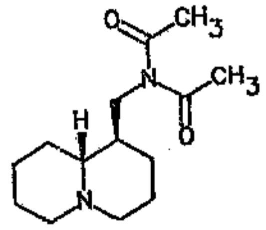
MeOH
170
160
150
140
130
120
110
100
ppm
90
80
70
60
50
40
30
20



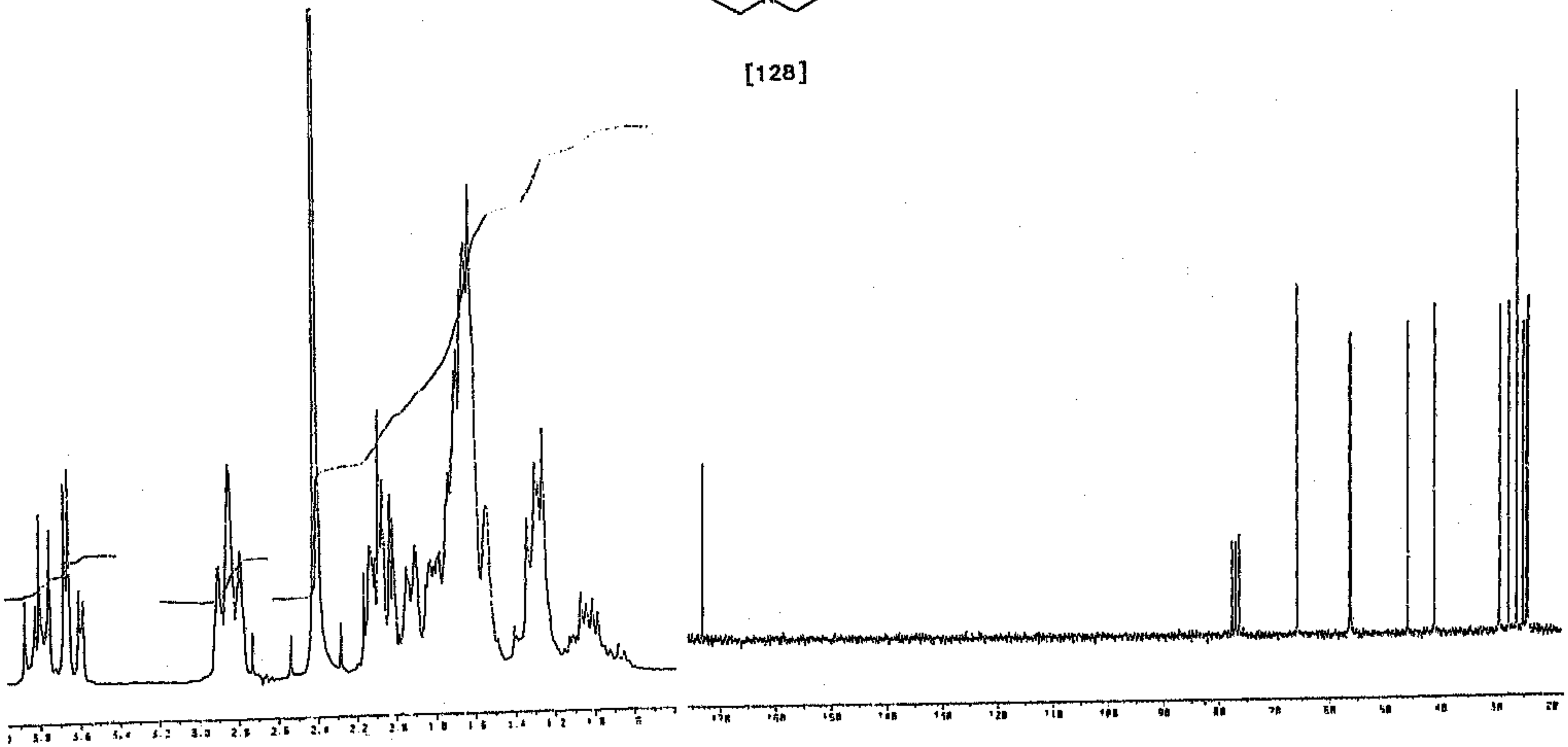
[127]

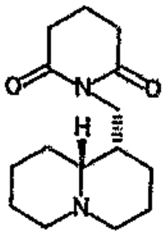

4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
.8
.6
ppm


170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

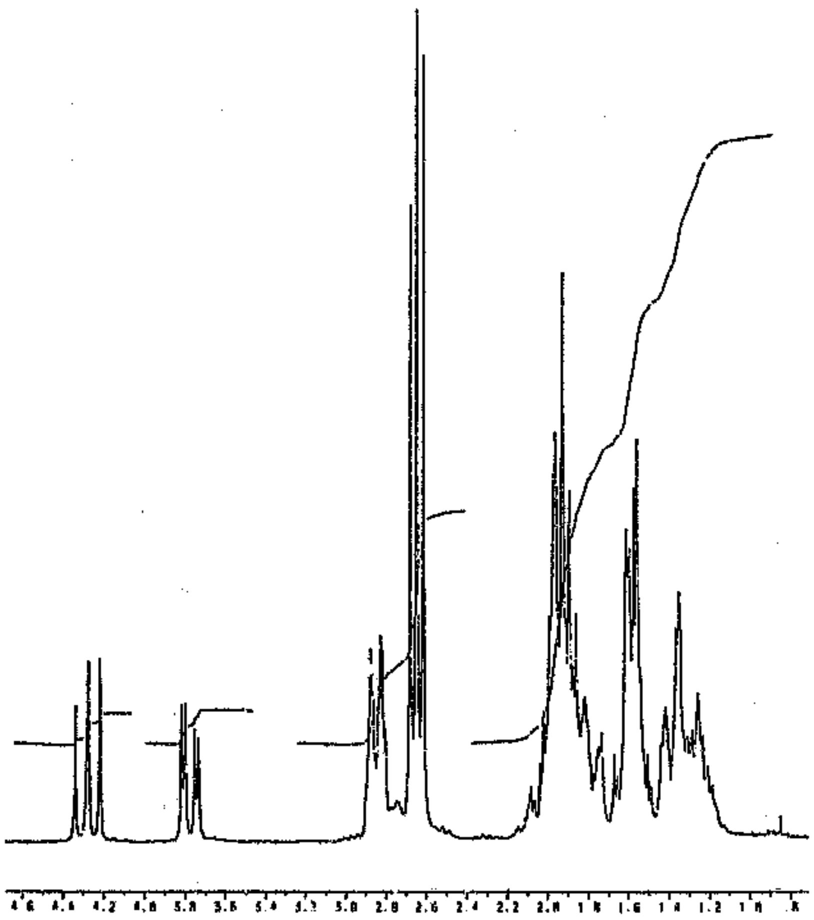

CH3
CH3
O
O
N
H
N

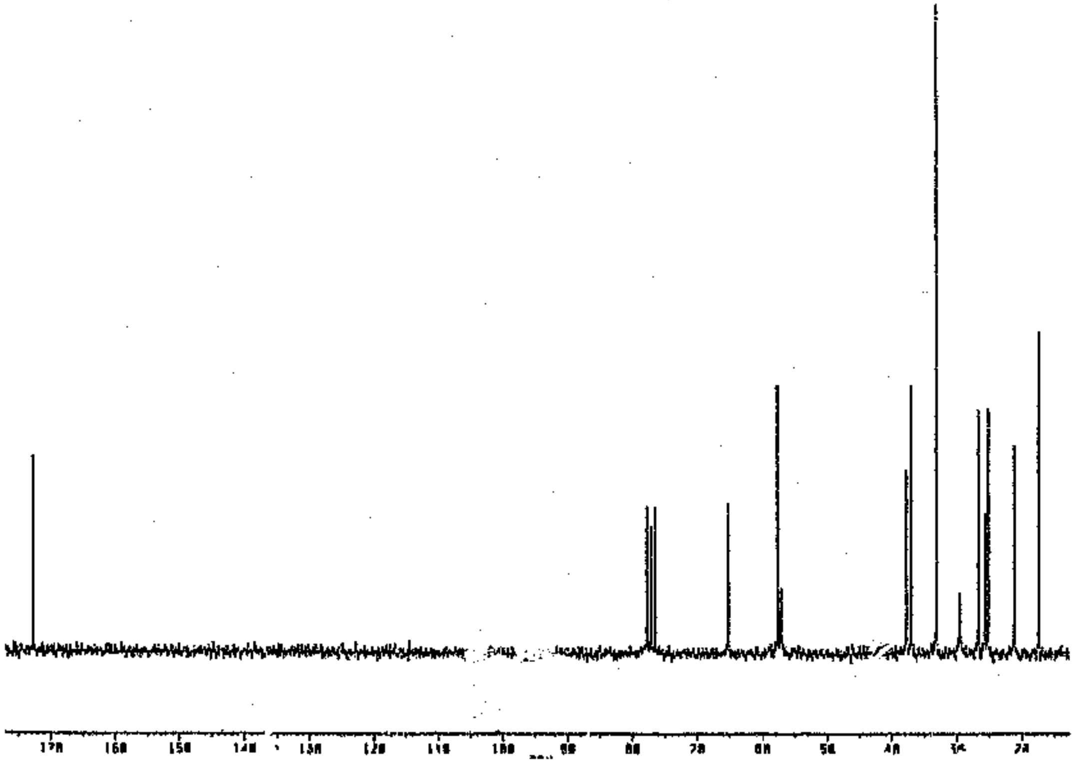
[128]

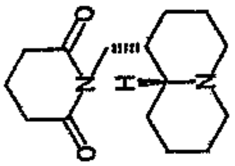

3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
.8
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20



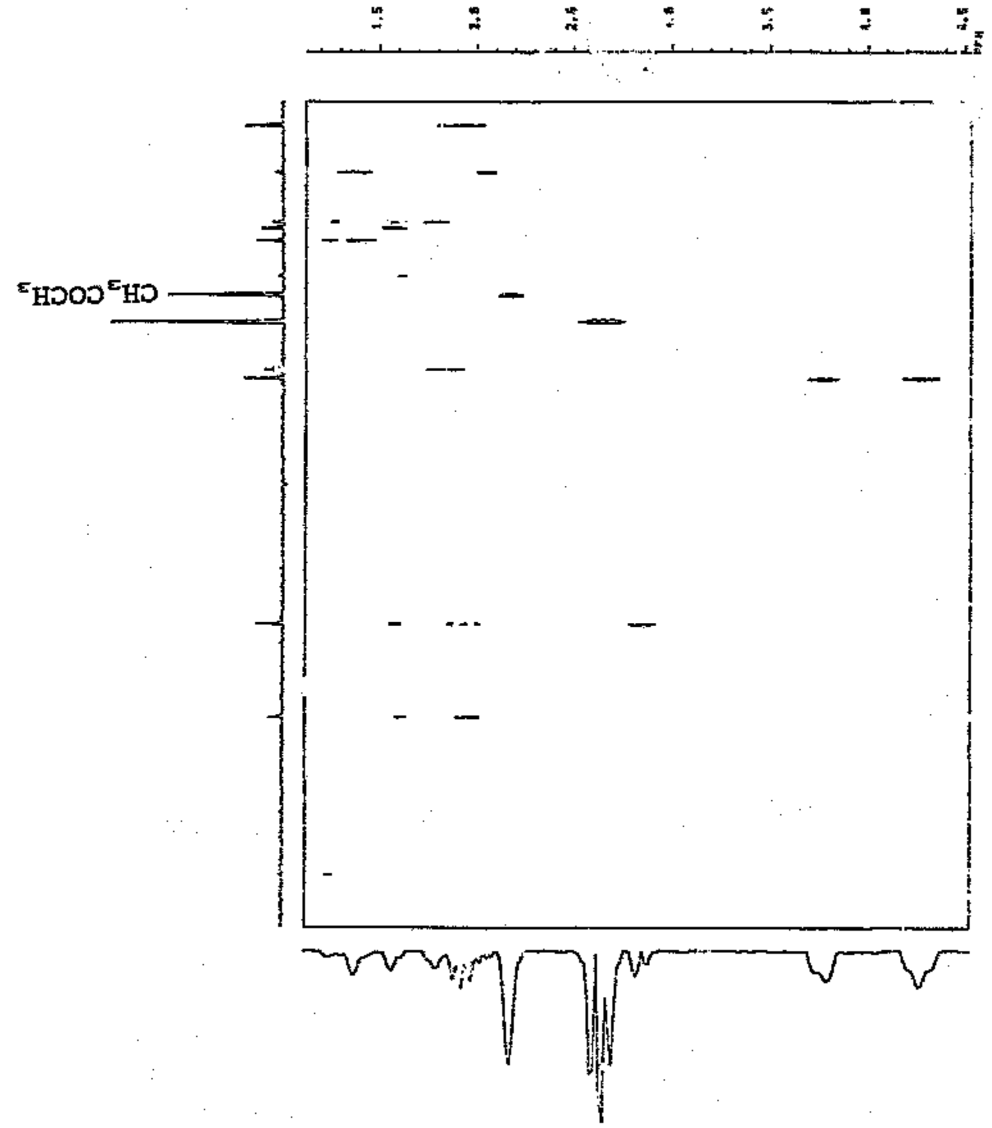
[2]

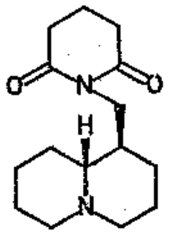

4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
.8


170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

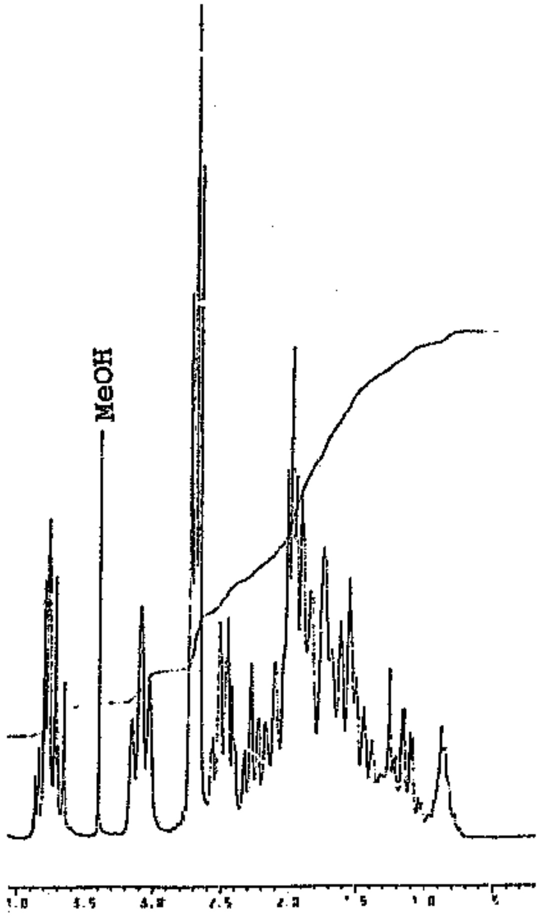


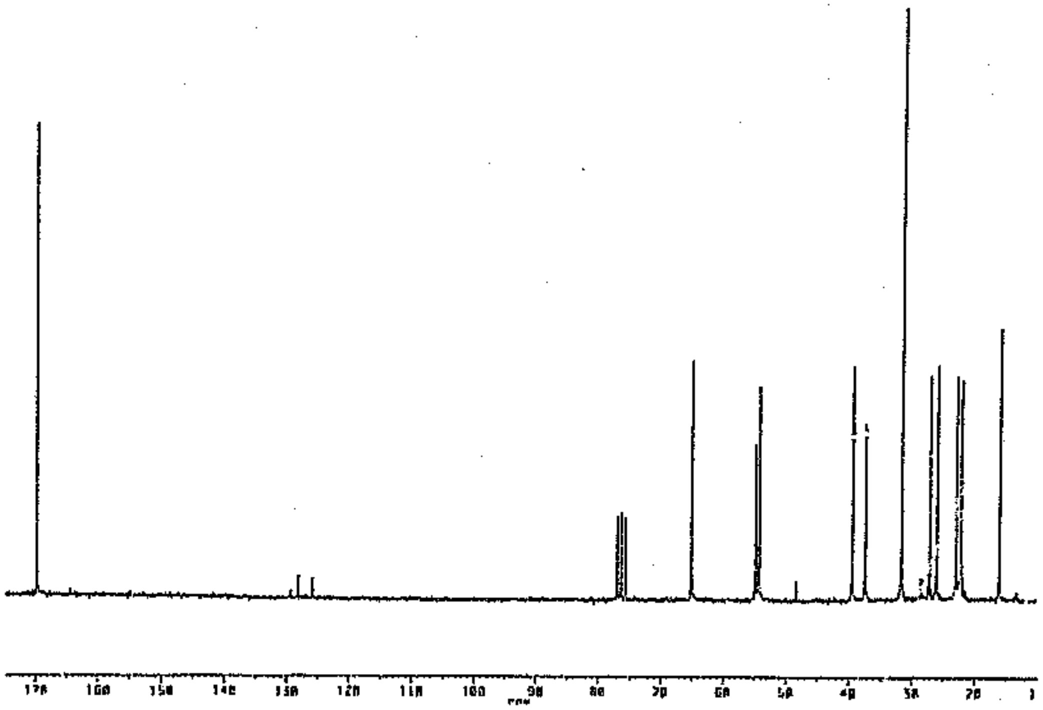
[2]

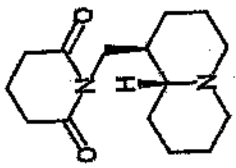




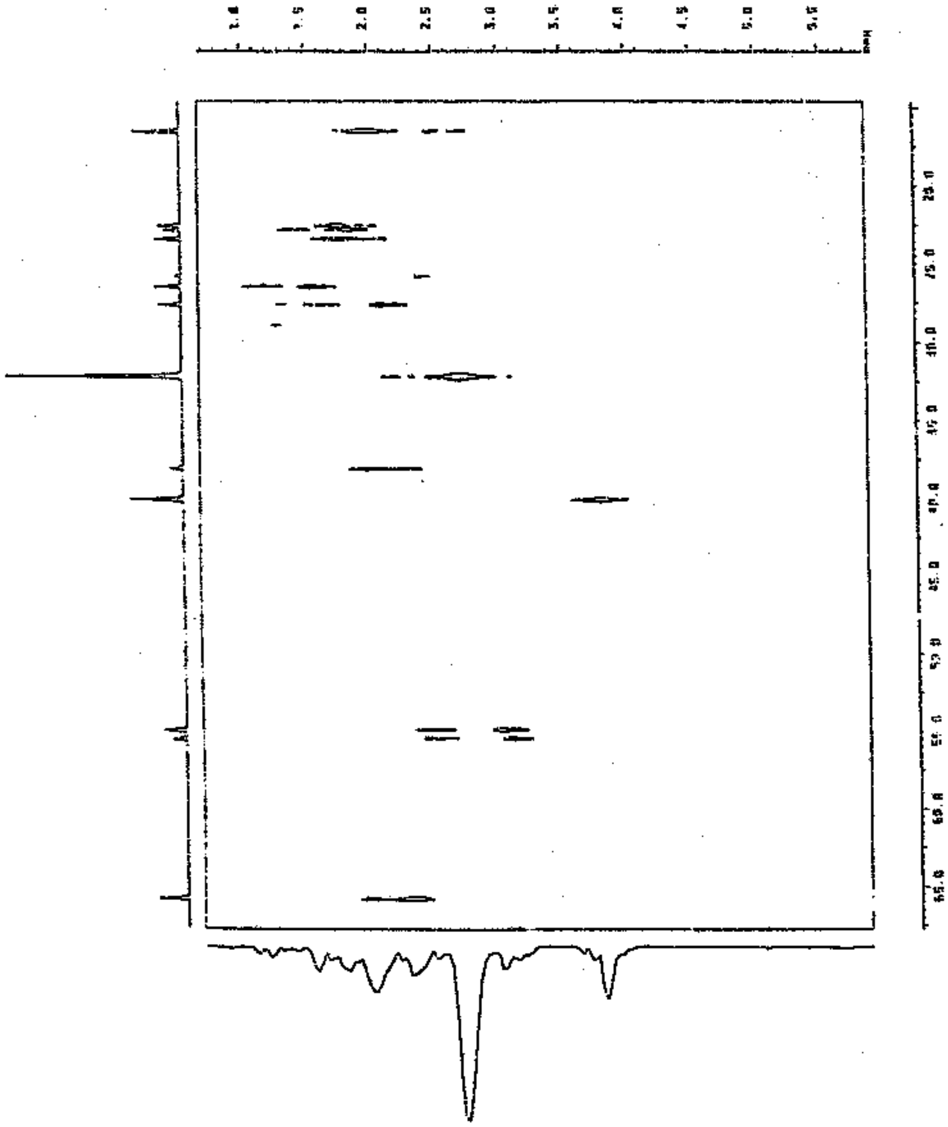
[3]


MeOH
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5


170
160
150
140
130
120
110
100
90
ppm
80
70
60
50
40
30
20
10



[3]


1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
ppm
20.0
25.0
30.0
35.0
40.0
45.0
50.0
55.0
60.0
65.0

Author: Jungmann Christa Maria.

Name of thesis: Synthetic approaches to quinolizidine alkaloids.

PUBLISHER:
University of the Witwatersrand, Johannesburg