Phosphorus- and Sulphur-Mediated Approaches to the Synthesis of Nitrogen and Nitrogen-Phosphorus Heterocycles

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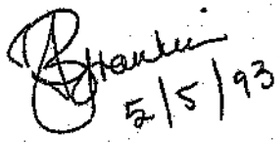
A Dissertation submitted to the Faculty of Science, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the Degree of Master of Science

Department of Chemistry
Johannesburg
May 1993

DECLARATION

I declare that the work presented in this dissertation was carried out by myself under the supervision of Prof J.P. Michael and Prof D.H. Reid. 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.



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Gail Taylor Brankin

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ABSTRACT

This dissertation is divided into two separate and unrelated sections.

Part A describes the attempted synthesis of a number of heterocyclic systems analogous to isoquinoline and ß-carboline, but containing P-N bonds, and with phosphorus in place of C-1. Reaction of ß-phenylethylamine [15] with (dichloro)phenylphosphine sulphide [16] or (dichloro)phenylphosphine oxide [39] gave rise to a number of compounds with acyclic rather than cyclic P-N bonds. *Cis*- and *trans*-1,3-di(phenethyl)-2,4-diphenyl-1,3-diaza-2λ^5,4λ^5-diphosphetidine-2,4-dithione [19], a cyclic compound containing a four-membered ring of alternating phosphorus and nitrogen atoms, was the exception, indicating that intermolecular reaction was preferred over cyclisation. A series of modifications was made to the starting amine [15] in an attempt to promote cyclisation. This approach was unsuccessful. In the reaction of homoveratrylamine [41] or *N*-methyl-2-(3,4-dimethoxyphenyl)ethylamine [44] with (dichloro)phenylphosphine sulphide [16], a side reaction predominated, yielding dimethyl phenyltrithiophosphonate [48] exclusively. To conclude, the synthetic route chosen was found to be useless for preparing P-N heterocycles.

In part B, a novel synthetic approach to the $\Delta^{6,7}$-indolizidine skeleton, as found in the alkaloids ipalbidine and septicine, is presented. An outline of reported synthetic routes to the alkaloids ipalbidine and septicine is described in Chapter 1, with the emphasis on the cyclisation step. This is followed by a presentation of our strategy for the synthesis of the $\Delta^{6,7}$-indolizidine skeleton. Three routes are proposed, each utilising a vinylogous urethane or vinylogous amide intermediate prepared by the sulphide contraction reaction.

Each route comprises four common steps: conjugate addition of a suitable acceptor (phenyl vinyl sulphone or dimethyl vinylphosphonate); salt formation with either ω-bromoacetophenone or ethyl bromoacetate followed by sulphide contraction; reduction; and cyclisation. In this way, 2-benzoylmethyl-1-(2-phenylsulphonyl-

ethyl)pyrrolidine [102] and 2-ethoxycarbonylmethyl-1-(2-phenylsulphonylethyl)-pyrrolidine [101] were prepared. However, reduction of the vinylogous amide (*E*/*Z*)-2-benzoyl-methylene-1-(2-dimethoxyphosphorylethyl)pyrrolidine [113] was unsuccessful.

The base-induced cyclisation step formed the focus of each route. Since the precursor 2-benzoylmethyl-1-(2-phenylsulphonylethyl)pyrrolidine [114] could not be prepared, only two of the cyclisation steps were examined. These base-induced sulphur-mediated cyclisations were unsuccessful. Further investigation is necessary to determine whether the three routes considered, in particular the cyclisation steps, offer a viable synthesis for the preparation of the $\Delta^{6,7}$-indolizidine skeleton.

TABLE OF CONTENTS

PART B

Phosphorus- and Sulphur-Mediated Routes to the $\Delta^{6,7}$-Indolizidine Ring

ABBREVIATIONS

α	*alpha*
β	*beta*
γ	*gamma*
δ	*delta*
υ	*upsilon*
Δ	heat
Å	angstrom(s)
Ac	acetyl
AR	analytical reagent
Ar	aromatic
br	broad
Bu	butyl
BuLi	butyllithium
ca.	*circa*
cm^{-1}	reciprocal centimeter (wave number)
d	doublet
DMF	dimethylformamide
DMSO	dimethyl sulphoxide
E	*entgegen*
Ed.	editor
EE	ethoxyethyl
e.g.	*exempli gratia*
eq.	equivalent
Et	ethyl
et al.	*et alii*
etc.	et cetera
EtOH	ethanol
EWG	electron withdrawing group
expt.	experiment
g	gram(s)

ABBREVIATIONS (continued)

HMPA	hexamethylphosphoric triamide
hr	hour(s)
HRMS	high resolution mass spectrum
Hz	hertz
i.e.	*id est*
i-Pr	*iso*-propyl
IR	infrared
J	coupling constant
L	levorotatory
LDA	lithium di*iso*propylamide
m	multiplet or medium
ml	millilitre
mm	millimetre
M	molar or Mega
M^+	molecular ion
Me	methyl
MeOH	methanol
min	minutes
mol	mole(s)
mp	melting point
m/z	mass-to-charge ratio (ms)
n	*normal*
NCS	*N*-chlorosuccinimide
NEt_3	triethylamine
NMR	nuclear magnetic resonance
no.	number
p	*para*
pp	page(s)
Ph	phenyl
ppm	parts per million

ABBREVIATIONS (continued)

q	quartet
qu	quintet
R	alkyl
R_F	retention factor
RT	room temperature
s	singlet or strong
S	*sinister* (="left")
sh	sharp
SM	starting material
t	*tertiary*
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
temp.	temperature
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
Ts	toluenesulphonyl
Z	*zusammen*

PART A

SYNTHESIS OF HETEROCYCLIC SYSTEMS

CONTAINING

PHOSPHORUS-NITROGEN BONDS

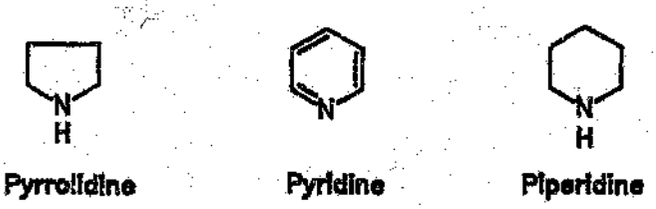
CHAPTER 1: INTRODUCTION, BACKGROUND AND AIMS

1.1 INTRODUCTION

Alkaloids are nitrogenous bases which occur naturally in plants, and to a limited extent in animals, fungi and bacteria. They nearly always contain their nitrogen as part of a heterocyclic system and are often quite complex in structure. A particular alkaloid is usually restricted to certain genera and families of the plant kingdom, rarely being present in large groups of plants. In addition, the alkaloids usually show specific pharmacological activity. However, there is no very sharp distinction between alkaloids and many other naturally occurring nitrogenous compounds. Over five thousand alkaloids have been isolated and the structures of most of them are known[1,2].

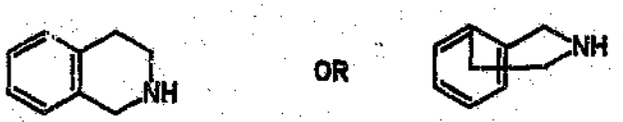
No systematic nomenclature or structural classification for alkaloids exists. The alkaloids are grouped essentially according to their structure, rather than according to their botanical origin[1,3].

SOME BASIC ALKALOID RING SYSTEMS[3]

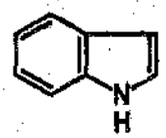


Pyrrolidine **Pyridine** **Piperidine**

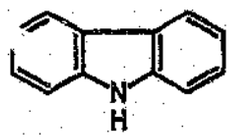
Isoquinoline **Quinoline**



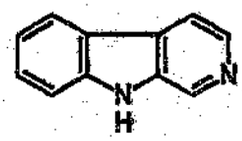
Tetrahydroisoquinoline **(Morphine Group)**



Indole



Carbazole

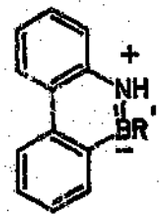


β–Carboline

The exploration of the plant kingdom for chemical compounds of medicinal value has been going on for thousands of years, and herbalism and folk medicine, ancient and modern, have been the source of much useful therapy. There is still plenty of scope for finding new and useful drugs, either by searching for alkaloids in plant species not previously investigated, or by studying synthetic analogues of known alkaloids[3]. The aim of this project was to synthesise new phosphorus-containing heterocyclic systems, based on the isoquinoline and β-carboline (Harmala Alkaloids) ring systems, by substituting phosphorus in place of C-1. The motivation for the preparation of these compounds lies in the fact that they are chemically interesting structures, and they may have useful biological activity.

1.2 BACKGROUND

This project derives its inspiration from publications describing heterocyclic analogs of the phenanthrene ring system containing nitrogen and phosphorus in the 9- and 10-positions. The idea of generating heteroaromatic phosphorus compounds isoconjugate with phenanthrene was devised by Dewar *et al.*[4] by analogy with a series of heteroaromatic boron compounds made by his group[5,6] in which carbons 9- and 10- were replaced by nitrogen and boron respectively. Some of the heteroaromatic boron compounds synthesised by Dewar *et al.*[5] are shown below.



R' = Cl

R' = Ph

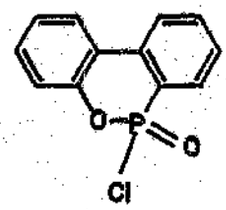
R' = Me

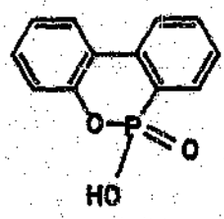
R' = Et

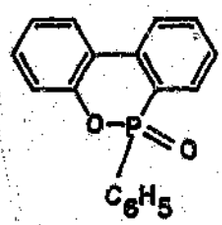
Chernyshev *et al.*[7] and Bhatia *et al.*[8-10] introduced oxygen and phosphorus in place of C-9 and C-10 in phenanthrene, and Bhatia *et al.*[11] extended this idea to the 3,4-

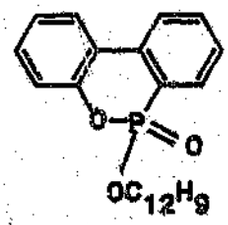
dihydrophenanthrene ring system in which C-1 and C-2 are replaced by oxygen and phosphorus. The properties of these systems have been studied in detail[5-12] owing to the possibility of their being biologically active.

Chernyshev *et al.*[7] synthesised compounds of the type shown below.

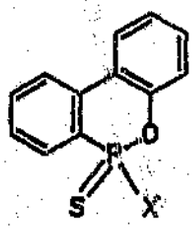








Biphenyl[13] and 2-hydroxybiphenyl[14] are important fungicides for citrus fruits. To explore fungicidal activity further, Bhatia *et al.*[8,9] prepared several phosphorus-containing biphenyls, including 6-chloro-6H-dibenz[c,e][1,2]oxaphosphorin-6-sulphide [1] and its 6-methoxy [2], 6-ethoxy [3] and 6-diethylamino [4] derivatives. Fungitoxicity of the seven-membered ring analogues [5] and [6] had previously been reported[15,16].

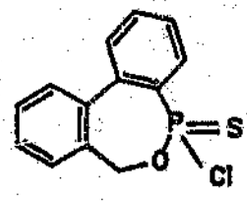


[1] X = Cl

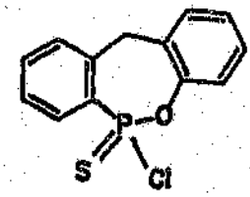
[2] X = OC_2H_5

[3] X = OCH_3

[4] X = $-N(C_2H_5)_2$



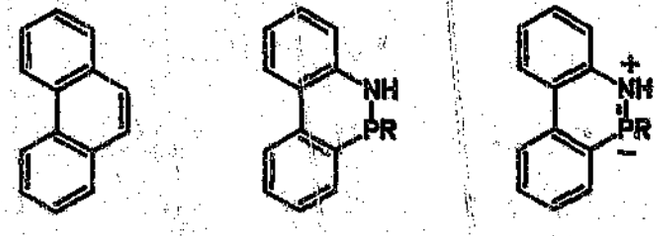
[5]



[6]

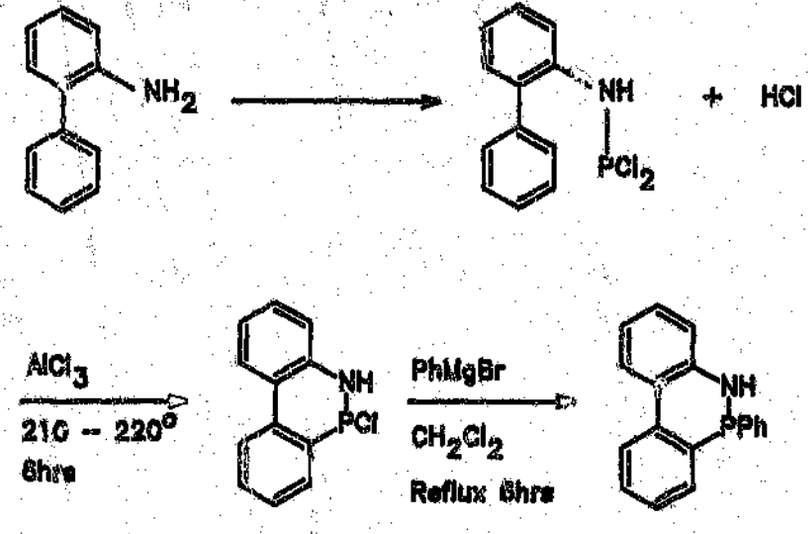
Dewar *et al.*[4] considered it possible to prepare a series of aromatic phosphorus compounds analogous to their boron compounds, by replacing a carbon atom in an aromatic system by P^-. The phenanthrene system was chosen since a number of analogous borazarophenanthrenes were already available to provide spectra for comparison, and few synthetic difficulties were expected[5].

For the series of heteroaromatic phosphorus compounds synthesised by Dewar *et al.*[4], each is derived from a carbocyclic aromatic compound by replacement of one carbon by P^- and a second by N^+, giving a neutral molecule isoconjugate with the aromatic hydrocarbon. The relation of compounds of type [8] to those of type [7] is indicated by the dipolar resonance structures e.g. [9].

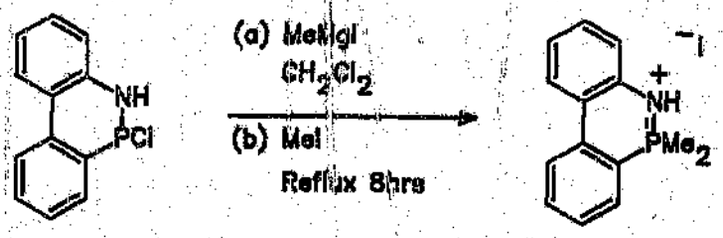


[7] [8] [9]

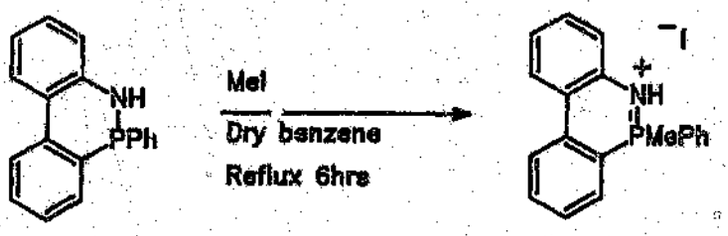
Schemes 1, 2 & 3 show three of the derivatives of 9,10-dihydro-9,10-azaphospha-phenanthrene [8] synthesised by Dewar *et al.*[4].



Scheme 1

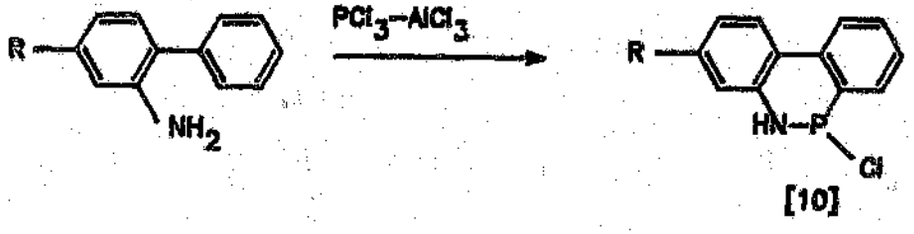


Scheme 2

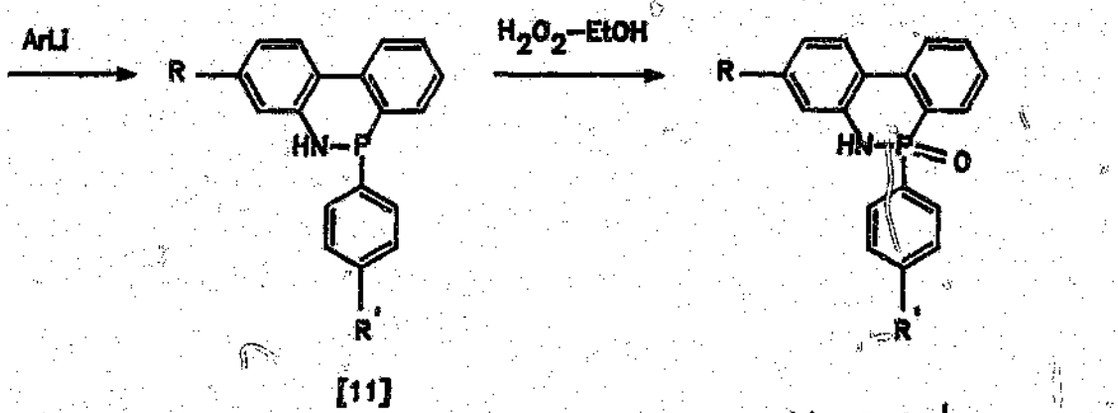


Scheme 3

Campbell and Way[17] attempted the synthesis of 10-aryl-9,10-dihydro-9-aza-10-phosphaphenanthrenes [11] by the method shown in Scheme 4. Interaction of phosphorus trichloride with 2-aminobiphenyl and with 2-amino-4-methylbiphenyl and treatment of the products with aluminium chloride gave cyclic chlorophosphines [10] which were too sensitive to moisture to be readily isolated in a pure state. The crude compounds were therefore arylated directly by means of an aryl-lithium or Grignard reagent and the azaphosphaphenanthrenes [11] were obtained in yields ranging from 5 to 25%. Like simple aromatic phosphines, the members of the group were stable in air but were readily oxidised by hydrogen peroxide in ethanol at room temperature.



[10]

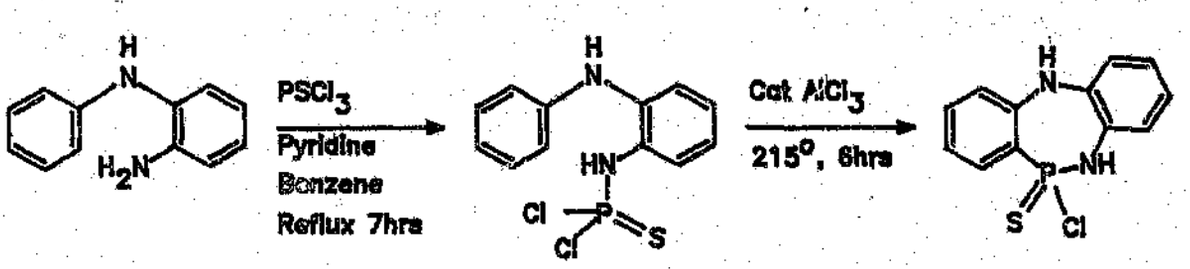


[11]

(a) R = R' = H
(b) R = Me, R' = H
(c) R = H, R' = Me
(d) R = H, R' = Br
(e) R = H, R' = NMe_2

Scheme 4

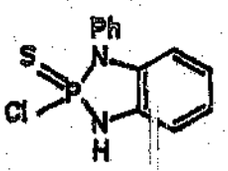
Bhatia *et al.*[16] claimed to have prepared the seven-membered ring system [12] according to the reaction sequence shown in Scheme 5.



[12]

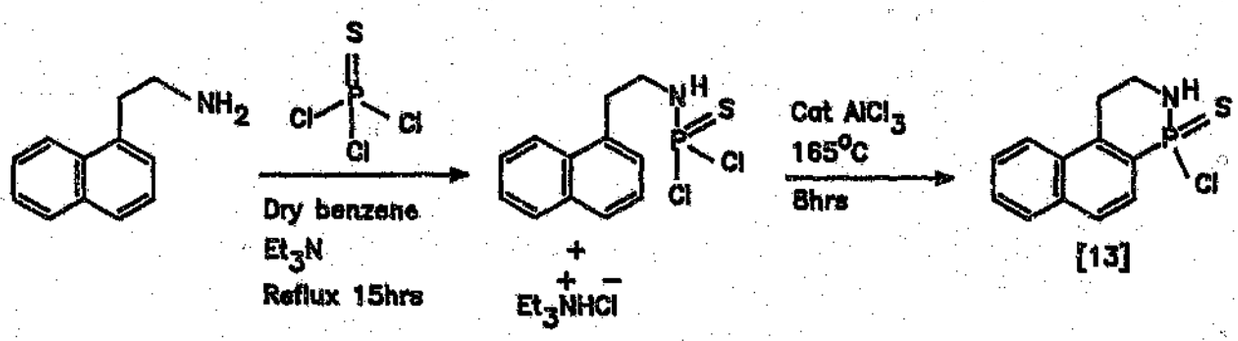
Scheme 5

This is an unusual reaction, and we suspect that the product may actually have the alternative structure shown below.



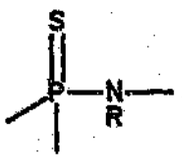
A number of novel heterocyclic compounds have been described above. The ultraviolet spectra of these compounds were compared with those of the analogous boron compounds. It was concluded that the close resemblance indicates that both types of compounds have similar electronic structures. Since the boron compounds are known to be aromatic i.e. they obey the Hückel number of $4n+2$ where $n = 0, 1, 2 \ldots$, this suggests that the phosphorus analogues may be aromatic too. The above discussion describes a preliminary study and further work is needed to clarify the electronic structures and chemical properties[9].

The main synthetic route to be considered during this project is based on the reported formation of 4-chloro-1,2,3,4-tetrahydronaphth[3,4-c]-[1,2]azaphosphorine-4-sulphide [13], a new ring system in which nitrogen and phosphorus replace C-3 and C-4 respectively in the phenanthrene ring. The synthesis was achieved as indicated in Scheme 6[18].



Scheme 6

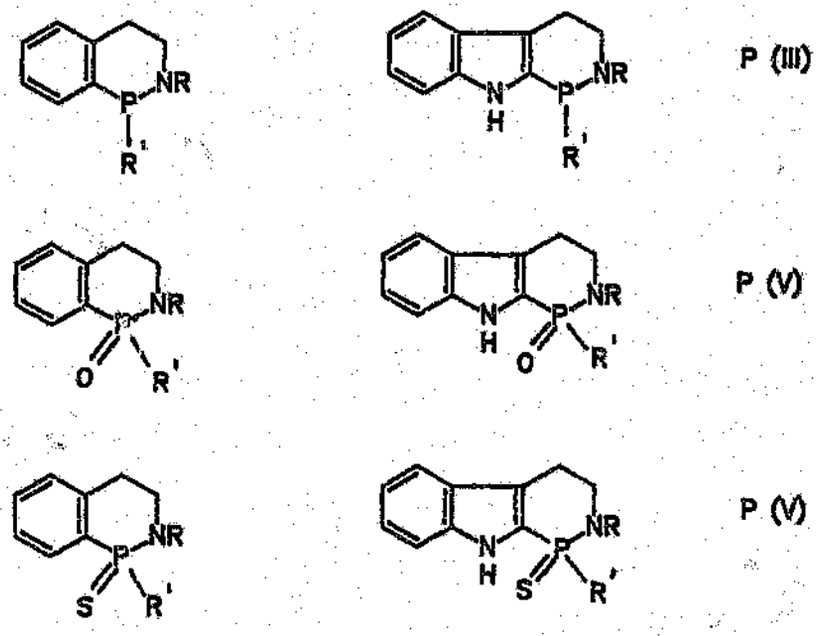
It should be noted that thiophosphoryl ester linkages and dialkylamine groups attached to phosphorus are structural features thought to increase biological activity[9,19]. In this project, these two features are combined to give a thiophosphoryl amide linkage [14] shown below. Our work, described in this dissertation, involved attempts to synthesise a series of compounds containing this group.



[14]

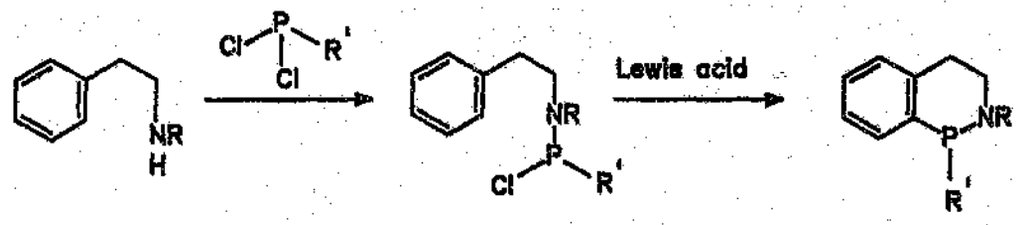
1.3 AIMS OF THIS PROJECT

Phosphorus exists in both the P(III) and P(V) state. In the P(V) state, the phosphorus atom may be bonded to oxygen or sulphur. Phosphorus analogues hitherto unknown and of interest in this project are as follows:

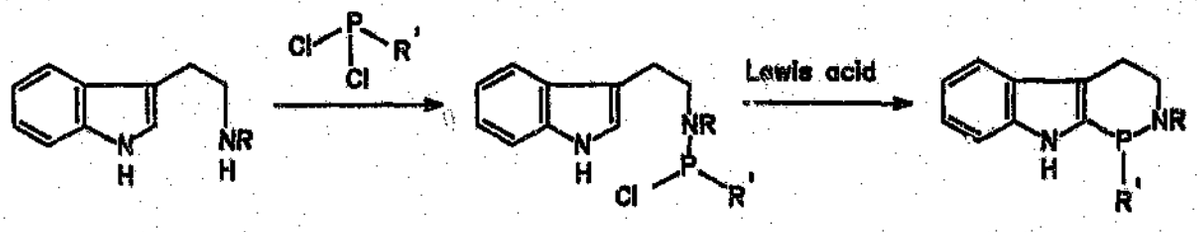


All these structures may have substituents attached to the aromatic ring.

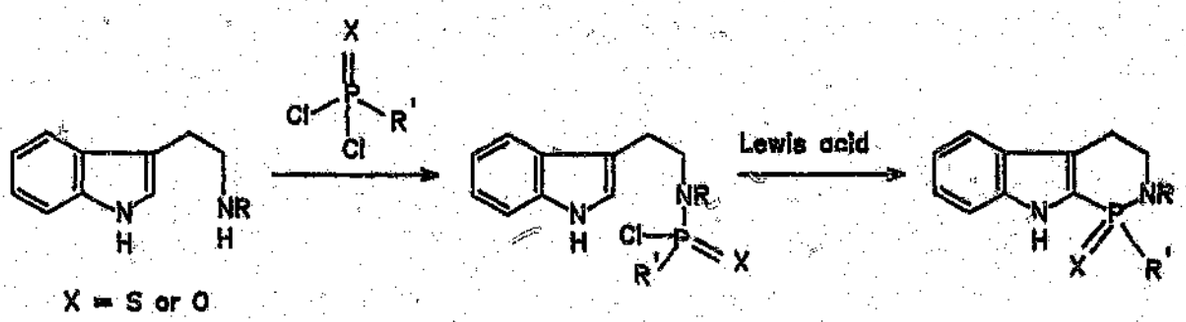
Proposed routes to these compounds are shown in Schemes 7 - 10 below.



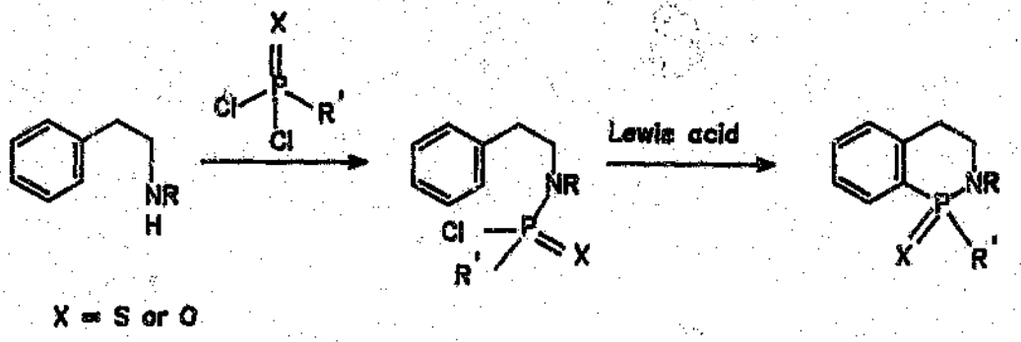
Scheme 7



Scheme 8



Scheme 9



Scheme 10

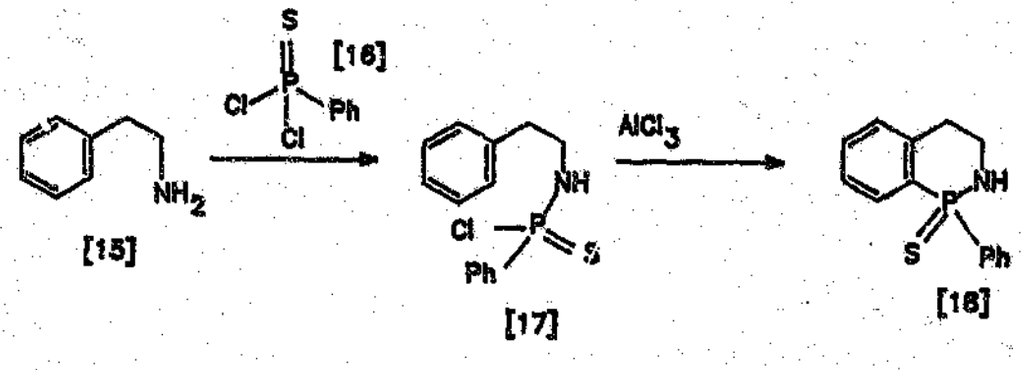
All reactions are likely to occur in two steps. In the first step a phosphorus-nitrogen bond is established and the second step involves cyclisation catalysed by a Lewis acid. A variety of Lewis acids to effect cyclisation were to be tested. Those to be considered were aluminium chloride ($AlCl_3$), stannic chloride ($SnCl_4$) and boron trifluoride (BF_3). The effect of activating groups on cyclisation was also to be examined.

CHAPTER 2: RESULTS AND DISCUSSION

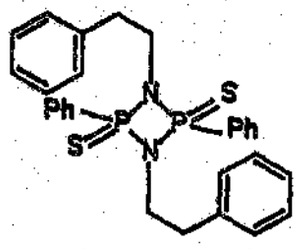
At the beginning of this project, we set out with a number of synthetic targets in mind. The aim was to synthesise heterocyclic systems containing phosphorus-nitrogen bonds. The project was unsuccessful in terms of the targets we chose, but a number of new compounds containing P-N bonds were prepared.

2.1 PREPARATION OF CYCLOPHOSPHAZANE [19]

Our objective was to prepare the heterocyclic system [18] through the reaction of (dichloro)phenylphosphine sulphide [16] with β-phenylethylamine [15], followed by cyclisation of the intermediate [17] in the presence of anhydrous aluminium chloride (Scheme 11).



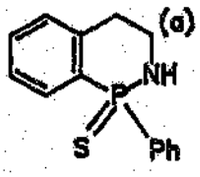
Scheme 11



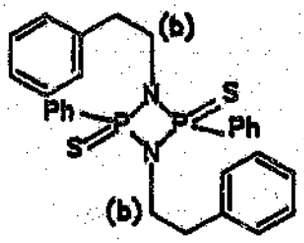
[19]

Compound [18] was not obtained; instead, compound [19] was isolated readily on a number of occasions.

Microanalysis results agreed with both structures [18] and [19]. Careful scrutiny of the ^{1}H and ^{13}C NMR spectra showed that structure [18] could not accomodate the spectral pattern. The ^{1}H NMR spectrum lacked the signal one would expect to see for the NH proton in [18]. In addition, there was a high field triplet at 36.52ppm in the ^{13}C NMR spectrum that could not be accounted for by structure [18].



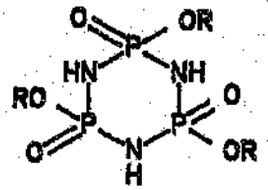
[18]



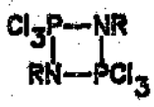
[19]

Equivalent methylene carbons (b) would couple to two phosphorus atoms, resulting in a triplet. In contrast, carbon (a) would give only a doublet. This eliminates [18] as a possible structure. The ^{13}C NMR data thus support structure [19] for the reaction product.

Compound [19] belongs to the class of compounds known as phosphazanes, which may be acyclic or cyclic compounds. The cyclophosphazanes, for example compound [19], constitute a diverse group which have the common characteristic of a formally saturated P-N ring bond. Several different types of phosphazane compounds are known including the cyclotriphosphazanes or trimetaphosphimates depicted in [20] and the cyclic dimeric derivatives of the types shown in [21] and [22][20]. Although the six-membered cyclophosphazanes are known, the four-membered cyclic structure is more prevalent.



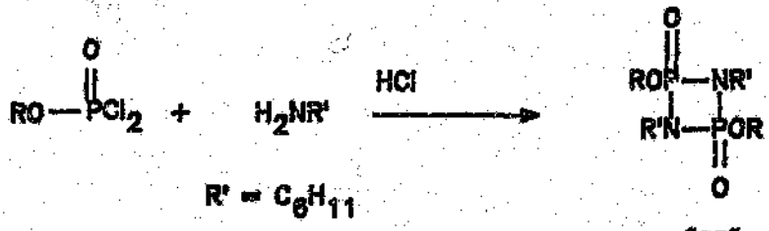
[20]



[21]

[22]

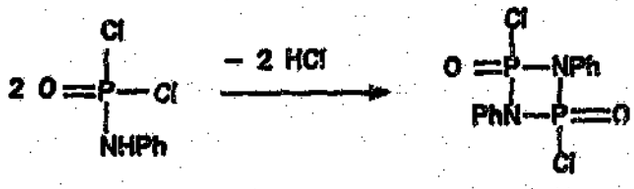
Phosphazanes are easily prepared from amines and varicus phosphorus halides. For example, the cyclohexyl ester of dichlorophosphoric acid reacts with cyclohexylamine to yield a cyclophosphazane with structure [23][21]. Similarly, thiophosphoryl chloride reacts with aniline hydrochloride to yield [24][22].



[23]

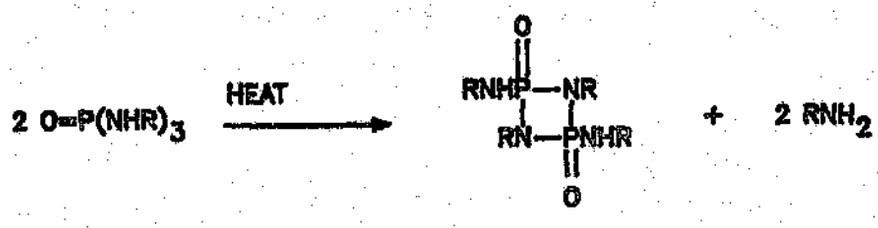
[24]

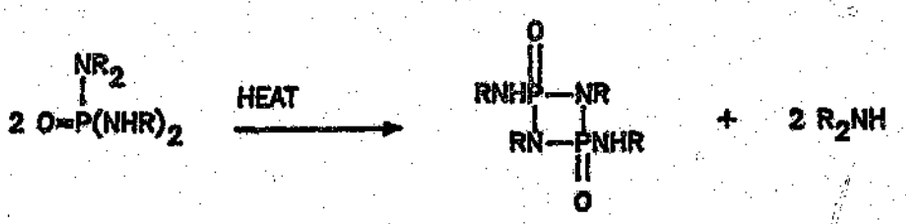
Stokes reported the pyrolytic condensation of $Cl_2P(O)NHPh$ to the cyclodiphosphazane [25] in 1893[23]. Further reaction of this product with amine hydrochloride resulted in the replacement of the halogen atoms and the formation of species such as $[R'NH(O)P(Cl)\text{-}NPh]_2$[24,25].



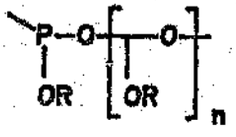
[25]

The thermal decomposition of organophosphorus triamides also results in the formation of cyclophosphazane dimers[25,26].

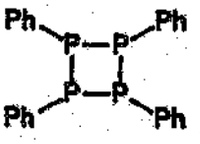




Examples of phosphorus compounds which show multiple bonding involving p-orbitals are rare. A number of compounds which were originally thought to possess multiple bonds have since been shown to be dimers or higher polymers[27]. Any comparison of compounds of nitrogen and phosphorus reveals the reluctance of phosphorus to form multiple bonds, for example, the totally different structures of the nitrites and their phosphorus analogues. R-O-N=O is a monomer, while attempts to prepare R-O-P=O lead to polymeric material [26]. "Phosphobenzene" $(PhP)_n$ was thought to have the structure PhP=PPh, but has since been shown to comprise mainly the cyclic compound [27]. The analogous nitrogen compound is azobenzene, Ph-N=N-Ph. It is important to realise that π-bonding which involves d-orbitals may well have a wide existence in phosphorus compounds, but π-bonding involving p-orbitals plays very little part in the bonding of stable phosphorus compounds[27].

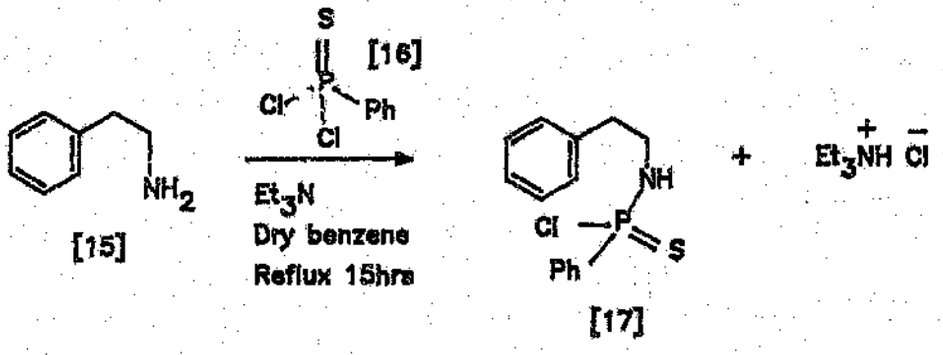


[26]

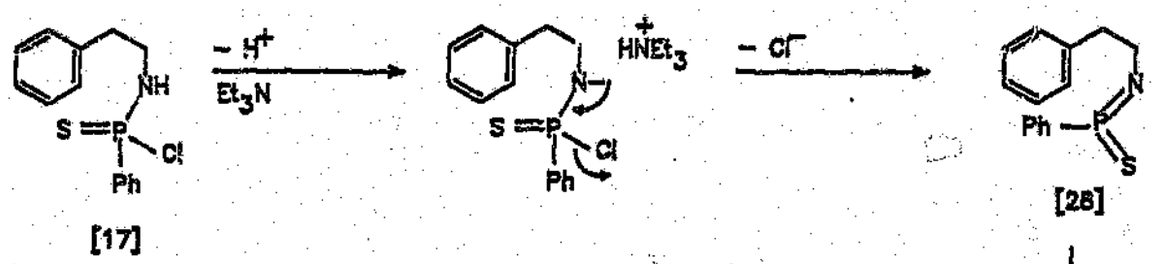


[27]

For the reaction under consideration, two possible routes are envisaged (Schemes 12 & 13). The primary step involves the reaction of (dichloro)phenylphosphine sulphide [16] on β-phenylethylamine [15] to give the intermediate [17].

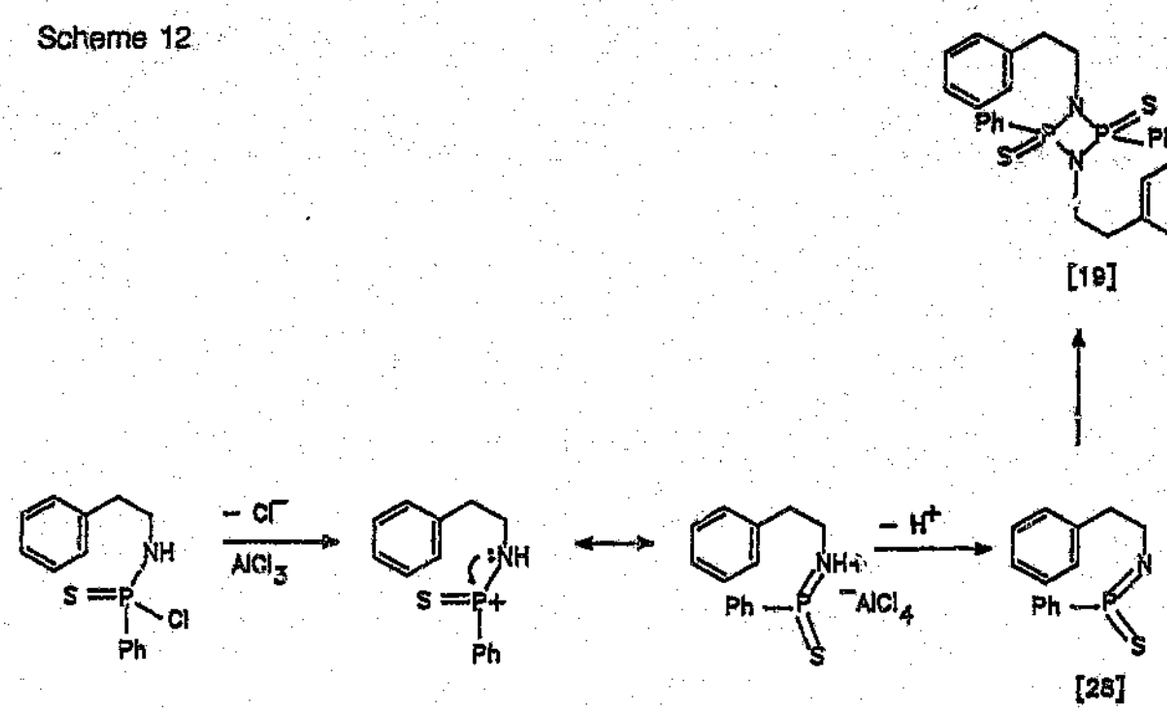


[17]



[17] [28]

Scheme 12



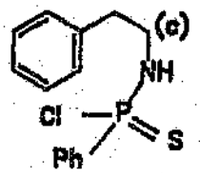
[19] [28]

Scheme 13

In Scheme 13, loss of Cl^- occurs in the first step of the reaction sequence, while in Scheme 12 it occurs in the second step. If route 12 is the mechanism by which the reaction takes place, then one would expect to detect product [19] in the reaction mixture at the end of the first step. When the reaction mixture was analysed for product by TLC, none was found, thereby indicating that the Lewis acid is indeed required to complete the reaction. Both routes have [28] as a common intermediate. The dimerisation of intermediate [28] is consistent with the known tendency of

phosphorus to avoid multiple bond formation.

A second product was isolated from the reaction mixture which gave compound [19]. This product has been assigned structure [17] on the basis of spectral data.



[17]

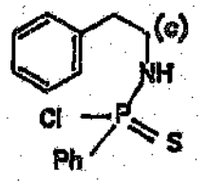
The ^{13}C NMR spectrum of [17] showed a doublet arising from the coupling of carbon (c) to one phosphorus atom. Further evidence was obtained from a comparison of the non-aromatic regions of the relevant ^{1}H NMR spectra. For [19] signals are present arising from four protons in the non-aromatic region. In moving from the spectrum of [19] to that of [17], an additional proton was observed upfield in the non-aromatic region. A D_2O exchange experiment showed this to be an exchangeable proton. Structure [18] also appeared to be able to accommodate the ^{1}H and ^{13}C NMR spectral data, but was ruled out as a possible structure since the aromatic ring of the phenethyl group did not exhibit coupling to phoshorus, as expected for the bicyclic compound. Compound [17] was found to decompose readily.

Reference (19) describes the synthetic route which this project has as its basis (see section 1.2), but the catalytic amount of aluminium chloride used for the cyclisation step was not actually quantified. For the specific reaction in which the four-membered ring compound was prepared, it was found that the starting amine had to be present in an amount four times greater than the aluminium chloride before product was isolated.

We now have to consider why cyclisation to the four-membered ring compound is preferred over cyclisation to the desired bicyclic compound. We have already shown that the catalyst is essential for reaction to take place. It seems reasonable to suppose that the catalyst functions to facilitate removal of chloride from phosphorus to produce

phosphorus to avoid multiple bond formation.

A second product was isolated from the reaction mixture which gave compound [19]. This product has been assigned structure [17] on the basis of spectral data.



[17]

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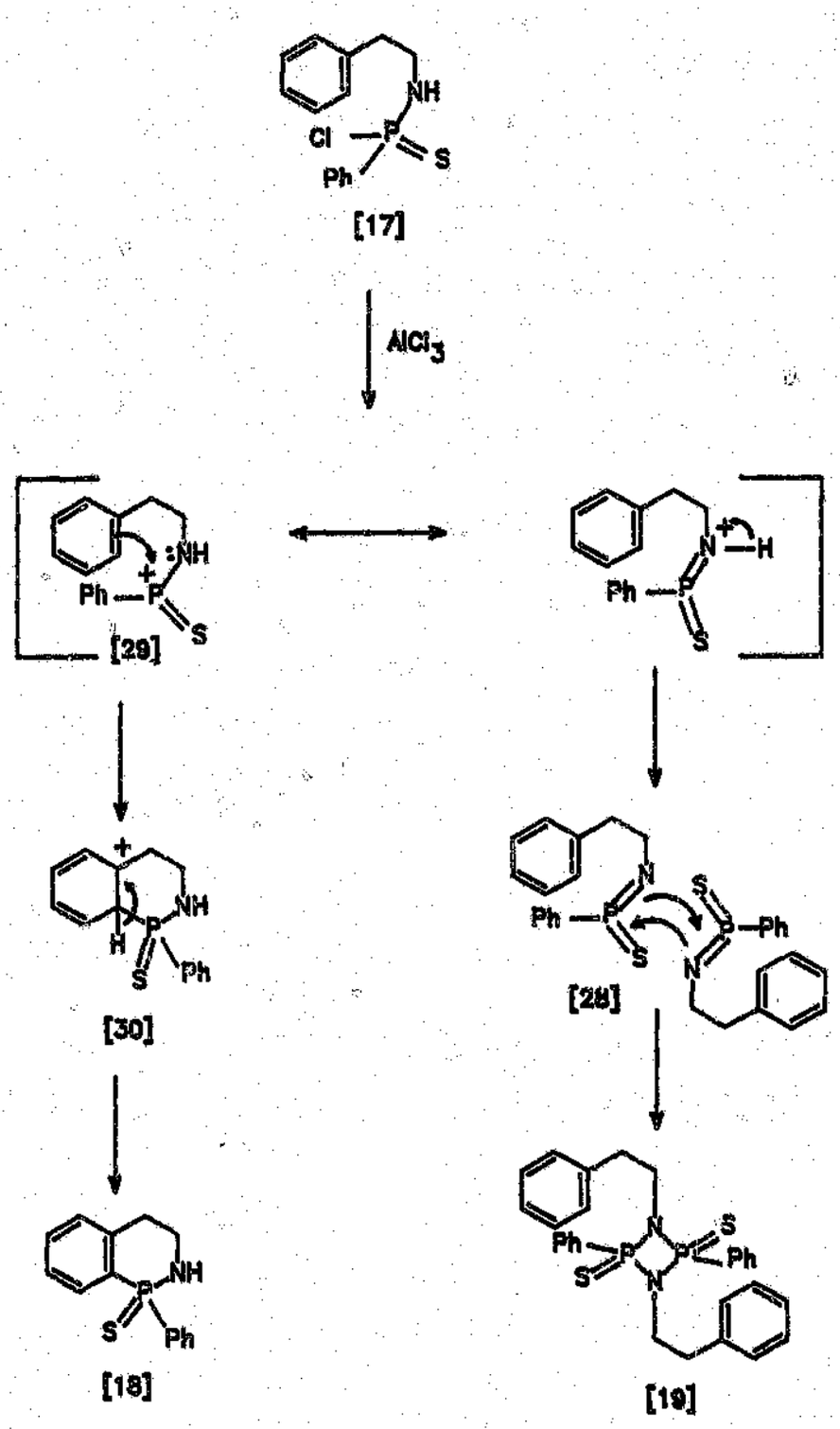
an electrophilic site at phosphorus, as shown in structure [29].



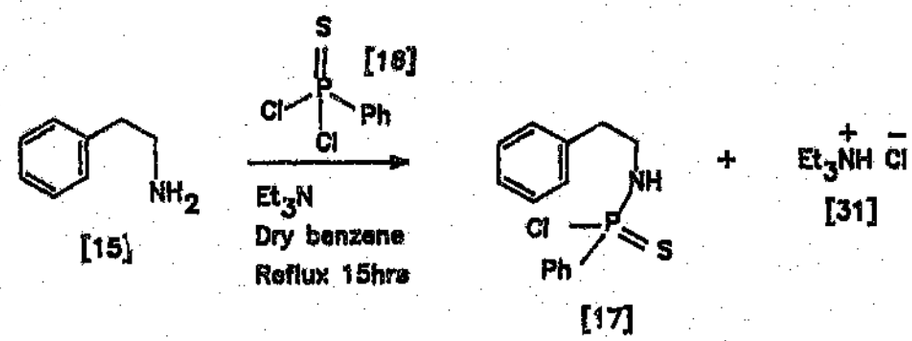
Scheme 14

Scheme 15

Two subsequent paths are envisaged for intermediate [17]. In Scheme 14, cyclisation takes place to the desired bicyclic compound. Once the electrophilic species [29] has been generated, it undergoes electrophilic attack on the aromatic ring, with hydrogen chloride and aluminium chloride being liberated. The key feature of this mechanism involves temporarily destroying the aromaticity of the ring to generate the intermediate [30]. This is an unfavourable process. Aromaticity is restored after cyclisation is completed.

The second option is indicated in Scheme 15. Present in intermediate [28] is a double bond involving phosphorus. We have already seen that phosphorus is reluctant to be involved in multiple bonding. By dimerising, intermediate [28] can lose the unwanted double bond and form a four-membered ring compound, which is a favoured structural feature with phosphorus.

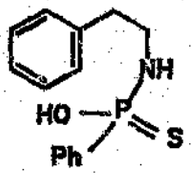
After our lack of success at isolating the desired compound [18], a new approach was taken in which the aim was to isolate and purify the intermediate [17] before attempting the cyclisation step (Scheme 16). (In the previous reaction, compound [17] was isolated at the end of the reaction sequence).



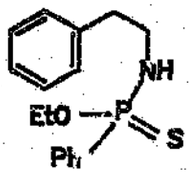
Scheme 16

There was no doubt that the intermediate was indeed being formed. Triethylamine hydrochloride [31] precipitated out of solution in large quantities, merely upon addition of the two starting reagents to each another. Removal of this solid and concentration of the resulting solution *In vacuo* gave crude [17]. This material was extremely sticky

and difficult to work with, making purification by column chromatography almost impossible. To try to overcome this problem, attempts were made to replace the remaining chlorine atom by a hydroxy or ethoxy group, and isolate [32] or [33] instead.



[32]



[33]

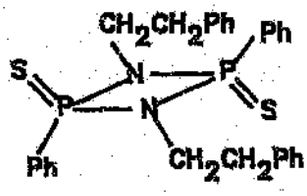
Again, the material recovered was difficult to work with. This approach was abandoned and we returned to executing both steps before proceeding with the work-up and purification procedures.

The reaction shown in Scheme 11 employed aluminium chloride as the catalyst. The reaction was repeated using stannic chloride in place of the aluminium chloride. Comparison of the reaction mixture by TLC with an authentic sample of the four-membered ring compound indicated that compound [19] had again been prepared. However, the formation of tin by-products during work-up made the reaction impractical.

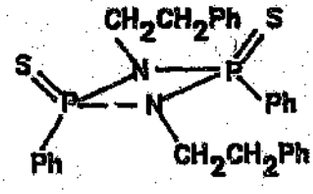
Repetition of the reaction of (dichloro)phenylphosphine sulphide [16] with β-phenylethylamine [15], followed by attempted cyclisation of the intermediate [17] with aluminium chloride to prepare the bicyclic compound [18], led to the isolation of a third product. Accurate mass determination gave m/z = 518.1120 as the molecular ion, thereby indicating the presence of the four-membered ring compound. Since the R_F value was not identical to that of the first cyclic compound isolated, it was concluded that a second isomer had been prepared.

The cyclophosphazane $[PhCH_2CH_2N\text{-}P(S)Ph]_2$ comprises a symmetrically substituted four-membered ring system. There are two geometrical isomers in which the two phenyl groups attached to phosphorus are respectively on the same side and opposite sides of the planar four-membered ring. The first isomer [19] isolated has been

assigned the geometry indicated in [34]. This is the lower energy configuration, with the two bulky phenyl groups being *trans* to one another. This assignment is in accordance with the ease of preparation and stability observed for the compound. A crystal structure determination was attempted in order to establish the actual geometry. However, resolution of the data was not possible due to micro-twinning of the crystals. The other isomer is assumed to have the *cis*-geometry indicated in [35].

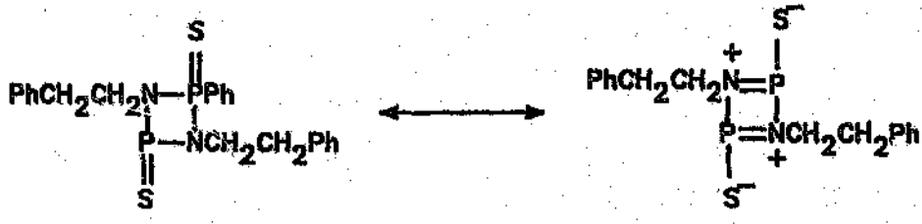


[34]



[35]

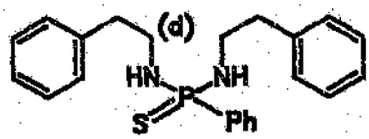
These dimers are stabilised by resonance as in [36]. These "cyclobutadiene" structures [36] have been postulated to be of importance in the resonance picture of such ring systems[26,28,29]. The lone pairs of electrons on the nitrogen are readily available for donation into the vacant phosphorus d-orbitals. The phosphorus in turn stabilises the negative charge by passing it on to sulphur.



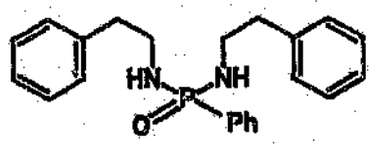
[36]

2.2 PREPARATION OF REFERENCE COMPOUNDS

After compound [19] had been isolated, we decided to prepare structurally similar model compounds for spectral comparisons. The compounds chosen were [37] and [38] shown below. Although prepared primarily to afford spectral data, they also happen to be new compounds containing P-N bonds, albeit open-chain compounds.

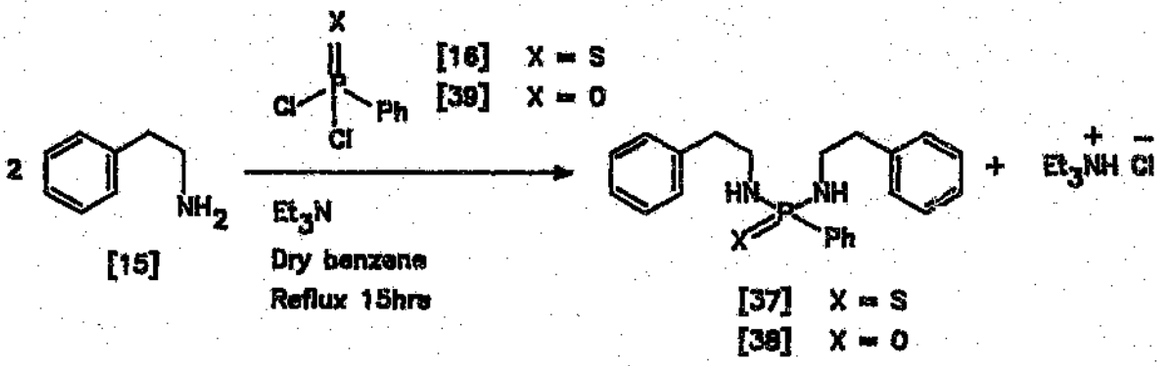


[37]



[38]

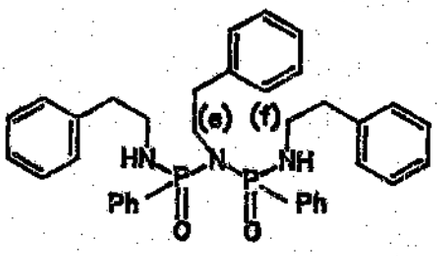
Compounds [37] and [38] were prepared by reacting two equivalents of ß-phenylethylamine [15] with one equivalent of the thiophosphoryl [16] or phosphoryl [39] reagent (Scheme 17). Both compounds were obtained as solids, although the sulphur compound was initially isolated as an oil that crystallised very slowly.



Scheme 17

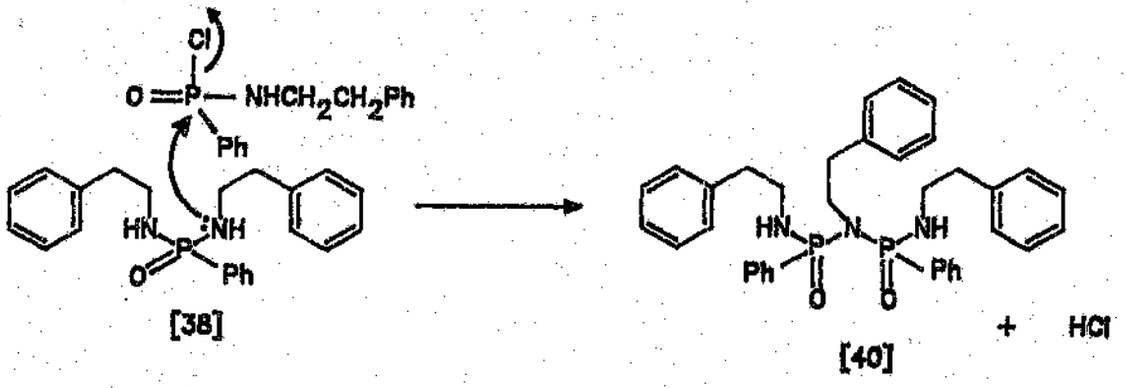
Microanalysis results were consistent with the structures for compounds [37] and [38]. The ^{13}C NMR spectra of compounds [37] and [38] were of particular interest. The important feature was the signal arising from coupling of methylene carbons (d) to the single phosphorus atom. This gave a doublet as expected, contrasting with the triplet observed for a similar carbon atom in compound [19] which couples to two phosphorus atoms. A doublet was also observed for the corresponding carbon in the oxygen analogue [38].

The preparation of the oxygen compound was not as straightforward as that of the sulphur analogue. The first two attempts gave compound [40] exclusively. It was only on the third attempt that compound [38], as well as compound [40], was isolated.



[40]

Structurally, compound [40] corresponds to [38] to which an additional (dichloro)phenylphosphine oxide and β-phenylethylamine residue have been added (Scheme 18). The presence of the corresponding sulphur compound of [37] was not detected.



Scheme 18

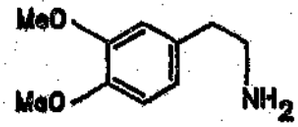
A high field triplet was observed at 38.41ppm in the ^{13}C NMR spectrum of compound [40]. This indicated the presence of two equivalent phosphorus atoms in the molecule. However, one odd feature about the ^{13}C NMR spectrum was the lack of a doublet expected for coupling of methylene carbons (f) to phosphorus. It may be possible that coupling for this structure is zero. Duplication of all signals in the ^{1}H NMR spectrum (particularly evident in the region 2.5-3.5ppm) indicated similar groups in distinct chemical environments. One set of signals integrated for twice as many protons as the other. On the basis of this information, the compound was assigned structure [40]. Addition of D_2O confirmed the presence of the exchangeable protons. The CH-correlated spectrum proved to be of no use in assigning the high field signals in the ^{13}C NMR spectrum. There are four signals, with two being of much greater intensity. These signals were assigned on the basis of their relative intensities and

spectroscopic comparison with simpler compounds in the series. In the mass spectrum an accurate mass determination of the molecular ion gave m/z = 607.2516, corresponding to $C_{36}H_{39}N_3O_2P_2$.

For all reactions considered so far, yields were found to be low (< 20%) and therefore not of preparative use. Reasons suggested to account for these observations were hydrolysis of the phosphoryl and thiophosphoryl reagents, or loss of the amine as a hydrochloride complex along with triethylamine hydrochloride. To test the latter possibility, the hydrochloride complex was filtered off and basified (4M NaOH) to release organic material trapped in this manner. The resulting solution was extracted and any organic material recovered. The loss of starting material in this manner corresponded to only 10%.

2.3 OTHER ATTEMPTS AT CYCLISATION

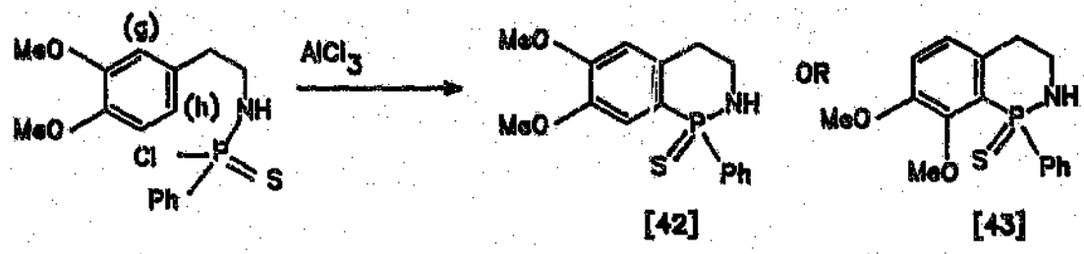
Since cyclisation of compound [17] did not appear to take place readily, a new approach was developed. Methoxy groups were included on the aromatic ring in an attempt to promote reactivity towards ring closure. Homoveratrylamine [41] was the substrate employed.



[41]

Homoveratrylamine

There are two sites, (g) & (h), on the ring at which cyclisation can take place (Scheme 19).



[42] [43]

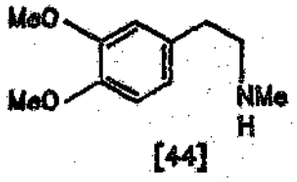
Scheme 19

In principle, cyclisation at both sites is possible. In practice cyclisation will occur largely at one site. Site (h) is preferred to site (g) due to steric factors, but a mixture of products is expected.

As with β-phenylethylamine, there is still a primary amine group present. This therefore affords the opportunity of formation of a four-membered ring compound, as well as the cyclised compounds.

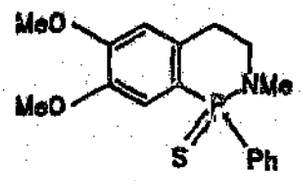
These ideas were tested through the reaction of (dichloro)phenylphosphine sulphide **[16]** with homoveratrylamine **[41]**, followed by a catalytic amount of aluminium chloride to induce cyclisation of the resulting intermediate to the desired bicyclic compound **[42]**. However, neither the bicyclic compounds **[42]** or **[43]**, nor a four-membered ring compound was isolated or detected.

To exclude the possibility of formation of a four-membered ring structure, *N*-methyl-2-(3,4-dimethoxyphenyl)ethylamine **[44]** was used, in which the *N*-methyl group blocks four-membered ring formation. (Dichloro)phenylphosphine sulphide **[16]** was reacted with compound **[44]**, followed by attempted cyclisation of the resulting intermediate with aluminium chloride, to prepare compound **[45]**. Despite the presence of a blocking group on nitrogen, cyclisation was still not achieved.



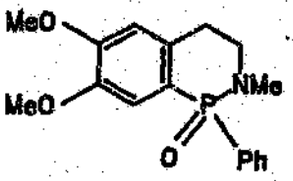
[44]

N–Methyl–2–(3,4–dimethoxyphenyl)ethylamine

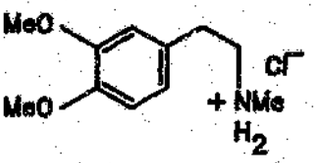


[45]

Attempts were made to prepare compound **[46]** by reaction of (dichloro)phenylphosphine oxide with *N*-methyl-2-(3,4-dimethoxyphenyl)ethylamine. The starting amine was recovered as the hydrochloride **[47]** (36%).

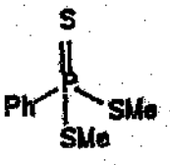


[46]



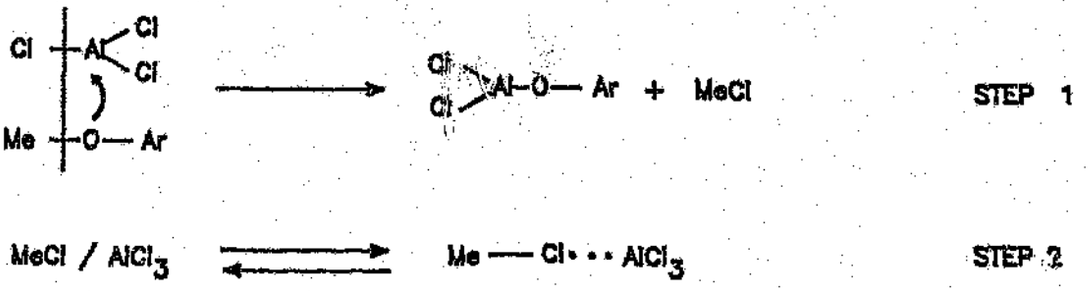
[47]

A problem associated with working with aluminium chloride is that it can bring about the demethylation of methoxy groups, with concomitant conversion into the hydroxyl group. We observed that, for the reaction of the thiophosphoryl reagent [16] on [41] and [44], the major reaction taking place was a demethylation reaction, with the (dichloro)phenylphosphine sulphide picking up the methyl groups. The product isolated has been assigned structure [48]. Microanalysis results and ^{1}H and ^{13}C NMR data concur with this structure.



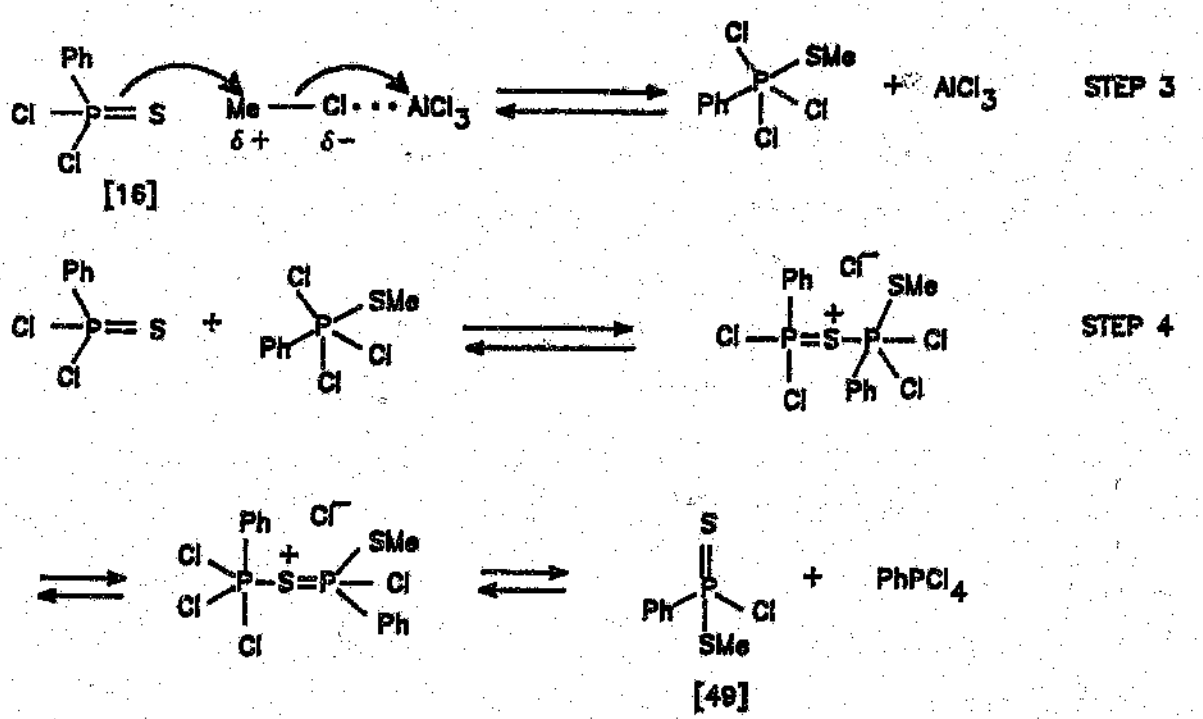
[48]

From this result we can see that it is not simply a case of a methyl group replacing a chlorine atom. The formation of compound [48] is not extraordinary, as both elemental and bound phosphorus are known to react readily with sulphur and with sulphur compounds. Phosphorus compounds frequently abstract sulphur atoms from sulphur-containing substrates to yield the desulphurised substrates and a thiophosphoryl compound[30]. Scheme 20 below outlines a plausible mechanism for the formation of [48].



STEP 1

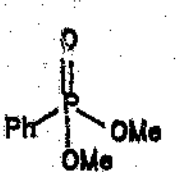
STEP 2



Scheme 20

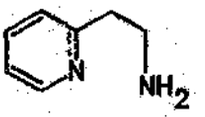
Further methylation of [49] followed by attack by another molecule of [16] would yield the isolated compound [48]. This mechanism is lent further credibility, since intermediate [49] was isolated and characterised. That it was isolated only once is indicative of its transient nature. In the case of *N*-methyl-2-(3,4-dimethoxyphenyl)-ethylamine, the N-Me group can also be demethylated. This will yield MeCl which would be incorporated in the second step of the reaction sequence. We did not isolate any material - starting material or cyclised product - in which the methoxy groups had undergone conversion to the alcohol. The only evidence we have for demethylation occurring is the isolation of [48].

In the case of the oxygen analogue, demethylation is still possible but formation of [50] was not expected. The P=O bond is a strong one and so a reaction analogous to that in Step 2 of Scheme 20 is unlikely. Demethylation will give MeCl which can be readily lost. Again demethylated starting material or products were not observed.



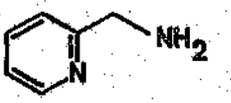
[50]

Activating groups did not assist in the cyclisation process. Consequently, we turned our attention to two new substrates; namely, 2-(2-aminoethyl)pyridine and 2-picolyamine.



[51]

2-(2-Aminoethyl)pyridine

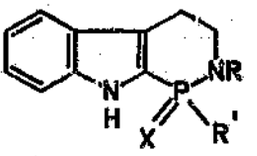


[52]

2-Picolyamine

The logic behind this was, that with nitrogen in the ring, with an available lone pair of electrons, cyclisation may be promoted since the aromaticity of the ring did not need to be disturbed. Compounds with phosphorus present in a 5- or 6-membered ring are known. Compound [51] will lead to a structure with phosphorus in a 6-membered ring, while compound [52] will yield the 5-membered analogue. We wished to see whether, for our type of compounds, one ring size was preferred to another. This approach was unsuccessful.

In our discussion so far, no mention has been made of the preparation of compounds of the type below.



X = S or O

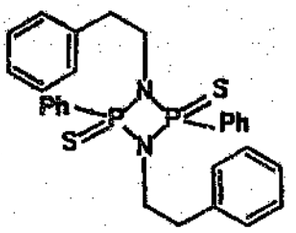
In order to investigate the preparation of the above compounds, one equivalent of tryptamine and one equivalent of the thiophosphoryl [16] or phosphoryl [38] reagent were combined under "standard" conditions. Approximately 70% of the starting amine was recovered each time. The problem was attributed to the solvent used, namely, benzene. The starting material did not dissolve readily in this medium; consequently, varying the solvent needs further investigation. This was not done, however, because of time pressure.

From the above discussion, it is clear that the project was unsuccessful in the

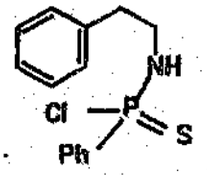
preparation of the desired bicyclic and tricyclic compounds, consequently it was abandoned. A number of the reactions considered warrant further investigation, but since they did not further the main aims of the project, they were not followed up.

CHAPTER 3: CONCLUSION

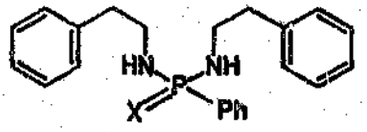
The aim of the project was to synthesise analogues of isoquinolines and β-carbolines containing P-N bonds, and with phosphorus in place of C-1. We set out with a number of specific synthetic targets in view, but were unsuccessful in their preparation. However, a number of other compounds still encompassed by the project description were obtained. These are shown below. With the exception of compound [19], the compounds prepared had acyclic rather than cyclic P-N bonds.



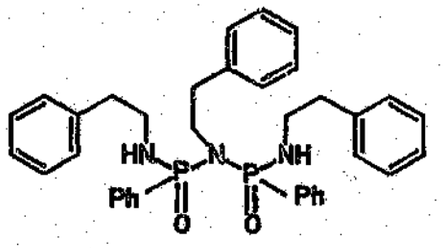
Cis– & Trans–[19]



[17]

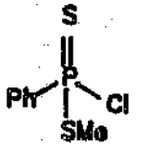


[37] X = S
[38] X = O

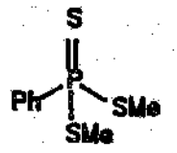


[40]

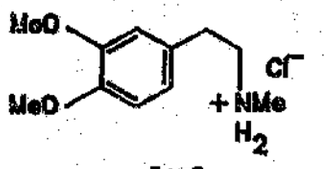
The following products were isolated as by-products:



[49]



[48]



[47]

Yields of the compounds with P-N bonds were low (20%) and the reactions were therefore not of preparative use.

Modifications were made to the starting amine-containing material in an attempt to promote cyclisation. Further activating the aromatic ring with electron-releasing methoxy groups did not promote cyclisation. Blocking the nitrogen with a methyl group prevented four-membered ring formation but did not promote the cyclisation step. No product whatsoever was obtained using aminomethyl-pyridine, deliberately chosen so as not to destroy aromatic character in the presumed cyclisation intermediate. The influence of the size of ring arising from cyclisation was also examined by comparing formation of a 5-membered versus a 6-membered ring; however, this approach was unsuccessful. In some cases side reactions predominated, as indicated by the exclusive formation of **[47]**, **[48]** and **[49]**.

From these investigations, we have found that the route chosen is not a good one for the preparation of P-N bonds, and quite useless for preparing P-N heterocycles.

CHAPTER 4: EXPERIMENTAL

4.1 GENERAL DETAILS

4.1.1 Solvents, Reagents and General Procedures

All solvents used for reactions and for preparative chromatography were distilled before use. THF was dried and purified by distillation under nitrogen from sodium-benzophenone. DMSO was distilled from calcium hydride and stored over molecular sieves (4Å). Benzene was dried azeotropically using a Dean-Stark apparatus, and then distilled from calcium hydride. Chloroform for infrared (IR) spectroscopy was dried by passage through a column of basic alumina (Merck, activity grade 1) immediately prior to use. Water used as the aqueous phase in extraction procedures was also distilled. Aluminium chloride was freshly sublimed prior to use.

Aqueous mixtures were extracted with an organic solvent and the organic phase after separation was dried over anhydrous magnesium sulphate or anhydrous sodium sulphate before removal of the solvent. Evaporation of solvent *in vacuo* refers to the removal of the solvent under reduced pressure on a rotary evaporator, followed by further drying on an oil pump at below 1mm Hg.

4.1.2 Chromatographic Separations

Products were separated and purified by means of column chromatography. Merck Kieselgel 60 (particle size 0.063 - 0.200mm) was used as the adsorbent for preparative column chromatography. All solvents used as eluents were purified by distillation, except for AR methanol. The progress of the column chromatography separation, as well as the reactions, was monitored by thin layer chromatography (TLC). The R_F values quoted are for TLC on pre-coated Merck DC-Plastikfolien Kieselgel 60 F_{254} plates, pre-coated Whatman Silica Gel 60 F_{254} glass plates or pre-coated Merck DC-Alufolien Kieselgel 60 F_{254} plates.

4.1.3 Spectroscopic and Physical Data

All melting points were obtained on a Reichert hot stage apparatus, and are uncorrected.

Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Bruker AC-200 spectrometer in deuteriochloroform (unless otherwise specified) at 200.13 and 50.32MHz, respectively. A few ^{1}H NMR spectra were recorded with a Varian EM-360A spectrometer (60MHz). Phosphorus nuclear magnetic resonance (^{31}P NMR) spectra were recorded at 81MHz. Chemical shifts are reported on a δ scale (ppm) relative to tetramethylsilane (TMS) for ^{1}H and ^{13}C NMR spectra, and relative to phosphoric acid for ^{31}P NMR spectra. DEPT, CH-correlated spectra and decoupling techniques were routinely used for the complete assignment of NMR signals. The chemical shifts are reported as follows: value (number of protons, description of absorption, coupling constant(s) in Hz where applicable, assignment). Abbreviations used: **s** = singlet, **d** = doublet, **t** = triplet, **q** = quartet, **qu** = quintet and **m** = multiplet.

Infrared spectra were recorded with a Pye-Unicam PU9512 or an IR Report-100 infrared spectrophotometer as 10% solutions in chloroform using a cell with a path length of 0.1mm and sodium chloride windows. A few spectra were recorded with samples as dispersions in potassium bromide. In some cases, infrared spectra of neat compounds were recorded between sodium chloride plates. Abbreviations used: **v** = very, **w** = weak, **m** = medium, **s** = strong, **sh** = sharp and **br** = broad.

Microanalyses were carried out by Energy Technology, CSIR, Pretoria. Elemental analyses were performed on solid samples wherever possible. The microanalytical service available to us provided unreliable results for liquid samples. For these, high resolution mass spectrometry was used for accurate mass determination on the molecular ion if it was present, or otherwise on the highest significant figure. One of the oils was sent for microanalysis to the Analytical Laboratories, Gummersbach 1 Elbach, West Germany. Mass spectra were recorded on an AEI MS5 (Cape

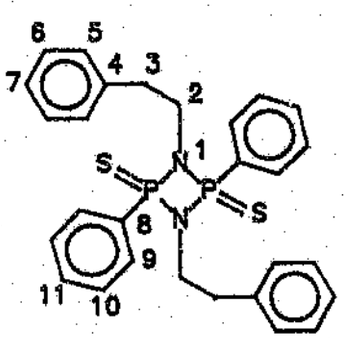
Technikon) high resolution mass spectrometer. Data are quoted as follows: *m/z* value (assignment if known, relative % abundance). Peaks in the mass spectra below 20% abundance have not been quoted except in the case of the molecular ion.

4.1.4 Other General Procedures

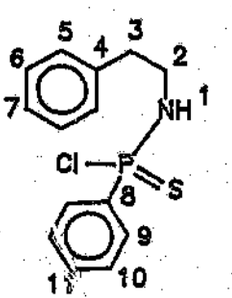
All details discussed above are applicable to Part B also. In Part A, yields are calculated from the mass of the relevant starting material; while in Part B, yields are calculated from the mass of the intermediate synthetic precursor used.

4.2 EXPERIMENTAL DETAILS

A ***Trans*-1,3-Di(phenethyl)-2,4-diphenyl-1,3-diaza-2λ^5,4λ^5-diphosphetidine-2,4-dithione [19], *N*-phenethyl-*P*-(chloro)phenylphosphonothioic amide [17] and *cis*-1,3-di(phenethyl)-2,4-diphenyl-1,3-diaza-2λ^5,4λ^5-diphosphetidine-2,4-dithione [19]**



Cis– & Trans–[19]



[17]

To a mixture of β-phenylethylamine (6.09g; 50.2mmol) and triethylamine (5.23g; 51.7mmol) in dry benzene (200ml), a solution of (dichloro)phenylphosphine sulphide (10.63g; 50.4mmol) in dry benzene (200ml) was added. During addition of the (dichloro)phenylphosphine sulphide/benzene solution, triethylamine hydrochloride was observed separating out. The reaction mixture was then refluxed for 15hrs and protected from extraneous moisture by means of a calcium chloride drying tube. The mixture was allowed to cool, the solid triethylamine hydrochloride was filtered off and

excess solvent was removed *in vacuo* to yield a cream-coloured syrupy material containing the intermediate [17] (16.18g). This intermediate was heated in the presence of anhydrous aluminium chloride (1.64g; 12.3mmol) at 165°C for 8hrs in order to effect cyclisation. The resulting hard brown residue was dissolved with difficulty in a dichloromethane/water mixture (300ml; CH_2Cl_2-H_2O 2:1). Water was added to destroy any excess aluminium chloride. The organic extracts were dried with anhydrous magnesium sulphate, filtered and solvent removed *in vacuo* to yield a dark brown oil (11.37g). Column chromatography of this oil with benzene-hexane (1:1) as solvent gave two products: ***trans*-1,3-di(phenethyl)-2,4-diphenyl-1,3-diaza-2λ^5,4λ^5-diphosphetidine-2,4-dithione [19]** (2.15g; 4.15mmol;16.5%) and ***N*-phenethyl-*P*-(chloro)phenylphosphonothioic amide [17]** (0.586g; 1.98mmol; 3.95%). Compound [19] was obtained as a powdery white solid. This was recrystallised from cyclohexane to give almost transparent cubes, mp 126-129°C, R_F (benzene) 0.93, R_F (benzene-hexane 1:1) 0.66.

Found: C, 65.10; H, 5.51; N, 5.41%.
$C_{28}H_{28}N_2P_2S_2$ requires C, 64.84; H, 5.45; N, 5.40%.

^{1}H NMR

δ_H 8.20 - 8.32 (4H, m, H-9); 7.43 - 7.60 (6H, m, H-10 + H-11); 7.02 - 7.12 (6H, m, H-6 + H-7); 6.90 - 6.96 (4H, m, H-5); 3.17 - 3.48 (2H, m, H-2a); 2.58 - 3.08 (2H, m, H-2b); 2.51 - 2.56 (4H, m, H-3).

^{13}C NMR

δ_C 137.90 (s, C-4); 133.37 (d, C-9, $^2J_{CP}$ = 14.27Hz); 132.93 (s, C-11); 132.30 (d, C-8, $^1J_{CP}$ = 108.07Hz); 128.55 (d, C-10, $^3J_{CP}$ = 15.48Hz); 128.48 (s, C-5); 128.17 (s, C-6); 126.27 (s, C-7); 41.85 (s, C-3); 36.52 (t, C-2, $^2J_{CP}$ = 2.85Hz).

^{31}P NMR: Singlet at 78.95ppm.

IR

υ_{max} ($CHCl_3$) 3070 (w, sh); 3040 (w, sh); 2970 (w, sh); 2925 (shoulder), 2902 (w,

sh); 2850 (w, sh); 1615 (w, sh); 1600 (w, sh); 1510 (w,sh), 1500 (shoulder); 1470 (m, sh); 1450 (s, sh); 1365 (w, sh); 1325 (w,sh); 1300 (w, br); 1155 (s, sh); 1120 (s, sh); 1100 (m, sh); 1040 (s, sh); 880 (s, sh), 845 (shoulder); 700 (s, sh); 660 (s, sh).

m/z 518 (M^+ $[PhCH_2CH_2N\text{-}P(S)Ph]_2^+$, 33%); 427 ($[M - PhCH_2]^+$, 100%); 399 ($PhCH_2CH_2N[P(S)Ph]_2^+$, 20%); 398 (20%); 294 ($[PhP(S)]_2N^+$, 37%); 168 (35%); 136 (27%); 105 ($PhCH_2CH_2^+$, 30%); 91 ($PhCH_2^+$, 50%).
HRMS (Found: M^+ 518.1168. $C_{28}H_{28}N_2P_2S_2$ requires 518.1170).

***N*-Phenethyl-*P*-(chloro)phenylphosphonothioic amide [17]** was obtained as a pale yellow oil which decomposed readily. R_F (benzene-hexane 1:1) 0.27.

^1H NMR

δ_H 7.84 - 7.97 (2H, m, H-9); 7.41 - 7.62 (3H, m, H-10 + H-11); 7.22 - 7.38 (3H, m, H-6 + H-7); 7.14 - 7.20 (2H, m, H-5); 3.30 - 3.57 (1H, m, H-1); 3.15 - 3.44 (2H, m, H-2); 2.85 (2H, t, H-3, $^3J_{HH}$ = 6.79Hz).
D_2O exchange: multiplet at 3.30 - 3.37ppm disappears and the HOD peak appears at 4.87ppm. Decouple at 2.84ppm, multiplet at 3.15 - 3.44ppm simplifies. Decouple at 3.30ppm, triplet at 2.85ppm collapses into a singlet. Decouple at 3.50ppm, multiplet at 3.15 - 3.44ppm simplifies.

^{13}C NMR

δ_C 137.88 (s, C-4); 135.69 (d, C-8, $^1J_{CP}$ = 129.65Hz); 132.56 (d, C-11, $^4J_{CP}$ = 3.53Hz); 130.11 (d, C-9, $^2J_{CP}$ = 12.62Hz); 128.82 (s, C-5); 128.76 (s, C-6); 128.73 (d, C-10, $^3J_{CP}$ = 16.07Hz); 126.79 (s, C-7); 43.95 (d, C-3, $^3J_{CP}$ = 4.31Hz); 36.82 (d, C-2, $^2J_{CP}$ = 8.42Hz).

^{31}P NMR: Singlet at 76.61ppm.

IR

υ_{max} ($CHCl_3$) 3040 (s, v.br); 2975 (s, v.br); 2300 (w, br); 1617 (s, sh), 1610 (shoulder); 1520 (shoulder), 1510 (s, sh); 1480 (m, sh); 1465 (m, sh); 1450 (s, sh);

1395 (w, sh); 1325 (w, sh); 1245 (w, sh); 1170 (shoulder), 1150 (s, sh); 1135 (s, sh); 1075 (w, sh); 960 (s, br); 925 (s, sh); 700 (s, sh); 645 (m, sh); 625 (w, sh).

In a similar preparation, (dichloro)phenylphosphine and one equivalent of sulphur were refluxed in dry benzene for 2hrs to generate the (dichloro)phenylphosphine sulphide, which was then used *insitu*. ***Trans*-1,3-Di(phenethyl)-2,4-diphenyl-1,3-diaza-2λ^5,4λ^5-diphosphetidine-2,4-dithione [19]** (0.192g; 0.370mmol; 1.75%) and ***cis*-1,3-di(phenethyl)-2,4-diphenyl-1,3-diaza-2λ^5,4λ^5-diphosphetidine-2,4-dithione [19]** (0.038g; 0.073mmol; 0.35%) were isolated. The *cis*-compound was recovered as a dirty-white solid. Mp 100-105°C (there was insufficient for recrystallisation), R_F (benzene-hexane 1:1) 0.44.

^{1}H NMR

δ_H 7.52 -7.67 (6H, m, H-10 + H-11); 7.29 - 7.38 (4H, m, H-9); 7.01 - 7.18 (6H, m, H-6 + H-7); 6.72 - 6.78 (4H, m, H-5); 3.58 (4H, tt, H-2, $^3J_{HH}$ = 7.31Hz, $^3J_{HP}$ = 15.85Hz); 2.72 (4H, t, H-3, $^3J_{HH}$ = 7.25Hz).
Decouple at 2.72ppm, triplet of triplets at 3.58ppm collapses to a triplet.

^{13}C NMR

δ_C 138.40 (s, C-4); 136.96 (d, C-8, $^1J_{CP}$ = 90.81Hz); 131.54 (d, C-10, $^3J_{CP}$ = 13.51Hz); 131.54 (s, C-11); 128.55 (s, C-5); 128.42 (d, C-9, $^2J_{CP}$ = 8.57Hz); 128.34 (s, C-6); 126.30 (s, C-7); 42.14 (s, C-3); 35.95 (t, C-2, $^2J_{CP}$ = 3.75Hz).

^{31}P NMR: Singlet at 82.45ppm.

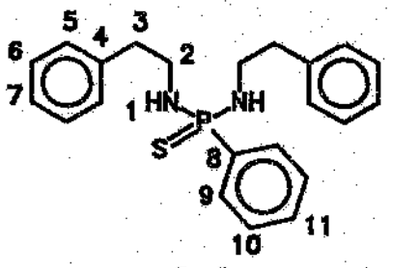
IR

υ_{max} (KBr disc) 3045 (m, sh); 3015 (m, sh); 3010 (m, sh); 2850 (m, sh); 1725 (w, br); 1605 (w, sh); 1585 (w, sh); 1495 (m, sh); 1483 (w, sh); 1455 (m, sh); 1435 (s, sh); 1365 (m, sh); 1310 (m, sh); 1290 (w, sh); 1280 (w, sh); 1265 (w, sh); 1215 (w, br), 1200 (shoulder); 1190 (w, sh); 1180 (w, sh); 1125 (s, sh); 1105 (s, sh); 1085 (m, sh); 1030 (m, sh); 1010 (w, sh); 1000 (w, sh); 965 (w, br); 920 (m, sh); 905 (m, sh); 885 (m, br); 855 (m, br); 785 (s, sh); 755 (shoulder), 745 (s, sh); 725 (s, sh); 695

(shoulder), 687 (s, sh); 677 (w, sh); 655 (w, sh); 645 (w, sh); 610 (w, sh).

m/z 519 (22%); 518 (M^+ $[PhCH_2CH_2N\text{-}P(S)Ph]_2^+$, 67%); 485 (30%); 434 (24%); 428 (27%); 427 ($[M - PhCH_2]^+$, 100%); 414 (22%); 399 ($PhCH_2CH_2N[P(S)Ph]_2^+$, 56%); 398 (33%); 294 ($[PhP(S)]_2N^+$, 54%); 226 (26%); 217 ($PhP(S)\text{-}N\text{-}P(S)^+$, 23%); 167 (27%); 136 (26%); 105 ($PhCH_2CH_2^+$, 31%); 91 ($PhCH_2^+$, 46%); 30 (55%).
HRMS (Found: M^+ 518.1120. $C_{28}H_{28}N_2P_2S_2$ requires 518.1170).

B ***N,N'*-Di(phenethyl)-*P*-phenylphosphonothioic diamide [37]**



[37]

To a mixture of β-phenylethylamine (2.78g; 22.9mmol) and triethylamine (2.58g; 25.5mmol) in dry benzene (200ml), was added a solution of (dichloro)phenylphosphine sulphide (2.12g; 10.1mmol) in dry benzene. Solid triethylamine hydrochloride separated out upon addition of the thiophosphoryl reagent, turning the initially colourless reaction mixture milky. The reaction mixture was then refluxed for 15hrs, and protected from extraneous moisture by means of a calcium chloride drying tube. At the end of this time, the mixture was left to cool. The solid triethylamine hydrochloride was filtered off and excess solvent removed *in vacuo* to yield a thick dark yellow oil as crude product (4.19g). Column chromatography with benzene as solvent gave ***N,N'*-di(phenethyl)-*P*-phenylphosphonothioic diamide [37]** (0.597g; 1.57mmol; 15.5%) as a pale yellow oil which crystallised very slowly to a cream-coloured solid. This was recrystallised from cyclohexane to give cream-coloured rods, mp 47-48.5°C, R_F (benzene) 0.28.

Found: C, 69.54; H, 6.72; N, 7.35%.
$C_{22}H_{25}N_2PS$ requires C, 69.45; H, 6.62; N, 7.36%.

^{1}H NMR

δ_H 7.78 - 7.90 (2H, m, H-9); 7.37 - 7.46 (3H, m, H-10 + H-11); 7.18 - 7.34 (6H, m, H-6 + H-7); 7.08 - 7.16 (4H, m, H-5); 3.13 (4H, broad singlet, H-2); 2.70 (4H, t, H-3, $^3J_{HH}$ = 6.80Hz); 2.35 (2H, broad singlet, H-1).

D_2O exchange: peak at 2.35ppm disappears, the HOD peak appears at 4.82ppm and the broad singlet at 3.13ppm becomes a complex multiplet.

^{13}C NMR

δ_C 138.76 (s, C-4); 134.91 (d, C-8, $^1J_{CP}$ = 120.68Hz); 131.46 (d, C-11, $^4J_{CP}$ = 3.13HZ); 130.75 (d, C-9, $^2J_{CP}$ = 11.05Hz); 128.77 (s, C-5); 128.43 (s, C-6); 128.14 (d, C-10, $^3J_{CP}$ = 15.25Hz); 126.34 (s, C-7); 42.40 (d, C-3, $^3J_{CP}$ = 1.05Hz); 37.56 (d, C-2, $^2J_{CP}$ = 7.25Hz).

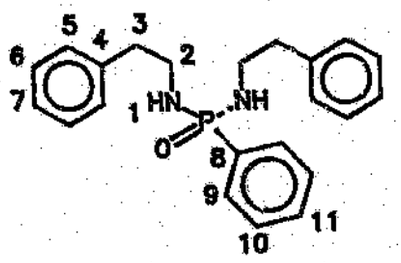
^{31}P NMR: Singlet at 64.75ppm.

IR

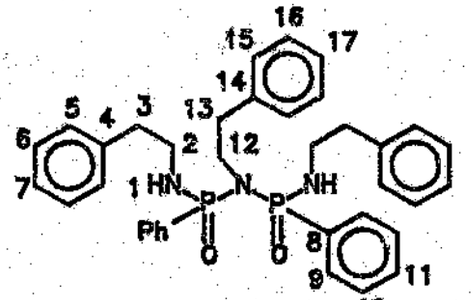
υ_{max} ($CHCl_3$) 3420 (m, sh); 3100 (m, sh); 3080 (m, sh); 2990 (s, sh); 2950 (s, sh); 2900 (shoulder), 2880 (m, sh); 1960 (w, br); 1735 (m, sh); 1710 (m, sh); 1690 (m, sh); 1685 (m, sh); 1675 (m, sh); 1610 (m, sh); 1600 (m, sh); 1590 (m, sh), 1580 (shoulder); 1555 (w, sh); 1500 (m, sh); 1480 (m, sh); 1460 (s, sh); 1445 (s, sh); 1400 (s, sh), 1390 (shoulder); 1310 (w, sh); 1277 (w, sh); 1263 (w, sh); 1250 (w, sh); 1180 (w, sh); 1160 (w, sh); 1140 (m, sh); 1120 (s, sh); 1090 (s, sh); 1030 (m, sh); 1005 (vw, sh); 980 (vw, sh); 945 (vw, sh); 910 (w, sh); 870 (vw, sh); 835 (vw, sh); 825 (vw, sh); 700 (s, sh); 650 (m, sh), 645 (shoulder); 619 (w, sh), 607 (shoulder).

m/z 380 (M^+ $[PhCH_2CH_2NH]_2P(S)Ph^+$, 18%), 289 ($PhCH_2CH_2NH$-P(S)Ph-$NHCH_2^+$, 41%); 260 ($PhCH_2CH_2NH$-P(S)Ph^+, 86%); 228 ($PhCH_2CH_2NH$-PPh^+, 22%); 156 (25%); 120 ($PhCH_2CH_2NH^+$, 100%); 105 ($PhCH_2CH_2^+$, 72%); 91 ($PhCH_2^+$, 44%). HRMS (Found: M^+ 380.1467. $C_{22}H_{25}N_2PS$ requires 380.1476).

C ***N,N'*-D. henethyl)-*P*-phenylphosphonic diamide [38] and 2-phenethyl-1,3-diphenyl-1,3-bis(phenethylamino)-diphosphazane-1,3-dione [40]**



[38]



[40]

A solution of (dichloro)phenylphosphine oxide (4.91g; 25.2mmol) in dry benzene (100ml) was added to a mixture of ß-phenylethylamine (6.13g; 50.6mmol) and triethylamine (5.09g; 50.3mmol) in dry benzene (200ml). Addition of the (dichloro)phenylphosphine oxide/benzene solution caused the reaction mixture to turn milky as solid triethylamine hydrochloride separated out. The reaction mixture was then refluxed for 15hrs, and protected from extraneous moisture by means of a calcium chloride drying tube. By the end of this time, the reaction mixture had turned dark yellow. The mixture was allowed to cool, the hydrochloride salt mixture was filtered off, and solvent was removed *in vacuo* from the filtrates to yield a viscous orange oil (11.9g). Column chromatography with ethyl acetate-hexane (20%) as solvent gave two products: ***N,N'*-di(phenethyl)-*P*-phenylphosphonic diamide [38]** (0.764g; 2.10mmol; 8.32%) and **2-phenethyl-1,3-diphenyl-1,3-bis(phenethylamino)-diphosphazane-1,3-dione [40]** (0.445g; 0.732mmol; 5.81%). Compound **[38]** was recovered as a pale yellow solid. This was recrystallised from ethyl acetate to give a white solid, mp 85-86°C, R_F (ethyl acetate-hexane {20%}) 0.11.

Found: C, 71.13; H, 6.88; N, 7.55%.

$C_{22}H_{25}N_2OP$ requires C, 72.51; H, 6.91; N, 7.69%.

^1H NMR

δ_H 7.64 - 7.75 (2H, m, H-9); 7.33 - 7.52 (3H, m, H-10 + H-11); 7.18 - 7.30 (6H, m, H-6 + H-7); 7.08 - 7.17 (4H, m, H-5); 3.07 - 3.22 (4H, m, H-2); 2.70 (4H, t, H-3,

$^3J_{HH}$ = 6.83Hz); 2.35 -2.46 (2H, m, H-1).
D_2O exchange: multiplet at 2.35 - 2.46 disappears and the HOD peak appears at 4.84ppm.

^{13}C NMR
δ_C 138.72 (s, C-4); 134.80 (d, C-8, $^1J_{CP}$ = 120.28Hz); 131.38 (d, C-11, $^4J_{CP}$ = 3.06Hz); 130.68 (d, C-9, $^2J_{CP}$ = 10.96Hz); 128.71 (s, C-5); 128.35 (s, C-6); 128.07 (d, C-10, $^3J_{CP}$ = 14.14Hz); 126.26 (s, C-7); 42.34 (s, C-3); 37.49 (d, C-2, $^2J_{CP}$ = 7.33Hz).

^{31}P NMR: Singlet at 21.09ppm.

IR
υ_{max} (KBr disc) 3250 (s, sh); 3060 (w, sh); 3025 (w, sh); 2955 (shoulder), 2940 (w, sh), 2935 (shoulder); 2875 (w, sh); 2860 (w, sh); 1600 (w, sh); 1580 (w, br); 1490 (m, sh); 1470 (w, sh); 1445 (s, sh); 1435 (s, sh), 1420 (shoulder); 1360 (w, sh); 1270 (w, sh); 1180 (s, sh); 1160 (s, sh); 1120 (m, sh); 1105 (m, sh); 1085 (shoulder), 1080 (s, sh), 1060 (shoulder); 1020 (m, sh); 902 (m, sh); 885 (m, sh); 800 (w, br); 875 (w, br); 742 (s, sh); 690 (s, sh).

m/z 364 (M^+ $[PhCH_2CH_2NH]_2P(O)Ph^+$, 0.02%); 273 ($PhCH_2CH_2NH$-P(O)Ph-CH_2^+, 100%); 244 ($PhCH_2CH_2NH$-P(O)Ph^+, 98%); 105 ($PhCH_2CH_2^+$, 20%).
HRMS (Found: M^+ 364.1721. $C_{22}H_{25}N_2OP$ requires 364.1704).

2-Phenethyl-1,3-diphenyl-1,3-bis(phenethylamino)-diphosphazane-1,3-dione [40] was recovered as a pale yellow solid. This was recrystallised from ethyl acetate to give a white solid, mp 166-167°C, R_F (ethyl acetate) 0.64, R_F (ethyl acetate-hexane {20%}) 0.54.

An NMR sample recovered after exchange with D_2O was also purified and submitted for elemental analysis.
Found C, 70.18; H, 6.47; N, 6.81%.

$C_{36}H_{39}N_3O_2P_2$ requires C, 71.16; H, 6.47; N, 6.97%.
Found C, 70.65, (H+D), 6.39; N, 6.85%.
$C_{36}H_{37}D_2N_3O_2P_2$ requires C, 70.92; (H+D), 6.12; N, 6.89%.

^{1}H NMR

δ_H 7.83 - 7.94 (4H, m, H-9); 7.39 - 7.55 (6H, m, H-10 + H-11); 7.14 - 7.29 (9H, m, H-6 + H-7 + H-16 + H-17); 7.05 - 7.10 (4H, m, H-5); 6.87 - 6.91 (2H, m, H-15); 3.73 - 3.84 (2H, m, H-1); 3.21 - 3.42 (2H, m, H-12); 2.93 - 3.18 (4H, m, H-2); 2.72 (4H, t, H-3, $^3J_{HH}$ = 6.75Hz); 2.53 - 2.62 (2H, m, H-13).
D_2O exchange: multiplet at 3.73 - 3.84 disappears and the HOD peak appears at 4.82ppm.

^{13}C NMR

δ_C 138.76 (s, C-4); 133.05 (d, C-8, $^1J_{CP}$ = 157.96Hz); 131.86 (s, C-14); 131.80 (s, C-11); 131.64 (d, C-9, $^2J_{CP}$ = 4.82Hz); 128.80 (s, C-5); 128.73 (s, C-15); 128.49 (s, C-6); 128.47 (d, C-10, $^3J_{CP}$ = 7.27Hz); 128.35 (s, C-16); 126.39 (s, C-7); 126.29 (s, C-17); 47.38 (s, C-13); 41.42 (s, C-3); 38.41 (t, C-12, $^2J_{CP}$ = 3.17Hz); 37.34 (s, C-2).

^{31}P NMR: Singlet at 23.74ppm.

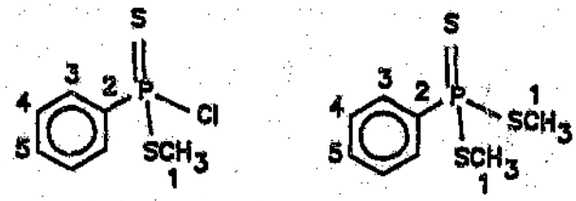
IR

υ_{max} ($CHCl_3$) 3665 (s, br); 3375 (m, v.br); 3075 (m, sh); 3060 (m, sh); 3025 (m, sh); 2995 (s, sh); 2925 (m, sh); 2865 (m, br); 2480 (m, br); 1955 (w, br); 1815 (w, br); 1680 (w, sh); 1600 (m, sh); 1590 (m, sh); 1555 (w, br); 1495 (s, sh); 1450 (s, sh); 1435 (s, sh); 1400 (s, sh); 1365 (w, sh); 1310 (w, sh); 1230 (s, sh); 1220 (s, sh); 1210 (s, sh); 1200 (s, sh); 1120 (s, sh); 1090 (s, sh); 1070 (s, sh); 1030 (m, sh); 910 (s, sh); 830 (w, sh); 725 (m, sh); 700 (s, sh); 667 (s, sh).

m/z 607 (M^+ $[PhCH_2CH_2NHP(O)Ph]_2$-$NCH_2CH_2PH^+$, 0.03%); 516 ($[PhCH_2CH_2NHP(O)Ph]_2$-NCH_2^+, 23%); 488 (32%); 487 ($PhCH_2CH_2NHP(O)Ph$-$N[CH_2CH_2Ph][P(O)Ph]^+$, 100%); 395 (23%); 383 (26%); 244 ($PhCH_2CH_2NH$-

P(O)Ph$^+$, 36%); 105 ($PhCH_2CH_2^+$, 25%); 91 ($PhCH_2^+$, 20%).
HRMS (Found: M^+ 607.2516. $C_{36}H_{39}N_3O_2P_2$ requires 607.2517).

D **Methyl (chloro)phenyldithiophosphonate [49] and dimethyl phenyltrithiophosphonate [48]**



[49] [48]

To a mixture of homoveratrylamine (4.62g; 25.5mmol) and triethylamine (2.54g; 25.1mmol) in dry benzene (200ml), a solution of (dichloro)phenylphosphine sulphide (5.30g; 25.1mmol) in dry benzene (100ml) was added. Addition of the (dichloro)phenylphosphine sulphide/benzene solution caused the reaction mixture to turn milky as solid triethylamine hydrochloride separated out. The reaction mixture was then refluxed for 15hrs, and protected from extraneous moisture by means of a calcium chloride drying tube. By the end of this time, the reaction mixture had turned bright yellow. The mixture was allowed to cool before the hydrochloride complex was filtered off. Excess solvent was removed *in vacuo* to yield a dark yellow-brown oil. This intermediate was heated in the presence of anhydrous aluminium chloride (3.33g; 25.0mmol) at 110°C for 8hrs. The resulting material was a black glassy material, which dissolved with difficulty in a dichloromethane/water mixture (400ml; CH_2Cl_2-H_2O 2:1). Water was added to destroy excess aluminium chloride. The combined organic extracts were washed with a saturated sodium chloride solution, dried with anhydrous sodium sulphate, filtered and excess solvent removed *in vacuo* to yield a dark brown oil (6.23g). Column chromatography with benzene-hexane (1:1) as solvent gave two products: **methyl (chloro)phenyldithiophosphonate [49]** (0.0375g; 0.168mmol; 1.34%) and **dimethyl phenyltrithiophosphonate [48]** (0.277g; 1.18mmol; 14.1%). Compound [49] was obtained as a pale yellow oil, R_F (benzene-hexane 1:1) 0.72.

^{1}H NMR

δ_H 8.04 - 8.19 (2H, m, H-3); 7.48 - 7.66 (3H, m, H-4 + H-5); 2.52 (3H, d, H-1, $^3J_{HP}$ = 18.62Hz).

^{13}C NMR

δ_C 136.03 (d, C-2, $^1J_{CP}$ = 99.96Hz); 133.23 (d, C-5, $^4J_{CP}$ = 3.64Hz); 130.48 (d, C-3, $^2J_{CP}$ = 12.99Hz); 128.72 (d, C-4, $^3J_{CP}$ = 15.66Hz); 15.46 (d, C-1, $^2J_{CP}$ = 4.06Hz).

IR

υ_{max} ($CHCl_3$) 3050 (w, sh); 2980 (m, sh); 2920 (w, sh); 1685 (w, br); 1597 (w, br); 1495 (w, sh); 1450 (s, sh); 1350 (w, sh); 1330 (w, sh); 1320 (w, sh); 1110 (s, sh); 1010 (w, sh); 980 (w, sh); 920 (w, br); 900 (w, br).

m/z 224 (25%); 222 (M^+ $PhClP(S)SMe^+$, 62%); 176 (34%); 175 ($PhP(S)Cl^+$, 39%); 145 ($ClP(S)SMe^+$, 28%); 143 ($PhPCl^+$, 78%); 139 (66%); 107 (41%); 78 (23%); 77 (Ph^+, 86%); 63 ($P{=}S^+$, 100%); 51 (96%); 50 (31%); 45 (21%).
HRMS (Found: M^+ 221.9490. $C_7H_8ClPS_2$ requires 221.9494).

Dimethyl phenyltrithiophosphonate [48] was recovered as a pale yellow oil. This was distilled under reduced pressure to give a colourless oil, which solidified very slowly to a white solid, mp 30-32°C, R_F (benzene) 0.90, R_F (benzene-hexane 1:1) 0.56. Dimethyl phenyltrithiophosphonate (15.7%) was again recovered when attempting the same reaction on the substrate *N*-methyl-2-(3,4-dimethoxy-phenyl)ethylamine. In addition, the reaction temperature was 169°C.

Found C, 40.83; H, 4.63; P, 13.38%.
$C_8H_{11}PS_3$ requires C, 41.00; H, 4.73; P, 13.22%.

^{1}H NMR

δ_H 8.00 - 8.13 (2H, m, H-3); 7.45 - 7.58 (3H, m, H-4 + H-5); 2.35 (6H, d, H-1, $^3J_{HP}$ = 16.00Hz).

^{13}C NMR

δ_C 134.71 (d, C-2, $^1J_{CP}$ = 86.00Hz); 132.39 (d, C-5, $^4J_{CP}$ = 3.54Hz); 130.62 (d, C-3, $^2J_{CP}$ = 11.33Hz); 128.57 (d, C-4, $^3J_{CP}$ = 13.95Hz); 14.94 (d, C-1, $^2J_{CP}$ = 3.57Hz).

^{31}P NMR: Singlet at 84.45ppm.

IR

υ_{max} ($CHCl_3$) 3050 (w, sh); 3025 (m, sh); 2950 (s, sh); 2895 (s, sh); 2795 (w, sh); 1670 (w, br); 1590 (w, br); 1480 (m, sh); 1435 (s, sh); 1420 (s, sh); 1320 (m, sh); 1310 (m, sh); 1235 (w, br), 1220 (shoulder); 1185 (w, sh); 1105 (s, sh); 1075 (w, sh); 1030 (w, sh); 1005 (w, sh); 970 (m, sh); 690 (s, sh); 680 (shoulder), 670 (s, sh).

m/z 234 (M^+ $PhP(S)(SMe)_2^+$, 42%); 187 ($PhP(S)SMe^+$, 88%); 155 ($PhPSMe^+$, 34%); 140 ($PhP(S)^+$, 22%); 139 (52%); 109 (22%); 107 (24%); 77 (Ph^+, 52%); 63 ($P{=}S^+$, 100%); 51 (39%).

HRMS (Found: M^+ 233.9736. $C_8H_{11}PS_3$ requires 233.9761).

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PART B

PHOSPHORUS- AND SULPHUR-MEDIATED ROUTES

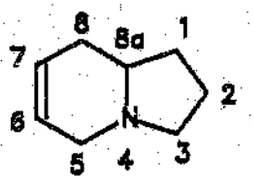
TO THE

^{6,7}-INDOLIZIDINE RING

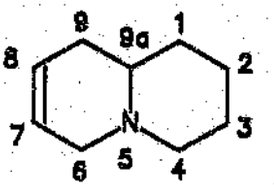
CHAPTER 1: INTRODUCTION, BACKGROUND AND AIMS

1.1 INTRODUCTION

The focus of this project is to devise new synthetic routes to the $\Delta^{6,7}$-indolizidine ring system shown in [1] (numbering scheme shown). By extension the routes developed should also be applicable to the closely related $\Delta^{7,8}$-quinolizidine system [2].

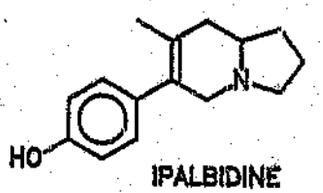


[1]



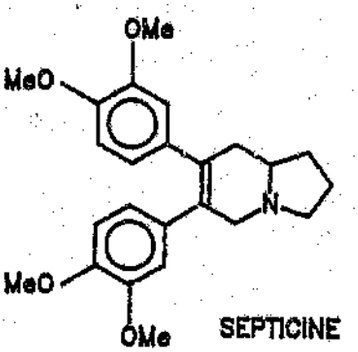
[2]

Interest in these ring systems derives from their occurrence in a number of alkaloids typified by ipalbidine [3], septicine [4] and julandine [5]. The bicyclic system may also be embedded in a fused polycyclic ring, as found in the phenanthroindolizidine [6] and phenanthroquinolizidine alkaloids [7].



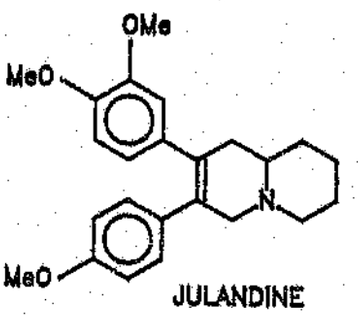
IPALBIDINE

[3]



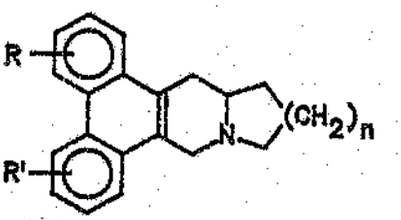
SEPTICINE

[4]



JULANDINE

[5]

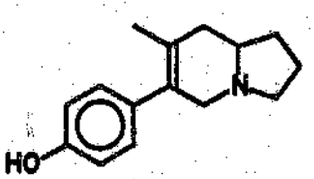


[6], n = 1
[7], n = 2

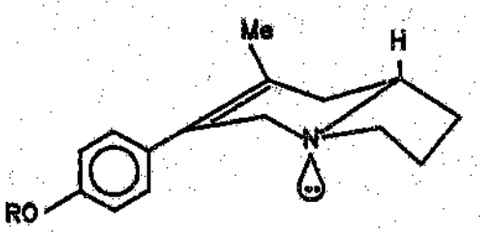
The following sections contain a brief account of the natural occurence of [3] - [5], and their relationship to the more complex phenanthro analogues. Aspects of some reported synthetic approaches to the systems of interest will be outlined. The project will then be put into perspective by a general discussion of the "Wits Alkaloids" programme. Finally, the specific aims and strategies of this project will be outlined.

1.2 $\Delta^{6,7}$-INDOLIZIDINE AND $\Delta^{7,8}$-QUINOLIZIDINE ALKALOIDS

1.2.1 Occurrence

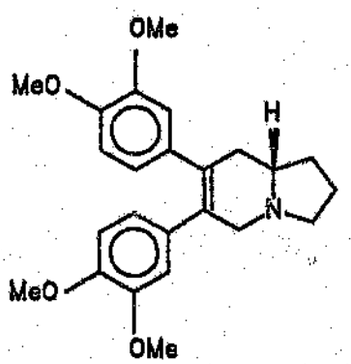


[3]

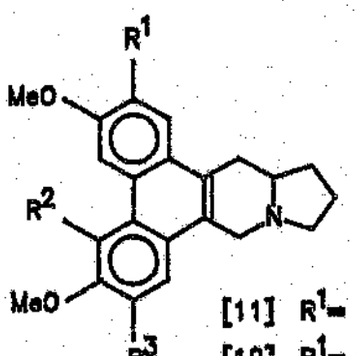


(+) – IPALBINE [8] R = β–D–GLYCOSYL
(+) – IPALBIDINE [9] R = H

Simple indolizidine alkaloids have been isolated from two species of *Ipomoea* (family Convolvulaceae). From the basic extracts of the crushed seeds of *Ipomoea alba* L., the common moonflower, were isolated ipalbidine [3], (+)-ipalbine [8], and a minor unidentified base[1]. (+)-Ipalbidine [9] is the aglycone of natural (+)-ipalbine [8]. The crushed seeds of *Ipomoea muricata*. Jacq. gave ipalbidine [3] as the minor product and a new alkaloid, (+)-ipomine, as the major[2]. Natural ipalbidine [3] is racemic, but both enantiomers have been synthesised by Dolphin and co-workers[3]. (+)-Ipalbidine [9] has been shown to have the (*S*)-configuration[4,5].



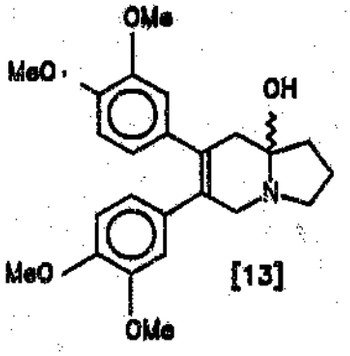
[10]



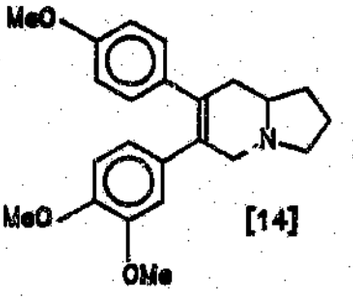
[11] R^1= R^3= OMe, R^2= H
[12] R^1= R^2= OMe, R^3= H
[15] R^1= R^2= H, R^3= OMe

(-)-Septicine [10] is the first simple indolizidine alkaloid to have been discovered. The alkaloid is a close relative of the phenanthroindolizidine alkaloids (see below). It was isolated along with (-)-tylophorine [11] and (+)-tylocrebine [12], from the tree *Ficus septica* Forsk. (family Moraceae)[6]. The structure was confirmed by a synthesis from L-prolinol, a synthesis that established (-)-septicine as being of the *S*-configuration, as shown in [10][7]. A later group of workers reinvestigated the root and leaves of *Ficus septica*, but failed to confirm the previous findings. (-)-Septicine has also been isolated from *Tylophora crebriflora* S.T.Blake, an Australian vine belonging to the family Asclepiadaceae (taxonomically quite remote from the family Moraceae) in which it occurs alongside tylocrebine [12] and five similar phenanthroindolizidine alkaloids[8,9].

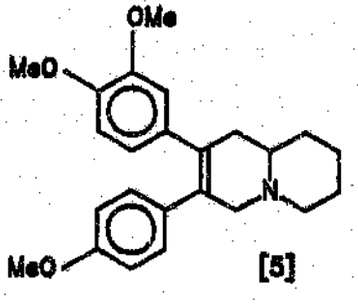
(+)-Septicine has been obtained from another species, *Tylophora asthmatica* Wright et Arn [syn. *T. indica* (Burm) Merril][10]. A third species, *T. hirsuta*, contains a related alkaloid, (+)-8a-hydroxysepticine [13][11]. The orientation of the hydroxy group in this compound has not been determined, though the ring junction is probably *cis*. A demethoxy derivative of septicine, named hispidine [14] has been isolated from the leaves of *Ficus hispida*[12]. The compound is a seco version of (-)-deoxypergularine [15], with which it occurs.



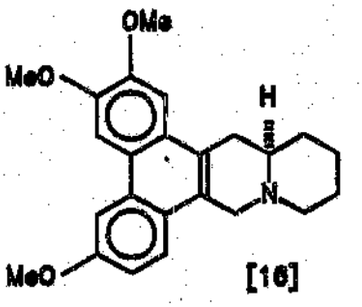
[13]



[14]



[5]

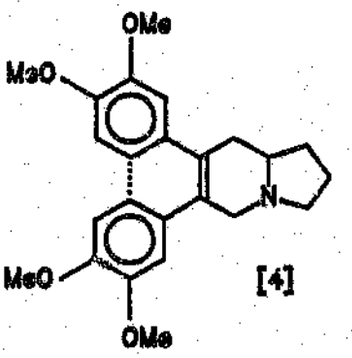


[16]

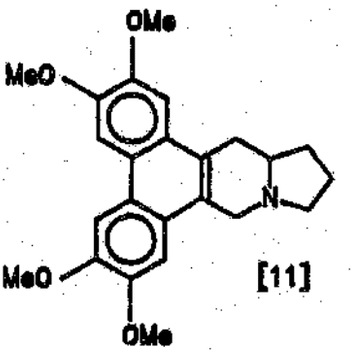
Julandine [5] is a minor alkaloid from *Boehmeria platyphylla* Don. (family Urticaceae)[13]. Julandine has a clear structural similarity to the phenanthroquinolizidine alkaloids e.g. cryptopleurine [16] which have excited interest as antimicrobial and antitumour agents. The natural product may be largely racemic.

The phenanthroindolizidine and phenanthroquinolizidine groups of alkaloids are closely related to the alkaloids under consideration in this project. These two groups of alkaloids have been the subject of detailed studies in recent years, particularly by Indian chemists. Various aspects of their chemistry and pharmacology have been reviewed by Govindachari[14-16] and by Wiegrebe[17]. Short reports of progress in the chemistry[18] and biosynthesis[19] of the phenanthroindolizidine alkaloids, and on the synthesis[20] of the phenanthroquinolizidines have also been published. Interest in the phenanthroindolizidine alkaloids has centered in particular around reports of their antitumour activity[21-24]. At the same time, their extremely toxic and vesicant nature has been noted by several investigators[25-28]. However the toxicity appears to be variable.

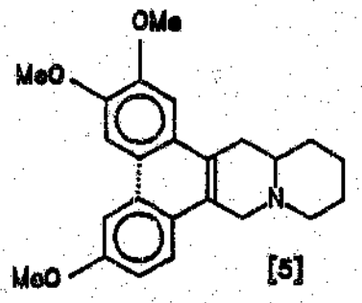
The name *Tylophora* alkaloids is often applied to the phenanthroindolizidines from the frequency with which they occur in this genus. They are also found in other genera of the Asclepidaceae, as well as in the Moraceae and Urticaceae, which are phylogenetically remote from the latter family but related to one another. The Lauraceae, which produce both phenanthroindolizidines and phenanthroquinolizidines, are likewise considered much less advanced than the Asclepidaceae[29].



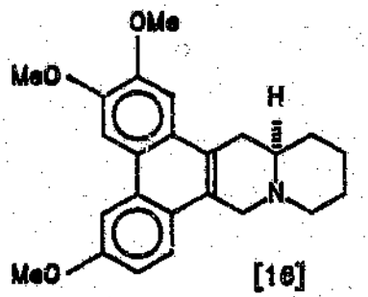
[4]



[11]

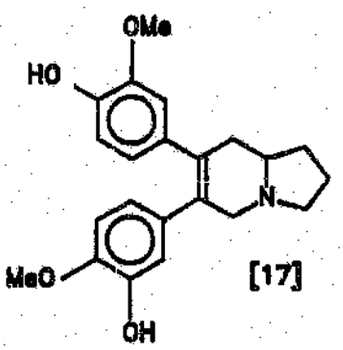


[5]



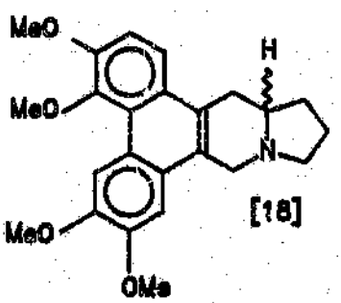
[16]

Looking at the structures of tylophorine [11] and its seco-analogue septicine [4] shown above, one can readily imagine a biosynthetic relationship between them. By forming a bond positioned along the dotted line, [4] can be converted to [11]. A similar relationship can be envisaged for julandine [5] and its seco-analogue, cryptopleurine [16]. In nature, a central role is allocated to compound [17] in the biosynthesis of these alkaloids, because oxidative phenolic coupling is postulated to lead to the fused pentacyclic alkaloids.

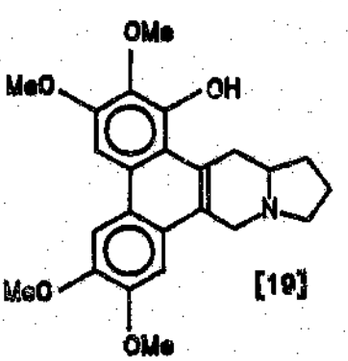


[17]

In the laboratory, this kind of coupling has been accomplished with thallium(III) trifluoroacetate[30,31]. One equivalent of this reagent very efficiently converted septicine [4] into tylophorine [11]; none of the isomeric, more sterically hindered alkaloids eg tylocrebrine [12] or isotylocrebrine [18], was obtained. When two equivalents of thallium(III) trifluoroacetate were used, a different product [19] was obtained.



[18]

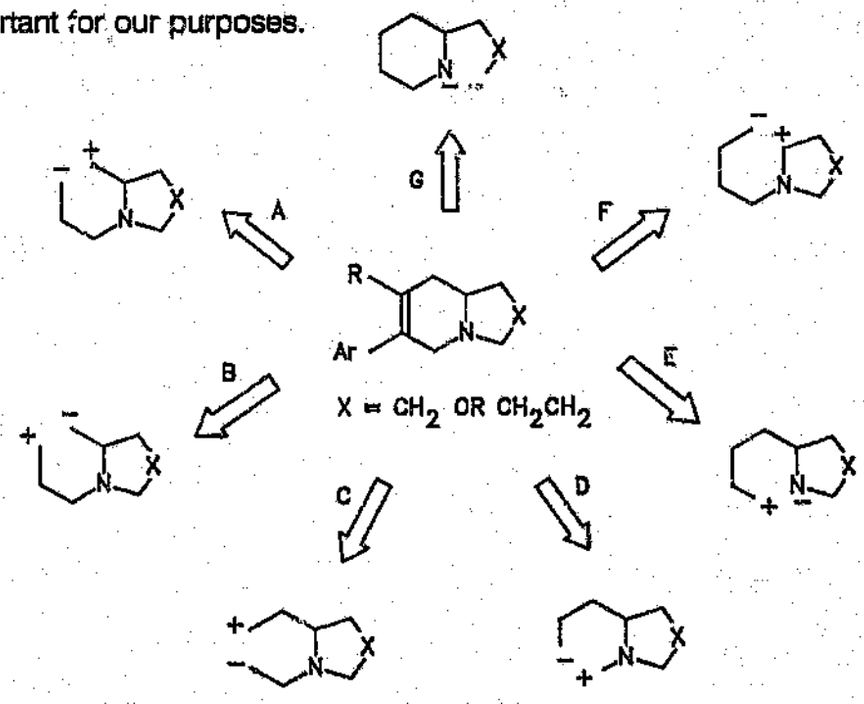


[19]

1.2.2 Reported Synthetic Approaches

Ipalbidine [3], septicine [4] and, to a lesser extent, julandine [5], have all been popular targets for total synthesis. In view of the structural similarities between these compounds, several common approaches to their synthesis have been developed. The documented syntheses of these compounds have been classified on the basis of the mode of ring closure of the aryl-substituted ring. Scheme 1 shows the disconnections involved. The scheme follows the classification method employed by Howard and Michael[32], with the addition of a new route (disconnection G), which has appeared since the earlier classification was published.

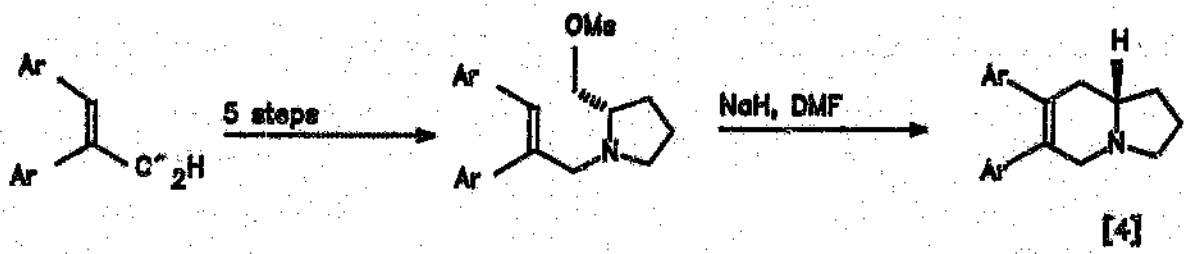
We will not go into great detail on the various syntheses of these alkaloids. Rather, our attention will be focussed on the central ring closure step. Only a few select examples will be illustrated for each mode of ring closure. For full details on the total synthesis of the three alkaloids, reviews are available by Howard and Michael[32], and Herbert[33]. In view of the strategy chosen for this project (see section 1.4), disconnection B is the most important for our purposes.



Scheme 1: Disconnections for reported syntheses of ipalbidine, septicine, and julandine.

Disconnection A

This route is largely historic, being the first by which septicine [4] was made. In addition, it is the only route to have led to the optically active alkaloid[7]. L-Prolinol was used in the synthesis in order to confer optical activity on the product, which may nevertheless still be partly racemic.

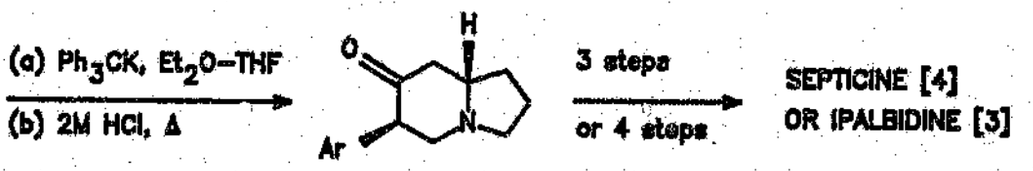


Scheme 2: Synthesis of (-)-septicine by Russel and Hunziker[7].

Disconnection B

Govindachari and co-workers accomplished ring closure to the indolizidine ring system by means of a Dieckmann condensation. This provided a generalised route to both (±)-ipalbidine [3][34] and (±)-septicine [4][35]. The condensations were carried out on the diesters [20a] and [20b]. The ketones [21a] and [21b] that were prepared in this manner are very important intermediates, since a number of other formal syntheses converge to these compounds. The perdemethoxy analogue of septicine has also been synthesised by this route[35].

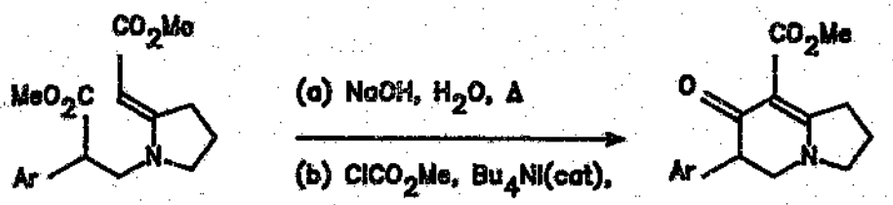
a X = H
b X = OMe



[21a] 42%
[21b] 65%

Scheme 3: Synthesis of ipalbidine and septicine by Govindachari and co-workers[34,35].

In a later formal synthesis of (±)-ipalbidine [3] by Howard, Gerrans and Michael[36], the object was the preparation of the ketone [21a]. In this synthesis, ring closure depends on the enamine-like nucleophilicity of the vinylogous urethane [22].



[22] 77%

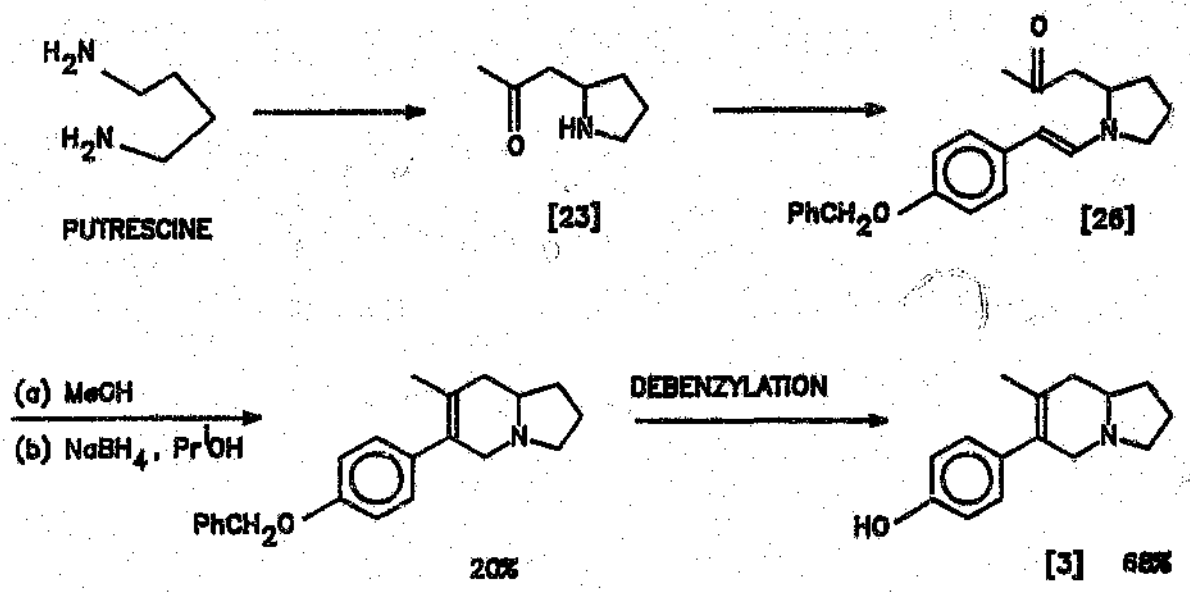
Scheme 4: Formal synthesis of ipalbidine by Howard, Gerrans and Michael[36].

This synthesis forms part of the "Wits Alkaloids" project. The approach employed by Howard *et al.*[36] complements my proposed construction of the indolizidine ring in the preparation of ipalbidine. Consequently this synthesis will be discussed in more detail in section 1.3.3, where it will also be seen in context with the rest of the Wits approach to alkaloid synthesis.

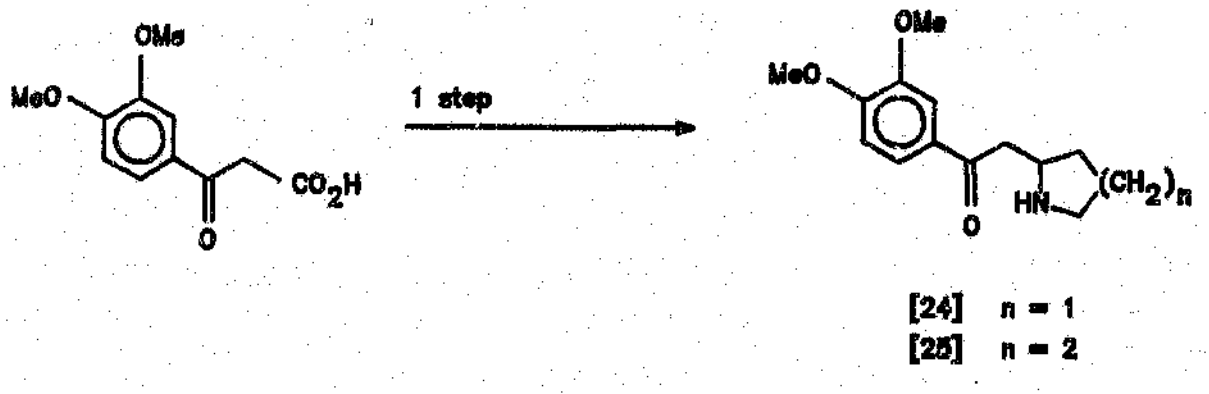
Disconnection C

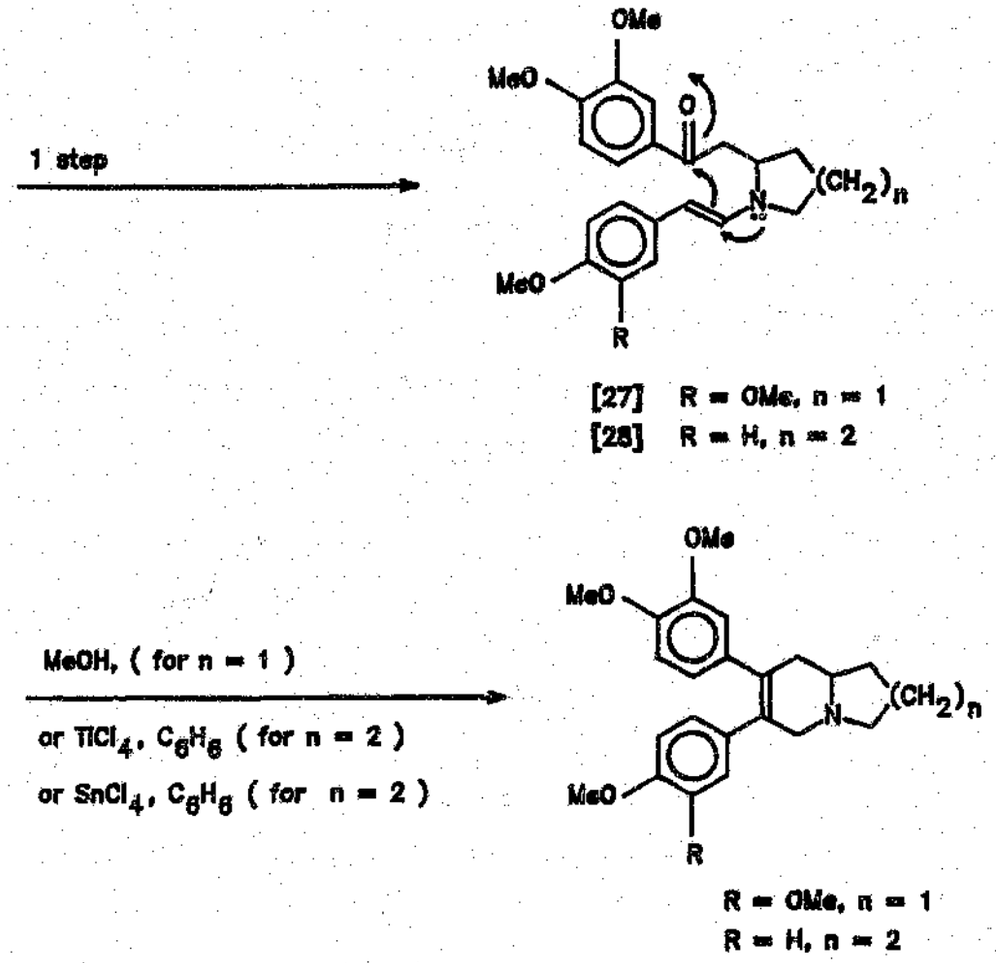
Herbert and co-workers have designed biogenetically-patterned syntheses of ipalbidine [3], septicine [4] and julandine [5][37-42] (Schemes 5 & 6). When the compounds [23], [24], [25] are treated with appropriately substituted arylacetaldehydes, enamines [26], [27] and [28] result. It is not necessary to isolate these compounds,

these compounds, as they undergo cyclisation and dehydration upon being left to stand in methanolic solution[40]. These crude products can then be transformed into the desired bicyclic alkaloids. Cyclisation of the enamine-ketone (and subsequent dehydration) can also be achieved using selected Lewis acid catalysts, notably titanium(IV) chloride and silicon(IV) chloride in benzene, and magnesium iodide in ether[37,39,42].

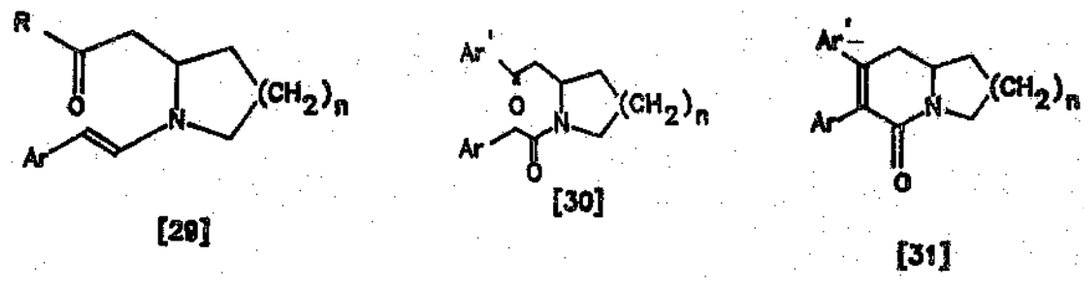


Scheme 5: Biogenetically patterned synthesis of (±)-ipalbidine by Hedges and Herbert[39].





Scheme 6: Synthesis of septicine and julandine by Herbert[37].



[29] [30] [31]

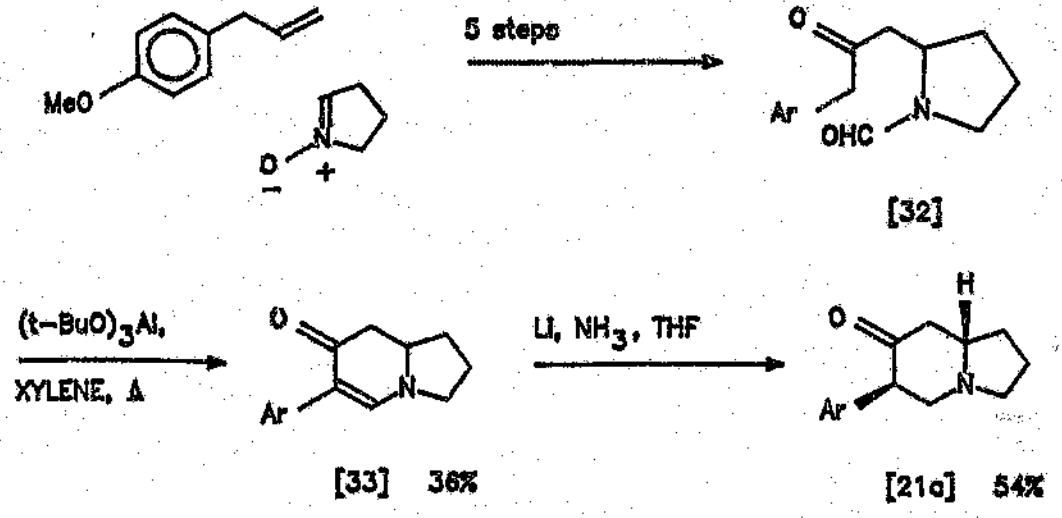
Very similar approaches have been devised which rely on the intramolecular cyclisation of keto amides [30] instead of enamines [29]. Cyclisation is now base induced, e.g. with sodium ethoxide, potassium *t*-butoxide or alcoholic alkali. The lactams [31] prepared by means of this condensation can subsequently be reduced to the alkaloids septicine [4][43-47] and julandine [5][47-49], as well as to several

unnatural analogs[50,51]. They can also serve as precursors to the phenanthroindolizidine and phenanthroquinolizidine alkaloids[46,47,49,52].

The above discussion is a short summary of some of the many approaches that fit into this disconnection scheme, and the following references should also be consulted: synthesis of septicine and julandine, by Kibayashi *et al.*[46,47,49]; ipalbidine, by Dolphin *et al.*[3] and Liu *et al.*[53]; julandine and analogues by Trigo *et al.*[51] and Paton *et al.*[48].

Disconnections D & E

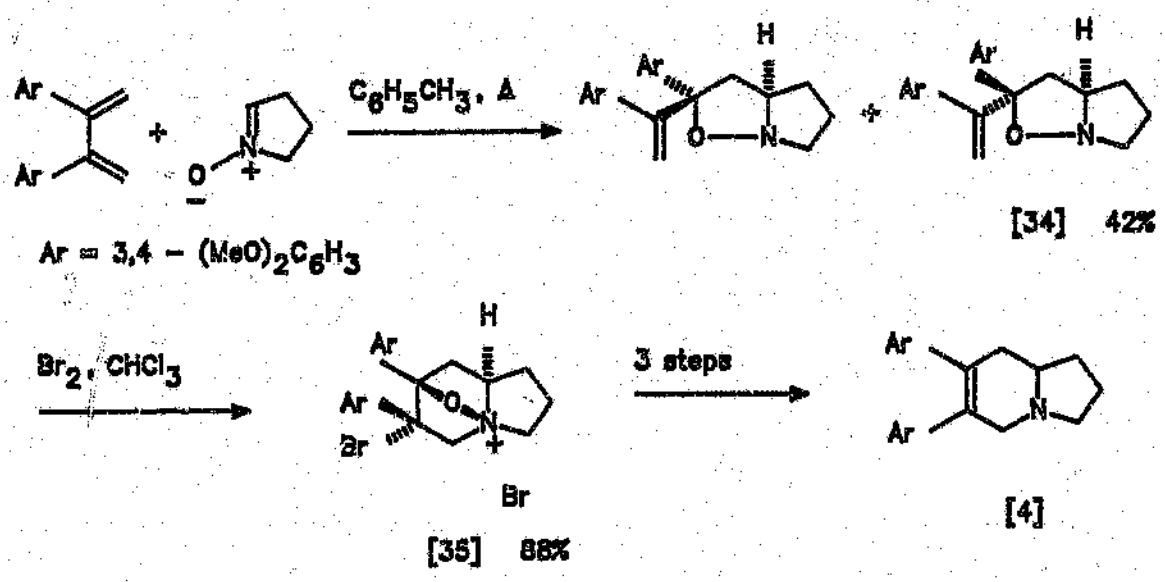
Two syntheses employing disconnections D and E are illustrated. Both exhibit interesting features in the early stages of the synthesis as well as in the cyclisations. Nitrone methodology is employed to introduce a carbon chain into the 2 position of a pyrrolidine ring. Scheme 7 outlines a recent formal synthesis of (±)-ipalbidine [3] by Iida *et al.*[54,55]. The *N*-formyl intermediate [32] undergoes base-initiated cyclisation to the vinylogous amide [33]. The olefinic bond is then reduced selectively to yield the much synthesised ketone [21a].



Scheme 7: Formal synthesis of ipalbidine by Iida, Watanaba and Kibayashi[54,55].

The synthesis of (±)-septicine [4] by Iwashita *et al.*[56] also uses nitrone methodology.

This synthesis deviates from the "condensation" feature observed in many of the syntheses described so far, by employing a disconnection-E annulation procedure. The major isoxazolidine [34] undergoes bromination with intramolecular participation by nitrogen to set up the indolizidine system in [35]. Compound [35] is then converted in three steps to (±)-septicine [4] (Scheme 8).

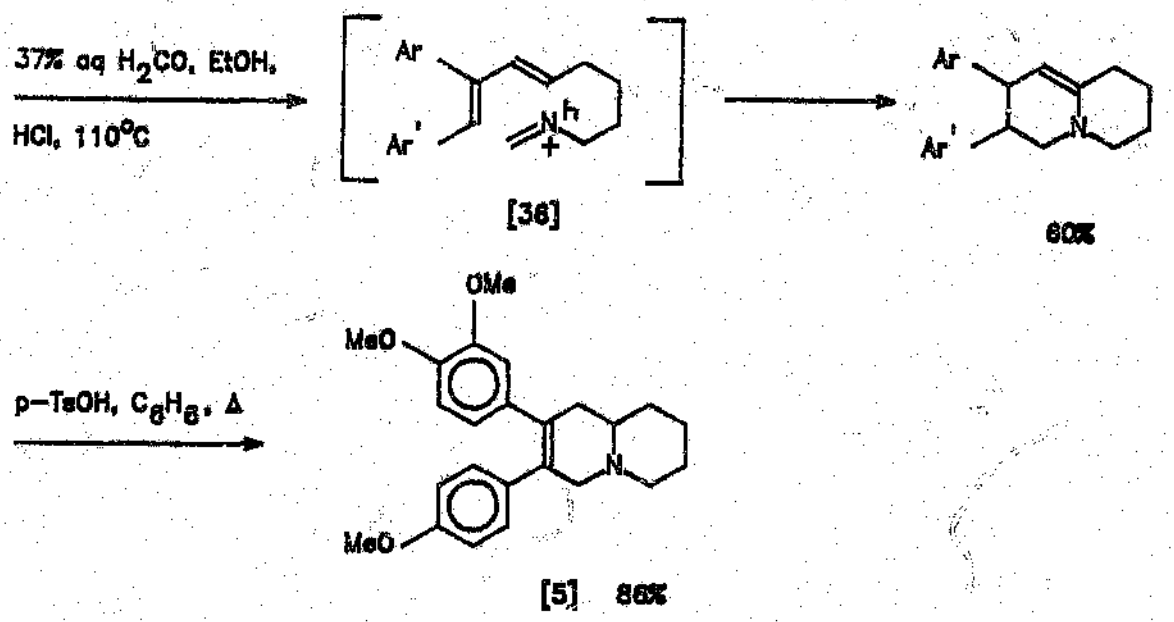


Scheme 8: Synthesis of septicine by Iwashita *et al.*[56].

Grieco and Parker[57] have synthesised julandine [5], employing disconnection D (Scheme 9). The central transformation involves an intramolecular Diels-Alder cycloaddition of a transient iminium intermediate [36].

Ar = 3,4 – $(MeO)_2C_6H_3$

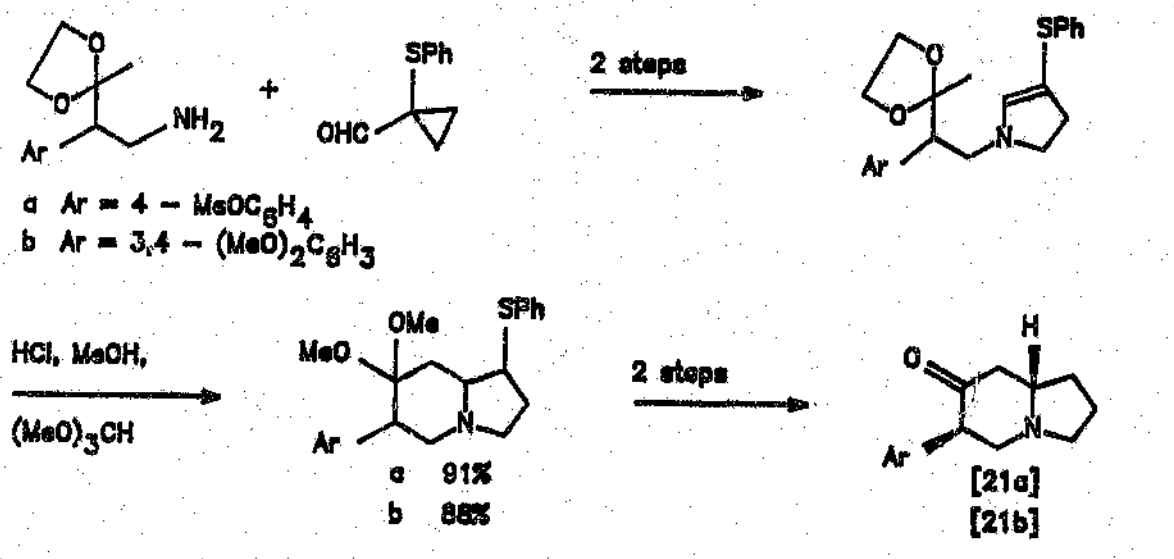
Ar' = 4 – $MeOC_6H_4$



Scheme 9: Synthesis of julandine by Grieco and Parker[57].

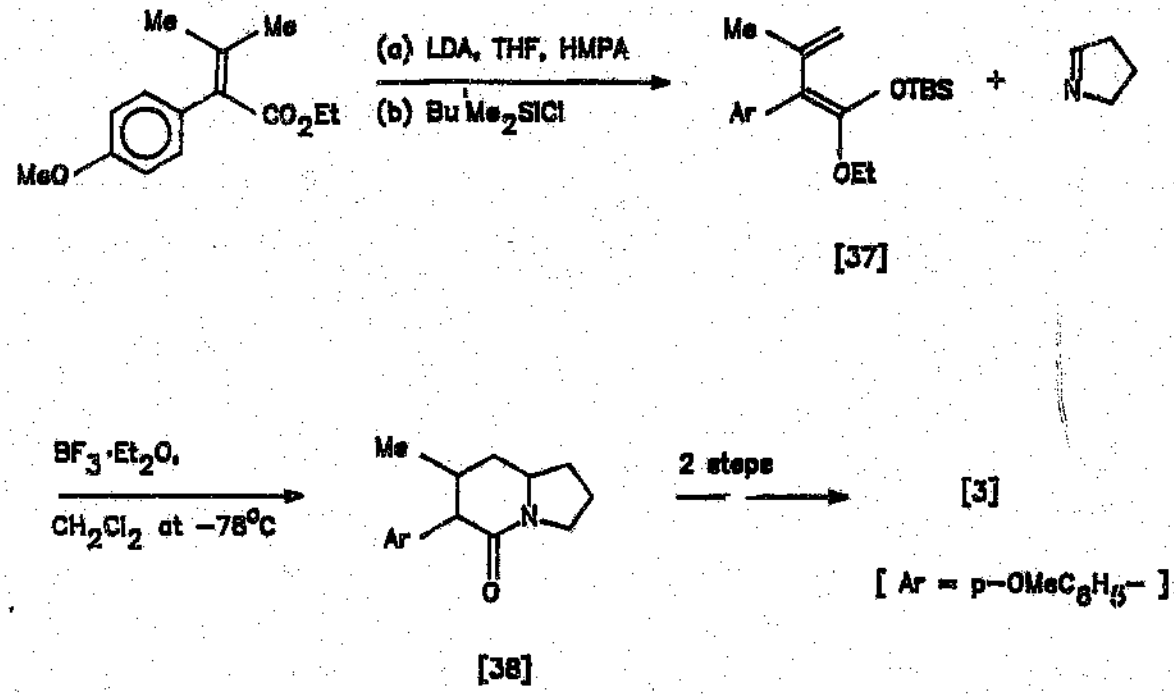
Disconnection F

Stevens has applied the cyclopropylimine-Δ^2-pyrroline rearrangement[58] successfully to the synthesis of both (±)-ipalbidine [3] and (±)-septicine [4][59](Scheme 10). Formation of the bicyclic systems was subsequently accomplished by an intramolecular Mannich reaction. Ketones [21a] and [21b] are again key intermediates.



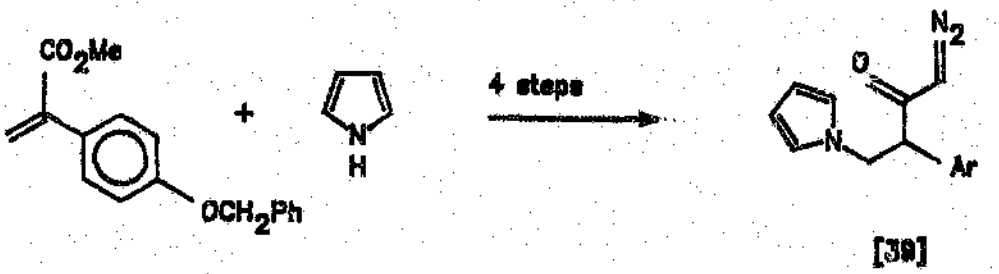
Scheme 10: Synthesis of ipalbidine and septicine by Stevens and Luh[59].

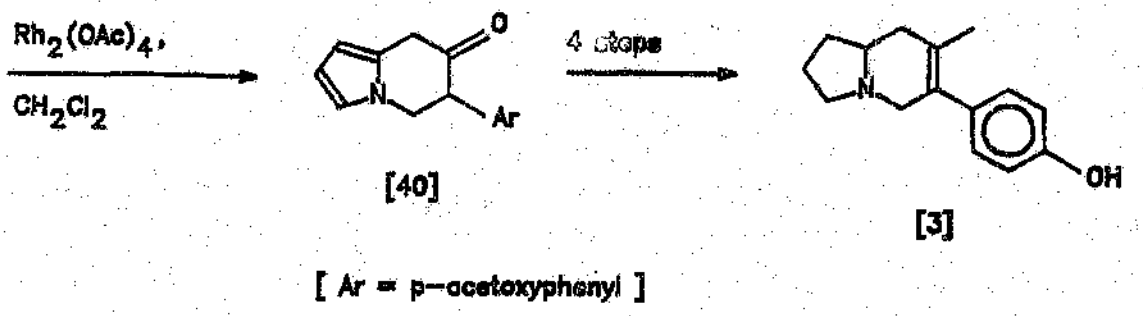
Danishefsky and Vogel[60] have shown that silyl ketene acetal [37] undergoes acid-catalysed cyclocondensation with an imine to give the indolizidine [38] (Scheme 11).



Scheme 11: Synthesis of ipalbidine by Danishefsky and Vogel[60].

Jefford *et al.*[61] carried out a synthesis of (±)-ipalbidine by an intramolecular carbene cyclisation of diazo ketone [39] (Scheme 12). The cyclisation [39] to [40] was catalysed by rhodium(II) acetate and the product was converted in four steps to ipalbidine [3]. These workers also investigated the influence of other aryl groups on the ease of cyclisation of [39] to [40].





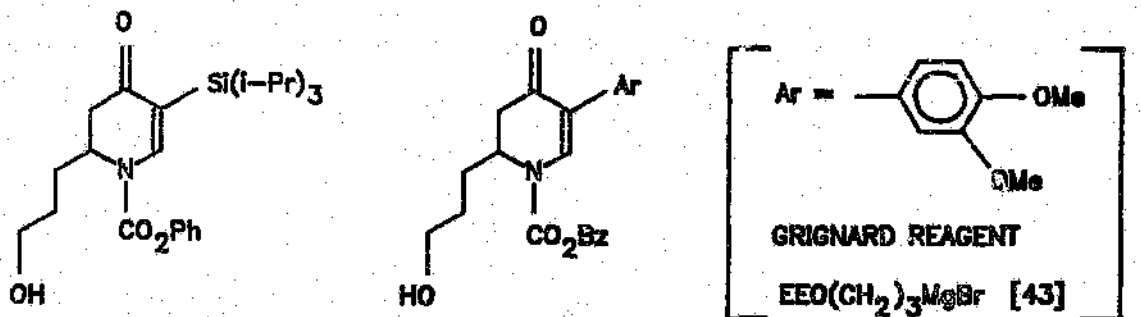
[40] [3]

[Ar = p–acetoxyphenyl]

Scheme 12: Formal synthesis of ipalbidine by Jefford and co-workers[61].

Disconnection G

Comins and Lawrence[62] have been using *N*-acyldihydropyridones as synthetic intermediates. They now report the conversion of *N*-acyldihydropyridone [41] to the indolizidine alkaloid (±)-septicine [4]. This disconnection approach differs from the others in that we are looking at ring closure to the 5-membered indolizidine ring.

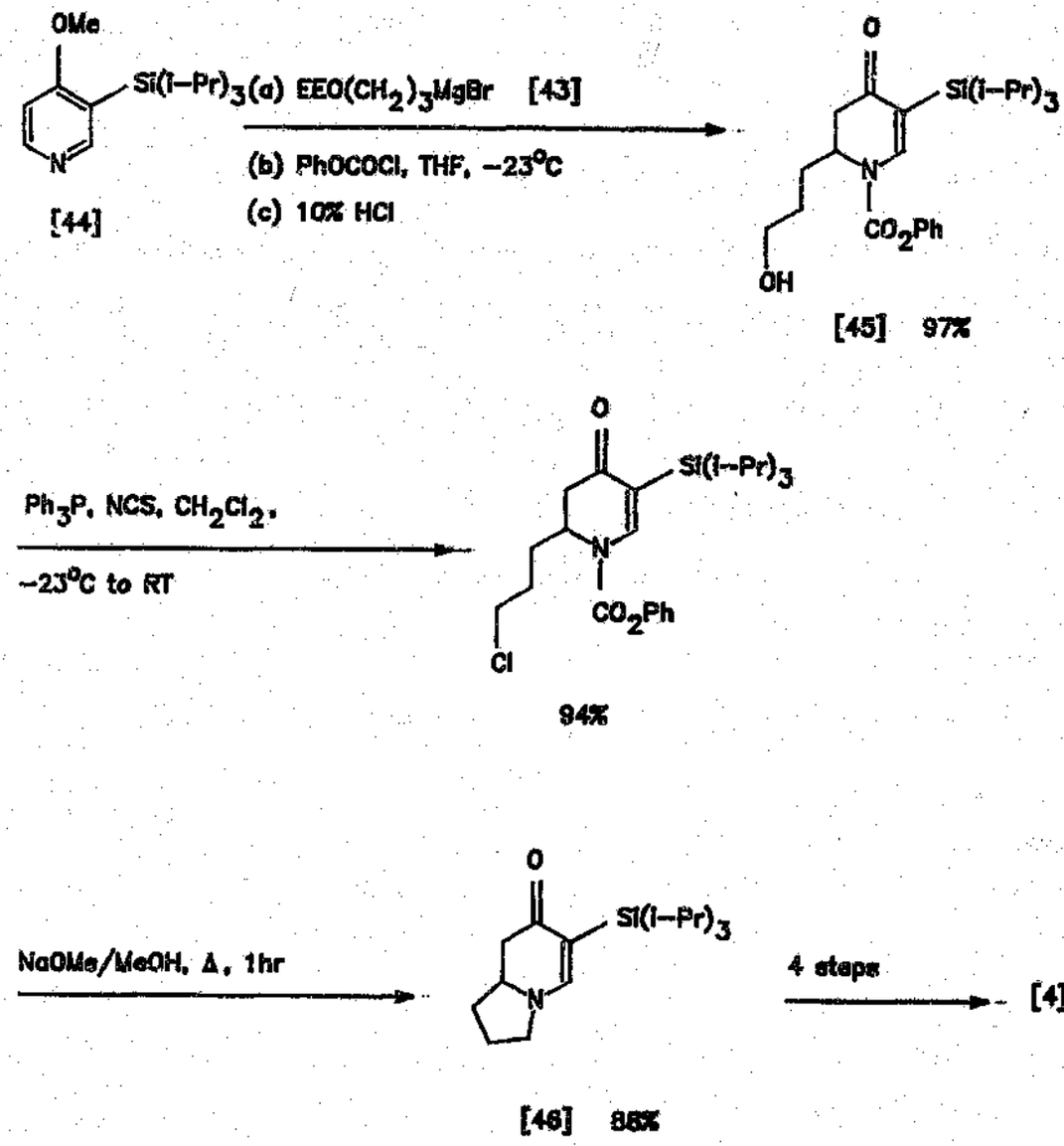


[41] [42]

Their initial approach was to prepare (±)-septicine via dihydropyridone [42]. The aryl group at C-3 was not sufficiently large to prevent attack by the Grignard reagent [43][63] at C-2, with the result that a mixture of dihydropyridones was obtained. Although the approach was successful, they were looking for a shorter and more regioselective route.

Previous work from their laboratories showed that a 3-triisopropylsilyl (TIPS) group can effectively block the C-2 position of a 1-acylpyridinium salt against attack by Grignard reagents[64]. Treatment of [44] with Grignard reagent [43] gave alcohol [45] in nearly

quantitative yield. (±)-Septicine was generated from the crude product [46] in 4 steps.



Scheme 13: Synthesis of septicine by Comins and Lawrence[62].

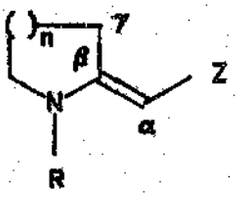
1.3 THE "WITS APPROACH" TO ALKALOID SYNTHESIS

A long-term goal in this department has been the development of novel methodology for the synthesis of alkaloids belonging to specific classes. Indolizidines and quinolizidines have featured predominantly as targets. In most cases, the perfection

of methodology has been the chief objective, and the preparation of alkaloids has been a subsidiary objective to be achieved once suitable methodology has been explored.

1.3.1 Overview

Research in alkaloid synthesis using the "Wits approach" dates back about two decades, during which time eight Ph.D. theses[65], three M.Sc. dissertations[66] and numerous honours projects have been completed, and several papers have been published[30,67-78]. This work is characterised by the exploitations of the properties of exocyclic vinylogous amides, urethanes and related compounds in the synthesis of various alkaloids. These systems [47] are illustrated below.



[47]

where n = 1 or 2

Z = CO_2R' (vinylogous urethane)

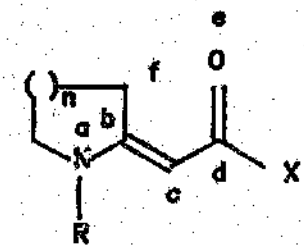
or Z = COR' (vinylogous amide)

or Z = CN (vinylogous cyanamide)

R = alkyl

The chemistry of vinylogous amides and urethanes, collectively also known as enaminones, has been reviewed by Greenhill[79]. The versatility of exocyclic extended enamines warrants their use as synthetic intermediates. It is unrealistic to think of enaminones as enamines or conjugated carbonyl compounds, as their extended π-system imparts to them a reactivity that, though at times resembling that of these

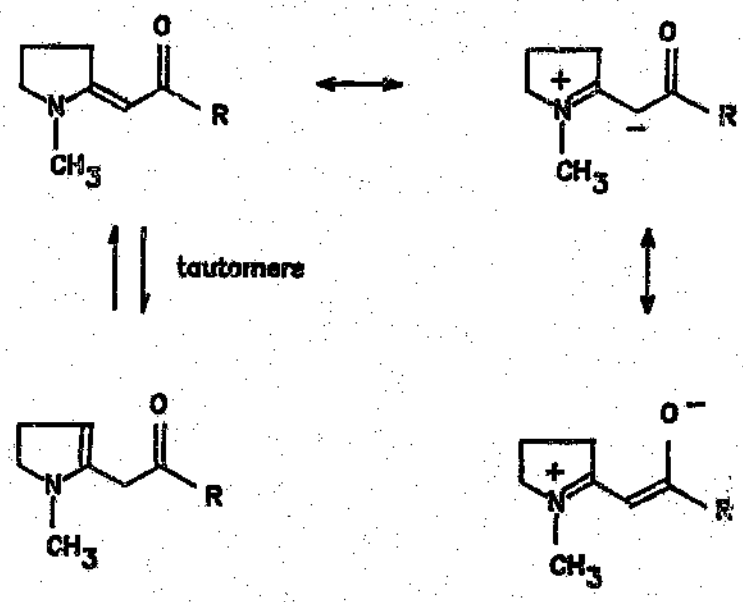
functional groups, is very often quite different[79]. The enaminone systems [48] possess ambident nucleophilicity and electrophilicity. They have potentially six reaction sites, four of which (a, c, e and f) are nucleophilic in nature and the other two sites (b, d) are electrophilic in nature.

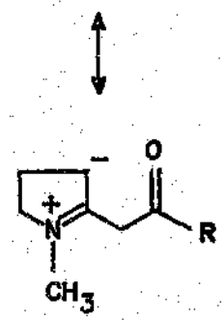


X = alkyl
or X = aryl
or X = alkoxy
R = alkyl

[48]

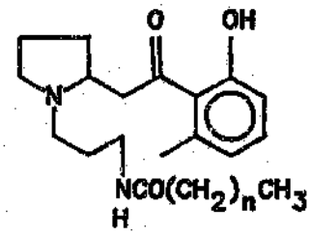
Extended delocalisation and tautomerism renders the oxygen and the γ-carbon competitive nucleophilic sites (Scheme 14). It is as a result of this ambident behaviour that they are envisaged as very versatile intermediates in organic synthesis. These chemistries have been studied fairly extensively in these laboratories and also by other workers.





Scheme 14

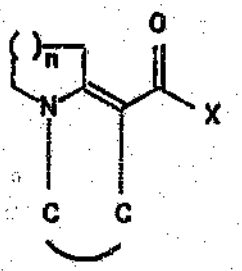
Our group is interested in searching for new or improved methods for synthesising vinylogous amides and urethanes as we have recognised them as potential intermediates for pyrrolizidine[65b], indolizidine[36,65d,69], quinolizidine, and more recently, perhydroindole[65e,80] alkaloid ring systems. Simple pyrrolidine and piperidine alkaloids are also readily accessible through various vinylogous urethanes and amides[71]. Slightly more complex pyrrolidine alkaloids such as peripentadenine **[49]** and dinorperipentadenine **[50]** have been synthesised recently in these laboratories via these intermediates[73].

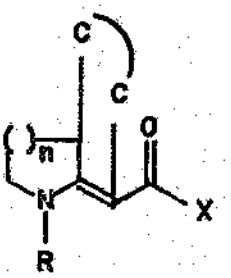


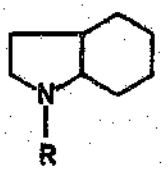
[49] n = 4
[50] n = 2

For the most part, we have exploited the ambident nucleophilicity of enaminones at two selected sites in cyclisations with bifunctional electrophiles. These intermediates have been used as a means to pyrrolizidine, indolizidine and quinolizidine bicyclic ring structures based upon an appropriate choice of ring size of the exocyclic enamine system and chain length of the substituent on the nitrogen atom.

Rings can be constructed around a pyrrolidine (n=1) or piperidine (n=2) nucleus as shown below. This, in theory, allows the synthesis of pyrrolizidine [51,n=m=1], indolizidine [51, n=1,m=2], quinolizidine [51, n=m=2] and hydroindole [52] ring systems.

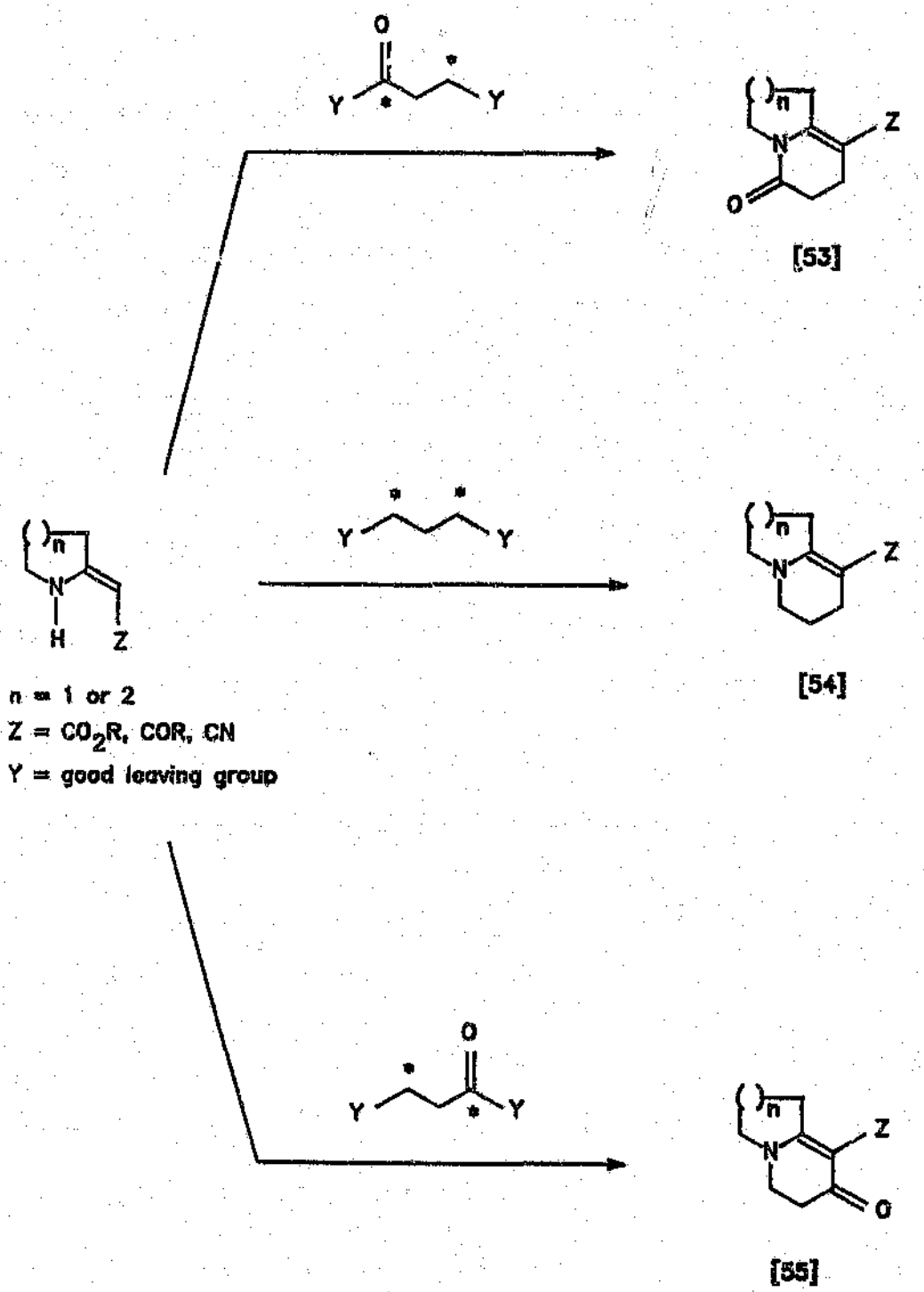






[51] [52]

The bifunctionalised electrophile may be employed to bridge between any two of the nucleophilic sites present in the exocyclic extended enamine intermediate. In the synthesis of functionalised indolizidine and quinolizidine systems, the nucleophilic properties of the nitrogen atom and the α-carbon are exploited. Scheme 15 shows how alkylative and acylative cyclisations may be achieved, depending on the oxidation level of the electrophilic carbon (*).

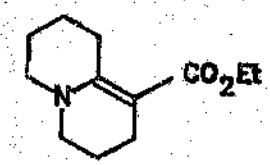


Scheme 15

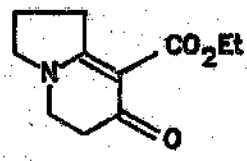
Bicyclic system [54] is the product of intramolecular alkylative ring closure, while [53] and [55] represent intramolecular acylative ring closures. The question of timing now becomes all-important. In all three cases, one has the choice of forming the bond to nitrogen before that to the α-carbon, or vice versa.

The "Wits approach" can further be used in the construction of bicyclic systems in which the nitrogen is α to the bridgehead position. Here, the nucleophilicity of the anion formed at the γ-carbon position and the α-carbon is used.

The principles discussed above have been applied successfully in the synthesis of compounds such as [56] and [57], which are precursors of *Lupin*[67] and *Elaeocarpus*[69] alkaloids respectively.

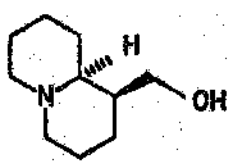


[56]

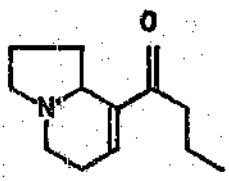


[57]

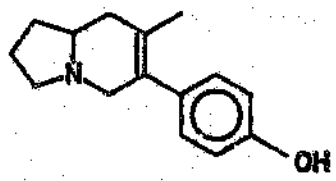
By exploiting the above characteristics of vinylogous urethanes and/or amides, formal total syntheses have been developed for the following bi- and tricyclic nitrogen bridgehead alkaloid systems: the quinolizidine alkaloid (±)-lupinine [58][65c,67], the indolizidine alkaloids ipalbidine [3][30], elaeokanines [59a], [59b] and [59c], and elaeocarpine [59d][65d,69], and the hexahydrojulolidine derivative [60][67], which is derived from the intermediate endocyclic enamine [61].



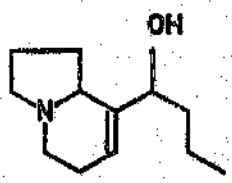
[58]



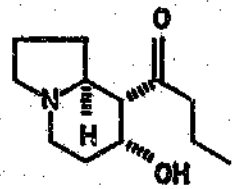
[59a]



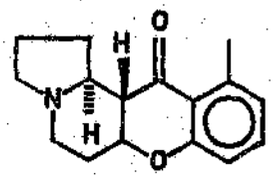
[3]



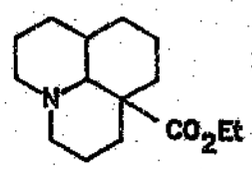
[59b]



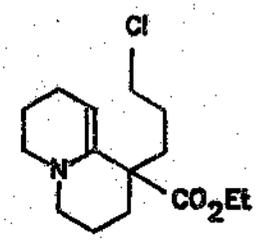
[59c]



[59d]

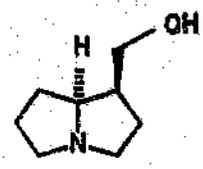


[60]



[61]

The pyrrolizidine alkaloid derivatives were shown not to be accessible *via* suitable vinylogous urethanes or amides[65b]. However, isoretronecanol **[62]** was later sythesised from a vinylogous urethane by Pinnick and co-workers[81,82].



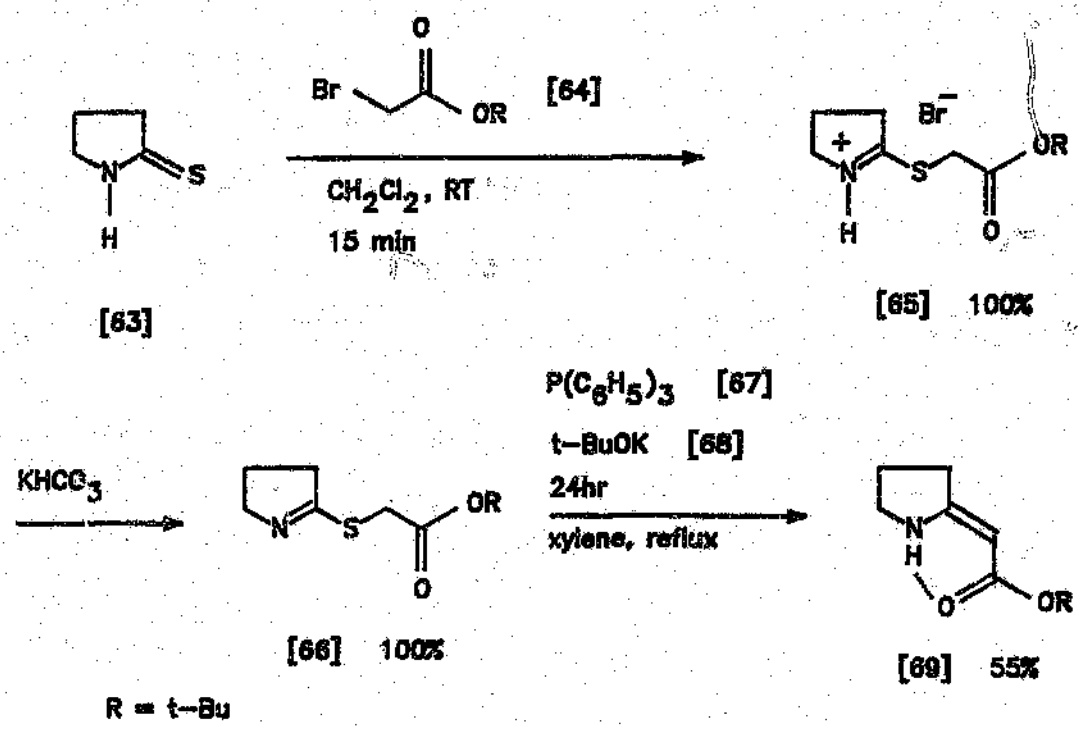
[62]

To date, a number of systems have been investigated by us. A few of our approaches are discussed below, but this discussion will be preceded by a consideration of the principal route that we have used in the preparation of enaminones.

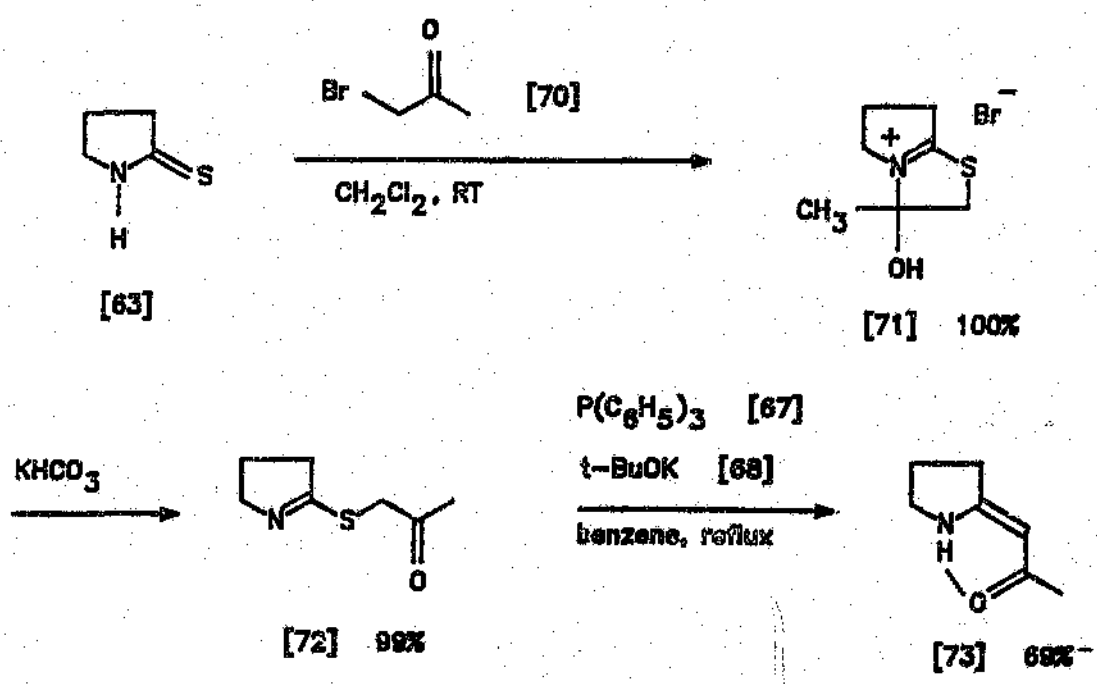
1.3.2 The Eschenmoser Sulphide Contraction Reaction

Despite the existence of other methods[81,83-85], the sulphide contraction reaction developed by Eschenmoser and co-workers for making secondary vinylogous urethanes and amides (Scheme 19)[86-88] still remains an excellent synthetic route to exocyclic extended enamines. Although this reaction was initially used as part of his vitamin B_{12} work[86], its potential has been recognised by us[36,65-78] and other workers[89] in the preparation of valuable intermediates for alkaloids and medically useful compounds. Two reactions representative of Eschenmoser's original work[88] are illustrated in Schemes 16 & 17. Condensation of the α-halocompounds **[64]** or **[70]** with the thiolactam **[63]** (in which the nitrogen is secondary) generated the thioiminoethers **[66]** or **[72]**, respectively, via the α-thioiminium salts **[65]** or **[71]**, respectively. Extrusion of sulphur was achieved using a strong base **[68]**, a sulphur

scavenger [67], and heating under reflux in a suitable solvent.

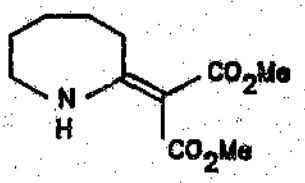


Scheme 16

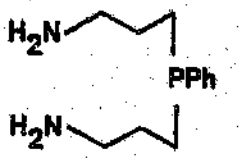


Scheme 17

Eschenmoser *et al.* also used 2-bromo-1,3-dicarbonyl compounds[86] to prepare compounds such as [74]. Another variation was the use of the combined phosphorus-base [75][86].

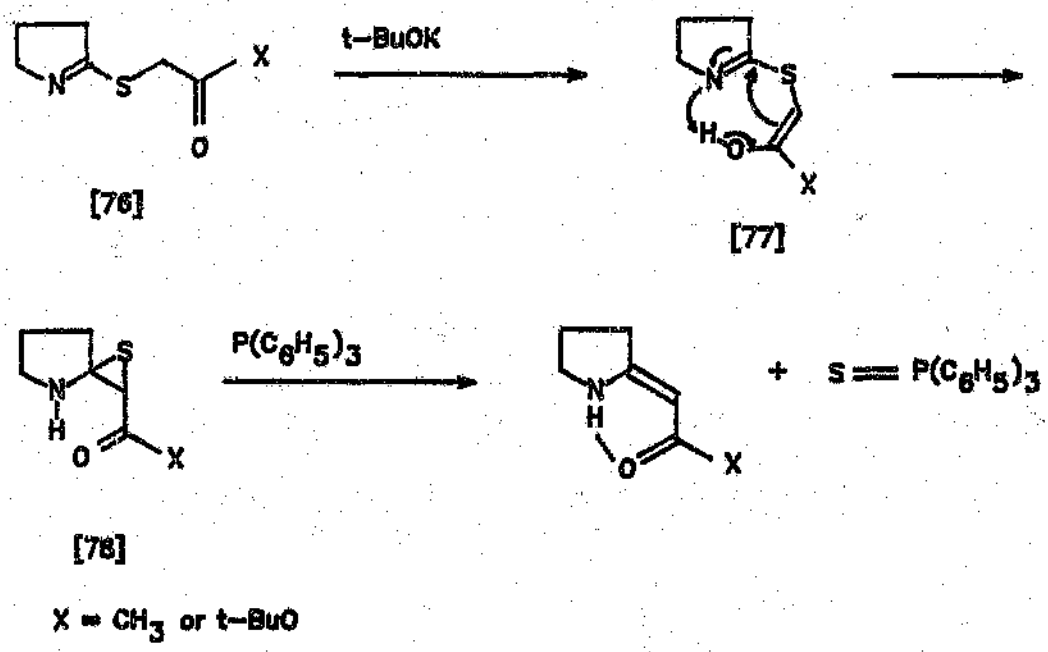


[74]



[75]

The proposed mechanism of the sulphide contraction reaction is shown in Scheme 18. The reaction occurs in two stages: salt formation between the thiolactam and an α-halo-carbonyl compound; and sulphur extrusion (sulphide contraction) induced by a base in the presence of a sulphur acceptor. The sulphide contraction reaction assumes the production of an episulphide intermediate [78] formed by an intramolecular attack at the imine carbon of the base-catalysed enol form [77] of the thioiminoether [76]. In both the vinylogous urethane [69] and the vinylogous amide [73] the geometry around the carbon-carbon double bond is *Z*. The formation of the *cis-s-cis* structure is favoured by the 6-membered hydrogen-bonded ring.

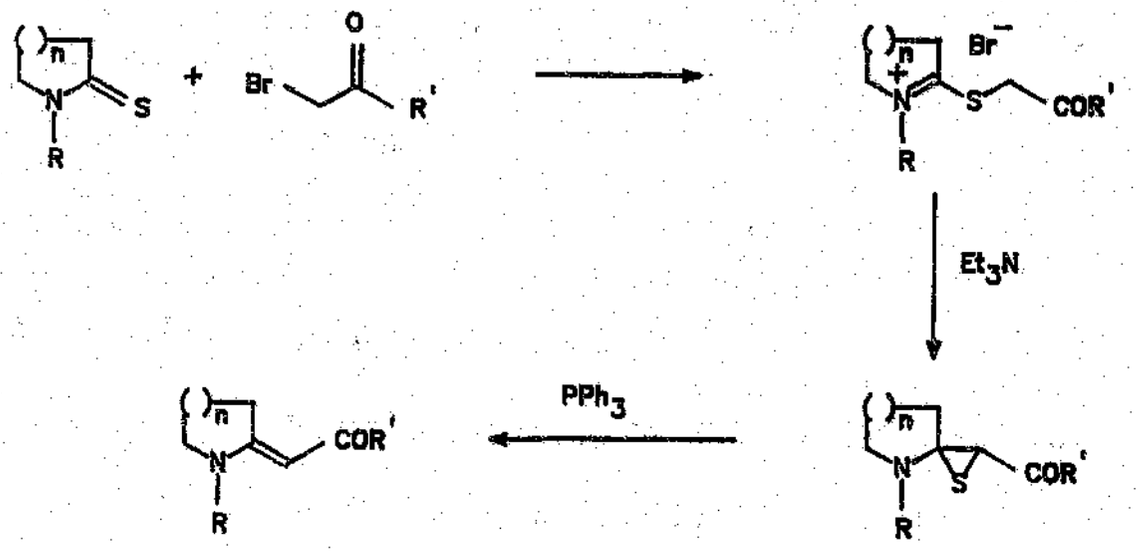


[76] [77] [78]

X = CH_3 or t-BuO

Scheme 18

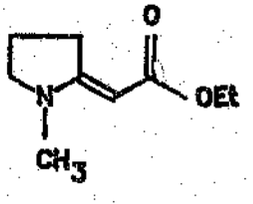
In these laboratories[71], the scope of Eschenmoser's procedure has been extended to include tertiary vinylogous urethanes and amides in greatly improved yields (40-90%) under milder reaction conditions by using acetonitrile in the presence of a thiophile and a weaker base such as triethylamine at room temperature. Harsher conditions are required for the secondary nitrogen analogues, since when R=H, the base will remove this proton first, and subsequent deprotonation α to the carbonyl group becomes a more difficult process to achieve.



n = 1 or 2

Scheme 19

It has been reported[71] that in some cases (e.g. where R=CH_3), sulphur extrusion is accomplished in the presence of either a thiophile or base, but a dramatic increase in yields is achieved by utilisation of both entities. The geometry of a sulphide contracted product bearing a tertiary nitrogen has been found to be *E*, e.g. [79]. This feature prevails in such systems to avoid intramolecular congestion.



[79]

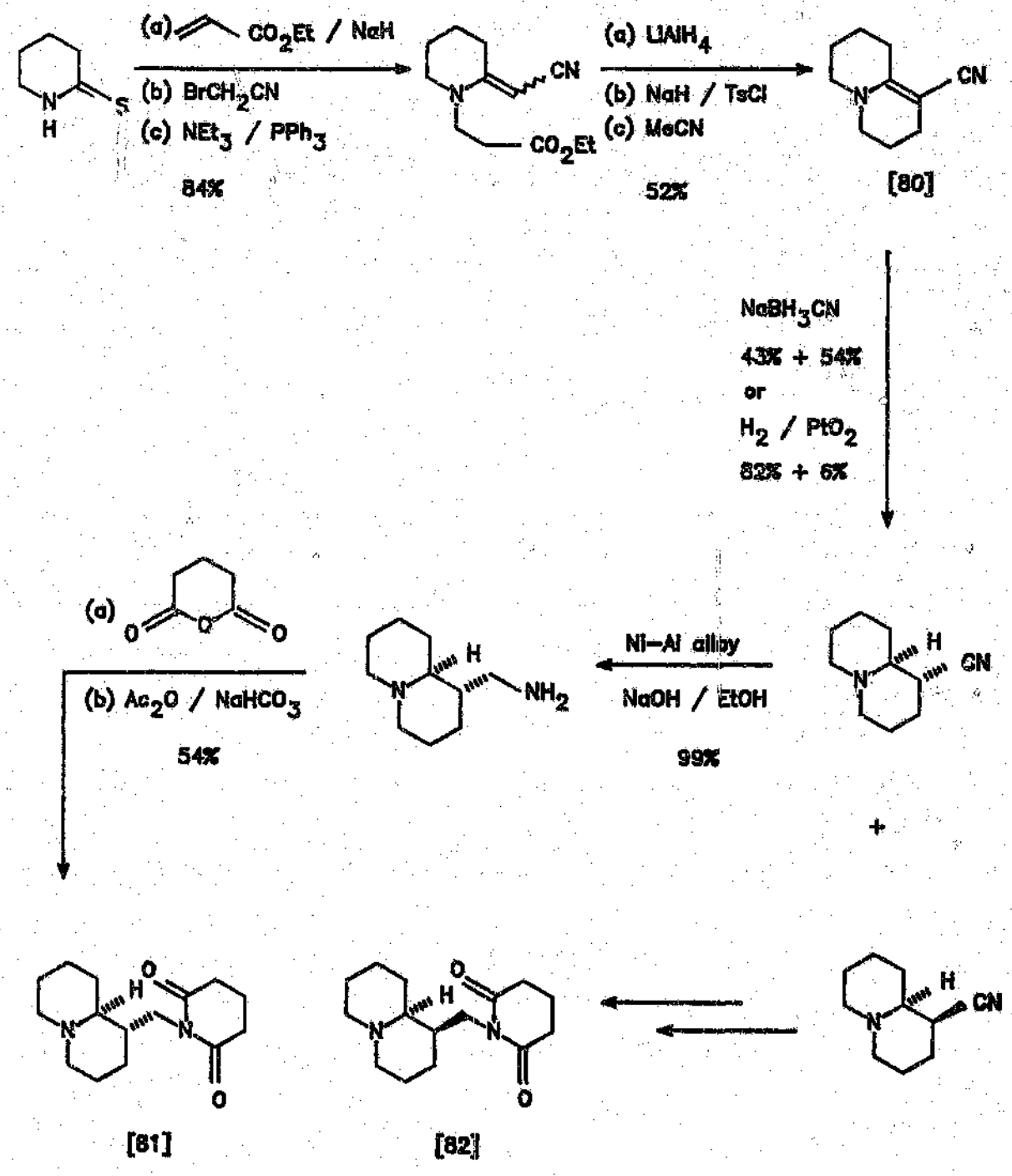
It was, however, observed that this extension of the sulphide contraction reaction could not be well utilised for the preparation of *N*-aryl vinylogous urethanes and amides[66a], perhaps because conjugation between the thioamide and the aromatic ring decreases the nucleophilicity of sulphur. However with an *o*-bromo substituent, there is steric hindrance to mesomerism. Wilson[66c] prepared a series of *N*-(*o*-bromoaryl) vinylogous amides and urethanes by the sulphide contraction method, the lowest yield obtained being 66%.

1.3.3 Illustrations of the Sulphide Contraction

As already mentioned in section 1.3.1, we have made use of Eschenmoser's sulphide contraction over the years to prepare numerous enaminones. A full discussion of the "Wits Alkaloids" project is too extensive to be included here. Section 1.3.1 is essentially a summary of the work to date, consequently I have chosen to review only three examples. The first two are representative of the most recent work completed here at Wits. The third example gives a detailed discussion of the synthesis of ipalbidine by Howard *et al.*[36].

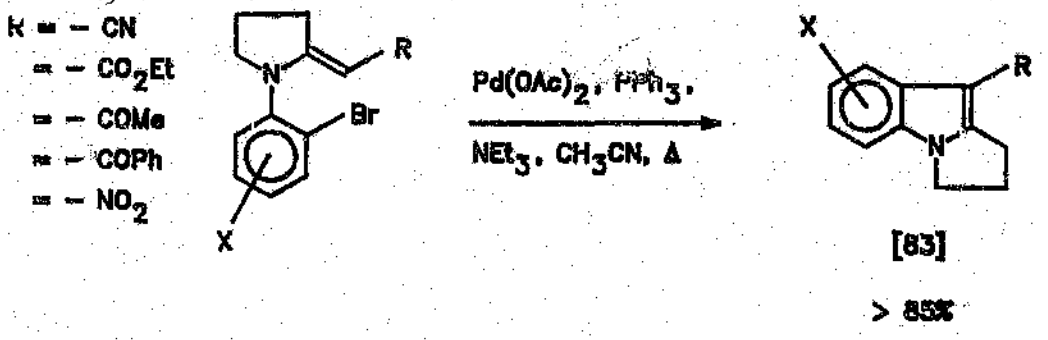
Jungmann[66b] used the sulphide contraction in her preparation of (±)-lamprolobine **[81]**[90] and (±)-epilamprolobine **[82]**[91]. She used an electron-withdrawing group α to the halogen that is not a carbonyl functionality, and her results show the flexibility possible with the sulphide contraction in introducing different elements into an alkaloid backbone. The procedure for the formation of the quinolizidine nucleus initially involved chemoselective reduction of the ester carbonyl group. This was done using lithium aluminium hydride to form a primary alcohol, leaving the vinylogous cyanamide 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. Reduction of the carbon-carbon double bond of the product **[80]** could be carried out in high yield using either hydrogen over Adams catalyst or sodium cyanoborohydride. The hydride reagent provided the *cis*- and *trans*-dihydro isomers in almost equal amounts, while the *trans* isomer was strongly favoured by the catalytic hydrogenation procedure. The

nitrile functions were reduced in good yield using nickel-aluminium alloy. The resulting amine was acylated with glutaric anhydride to give the desired alkaloids in reasonable yields (Scheme 20).



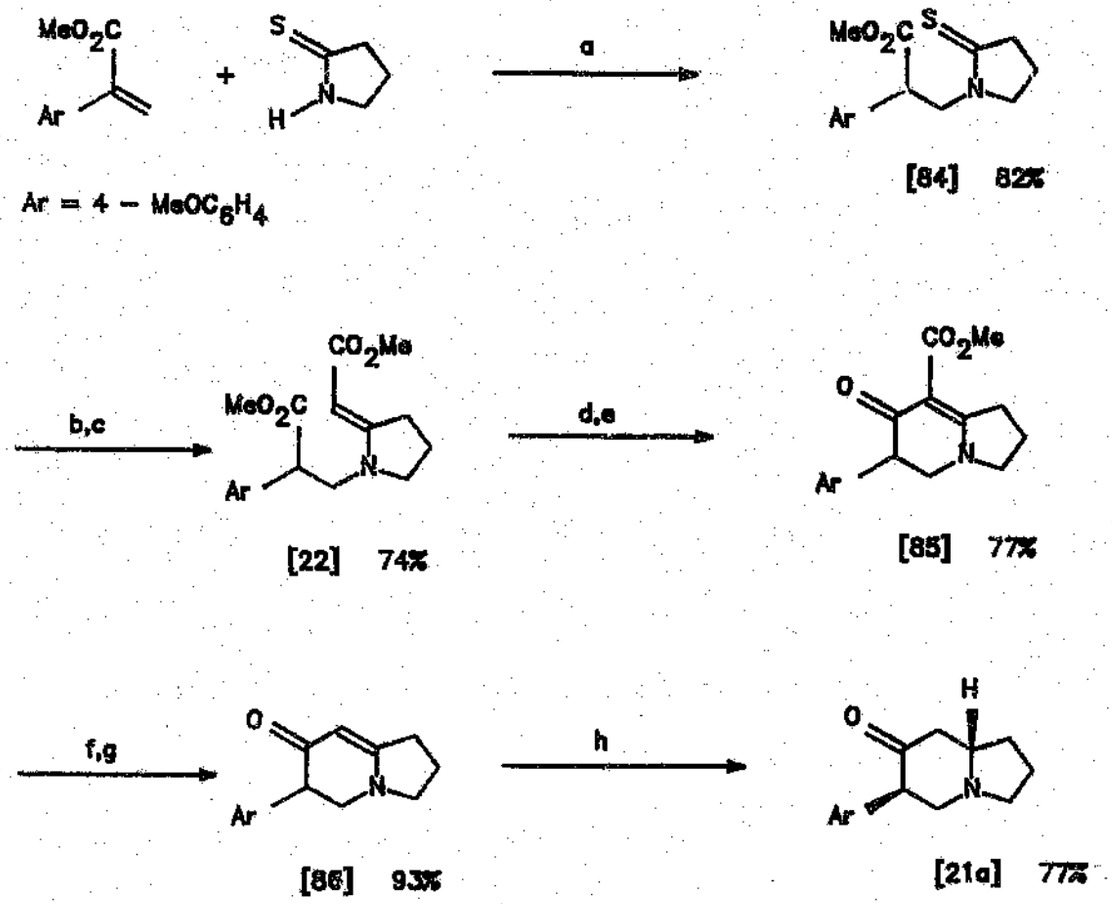
Scheme 20

In her M.Sc. project, Wilson[66c] prepared a series of differently substituted *N*-aryl vinylogous urethanes and then used the Heck-type palladium catalysed ring closure reaction developed by Chang[65f] in his Ph.D. study to prepare a range of pyrrolo[1,2-*a*]indoles [83] (Scheme 21). The interest in this work stems from the fact that compounds [83] serve as precursors to the mitomycins.



Scheme 21

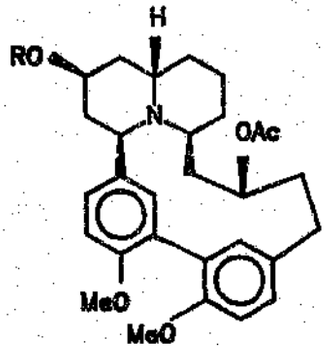
Howard *et al.*[36] employed disconnection B in the design of a formal synthesis of (±)-ipalbidine [3]. The objective was the synthesis of the popular target, ketone [21a]. The reaction sequence (Scheme 22) begins with Michael reaction of a 2-aryl ester onto the nitrogen atom of the pyrrolidine-2-thione. The resulting thiolactam [84] was alkylated on sulphur using methyl bromoacetate; following which the salt was subjected to the sulphide contraction procedure to generate the vinylogous urethane [22]. Ring closure is dependent on the enamine-like nucleophilicity of this vinylogous urethane [22]; and takes place only when the saturated ester group has been converted to the mixed anhydride. The vinylogous amide [86] was prepared by hydrolysis and decarboxylation of the cyclised product [85]. Reduction of [86] under controlled conditions gives the target ketone [21a]. This intermediate can then be taken through a series of reactions to afford ipalbidine [3]. This route is significant in that it complements my route to ipalbidine as proposed in the next section.

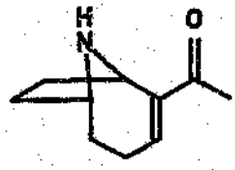


Scheme 22: Formal synthesis of ipalbidine by Howard, Gerrans and Michael[36].
Reagents: (a) NaOH(cat), THF; (b) $BrCH_2CO_2Me$, THF; (c) Ph_3P, NEt_3, MeCN; (d) NaOH, H_2O, Δ; (e) $ClCO_2Me$, Bu_4NI(cat), THF; (f) KOH, H_2O, Δ; (g) HCl, H_2O, Δ; (h) $LiAlH_4$, THF.

The use of vinylogous amides and urethanes as intermediates in alkaloid synthesis is not unique to the "Wits approach". As many as fifty papers have been published by other research groups since Eschenmoser's first report. Principal workers in the field include Hart and Rapoport. Hart used the method to prepare the Lythraceae alkaloids (±)-lythrancepine II [87] and III [88][92], and gephyrotoxin-223AB[93], a biologically active alkaloid from Dendrobatid frogs. Examples by Rapoport[94] include his chirospecific and enantiodivergent synthesis of anatoxin-a [89], a potent neurotoxin and neurotransmitter, along with its analogues[95-97]. He has also used vinylogous urethanes in model studies towards the synthesis of antitumour antibiotics, mitomycins

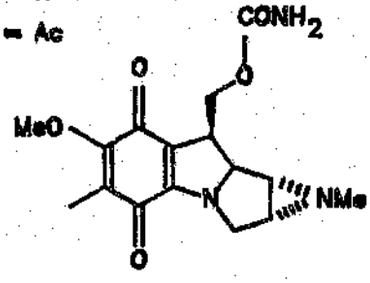
[90][98,99], and in the synthesis of *trans*-5-butyl-heptylpyrrolidine[100], an active and major component of the repellent venom of the ant *Solenopsis fugax*. This brief survey by no means covers the full use of the sulphide contraction by other workers. A comprehensive review by Shiosaki[89] is available.





[89]

[87] R = H
[88] R = Ac



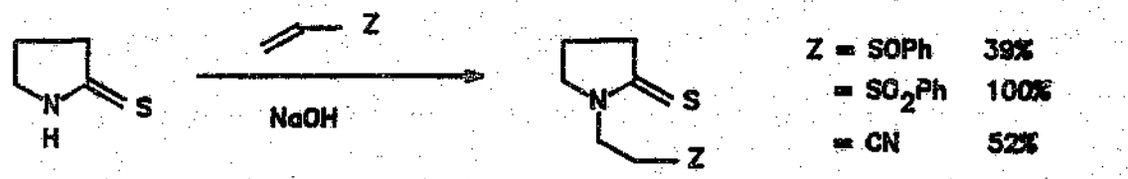
[90] MITOMYCIN B

1.4 THE ORIGINS AND AIMS OF THIS PROJECT

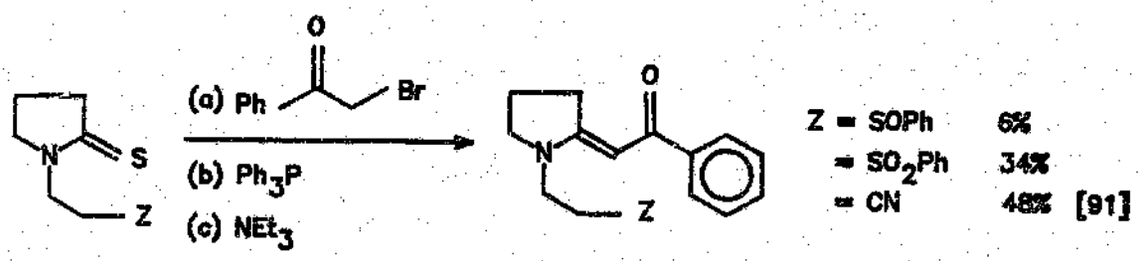
I will begin this section with a presentation, in summary, of some relevant details from the Ph.D. study by Andrew Parsons. This will be followed by a discussion of the aims of this project.

In 1987, Parsons carried out in these laboratories an Honours project[101] concerned with the conjugate addition reactions of pyrrolidine-2-thione with several Michael acceptors, *viz.* 2-nitropropene, phenyl vinyl sulphoxide, phenyl vinyl sulphone and

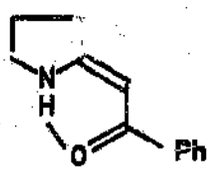
acrylonitrile (Scheme 23). The use of these Michael acceptors extended the scope of previous efforts by workers here, which have centred mainly on acrylates[36,67,69]. Except for the 2-nitropropene adduct, which was formed in very low yield, the resulting thiolactams were subjected to sulphide contraction after salt formation with phenacyl bromide (Scheme 24).



Scheme 23



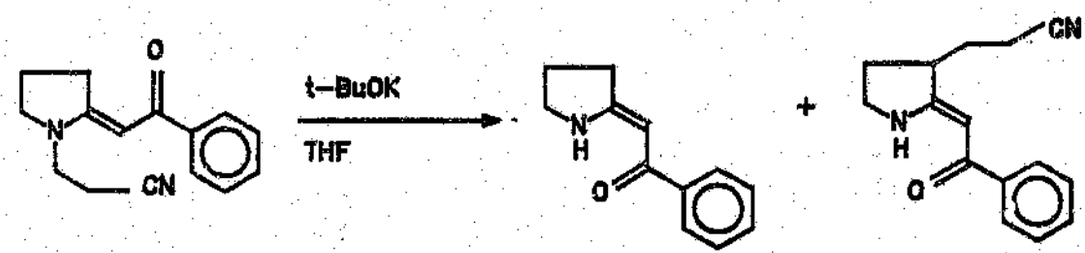
Scheme 24



[92]

In further reaction of [91,Z=CN], it was found that basic conditions could induce a retro-Michael reaction, yielding [92]. This result has a bearing on the present project (see page 110). Sulphide contraction reactions with tertiary thiolactams generally take place in higher yields and require milder conditions. Consequently a suitable protecting group for nitrogen has been sought in these laboratories for many years. Parsons recognised that the cyanoethyl group was acting as just such a protecting group. Conditions were optimised, so when compound [93] was stirred at room temperature

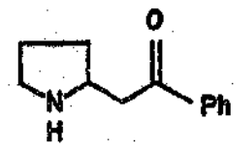
in THF with two equivalents of *t*-BuOK, a yield of 93% of 2-benzoylmethylene-pyrrolidine [92] was obtained (Scheme 25).



[93] [92]

Scheme 25

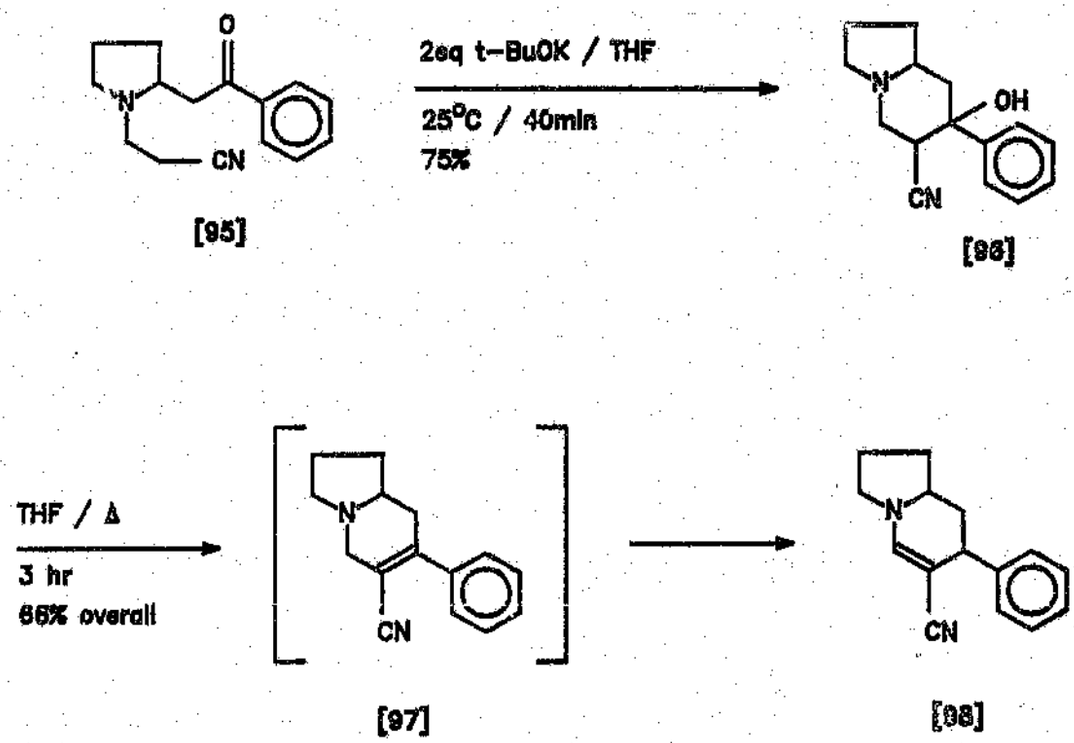
Parsons was also interested in the synthesis of compound [94]. His approach comprised reduction of the carbon-carbon double bond of compound [93] to generate [95], followed by removal of the cyanoethyl group in a retro-Michael reaction.



[94]

When removal of the cyanoethyl group from aminoketone [95] was attempted using the conditions that worked best with the corresponding vinylogous amide (2 eq *t*-BuOK/THF/25°C/40min), a new product was formed. Analysis of its NMR spectra showed that it had structure [96]; the yield was 75% (Scheme 26). Obviously, though deprotonation had occurred α to the nitrile, retro-Michael reaction did not result, but rather intramolecular attack of the carbonyl group to give the indolizidine product. In another attempt, compound [95] was stirred at room temperature with two equivalents of *t*-BuOK for one hour, but instead of being worked up, the mixture was heated under reflux for three hours. Base-induced elimination from [96] took place, but instead of compound [97] being the product, its isomer [98] was formed in 66% yield (Scheme 26). For the observed isomer to be formed, there must be better π-orbital

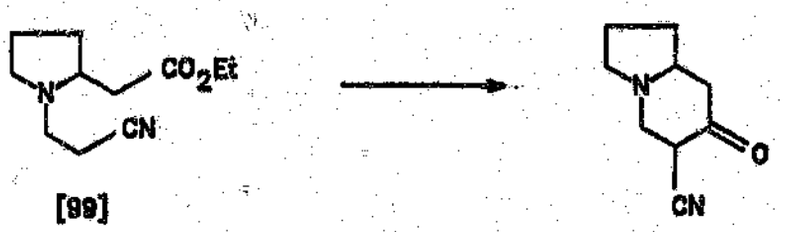
overlap than in the alternative isomer. This is because the two electron-rich groups conjugated through the double bond are orientated in a *trans*, as opposed to a *cis*, geometry. In addition, nitrogen is more electron-rich than the phenyl group, and therefore a better π-donor.



Scheme 26

We are extremely interested in the cyclisation step [95]-[96], as it is this reaction upon which the current project is based. The production of the desired compound from [95] was abandoned at this point because it seemed unlikely that mild base conditions would cause retro-Michael reaction rather than intramolecular condensation. These results are in agreement with earlier results of Parsons[65h] that vinylogous amides with CH_2-CH_2-EWG (EWG = electron-withdrawing group) attached to nitrogen are more prone to retro-Michael reactions than are amines with the same group attached to nitrogen. In the presence of a base, such amines are more likely to undergo an internal condensation reaction (if possible) than a retro-Michael reaction.

The preparation of indolizidine compounds [96] and [98] was not intended, though not unexpected. The substituent at the 7-position could be altered simply by carrying out the initial sulphide contraction with a different α-bromocarbonyl compound. Furthermore, if compound [99] can be prepared, it should allow the synthesis of 6-cyano-octahydroindolizin-7-one [100] (Scheme 27), which can itself be manipulated further.



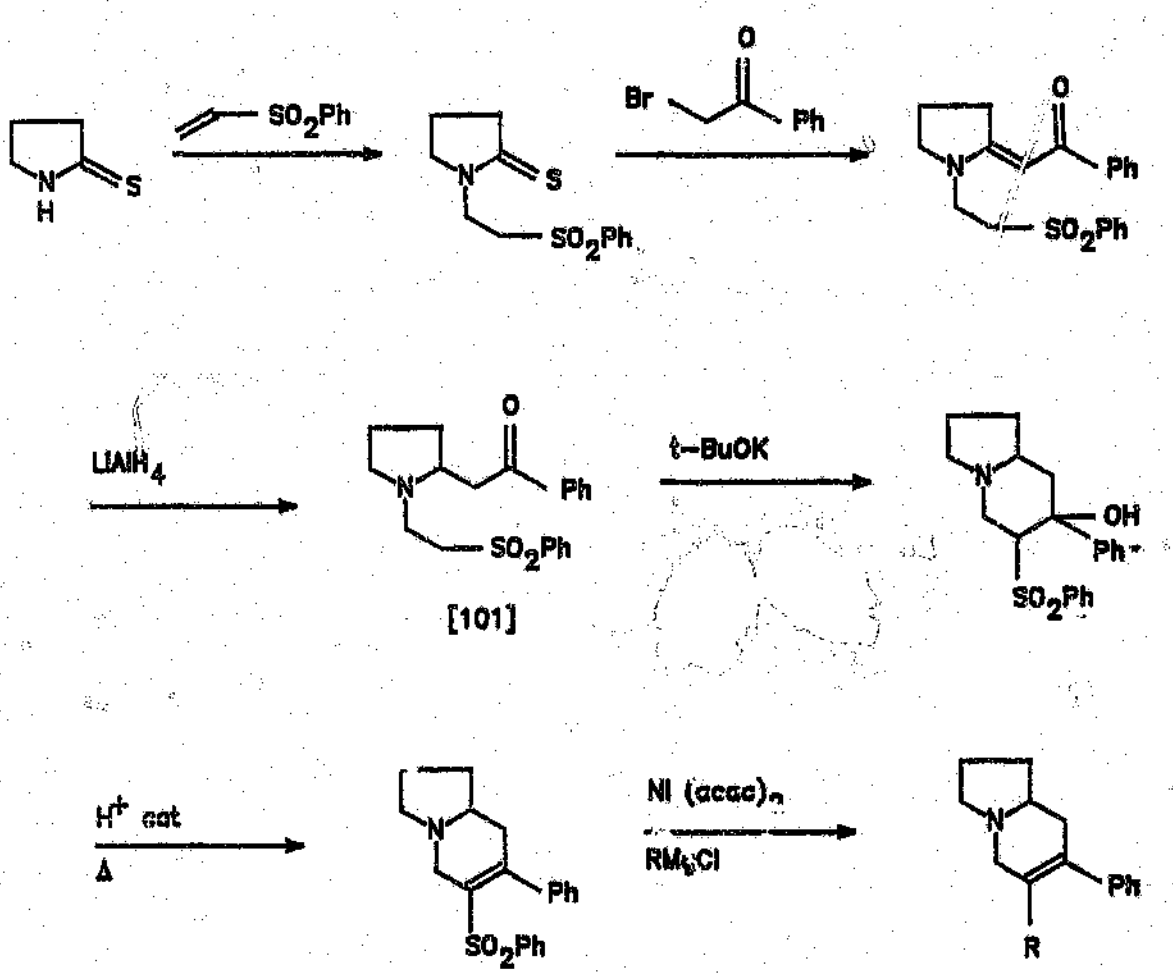
[99] [100]

Scheme 27

The main objective of the present project is to transfer the methodology developed by Parsons[65h], relating to intramolecular cyclisations, to new systems. This will allow us access to the indolizidine skeleton as found in the alkaloids ipalbidine [3] and septicine [4]. The synthesis of these specific alkaloids is not intended; rather, we hope to develope general methodology for gaining access to the unsaturated bicyclic parents. In addition we will extend the range of Michael acceptors that can add to pyrrolidine-2-thione at nitrogen. Again the synthesis and reactions of vinylogous urethanes and/or amides form the core of the approach to the desired alkaloids.

Three approaches are envisaged. The first, route A, is an extension of the work carried out by Parsons[101] in his honours project. It involves the synthesis of sulphone [101] from the vinylogous amide precursor prepared before by him. A cyclisation similar to that seen in his Ph.D. study will be attempted (Scheme 28).

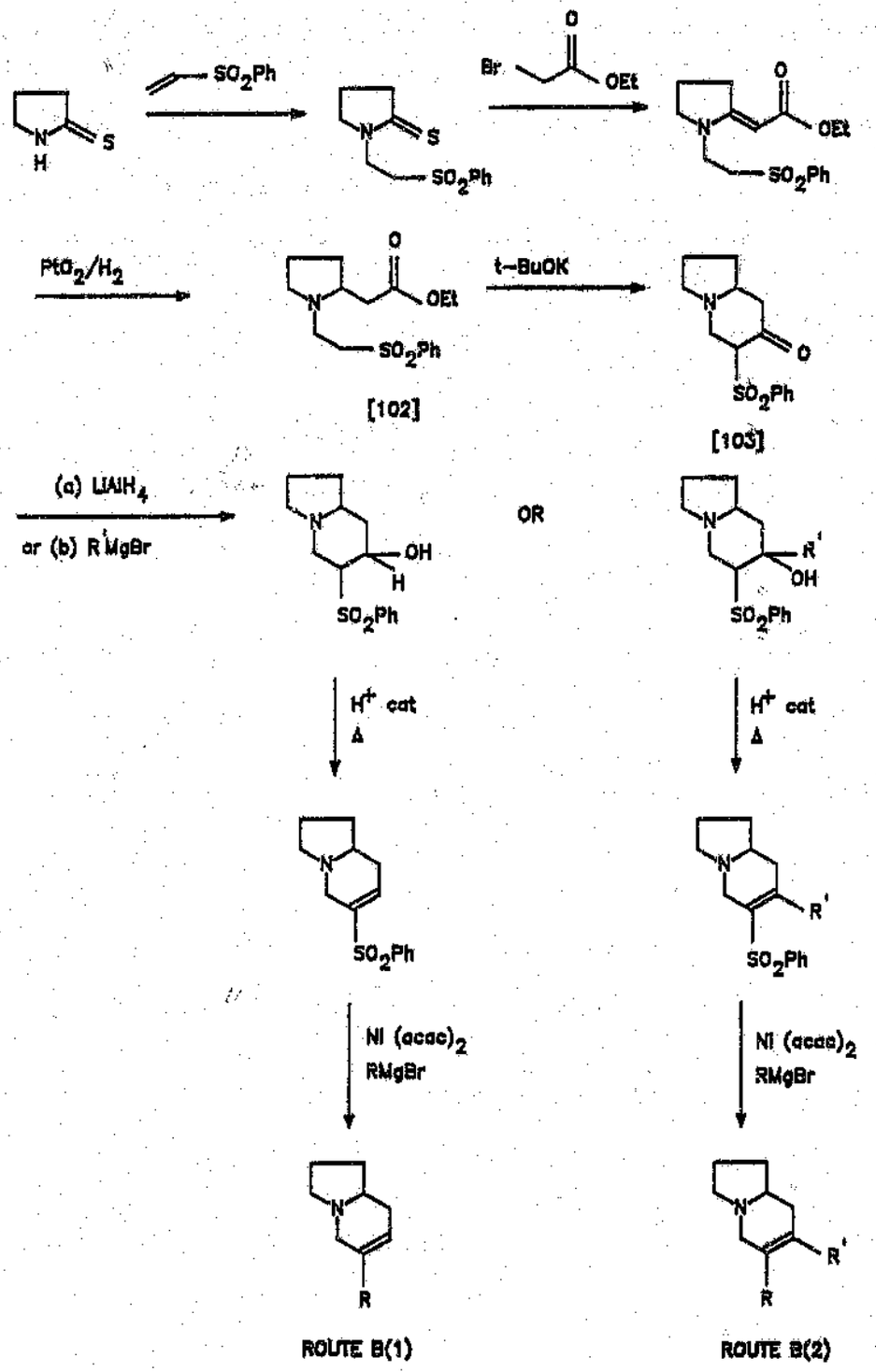
Route A



Scheme 28

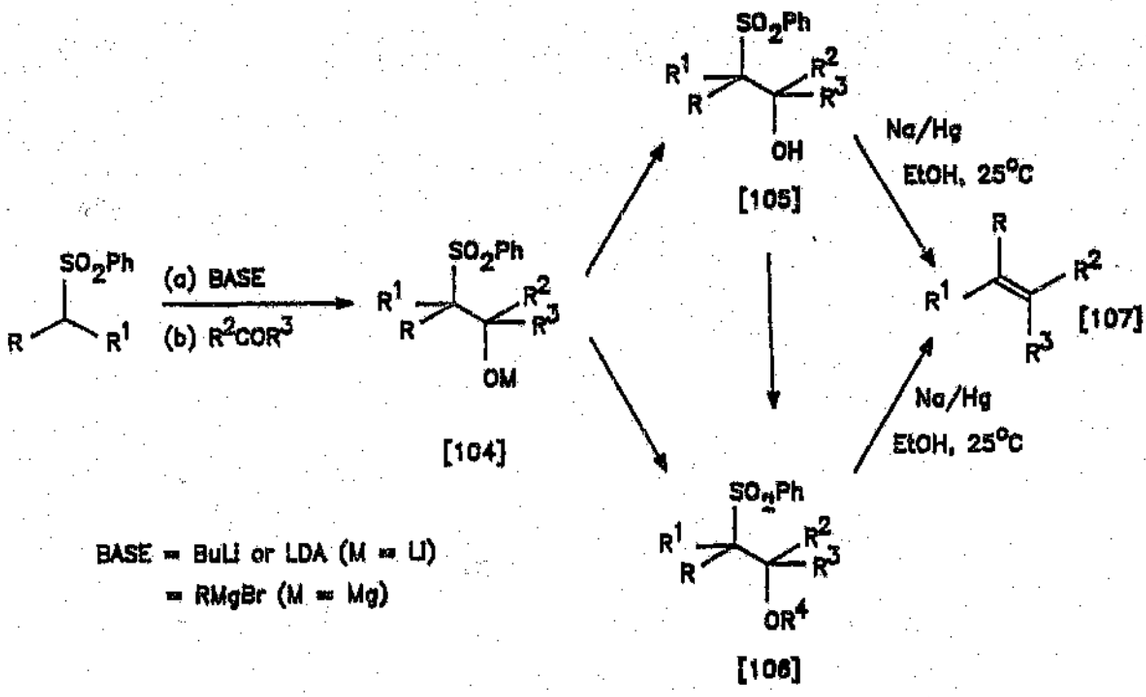
The second route is a variation of the first, and employs the idea of changing the substituent at the 7-position. If compound [102] can be prepared, it would then allow the synthesis of 6-sulphonyloctahydroindolizin-7-one [103] (Scheme 29). Manipulation of the carbonyl group of [103] should give one control over the substituent at the 7-position. For example, after reduction of the carbonyl group, route B(i) converges with route A.

Route B



Scheme 29

In both routes A and B, we see that after formation of the double bond the sulphonyl group remains the molecule. An alternative exists whereby the sulphonyl and hydroxy groups simultaneously eliminated to create the double bond. Julia and Paris[102] reported this new olefin synthesis based on the reductive elimination of β-substituted sulphones. The reaction is known as the Julia reaction and is outlined in general form in Scheme 30.



Scheme 30

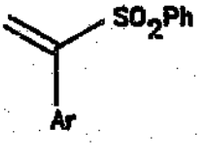
A sulphone carbanion is treated with an aldehyde or ketone to give the metal alkoxide adduct [104]. This intermediate is then usually derivatised *in situ* to give [106], where R^4 is COMe, COPh, SO_2Me or *p*-toluenesulphonyl. Treatment of derivative [106] with sodium amalgam yields the alkene product [107]. In a few cases direct reductive elimination of the β-hydroxy sulphone [105] is effective (*vide infra*); however the method is rarely as efficient as elimination from the derivative [106].

The Julia reaction resembles the Wittig reaction in that an α-hetero substituted carbanion and a carbonyl compound are combined, followed by vicinal elimination of two functional groups to give a double bond. The two reactions are therefore both

connective and regiospecific, but produce complementary stereochemical results.The main difference between the two reactions is the subsequent manipulations needed in the Julia procedure, whereas the Wittig elimination occurs *in situ*. This disadvantage of the two stage Julia olefination is somewhat offset by the ready preparation of the ß-alkoxy sulphones and the relative ease of removal of elimination by-products during work-up.

Of key importance is the overall stereochemical outcome of the reaction. The Julia olefination procedure has been shown to give essentially *trans*-olefins[103]. This high *trans*-stereoselectivity was unexpected and investigated further. A pair of diastereomeric sulphones were separated into the pure *threo* and *erythro* isomers and individually treated with sodium amalgam. Only the *trans*-olefin was obtained from both isomers[103a], thereby indicating the overall stereochemistry of the reaction is independent of the stereochemistry of the sulphone precursor.

The Julia reaction is a possible alternative that can be employed in routes A and B. In addition it assists in making the connection between routes A & B and C clearer. Note, however, that if the Julia reaction is applied as an alternative in routes A and B, then the substituent is lost from C-7 of the indolizidine, and there is no easy way of introducing the aryl group required for the target alkaloids other than by starting with an α-arylated vinylsulphone such as **[108]**.

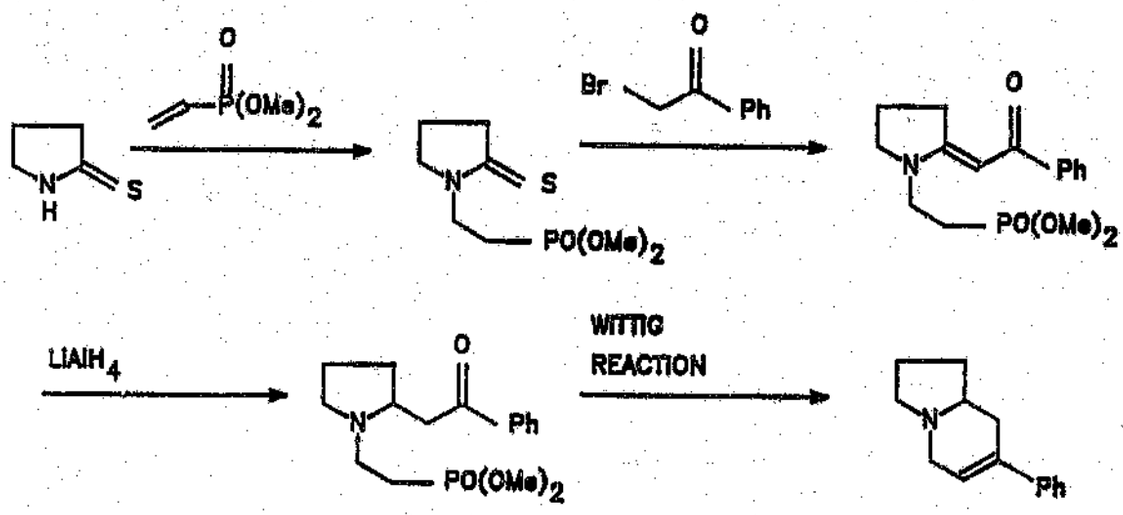


[108]

Route C allows us to meet the second aim of the project, namely to extend the range of Michael acceptors that add to pyrrolidine-2-thione. The Michael acceptor under consideration is dimethyl vinylphosphonate. This route differs from the other two in that cyclisation takes place by a Wittig-type reaction, in contrast to simple base induced cyclisation. Route C does not allow for modification of substituents on the

indolizidine ring at a late stage in the synthesis. All changes have to be made to the starting materials themselves. This contrasts markedly with routes A and B, where the nature of the second substituent is decided in the final step of the synthesis, but complements the Julia procedure.

Route C



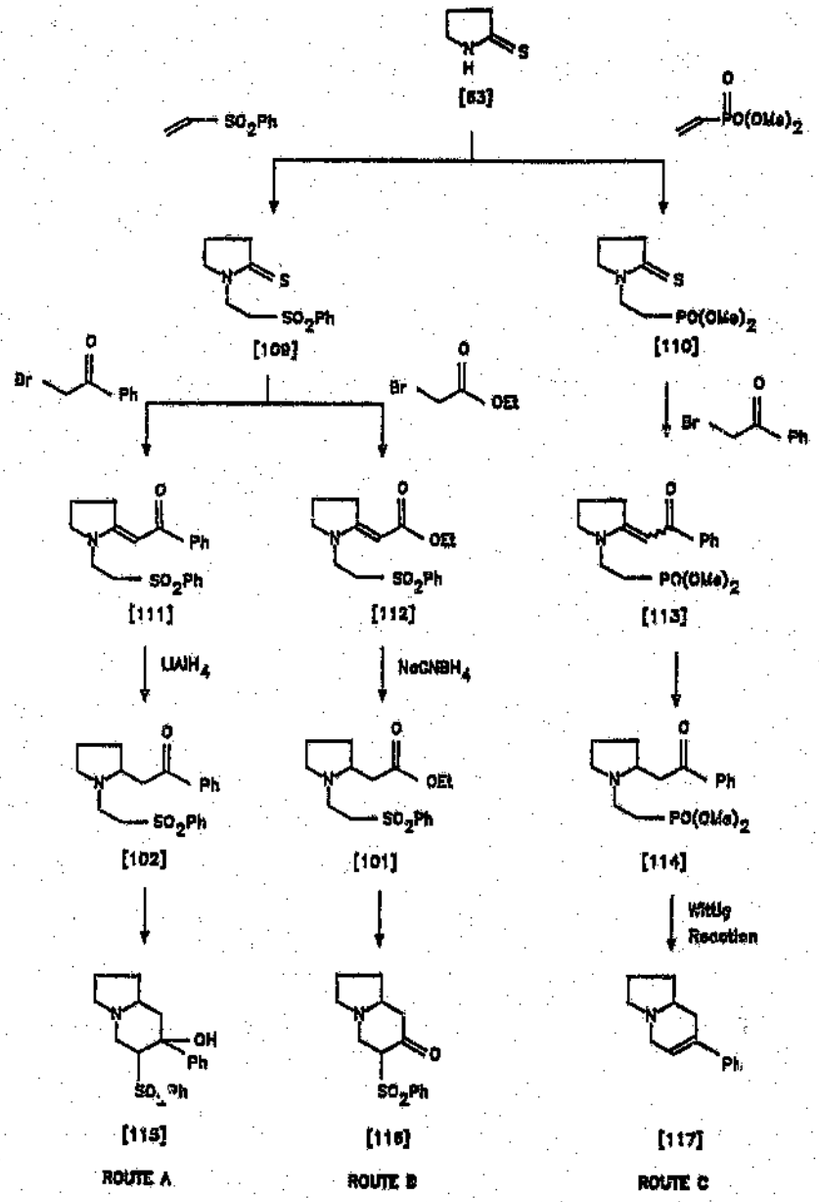
In routes A, B & C shown above, I have outlined the total synthesis of a number of alkaloids. It is essential to remember that the synthesis of the alkaloid itself is not a main objective, rather the cyclisation step leading to the bicyclic skeleton. I have included the full synthesis for the sake of clarity and completeness.

The aims of this project may be summarised as follows:

- To extend the range of Michael acceptors which react with pyrrolidine-2-thione.
- To demonstrate further the synthetic utility of the sulphide contraction reaction in alkaloid synthesis.
- To develop a new route to the synthesis of the indolizidine skeleton as found in the alkaloids ipalbidine and septicine.

CHAPTER 2: RESULTS AND DISCUSSION

The main aim of this project was to synthesise the $\Delta^{6,7}$-indolizidine skeleton as found in the alkaloids ipalbidine and septicine. Three different routes (Scheme 31) were envisaged for achieving this goal. Each route comprised four common steps. In the sections that follow (2.1 - 2.4), each of the four reactions, conjugate addition, sulphide contraction, reduction and cyclisation, will be discussed in turn.



Scheme 31

2.1 CONJUGATE ADDITION WITH PYRROLIDINE-2-THIONE AS NUCLEOPHILE

2.1.1 Preparation of 1-(2-phenylsulphonylethyl)pyrrolidine-2-thione [109]

Pyrrolidine-2-thione was selectively alkylated at nitrogen by using an activated olefin in a Michael reaction. Specifically, pyrrolidine-2-thione [63] was treated with phenyl vinyl sulphone in tetrahydrofuran in the presence of a catalytic quantity of sodium hydroxide to afford 1-(2-phenylsulphonylethyl)pyrrolidine-2-thione [109] in nearly quantitative yield (96%). Preparation of this material comprised the first step of both routes A & B.

The appearance of aromatic signals at 7.55 - 7.74ppm and 7.90 - 7.96ppm in the ^{1}H NMR spectrum of the product indicated the presence of the phenylsulphonyl group. The data afforded by the ^{13}C NMR spectrum corroborate those of the ^{1}H NMR spectrum. Further evidence of the Michael product was provided by the IR spectrum. The prominent N-H stretch observed at 3175cm^{-1} for the secondary thiolactam precursor [63] was absent in the tertiary Michael product. Microanalysis results confirmed these findings. S-alkylation of pyrrolidine-2-thione by the Michael acceptor to form a thioiminoester was not observed.

2.1.2 Preparation of 1-(2-dimethoxyphosphorylethyl)pyrrolidine-2-thione [110]

In preparing this compound, a secondary aim of the project was fulfilled: namely, to extend the range of Michael acceptors reacting with pyrrolidine-2-thione at nitrogen. Dimethyl vinylphosphonate was chosen as the acceptor. This reaction proved to be extremely challenging.

Initial attempts at this reaction employed the conditions described above for the

preparation of 1-(2-phenylsulphonylethyl)pyrrolidine-2-thione [**109**]. On all occasions, fairly substantial quantities of both starting materials were recovered, in addition to a third compound isolated as a pale yellow oil. From ^{1}H NMR data, this material contained traces of the desired product. When distillation of the product was attempted, the distillate yielded dimethyl vinylphosphonate. The residue, which had changed to a dark orange-brown gum, was discovered to be 1-(2-dimethoxy-phosphorylethyl)pyrrolidine-2-thione [**110**] (19%).

Since "heat" appeared to be necessary for the reaction, the next attempts involved sealed tube reactions. Dimethylformamide was used as solvent for the first attempt. The reaction mixture was heated to 130°C for 5hrs, but only the thiolactam precursor [**63**] (44%) was recovered. For the second attempt, excess dimethyl vinylphosphonate was used as solvent, and the mixture was heated to 170°C for 6hrs. Dimethyl vinylphosphonate (39%) was recovered, but product [**110**] was not isolated.

Formation of the desired product [**110**] was accomplished by changing the base to *n*-butyllithium. TABLE 1 summarises the conditions used and the outcome. 1-(2-Dimethoxyphosphorylethyl)pyrrolidine-2-thione [**110**] was isolated in all cases except the first.

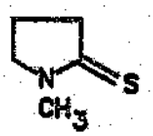
TABLE 1: Reaction details for the preparation of [**110**] using *n*-BuLi.

Expt. No.*	Eq. *n*-BuLi	[110] /%	[118]# /%	[63] /%	Time /hrs
1	1.61	-	2.3	6.3	18.5
2	1	9.7	4.1	-	24
3	0.42	30.2	1.9	trace	23
4	0.32	63.9	2.3	-	5.5

TABLE 1: Continued.

Expt. No.*	Eq. *n*-BuLi	[110] /%	[118]# /%	[63] /%	Time /hrs
5	2.88E-3	77.5	0.9	-	67.5
6	1.94E-3	65.7	2.2	1.1	67.5

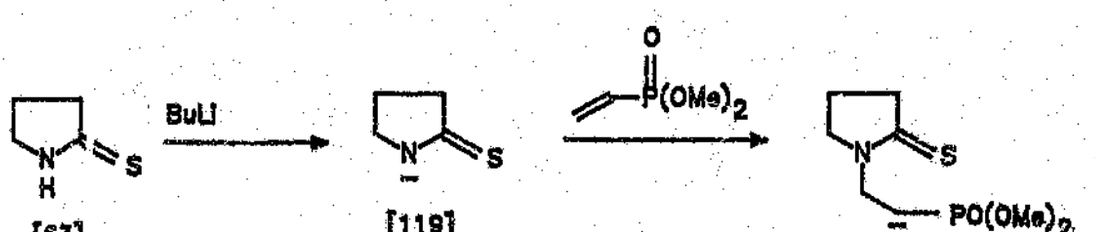
* All reactions were carried out at room temperature.



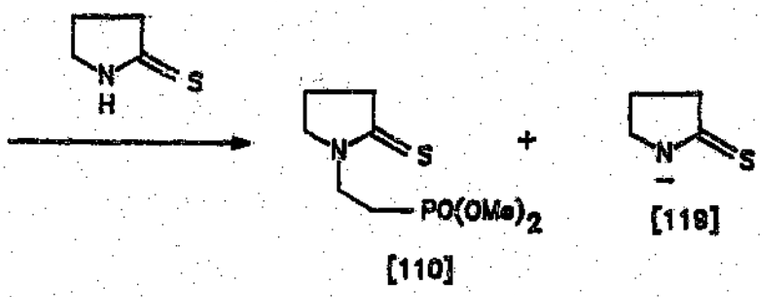
[118]

Experiment 1 differs from the rest in that the ratio of the thiolactam precursor [63] to *n*-butyllithium is less than one. For the remaining experiments, this ratio is one or greater. In experiments 2 through 5, as the quantity of *n*-butyllithium approaches catalytic, there is a corresponding marked increase in the yield of the product [110]. However, there is a limit to this ratio as indicated by the drop in yield in going from experiment 5 to experiment 6. The conclusion drawn was that the quantity of *n*-butyllithium used must be catalytic.

The *n*-butyllithium was used to deprotonate the pyrrolidine-2-thione [63]. The resulting anionic species [119] would react with the dimethyl vinylphosphonate to set up the catalytic cycle shown in Scheme 32.



[63] [119] [120]



Scheme 32

If a full equivalent (or more) of *n*-butyllithium was used, all the thiolactam **[63]** would be deprotonated at once, thereby eliminating the possibility to quence the negative charge in intermediate **[120]**. Participation of **[120]** in unwanted side reactions possibly accounts for failure to isolate **[110]**.

Methyl transfer from the starting material, dimethyl vinylphosphonate, was observed resulting in preparation of *N*-methylpyrrolidine-2-thione **[118]**. The highest yielding reaction gave ~4% of **[118]**, therefore loss of thiolactam in this manner was considered negligible.

Reaction time was investigated. However, from the data gathered, the yield of **[110]** does not appear to be time-dependent. This is borne out by comparison of expt. 2 with 3, and expt. 5 with 6. In both instances, time is the constant, with the ratio **[63]** : *n*-BuLi being the variable. A change in this ratio is accompanied by an inverse change in the yield of **[110]**. Further investigation is required to confirm these ideas.

Product **[110]** was characterised fully by spectroscopic techniques. The signal due to the methoxy protons was extremely prominent in the ^{1}H NMR spectrum. It was split into a doublet due to coupling to phosphorus. The signals for protons close to the phosphorus atom were quite complex as both hydrogen-hydrogen and hydrogen-phosphorus coupling was taking place. Some doubling up of signals was observed in the ^{13}C NMR spectrum. Again, this was due to coupling to phosphorus. The IR spectrum of the product contained an absorption band for a P=O stretch at 1240 cm^{-1}. The N-H stretch at 3175cm^{-1} for the thiolactam precursor **[63]**, was absent. The

high resolution mass spectrum gave a molecular ion peak at m/z = 237.0587, corresponding to $C_8H_{16}NO_3PS$.

The difference in ease of preparation of [110] compared with [109] is discussed below.

[121] [122]

[123] [124]

[125] [126]

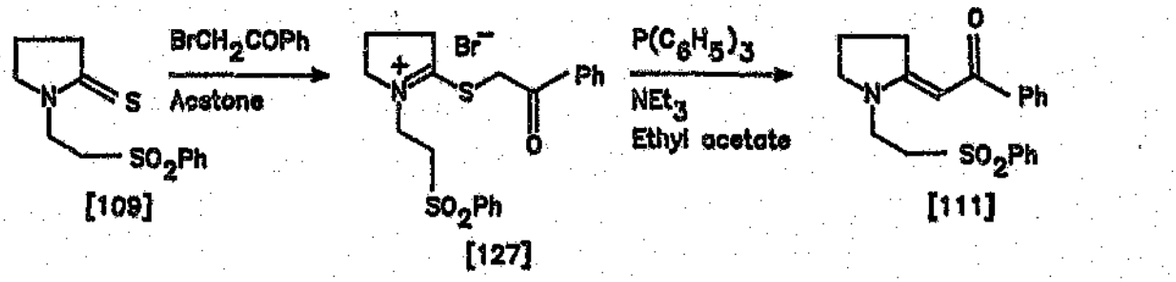
In the example of an α,β-unsaturated carbonyl compound [121], all orbitals are aligned as indicated in [125]. This allows for ready addition of the thiolactam, since delocalisation of electrons to form the transient species [122] is not hindered. This is not the case for the phosphorus analogue. In [123], the geometry at phosphorus is essentially tetrahedral. The P=O double bond is formed by back donation from a filled p-orbital on oxygen into an empty d-orbital on phosphorus. Involvement of a d-orbital results in the orbitals no longer being aligned, as shown in [126]. This makes generation of the transient species [124] more difficult. Since sulphur is also a third-period element, it exhibits the same kind of $p\pi$-$d\pi$ overlap. The diminished reactivity of phosphorus versus sulphur can probably be ascribed to back donation by the methoxy groups in the phosphorus reagent [123]. Consequently harsher conditions are required in the preparation of the phosphorus compound [110], as indicated by

the use of *n*-butyllithium, longer reaction times and lower yields compared with those for the preparation of the sulphonyl equivalent [109].

2.2 SULPHIDE CONTRACTION REACTIONS

2.2.1 Preparation of (*E*)-2-benzoylmethylene-1-(2-phenylsulphonylethyl)pyrrolidine [111]

2-Benzoylmethylene-1-(2-phenylsulphonylethyl)pyrrolidine [111] was prepared according to the sequence illustrated in Scheme 33.



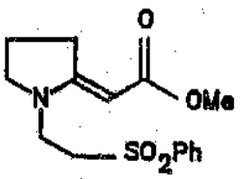
Scheme 33

Salt formation [127] was accomplished by the addition of ω-bromoacetophenone to a solution of 1-(2-phenylsulphonylethyl)pyrrolidine-2-thione [109] in acetone. Subsequent sulphur extrusion was effected by the consecutive addition of triphenylphosphine and triethylamine in ethyl acetate. The product was obtained in a good yield (93%, chromatographically pure). The ^{1}H NMR spectrum showed the distinguishing vinyl proton singlet at 5.58ppm, while the vinyl carbon signal appeared at 86.88ppm in the ^{13}C NMR spectrum. No doubling up of signals in the ^{13}C NMR spectrum was observed, indicating that only one geometrical isomer had been prepared. The geometry around the carbon-carbon double bond was predicted as being *E*, as this would relieve intramolecular congestion within the molecule. Comparison of the chemical shift for H-3 (3.28ppm) with other similar compounds, indicated that δ for the *E*-isomer is 0.5ppm more downfield than for the *Z*-isomer. The

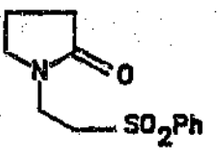
IR spectrum of the product contained two absorption bands indicative of a C=C-C=O system i.e. a C=O stretch at 1730cm^{-1} and a C=C stretch at 1620cm^{-1}. Microanalysis confirmed the formula $C_{20}H_{21}NO_3S$.

2.2.2 Preparation of (*E*)-2-ethoxycarbonylmethylene-1-(2-phenylsulphonylethyl)pyrrolidine [112]

The original idea was to prepare 2-methoxycarbonylmethylene-1-(2-phenylsulphonylethyl)pyrrolidine [128], the analogous methoxy compound of [112]. For this purpose a solution of 1-(2-phenylsulphonylethyl)pyrrolidine-2-thione [109] in acetone was treated with methyl bromoacetate, followed by sulphur extrusion of the resultant salt with triphenylphosphine and triethylamine .The sulphide contraction reaction did not produce the expected sulphide contracted product. Hydrolysis occurred instead, producing the oxygen analogue of the starting material, 1-(2-phenylsulphonylethyl)-pyrrolidine-2-one [129], in 36 - 47% yields. The remaining unhydrolysed starting material [109] was also recovered.



[128]



[129]

For compound [129], the carbonyl carbon peak was observed at 175.01ppm in the ^{13}C NMR spectrum. The C=O stretch of the 5-ring lactam system was observed at 1675cm^{-1} in the IR spectrum. Conclusive evidence of the lactam product was provided by the high resolution mass spectrum which gave a molecular ion peak at m/z = 253.0792, corresponding to $C_{12}H_{15}NO_3S$. Microanalysis further confirmed this structure.

2-Ethoxycarbonylmethylene-1-(2-phenylsulphonylethyl)pyrrolidine [112] was eventually synthesised by the addition of ethyl bromoacetate to a solution of 1-(2-phenylsulphonylethyl)pyrrolidine-2-thione [109] in acetone, followed by sulphur extrusion of the resultant salt with triphenylphosphine and triethylamine. The product [112] was

obtained in 72% yield after column chromatography.

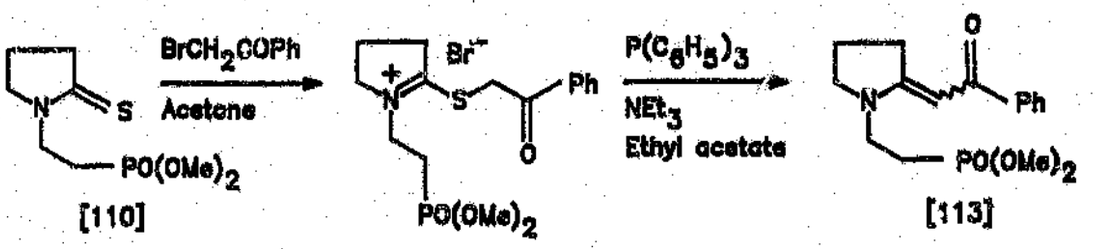
The structure of 2-ethoxycarbonylmethylene-1-(2-phenylsulphonylethyl)pyrrolidine [112] was substantiated by ^{1}H NMR and ^{13}C NMR data. The quartet at 4.07ppm and the triplet at 1.24ppm in the ^{1}H NMR spectrum indicated the presence of the ethoxy group. The ester carbonyl signal was observed at 168.81ppm in the ^{13}C NMR spectrum. The vinyl proton resonated at 4.33ppm and the vinyl carbon signal appeared at 79.23ppm. Using the same argument as for [111], the geometry around the carbon-carbon double bond in [112] was again believed to be *E*.

Further evidence of the sulphide contracted product was provided by the IR spectrum which showed a C=O stretch at 1725cm^{-1}, asymmetrical C-O stretches at 1305cm^{-1} & 1290cm^{-1} and a symmetrical C-O stretch at 1142cm^{-1} for the ester group. The high resolution mass spectrum showed a molecular ion peak at m/z = 323.1174, corresponding to $C_{16}H_{21}NO_4S$.

The failure of the original reaction to prepare compound [128] is mysterious, as the conditions used were identical to those for the successful preparation of compound [112].

2.2.3 Preparation of (*E*/*Z*)-2-benzoylmethylene-1-(2-dimethoxyphosphorylethyl)pyrrolidine [113]

A mixture of isomers of 2-benzoylmethylene-1-(2-dimethoxyphosphorylethyl)pyrrolidine [113] was prepared according to the reaction sequence illustrated in Scheme 34.



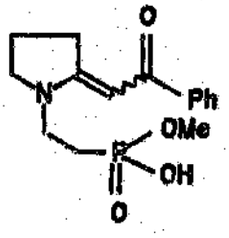
Scheme 34

Addition of ω-bromoacetophenone to a solution of 1-(2-dimethoxyphosphorylethyl)-pyrrolidine-2-thione [110] in acetone, followed by sulphur extrusion, gave the product mixture [113] in a good yield (74%, chromatographically pure).

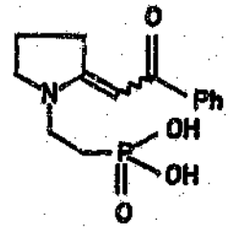
Doubling up of the characteristic vinyl proton in the ^{1}H NMR spectrum immediately indicated the presence of both the *E*- and *Z*-isomers. This doubling up of signals was also observed in the ^{13}C NMR spectrum. The *E*-isomer vinyl proton singlet appeared at 5.77ppm, while that of the *Z*-isomer was found at 5.72ppm in the ^{1}H NMR spectrum. The vinyl carbon signals for the *E*- and *Z*-isomer appeared in the ^{13}C NMR spectrum at 85.43ppm and 84.76ppm respectively. Comparison of the ^{1}H NMR integrals for the two vinyl proton signals indicated the *E*-isomer to be present in an amount four times greater than that for the *Z*-isomer. This excess of one of the isomers is not unexpected as the *E*-isomer is the less intramolecularly congested of the two molecules. The IR spectrum showed a P=O stretch at 1230cm^{-1}.

It was not possible to separate the two molecules by column chromatography. However it was found that the *Z*-isomer was insoluble in most common organic solvents available to us. The *E*-isomer was extracted from the mixture with chloroform. For a mixture of the isomers, the high resolution mass spectrum gave a molecular ion peak at m/z = 323.1306, corresponding to $C_{16}H_{22}NO_4P$. The *Z*-isomer alone failed to give a spectrum.

Isolated along with the *E*/*Z*-isomer mixture were copious quantities of a second compound of unknown structure. On the basis of the ^{1}H NMR, ^{13}C NMR and IR spectral data, [130] and [131] were put forward as possible structures. The high resolution mass spectrum results failed to correspond with these proposed structures, nor were these results of assistance in elucidating the actual structure.

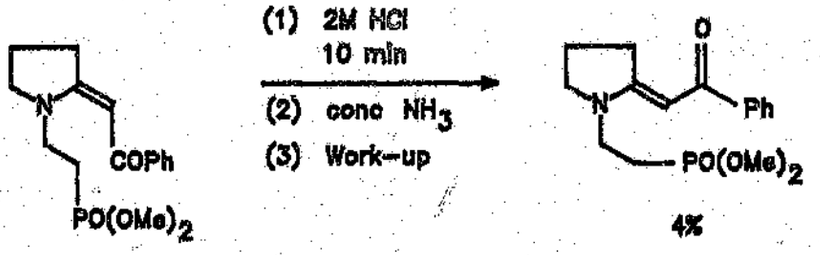


[130]



[131]

To confirm the geometry of the *Z*-isomer, it was epimerised to the thermodynamically more stable *E*-isomer, according to the sequence illustrated in Scheme 35 below. Displacement of the methoxy groups by ammonia to generate a phosphonamide which can be lost during work-up, may account for the low yield observed.



Scheme 35

2.3 REDUCTION REACTIONS

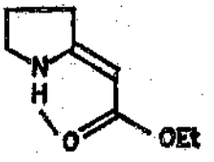
2.3.1 Preparation of 2-benzoylmethyl-1-(2-phenylsulphonylethyl)-pyrrolidine [102]

The carbon-carbon double bond in the vinylogous amide system of [111] was reduced using lithium aluminium hydride. 2-Benzoylmethyl-1-(2-phenylsulphonylethyl)-pyrrolidine [102] was prepared in a good yield (85%, chromatographically pure) by treating (*E*)-2-benzoylmethylene-1-(2-phenylsulphonylethyl)pyrrolidine [111] with lithium aluminium hydride in tetrahydrofuran at 0°C. The absence of the vinyl proton singlet at 5.58ppm and the increased complexity of all signals in the ^{1}H NMR spectrum indicated the presence of the desired product [102]. The IR-absorption due to the C=O group was observed at 1680cm^{-1}. The high resolution mass spectrum gave a molecular ion peak at m/z = 357.1389 corresponding to $C_{20}H_{23}NO_3S$, which confirmed the structure of the product as [102].

2.3.2 Preparation of 2-ethoxycarbonylmethyl-1-(2-phenyl-sulphonylethyl)pyrrolidine [101]

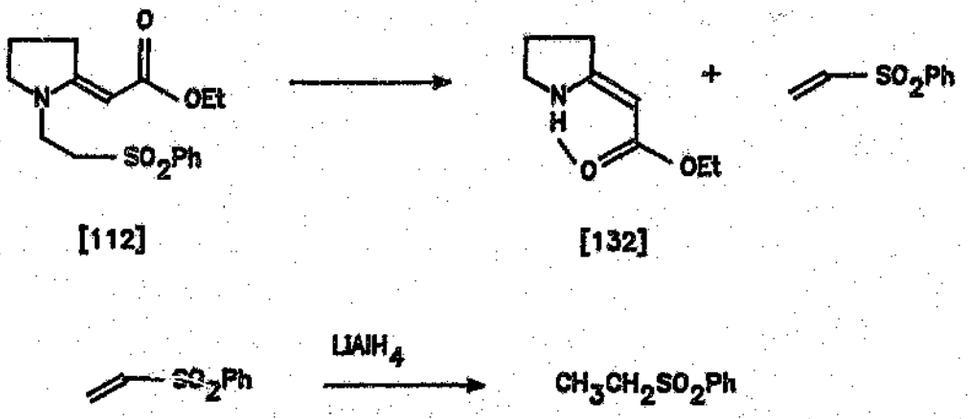
Lithium aluminium hydride is a well-established common reducing agent, but is not suitable for reduction of the carbon-carbon double bond in the vinylogous urethane system of [112]. However, it was tried out of curiosity.

(*E*)-2-Ethoxycarbonylmethylene-1-(2-phenylsulphonylethyl)pyrrolidine [112] and lithium aluminium hydride were reacted in tetrahydrofuran at 0°C. The presence of a vinyl proton peak at 4.54ppm in the ^{1}H NMR spectrum confirmed that the material isolated was not the reduced product [101]. The δ_H-value of this singlet did not correspond to that for the starting material [112]. On this basis, the new product was suspected to be the *Z*-isomer of 2-ethoxycarbonylmethylene-1-(2-phenylsulphonyl-ethyl)pyrrolidine [112]. However, the high resolution mass spectrum gave a molecular ion peak at m/z = 170.0392, which did not correspond with the assignment of this structure.



[132]

Further investigation indicated that the ^{1}H NMR spectrum corresponded to a mixture of (*Z*)-2-ethoxycarbonylmethylenepyrrolidine [132] and ethyl phenyl sulphone. A mechanism proposed to account for these observations is given in Scheme 36. Retro-Michael reaction of (*E*)-2-ethoxycarbonylmethylene-1-(2-phenylsulphonylethyl)-pyrrolidine [112], induced by lithium aluminium hydride acting as base rather than reducing agent, yielded (*Z*)-2-ethoxycarbonylmethylenepyrrolidine [132] and phenyl vinyl sulphone. The carbon-carbon double bond of the phenyl vinyl sulphone was then reduced by the hydride reagent. The presence of [132] was confirmed by comparison of the ^{1}H and ^{13}C NMR data obtained with that for an authentic sample.



Scheme 36

A few reports describing the use of hydride reducing reagents for the conversion of vinyl sulphones to their saturated analogues are known[104,105]. These reductions are presumed to occur by Michael addition of the hydride, but no detailed study of this type of reaction of vinyl sulphones has appeared[106].

2-Ethoxycarbonylmethylene-1-(2-phenylsulphonylethyl)pyrrolidine **[112]** was successfully reduced with sodium cyanoborohydride in ethanol at pH *ca.* 4. The product was obtained in 86% yield after column chromatography. As observed before for **[102]**, the absence of the vinyl proton singlet at 4.33ppm and the increased complexity of all signals in the ^{1}H NMR spectrum indicated the presence of the desired product **[101]**. The quartet at 4.10ppm and the triplet at 1.25ppm in the ^{1}H NMR spectrum indicated that the ethoxy group was still present. The ester carbonyl signal was observed at 171.92ppm in the ^{13}C NMR spectrum. The IR spectrum showed a C=O stretch at 1700cm^{-1} and a C-O stretch at 1265cm^{-1} for the ester group.

2.3.3 Attempted preparation of 2-benzoylmethyl-1-(2-dimethoxy-phosphorylethyl)pyrrolidine [114]

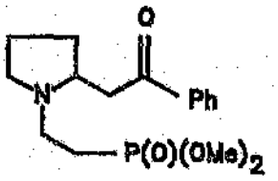
The reducing agents lithium aluminium hydride and sodium cyanoborohydride were used in an attempt to reduce the carbon-carbon double bond in the vinylogous amide system of **[113]**. TABLE 2 contains a summary of the conditions employed and the results obtained.

TABLE 2: Reaction details for the attempted preparation of [114] from [113]

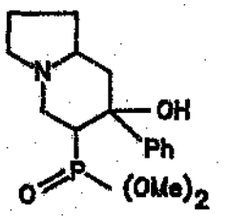
Expt. No.*	Reducing Agent	Eq. Reducing Agent	Solvent	Temp. /°C	Time /hrs	Recovered /%#
1	$LiAlH_4$	1.11	THF	0 25	3.0 19.5	SM 42%
2	$LiAlH_4$	1.23	THF	0	1.0	SM 62%
3	$NaCNBH_4$	1.32	EtOH	25	1.3	[114] & [133]

* All reactions were carried out under an inert atmosphere of nitrogen.
# SM = Starting Material.

In experiment 1, the starting material comprised a mixture of the *E/Z*-isomers. Dissolution of this material in dichloromethane gave a heterogenous mixture, thereby reducing the efficiency of the reaction. The insolubility of the *Z*-isomer in suitable organic solvents was a problem; consequently, subsequent attempts at preparation of [114] made use of the *E*-isomer only.



[114]



[133]

Lithium aluminium hydride was found not to be a suitable reductant. This result contrasts with that for a similar system in [111]. The sodium cyanoborohydride reaction appears to have yielded a mixture of the desired reduced product [114] and the cyclised product [133]. From the ^1H NMR spectrum, the C=C bond of the vinylogous amide was definitely no longer intact, as indicated by the lack of the vinyl proton at 5.77ppm and the complexity of the signals that were observed. A broad

peak at 4.58ppm was assigned to the alcohol proton in [133]. The ^{13}C NMR spectrum provided further evidence for the presence of more than one compound, since there were many peaks. The vinyl signal at 85.46ppm, characteristic of the vinylogous amide [113], was absent. A carbonyl peak was observed at 199.26ppm and assigned to the reduced compound [114]. The most convincing piece of evidence that allowed us to tentatively conclude the presence of [114] and [133] was provided by the ^{31}P NMR spectrum. There were three signals in the ^{31}P NMR spectrum, a singlet and what appeared to be a doublet. The singlet at 33.59ppm was assigned to 2-benzoylmethyl-1-(2-dimethoxyphosphorylethyl)pyrrolidine [114], while the two peaks at 32.52ppm and 32.71ppm were thought to arise from the two possiblediastereomersof4-phenyl-3-dimethoxyphosphoryl-1-azabicyclo[4.3.0]nonan-4-ol [133].

The reduction step in Route C (Scheme 31), was the last to be considered. Time constraints prevented further investigation, although from the above discussion the approach appears promising.

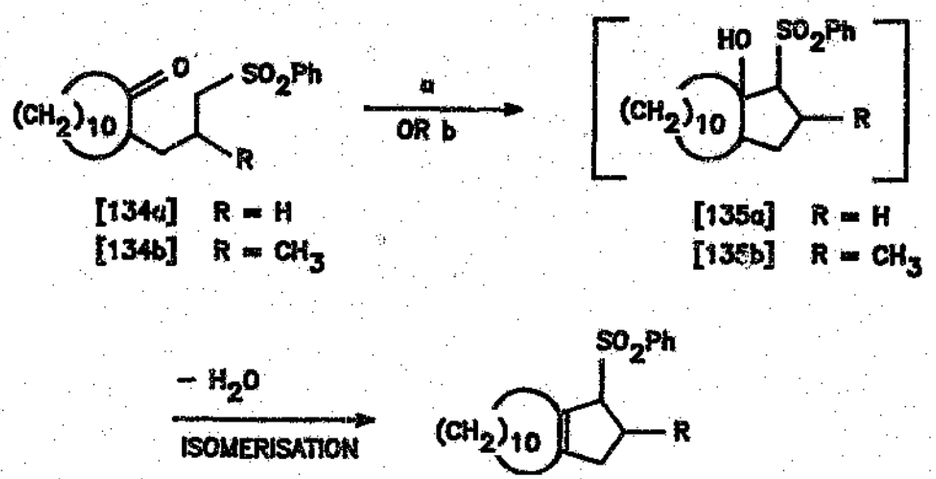
2.4 ATTEMPTED CYCLISATION REACTIONS

In section 1.4, three novel routes to the $\Delta^{6,7}$-indolizidine skeleton were proposed. Routes A and B included a base-induced, sulphur-mediated cyclisation step, while a phosphorus-mediated process was envisaged in Route C. Sections 2.4.1 and 2.4.2 describe attempts to induce cyclisation by taking advantage of condensation involving α-sulphonyl anions, while in the third case, the aim was to prepare the $\Delta^{6,7}$-indolizidine skeleton patterned on a Wittig reaction. In the latter case, attempts to prepare the precursor, 2-benzoylmethyl-1-(2-dimethoxyphosphorylethyl)pyrrolidine [114], were unsuccessful. Consequently this cyclisation reaction was not attempted.

2.4.1 Attempted preparation of 4-phenyl-3-phenylsulphonyl-1-azabicyclo[4.3.0]nonan-4-ol [115]

An outline of reported intramolecular cyclisations of sulphonyl ketones precedes the discussion for an analogous reaction in our strategy for the synthesis of the bicyclic compound [115].

Fehr[107] described the intramolecular condensation of sulphonyl ketones [134a] or [134b] to give the β-hydroxy sulphones [135a] or [135b] (Scheme 37).



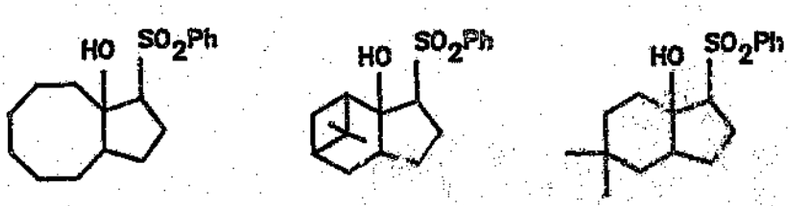
[134a] R = H
[134b] R = CH_3

[135a] R = H
[135b] R = CH_3

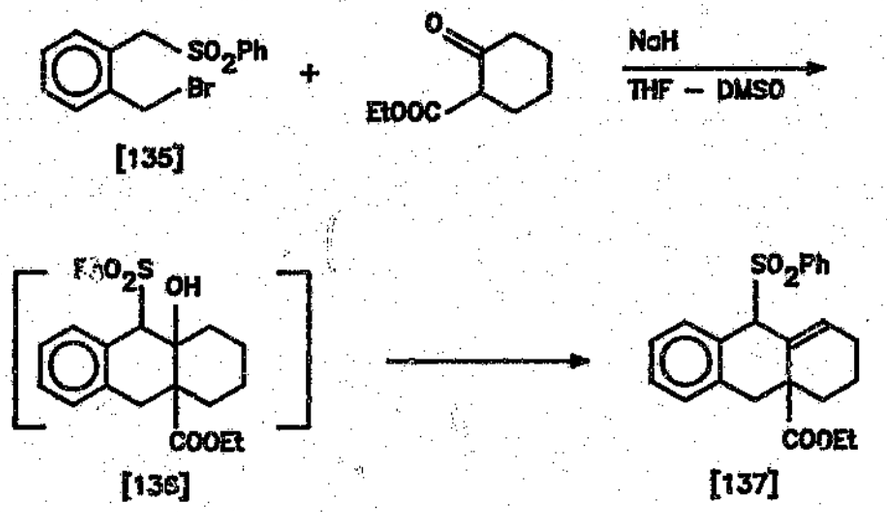
(a) *t*-BuOK (1.5eq.), toluene/50°C/1hr or KOH (7eq.), toluene/110°C/30min.
(b) *t*-BuOK (2.5eq.), toluene/110°C/1hr or KOH (6.5eq.), toluene, DMSO (2.8eq.)/110°C/15hrs.

Scheme 37

Other β-hydroxy sulphones prepared by this method are shown below[107].

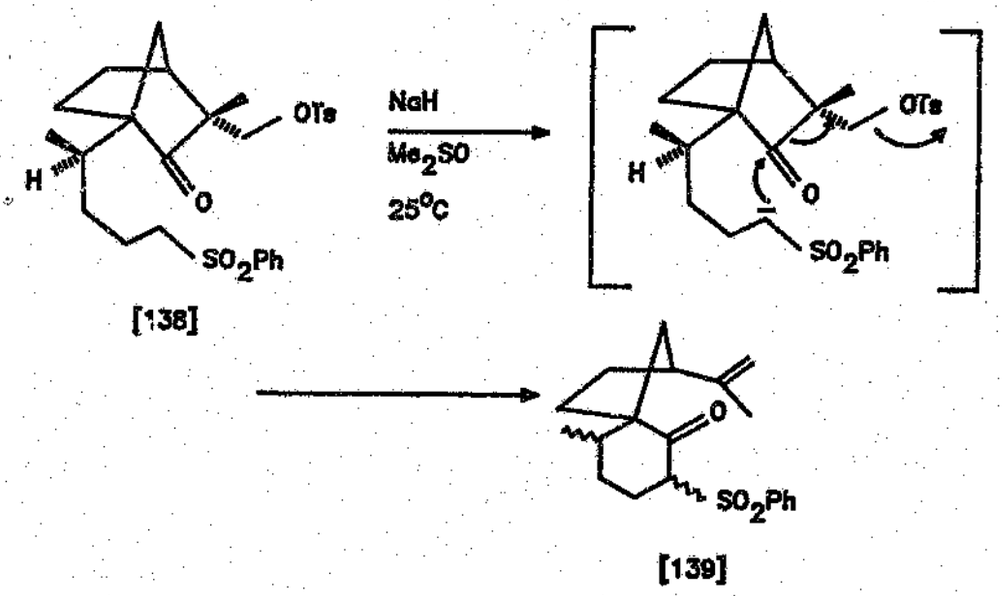


Ghera *et al.*[108,109] found that bromosulphone [135] reacted with ethyl cyclohexanone-2-carboxylate in two consecutive steps, by preferential attack of the α-sulphonyl carbanion on the carbonyl group to give tricyclic compound [137], via the β-hydroxy sulphone intermediate [136] (Scheme 38).



Scheme 38

Chass *et al.*[110] synthesised the spiro[4.5]decane [139] from the fragmentation of [138], as shown in Scheme 39.



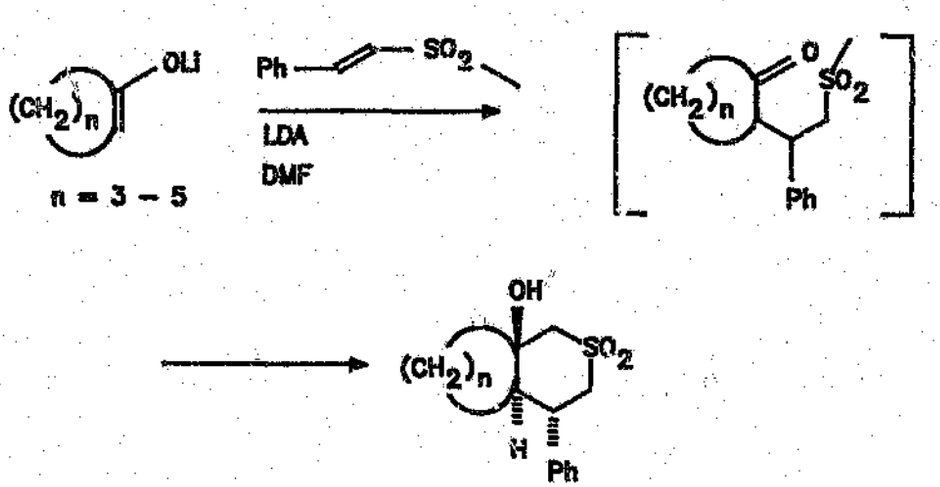
Scheme 39

Anderson *et al.*[111] formed the α-silyl sulphone [140], by Michael addition to a vinyl sulphone. Fluoride was used to regenerate the α-sulphonyl carbanion, thereby enabling an intramolecular aldol-type reaction to occur (Scheme 40).

[140]

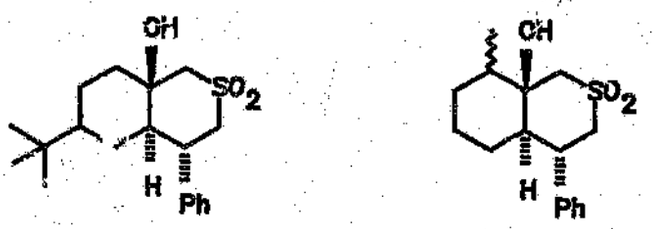
Scheme 40

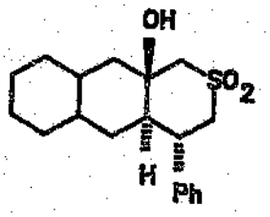
Takaki *et al.*[112,113] developed a useful method of utilising vinyl sulphones (specifically methyl styryl sulphones) for the preparartion of thiane dioxides in good yields (Scheme 41). The ketone enolates add to the vinyl sulphone, followed by an intramolecular ketone sulphonyl condensation that leads to the thiane sulphone.

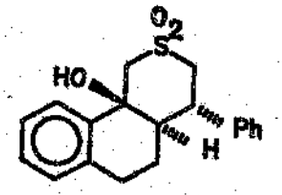


Scheme 41

Other thiane sulphones prepared in this manner are shown below[112].







A number of these examples at first appear unrelated to the strategy we employed. However, all include formation of an α-sulphonyl anion followed by intramolecular nucleophilic attack at a ketone carbonyl group. The methodology employed is the feature of interest, rather than the products synthesised.

Attempts were made to prepare our system, 4-phenyl-3-phenylsulphonyl-1-azabicyclo-[4.3.0]nonan-4-ol **[115]** by reacting 2-benzoylmethyl-1-(2-phenylsulphonylethyl)-pyrrolidine **[102]** with at least one equivalent of base to create an α-sulphonyl anion and thereby induce cyclisation. A number of different bases were tried[107-114]. The details are summarised in TABLE 3 along with the outcome of the various reactions.

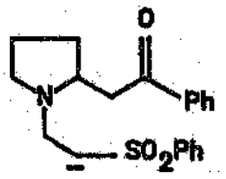
TABLE 3: Reaction details for the attempted preparation of **[115]** from **[102]**

Expt. No.*	Base	Eq. Base	Solvent	Temp. /°C	Time /hrs	Recovered /%#
1	NaOEt	10.9	EtOH	Reflux	1.5	SM 57%
2	*t*-BuOK	2.01	THF	Reflux	16.3	-
3	*t*-BuOK	2.19	THF	25	5.0	SM 0.8%
4	*t*-BuOK	2.33	THF	25 Reflux	45.0 21.5	[92] ~51%∞
5	*n*-BuLi	1.55	THF	25	5.5	SM 14%
6	*n*-BuLi	2.33	THF	Reflux	114.5	SM 15%

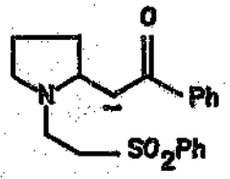
* All reactions were carried out under an inert atmosphere of nitrogen.

SM = Starting Material.

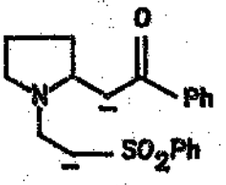
∞ Discussed in section 2.4.3.



[141]



[142]



[143]

Route A in Scheme 31 proposed formation of the desired bicyclic system via the α-sulphonyl anionic species [141]. However, the molecule contains a second, more acidic set of protons, α to the carbonyl group. Deprotonation at this site is preferred, giving rise to the anionic species [142]. Since the sulphonyl group is relatively inert to nucleophilic attack[106], this species would not undergo further reaction, but rather would exist in equilibrium with the desired anion [141].

The sulphonyl group enables deprotonation of attached alkyl, alkenyl and aryl groups, but is also able to allow multiple deprotonation to form a range of polyanions[106]. Upon examination of the data in TABLE 3, we see that in most cases, two equivalents of base were employed. This would allow formation of the dianionic species [143]. Species [143] is unable to undergo further reaction, and is likely to be involved in an equilibrium process with both species [141] and [142]. Formation of the cyclised product is therefore expected, made possible through this equilibrium reaction.

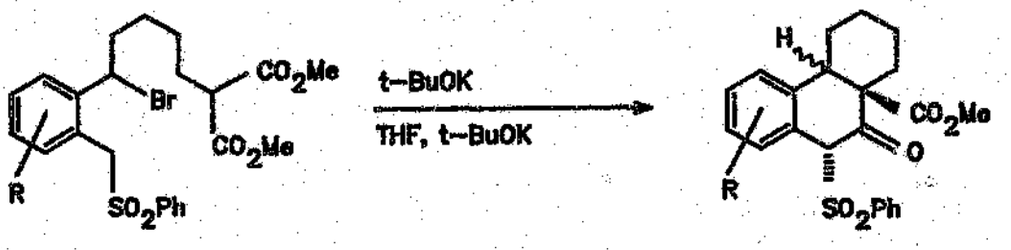
At no time was the cyclised product [115] detected or isolated. In additon to the above difficulties, steric effects must certainly impede the desired reaction, and may contribute to the failures recorded in TABLE 3. The cyclised product [115] would contain a sulphonyl group and a phenyl group on adjacent carbon atoms. This would lead to much steric congestion within the molecule and possibly accounts for cyclisation not being observed.

2.4.2 Attempted preparation of 3-phenylsulphonyl-1-azabicyclo-[4.3.0]nonan-4-one [116]

Reported syntheses containing an intramolecular sulphonyl acylation reaction, analogous to that proposed for the synthesis of the bicyclic system [116], are outlined

below.

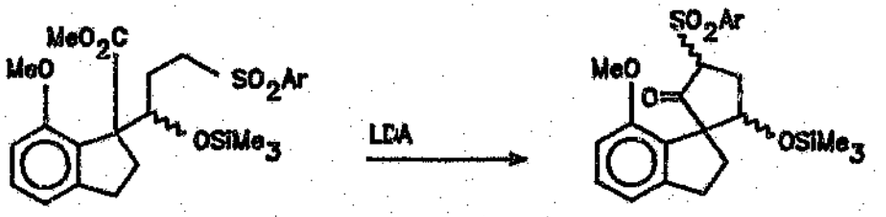
Ghera *et al.*[115] treated [144] with an excess of base, resulting in successive intramolecular malonate alkylation and sulphone acylation. The tricyclic products such as [145] were obtained stereoselectively, the major products having *trans*-ring fusion (Scheme 42).



[144] [145]

Scheme 42

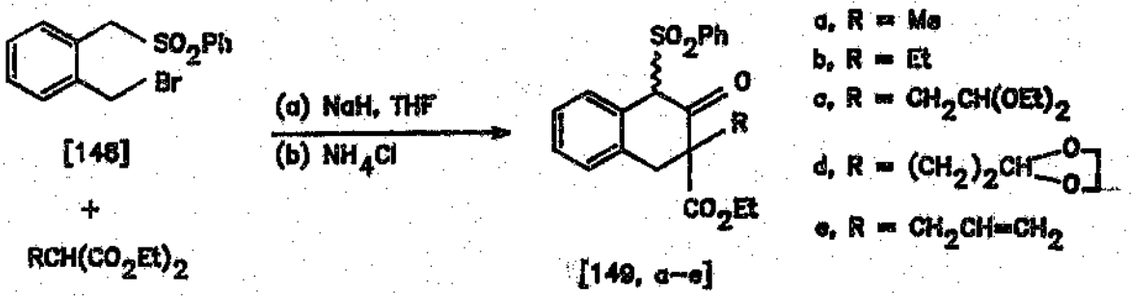
Bennet *et al.*[116] observed that cyclisation of [146] occurred in a similar fashion, using LDA at -78°C with warming to 0°C, to give the spirocyclic product [147] in good yield (Scheme 43).



[146] [147]

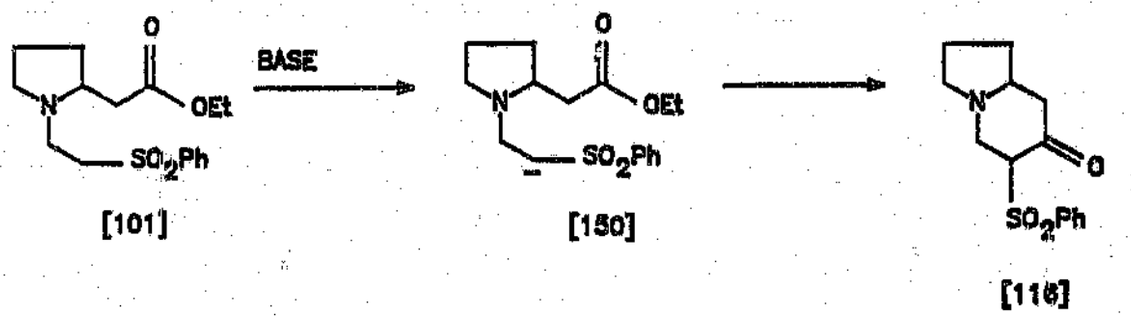
Scheme 43

Ghera *et al.*[109] treated bromosulphone [148] with a series of monosubstituted malonate enolates in an alkylation-acylation sequence (Scheme 44). Bicyclic crystallizable diastereomeric mixtures [149, a-e] were obtained as products.



Scheme 44

In an approach similar to that in section 2.4.2, preparation of 3-phenylsulphonyl-1-azabicyclo[4.3.0]nonan-4-one **[116]** was attempted according to the reaction sequence illustrated in Scheme 45.



Scheme 45

TABLE 4 contains a summary of the reaction conditions employed.

TABLE 4: Reaction details for the attempted preparation of **[116]**

Expt. No.*	Base	Eq. Base	Temp. /°C	Time /hrs	Recovered /%#
1	*t*-BuOK	1.21	Reflux	16.3	SM 63%
2	*n*-BuLi	0.44	25	45	SM 65%

* All reactions were carried out in THF and under an inert atmosphere of nitrogen.

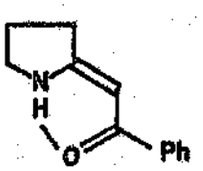
SM = Starting Material

Again, there are two sets of acidic protons in the precursor [101], but in this case they are approximately of equal acidity. Since a sulphonyl group was present in the molecule, it was possible to form a dianionic species similar to [143]. Less than two equivalents of base were employed to promote cyclisation, thereby avoiding this possible problem. Difficulties were not envisaged in the preparation of the anionic species [150], but cyclisation was not observed. However, since the reaction was only attempted twice, it would be premature to attempt to draw conclusions from the results obtained. Time constraints prevented a more thorough investigation.

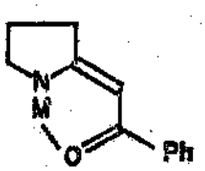
To conclude, the step that was to provide the main focus of the project turned out to be unsuccessful. The investigation undertaken warrants further study to determine adequately whether the cyclisation steps proposed constitute part of a useful synthesis to the $\Delta^{6,7}$-indolizidine skeleton or not.

2.4.3 Preparation of (*Z*)-2-benzoylmethylenepyrrolidine [92]

The following discussion details work which comprises a spin-off from the main theme of the project. It is discussed here as it adds to similar material already investigated by Parsons[65h].



[92]



[151]

Interest in compound [92] revolves around its use as a possible ligand for transition metals. Compounds of the type [151] have been proposed as ligands for transition metals[65h]. Geometry around the carbon-carbon double bond is *Z* owing to the 6-membered hydrogen-bonded structure that is formed. Synthesis of compounds of this type by way of the sulphide contraction reaction can be difficult. Vigorous reaction conditions are required, and yields are generally low. On the other hand, sulphide contraction reactions with tertiary thiolactams generally take place in higher yields and require milder conditions. Consequently a suitable protecting group for nitrogen has

been sought in these laboratories for many years. Parsons found that basic conditions (*t*-BuOK) could induce a retro-Michael reaction in (*E*)-2-benzoylmethylene-1-(2-cyanoethyl)pyrrolidine [91], yielding [92]. He recognised that the cyanoethyl group was acting as the sought-after protecting group.

(*Z*)-2-Benzoylmethylenepyrrolidine [92] was synthesised by accident during attempted cyclisation of [102] to 4-phenyl-3-phenylsulphonyl-1-azabicyclo[4.3.0]nonan-4-ol [115]. The starting material used for the cyclisation step was contaminated with a small quantity of 2-benzoylmethylene-1-(2-phenylsulphonylethyl)pyrrolidine [111]. The reaction conditions used were similar to those employed by Parsons. A mixture of compounds [102] and [111] was stirred at room temperature in THF with *t*-BuOK. A retro-Michael reaction was observed in [111] to yield [92], thereby also establishing the phenylsulphonylethyl group as a suitable protecting group for nitrogen. To render the reaction of preparative use, further investigation is needed. Optimum conditions still need to be determined.

CHAPTER 3: SUMMARY AND CONCLUSION

The aims of this project have been presented in Chapter 1. Each of the three aims is discussed in turn below.

(1) *To extend the range of Michael acceptors which react with pyrrolidine-2-thione at nitrogen.*

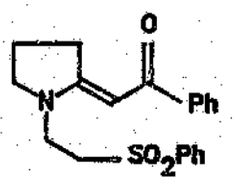
The synthetic utility of dimethyl vinylphosphonate and phenyl vinyl sulphone as Michael acceptors in adding to pyrrolidine-2-thione was investigated. Parsons[65h] had already determined that phenyl vinyl sulphone added in quantitative yield. We reconfirmed this result, but found that retro-Michael reaction occurred if the optimum reaction time of 24hrs was exceeded excessively.

Numerous attempts were made to attach dimethyl vinylphosphonate to pyrrolidine-2-thione. Using a catalytic quantity of sodium hydroxide as the base was unsuccessful, as was heating the two reactants together in a sealed tube at a high temperature. Formation of the desired product [110] was accomplished by changing the base to *n*-butyllithium. However, to obtain [110] in good yield, a catalytic quantity of base had to be used.

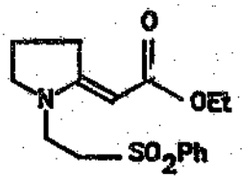
(2) *To demonstrate further the synthetic utility of the sulphide contraction reaction in alkaloid synthesis.*

The sulphide contraction reaction is a well known procedure, and is used frequently in these laboratories in the synthesis of alkaloids. It allows the synthesis of exocyclic vinylogous amides and urethanes, which upon further manipulation can be taken through to a number of different alkaloids or alkaloidal intermediates. Its usefulness lies in being able to introduce functionalised carbon-carbon bonds into a molecule. The ambident electrophilicity and nucleophilicity of the resulting enaminones in turn makes them versatile organic intermediates.

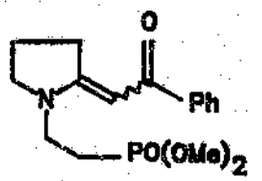
In this project we prepared vinylogous amides [111] and [113], and the vinylogous urethane [112]; thereby providing further examples of the synthetic utility of this well known reaction.



[111]



[112]



[113]

(3) *To develop a new route to the synthesis of the indolizidine skeleton as found in the alkaloids ipalbidine and septicine.*

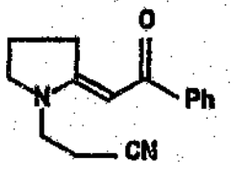
This project was concerned with the development of a new route to the $\Delta^{6,7}$-indolizidine skeleton. At the core was the development of efficient methodology, rather than the total synthesis of the alkaloids ipalbidine, septicine and some of their analogues. Three different routes were outlined for the construction of the desired skeleton, with emphasis placed on the cyclisation step. Stereoselectivity was not considered.

The two routes involving sulphur-mediated ring closure were successful up to the cyclisation step. Different reagents and reactions were investigated, but the cyclised products were not detected nor isolated. The third route had as its basis a phosphorus-mediated ring closure step, and proved to be extremely challenging. Although the route was proceeding successfully, progress was slow and time constraints prevented the cyclisation step being attempted. However, during the preparation of compound [114], a by-product apparently having the structure of the desired product [133] was isolated, which gives hope for the successful completion of this route in the future.

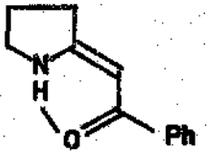
In summary, the first two aims of the project were achieved successfully, but the third aim was not met. From this investigation we cannot conclude that the cyclisation step is not a viable reaction. Rather, suitable reaction conditions have not yet been found.

Further work on the cyclisation step is therefore necessary. Once cyclisation has been achieved, further manipulation of the cyclised product can lead to a number of different alkaloids. Some of our ideas are expressed in section 1.4.

To conclude this chapter, a brief discussion about an unexpected result follows.



[91]



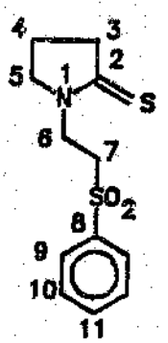
[92]

(*Z*)-2-Benzoylmethylenepyrrolidine [92] was first obtained by Parsons[65h] as an unwanted side product in a base-mediated reduction of [91]. The cyanoethyl group in compound [91] was acting as a protecting group for nitrogen, which could be removed by base-induced retro-Michael reaction to yield [92]. We accidentally prepared compound [92] in a similar manner from (*E*)-2-benzoylmethylene-1-(2-phenylsulphonylethyl)pyrrolidine [111] (section 2.4.3.). The phenylsulphonylethyl group in compound [111] was also found to act as a protecting group for nitrogen.

CHAPTER 4: EXPERIMENTAL

General details pertaining to this project have been included in the experimental section of Part A (pages 31-33).

A 1-(2-Phenylsulphonylethyl)pyrrolidine-2-thione [109]



[109]

Pyrrolidine-2-thione **[63]** (1.38g; 13.6mmol) was stirred in dry THF (36ml) with a catalytic amount of sodium hydroxide (*ca.* 10mg) and phenyl vinylsulphone (2.30g; 13.7mmol). After 24hrs, the reaction mixture was washed with water (40ml). The aqueous phase was extracted with dichloromethane (2x50ml) and the organic extracts dried ($MgSO_4$) and evaporated *in vacuo* to give a cream-coloured solid. Column chromatography with ethyl acetate as solvent gave **1-(2-phenylsulphonylethyl)-pyrrolidine-2-thione [109]** (3.53g; 13.1mmol; 96.3%) as a cream-coloured solid. This was recrystallised from benzene-hexane (1:1) to give small white needles, mp 95-96°C, R_F (ethyl acetate) 0.71.

Found: C, 53.22; H, 5.43; N, 5.30%.
$C_{12}H_{15}NO_2S_2$ requires C, 53.51; H, 5.61; N, 5.20%.

^1H NMR

δ_H 7.90 - 7.96 (2H, m, H-9); 7.55 - 7.74 (3H, m, H-10 + H-11); 4.11 (2H, t, $^3J_{HH}$ = 6.49Hz, H-6); 3.87 (2H, t, $^3J_{HH}$ = 7.28Hz, H-5); 3.60 (2H, t, $^3J_{HH}$ = 6.48Hz, H-7); 2.94 (2H, t, $^3J_{HH}$ = 7.93Hz, H-3); 2.04 (2H, qu, $^3J_{HH}$ = 7.62Hz, H-4).

Decouple at 2.05ppm, the triplets at 2.94ppm and 3.87ppm collapse to singlets.

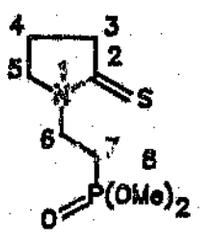
^{13}C NMR

δ_C 202.41 (C-2); 138.78 (C-8); 134.01 (C-11); 129.36 (C-10); 127.63 (C-9); 56.17 (C-5); 51.68 (C-7); 44.52 (C-3); 41.64 (C-6); 19.83 (C-4).

IR

υ_{max} ($CHCl_3$) 2990 (m, sh); 2980 (m, sh); 2900 (w, sh); 2880 (w, sh); 1590 (w, br); 1500 (s, sh); 1465 (m, sh); 1445 (m, sh); 1420 (w, sh); 1410 (w, sh); 1395 (w, sh); 1360 (w, sh); 1330 (s, sh); 1310 (s, sh); 1300 (s, sh); 1260 (w, sh); 1225 (w, sh), 1210 (broad shoulder); 1140 (s, sh); 1110 (m, sh); 1075 (m, sh); 675 (m, sh) cm^{-1}.

B 1-(2-Dimethoxyphosphorylethyl)pyrrolidine-2-thione [110]



[110]

Pyrrolidine-2-thione **[63]** (0.526g; 5.20mmol) was stirred in THF (15ml) under a nitrogen atmosphere with a catalytic amount of *n*-butyllithium (0.60ml; 0.61mg; 0.96mmol) and dimethyl vinylphosphonate (0.801g; 5.89mmol). After 67.5hrs, the reaction mixture was washed with water (50ml). The aqueous phase was extracted with dichloromethane (2x50ml) and the organic extracts dried ($MgSO_4$) and evaporated *in vacuo* to give a pale-yellow oil (1.17g). Column chromatography with ethyl acetate- methanol (6:1) as solvent gave **1-(2-dimethoxyphosphorylethyl)pyrrolidine-2-thione [110]** (0.956g; 4.03mmol; 77.5%) as a pale-yellow oil, R_F (ethyl acetate-methanol {20%}) 0.52, R_F (ethyl acetate) 0.09.

^{1}H NMR

δ_H 3.96 (2H, dt, H-6, $^3J_{HH}$ = 7.79Hz, $^3J_{HP}$ = 10.87Hz); 3.82 (2H, t, H-5, $^3J_{HH}$ = 7.30Hz); 3.79 (6H, d, H-8, $^3J_{HP}$ = 10.98Hz); 3.01 (2H, t, H-3, $^3J_{HH}$ = 7.92Hz); 2.27 (2H, dt, H-7, $^3J_{HH}$ = 7.71Hz, $^2J_{HP}$ = 18.42Hz); 2.10 (2H, q, H-4, $^3J_{HH}$ = 7.61Hz).

Decouple at 2.08ppm, triplets at 3.01ppm and 3.82ppm collapse to singlets.

Decouple at 2.27ppm, doublet of triplets at 3.96ppm collapses to a doublet.

Decouple at 3.00ppm, quintet at 2.10ppm collapses to a triplet.

Decouple at 3.82ppm, quintet at 2.10ppm collapses to a triplet.

Decouple at 3.96ppm,doublet of triplets at 2.27ppm collapses to a doublet.

^{13}C NMR

δ_C 201.09 (s, C-2); 54.97 (s, C-5); 52.29 (d, C-8, $^2J_{CP}$ = 6.48Hz); 44.41 (s, C-3); 41.71 (s, C-6); 20.62 (d, C-7, $^1J_{CP}$ = 139.14Hz); 19.38 (s, C-4).

^{31}P NMR: Singlet at 30.49ppm.

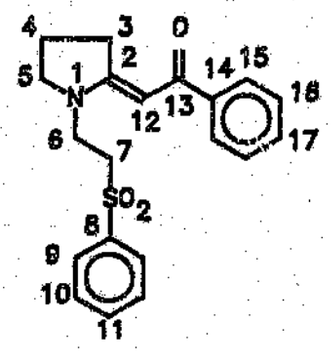
IR

υ_{max} ($CHCl_3$) 3665 (w, sh); 3430 (w, br); 3000 (s, sh); 2950 (s, sh); 2880 (m, sh); 2850 (m, sh); 2460 (w, br); 1710 (w, br); 1670 (w, sh); 1610 (w, br); 1510 (s, sh); 1465 (m, sh); 1450 (m, sh); 1430 (m, sh); 1420 (m, sh); 1400 (w, sh); 1365 (m, sh); 1330 (s, sh); 1300 (s, sh); 1287 (s, sh); 1240 (s, br); 1210 (m, sh); 1185 (m, sh); 1145 (m, sh); 1120 (m, sh); 1060 (s, sh); 1040 (s, sh); 1000 (m, sh); 940 (vw, sh); 845 (s, sh); 820 (s, sh); 785 (m, sh); 775 (s, sh); 760 (m, sh); 750 (s, sh); 745 (s, sh); 735 (m, sh); 730 (s, sh); 700 (m, sh); 665 (s, sh).

m/z 237 (M^+ $C_8H_{16}NO_3PS^+$); 137 ($(MeO)_2P(O)CH_2CH_2^+$, 24%); 128 ($[M - P(O)(OMe)_2]^+$, 100%); 127 (23%); 126 (56%); 109 ($(MeO)_2P(O)^+$, 20%); 85 (25%); 42 (25%).

HRMS (Found: M^+ 237.0587. $C_8H_{16}NO_3PS$ requires 237.0589).

C (E) 2-Benzoylmethylene-1-(2-phenylsulphonylethyl)pyrrolidine [111]



[111]

ω-Bromoacetophenone (0.420g; 2.11mmol) was added to a solution of 1-(2-phenylsulphonylethyl)pyrrolidine-2-thione [109] (0.539g; 2.00mmol) in acetone (3ml). The mixture was swirled and left at 3°C for 24hrs in order to facilitate salt formation. The solvent was evaporated *in vacuo* and the product, a solid, was dissolved in acetonitrile (10ml). Triphenylphosphine (0.584g; 2.22mmol) was added, followed by triethylamine (5.00ml; 3.63g; 35.2mmol). Ethyl acetate (100ml) was added. The reaction mixture was filtered through Celite, dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil/solid mixture (1.50g). Column chromatography with ethyl acetate as solvent gave **(*E*)-2-benzoylmethylene-1-(2-phenylsulphonylethyl)pyrrolidine [111]** (0.659g; 1.85mmol; 92.7%). This was recrystallised from ethyl acetate to give pale yellow cubes, mp 151-151.5°C, R_F (ethyl acetate) 0.33.

Found: C, 67.55; H, 5.99; N, 3.92%.
$C_{20}H_{21}NO_3S$ requires C, 67.58; H, 5.95; N, 3.94%.

^1H NMR

δ_H 7.91 - 7.96 (2H, m, H-9); 7.75 - 7.81 (2H, m, H-15); 7.53 - 7.74 (3H, m, H-10 + H-11); 7.34 - 7.45 (3H, m, H-16 + H-17); 5.58 (1H, s, H-12); 3.78 (2H, t, $^3J_{HH}$ = 7.10Hz, H-6); 3.42 (2H, t, $^3J_{HH}$ = 7.23Hz, H-5); 3.41 (2H, t, $^3J_{HH}$ 7.05Hz, H-7); 3.28 (2H, t, $^3J_{HH}$ = 7.54Hz, H-3); 1.91 (2H, qu, $^3J_{HH}$ = 7.53Hz, H-4).
Decouple at 1.90ppm, the triplets at 3.28ppm and 3.42ppm collapse to singlets.
Decouple at 3.28ppm, the quintet at 1.91ppm collapses to a triplet.

Decouple at 3.78ppm, the triplet at 3.41ppm collapses to a singlet.

^{13}C NMR

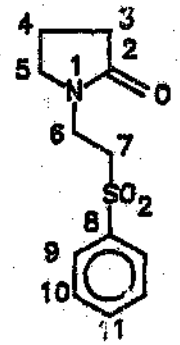
δ_C 187.67 (C-13); 166.05 (C-2); 141.21 (C-14); 138.72 (C-8); 134.15 (C-11); 130.62 (C-17); 129.49 (C-10); 128.05 (C-16); 127.71 (C-9); 127.15 (C-15); 86.88 (C-12); 52.69 (C-5); 51.47 (C-7); 39.99 (C-6); 33.41 (C- 3); 20.84 (C-4).

IR

υ_{max} ($CHCl_3$) 3665 (w, br); 3400 (w, br); 3060 (w, sh); 3030 (w, sh); 3000 (m, sh); 2860 (w, br); 2450 (w, br); 1960 (vw, br); 1890 (vw, br); 1810 (vw, br); 1765 (vw, br); 1730 (vw, br); 1620 (s, sh); 1595 (m, sh); 1575 (s, sh); 1530 (s, sh); 1478 (s, sh); 1460 (w, sh); 1445 (m, sh); 1400 (m, sh); 1360 (m, sh); 1320 (s, sh); 1305 (s, sh); 1290 (s, sh); 1225 (s, sh); 1210 (m, sh); 1180 (m, sh); 1150 (s, sh); 1085 (s, sh); 1065 (w, sh); 1035 (w, sh); 1010 (m, sh); 1000 (w, sh); 960 (m, sh); 930 (w, sh); 885 (w, sh); 840 (m, sh); 810 (w, br); 720 (w, sh); 705 (m, sh); 690 (s, sh); 665 (s, sh) cm^{-1}.

m/z 355 (M^+ $C_{20}H_{21}NO_3S^+$, 0.03%); 215 (13%); 214 ($[M - SO_2Ph]^+$, 100%); 108 (11%); 105 ($PhC(O)^+$, 36%); 77 (Ph^+, 16%).
HRMS (Found: M^+ 355.1263. $C_{20}H_{21}NO_3S$ requires 355.1242).

D 1-(2-Phenylsulphonylethyl)pyrrolidine-2-one [129]



[129]

Methyl bromoacetate (0.571g; 3.73mmol) was added to a solution of 1-(2-phenyl-

sulphonylethyl)pyrrolidine-2-thione **[109]** (1.01g; 3.75mmol) in acetone-dichloromethane (1:1) (5ml). The mixture was swirled and left at 3°C for 24hrs to facilitate salt formation. The solvent was evaporated *in vacuo* and the product, an oil, was dissolved in ethyl acetate (10ml). Triphenylphosphine (0.991g; 3.76mmol) was added, followed by triethylamine (1.60ml; 1.16g; 11.2mmol). Ethyl acetate (100ml) was added. The reaction mixture was filtered through Celite, dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil (2.34g). Column chromatography with ethyl acetate as solvent gave **1-(2-phenylsulphonylethyl)pyrrolidine-2-one [129]** (0.442g; 1.74mmol; 46.5%) and starting material (0.568g; 2.11mmol; 56.2%). Compound **[129]** was recrystallised from benzene-hexane (1:1) to give small white needles, mp 95-96°C, R_F (ethyl acetate) 0.71.

Found: C, 56.60; H, 6.09; N, 5.54%.
$C_{12}H_{15}NO_3S$ requires C, 56.90; H, 5.97; N, 5.53%.

^1H NMR

δ_H 7.89 - 7.06 (2H, m, H-9); 7.54 - 7.73 (3H, m, H-10 + H-11); 3.66 (2H, t, H-6, $^3J_{HH}$ = 6.68Hz); 3.41 (2H, t, H-7, $^3J_{HH}$ = 6.57Hz); 3.39 (2H, t, H-5, $^3J_{HH}$ = 6.99Hz); 2.24 (2H, t, H-3, $^3J_{HH}$ = 8.16Hz); 1.91 (2H, q, H-4, $^3J_{HH}$ = 7.50Hz).
Decouple at 1.89ppm, triplets at 2.24ppm and 3.39ppm collapse to singlets.
Decouple at 3.66ppm, triplet at 3.41ppm collapses to a singlet.

^{13}C NMR

δ_C 175.01 (C-2); 138.60 (C-8); 133.63 (C-11); 129.02 (C-10); 127.43 (C-9); 52.43 (C-7); 47.14 (C-5); 36.52 (C-6); 30.19 (C-3); 17.48 (C-4).

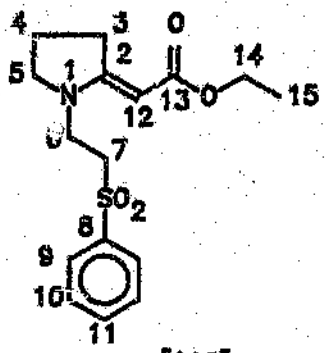
IR

υ_{max} ($CHCl_3$) 3670 (w, sh); 3450 (s, br); 3350 (s, br); 3065 (m, sh); 3025 (s, sh); 3010 (s, sh); 2925 (m, sh); 2875 (m, sh); 2450 (w, br); 1675 (s, sh); 1580 (w, sh); 1490 (m, sh); 1460 (m, sh); 1445 (s, sh); 1430 (m, sh); 1420 (m, sh); 1400 (m, sh); 1360 (m, sh); 1315 (s, sh); 1305 (s, sh); 1290 (s, sh); 1230 (s, sh); 1218 (s, sh); 1210 (m, sh); 1207 (s, sh); 1150 (s, sh); 1090 (s, sh); 1065 (w, sh); 1045 (w, sh);

1025 (w, sh); 1010 (w, sh); 1000 (w, sh); 970 (w, sh); 928 (w, sh); 880 (w, sh); 840 (w, sh); 810 (w, sh); 790 (m, sh); 785 (s, sh); 762 (s, sh); 760 (s, sh); 738 (s, sh); 730 (m, sh); 725 (m, sh); 690 (s, sh); 670 (s, sh).

m/z 253 (M^+ $C_{12}H_{15}NO_3S^+$, 23%); 112 ($[M - SO_2Ph]^+$, 45%); 111 (100%); 98($[M - PhSO_2CH_2]^+$, 27%); 83 (25%); 56 (29%).
HRMS (Found: M^+ 253.0792. $C_{12}H_{15}NO_3S$ requires 253.0773).

E **(*E*)-Ethoxycarbonylmethylene-1-(2-phenylsulphonylethyl)pyrrolidine [112]**



[112]

Ethyl bromoacetate (0.443g; 2.65mmol) was added to a solution of 1-(2-phenylsulphonylethyl)pyrrolidine-2-thione [109] (0.522g; 1.94mmol) in acetone (4ml). The mixture was swirled and left at 3°C for 24hrs in order to facilitate salt formation. The solvent was evaporated *in vacuo* and the product, an oil, was dissolved in acetonitrile (10ml). Triphenylphosphine (0.703g; 2.67mmol) was added, followed by triethylamine (10.0ml; 7.26g; 70.4mmol). Ethyl acetate (150ml) was added. The reaction mixture was filtered through Celite, dried ($MgSO_4$) and evaporated *in vacuo* to give an orange-brown gum/solid (1.71g). Column chromatography with ethyl acetate as solvent gave **(*E*)-2-ethoxycarbonylmethylene-1-(2-phenylsulphonylethyl)pyrrolidine [112]** (0.453g; 1.40mmol; 72.2%) as a yellow oil/solid, R_F (ethyl acetate) 0.66.

^1H NMR
δ_H 7.90 - 7.95 (2H, m, H-9); 7.55 - 7.74 (3H, m, H-10 + H-11); 4.33 (1H, s, H-12); 4.07 (2H, qt, H-14, $^3J_{HH}$ = 7.12Hz); 3.64 (2H, t, H-6, $^3J_{HH}$ = 6.85Hz); 3.37 (2H, t,

H-5, $^3J_{HH}$ = 6.98Hz); 3.34 (2H, t, H-7, $^3J_{HH}$ = 9.82Hz); 3.04 (2H, td, H-3, $^2J_{HH}$ = 1.09Hz, $^3J_{HH}$ = 7.81Hz); 1.85 (2H, q, H-4, $^3J_{HH}$ = 7.45Hz); 1.24 (3H, t, H-15, $^3J_{HH}$ = 7.10Hz).

Decouple at 1.85ppm, triplets at 3.04ppm and 3.37ppm collapse to singlets.

Decouple at 3.04ppm, quintet at 1.85ppm collapses to a triplet.

Decouple at 3.65ppm, triplet at 3.34ppm collapses to a singlet.

^{13}C NMR

δ_C 168.81 (C-13); 163.79 (C-2); 138.93 (C-8); 134.03 (C-11); 129.43 (C-10); 127.67 (C-9); 79.23 (C-12); 58.40 (C-14); 52.72 (C-5); 51.58 (C-7); 39.68 (C-6); 32.17 (C-3); 20.96 (C-4); 14.58 (C-15).

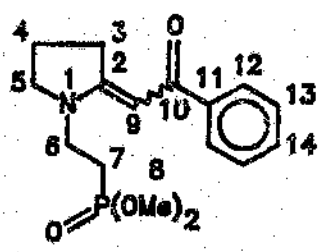
IR

υ_{max} ($CHCl_3$) 3025 (shoulder), 2985 (w, sh), 2950 (shoulder); 2900 (w, sh); 2875 (w, sh); 1725 (w, sh); 1675 (m, sh); 1590 (s, sh); 1475 (w, sh); 1455 (w, sh); 1440 (w, sh); 1420 (w, sh); 1395 (w, sh); 1375 (w, sh); 1360 (w, sh); 1320 (m, sh); 1305 (m, sh); 1290 (m, sh); 1245 (w, br); 1200 (w, br); 1142 (s, sh), 1125 (shoulder); 1080 (m, sh); 1058 (m, sh); 1020 (w, sh); 995 (w, sh); 710 (w, br); 680 (w, sh); 565 (w, sh); 525 (w, br).

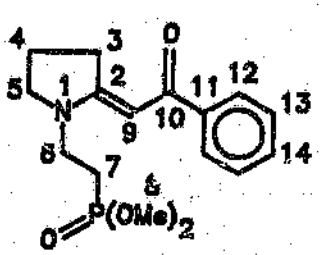
m/z 323 (M^+ $C_{16}H_{21}NO_4S^+$, 21%); 278 ($[M - OEt]^+$, 40%); 182 ($[M - SO_2Ph]^+$, 100%); 128 (58%); 110 (92%); 108 (62%); 73 ($(EtC)C(O)^+$, 23%).

HRMS (Found: 323.1174. $C_{16}H_{21}NO_4S$ requires 323.1192).

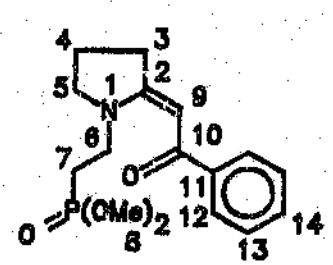
F **(*E/Z*)-Benzoylmethylene-1-(2-dimethoxyphosphorylethyl)pyrrolidine [113]**



[113]



[113]



[113]

ω-Bromoacetophenone (0.476g; 2.39mmol) was added to a solution of 1-(2-dimethoxyphosphorylethyl)pyrrolidine-2-thione [110] (0.507g; 2.14mmol) in acetone (2ml). The mixture was swirled and left at 3°C for 24hrs in order to facilitate salt formation. The solvent was evaporated *in vacuo* and the product, a gum, was dissolved in acetonitrile (8ml). Triphenylphosphine (0.636g; 2.41mmol) was added, followed by triethylamine (10.0ml; 7.26g; 70.4mmol). Ethyl acetate (150ml) was added. The reaction mixture was filtered through Celite, dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil/solid (1.52g). Column chromatography with ethyl acetate- methanol (20%) gave **(*E/Z*)-benzoylmethylene-1-(2-dimethoxy-phosphorylethyl)pyrrolidine [113]** (0.546g; 1.69mmol; 78.9%) as an orange gum, R_F (ethyl acetate) 0-0.34, R_F (ethyl acetate-methanol{50%}) 0.73; and an unknown compound (0.144g), R_F (ethyl acetate-methanol{50%}) 0.36. The *Z*-isomer was found to be insoluble in most common solvents available to us. The *E*-isomer was extracted from the isomer mixture with chloroform, while the *Z*-isomer was recovered from the aqueous layer by allowing the water to evaporate. The *E*-isomer was obtained as a yellow oil, R_F (ethyl acetate-methanol {10%}) 0.47 (*E*-isomer). The *Z*-isomer was obtained as an orange gum, R_F (ethyl acetate-methanol {10%}) 0.52 (*Z*-isomer).

^{1}H NMR (*E*-isomer, DMSO-d_6)

δ_H 7.82 - 7.88 (2H, m, H-12); 7.39 - 7.47 (3H, m, H-13 + H-14); 5.77 (1H, s, H-9); 3.67 (6H, d, H-8, $^3J_{HP}$ = 10.96Hz); 3.62 (2H, dt, H-6, $^3J_{HH}$ = 8.44Hz, $^3J_{HP}$ = 2.56Hz); 3.50 (2H, t, H-3, $^3J_{HH}$ = 7.23Hz); 3.20 (2H, t, H-5, $^3J_{HH}$ = 7.74Hz); 2.19 (2H, dt, H-7, $^3J_{HH}$ = 7.48Hz, $^2J_{HP}$ = 17.95Hz); 1.92 (2H, q, H-4, $^3J_{HH}$ = 7.51Hz). Decouple at 2.19ppm, doublet of triplets at 3.62ppm collapses to a doublet, $^3J_{HP}$ = 28.85Hz.

^{13}C NMR

δ_C 185.25 (s, C-10); 165.79 (s, C-2); 141.61 (s, C-11); 130.14 (s, C-14); 127.95 (s, C-13); 126.76 (s, C-12); 85.46 (s, C-9); 52.10 (d, C-8, $^2J_{CP}$ = 6.40Hz); 51.70 (s, C-5); the peak for C-6 is obscured by the DMSO-d_6 signal; 33.41 (s, C-3); 20.48 (d, C-7, $^1J_{CP}$ = 136.21Hz); 20.29 (s, C-4).

^{31}P NMR: Singlet at 37.54ppm.

^{1}H NMR (*E*-isomer, $CDCl_3$)

δ_H 7.87 - 7.91 (2H, m, H-12); 7.40 - 7.44 (3H, m, H-13 + H-14); 5.76 (1H, s, H-9); 3.78 (6H, d, H-8, $^{3}J_{HP}$ = 10.90Hz); 3.64 (2H, dt, H-6, $^{3}J_{HH}$ = 7.78Hz, $^{3}J_{HP}$ = 10.76Hz); 3.50 (2H, t, H-5, $^{3}J_{HH}$ = 7.23Hz); 3.40 (2H, t, H-3, $^{3}J_{HH}$ = 7.65Hz); 2.13 (2H, dt, H-7, $^{2}J_{HP}$ = 19.13Hz, $^{3}J_{HH}$ = 8.06Hz); 2.04 (2H, q, H-4, $^{3}J_{HH}$ = 7.14Hz).

^{13}C NMR

δ_C 187.83 (s, C-10); 166.23 (s, C-2); 141.70 (s, C-11); 130.47 (s, C-14); 128.05 (s, C-13); 127.20 (s, C-12); 86.78 (s, C-9); 52.59 (d, C-8, $^{2}J_{CP}$ = 5.84Hz); 52.53 (s, C-5); 40.34 (s, C-6); 33.69 (s, C-3); 21.60 (d, C-7, $^{1}J_{CP}$ = 139.63Hz); 20.97 (s, C-4).

^{1}H NMR (*Z*-isomer, DMSO-d_6)

δ_H 7.77 - 7.82 (2H, m, H-12); 7.35 - 7.40 (3H, m, H-13 + H-14); 5.70 (1H, s, H-9); 3.40 (6H, d, H-8, $^{3}J_{HP}$ = 10.12Hz); the signal for H-6 is obscured by the broad based methoxy signal; 3.16 (2H, t, H-5, $^{3}J_{HH}$ = 7.65Hz); 1.85 (2H, t, H-3, $^{3}J_{HH}$ = 7.28Hz); 1.74 (2H, q, H-4, not possible to determine the coupling constant); the signal for H-7 is obscured by the quintet at 1.74ppm and the triplet at 1.85ppm.

^{13}C NMR

δ_C 184.70 (s, C-10); 165.70 (s, C-2); 141.73 (s, C-11); 129.89 (s, C-14); 127.88 (s, C-13); 126.63 (s, C-12); 84.72 (s, C-9); 51.63 (s, C-5); 50.31 (d, C-9, $^{2}J_{CP}$ = 5.44Hz); 42.10 (s, C-6); 33.56 (s, C-3); 22.93 (d, C-7, $^{1}J_{CP}$ = 130.58Hz); 20.13 (s, C-4).

^{31}P NMR: Singlet at 33.27ppm.

IR

υ_{max} (Smear, *E/Z*-isomers) 3460 (s, br); 3070 (w, sh); 2960 (s, sh); 2885 (m, sh); 2865 (m, sh); 1670 (w, br); 1625 (s, br); 1600 (s, sh); 1580 (s, sh); 1540 (s, br); 1480 (s, sh), 1475 (shoulder); 1445 (m, sh); 1420 (w, br); 1370 (s, sh); 1320 (s, sh);

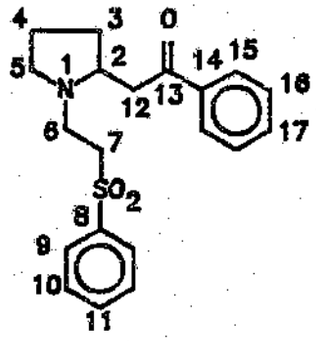
1305 (s, sh); 1270 (shoulder), 1230 (s, br), 1190 (shoulder); 1150 (w, sh); 1050 (s, v.br); 955 (w, sh); 935 (w, sh); 845 (m, sh); 820 (m, sh); 765 (m, sh); 710 (m, sh); 675 (w, sh); 650 (w, sh).

IR

υ_{max} (Smear, *E*-isomer) 3407 (m, v.br); 3025 (w, sh); 2925 (m, sh); 2855 (m, sh); 2825 (m, sh); 1615 (m, br); 1590 (m, sh); 1568 (s, sh); 1535 (br shoulder), 1525 (s, sh); 1475 (s, sh); 1435 (m, sh); 1405 (w, br); 1360 (m, sh); 1315 (m, sh); 1295 (m, sh); 1255 (br shoulder), 1225 (s, sh); 1175 (m, sh); 1140 (s, br); 1050 (s, br); 1025 (s, br), 1010 (shoulder); 963 (w, sh); 945 (w, sh); 925 (w, sh); 835 (m, sh); 815 (m, sh); 760 (shoulder), 755 (m, sh); 705 (m, sh); 663 (w, sh); 643 (w, sh).

m/z (*E/Z*-isomers) 323 (M^+ $C_{16}H_{22}NO_4P^+$); 220 (35%); 195 (48%); 194 (100%); 192 (38%); 166 (34%); 122 (75%); 120 (82%); 44 (22%); 41 (33%).
HRMS (Found: 323.1306. $C_{16}H_{22}NO_4P$ requires 323.1286).
The *Z*-isomer failed to give a spectrum.

F **2-Benzoylmethyl-1-(2-phenylsulphonylethyl)pyrrolidine [102]**



[102]

Lithium aluminium hydride (13.1mg; 0.345mmol) was added under nitrogen to a stirred solution of (*E*)-2-benzoylmethylene-1-(2-phenylsulphonylethyl)pyrrolidine **[111]** (0.108g; 0.304mmol) in dry THF (8ml) at 0°C. Water was added after 50min to quench unreacted lithium aluminium hydride. The mixture was dried ($MgSO_4$) and evaporated *in vacuo* to give a brown oil, which was purified by column chromatography using ethyl acetate as solvent to give 2-benzoylmethyl-1 (2-

phenylsulphonylethyl)pyrrolidine [102] (92.2mg; 0.258mmol; 84.6%) as a red-brown oil, R_F (ethyl acetate) 0.49.

^1H NMR

δ_H 7.89 - 7.94 (4H, m, H-9 + H-15); 7.57 - 7.63 (2H, m, H-11 + H-17); 7.41 - 7.56 (4H, m, H-10 + H-16); 3.18 - 3.39 (4H, m, H-7 + H-6a + H-12a); 2.82 - 3.07 (3H, m, H-2 + H-5a + H-12b); 2.58 -2.70 (1H, m, H-6b); 1.94 -2.21 (2H, m, H-5b + H-3a); 1.58 -1.73 (2H, m, H-4); 1.32 - 1.48 (1H, m, H-3b).

Decouple at 1.40ppm, multiplets at 1.32 - 1.48ppm, 1.58 - 1.73ppm and 2.82 - 3.07ppm simplify. Decouple at 1.66ppm, multiplets at 1.32 - 1.48ppm, 1.94 - 2.21ppm and 2.82 - 3.07ppm simplify. Decouple at 2.65ppm, multiplet at 3.18 - 3.39 simplifies.

^{13}C NMR

δ_C 139.01 (C-13); 139.49 (C-14); 136.85 (C-8); 133.53 (C-11); 133.07 (C-17); 129.03 (C-10); 128.51 (C-16); 127.92 (C-9); 127.85 (C-15); 59.90 (C-2); 54.46 (C-7); 52.87 (C-5); 46.96 (C-6); 43.39 (C-12); 31.06 (C- 3); 22.30 (C-4).

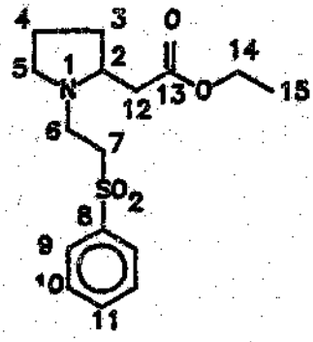
IR

υ_{max} ($CHCl_3$) 3025 (w, sh); 3000 (w, sh); 2960 (w, br); 2875 (w, br); 2800 (w, br); 1680 (s, sh); 1610 (w, sh); 1595 (w, sh); 1580 (w, sh); 1535 (vw, sh); 1530 (vw, sh); 1445 (s, sh); 1400 (w, sh); 1370 (w, sh); 1315 (s, sh); 1305 (s, sh); 1290 (s, sh); 1235 (w, br); 1210 (w, sh); 1205 (w, sh); 1180 (w, sh); 1150 (s, sh); 1085 (m, sh); 1025 (w, br); 1000 (m, br); 785 (s, sh); 775 (s, sh); 740 (m, sh); 725 (m, sh); 720 (w, sh); 690 (s, sh); 668 (s, sh); 666 (m, sh); 605 (m, br) cm^{-1}.

m/z 357 (M^+ $C_{20}H_{23}NO_3S^+$, 0.11%); 239 (24%); 238 (100%); 214 (32%); 188 ([M - $PhSO_2CH_2CH_2]^+$, 21%); 105 ($PhC(O)^+$, 81%); 96 (46%); 77 (Ph^+, 61%); 70 (38%); 28 (29%).

HRMS (Found: M^+ 357.1389. $C_{20}H_{23}NO_3S$ requires 357.1399).

G 2-Ethoxycarbonylmethyl-1-(2-phenylsulphonylethyl)pyrrolidine [101]



[101]

(*E*)-2-Ethoxycarbonylmethylene-1-(2-phenylsulphonylethyl)pyrrolidine [112] (0.212g; 0.656mmol) was dissolved in absolute ethanol (2.20ml) to make up a 0.3M solution. Sodium cyanoborohydride (0.0571g; 0.909mmol) 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, under an atmosphere of nitrogen. Water (30ml) was added, and the solution was made basic with concentrated NH_3 (25%). The aqueous phase was extracted with dichloromethane (2X30ml) and the organic extracts dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil (0.194g). Column chromatography with ethyl acetate as solvent gave **2-ethoxycarbonylmethyl-1-(2-phenylsulphonylethyl)-pyrrolidine [101]** (0.184g; 0.565mmol; 86.4%) as a pale-yellow oil, R_F (ethyl acetate) 0.60.

^{1}H NMR

δ_H 7.89 - 7.96 (2H, m, H-9); 7.52 - 7.70 (3H, m, H-10 + H-11); 4,10 (2H, qt, H-14, $^3J_{HH}$ = 7.13Hz); 3.23 - 3.34 (2H, m, H-7); 3.10 - 3.21 (1H, m, H-6a); 2.71 - 2.88 (2H, m, H-5a + H-2); 2.64 (1H, ddd, H-6b, $^2J_{HH}$ = 11.73Hz, $^3J_{HH}$ = 5.75Hz, $^3J_{HH}$ = 1.91Hz); 2.52 (1H, dd, H-12a, $^2J_{HH}$ = 14.99Hz, $^3J_{HH}$ = 4.54Hz); 2.17 (1H, dd, H-12b, $^2J_{HH}$ = 15.25Hz, $^3J_{HH}$ = 8.66Hz); 2.06 - 2.15 (1H, m, H-5b); 1.87 - 2.00 (1H, m, H-3a); 1.58 - 1.70 (1H, m, H-3b); 1.41 - 1.57 (2H, m, H-4); 1.25 (3H, t, H-15, $^3J_{HH}$ = 7.11Hz).

Decouple at 1.64ppm, multiplets at 1.41 - 1.57ppm, 1.87 - 2.00ppm, 2.06 - 2.15ppm

and 2.71 - 2.88ppm simplify. Decouple at 1.98ppm, multiplets at 1.41 - 1.57ppm, 1.58 - 1.70ppm and 2.71 - 2.88ppm simplify. Decouple at 2.52ppm, doublet of doublets at 2.17ppm collapses to a doublet and the multiplet at 2.71 - 2.88 simplifies. Decouple at 3.30ppm, doublet of doublet of doublets at 2.64ppm and the multiplet at 3.10 - 3.21ppm simplifies.

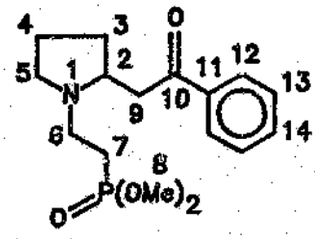
^{13}C NMR

δ_C 171.92 (C-13); 139.61 (C-8); 133.58 (C-11); 129.09 (C-10); 127.94 (C-9); 60.32 (C-2); 60.28 (C-14); 54.65 (C-7); 53.05 (C-5); 46.95 (C-6); 39.38 (C-12); 30.64 (C-3); 22.23 (C-4); 14.15 (C-15).

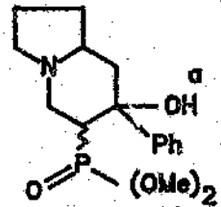
IR

υ_{max} (Smear) 3565 (w, v.br); 3455 (w, v.br); 3040 (w, sh); 2950 (s, sh); 2900 (s, sh); 2860 (s, sh), 2840 (shoulder); 1700 (w, sh); 1650 (s, sh); 1565 (s, br); 1480 (m, sh); 1450 (w, sh); 1438 (m, sh); 1420 (s, sh); 1400 (m, sh); 1375 (m, sh); 1350 (m, sh); 1340 (m, sh); 1295 (br shoulder), 1280 (s, sh); 1265 (s, sh); 1220 (m, sh); 1180 (m, sh); 1120 (s, br); 1060 (s, sh); 1040 (s, sh); 1010 (m, sh); 1000 (m, sh); 970 (m, sh); 918 (w, sh); 900 (w, sh); 850 (w, br); 822 (w, br); 760 (m, sh); 738 (m, sh); 705 (s, sh); 660 (s, sh).

H **2-Benzoylmethyl-1-(2-dimethoxyphosphorylethyl)pyrrolidine [114] and 4-phenyl-3-dimethoxyphosphoryl-1-azabicyclo[4.3.0]nonan-4-ol [133]**



[114]



[133]

(*E*)-2-Benzoylmethylene-1-(2-dimethoxyphosphorylethyl)pyrrolidine [113] (0.115g; 0.356mmol) was dissolved in absolute ethanol (1.01ml) to make up a 0.4M solution. Sodium cyanoborohydride (0.0306g; 0.487mmol) 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, under an atmosphere of nitrogen. Water (32ml) was added, and the solution was made basic with concentrated NH_3 (25%). The aqueous phase was extracted with dichloromethane (2X50ml) and the organic extracts dried ($MgSO_4$) and evaporated *In vacuo* to give a pale-yellow oil (0.093g). Column chromatography with ethyl acetate-methanol (1:1) as solvent gave a mixture of **2-benzoylmethyl-1-(2-dimethoxyphosphorylethyl)pyrrolidine[114]and4-phenyl-3-dimethoxy-phosphoryl-1-azabicyclo[4.3.0]nonan-4-ol [133]** as a colourless oil, (30.4mg), R_F (ethyl acetate-methanol (1:1)) 0.62.

^{1}H NMR

δ_H. Discernible peaks for compounds **[114]** and **[133]**: 7.94 - 7.99 (2H, m, H-12); 4.54 (br.s, H-a); 3.77 (6H, d, H-a or b. $^3J_{HP}$ = 10.91Hz), 3.75 (6H, d, H-a or b, $^3J_{HP}$ = 10.63Hz) 3.74 (6H, d, H-a or b, $^3J_{HP}$ = 10.95Hz), 3.72 (6H, d, H-a or b, $^3J_{HP}$ = 10.84Hz); 2.20 (2H, qu, H-4, $^3J_{HH}$ = 8.54Hz).

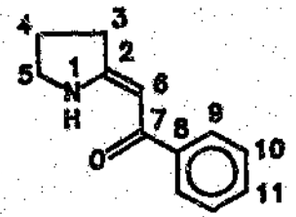
^{13}C NMR

δ_C for compound **[114]**: 199.26 (s, C-10); 137.06 (s, C-11); 133.05 (s, C-14); 128.55 (s, C-13); 128.01 (s, C-12); 60.16 (s, C-2); 52.87 (s, C-5); 52.11 (d, C-8, $^3J_{CP}$ = 6.50Hz); 47.16 (s, C-6); 43.68 (s, C-9); 31.28 (s, C-3); 24.26 (d, C-7, $^1J_{CP}$ = 138.73Hz); 22.34 (s, C-4).

δ_C for compound **[133]**: 128.20; 128.16; 126.99; 126.86; 125.55; 125.43; 73.78; 71.03; 64.59; 63.12; 53.34; 52.41; 52.28; 49.32; 47.62; 43.32; 38.77; 30.14; 28.37; 23.58; 23.40; 22.99; 22.75.

^{31}P NMR: Singlets at 32.52ppm and 32.71ppm are due to **[133]**, while the singlet at 33.59ppm is due to **[114]**.(The ratio of **[114]** to **[133]** is approximately 2:1, as estimated from the NMR spectrum).

(*Z*)-2-Benzoylmethylenepyrrolidine [92]



[92]

Potassium tertiary butoxide (54.5mg; 0.486mmol) was added with stirring to a solution of 2-benzoylmethyl-1-(2-phenylsulphonylethyl)pyrrolidine **[102]** and (*E*)-benzoylmethylene-1-(2-phenylsulphonylethyl)pyrrolidine **[111]** (75.1mg) in dry THF (10ml). The mixture was stirred under nitrogen at room temperature for 45hrs and then heated under reflux for 21.5hrs. Water was added to destroy unreacted potassium tertiary butoxide. The aqueous phase was extracted with dichloromethane (2x25ml) and the organic extracts dried ($MgSO_4$) and evaporated *in vacuo* to give a brown solid. Column chromatography with ethyl acetate as solvent gave **(*Z*)-2-benzoylmethylene-pyrrolidine [92]** (14.8mg, 0.080mmol) and **1-(2-phenylsulphonylethyl)pyrrolid-2-one [129]** (4.41mg; 0.0174mmol), R_F (ethyl acetate) 0.18. (For characterisation of **[129]** see page 119).

Compound **[92]** was obtained as cream-coloured cubes, mp 115.5-117.5°C[65h], R_F (ethyl acetate) 0.68.

Found: C, 76.70; H, 6.95; N, 7.49%.

$C_{12}H_{13}NO$ requires C, 76.98; H, 7.00; N, 7.48%[65h].

^1H NMR

δ_H 10.28 (1H, br s, H-1); 7.85 - 7.90 (2H, m, H-9); 7.38 - 7.42 (3H, m, H-10 + H-11); 5.81 (1H, s, H-6); 3.66 (2H, t, $^3J_{HH}$ = 7.04Hz, H-5); 2.74 (2H, t, $^3J_{HH}$ = 7.82Hz, H-3); 2.05 (2H, qu, $^3J_{HH}$ = 7.50Hz, H-4).

^{13}C NMR

δ_C 187.97 (C-7); 169.24 (C-2); 140.25 (C-8); 130.39 (C-11); 128.09 (C-10); 126.93 (C-9); 86.47 (C-6); 47.69 (C-5); 32.85 (C-3); 21.32 (C-4).

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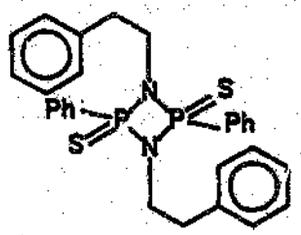
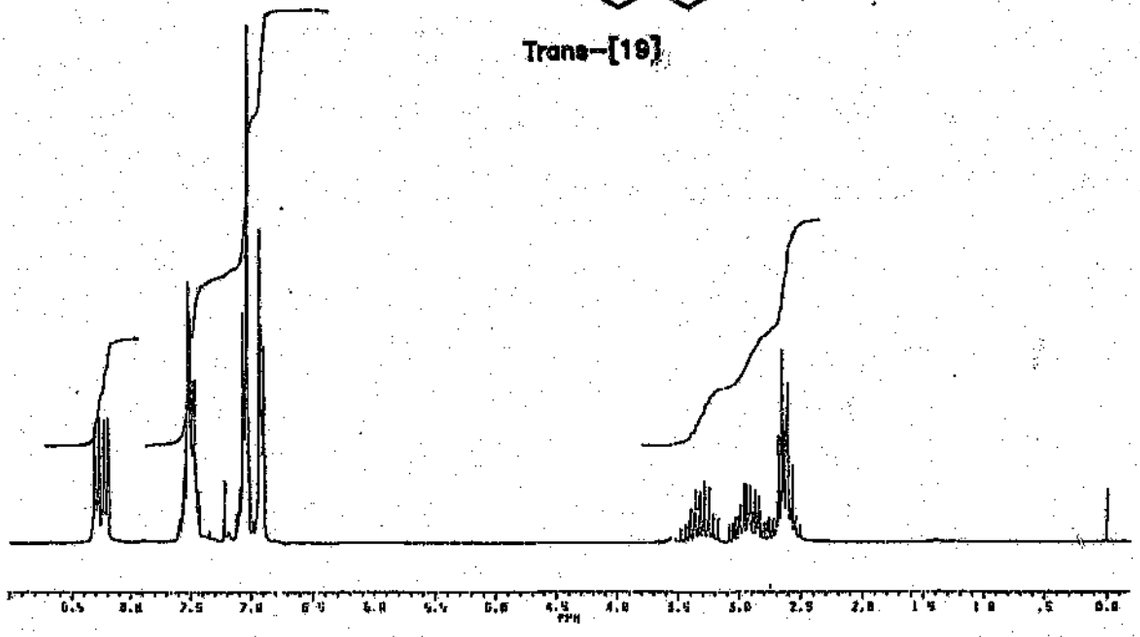
APPENDIX: NMR SPECTRA

^{1}H NMR, ^{13}C NMR, ^{1}H-^{13}C CORRELATED and other relevant spectra of selected compounds have been included in this appendix. Chemical shifts are reported on a δ scale (ppm) relative to tetramethylsilane (TMS). All NMR spectra were recorded in *deuteriochloroform, unless otherwise specified.*

SPECTRUM	COMPOUND NAME AND NUMBER	PAGE
^{1}H-19, ^{13}C-19, CORR-19, DEPT-19, ^{1}H EXPAN-19	2-Ethoxycarbonylmethyl-1-(2-phenyl-sulphonylethyl)pyrrolidine [101]	162,163
^{1}H-20, ^{13}C-20, ^{31}P-20	2-Benzoylmethyl-1-(2-dimethoxyphosphoryl-ethyl)pyrrolidine [114] and 4-phenyl-3-dimethoxyphosphoryl-1-azabicyclo[4.3.0]-nonan-4-ol [133]	164
^{1}H-21, ^{13}C-21	(*Z*)-2-Benzoylmethylenepyrrolidine [92]	165



Trans–[19]



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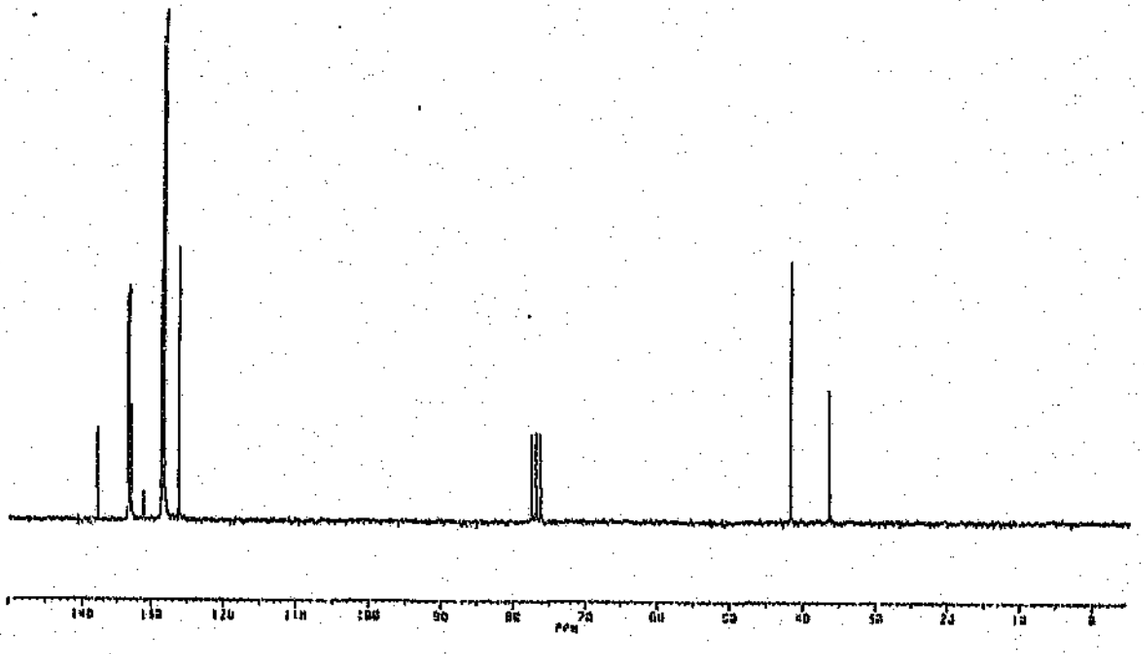

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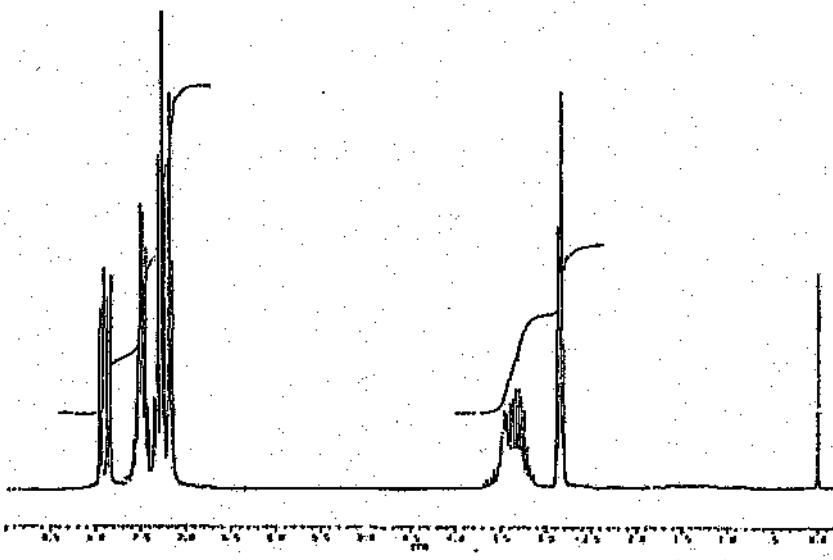

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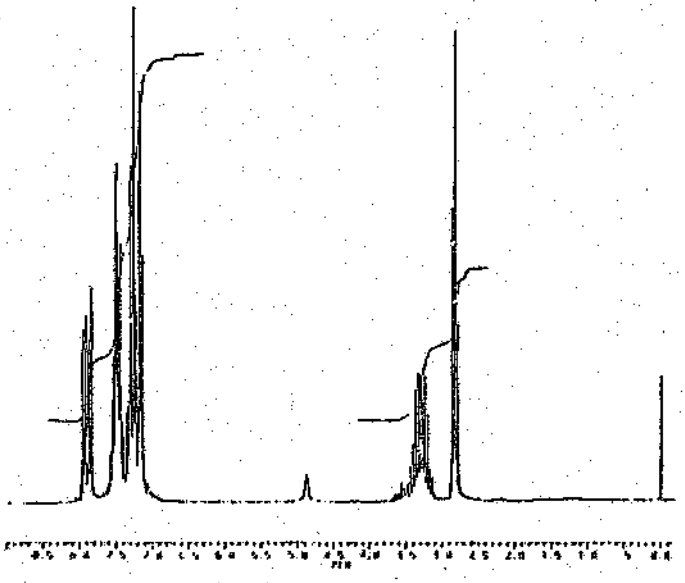

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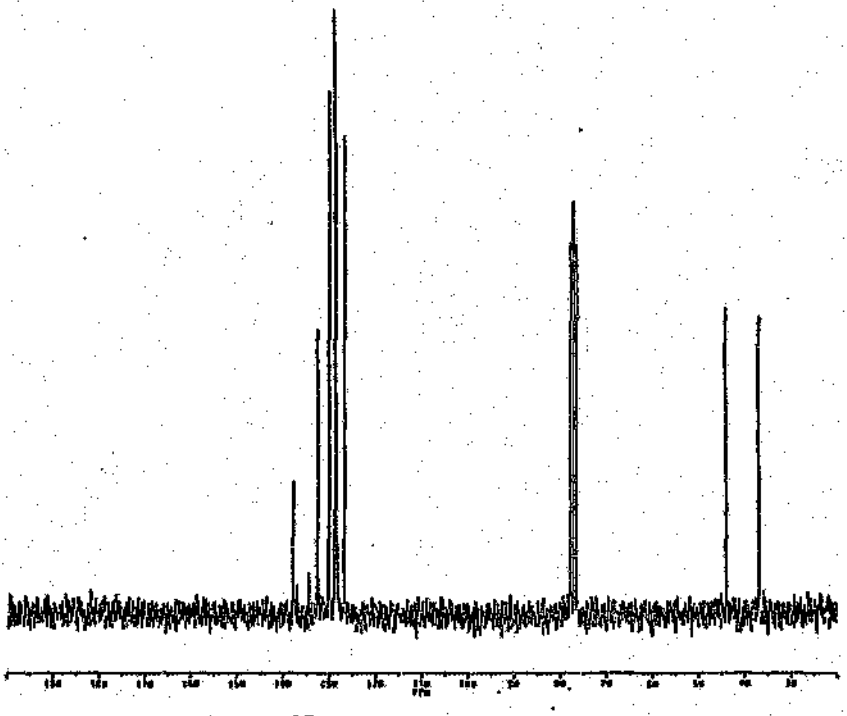

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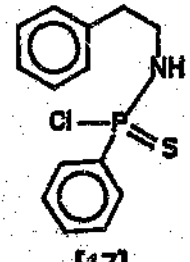

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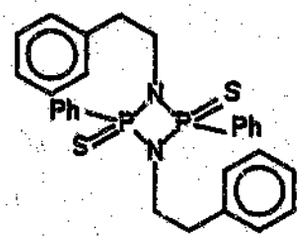

Cis–[19]

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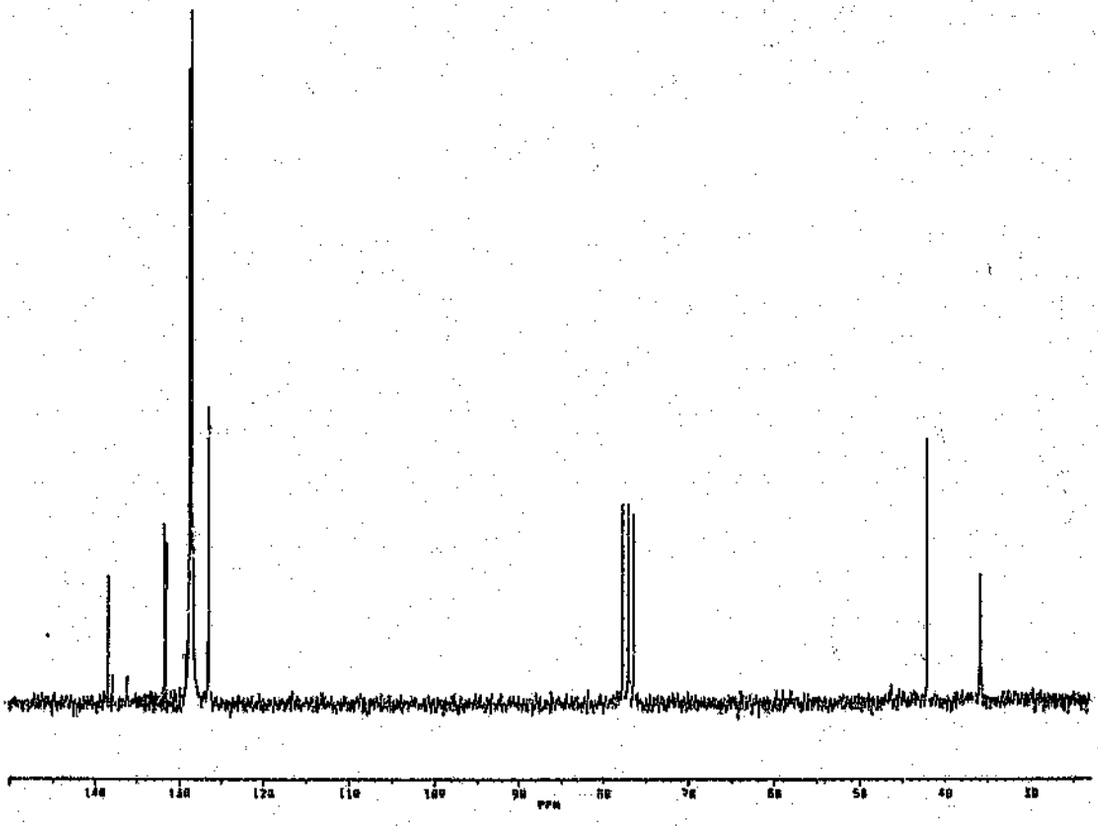

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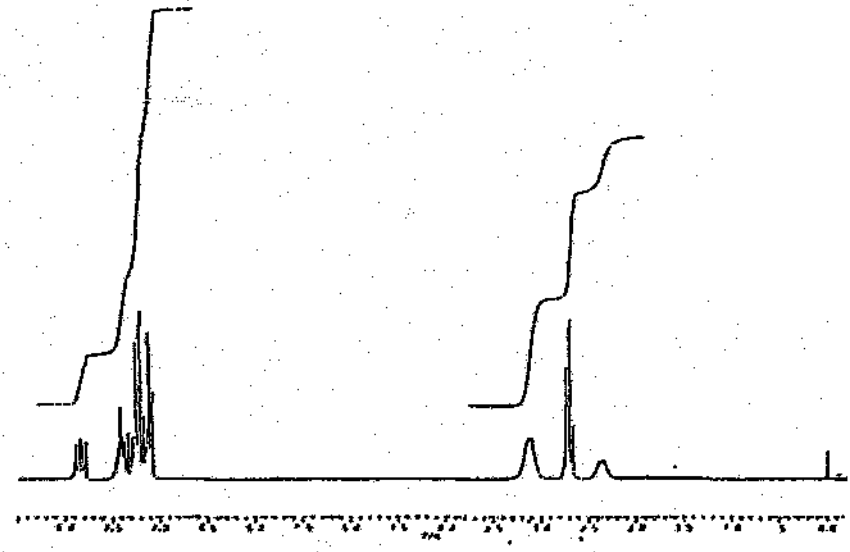

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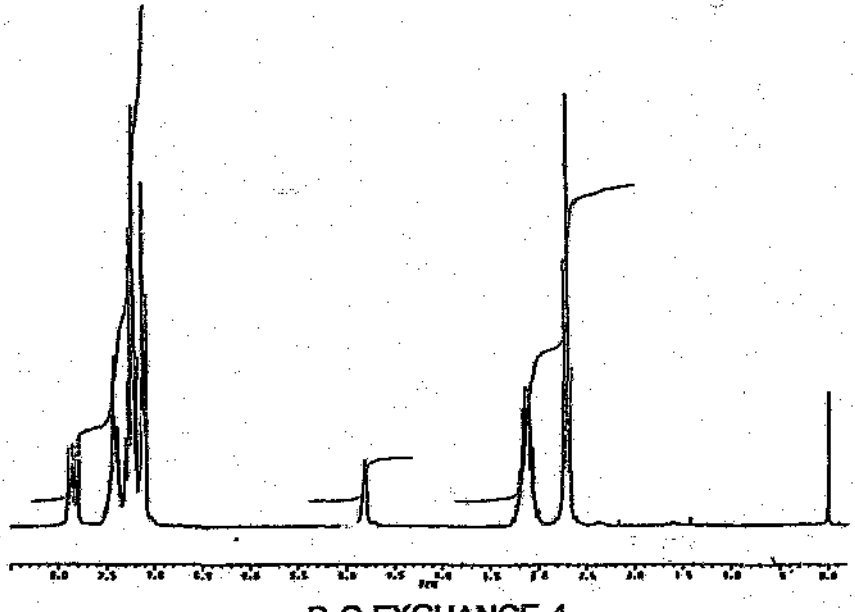

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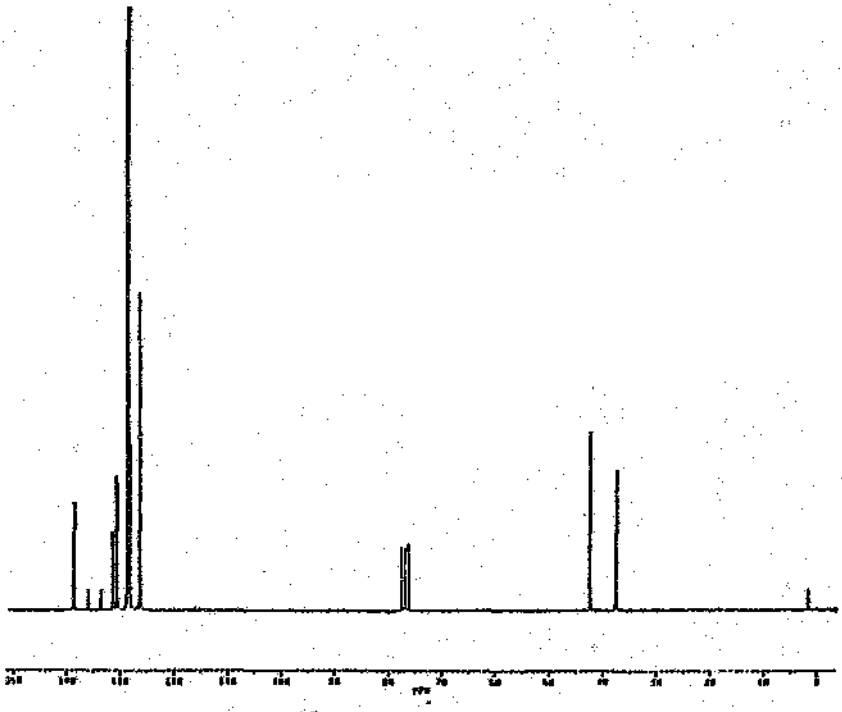

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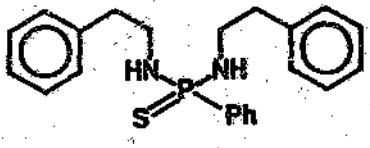

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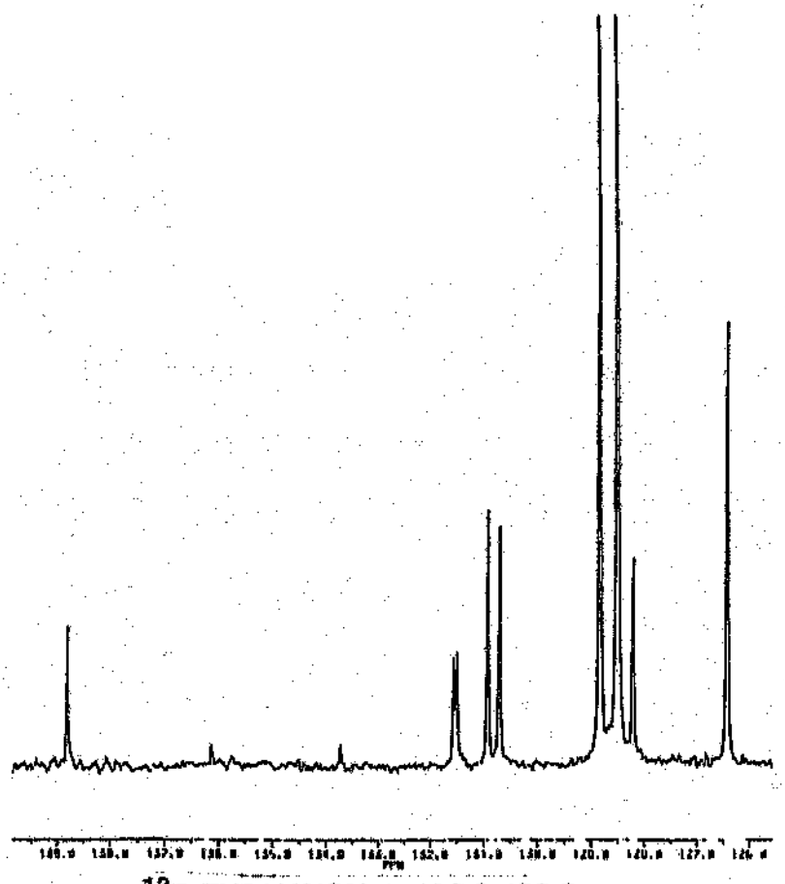

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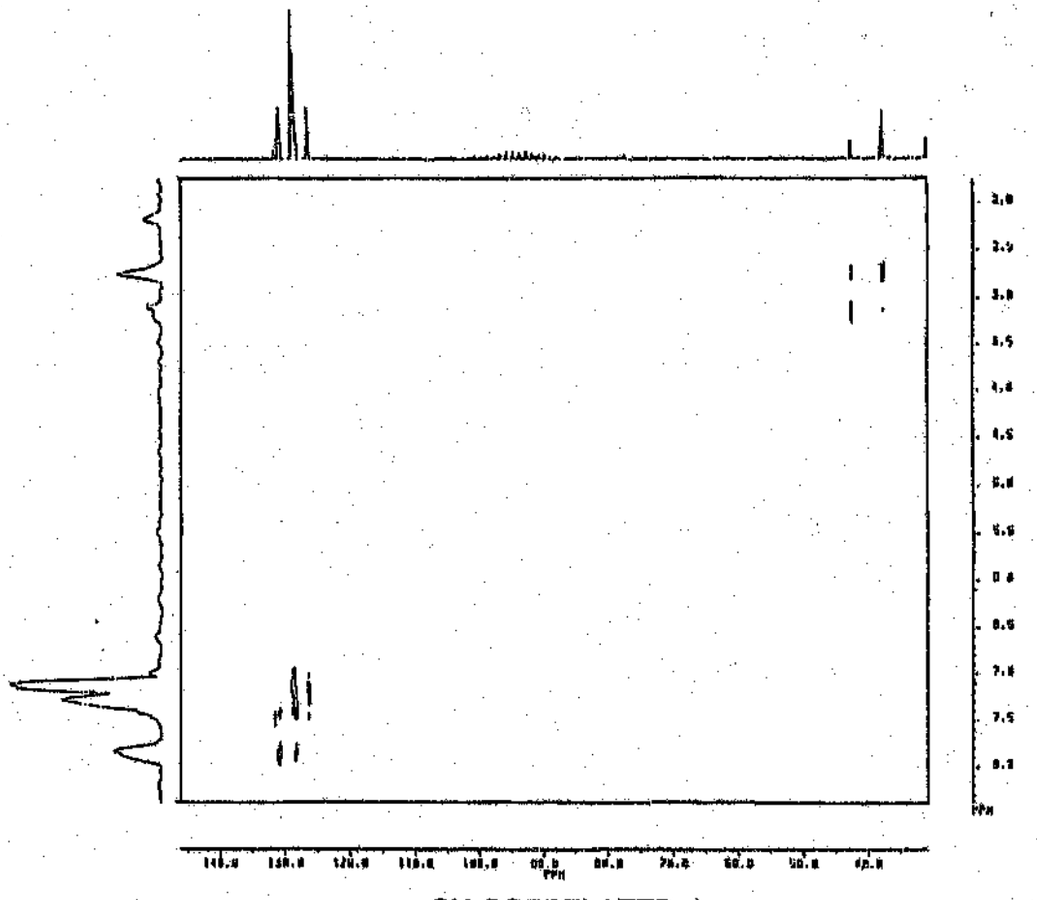
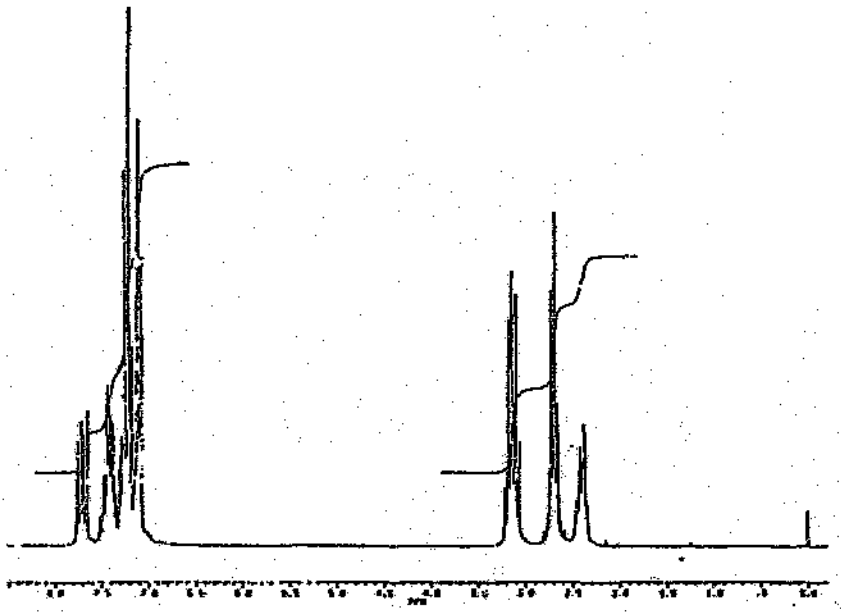


CH-CORRELATED 4



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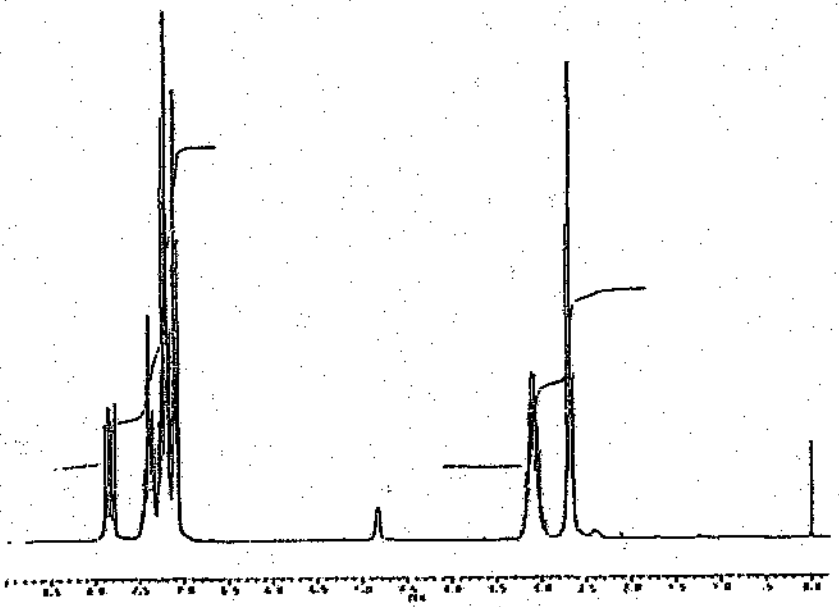

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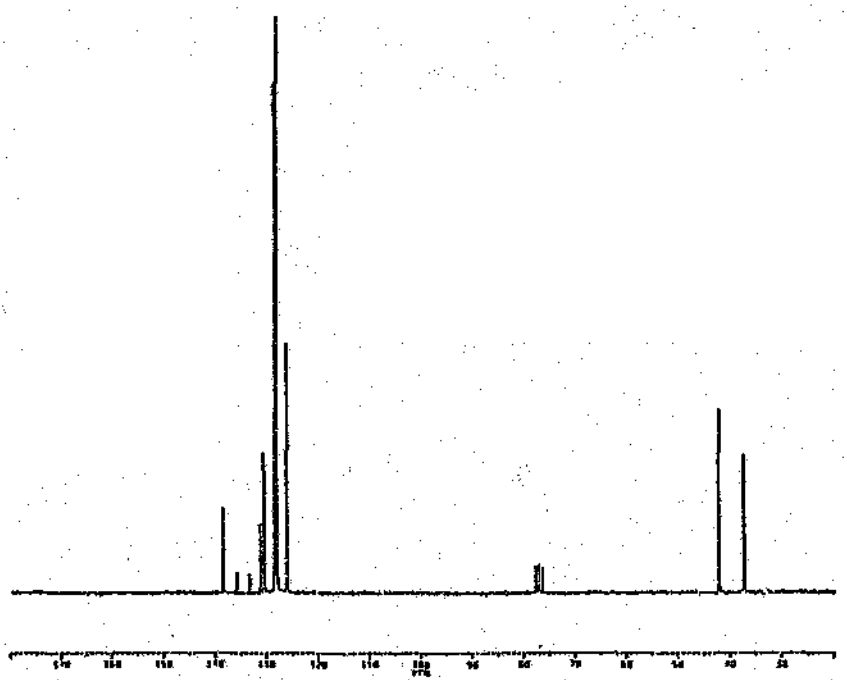

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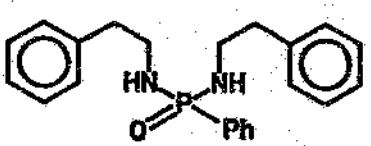

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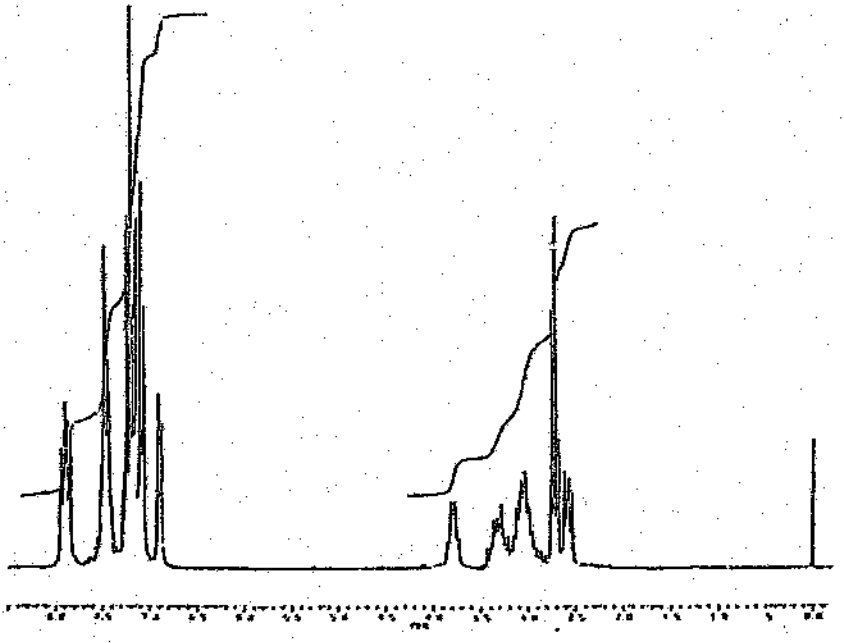

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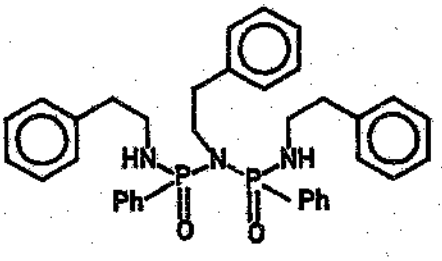

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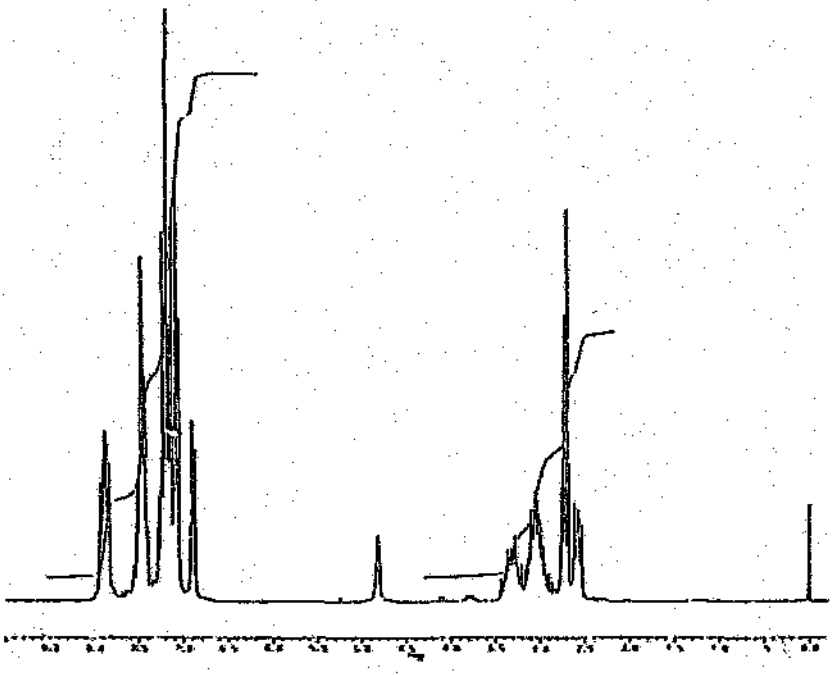
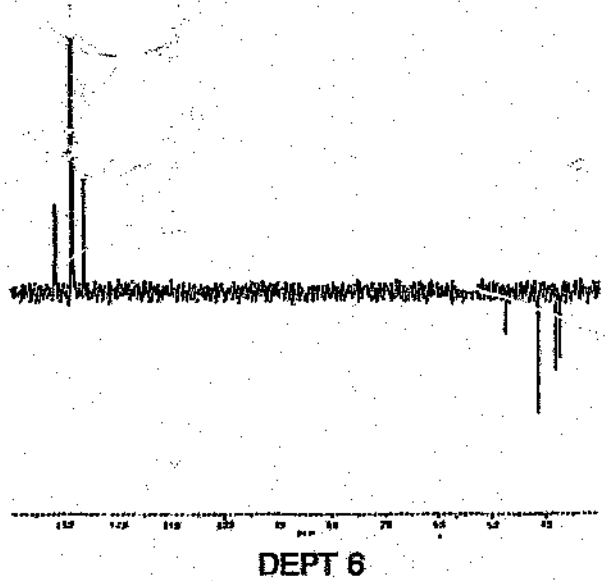
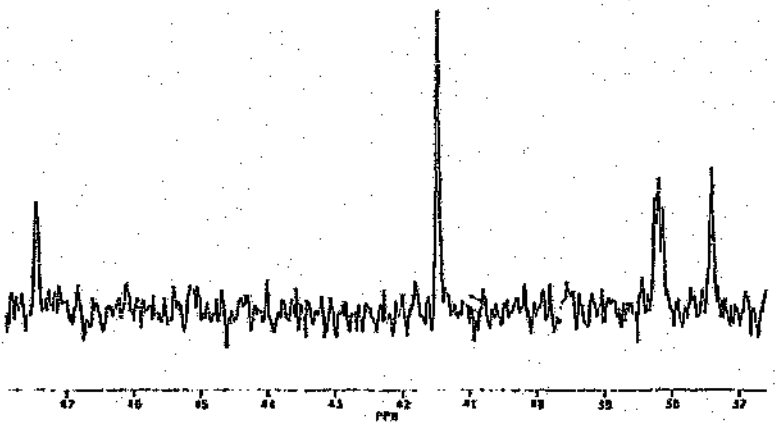


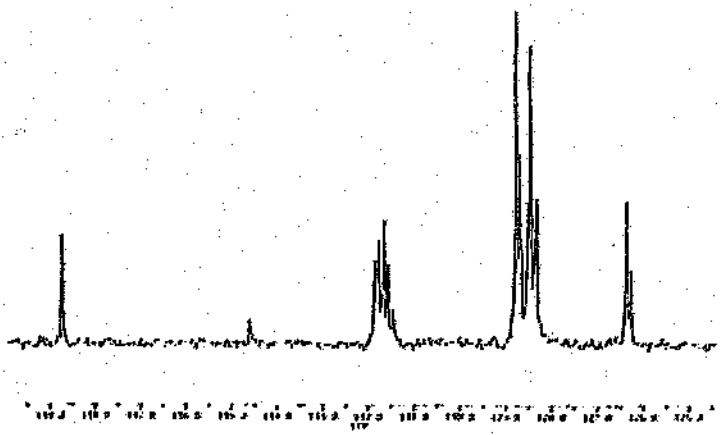
D_2O-EXCHANGE 6



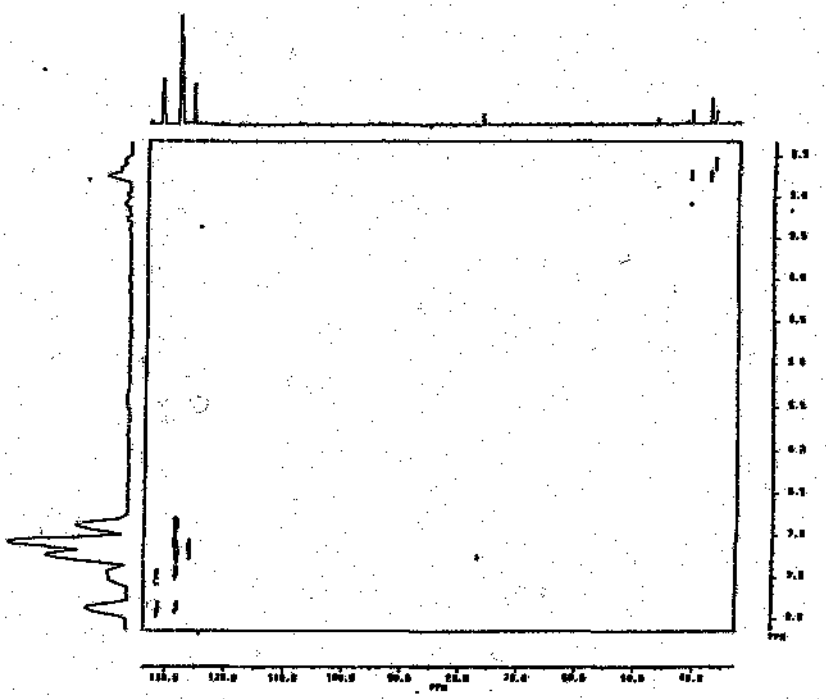
DEPT 6



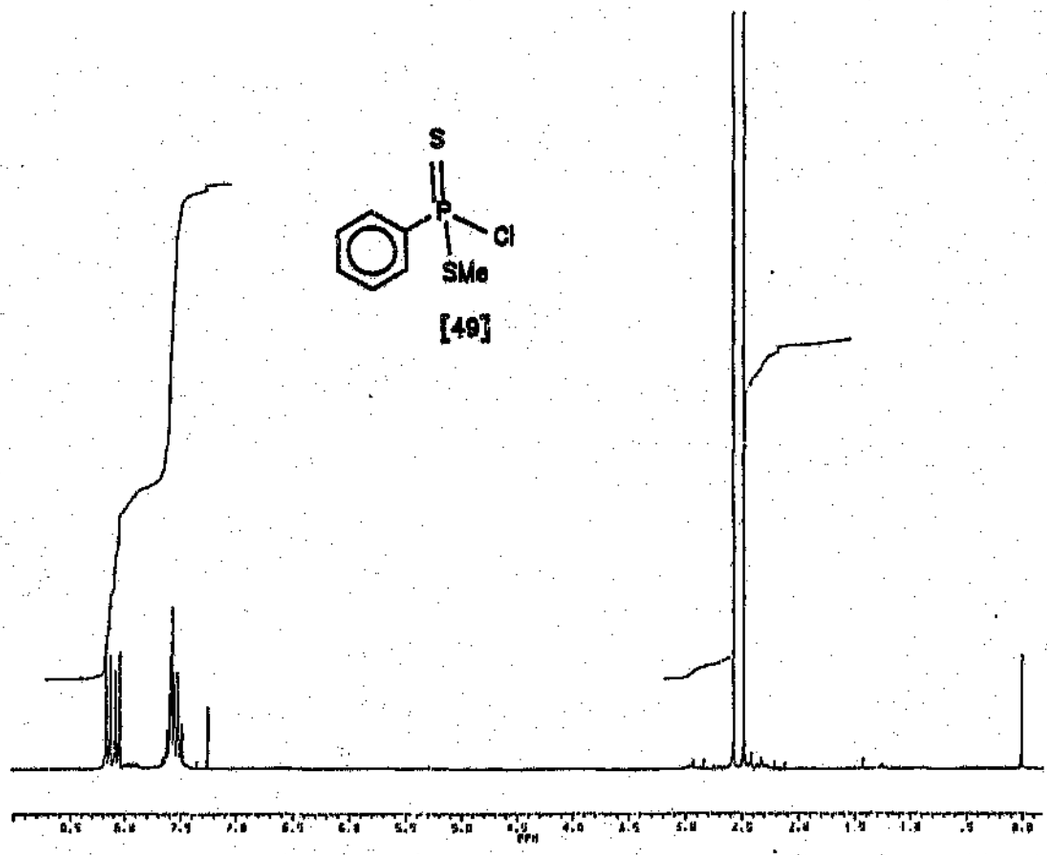
^{13}C-EXPANSION 6, 37-48ppm



^{13}C-EXPANSION 6, 125.0-139.5ppm

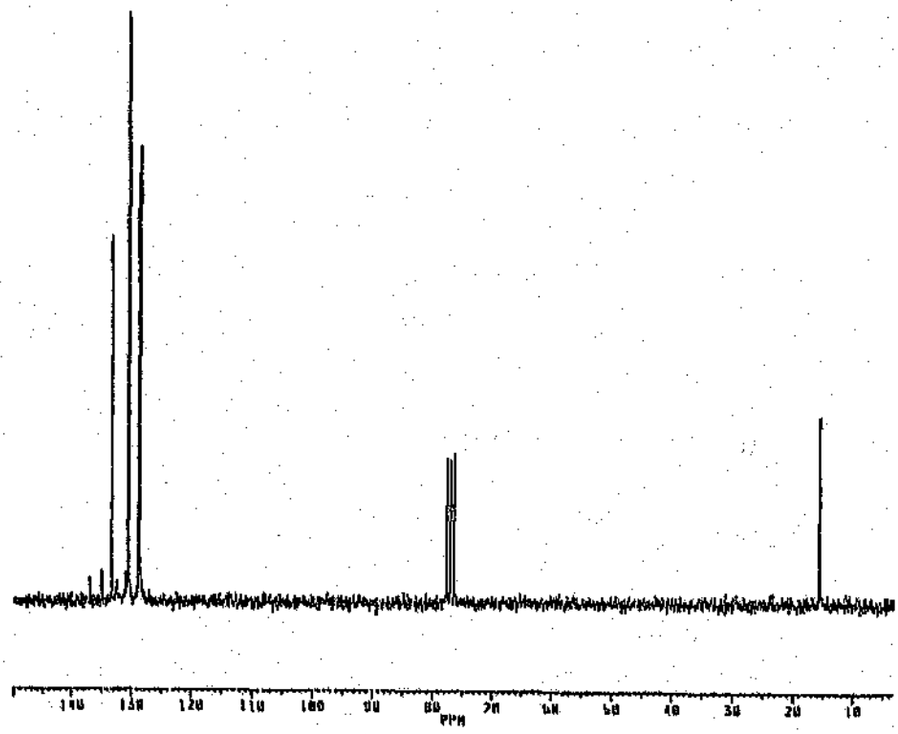


CH-CORRELATED 6

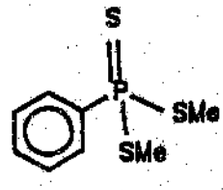


[49]

^{1}H-SPECTRUM 7



^{13}C-SPECTRUM 7



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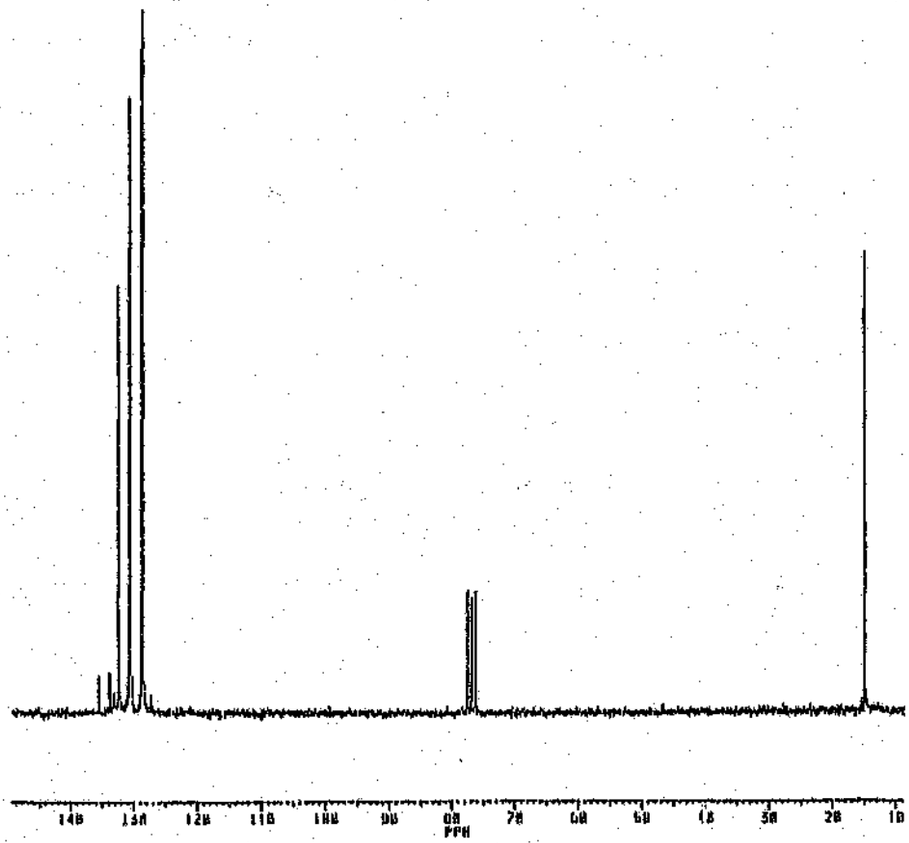
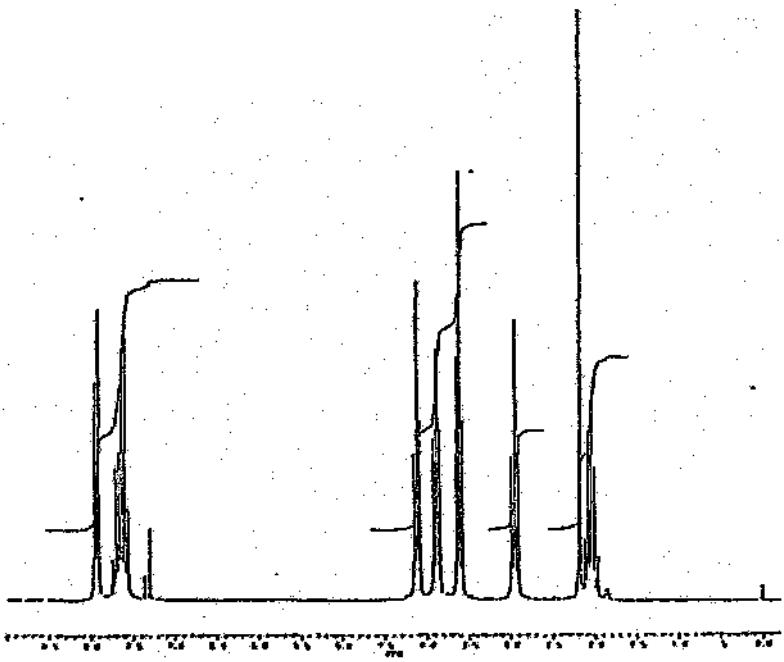
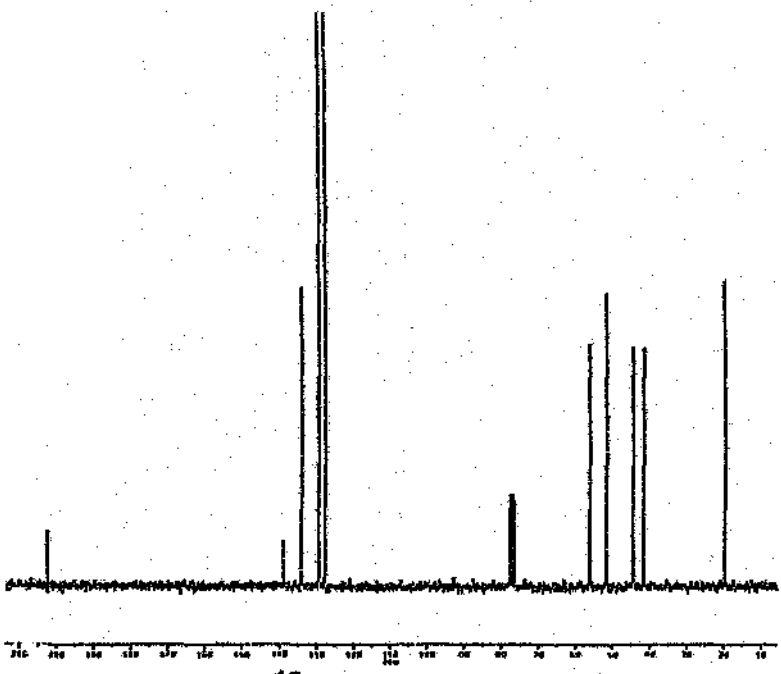
^{1}H-SPECTRUM 8



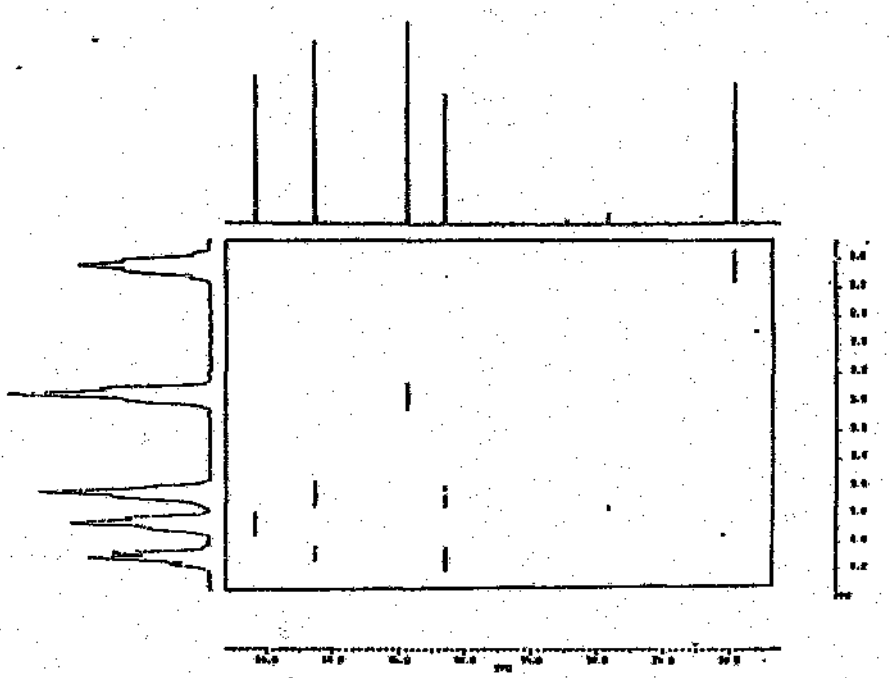
^{13}C-SPECTRUM 8



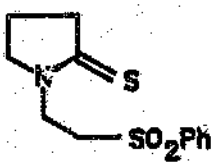
^{1}H-SPECTRUM 9



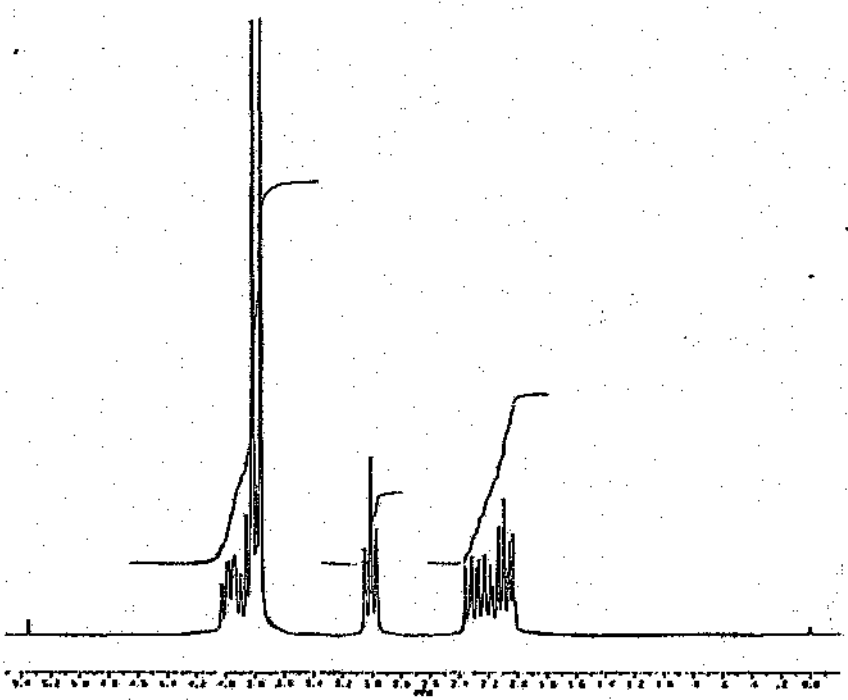
^{13}C-SPECTRUM 9



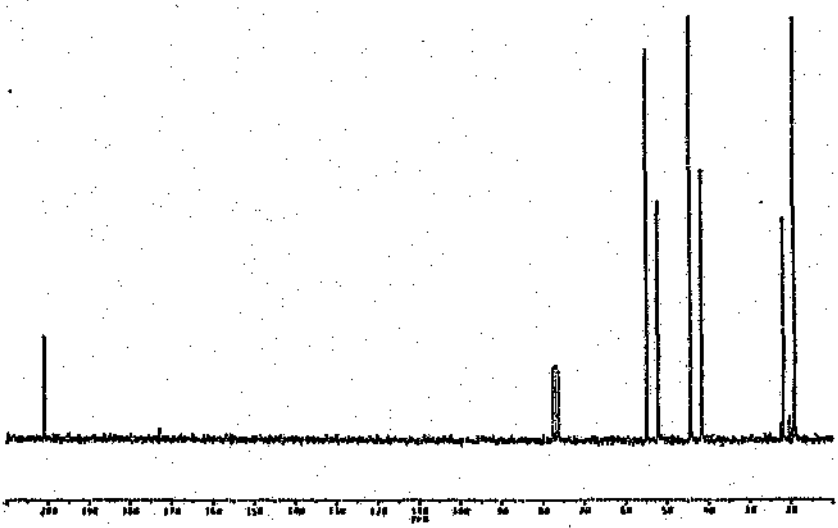
CH-CORRELATED 9



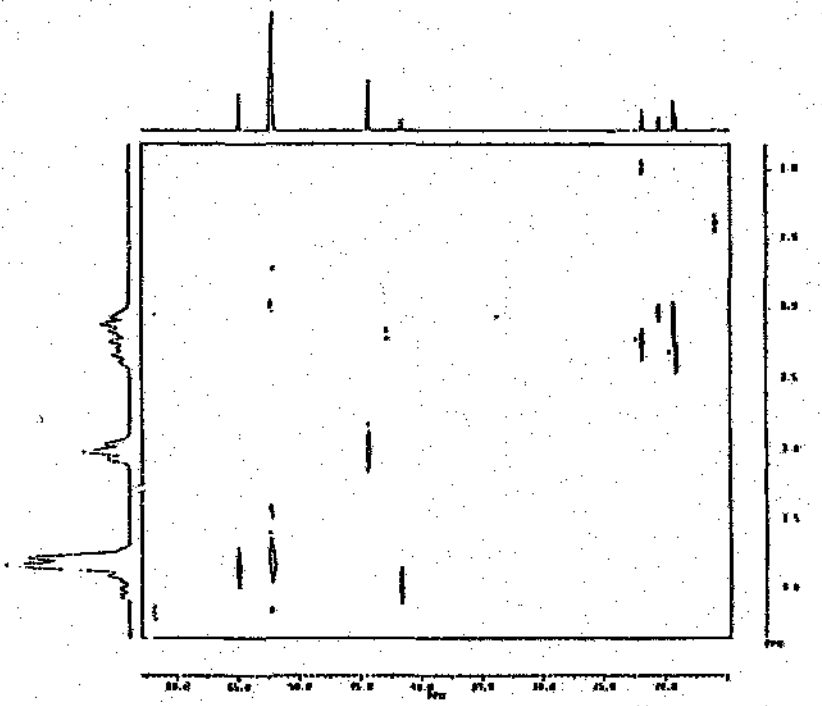
[109]



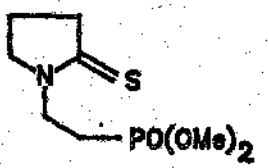
^{1}H-SPECTRUM 10



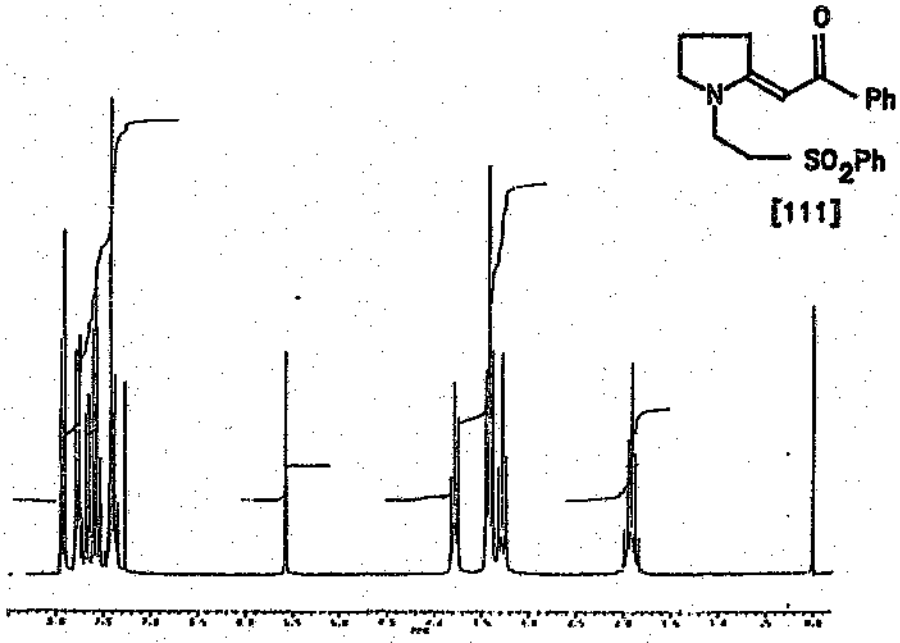
^{13}C-SPECTRUM 10



CH-CORRELATED 10



[110]



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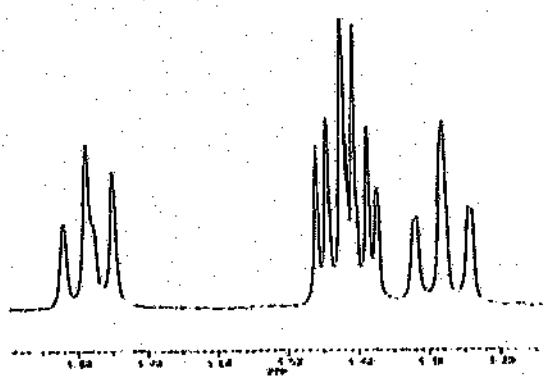
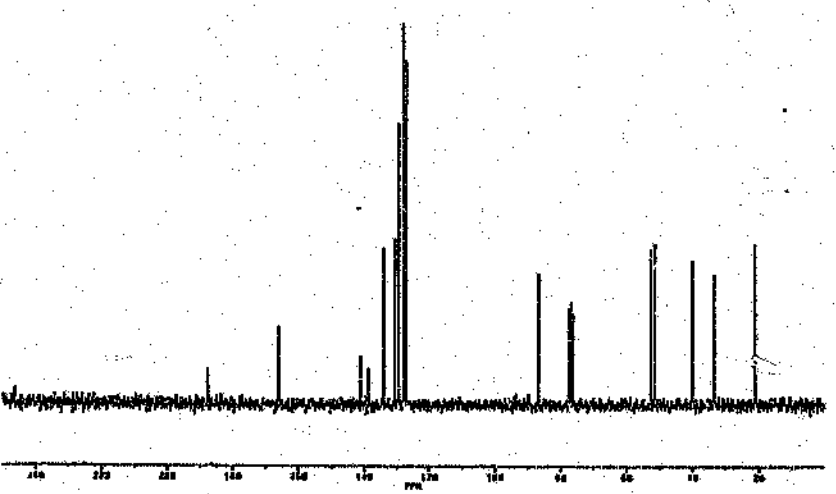
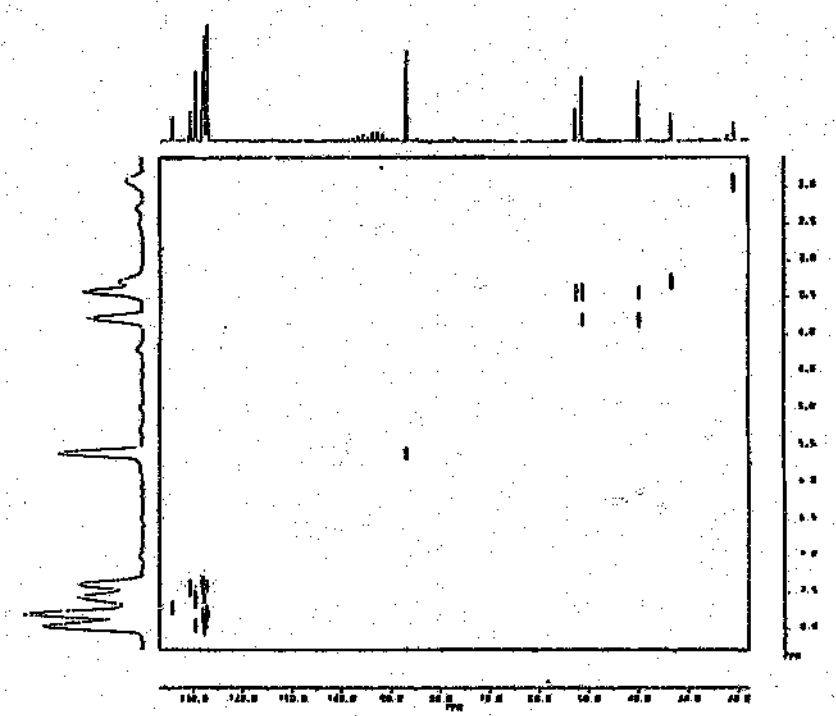
^{1}H-SPECTRUM 11



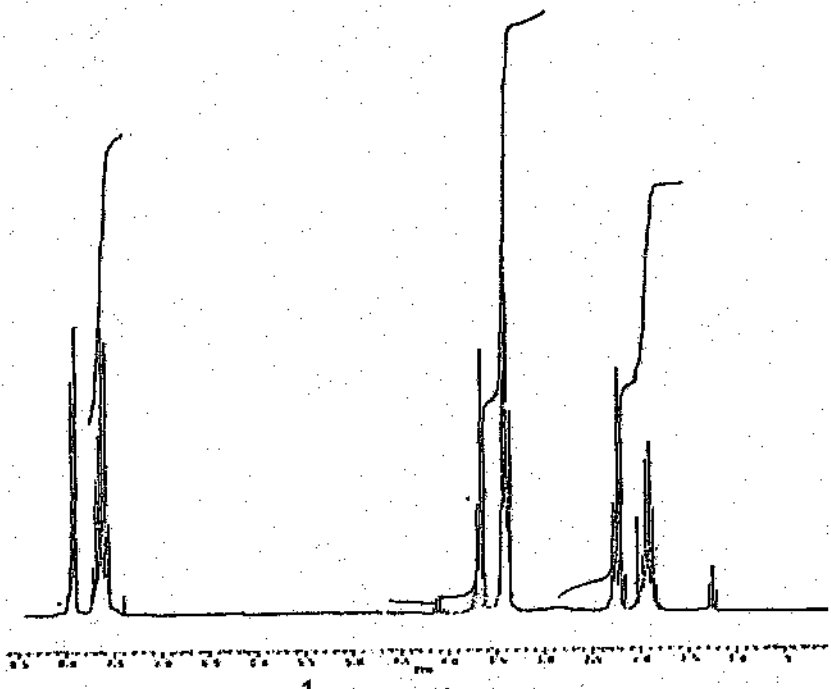
^{1}H-EXPANSION 11, 3.15-3.90ppm



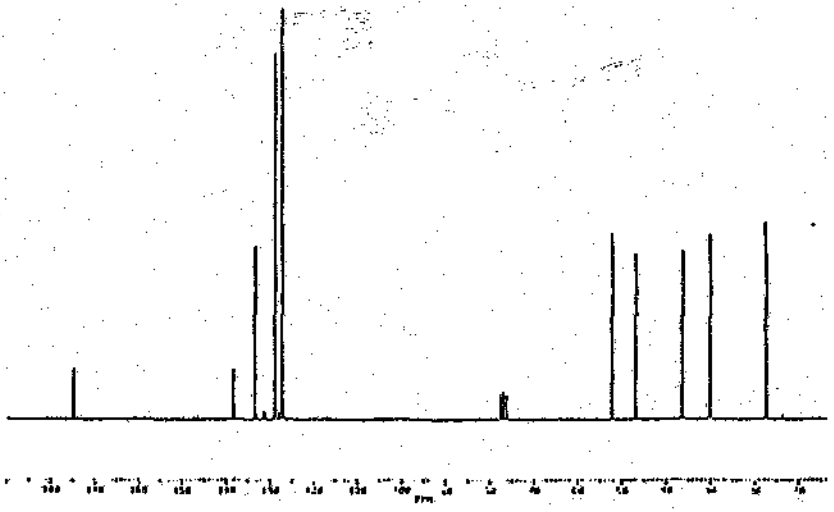
^{13}C-SPECTRUM 11



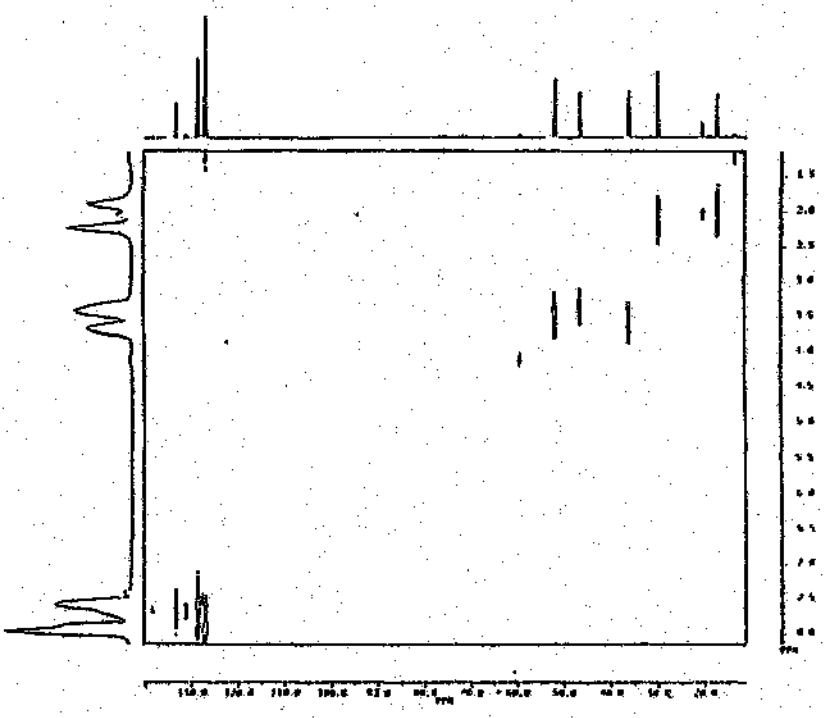
CH-CORRELATED 11



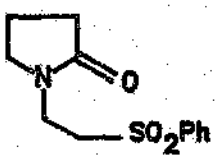
^{1}H-SPECTRUM 12



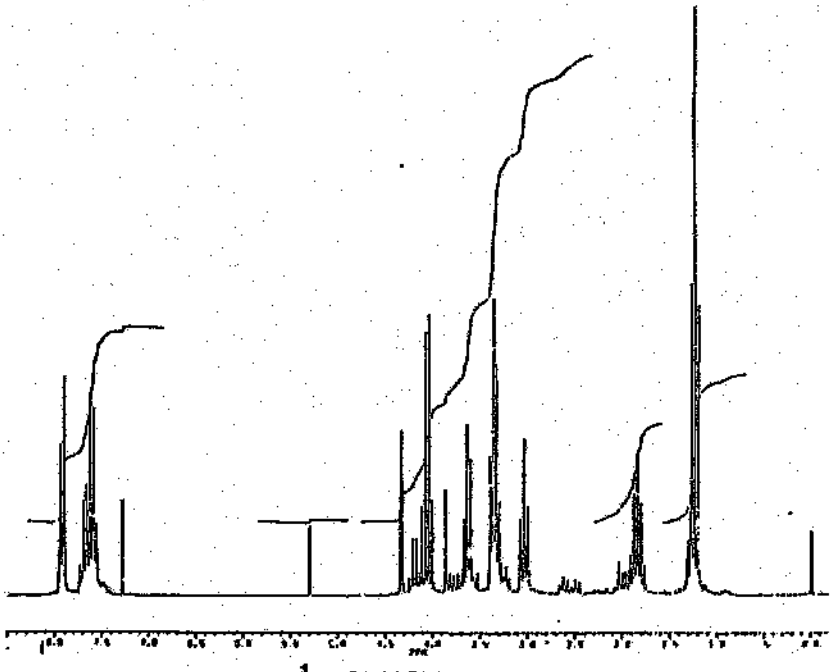
^{13}C-SPECTRUM 12



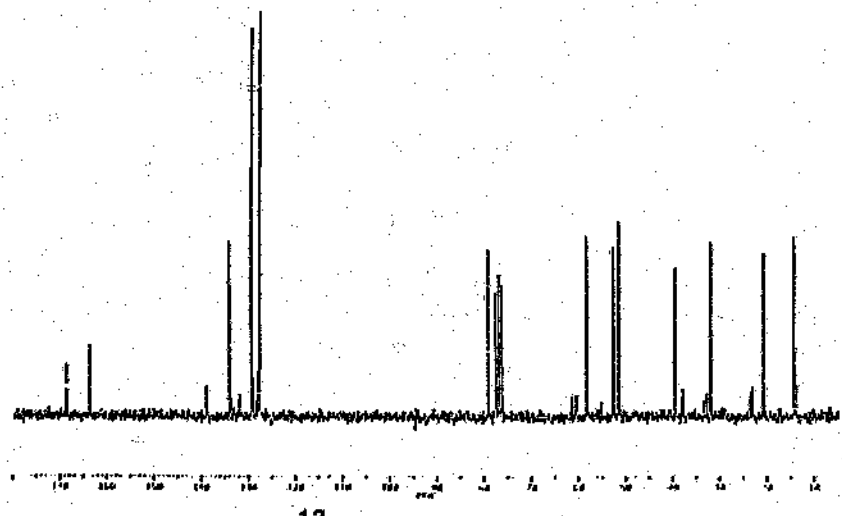
CH-CORRELATED 12



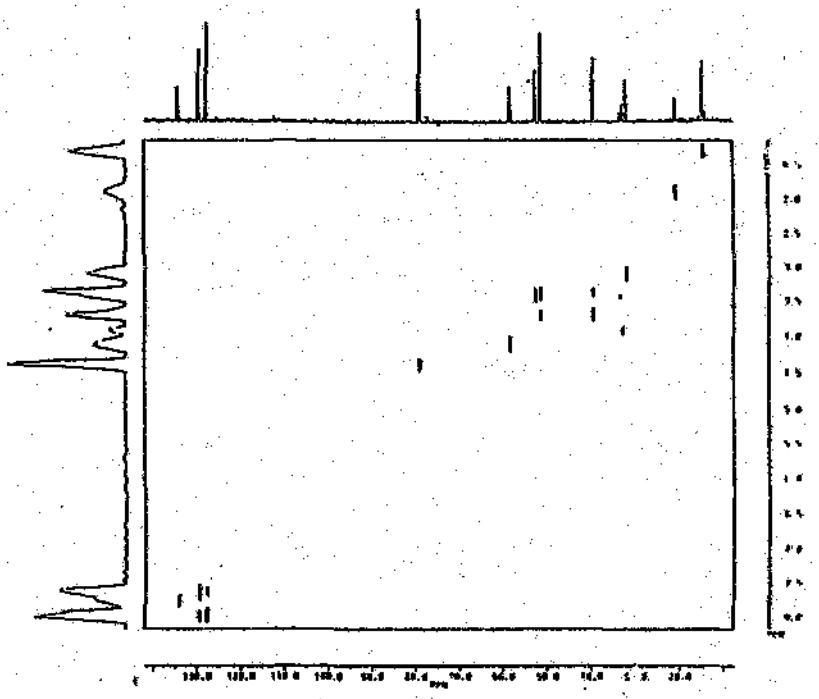
[129]



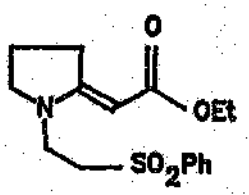
^{1}H-SPECTRUM 13



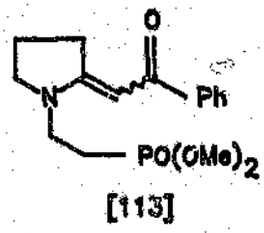
^{13}C-SPECTRUM 13



CH-CORRELATED 13



[112]



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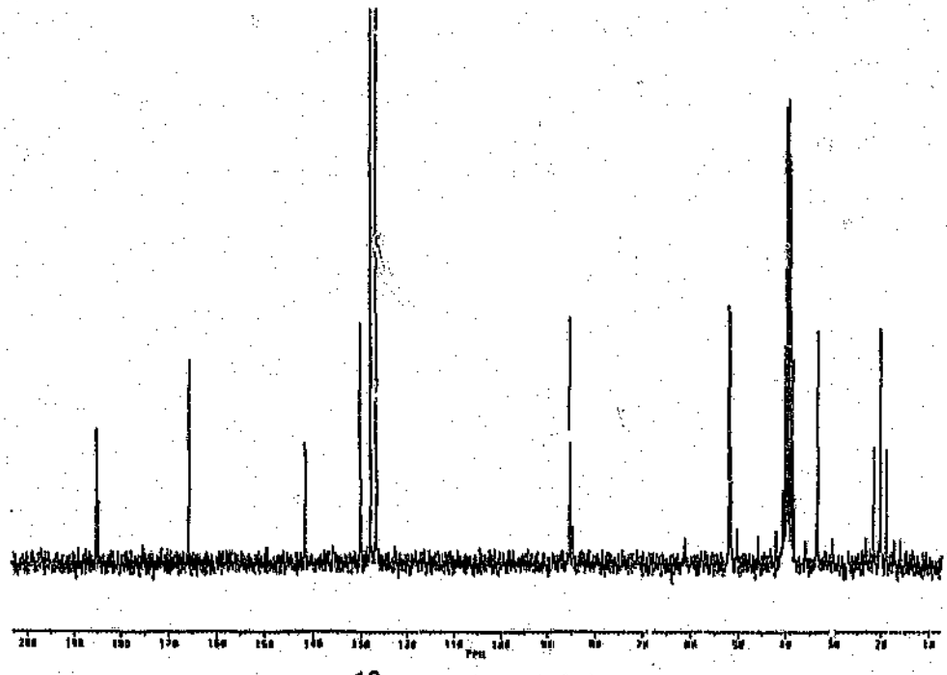
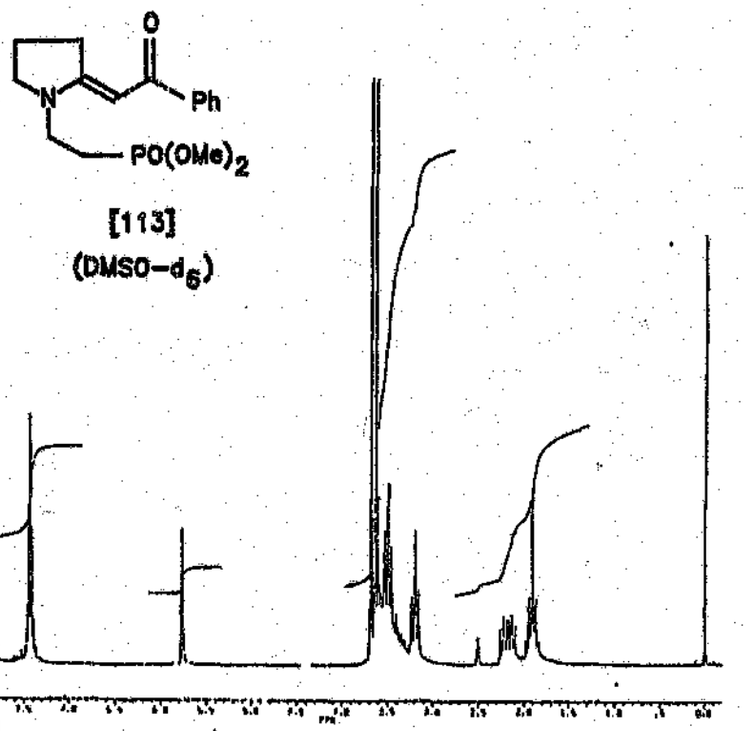
^{1}H-SPECTRUM 14

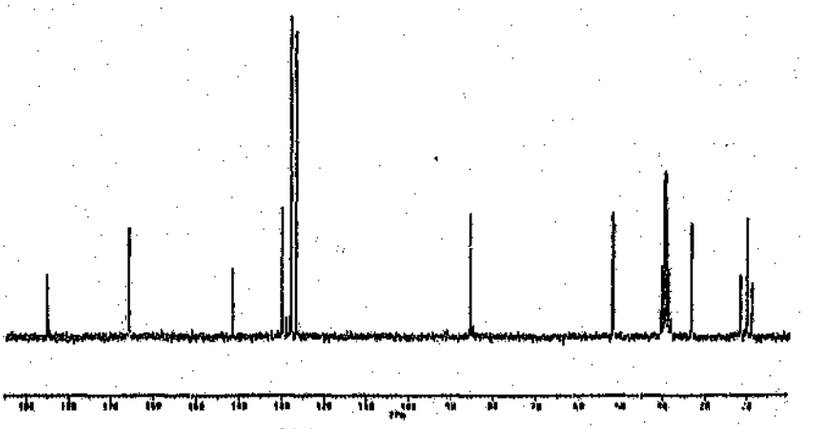


^{13}C-SPECTRUM 14

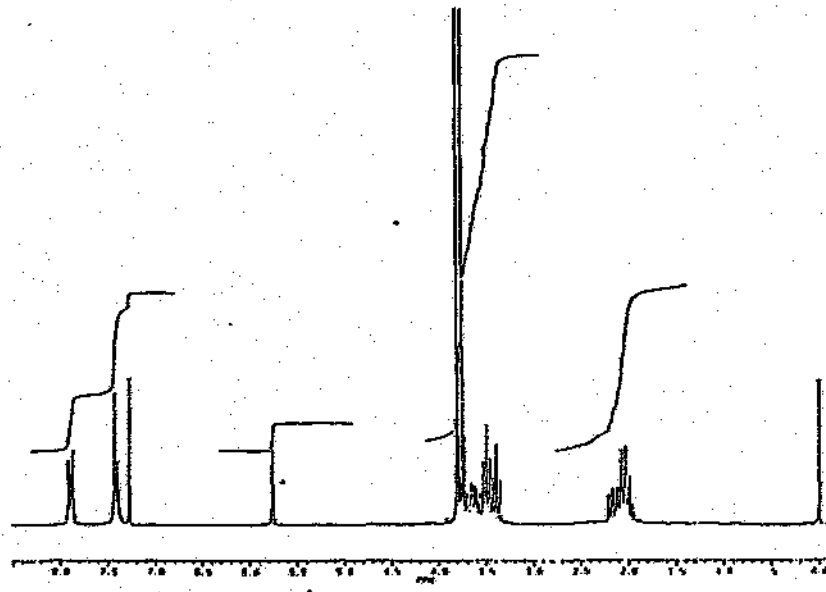


[113]
(DMSO–d_6)

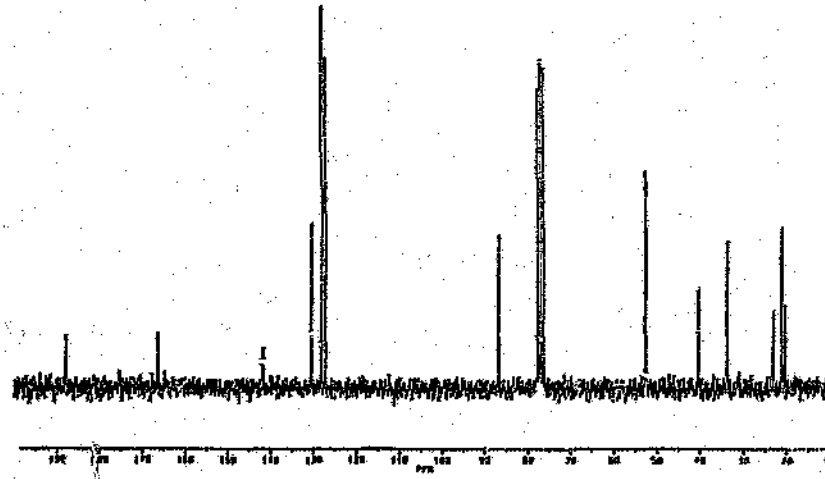
^{1}H-SPECTRUM 15



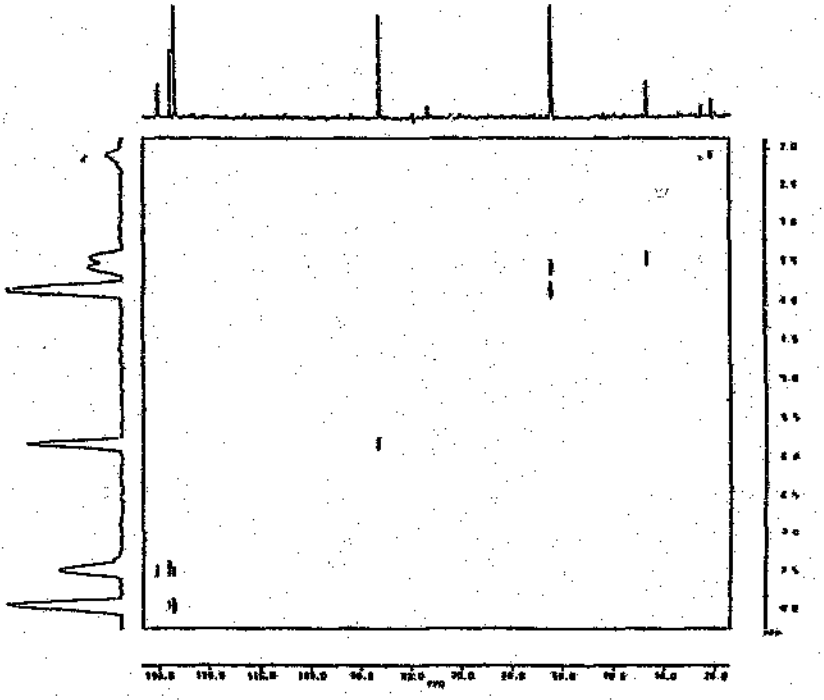
^{13}C-SPECTRUM 15



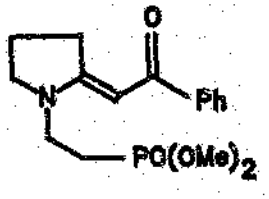
^{1}H-SPECTRUM 16



^{13}C-SPECTRUM 16



CH-CORRELATED 16

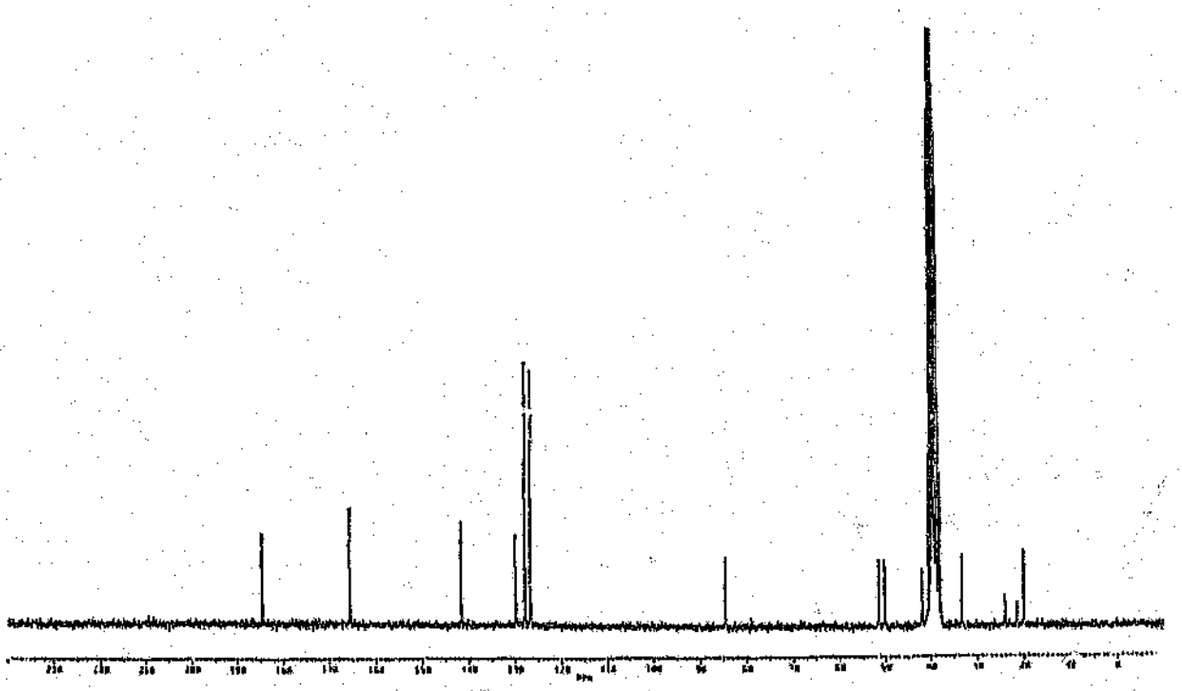


[113]

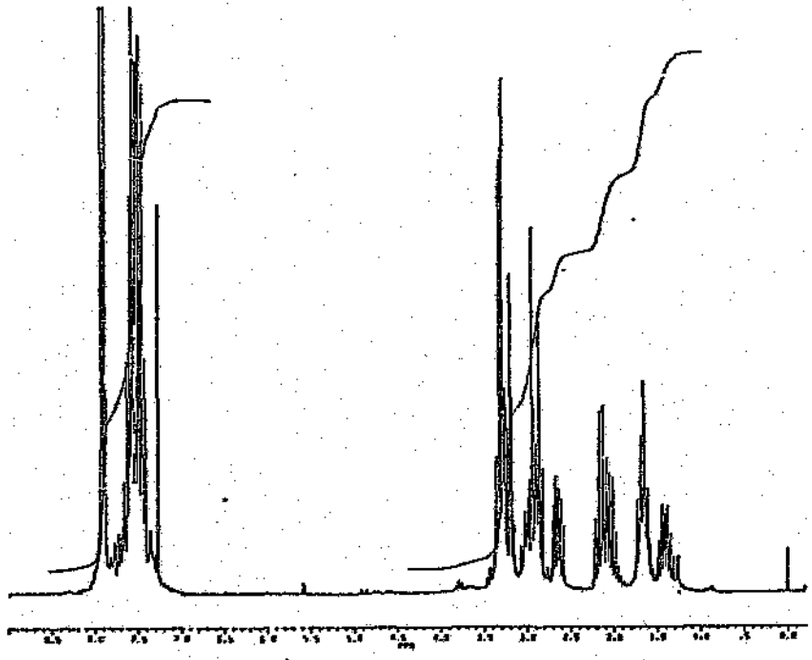
($CDCl_3$)

[113]

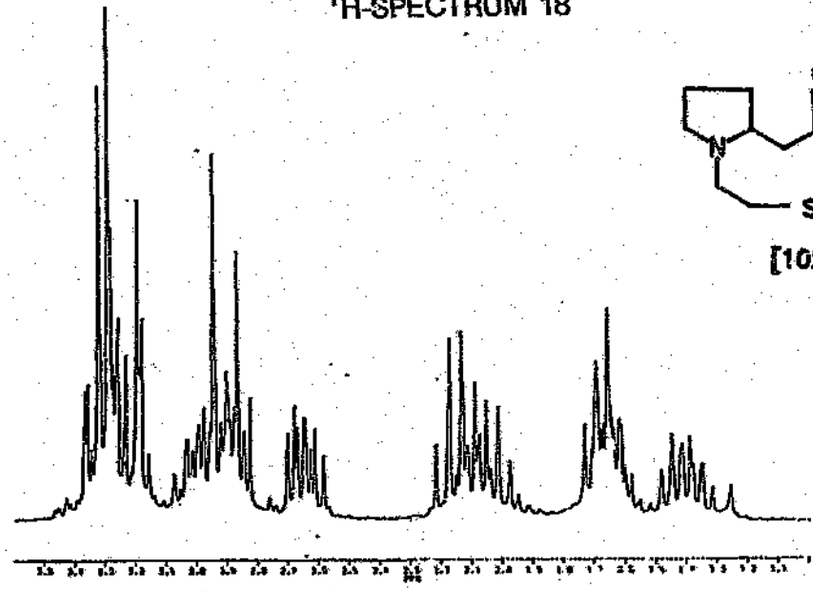
^{1}H-SPECTRUM 17



^{13}C-SPECTRUM 17

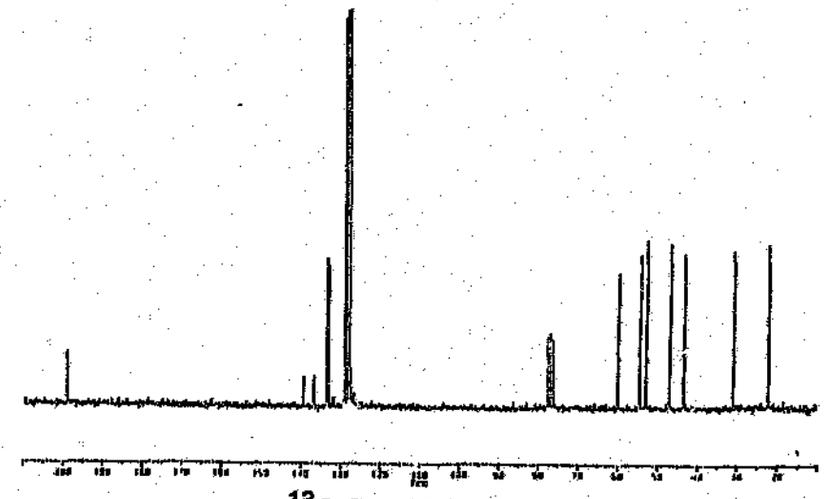


^{1}H-SPECTRUM 18

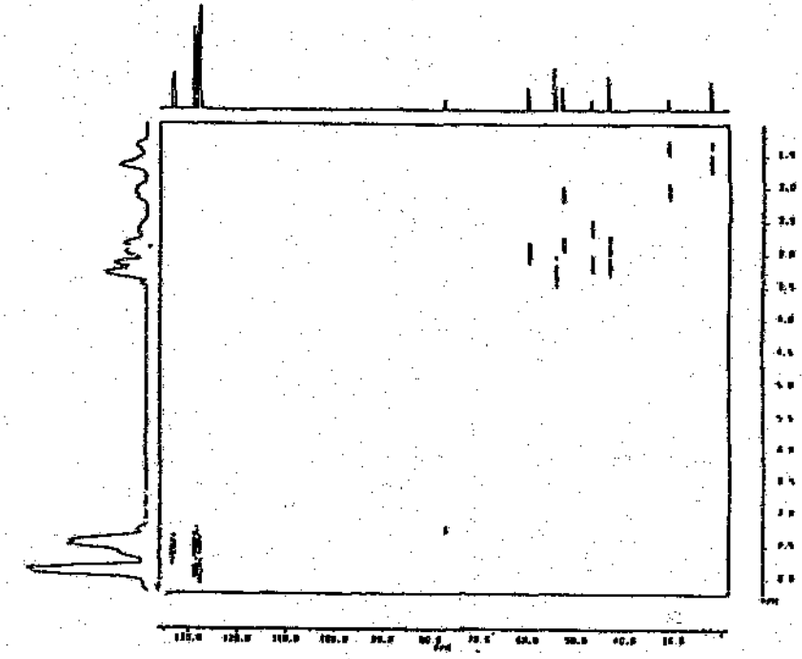


^{1}H-EXPANSION 18, 1.1-3.5ppm

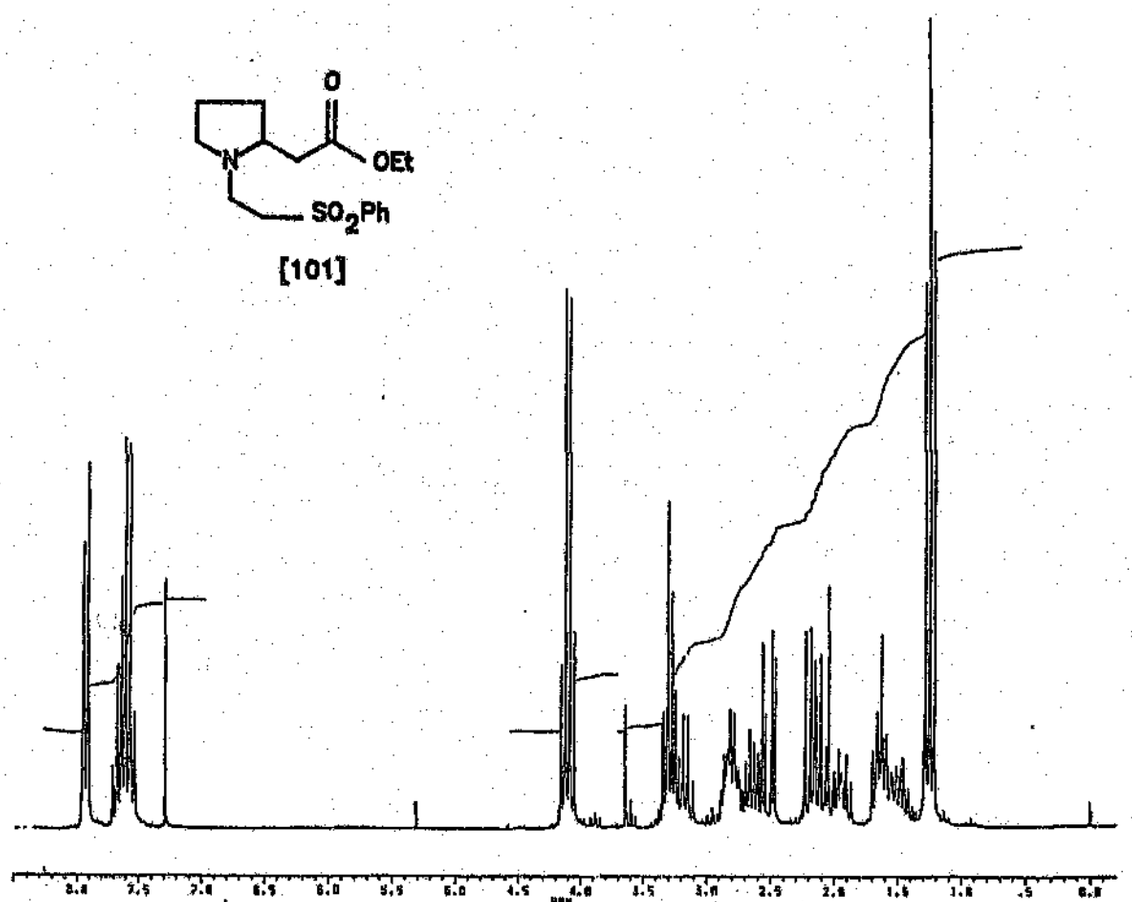
[102]



^{13}C-SPECTRUM 18

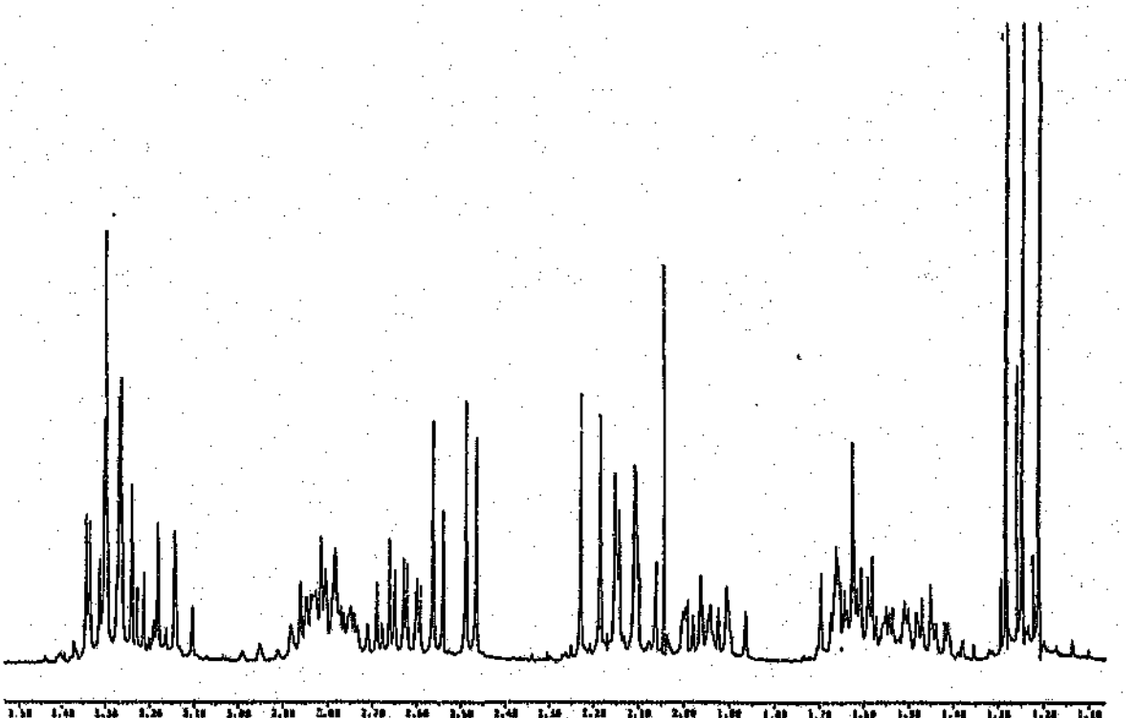


CH-CORRELATED 18

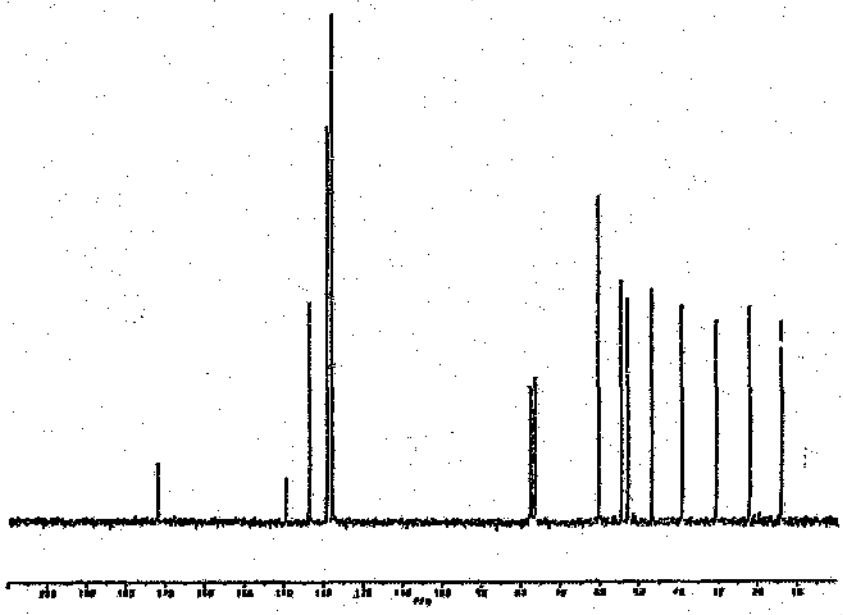


[101]

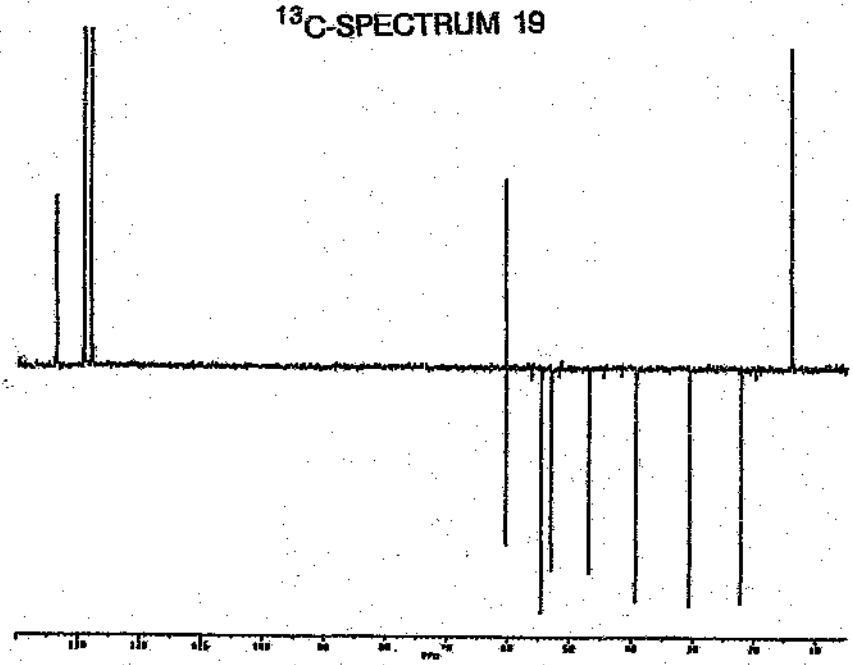
^{1}H-SPECTRUM 19



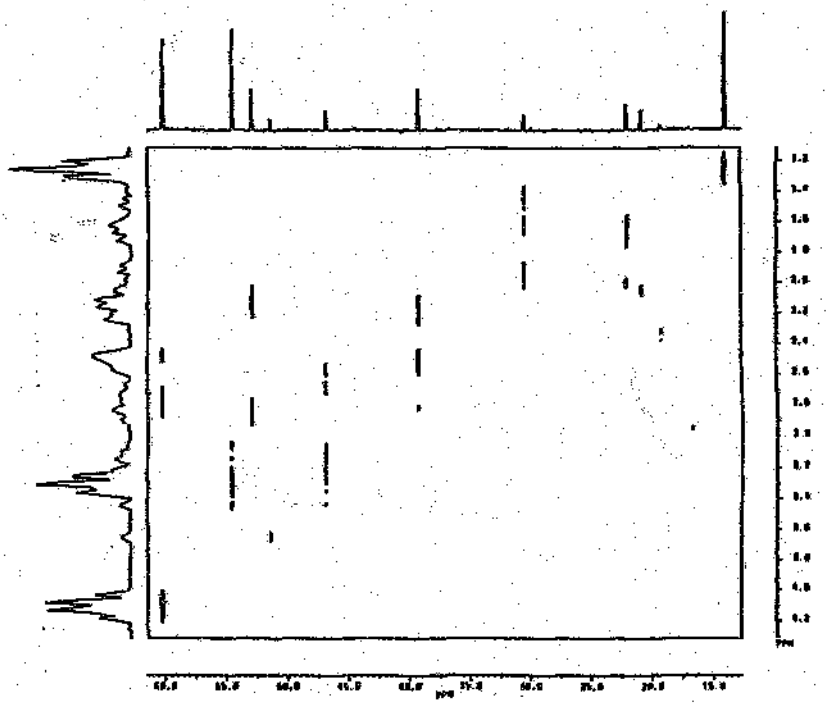
^{1}H-EXPANSION 19, 1.10-3.50ppm



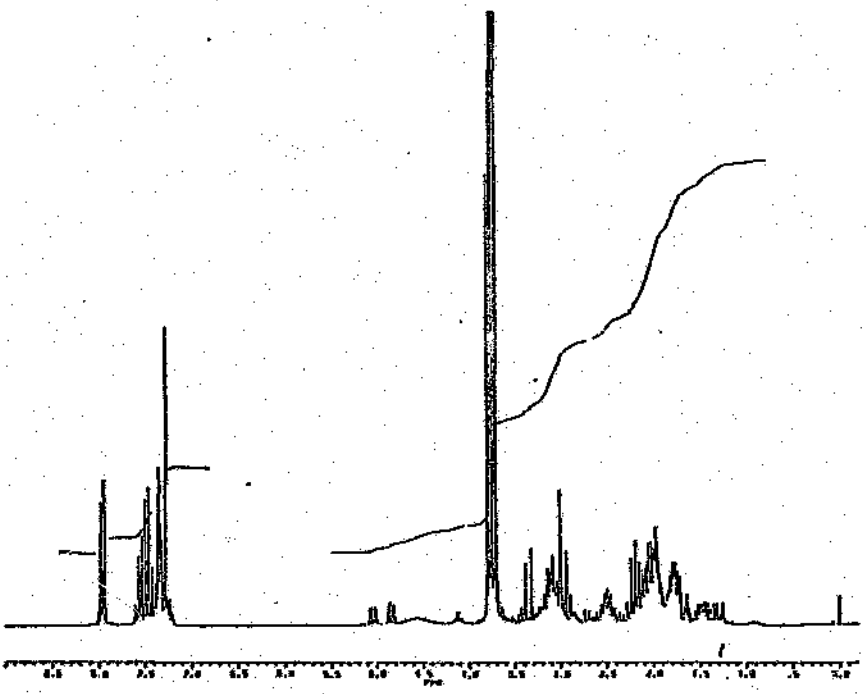
^{13}C-SPECTRUM 19



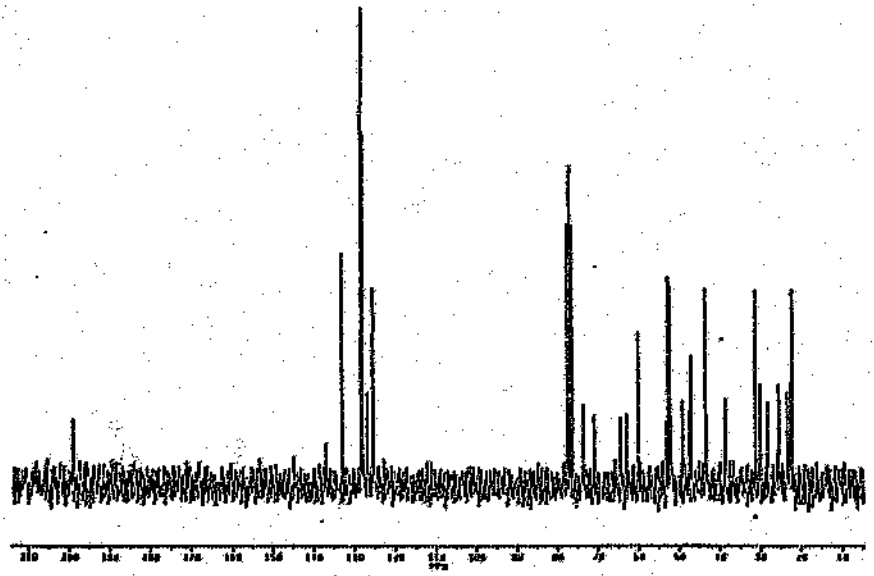
DEPT 19



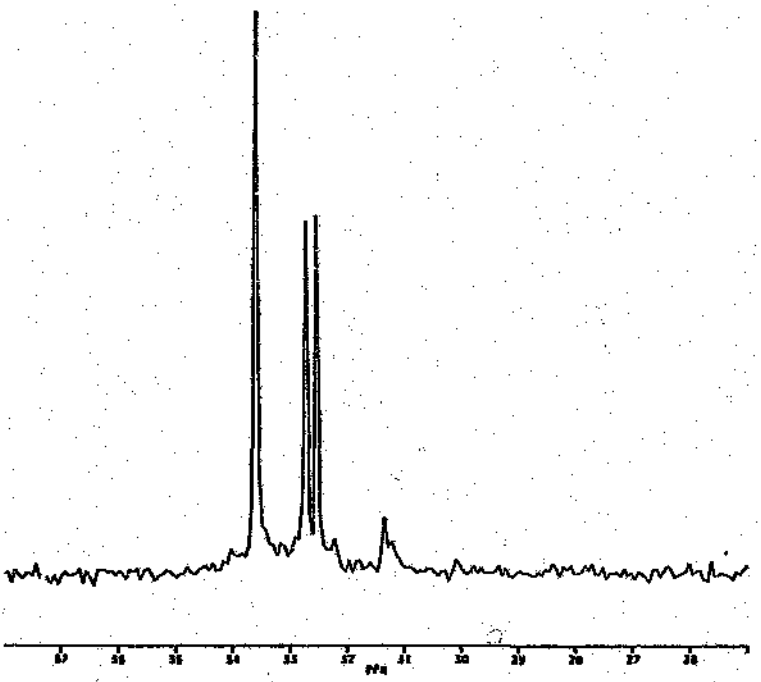
CH-CORRELATED 19



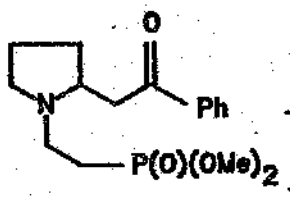
^{1}H-SPECTRUM 20



^{13}C-SPECTRUM 20



^{31}P-SPECTRUM 20



[114]

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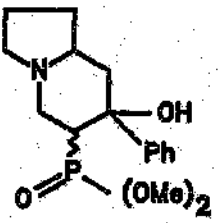

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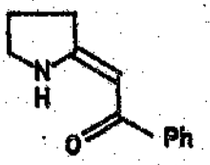
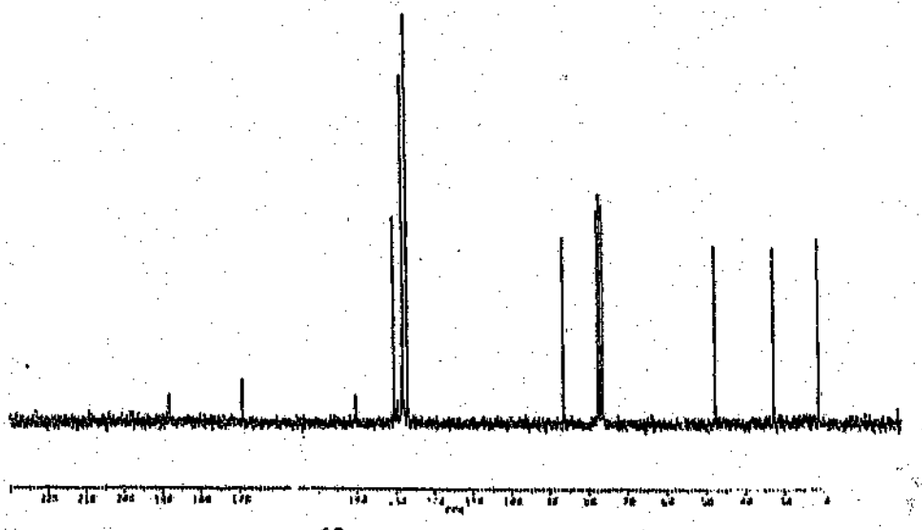


[92]

^{1}H-SPECTRUM 21



^{13}C-SPECTRUM 21

The Road Not Taken

Two roads diverged in a yellow wood,
And sorry I could not travel both
And be one traveller, long I stood
And looked down one as far as I could
To where it bent in the undergrowth;

Then took the other, as just as fair,
And having perhaps the better claim,
Because it was grassy and wanted wear;
Though as for the passing there
Had worn them really about the same,

And both that morning equally lay
In leaves no step had trodden black.
Oh, I kept the first for another day!
Yet knowing how way leads on to way,
I doubted if I should ever come back.

I shall be telling this with a sigh
Somewhere ages and ages hence:
Two roads diverged in a wood, and I-
I took the one less travelled by,
And that has made all the difference.

Robert Frost