INTRAMOLECULAR ARYLATION OF VINYLOGOUS AMIDES AND URETHANES

BY

STEVEN (SHIH-FANG) CHANG, B.Sc. HONS (WITWATERSRAND)

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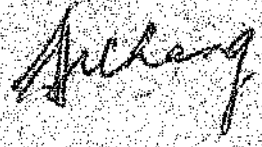
A thesis presented in
the University of the Witwatersrand
for the degree of Doctor of Philosophy

This research was carried out in the Department of Chemistry in the University of the Witwatersrand under the supervision of
Prof. J. P. Michael, B.Sc. Hons, Ph.D. (Witwatersrand),
Associate Professor, Department of Chemistry

August, 1991

DECLARATION

I declare that this thesis is my own unaided work. It is being submitted for the degree of Doctor of Philosophy 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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I would like to express my sincere gratitude to the following:

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ABSTRACT

Aspects of the literature on the chemistry of enaminones, the syntheses of *Cephalotaxus* alkaloids, and the intramolecular arylation of enaminones are reviewed.

Three classes of model compounds, *viz.* N-aryl, N-benzyl and N-[illegible]yl vinylogous amides and urethanes, were prepared for subsequent cyclisation studies. The synthetic sequence in most cases involved making 4-substituted pyrrolidinones, converting them to thiones, and preparing the cyclisation precursors from these by the sulphide contraction reaction. Unsuccessful vinylic substitution reactions on (*E*)-2-ethoxycarbonyl methylene-1-methylpyrrolidine and (*E*)-2-acetylmethylene-1-methylpyrrolidine were attempted using various reagents, including N-bromosuccinimide, bromine, and cyanogen bromide. Successful preparation of (*Z*)-2-(1-ethoxycarbonyl-1-chloromethylene)-1-methylpyrrolidine was achieved from (*E*)-2-ethoxycarbonylmethylene-1-methylpyrrolidine by the action of trimethylsilyl trifluoromethanesulphonate and ferric chloride. Phenylsulphenyl chloride reacted with (*E*)-2-ethoxycarbonylmethylene-1-methylpyrrolidine to produce a mixture of *cis* and *trans* α-sulphenylated isomers, while (*E*)-2-acetylmethylene-1-methylpyrrolidine underwent a deacetylation reaction at the same time as α-sulphenylation to produce (*E*)-2-phenylthiomethylene-1-methylpyrrolidine.

Cyclisations were attempted under a variety of conditions. The results include successful palladium(0)-catalysed Heck reactions on three N-(*o*-bromoaryl) vinylogous urethanes, resulting in the formation of various 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles. Under the same conditions, two N-benzyl enaminones failed to cyclise, giving instead the debrominated compounds. Free radical reactions involving Co(I)-salen resulted in the debromination of a homologous series of *o*-bromoarylated vinylogous urethanes. Unsatisfactory results were obtained from the photochemical reactions of the abovementioned compounds and from the reactions of two N-benzyl enaminones under strongly basic conditions. One attempt was made to induce radical cyclisation with *n*-tributyltin hydride on (*E*)-1-(2-bromo-4,5-dimethoxybenzyl)-2-acetylmethylenepyrrolidine. The debrominated compound was produced.

Successful complexation was observed between chromium hexacarbonyl and 1-(2-(2-bromo-4,5-dimethoxyphenyl)ethyl)pyrrolidin-2-one or (E)-1-(2-(3,4-dimethoxyphenyl)ethyl)-2-ethoxycarbonylmethylenepyrrolidine. No spontaneous cyclisation was observed in the case of the vinylogous urethane.

Reactions with lead tetraacetate resulted in the cleavage of the enaminone double bond of N-benzyl and N-phenylethyl vinylogous amides and urethanes. The corresponding lactams were formed.

Electrochemical information relating to the enaminones and 1-(2-(2-bromo-4,5-dimethoxyphenyl)ethyl)pyrrolidin-2-one was collected. Two unsuccessful anodic oxidation reactions were attempted on (E)-1-(2-bromo-4,5-dimethoxybenzyl)-2-acetylmethylenepyrrolidine.

Successful Sml$_2$ reactions on 1-(2-(2-bromo-4,5-dimethoxyphenyl)ethyl) pyrrolidin-2-one were achieved using acetone enolate and solvated electrons in liquid ammonia. The product obtained here failed to undergo cyclisations in Vilsmeier reaction conditions

CONTENTS

CHAPTER ONE: BACKGROUND, LITERATURE REVIEW, AND AIMS 1

1.1 The "Wits approach" to alkaloid synthesis 1

1.2 The "Wits approach" to the *Cephalotaxus* alkaloids 7

1.3 The aims of this project 15

CHAPTER TWO: PREPARATION OF VINYLOGOUS AMIDES AND URETHANES 18

2.1 Introduction 18

2.2 Preparation and characterisation of lactams 19
2.2.1 Synthesis of N-aryl and N-phenylethyllactams 19
2.2.2 Synthesis of 1-(3,4-dimethoxybenzyl)pyrrolidin-2-one 20
2.2.3 Bromination of lactams 22
2.2.4 Spectroscopic characterisation of lactams 23

2.3 Preparation and characterisation of thiolactams 27
2.3.1 Synthesis 27
2.3.2 Spectroscopic characterisation 28

2.4 Preparation and characterisation of vinylogous amides and urethanes 31
2.4.1 N-Aryl systems by sulphide contraction 32
2.4.2 Alternative synthesis of N-aryl vinylogous urethanes 35
2.4.2 a) Vinylogous urethane [53b] 35
2.4.2 b) Preparation of other N-aryl vinylogous urethanes 38
2.4.3 N-Benzyl and N-phenylethyl vinylogous amides and urethanes 40
2.4.4 Characterisation by nuclear magnetic resonance spectroscopy 41
2.4.5 Infrared spectroscopy 49

2.5 Attempted vinyl substitution reactions of vinylogous amides and urethanes, and related reactions 50
2.5.1 Reactions with N-bromosuccinimide 51
2.5.2 Reactions with trimethylsilyl trifluoromethanesulphonate (TMSOTf) and transition metal salts 58
2.5.3 Reactions with phenylsulphenyl chloride 62

CHAPTER THREE: THE INTRAMOLECULAR HECK REACTION 64

3.1 Introduction 64

3.2 Literature survey and analogies 64

3.3 Results and discussion 80

3.4 Postscript: π-allyl palladium compounds 87

CHAPTER FOUR: INTRAMOLECULAR ARYLATION MEDIATED BY OTHER METALS 89

4.1 Introduction 89

4.2 Cobalt(I)-mediated cyclisation attempts 90
4.2.1 Literature 90
4.2.2 Results 93

4.3 SmI2-initiated cyclisation attempts 96
4.3.1 Literature 96
4.3.2 Results 101

4.4 Chromium complexation of N-phenylethyl compounds 103
4.4.1 Literature 103
4.4.2 Results 105

4.5 Reactions with lead tetraacetate 108
4.5.1 Literature 108
4.5.2 Results 108

CHAPTER FIVE: OTHER CYCLISATION ATTEMPTS 111

5.1 Introduction 111

5.2 Cyclisation via aryne intermediates 111
5.2.1 Literature 111
5.2.2 Results 115

5.3 Photochemically induced intramolecular arylations 116
5.3.1 Literature 116
5.3.2 Results 122

5.4 Electrochemistry of enaminon and related compounds 123
5.4.1 Introduction 123
5.4.2 Results 129

5.5 Sml reactions on lactam [250] 132
5.5.1 Introduction 132
5.5.2 Results 135

CHAPTER SIX: CONCLUSION, AND RECOMMENDATIONS 139

EXPERIMENTAL 144

General Details 144
Experimental procedures relating to Section 2.2 145
Experimental procedures relating to Section 2.3 152
Experimental procedures relating to Section 2.4 157
Experimental procedures relating to Section 2.5 172
Experimental procedures relating to Section 3.3 183
Experimental procedures relating to Section 4.2.2 191
Experimental procedures relating to Section 4.3.2 193
Experimental procedures relating to Section 4.4.2 194
Experimental procedures relating to Section 4.5.2 195
Experimental procedures relating to Section 5.2.2 199
Experimental procedures relating to Section 5.3.2 200
Experimental procedures relating to Section 5.4.2 203
Experimental procedures relating to Section 5.5.2 204

APPENDIX 208

REFERENCES 240

The answer, my dear, is blowing in the wind. 253

For my parents,

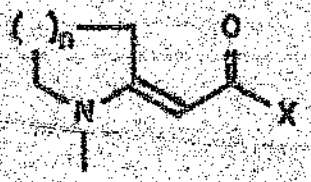
without whose love and attention this project would not have been possible.

CHAPTER ONE: BACKGROUND, LITERATURE REVIEW, AND AIMS

1.1 The "Wits approach" to alkaloid synthesis

Alkaloids have interested organic chemists for centuries. They are natural compounds derived from plant or animal sources, and many of them possess pharmacological potential. To the organic chemist, synthesis of these sometimes very complex molecules can be a daunting challenge.

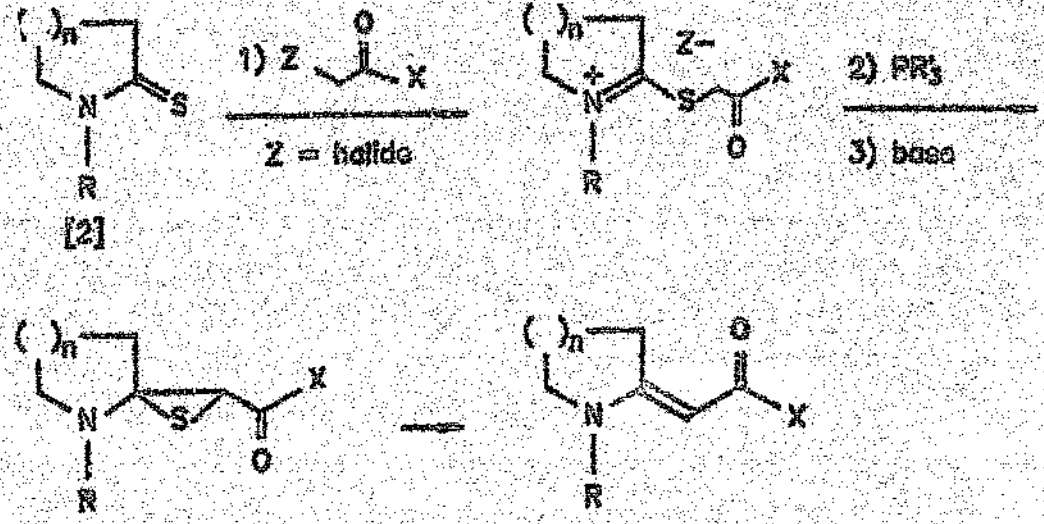
Since the early 1970's, an active research programme on alkaloid synthesis at this University has produced fruitful results. Five Ph.D. theses,[1-5] one M.Sc. dissertation[6] and numerous honours projects have been completed, and several papers have been published.[7-9] All these works have a common central feature: the exploitation of the reactivity of enecyclic vinylogous amides and urethanes of the type shown as [1].



n = 1 or 2
X = alkyl, aryl, or alkoxy
R = alkyl or substituted alkyl

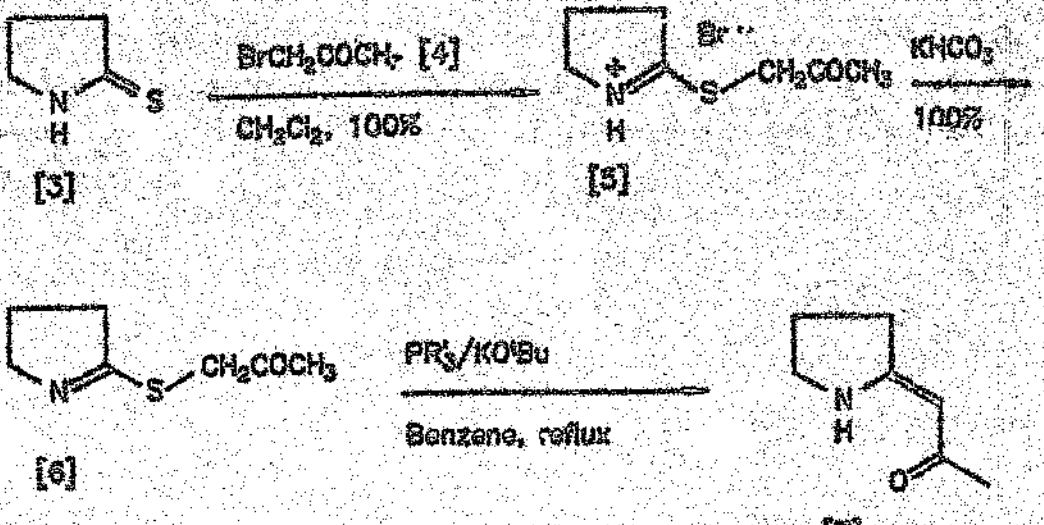
[1]

In general these compounds are most readily obtained from thiolactams [2] by application of Eschenmoser's sulphide contraction procedure (Scheme 1).[35] The reaction occurs into two stages: salt formation between the thiolactam [2] and an α-halo-carbonyl compound; and sulphur extrusion (sulphide contraction) induced by a base in the presence of a sulphur acceptor.



Scheme 1

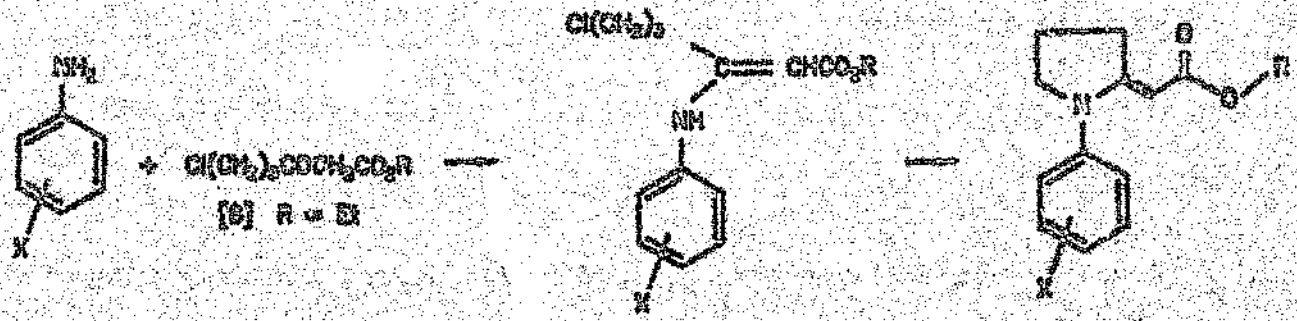
Scheme 2 illustrates the original work of Eschenmoser.[15,16] The salt [5] was formed by mixing 1-pyrrolidine-2-thione [3] with bromoacetone [4]. A weak base, potassium bicarbonate, was used to generate the thioiminoether [6]. The extrusion of sulphur was achieved by refluxing [6] together with a strong base, potassium *t*-butoxide, and a thiophile (triphenylphosphine or triphenyl phosphite) in benzene. The secondary vinylogous amide [7] was obtained in a fair yield (69%). Other secondary vinylogous amides were prepared similarly.



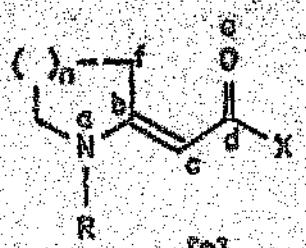
Scheme 2

It has been shown in these laboratories[12] that milder reaction conditions (usually room temperature for both salt formation and the sulphur extrusion stage), a relatively weak base (triethylamine), and triphenylphosphine, are required to prepare tertiary vinylogous amides and urethanes (R = alkyl or substituted alkyl, Scheme 1). Fair to good yields (40-90%) are often obtained. The procedure, however, is unreliable

when R = aryl. Hoeben in her M.Sc. study devised an alternative approach to obtain these N-aryl vinylogous urethanes.[6,13] It effectively involves two consecutive condensation reactions between a substituted aniline and ethyl 6-chloro-3-oxohexanoate [8] (R = Et). Various N-aryl vinylogous urethanes were prepared this way in yields ranging from 41% to 80%. The yields are usually higher than those from the corresponding sulphide contraction approach with N-aryl thiolactams.

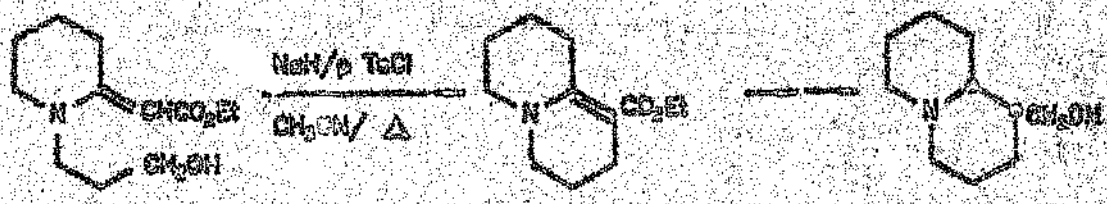


The chemistry of vinylogous amides and urethanes, collectively also known as enaminones, has been reviewed by Greenhill.[17] These compounds show very interesting behaviour. The enaminone systems [9] possess ambident nucleophilicity and electrophilicity. They have potentially six reaction sites, four of which (a, c, e, and f) are nucleophilic in nature and the other two sites (b, d) are electrophilic in nature. These chemistries have been studied in these laboratories to a large extent and also by other workers.



[9]

In these laboratories, the nucleophilicity of site c has been employed in cyclisations to reconstruct the backbones of alkaloids. Suitably positioned electrophiles within precursor molecules render intramolecular cyclisation possible. Howard *et al.* used such an approach to achieve the cyclisations shown overleaf. The bicyclic compounds [10] and [11] serve as precursors to Lupin[7] and *Elaeocarpus*[18] alkaloids respectively.



[10], cois

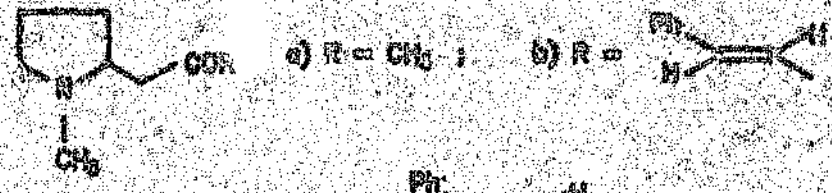
(±)-lupinine



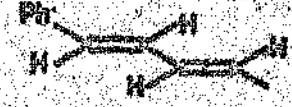
[11], 713

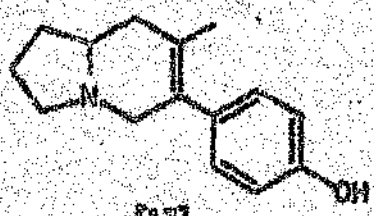
elaeokanine C

Other alkaloids synthesised from vinylogous amides or urethanes in these laboratories include simple pyrrolidines such as hygrine [12a],[12] dehydroderlinine [12b],[12] dehydroderlingionine [12c],[12] and more complex compounds such as hyalbidine [13][7] and the hexahydrojulolidine derivative [14][7] which is derived from intermediate [10].

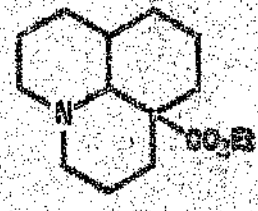


[12]



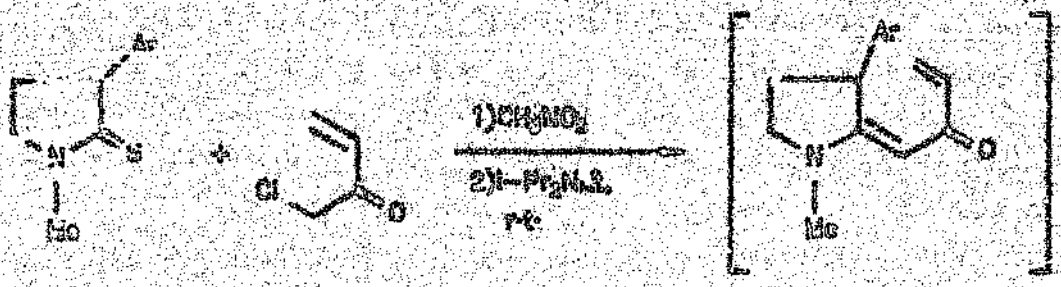


[13]



[14]

In the synthesis of Δ^7-mesembrenone [16] by Katz *et al.*[8,11] in these laboratories, the final cyclisation reaction uses the nucleophilicity of the γ carbon centre (site f) of the vinylogous amide [15], which was not isolated.

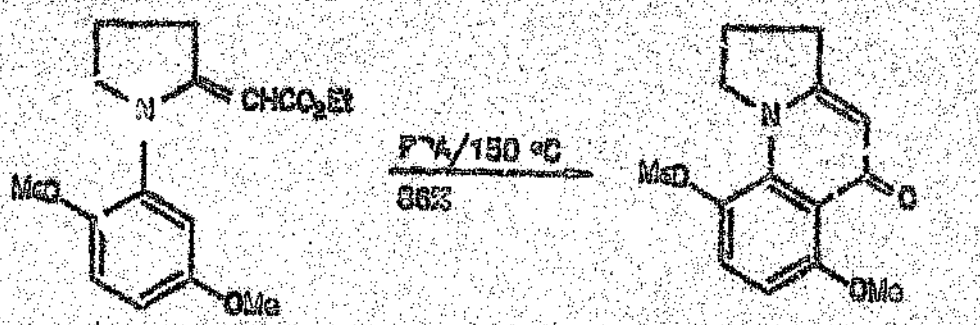


[15]



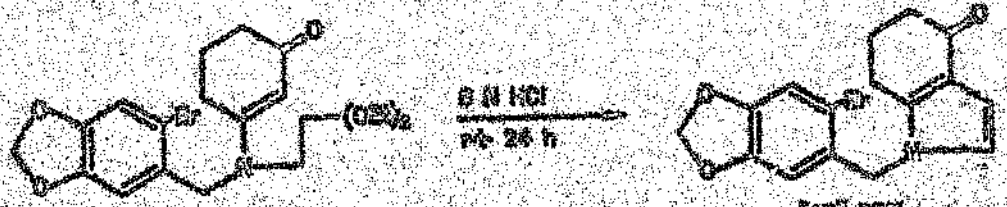
[16]

The 4-quinolinone structural unit is found in many of the quinolinone alkaloids, some of which have been found to possess antibiotic properties. One of the ways of preparing these compounds is to use the Conrad-Limpach reaction on the N-aryl vinylogous urethanes. This formed the central theme for Hosken's M.Sc. dissertation.[6] The reaction centered on the electrophilicity of site d. An example from Hosken's work is shown.

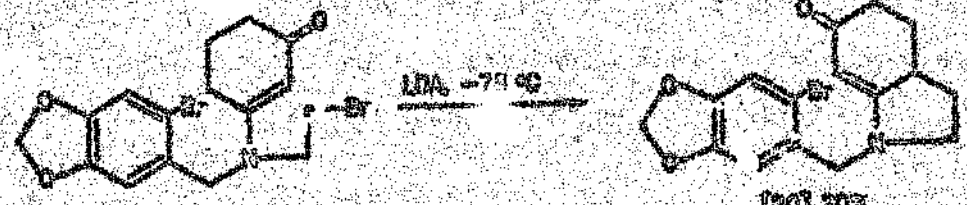


In practice, in these laboratories, the routine work on the vinylogous amides and urethanes is on model studies designed to explore the potential of the systems. The synthesis of alkaloids is in general a long-term aim.

It must be mentioned in conclusion that other workers have also used vinylogous amides and urethanes as intermediates for alkaloid synthesis. Kibayashi *et al.* used the vinylogous amide [17] to prepare the oxodihydroindole [18]. Under strongly basic conditions a similar substrate [19] cyclised differently. In this case, the reactivity of the γ carbon was employed.[18] Both the cyclised products [18] and [20] can serve as potential precursors to lycoranes. In fact, it has been demonstrated by the same group that [20] is subject to intramolecular electrophilic α-arylation via an aryne intermediate to yield a phenanthridone derivative which can further be converted to γ-lycorane[220] (see Section 5.2.1 page 113).



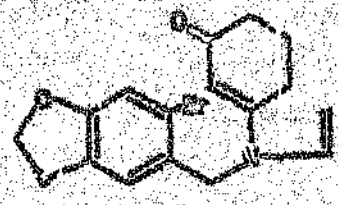
[17]



[19]

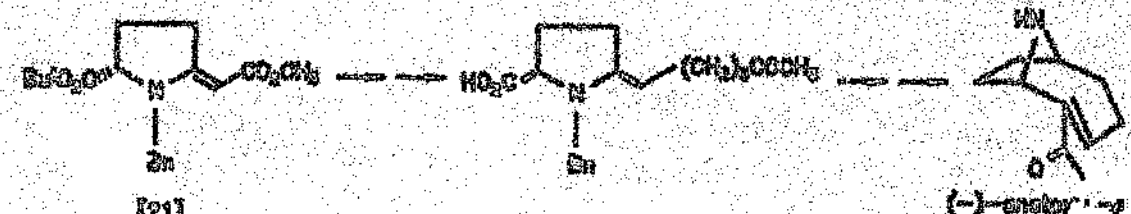
[20] 20%

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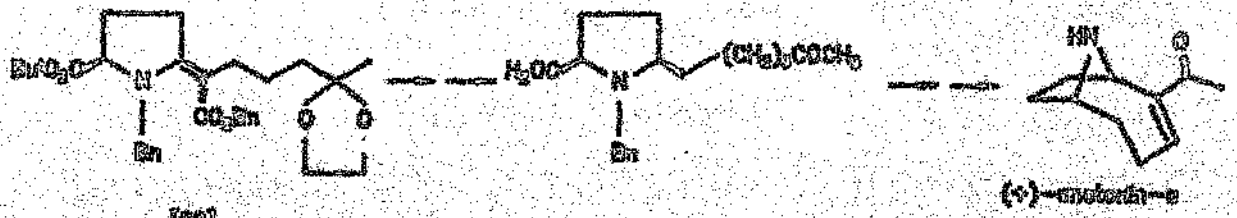


25%

Rapoport *et al.* in the synthesis of anatoxin-a, a potent nerve-depolarizing agent, made use of vinylogous urethanes, [21] and [22], as intermediates. Both (+)- and (-)-anatoxin-a of high optical purity were obtained.[19]



[21]

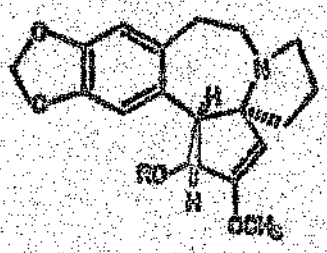


[22]

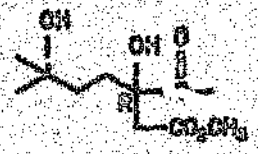
Other workers who have made use of vinylogous urethanes in syntheses include Negasaka in his synthesis of a carbapenam[20] related to the highly potent antibiotic thienamycin; Hart in his syntheses of the *Lythraceae* alkaloids (±)-lythrancepine II and III[21] and gephyrotoxin-222AB,[22] a biologically active alkaloid from Dendrobatid frogs; Feiner in the synthesis of the antibiotic enisomycin;[23] Kishi in his synthesis of gephyrotoxin;[24] and Pinnick in the synthesis of a pyrrolizidine alkaloid isoretronecanol.[25]

1.2 The 'Wits approach" to the *Cephalotaxus* alkaloids

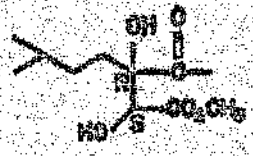
Cephalotaxine [23] is the parent alkaloid produced by the *Cephalotaxus* genus. It was first isolated in 1963 by Paudler *et al.*[26] Six years later the structure of cephalotaxine was finally determined by X-ray crystallographic analysis.[27] The skeleton of this structure is unique to the genus *Cephalotaxus*, which is the only member of the family Cephalotaxaceae of the order of Coniferae. These evergreen shrubs are widely distributed around the world. The genus contains eight species. Of particular interest are four esters of cephalotaxine, which have been found to exhibit significant antitumour activity in animal tests.[28,29] They are harringtonine [24], isoharringtonine [25], homoharringtonine [26], and deoxyharringtonine [27]. Recently these four esters have been evaluated in phase II clinical trials as antileukemia agents.[30-32]



[23] R = H

[24] R = 

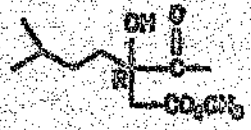
harringtonine

[25] R = 

isoharringtonine

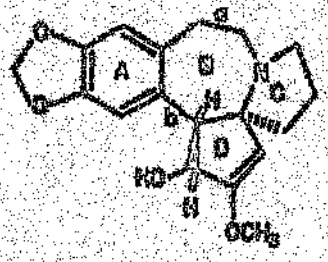
[26] R = 

homoharringtonine

[27] R = 

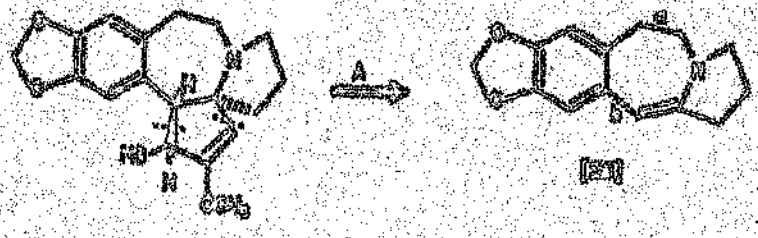
deoxyharringtonine

Although cephalotaxine itself displays no significant antileukemia activity,[23] it is an obvious intermediate in a total synthesis of the harringtonines [24-27]. Consequently many papers have appeared on the synthesis of [23] and its analogues.[29-32,34-61] Huang and Xue classified the various syntheses of cephalotaxine into a number of categories according to the strategies used.[29]



Strategy A

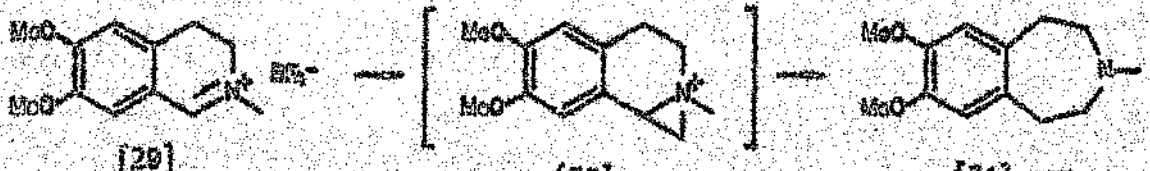
The specific feature of strategy A is the connection of rings A and C to form the key intermediate [28] first. The synthesis is then completed with construction of ring D. Many papers have appeared on such an approach where rings A and C are connected first by the "a" linkage followed by cyclisation through bond "b" formation.[34,50,39,44] Dolby,[37] however, formed bond "b" first.



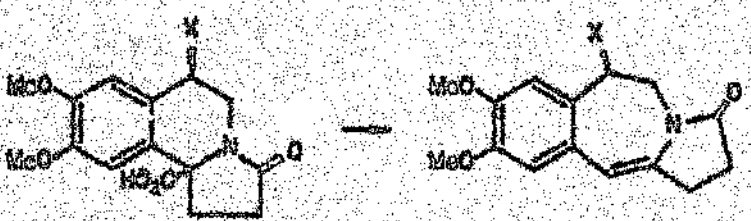
[28]

Many groups have turned their interest towards modified ring systems, *e.g.* with methoxy groups replacing the methylenedioxy ring A,[44,50,51] and more highly substituted analogues. Notably, hydroxy- and oxo- derivatives have been identified as important targets.[30,47,50]

In an approach to cephalotaxine via ring expansion of an isoquinoline aziridinium ion of type [30], Mill reported a successful transformation of [29] to benzazepine [31][45] as a prelude to the transformation of a more complex compound, such as [32], to cephalotaxine.[52]



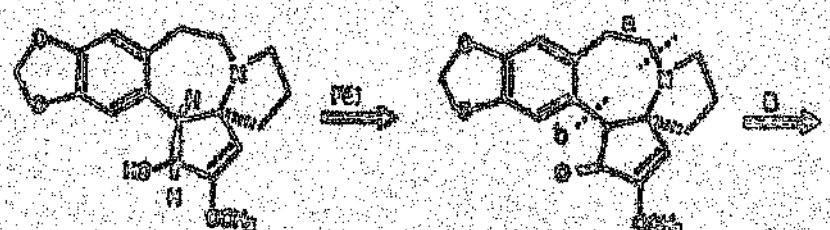
[29] [30] [31], 66%



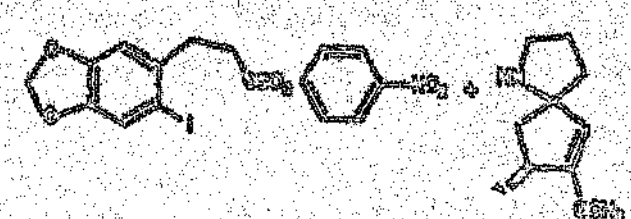
[32] X = H, OH

Strategy B

Semmelhack *et al.* designed a synthetic scheme that connected the pre-formed spiro CD ring moiety [33] to the aromatic ring through bridge "a". They completed the ring closure to form cephalotaxinone [34] by bond "b" formation.[35a] Other groups have developed similar approaches.[45,47]

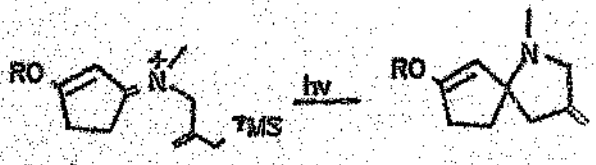


[34]

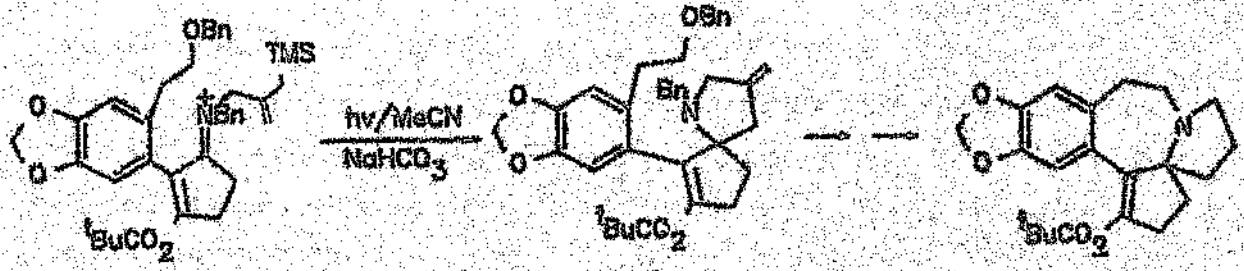


[33]

Mariano *et al.* suggested the utility of the electron transfer-initiated iminium salt photospirocyclisation method for the synthesis of cephalotaxine. A model cyclisation of an iminium salt [35] to a spirocyclic amine was investigated.[63] The reaction was then carried out on the iminium ion [36] to obtain the amine [37].[31] The important point of this strategy lies in the use of a hindered ester on incipient D ring. This approach has enabled Mariano *et al.* to produce a direct synthesis of [38], a compound related to the cephalotaxine esters.[31] The approach is contrasted to that used by Semmelhack *et al.*[35a] in that bond "b" formation precedes that of bond "a". Attempts to form ring B prior to photocyclisation to construct ring C failed.[31]

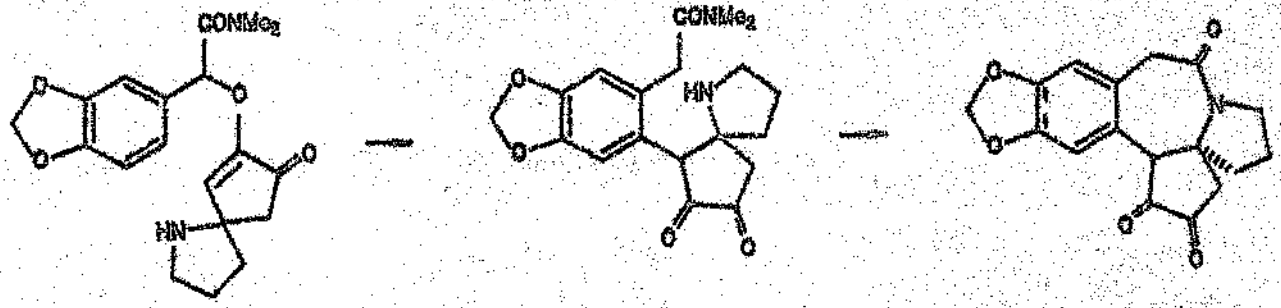


[35], R = CH_3, 91%
R = $COC(CH_3)_3$, 87%

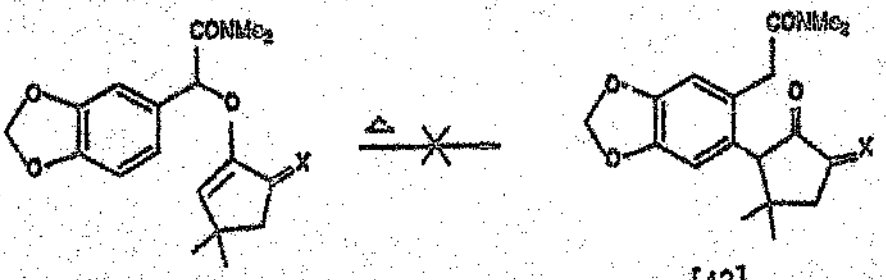


[36] [37] [38]

Recently, approaches based on rearrangement reactions have also been attempted. Raucher *et al.* designed their approach based on an important [3,3] sigmatropic rearrangement of the benzyl vinyl ether [39].[64] Although the synthesis for the precursor before the last crucial cyclisation reaction is different to that used by Mariano *et al.*,[31] this last cyclisation reaction is similar in principle. Model studies, however, gave different results. Compound [40] failed to react under thermolysis conditions. Compound [41] reacted to give an unexpected alcohol [43] instead of [42, X = NOMe].

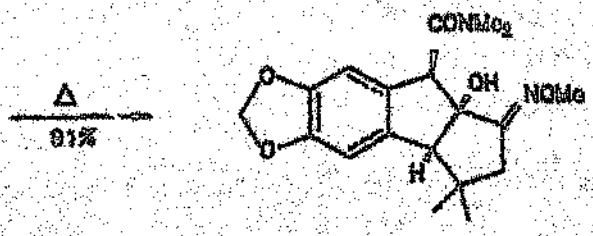


[39]



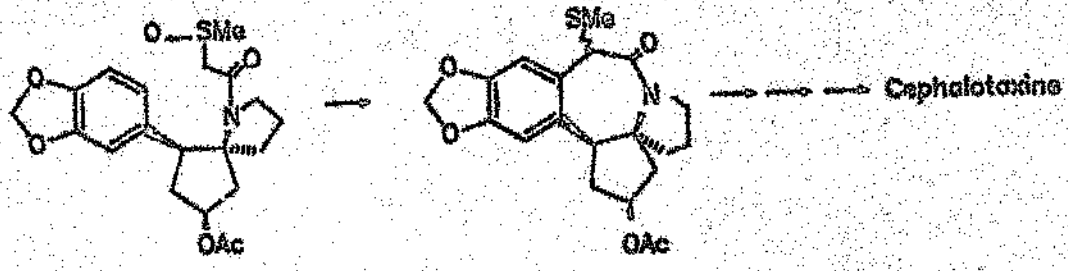
[40] X = O
[41] X = NOMe

[42]



[43]

In the total synthesis of cephalotaxine [23] by Ishibashi *et al.*,[50] the crucial cyclisation step is contrasted to those employed by Mariano[31] and Raucher[43] in that the electrophilic centre is linked to the nitrogen atom instead of the aryl group, and the aryl group is the nucleophile instead of the nitrogen atom.

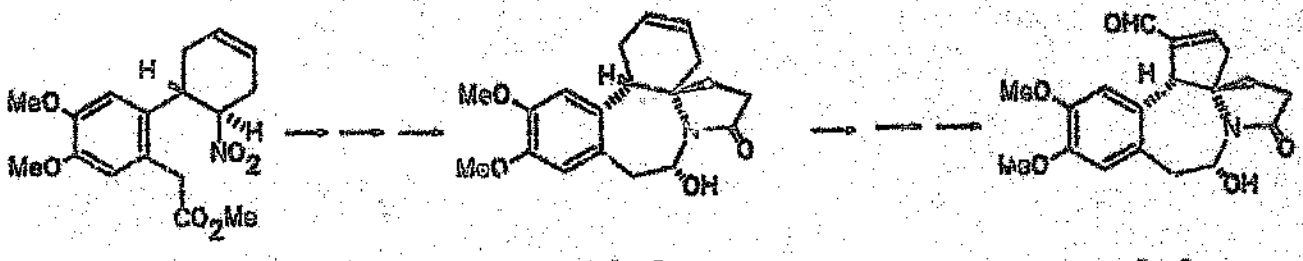


Cephalotaxine

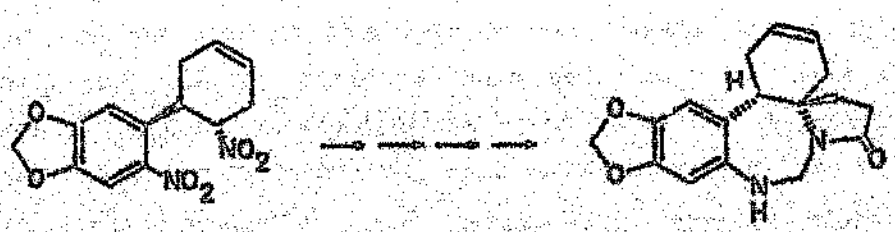
Other strategies

Other new approaches to synthesis of cephalotaxine have been attempted. Bryce *et al.*[51] using [44] as an intermediate prepared the fused benzazepine system [45] in an elaborate synthesis. Compound [45] has been further converted to functionalised cephalotaxine analogue [46]. Using the same approach they also managed to prepare the spiro-fused benzo-1,3-

diazepine skeleton [47], an azacephalotaxine derivative.[32]

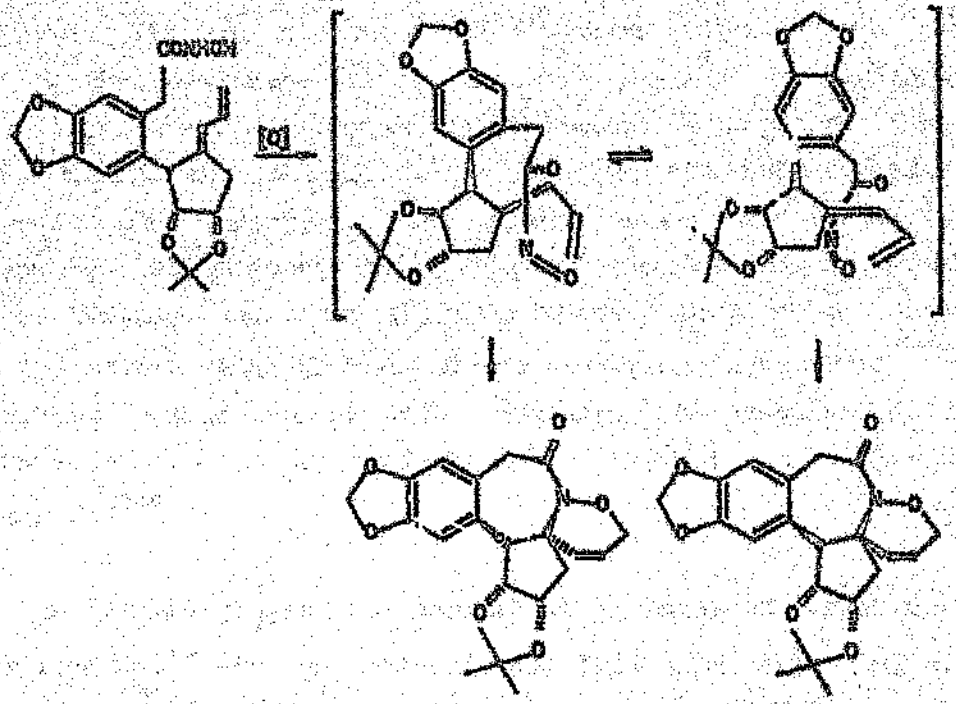


[44] [45] [46]

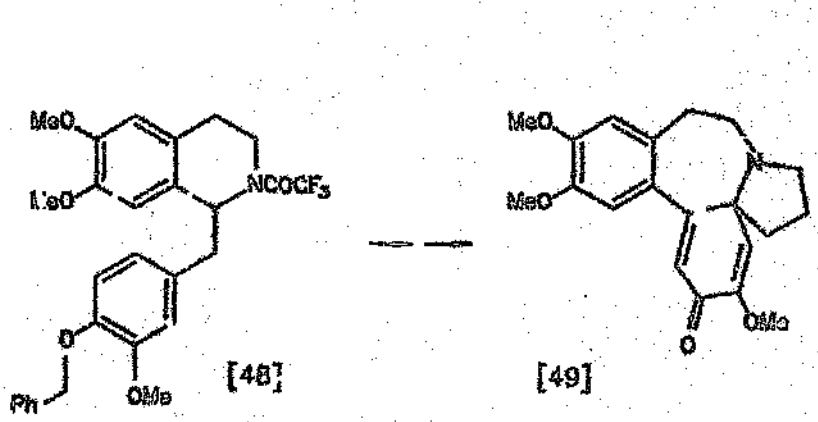


[47]

The synthetic approach of Fuchs *et al.* is based on an important [4+2] cycloaddition reaction.[30]



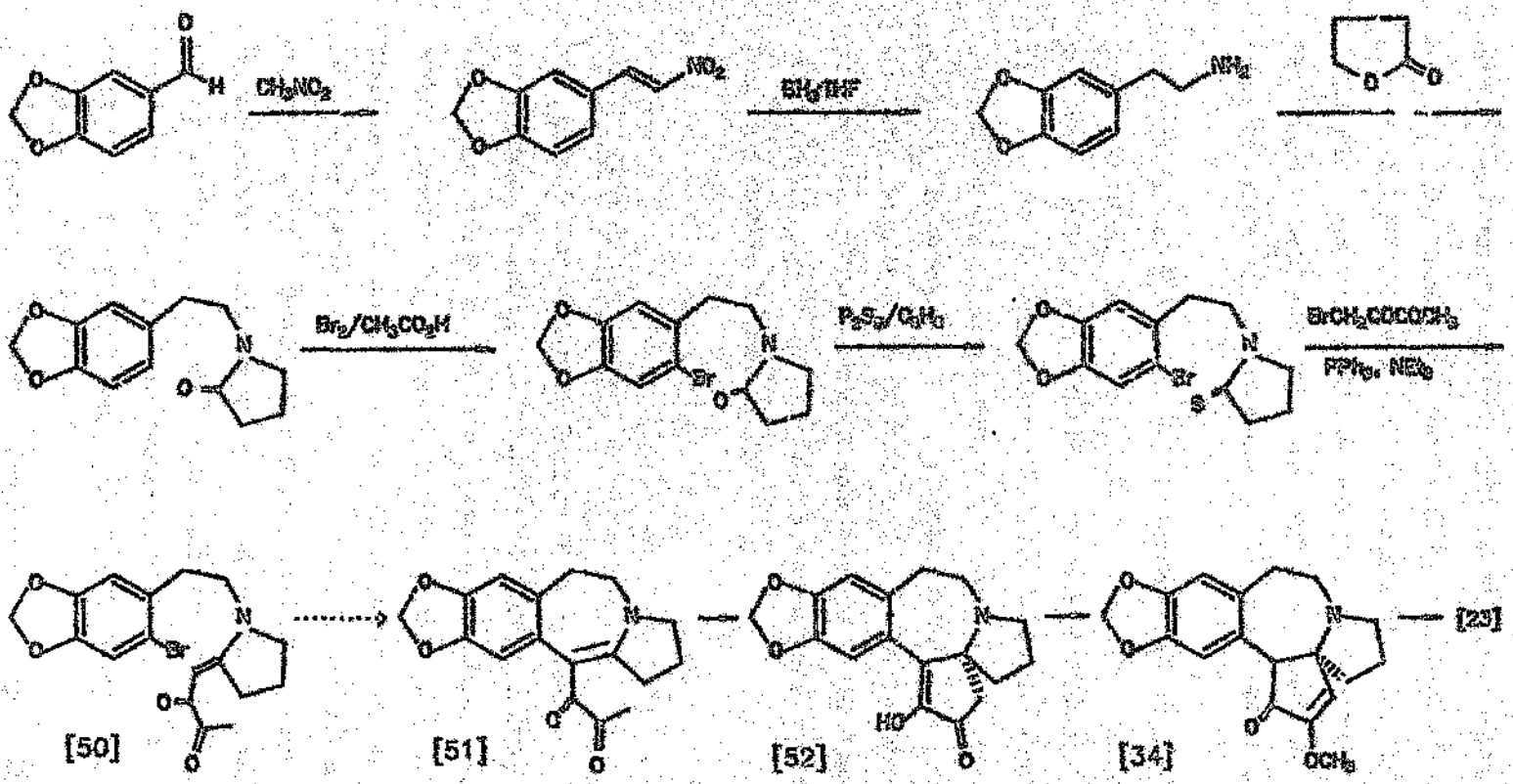
Biomimetic approaches to the synthesis of cephalotaxine have been attempted by several investigators. Kupchan *et al.* prepared the quinone [49], the assumed biogenic precursor to cephalotaxine, from the tetrahydroisoquinoline [48].[31]



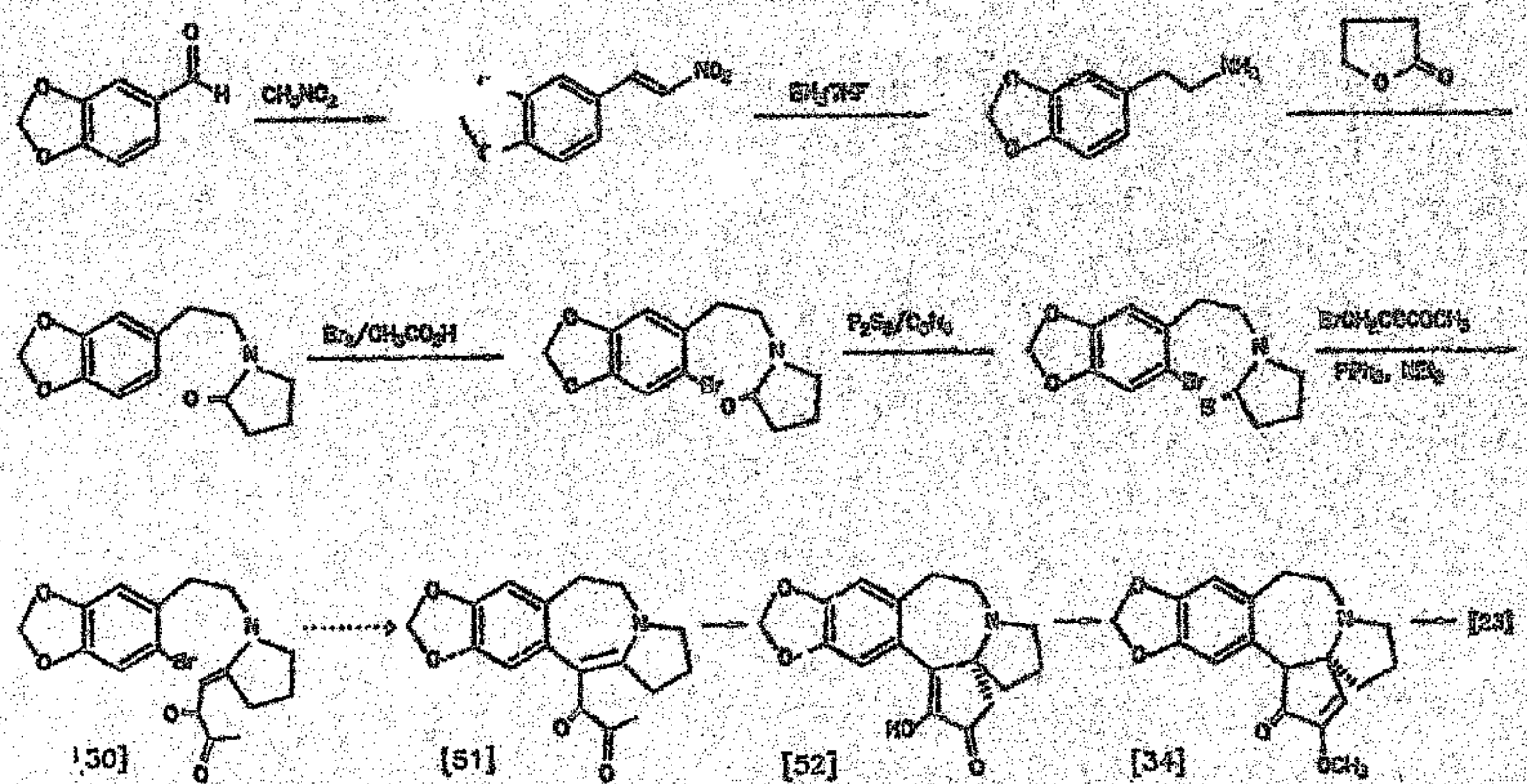
[48] [49]

Finally, serious attempts have been made by several groups to produce cephalotaxins and its esters by callus and suspension tissue cultures. Pioneering work in this novel approach was performed by Delfel and co-workers, who demonstrated that both cephalotaxine and its esters are produced by cultures.[54-58] Brief mention must also be made of the synthesis of the four important esters of cephalotaxine, which have also received active attention in the field of synthetic organic chemistry.[59] The seemingly simple esterification reactions between cephalotaxine and the various side-chain acid derivatives were accomplished with difficulty. The lack of success was attributed to two factors. Firstly, the steric environment of the hydroxyl group of cephalotaxine is extremely hindered, allowing the approach of an incoming acyl chain only from the direction perpendicular to the plane bisecting the pentacyclic skeleton. This phenomenon thus greatly reduces the probability of favourable configurations leading to bond formation in the transition state. Secondly, the esters are quite resistant to hydrolysis, attesting to the extreme steric hindrance of the carboxylate environment.[59b] Other strategies, leading to some brilliant syntheses, were developed. For more information on these syntheses two excellent reviews can be consulted.[29,59]

In my honours project I undertook the synthesis of demethoxycephalotaxinone [52].[60] Although compound [52], like cephalotaxine [23], is not pharmacologically active, it has been converted to cephalotaxinone [34], metal hydride reduction of which produces a single product, cephalotaxine [23].[35b] Hence the harringtonines can be obtained. I worked on the approach shown in Scheme 3 overleaf.


CH3NO2
BH3/THF
Br2/CH3CO2H
P2S5/C6H6
BrCH2COCO2CH3
PPh3, NEt3
[50]
[51]
[52]
[34]
[23]

Schema 3


CH3NO2
LiAlH4/THF
Br2/CH3CO2H
P2S5/C5H5N
BrCH2COCOCH3
PPh3, NEt3
[30]
[51]
[52]
[34]
[23]

Schema 3

The synthesis of the tetracyclic compound [51] would in fact constitute a formal synthesis to demethylcephalotaxinone [52] as Weinreb *et al.*[34] have already successfully cyclised [51] in an intramolecular Michael reaction to [52] using conditions developed by Muxfeldt *et al.*[61] In my honours project, however, only as far as vinylogous amide [50] was achieved. Two cyclisation attempts using palladium(II) as a catalyst failed to produce the desired compound [51]. Our approach would in fact fall under the category of strategy A according to the classification of Huang and Xie.

The crucial ring closure is, in effect, an arylation of a vinylogous amide. Mention has already been made on alkylation at site c of vinylogous amides and urethanes on page 4. Despite the rather abundant literature on intramolecular alkylation and acylation reactions of these systems at site c, there appear to have been remarkably few reports of arylation, although such a process would be potentially useful in synthesis. This problem in fact gives rise to the main aim of this Ph.D. project, which can be stated concisely: it is to examine intramolecular arylation at site c of vinylogous amides and urethanes. Detailed aims will be presented in Section 1.3.

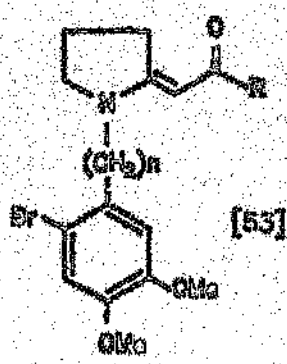
1.3 The aims of this project

The desired cyclisation in Scheme 3 is in fact an aromatic nucleophilic substitution reaction in which the nucleophilicity of site c of a vinylogous amide is employed. The electrophilic site is the carbon to which bromine is attached in the phenyl moiety. Simple nucleophilic displacement of halide ion from an aromatic ring is an unusual reaction; and known cases of this sort of reaction are often not straightforward mechanistically. Some literature analogies exist for the desired intramolecular transformation in which the nucleophile is an alkene carbon centre. In general, depending on the size of the ring formed, three approaches have been employed. They are:

1) Organometallic-assisted cyclisation. The Heck-type reactions are the most useful ones here.
2) Free-radical induced cyclisation. Both photochemical and organometallic routes are possible.
3) Cyclisation of aryne intermediates generated by strong bases.

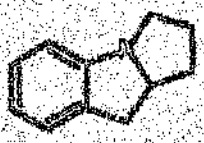
Detailed literature examples will be presented immediately preceding each method to be described in chapters THREE, FOUR, and FIVE. It is clear that the long-term aim of this project is to develop a method by which the desired ring closure reaction of [50] to [51] in the synthesis of demethylcephalotaxinone [52] can be effected.

We intend to study this kind of transformation in more detail and to approach the problem systematically. The immediate purpose of this project is to investigate this kind of intramolecular arylation of an enamine by studying a range of model compounds in which certain structural features are varied. Most importantly, we wish to understand the changes in conditions that might be necessary if we vary the size of the ring being formed from five-membered to six- and seven-membered. For convenience and ease of access, the model studies will be performed with 3,4-dimethoxyphenyl-substituted compounds rather than 3,4-methylenedioxy. Finally, since reactivity may change depending on the substituent on the enamine, we shall examine both vinylogous amides and vinylogous urethanes. In summary, the model compounds for this study will be systems such as [53], with n = 0, 1, or 2, and R = alkyl or alkoxy.



[53]

These important precursors will be subjected to cyclisation conditions reported in successful literature examples. The final cyclised model compounds would constitute three classes of compounds whose backbone structures are widely found in various alkaloids. For example the benzannelated pyrrolizidine system [54] occurs in the mitomycin antibiotics, many of which possess antitumour properties.[62] The example shown here is mitomycin B, in which the aryl moiety has been disguised as a *p*-benzoquinone derivative. The benzannelated indolizidines [55] are found in many alkaloid families. γ-Lycorane is given here as an example. Finally the benzannelated 1-azabicyclo[5.3.0]decanes [56] form part of the skeleton of the *Cephalotaxus* alkaloids.



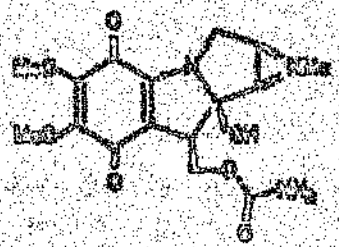
[54]



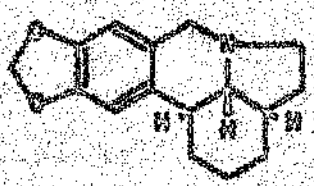
[55]

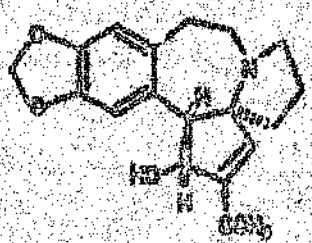


[56]



mitomycin B





cephalotaxine

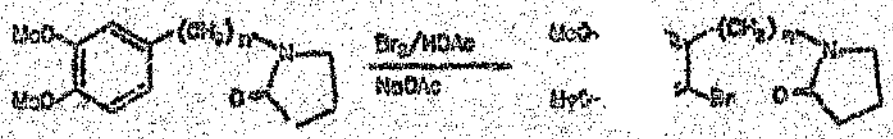
The aims of this project can therefore be summarised as follows:

1) To prepare and characterise the different series of model compounds;
2) To apply cyclisation reactions to the different classes of vinylogous amides and urethanes;
3) To use the results from 2) to complete the synthesis of the cephalotaxine structure [52].

CHAPTER TWO: PREPARATION OF VINYLOGOUS AMIDES AND URETHANES

2.1 Introduction

In this chapter the preparation and characterisation of various model vinylogous amides and urethanes for the cyclisation studies will be discussed. The three classes of model compounds (53, n = 0, 1 or 2) were prepared according to Scheme 4. In view of some results that will be presented in later chapters, the unbrominated chlolactams (59) and vinylogous urethanes (61) were also prepared for purposes of comparison.



[57] a, n = 0
b, n = 1
c, n = 2



[58] a, n = 0
b, n = 1
c, n = 2



[59] a, n = 1
b, n = 2



[60] a, n = 0
b, n = 1
c, n = 2



[61] a, n = 0, R = OEt
b, n = 1, R = OEt
c, n = 2, R = OEt
d, n = 1, R = CH_3

[53] a, n = 0, R = CH_3
b, n = 0, R = OEt
c, n = 1, R = CH_3
d, n = 1, R = OEt
e, n = 2, R = CH_3
f, n = 2, R = OEt

Scheme 4

The preparation of the N-benzyl lactam [57b] was different from those of the other two. Section 2.2.2 details its preparation. Sulphide contraction was employed to prepare the important precursors [53] except for the N-aryl vinylogous amides and urethanes [53a] and [53b], where an alternative route was used (see Section 2.4.2). The other model compounds at different stages along the series were prepared using conditions quoted in the Scheme, and the syntheses will be discussed in the appropriate sections in the rest of this chapter. The contracted products [53] were subjected to cyclisation reactions according to successful literature methods, and these results form the main body of Chapters Three, Four and Five.

2.2 Preparation and characterisation of lactams

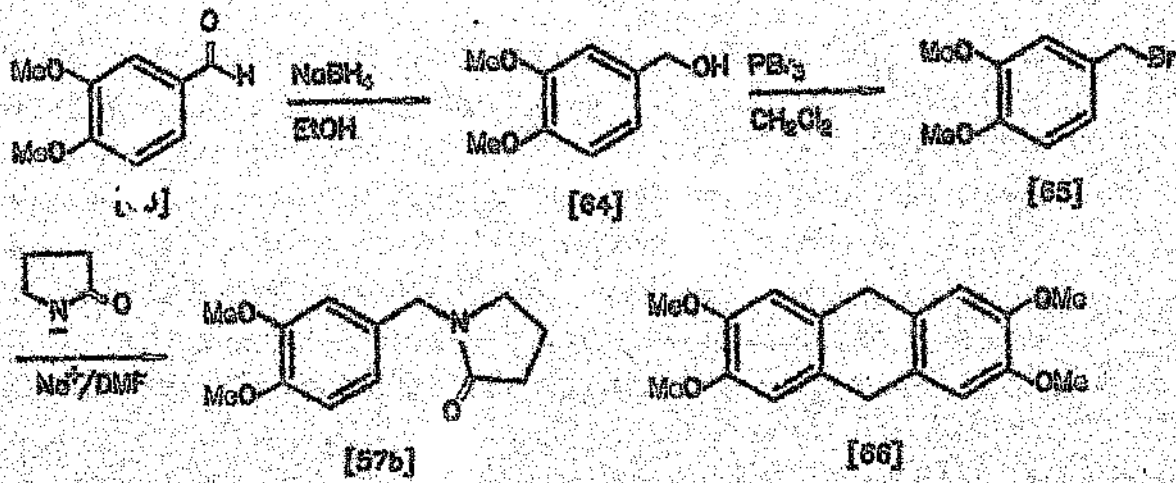
2.2.1 Synthesis of N-aryl and N-phenylethyllactams

1-(3,4-Dimethoxyphenyl)pyrrolidin-2-one [57a] was prepared by heating γ-butyrolactone and 3,4-dimethoxyaniline [62] under sealed tube conditions at 220 °C. The procedure is similar to that reported by Reppe.[63] This is a condensation reaction in which water is eliminated. A 60% yield was obtained after distillation. An initial attempt to prepare [57a] by heating the two substances together at 176 °C for two hours followed by addition of a catalytic amount of concentrated sulphuric acid failed; the aniline was recovered (80%). This is somewhat surprising, since we have made several other N-arylactams this way.[6,12] Spectral characterisation will be presented in Section 2.2.4.

1-[2-(3,4-Dimethoxyphenyl)ethyl]pyrrolidin-2-one [57c] was prepared in bulk quantity from 3,4-dimethoxyphenylethylamine and γ-butyrolactone under sealed tube conditions at ca 210 °C. A 63% crude yield was obtained. An initial attempt at heating the two reagents together followed by the addition of a catalytic amount of concentrated sulphuric acid gave a very poor yield (36%). Compound [57c] was a viscous oil after distillation; it very slowly turned semi-solid on standing at room temperature. Its spectroscopic characterisation will also be presented in Section 2.2.4.

2.2.2 Synthesis of 1-[3,4-dimethoxybenzyl]pyrrolidin-2-one

The following scheme depicts our approach to this model compound. The idea was to make an electrophilic benzylic compound with an appropriate leaving group, which could then react with pyrrolidinone anion to produce the desired lactam.



[63] [64] [65]

[57b] [66]

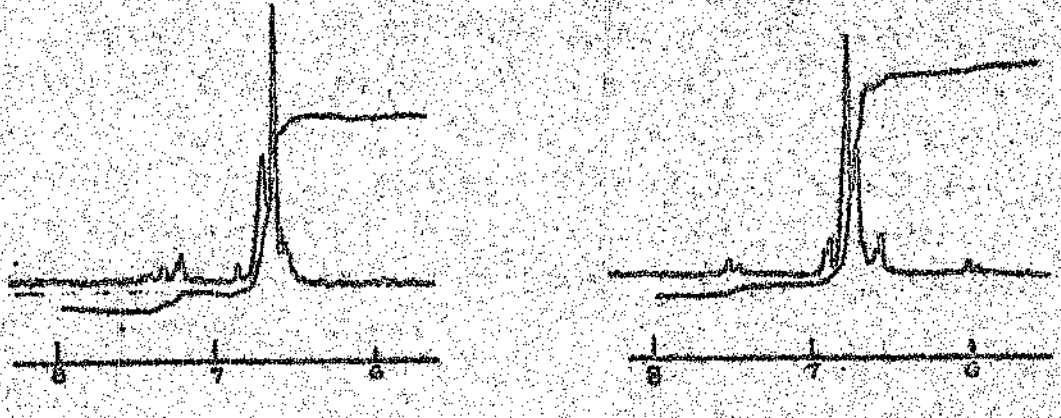
The benzaldehyde [63] was easily reduced by sodium borohydride in absolute ethanol to the corresponding alcohol [64] in quantitative yields. Tosylation of the benzyl alcohol proved problematic. Many trials were attempted, but no tosylated benzyl compound was ever isolated. We therefore turned to the preparation of the benzyl bromide [65]. Attempts to substitute the hydroxyl group by bromide were carried out by stirring the benzyl alcohol in dichloromethane with 48% aqueous hydrobromic acid. Zinc bromide (0.50 mol %) was also present as a catalyst.[64a]

In one larger scale attempt, ca. 1 g benzyl alcohol with 0.50 mol % zinc bromide, 2,3,6,7-tetramethoxy-9,10-dihydroanthracene [66] was isolated in quantitative yield (100%). The probable sequence of reaction was conversion of the benzyl alcohol to the bromide, which then dimerised by a Friedel-Crafts process in the presence of zinc bromide to produce [66]. Such a compound and many analogues have already been prepared similarly[65] and their proton spectra studied in detail. Compound [66] shows interesting coupling patterns in the proton spectrum. The signals of the benzylic protons at C-9 and C-10 correspond to an AB system. In 9,10-dihydroanthracene itself there is only one signal for the methylene protons at 3.87 ppm. This has been explained by a rapid interconversion between two extreme boat conformations. The introduction of four methoxy groups in positions 2, 3, 6, and 7 of the 9,10-dihydroanthracene skeleton

reduces the rate of interconversion and the differences between the axial and the equatorial protons are now evident. The axial protons absorb at 3.54 ppm and the equatorial protons at 4.75 ppm. This difference is due to the shielding of the axial hydrogens by the aromatic magnetic fields. A large geminal coupling, $J = 13.8$ Hz, was also observed.

Because of this competitive formation of compound [66], subsequent substitution attempts using hydrobromic acid had to be carefully performed. Although crude yields were good (79-98%) using this method, the yields were much reduced after distillation (38-61%). T.l.c. also indicated the formation of several by-products. An alternative procedure was therefore used.[65] When the benzyl alcohol was stirred together with phosphorus tribromide in dichloromethane, good yields of benzyl bromide [65] were obtained (86-93%) and t.l.c. indicated a clean reaction.

The proton spectra (60 MHz) of the alcohol [64] and the bromide [65] are remarkably similar. The benzylic signal is at exactly the same position (4.30 ppm) for both compounds. The only difference in their proton spectra is the pattern for aromatic protons. Thus the alcohol has pattern A and the bromide pattern B. Hence the crude PMR data obtained here could not tell us with certainty that the reaction had occurred. Other physical properties such as t.l.c. and i.r. spectra had to be consulted. Also the alcohol is a viscous oil, and the bromide a solid. This was not expected as the alcohol can hydrogen-bond, therefore creating stronger intermolecular forces than those in the bromide.



A B

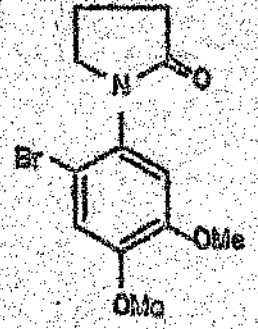
The reaction between 2-pyrrolidinone anion and the bromide was slightly exothermic. The 2-pyrrolidinone anion was generated from 2-pyrrolidinone by the action of sodium hydride in DMF. Isolated yields were good (72-

(60%). N.m.r. spectral discrimination will be presented in Section 2.2.4.

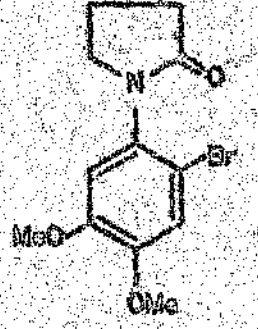
2.3.3 Bromination of lactams

Bromination at the desired position on the aryl r[illegible] all the lactams [57a, b, c] was easily achieved in almost quantitative crude yield with bromine in acetic acid. The 6 position of the aromatic ring is the most nucleophilic site owing to a combination of *o* and *p* activating effects from methoxy group at the 3 position and lactam nitrogen. Although the 2 position is also nucleophilic it is sterically hindered. The effective bromination electrophile could be BrOAc[87] from bromine and acetic acid. Approximately three equivalents of sodium acetate were always present. The sodium acetate, acting as a buffer, stabilizes the pH of the solution during the progress of the reaction. In general these bromination reactions were also very quick (30-60 min), but longer reaction times were allowed to ensure completion of reaction. Spectroscopic characterization of all products will be discussed in the next section.

High isolated yields (94-99%) were obtained for the preparation of 1-(2-bromo-4,6-dimethoxy[illegible]oyl)pyrrolidin-2-one [58a]. Interestingly though, during two different recrystallization attempts using ethyl acetate: hexane mixture, two distinct melting point ranges were detected (112-113 °C, 98-99 °C). This could arise from the two possible rotamers [58a], [58a'] that this compound might possess. The rotamer study of various N-aryl lactams has been widely investigated in these laboratories, and some crystal structures have been determined by the Structural Chemistry group.[88] These studies indicate that the two rings (the lactam and the aryl ring) are never coplanar in the solid state; nonetheless, conformations appear to be sufficiently rigid that non-planar forms of [58a] with bromine pointing towards and away from the carbonyl are certainly feasible.



[58a]



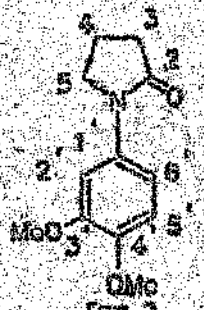
[58a']

1-(2-Bromo-4,5-dimethoxybenzyl)pyrrolidin-2-one [58b] was prepared in high isolated yields (92-100%). The product is a viscous oil.

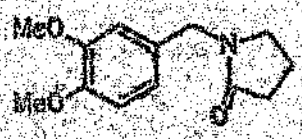
Excellent yields (95-98%) were obtained in the preparation of 1-(2-(2-bromo-4,5-dimethoxyphenyl)ethyl)pyrrolidin-2-one [58c]. Recrystallisation from acetone: hexane mixture gave colourless cubes.

2.2.4 Spectroscopic characterisation of lactams

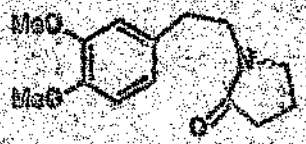
Proton and carbon NMR signals for the various lactams [57] and bromolactams [58] are summarised in Tables 1-2 (see Appendix for spectra).



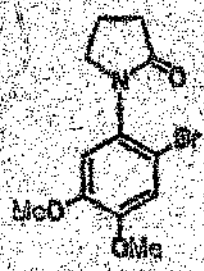
[57a]



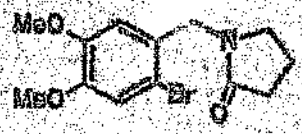
[57b]



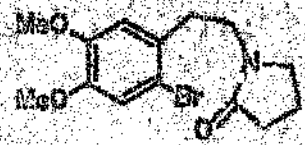
[57c]



[58a]



[58b]



[58c]

	57a	58a	57b	58b	57c	58c
H-3	2.56, t	2.56, t	2.43, t	2.42, t	2.35, t	2.37, t
H-4	2.13, quintet	2.23, quintet	1.98, quintet	2.00, quintet	1.95, quintet	1.97, quintet
H-5	3.82, t	3.75, t	3.26, t	3.32, t	3.27, t	3.31, t
2xOMe	3.89, 3.86	3.87, 3.85	3.86	3.87, 3.84	3.87, 3.85	3.86
arom H's	7.52, d; 6.85, m	7.08, 6.77	6.80-6.76	7.00, 6.86	6.83-6.72	7.00, 6.79
CH_2Ar	—	—	4.38	4.53	2.79, t	2.91, t
CH_2CH_2Ar	—	—	—	—	3.51, t	3.52, t

Table 1 PMR Chemical shifts (δ, ppm) for lactams [57] and [58].

	57a	58a	57b	58b	57c	58c
C-2	173.73	174.82	174.69	174.65	174.63	174.72
C-3	32.39	30.61	30.84	30.43	33.05	33.29
C-4	17.62	18.78	17.50	17.51	17.72	17.85
C-5	48.94	49.85	46.37*	46.42	47.39	47.52
2xOMe	55.65, 55.76	56.11 55.92	55.73, 55.59	55.81 55.76	55.55	55.93
CH_2Ar	—	—	46.18*	45.61	30.77	30.86
CH_2CH_2Ar	—	—	—	—	43.77	43.24
Ar C-1'	132.86	130.01	129.00	127.54	131.01	129.76
Ar C-2'	with C-5' & 6'	112.10	with C-5' & 6'	113.63	with C-5' & 6'	113.84
Ar C-3'	148.56, 145.75	115.26 111.68	149.01, 148.33	114.91 115.54	148.60, 147.27	115.21 112.92
Ar C-4'		149.05 148.76		149.47		148.25 148.01
Ar C-5'	111.48, 110.69, 104.89		120.40, 111.23, 110.94		120.35, 111.49, 110.94	
Ar C-6'		with C-3'		with C-3'		with C-3'

* Interchangeable

Table 2 CMR Chemical shifts (δ, ppm) for lactams [57] and [58].

The aromatic region of the proton spectrum of 1-(3,4-dimethoxyphenyl) pyrrolidin-2-one [57a] shows two signals. One at 7.52 ppm has a relative integration of one. It is a broad singlet with weak coupling (ca. 1 Hz). This is too small for *ortho* coupling, hence this signal must arise from aromatic H-2. The other aromatic signal appears at around 6.85 ppm. It is a multiplet with a relative integration of two. H-3 and H-5 protons of the heterocyclic ring appear as triplets, although the H-5 signal (3.62 ppm) overlaps with one of the signals from the two methoxy groups. This is an unusual position for H-5 protons to occur. In N-alkyl lactams the signals from H-5 protons appear around 3.2 to 3.4 ppm.[60] The observed downfield shift is caused by the deshielding effect of the aromatic magnetic field. For the same reason the signals from the methoxy groups appear more downfield than those from methyl alkyl ethers. This deshielding effect on H-5 protons is also observed for the compounds derived from [57a], which will be described later in this section. The appearance of triplets from H-3 and H-5 protons indicates there is free inversion of the ring, causing these protons to be magnetically equivalent. The triplet from H-3 is broad, and the multiplet, effectively a quintet, from H-4 shows fine splitting, indicating that C-3 is relatively rigid compared with C-5.

In all brominated lactams, the aromatic region of the proton spectra of the products always simplifies to two singlets. This is because the two aromatic hydrogens are *para* to each other and *para* coupling in aryl compounds is indeed very small.

The aromatic region of the proton spectrum for 1-(2-bromo-4,5-dimethoxyphenyl)pyrrolidin-2-one [57b] shows two sharp singlets with relative integration of one each (v. Table V). The singlet at 7.08 ppm, the furthest downfield signal, could arise from aromatic H-6. Molecular models indicate that the preferred rotamer might be one in which aromatic H-6 could lie in the deshielding zone of the carbonyl group, i.e. spatially outside the C=O double bond, causing this proton to be deshielded. A direct proof could come from an NOE study, but this was not attempted. Again, the deshielding effect of the aromatic magnetic field causes the signals from H-5 in the ring to appear more downfield (3.75 ppm) than they do in N-alkyl lactams. They are, however, slightly more upfield than those of the corresponding unbrominated lactam. The

bromine ... the aryl group has mesomerically shielded these protons. The signals from H-3 in the heterocyclic ring, those next to the carbonyl group, have the appearance of a triplet of doublets. The fine splitting causing the appearance of a doublet arises from the fact that these two protons are non-equivalent, thereby creating two triplets almost superimposed on each other (1 Hz apart). This indicates that there is some degree of rigidity at this carbon centre. Consequently the appearance of the signals from H-4 protons becomes more complicated (quintet with further fine splitting). In the ^{13}C spectrum the two peaks from 115.4 and 111.7 ppm come from aromatic C-2 and C-6, but absolute assignment of these peaks is not possible. More work, ^{13}C-^{1}H correlation and NOE experiments, would have to be done to clarify this uncertainty. However, it was felt that their assignment was not of vital importance.

There are no unusual features in the proton spectrum of lactam 1-[3,4-dimethoxybenzyl]pyrrolidin-2-one [57b]. Introduction of bromine at the desired position in the aryl group caused the methoxy signals of [58b] to separate into two clear singlets, although the position is little changed. The most pronounced shift on bromination comes from the signals of the benzylic protons. A 0.15 ppm downfield shift relative to the unbrominated lactam [57b] is observed. This is probably more a field effect than an electronic effect through bonds. In the carbon spectrum, differentiation of the two methylene carbon peaks next to the nitrogen is difficult since they appear close together. Although the identification of these signals is not of vital importance, a ^{13}C-^{1}H correlation spectrum was obtained to clarify this ambiguity. The benzylic carbon is slightly more upfield, by 0.81 ppm, than the signal from the carbon next to nitrogen in the ring. The signal from the phenyl carbon with bromine attached is more upfield by 6.77 ppm than the corresponding signal from the unbrominated carbon in [57b]. Bromine, although electronegative, can also mesomerically release electron density into the ring, thereby shielding this carbon. This upfield shift due to the shielding effect of bromine is observed in all similar brominated compounds.

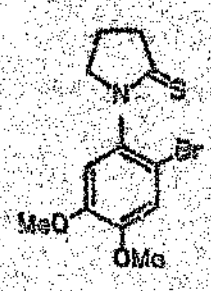
For the N-phenylethyllactams [57c] and [58c], four sets of triplets are observed in the proton spectra. Assignments were made on the basis of the PMR spectrum of [58c] and similar effects appear to hold for [57c]. Decoupling at 1.97 ppm, the centre of the quintet from the methylene

protons in the ring, simplifies two triplets at 2.37 ppm and 3.31 ppm to singlets. Thus one can see that the methylene protons next to nitrogen in the chain give signals more downfield than those from the methylene protons next to the nitrogen in the ring. The methylene protons adjacent to the aryl group in the chain give signals more downfield, by 0.54 ppm, than the signals from the methylene protons adjacent to the carbonyl group in the ring. This shows that the deshielding effect of the aromatic magnetic field is stronger than that from an amide carbonyl group. As was found for the N-benzyl lactams, the introduction of bromine in the aryl group shifts the signals from the methylene protons adjacent to the aryl group in the chain more downfield (0.12 ppm) than in the corresponding unbrominated compound. For compound [57c], a ^{13}C-^{1}H correlation spectrum was necessary to distinguish between the aliphatic carbons both in the chain and in the ring. Thus the methylene carbon next to nitrogen in the ring is furthest downfield of all the methylene signals.

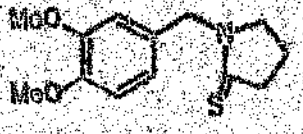
2.3 Preparation and characterisation of thiolactams

2.3.1 Synthesis

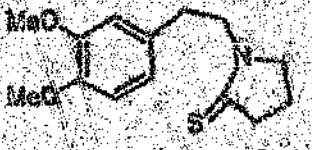
The five thiolactams [59] and [60] shown below were prepared in this project by thionation of lactams [57] and [58].



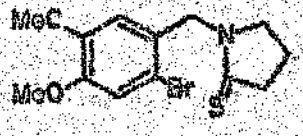
[60a]



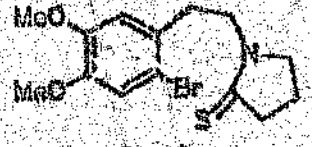
[59a]



[59b]



[60b]



[60c]

Thionation of the bromolactam [58a] was brought about by heating [58a] and phosphorus pentasulphide together under reflux in benzene. 1-(2-Bromo-4,5-dimethoxyphenyl)pyrrolidine-2-thione [60a] was obtained in 62% yield together with 20% recovered starting material. Recrystallisation of the compound proved difficult. The thiolactam is barely soluble in acetone or ethyl acetate. The best solvent system found

was a chloroform ethyl acetate mixture. Boiling acetonitrile also works well. The same problem was encountered in these laboratories by Hocken when she tried to recrystallise the various N-arylthiolactams she prepared.[70a]

Thionation of the N-benzyllactam [58b] was easily achieved using the usual procedure by heating together lactam [58b] and phosphorus pentasulphide in benzene under reflux. Good isolated yields (92-93%) were obtained. The crude thiolactam, 1-(2-bromo-4,5-dimethoxybenzyl) pyrrolidine-2-thione [60b], was recrystallised from acetonitrile to yield colourless crystals.

Good isolated yields were obtained (96-100%) for the preparation of 1-(2-(2-bromo-4,5-dimethoxyphenyl)ethyl)pyrrolidine-2-thione [60c]. After recrystallisation from acetonitrile colourless cubes were obtained.

Thiolactams [59a] and [59b] were also prepared. Their preparation is necessary for preparing compounds described in Section 3.3. 1-(3,4-Dimethoxybenzyl)pyrrolidine-2-thione [59a] was obtained in a 76% yield. The thionation reaction of lactam [57c] gave a fair yield of [59b], 69%, although only one attempt was made.

Lawesson's reagent can also be used to cause thionation.[70a] Recently a new method for thionation of amides and lactams has been reported.[70b] It uses the action of sodium carbonate on phosphorus pentasulphide to form a complex. The procedure provides milder and faster reaction conditions (THF/r.t.) with yields comparable to those obtained here. In these laboratories, other workers have found the new procedure to be superior to the standard thionation with phosphorus pentasulphide, and it is recommended if the work reported here should ever be repeated.

2.3.2 Spectroscopic characterisation

The signal positions for both the proton and carbon NMR spectra for the thiolactams prepared in Section 2.3.1 are collected in Tables 3-4 (see Appendix for spectra).

	60a	59a	60b	59b	60c
C-2	204.15	201.02	201.72	200.87	200.73
C-3	44.71	44.76	44.80	44.80	44.71
C-4	20.04	19.15	19.57	19.63	19.56
C-5	57.35	53.68	54.10	55.56,	55.50
2xOMe	55.99	55.69	56.22, 56.19	55.74, 55.79	55.92, 55.89
CH2Ar	———	51.13	50.74	31.64	31.59
CH2CH2Ar	———	———	———	49.39	47.43
Ar C-1'	131.72	127.52	126.76	130.62	129.20
Ar C-2'	110.76	with C-5' & 6'	114.26	with C-5' & 6'	113.72
Ar C-3'	115.11	148.61, 148.96	113.02, 115.19	147.59, 148.83	113.09, 115.15
Ar C-4'	148.65,		148.86,		148.15,
Ar C-5'	149.31	120.85, 111.31,	149.46	120.50, 111.68,	148.36
Ar C-6'	with C2'	110.81	with C3'	111.13	with C3'

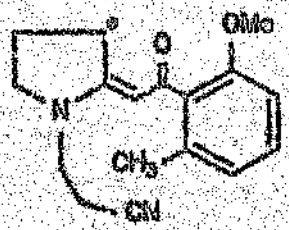
Table 3 CMR Chemical shifts (δ, $p_{p.m.}$) for thiolactams [59] and [60].

	60a	59a	60b	59b	60c
H-3	3.19, t	3.08, t	3.08, t	2.92, t	2.91, t
H-4	2.30, quintet	2.02, quintet	2.03, quintet	1.92, quintet	2.02, quintet
H-5	4.10, broad hump	3.60, t	3.64, t	3.47, t	3.56, t
2xOMe	3.86, 3.89	3.86, 3.87	3.83, 3.88	3.82, 3.84	3.86
arom H's	6.81, 7.11	6.88, m 6.96, d	7.01, 7.14	6.75	6.82, 7.00
CH2Ar	———	4.92	5.08	2.96, t	3.14, t
CH2CH2Ar	———	———	———	3.92, t	3.96, t

Table 4 PMR Chemical shifts (δ, ppm) for thiolactams [59] and [60].

In the proton spectrum of 1-(2-bromo-4,5-dimethoxyphenyl)pyrrolidine-2-thione [60a], the signals from H-5 protons, those next to nitrogen in the

ring, show up as a broad hump (δ ≈ 4.1 ppm) near the two methoxy signals. The marked downfield shift is caused by the deshielding effect from both the aromatic magnetic field and the mesomeric effect from the thiocarbonyl group. Changing solvent from $CDCl_3$ to C_6D_6 did not help to solve the problem. If the two protons on C-5 were interconverting with ease by ring inversion then an average signal should be obtained. Indeed by running the PMR spectrum at 50 °C in $CHCl_3$, we resolved the broad hump from H-5 protons into a poor triplet (4.00 ppm, J = 5.45 Hz). [In these laboratories Parsons[70b] also resolved the broad hump (3.16 ppm) of C-3 protons in the heterocyclic ring in vinylogous amide [67] to a clear triplet (3.13 ppm, J = 7.71 Hz) by running the PMR spectrum at 50 °C.] The ^{13}C spectrum of [60a] shows only ten peaks.



[67]

The aromatic region of the proton spectrum of 1-(3,4-dimethoxybenzyl) pyrrolidine-2-thione [59a] is quite complex. Two regions of multiplets were recorded. One region, centred on 6.96 ppm, has a relative integration of one. A doublet with a coupling constant of 1.8 Hz was observed. This is probably due to a *meta* coupling because of the small coupling constant recorded. Other signals were centred on 6.85 ppm. A close inspection of these signals reveals that the integration is split up into two regions corresponding to relative integration of one each. The signal centred on 6.86 ppm is a doublet with a coupling constant of 1.8 Hz. Thus this signal comes from a proton that is *meta* to the one described above. Although it is suggested that these signals come from aromatic H-2 and H-6, one can not be certain of the assignment. A singlet at 6.84 ppm probably comes from aromatic H-5, i.e. no *ortho* coupling was observed between aromatic H-5 and H-6. In going from unbrominated thiolactam [59a] to 1-(2-bromo-4,5-dimethoxybenzyl)pyrrolidine-2-thione [60b], comparable peak shifts were observed as those obtained in going from unbrominated lactam [57b] to lactam [56b]. The benzylic proton signal has shifted more downfield (0.16 ppm) from [59a] to [60b]. In the

^{13}C spectra of [60b], the phenyl carbon with bromine attached moves more upfield by 6.59 ppm compared with the analogous carbon in the unbrominated compound [59a].

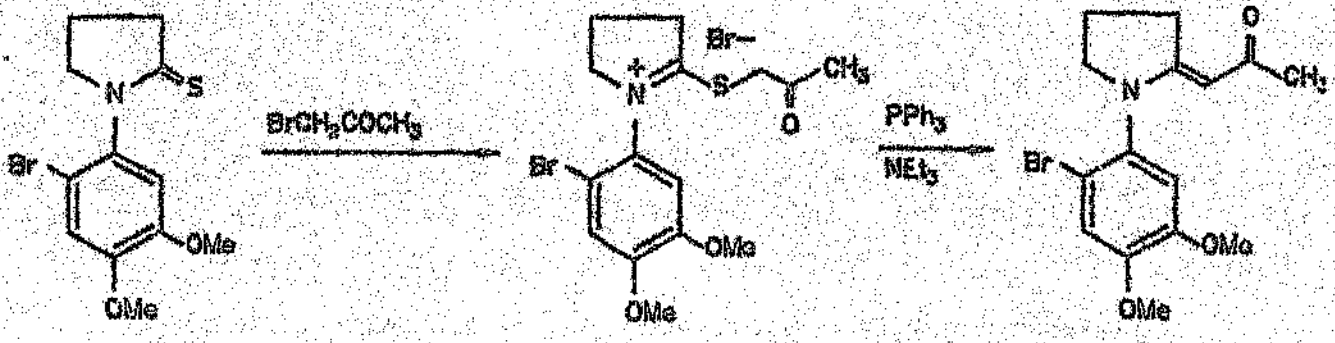
The same sequence of position of triplets as those observed for the corresponding lactams appeared for 1-(2-(2-bromo-4,5-dimethoxyphenyl) ethyl)pyrrolidine-2-thione [60c]. This was revealed by a ^{13}C-^{1}H correlation and decoupling experiments. But now the triplets from methylene groups adjacent to the aryl group in the chain and adjacent to the thiocarbonyl group in the ring have overlapped each other slightly to produce a multiplet at about 3.10 ppm, because the ring methylene protons have moved downfield in the thiated compound. The triplet from the methylene protons next to nitrogen in the chain appears far downfield (3.95 ppm). Several factors cause this downfield shift. Electronically these protons are deshielded by the aromatic magnetic field, the electronegative nitrogen and the thioamide. Finally, the mesomeric effect from the thiocarbonyl group must also have some deshielding effect for these protons to shift downfield, by 0.5 ppm from about 3.52 ppm in bromolactam [58c]. The aromatic protons in 1-(2-(3,4-dimethoxyphenyl) ethyl)pyrrolidine-2-thione [59b] coalesce to give a broad singlet in the proton spectrum.

2.4 Preparation and characterisation of vinylogous amides and urethanes

In general, exocyclic vinylogous amides and urethanes are best prepared by the sulphide contraction reaction.[15] From experience, a salt formation between a thiolactam and an α-halocarbonyl compound is best achieved by simply mixing the two compounds in as little solvent as possible. Suitable solvents include acetone, acetonitrile, chloroform, and dichloromethane. The mixture is usually stoppered in a flask and left to stand at room temperature. The reaction may be quick and sometimes the insoluble salt crystallises out of the solution. Higher temperatures have been tried to speed up sluggish salt formations which may drag into days. Excess (10%) α-halocarbonyl compound is usually used. The sulphur extrusion step is best achieved when both a thiophile and a base are used.

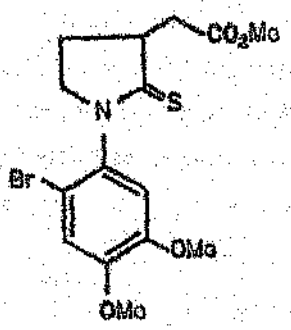
2.4.1 N-Aryl systems by sulphide contraction

In the N-aryl series, bromoacetone was chosen as the α-halocarbonyl compound. Salt formation between thiolactam [60a] and bromoacetone [4] in chloroform proved difficult. This is due partially to the low solubility of [60a] and the sluggish progression of the reaction. After twelve days at room temperature, an initial attempt at salt formation still showed the presence of [60a] even though 2.2 equivalents of bromoacetone were used. Leaving the reaction mixture in an oven at 50 °C did not improve the situation. After contraction and chromatography, less than 22% of the vinylogous amide [53a] was obtained. Some starting thiolactam and lactam were also isolated. Changing the solvent from chloroform to acetonitrile presented the same problem. Again switching temperature to 50 °C did little to help. An even lower yield (14%) was obtained. The diminished nucleophilicity of sulphur is associated with the mesomeric interaction between the thioamide group and the N-aryl substituent. It is known that amines having an aryl group attached to nitrogen are characterised by somewhat larger HNH and HNC angles,[94b] *i.e.* nitrogen is more nearly planar than in alkylamines. This is caused by the mesomeric release of the lone pair on nitrogen into the aromatic ring, giving the N-C bond some double bond character and making the amine approach planarity.

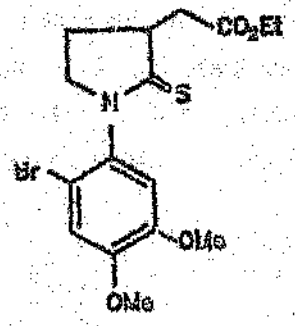


Changing the α-halo compound to methyl bromoacetate did speed up the salt formation process. This is not necessarily expected. However, the major compound isolated after contraction was the 3-alkylated compound [68] (11%). Similar results were obtained when ethyl bromoacetate was used. This time the 3-alkylated compound [69] was obtained in 20% yield, together with the desired vinylogous urethane [53b], also in 20% yield. Some thiolactam and lactam were also isolated. Acid extraction did not transfer [53b] into the aqueous phase. This indicates that the system [53b] is not very basic, probably because the lone pair on nitrogen is

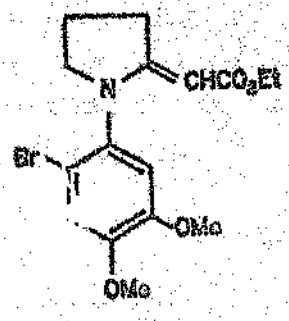
further delocalised with the aryl moiety, as well as with the vinylogous urethane system.



[68]

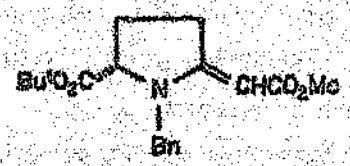


[69]

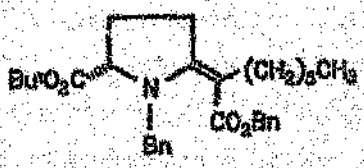


[33b]

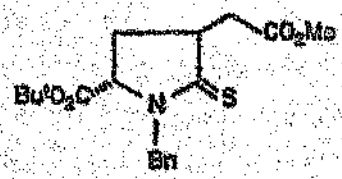
The problem of 3-alkylation in sulphide contraction reactions of N-aryl thiolactams has been experienced by Hosken.[6,13] Rapoport had the same problem when he tried to prepare the vinylogous urethanes [21][19] and [70],[72] although his starting thiolactams were not of the N-aryl class. Both [71] and [72] were obtained.



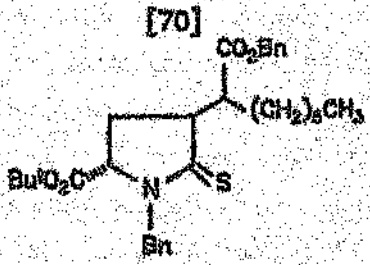
[21]



[70]



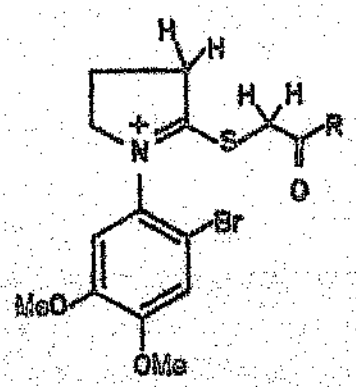
[71]



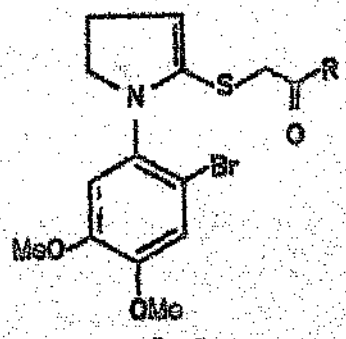
[72]

The following explanation for the formation of 3-substituted thiolactams has been proposed.[19,72] α-Thioiminoether salts [73] possess not only an acidic α-proton in the alkyl side chain, but also an acidic proton in the α-position of the pyrrolidine ring. Abstraction of either of these is possible. According to Rapoport, proton abstraction at the α-position of the ring would lead to the formation of an intermediate ketene S,N-acetal [74]. Transalkylation of [74] would lead to the formation of [68] and [69], while hydrolysis during isolation would lead to the formation of the lactam [58a], although no effort was made to isolate the lactam. Using the same reasoning, Hosken could explain the formation of 3-alkylated thiolactams together with the isolation of the corresponding

lactams in her sulphide contraction attempts with various N-aryl thiolactams. It appears that the presence of an aryl group on nitrogen in the α-thioiminoether salts makes the α ring protons more acidic than the alkyl side chain α-protons. Steric factors are less probable than electronic factors since in work in these laboratories, the problem of 3-alkylation is little encountered outside the N-aryl thiolactam class.



[73]



[74]

In the present study only two 3-substituted thiolactams, [68] and [69], were isolated and characterised by NMR. The alkylation at the 3 position has introduced a stereogenic carbon centre into the molecule, and as a result all methylene hydrogens are diastereotopic, hence intrinsically non-equivalent. Alkylation at the 3 position also appears to introduce rigidity to the ring, and this further complicates the proton spectra. Non-equivalent signals from the ring methylene protons and those next to the ester carbonyl group were detected, and complex splitting patterns were observed (see Appendix for spectra). Alkylation at the 3 position causes the signals from the ring carbons to shift slightly in their CMR spectra relative to unsubstituted thiolactams. Signals from the aryl carbons and those from the two methoxy groups stay relatively unchanged. As can be seen from Table 5, downfield shift is observed in the signals from the ring carbons, except those from C-5. This is most pronounced in the signals from C-4, where a downfield shift of 7 ppm was detected. Signals from C-3 are also about 5 δ units downfield. This downfield shift is caused by the deshielding effect from the alkoxycarbonylmethyl group present in the 3 position. However, the signal due to the carbon adjacent to nitrogen (C-5) is not affected by this deshielding, and it shifts upfield by some 2.5 ppm.

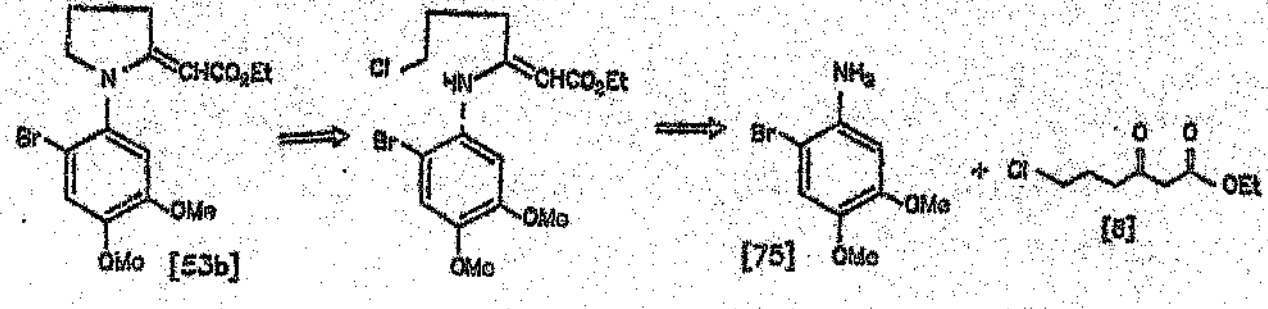
compound	C_2 ppm	C_3 ppm	C_4 ppm	C_5 ppm
60a	204.15	44.71	20.94	57.35
68	205.74	50.00	27.85	55.11
69	205.36	49.69	27.43	54.60

Table 5 Comparison of CMR chemical shifts between thiolactam [60a] and the 3-alkylated thiolactams [68] and [69].

2.4.2 Alternative synthesis of N-aryl vinylogous urethanes

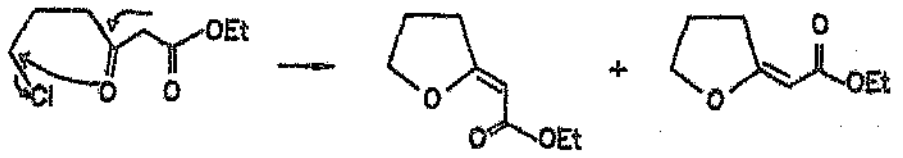
2.4.2 a) Vinylogous urethane [53b]

Because of the disappointing performance of the sulphide contraction in the preparation of N-aryl vinylogous amides and urethanes, the poor yield and competition from 3-alkylation, another method for their preparation was sought. In a disconnection approach it is not difficult to see that [53b] can be constructed from 2-bromo-4,5-dimethoxyaniline [75] and ethyl 6-chloro-3-oxohexanoate [8]. Such an approach was adopted by Hosken, who prepared several N-aryl vinylogous urethanes this way by modifying a published synthesis[73] of N-H vinylogous urethane to suit her purposes.



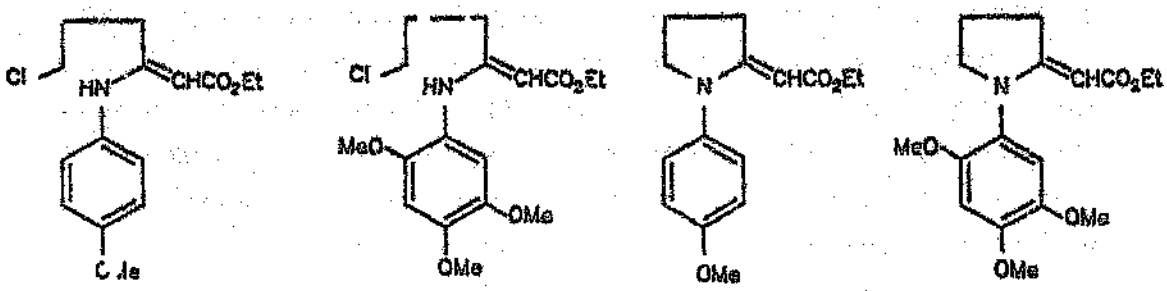
In Hosken's optimised method, an aniline was heated at 70 °C together with [8], preferably in the absence of a solvent. A catalytic amount of iodine was also present, because it was reported[74] that molecular iodine catalytically promotes the formation of acyclic N-aryl vinylogous urethanes by condensation of anilines at the keto group of β-ketoesters. During the reaction both water and HCl are eliminated; therefore, to promote the forward reaction, a drying agent (sodium sulphate) and a solid base (disodium hydrogen phosphate) were present. Sodium sulphate instead of magnesium sulphate was used as drying agent because it was

feared that magnesium(II) could form a co-ordination complex with the β-ketoester [8] in the reaction. A weak base was employed because stronger bases lead to the formation of compounds [76] and [77] through the formation of the anion of [8], as shown below.



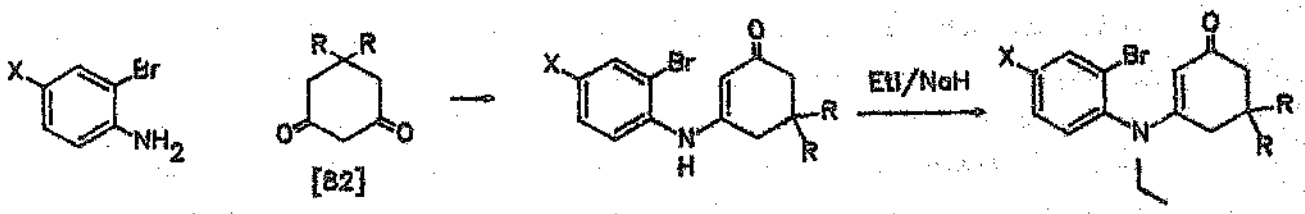
[76] [77]

Compound [8] possesses three electrophilic centres. In the absence of strong bases, the ester carbonyl centre will be the least reactive site. It was found by Hos' .. that the aniline first attacks at the ketonic carbonyl centre of [.. to give an acyclic N-aryl vinylogous urethane. This observation was supported by the isolation of the intermediates [78] and [79] in the preparation of vinylogous urethanes [80] and [81] respectively. Further heating of intermediate [78] in acetonitrile completed the desired cyclisation. Vinylogous urethane [79] cyclised to [81] on standing in solution. Hence a higher reaction temperature was required for complete effective cyclisation, and 70 °C appears to be optimal.

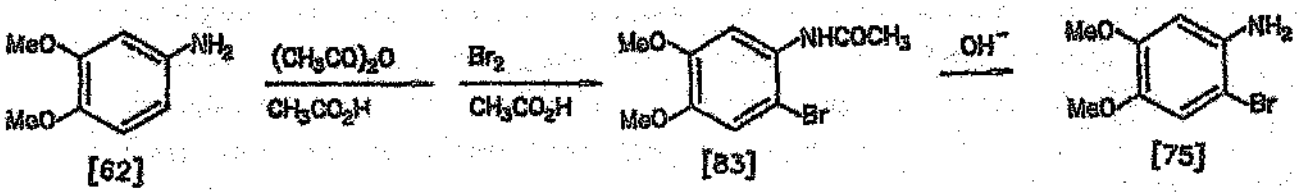


[78] [79] [80] [81]

It is worth mentioning that Kibayashi *et al.* have prepared several N-aryl vinylogous amides using a similar approach by heating together substituted *o*-bromoaromatic amines and cyclohexane-1,3-dione [82, R = H] or dimedone [82, R = CH3] without any solvent in nitrogen.[75] Good yields were obtained (67-90%). These secondary vinylogous amides could easily be N-ethylated with ethyl iodide and sodium hydride to give the corresponding tertiary enaminones. Yamanaka *et al.* have prepared many N-aryl enaminones similarly.[76]



Before the Hosken procedure could be carried out to prepare [53b], the appropriate aniline, *i.e.* 2-bromo-4,5-dimethoxyaniline [75], had to be made. Hosken had tried to brominate some N-aryl vinylogous urethanes on the benzene ring, but the reaction was unsuccessful. Therefore introduction of bromine onto the benzene ring at the aniline stage was necessary, and a protection/deprotection strategy was followed.[77] The aniline [62] was converted to the corresponding anilide, which could then be selectively brominated. The following scheme illustrates the conversion of [62] to [75].



The reaction between [62] and acetic anhydride was very exothermic and quick. When t.l.c. indicated that all [62] was consumed, bromine in acetic acid was added. Again an exothermic reaction was observed. After aqueous work-up, anilide [83] was isolated in high yields. The deprotection step, however, proved problematic. Firstly, acid hydrolysis of the anilide was attempted. Unsatisfactory results were obtained. Almost all anilide was destroyed by concentrated hydrochloric acid to give an uncharacterisable black substance which dissolved in basic aqueous solution and could not be extracted by dichloromethane or ethyl acetate. Moderately strong acid gave incomplete hydrolysis. However, base hydrolysis produced an almost quantitative yield of the desired aniline [75] as a purplish crystalline solid.

Two attempts were then carried out to prepare [53b]. The first one used the reaction conditions suggested by Hosken. During the progress of the reaction so much solid developed out of the solution that stirring was made impossible. After work-up, recrystallisation, and column chromatography, the desired vinylogous urethane was obtained in a 40%

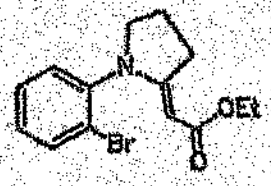
yield. No attempt was made to isolate and characterise the other products. Although this was better than the sulphide contraction approach, the low yield was still disappointing. It was reasoned that perhaps the solid formation during the reaction had provided a poor medium for reaction, thus giving a low yield for the desired compound. In the second attempt some DMF was introduced as solvent. This, however, gave an even poorer yield (16%) after chromatography. Since this reaction is the same in nature as the one used to prepare lactams between an appropriate amine and γ-butyrolactone, two sealed tube experiments were also carried out. The first attempt used all the ingredients suggested by Hosken plus some acetonitrile (1ml), and the contents were heated at 130 °C in a sealed tube. In the second attempt, just the aniline [75], β-ketoester [8], and toluene (2ml) were heated at 130 °C in a sealed tube. Both attempts failed to produce the desired vinylogous urethane [53b]. In the latter case starting aniline [75] was recovered. Hence it can be concluded that the procedure suggested by Hosken is the best one available. Although a low yield was obtained using this approach, it nevertheless has the advantage of time-saving over the sulphide contraction approach in that fewer steps are required.

2.4.2 b) Preparation of other N-aryl vinylogous urethanes

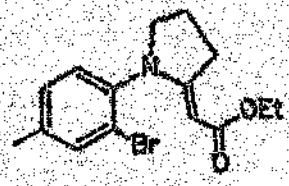
The preparation of other N-aryl vinylogous urethanes is necessary for the study of palladium-catalysed Heck reaction described in Section 3.3. Reactions between various 2-bromoaromatic amines and β-ketoester [8] were tried, but only two successful preparations resulted.

The various 2-bromoaromatic amines required were prepared from the corresponding aromatic amines by the action of bromine in dioxane,[78] except in the case of 2-naphthylamine, where a protection and deprotection strategy was used.[79] The use of bromine in dioxane provides a direct mono-*ortho*-bromination of certain aromatic amines. In the case of *p*-toluidine, the yield was poor (12%), and some 2,6-dibromo-4-methylaniline and starting aniline were also detected, but for *p*-nitroaniline, the yield of 2-bromo-4-nitroaniline was excellent (100%). However, in the case of 3,5-dimethylaniline [84], a mixture of tribrominated compound and starting material was obtained.

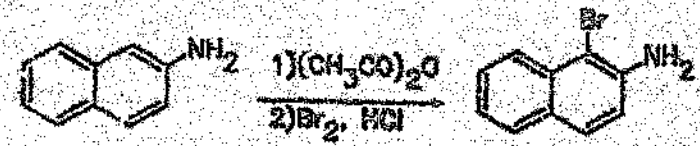
The reaction between o-bromoaniline and [8] gave the 2-bromo substituted N-aryl vinylogous urethane [85] in 41% after chromatography. [This is comparable to the yield obtained for the reaction between aniline itself or [8], 52%.][6,13] Vinylogous urethane [86] from o-bromotoluidine, was obtained in a 63% yield after chromatography. Unsatisfactory results were obtained from the reactions of 2-bromo-4-nitroaniline [87] and 1-bromo-2-naphthylamine [88] with β-ketoester [8] respectively. 2-Bromo-4-nitroaniline [87] was recovered unchanged after reaction with [8], in agreement with the observation for similar reaction between p-nitroaniline and [8].[6,13] 1-Bromo 2-naphthylamine [88] reacted with β-ketoester [8], giving an unidentifiable yellow liquid. This disappointing result contrasts with the 90% yield of vinylogous urethane from reaction between 2-naphthylamine itself and [8].[6,13] It is noteworthy that in a similar reaction carried out by Kihayashi *et al.* the desired secondary vinylogous amides [89] were obtained in good yields (R = H, 90%, R = CH3, 67%).[76]



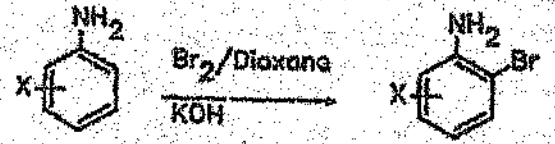
[85]



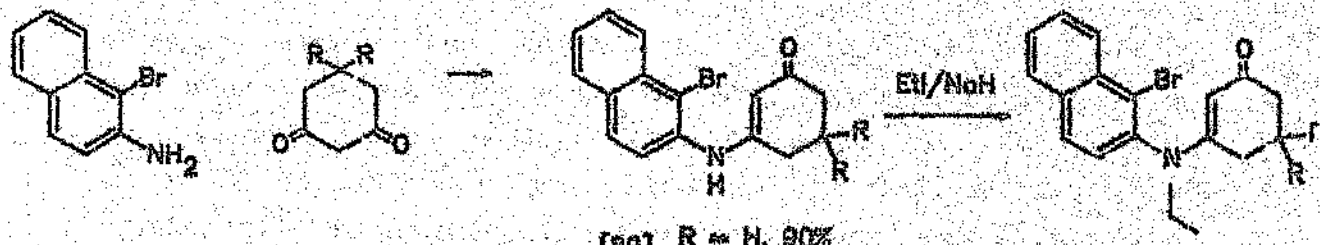
[86]



[88]



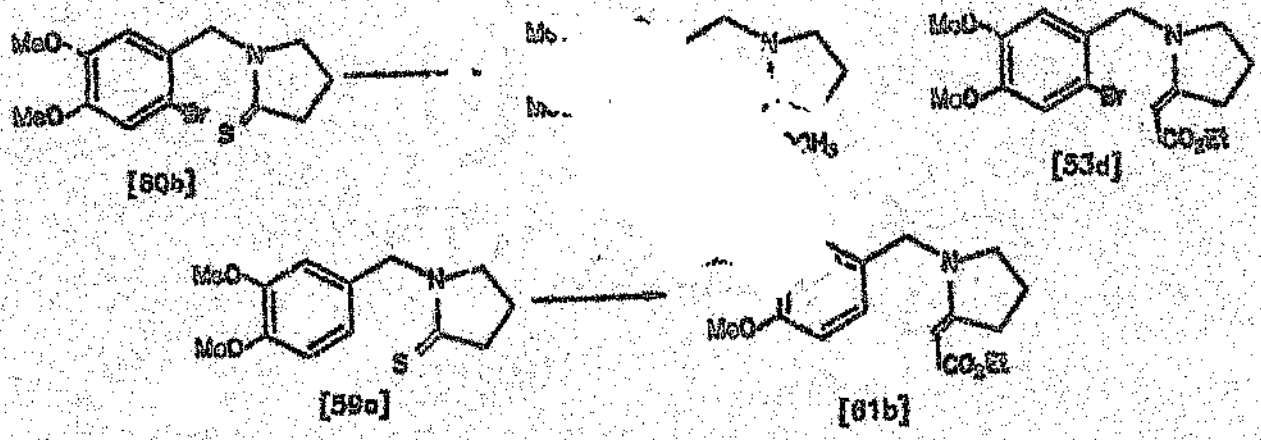
[84], X=3,5-dimethyl [87], X=4-nitro



[89], R = H, 90%
R = Me, 67%

2.4.3 N-Benzyl and N-phenylethyl vinylogous amides and urethanes

As expected, sulphide contraction reactions were achieved smoothly with thiolactams [59] and [60] in the presence of triethylamine and triphenylphosphine. Good yields were obtained with both ethyl bromoacetate and bromoacetone. It was found that the yield of sulphide contraction is strongly dependent on the solvent used in the salt formation step. In general polar solvents such as acetone were found to give better yields in these reactions than less polar solvents such as dichloromethane. In all the sulphide contraction reactions the addition of triethylamine produced an exothermic reaction, accompanied by a colour change. Fuming was usually observed too. Crystallisation of phosphine compounds could sometimes be observed. A solid precipitated in the salt formation stage for the preparation of [53c], [53d], and [61b].



Compounds [53c] and [53d] are different in two ways. Vinylogous amide [53c] was isolated as an oil (67% after chromatography), which later solidified. After recrystallisation, a colourless crystalline solid was obtained. Crude vinylogous urethane [53d] was isolated as a solid (65% after acid work-up). The products showed different basicities: compound [53d] could be purified by extraction into aqueous acid, but [53c] could not be extracted in this way. The reason for compound [53d] being more basic than compound [53c] is not clear.

Vinylogous urethane [61b] was prepared from thiolactam [59a]. Its preparation is necessary for comparison with a product obtained in a procedure to be described in Chapter Three, Section 3.3. Acetone was used in the salt formation step. After contraction t.l.c. indicated that the reaction was amazingly clean. The desired compound was easily isolated in a remarkable 90% yield after column chromatography.

Compound	83b	61a	85	86
C-2	165.29	169.59	168.52	163.09
C-3	31.83	32.66	31.44	31.09
C-4	22.13	21.60	21.70	21.94
C-5	53.73	55.12	53.36	52.94
>C=N	81.11	80.67	80.82	80.36
$\geq$CNO	54.20, 56.32	56.01, 58.06	———	19.90 CH_3Ar
>C=O	165.38	164.90	164.42	164.13
$-OCH_2CH_3$	58.63	58.39	57.81	57.31
$-OCH_2CH_3$	14.60	14.63	14.15	13.92
Ar C-1'	131.04	134.36	132.12	126.11
Ar C-2'	112.70	with C-5' & 6'	132.17	131.41
Ar C-3'	111.79, 115.73	147.53, 149.53	133.46, 129.36, 129.06, 128.64	with C-5' & 6'
Ar C-4'	149.32			130.97
Ar C-5'	149.27	117.52, 112.59, 108.89		130.10, 128.97, 128.57
Ar C-6'	with C3'			

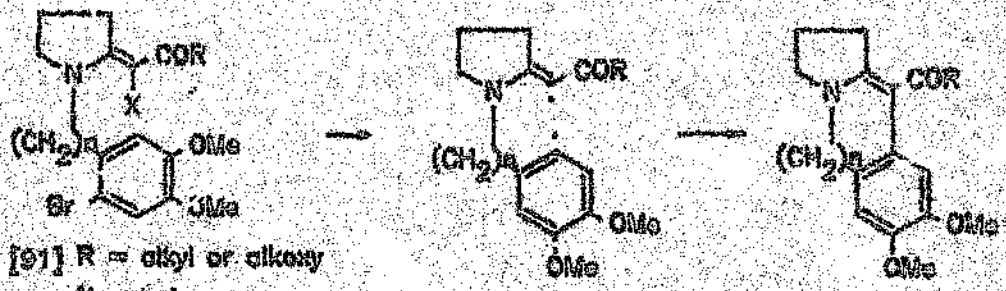
Table 7a CMR Chemical shifts (δ, ppm) for N-aryl enaminones.

Compound	53e	53f	61c
R =	CH_3	OEt	OEt
C-2	164.51	169.39	169.45
C-3	33.08	32.58	32.61
C-4	20.77	21.08	21.09
C-5	52.74	53.15	53.30
>C=CH	89.39	77.73	77.64
2xOMe	55.89	56.07	56.10, 55.95
>C=O	193.77	164.45	164.49
$-OCH_2CH_3$	———	58.20	58.21
$-OCH_2CH_3$	———	14.68	14.72
>C=OCH_3	30.44	———	———
CH_2CH_2Ar	32.03	32.04	31.70
CH_2CH_2Ar	45.96	45.99	48.09
Ar C-1'	129.48	129.90	131.34
Ar C-2'	113.82	113.95	with C-5' & 6'
Ar C-3'	115.34, 113.14	115.51, 113.98	148.01, 147.66
Ar C-4'	148.25	148.39, 148.35	120.51, 111.85, 111.38
Ar C-5'			
Ar C-6'	with C3'	with C3'	

Table 7c CMR Chemical shifts (δ, ppm) for N-phenylethyl enaminones.

This class of compounds produces interesting proton spectra. The appearance of the pyrrolidine ring protons reveals vital dynamic stereochemical information about these compounds. In all these compounds the *trans-s-cis* configuration was observed. This is clearly indicated by the position of the H-3 protons in the pyrrolidine ring. The (E) geometry around the carbon-carbon double bond enables the carbonyl group to come into close proximity with the H-3 protons; hence these protons are deshielded and they appear downfield at between 3.20 to 3.40 ppm. In the

compounds such as [91]. Substitution at the vinylic position is expected to increase the reactivity at that site because of alternative reactions that now become possible. This increased reactivity should enhance the success rate of the final coupling reaction between the aryl and vinyl centre. Suitable coupling reactions should be radical in nature, as [91] is effectively the precursor of a diradical. Appropriate reactions include Wurtz coupling reactions and radical reactions involving reagents such as Bu_3SnH and Co(I)-salen. Photochemistry can also be tried, although isolation of dibromo species similar to [91] from the photochemistry of some monobrominated compounds gives one reason to doubt that the coupling would work using a photochemical approach.



[91] R = alkyl or alkoxy
X = halogen

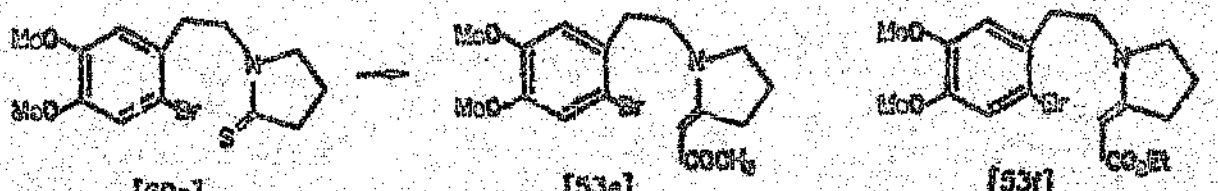
In the following sections, attempts to introduce halogens and sulphur at this position will be described. Different reagents including bromine, N-bromosuccinimide, cyanogen bromide, and related compounds were investigated.

2.5.1 Reactions with N-bromosuccinimide

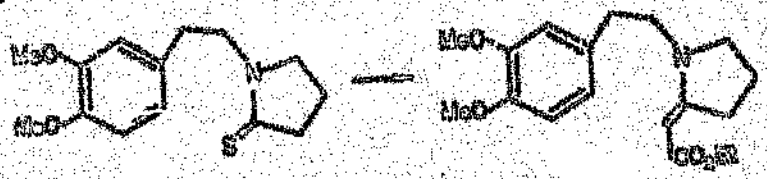
Halogenation of enamines has been widely investigated. A review has been presented by Hickmott.[92] Various halogenating materials ranging from molecular halogen to compounds such as bromodimethylsulphonium bromide have been used. Fluorinations have been carried out with NaF's. Regioselectivity can be achieved partially by employing the correct halogenating agent and the right conditions.

Literature examples exist for introduction of a halide at the vinyl position of enaminones. Kibayashi et al. succeeded in carrying out the bromination reactions shown overleaf.[93,94]

From the phenylethyl thiolactam [60c], vinylogous amide [53e] and urethane [53f] were obtained in good yields. A 63% yield after column chromatography was obtained for compound [53e] when dichloromethane was used in the salt formation step. This yield was pushed up to 84%, also after column chromatography, when acetone was used in the salt formation step. Similar differences in basicity as between [53c] and [53d] were observed here between [53e] and [53f]. Again acid work-up poorly separated compound [53e] from the other components, while good isolated yields were obtained for compound [53f] from acid work-up (90%). Again this yield was improved (92%) when acetone was used in the salt formation stage. Compound [53e] is a solid and [53f] a very thick yellow oil. Finally, the unbrominated vinylogous urethane [61c] was prepared as a crystalline solid from thiolactam [59b] (79%).



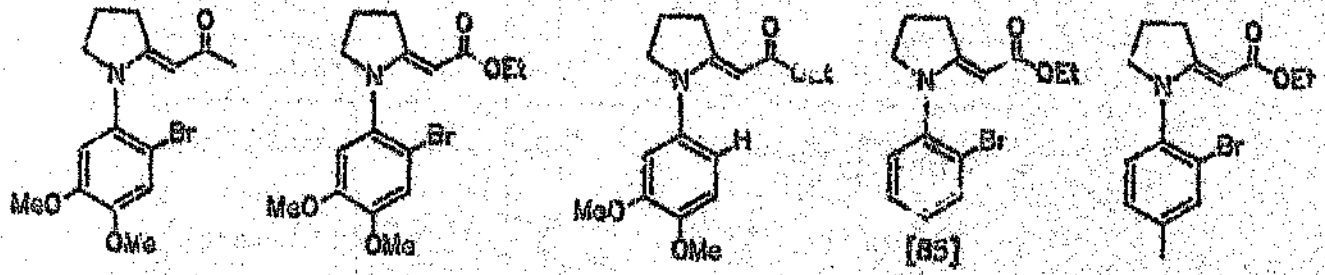
[60c] [53e] [53f]



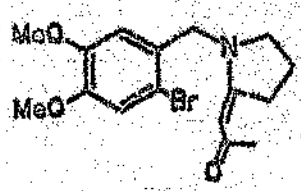
[59b] [61c]

2.4.4 Characterisation by nuclear magnetic resonance spectroscopy

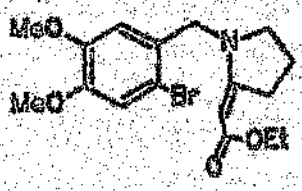
Proton and carbon NMR spectra for vinylogous amides [53a, 53c, 53e, 61d] and vinylogous urethanes [53b, 53d, 53f, 61a, 61b, 61c, 85, 86, 90] are summarised in Tables 6-7. Included in these tables for convenience are the unbrominated compounds [61a], [61b], [61c], and [61d], the isolation of which, by metal-induced debromination of [53b], [53d], [53f], and [53c], will be discussed in Chapter Four (see Appendix for spectra). The debrominated vinylogous urethane [90] with *t*-butoxide exchange was isolated from a Bu_3SnH experiment (see Section 5.2.2).



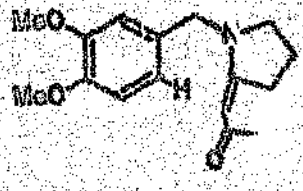
[53a] [53b] [61a] [85] [86]



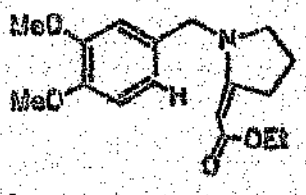
[53c]



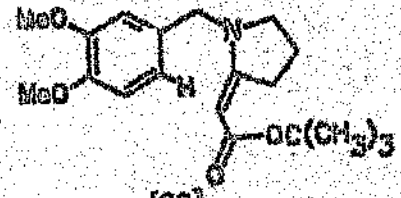
[53d]



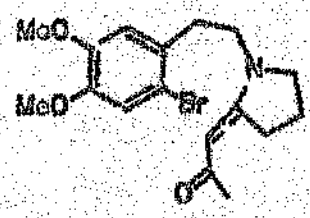
[61d]



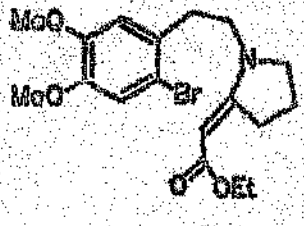
[61b]



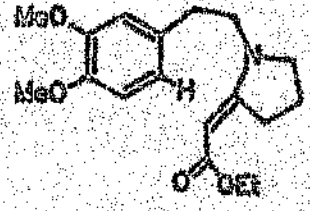
[90]



[53e]



[53f]



[61c]

Compound	53a	53b	61a	85	86
R =	CH_3	OEt	OEt	OEt	OEt
H-3	3.35, 2xdt	3.30, 2xdt	3.30, dt	3.31, tdd	3.28, q
H-4	2.15, quintet	2.15, quintet	2.09, quintet	2.13, quintet	2.10, quintet
H-5	3.30,dt 3.79,dt	3.31,dt 3.75,dt	3.69, t	3.30,dt 3.80,dt	3.46,dt 3.75,dt
>C=CH-	4.77, t	4.27, t	4.72, t	4.26, t	4.24, s
2xOMe	3.88, 3.92	3.85, 3.89	3.87, 3.89	———	2.31, s CH_3Ar
-OCH_2CH_3	———	4.05, q	4.06, q	4.03, q	4.01, q
-OCH_2CH_3	———	1.20, t	1.21, t	1.17, t	1.14, t
-$COCH_3$	1.96	———	———	———	———
arom H's	6.72, 7.11	6.74, 7.09	6.75-6.90	7.65,dd,H-3, 7.36, ddd, H-5, 7.25, dd, H-6, 7.19, ddd, H-4	7.46, s H-3 7.14, s H-5 & H-6

Table 6a PMR Chemical shifts (δ, ppm) for N-aryl enaminones.

Compound	53c	61d	53d	61b	60
R =	CH_3	CH_3	OEt	OEt	O-t-Bu
H-3	3.27, t	3.31, t	3.25, t	3.23, t	3.16, t
H-4	1.92, quintet	1.96, quintet	1.99, quintet	1.96, quintet	1.93, quintet
H-5	3.31, t	3.33, t	3.33, t	3.32, t	3.27, t
>C=CH-	5.10, s	5.25, t	4.63, s	4.72, s	4.66, s
2xOMe	3.74, 3.81	3.86, 3.88	3.81, 3.87	3.86, 3.87	3.86, 3.87
-OC$\underline{H}_2CH_3$	———	———	4.08, q	4.09, q	1.47, s $OC(CH_3)_3$
-$OCH_2C\underline{H}_3$	———	———	1.24, t	1.25, t	
-$COCH_3$	1.98	2.07	———	———	———
$ArCH_2$	4.32	4.34	4.34	4.29	4.27
arom H's	6.53, 6.98	6.71-6.86	6.60, 7.03	6.70-6.84	6.71-6.85

Table 6b PMR Chemical shifts (δ, ppm) for N-benzyl enaminones.

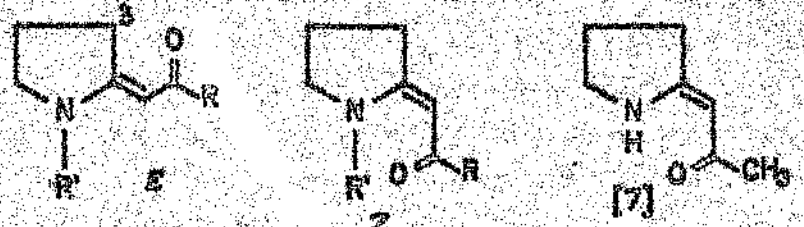
Compound	43e	53f	61c
R =	CH_3	OEt	OEt
H-3	3.12, t	3.15, t	3.13, t
H-4	1.79, quintet	1.86, quintet	1.85, quintet
H-5	3.15, t	3.20, t	3.15, t
>C=CH-	5.08, s	4.65, s	4.61, s
2xOMe	3.75, 3.77	3.85, 3.86	3.87, 3.88
-$OC\underline{H}_2CH_3$	———	4.11, q	4.11, q
-$OCH_2C\underline{H}_3$	———	1.27, t	1.27, t
-$COCH_3$	1.98	———	———
$CH_2C\underline{H}_2Ar$	2.85, t	2.93, t	2.90, t
$C\underline{H}_2CH_2Ar$	3.37, t	3.42, t	3.40, t
arom H's	6.53, 6.98	6.69, 7.01	6.69, 6.83

Table 6c PMR Chemical shifts (δ, ppm) for N-phenylethyl enaminones.

Compound	53c	61d	53d	61b	90
R =	CH_3	CH_3	OEt	OEt	O-t-Bu
C-2	165.22	165.63	169.34	169.59	169.40
C-3	93.06	93.47	92.37	92.66	92.55
C-4	20.91	20.93	21.20	21.03	21.19
C-5	51.87	51.99	52.17	52.18	51.95
>C=CH	90.03	89.79	78.77	78.21	80.17
2xOMe	55.94 56.03	55.94	56.02, 56.12	55.98	55.93
>C=O	194.43	194.54	165.01	165.26	164.50
-OCH$_2$CH$_3$	———	———	58.38	59.78	77.93 OC(CH$_3$)$_3$
-OCH$_2$CH$_3$	———	———	14.58	14.68	28.79 OC(CH$_3$)$_3$
>C=OCH$_3$	90.54	91.06	———	———	———
ArCH$_2$	49.84	49.78	49.99	49.75	49.76
Ar C-1'	130.14	128.12	126.56	128.48	128.76
Ar C-2'	113.25	with C-5' & 6'	113.24	with C-5' & 6'	with C-5' & 6'
Ar C-3'	110.98, 115.56	149.29	111.03, 115.59	149.17,	149.17,
Ar C-4'	148.91,	148.57	148.85,	148.41	148.39
Ar C-5'	148.58	119.55,	148.59	119.56,	119.63,
Ar C-6'	with C3'	111.27, 110.43	with C3'	111.16, 110.49	111.19, 110.60

Table 7b CMR Chemical shifts (δ, ppm) for N-benzyl enaminones.

Z isomers these protons appear more upfield, as exemplified by vinylogous amide [7], for which the C-3 protons appear at 2.70 ppm.[18]



E Z [7]

The proton spectra of the N-aryl vinylogous amide [53a] and urethanes [53b], [95] and [96] are worthy of comment here. The H-5 protons in the pyrrolidine ring exhibit AB system splitting patterns, further coupled to C-4 protons to produce signals that are approximately doublets of triplets. This might indicate a rigidity of the ring, as the two protons find themselves in different environments. This ring rigidity is caused by the presence of the nearby aryl group since this phenomenon is not observed in the other two classes of enaminone compounds. Another more likely explanation invokes restricted rotation around the N-aryl bond. The bulky o-bromo substituent on the aryl group introduces severe steric effects around the N-aryl bond, causing rotation around this bond to be restricted. The two C-5 protons thus are forced into different chemical environments, making one of the protons closer in space to the aryl ring. This restricted rotation also makes the aryl ring non-coplanar with the vinylogous amide system. When the bromine is removed as in [61a], free rotation around the N-aryl bond is established. The two C-5 protons are now equivalent, and they appear as a triplet. This is in agreement with the PMR data of the various N-aryl vinylogous urethanes with no substituent on C-2 of the phenyl ring, prepared by Hocken.[5,13] The C-5 protons in all these compounds are equivalent and they appear as triplets. The removal of bromine also causes the H-5 proton signal to have a slight upfield shift. Outside the N-aryl system, the H-3 and H-5 signals are close together because H-5 is shifted upfield. The aryl group is too far away to have any effect on these protons, as it has in the N-aryl compounds, although in the N-phenylethyl compounds the H-3 signals have also shifted upfield.

The position of the NH resonance is also very informative. It appears more downfield for the vinylogous amides than for the vinylogous urethanes. This can best be accounted for by the stronger deshielding

effect of the ketonic carbonyl group than the corresponding one of the ester carbonyl group, in which back-donation of electron density of the alkoxy portion shields the proton in question. The vinyl proton signal for vinylogous amide [53c] appears at 5.10 ppm, the furthest downfield signal in the three vinylogous amides, [53a], [53c], and [53e]. The absence of bromine as in [61d] shifts the vinyl signal even more downfield. Thus the vinyl signal of [61d] appears the most downfield of the vinylogous amides characterised (5.25 ppm). Except in the case of [61e], where an upfield shift of 0.04 ppm was observed, the removal of bromine shifts the vinyl signal downfield in the enaminone compounds. This is most pronounced in the N-aryl enaminone compounds, where a downfield shift of 0.45 ppm was observed from [53b] to [61a]. Such an effect has also been observed by Kikuchi *et al.* in some N-phenylethyl enaminones.[39,40] The signals of H-3 and H-4 protons of the N-aryl enaminone compounds in general occur more downfield than those of the N-benzyl and N-phenylethyl analogues. This could be attributed to the inductive effect of the aryl group that operates in the N-aryl case. Unlike those of the vinyl protons, the positions of the C-3 protons in the heterocyclic ring differ very little from vinylogous amides to vinylogous urethanes.

Allylic coupling between the H-3 protons and the vinyl proton is present in most of the enaminone spectra, a coupling constant of 1.0 Hz to 1.5 Hz being observed. For example a coupling constant of 1.37 Hz was observed for the case of compound [53b]. As a result of this coupling, the H-3 protons appear as triplets of doublets, while the vinyl proton appears as a triplet. In most spectra [*e.g.* 53c, 53e, 53f, 61b, 61c, 61l, the effect was not clear, the H-3 protons appearing as broad triplets and the vinyl signal as broad singlet. Evidence of the allylic coupling was obtained unambiguously by decoupling experiments. Irradiation at the H-3 signal caused the vinyl triplet to collapse to a singlet, or, if already a singlet, to sharpen; while irradiation at the vinyl proton signal caused a collapse of the H-3 triplet of doublets to a triplet (or sharpening of the triplet).

In the aromatic region, two sharp, distinct, signals were observed for the enaminones prepared with tetrasubstituted phenyl groups. They are separated by 0.33 ppm in [53f] and 0.45 ppm in [53e]. The separation has

been found to be greater for the vinylogous amides than for the vinylogous urethanes. The exact origin of these different separations can not even be speculated. No attempt was made to assign these two aromatic protons since this was not of vital importance. In the trisubstituted enaminones [61a], [61b], [61c], [61d], and [90] the aromatic protons show *ortho* and *meta* coupling, producing interesting splitting patterns that are amenable to simple analysis.

In the ^{13}C spectra, vinylogous amides have a carbonyl peak at around 194 ppm while that of the vinylogous urethanes appears at approximately 164-165 ppm. Similarly the proton-bearing vinyl carbon peak for the vinylogous amides appears at around 90 ppm, more downfield than that for the vinylogous urethanes, which appears at between 77 and 82 ppm. The absence of bromine from the phenyl group in these compounds results in a downfield shift of the aromatic carbon signal relative to the analogous signal in the unbrominated compound. This is indicated by the presence of a more intense peak in the aromatic region of their ^{13}C spectra. The absence of bromine from the phenyl group in [61c] has also shifted the chain carbon next to the nitrogen atom downfield by 2 ppm. This effect however is not observed in the N-benzyl enaminones. The benzylic signal appears at just below 50 ppm in all cases examined.

2.4.5 Infrared spectroscopy

The different series of compounds prepared show characteristic infrared spectra. Although infrared spectroscopy is not as powerful a tool as nuclear magnetic resonance spectroscopy, it indirectly reveals a side of molecular structure that can not be obtained from nuclear magnetic resonance spectroscopy, viz. the nature of the different bonds. It therefore is a complementary tool to nuclear magnetic resonance spectroscopic techniques.

The lactams [57] and [59] show a strong absorption just below 1700 cm^{-1} corresponding to the cyclic amide carbonyl stretch. Thus N-phenylethyllactam [57c] shows a strong absorption at 1665 cm^{-1} and N-aryllactam [57a] at 1675 cm^{-1}. The fact that N-aryllactam [57a] shows an absorption slightly higher than that of N-phenylethyllactam [57c] indicates delocalisation of the amide moiety is less in [57a] than in

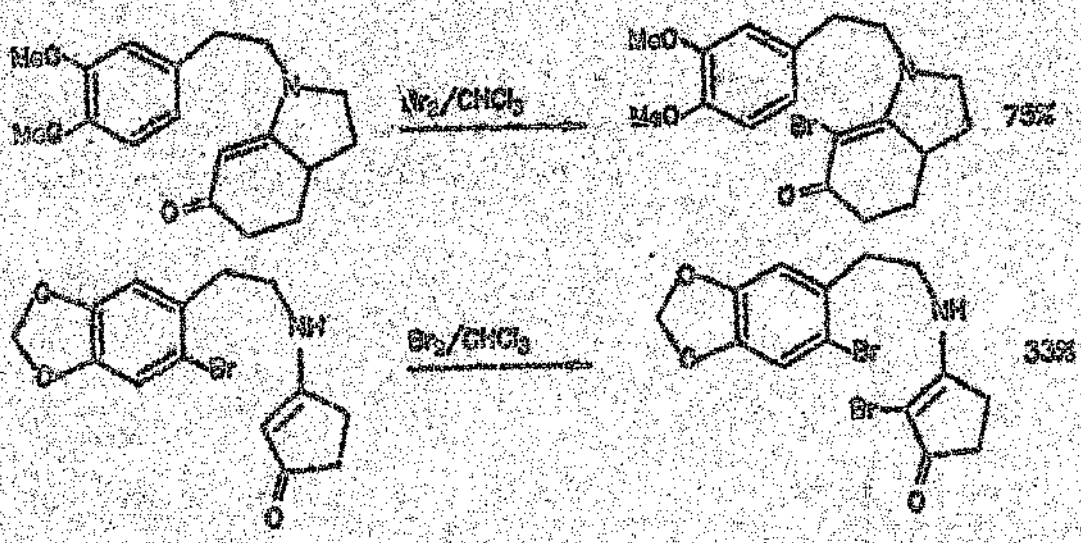
[57c]. This can be attributed to the electron withdrawing effect of the aryl group in [57a]. Bromination of the aryl group generally increases the lactam carbonyl absorption. Thus the peak shifts from 1675 cm^{-1} in [57a] to 1690 cm^{-1} in N-aryllactam [58a]. This implies that the lactam carbonyl bond in [58a] is slightly stronger than that in [57a]. Thus the bromine inductively withdraws electron density from the nitrogen. The same was observed for N-benzyllactams [57b] and [58b]. Bromination at the desired position in N-phenylethyllact. a [57c] did not change the lactam carbonyl absorption, since the aryl group is too far away to have any effect on the lactam group.

Thiolactams have a characteristic strong absorption around 1500 cm^{-1}. The bands are usually sharper than those for lactams. Thus N-aryl thiolactam [60a] shows a strong absorption at 1490 cm^{-1}. Bromination on the aryl group does not seem to have any effect on the thiocarbonyl stretching frequency. The N-benzyl thiolactams [60b] and [59a] have the same absorption frequency at 1490 cm^{-1}. The same is true for the N-phenylethyl thiolactams [60c] and [59b] at 1505 cm^{-1}. The 3-alkylated thiolactams [68] and [69] have a lower stretching frequency at 1475 cm^{-1}.

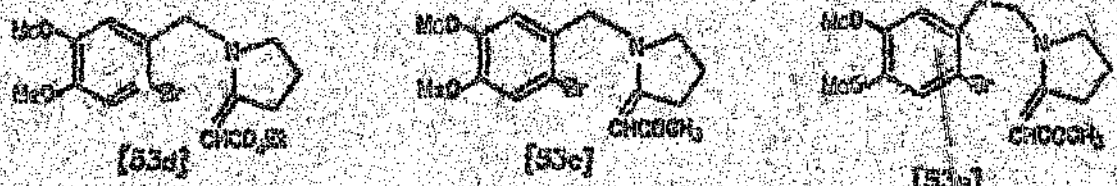
Vinylogous amides and urethanes show two characteristic absorption peaks at around 1700 and 1600 / cm^{-1} corresponding to carbonyl and vinyl C=C stretch. In the N-benzyl and N-phenylethyl vinylogous amides and urethanes, the carbonyls of the vinylogous urethanes have an absorption just stronger than that of the corresponding carbonyls from the vinylogous amides. This, however, is not the case for the N-aryl compounds. The vinyl C=C stretch ranges from 1600 cm^{-1} in N-phenylethyl vinylogous amide [53c] to 1580 cm^{-1}, which occurs in many vinylogous amides and urethanes. The unbrominated compounds show similar stretching frequencies at the same regions.

2.5 Attempted vinyl substitution reactions of vinylogous amides and urethanes, and related reactions

This section is devoted entirely to vinyl substitution reactions of vinylogous amides and urethanes. Successful reactions here would produce

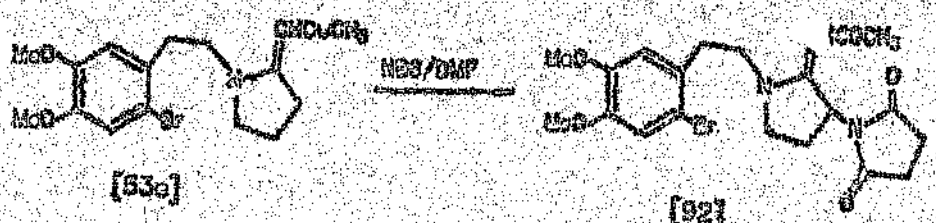


However, when Kibayashi's procedure was tried on the compounds shown below, it failed. Every attempt produced some sticky material which was not possible to purify by chromatography. No characterisable compound was ever isolated.



[53d] [53c] [53e]

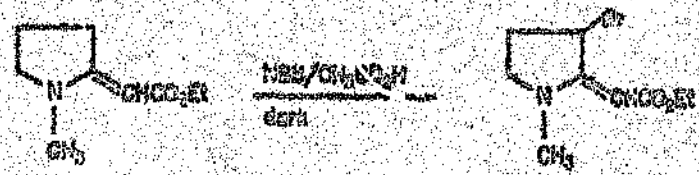
Another literature procedure using N-bromosuccinimide in DMF[39] was tried out on the compound [53e]. Vinylogous amide [92] was produced (64%). Probably it goes through a γ-Br compound, from which Br is then displaced by succinimide anion. A radical mechanism can also be called upon to explain the formation of compound [92], although this is less likely in a polar medium. Compound [92] decomposed on standing in air.



[53e] [92]

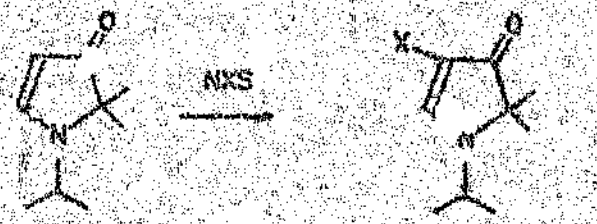
The bromination reaction was studied further using a model compound [93]. An acidic medium (CH_3CO_2H) was chosen. The acid was intended to quench succinimide anion formed in the reaction. Radical reaction is minimised by the use of a polar solvent and the fact that the reaction was carried out in the dark. Vinylogous urethane [94] was isolated in 41% yield after

column chromatography. (The same compound was obtained by Sack[94] who used the same reagents but tried different reaction conditions.) No succinimide anion participation was observed.



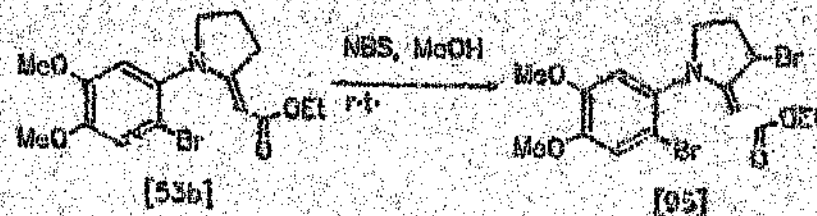
[93] [94]

McNab et al. achieved the following halogenation reactions in excellent yields using the appropriate N-halogenosuccinimide.[95] The reactions were carried out in methanol at 20 °C. They found that even molecular bromine in methanol could do the job, but solid potassium carbonate had to be added as well to mop up hydrogen bromide eliminated in the reaction or else a 1 : 1 mixture of starting material and product was the result.

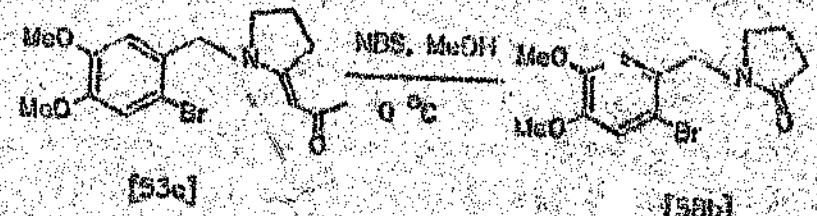


X = Cl, 91%
X = Br, 88%
X = I, 76%

When vinylogous urethane [53b] was reacted under the conditions specified above the γ-brominated compound [95] was isolated as a solid in a 76% yield after column chromatography. However when the vinylogous amide [53c] was treated similarly the corresponding lactam [58b] was isolated in a 94% yield after column chromatography.



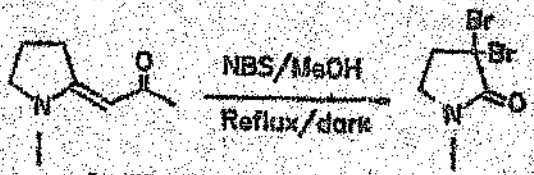
[53b] [95]



[53c] [58b]

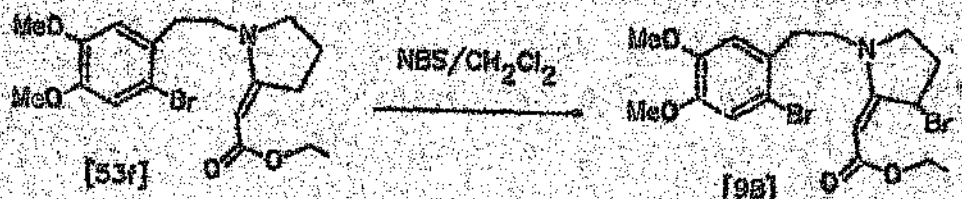
This reaction was studied further using a model vinylogous amide [96].

When [96] was treated with NBS in methanol at room temperature in the dark there was no reaction after 170 h and starting material was recovered. When the solution was refluxed in the dark, vinylogous amide [96] decomposed and the only compound isolated as a trace component appears to be the dibromide of N-methylpyrrolidinone [97]. This is indicated by the PMR spectrum of [97], which exhibited two sets of triplets (2x2H, 3.40 and 3.10 ppm, J 5.9 Hz) and a singlet (3H, 2.96 ppm).



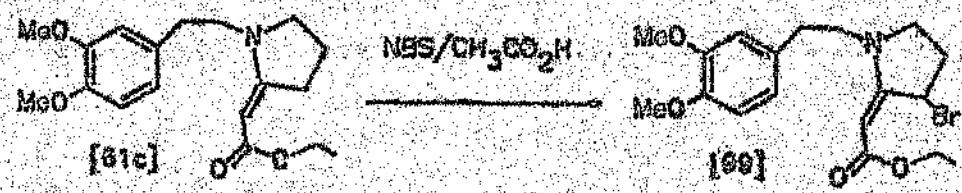
[96] [97]

The bromination reaction of [53f] was carried out in dichloromethane, a less polar solvent to enhance radical bromination. This, however, gave a very poor yield. The desired dibromide [98] was isolated as an oil in a 22% yield after column chromatography.



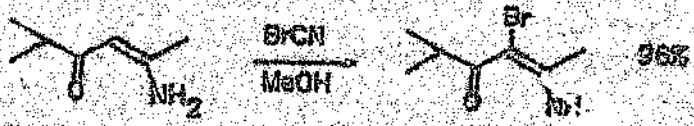
[53f] [98]

The γ-brominated vinylogous urethane [99] was prepared by the action of NBS in glacial acetic acid on [61c]. A 58% yield was obtained after column chromatography. No aromatic bromination was observed.



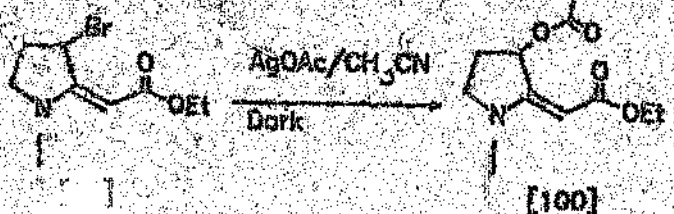
[61c] [99]

Cyanogen bromide is also a useful brominating agent. Bromination at the vinyl position of some acyclic vinylogous amides has been achieved in excellent yield in methanol at 0°C using this reagent.[66] However when vinylogous urethane [93] was treated accordingly a mixture of γ-brominated compound and starting material was obtained. No substitution of the bromide by cyanide anion was observed.

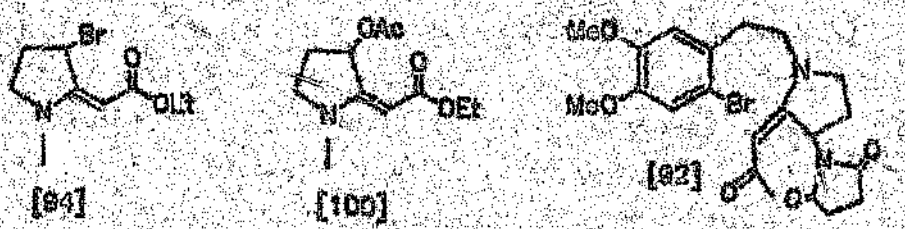


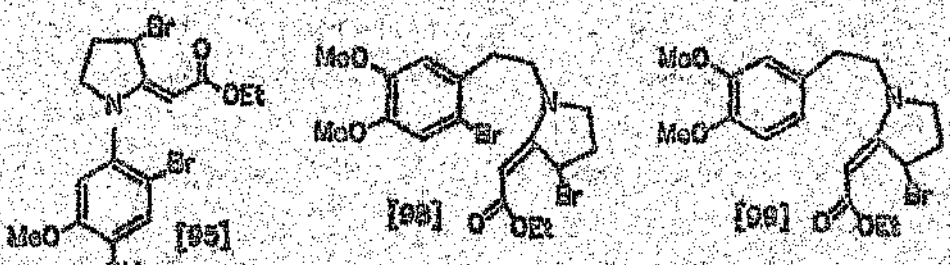
Except for vinylogous amide [53c] which produced [92], the other vinylogous amides studied here, [53c] and [95], decomposed when reacted with NBS to give mainly the lactam. These allylic bromination reactions are not new. Such processes are believed to be free radical in nature.[57,58]

For subsequent work to be discussed in CHAPTER THREE, γ-acetoxy vinylogous urethanes were required, and we felt that they should be accessible via the γ-bromo compounds. However, the substitution reaction of the bromide [94] with silver acetate, proved challenging. The desired acetate [100] was isolate as an oil after column chromatography in a 20% yield. During the reaction it was observed that silver acetate was not totally soluble in acetonitrile. When glacial acetic acid was used as solvent no reaction took place at room temperature. After reflux no characterisable compounds were obtained. It is possible that this substitution reaction by acetate anion may be improved by π-allyl palladation using Pd(0).[59]



The NMR data for the γ-substituted oxamigones are collected in Tables 8 and 9.





Compound	94	100	95	92	98	99
R =	OEt	OEt	OEt	CH_3	OEt	OEt
H-3	5.94, d	6.40, d	6.07, d	6.08, dd	5.93, d	5.96, dd
H-4	2.34, m	2.35; m	2.55, m	2.28, m	2.20, m	2.21, m
H-5	3.74; dt 3.31; dt$_d$	3.69; td 3.31; td$_d$	3.7-3.9	3.55, t	3.15; m 3.08; m	3.09; m 3.05; m
>C=CH-	4.42, s	4.52, s	4.27, s	5.10, s	4.63, s	4.55, s
2xOMe	———	2.06, s acetate methyl gp.	3.90, 3.88	3.87, s with br base	3.85, 3.86	3.85, 3.87
-OCH$_a$CH$_3$	4.12, 2xq	4.09, q	4.11, 2xq	3.78 signal under	4.16, 2xq	4.15, 2xq
-OCH$_2$CH$_3$	1.27, t	1.23, t	1.22, t	———	1.29, t	1.28, t
-COCH$_3$	2.85, s N-CH$_3$	2.85, s N-CH$_3$	———	2.15, s	———	———
CH$_a$CH$_a$Ar			———	2.97, t	2.94, t	2.82, t
CH$_a$CH$_a$Ar	———	———	———	3.0-3.4 2xCH$_2$	3.48, t	3.45, m*
aroa H's	———	———	6.75, 7.10	5.75, 7.03	6.71, 7.02	6.73- 6.84

* Signal coincides with that of one of the NCH$_2$ protons in the ring.

Table 8 PMR Chemical shifts (δ, ppm) for γ-substituted enamilnones.

γ-Substitution at the 3 position of the heterocyclic ring introduces a stereogenic centre into these compounds, and as a result the two protons at the 5 position show up as an AB pattern. This is clearly evident in the PMR spectra of the N-methyl substituted vinylogous urethanes [94] and [100]. In the other vinylogous urethanes, because of overlapping from other signals, they appear as multiplets. The alkoxy methylene protons are diastereotopic. They appear as two sets of quartets at between 4.11 - 4.12 ppm for [95] and [135], and 4.15 - 4.16 ppm for [99] and [98]. They are separated by between 0.84 Hz in the dibromide [98] to 1.55 Hz in [99]. In the case of the acetate [100], however, the alkoxy methylene protons appear as a clean quartet at 4.09 ppm. The only proton left at the 3 position usually gives broad doublets appearing far downfield. This doublet coupling comes from vicinal coupling with one of the C-4 protons, the other usually showing negligible coupling. This is unambiguously proven by decoupling experiments. For example, in the case of the acetate [100], irradiation at 2.25 ppm, signal from one of the C-4 protons, the doublet collapses to a broad singlet at 6.40 ppm. Irradiation at the other C-4 methylene proton at 2.20 ppm only sharpens this doublet. In the

bromides these protons appear between 5.93 ppm, as in [98], and 6.07 ppm, as in [95]. In the acetate [100] this proton appears at 6.40 ppm, thus showing the more powerful deshielding effect of the acetate over the bromide. In the case of [92] and [99], doublets of doublets were observed for H-3. From decoupling experiments, this additional doublet coupling must also come from vicinal coupling with the other C-4 methylene proton.

Compound	94	100	95	92	98	99
R =	OEt	OEt	OEt	CH_3	OEt	OEt
C-2	167.62	167.62	167.64	162.82	167.83	167.53
C-3	47.52	73.95	47.33	48.30	47.95	47.85
C-4	33.74	20.86	34.49	33.62	33.09	33.60
C-5	51.59	52.27	51.38	50.86	50.79	50.69
>C=CH	78.36	80.42	82.38	88.89	79.10	78.34
2xOMe	———	170.90 $CH_3O-C=O$	56.28	55.99	55.98	55.55, 55.50
>C=O	162.95	160.21	163.01	193.60	161.33	161.83
$-O\underline{C}H_3$	58.38	58.66	58.92	178.13 $\underline{C}=O$ ppm Ido	58.65	58.35
$-OCH_2\underline{C}H_3$	14.39	14.53	14.40	28.44 $\underline{C}H_2$ ppm Ido	14.45	14.26
$>C=O\underline{C}H_3$	33.30, N-methyl	33.34, N-methyl	———	30.46	———	———
$CH_2\underline{C}H_2Ar$	———	———	———	32.19	31.99	31.10
$\underline{C}H_2CH_2Ar$	———	———	———	46.42	46.03	48.07
Ar C-1'	———	———	131.12	128.11	129.49	130.79
Ar C-2'	———	———	112.77	113.79	113.74	with C-5' & 6'
Ar C-3'	———	———	115.43, 110.73	115.43, 113.60	115.43, 113.61	146.58, 147.38
Ar C-4'	———	———	149.51	148.42, 146.34	148.33	
Ar C-5'	———	———				120.41, 111.66, 111.05
Ar C-6'	———	———	with C3'	with C3'	with C3'	

Table 9 CMR Chemical shifts (δ, ppm) for γ-substituted enaminones.

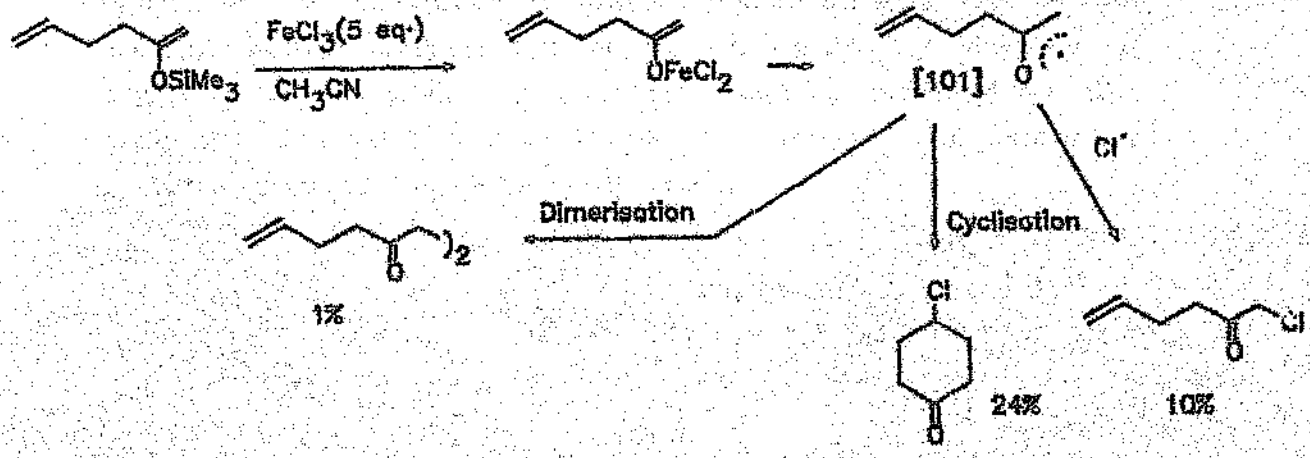
For the γ-brominated vinylogous urethanes [94], [95], [92], and [99], their carbonyl peak signals have all shifted upfield by some 2.00 ppm from those of the corresponding γ-unbrominated vinylogous urethanes. In

the case of the acetate [100], the carbonyl peak signal has shifted downfield the most, 5.33 ppm. It now appears at 160.21 ppm. In the case of the succinimide [92] however, the carbonyl peak signal has stayed relatively unchanged. Similarly the non proton-bearing vinyl peak signals have also shifted upfield. Their movement, however, is not as pronounced as those observed for the carbonyl peak signals. The bromine at C-3 in the heterocyclic ring has shielded the carbonyl carbon and this vinyl carbon mesomerically in these compounds. However C-3 and C-4 signals have appeared more downfield (by ca. 15-12 ppm) in these γ-brominated vinylogous urethanes. The C-3 signals now appear at ca. 47 ppm. In the succinimide [92] this carbon appears at 48.30 ppm. In the acetate [100] it appears most downfield at 73.95 ppm. The C-4 signal strangely enough stayed unchanged at 20.86 ppm. Except for the succinimide [92] the proton-bearing vinyl carbon signals in these γ-substituted enaminones have also all shifted marginally downfield. This can best be explained by the inductive effect of the nearby electronegative bromine. This effect is observed in all γ-substituted enaminones where an electronegative element has replaced one of the C-3 protons. This inductive effect however weakens with distances. The C-5 signals in these compounds not only do not experience this inductive effect, instead they shift upfield by ca. 2.5 ppm. The absence of bromine from the phenyl group in [99] has also shifted the chain carbon next to the nitrogen atom downfield by 2 ppm. The aromatic carbon bearing methoxy substituent produces a signal between 147 and 150 ppm in these enaminones. They appear close together where bromine is present in the phenyl group and they coincide exactly in [98] and [95] at 148.33 and 149.51 ppm respectively.

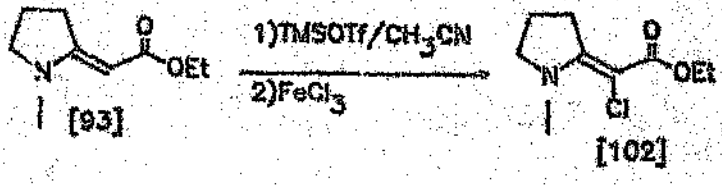
2.5.2 Reactions with trimethylsilyl trifluoromethanesulphonate (TMSOTf) and transition metal salts

In view of the failure to accomplish α-bromination of vinylogous amides and urethanes with conventional brominating agents, alternative procedures were investigated. An alternative method pioneered for enol silyl ethers[89,90,91] seemed to hold potential for our systems. Saegusa *et al.* have shown that the silyl group in enol silyl ethers can be exchanged with transition metal salts such as ferric chloride or cupric chloride.[91] The new enolate formed then breaks down to form a vinyloxy radical [101] which abstracts a chlorine atom from the metal salt to produce the

corresponding α-chlorocarbonyl compounds. In fact cyclisation has also been observed by trapping of this radical by suitably positioned functionalities. Dimerisation has also been observed, which strongly suggests the radical nature of the reaction. A large excess of the metal salts is necessary to obtain satisfactory yields. Fair yields were obtained by them.



It seemed to us that O-silylation of vinylogous amides and urethanes should produce enol silyl ethers, which might be halogenated by Saegusa's procedure. When vinylogous urethane [93] was reacted with trimethylsilyl trifluoromethanesulphonate (TMSOTf) in acetonitrile in the presence of zinc under sonication,[92] followed by addition of ferric chloride, vinylic chlorinated compound [102] was produced in a G.C. yield of 37%. Also present was 16% of starting material. The reaction was repeated several times but the isolated yield of [102] could not be improved.

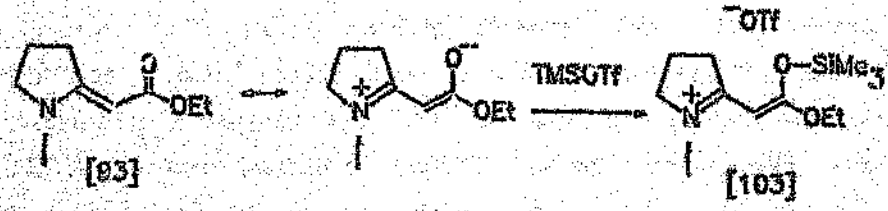


[93] [102]

The low yield may be due to problems encountered during the work-up stage. The reaction solution is very acidic after addition of ferric chloride, and basification to liberate the expected vinylogous urethane was necessary. This was achieved by adding solid potassium bicarbonate. Much effervescence was observed, and inorganic solids precipitated out of the solution. Filtration of this mixture to remove the solids was difficult, and the organic component was produced as an oil with a poor mass balance. Organic compounds were almost certainly trapped in the

inorganic precipitate, and this resulted in the low recovery from this reaction.

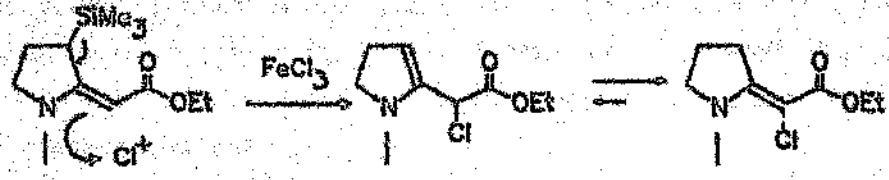
The vinylic chloride [102] probably formed through the intermediate [103], an enol silyl ether, which was formed by trapping one of the resonance forms of the vinylogous urethane by TMSOTf. As mentioned already in the introduction in Chapter One, enaminones have several ambident nucleophilic sites; here we see the reactivity of the carbonyl oxygen atom being used. Addition of FeCl3 probably exchanged the silyl group for iron. This then breaks down according to the previously presented scheme to produce the vinylic chloride.



[93] [103]

It was questioned that perhaps the reaction took place through [104], an allylsilane, instead of the enol silyl ether [103]. The allylsilane [104] has previously been prepared by Michael[70a] by treating vinylogous urethane [93] with butyllithium in THF followed by chlorotrimethylsilane (TMSCl). In this work three attempts were made to repeat the synthesis of [104] but to no avail. Each time only starting material was recovered. Thus the hypothesis could not be tested.

However, the formation of the vinylic chloride through this allylsilane is unlikely as chlorine cation is needed for further reaction.



[104] [102]

When chlorotrimethylsilane was used in conjunction with triethylamine for this vinylic chlorination reaction, starting material was recovered. Thus the carbonyl oxygen of the vinylogous urethane may not be nucleophilic enough to react with TMSCl. This shows that the oxygen atoms from enols formed from carbonyl compounds are more nucleophilic than the oxygen atom of the vinylogous urethane here as many enol silyl ethers are obtained

from reaction of carbonyl compounds with TMSCl and NEt3.

The zinc does not seem to play a very important role here.[92] It probably reacts with any acid that may be formed from hydrolysis of TMSOTf, thereby ensuring neutral reaction conditions. An attempt was made without zinc and a 29% yield of [102] was obtained.

Both bromine and NBS have also been used to react with enol silyl ethers to produce the corresponding α-bromocarbonyl compounds.[89,90] When NBS was used instead of FeCl3 in conjunction with TMSOTf poor results were obtained. The γ-brominated vinylogous urethane [94] was isolated in a 5% yield together with some starting material (8%). The γ-brominated compound was probably formed between NBS and the enol silyl ether [103]. This assumption is supported by the fact that no reaction was observed when TMSCl was used instead of TMSOTf. For some reason NBS is not even reactive towards the vinylogous urethane here.

When cupric bromide was used in the presence of TMSOTf the γ-brominated compound [94] was isolated in a 12% yield after column chromatography. Both zinc bromide and ferric bromide failed to give any reaction. In the case of ferric bromide, inorganic precipitates were formed during the work-up stage. Two attempts were made and in both cases vinylogous urethane [93] was recovered in very poor yield.

Finally silylation was attempted on the N-aryl vinylogous urethane [53b]. It was hoped that when ferric chloride was added, the hypothetical vinyloxy radical formed, would trigger off a cyclisation reaction on the aromatic ring. A very poor result was obtained here, and PMR of reaction mixture indicated the presence of possible vinylic chlorinated compound, but no cyclised compound.

In the PMR spectrum of the vinylic chloride [102] the alkoxy proton signals have shifted downfield slightly. The biggest shift came from the N-methyl protons which now appear at 3.32 ppm, as compared with 2.80 ppm before reaction. The changes in the ring proton signals are irregular. The proposed structure (Z-isomer) is based on the observation that C-3 ring protons, which are deshielded by the ester carbonyl, appear at 3.14 ppm, no change from the unchlorinated compound. In the CMR spectrum most

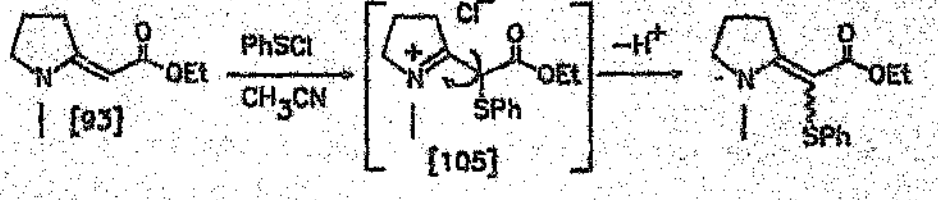
of the signals have moved downfield relative to those from the vinylogous urethane [93]. The biggest downfield shift came from the vinyl carbon attached to the chlorine. It now appears at 85.36 ppm. The only significant upfield shift came from the carbonyl carbon and the other vinyl carbon signal.

This work was discontinued because vinylic chlorides are expected to react poorly in radical coupling reactions, and vinylic bromination with FeBr3 instead of FeCl3 could not be achieved.

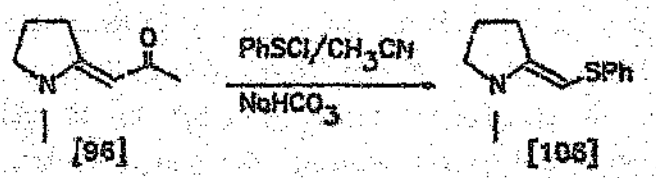
2.5.3 Reactions with phenylsulphenyl chloride

Substitution by phenylsulphenyl group at the vinyl position is also appropriate to study since C-SPh bonds are known to undergo radical reactions (see CHAPTER FOUR for further discussion).

Phenylsulphenyl chloride was prepared from the reaction of thiophenol with sulphuryl chloride in carbon tetrachloride in the presence of triethylamine at 0 °C.[93] A clear red liquid was obtained after distillation (87%). When vinylogous urethane [93] was reacted with phenylsulphenyl chloride in the presence of NEt_3 no desired compound was obtained, but some diphenyl disulphide was isolated. In this reaction the addition of PhSCl produced an immediate exothermic reaction, leading to precipitation of crystalline solids from the solution. This is probably the reaction between the base and PhSCl to form a salt which precipitated out of solution. When the reaction was carried out without a base the desired reaction was achieved and the product isolated as a clear yellow oil after column chromatography in a 75% yield. PMR of this compound, however, shows that it is a mixture of *cis* and *trans* isomers. Isomerisation must have arisen from the intermediate [105] formed during the reaction where free rotation, impossible in the precursor's double bond, is now possible

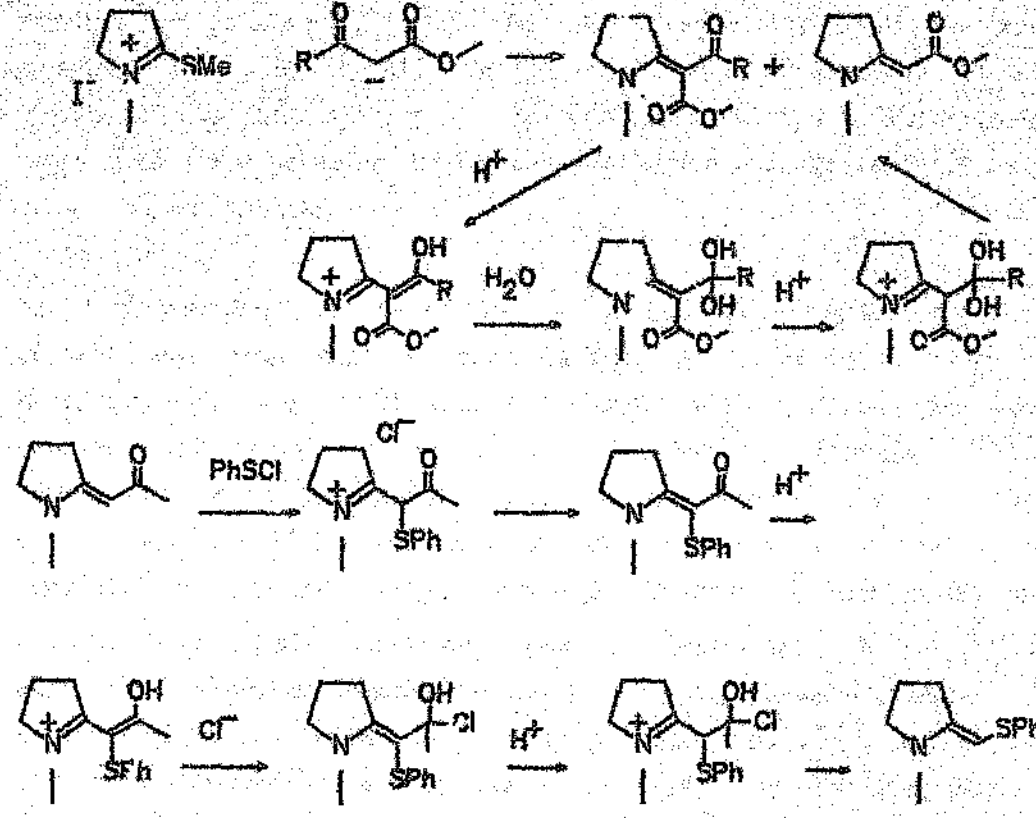


Again vinylogous amide [96] showed different reactivity towards phenylsulphenyl chloride compared with the vinylogous urethane [93]. Phenylsulphenation accompanied by deacetylation leading to the formation of [106] was the result. A 38% yield was obtained after column chromatography. By doing the reaction in dichloromethane produced the same result with a poorer yield (23%).



[96] [106]

Similar deacylation reactions have been reported by Zwane in these laboratories.[70d] Possible explanations have been put forward by Zwane. These include the ease of protonation of vinylogous amide carbonyl, the product of which can be hydrolysed or attacked by other nucleophiles (e.g. Cl^- as was proposed to explain the formation of [106]). Vinylogous urethane carbonyl appears to be more resistant to protonation reaction.



This approach was thus abandoned due to the unexpected complications that have arisen in the reaction.

CHAPTER THREE: THE INTRAMOLECULAR HECK REACTION

3.1 Introduction

This chapter is entirely devoted to Heck reactions. This reaction is now recognised as an important method for coupling an alkenyl carbon to aryl or vinyl halides. Literature examples, especially the intramolecular ones, including mechanism and shortcomings of the reaction, will be discussed in detail in the following section. Emphasis will be placed on the coupling between enaminic type carbons and aryl bromides or iodides. In Section 3.3, our results in this regard will be presented.

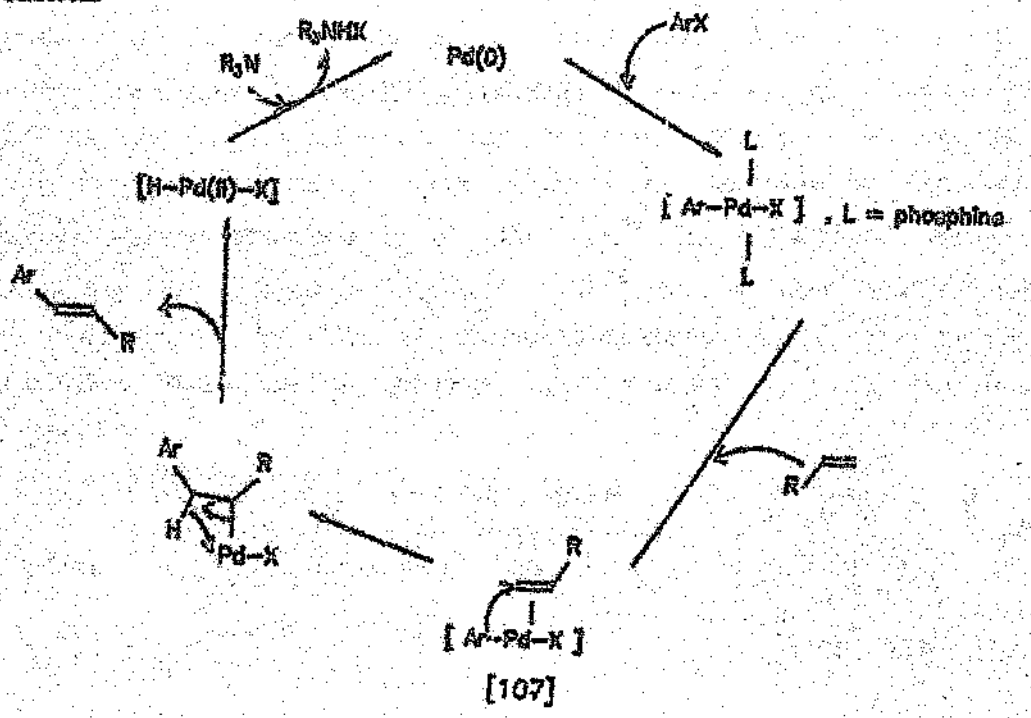
3.2 Literature survey and analogies

It is apparent from recent literature that organometallic compounds, especially those of the transition metals, are receiving more and more attention in organic synthesis. The metal-containing reagents have been used both stoichiometrically and catalytically. We shall focus our attention on palladium here.[94-96] The characteristics of readily variable oxidation state (0, II, IV), flexible coordination number (2 to 6), kinetic lability, and affinity for a very wide range of ligand types, combine to make palladium an extremely effective and versatile promoter of organic transformations.

The Heck reaction[97] can be defined as the palladium-catalysed vinylation of aryl, heteroaryl, vinyl or benzyl halides. Ever since its discovery by Heck, numerous reports of this synthetically useful method have been recorded. This reaction is a very useful method for obtaining arylated alkenes because of the catalytic nature of the reaction, the availability of starting materials, tolerance of the reaction to a variety of functional groups, good stereo- and regioselectivity in most cases, and the relatively simple conditions. Typically temperatures of 100 °C or higher are required. Neutral ligands such as triphenylphosphine are always present to stabilise intermediate palladium complexes, and a base is used to neutralise the acid HX that is liberated during the reaction.

The probable mechanism,[96] shown in Scheme 5, involves oxidative addition

of the halide to Pd(0), producing a σ-aryl-palladium bond. Such a divalent palladium complex is usually stabilised by some neutral ligands, such as triphenylphosphine or solvent molecules. This is followed by the coordination of palladium to the vinyl system. This reduces the π electron density of the alkene and makes this palladium(II)-π complex [107] susceptible to nucleophilic attack at the alkenyl centres. This can also be viewed as "insertion" of the alkene into the σ-aryl-palladium bond. β-Hydride elimination then follows to remove palladium hydride, and regeneration of Pd(0) via base-promoted dehydrohalogenation completes the reaction.

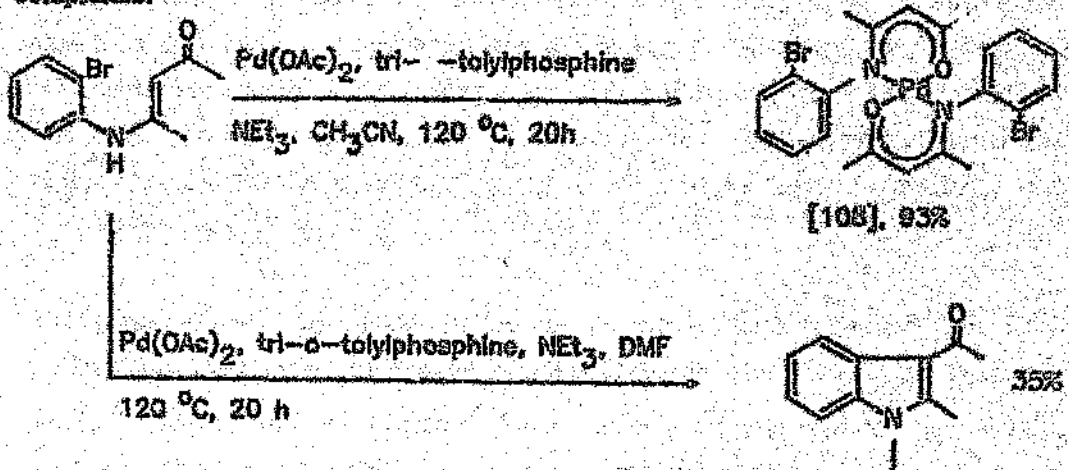


[107]

Scheme 5

The Pd(0) is usually generated *in situ* and is present as a phosphine complex, but with iodoarenes it can even be in the form of very finely divided palladium metal.[94,95] Often the palladium is added in the form of palladium(II) acetate because of the solubility of this salt in organic solvents and its ease of reduction. However, one should be aware of the various forms of palladium(II) acetate that can be prepared by recrystallisation depending on the solvent ur [98] They behave differently mechanistically. Various other palladium acetate complexes are available. They include Pd(OAc)2(PPh3)2 and Pd(OAc)2[P(o-Tol)3]2. Other palladium reagents used include Li2PdCl4, Pd(PPh3)4 and palladium on carbon. Other variables employed in Heck reactions include different

bases and solvents. Consequently several reaction protocols have resulted. The different bases employed can be divided into liquid bases, which include NEt3 and NBu3, and solid bases, often NaHCO3, K2CO3, NaOAc and KOAc. Amorese *et al.* have discovered that tertiary amines tend to favour the formation of conjugate addition-type products in the reaction of β-substituted-α,β-enones and enals with aryl halides in the presence of a palladium catalyst.[99] Similar observations were reported when the alkene component comes from an acyclic α,β-unsaturated carbonyl compound.[100] Sodium bicarbonate or sodium acetate favours the formation of vinylic substitution products. Usually, the use of sodium acetate produced results comparable to, or better than, those obtained with sodium bicarbonate.[99] Usually acetonitrile is used as the solvent, but DMF and acetone are sometimes used. The nature of the solvent can also play an important role in Heck reactions as the following reactions carried out by Yamanaka *et al.* illustrate.[76] The palladium(II) complex [108] was also isolated by Kibayashi *et al.*[101] It was found that the use of triethylamine in place of sodium bicarbonate as a base in the respective Heck reaction prevents the formation of such palladium complexes.



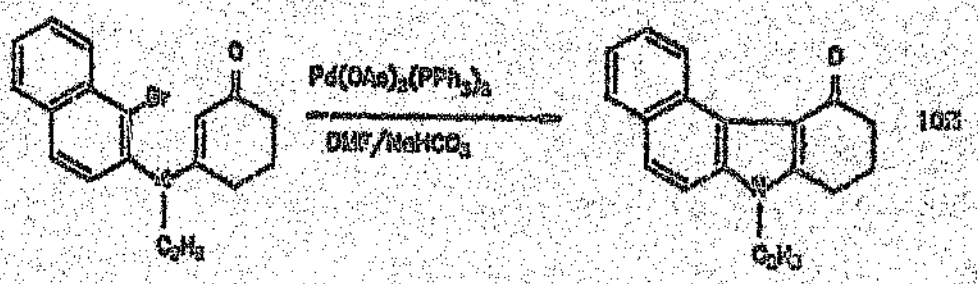
The reaction does not proceed satisfactorily with aryl bromides bearing strongly electron-donating substituents such as hydroxyl and amino groups owing to competing formation of tetraarylphosphonium salts from aryl bromides and triarylphosphine. Better results may be obtained by using sterically hindered tri-o-tolylphosphine in place of triphenyl phosphine.[102] In general, palladium-mediated Heck-type reactions are poor yielding and require high temperatures. Both of these problems can be overcome by introducing a phase transfer catalyst, usually

tetrabutylammonium chloride, as shown by Jeffery and others,[103-107] who achieved near-room temperature conditions.[103,104] The reaction rate was found to increase with increasing concentration of tetrabutylammonium chloride.

Perhaps it is the chloride ion that assisted in bringing about better yields and moderate reaction temperatures, as Merlic *et al.* also reported that addition of chloride ion is found to enhance the yields of cross-couplings between aryl iodides and selected olefin acceptors.[108] It has been speculated that the addition of chloride ion might promote the reaction either by helping to solubilise surface-bound palladium (as in palladium on carbon) or by transmetallating with the arylpalladium iodide to generate a more electrophilic arylpalladium chloride intermediate. Other additives which are found to bringing down reaction temperatures are silver salts ($AgNO_3$, $AgCO_3$).[109,110]

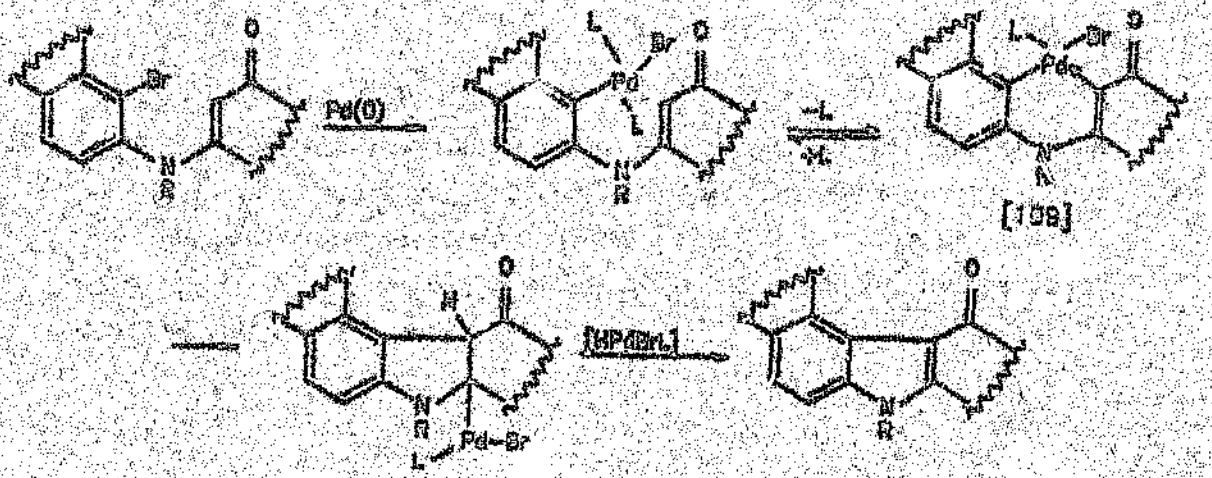
While examples of intermolecular coupling of aryl halides with alkenes using palladium reagents are abundant in the literature, the corresponding intramolecular analogues are relatively few. Examples in which five-membered rings are formed are far more common than those in which larger rings are formed. In the following examples, enamines, enamides and vinylogous amides or urethanes are illustrated as the alkene component as far as possible, because these will be more relevant for the present project.

Kibayashi *et al.*, by using palladium reagents, have effected the Heck cyclisation in N-aryl vinylogous amides although the yields are generally poor.[76] Many indole systems have been prepared this way. Both stoichiometric and catalytic cyclisation were investigated. An example of their work is given below.



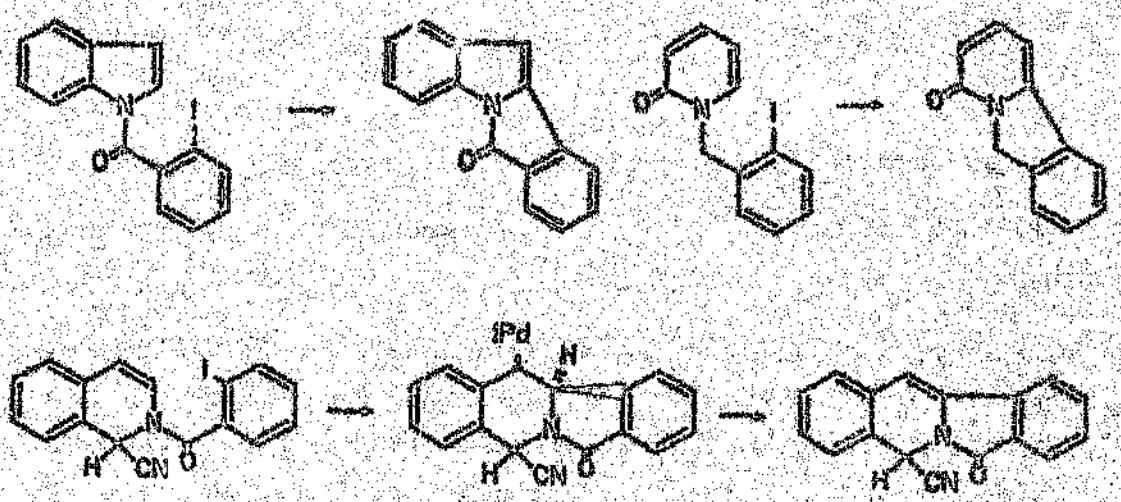
103

The probable mechanism for catalytic cyclization suggested by Kibayashi is described pictorially below. The active palladium(0) species undergoes oxidative addition to an aryl halide bond. This is followed by insertion of the double bond in the vinylogous amide system into the σ-aryl-palladium bond and the loss of palladium hydride species by β-hydride elimination to produce the desired compound. A reactive six-membered cyclic intermediate [109] involving palladium was invoked. The addition of palladium-aryl bond to the alkene is believed to be in a *cis* fashion.[111] This results in an unstable σ-alkylpalladium species which undergoes a rapid, spontaneous *syn*-β-elimination of HPdBr to form the vinylic substitution product.[94,96,97,112]



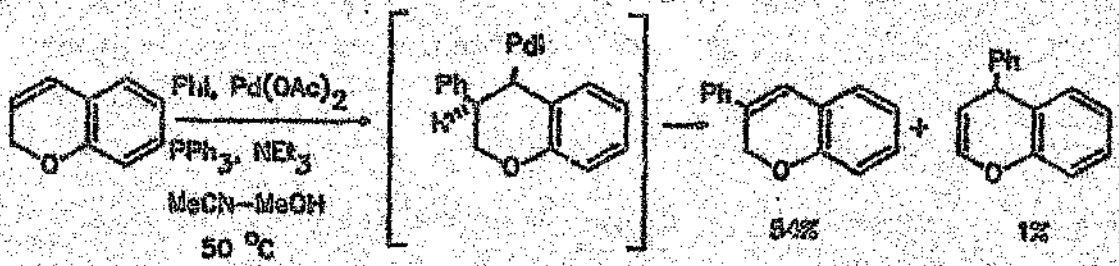
[108]

Recently, however, Grigg *et al.* reported examples in which the intermediate σ-alkylpalladium species have the wrong stereochemistry to undergo the necessary *syn*-elimination of HPdX.[113] The following examples illustrate their argument:

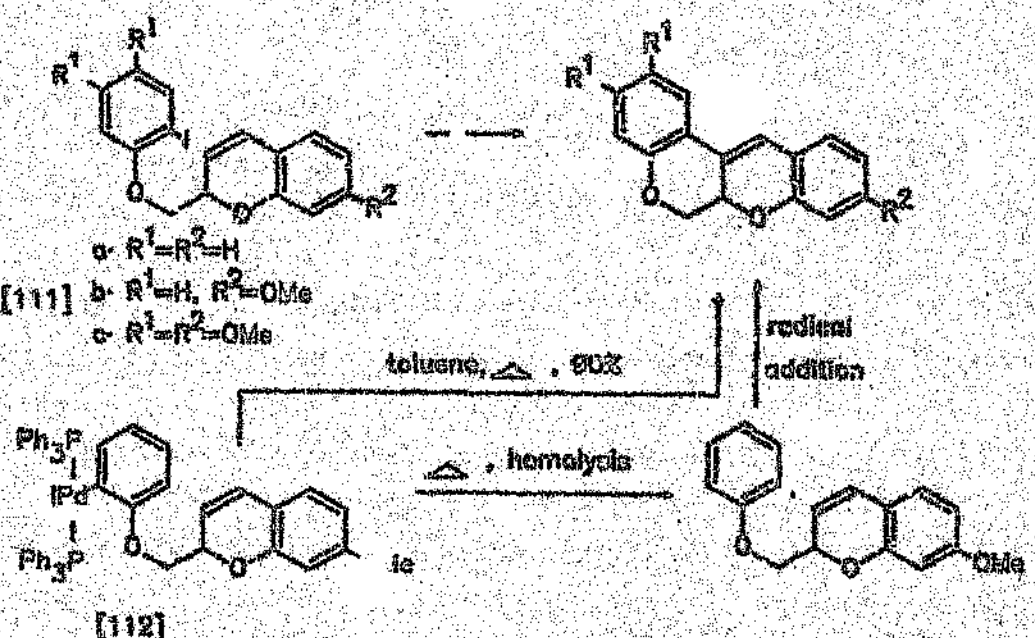


[110]

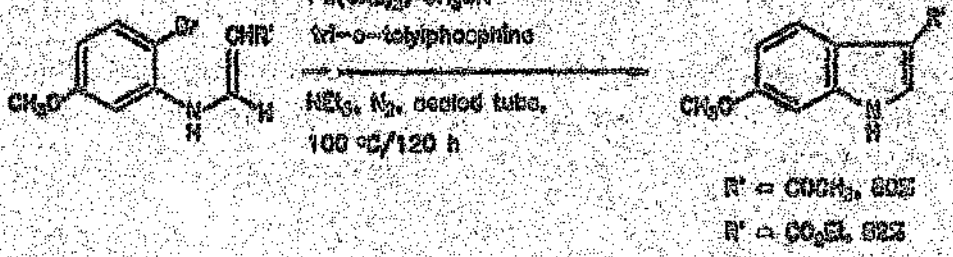
The wrong stereochemistry arises from the *cis*-addition of Pd-Ar bond to the alkene as depicted by [110]. Since in all cases the expected Heck products are obtained, the PdI moiety either undergoes a facile stereomutation furnishing the required *cis*-stereochemistry, or elimination is *anti*. A similar observation was reported by Amos *et al.* for an intermolecular Heck reaction.[116]



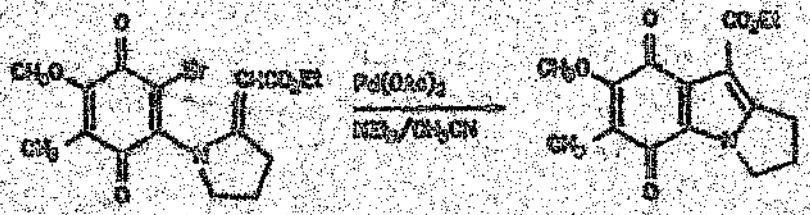
Amos *et al.* then studied the intramolecular cases and found that the "expected" Heck products were obtained in moderate yields.[116] In the case of [111b] the palladium complex [112] was isolated, which upon reflux in toluene gave the desired product in 90% yield. A radical mechanism was used to explain the formation of the stereochemically disallowed inter- and intramolecular product.



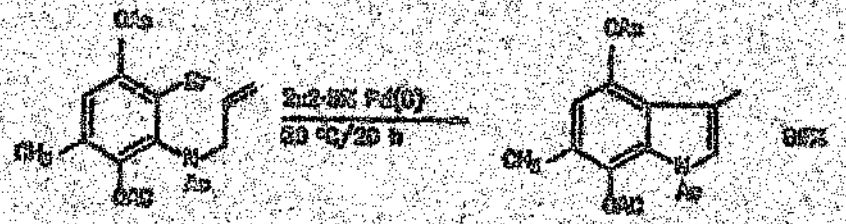
Kasahara *et al.*[115] and Yamanaka *et al.*[76] on the other hand claimed high yields by employing different reaction conditions. Both N-aryl vinylogous amides and urethanes were successfully cyclised using catalytic amounts of $Pd(OAc)_2$ to give the corresponding indole compounds. Two examples of Kasahara's work are given overleaf.



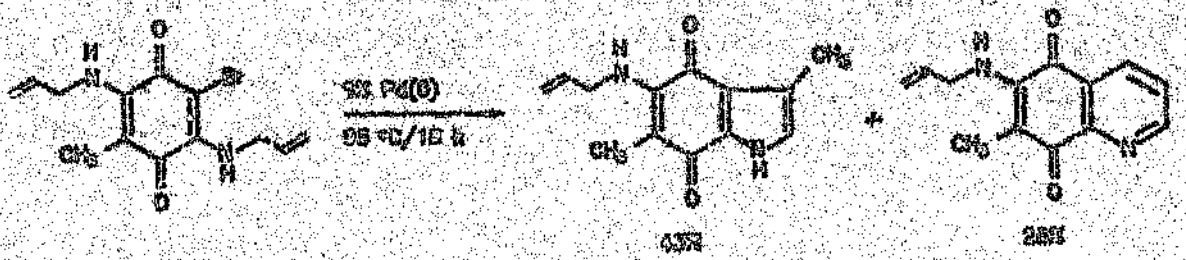
Rapoport *et al.* in the synthesis of mitomycins make frequent use of vinylogous urethanes as intermediates. They claimed a 97% yield for the following step.[116]



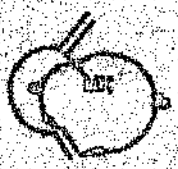
Other intramolecular five-membered ring-forming reactions using palladium reagents as catalyst exist in the literature although they do not have direct relevance to our work here. An example by Negedas is given below.[117]



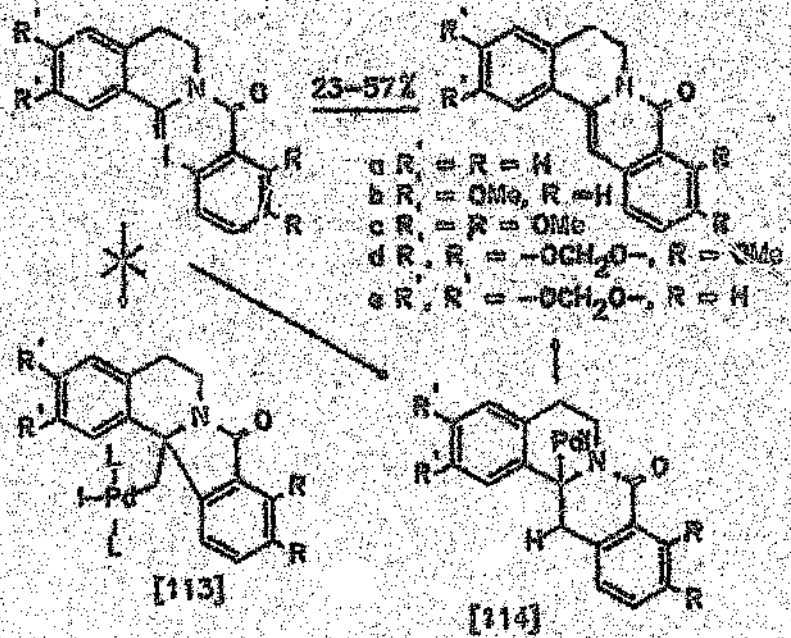
Although Heck-type reactions are useful in forming five-membered rings intramolecularly,[118] the corresponding intramolecular six- and seven-membered ring formations are relatively few indeed. The above example by Negedas *et al.* could potentially form a five- or a six-membered ring intramolecularly. A case in which both products were formed was also reported by Negedas *et al.* in the following reaction.[117]



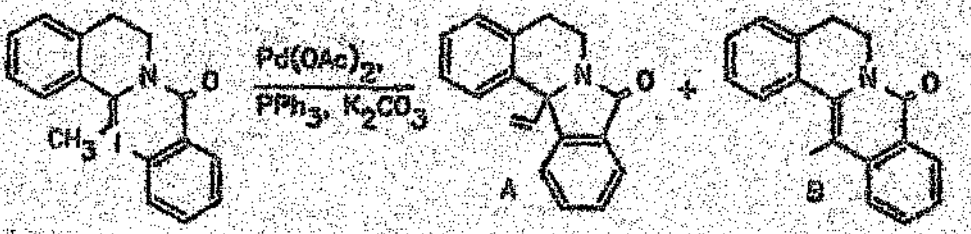
The preference of *exo*-trig mode (a) versus *endo*-trig (b)[119] in an intramolecular cyclisation has been investigated in detail by Grigg in various systems of compounds under different conditions.[116,120-123]



It was found that depending on the availability of β-hydrogen in the intermediate organopalladium species [113] and [114], both *exo*-trig and *endo*-trig cyclisations can be made to occur. Thus the following enamides are forced to cyclise by the 6-*endo*-trig mode since 5-*exo*-trig cyclisation would create an organopalladium intermediate lacking the necessary β-hydrogen for elimination.[113,126]

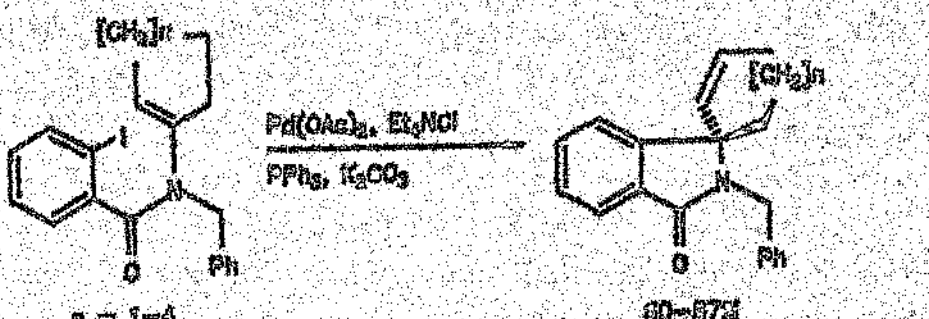


When both modes of cyclisation can potentially occur, depending on the substrates and reaction conditions, one of the two possible modes can be favoured as the cyclisation reaction shown overleaf illustrates.[113,126] It can be seen from the table that the addition of tetraethylammonium chloride permitted the reaction to be carried out at lower temperatures and resulted in increased selectivity for A.

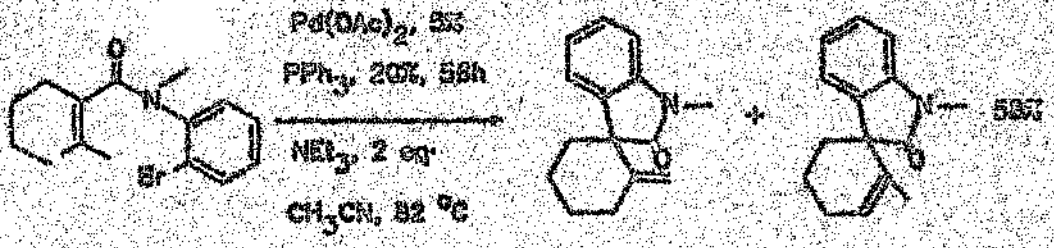


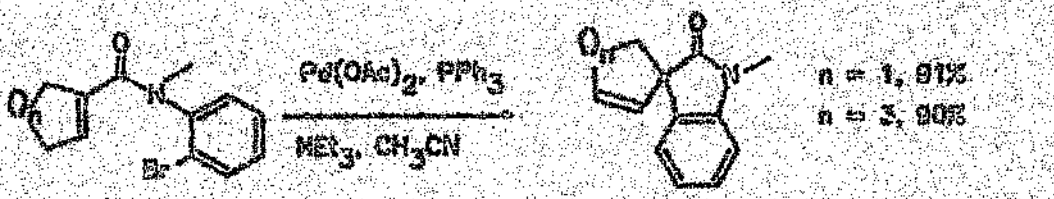
Catalyst system	Conditions	Yield (%)	A : B
10 mol% $Pd(OAc)_2$ 20 mol% PPh_3	DMF, 100 °C, 1 h	80	3·3 : 1
5 mol% $Pd(OAc)_2$ 10 mol% PPh_3	DMF, 100 °C, 2 h	84	6·7 : 1
10 mol% $Pd(OAc)_2$ 20 mol% PPh_3	CH_3CN, 80 °C, 1 h, Et_4NCl, 1 mol	91	10 : 1
12·5 mol% $Pd(OAc)_2$ 25 mol% PPh_3	CH_3CN, 30–50 °C, 168 h, Et_4NCl, 1 mol	83	13 : 1

It was also observed that 5-*exo*-trig cyclisations are kinetically favoured over 6-*endo*-trig cyclisations, resulting in intramolecular attack at the more substituted end of the double bond.[120] This finding contrasts with the intermolecular reactions where the terminal position is most reactive.[120] Similar results have been reported by Negishi,[125] Larock[126,127] and others.[128-130] Thus the following enamides cyclise to give products bearing tetrasubstituted carbon centres which could be valuable in natural product synthesis.[120,113]

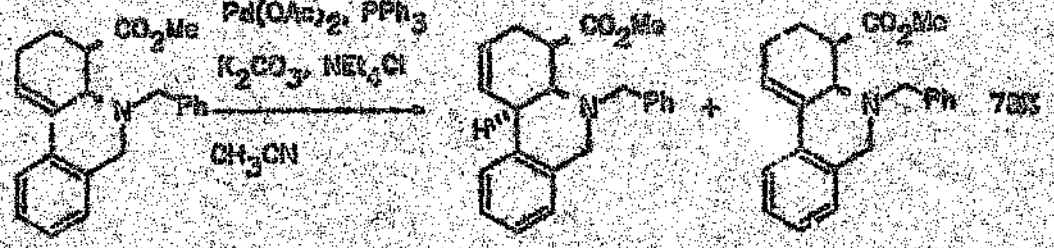


Other groups have also employed the intramolecular Heck-type cyclisations to produce spiro compounds.[115,131-135] As model studies for the complex hexacyclic alkaloid gelsemine, the intramolecular Heck arylations shown overleaf were carried out. Various 3-spiro-2-oxindoles were prepared.[133]





The formation of six-membered rings can also be obtained by performing a 6-exo-trig cyclisation on an appropriate substrate.[113]



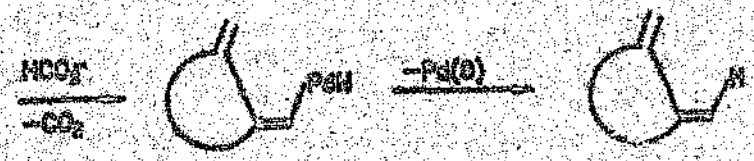
[115] [116]

Double bond isomerisation is always a potential problem in Heck-type reactions. It arises if the rate of readdition of the hydridopalladium halide to the alkene is faster than dissociation of the π-complexed alkene.[97] Addition of either tetraalkylammonium chloride[103,109] or silver salts (nitrate, carbonate),[109,126,135] known to trap hydrohalic acids, suppresses this. The latter salts are claimed to be the more efficient.[110,119,193] Modification of the catalyst system in the above example by addition of silver nitrate or silver carbonate in place of tetraethylammonium chloride resulted in a slower reaction but the reaction was now selective for [116]. Thus [116] (36%) was formed after one day in boiling acetonitrile together with substantial amounts of unreacted [115].

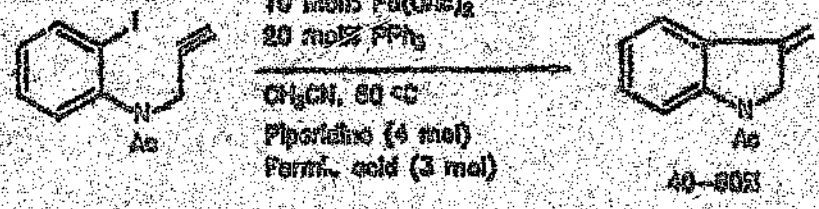
Recently Grigg has reported hydride ion capture, by vinylpalladium species, generated by internal capture of an allyne.[122] The hydride is generated *in situ* by decomposition of formate ion.



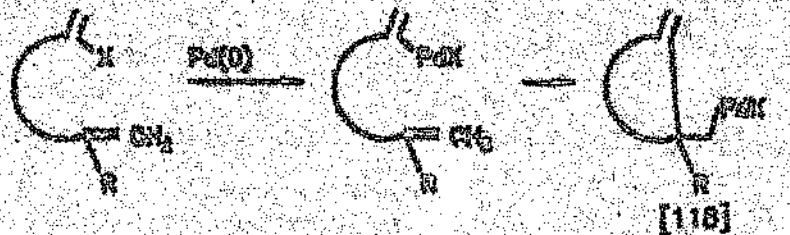
[117]



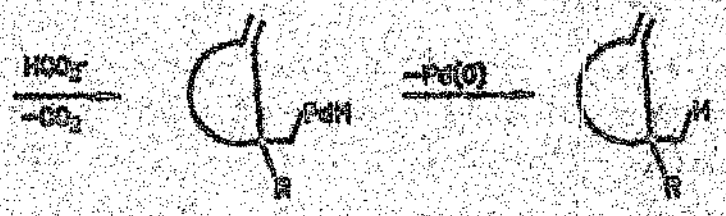
β-Hydride elimination from [117] is not possible. However, an anion exchange is possible. Thus the vinyl iodide below cyclises regio- and stereo-specifically via a 5-exo-dig process with hydride capture by the vinylpalladium intermediate to give a compound with an exocyclic double bond.



This idea was extended to alkylpalladium species, generated by internal capture of alkenes.[123] Larock *et al.* have reported a similar observation.[127] When R = H then β-hydride elimination is possible from [118].

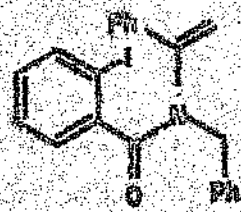


[118]



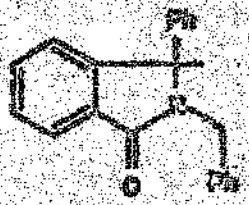
Thus the compound [119], which without a hydride ion source could only undergo 6-*endo*-trig cyclisation, was cyclised in a 5-*exo*-trig mode followed by hydride capture by the alkylpalladium intermediate to produce

[120] with a quaternary carbon centre. Different reaction conditions have to be employed to prevent the 6-*endo*-trig cyclisation process from taking place.[123]



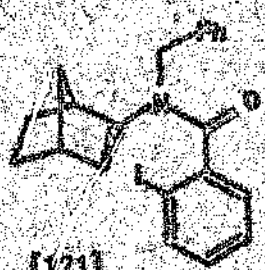
[119]

10 mol% $Pd(OAc)_2$
20 mol% PPh_3
HCO_2Na (1-1 mol)
DMF, 80 °C, 18 h



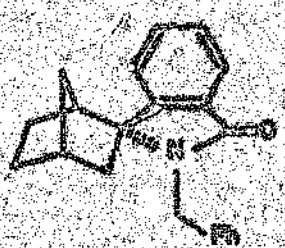
[120], 82%

The bridged ring enamides [121] and [122] are cyclised regio- and stereospecifically to give [123] and [124] respectively. Although the alkylpalladium intermediates can potentially undergo β-hydride elimination, the resultant products would end up with a double bond in the bridgehead position. Instead, reductive conditions ensure that 5-*exo*-trig cyclisation occurs. Similar bridged, spiro-cyclic compounds and the creation of tetrasubstituted carbon centres using Heck-type cyclisations have been reported by others.[119,133]

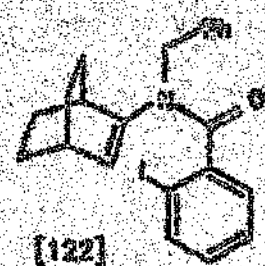


[121]

$Pd(OAc)_2$, PPh_3,
piperidine, CH_3CN
HCO_2H, 80 °C, 1–2 h

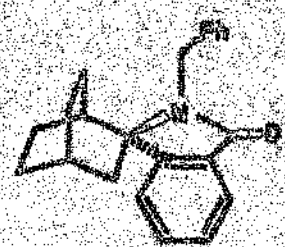


[123], 93%



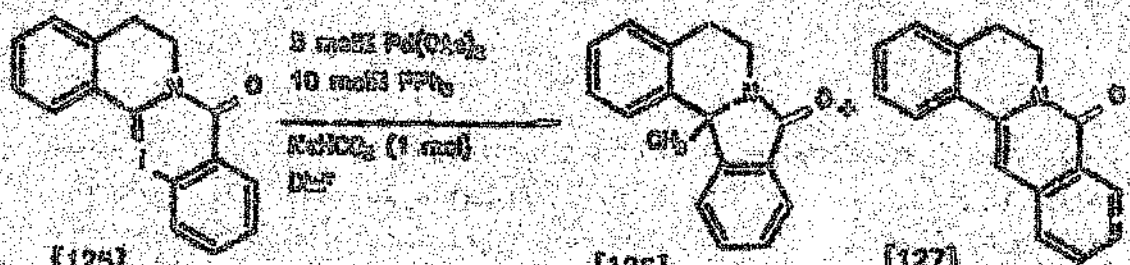
[122]

$Pd(OAc)_2$, PPh_3,
piperidine, CH_3CN
HCO_2H, 80 °C, 1–2 h



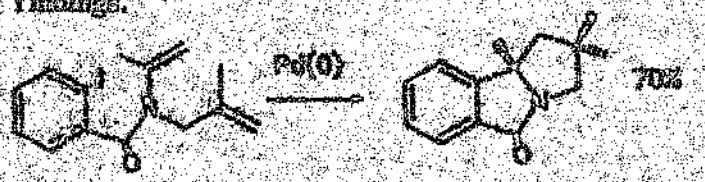
[124], 88%

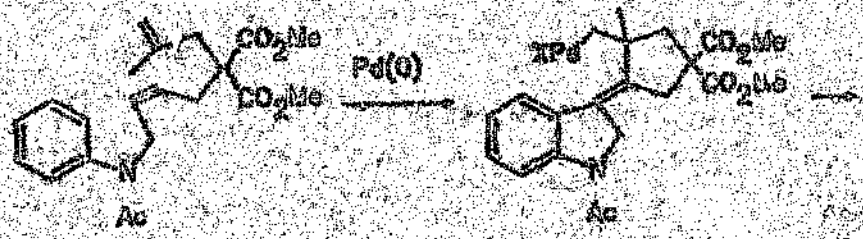
The previously mentioned enamide [125] under reductive cyclisation conditions displays competition between 5-*exo*-trig and 6-*endo*-trig cyclisations giving a 2 : 1 mixture of [126] and [127] in a 74% combined yield.[123] Under non-reductive conditions, however, it slowly cyclises to [127] as shown on page 71.[120]



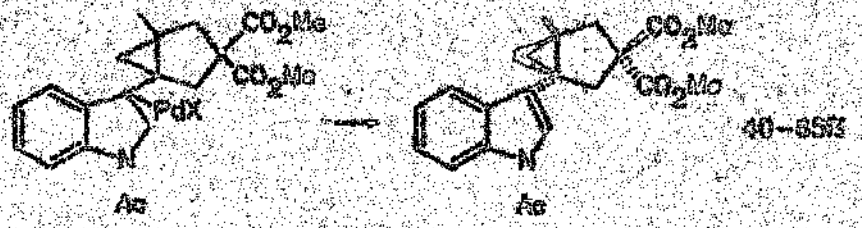
[125] [126] [127]

The idea of anion capture was extended further by Grigg by having multiple appropriately positioned functionalities in the substrate.[126] The action of palladium causes a cascade effect resulting in *bis*- and *tris*-cyclisation.[126] In the case of [128] cyclisation of the alkylpalladium species [129] is energetically more favourable than anion exchange and reductive elimination. Other researchers have reported similar findings.[118,127]





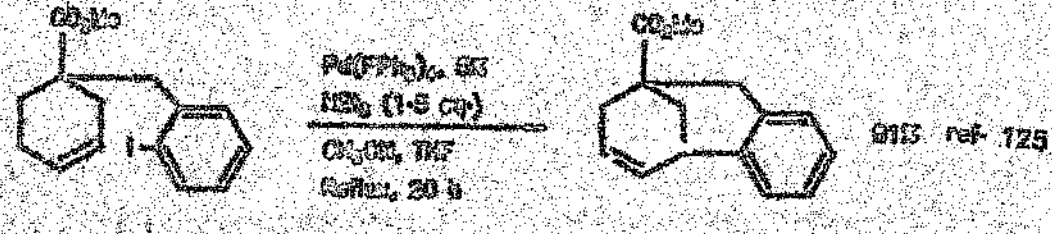
[128] [129]



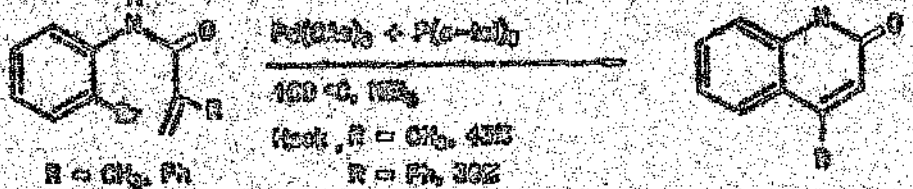
Other well documented nucleophiles to intercept alkylpalladium intermediates include O, N, and carbon nucleophiles.[118,126] When such interceptions occur intramolecularly, heterocycles are produced. Even enol silyl ethers have been used to intercept alkylpalladium intermediates.[130-131]

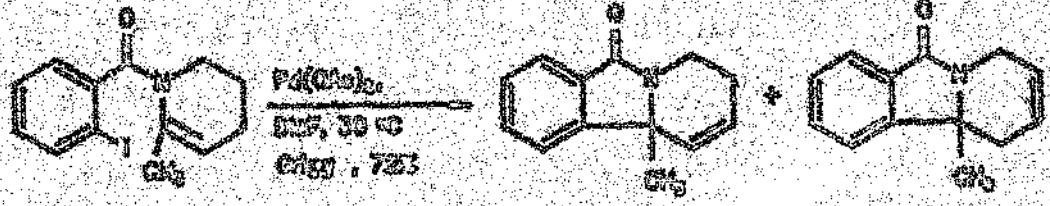
Other reports of the rather uncommon intramolecular cyclisation to

produce six-membered rings are available.[116,125,127,131,142-144] Where a competition exists between the formation of five-membered and six-membered rings, five-membered rings are always favoured. In general, six-membered rings are formed only when the double bond is so positioned in the reactant that a five-membered ring cannot be obtained. No examples where the alkene is part of an enamine system were found, so the following examples, not particularly relevant for this work, are given by way of illustration.



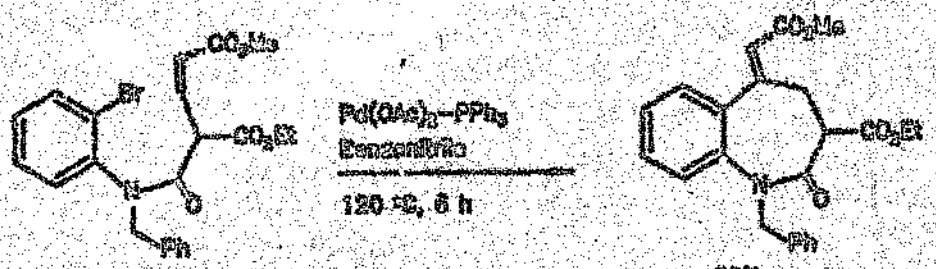
Attempts to block a carbon site in the double bond by alkyl groups to force other cyclisation modes have resulted in migration of bonds leading to some interesting results. Heck *et al.* reported the rearrangement reactions shown below,[129] while Grigg *et al.* with a similar substrate observed a simple migration of the double bond.[130,133] Such an observation had been reported by others.[107,125,127,128,130,144,149]





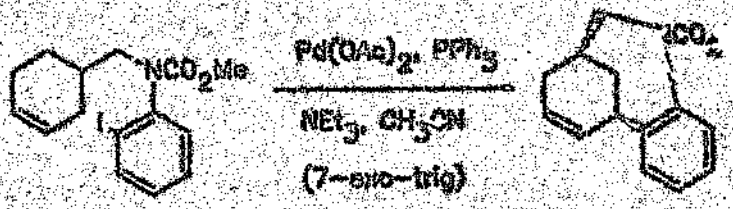
Few Heck reactions have been reported to give seven-membered rings by intramolecular arylation. Mori and Ban, in a study of *exo*- versus *endo*-

intramolecular cyclisation, carried out the reaction shown below.[148] The cyclisation mode was found to be 7-exo-trig rather than 8-endo-trig. This cyclisation is similar to the desired one in the synthesis of demethylcephalotaxinone [52] (page 14) in that the desired sized ring is formed.



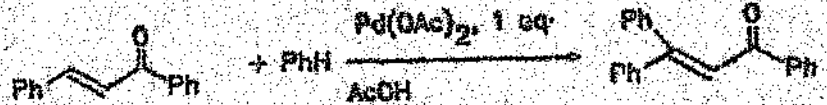
38%

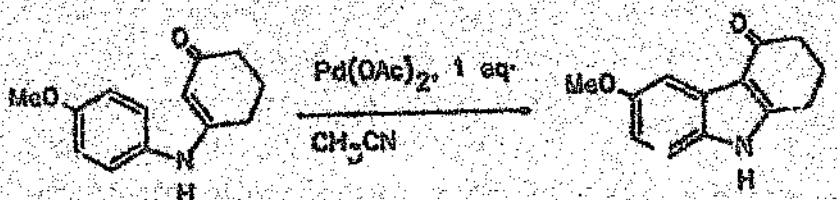
As was observed for six-membered ring formation, seven-membered rings are formed when no other options are available. Even bigger rings are obtainable this way.[145,149]

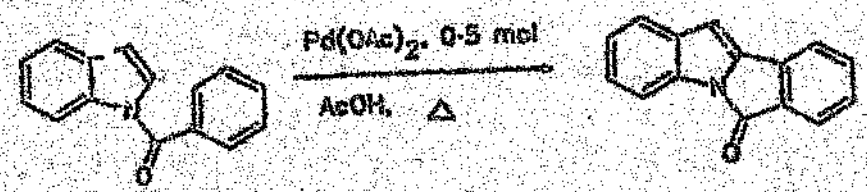


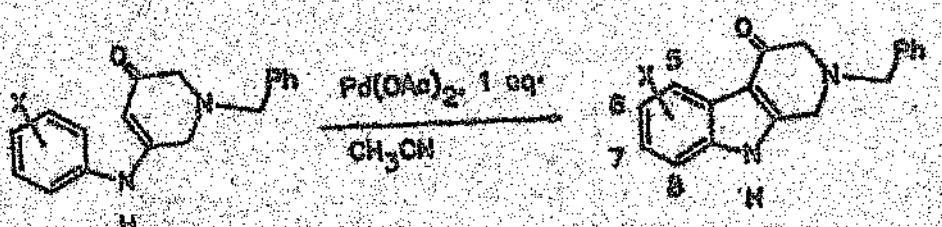
87%

Mention must also be made of Heck reactions between an aryl moiety bearing no halides and an alkene component, as these examples are increasing in number in the literature. Both inter- and intramolecular examples are available.[76,105-148] In all the cases shown overleaf no phosphine ligands were present. In the last two examples the low yields suggest that these processes cannot be catalytic in palladium.[147,149] In the last example the reaction is considered as aromatic electrophilic palladation,[148] therefore the yield is accounted for by the position of the methoxy group on the phenyl ring.[149] It can be seen from the three intramolecular examples that ortho substitution (palladation) of the aromatic ring is dominant. Besides the substituent effect in electrophilic aromatic substitution, there is the added coordination (complexing) effect by ortho group participation to stabilise the palladium intermediate.[150-152]

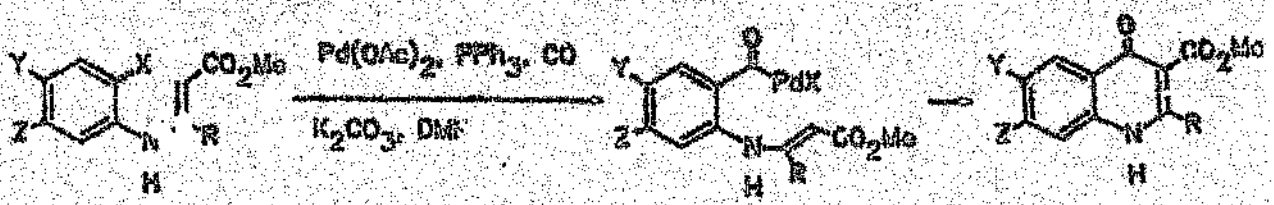








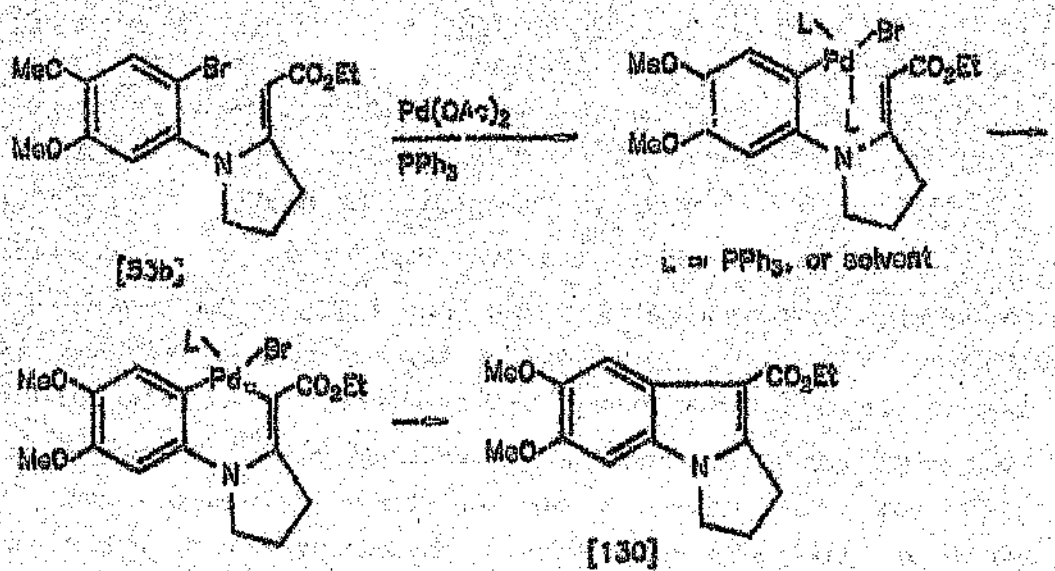
A modification to the Heck reaction has been found. Carbonylation of aromatic halides with palladium catalyst has been widely used in organic synthesis.[96a,97] Tarli *et al.* ed such a method to prepare substituted 4-oxoquinolines.[153] They found the cyclisation to be *endo*. Other groups have reported *exo* cyclisations.[154-159]



In view of the literature analogies it is apparent that while intermolecular Heck reactions prevail in the literature, their intramolecular counterparts are more suitable to form five-membered rings in the vinylogous amide and urethane systems. Indeed in our own work, reported in the following section, it was found that the formation of five-membered rings intramolecularly was successful, while attempted cyclisation intramolecularly to form six-membered rings failed.

3.3 Results and discussion

When vinylogous urethane [53b] was stirred at room temperature with a catalytic amount (0.12 eq.) of palladium acetate in the presence of triethylamine in acetonitrile, no reaction was observed. However, upon reflux in the presence of triphenylphosphine, the desired indole compound [130] was obtained in a 36% yield after chromatography. Another attempt was made with propionitrile as the solvent. The increase in reaction temperature did not help to improve the yield of the reaction (34%). In both cases the reaction was carried out under nitrogen and the solution turned black during the reaction, indicating the presence of palladium(0), which is believed to be the active species. The low yield, although disappointing, is comparable to those obtained by Kibayashi *et al.*[75] Successful literature examples in similar systems have employed sealed tube conditions.[74,116] [Perhaps an increase in both temperature and pressure is what is needed to push up the yield, but this was not attempted.]



[53b]

[130]

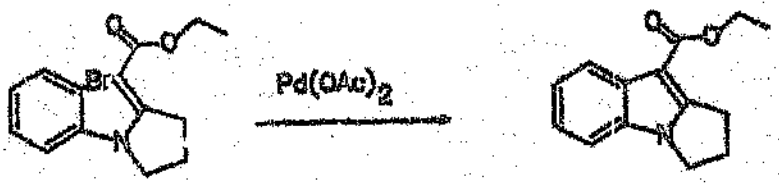
When a stoichiometric amount of palladium acetate was added, the yield was much improved (63%). This provides a way to obtain this indole compound, which can serve as a model compound to mitomycin antibiotics,[92] in a fair yield. The extent of improvement suggests that the reaction is not truly stoichiometric in palladium but rather more catalytic in nature. The failure for total conversion of the reaction suggests that the active palladium(0) species is tied up somehow in the reaction. Simple palladation of the reaction vessel, a problem in our experience,

is not enough to use up all the palladium(0) particles. Although the palladium produced during reaction gives the solution a black appearance, after filtration the solution is in fact golden brown, and column chromatography also separates a yellow solid. This could be unreacted palladium acetate, or palladium acetate bis-phosphine complex. This suggests that palladium(II) acetate is not reduced as easily as reported. Literature examples, however, have shown that Heck reaction does not proceed satisfactorily with aryl bromides bearing strongly electron-donating substituents on the phenyl ring owing to competing formation of tetraarylphosphonium salts from aryl bromides and triarylphosphine. Better results may be obtained by using sterically hindered tri-o-tolylphosphine in place of triphenylphosphine.[102] Hence the low yield obtained for [130] in this Heck reaction may be attributed to the electronic factor of the substrate [53b].

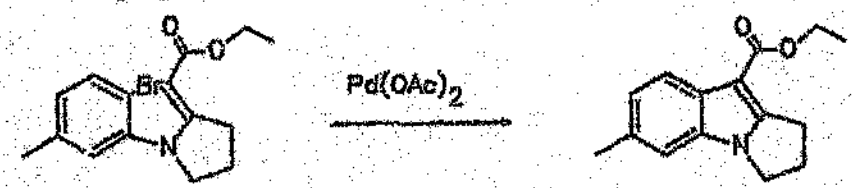
Attempts to use a phase transfer reagent to improve the yield of this catalytic Heck reaction, as suggested by Jeffery,[103-105] failed completely. No reaction was observed when [53b], palladium acetate, triphenylphosphine, potassium carbonate or triethylamine and tetraethylammonium bromide were heated under reflux in acetonitrile. Starting vinylogous urethane [53b] was recovered quantitatively. (Although the chloride salt has been the popular one used in many examples including those initial reactions carried out by Jeffery,[103-105] the bromide salt has also been quoted in the literature.[107]) Merlic et al. have also recently reported that chloride ion (KCl, LiCl, or NaCl) enhances the yields of cross-couplings between aryl iodides and selected olefin acceptors.[109] The inhibition of the conversion by the introduction of tetraethylammonium bromide, not even a trace by t.l.c., was totally unexpected. Tetraethylammonium bromide may have tied up active palladium(0) species, resulting in no reaction.

The fact that this Heck reaction operating in our system is catalytic is proved by the conversion of vinylogous urethane [85] to the desired indole compound [131] using palladium acetate (0.2 eq.). A 98% yield was obtained. This yield is exceptionally high, better than those obtained for the palladium-catalysed cyclisation of some β-(2-halophenyl)amino-substituted α,β-unsaturated ketones and esters carried out by Yamanaka et

al.,[76] who used sealed tube conditions. Their yields ranged from 35 to 83%. The conversion of vinylogous urethane [86] to the indole compound [132] was also achieved in a good yield (78%) with a catalytic amount of palladium acetate (0.2 eq.).

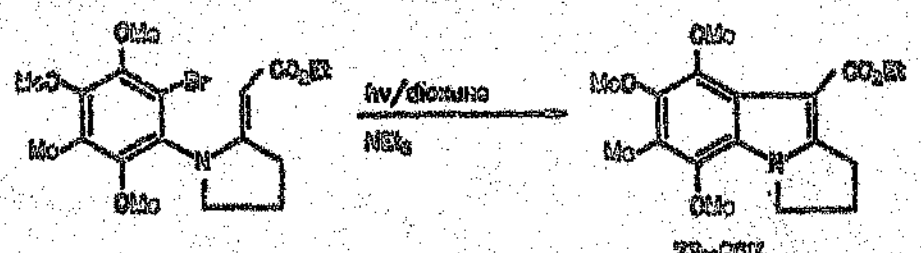


[85] [131]



[86] [132]

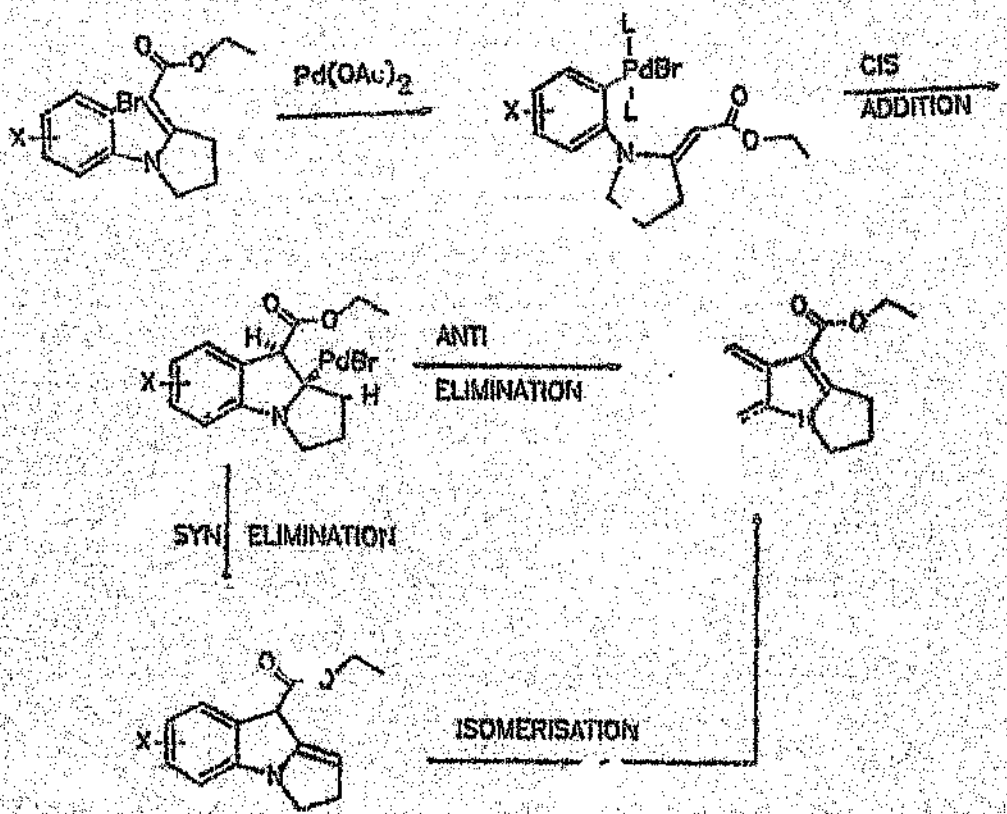
The yields obtained for the three successful Heck reactions carried out in this project show the trend that electron donating substituents on the aryl ring lower the yield of the reaction. Such a finding has already been reported by Hegedus[117] and Grigg.[120] According to such an observation the cyclisation shown below is expected to give a poor yield when using Heck reaction conditions. Perhaps this is why Rapoport *et al.* used a photochemical approach to effect the desired cyclisation.[163] It is on the agenda in this laboratory to repeat Rapoport's reaction with palladium(II) for comparison, though we do not expect to improve his yields.



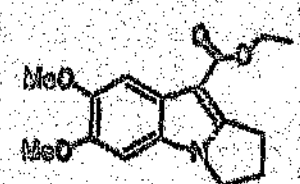
78–88%

The mechanism of the Heck reaction operating in our system also produces an interesting question. Since the addition of the aryl-palladium species to the alkene component in the vinylogous urethane is *cis* in fashion,[111] the intermediate produced (two enantiomeric forms) has the wrong stereochemistry for the required *syn*-elimination of HPdBr,[94,95,97,112] the hydrogen in question being the only one left in the newly formed

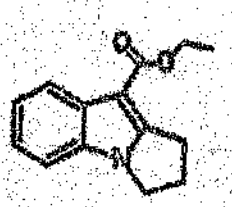
heterocycle. The PdBr moiety either undergoes an *anti*-elimination,[113] or undergoes a *syn*-elimination with the *syn* hydrogen from position 3 of the original heterocyclic ring. The product would then isomerise to the desired indole compound.



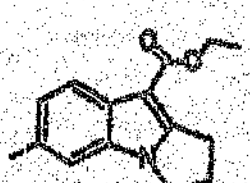
The NMR data for the three indole compounds are collected in Tables 10 and 11.



[130]



[131]



[132]

Compound	130	131	132
C-1	44.36	44.09	44.33
C-2	26.47	26.22	26.43
C-3	26.11	25.85	26.11
C-3a	150.56	152.69	152.72
C-4	96.64	98.86	98.61
OCH_2CH_3	59.01	59.04	59.10
OCH_2CH_3	14.53	14.52	14.63
>C=O	165.49	165.30	165.54
C-4a	126.58 or 123.61	132.43 or 130.76	131.14 or 130.90
C-5	103.03 or93.26	121.37,	122.94,
C-6	146.15,	121.28,	109.34
C-7	145.90	121.08,	131.14 or 130.90
C-8	103.03 or93.26	109.67	121.09
C-8a	126.58 or 123.61	132.43 or 130.76	131.14 or 130.90
2xOMe	56.04	———	———
$ArCH_3$	———	———	21.61

Table 10 CMR Chemical shifts (δ, ppm) for the three indole compounds [130], [131], and [132].

Compound	130	131	132
CH_2N	4.04	3.88	4.00
$CH_2CH_2CH_2$	2.62	2.49	2.57
$CH_2C{=}CC{=}O$	3.23	3.11	3.21
OCH_2CH_3	4.34, 1.40	4.33, 1.39	4 35, 1.40
H-5	7.63	8.10	7.90
H-6	———	7.14, 3H,	7.08
H-8	6.72	Includes H-7	6.99
2xOMe	3.97, 3.92	———	———
$ArCH_3$	———	———	2.47

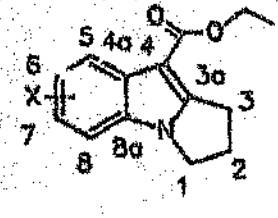


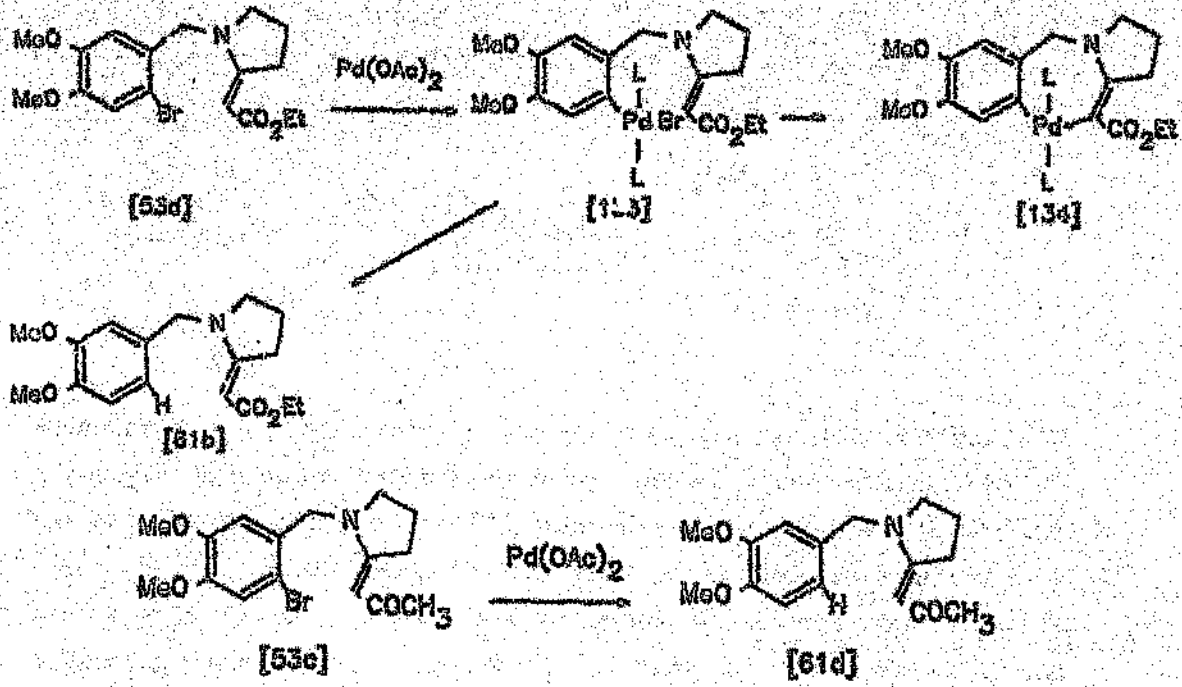
Table 11 PMR Chemical shifts (δ, ppm) for the three indole compounds [130], [131], and [132].

In general the proton peak positions have all shifted slightly downfield compared to those of the corresponding starting vinylogous urethane. In the aromatic region one proton always stands out most downfield. This must come from aromatic H-5 as this proton in the indole structure falls within the deshielding zone of the ester carbonyl group. The other signals stay relatively unchanged. The protons next to nitrogen in the ring have shifted downfield remarkably; in fact they are more downfield than the two methoxy signals as in [131]. Also now they appear as triplets, in contrast to two sets of doublets of triplets observed in the spectra for the corresponding starting vinylogous urethane. In the indole compound the aryl ring is forced to be coplanar with the vinylogous urethane because of ring fusion. This creates the same chemical environment for the two protons next to nitrogen in the ring. The marked downfield shift of these protons is thus ascribed to the powerful deshielding effect of the indole magnetic field. The effect also causes a substantial downfield shift of the side chain alkoxy proton and the $CH_2\underline{CH_2}CH_2$ signals. The $\underline{CH_2}C{=}CHC{=}O$ proton signals on the other hand have shifted upfield slightly. This is not because the deshielding effect from the indole structure does not reach them, but because now they are out of reach of the deshielding zone of the carbonyl group. It should be appreciated that the position of the signals of these protons is far more downfield than that for H-3 of the *cis-s-cis* structures in our cyclic enaminones, which usually appears *c.f.* δ = 2.70 ppm. The signals from the aryl substituents have also shifted downfield after cyclisation, but their movements are not as pronounced as the others.

In contrast to the more predictable trend of changes observed in the PMR of the indole compounds, the changes in their CMR are more irregular when compared to the peaks from the corresponding vinylogous urethanes. They however do show a trend amongst themselves, as illustrated in Table 10. The carbonyl peaks stay relatively unchanged, as do the signals from the ethoxy carbons and those from the aryl substituents. The aryl aromatic peaks have in general moved upfield. The signals from C-1 and C-3 have also shifted distinctly upfield. The signals from C-3a have also moved upfield by *ca.* 16-19 ppm units. The only marked downfield shift comes from the C-2 signals, which have moved by between 4-5 ppm.

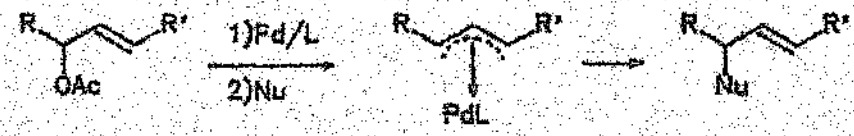
When the N-benzyl vinylogous urethane [53d] was subjected to

stoichiometric palladium reaction conditions in which [53d], palladium acetate (1.10 eq.), triphenylphosphine (2 eq.) and triethylamine (1.00 eq.) were heated under reflux in acetonitrile, the debrominated vinylogous urethane [61b] was isolated in a 13% yield after column chromatography. The NMR data of [61b] were summarised in Tables 6 and 7, Chapter Two. This product must be formed from the hydrolysis of the organopalladium compound [133]. Such reduced species have never been reported in Heck reactions. If the reaction worked as desired, the intermediate [134] would contain the unfavourable palladium-containing seven-membered ring. This may be the cause for the failure of cyclisation although seven-membered palladacycles have been proposed to explain formation of six-membered rings.[164] Even bigger ring palladacycles (9- & 11-membered) have been invoked as reaction intermediates.[133,143,164,165] But one has to bear in mind that these successful literature examples have different systems to ours. The N-benzyl vinylogous amide [53c] also failed to undergo the Heck reaction. The debrominated product [61d] was isolated in an 8% yield. No attempt was made to cyclise the N-phenylethyl precursors using the Heck reaction in this project although during the Honours project (see Introduction in Chapter One) two unsuccessful palladium-catalysed cyclisation attempts were carried out on vinylogous amide [50]. The failure could be reasoned with the same arguments as for [53c] and [53d].

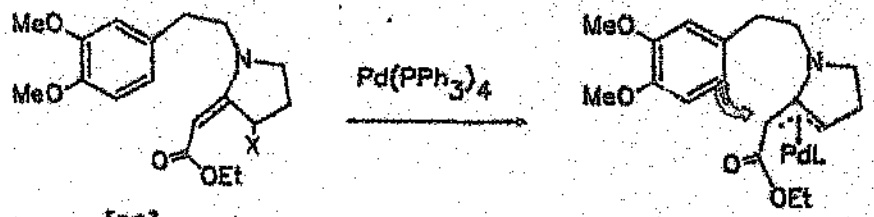


3.4 Postscript: π-allyl palladium compounds

Alkenyl species bearing a suitable leaving group on the allylic position are known to undergo facile palladation reactions, producing the corresponding π-allylpalladium complexes. Such reactions have been well documented.[94b],159 Usually $PdCl_2$ or $Pd(PPh_3)_4$ is used to do the required transformation. Both allyl halides and acetates can be palladated. Such species are electrophilic in nature and are therefore susceptible to nucleophilic attack. Nucleophiles that have been employed include the anions of active methylene compounds, enamines and amines. Both inter- and intramolecular examples have been reported.[160-162]



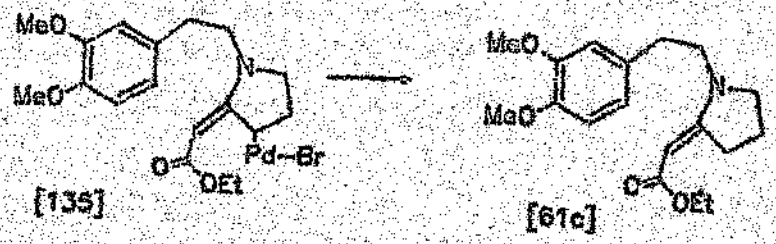
Aryl groups acting as nucleophiles have never been reported in π-allylic palladation reactions. It was felt that such an approach may be possible for the required cyclisation. This approach, however, reverses the role of both the aryl group and the vinylogous urethane system. The aryl group now acts as the nucleophile, and the introduction of a leaving group in the α position of the heterocycle makes the enaminic carbon electrophilic when palladated. The bromide [99, X = Br] is easily prepared, although the preparation of the corresponding acetate by exchange is expected to be difficult from model studies (see Section 2.5, page 55).



[99]

When the reaction was carried out by refluxing together [99, X = Br] with a catalytic amount of $Pd(PPh_3)_4$ (0.04 eq.) in THF under nitrogen, half of the bromide was recovered and the debrominated vinylogous urethane [61c] was isolated in an 8% yield. The low yield may reflect the resistance of the bromide to undergo palladation reaction or other factors such as temperature and pressure may need to be increased. The presence of the debrominated compound [61c] shows that palladation of the bromide must

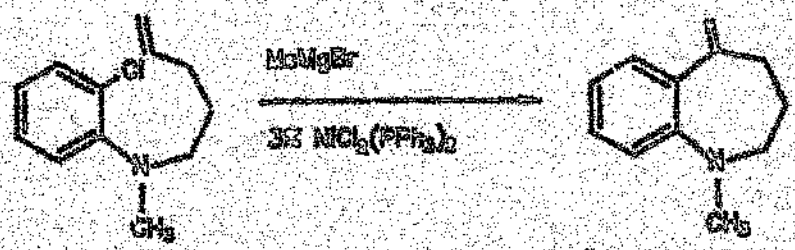
have occurred to some extent. Hence either the aryl group is too weak a nucleophile here or π-allylic palladation did not occur and a simple σ-palladium species [135] formed, in which case cyclisation would be impossible. If π-allylic palladation did occur then one can say with certainty that the aryl group is not strong enough as a nucleophile here. Perhaps an increase in reaction temperature would force cyclisation to occur. However, it is just as likely that this approach is simply not viable.



CHAPTER F . R: INTRAMOLECULAR ARYLATION MEDIATED BY OTHER METALS

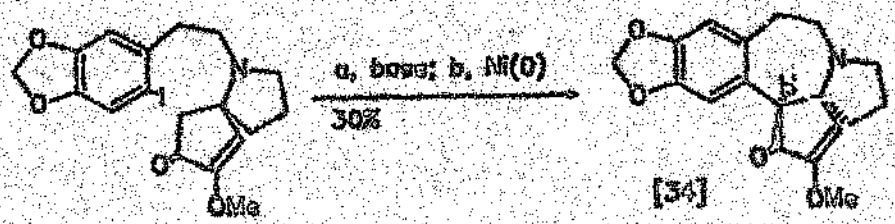
4.1 Introduction

Coupling between an aryl halide and an alkene has been achieved by transition metals other than palladium. The most frequently used metals include nickel[166-168] and copper.[169,170] For example Ban et al. prepared many heterocycles using nickel catalysts. They succeeded in bringing about an intramolecular arylation using nickel to generate benzazepine derivative [136].[166] The cyclisation mode was 7-exo-trig.



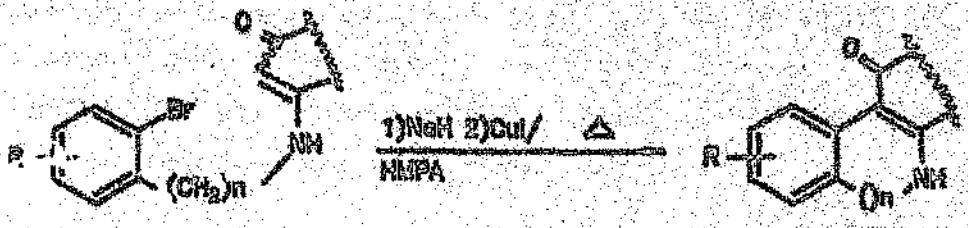
[136] , 62%

Semmelhack et al. also tried zero-valent nickel complex to effect the crucial ring closure reaction in the synthesis of cephalotaxinone [34]. The yield is much lower than that obtained from the SRN1 approach.[35a]



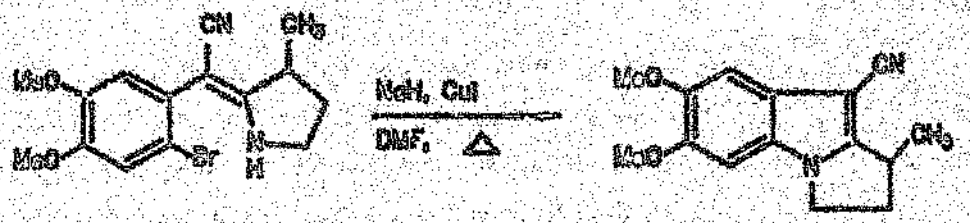
[34]

Osuka and Suzuki cyclised many N-2-haloaryl-vinylogous amides to give different indoles using a copper(I) catalyst.[169] Many dihydro isoquinolines were also prepared similarly. Kametani et al. treated a vinylogous cyanamide [137] under similar reaction conditions.[170] Owing to the structure of the substrate, N-arylation was forced to occur, and gave the indole derivative in excellent yield (93%).



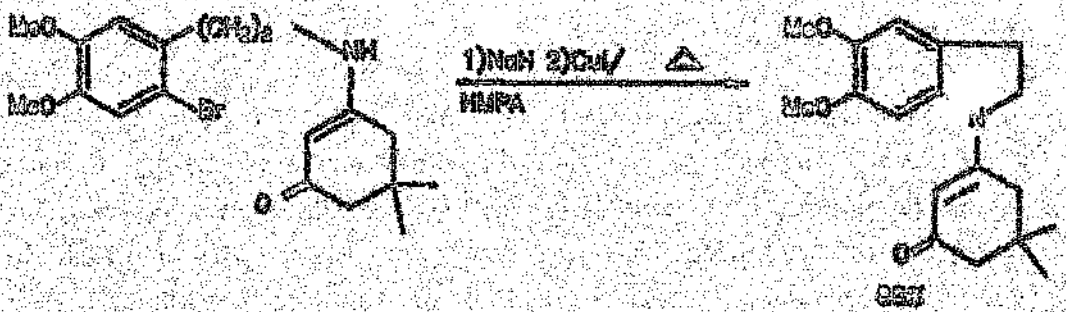
n = 0, or 1

42-82%



[137] 933

Attempts to prepare benzazepine derivatives failed. Instead, N-arylation resulted in indoline compounds in high yields.[169] Similar results were reported by Kibayashi[230,241b] under different conditions, in which the same substrate was subjected to lithium diethylamide (see Section 5.2.1).



934

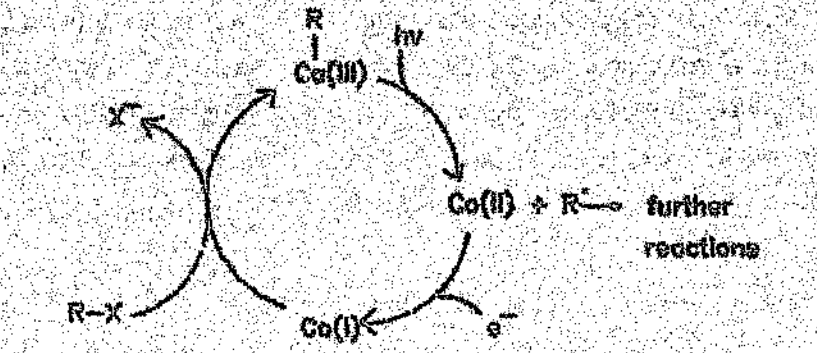
Although these examples are interesting, we did not pursue reaction with copper and nickel. More appropriate for our purposes were reactions employing cobalt, tin, lead, and chromium. In the rest of this chapter, we shall present reported cyclisations based on these metals, and in each case the brief literature survey will be followed by an account of our own attempts to use these metals to achieve the desired cyclisations.

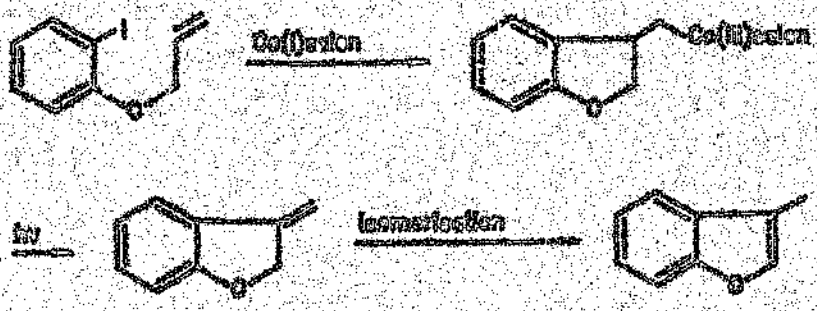
4.2 Cobalt(I)-mediated cyclisation attempts

4.2.1 Literature

It is well known that tin hydrides can be used to generate free radicals from alkyl, vinyl, and aryl halides, and that these radicals can be involved in carbon/carbon bond formation (see also Section 4.3). A major drawback of this method is the reductive nature of the carbon/carbon bond formation, which leads to the loss of two functional groups in exchange for the new carbon/carbon bond. Owing to this problem, other methods have been explored for the generation of the requisite free radical which do not involve such loss of functionality.[171b] Among the methods available, the use of less toxic, low valent cobalt complexes to generate organo-

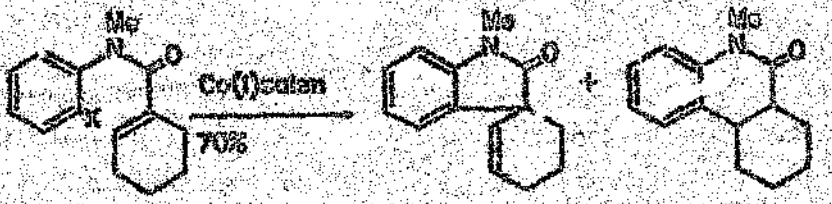
cobalt intermediates which undergo radical type cyclisations has been explored as an alternative approach. Various cobalt reagents are available. Cobalt(I) complexes are among the most powerful nucleophiles known and they have been called supernucleophiles.[172] They are reactive towards saturated carbon, and are capable of displacing halide, tosylate, carboxylate, sulphate and phosphate from the corresponding alkyl derivatives. Even aryl halides are no exception.[172] The mechanism for Co(I) radical reactions is given below. An example of intramolecular coupling between an alkene and an aryl iodide by Pattenden is also described.[173] Co(I) is such a powerful reductant that it readily gives up an electron to go to a more stable Co(II) species. Co(I) reagents can give up electrons to alkyl and aryl halides, producing the corresponding alkyl and aryl radicals which can undergo radical cyclisation with suitably positioned functionalities. The radical species generated in this process can be trapped by the Co(II) species to produce effectively an organo-Co(III) species. The Co(III) part can then be removed *in situ* by 1,2-elimination of Co-H, or it can be removed photochemically. Thus the functionality of the alkene moiety is restored with the aid of light. Successful literature examples of cyclisation almost always report the formation of five-membered rings. Few other sized rings have been reported.



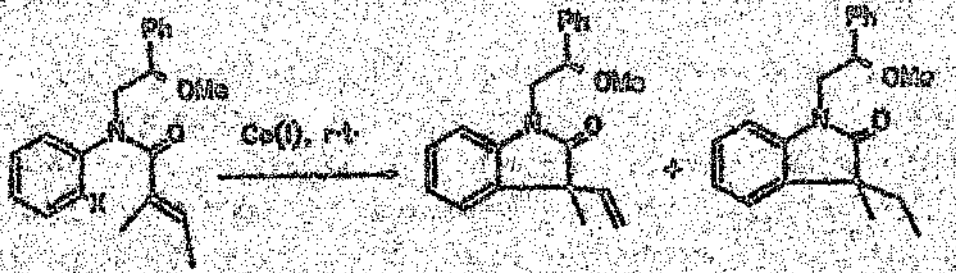


Recently Jones *et al.* have observed that cobalt-mediated aryl radical cyclisations involve simple free radicals.[174] Their conclusion is based

on regiochemical and stereochemical evidence.

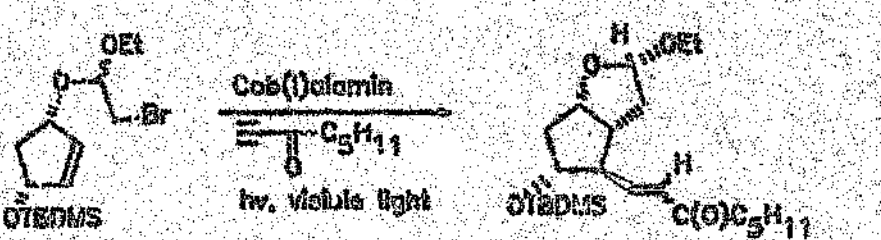


The above cyclisation could also be achieved using Bu_3SnH (X = Br, 91%, with loss of the double bond in the 1,5-cyclisation product). The fact that the ratio of 1,5- : 1,6-cyclisation is independent of whether tin hydride or cobalt(I) is used suggests that a common free-radical intermediate is involved.[174]



Compound [138] was obtained in 40% yield with a d.e. of 15%. When Bu_3SnH was used (X = Br, 79%), compound [139] was obtained also with a d.e. of 15%. This again points out that the cobalt-mediated aryl radical cyclisation involves simple free radicals. They concluded that attempts to use a chiral cobalt complex to induce enantioselectivity in such reactions will probably lead to poor results as the cobalt plays no direct role in cyclisation.[174,175]

Scheffold *et al.*, in the synthesis of prostaglandins, used cobalt(I) reagent in the form of Cob(I)alamin (B_{12a}) to carry out a crucial cyclisation reaction. This reductive B_{12}-catalysed radical cyclisation with concomitant trapping of the intermediate secondary radical by 1-octyne-3-one again indicates the radical nature of cobalt(I) reactions.[176]



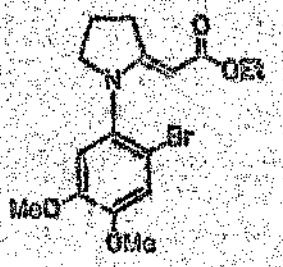
Pattenden *et al.* have used a similar approach to achieve several cyclisations.[173,177-179]

No examples including enamines or enaminones have been found. The use of cobalt(I) reagents to mediate cyclisation reactions in our system would thus constitute a genuinely new approach if successful.

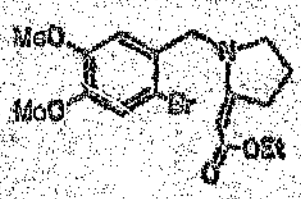
4.2.2. Results

The decomposition of the organo-cobalt species implicated in the cyclisation process generates radicals, so the reaction should be suitable for the formation of rings of various sizes. However, successful literature examples of ring formation involve mainly five-membered rings.

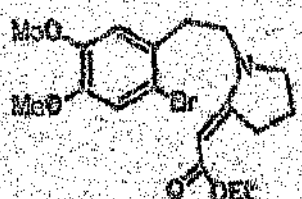
In this project three vinylogous urethanes [53b], [53d], and [53f] were subjected to cobalt(I) radical reactions. As the reactive species Co(I) is sensitive to light, all Co(I)-mediated reactions were carried out in the dark and under an argon atmosphere. The mechanism of the reaction involve Co(I), Co(II) and Co(III) species as mentioned already in the literature survey in Section 4.2.1. The scheme shown overleaf, with [53d] as an example, shows the steps expected.



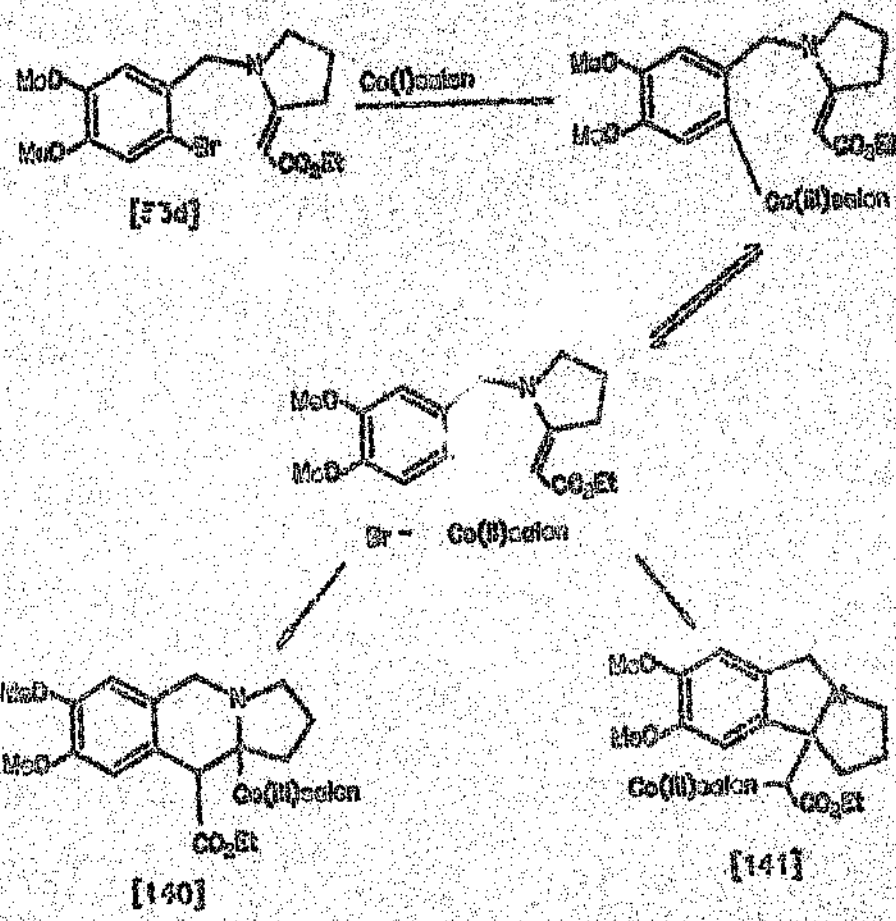
[53b]



[53d]

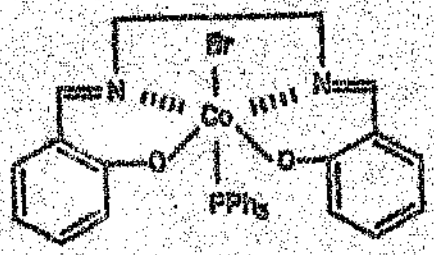


[53f]



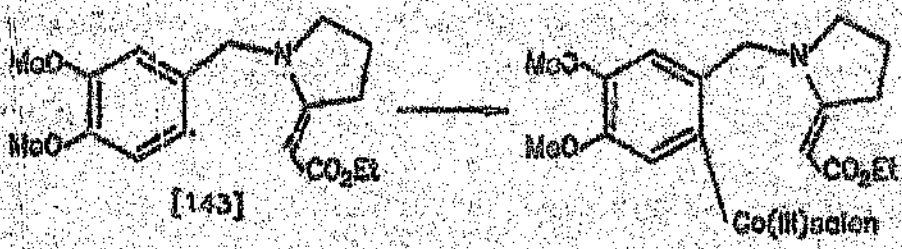
The aryl radical intermediate should undergo a radical cyclisation reaction with the alkenyl component of the vinylogous urethane system. Two different modes of cyclisation are possible, producing two different alkyl radicals which are then trapped by the Co(II) species. Cobalt complex [140] can undergo 1,2 Co-H elimination to give the desired compound in which a vinylogous urethane is regenerated. Compound [141], however, cannot undergo such a process.

In our cases the Co(I) was used in the form of the cobalt(I) complex of the bis-imine of salicylaldehyde and 1,2-ethylenediamine, with the remaining coordination site occupied by triphenylphosphine. This complex is more commonly referred to as Co(I)-salen. It is derived from the reduction of the corresponding Co(III)-salen [142] with sodium amalgam. Sodium borohydride and electrochemical reduction have been used by others in the literature.[175,180] The completion of reduction is indicated by change in colour from rust brown (Co(III)-salen) to green, typical of Co(I) species. The green Co(I)-salen was transferred to the organic substrate under argon pressure using a cannula.

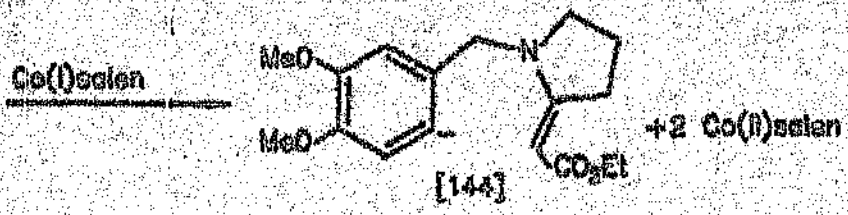


[142]

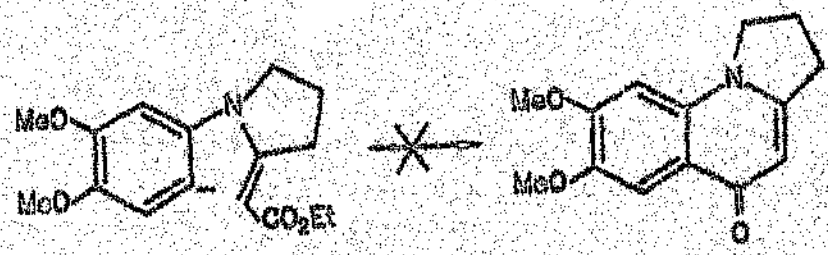
In all three cases only starting materials and debrominated vinylogous urethanes were obtained after chromatography. Yields of the latter range from 23% for [53b], 41% for [53c] to 45% for [53a]. It appears that the cyclised complexes such as [140] and [141] were not formed. The failure to cyclise could be attributed to the delocalised nature of the vinylogous urethane system, rendering the alkenyl component inactive towards radicals. Literature examples are based on localised double bonds. What may happen instead is that the radical [143] formed is trapped with Co(II) salen to give the corresponding Co(III) species. This Co(III) complex then reacts with a Co(I) species to give an aryl carbanion species and two Co(II) species.



Br – Co(II)salen



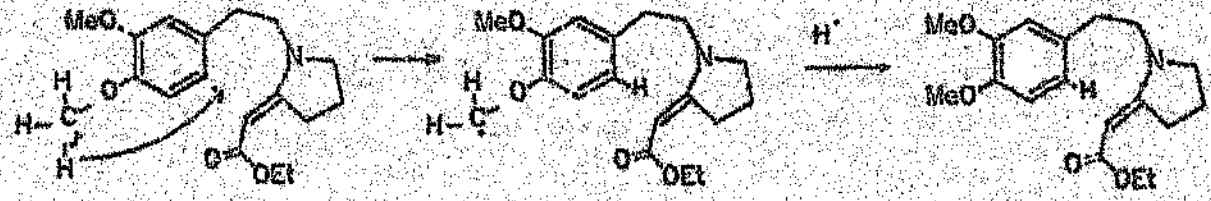
No cyclised compound of the desired type is possible from [144], although there is always the possibility of cyclisation by attack at the conjugate position. In the case of [53b] the aryl carbanion could possibly attack at the carbonyl centre of the ester group (c.f. Conrad-Limpach reaction) to give [145] if the geometry of the double bond were (Z) and not (E). The radicals and/or anion can thus only pick up hydrogen from other sources, such as the solvent.



[145]

Beckwith[27f] and Snieckus[101] have observed that aryl radicals easily undergo 1,5 alkyl hydrogen transfer. This may be the most likely cause for the failure of the reaction here. To prove such a theory, deuterated solvents would have to be used in the reaction. If deuterium simply replaces bromine then hydrogen atom abstraction from the solvent is taking place. A change of solvent to e.g. benzene may solve this problem. If deuterium lands up elsewhere in the molecule, then 1,5 alkyl to aryl hydrogen atom transfer is taking place. The inherent nature of this problem renders it difficult to solve. Both aryl radicals from [53b] and [53d] can undergo 1,5 hydrogen atom transfer with the heterocyclic hydrogens. The aryl radical from the N-phenylethyl precursor [53f] can only undergo 1,5 hydrogen atom transfer with the 4-methoxy hydrogens on the aryl ring.

In the present case, it was not felt worthwhile to devote time to investigate these mechanistic aspects.

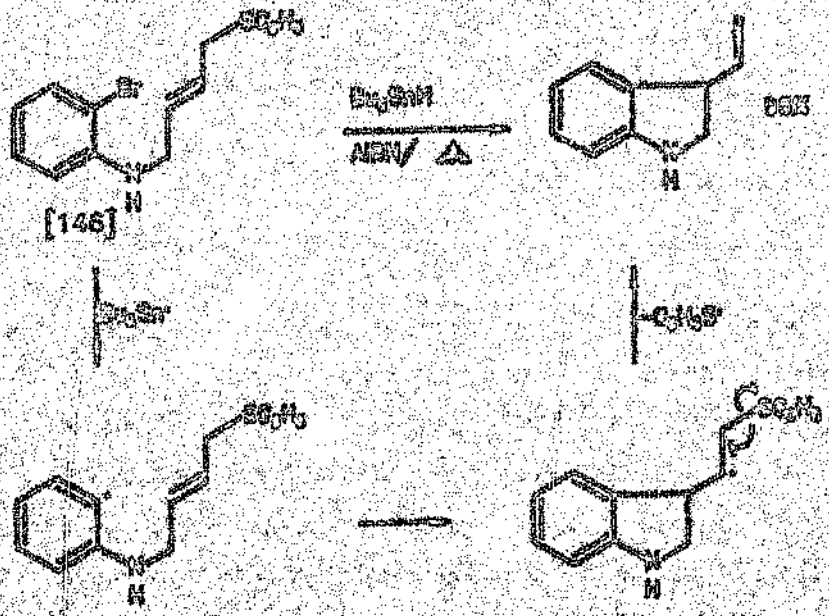


4.3 Bu$_3$SnH-initiated cyclisation attempts

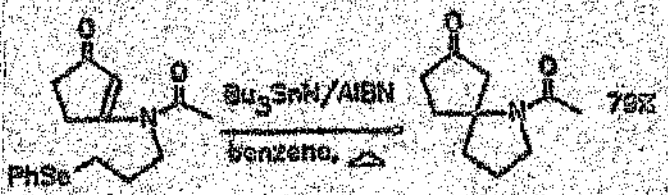
4.3.1 Literature

Tin, used in the form of tributylstannane, is receiving more and more attention in organic syntheses as a radical initiator.[17a,b,102-105] Radicals from alkyl and aryl halides can be generated using this reagent. The formation of radicals, however, destroys the double bond in the reactant. Thus, the reaction of bromide [146] with Bu$_3$SnH gives the

indoline compound in excellent yield.[193] Another double bond is created by the departure of phenylthio radical. Boger *et al.* used a similar system as model in the synthesis of complex antitumor antibiotics.[194]



As the above example illustrates, because of the radical nature of the reaction, groups other than halides which can be cleaved homolytically from carbon can also be used. Phenylselene group has been used as a radical source.[192,193] Simpkins *et al.* prepared the azaspiro[4.4]nonane [147] which may prove useful in cephalotaxine synthesis.[195]

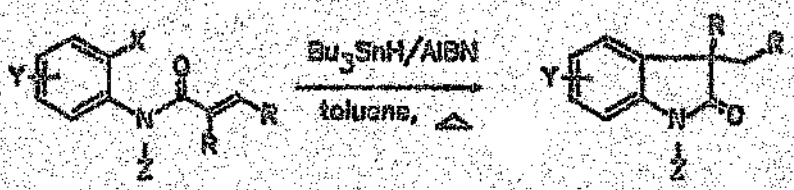


[147]

In general, however, a carbon halide bond is used to generate a carbon radical by Bu_3SnH. Beckwith *et al.* have studied the aryl radicals generated by Bu_3SnH in great depth.[189-191] Even an aryl diazonium salt can be used to generate an aryl radical.[196b]

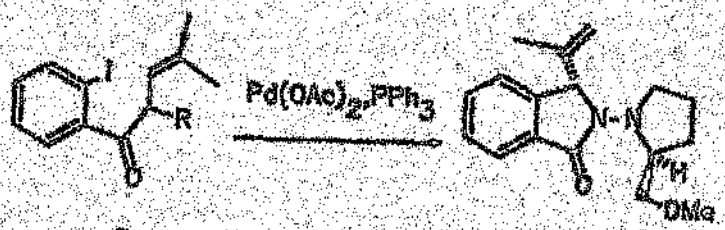
Various crucial ring cyclisations are achieved using Bu_3SnH, leading in some cases to the syntheses of natural products.[175,192,193] Jones *et al.* prepared various 3,3-disubstituted oxindoles from ortho-haloacetoxyl anilides.[175] No 1,6 cyclisation products were obtained.[194-196] This

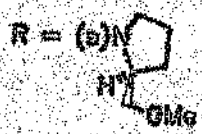
approach complements the preparation of tetrasubstituted carbon centres as obtained using palladium reagent.[110,120,123,131-136] Here the alkene functionality is lost in the reaction.



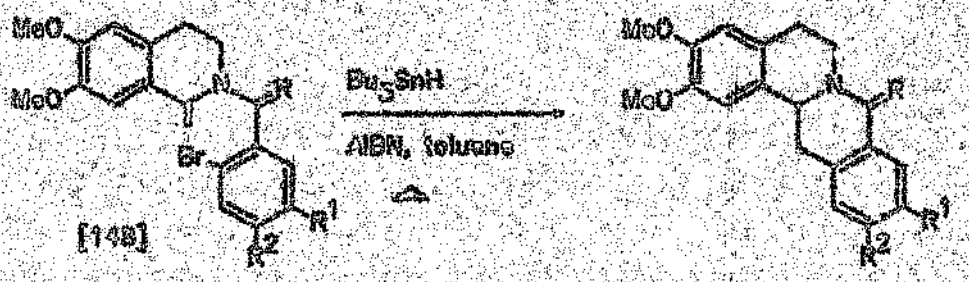
Y = H or OMe
X = Br or I
R = H or Me

The overall yield ranges from fair to good. By introducing chiral auxiliaries, Z, on N, oxindoles with optical yields up to 39% are obtained (Y = OMe, X = Br, Z = α-methylbenzyl).[178] The same aim has been achieved by Grigg and the others using palladium acetate and chiral phosphines with higher d.e.'s than the Bu_3SnH approach.[144,197] The following was achieved without chiral phosphines. The chirality induction carried by the group on nitrogen was enough to produce a d.e. > 95% of the product.[197]





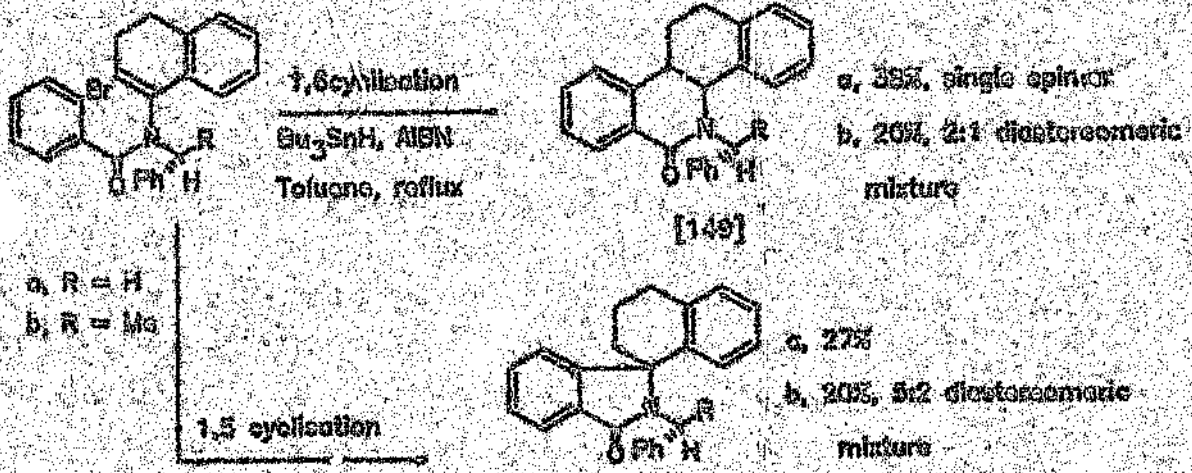
The problem of regioselectivity is also encountered in radical chemistry. Often mixtures are obtained but sometimes exclusive regioselectivity is observed.[194-196] Takano et al. reported exclusive 1,6-cyclisation for the enamide and enamine substrates (1/2) bearing exo-olefin.[196] When R = 2H, this radical approach is superior to both the photochemical[199,200] and palladium mediated methods,[120,134] which would not be able to furnish the cyclisation products directly from the enamine substrate. When R = O, the yields are better than those obtained using the palladium-mediated method (see page 71), and those from the photochemical approach (R_1 = R_2 = OMe, see page 118). But as Bu_3SnH reduces the alkene to a single bond in the process, comparison of the yields is meaningless since different products are obtained.



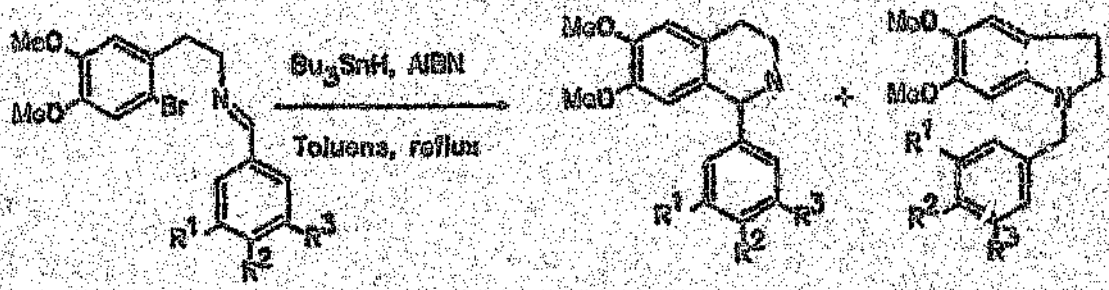
when R = O
$R^1 = R^2 = H$, 61%
$R^1 = R^2 = OMe$, 62%

when R = 2H
$R^1 = R^2 = -OCH_2O-$, 51%
$R^1 = R^2 = OMe$, 32%

However when the enamide substrates bearing *endo*-olefin moiety were treated under the same conditions, competitive 1,6- and 1,5-cyclisation occurred.[148] In [149b] a 2 : 1 diastereomeric mixture was obtained, reflecting asymmetric induction from the amine substituent.

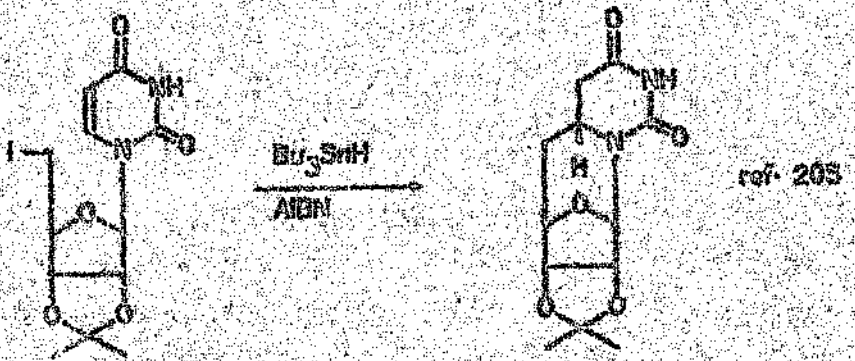


In Bu_3SnH radical reactions the unsaturated component may contain a heteroatom. Takano *et al.* reported intramolecular coupling between an imine double bond and an aryl halide, which occurred with a competition between 1,5- and 1,6-cyclisation.[201]



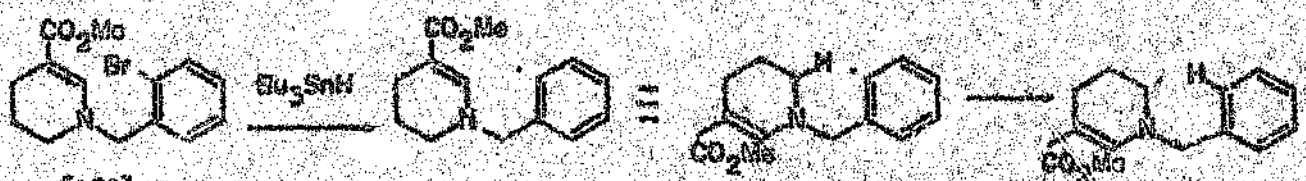
$R^1 = R^2 = -OCH_2O-$, $R^3 = H$	56%	10%
$R^1 = R^2 = OMe$, $R^3 = H$	51%	9%
$R^1 = R^2 = R^3 = OMe$	36%	8%

Beckwith et al. studied the intramolecular coupling between the enamine double bond of vinylogous urethanes and various bromides, including aryl bromide.[202] Some precedent for the viability of a cyclisation of this type has been provided by the work of Ueda, who reported successful radical cyclisations onto the heterocyclic ring in suitable N-substituted uracils.[203-207]

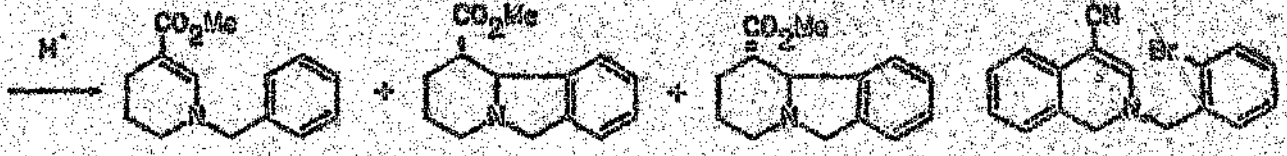


ref. 203

Beckwith *et al.* found that the cyclisation is less efficient than in the all-carbon analogue. Yield ranges from poor to fair. In all their examples, a significant amount (10-20%) of the simple reduction product was observed. In the case of [150] the reduced material predominantly arises not by direct reduction of the initial radicals, but rather by initial 1,6 alkyl to aryl hydrogen atom transfer followed by reduction of the rearranged radical since either direct addition or reverse addition over a period of several hours produces roughly the same percentage yield for the reduced compound. Such 1,5 transfers occur readily to an aryl or vinyl radical ($k_t \approx 10^7$ s^{-1}), and in this case the rearrangement results in the formation of a secondary alkyl radical stabilised by an adjacent nitrogen atom.[202] Saicahus has observed a similar phenomenon.[154] In the case of vinylogous cyanamide [151] only the reduced material was produced. For this compound there appears to be a complete preference for 1,5-hydrogen transfer resulting in the formation of a radical that is both benzylic and stabilised by an α-nitrogen atom.

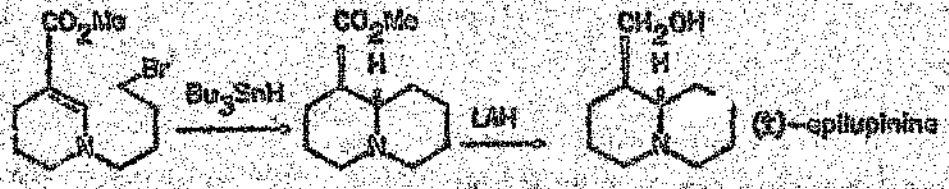


[150]



13% 15% 48% [151]

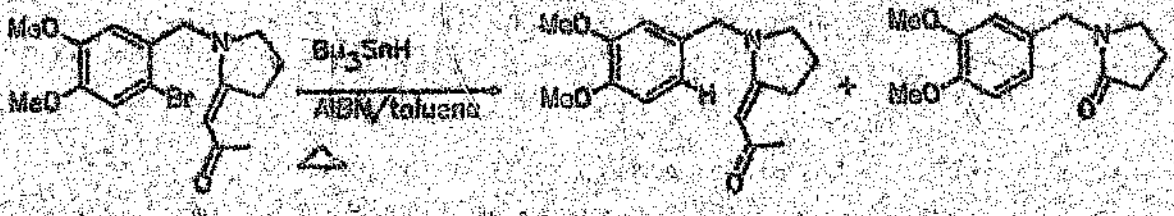
Various indolizidine compounds and one quinolizidine compound which eventually led to the synthesis of (±)-epilupinine were prepared this way. This synthesis is similar in approach to that of Howard et al.[7] (see page 4).



Successful examples of vinylogous urethane and vinylogous amide involve cyclisation on to the conjugate position. No cases of cyclisation α to the carbonyl group have been reported. What we are hoping for is therefore not a highly *anti* endo reaction, however, with the N-benzyl and N-phenylethyl enaminones of our system, a cyclisation on to the conjugate position would still be of considerable interest, in view of the occurrence of natural products containing such ring systems (e.g. *Erythrina* alkaloids).

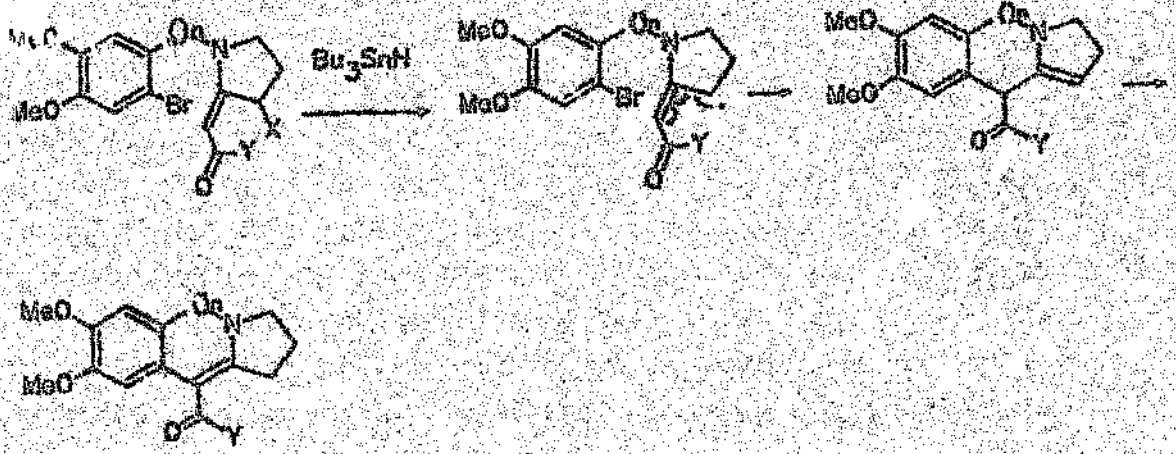
6.2 Results

When vinylogous amide [53c] was treated with Bu_3SnH/AIBN at reflux in toluene, the debrominated compound [61d] was isolated in a 25% yield together with the debrominated lactam [57b] in a 12% yield. The isolation of debrominated vinylogous amide [61d] could be explained using the 1,5 hydrogen transfer process. But the formation of the lactam [57b] is not easily understood.

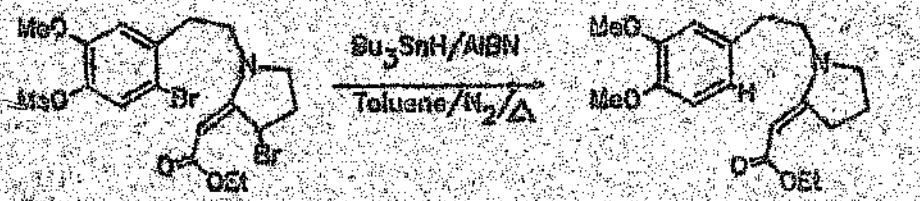


[53c] [61d] [57b]

Allylic functionalities can also be cleaved homolytically by Bu_3SnH.[104,105] It was reasoned that perhaps a generation of radical first at the γ position of the heterocycle of enaminones in our system would lead to cyclisation. This approach is described pictorially on the next page.

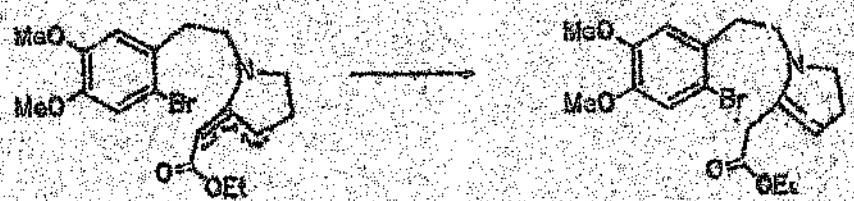


For this reaction to be applicable in the present work, the dibromide [98] was prepared. The γ-brominated compound was easily obtained by treating the corresponding vinylogous urethane [53f] in the presence of NBS (see Section 2.5). The dibromide [98] was treated with Bu_3SnH (2.70 eq.)/AIBN in reflux toluene. After chromatography the doubly debrominated vinylogous urethane [61c] was obtained in a 68% yield.



[98] [61c]

In this last example, if the allyl bromide reacted first and the radical reacted further with the double bond in the vinylogous urethane to produce a secondary radical α to the carbonyl group, [152], then there should have been cyclisation, since from the Co(I) reactions we observed that the aryl-bromine bond in our system reacted favourably towards radical initiators. The allylic radical formed did not react with the double bond in the vinylogous urethane system because of the delocalised nature of the system, then there was no chance of cyclisation. If however the aryl bromide reacted first, this aryl radical may undergo 1,5 allyl to aryl hydrogen atom transfer faster than reaction at the allyl bromide,[111,202] the product of which is then reduced further by more Bu_3SnH to produce the doubly debrominated vinylogous urethane [61c].



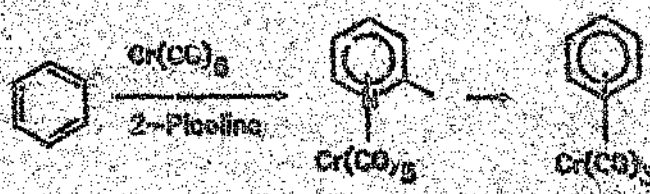
[152]

When vinylogous urethane [52f] was stirred together with Bu_3SnH/AIBN in toluene at r.t., no reaction was observed and [52f] was isolated quantitatively. More vigorous conditions are required here than in the reactions involving Co(I) since all the Co(I) reactions were carried out at r.t. The results obtained here also indicate that the enaminone system in our project may be inert to aryl radicals or they are too slow to react and the aryl radicals produced simply abstract a hydrogen elsewhere in the system or from the reagent.

4.4 Chromium complexation of N-phenylethyl compounds

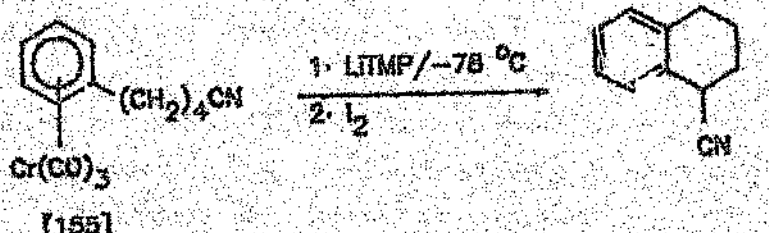
4.4.1 Literature

Zero-valent transition metal complexation of aryl compounds followed by reaction at the aromatic ring is becoming more and more important as a synthetic process. Since the discoveries of arenetricarbonylmetal complexes in the late 1950's,[200-202] this class of organometallic compounds has been rather extensively investigated.[203] The parent member of this series, benzenetricarbonylchromium [153], has been shown to undergo a variety of interesting reactions, including ligand exchange,[204-206] Friedel-Crafts acetylation,[216-218] and reactions with *n*-butyllithium resulting in metallation.[219,220] Many methods are available for the preparation of [153]. Rausch[221] uses the general procedure developed by Fruett *et al.* for the syntheses of arenetricarbonylmetal complexes,[222,223] which involves the refluxing under nitrogen of equal volumes of benzene and 2-picoline containing chromium hexacarbonyl. Under these conditions, carbon monoxide is rapidly evolved and little or no sublimation of chromium hexacarbonyl occurs. This reaction is believed to go through the intermediate [154], (2-picoline)pentacarbonylchromium, or related complexes which subsequently react with benzene present to form [153].[221,224]

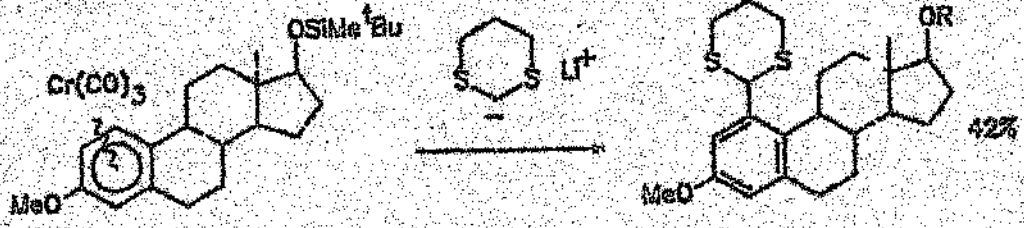


[154] [153]

Aryl groups are electro. rich and are considered as η^6 six-electron donors. Therefore, after complexation, the chromium has only three carbonyl groups attached to it. The chromium stays zero-valent before and after the reaction. The chromium carbonyl moiety is electron-withdrawing in nature. This makes the aryl ring electrophilic and thus it becomes susceptible to nucleophilic attack. Hard carbon nucleophiles such as in examples [155][213c] and [156][226] have been used. The chromiumtricarbonyl group is conveniently removed by mild oxidation with iodine.[209b),213a]



[155]



[156]

This idea was applied to some of the N-phenylethyl compounds in our system, and it formed the main theme for an Honours project.[226] The intention was to use the vinylogous urethane moiety as the internal nucleophile to attack the chromium-complexed arene ring.

Chromium-arene complexes are air and light sensitive; they easily undergo aerial oxidation to produce the corresponding chromium(III) species which are characterised by a green colour, therefore care has to be taken in their preparation. The method for preparing arenechromium complexes by Mahaffy and Pauson was used,[227] in which because of the volatility of $Cr(CO)_6$ and the slowness of the reaction a mixture of THF and dibutyl ether was used to keep the reagent in solution at reflux. The viability of the idea was first tested on the lactam [57c] and the thiolactam [59b] before it was extended to the vinylogous urethanes [61c] and [53f].

4.4.2 Results

The first reaction carried out was complexation of lactam [57c]. T.l.c. indicated the presence of a new compound even though the solution turned green during reflux. The desired complex [157] was obtained as a yellow oil in 20% yield after chromatography. Because these transition metal complexes are usually highly coloured, column chromatography of them becomes easier owing to the presence of the coloured bands moving along the column. The i.r. spectrum of [157] clearly indicated the presence of the complex by the appearance of two new strong signals at 1960 and 1880 cm^{-1}, which are ascribed to carbonyl absorptions on the chromium group. The lactam carbonyl absorption appeared at 1690 cm^{-1}. The compound decomposed before NMR data could be obtained. Attempted complexation reaction on thiolactam [59b] failed. After reflux a green solution was obtained, indicating that the chromium species have been oxidised to some chromium (III) compounds. Column chromatography yielded no chromium complexes.

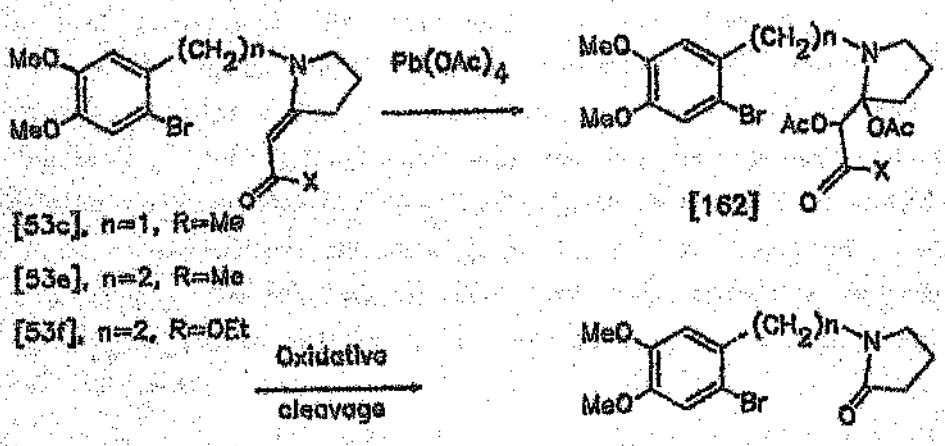


[57c] [157]

When vinylogous urethane [61c] was treated with $Cr(CO)_6$, the desired complex [158] was obtained as a yellow oil (58%). Starting material was also recovered (34%). The i.r. spectrum of [158] indicated two new strong absorptions (1966 cm^{-1}, sharp; 1888 cm^{-1} broad) due to the chromium carbonyl groups. The vinylogous urethane carbonyl group now produces a strong absorption at 1590 cm^{-1}. Again the complex decomposed during NMR characterisation. The paramagnetic nature of Cr(III) broadened the PMR spectrum; the peaks have in general moved upfield, especially the aromatic signals. There were no significant signals below 5.5 ppm. This is not expected; the chromium moiety is expected to be electron-withdrawing, causing the aromatic signals to appear more downfield. The shielding effect observed comes from the three carbonyl groups attached to the chromium. Exact assignment of the peaks is impossible due to the broadening of the peaks. However, the broadening effect of the Cr(III) does not seem to affect the NMR spectrum. Here the strong shielding

the corresponding lactam was produced. Thus vinylogous urethane [53f] was reacted with $Pb(OAc)_4$ in glacial acetic acid, and lactam [58c] was obtained in a 84% yield before column chromatography. The same is true for vinylogous amides [53c] and [53e], where lactam yields of 21% and 14% respectively were obtained after column chromatography. Material may have been lost during chromatography since these lactams are very polar and difficult to remove from the column.

If intermediate diacetates [162] were produced when tetrasubstituted aryl enaminones were reacted, then attack by the aryl group on α-carbon to the carbonyl group resulting in cyclisation would be unlikely. The diacetates may be cleaved hydrolytically to produce the lactams.



Lead tetraacetate is known as an oxidant in organic reactions.[229-231] Such reactions could also go through radical intermediates although this is less likely in acetic acid. However such a possibility can not simply be dismissed. Thus vinylogous urethane [53f] was reacted with lead tetraacetate in the non-polar solvent benzene. Inconclusive results were obtained. Reaction appeared to have taken place both at the aryl group and the vinylogous urethane system, and fragmentation of the molecule appeared likely from the PMR data.

The vinyl substitution reaction, which appears to go through a radical mechanism, would also be a useful process for us, since the vinyl radical produced might possibly cyclise on to the aryl ring. Attempts to see if such an approach could lead to cyclisation was carried out on the N-aryl vinylogous urethane [53b]. In one attempt, from PMR of the reaction mixture, it appeared that a new compound had formed and it looked like the vinyl chlorinated compound (two sets of some of the signals but only

CHAPTER FIVE: OTHER CYCLISATION ATTEMPTS

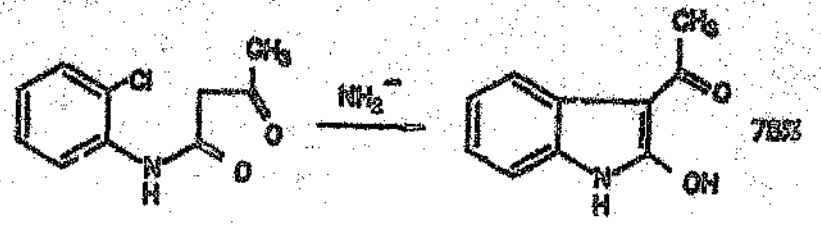
5.1 Introduction

The desired cyclisation can also be achieved in principle by methods that are not mediated by metals. This chapter is devoted to these other cyclisation methods reported in the literature. Among these, the "benzyne approach" and "photochemical coupling" are the most common ones.

5.2 Cyclisation via aryne intermediates

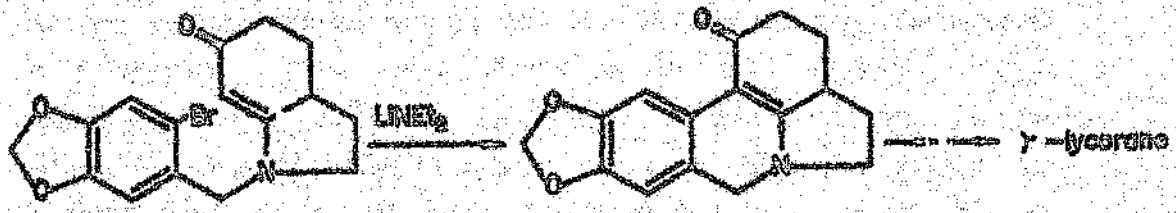
5.2.1 Literature

Another possible cyclisation approach is to go through the aryne intermediates. Strong bases have to be used. Perhaps it is because of these harsh conditions required for aryne formation that little reported work deals with intramolecular cyclisation via arynes. Ever since Roberts et al.[232,233] elegantly demonstrated the existence of benzyne, it has been used to trap many nucleophiles. In principle, if the nucleophile is suitably positioned intramolecularly, then cyclisation is possible. The following example is given by way of illustration. Bunnett et al. prepared many heterocyclic systems this way. The behaviour of other nucleophiles including nitrogen, oxygen and sulphur was investigated.[234]

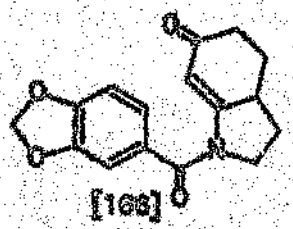


Semmelhack *et al.* in the synthesis of cephalotaxinone also tried the benzyne approach to effect the crucial ring closure reaction.[35a] A very poor yield was obtained, despite the strong bulky bases that were used. LDA, potassium hexamethyldisilazide, and potassium tertiarybutoxide failed to do the necessary conversion. Potassium amide in liquid ammonia gave a compound which was suspected to be an aromatic amine, which probably came from amide attack on the benzyne intermediate.

Fair yields were obtained when six-membered rings were formed as illustrated by the example shown below for the synthesis of γ-lycorane. The yield is considerably lower than the photocyclisation on a similar substrate [166] (see page 119). However, the benzyne route is better than the photochemical one for substrate [20].

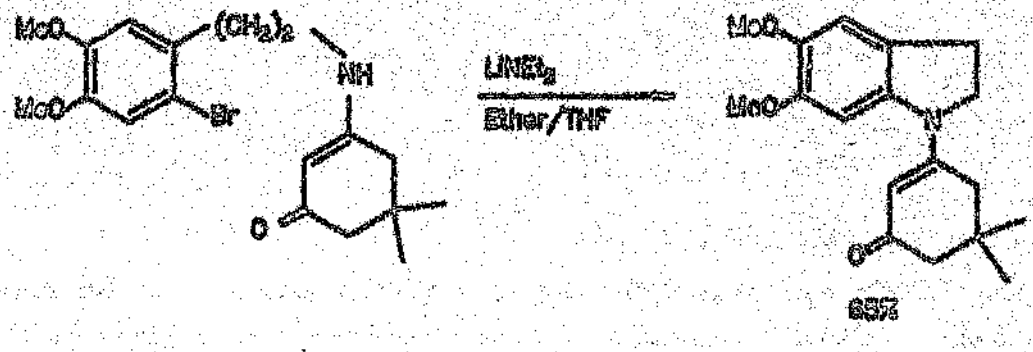


[20] 49%



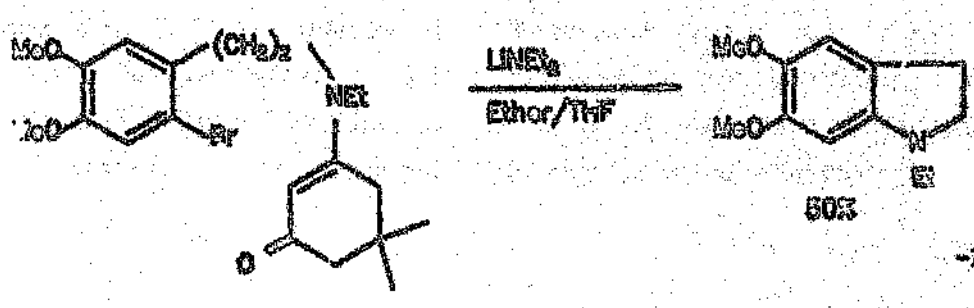
[166]

Attempts to form benzazepine derivatives proved to be complicated.[238,240] N-Arylation was preferred to C-arylation in secondary vinylogous amide systems, giving indoline compounds in fair yields. Similar results but better yields have been reported with copper catalysis (see Section 4.1, page 90).



65%

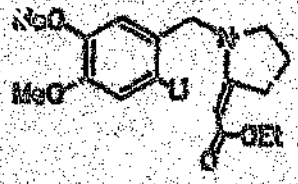
When the nitrogen was made tertiary in an attempt to prevent N-arylation by alkylation with ethyl iodide, the resultant compound fragmented on treatment with lithium diethylamide.[238,240] In all these cases no C-arylation was observed and fair yields were obtained.



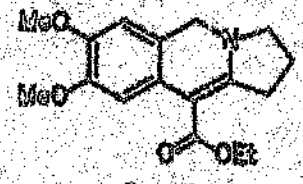
60%

Despite the successful literature examples, the results obtained here were disappointing. LDA was prepared from diisopropylamine and n-butyllithium in THF. Vinylogous urethane [53d] dissolved in THF was then added. The reaction was carried out under nitrogen at -78 °C. Often inseparable mixtures were obtained. In one case the debrominated compound [61b] was obtained in a 5% yield. The same compound was produced in cobalt(I) initiated cyclisations. This compound was confirmed by independent synthesis by a sulphide contraction approach.

This debrominated compound was probably produced by a metal-halogen exchange process in accordance with Kibayashi's explanation.[238] Hydrolysis of this organometallic compound [176] produces the debrominated compound [61b]. There is some n.m.r. evidence for the formation of the desired compound [177], however. Often the desired compound was probably present in the mixture, as indicated by the presence of two new aromatic signals at 8.14 and 7.79 ppm. As will be described in the next section, the desired compound was isolated in a photochemical approach, thereby allowing one to claim its formation in this reaction with some confidence.



[176]



[177]

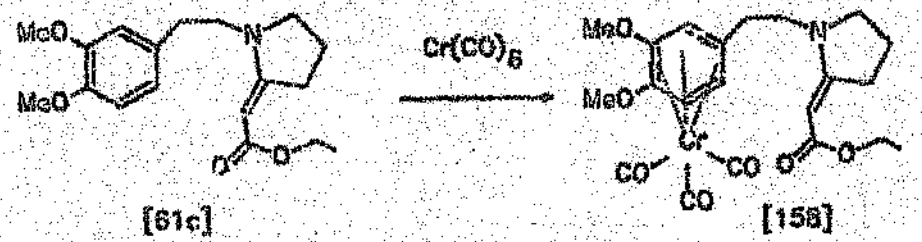
Two attempts were also carried out on the vinylogous amide [53c]. In both cases the starting material was recovered quantitatively. Hence these two compounds [53c] and [53d] react differently in strongly basic conditions.

5.3. Photochemically Induced Intramolecular Arylations

5.3.1 Literature

Although few examples of Heck reaction exist in which seven-membered rings are formed by intramolecular cyclisation, many reports exist of the corresponding photochemically induced cyclisation to seven-membered rings. Indeed many reports on the synthesis of cephalotaxine and its analogues involve such a crucial step.[36a],37,38 Sniekus et al.

effect of the three carbonyl groups on chromium is clearly evident. Table 12 compares the signals from vinylogous urethane [61c] and the complex [158]. The carbonyl signal from the chromium tricarbonyl moiety appears at 233.22 ppm.



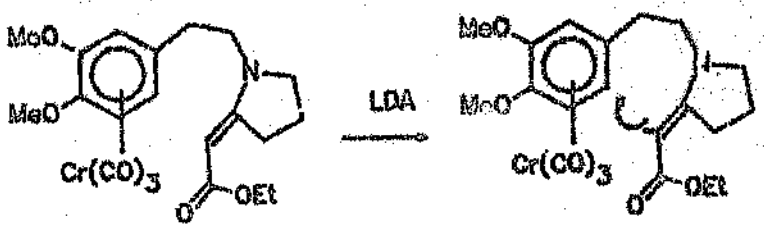
[61c] [158]

In general the peak positions have not changed too much except those from the aryl carbons, which have all shifted upfield significantly. The tertiary aryl carbon signals have all shifted upfield by between 33-35 ppm. These carbons must be strongly shielded by the carbonyl groups. Aryl carbons 3 and 4 have moved upfield the least by ca. 16 ppm. The electron donating nature of the methoxy groups has lessened the shielding effect from the carbonyl groups. Aryl carbon 1 has also shifted upfield significantly, 27.5 ppm. The shielding effect from the $Cr(CO)_3$ group does not reach beyond the aryl carbons as the other signals stay relatively unchanged. Even the methoxy carbons are little changed.

Compound	61c	158
C-2	169.45	169.01
C-3	32.63	32.39
C-4	21.09	21.06
C-5	53.20	53.04
>C=CH	77.64	78.51
OCH$_a$CH$_3$	58.24	58.29
OCH$_a$CH$_3$	14.72	14.56
>C=O	164.49	164.12
2xOMe	55.85, 56.10	57.41, 56.67
CH$_a$CH$_a$Ar	31.70	30.90
CH$_a$CH$_a$Ar	48.09	47.26
arom C-1'	131.34	103.84
arom C-2'	with arom C-5' & arom C-6'	with arom C-5' & arom C-6'
arom C-3'	148.91	133.82
arom C-4'	147.66	131.17
arom C-5'	120.61, 111.85	85.82, 78.85
arom C-6'	111.28	78.56

Table 12 Comparison of CMR chemical shifts (δ, ppm) between vinylogous urethane [61c] and the chromium complex [158].

The isolation of this complex also implies that the expected spontaneous attack by the enaminic carbon from the vinylogous urethane system on the aryl group during the complexation reaction did not occur. This probably suggests that the enaminic carbon in the vinylogous urethane system is not nucleophilic enough to undergo an attack at the aryl ring of the chromium-arene complex [158]. Deprotonation at the γ position of the heterocyclic ring of the complex, producing the anion [159], may be what is needed to activate this enaminic carbon thereby causing cyclisation, as many successful literature examples involve generation of such hard carbanions as nucleophiles.[213a],225



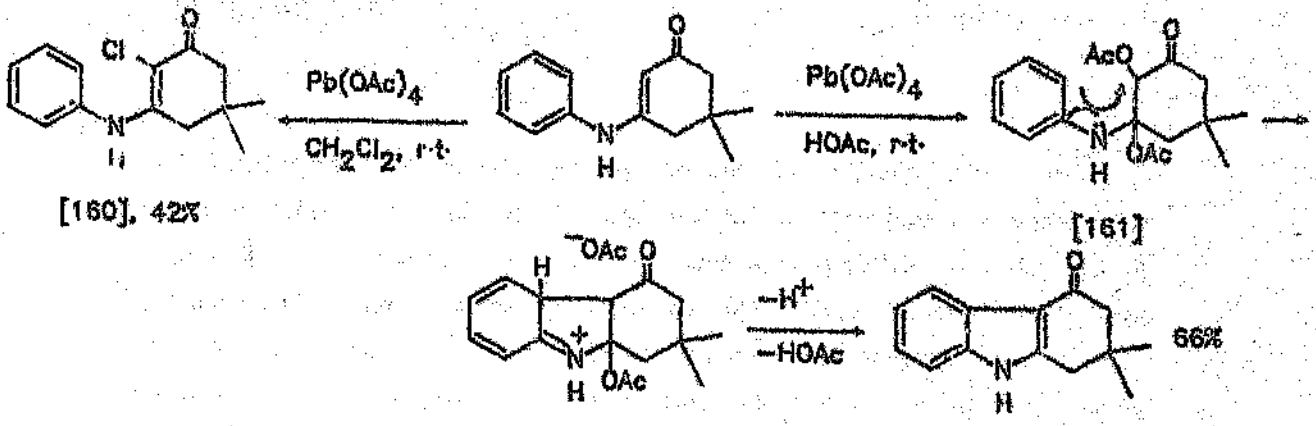
[158] [159]

Vinylogous urethane [53f] did not react with $Cr(CO)_6$. The starting material was recovered quantitatively. Steric effect is unlikely to be the factor as the aryl group is planar. The introduction of bromine on the aryl group has apparently made the aryl group electron deficient, rendering it inactive towards $Cr(CO)_6$.

4.5 Reactions with lead tetraacetate

4.5.1 Literature

Schäfer and Ellenberg reported the cyclisation shown below using lead tetraacetate.[229] It is interesting to note that in different solvents, different products are formed. Thus in dichloromethane the vinyl chloride [160] was obtained. The formation of this product appears to go through a radical mechanism, while cyclisation goes through a polar mechanism in which the diacetate [161] is a possible intermediate. Enamines are known to react with lead tetraacetate to produce such species.[229-231] Both ionic and radical reactions are possible with lead tetraacetate.

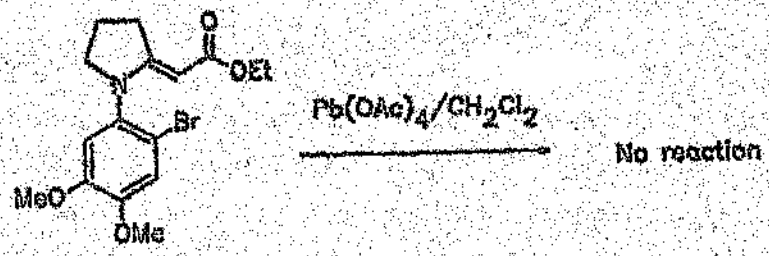


Since lead tetraacetate can react both as a radical and as a polar reagent depending on the solvent employed, we hope to investigate and effect both of these reactions using different solvents in our system.

4.5.2 Results

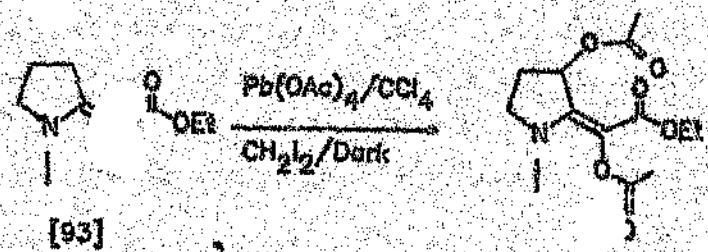
When vinylogous urethane [61c] was treated with lead tetraacetate in acetic acid, starting material was recovered (56%) after 8h of stirring at room temperature. No new signals were observed in the PMR of the reaction mixture. However when tetrasubstituted aryl enaminones were reacted similarly, cleavage of the enaminone double bond was observed and

one vinyl signal due to the presence of the starting material [53b]). However subsequent attempts all failed and starting material was recovered.



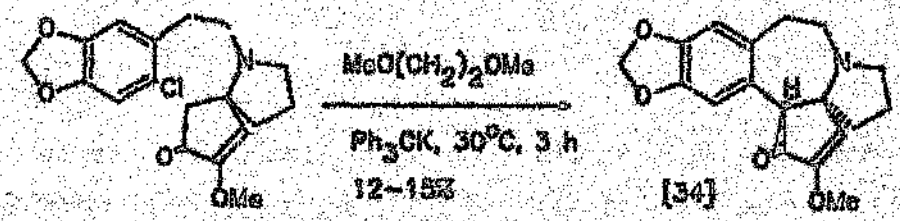
[53b]

It was reasoned that perhaps vinylogous urethane [53b] does not react with lead tetraacetate in dichloromethane. The reaction was studied further on the model N-methyl vinylogous urethane [93], where methylene iodide was substituted for dichloromethane, and carbon tetrachloride used as the solvent. The vinyl iodinated compound was the expected product. An interesting reaction was observed. The only characterisable compound was the highly oxygenated diacetate [163] in a 17% yield after column chromatography. The vinyl acetate could have come from a polar reaction, while that at the γ position of the heterocycle from a radical reaction of lead tetraacetate.



[93] [163]

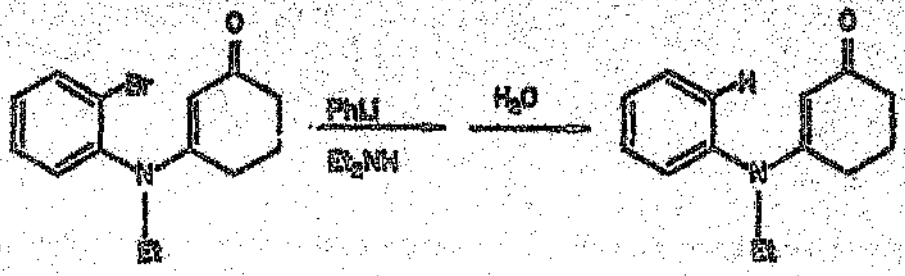
It can be seen that reactions with lead tetraacetate are very sensitive towards solvents. Future reactions may require careful choice of solvent to achieve desired reactions. However, indications are that they may not be worth the effort.



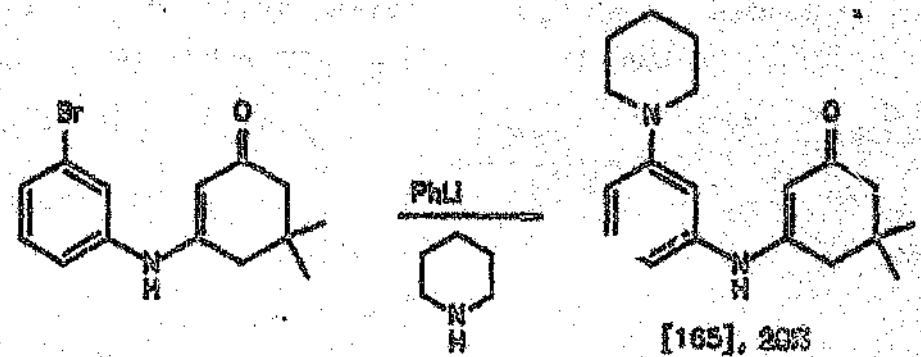
12–153 [34]

The one serious drawback of using alkali metal amide, such as sodamide or potassium amide, as the strong base to generate benzyne is its participation as a nucleophile.[235] Perhaps it is this reason that prompted many authors to seek different non-nucleophilic bases. For example Huisgen used phenyllithium to generate the aryne species.[235,237] Kibayashi *et al.*,[238] however, have pointed out that halogen-metal exchange may dominate in cases where the halogen has *ortho* substituents that can donate electrons inductively. This results in reduced products after hydrolysis.[230,239]

Quite a few examples are found in which vinylogous amides are used as substrates for intramolecular cyclisation using the aryne approach. Kibayashi et al. used lithium diethylamide to generate aryne intermediates from the vinylogous amide system.[15,239-241] The best results were obtained when a six-membered ring was formed.[230,239] Attempts to form five-membered rings failed.[239] Halogen-metal exchange and base participation were observed. The reduced product [164] could only be accounted for if halogen-metal exchange had occurred. The substituted product [165] indicates the presence of an aryne intermediate in the reaction. The lack of cyclisation here was attributed to reduction of the nucleophilicity of the α carbon by attachment of an aryne substituent in the reaction.[238]

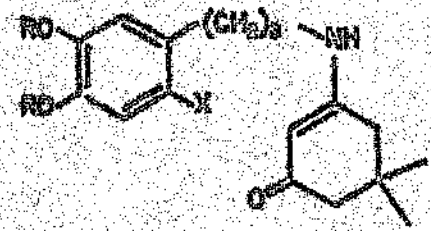


[164], 203

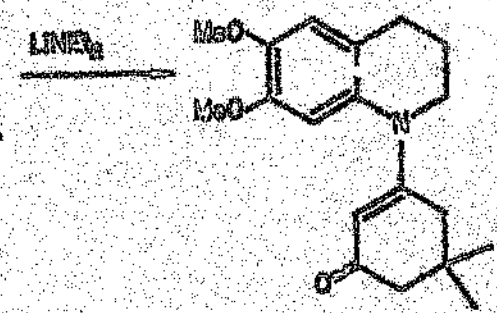


[165], 203

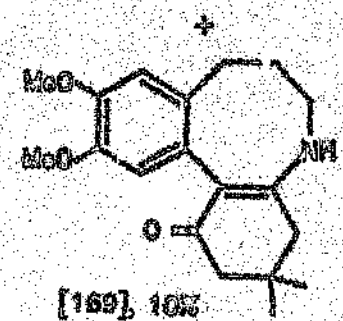
When the chain length was increased further by one methylene unit different results were obtained.[241a] Thus vinylogous amide [167, X = Br, R = Me] was prepared and treated with lithium diethylamide. Both N-arylated product, leading to a tetrahydroquinoline derivative [168], and C-arylated product, leading to a benzazocine system [169], were obtained. Furthermore, the reduced product [167, X = H, R = Me] was also isolated in a competitive yield (24%). Similar results were obtained using a photochemical approach[81] (page 120), which is superior to the benzyne method in producing the C-arylated compound [169]. No mention of dehalogenated product was made in the photochemical report. Similar results were obtained when the dimethoxyphenyl moiety was replaced by a methylenedioxy moiety [167, X = Br, R, R = CH_2].



[167]



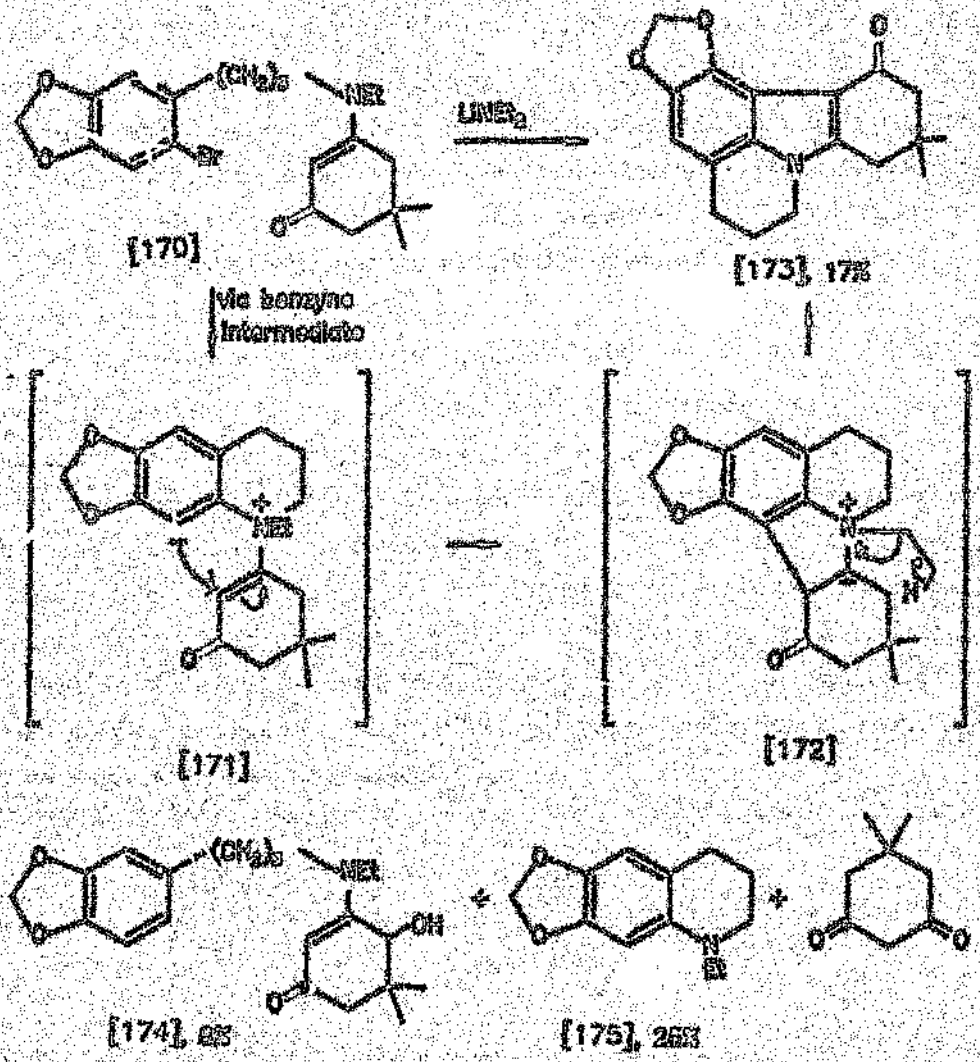
[168], 32%



[169], 10%

When the corresponding tertiary vinylogous amide [170] was treated with lithium diethylamide, interesting results were obtained. The formation of compound [173] was explained by the intermediacy of ylides [171] and [172]. Compound [171] was formed by N-attack on the aryne intermediate. If compound [171] is hydrolysed, the tetrahydroquinoline derivative [175] plus the diketone can be obtained. However, if [171] reacts further as shown then [173] is obtained. It is interesting to note that the ylide formation in the reaction of [171] to [172] arises from *umpol*ung of the normal reactivity (nucleophilic) of the α carbon atom in the vinylogous amide system. Finally, compound [174] may arise via another pathway

involving halogen-metal exchange, causing debromination and concomitant base-catalysed air oxidation at the allylic position.



[170] [173], 17%

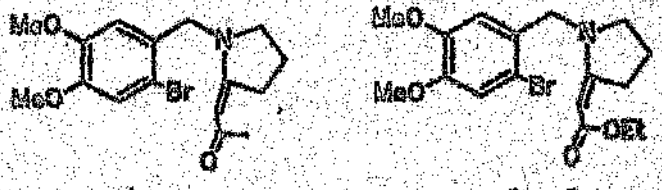
[171] [172]

[174], 8% [175], 26%

5.2.2 Results

Successful literature examples mainly involve the formation of six-membered rings. In the enaminone system, base participation was encountered when formation of five-membered rings was attempted and N-arylation leading to breakdown of the molecular skeleton was the result when formation of seven-membered rings was attempted.

As a result, in this work only the N-benzyl enaminones [53c] and [53d] were subjected to this strongly basic reaction condition.



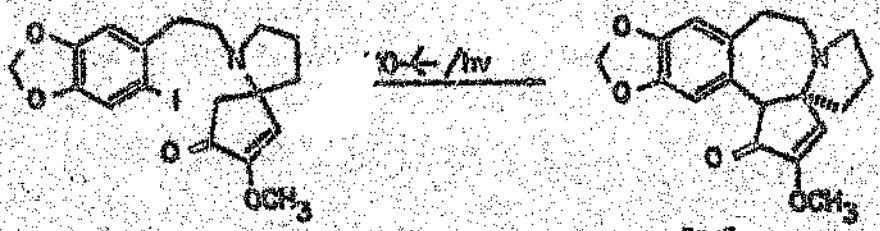
[53c] [53d]

irradiated enamide [178] to obtain the tetracyclic benzazepine deriva [179] in a 46% yield.[35]



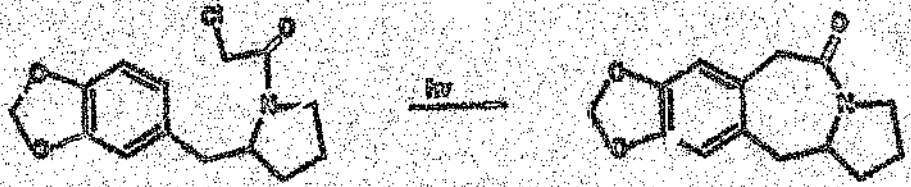
[178] [179]

Semmelhack *et al.* r photo-Sml reaction to effect the ring closure in the synth sis of cephalotaxinone [34].[35d] The yield was exceptionally high (94%).

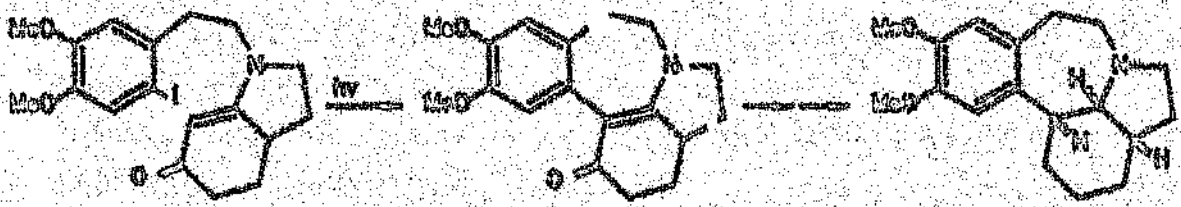


[34]

Dolby *et al.* also used a photochemical approach for the crucial cyclisation in the synthesis of cephalotaxine.[37] The yield for this step was very poor (25%).



Kibayashi *et al.*, in the synthesis of hexahydroaporyscpine dimethyl ether [182], subjected the vinylogous amide [180] to photochemical condi ne. The desired cyclisation gave the benzazepine derivative [181] in 50% yield.[38]

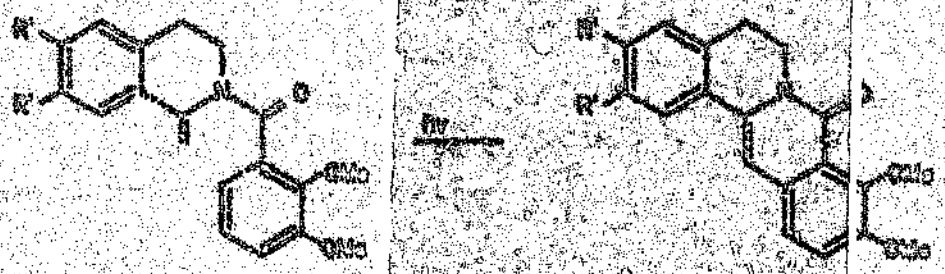


[180] [181] [182]

The examples shown already illustrate intramolecular cyclisations to give seven-membered rings. Photocyclisation is in fact more general and the examples shown on next page show photoarylations of alkenes in which

other sized rings are formed.

It is clear from Grigg's work that enamides are important synthetic intermediates. They have also been widely used as precursors in photochemistry. Intramolecular photoarylations of enamides to heterocyclic ring systems have been extensively studied, particularly in the field of alkaloid synthesis.[243-244] Ninomiya *et al.* prepared the important intermediates [183a and 183b] in the synthesis of the alkaloids tetrahydropalmatine[245] and sinactine[246] respectively by photolysis. The palladium catalysed route is claimed by Grigg *et al.*[120] to be superior to the photocyclisation for the production of [183a] but less efficient for [183b] (see page 71, see also page 98 for Buchwald reactivity).



[183] a, R' = OMe, 20%
b, R' = -OCH$_2$O-

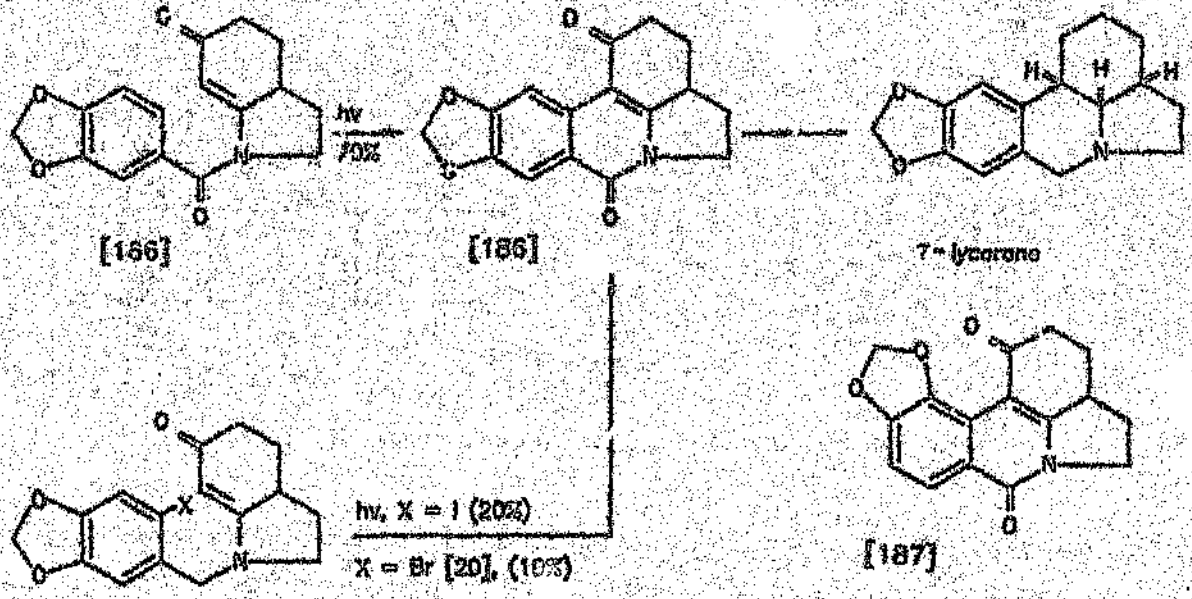
Schultz *et al.* have also used enamides as important intermediates in photocyclisation for alkaloid synthesis.[247,248]

Although not as widely documented in the literature as the photochemistry of enamides, that of vinylogous amides and urethanes has also been employed in the synthesis of alkaloids.[31,163,249-253] The photocyclisation of vinylogous amides and urethanes proceeds by a homolytic mechanism involving aryl radicals [184].[31,251,252] This aryl radical couples with the vinyl carbon with extrusion of a hydrogen atom to produce the cyclised product [185].

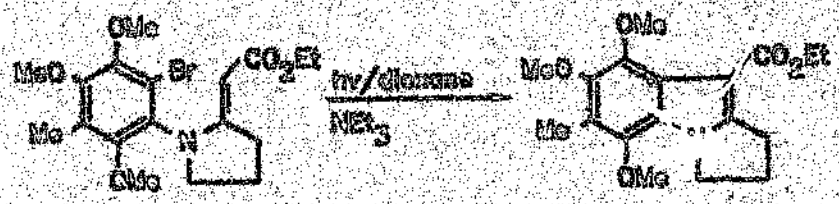


[184] [185]

The isolation of photo-reduced species[20,163,251,252] and sometimes that of dimeric species[21,252] clearly indicates the involvement of radicals in the reaction. Kibayashi *et al.*, in the synthesis of γ-lycorane, achieved the cyclisation shown below in a 70% yield.[250] The precursor before the photolysis, compound [165], is an N-aroyl vinylogous amide. It is important to note that in this photocyclisation the centres undergoing coupling all bear hydrogen. This result shows that such species, the reduced compounds, which have been isolated in photocyclisation attempts, may themselves undergo photocyclisation. Also note that two modes of cyclisation are possible with [166]. Compound [187], the structural isomer of [186], is not sterically favoured because of serious non-bonded interaction between the 1-carbonyl group and the 11-ether oxygen atom. Interestingly enough, a similar substrate [188], now bearing a halogen (X = Br or I) on the aryl ring, also undergoes photocyclisation to give the same compound [186].[81,251] However, poor yields along with reduced product [188, X = H] were obtained here. Thus the reduced compound [188, X = H] apparently did not undergo photocyclisation here. This renders photochemistry an inconsistent technique.



Photochemistry is sometimes associated with non-selectivity. It may lead to a wide distribution of products and low yields, but successful examples abound in the literature. The example shown overleaf was achieved by Rapoport *et al.* in the synthesis of mitomycins.[163]



73–80%

The size of the ring formed intramolecularly does not appear to be a big problem in photocyclisation. One might expect that the bigger the ring to be formed, the further away the two radical centres will be from each other. Owing to their short life times they may not couple; yet this does not seem to affect the process. Kibayashi *et al.* studied the ease of intramolecular photocyclisation of a class of vinylogous amides.[25a] The results are summarised in Table 13. Thus it can be deduced that the photocyclisation of this class of vinylogous amides is both selective and high yielding.



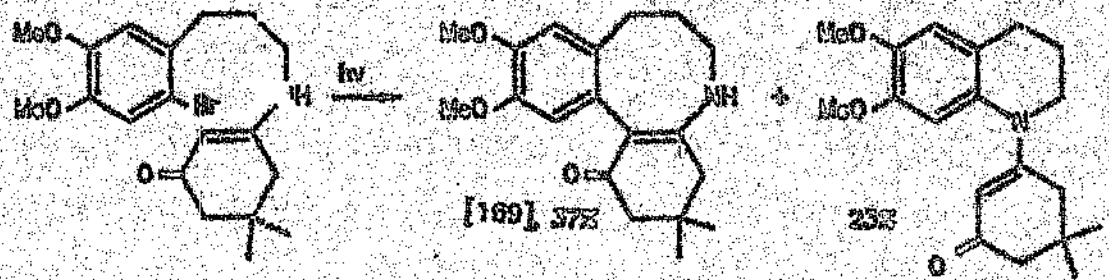
n	R^1	R^2	R^3	% yield
0	H	H	H	79
0	Me	H	H	96
0	Me	Et	H	64
1	Me	H	-OCH2-	25[a]
2	Me	H	OMe	91
2	Me	Et	OMe	94

[a] yield for the the oxidised product [189].

[189]

Table 13 Yields for above photocyclisation reported by Kibayashi.[25a]

In another report even an eight-membered ring was prepared, giving a benzazocine derivative [169]. Here a competition existed between N-arylation and C-arylation.[25]

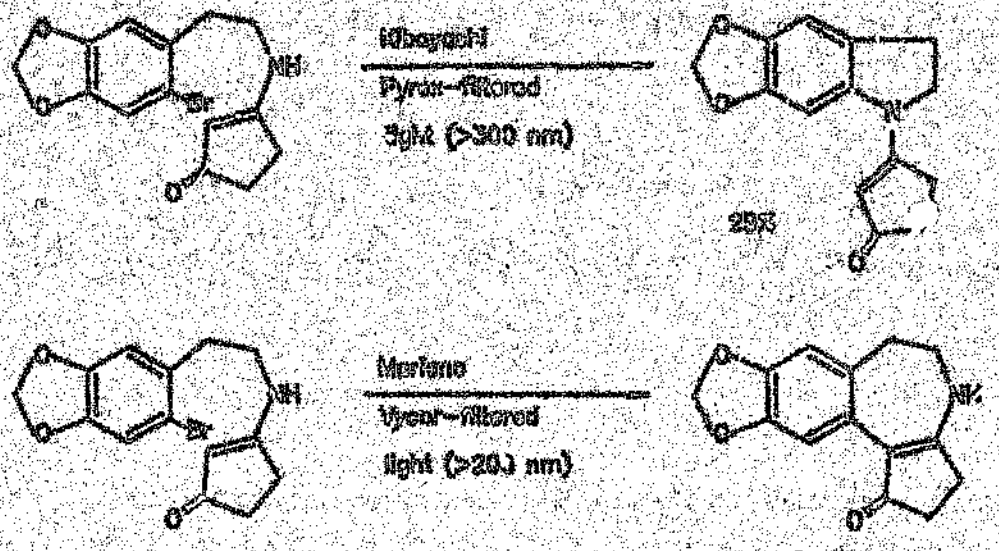


[169] 37%

23%

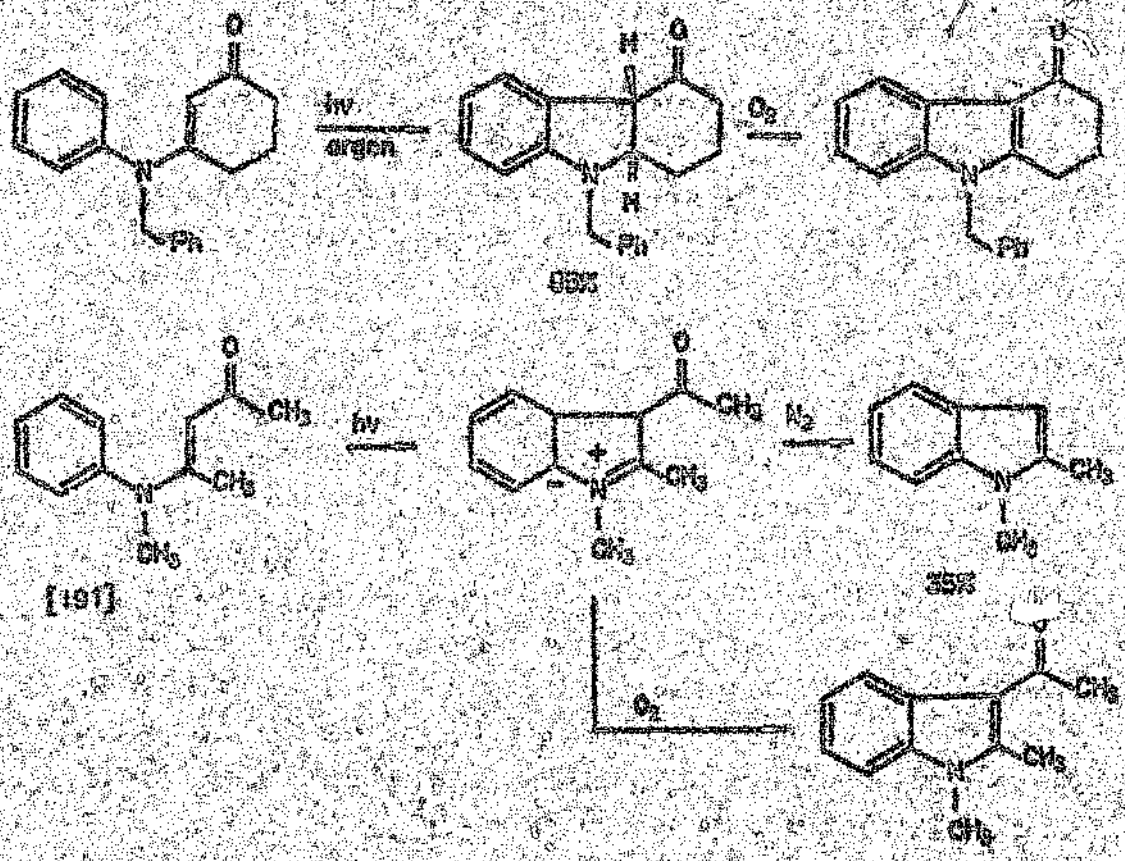
Such a competition has been observed in the photocyclization of secondary vinylogous amides when the ring size desired is seven or eight.[91,252] Thus Kibayashi *et al.* in the same report[91] failed to effect the cyclization shown below. The benzazepine derivative [190] can serve as a synthetic precursor to the alkaloid family of cephalotaxine. However, N-arylation leading to an indoline compound was obtained.

The competition of N- versus C-arylation was studied further by Mariano *et al.*[252] It was found that the efficiencies of intramolecular photoarylations of the N-(haloaryl)ethyl-β-vinylogous amides are dependent upon the wavelength of irradiation. Kibayashi observed that irradiation of the vinylogous amide system with light > 300 nm (Pyrex filtered) can result in the formation of a variety of products. This drawback is avoided by the use of Vycor-filtered light (> 200 nm), which also shortens the reaction time. Thus the previously unattainable tricyclic cyclopentenone derivative [190] is now furnished in a 47% isolated yield.

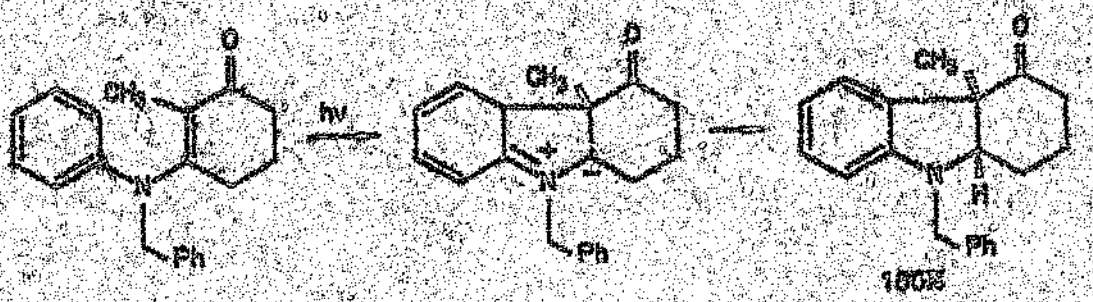


[190], 47%

N-aryl vinylogous amides have been used as precursors for the synthesis of indoles.[91,252-256] Ylide mechanisms are proposed.[252,256] Notice again that in these reactions the coupling centres all bear hydrogen. When oxygen is present, the compounds couple to retain the vinylogous amide system.[254,255] However, in the absence of oxygen, reduced compounds are produced. In the case of [191] the compound actually fragmented.[255]

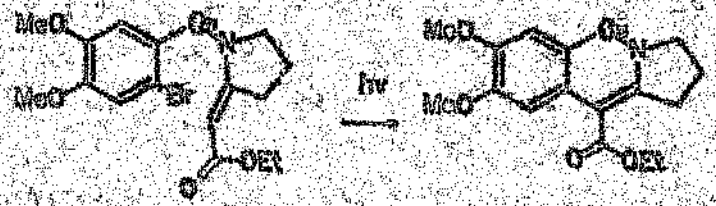


When the α carbon is blocked by an alkyl group the corresponding indoline derivative is obtained.[253]



5.2.2 Results

Based on the literature survey this radical-mediated intimted reaction should work for all three classes of enaminones. The photochemical approach was tried on the three vinylogous urethanes [53b], [53d], and [53f].



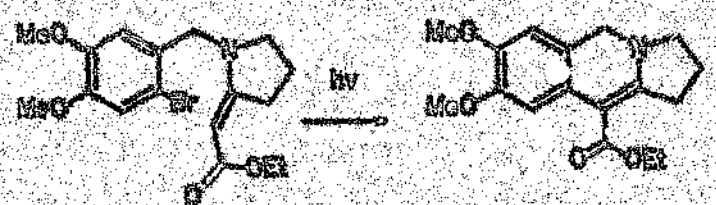
[53], b, n = 0

d, n = 1

f, n = 2

In all photochemical attempts, a medium pressure, 450 w Hanovia mercury lamp equipped with a quartz filter was used. In general, inseparable product mixtures were obtained owing to the presence of minor components which only became evident during the chromatography stage.

In the case of vinylogous urethane [53d], the desired compound [177] was actually isolated as a trace component (1%). Table 14 illustrates the differences between [53d] and the cyclised compound [177] in their PMR spectra. In general the signals have shifted downfield except that for the benzylic protons (see spectrum H-23 in Appendix). The cyclisation brings the ester carbonyl group into close proximity with aromatic H-8, thereby deshielding it and causing a tremendous downfield shift. No clear reason can be found for the downfield shifts for the other aromatic signal, or for the aliphatic C-H signals. In the cyclised compound, models seem to show that the ester carbonyl group is further away from the heterocyclic ring C-3 protons; yet these protons appear more downfield than those of the starting vinylogous urethane. The benzylic protons have limited movement as they are effectively fixed in a fused ring. The two protons exhibit magnetic non-equivalence, but appear close together at 3.94-3.85 ppm (cf. the spectrum of 2,3,6,7-tetramethoxy-9,10-dihydroanthracene [60]).



[53d] [177]

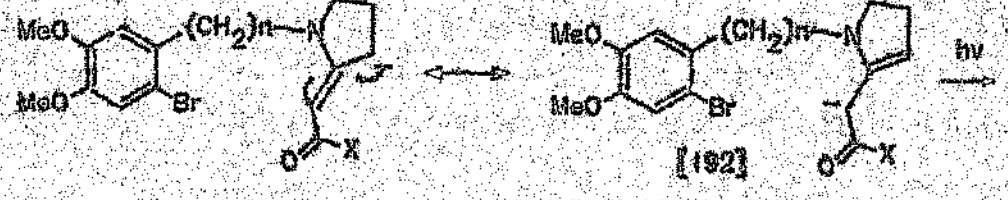
The fact that compound [177] was produced, although only in a very low yield, implies the photochemical approach is viable (at least so for the N-benzyl vinylogous urethane [53d]). However, the low yield together with the failure to reproduce the result and the observation of decomposition of starting material in many cases all seem to suggest that perhaps the desired product did form but it could not stand continuing photolytic conditions and decomposed afterwards. Acidic conditions were then tried by adding some trifluoroacetic acid (5 ml) to a solution of vinylogous urethane [53d] (0.30 mmol) in dioxane (220 ml). After irradiation, again decomposition of [53d] was observed.

Compound	534	177
aromatic H's	7.03; 6.60	8.14; 7.79
2xOMe	3.97; 3.81	4.02; 4.01
benzylic H's	4.34	3.94-3.85
CH_2N	3.33	4.25
$CH_2C{=}CC{=}O$	3.25	3.52
$CH_2CH_2CH_2$	1.99	2.21
OCH_2CH_3	4.09; 1.24	4.41; 1.44

Table 14 Comparison of PMR chemical shifts (δ, ppm) between [534] and [177].

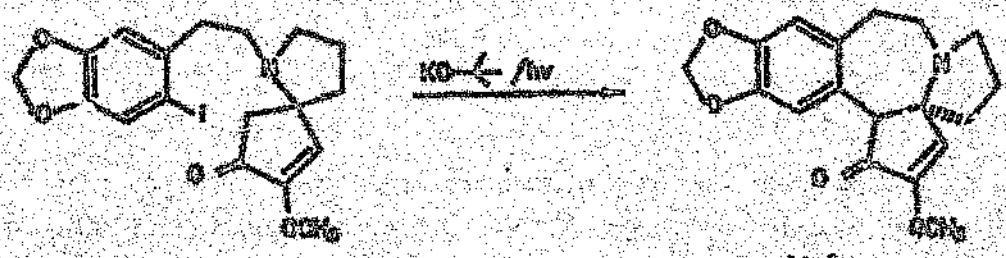
The photolyses of vinylogous urethanes [534b] and [534f] produced very inconclusive results. They certainly produced the debrominated species [61a] and [61a], as indicated by the presence of new vinyl peaks in the PMR spectra of product mixtures. In the case of [534b], cyclised compound [130] was probably present in the mixture as indicated by the two new aromatic signals. As for [534f], the presence of cyclised compound was quite uncertain. The reduced compounds may have come by the 1,5 alkyl to aryl hydrogen atom transfer process mentioned already in the radical initiated reactions.[121,202]

Doing the irradiation under basic conditions introduces a new approach to our cyclisation problem. The idea of photo-SRN1 reaction is certainly not new. The reaction has already been applied widely, and arylations with various nucleophiles have been successfully achieved both inter- and intramolecularly. However, anions derived from the enaminone system have never been reported as nucleophiles in photo-SRN1 reactions. The γ-protons in the heterocycle in the enaminone system can be abstracted by a base. The charge is then delocalised into the enaminone system. One of the resonance forms actually produces an enolate, [192]. This idea of using this anion as the nucleophile in an SRN1 reaction therefore looks plausible.



[192]

Vinylogous urethane [53d] was dissolved in toluene together with potassium-t-butoxide. This solution was irradiated with a 450 W medium pressure, Hanovia UV(mercury) lamp equipped with a quartz jacket (filter). After column chromatography only 10% of starting material was recovered. It was felt that perhaps the t-butoxide was not basic enough to abstract a γ proton from the heterocycle, although this should not be the case since Semmelhack *et al.* used the same base to generate the enolate which undergoes the photo-SRN1 reaction to effect the ring closure in the synthesis of cephalotaxinone [34].[35a]



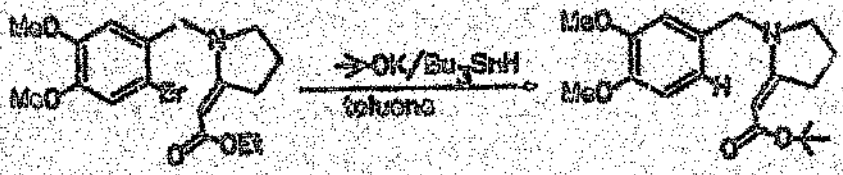
[34]

When sodamide was used in THF it was observed that the base was insoluble in the solvent of choice. Ultrasound was used to agitate the base particles but after a prolonged period (4 h) of sonication, t.l.c. indicated little reaction and most of the vinylogous urethane [53d] was recovered after work-up. Typical SRN1 reactions are carried out in liquid ammonia. Thus vinylogous urethane [53d] was added to a solution of sodamide in liquid ammonia. After irradiation and work-up it was learnt that most of the vinylogous urethane [53d] did not dissolve in liquid ammonia and 81% of it was recovered.

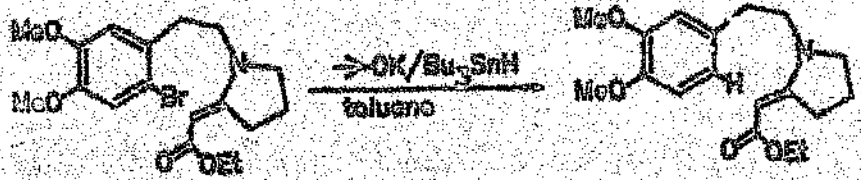
However, when the N-benzyl vinylogous amide [53c] was treated with potassium-t-butoxide in dioxane, irradiation produced the corresponding lactam in a 12% yield. Hence [53c] and [53d] behave differently in strongly basic conditions under irradiation.

In the photo-SRN1 reactions the aryl radicals can also be produced by radical initiators, although tributyltin hydride has never been tried in conjunction with irradiation. Thus vinylogous urethane [53d] was treated with potassium-t-butoxide and Bu_3SnH in toluene at reflux. After chromatography the debrominated compound was isolated as a trace component (4%), but an alkoxide exchange at the ester carbonyl was also detected producing [90]. The same conditions were applied to the N-

phenylethyl vinylogous urethane [53f]. Thus [53f] was refluxed in THF together with potassium-t-butoxide and [illegible]. After chromatography the debrominated compound [61n] was isolated in a 14% yield.

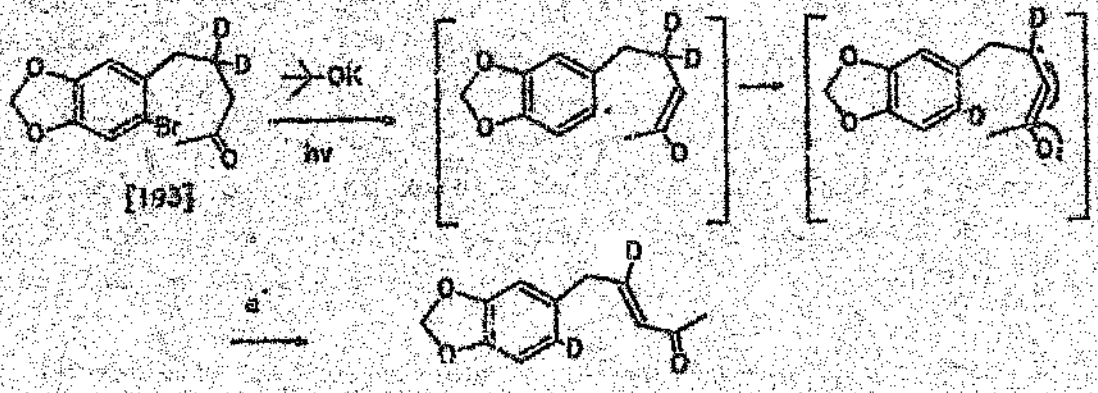


[53d] [60]



[53f] [61e]

Thus the 1,5 alkyl to aryl hydrogen atom transfer process may still be in operation here. Semmelhack *et al.* have observed such a process occurring in photo-Sn2 reactions.[259] They proved their point by subjecting a deuterated sample [193] to photo-Sn2 reaction conditions. The bromine was replaced by deuterium and a conjugated enone was also produced.



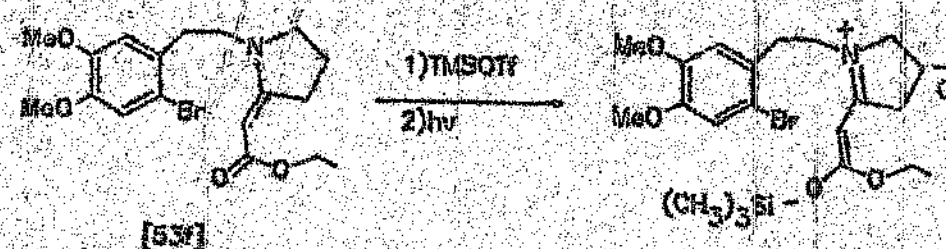
[193]

The required aryl radical can also be produced by solvated electrons, such as potassium or sodium in liquid ammonia[259] (see also Section 5.3). However the most frequently reported method to generate aryl radicals in Sn2 reactions employs the use of irradiation with a suitable frequency. Perhaps it is the powerful reducing conditions used that make this method less appealing. Under such conditions any product formed is likely to undergo further reductions. However no guarantee is provided for prevention of further reactions when radical formation is induced by irradiation as earlier results suggested.

This SnaI approach was tested on the N-aryl vinylogous urethane [53b]. Sodium hydride was used to generate the enolate. Thus [53b] was added to liquid ammonia in the presence of sodium hydride. No reaction was observed. Liquid ammonia was allowed to evaporate in a nitrogen atmosphere. DMF was then introduced. Effervescence was observed. After ca. 25 minutes liquid ammonia was added followed by pieces of potassium metal. However the metal did not dissolve well in this mixture of DMF and liquid ammonia (ca. 1 : 10). After work-up it was observed that [53b] had fragmented and no useful compounds were isolated. The formation of the enolate was next performed in THF, still using sodium hydride. THF was later removed before the addition of liquid ammonia. Pieces of potassium were added until a blue colour persisted. After work-up, however, only minor traces of debrominated compound [61a] and starting material were indicated by proton n.m.r. characterisation of the reaction mixture. Other uncharacterisable components were also present. No cyclised indole compound [130] was detected. When butyllithium was used to generate the enolate from [53b], the major compound detected after work-up was the debrominated vinylogous urethane [61a]. This could have come about either by halogen-metal exchange as was observed in the benzyne approach for [53d] (see preceding Section 5.2), or the reduction of [53b] by potassium in liquid ammonia.

The absence of indole compound [130] in the above trials may not be at all surprising as such compound is certain to undergo further reactions under these powerful reducing conditions. This makes this approach of the SnaI reaction a tricky and risky one.

The enolate in question may also be generated in the form of an enol silyl ether by treating the appropriate enaminone with TMSOTf (see Section 2.5.2). Thus vinylogous urethane [53f] was treated with TMSOTf in acetonitrile. T.l.c indicated the formation of the endi silyl ether as quantitative (a base line spot with little starting vinylogous urethane present). The solution was then irradiated, but after work-up t.l.c. indicated only the presence of starting material.



[53f]

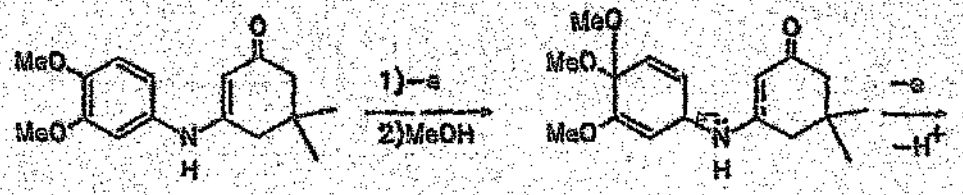
The photo-Sn2 strategy may also be a poor approach because of the inherent destructive nature of the aryl radicals in our system.

The mechanism for the photo-excitation of the enaminone system implies that the radical generation is stepwise; the probability of simultaneous production of a diradical species must be very low. Also it is the aryl halide bond that responds to the photons first. This is strongly supported by reports of dehalogenated compounds in the literature. In our cases, it is likely that the vinylogous urethane system does not react with such aryl radicals fast enough (see Section 4.2 on cobalt(I)-mediated cyclisations). Such radicals may not survive long enough to wait for the generation of a vinyl radical centre at the vinylogous urethane system such that the two radicals couple to give cyclised products. Instead, they may form reduced products by hydrogen radical abstraction from some other sources, e.g. the 1,5 alkyl to aryl hydrogen atom transfer,[201,202] or from the solvent. Whatever the fate of the radicals, this set of reactions was very disappointing. It is possible that use of a different filter (e.g. Vycor glassware) may improve matters, but such equipment was not available for this study.

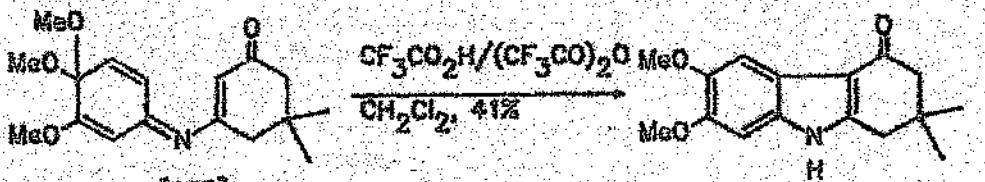
5.4 Electrochemistry of enaminones and related compounds

5.4.1 Introduction

Schäfer and Ellenberg also reported anodic cyclisation of enaminones.[229,257] Both vinylogous amides and one vinylogous urethane were successfully cyclised leading to the formation of five-, six- and seven-membered rings.[257] Both aryl and enaminone cation radicals are involved. Attack by the enaminone system and aryl group respectively leading to cyclisation is possible. Such intermediate species have been intercepted by solvent molecules as exemplified in the case of vinylogous amide [194]. The imino acetal [195], which could not be oxidised any further, was isolated. Compound [195] could be converted to the desired indole compound by treating it in dichloromethane with a catalytic amount of $CF_3CO_2H/(CF_3CO)_2O$ (20 : 1).



[194]

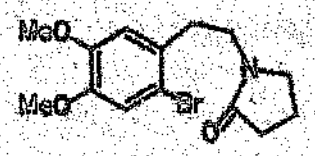


[195]

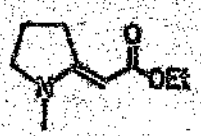
This work is especially important since we have never looked at electrochemistry of vinylogous amide and vinylogous urethane. In view of potential for oxidation and reduction of the systems, this breaks new ground for us.

5.4.2 Results

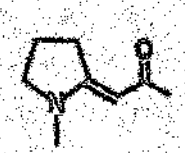
Cyclic voltammetry of some of the enaminones and lactam [58c] was done. The electrolyte used was 0.30 M $NaClO_4$ in methanol and about 3.00 mM solutions of samples were prepared. Since the electrolyte itself undergoes oxidation at ca. 1.90 V, an interval of 0.50 V to 1.90 V versus S.C.E. was scanned on the samples. A series of oxidation potentials was obtained. They are collected in Table 15 shown on next page. A typical picture of anodic voltammogram is presented here for [53d].



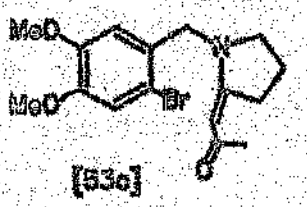
[58c]



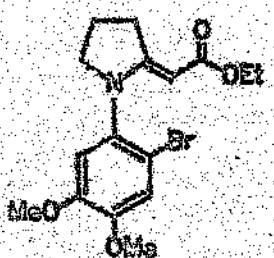
[93]



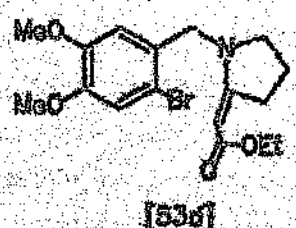
[96]



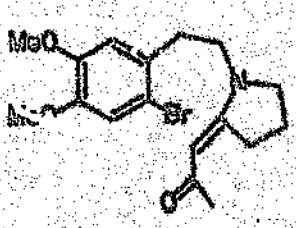
[53a]



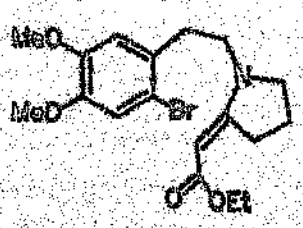
[53b]



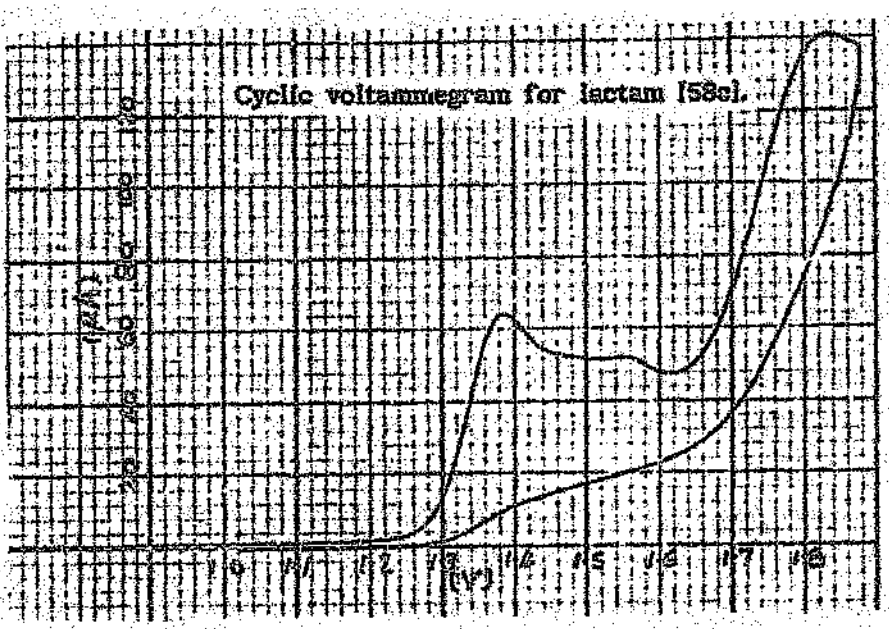
[53d]



[53e]



[53f]



Compound	58c	96	93	53b	53c	53d	53e	53f
Oxidation potentials (V)	1.39 1.56 1.84	0.98	0.96	1.16 1.70	1.04 1.53	1.04 1.54	0.98 1.43	0.98 1.44

Table 15 Oxidation potentials for lactam [58c] and some enaminones.

According to Schäfer and Ellenberg,[257] the lowest peak potential is attributed to the oxidation of the enaminone system while the second to that of the aryl group. Their observations are strongly supported by our results. Thus the N-methyl enaminones [93] and [96] contain only one oxidation potential at 0.96 and 0.98 V respectively. From this study it can be seen that the aryl group requires a higher potential to be oxidised. This is because oxidation disrupts aromaticity of the aryl group in these compounds. It can also be viewed that the enaminone system is more electron rich than the aryl group, thus the oxidation potentials for the enaminone system are lower than those for the aryl group. In the N-aryl vinylogous urethane [53b] the oxidation of the vinylogous urethane system is the highest of the samples investigated at 1.16 V. This can be attributed to a deficiency of electron density in the vinylogous urethane system due to the presence of the aryl group which withdraws electron density, therefore a higher oxidation potential is required. This is in contrast to the literature report, where the first oxidation potential is lowest for the N-aryl enaminones, although one has to bear in mind that their samples contain no bromine in the aryl group. $^{-}$ is certainly must have changed the oxidation potential of the aryl group. In the N-benzyl compounds [53c] and [53d], the first oxidation potential is also slightly higher, at 1.04 V. This can also be attributed to the inductive pull of the nearby aryl group. The first oxidation potentials for the N-

phenylethyl compounds [53e] and [53f] are similar to those for the N-methyl compounds thus the aryl group has little influence on the electronic property of the enaminone system here.

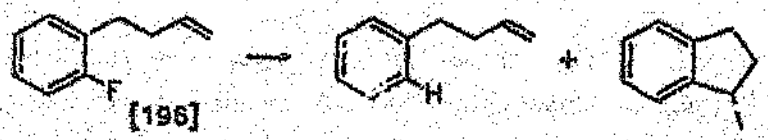
The oxidation potential for the aryl group in our samples appears at ca. 0.50 V higher than the corresponding first oxidation potential. It is highest for the N-aryl vinylogous urethane [53b] at 1.70 V. This can be explained on the ground that the aryl cation radical formed contains one of the resonance forms in which the positive charge is next to the electronegative nitrogen. Although the lone pair on nitrogen can stabilise this cation, this appears not to have taken place here. The N-benzyl enaminones have their second oxidation potential about 0.10 V higher than those for the N-phenylethyl enaminones, thus indicating that in the N-benzyl enaminones the aryl radical cations are more difficult to form compared to those for the N-phenylethyl enaminones. This again is in contrast to the literature report. The anodic oxidation potentials for the lactam [58c] were also determined. It served as a reference for oxidation of the aryl group in our system although it is not clear here which of the three values is due to the oxidation of the aryl group. No significant cathodic reduction potentials were detected for these samples, with potential scanned down to -0.90 V where the electrolyte reduction starts to interfere. Hence it can be seen from the cyclic voltammograms that oxidation of the samples investigated appear irreversible.

Two electrolyses were then attempted on the vinylogous amide [53c]. The first was done with an applied potential of 1.0 V, *i.e.* oxidation of the enaminone system was intended. Inconclusive results were obtained. Extra methoxy peaks were observed from PMR. This indicates possible incorporation of the methanol molecules in the reaction. Lactam [58b] was present in the mixture. The second electrolysis was done with an applied potential of 1.55 V *i.e.* oxidation of the aryl group of vinylogous amide [53c] was intended. After work-up and chromatography lactam [58b] was isolated in a 16% yield together with starting material.

In both cases the presence of lactam [58b] was detected. This indicates that the enaminone system responded more to the two different applied potentials and underwent oxidation reactions. The aromaticity of the aryl

group prevented the aryl group to undergo any oxidation reactions. Oxidation of the enaminone system could not have generated a neutral vinyl radical, as such species is likely to undergo radical cyclisation with the nearby aryl bromide. The formation of enaminone cation radical as suggested by Schäfer and Ellenberg[228,257] is possible. This however would not lead to cyclisation as the aryl group is already tetrasubstituted. The presence of bromine also reduces electron density of the aryl group through inductive effect. The net result is the hydrolysis of the enaminone radical cation to produce the lactam, similar to those observed when N-phenylethyl enaminones [53e and f] were treated with lead tetraacetate. Maybe an unbrominated analogue would lead to cyclisation under similar conditions.

With our samples here it is possible that a cathodic reduction may lead to cyclisation since halobenzenes with suitably positioned alkenes such as [196] have been successfully cyclised using a reductive approach.[258] The applied potential was as negative as 2.95 V. This is outside the window of the electrolyte used in this study. Another electrolyte would have to be employed. Such processes involve aryl radicals and as a result the reduced compound is always a by-product. This approach may thus not work well in our system.



[196]

$$PhX + 1e^{-} \longrightarrow PhX^{\cdot -} \longrightarrow Ph^{\cdot} + X^{-}$$

The following section deals with a totally new approach to the synthesis of the target systems. Scheme 6 describes this approach mechanistically in detail.

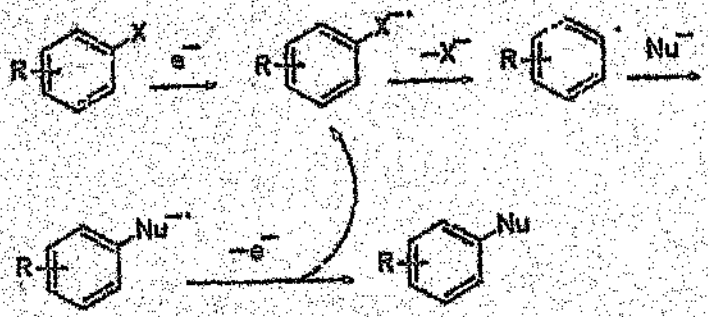
5.5 Sml reactions on lactam [58c]

5.5.1 Introduction

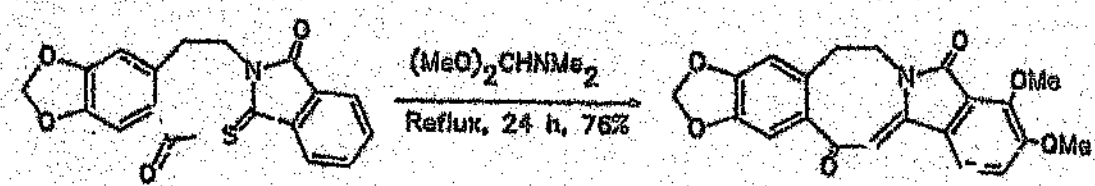
It is apparent that in the synthesis of target systems, the last crucial cyclisation reaction is the stumbling block of the whole synthesis. This problem can perhaps be overcome by accomplishing this nucleophilic aromatic substitution at the beginning of the synthesis. In effect, it

means that an entirely different approach to the target systems would have to be developed.

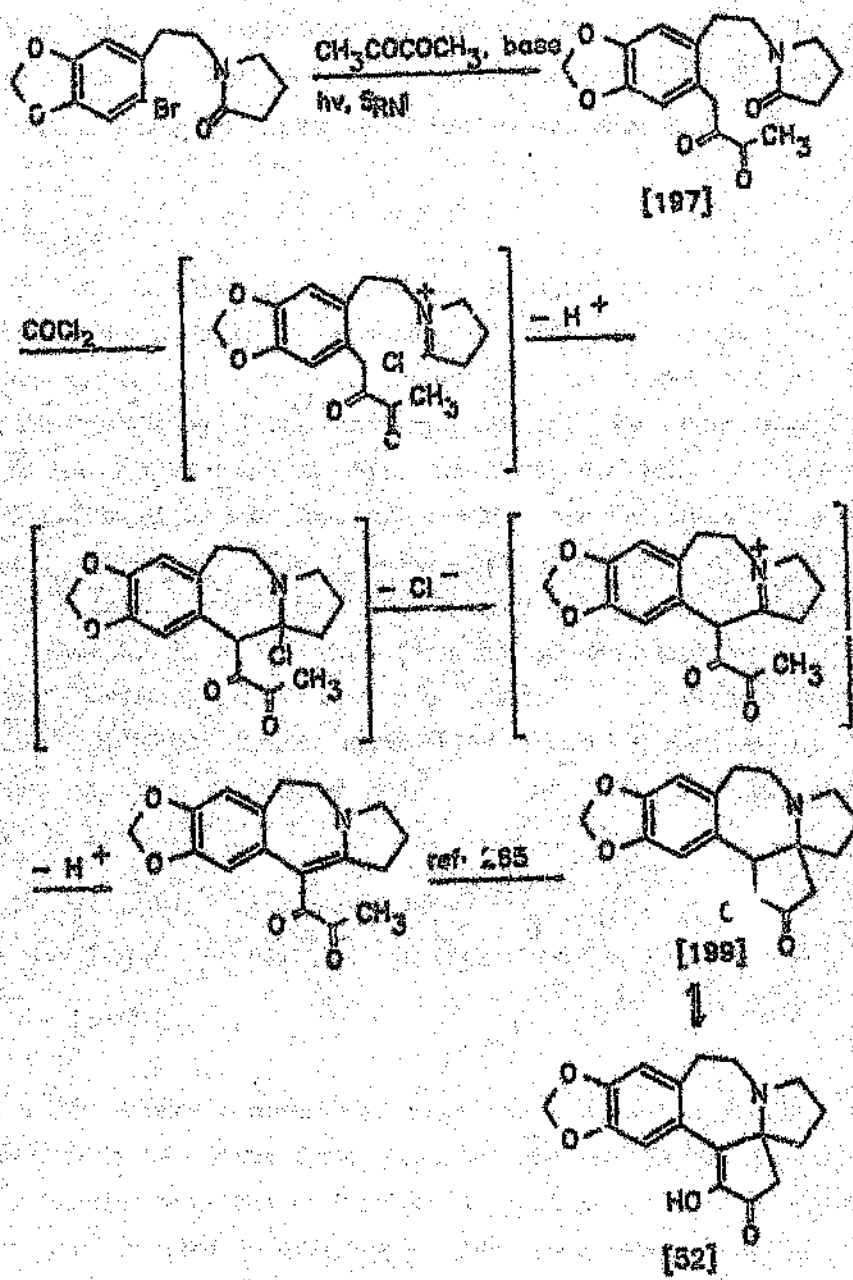
Consider the following approach to the synthesis of (52) (Scheme 6, overleaf). The nucleophilic aromatic substitution reaction is achieved by an SrnI reaction. SrnI reactions are good ways to alkylate aromatic halides; the products formed are difficult to prepare otherwise. The mechanism of an SrnI reaction is depicted below.[259] Both aromatic bromides and iodides are suitable for the reaction. Typical nucleophiles include carbonyl enolates and cyanide anions. Radical initiation is usually carried out by irradiation of the reaction solution. Note that the radicals behave catalytically here. Many analogies exist in the literature for this SrnI reaction.[259]



Since a symmetrical dicarbonyl compound is involved in Scheme 6 there would be no selectivity problem. The next stage would be for lactam (197) to undergo a reaction similar to the first stage of the Vilsmeier reaction. The intermediate chloroiminium salt can be intercepted by the benzylic carbon α to the carbonyl group in the chain. Many similar approaches in the literature leading to cyclisation have been reported.[250-254] For example, Danishefsky et al. used such an approach for the synthesis of magallanesine (198).[254]



[198]

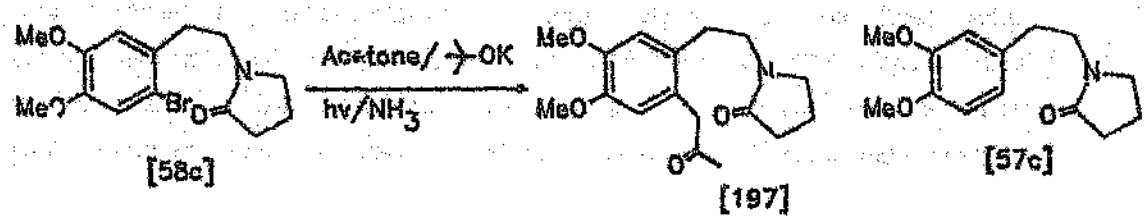


Schema 6

Compound [199] is in fact a tautomer of demethylcephalotaxinone [52], methylation of which can be made to occur in the proper direction under carefully controlled conditions to give cephalotaxinone.[265] The proposed approach has not been attempted before and it falls into category A according to Huang and Kue's classification (see page 8).[29]

5.5.2 Results

Typical SRN1 reactions are carried out in liquid ammonia in the presence of strong bases such as sodamide or potassium amide. The reaction solution is usually irradiated internally. Our model studies for this approach used lactam [58c]. An initial attempt used liquid ammonia as the solvent and acetone enolate generated from the action of potassium *t*-butoxide (formed *in situ* from the reaction between potassium and *t*-butyl alcohol) on acetone. The solution was irradiated internally using a medium pressure mercury lamp. The desired lactam [197] was isolated as a thick yellow oil in a 42% yield after column chromatography. Subsequent attempts, however, either gave poor yields of the desired lactam [197] together with debrominated lactam [57c] or no reaction at all. When no reaction occurred it implied that the aryl bromide bond is inert to photolysis here.



[58c] [197] [57c]

Thus in the initial successful attempt the aryl radical required for SRN1 reaction could have come from traces of unreacted potassium metal, which led to reaction with the aryl halide. In another attempt the debrominated lactam was isolated quantitatively. This could imply that formation of the aryl radicals was successful while enolate formation failed. Beugelmans *et al.* reported successful SRN1 reactions in DMSO.[266] When lactam [58c] was reacted with acetone enolate in DMSO, photolysis of the solution produced no reaction, and lactam [58c] was recovered quantitatively. Using biacetyl as the enolate precursor and sodamide as the base also gave no reaction. Also using biacetyl, dioxane was used as the solvent and potassium hydride as the base, but there was still no reaction. Finally *t*-butyl acetoacetate was used as the enolate

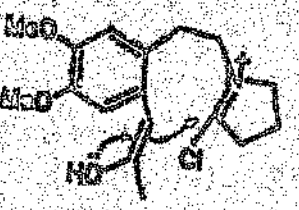
precursor.[267] Decomposition of starting material was observed. The debrominated lactam was isolated as a trace component.

The results obtained here seem to indicate that the aryl radicals required for reaction could have come from traces of excess potassium metal. Addition of acetone after presumably the completion of formation of potassium t-butoxide would destroy any trace of potassium, resulting in the formation of acetone enolate and isopropyl alcohol.[268] Thus formation of the enolate could have been successful but there was no metal to produce the aryl radical for SRN1 reactions. This would result in the recovery of starting material. Conversely when large excess of potassium was present the formation of the enolate would be poor and the reduced lactam [57c] would be the major product.

This finding is backed up by reports of successful SRN1 reactions where solvated electrons were used to generate the required aryl radicals.[269] We tested the hypothesis that potassium metal might be involved as follows. Lactam [58c] was added to acetone enolate in liquid ammonia, generated by either potassium t-butoxide or sodamide. Potassium was then added bit by bit until the solution stayed blue. The desired lactam [197] was isolated in yields similar to that obtained in the first trial. Little debrominated lactam [57c] was also present. This result also proves that the light frequency used in previous unsuccessful attempts was redundant, hence the recovery of starting lactam [58c] in many cases.

Lactam [197] was now ready and was subjected to cyclisation conditions. However, disappointing results were obtained. When phosgene was added to lactam [197] in chloroform, starting material was recovered quantitatively, even after prolonged stirring and reflux. When phosphoryl chloride was used in conjunction with triethylamine, lactam [197] was recovered with a poor mass balance after reflux. Amides are known to react with phosphoryl chloride to produce the corresponding chloroiminium salts. Such species are very sensitive to water. Hydrolysis of these compounds reverses the reaction direction and the starting amide is regenerated. Perhaps the failure of cyclisation is not due to the failure of formation of the chloroiminium salt but rather the lack of response of the benzylic carbon α to the carbonyl group in the chain. This was unexpected as it was proposed that the enol form is favoured due to

conjugation. Addition of triethylamine also failed to produce the desired cyclisation.



Although unsuccessful, this cyclisation attempt still warrants more investigation. A stronger base such as sodium hydride may be used to generate the enolate after the formation of the chloroiminium salt. A catalytic amount of acid (*e.g.* CF_3CO_2H) may be added to promote the formation of the enol. Perhaps even the enol allyl ether of lactam [197] can be used. Although this cyclisation appears to be obvious it may again prove to be stubborn in the light of the above observations.

CHAPTER SIX: CONCLUSION, AND RECOMMENDATIONS

The work of this Ph.D. project can be summarised as follows:

(1) A range of model vinylogous amides and urethanes has been synthesised. These syntheses have been successful, and high yields were usually obtained, except in the preparation of N-aryl vinylogous amides and urethanes. An alternative approach for their preparation has not yet been optimised in yield.

(2) Vinylic bromination of the enaminone system has proved difficult in our system. Allylic bromination resulting in γ-brominated compounds was often observed. The successful preparation of the vinylic chloride [102], obtained by the action of trimethylsilyl trifluoromethanesulphonate on vinylogous urethane [93], followed by the addition of ferric chloride, may indicate the presence of the enol silyl ether [103] in the intermediate stage. In these reactions, the reactivity of the vinylogous amides and urethanes is quite different: vinylogous amides show resistance to bromination reactions, or decomposition when forcing conditions were used.

(3) N-Methyl vinylogous urethane [93] and vinylogous amide [96] react with phenylsulphenyl chloride differently. A mixture of *cis* and *trans* α-sulphenylated isomers was obtained in the case of [93], while vinylogous amide [96] undergoes a deacetylation reaction at the same time as α-sulphenylation to produce [106].

(4) The palladium(0)-mediated Heck reactions appear to be quite general for the N-(*o*-bromoaryl) vinylogous urethanes, resulting in the formation of 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles. Yields decrease with increasing electron-donating substituents on the aryl ring. Addition of tetraethyl ammonium bromide resulted in no reaction at all for the N-aryl vinylogous urethane [53b]. The reaction does not work at all for the N-benzyl compounds, from which the corresponding dehalogenated analogues were obtained. This work may prove useful for the construction of mitomycin compounds.[62]

(5) Free radical reactions involving both Co(I) and Bu_3SnH all produced the debrominated compounds. Failure of reaction may be due to the inertness of the enaminone system towards radicals. Abstraction of a hydrogen atom by the aryl radicals can be achieved many ways. 1,5-Alkyl to aryl hydrogen atom transfer is a very likely process here as it has been reported by others.[161,202]

(6) Chromium hexacarbonyl complexation of vinylogous urethane [61c] was successful. However no spontaneous cyclisation occurred. Perhaps the anion of the complex, deprotonation at the γ carbon in the heterocycle, would undergo such a cyclisation reaction, as many literature examples involve the formation of carbanions as the attacking nucleophiles.[213c,225]

(7) Cyclisation of [53d] under strongly basic conditions (the benzyne approach) produced the debrominated compound [61b], and traces of the desired product. The corresponding N-benzyl vinylogous amide [53c] failed to undergo any reaction. Disappointing results were obtained in the photochemistry of the enaminones. Many different reaction conditions were tried, including strong basic conditions which brings in the idea of SRN1 reaction in arylation of enaminones in our system. Decomposition of starting material was often observed, leading in some cases to the formation of the corresponding lactam and the debrominated analogue.

(8) Reactions of the enaminones [53c], [53e], and [53f] with lead tetraacetate produced the corresponding lactam.

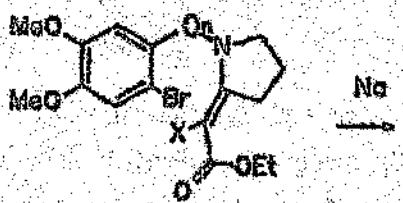
(9) Electrochemical information relating to the enaminones and lactam [58c] was collected. Anodic oxidation of vinylogous amide [53c] failed to produce any cyclised compound; instead the corresponding lactam was formed. Cathodic reduction may prove to be more appropriate in our system.[252]

(10) All the approaches to the target compounds were based on intramolecular arylation of vinylogous amide and urethane. When these ideas were exhausted, a completely new approach was briefly examined. SRN1 reactions on lactam [53c] were successful, although the yields have not been optimised yet.

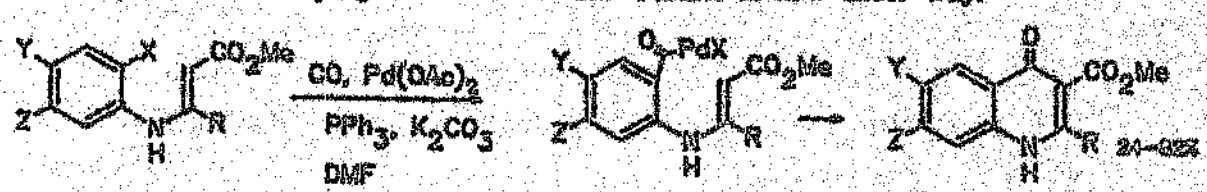
In our molecules we have two electron rich systems, the enaminone and the aryl groups. But on the average, the enaminone group is more electron rich than the aryl group as the above observations show: i.e. under reducing conditions, such as in the presence of Bu_3SnH and Co(I)-salen, the aryl bromide bond is susceptible to reaction and the enaminone system stays intact. On the other hand under oxidising conditions such as in the presence of $Pb(OAc)_4$ and anodic oxidation conditions, the enaminone system becomes oxidised and the aryl bromide bond remains untouched.

Hence our approach to the cyclisation of this nature is justified, i.e. using an electron rich enaminone group to attack at the less electron rich aryl group intramolecularly. However the problem is more complicated than it appears as areas such as the stability of the size of the ring being formed and the stability of the reaction intermediates are inevitably involved. From literature examples a neutral approach (i.e. the radical approach) has been shown to be viable. However many of the radical initiating reagents present today tend to react only with the aryl bromide bond and as the enaminone group fails to react accordingly, the debrominated analogue is the only result. Even photochemistry failed to achieve the desired cyclisation, although only one source of light was used.

Future work should still be directed at the vinylic substitution reactions of the enaminones. Preparation of vinylic substituted enaminones opens up new area of reactivity for these compounds. Such species may still be coupled by the Wurtz coupling reaction, or perhaps Ullmann methods.

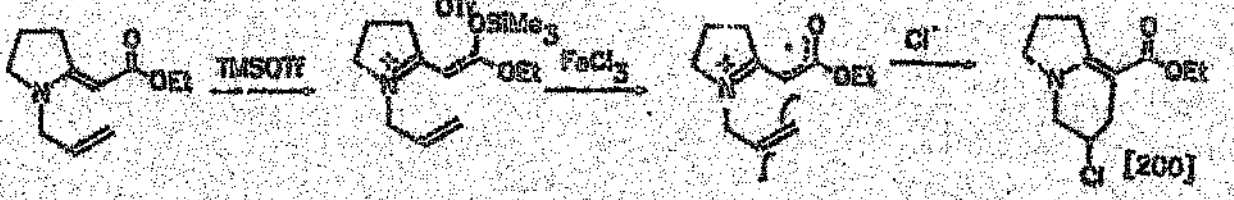


There is scope for expansion of the Heck reactions studied in this project by incorporating carbon monoxide into the system. Substituted 4-oxoquinolines, of interest as antibacterials, would be obtained this way.[153] An M.Sc. project to extend these results is now under way.[269]



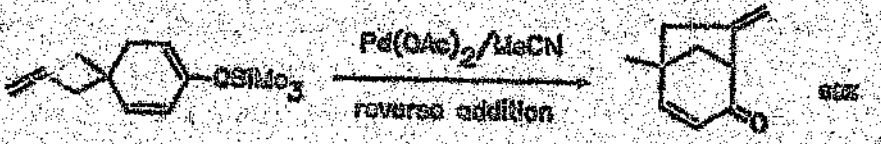
24-02%

The formation of the vinylic chloride [102] suggests the formation of the intermediate enol silyl ether [103]. Such species have been broken down by addition of ferric chloride to produce vinyloxy radicals. These radicals have been trapped intramolecularly by alkenes to form cyclic compounds. This approach may be applied in these laboratories to enaminones with appropriately positioned alkenes to form bicyclic systems such as [200], which may prove useful in natural product synthesis.

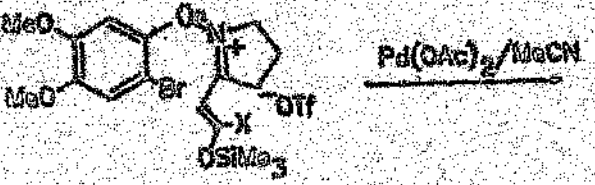


[200]

Enol silyl ethers have been shown to attack alkenes in palladium catalysed reactions. Many spirocyclic bicyclo alkenones have been produced this way.[137]



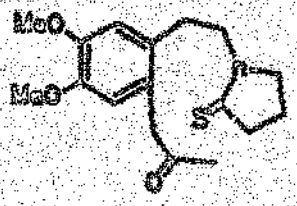
Such an approach may be worth a trial in our system.



The SrnI reactions on the enaminones in our system should still be investigated further, as aryl radicals are known to react with stabilised carbanions. Deprotonation at the γ carbon to form the carbanion and aryl radical formation still need to be studied, but solubility problem of the substrates in liquid ammonia must be overcome. Solvated electrons to initiate aryl radicals may not be appropriate here as such powerful reducing conditions make possible for further reactions for the products.

The study of the alternative approach to the synthesis of demethylcephalotaxinone [52] can also be resumed. Formation of the ketone

[197] by the Stoll reaction is a viable route, although the yield has not yet been optimised. Cyclisation of this ketone to produce the desired compound using the Vilsmeier reaction conditions is still a possible reaction. The thiated analogue of ketone [197] introduces another solution to this cyclisation problem. A similar literature example is presented below.[279]





Both inter- and intramolecular alkylation and acylation reactions of enaminones at the α position have been reported. The corresponding intramolecular arylation reactions are relatively few indeed. The potential of such a reaction, which formed the central theme of this *Ph.D.* project, is immeasurable in organic synthesis. The study shown in this project explores the different possibilities for such a reaction to be successful. While successful intramolecular arylation reactions of N-(o-bromoaryl) vinylogous urethanes were achieved using the Heck reactions, the results obtained for the corresponding formation of six- and seven-membered rings were disappointing. These reactions, direct arylation of enaminones at the α position to form six- and seven-membered rings, are probably difficult to achieve if they are at all possible. However, in these studies several approaches which we have previously not looked at for vinylogous amide and urethane have been explored for the first time: photochemistry, radical, electrochemistry and transition metal-mediated metals. This project thus breaks new ground in devising new ways of manipulating enaminones, and even if the rate of success was not encouraging, the foundations have been laid for future workers to build on.

This project, although only partially successful, has provided many insights into the nature of the problem. The great depth of difficulty of

this reaction is now appreciated. Much more work, especially in the preparation of diradicals of vinylogous amides and ureidenes, i.e. the preparation of vinyl substituted enaminones, still needs to be done. With time, we believe that the goal that provided the main inspiration of this project, the synthesis of the cephalotaxus ring system, will be achieved.

EXPERIMENTAL

General Details

A. Purification of solvents and reagents

All solvents were distilled before use. THF and dioxane were distilled from sodium/benzophenone, and dichloromethane from phosphorus pentoxide. Acetonitrile, triethylamine and DMF were distilled from calcium hydride.

B. Chromatographic separations

The R_f values quoted are for thin-layer chromatography (t.l.c.) on Merck DC-Fertigplatten Kieselgel F-254 plates. Merck Kieselgel 60 (particle size 0.063-0.200 mm) was used as the absorbent for conventional preparative column chromatography, while Merck Kieselgel 60 (particle size 0.040-0.063 mm) was used for preparative flash chromatography.[276]

C. Spectroscopic and physical data

All melting points were obtained on Reichart micro hotstage apparatus and are uncorrected. Proton nuclear magnetic resonance spectra (^1H n.m.r.) were recorded in deuterated chloroform on a Bruker AC-200 spectrometer (200.13 MHz) or a Varian EM-360A spectrometer (60 MHz). Spectra listed in the following pages were recorded at 200.13 MHz unless otherwise stated. Chemical shifts are reported on the δ scale relative to tetramethylsilane. Coupling constants are in Hertz. The chemical shifts are reported: 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, m = multiplet, and br = broad.

Carbon nuclear magnetic resonance spectra (^{13}C n.m.r.) were obtained on a Bruker AC-200 spectrometer (50.32 MHz). Chemical shifts are reported on the δ scale relative to the central peak of chloroform peak taken as δ 77.00. The DEPT technique, and if necessary, ^{13}C-^1H correlated spectra,

were used to assign ^{13}C signals. I.r. spectra were recorded on a Pye-Unicam SP3-300 spectrometer as 0.05 g ml^{-1} solutions in chloroform, using a cell with a path length of 0.1 mm and sodium chloride windows. Band positions are given in cm^{-1}. Abbreviations used in quoting spectra are: s = strong, m = medium, w = weak.

Elemental analyses were performed on solid samples wherever possible; the microanalytical service available to us invariably provided unreliable results for liquid samples. For these, purity was estimated in terms of chromatographic and n.m.r. spectroscopic homogeneity; high-resolution mass spectrometry was then used for accurate mass determination on the molecular ion if it was present, or otherwise on the highest significant fragment. Low resolution mass spectra were recorded on a Kratos MAT 90 spectrometer, while those for high resolution were done on a Varian MAT 311 spectrometer. All peaks in the higher mass ranges having a relative abundance greater than 10% have been quoted, unless otherwise stated. Data are quoted: m/z value (assignment if known, relative abundance, %).

D. Other general procedures

When aqueous solutions were extracted with an organic solvent, the organic phase after separation was dried over anhydrous magnesium sulphate before removal of the solvent. Evaporation of solvent *in vacuo* refers to the removal of solvent under reduced pressure at a rotary evaporator, followed by final drying on an oil pump at ca. 1 torr.

EXPERIMENTAL PROCEDURES RELATING TO SECTION 2.2

1) 1-(3,4-Dimethoxyphenyl)pyrrolidin-2-one [87a]

3,4-Dimethoxyaniline (3.17 g, 20.7 mmol) and γ-butyrolactone (1.75 ml, 22.[illegible] mmol) were sealed into a Carius tube, which was heated on a [illegible] 220 °C for 15 h. When cooled the tube was cut open and the contents, a black liquid, were dissolved in dichloromethane (25 ml). The organic solution was then washed with hydrochloric acid (2.0M, 2x20 ml), followed by sodium hydroxide (2.0M, 2x50 ml), and finally with salt water (2x50 ml). The combined organic extracts were dried ($MgSO_4$) and filtered. After evaporation a black crystalline solid was obtained. This solid was distilled in vacuo. A purple distillate was collected (193-196 °C/2-2.5 torr). The distillate solidified on cooling (2.74 g, 12.4 mmol, 60%). Recrystallisation from ethyl acetate/hexane produced colourless cubes, m.p. 85-86 °C, Rf (ethyl acetate) 0.44.

Analysis. Found: C, 64.89; H, 7.01; N, 6.30.
$C_{12}H_{15}NO_3$ requires C, 65.14; H, 6.83; N, 6.33%.

^1H n.m.r.

7.52 (1H, br s with fine coupling, J ca. 1.1 Hz, aromatic H-2); 6.85 (2H, m, aromatic H-5 and H-6); 3.89, 3.86 (6H, 2xs, 2xOMe); 3.82 (2H, t, J 7.1 Hz, $-CH_2N<$); 2.53 (2H, t, J 8.0 Hz, $-CH_2C=O$); 2.13 (2H, quintet with further fine splitting, J 7.7 Hz, $-CH_2CH_2CH_2-$).

^{13}C n.m.r.

173.73 (>C=O); 148.56, 145.75 (aromatic C-3 and C-4); 132.86 (aromatic C-1); 111.48, 110.69 (aromatic C-5 and C-6); 104.89 (aromatic C-2); 55.76, 55.65 (2xOMe); 48.94 ($-CH_2N<$); 32.39 ($-CH_2C=O$); 17.62 ($-CH_2CH_2CH_2-$).

I.r.

2935(m); 2820(w); 1675(s); 1590(w); 1510(m); 1450(m); 1410(m); 1320(w); 1220(s); 1155(m); 1140(m); 1115(m); 1030(m); 855(w); 810(w) cm^{-1}.

2) General method for bromination of lactams

Lactam was dissolved in glacial acetic acid. Sodium acetate (3 eq.) was added. Heating usually was required to dissolve all the solid: more acetic acid was necessary if the lactam was a solid. When a homogeneous solution had formed, bromine (1 eq.) in glacial acetic acid (1-2 ml) was added quickly. An exothermic reaction usually resulted. The solution was stirred at r.t. and reaction was monitored by t.l.c. Upon completion of reaction the mixture was basified with concentrated ammonia liquid. The basic aqueous solution was extracted with dichloromethane. The combined organic extracts were dried and evaporated *in vacuo*. The product was purified by column chromatography and recrystallisation. The following compounds were prepared and characterised.

1-(2-Bromo-4,5-dimethoxyphenyl)pyrrolidin-2-one (58a) was obtained as a purple solid (2.842 g, 96%) from 1-(3,4-dimethoxyphenyl)pyrrolidin-2-one (2.11 g, 9.54 mmol). A colourless solid was obtained after recrystallisation from ethyl acetate/hexane mixture, m.p. 98-99 °C, Rf (ethyl acetate) 0.32.

Analysis. Found: C, 47.86; H, 4.90; N, 4.66.
$C_{12}H_{14}BrNO_3$ requires C, 48.02; H, 4.70; N, 4.67%.

^{1}H n.m.r.
7.08, 6.77 (2H, 2m, aromatic protons); 3.87, 3.85 (6H, 2ms, 2xOMe); 3.75 (2H, t, *J* 7.0 Hz, -CH$_2$N<); 2.56 (2H, t with further fine splitting, *J* 8.1 Hz, -CH$_2$C=O); 2.23 (2H, quintet with further fine splitting, *J* 7.6 Hz, -CH$_2$CH$_2$CH$_2$-).

^{13}C n.m.r.
174.82 (>C=O); 149.05, 148.76 (aromatic C-4 and C-5); 130.01 (aromatic C-1); 115.26, 111.68 (aromatic C-3 and C-6); 112.10 (aromatic C-2); 56.11, 55.92 (2xOMe); 49.85 (-CH$_2$N<); 30.61 (-CH$_2$C=O); 18.78 (-CH$_2$CH$_2$CH$_2$-).

I.r.
3000(m); 1950(w); 1685(s); 1600(w); 1500(s); 1460(m); 1455(s); 1420(m); 1385(m); 1340(w); 1320(w); 1290(m); 1255(s); 1175(s); 1125(m); 1035(w); 1000(m); 885(w); 855(m); 640(w) cm^{-1}.

1-(2-Bromo-4,5-dimethoxybenzyl)pyrrolidin-2-one [58b] was obtained as a light yellow oil (1.336 g, 92%) from 1-(3,4-dimethoxybenzyl)pyrrolidin-2-one [57b] (1.091 g, 4.54 mmol). The oil was purified by column chromatography on silica gel with hexane/acetone mixtures. A clear oil was obtained (1.169 g, 80%); Rf (ethyl acetate) 0.28.

^{1}H n.m.r.
7.00, 6.86 (2H, 2xs, aromatic protons); 4.53 (2H, s, benzylic protons); 3.87, 3.84 (6H, 2xs, 2xOMe); 3.32 (2H, t, J 7.0 Hz, -CH$_2$N<); 2.42 (2H, t, J 8.1 Hz, -CH$_2$C=O); 2.00 (2H, quintet, J 7.7 Hz, -CH$_2$CH$_2$CH$_2$-).

^{13}C n.m.r.
174.66 (>C=O); 149.47 (aromatic C-4 and C-5); 127.54 (aromatic C-1); 116.91, 112.54 (aromatic C-3 and C-6); 113. (aromatic C-2); 55.81, 55.76 (2xOMe); 46.42, 45.61 (-CH$_2$NCH$_2$-); 30.45 (-CH$_2$C=O); 17.51 (-CH$_2$CH$_2$CH$_2$-).

I.r.
3000(w); 2940(w); 2850(w); 1670(s); 1605(w); 1500(m); 1460(m); 1440(m); 1385(w); 1355(w); 1305(w); 1285(w); 1230(s); 1160(s); 1125(w); 1065(w); 1035(w); 985(w); 945(w); 915(w); 865(w); 840(w); 640(w); 590(w) cm^{-1}.

1-(2-(2-Bromo-4,5-dimethoxyphenyl)ethyl)pyrrolidin-2-one [58c] was obtained as a brown oil (1.239 g, 98%) from 1-(2-(3,4-dimethoxyphenyl)ethyl)pyrrolidin-2-one[59] [57c] (0.957 g, 3.84 mmol). The oil solidified on standing. Recrystallisation from acetone/hexane produced colourless needles, m.p. 92-93 °C, Rf (hexane/acetone 1:1) 0.28.

Analysis. Found: C, 51.22; H, 5.49; N, 4.27.
C$_{14}$H$_{18}$BrNO$_3$ requires C, 51.23; H, 5.53; N, 4.27%.

^{1}H n.m.r.
7.00, 6.79 (2H, 2xs, aromatic protons); 3.860, 3.857 (6H, 2xs, 2xOMe); 3.52 (2H, t, J 7.41 Hz, ArCH$_2$CH$_2$N<); 3.21 (2H, t, J 7.0 Hz, -CH$_2$CH$_2$CH$_2$N<); 2.91 (2H, t, J 7.41 Hz, ArCH$_2$CH$_2$N<); 2.37 (2H, t, J 8.1

Hz, -CH2C=O); 1.97 (2H, quintet, J 7.5 Hz, -CH2CH2CH2-).

Irradiation at 1.97 : t at 2.37 collapses to s. t at 3.31 collapses to s.

^{13}C n.m.r.

174.72 (>C=O); 148.25, 148.01 (aromatic C-4 and C-5); 129.76 (aromatic C-1); 118.21, 112.92 (aromatic C-3 and C-6); 113.94 (aromatic C-2); 55.93 (2xOMe); 47.52 (-CH2CH2CH2N<); 42.24 (ArCH2CH2N<); 33.29 (-CH2C=O); 30.86 (ArCH2CH2N<); 17.85 (-CH2CH2CH2-).

I.r.

2990(m); 2970(m); 2940(m); 2830(w); 1665(s); 1605(m); 1580(w); 1495(s); 1460(s); 1440(s); 1420(s); 1385(m); 1360(m); 1335(m); 1290(s); 1235(s); 1160(s); 1065(s); 1030(m); 990(w); 965(w); 900(w); 860(m); 795(w) cm^{-1}.

3) Sequence for the preparation of 1-(3,4-dimethoxybenzyl)pyrrolidin-2-one [576]

a) 3,4-Dimethoxybenzyl alcohol [64]

3,4-Dimethoxybenzaldehyde [63] (4.60 g, 27.7 mmol) and sodium borohydride (1.567 g, 41.6 mmol, 1.5 eq.) were heated under reflux in absolute ethanol (30.0 ml) for 17 h. More sodium borohydride (0.245 g) was added and the solution was heated under reflux for another 3 h. The solvent was evaporated *in vacuo*. Hydrochloric acid (2.4M, 50.0 ml) was added. The acidic solution was extracted with dichloromethane (4x20 ml). The combined organic extracts were dried and the solvent evaporated *in vacuo* to produce a milky, viscous oil (4.743 g, 100%). A distillate was collected at oven temperature as 140-180 °C and pressure as 2 Torr, (lit.[371] 165-167 °C/11 torr).

^{1}H n.m.r. (60 MHz)

6.8-6.5 (3H, m, aromatic protons); 4.35 (2H, s, benzylic protons); 3.65 (6H, s, 2xOMe).

b) 3,4-Dimethoxybenzyl bromide [65]

3,4-Dimethoxybenzyl alcohol [64] (5.170 g, 30.74 mmol) was dissolved in

dichloromethane (30.0 ml). The solution was stirred at 0 °C. Phosphorus tribromide (1.72 ml, 4.90 g, 18.1 mmol, 0.59 eq.) in dichloromethane (20.0 ml) was added over a period of 17 min. The operation was carried out under dry conditions. The resultant solution was stirred for 21 h at r.t. The organic solution was washed with saturated sodium chloride solution. The combined organic solution was dried and the solvent evaporated *in vacuo* to produce a yellow oil (6.637 g, 93%). The oil slowly solidified on standing in a refrigerator, m.p 43-55 °C (lit.[272] 59 °C), Rf (hexane/ethyl acetate 1 : 1) 0.77.

^{1}H n.m.r. (60 MHz)
6.0-6.6 (3H, m, aromatic protons); 4.35 (2H, s, benzylic protons); 3.70 (6H, s, 2xOMe).

g) 2,3,6,7-Tetramethoxy-9,10-dihydroanthracene (66)

Zinc bromide (0.643 g, 2.85 mmol) in hydrobromic acid (48% aqueous solution, 3.0 ml) was added to 3,4-dimethoxybenzyl alcohol [64] (0.965 g, 5.74 mmol). The mixture immediately turned into a paste. More acid (20.0 ml) was added. The mixture was stirred at r.t. for 15 h. Water (20.0 ml) was added and the aqueous solution washed with dichloromethane (4x20 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated *in vacuo* to yield a green crystalline solid (0.874 g, 100%). Recrystallisation from dichloromethane gave white needles, m.p. 230-240 °C (lit.[45,273] 230-250 °C depending on the rate of heating), Rf (hexane/ethyl acetate 1 : 1) 0.72.

^{1}H n.m.r.
6.83 (4H, s, aromatic protons); 4.76 (2H, d, *J* 13.8 Hz, 2xCH$_a$H$_b$Ar); 3.83 (12H, s, 4xOMe); 3.54 (2H, d, *J* 13.8 Hz, 2xCH$_a$H$_b$Ar).

^{13}C n.m.r.
147.53 (4 x aromatic C with OMe attached); 131.67 (4 x aromatic C attached to benzylic carbons); 112.98 (4 x aromatic C with hydrogen substituent); 55.88 (4xOMe); 36.25 (2 x benzylic carbon).

d) 1-(3,4-Dimethoxybenzyl)pyrrolidin-2-one [57]

2-Pyrrolidinone (1.83 ml, 2.048 g, 24.06 mmol) was dissolved in DMF (10.0 ml). Sodium hydride (50%, 1.155 g, 24.06 mmol) was added. The solution warmed up slightly. Slight effervescence was observed. The solution was stirred under nitrogen for $2^1/_2$ h. 3,4-Dimethoxybenzyl bromide [65] (5.56 g, 24.06 mmol) in DMF (12.0 ml) was then added slowly over $1^1/_2$ h. The solution was then stirred at r.t. under nitrogen for $16^1/_2$ h. DMF was evaporated *in vacuo*. The residual yellow oil was partitioned between dichloromethane and water. The combined organic extracts were dried and the solvent evaporated *in vacuo*. The desired lactam was obtained as a light yellow oil (4.778 g, 72%). R_f (ethyl acetate) 0.28.

^{1}H n.m.r.

6.80-6.76 (3H, m, aromatic protons); 4.38 (2H, s, benzylic protons); 3.86 (6H, br s, 2xOMe); 3.26 (2H, t, *J* 7.1 Hz, >NCH$_2$CH$_2$CH$_2$-); 2.43 (2H, t, *J* 8.1 Hz, -CH$_2$C=O); 1.98 (2H, quintet with further fine splitting, *J* 7.4 Hz, -CH$_2$CH$_2$CH$_2$-).

^{13}C n.m.r.

174.69 (>C=O); 149.01, 148.33 (aromatic C-3 and C-4); 129.00 (aromatic C-1); 120.40, 111.23, 110.94 (aromatic C-2, C-5, and C-6); 55.73, 55.59 (2xOMe); 46.37, 46.18 (-CH$_2$NCH$_2$-); 30.84 (-CH$_2$C=O); 17.50 (-CH$_2$CH$_2$CH$_2$-).

I.r.

2990(s); 2955(s); 2930(m); 2910(m); 2835(m); 1660(s); 1605(m); 1590(m); 1500(m); 1490(m); 1455(s); 1435(s); 1410(s); 1355(m); 1335(w); 1300(m); 1255(s); 1150(s); 1135(s); 1020(s); 950(w); 910(w); 870(w); 810(w); 635(w); 595(w); 560(w) cm^{-1}.

EXPERIMENTAL PROCEDURES RELATING TO SECTION 2.3

General method for thionation reactions

Lactam was dissolved in benzene (ca. 10 ml per g) unless otherwise stated. Phosphorus pentasulphide (one equivalent of sulphur per mole lactam) was added. The mixture was heated under reflux, additional phosphorus pentasulphide being added, if necessary, to drive the reaction towards completion. Upon completion of reaction the supernatant benzene was decanted off and filtered. Dichloromethane was added to the residue, and the mixture was heated for ca. 2 min, prior to the decantation and filtration of the dichloromethane. To the residue, concentrated ammonia was added and the mixture was stirred until a solution formed. The basic solution was extracted with dichloromethane. The combined organic extracts were dried and evaporated *in vacuo*. The resulting solid was purified by chromatography and recrystallisation.

1-(2-Bromo-4,5-dimethoxyphenyl)pyrrolidine-2-thione [60a] was obtained as a cream white solid (1.425 g, 90%) from 1-(2-bromo-4,5-dimethoxy phenyl)pyrrolidin-2-one [59a] (1.508 g, 5.02 mmol) and P_2S_5 (0.931 g, 4.19 mmol) in benzene (20 ml). Recrystallization from chloroform/ethyl acetate produced colourless cubes, m.p. 175-176 °C. Rf (ethyl acetate/hexane 1:1) 0.65.

Analysis. Found: C, 46.06; H, 4.35; N, 4.39.
$C_{12}H_{14}BrNO_2S$ requires C, 45.58; H, 4.46; N, 4.43%.

^1H n.m.r.
7.11, 6.81 (2H, 2xs, aromatic protons); 4.1 (2H, br s, $-CH_2N<$); 3.89, 3.86 (6H, 2xs, 2xOMe); 3.19 (2H, t, *J* 7.9 Hz, $-CH_2C=S$); 2.30 (2H, quintet, *J* 7.5 Hz, $-CH_2CH_2CH_2-$).

^{13}C n.m.r.
204.15 (>C=S); 149.31, 148.95 (aromatic C-4 and C-5); 131.72 (aromatic C-1); 115.11 (aromatic C-3); 110.76 (aromatic C-2 and C-6); 57.36 ($-CH_2N<$)

55.99 (2xOMe); 44.71 (-$\underline{CH_2}$C=S); 20.94 (-$CH_2\underline{CH_2}CH_2$-).

I.r.
2975(s); 2850(w); 1600(w); 1580(w); 1490(s); 1455(s); 1440(s); 1425(s); 1390(m); 1345(m); 1305(s); 1285(s); 1255(s); 1240(s); 1175(s); 1150(s); 1070(w); 1030(s); 975(w); 850(m); 630(w) cm^{-1}.

1-(2-Bromo-4,5-dimethoxybenzyl)pyrrolidine-2-thione [60b] was obtained as a brown solid (0.866 g, 93%) from 1-(2-bromo-4,5-dimethoxy benzyl)pyrrolidin-2-one [59b] (0.883 g, 2.81 mmol) and P_2S_5 (0.349 g, 1.57 mmol) in benzene (10 ml). Recrystallisation from acetonitrile produced colourless cubes, m.p. 121-122 °C, Rf (ethyl acetate) 0.60.

Analysis. Found: C, 47.26; H, 4.37; N, 4.20%.
$C_{13}H_{16}BrNO_2S$ requires C, 47.28; H, 4.89; N, 4.24%.

^1H n.m.r.
7.14, 7.01 (2H, 2xs, aromatic hydrogens); 5.08 (2H, s, benzylic protons); 3.88, 3.83 (6H, 2xs, 2xOMe); 3.64 (3H, t, *J* 7.3 Hz, -$CH_2\underline{CH_2}N$<); 3.08 (2H, t, *J* 7.9 Hz, -$\underline{CH_2}$C=S); 2.03 (2H, quintet, *J* 7.6 Hz, -$CH_2\underline{CH_2}CH_2$-).

^{13}C n.m.r.
201.72 (>C=S); 149.46, 148.86 (aromatic C-4 and C-5); 126.76 (aromatic C-1); 115.19, 113.02 (aromatic C-3 and C-6); 114.26 (aromatic C-2); 56.22, 56.18 (2xOMe); 54.18 (-$CH_2\underline{CH_2}N$<); 50.74 (benzylic carbon); 44.80 (-$\underline{CH_2}$C=S); 19.57 (-$CH_2\underline{CH_2}CH_2$-).

I.r.
2960(m); 2940(m); 2905(w); 2890(w); 2840(w); 1600(w); 1490(s); 1455(s); 1435(s); 1380(m); 1345(w); 1320(m); 1305(m); 1255(s); 1245(s); 1155(s); 1105(m); 1025(m); 995(w); 960(w); 905(w); 870(w); 860(w); 835(w); 585(w) cm^{-1}.

1-[2-(2-Bromo-4,5-dimethoxyphenyl)ethyl]pyrrolidine-2-thione [60c] was obtained as a light yellow solid (1.413 g, 100%) from 1-(2-(2-bromo-4,5-

dimethoxyphenyl)ethyl)pyrrolidin-2-one [58c] (1.332 g, 4.06 mmol) and P_2S_5 (0.33 g, 1.95 mmol) in benzene (10 ml). Recrystallisation from acetonitrile gave colourless needles, m.p. 113.5-114.5 °C, Rf (hexane/acetone 1 : 1) 0.53.

Analysis. Found: C, 48.79; H, 4.90; N, 4.12.
$C_{14}H_{18}BrNO_2S$ requires C, 48.84; H, 5.27; N, 4.07%.

^1H n.m.r.
7.00, 6.82 (2H, 2xs, aromatic protons); 3.96 (2H, t, *J* 7.40 Hz, $ArCH_2\underline{CH_2}N<$); 3.86 (6H, s, 2xOMe); 3.56 (2H, t, *J* 7.3 Hz, $-CH_2CH_2\underline{CH_2}N<$); 3.14 (2H, t, overlaps with the following triplet, *J* 7.40 Hz, $Ar\underline{CH_2}CH_2N<$); 3.01 (2H, t, *J* 8.0 Hz, $-\underline{CH_2}C=S$); 2.02 (2H, quintet with further fine splitting, *J* 7.6 Hz, $-CH_2\underline{CH_2}CH_2-$).
Irradiation at 2.02 : t at 3.56 collapses to s. t at 3.01 collapses to s.

^{13}C n.m.r.
200.73 (>C=S); 148.26, 148.15 (aromatic C-4 and C-5); 129.20 (aromatic C-1); 113.15, 113.09 (aromatic C-3 and C-6); 113.72 (aromatic C-2); 55.92, 55.89 (2xOMe); 55.50 ($-CH_2CH_2\underline{CH_2}N<$); 47.43 ($ArCH_2\underline{CH_2}N<$); 44.71 ($-\underline{CH_2}C=S$); 31.59 ($Ar\underline{CH_2}CH_2N<$); 19.56 ($-CH_2\underline{CH_2}CH_2-$).

I.r.
2990(s); 2960(m); 2850(w); 1675(w); 1610(w); 1505(s); 1470(m); 1445(m); 1430(m); 1395(m); 1360(w); 1330(m); 1295(m); 1260(s); 1165(s); 1120(m); 1045(m); 1035(m); 970(w); 935(w); 865(w); 600(w) cm^{-1}.

1-(3,4-Dimethoxybenzyl)pyrrolidine-2-thione [59a] was obtained as a brown oil (0.542 g, 76%) from 1-(3,4-dimethoxybenzyl)pyrrolidin-2-one [57b] (0.665 g, 2.83 mmol) and P_2S_5 (0.396 g, 1.78 mmol) in toluene (15 ml). The oil was purified by column chromatography on silica gel with hexane/acetone mixtures to give a white solid. Recrystallisation from acetonitrile produced colourless plates, m.p. 109-110 °C, Rf (hexane/acetone 2 : 1) 0.47.

Analysis. Found: C, 62.20; H, 6.88; N, 5.48.
$C_{13}H_{17}NO_2S$ requires C, 62.12; H, 6.82; N, 5.57%.

^{1}H n.m.r.

6.96 (1H, d, *J* ca. 1.80 Hz, aromatic H-2); 6.85 (2H, m, aromatic H-5 and H-6); 4.92 (2H, s, benzylic protons); 3.87, 3.86 (6H, 2xs, 2xOMe); 3.60 (2H, t, *J* 7.3 Hz, -$CH_2CH_2\underline{CH_2}N$<); 3.08 (2H, t, *J* 7.92 Hz, -CH_2C=S); 2.02 (2H, quintet with further fine splitting, *J* 7.6 Hz, -$CH_2\underline{CH_2}CH_2$-).

^{13}C n.m.r.

201.02 (>C=S); 148.96, 148.61 (aromatic C-3 and C-4); 127.52 (aromatic C-1); 120.85 (aromatic C-6); 111.31, 110.81 (aromatic C-2 and C-5); 55.69 (2xOMe); 53.68 (-$CH_2\underline{CH_2}N$<); 51.13 (benzylic carbon); 44.76 (-$\underline{CH_2}$C=S); 19.15 (-$CH_2\underline{CH_2}CH_2$-).

I.r.

2940(s); 2850(s); 2840(m); 1595(s); 1490(s); 1440(s); 1415(s); 1345(s); 1305(s); 1205(s); 1150(s); 1140(s); 1110(s); 1060(w); 1030(m); 1005(w); 950(w); 850(m); 645(w); 590(w); 555(w) cm^{-1}.

1-(2-(3,4-Dimethoxyphenyl)ethyl)pyrrolidine-2-thione [59b] was obtained as a brown oil (0.459 g, 69%) from 1-(2-(3,4-dimethoxyphenyl)ethyl) pyrrolidin-2-one [57c] (0.629 g, 2.52 mmol) and P_2S_5 (0.490 g, 2.20 mmol) in toluene (10 ml). The oil was purified by column chromatography on silica gel with hexane/acetone mixtures to give a yellow solid. Recrystallisation from acetone/hexane mixture produced colourless cubes, m.p. 81.5-82.5 °C, R_F (hexane/acetone 2 : 1) 0.42.

Analysis. Found: C, 63.50; H, 7.19; N, 5.50.
$C_{14}H_{19}NO_2S$ requires C, 63.37; H, 7.22; N, 5.28%

^{1}H n.m.r.

6.75 (3H, s, aromatic protons); 3.92 (2H, t, *J* 7.4 Hz, $ArCH_2\underline{CH_2}$-); 3.84, 3.82 (6H, 2xs, 2xOMe); 3.47 (2H, t, *J* 7.29 Hz, >$N\underline{CH_2}CH_2CH_2$-); 2.96 (2H, t, *J* 7.4 Hz, $Ar\underline{CH_2}CH_2$-); 2.92 (2H, t, *J* 7.3 Hz, -CH_2C=S); 1.92 (2H, quintet, *J* 7.6 Hz, -$CH_2\underline{CH_2}CH_2$-).

^{13}C n.m.r.

200.67 (>C=S); 148.83, 147.59 (aromatic C-3 and C-4); 130.62 (aromatic C-1); 120.50, 111.68, 111.13 (aromatic C-2, C-5, and C-6); 55.78, 55.74, 55.56 (CxOMe and $-CH_2\underline{C}H_2\underline{C}H_2N<$); 49.39 ($ArCH_2\underline{C}H_2-$); 44.80 ($-\underline{C}H_2CH_2\underline{C}H_2C=S$); 31.64 ($Ar\underline{C}H_2CH_2-$); 19.63 ($-CH_2\underline{C}H_2CH_2-$).

I.r.

2960(m); 2930(m); 2880(w); 2840(w); 1590(w); 1505(s); 1465(s); 1450(m); 1440(m); 1420(m); 1360(w); 1330(m); 1310(m); 1290(m); 1260(s); 1155(s); 1140(s); 1120(m); 1030(m); 855(w); 800(w) cm^{-1}.

EXPERIMENTAL PROCEDURES RELATING TO SECTION 2.4

General procedure for the sulphide contraction

The appropriate thiolactam was dissolved in a small quantity of a suitable solvent and the appropriate α-bromocarbonyl compound (1.1 eq.) was added. Suitable solvents include dichloromethane, chloroform, acetonitrile, and acetone. α-Bromocarbonyl compounds used include bromoacetone, methyl and ethyl bromoacetate. Unless otherwise stated the salt was then formed at r.t. in a stoppered flask and the reaction monitored by t.l.c. Upon completion of the reaction the salt was dissolved in acetonitrile (amount required depends on the solubility of the salt). Triphenylphosphine (ca. 1.1 eq.) in the minimal amount of dichloromethane followed by triethylamine (1.1 eq.) were added. The ensuing reaction was usually exothermic, and the colour tended to darken. Immediate acid extraction was done (2.0M HCl). The combined aqueous extracts were basified with concentrated ammonia liquid. The basic solution was extracted with dichloromethane. The combined organic extracts were dried and evaporated *in vacuo*. The residue was purified by chromatography and recrystallisation. If the desired compound was not basic enough to be extracted, the organic solution was dried and evaporated. The residue was purified by column chromatography on silica eluted with hexane/ethyl acetate mixtures unless otherwise stated to give the desired compound.

(*E*)-1-(2-Bromo-4,5-dimethoxyphenyl)-2-acetylmethylenepyrrolidine [53a]

The salt was produced by refluxing 1-(2-bromo-4,5-dimethoxyphenyl) pyrrolidine-2-thione [60a] (106 mg, 0.336 mmol) together with bromoacetone (98.1 mg, 0.716 mmol) in acetonitrile (1.0 ml). After 1½ h of reflux t.l.c. indicated that there was only a trace of thiolactam. Triphenylphosphine (96.9 mg, 0.370 mmol, 1.1 eq.) dissolved in dichloromethane (1.0 ml) was added quickly followed by triethylamine (0.047 ml, 0.337 mmol). Addition of base resulted in an exothermic evolution of white fumes. The organic solution was then diluted with dichloromethane (20.0 ml) and washed with 4.0M HCl (5x20 ml). The combined aqueous solution was back-washed with ether (2x20 ml). The

i.r.

2960(m); 2940(m); 2870(m); 1710(m); 1660(s); 1585(s); 1570(s); 1470(s); 1450(m); 1435(m); 1395(m); 1370(m); 1345(m); 1295(s); 1155(m); 1130(s); 1085(m); 1065(m); 1040(m); 850-825(w); 795-705(m) cm^{-1}.

2.3) (E)-1-(2-bromo-4-methylphenyl)-2-ethoxycarbonylmethylenepyrrolidine [86]

2-Bromo-4-methylaniline (0.661 g, 3.55 mmol) was added to ethyl 6-chloro-3-oxohexanoate [8] (0.901 g, 4.69 mmol, 1.32 eq.). Sodium sulphate (0.506 g, 3.55 mmol) and disodium hydrogen phosphate (0.509 g, 3.55 mmol) together with a crystal of iodine were added. The flask with its contents were flushed with nitrogen and it was stoppered and heated at 80 °C for 22 h. The contents were partitioned between dichloromethane (3x20 ml) and water (20 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a brown oil (1.372 g). This oil was purified by column chromatography using hexane/ethyl acetate mixtures. (E)-1-(2-Bromo-4-methylphenyl)-2-ethoxycarbonylmethylenepyrrolidine [86] was isolated as a yellow oil (0.720 g, 63%), which later solidified. Vinylogous urethane [86] was recrystallised from ethyl acetate to give colourless crystals, m.p. 87-88 °C, Rf (hexane/ethyl acetate 2 : 1) 0.65.

Analysis. Found : C, 70.33; H, 7.42; N, 6.80.
$C_{15}H_{18}BrNO_2$ requires C, 70.22; H, 7.37; N, 6.82%.

^1H n.m.r.

7.46 (1H, s, aromatic H-3); 7.14 (2H, s, aromatic H-5 and H-6); 4.24 (1H, s, >C=CH); 4.01 (2H, q, *J* 6.8 Hz, $-OCH_2CH_3$); 3.75 (1H, dt, *J* 9.1 and 6.7 Hz, $>NCH_aH_b-$); 3.46 (1H, dt, *J* 9.2 and 7.3 Hz, $>NCH_aH_b-$); 3.28 (2H, q, *J* 7.0 Hz, $-CH_2C=C<$); 2.31 (3H, s, $ArCH_3$); 2.10 (2H, quintet, *J* 7.5 Hz, $-CH_2CH_2CH_2-$); 1.14 (3H, t, *J* 7.1 Hz, $-OCH_2CH_3$).

^{13}C n.m.r.

168.08 (>NC=CH); 164.13 (>C=O); 139.10, 128.97, 123.57 (aromatic C-3, C-5 and C-6); 136.11 (aromatic C-1); 133.37 (aromatic C-4); 121.41 (aromatic C-2); 90.36 (>NC=CH); 57.31 ($-OCH_2CH_3$); 52.94 ($-CH_2N<$); 31.09 ($-CH_2C=CH$); 21.34 ($-CH_2CH_2CH_2-$); 19.88 ($ArCH_3$); 13.82 ($-OCH_2CH_3$).

aqueous solution was then basified with concentrated ammonia solution and extracted with dichloromethane (3x20 ml). The combined organic extracts were dried and evaporated *in vacuo* to yield a brown solid (79 mg). After three recrystallisations with ethyl acetate a yellow solid was obtained (6.5 mg, 5.7%); m.p. 171-175 °C, R_F (ethyl acetate) 0.45.

^{1}H n.m.r.

7.11, 6.72 (2H, 2xs, aromatic protons); 4.77 (1H, t, *J* 1.2 Hz, >C=CH-); 3.92, 3.88 (6H, 2xs, 2xOMe); 3.79, 3.50 (2H, 2xdt, *J* 9.6 Hz, 7.1 Hz, $CH_2N<$); 3.35 (2H, 2xtd, *J* 7.2 Hz, 1.2 Hz, >NCH$_2$CH$_2$CH$_2$-); 2.15 (2H, quintet, *J* 7.4 Hz, -CH$_2$CH$_2$CH$_2$-); 1.96 (3H, s, CH_3C=O).

Irradiation at 4.77 : 2xdt at 3.34 collapse to td.

at 3.35 : quintet at 2.11 collapses to t, *J* 6.3 Hz, t at 4.77 collapses to s.

at 2.15 : 2xtd at 3.79 and 3.50 collapse to 2xd, *J* 6.6 Hz.

2xdt at 3.34 collapse to 2xd *J* 1.2 Hz. *J* 1.2 Hz.

I.r.

2990(s); 2960(s); 2930(s); 2905(s); 2830(m); 1680(s); 1635(s); 1595(s); 1535(s); 1495(s); 1460(s); 1435(s); 1405(s); 1320(s); 1310(s); 1290(s); 1250(s); 1170(s); 1140(s); 1120(s); 1110(s); 1095(s); 1075(m); 1045(s); 1035(s); 1000(w); 975(w); 920(w); 850(s); 840(s); 820(m); 690(m); 650(w); 570(w); 530(m) cm^{-1}.

M.s.

44(15); 183(5); 185(6); 199(7); 201(11); 202(5); 206(11); 220(20); 221(17); 244(7); 245(5); 260(M^+ - Br, 100); 261(17); 277(89); 278(42); 279(7).

Accurate mass. Found: M^+ - Br, 260.1292.

$C_{14}H_{18}NO_3$ requires 260.1287.

1-(2-Bromo-4,5-dimethoxyphenyl)-3-methoxycarbonylmethylpyrrolidine-2-thione [68]

1-(2-Bromo-4,5-dimethoxyphenyl)pyrrolidine-2-thione [60a] (92 mg, 0.29 mmol) and methyl bromoacetate (52 mg, 0.34 mmol) were mixed in chloroform. After two days of standing at r.t. the mixture was diluted

with dichloromethane (1.0 ml) and triphenylphosphine (83 mg, 0.31 mmol) in dichloromethane (1.0 ml) was added followed by triethylamine (0.05 ml, 33 mg, 0.32 mmol). The solvent was evaporated and the residue was purified by column chromatography on silica gel with hexane/ethyl acetate mixtures. 1-(2-Bromo-4,5-dimethoxyphenyl)-3-methoxycarbonylmethylpyrrolidine-2-thione [68] (13 mg, 11%) was isolated as a black-brown solid; m.p. 107-113 °C, Rf (ethyl acetate) 0.5.

^{1}H n.m.r.
7.10, 6.77 (2H, 2xs, aromatic hydrogens); 4.30-3.95 (2H, m, >NCH$_2$-); 3.90, 3.87 (6H, 2xs, 2xOMe); 3.74 (3H, s, -CO$_2$CH$_3$); 3.55-3.25 (2H, m, -CHC=S and -CH$_a$H$_b$CO$_2$CH$_3$); 2.72-2.57 (2H, m, -CH$_2$CH$_c$H$_d$CH- and -CH$_a$H$_b$CO$_2$CH$_3$); 2.13-1.93 (1H, m, -CH$_2$CH$_c$H$_d$CH-).

^{13}C n.m.r.
205.74 (>C=S); 172.48 (>C=O); 149.77, 149.33 (aromatic C-4 and C-5); 132.22 (aromatic C-1); 115.55, 111.09 (aromatic C-2, C-3 and C-6); 56.28 (2xOMe); 55.11 (>NCH$_2$); 51.77 (-CO$_2$CH$_3$); 50.00 (-CHC=S); 32.43 (-CH$_2$CO$_2$CH$_3$); 27.85 (-CH$_2$CH$_2$CH-).

I.r.
2940(s); 2840(w); 1720(s); 1590(w); 1475(s); 1430(s); 1380(m); 1365(m); 1335(m); 1320(m); 1285(s); 1235(s); 1170(s); 1065(m); 1030(m); 870(w); 850(m); 630(w) cm^{-1}.

M.s.
124(3); 220(5); 292(9); 308.1(M$^+$ - Br, 100); 310(6); 356(M$^+$ - OMe, 3); 358(3)

Accurate mass. Found: M$^+$ - OMe, 355.9963.
$C_{14}H_{18}BrNO_3S$ requires 355.9956.

1-(2-Bromo-4,5-dimethoxyphenyl)-3-ethoxycarbonylmethylpyrrolidine-2-thione [69]

1-(2-Bromo-4,5-dimethoxyphenyl)pyrrolidine-2-thione [60a] (0.475 g, 1.50 mmol) was dissolved in acetonitrile (2.0 ml). Heating was required to dissolve all the thiolactam. Ethyl bromoacetate (0.18 ml, 0.273 g, 1.63

mmol, 1.1 eq.) was added. This solution was allowed to stand at r.t. After 38 h more ethyl bromoacetate (0.01 ml) was added. After this has stood at r.t. for another six days, fine crystals were observed in the solution. The solid dissolved on heating in acetonitrile (10.0 ml). Triphenylphosphine (0.394 g, 1.50 mmol, 1 eq.) dissolved in dichloro methane (2.0 ml) was added, followed by triethylamine (0.23 ml, 1.63 mmol, 1.1 eq.). The reaction solution warmed up and crystals of phosphine compounds precipitated out of the solution. The solvent was evaporated and the residue was purified by flash column chromatography using ethyl acetate/hexane (1 : 3). The desired compound (0.112 g, 0.30 mmol, 20%) was obtained as a brown solid. 1-(2-Bromo-4,5-dimethoxyphenyl)-3-ethoxy carbonylmethylpyrrolidine-2-thione [69] (0.122 g, 20%) was obtained as a yellow oil which slowly solidified on standing. It was recrystallised from acetone/hexane mixture to produce yellow cubes, m.p. 96-98 °C. Rf (heptane/acetone 2 : 1) 0.29.

^{1}H n.m.r.

7.10, 6.78 (2H, 2xs, aromatic protons); 4.19 (2H, q, *J* 7.1 Hz, OCH_2CH_3); 4.10-3.65 (2H, m, $>NCH_2-$); 3.89, 3.86 (6H, 2xs, 2xOMe); 3.50-3.20 (2H, m, $-CHC=S$ and $-CH_aH_bCO_2Et$); 2.75-2.50 (2H, m, $-CH_2CH_cH_dCH-$ and $-CH_aH_bCO_2Et$); 2.20-1.90 (1H, m, $-CH_2CH_cH_dCH-$); 1.29 (3H, t, *J* 7.1 Hz, $-OCH_2CH_3$).

^{13}C n.m.r.

205.36 (>C=S); 171.56 (>C=O); 149.29, 148.85 (aromatic C-4 and C-5); 131.85 (aromatic C-1); 115.06, 110.73, 110.65 (aromatic C-2, C-3, and C-6); 60.25 ($-OCH_2CH_3$); 55.92 (2xOMe); 54.60 ($>NCH_2-$); 49.69 ($>CHC=S$); 36.37 ($-CH_2CO_2Et$); 27.43 ($-CH_2CH_2CH-$); 13.90 ($-OCH_2CH_3$).

I.r.

2950(s); 2920(s); 2830(m); 1710(s); 1590(m); 1575(m); 1475(s); 1425(s); 1370(s); 1330(s); 1280(s); 1165(s); 1060(m); 1025(s); 865(m); 845(m); 625(w) cm^{-1}.

M.s.

2940(9); 306(15); 321.9(M^+ - Br, 100), 323(19); 324(6).

Accurate mass. Found: M^+ - Br, 322.1113.

$C_{16}H_{20}NO_4S$ requires 322.1...

1) Preparation of ortho bromoanilines

1.1) Sequence for the preparation of 2-bromo-4,5-dimethoxyaniline [75]

a) 2-Bromo-4,5-dimethoxyphenylacetamide [83]

3,4-Dimethoxyaniline [62] (1.313 g, 8.57 mmol) was dissolved in glacial acetic acid (5.0 ml). Acetic anhydride (1.30 ml, 1.40 g, 13.7 mmol, 1.6 eq.) was added. An exothermic reaction resulted. This solution was then heated under reflux for 30 min. After cooling bromine (0.62 ml, 1.92 g, 12.0 mmol, 1.4 eq.) in glacial acetic acid (3.0 ml) was added. A very exothermic reaction resulted. This solution was then stirred. Solid precipitate was observed after 5 min. Water (5.0 ml) was added after 10 min. A homogeneous black solution was formed. Stirring was resumed for 18 h. The black solution was basified (NH4OH). Brown solid chunks precipitated out of the solution. This aqueous mixture was extracted with dichloromethane (4x20 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated *in vacuo* to yield light whitish purple needles (2.300 g, 96%), m.p. 125-127 °C (lit.[274] 127 °C).

^{1}H n.m.r. (60 MHz)

7.8, 6.8 (2H, 2xs, aromatic protons); 7.4 (1H, broad s, >NHC=O); 3.8, 3.7 (6H, 2xs, 2xOMe); 2.1 (3H, s, CH_3C=O).

b) 2-Bromo-4,5-dimethoxyaniline [75]

2-Bromo-4,5-dimethoxyphenylacetamide [83] (1.103 g, 4.02 mmol) was heated under reflux in sodium hydroxide solution (0.42M, 50.0 ml) for 20 1/2 h. On cooling long blade-like crystals came out of solution. The basic solution was washed with dichloromethane. The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated *in vacuo* to give the desired aniline (0.870 g, 94%) as a brown needles, m.p. 50-54 °C (lit.[276] 51 °C).

^{1}H n.m.r. (60 MHz)

6.8, 6.2 (2H, 2xs, aromatic protons); 3.8 (2H, br s, $-NH_2$); 3.7, 3.63 (6H, 2xs, 2xOMe).

1.2) 2-Bromo-4-methylaniline

p-Toluidine (6 g, 56 mmol) was dissolved in dioxane (8 ml). Potassium hydroxide (3.14 g, 56 mmol) in water (14 ml) was added. Bromine (8.97 g, 56 mmol) in dioxane (70 ml) was then added dropwise over a period of 1 h and 50 min. The resultant solution was stirred at r.t. for 22 h. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane (5x20 ml) and basic aqueous solution (20 ml, NH_4OH). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a mixture of purple solid and oil (10.70 g). This was purified by column chromatography using hexane/ethyl acetate mixtures. The desired aniline was isolated as an oil (1.934 g, 12%). Another solid was also isolated (1.225 g). This is probably 2,6-dibromo-4-methylaniline, m.p. 70 °C. Lit 73.5-74.5 °C.[276] Some mixtures were also obtained.

1.3) 1-Bromo-2-naphthylamine [88]

β-Naphthylamine (1.033 g, 7.21 mmol) was added to glacial acetic acid (7 ml). Acetic anhydride (0.92 ml, 9.75 mmol, 1.35 eq.) was added. An exothermic reaction resulted. The solution was heated for 30 min on a boiling water bath. Bromine (0.38 ml, 7.42 mmol, 1.03 eq.) was added. Immediate precipitation was observed. The precipitate was washed with water, then hydrolysed using hydrochloric acid (1.10 ml)/ethanol (10 ml) at reflux for 40 min. More hydrochloric acid was added (2 ml), and after another 30 min of reflux complete dissolution of the solid was observed, immediately followed by solid formation. The solution was basified (NaOH) and the aqueous solution extracted with dichloromethane (5x20 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a purple oil. This oil was purified by column chromatography using hexane/ethyl acetate mixtures. The desired 1-bromo-2-naphthylamine [88] was obtained as a light purple crystalline solid (1.102 g, 69%). M.p. 60 °C. Lit. 63 °C.[277]

1.4) 2-Bromo-4-nitroaniline [87]

p-Nitroaniline (5 g, 36 mmol) was dissolved in dioxane (11 ml). Potassium hydroxide (2.02 g, 36 mmol) in water (7.2 ml) was then added. The

solution was cooled to 0.5 °C and bromine (5.90 g, 36 mmol) in dioxane (58 ml) was added over a period of 1½ h. The solution was then stirred at r.t. for 2 h. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane (3x20 ml) and basic aqueous solution (20 ml, NH_4OH). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield 2-bromo -nitroaniline [57] as a yellow solid (8.575 g). After one recrystallisation (ethyl acetate) m.p 96-102 °C. Lit. m.p. 104 °C.[278]

2) Condensation reactions between o-bromoanilines and 6-chloro-3-oxohexanoate [8][73]

2.1) (*E*)-1-(2-Bromo-4,5-dimethoxyphenyl)-2-ethoxycarbonylmethylenepyrrolidine [53b]

2-Bromo-4,5-dimethoxyaniline [75] (3.000 g, 12.93 mmol) was dissolved in ethyl 6-chloro-3-oxohexanoate [8] (2.856 g, 14.8 mmol, 1.15 eq.). Some dichloromethane (ca. 2-3 ml) was added to help to dissolve aniline [75]. A mixture of disodium hydrogen phosphate (1.848 g, 13.06 mmol), sodium sulphate (1.853 g, 13.06 mmol) and a crystal of iodine was introduced. This mixture was then stirred and heated at 70 °C in a stoppered flask. After 67½ h the mixture had gone solid. Water (20.0 ml) was added to dissolve the solid and this aqueous solution was washed with dichloromethane. After drying and evaporation a dark crystalline solid (4.038 g) was obtained. This crude solid was recrystallised from acetonitrile to produce colourless needles (1.583 g) and the mother liquor was purified by column chromatography to produce more title compound as a light brown crystalline solid (0.315 g). Total mass obtained = 1.90 g, 40%. In yet another attempt some DMF was introduced as solvent; an even poorer yield was obtained. Attempts using sealed tube conditions failed to give any significant results. Starting materials were recovered. (*E*)-1-(2-Bromo-4,5-dimethoxyphenyl)-2-ethoxycarbonyl methylenepyrrolidine [53b] was recrystallised from acetonitrile to yield colourless crystals, m.p. 163-164 °C, Rf (hexane/acetone 2 : 1) 0.52.

Analysis. Found: C, 51.74; H, 5.42; N, 3.82.
$C_{15}H_{20}BrNO_4$ requires C, 51.9%; H, 5.44; N, 3.78%.

^1H n.m.r.

7.09, 6.74 (2H, 2xs, aromatic protons); 4.27 (1H, t, *J* 1.4 Hz, >C=CH); 4.05 (2H, q, *J* 7.2 Hz, -OCH$_2$CH$_3$); 3.89, 3.85 (6H, 2xs, 2xOMe); 3.75, 3.51 (2H, 2xdt, *J* 9.3 and 7.0 Hz, -CH$_2$N<); 3.30 (2H, 2xtd, *J* 7.8 and 1.4 Hz, -CH$_2$C=C<); 2.15 (2H, quintet, *J* 7.5 Hz, -CH$_2$CH$_2$CH$_2$-); 1.20 (3H, t, *J* 7.1 Hz, -OCH$_2$CH$_3$).

Irradiation at 4.27 : 2xdt at 3.30 collapse to 2xt.

3.77 : td at 3.51 collapses to t, *J* 6.8 Hz. Quintet at 2.15 collapses to q, *J* 7.5 Hz.

3.30 : t at 4.27 collapses to s. Quintet at 2.15 collapses to t, *J* 7.9 Hz.

2.15 : 2xtd at 3.75 and 3.51 collapse to 2xd, *J* 9.3 Hz; 2xdt at 3.30 collapse to 2xd, *J* 1.4 Hz.

^{13}C n.m.r.

169.29 (>NC=CH); 165.28 (>C=O); 149.32, 149.27 (aromatic C-4 and C-5); 131.94 (aromatic C-1); 115.73, 111.79 (aromatic C-3 and C-6); 112.70 (aromatic C-2); 81.11 (>NC=CH); 56.42 (-OCH$_2$CH$_3$); 56.32, 56.20 (2xOMe); 53.73 (-CH$_2$N<); 31.85 (-CH$_2$C=CH); 22.13 (-CH$_2$CH$_2$CH$_2$-); 14.60 (-OCH$_2$CH$_3$).

I.r.

2990(s), 2950(s), 2910(s), 2860(m), 2855(m), 1670(s), 1605(s), 1580(s), 1495(s), 1460(s), 1440(s), 1420(s), 1395(s), 1380(s), 1350(s), 1340(s), 1285(s), 1250(s), 1210(s), 1165(s), 1135(s), 1095(s), 1070(s), 1050(s), 1035(s), 1010(s), 960(w), 875(w), 855(m), 835(m), 635(w) cm^{-1}.

2.2) (E)-1-(2-bromophenyl)-2-ethoxycarbonylmethylenepyrrolidine [85]

o-Bromoaniline (0.593 g, 3.45 mmol) was dissolved in ethyl 6-chloro-3-oxohexanoate (0.684 g, 3.55 mmol, 1.03 eq.). A mixture of disodium hydrogen phosphate (0.494 g, 3.49 mmol), sodium sulphate (0.486 g, 3.42 mmol), and a crystal of iodine was introduced. The flask was flushed with nitrogen and then stoppered and heated with stirring at ca. 78 °C for ca.

26 h. White crystalline solid formed at the end of stirring. The contents of the flask were partitioned between dichloromethane (3x20 ml) and brine (20 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to produce a brown oil (1.091 g). This was purified by column chromatography using hexane/ethyl acetate (30 : 1, 28 : 1, 26 : 1). (E)-1-(2-Bromophenyl)-2-ethoxycarbonylmethylenepyrrolidine [85] was isolated as a light yellow crystalline solid (0.433 g, 41%). Some aniline was also recovered (0.077 g). Vinylogous urethane [85] was recrystallised from acetone to give colourless crystals, m.p. 84-86 °C, Rf (hexane/ethyl acetate 2 : 1) 0.67.

Analysis. Found : C, 54.24; H, 5.07; N, 4.53.
$C_{14}H_{16}BrNO_2$ requires C, 54.21; H, 5.20; N, 4.52%.

^1H n.m.r.

7.65 (1H, dd, *J* 7.9 and 1.5 Hz, aromatic H-3); 7.36 (1H, ddd, *J* 7.9, 7.1, and 1.5 Hz, aromatic H-5); 7.25 (1H, dd, *J* 8.3 and 1.9 Hz, aromatic H-6); 7.19 (1H, ddd, 7.9 7.2, and 2.0 Hz, aromatic H-4); 4.26 (1H, t, *J* 1.3 Hz, >C=CH); 4.03 (2H, q, *J* 7.1 Hz, -OCH_2CH_3); 3.80 (1H, dt, *J* 9.2 and 6.7 Hz, >NCH_aH_b-); 3.50 (1H, dt, *J* 9.2 and 7.3 Hz, >NCH_aH_b-); 3.31 (2H, tdd, *J* 7.6, 6.8, and 1.3 Hz, -CH_2C=C); 2.13 (2H, quintet, *J* 7.4 Hz, -$CH_2CH_2CH_2$-); 1.17 (3H, t, *J* 7.1 Hz, -OCH_2CH_3).

Irradiation at 7.64 : ddd at 7.36 collapses to t, *J* 7.3 Hz. Dd at 7.25 collapses to d, *J* 2.0 Hz. Ddd at 7.19 becomes a multiplet.

2.13 : dt at 3.80 collapses to d, *J* 9.3 Hz. Dt at 3.50 collapses to a d, *J* 9.2 Hz. Tdd at 3.31 collapses to a dd, *J* 6.4 and 1.4 Hz.

3.50 : quintet at 2.13 collapses to q, *J* 6.9 Hz. Dt at 3.80 becomes a multiplet.

^{13}C n.m.r.

168.52 (>NC=CH); 164.42 (>C=O); 139.12 (aromatic C-1); 133.46, 129.36, 129.06, 128.54 (aromatic C-3, C-4, C-5, and C-6); 122.17 (aromatic C-2); 80 .82 (>NC=CH); 57.81 (-OCH_2CH_3); 53.26 (-CH_2N<); 31.44 (-CH_2C=CH); 21.70 (-$CH_2CH_2CH_2$-); 14.15 (-OCH_2CH_3).

I.r.

3010, 2980(s); 2950(m); 2925(m); 2870(m); 1689(s); 1670(s); 1610(s); 1580(s); 1510(w); 1490(s); 1460, 1450, 1440(m); 1410(s); 1390(m); 1375(s); 1350(m); 1300(s); 1290(m); 1265(m); 1255(m); 1235(s); 1200(s); 1140(s); 1100(s); 1075(w); 1050(s); 990(w); 975(w); 940(w); 920(w); 875(w); 860(w); 830(m); 825(m); 800(m) cm^{-1}.

M.s.

Accurate mass. Found : M^+, 323.0669.

$C_{15}H_{18}BrNO_2$ requires 323.0521.

2.4) Two attempts of condensation between 1-bromo-2-naphthylamine [68] and ethyl 6-chloro-3-oxo-hexanoate [8] failed. Non characterisable compounds were obtained. 2-Bromo-4-nitroaniline also failed to undergo condensation reactions with [8]. Starting material was recovered.

(E)-1-(2-Bromo-4,5-dimethoxybenzyl)-2-ethoxycarbonylmethylenepyrrolidine [53d]

1-(2-Bromo-4,5-dimethoxybenzyl)pyrrolidine-2-thione [60b] (0.355 g, 1.08 mmol) was dissolved in dichloromethane (1.0 ml). Ethyl bromoacetate (0.13 ml, 0.20 g, 1.19 mmol, 1.1 eq.) was added. After standing at r.t. for 4h, crystalline solids precipitated out of the solution. After 24 h acetonitrile was added to dissolve the salt; heating was necessary to get all solids to dissolve. Triphenylphosphine (0.297 g, 1.13 mmol, 1.05 eq.) in dichloromethane (1.0 ml) was added followed by triethylamine (0.17 ml, 1.19 mmol, 1.1 eq.). The solution turned yellow slowly and heated up slightly. The organic solution was washed with acid (2.0M HCl, 4x25 ml). The combined aqueous solution was basified (NH4OH) and extracted with dichloromethane. After evaporation the desired vinylogous urethane was obtained as an orange fluffy solid (0.267 g, 65%). Vinylogous urethane [53d] was recrystallised from acetone/hexane mixture to produce white cotton-like needles, m.p. 109-110.5 °C, Rf (hexane/acetone 3:1) 0.35.

Analysis. Found: C, 53.21; H, 5.71; N, 3.85.

$C_{17}H_{22}BrNO_4$ requires C, 53.14; H, 5.77; N, 3.64%.

^{1}H n.m.r.

7.03, 6.60 (2H, 2xs, aromatic protons); 4.63 (1H, br s, >C=CH); 4.34 (2H, s, benzylic protons); 4.09 (2H, q, *J* 7.1 Hz, -OCH$_2$CH$_3$); 3.87, 3.81 (6H, 2xs, 2xOMe); 3.33 (2H, t, *J* 7.1 Hz, >NCH$_2$CH$_2$-); 3.25 (2H, t, *J* 7.1 Hz, -CH$_2$C=C<); 1.99 (2H, quintet, *J* 7.4 Hz, -CH$_2$CH$_2$CH$_2$-); 1.24 (3H, t, *J* 7.1 Hz, -OCH$_2$CH$_3$).

^{13}C n.m.r.

169.34 (>NC=CH); 169.01 (>C=O); 148.85, 148.59 (aromatic C-4 and C-5); 126.56 (aromatic C-1); 115.59, 111.03 (aromatic C-3 and C-6); 113.24 (aromatic C-2); 78.77 (>NC=CH); 68.23 (-OCH$_2$CH$_3$); 56.13, 56.02 (2xOMe); 52.17 (>NCH$_2$CH$_2$-); 49.99 (benzylic carbon); 33.37 (-CH$_2$C=CH); 21.20 (-CH$_2$CH$_2$CH$_2$-); 14.58 (-OCH$_2$CH$_3$).

I.r.

2970(m); 2930(m); 2895(w); 2835(w); 1700(m); 1655(s); 1580(s); 1490(m); 1450(m); 1375(m); 1345(m); 1290(m); 1245(s); 1130(s); 1090(m); 1055(s); 1025(m); 955(m); 915(w); 875(w); 850(w); 590(w) cm^{-1}.

(*E*)-1-(2-Bromo-4,5-dimethoxybenzyl)-2-acetylmethylenepyrrolidine [53c]

1-(2-Bromo-4,5-dimethoxybenzyl)pyrrolidine-2-thione [60b] (0.257 g, 0.78 mmol) was dissolved in dichloromethane (1.5 ml). Bromoacetone (0.072 ml, 0.86 mmol, 1.1 eq.) was added. The solution was allowed to stand at r.t in a stoppered flask. After 3 h some white solids precipitated out of the solution. After 24 h acetonitrile (10 ml) was added to the salt and with the aid of heating everything dissolved. Triphenylphosphine (0.204 g, 0.78 mmol) dissolved in dichloromethane (2.0 ml) was added. This was followed by the addition of triethylamine (0.12 ml, 0.9 mmol, 1.1 eq.). A reddish solution was formed. Acid (4.0M HCl) extraction gave unsatisfactory results. The organic solution was dried (MgSO$_4$) and evaporated to dryness. The residue was purified by flash column chromatography to produce a brown oil (0.187 g, 69%). The percentage yield was based on thiolactam [60b] reacted. Thiolactam [60b] (0.061g) was also recovered. Recrystallisation from ethyl acetate gave colourless cubes, m.p. 103-104 °C, *Rf* (hexane/acetone 2 : 1) 0.30.

Analysis. Found: C, 53.98; H, 5.62; N, 4.00.
$C_{16}H_{20}BrNO_3$ requires C, 54.25; H, 5.69; N, 3.95%.

^1H n.m.r.
6.78, 6.83 (2H, 2xs, aromatic protons); 5.10 (1H, br s, >C=CH); 4.32 (2H, s, benzylic protons); 3.81, 3.74 (6H, 2xs, 2xOMe); 3.31 (2H, t, J 7.1 Hz, overlaps with the next triplet, >NCH$_2$CH$_2$); 3.27 (2H, t, J 7.3 Hz, -CH$_2$C=CH); 1.98 (3H, s, overlaps with the next quintet, CH$_3$C=O); 1.92 (2H, quintet, -CH$_2$CH$_2$CH$_2$-).

^{13}C n.m.r.
194.46 (>C=O); 165.22 (>NC=CH); 148.91, 148.58 (aromatic C-4 and C-5); 126.14 (aromatic C-1); 115.56, 110.98 (aromatic C-3 and C-6); 113.25 (aromatic C-2); 98.03 (>NC=CH); 56.03, 55.94 (2xOMe); 51.87 (>NCH$_2$CH$_2$-); 49.84 (benzylic carbon); 33.06 (-CH$_2$C=CH); 30.54 (CH$_3$C=O); 20.91 (-CH$_2$CH$_2$CH$_2$-).

I.r.
3010(m); 2990(m); 2980(m); 2950(m); 2920(w); 2860(w); 1710(w); 1635(m); 1605(m); 1580(m); 1535(s); 1505(s); 1385(s); 1465(m); 1440(m); 1395(m); 1355(m); 1300(m); 1260(s); 1180(m); 1175(m); 1165(m); 1120(w); 1075(w); 1035(w); 970(w); 955(w); 925(w); 860(w); 815(w); 640(w); 605(w); 575(w) cm^{-1}.

(E)-1-(2-(2-Bromo-4,5-dimethoxyphenyl)ethyl)-2-ethoxycarbonylmethylenepyrrolidine [53f]

1-(2-(2-Bromo-4,5-dimethoxyphenyl)ethyl)pyrrolidine-2-thione [60c] (0.501 g, 1.46 mmol) was dissolved in dichloromethane (2.0 ml). Ethyl bromo acetate (0.18 ml, 0.263 g, 1.61 mmol, 1.1 eq.) was added. This solution was allowed to stand at for 22½ h. Triphenylphosphine (0.403 g, 1.53 mmol, 1.05 eq.) in dichloromethane (2.0 m.) was added, followed immediately by the addition of triethylamine (0.23 ml, 0.163 g, 1.61 mmol, 1.1 eq.). The solution turned yellow and heated up to such an extent that it l ,led. Crystals of phosphine compounds precipitated out

of the solution. Addition of more dichloromethane resulted in a homogeneous solution. Acid (2.0M HCl, 4x25 ml) extraction was carried out. The aqueous solution was basified (NH_4OH) and washed with dichloromethane (3x20 ml). The combined organic extracts were dried ($MgSO_4$). Evaporation of the organic solution *in vacuo* produced a brown oil (0.521 g, 90%). The crude oil was purified by flash column chromatography on silica gel using benzene/acetone (3 : 1) to produce a yellow oil, Rf (benzene/acetone 3 : 1) 0.38. The yield increased to 97% when dry stirring was used in the salt formation step.

^{1}H n.m.r.

7.04, 6.69 (2H, 2xs, aromatic protons); 4.65 (1H, br s, >C=CH); 4.11 (4H, q, *J* 7.1 Hz, -OCH$_2$CH$_3$); 3.86, 3.85 (6H, 2xs, 2xOMe); 3.42 (2H, t, *J* 7.2 Hz, >NCH$_2$CH$_2$Ar); 3.20 (2H, t, *J* 7.1 Hz, overlaps with the next triplet, >NCH$_2$CH$_2$CH$_2$); 3.15 (2H, t, *J* 7.6 [illegible] -CH); 2.93 (2H, t, *J* 7.2 Hz, >NCH$_2$CH$_2$Ar); 1.86 (2H, quinot, *J* [illegible] 7. -); 1.27 (3H, t, *J* 7.1 Hz, -OCH$_2$CH$_3$).

^{13}C n.m.r.

169.39 (>NC=CH); 164.48 (>C=O); 148.39, 148.25 (aromatic C-4 and C-5); 129.20 (aromatic C-1); 115.51, 113.38 (aromatic C-3 and C-6); 113.55 (aromatic C-2); 77.73 (>NC=CH); 59.20 (-OCH$_2$CH$_3$); 56.07 (2xOMe); 53.15 (>NCH$_2$CH$_2$CH$_2$-); 45.99 (>NCH$_2$CH$_2$Ar); 32.58 (-CH$_2$C=CH); 32.04 (>NCH$_2$CH$_2$Ar); 21.09 (-CH$_2$CH$_2$CH$_2$-); 14.69 (-OCH$_2$CH$_3$).

I.r.

2980(m); 2945(m); 2910(m); 2858(w); 1705(m); 1665(s); 1595(s); 1500(m); 1460(m); 1440(m); 1380(m); 1360(m); 1325(w); 1300(m); 1255(s); 1160(s); 1135(s); 1075(m); 1065(m); 1040(m); 1005(w); 965(w); 860(w) cm^{-1}.

M.s.

122(5); 140(9); 168(57); 169(60); 242(52); 244(51); 245(10); 318(100); 319(19); 352(M$^+$ - OEt, 12); 354(12).

Accurate mass. Found. M$^+$ - OEt, 352.0548.

$C_{18}H_{26}NO_6P$ requires 352.0549.

1.3) (E)-3-Bromo-1-(2-bromo-4,5-dimethoxyphenyl)-2-ethoxycarbonylmethylene pyrrolidine (95)

(E)-1-(2-Bromo-4,5-dimethoxyphenyl)-2-ethoxycarbonylmethylenepyrrolidine (93b) (0.094 g, 0.253 mmol) was partly dissolved in methanol (6 ml). NBS (0.047 g, 0.266 mmol) was added in small portions. The flask was stoppered and stirred at r.t. for 16 h, t.l.c. indicated the presence of starting material (93b). More NBS (0.014 g, 0.076 mmol) was added. The solution was stirred for a further period of 30 min at r.t before it was put to reflux under nitrogen for 2 h and 20 min. It was stirred further at r.t. for another 2 h. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane (3x20 ml) and sodium bicarbonate solution (1 g/20 ml H_2O). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to produce an oil (0.134 g). The oil was purified by column chromatography using hexane/ethyl acetate mixtures. (E)-3-Bromo-1-(2-bromo-4,5-dimethoxyphenyl)-2-ethoxycarbonyl methylenepyrrolidine (95) was isolated (0.090 g, 78%) as an oil which turned solid slowly. Unsuccessful crystallisation of the compound was observed. M.p. 123-133 °C, R_f (hexane/acetone 4 : 1) 0.36.

^{1}H n.m.r.

7.10, 6.75 (2H, 2xs, aromatic protons); 6.07 (1H, d, *J* 5.0 Hz, >CHBr); 4.27 (1H, s, >C=CH); 4.11 (2H, 2xq almost superimposed on each other, separated by 1.45 Hz, *J* 7.1 Hz, -OCH_2CH_3); 3.90, 3.88 (6H, 2xs, 2xOMe); 3.7-3.9 (2H, 2xm, >NCH_2CH_2-); 2.55 (2H, m, -CH_2CHBr); 1.22 (3H, t, *J* 7.2 Hz, -OCH_2CH_3).

^{13}C n.m.r.

167.64 (>NC=CH); 163.01 (>C=O); 148.51 (aromatic C-4 and C-5); 131.12 (aromatic C-1); 115.43, 110.73 (aromatic C-3 and C-6); 112.77 (aromatic C-2); 82.38 (>NC=CH); 59.92 (-OCH_2CH_3); 56.28 (2xOMe); 51.23 (>NCH_2CH_2-); 47.33 (>$CHBr$); 34.49 (>NCH$_2CH_2$-); 14.40 (-OCH_2CH_3).

I.r.

2930(w); 1670(m); 1610(s); 1590(s); 1455(s); 1435(m); 1370(w); 1353(w); 1300(w); 1290(w); 1195(m); 1170(m); 1135(s); 1035(w); 850(w) cm^{-1}.

phenylsulphenyl chloride (0.149 g, 1.03 mmol, 1.28 eq.) in acetonitrile (1 ml) was added. This solution was stirred at -63 °C for ca. 3 h before it was allowed to warm up to r.t. and stirred for 68 h. The organic solution was washed with sodium bicarbonate solution. Effervescence was observed. The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to produce a dark green oil (0.187 g). This oil was purified by flash column chromatography using hexane/ethyl acetate (25 : 1). (*E*)-2-Phenylthiomethylene-1-methylpyrrolidine [106] was isolated as an oil (0.064 g, 38%). When the reaction was carried out in dichloromethane, (*E*)-2-phenylthiomethylene-1-methylpyrrolidine [106] was obtained in a 23% yield. Rf (hexane/ethyl acetate 2 : 1) 0.42.

^1H n.m.r.

7.50-7.10 (5H, m, aromatic hydrogens); 4.38 (1H, br s, >C=CH); 3.30 (2H, t, *J* 6.7 Hz, $>NCH_2-$); 2.80 (3H, s, $>NCH_3$); 2.70 (2H, t, *J* 7.7 Hz, $>NCH_2CH_2\underline{CH_2}-$); 1.84 (2H, q, *J* 7.2 Hz, $-CH_2\underline{CH_2}CH_2-$).

^{13}C n.m.r.

161.74 ($>N\underline{C}=CH$); 142.38 (aromatic C-1); 128.40(aromatic C-3 and C-5); 124.34 (aromatic C-2 and C-6); 123.71 (aromatic C-4); 69.73 ($>NC=\underline{C}H$); 55.20 ($>NCH_2-$); 33.37 ($>NCH_3$); 30.67 ($>NCH_2CH_2\underline{CH_2}-$); 21.06 ($-CH_2\underline{CH_2}CH_2-$).

I.r.

3050(m); 3000-2850(s-m); 1600(s); 1580(s); 1470(s); 1430(s); 1400(s); 1280(s); 1270(m); 1240(s); 1220(m); 1210(m); 1170(w); 1100(m); 1080(m); 1020(m); 1000(w); 970(w); 900(w); 860(w); 830(w); 760(m); 690(s); 670(s) cm^{-1}.

M.s.

Accurate mass. Found : M^+, 205.0940.

$C_{12}H_{15}NS$ requires 205.0925.

4) (*E*)-3-Acetoxy-2-ethoxycarbonylmethylene-1-methylpyrrolidine [100]

(*E*)-3-Bromo-2-ethoxycarbonylmethylene-1-methylpyrrolidine [94] (0.118 g, 0.475 mmol) was dissolved in acetonitrile (2 ml). Silver acetate (0.091 g, 0.543 mmol, 1.14 eq.) was added. The solution was stirred in the dark

(E)-1-(2-[2-Bromo-4,5-dimethoxyphenyl]ethyl)-2-acetylmethylenepyrrolidine [53c]

1-(2-(2-Bromo-4,5-dimethoxyphenyl)ethyl)pyrrolidine-2-thione [60c] (0.339 g, 0.98 mmol) was dissolved in acetone (2.0 ml). Bromoacetone (0.087 ml, 1.03 mmol, 1.05 eq.) was added. Immediate solid formation was observed. After one week more bromoacetone (0.02 ml) was added. After altogether nine days there was a substantial amount of solid. The entire mixture was dissolved in acetonitrile (10.0 ml). Triphenylphosphine (0.259 g, .999 mmol, 1 eq.) in dichloromethane (2.0 ml) was added followed by triethylamine (0.18 ml, 1.28 mmol, 1.31 eq.). The solvent was removed *in vacuo*. The residue was purified by column chromatography using hexane/acetone mixtures to give the desired vinylogous amide [53c] (0.306 g, 84%) along with thiolactam [60c] (60 mg). Vinylogous amide [53c] was recrystallised from chloroform/acetone mixture to yield colourless cubes, m.p. 147-148 °C, R_f (hexane/acetone 2 : 1) 0.14.

Analysis. Found: C, 54.91; H, 5.03; N, 3.81.

$C_{17}H_{22}BrNO_3$ requires C, 55.44; H, 6.02; N, 3.80%.

^1H n.m.r.

6.93, 6.58 (2H, 2xs, aromatic protons); 5.08 (1H, s, >NC=CH); 3.77, 3.76 (6H, 2xs, 2xOMe); 3.37 (2H, t, *J* 7.2 Hz, >NCH$_2$CH$_2$Ar); 3.15 (2H, t, *J* 7.0 Hz, >NCH$_2$CH$_2$CH$_2$-); 3.12 (2H, t, *J* 7.0 Hz, >NCH$_2$CH$_2$CH$_2$-); 2.35 (2H, t, *J* 7.2 Hz, >NCH$_2$CH$_2$Ar); 1.98 (3H, s, CH$_3$C=O); 1.79 (2H, quintet, *J* 7.4 Hz, -CH$_2$CH$_2$CH$_2$-).

^{13}C n.m.r.

193.77 (>C=O); 164.51 (>NC=CH); 148.25 (aromatic C-4 and C-5); 129.48 (aromatic C-1); 115.34, 113.14 (aromatic C-3 and C-6); 113.82 (aromatic C-2); 89.39 (>NC=CH); 55.89 (2xOMe); 52.74 (>NCH$_2$CH$_2$CH$_2$-); 48.96 (>NCH$_2$CH$_2$Ar); 33.08 (-CH$_2$C=CH); 32.03 (>NCH$_2$CH$_2$Ar); 30.44 (CH$_3$C=O); 20.77 (-CH$_2$CH$_2$CH$_2$-).

I.r.

2930(m); 2950(m); 2930(m); 2840(w); 1620(s); 1600(m); 1535(s); 1495(s); 1475(s); 1455(s); 1435(s); 1390(m); 1350(m); 1330(m); 1295(s); 1230(s); 1180(s); 1160(s); 1030(w); 970(w); 935(w); 900(w); 855(m); 845(w); 575(w) cm^{-1}.

EXPERIMENTAL PROCEDURES RELATING TO SECTION 2.3

1) Attempted vinyl bromination reactions of enecarbamates using N-bromo succinimide (NBS)

1.1) (S)-1-(2-(2-Bromo-4,5-dimethoxybenzyl)ethyl)-6-acetylmethylene-3-succinimidopyrrolidine [92]

Vinylogous amide [53a] (79 mg, 0.21 mmol) and NBS (38 mg, 0.21 mmol) were dissolved in DMF (2.0 ml) and stirred at r.t. After 48 h more NBS (11 mg, 0.06 mmol) was added. After another 60 h the reaction was stopped. A brown oil was obtained which was purified by column chromatography on silica gel with hexane/acetone mixture. Vinylogous amide [92] was obtained as a black crystalline solid (63 mg, 64%), R_f (hexane/acetone 2 : 1) 0.32.

^{1}H n.m.r.

7.03, 6.75 (2H, 2xs, aromatic protons); 6.08 (1H, dd, *J* 4.7 Hz, 1.1 Hz, -CH=C<); 5.10 (1H, s, -CH=C<); 3.87 (6H, s with broad base, 2xOMe and >NCH$_2$CH$_2$Ar); 3.55 (2H, t, *J* 7.0 Hz, >NCH$_2$CH$_2$CH-); 2.97 (2H, t, *J* 6.9 Hz, -CH$_2$Ar); 2.78 (4H, s, 2xCH$_2$C=O); 2.28 (2H, m, >NCH$_2$CH$_2$CH-); 2.15 (3H, s, CH$_3$C=O).

^{13}C n.m.r.

193.60 (>C=O); 178.13 (2x>NC=O); 162.82 (>NC=CH); 148.42, 148.34 (aromatic C-4 and C-5); 129.11 (aromatic C-1); 115.43, 113.60 (aromatic C-3 and C-6); 113.79 (aromatic C-2); 88.89 (>C=CH); 55.99 (2xOMe); 50.86 (>NCH$_2$CH$_2$CH-); 48.30 (>NCH$_2$CH$_2$A-); 46.43 (>NCH$_2$CH$_2$Ar); 33.62 (>NCH$_2$CH$_2$CH-); 32.19 (>NCH$_2$CH$_2$Ar); 30.46 (CH$_3$C=O); 28.43 (2xCH$_2$C=O).

i.r.

3000(m); 2960(m); 2930(m); 2850(m); 1770(w); 1750(m); 1715(s); 1600(m); 1550(s); 1500(s); 1460(m); 1435(m); 1380(m); 1350(m); 1340(m); 1305(m); 1290(m); 1250(s); 1155(s); 1040(w); 1030(w); 970(w); 905(w); 875(w); 860(m); 835(m) cm^{-1}.

1.2) (E)-3-Bromo-2-ethoxycarbonylmethylene-1-methylpyrrolidine [94]

(E)-2-Ethoxycarbonylmethylene-1-methylpyrrolidine [93] (0.148 g, 0.88 mmol) and NBS (0.157 g, 0.88 mmol) were dissolved in glacial acetic acid (2.0 ml). The flask was stoppered and the solution was stirred in the dark at r.t. for 40 h. The solution was basified and the aqueous solution extracted with dichloromethane (4x20 ml). The oil obtained was purified by column chromatography on silica gel using ethyl acetate/hexane mixture. A yellow oil was obtained (89 mg, 41%), Rf (hexane/acetone 2 : 1) 0.66.

^{1}H n.m.r.

5.94 (1H, d, *J* 5.6 Hz, >CHBr); 4.42 (1H, s, >C=CH); 4.12 (2H, 2xq almost superimposed on each other, separated by 1.12 Hz, *J* 7.1 Hz, -OCH$_a$H$_b$CH$_3$); 3.74 (1H, dt, *J* 12.3 Hz, 7.9 Hz, >NCH$_a$H$_b$); 3.31 (1H, m made up of dtd, >NCH$_a$H$_b$, possibly W coupled to -CHBr); 2.95 (3H, s, >NCH$_3$); 2.34 (2H, m, >NCH$_2$CH$_a$H$_b$CHBr-); 1.27 (3H, t, *J* 7.1 Hz, -OCH$_2$CH$_3$).

Irradiation at 2.34 ; d at 5.94 collapses to s at 5.94. dt at 3.74 collapses to d, *J* 9.9 Hz. m at 3.31 collapses to dd, *J* 9.8 Hz, 1.7 Hz.

^{13}C n.m.r.

167.62 (>C=CH); 162.95 (>C=O); 78.36 (>C=CH); 58.30 (-OCH$_2$CH$_3$); 51.59 (>NCH$_2$CH$_2$-); 47.52 (>CHBr); 33.74 (>NCH$_2$CH$_2$-); 33.30 (>NCH$_3$); 14.39 (-OCH$_2$CH$_3$).

I.r.

3000(m); 2980(m); 2930(m); 2860(m); 2800(w); 1665(s); 1610(s); 1440(m); 1405(m); 1390(m); 1370(m); 1360(m); 1310(m); 1295(s); 1265(m); 1240(m); 1195(s); 1145(s); 1105(s); 1050(s); 1000(w); 895(w); 855(w); 845(m); 800(m); 730(m); 715-705(m); 655(w) cm^{-1}.

M.s.

44(100, OEt$^+$); 94(7); 122(12); 124(10); 167(13, M$^+$ - Br); 246.9(M$^+$, 9).

Accurate mass. Found: M$^+$, 247.0209.

$C_9H_{14}NO_2Br$ requires 247.0208.

1.4) (E)-1-(2-Bromo-4,5-dimethoxybenzyl)-2-acetylmethylenepyrrolidine [53c] (0.052 g, 0.146 mmol) was dissolved in methanol (3 ml). NBS (0.029 g, 0.160 mmol) was added in small portions while the solution was stirred at 0 °C. The flask was then stoppered and stirred at r.t. for 18 h. The solvent was removed *in vacuo* to produce a brown oil (0.057 g). This was purified by column chromatography to yield 1-(2-bromo-4,5-dimethoxy benzyl)pyrrolidin-2-one [58b] (0.0039 g, 34%).

1.5) N-Methyl-3,3-dibromopyrrolidin-2-one [97]

(E)-2-Acetylmethylene-1-methylpyrrolidine [96] (0.038 g, 0.27 mmol) was dissolved in methanol (2 ml). NBS (0.128 g, 0.72 mmol, 2.7 eq.) was added in the dark. The solution was allowed to reflux for 14½ h. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane (3x10 ml) and potassium bicarbonate solution (10 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to produce a brown solid (0.041 g). This was purified by column chromatography to yield a compound tentatively identified as N-methyl-3,3-dibromopyrrolidin-2-one [97] (6 mg). Doing the reaction in the dark without reflux produced no results. Starting material was recovered.

^{1}H n.m.r.
3.40 (2H, t, *J* 5.9 Hz, $-CH_2CBr_2$); 3.10 (2H, t, *J* 5.9 Hz, $-CH_2CH_2CBr_2$); 2.96 (3H, s, $>NCH_3$).

1.6) (E)-3-Bromo-2-ethoxycarbonylmethylene-1-methylpyrrolidine [94]

(E)-2-Ethoxycarbonylmethylene-1-methylpyrrolidine [93] (0.146 g, 0.86 mmol) was dissolved in methanol (2 ml). The solution was cooled to 0 °C. Bromocyanogen (0.101 g, 0.96 mmol, 1.12 eq.) in methanol (2 ml) was added over a period of 20 min. The solution was stirred at 0 °C for 1 h and at r.t. for 18 h. The solvent was removed *in vacuo*. A brown oil was obtained (0.221 g). This was purified by column chromatography using hexane/ethyl acetate. A mixture of starting material and γ-brominated compound [94] was obtained (0.150 g).

1.7) (E)-3-Bromo-1-(2-(2-bromo-4,5-dimethoxyphenyl)ethyl)-2-ethoxycarbonylmethylenepyrrolidine [98]

(E)-1-(2-(2-Bromo-4,5-dimethoxyphenyl)ethyl)-2-ethoxycarbonylmethylenepyrrolidine [53f] (0.285 g, 0.714 mmol) was dissolved in dichloromethane (2 ml). NBS (0.139 g, 0.785 mmol, 1.1 eq.) was added. The solution warmed up slightly and turned black. The solution was stirred at r.t. for 16½ h. The solution was partitioned between dichloromethane (3x20 ml) and water (20 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to produce an oil (0.347 g). This oil was purified by flash column chromatography using hexane/ethyl acetate (6 : 1). (E)-3-Bromo-1-(2-(2-bromo-4,5-dimethoxyphenyl)ethyl)-2-ethoxycarbonylmethylenepyrrolidine [98] was obtained as an oil (0.076 g, 22%). Rf (hexane/ethyl acetate 2 : 1) 0.57.

^{1}H n.m.r.

7.02, 6.71 (2H, 2xs, aromatic protons); 5.93 (1H, d, *J* 5.0 Hz, >CHBr); 4.63 (1H, s, >C=CH); 4.16 (2H, 2xq almost superimposed on each other, separated by 0.04 Hz, *J* 7.2 Hz, $-OCH_2CH_3$); 3.86, 3.85 (6H, 2xs, 2xOMe); 3.48 (2H, t, *J* 6.9 Hz, $>NCH_2CH_2Ar$); 2.94 (2H, t, *J* 6.9 Hz, $>NCH_2CH_2Ar$); 3.55 (1H, m, $>NCH_aH_b$); 3.15 (1H, m, $>NCH_aH_b$); 2.20 (2H, m, $>NCH_2CH_2CHBr$); 1.29 (3H, t, *J* 7.1 Hz, $-OCH_2CH_3$).

^{13}C n.m.r.

167.83 (>NC=CH); 161.33 (>C=O); 148.33 (aromatic C-4 and C-5); 129.49 (aromatic C-1); 115.43, 113.61 (aromatic C-3 and C-6); 113.74 (aromatic C-2); 79.10 (>NC=CH); 58.62 ($-OCH_2CH_3$); 55.98 (2xOMe); 50.79 ($>NCH_2CH_2CHBr$); 47.95 (>CHBr); 46.03 ($>NCH_2CH_2Ar$); 33.09 ($>NCH_2CH_2CHBr$); 31.99 ($>NCH_2CH_2Ar$); 14.45 ($-OCH_2CH_3$).

I.r.

2920-2980(m); 2830(w); 1730(s); 1600(s); 1495(s); 1455(s); 1435(s); 1375(m); 1245(s); 1150(s); 1135(s); 1030(m); 855(m) cm^{-1}.

M.s.

Accurate mass. No M^+ found : $CH_2=CHAr^+$, 241.9915.

$C_{16}H_{21}BrO_2$ = M^+ - $C_5H_{12}BrNO_2$ requires 241.9943.

1.8) (E)-3-Bromo-1-[2-(3,4-dimethoxyphenyl)ethyl]-2-ethoxycarbonylmethylenepyrrolidine [99]

(E)-1-(2-(3,4-Dimethoxyphenyl)ethyl)-2-ethoxycarbonylmethylenepyrrolidine [61c] (0.221 g, 0.69 mmol) was dissolved in acetic acid (2 ml) and [illegible] (0.139 g, 0.782 mmol, 1.13 eq.) was then added. The flask was [illegible] and the solution stirred at r.t. for 16 2/3 h. T.l.c. indicated that the reaction was completed. The solution was basified (NH_4OH) and the aqueous solution extracted with dichloromethane (3x20 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a dark brown oil (0.271 g). This oil was purified by column chromatography using hexane/ethyl acetate mixtures. (E)-3-Bromo-1-[2-(3,4-dimethoxyphenyl)ethyl]-2-ethoxycarbonylmethylenepyrrolidine [99] was isolated as an oil (0.159 g, 56%). Rf (hexane/ethyl acetate 2 : 1) 0.47.

^{1}H n.m.r.

6.84-6.73 (3H, m, aromatic hydrogens); 5.98 (1H, dd, *J* 3.3 and 1.9 Hz, >CHBr); 4.55 (1H, s, >NC=CH); 4.15 (2H, 2xq almost superimposed on each other, separated by 1.55 Hz [illegible] .2 Hz, $-OCH_2CH_3$); 3.87, 3.85 (6H, 2xs, 2xOMe); 3.45 (3H, m, >NC[illegible]aCHBr- and >NCH_2CH_2Ar); 3.00 (1H, m, >$NCH_aH_bCH_2CH_b$.); 2.82 (2H, t, *J* 6.9 Hz, >NCH_2CH_2Ar); 2.21 (2H, m, >NCH_2CH_2CHBr-); 1.26 (3H, t, *J* 7.1 Hz, $-OCH_2CH_3$).

^{13}C n.m.r.

167.53 (>NC=CH); 161.23 (>C=O); 148.59, 147.38 (aromatic C-3 and C-4); 130.79 (aromatic C-1); 120.41 (aromatic C-6); 111.66, 111.08 (aromatic C-2 and C-5); 78.34 (>NC=CH); 59.38 ($-OCH_2CH_3$); 55.55, 55.50 (2xOMe); 50.69 (>NCH_2CH_2CHBr-); 46.07 (>NCH_2CH_2Ar); 47.65 (>CHBr); 33.60 (>NCH_2CH_2CHBr-); 31.10 (>NCH_2CH_2Ar); 14.26 ($-OCH_2CH_3$).

I.r.

3000-2920(w); 1670(m); 1600(s); 1510(m); 1460(m); 1440(m); 1420(w); 1380(w); 1360(w); 1300(m); 1260(s); 1200(m); 1140(s); 1080(w); 1040(w); 840(w); 810-720(m) cm^{-1}.

M.s.

Accurate mass. Found : M^+-HBr, 317.1627.

$C_{18}H_{24}BrNO_4$-HBr requires 317.1727.

2) (Z)-2-(1-Ethoxycarbonyl-1-chloromethylene)-1-methylpyrrolidine (102)

Zinc (0.209 g, 3.19 mmol, 4.20 eq.) and trimethylsilyl trifluoromethanesulphonate (0.38 ml, 1.97 mmol, 2.58 eq.) were introduced to a round bottomed flask containing acetonitrile (1 ml). The mixture was sonicated for 10 min before (E)-2-ethoxycarbonylmethylene-1-methylpyrrolidine (93) (0.129 g, 0.765 mmol) was added. This mixture was sonicated for *ca.* 9 h before it was filtered and the filtrate added to ferric chloride (0.956 g, 5.90 mmol, 7.7 eq.) in acetonitrile (1 ml). An exothermic reaction followed. The mixture was sonicated for 20 min then it was basified ($KHCO_3$). Precipitation of inorganic solids was observed. The insoluble inorganic solids were filtered off and the filtrate extracted with dichloromethane (3x20 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to produce a brown oil (0.072 g). G.c. analysis shows that 74% by mass of this oil is (Z)-2-(1-ethoxycarbonyl-1-chloromethylene)-1-methylpyrrolidine (102). The rest being mostly starting material (93). This is equivalent to a yield of 37%. Rf (hexane/ethyl acetate 2 : 1) 0.63.

^1H n.m.r.

4.17 (2H, q, J 7.1 Hz, $-OC\underline{H}_2CH_3$); 3.42 (2H, t, J 7.0 Hz, $>NCH_2-$); 3.32 (3H, s, $>NCH_3$); 3.14 (2H, t, J 7.8 Hz, $>NCH_2CH_2C\underline{H}_2-$); 1.92 (2H, quintet, J 7.4 Hz, $-CH_2C\underline{H}_2CH_2-$); 1.30 (3H, t, J 7.1 Hz, $-OCH_2C\underline{H}_3$).

^{13}C n.m.r.

166.17($>N\underline{C}=CCl$); 160.09 ($>C=O$); 85.63 ($>NC=\underline{C}Cl$); 60.18 ($-O\underline{C}H_2CH_3$); 57.79 ($>NCH_2-$); 37.65 ($>NCH_2CH_2\underline{C}H_2-$); 36.26 ($>NCH_3$); 21.30 ($-CH_2\underline{C}H_2CH_2-$); 14.58 ($-OCH_2\underline{C}H_3$).

I.r.

2980(m); 2910-2840(m-w); 1650(m); 1560(s); 1360(w); 1250(s); 1225-1200(s); 1090(m); 1055(s); 820(w) cm^{-1}.

M.s.

Accurate mass. Found : M^+, 203.0717.

$C_9H_{14}NO_2Cl$ requires 203.0713.

3) Reactions of N-methyl enaminones [93] and [96] with phenylsulphenyl chloride (PhSCl)

3.1) (E)- and (Z)-2-(1-Ethoxycarbonyl-1-phenylthiomethylene)-1-methylpyrrolidine

(E)-2-Ethoxycarbonylmethylene-1-methylpyrrolidine [93] (0.059 g, 0.350 mmol) was dissolved in acetonitrile (1 ml). The solution was cooled to -63 °C. Phenylsulphenyl chloride (0.062 mg, 0.429 mmol, 1.23 eq.) in acetonitrile (1 ml) was added. The flask was then wrapped in aluminium foil and kept in the freezer at ca. -10 °C for 22 h. The solution was stirred at r.t. for 2½ h, basified ($NaHCO_3$) and extracted using dichloromethane (3x10 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. A yellow oil was obtained (0.095 g). This was purified by flash column chromatography using hexane/ethyl acetate (10 : 1 and 8 : 1). 2-(1-Ethoxycarbonyl-1-phenylthiomethylene)-1-methylpyrrolidine was isolated as a yellow oil in a mixture of *cis* and *trans* isomers (0.073 g, 75%). Rf (hexane/ethyl acetate 2 : 1) 0.53.

N.m.r. data are difficult to interpret due to the presence of the two isomers.

I.r.

3050(w); 2970(s); 2910(m); 2850(m); 1635(s); 1570(s); 1530(s); 1500(s); 1465(m); 1450(m); 1415(s); 1355(m); 1310(m); 1290(s); 1270(s); 1250-1180(s); 1165(s); 1145(m); 1090(m); 1045(m); 1020(w); 960(w); 855(w); 825(m); 810(m); 800(m); 795-715(m); 680(m); 655(w) cm^{-1}.

M.s.

Accurate mass. Found : M^+, 277.1126.

$C_{16}H_{19}NO_2S$ requires 277.1137.

3.2) (E)-2-Phenylthiomethylene-1-methylpyrrolidine [106]

(E)-2-Acetylmethylene-1-methylpyrrolidine [96] (0.112 g, 0.81 mmol) was dissolved in acetonitrile (2 ml). Under nitrogen in the dark at -63 °C

under nitrogen for 23½ h. The solution was basified ($NaHCO_3$) and extracted using dichloromethane (3x20 ml). The combined organic extracts were dried ($MgSO_4$) and solvent was removed *in vacuo* to produce a brown oil (0.092 g). This oil was purified by column chromatography using hexane/ethyl acetate (10 : 1). (*E*)-3-Acetoxy-2-ethoxycarbonylmethylene-1-methylpyrrolidine [100] was isolated as an oil (0.021 g, 20%). When the reaction was carried out in acetic acid unsatisfactory results were obtained. Rf (hexane/ethyl acetate 2 : 1) 0.25.

^{1}H n.m.r

6.40 (1H, d, *J* 6.7 Hz, >CHOCOCH$_3$); 4.52 (1H, br s, >C=CH); 4.09 (2H, q, *J* 7.1 Hz, -OCH$_2$CH$_3$); 3.60 (1H, td, *J* 9.2 and 6.9 Hz, >NCH$_a$H$_b$-); 3.31 (1H, ddd, *J* 9.7, 8.9, and 2.0 Hz, >NCH$_a$H$_b$-); 2.85 (3H, s, >NCH$_3$); 2.25 (1H, m, >NCH$_2$CH$_a$H$_b$-); 2.06 (3H, s, -OCOCH$_3$); 2.05 (1H, m, >NCH$_2$CH$_a$H$_b$-); 1.23 (3H, t, *J* 7.1 Hz, -OCH$_2$CH$_3$).

Irradiation at 2.00 : d at 6.40 sharpens, *J* 6.1 Hz. Td at 3.60 collapses to t, *J* 8.9 Hz. Ddd at 3.31 collapses to dd, *J* 9.7 and 8.2 Hz. M at 2.25 appears more complicated.

2.25 : d at 6.40 collapses to s. Td at 3.60 collapses to m. Ddd at 3.31 collapses to m. M at 2.05 shifts to 1.97.

^{13}C n.m.r.

170.00 (-OCOCH$_3$); 167.62 (>C=CH); 160.21 (-NCOEt); 80.42 (>C=CH); 73.95 (>CHOCOCH$_3$); 58.66 (-OCH$_2$CH$_3$); 52.77 (>NCH$_2$CH$_2$CH$_2$-); 33.34 (>NCH$_3$); 29.13 (-OCOCH$_3$); 20.86 (-CH$_2$CH$_2$CH$_2$-); 14.53 (-OCH$_2$CH$_3$).

I.r.

2990(m); 2930(m); 2870(m); 1730(s); 1670(s); 1645(s); 1610(s); 1440(m); 1410(m); 1370(m); 1300(s); 1235-1200(s); 1145(s); 1110(s); 1080(m); 1050(s); 865(m); 800-715(m) cm^{-1}.

M.s.

Accurate mass. Found : M^+, 227.1184.

$C_{11}H_{17}NO_4$ requires 227.1158.

5) Attempted γ-allylation reaction of N-methyl vinylogous urethane [93]

(E)-2-Ethoxycarbonylmethylene-1-methylpyrrolidine [93] (0.379 g, 2.24 mmol) was dissolved in dry THF (20 ml). Under nitrogen at 0 °C *n*-butyllithium (1.60 ml, 2.46 mmol, 1.1 eq.) was introduced by syringe. A yellow solution was formed. After 5 min trimethylsilyl chloride (0.32 ml, 2.46 mmol, 1.1 eq.) was added. The solution was stirred at 0 °C for 30 min before the solvent was removed using an oil pump. Dichloromethane was added to rinse the residue. A golden yellow liquid was obtained (0.416 g). Distillation yielded only starting material.

EXPERIMENTAL PROCEDURES RELATING TO SECTION 3.3

(*E*)-1-(3,4-Dimethoxybenzyl)-2-acetylmethylenepyrrolidine (61d)

(*E*)-1-(2-Bromo-4,5-dimethoxybenzyl)-2-acetylmethylenepyrrolidine [5...] (53 mg, 0.15 mmol), palladium acetate (8 mg, 0.04 mmol, 0.23 eq.), triphenylphosphine (0.022 g, 0.08 mmol, 0.46 eq.), triethylamine (0.025 ml, 0.18 mmol, 1.2 eq.) and acetonitrile (2.0 ml) were introduced into a flask (10 ml). A dark brown solution was formed. This was heated under reflux in the open for 18 h. Black metallic palladium deposit was observed on the inside of the flask. The solution was filtered. The solvent was evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel with hexane/acetone (1 : 1). The title compound was obtained as a white oil (3 mg, 8%), Rf (hexane/acetone 2 : 1) 0.42.

^{1}H n.m.r.

6.86-6.71 (3H, m, aromatic hydrogens); 5.25 (1H, br s, >NC=CH); 4.34 (2H, s, benzylic protons); 3.88 3.86 (6H, 2xs, 2xOMe); 3.. (2H, t, *J* 7.2 Hz, overlaps with the next triplet, >NCH2CH2CH2-); 3.31 (2H, t, *J* 7.5 Hz, >CH2C=CH-); 2.07 (2H, s, CH3C=O); 1.96 (2H, quintet, *J* 7.5 Hz, -CH2CH2CH2-).

^{13}C n.m.r.

194.54 (>C=O); 165.63 (>NC=CH); 149.29, 148.57 (aromatic C-3 and C-4); 128.12 (aromatic C-1); 119.55 (aromatic C-6); 111.27, 110.43 (aromatic C-2 and C-5); 89.79 (>NC=CH); 55.94 (2xOMe); 51.99 (>NCH2CH2-); 49.78 (benzylic carbon); 30.47 (>CH2C=CH); 31.06 (-COCH3); 20.93 (...d2CH2CH2-).

I.r.

3000(m); 2960(m); 2940(m); 2870(w); 2840(w); 1710(w); 1665(m); 1630(m); 1595(m); 1535(s); 1510(s); 1480(m); 1460(m); 1440(m); 1420(m); 1395(m); 1350(m); 1300(m); 1260(s); 1175(m); 1160(m); 1140(s); 1075(m); 1035(m); 980(w); 960(w); 940(w); 865(w); 815(m); 660(w); 650(w); 580(w) cm^{-1}.

(E)-1-(3,4-Dimethoxybenzyl)-2-ethoxycarbonylmethylenepyrrolidine [61b]

a) (E)-1-(2-Bromo-4,5-dimethoxybenzyl)-2-ethoxycarbonylethylenepyrrolidine [53d] (0.104 g, 0.27 mmol), palladium acetate (0.066 g, 0.29 mmol, 1.08 eq.), and triphenylphosphine (0.142 g, 0.54 mmol, 2 eq.) were introduced to a 20 ml round bottomed flask. Freshly distilled acetonitrile (3.5 ml) was added to the mixture, followed by triethylamine (0.038 ml, 0.27 mmol, 1 eq.). The solution turned black quickly and it was heated under reflux in a nitrogen atmosphere for 17 h. T.l.c. indicated presence of two spots. The solvent was removed *in vacuo* to produce a black oil (0.274 g). This oil was purified by flash column chromatography using hexane/ethyl acetate (2 : 1). The debrominated vinylogous urethane [61b] was isolated (10 mg, 13%).

b) In an independent synthesis 1-(3,4-dimethoxybenzyl)pyrrolidine-2-thione [59a] (97 mg, 0.39 mmol) was dissolved in acetone (1.0 ml). Ethyl bromoacetate (0.047 ml, 71 mg, 0.42 mmol, 1.1 eq.) was added. After 20 h standing at r.t. white solid particles precipitated out of the solution. After yet another 24 h acetonitrile (2.0 ml) was added to dissolve the solid. Triphenylphosphine (0.107 g, 0.41 mmol, 1.05 eq.) in dichloromethane (1.0 ml) was added, followed by triethylamine (0.06 ml, 44 mg, 0.43 mmol, 1.1 eq.). The solution turned yellow and warmed up. Crystals of phosphine compounds precipitated out of the solution. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography using hexane/acetone mixtures to yield the title compound (0.105 g, 90%) as a yellow oil, Rf (hexane/acetone 2 : 1) 0.54.

^{1}H n.m.r.

6.84-6.70 (3H, m, aromatic protons); 4.72 (1H, br s, >C=CH); 4.29 (2H, s, benzylic protons); 4.09 (2H, q, *J* 7.1 Hz, -OCH$_2$CH$_3$); 3.87, 3.86 (6H, 2xs, 2xOMe); 3.32 (2H, t, *J* 7.1 Hz, >NCH$_2$CH$_2$-); 3.23 (2H, t, *J* 7.8 Hz, -CH$_2$C=CH); 1.96 (2H, quintet, *J* 7.4 Hz, -CH$_2$CH$_2$CH$_2$-); 1.25 (3H, t, *J* 7.1 Hz, -OCH$_2$CH$_3$).

^{13}C n.m.r.

169.59 (>NC=CH); 165.26 (>C=O); 149.17, 148.41 (aromatic C-3 and C-4); 128.48 (aromatic C-1); 119.56, 111.16, 110.49 (aromatic C-2, C-5, and C-6); 78.21 (>NC=CH); 58.29 (-OCH$_2$CH$_3$); 55.88 (2xOMe); 52.14 (>NCH$_2$CH$_2$-);

49.75 (benzylic carbon); 32.66 ($\underline{C}H_2C=CH$); 21.03 (-$CH_2\underline{C}H_2CH_2$-); 14.68 (-$OCH_2\underline{C}H_3$).

I.r.
2960(w); 2930(w); 2840(w); 1725(m); 1660(m); 1580(s); 1560(m); 1505(m); 1455(m); 1435(m); 1415(m); 1295(m); 1255(s); 1135(s); 1090(m); 1065(m); 1040(m); 600(w) cm^{-1}.

M.s.
151($ArCH_2^+$, 100); 152(11); 232(20); 260(7); 305(M^+, 30).
Accurate mass. Found: M^+, 305.1627.
$C_{17}H_{23}NO_4$ requires 305.1627.

Ethyl 6,7-dimethoxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-4-carboxylate [130]

(*E*)-1-(2-Bromo-4,5-dimethoxyphenyl)-2-ethoxycarbonylmethylenepyrrolidine [53b] (52 mg, 0.14 mmol), palladium acetate (6 mg, 2.45×10^{-2} mmol, 0.18 eq.), triphenylphosphine (17 mg, 6.4×10^{-2} mmol, 0.46 eq.), and triethylamine (0.02 ml, 0.14 mmol, 1 eq.) were dissolved in acetonitrile (2.0 ml). The solution was heated under reflux under a nitrogen atmosphere. After 6 h a black solution was formed. More palladium acetate (10 mg) and acetonitrile (2.0 ml) were added. The solution was again heated under reflux under a nitrogen atmosphere for another 12 h. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane and water. The combined organic extracts were dried and the solvent evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel using hexane/ethyl acetate mixtures. The desired indole derivative was isolated as a light brown solid (15 mg, 36%). In another attempt propionitrile was used as solvent. A similar yield (34%) was obtained. When stoichiometric palladium acetate was added the desired compound was obtained in a 63% yield. Recrystallisation from ethyl acetate/hexane yielded the desired compound as a white cotton-like crystalline solid, m.p. 123.5-124 °C, Rf (hexane/acetone 2 : 1) 0.43.

No reaction was observed when tetraethylammonium bromide was present in the reaction procedure. This contradicts the literature findings.

Analysis. Found: C, 65.70; H, 6.53; N, 4.62.
$C_{16}H_{19}NO_4$ requires C, 66.42; H, 6.62; N, 4.84%.

^1H n.m.r.
7.63 (1H, s, H-5); 6.72 (1H, s, H-8); 4.34 (2H, q, *J* 7.1 Hz, $-OCH_2CH_3$); 4.04 (2H, t, *J* 7.2 Hz, $>NCH_2-$); 3.97, 3.92 (6H, 2xs, 2xOMe); 3.23 (2H, t, *J* 7.5 Hz, $-CH_2C=C-$); 2.62 (2H, quintet, *J* 7.3 Hz, $-CH_2CH_2CH_2-$); 1.40 (3H, t, *J* 7.1 Hz, $-OCH_2CH_3$).

^{13}C n.m.r.
165.49 (>C=O); 150.56 (C-3a); 146.15, 145.90 (C-6 and C-7); 126.58 (C-9a); 123.61 (C-4a); 103.03, 93.26 (C-5 and C-8); 96.64 (C-4); 59.01 ($-OCH_2CH_3$); 56.04 (2xOMe); 44.36 ($>NCH_2-$); 26.47 ($>NCH_2CH_2CH_2-$); 26.11 ($>NCH_2CH_2CH_2-$); 14.53 ($-OCH_2CH_3$).

I.r.
3000(m); 2980(m); 2960(m); 2935(m); 2910(w); 2840(w); 1670(s); 1545(s); 1490(s); 1485(s); 1460(s); 1440(s); 1420(s); 1395(w); 1370(w); 1340(s); 1320(s); 1295(s); 1245(s); 1155(s); 1105(s); 1035(m); 980(w); 855(m); 845(m); 840(m); 815(w); 650(w); 600(w) cm^{-1}.

M.s.
40(13); 44(26); 149(8); 244(11); 260(16); 274(30); 289(M^+, 100); 290(13).
Accurate mass. Found: M^+, 289.1315.
$C_{16}H_{19}NO_4$ requires 289.1314.

Ethyl 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-4-carboxylate [131]

(*E*)-1-(2-Bromophenyl)-2-ethoxycarbonylmethylenepyrrolidine [88] (0.203 g, 0.671 mmol), palladium acetate (0.153 g, 0.683 mmol, 1.02 eq.), and triphenylphosphine (0.348 g, 1.33 mmol, 1.98 eq.) were dissolved in acetonitrile (7 ml). Triethylamine (0.09 ml, 0.671 mmol) was then added. A yellow solution was formed which quickly turned black. This black solution was heated under reflux in a nitrogen atmosphere for 2½ h. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane (3x20 ml) and brine (20 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to produce a

black solid. This solid was purified by column chromatography using hexane/ethyl acetate mixtures. Ethyl 2,3-dihydro-1*H*-pyrrolo[1,2-a] indole-4-carboxylate [131] was isolated as a light yellow solid (0.165 g, 100%). A 98% yield was obtained when palladium acetate was used catalytically (0.20 eq.). Compound [131] was recrystallised from ethyl acetate to give colourless cubes, m.p. 95-97 °C, Rf (hexane/ethyl acetate 2 : 1) 0.61.

Analysis. Found : C, 73.42; H, 6.47; N, 6.10.
$C_{14}H_{15}NO_2$ requires C, 73.34; H, 6.59; N, 6.11%.

^{1}H n.m.r.
8.10 (1H, m, H-5); 7.14 (3H, m, H-6, H-7, and H-8); 4.33 (2H, q, *J* 7.1 Hz, -OC<u>H</u>$_2$CH$_3$); 3.88 (2H, t, *J* 7.1 Hz, >NCH$_2$-); 3.11 (2H, t, *J* 7.9 Hz, >NCH$_2$CH$_2$C<u>H</u>$_2$-); 2.49 (2H, quintet, *J* 7.3 Hz, -CH$_2$C<u>H</u>$_2$CH$_2$-); 1.39 (3H, t, *J* 7.1 Hz, -OCH$_2$C<u>H</u>$_3$).

^{13}C n.m.r.
165.30 (-O); 152.69 (C-3a); 132.43, 130.76 (C-4a and C-8a); 121.37, 121.28, 121.08, 109.67 (C-5, C-6, C-7, and C-8); 98.86 (C-4); 59.04 (-O<u>C</u>H$_2$CH$_3$); 44.09 (>NCH$_2$-); 26.22 (-CH$_2$<u>C</u>H$_2$CH$_2$-); 25.85 (>NCH$_2$CH$_2$<u>C</u>H$_2$-); 14.52 (-CH$_2$<u>C</u>H$_3$).

I.r.
3060(w); 3040(w); 2980(s); 2960(s); 2890(m); 1660(s); 1590(s); 1560(s); 1545(s); 1465(s); 1445(s); 1435(s); 1415(s); 1390(m); 1370(s); 1345(m); 1325(m); 1290(s); 1280(s); 1255(m); 1185(m); 1130(s); 1100(s); 1045(m); 1030(m); 1010(w); 840-830(m); 800-710(m) cm^{-1}.

<u>Ethyl 7-methyl-2,3-dihydro-1*H*-pyrrolo[1,2-a]indole-4-carboxylate [132]</u>

(*E*)-1-(2-Bromo-4-methylphenyl)-2-ethoxycarbonylmethylenepyrrolidine [86] (0.280 g, 0.864 mmol), palladium acetate (0.040 g, 0.173 mmol, 0.2 eq.) and triphenylphosphine (0.092 g, 0.346 mmol, 0.4 eq.) were introduced to a 20 ml round bottomed flask. Acetonitrile (9 ml) was added. A yellow solution was formed. Triethylamine (0.12 ml, 0.864 mmol) was added. The solution was heated under reflux in a nitrogen atmosphere. After 9 h of

reflux t.l.c. indicated that there was no apparent reaction (it was later realised that starting material [86] and the product [132] have the same Rf in hexane/ethyl acetate solvent system). After another 26 h of reflux the solvent was removed *in vacuo* and the residue partitioned between dichloromethane (3x20 ml) and water (20 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a black oil (0.384 g). Using hexane/ethyl acetate mixtures failed to separate the indole compound [132] from starting material [86]. Ethyl 7-methyl-2,3-dihydro-1*H*-pyrrolo[1,2-a]indole-4-carboxylate [132] was isolated as a light brown solid by column chromatography using hexane/dichloromethane mixtures (0.163 g, 78%). Compound [132] was recrystallised from ethyl acetate to produce colourless cubes, m.p. 90-91 °C, Rf (hexane/ethyl acetate 2 : 1) 0.66.

Analysis. Found ; C, 74.05; H, 7.01; N, 5.74.
$C_{15}H_{17}NO_2$ requires C, 74.05; H, 7.04; N, 5.76%.

^1H n.m.r.
7.90 (1H, t, *J* 0.75 Hz, H-5); 7.08 (1H, dd, *J* 8.2 and 0.46 Hz, H-7); 6.99 (1H, dd, *J* 8.2 and 0.37 Hz, H-8); 4.35 (2H, q, *J* 7.1 Hz, -OCH_2CH_3); 4.00 (2H, t, *J* 7.2 Hz, >NCH_2-); 3.21 (2H, t, *J* 7.6 Hz, >$NCH_2CH_2CH_2$-); 2.57 (2H, quintet, *J* 7.4 Hz, -$CH_2CH_2CH_2$-); 2.47 (3H, s, $ArCH_3$); 1.40 (3H, t, *J* 7.1 Hz, -OCH_2CH_3).

^{13}C n.m.r.
165.54 (>C=O); 152.72 (C-3a); 131.14, 130.90 (C-6, C-4a, and C-8a); 122.94, 109.34 (C-7 and C-8); 121.09 (C-5); 118.61 (C-4); 83.10 (-OCH_2CH_3); 44.33 (>NCH_2-); 26.43 (-$CH_2CH_2CH_2$-); 26.11 (>$NCH_2CH_2CH_2$-); 21.61 ($ArCH_3$); 14.63 (-OCH_2CH_3).

I.r.
3020, 2975, 2930(s); 1680(s); 1620(m); 1550(s); 1490(m); 1460(s); 1455(s); 1440(s); 1425(s); 1375(s); 1350(m); 1310(s); 1285(s); 1260(s); 1220(s); 1160(s); 1140(s); 1110(s); 1040(s) cm^{-1}.

(*E*)-1-(2-(3,4-Dimethoxyphenyl)ethyl)-2-ethoxycarbonylmethylenepyrrolidine [61c]

a) (*E*)-3-Bromo-1-(2-(3,4-dimethoxyphenyl)ethyl)-2-ethoxycarbonylmethylene pyrrolidine [99] (0.154 g, 0.387 mmol) was dissolved in THF (10 ml). Tetrakis(triphenylphosphine)palladium(0) (0.018 g, 0.016 mmol, 0.04 eq.) was added. The solution was heated under reflux in the dark in nitrogen atmosphere for 22½ h. A yellow solution was formed. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane (3x20 ml) and brine (20 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a mixture of solid and oil (0.147 g). This mixture was purified by column chromatography using hexane/ethyl acetate mixtures. Starting material was recovered (77 mg). The debrominated vinylogous urethane [61c] was also isolated (10 mg).

b) In an independent synthesis 1-(2-(3,4-dimethoxyphenyl)ethyl)pyrrolidine-2-thione (93 mg, 0.35 mmol) was dissolved in acetone (2.0 ml). Ethyl bromoacetate (0.043 ml, 0.39 mmol, 1.1 eq.) was introduced. After 1½ h solid formation in the flask was observed. After six days the solid was dissolved in acetonitrile (5.0 ml). Triphenylphosphine (96 mg, 0.37 mmol, 1.05 eq.) in dichloromethane (1.0 ml) was added, followed by triethylamine (0.054 ml, 0.39 mmol, 1.1 eq.). The solvent was evaporated and the crude solid purified by column chromatography using hexane/acetone mixtures to produce the title compound (89 mg, 79%) as a yellow solid. Recrystallisation from acetone produced colourless cubes, m.p. 108-109.5 °C, Rf (hexane/acetone 2 : 1) 0.53.

Analysis. Found: C, 67.82; H, 7.95; N, 4.43.
$C_{18}H_{25}NO_4$ requires C, 67.69; H, 7.89; N, 4.39%.

^{1}H n.m.r.
6.83-6.69 (3H, m, aromatic protons); 4.61 (1H, br s, >NC=CH); 4.11 (2H, *J* 7.1 Hz, -OC$\underline{H_2}$CH$_3$); 3.88, 3.87 (6H, 2xs, 2x(*Me*); 3.40 (2H, t, *J* 7.3 Hz, >NC$\underline{H_2}$CH$_2$Ar); 3.16 (2H, t, *J* 7.0 Hz, overlaps with the next triplet, >NC$\underline{H_2}$CH$_2$CH$_2$-); 3.13 (2H, t, *J* 7.0 Hz, -C$\underline{H_2}$C=CH); 2.80 (2H, t, *J* 7.3 Hz, >NCH$_2$C$\underline{H_2}$Ar); 1.85 (2H, quintet, *J* 7.4 Hz, -CH$_2$C$\underline{H_2}$CH$_2$-); 1.27 (3H, t, *J* 7.1 Hz, -OCH$_2$C$\underline{H_3}$).

^{13}C n.m.r.

169.43 (>NC=CH); 160.49 (>C=O); 148.91, 147.66 (aromatic C-3 and C-4); 131.34 (aromatic C-1); 120.61, 111.85, 111.28 (aromatic C-2, C-5, and C-6); 77.64 (>NC=CH); 58.24 (-OCH$_2$CH$_3$); 55.85, 56.10 (2xOMe); 53.20 (>NCH$_2$CH$_2$CH$_2$-); 48.09 (>NCH$_2$CH$_2$Ar); 32.63 (CH$_2$C=CH); 31.70 (>NCH$_2$CH$_2$Ar); 21.09 (-CH$_2$CH$_2$CH$_2$-); 14.72 (-OCH$_2$CH$_3$).

I.r.

3020(w); 2940(s); 2920(s); 2850(m); 2820(m); 1660(s); 1630(s); 1510(s); 1465(s); 1430(s); 1440(s); 1420(s); 1395(m); 1378(s); 1355(s); 1295(s); 1140(s); 1025(s); 1045(s); 1040(s); 1009(s); 945(w); 850(m) cm^{-1}.

M.s.

164($ArCH_2CH_2^+$, 100); 165(11); 168(M^+ - $ArCH_2$, 23); 274(M^+ - OEt, 10); 319(M^+, 4).

Accurate mass. Found: M^+, 319.1783.

$C_{18}H_{25}NO_4$ requires 319.1734.

EXPERIMENTAL PROCEDURES RELATING TO SECTION 4.2.2

Reactions with Co(III)-salen

(*E*)-1-(3,4-Dimethoxyphenyl)-2-ethoxycarbonylmethylenepyrrolidine [61a]

(*E*)-1-(2-Bromo-4,5-dimethoxyphenyl)-2-ethoxycarbonylmethylenepyrrolidine [53b] (42 mg, 0.111 mmol) was dissolved in dry THF (5.0 ml). Co(III)-salen (0.140 g, 0.221 mmol, 2 eq.) dissolved in dry THF (5.0 ml) was reduced to green Co(I)-salen by sodium amalgam (2%, 0.524 g, 4 eq.) in the dark and under argon atmosphere. The green Co(I)-salen solution was transferred to the organic solution under argon pressure by a cannula in ca. _ min. The solution was kept for 3 h in the dark. When taken out from the dark room the solution slowly turned from reddish to yellow. The stoppered flask was then exposed to sun light for 1 h. The solvent was evaporated and the residue was purified by flash column chromatography using hexane/ethyl acetate (4 : 1) to yield the title compound [61a] (8 mg, 23%). m.p. 105-128 °C, *Rf* (hexane/acetone 2 : 1) 0.53.

^{1}H n.m.r.

6.90-6.75 (3H, m, aromatic protons); 4.72 (1H, t, *J* 1.3 Hz, >C=CH); 4.06 (2H, q, *J* 7.1 Hz, -OCH$_2$CH$_3$); 3.89, 3.87 (6H, 2xs, 2xOMe); 3.69 (2H, t, *J* 7.0 Hz, >NCH$_2$); 3.30 (2H, dt, *J* 7.8 Hz, 1.3 Hz, -CH$_2$C=C<); 2.09 (2H, quintet, *J* 7.3 Hz, -CH$_2$CH$_2$CH$_2$-); 1.21 (3H, t, *J* 7.1 Hz, -OCH$_2$CH$_3$).

^{13}C n.m.r.

169.59 (>NC=CH); 164.90 (>C=O); 149.63, 147.53 (aromatic C-3 and C-4); 134.36 (aromatic C-1); 117.52, 111.59, 108.99 (aromatic C-2, C-5, and C-6); 80.67 (>NC=CH); 58.39 (-OCH$_2$CH$_3$); 56.06, 56.01 (2xOMe); 55.13 (>NCH$_2$-); 32.46 (>CH$_2$C=CH); 21.60 (-CH$_2$CH$_2$CH$_2$-); 14.63 (-OCH$_2$CH$_3$).

I.r.

2950(m); 2850(w); 1665(m); 1585(s); 1503(m); 1465(m); 1453(m); 1445(m); 1400(w); 1375(w); 1350(w); 1330(w); 1300(m); 1260(m); 1200(m); 1135(s); 1090(m); 1045(m); 860(w); 800(w) cm^{-1}.

M.s.

123(5); 166(5); 187(7); 202 7); 203(7); 204(9); 217(9); 218(32); 219(34); 230(12); 246(M$^+$ - OEt, 35); 247(5); 276(10); 290(12); 291(M$^+$, 100); 292(17).

Accurate mass. Found: M$^+$, 291.1471.

$C_{16}H_{21}NO_4$ requires 291.1471.

(*E*)-1-(3,4-Dimethoxybenzyl)-2-ethoxycarbonylmethylenepyrr idine [61b]

(*E*)-1-(2-Bromo-4,5-dimethoxybenzyl)-2-ethoxycarbonylmethylenepyrrolidine [53d] (45 mg, 0.118 mmol) was dissolved in dry THF (2.0 ml) and the solution stored under a stream of argon in the dark. Reddish Co(III)-salen (0.159 g, 0.238 mmol, 2 eq.) was introduced to a suspension of sodium amalgam (2%, 0.544 g, 4 eq.) in THF (0.5 ml). The corresponding Co(I)-salen reagent was produced in ca. 20 min. It was transferred to the organic solution by a cannula. The solution was kept for 2 h in the dark. A brown solution was obtained. The solvent was evaporated and the residue was purified by flash column chromatography using hexane/acetone (5 : 1) to give the title compound (15 mg, 41%) as an oil. Vinylogous urethane [61b] has already been fully characterised in EXPERIMENTAL SECTION 3.3.

(*E*)-1-(2-(3,4-Dimethoxyphenyl)ethyl)-2-ethoxycarbonylmethylenepyrrolidine [61c]

(*E*)-1-(2-(2-Bromo-4,5-dimethoxyphenyl)ethyl)-2-ethoxycarbonylmethylenepyr rolidine [53f] (48 mg, 0.12 mmol) was dissolved in THF (2.0 ml) and this yellow solution was stored under argon. Co(III)-salen (0.169 g, 0.25 mmol, 2 eq.) was introduced to a mixture of sodium amalgam (2%, 0.589 g, 4 eq.) in THF (2.0 ml). The green Co(I)-salen was produced in ca. 20 min. It was transferred to the organic substrate under argon pressure via a cannula. After 18 h of standing in the dark the solution was filtered and the filtrate was evaporated to dryness. The residue was purified by flash column chromatography using hexane/acetone (4 : 1) to give the title compound (17 mg, 45%). Vinylogous urethane [61c] has already been fully characterised in EXPERIMENTAL SECTION 3.3.

EXPERIMENTAL PROCEDURES RELATING TO SECTION 4.3.2

Reactions with *n*-Bu$_3$SnH

(*E*)-1-(3,4-Dimethoxybenzyl)-2-acetylmethylenepyrrolidine [61d]

(*E*)-1-(2-Bromo-4,5-dimethoxybenzyl)-2-acetylmethylenepyrrolidine [53c] (0.050 g, 0.141 mmol) was dissolved in dry toluene (11 ml). AIBN (5 mg, 0.064 mmol, 0.46 eq.) was added. *n*-Bu$_3$SnH (0.06 ml, 0.223 mmol, 1.58 eq.) was introduced by syringe. The solution was heated under reflux in a nitrogen atmosphere for 24 h. The solvent was removed *in vacuo* and the residue dissolved in dichloromethane (10 ml). Dilute aqueous potassium fluoride solution was added. This biphasic mixture was stirred for ca. 18 h. The organic layer was separated from the aqueous layer. The organic solution was dried ($MgSO_4$) and the solvent removed *in vacuo*. The tin compound was precipitated out of solution by using acetone as the solvent. A mixture of clear oil and yellow oil was obtained (0.152 g). This mixture was purified by column chromatography using hexane/ethyl acetate mixtures as eluent. From PMR a mixture of debrominated vinylogous urethane, (*E*)-1-(3,4-dimethoxybenzyl)-2-acetylmethylenepyrrolidine [61d] (0.011 g, 28%) and debrominated lactam, 1-(3,4-dimethoxybenzyl)pyrrolidin-2-one [57b] (3.9 mg, 12%) was obtained.

(*E*)-1-[2-(3,4-dimethoxyphenyl)ethyl]-2-ethoxycarbonylmethylenepyrrolidine [61c]

(*E*)-3-Bromo-1-[2-(2-bromo-4,5-dimethoxyphenyl)ethyl]-2-ethoxycarbonylmethylenepyrrolidine [98] (0.070 g, 0.147 mmol) and AIBN (*ca.* 5 mg) were introduced into a 25 ml round bottomed flask. The system was evacuated and nitrogen introduced. This process was repeated several times. Toluene (15 ml) was then added and *n*-Bu$_3$SnH (*ca.* 0.11 ml, 0.40 mmol, 2.69 eq.) introduced by syringe. A yellow solution was formed. This solution was heated under reflux in a nitrogen atmosphere for 3½ h after which it was stirred at r.t. for 18 h. The solvent was removed *in vacuo*. The brown residue obtained was purified by flash column chromatography using hexane/ethyl acetate (4 : 1). The doubly debrominated vinylogous urethane, (*E*)-1-[2-(3,4-dimethoxyphenyl)ethyl]-2-ethoxycarbonylmethylene pyrrolidine [61c] was isolated (0.032 g, 68%).

(η^6-Arene)chromium tricarbonyl complex of (E)-1-[2-(3,4-dimethoxyphenyl) ethyl]-2-ethoxycarbonylmethylenepyrrolidine, [158]

(E)-1-[2-(3,4-Dimethoxyphenyl)ethyl]-2-ethoxycarbonylmethylenepyrrolidine [61e] (0.205 g, 0.64 mmol) and chromium hexacarbonyl (0.339 g, 1.54 mmol, 2.4 eq.) were added to a two-necked flask. The system was evacuated and argon was then introduced. This process was repeated several times before freshly distilled dibutyl ether (18 ml) and THF (2 ml) were introduced. The yellow solution was heated under reflux for 17 h. The colour intensified and the solution became cloudier. At the end of the reflux some green/black slime formed on the sides of the flask, indicating that some chromium(III) species had been formed. T.l.c. indicated that the reaction was incomplete. The solution was refluxed for a further period of 3 h. The solvent was decanted into a clean round bottomed flask. The solvent was removed *in vacuo* to produce a yellow oil. This oil was purified by flash column chromatography under nitrogen using hexane/ethyl acetate (2 : 1, 1 : 1) and pure ethyl acetate. The desired (η^6-arene) chromium tricarbonyl complex [158] was isolated as a yellow oil (0.165 g, 58%). Some starting material was also recovered (0.069 g). R_f (ethyl acetate/hexane 2 : 1) 0.41.

^{1}H n.m.r. data are of no diagnostic value because of line broadening due to the presence of chromium(III) species.

^{13}C n.m.r.

233.22 ($Cr(CO)_3$); 169.01 (>NC=CH); 164.12 (>C=O); 133.52, 131.1. (aromatic C-3 and C-4); 103.84 (aromatic C-1); 85.82, 78.85, 78.55 (aromatic C-2, C-5, and C-6); 78.51 (>NC=CH); 58.29 (-OCH$_2$CH$_3$); 57.41, 56.87 (2xOMe); 53.04 (>NCH$_2$CH$_2$CH$_2$-); 47.26 (>NCH$_2$CH$_2$Ar); 32.39 (>NCH$_2$CH$_2$CH$_2$-); 30.50 (>NCH$_2$CH$_2$Ar); 21.06 (-CH$_2$CH$_2$CH$_2$-); 14.56 (-OCH$_2$CH$_3$).

I.r.

2950-2280(w); 1966(s); 1888(s); 1680(m); 1590(s); 1520(w); 1500(w); 1465(w); 1440(w); 1390(w); 1360(w); 1300(w); 1260(m); 1150(s); 1070(w); 1030(w); 630(w) cm^{-1}.

The same procedure was carried out on (S)-1-(2-(5'-bromo-4,5-dimethoxyphenyl)ethyl)-2-ethoxycarbonylmethylenepyrrolidine [33f] but no reaction was observed.

EXPERIMENTAL PROCEDURES RELATING TO SECTION 4.5.2

Reactions with lead tetraacetate

a) (E)-1-[2-(2-Bromo-4,5-dimethoxyphenyl)ethyl]-2-ethoxycarbonylmethylene pyrrolidine [53f] (0.081 g, 0.240 mmol) was dissolved in glacial acetic acid (25 ml). A light red orange solution was formed. The solution was stirred at r.t. for 40 min under nitrogen before lead tetraacetate (0.1664 g, 80%, 0.1331 g, 0.300 mmol, 1.47 eq.) was added. A dark red orange solution resulted after ca. 20 min of stirring. This solution was stirred at r.t. for 5½ h after which it was basified (NH_4OH). The aqueous solution was extracted with dichloromethane (5x20 ml). The combined organic extracts were back-washed with water (20 ml). The organic solution was dried ($MgSO_4$) and evaporated to dryness. The lactam [59e] was obtained in impure form as a dark brown oil (0.057 g, 84%). Inconclusive results were obtained when the reaction was carried out in benzene.

No reaction was observed when (E)-1-[2-(3,4-dimethoxyphenyl)ethyl]-2-ethoxycarbonylmethylenepyrrolidine [61c] was subjected under similar conditions. Starting material was recovered (56%).

b) (E)-1-[2-(2-Bromo-4,5-dimethoxyphenyl)ethyl]-2-acetylmethylenepyrrolidine [63c] (0.108 g, 0.293 mmol) was dissolved in glacial acetic acid (25 ml). A light brown solution was formed. This was stirred at r.t. for 10 min before lead tetraacetate (0.242 g, 80%, 0.1938 g, 0.437 mmol, 1.49 eq.) was added. The solution turned dark yellow very quickly. After stirring at r.t. for 24 h a red solution had formed. The solution was basified (NH_4OH), and diluted with water (20 ml). The aqueous solution was extracted with dichloromethane (5x20 ml). The combined organic solution was back-washed with water (20 ml). The organic solution was dried ($MgSO_4$) and the solvent removed *in vacuo* to produce a brown amorphous solid (0.100 g). This solid was purified by column chromatography on silica gel using hexane/ethyl acetate mixtures. Lactam [59c] was isolated (0.021 g, 21%).

c) (E)-1-(2-Bromo-4,5-dimethoxybenzyl)-2-acetylmethylenepyrrolidine [53c] (0.289 g, 0.810 mmol) was dissolved in glacial acetic acid (15 ml). The reddish solution was stirred at r.t. under nitrogen for 10 min before lead tetraacetate (0.673 g, 80%, 0.599 g, 1.21 mmol, 1.50 eq.) was added. A wine red solution was formed. After stirring at r.t. for 21½ h a dark blue solution had formed. The solution was basified (NH_4OH). The aqueous solution was extracted with dichloromethane (4x20 ml). The combined organic extracts were back-washed with water (20 ml). The organic solution was dried ($MgSO_4$) and the solvent removed *in vacuo* to produce an oil (0.205 g). This oil was purified by column chromatography using hexane/ethyl acetate mixtures. The benzyl lactam [56b] was obtained (0.035 g, 14%).

d) (E)-1-(2-Bromo-4,5-dimethoxyphenyl)-2-ethoxycarbonylmethylenepyrrolidine [53b] (0.102 g, 0.293 mmol) was dissolved in dichloromethane (6 ml). A light brown solution formed quickly. The solution was stirred at ca. -2.5 °C in a nitrogen atmosphere and lead tetraacetate (0.377 g, 0.85 mmol, 2.9 eq.) was added. The solution immediately turned yellow. The solution was stirred at between 2.5-3 °C for 15 h and 40 min. A brown solution was obtained. The organic solution was washed with sat. sodium bicarbonate solution and extracted using dichloromethane (3x20 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. Starting material was recovered (0.111 g).

e) <u>(E)-3-Acetoxy-2-[1-ethoxycarbonyl-1-acetoxymethylene]-1-methylpyrrolidine [163]</u>

(E)-2-Ethoxycarbonylmethylene-1-methylpyrrolidine [93] (0.107 g, 0.635 mmol) was dissolved in carbon tetrachloride (1 ml). Diiodomethane (0.05 ml, 0.657 mmol, 1.05 eq.) was injected. This was stirred under nitrogen in the dark at -23 °C for 10 min before lead tetraacetate (0.556 g, 1.26 mmol, 2.0 eq.) was added. The solution was stirred at -25 °C for 50 min, kept in the deep freezer for 40 min, then left to stir at r.t. for 16½ h. The solution was basified with aqueous sodium bicarbonate solution and extracted with dichloromethane (3x20 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a brown oil

(0.158 g). This was purified by flash column chromatography using hexane/ethyl acetate (6 : 1 and 5 : 1). (E)-3-Acetoxy-2-(1-ethoxycarbonyl-1-acetoxymethylene)-1-methylpyrrolidine [163] was isolated as an oil (0.031 g, 17%). R_F (hexane/ethyl acetate 2 : 1) 0.38.

^1H n.m.r.

6.37 (1H, dd, J 6.2 and 0.9 Hz, >CHOCOCH$_3$); 4.12 (2H, q, J 7.1 Hz, -OCH$_2$CH$_3$); 3.59 (1H, td, J 9.7 and 6.5 Hz, >NCH$_a$H$_b$-); 3.27 (1H, ddd, J 9.8, 8.6, and 1.4 Hz, >NCH$_a$H$_b$-); 3.10 (3H, s, >NCH$_3$); 2.21, 2.06(2x3H, 2xs, 2x-COOCH$_3$); 2.19 (1H, m, >NCH$_2$CH$_a$H$_b$-); 2.00 (1H, m, >NCH$_2$CH$_a$H$_b$-); 1.21 (3H, t, J 7.1 Hz, -OCH$_2$CH$_3$).

I.r.

3020(m); 3010(m); 2980(s); 2940(m); 2850(m); 1765(s); 1710(s); 1660(s); 1600(s); 1440(s); 1400(s); 1365(s); 1320(s); 1280(s); 1240(s); 1200(s); 1170(m); 1120(s); 1023(s); 1000(s); 1010(m); 980(w); 895(w); 860(m) cm^{-1}.

EXPERIMENTAL PROCEDURES RELATING TO SECTION 5.2.2

Arylation under strongly basic condition

a) The reaction apparatus was flame-dried before the reaction. n-Butyllithium (0.4 ml, ca. 0.6 mmol) was dissolved in ether (10.0 ml). Diisopropylamine (0.05 ml, 36 mg, 0.36 mmol) was added. The solution was stirred at 0 °C for 20 min. (E)-1-(2-Bromo-4,5-dimethoxybenzyl)-2-ethoxy carbonylmethylenepyrrolidine [53d] (65 mg, 0.17 mmol) in THF (10.0 ml) was added. A dark brown solution was formed which was stirred for 1½ h at r.t. Saturated ammonium chloride solution (2.0 ml) was added. The solvent was evaporated *in vacuo*. Water (20.0 ml) was added. The aqueous solution was extracted with dichloromethane (6x20.0 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The solid that remained was purified by column chromatography on silica gel with hexane/acetone (4 : 1). Debrominated compound [61b] was isolated (3 mg). Other fractions contained th cyclised product as indicated by the presence of the two new signals (8.14, 7.79 ppm) in the aromatic region.

b) All apparatus was flame-dried, and experiments were conducted under nitrogen. n-Butyllithium (ca. 0.24 ml, 0.39 mmol, 1.15 eq.) was added to a solution of diisopropylamine (0.048 ml, 0.34 mmol, 1 eq.) in THF (10 ml) at -78 °C and the solution stirred for 20 min. (E)-1-(2-Bromo-4,5-dimethoxybenzyl)-2-acetylmethylenepyrrolidine [53c] (0.120 g, 0.34 mmol) in THF (10 ml) was then injected over a period of 25 min. The solution was then stirred at -78 °C for 15 min before it was allowed to warm up to r.t. and stirred for 14½ h. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane (2x20 ml) and water (20 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. Starting material was recovered (0.111 g).

EXPERIMENTAL PROCEDURES RELATING TO SECTION 5.3.2

Photochemically induced intramolecular cyclisations

a) (E)-1-(2-Bromo-4,5-dimethoxyphenyl)-2-ethoxycarbonylmethylenepyrrolidine [53b] (86 mg, 0.23 mmol) was dissolved in dioxane (50.0 ml). Triethylamine (1.0 ml, 0.72 mmol, 3 eq.) was added. The solution was degassed with nitrogen for 20 min. The solution was irradiated with a 450 W medium pressure, Hanovia UV(mercury) lamp equipped with a quartz jacket (filter) for $2^1/_2$ h. A light yellow solution was obtained. The solvent was evaporated *in vacuo*. Dichloromethane was added to the residue and this organic solution washed with brine. The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The solid that remained was purified by flash column chromatography on silica gel with hexane/acetone (3 : 1). Starting material was isolated (28 mg). Other fractions contained mixtures of starting material and possibly debrominated starting material [61a] and the desired indole compound as judged from the analysis of ^1H n.m.r. spectrum of the mixture: δ 7.63 (H-5, cyclised compound), 4.72 (vinyl proton of the debrominated compound).

b) (E)-1-(2-Bromo-4,5-dimethoxybenzyl)-2-ethoxycarbonylmethylenepyrrolidine [53d] (94 mg, 0.25 mmol) and triethylamine (0.5 ml, 0.36 mmol, 1.4 eq.) were dissolved in dioxane (90.0 ml). The solution was degassed for 30 min with argon. It was irradiated for 17 h. A golden brown solution was formed. The solvent was evaporated *in vacuo*. The solid that remained was dissolved in dichloromethane and this organic solution washed with water. The combined organic extracts were dried and the solvent evaporated *in vacuo*. The residue (91 mg) was purified by flash column chromatography on silica gel with hexane/acetone mixtures. Different mixtures of products were obtained. The desired cyclised compound, ethyl 6,7-dimethoxy-1,2,3,9-tetrahydropyrrolo[1,2-*b*]isoquinoline-4-carboxylate [177], was also isolated in a very poor yield (1 mg, 1%) as a white solid. Other fractions also contained the desired compound as indicated by the two new aromatic peaks but they were contaminated. Attempts to reproduce the results failed. Decomposition of starting material was observed. By doing the photolysis in a catalytic acidic medium (CF_3CO_2H) also produced decomposition of the starting material.

^{1}H n.m.r.

3.14 (1H, s, aromatic H-5); 7.79 (1H, s, aromatic H-8); 4.41 (2H, q, *J* 7.1 Hz, -OCH$_2$CH$_3$); 4.25 (2H, t, *J* 7.4 Hz, >NCH$_2$CH$_2$CH$_2$-); 4.02, 4.0^4 (6H, 2xs, 2xOMe); 3.94-3.35 (2H, m, benzylic protons); 3.52 (2H, t, *J* 7.8 Hz, -CH$_2$C=CO$_2$Et); 2.21 (2H, quintet, *J* 7.5 Hz, -CH$_2$CH$_2$CH$_2$-); 1.44 (3H, t, *J* 7.1 Hz, -OCH$_2$CH$_3$).

Irradiation at 2.20 : t at 4.25 collapses to s at 4.25.

t at 3.52 collapses to s at 3.33.

I.r.

3000(w); 2970(w); 2940(w); 2870(w); 1695(m); 1640(s); 1615(m); 1600(m); 1500(m); 1460(m); 1405(m); 1365(m); 1325(m); 1310(m); 1280(m); 1255(m); 1170(m); 1125(s); 1090(s) cm^{-1}.

c) (*E*)-1-[2-(2-Bromo-4,5-dimethoxyphenyl)ethyl]-2-ethoxycarbonylmethylene pyrrolidine [53f] (0.118 g, 0.30 mmol) and triethylamine (1.0 ml, 0.72 mmol, 2.4 eq.) were dissolved in dioxane (30.0 ml). The solution was degassed for 20 min with argon. It was then irradiated for 2 h. More dioxane (50.0 ml) was added and the solution formed was irradiated for a further 16 h. The solution was diluted with water and extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The oil obtained was purified by flash column chromatography on silica gel with hexane/acetone (4 : 1). Mixtures of products were obtained. From the proton n.m.r. analysis it was speculated that possibly the desired cyclised compound, the debrominated compound and starting material were present in the mixtures: δ 6.96, 6.53 (new aromatic peaks), 4.63 (vinyl proton signal of the debrominated compound).

Syn reactions on enaminones

a) (*E*)-1-(2-Bromo-4,5-dimethoxybenzyl)-2-acetylmethylenepyrrolidine [53c] (0.050 g, 0.139 mmol) was dissolved in dioxane (35 ml). Potassium *t*-butoxide (0.141 g, 1.25 mmol, 7.4 eq.) was added. A golden orange solution was formed. This was irradiated under nitrogen for 5 h and 35

min. A light yellow solution resulted. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane (3x20 ml) and water (20 ml). A yellow oil was obtained (30.3 *mg*). This oil was purified by flash column chromatography using hexane/ethyl acetate (6 : 1 and 3 : 1). Lactam [58b] (5.6 mg, 12%) was obtained.

b) Sodium (37 mg, 1.61 mmol, 5.5 eq.) was added to liquid ammonia (20 ml). A crystal of ferric nitrate was added. A black-grey solution was formed. 15 Min was allowed for sodamide to form. (E)-1-(2-Bromo-4,5-dimethoxybenzyl)-2-ethoxycarbonylmethylenepyrrolidine [53d] (0.112 g, 0.291 mmol) was added as a solid. The solution was irradiated for 1 h. It was observed that most of the vinylogous urethane did not dissolve in liquid ammonia. The solution was poured into dilute aqueous ammonium chloride solution (50 *ml*). This aqueous solution was extracted with dichloromet (3x20 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield starting material (0.090 g). When THF was used it was observed that sodamide was sparingly soluble in it. Again no reaction was observed. Doing the reaction in toluene in the presence of potassium *t*-butoxide gave no significant results. Starting material was recovered (10%).

c) (E)-1-(2-(2-Bromo-4,5-dimethoxyphenyl)ethyl)-2-ethoxycarbonylmethylene pyrrolidine [53f] (0.115 g, 0.29 mmol) was dissolved in THF (20 ml). A yellow solution was formed. Potassium *t*-butoxide (0.255 g, 2.27 mmol, 7.8 eq.) was added. The solution quickly turned dark brown. The solution was stirred for 30 min before *n*-Bu_3SnH (0.082 ml, 0.30 mmol, 1.05 eq.) was introduced by syringe. A crystal of AIBN was also added. This was stirred at r.t. for $15^1/_2$ h then it was heated under reflux in nitrogen atmosphere for 25 h. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane (3x20 ml)and brine (20 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield an oil (0.126 g). This oil was purified by column chromatography using hexane/ethyl acetate mixtures. The debrominated vinylogous urethane, (E)-1-(2-(3,4-dimethoxyphenyl)ethyl)-2-ethoxy carbonylmethylenepyrrolidine [61e] was isolated (14 mg).

d) (E)-1-(2-Bromo-4,5-dimethoxybenzyl)-2-ethoxycarbonylmethylenepyrroli dine [53d] (0.203 g, 0.52 mmol) was dissolved in dry toluene (20 ml). A

light yellow solution was formed. Potassium *t*-butoxide (0.123 g, 1.09 mmol, 2.1 eq.) was added. The solution was heated under reflux for 15 min and a dark solution was obtained. The solution was then stirred at r.t. for 30 min before *n*-Bu_3SnH (0.15 ml, 0.55 mmol, 1.05 eq.) was introduced by syringe. This solution was heated under reflux for 17½ h. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane (3x20 ml) and brine (20 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield an oil (0.343 g). Most of the oil was removed by repeated extraction with hexane. After purification by column chromatography (*E*)-1-(3,4-dimethoxy benzyl)-2-(*t*-butoxycarbonylmethylene)pyrrolidine [90] was isolated (7.4 mg). R_f (hexane/ethyl acetate 2 : 1) 0.42.

^1H n.m.r.

6.95-6.71 (3H, m, aromatic hydrogens); 4.66 (1H, br s, >C=CH); 4.27 (2H, s, benzylic protons); 3.87, 3.86 (6H, 2xs, 2xOMe); 3.27 (2H, t, *J* 7.1 Hz, $>NCH_2-$); 3.16 (2H, t, *J* 7.4 Hz, $>NCH_2CH_2CH_2-$); 1.93 (2H, quintet, *J* 7.4 Hz, $-CH_2CH_2CH_2-$); 1.47 (9H, s, $-OC(CH_3)_3$).

^{13}C n.m.r.

169.49 (>NC=CH); 164.50 (>C=O); 149.17, 148.39 (aromatic C-3 and C-4); 123.76 (aromatic C-1); 119.63 (aromatic C-6); 111.19, 110.60 (aromatic C-2 and C-5); 90.17 (>NC=CH); 77.53 ($-OC(CH_3)_3$); 55.93 (2xOMe); 51.95 ($>NCH_2-$); 49.76 (benzylic carbon); 32.55 ($>NCH_2CH_2CH_2-$); 28.73 ($-OC(CH_3)_3$); 21.15 ($-CH_2CH_2CH_2-$).

I.r.

3020(s); 2975(s); 2930(m); 2870(m); 1710(m); 1675(m); 1580(s); 1510(s); 1460(m); 1450(m); 1440(m); 1420(m); 1390(m); 1360(m); 1300(m); 1260(s); 1220(s); 1130(s); 1050(s); 1030(s); 990(m); 910(m) cm^{-1}.

M.s.

Accurate mass. Found : M^+, 333.1948.

$C_{19}H_{27}NO_4$ requires 333.1940.

e) (*E*)-1-(2-(2-Bromo-4,5-dimethoxyphenyl)ethyl)-2-ethoxycarbonylmethylene pyrrolidine [53f] (0.179 g, 0.45 mmol) was dissolved in dry acetonitrile (10 ml). Trimethylsilyl trifluoromethanesulphonate (0.20 ml, 1.03 mmol, 2.30 eq.) was added. The solution was sonicated for 1½ h in a nitrogen atmosphere. It was then irradiated externally (i.e. with the light source right next to the reaction flask) for 1½ h. T.l.c. indicated little starting material left with a base line spot. The solution was irradiated for another hour, without further change. During irradiation the solution changed from light brown to dark brown. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane (3x20 ml), and basic aqueous solution (NaOH). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield starting material as a brown oil (0.162 g).

EXPERIMENTAL PROCEDURES RELATING TO SECTION 5.4.2

Cyclic Voltammetry and electrolysis of enaminones

Approximately 3.0 mM solutions of enaminones were prepared in 0.3 M $NaClO_4$/MeOH. Anode : glassy carbon (ca. 0.1 cm^2). Cathode : platinum rod. Reference electrode : s.c.e. Anodic cyclic voltammegrams of the samples were scanned. The results are summarised in Table 15.

Electrolysis of (*E*)-1-(2-Bromo-4,5-dimethoxybenzyl)-2acetylmethylenepyrrolidine [53c]

(*E*)-1-(2-Bromo-4,5-dimethoxybenzyl)-2-acetylmethylenepyrrolidine [53c] (0.105 g, 0.30 mmol) was dissolved in electrolyte (25 ml, 0.30 M $NaClO_4$/MeOH). A potential of 1.55 V was applied to the solution. After every 75 coulombs of electricity was produced a cyclic voltammegram of the solution was recorded. Current output ranged from 21 mA in the beginning to 16 mA at the end. After 2 h and 40 min the reaction was stopped. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane (3x20 ml) and water (20 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a brown solid (0.104 g). This was purified by column chromatography using hexane/ethyl acetate mixtures as eluent. The only characterisable compound obtained was 1-(2-bromo-4,5-dimethoxybenzyl)pyrrolidine-2-one [55b] (0.015 g, 16%).

Another attempt was done using an applied potential of 1 V. Again inconclusive results were obtained.

EXPERIMENTAL PROCEDURES RELATING TO SECTION 5.5.2

1-[2-(2-Acetonyl-4,5-dimethoxyphenyl)ethyl]pyrrolidin-2-one [197]

The equipment was flame-dried and the experiment conducted under nitrogen atmosphere. Liquid ammonia (30 ml) was transferred to the reaction vessel. Potassium (0.182 g, 4.65 mmol, 6.6 eq.) was added in small pieces after the addition of *t*-butanol (0.40 ml, 4.24 mmol, 6.24 eq.). A blue solution was formed. The solution was stirred for 15 min before acetone (0.30 ml, 4.09 mmol, 6.01 eq.) was added. A clear solution resulted immediately. After another 10 min of stirring 1-(2-(2-bromo-4,5-dimethoxy phenyl)ethyl)pyrrolidin-2-one [55c] (0.222 g, 0.68 mmol) was added. A light yellow solution resulted. More liquid ammonia (20 ml) was added and the solution irradiated for 1½ h. The ammonia was allowed to evaporate at r.t. A rust brown residue was left behind. This residue was partitioned between dichloromethane (3x20 ml) and water (20 ml). The combined extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. A brown oil was obtained. This was purified by column chromatography using hexane/ethyl acetate mixtures. 1-[2-(2-Acetonyl-4,5-dimethoxyphenyl) ethyl]pyrrolidin-2-one [197] was eluted using neat ethyl acetate, and isolated as a yellow oil (0.087 g, 42%). R_f (ethyl acetate) 0.82.

^1H n.m.r.

6.66, 6.55 (2H, 2xs, aromatic hydrogens); 3.78, 3.76 (6H, 2xs, 2xOMe); 3.68 (2H, s, $ArCH_2COCH_3$); 3.27 (4H, 2t overlapping each other, *J* 7.0 and 7.5 Hz, $-CH_2NCH_2-$); 2.63 (2H, t, *J* 7.8 Hz, $>NCH_2CH_2Ar$); 2.28 (2H, t, *J* 8.0 Hz, $>NCH_2CH_2CH_2-$); 2.13 (3H, s, $ArCH_2COCH_3$); 1.90 (2H, quintet, *J* 7.6 Hz, $-CH_2CH_2CH_2-$).

^{13}C n.m.r.

206.81 ($ArCH_2COCH_3$); 175.08 (>N-CO); 148.10, 147.56 (aromatic C-4 and C-5); 129.42 (aromatic C-1); 124.89 (aromatic C-2); 112.76, 113.93 (aromatic C-3 and C-6); 55.90, 55.96 (2xOMe); 47.81, 47.72 ($>NCH_2CH_2CH_2-$, $ArCH_2COCH_3$); 43.48 ($>NCH_2CH_2Ar$); 30.95, 30.49, ($>NCH_2CH_2Ar$, $>NCH_2CH_2CH_2-$); 29.39 ($ArCH_2COCH_3$); 17.96 ($-CH_2CH_2CH_2-$).

I.r.

2960(s); 2940(s); 2920(s); 2860(m); 2840(w); 1700(s); 1630(s); 1650(s); 1645(s); 1580(w); 1480(s); 1430(s); 1415(s); 1385(s); 1320(s); 1290(s); 1255(s); 1240-1170(s); 1120(s); 1090(w); 1010(m) cm^{-1}.

M.s.

Accurate mass. Found : M^+, 305.1620.

$C_{19}H_{23}NO_4$ requires 305.1627.

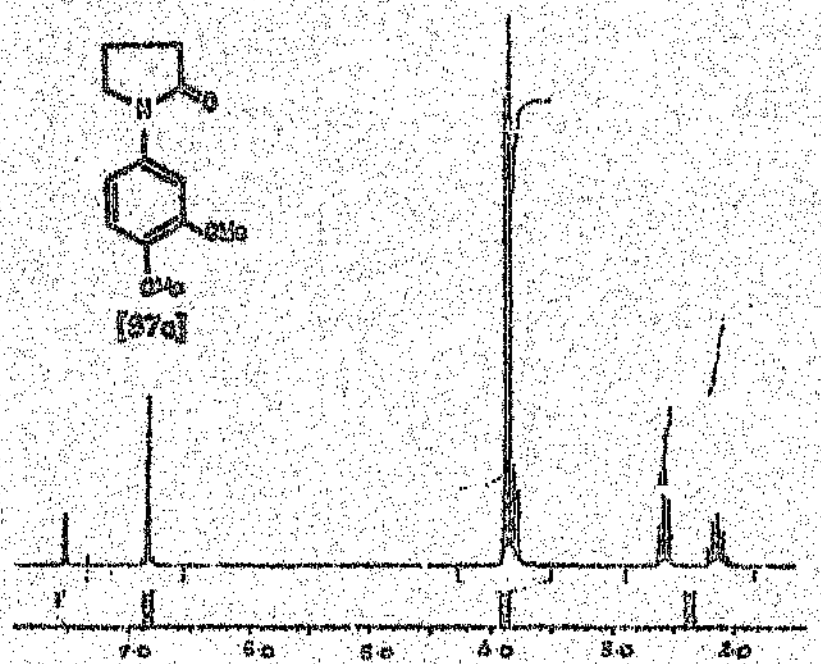
APPENDIX

Proton, carbon-13 and ^{13}C-^{1}H correlation spectra included in this appendix. Chemical shifts for the spectra are reported on the δ scale.

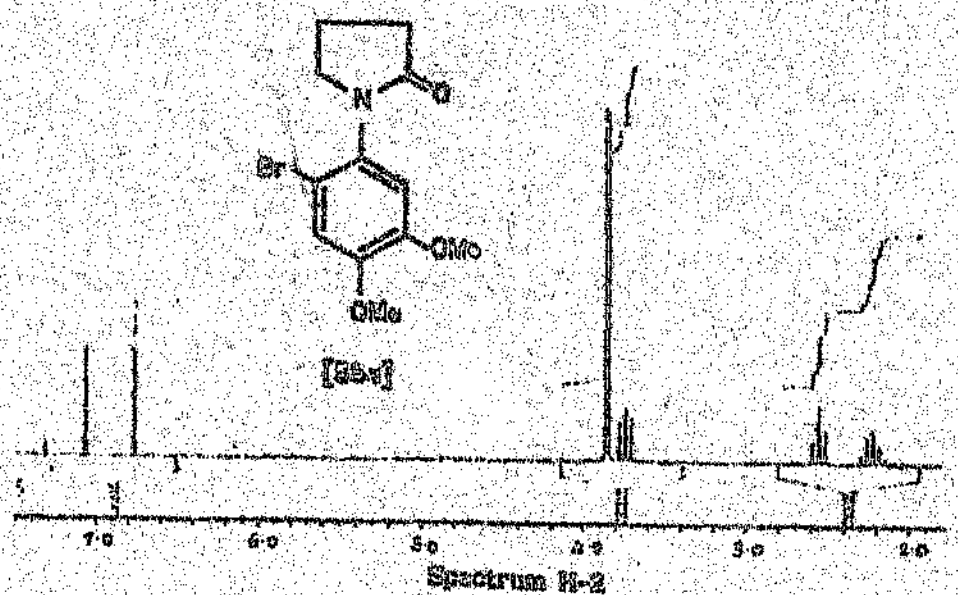
Spectrum	Compound name and number	Page
H-1 C-1	1-(3,4-Dimethoxyphenyl)pyrrolidin-2-one [57a]	211
H-2 C-2	1-(2-Bromo-4,5-dimethoxyphenyl)pyrrolidin-2-one [58a]	211
H-3 C-3	1-(2-Bromo-4,5-dimethoxyphenyl)pyrrolidine-2-thione [60a]	212
H-4 C-4	1-(2-Bromo-4,5-dimethoxyphenyl)-3-methoxycarbonylmethylenepyrrolidine-2-thione [68]	212
H-5 C-5	1-(2-Bromo-4,5-dimethoxyphenyl)-3-ethoxycarbonylmethylenepyrrolidine-2-thione [69]	213
H-6	(*E*)-1-(2-Bromo-4,5-dimethoxyphenyl)-2-acetylmethylenepyrrolidine [53a]	213
H-7, C-7 Corr-1	(*E*)-1-(2-Bromo-4,5-dimethoxyphenyl)-2-ethoxycarbonylmethylenepyrrolidine [53b]	214
H-8 C-8	(*E*)-1-(3,4-Dimethoxyphenyl)-2-ethoxycarbonylmethylenepyrrolidine [61a]	215
H-9 C-9	(*E*)-1-(2-Bromophenyl)-2-ethoxycarbonylmethylenepyrrolidine [85]	216
H-10 C-10	(*E*)-1-(2-Bromo-4-methylphenyl)-2-ethoxycarbonylmethylenepyrrolidine [86]	216
H-11, C-11 Corr-2	Ethyl 6,7-dimethoxy-2,3-dihydro-1*H*-pyrrolo[1,2-a]indole-4-carboxylate [130]	217
H-12, C-12 Corr-3	Ethyl 2,3-dihydro-1*H*-pyrrolo[1,2-a]indole-4-carboxylate [131]	218
H-13, C-13 Corr-4	Ethyl 7-methyl-2,3-dihydro-1*H*-pyrrolo[1,2-a]indole-4-carboxylate [132]	219 220
H-14 C-14	1-(3,4-Dimethoxybenzyl)pyrrolidin-2-one [57b]	221
H-15, C-15 Corr-5	1-(2-Bromo-4,5-dimethoxybenzyl)pyrrolidin-2-one [58b]	222
H-16 C-16	1-(3,4-Dimethoxybenzyl)pyrrolidine-2-thione [59a]	223
H-17 C-17	1-(2-Bromo-4,5-dimethoxybenzyl)pyrrolidine-2-thione [60b]	223

Spectrum	Compound name and number	Page
H-18, C-18 Corr-6	(*E*)-1-(2-Bromo-4,5-dimethoxybenzyl)-2-ethoxycarbonylmethylenepyrrolidine [53d]	224
H-19 C-19	(*E*)-1-(2-Brom›-4,5-dimethoxybenzyl)-2-acetylmethylenepyrrolidine [53c]	225
H-20 C-20	(*E*)-1-(3,4-Dimethoxybenzyl)-2-ethoxycarbonylmethylenepyrrolidine [61b]	225
H-21 C-21	(*E*)-1-(3,4-Dimethoxybenzyl)-2-acetylmethylenepyrrolidine [61d]	226
H-22 C-22	(*E*)-1-(3,4-Dimethoxybenzyl)-2-(t-butoxycarbonyl)methylenepyrrolidine [90]	226
H-23	Ethyl 6,7-dimethoxy-1,2,3,9-tetrahydropyrrolo[1,2-a]isoquinoline-4-carboxylate [177]	227
H-24 C-24	2,3,6,7-Tetramethoxy-9,10-dihydroanthracene [66]	227
H-25, C-25 Corr-7	1(2-(2-Bromo-4,5-dimethoxyphenyl)ethyl)pyrrolidin-2-one [58c]	228
H-26 C-26	1-(2-(3,4-Dimethoxyphenyl)ethyl)pyrrolidine-2-thione [59b]	229
H-27, C-27 Corr-8	1-(2-(2-Bromo-4,5-dimethoxyphenyl)ethyl)pyrrolidine-2-thione [60c]	230
H-28 C-28	(*E*)-1-(2-(2-Bromo-4,5-dimethoxyphenyl)ethyl)-2-ethoxycarbonylmethylenepyrrolidine [53f]	231
H-29 C-29	(*E*)-1-(2-(2-Bromo-4,5-dimethoxyphenyl)ethyl)-2-acetylmethylenepyrrolidine [53e]	231
H-30, C-30 Corr-9	(*E*)-1-(2-(3,4-Di ethoxyphenyl)ethyl)-2-ethoxycarbonylmethylenepyrrolidine [61c]	232
C-31	(η^6-Arene)chromium tricarbonyl complex of (*E*)-1-(2-(3,4-dimethoxyphenyl)ethyl)-2-ethoxycarbonylmethylenepyrrolidine, [158]	233
H-32 C-32	1-[2-(2-Acetonyl-4,5-dimethoxyphenyl)ethyl)pyrrolidin-2-one [157]	233
H-33 C-33	(*E*)-3-Bromo-2-ethoxycarbonylmethylene-1-methylpyrrolidine [94]	234
H-34	(*E*)-3-Acetoxy-2-(1-ethoxycarbonyl-1-acetoxymethylene)-1-methylpyrrolidine [163]	234
H-35	N-Methyl-3,3-dibromopyrrolidin-2-one [97]	234
H-36, C-36 Corr-10	(*E*)-3-Acetoxy-2-ethoxycarbonylmethylene-1-methylpyrrolidine [100]	235
H-37 C-37	(*Z*)-2-(1-Ethoxycarbonyl-1-chloromethylene)-1-methylpyrrolidine [102]	236
H-38 C-38	(*E*)-2-Phenylthiomethylene-1-methylpyrrolidine [136]	236
H-39 C-39	(*E*)-3-Bromo-1-(2-bromo-4,5-dimethoxyphenyl)-2-ethoxycarbonylmethylenepyrrolidine[95]	237
H-40 C-40	(*E*)-1-(2-(2-Bromo-4,5-dimethoxyphenyl)ethyl)-2-acetylmethylene-3-succinimidopyrrolidine [92]	237

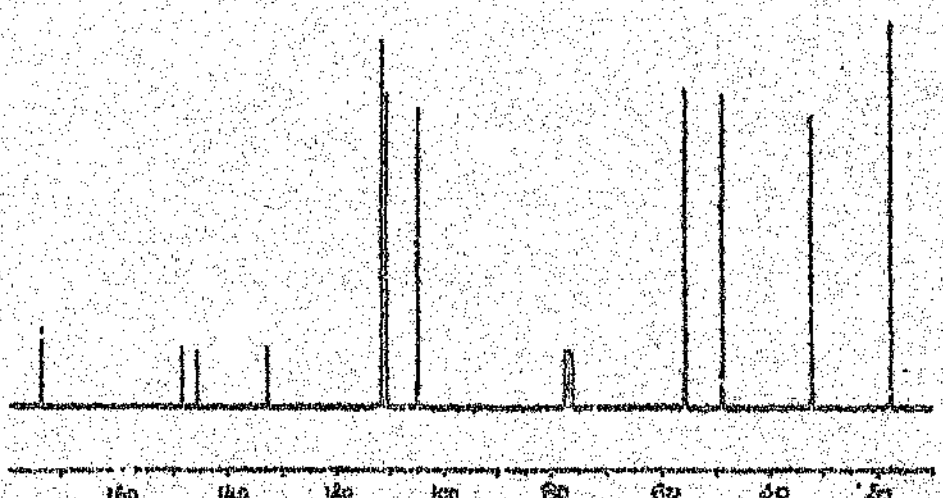
Spectrum	Compound name and numbe..	Page
H-41 C-41	(E)-3-Bromo-1-(2-(3-bromo-4,5-dimethoxyphenyl)ethyl)-2-ethoxycarbonylmethylenepyrrolidine [98]	238
H-42, C-42 Corr-11	(E)-3-Bromo-1-(2-(3,4-dimethoxyphenyl)ethyl)-2-ethoxycarbonylmethylenepyrrolidine [9	2.



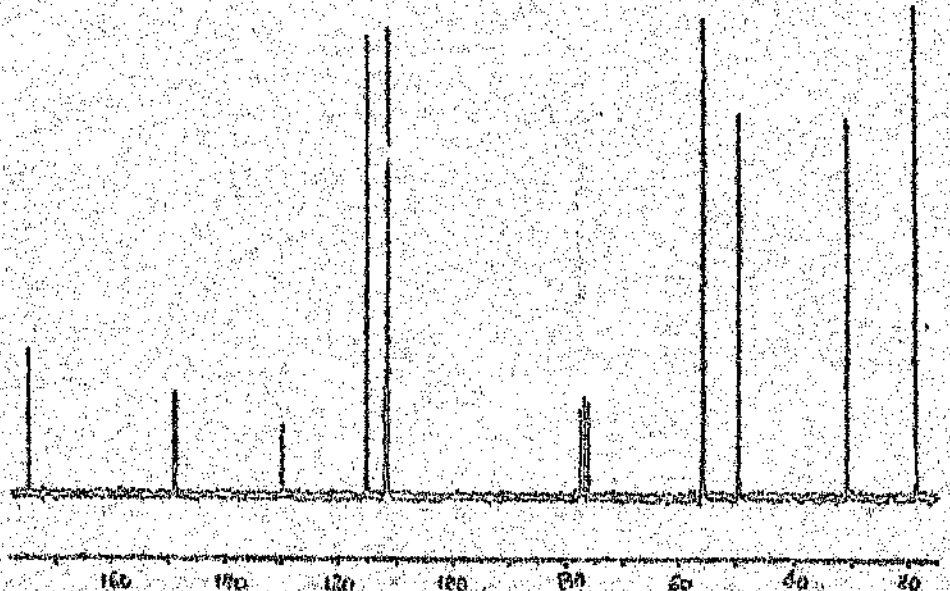
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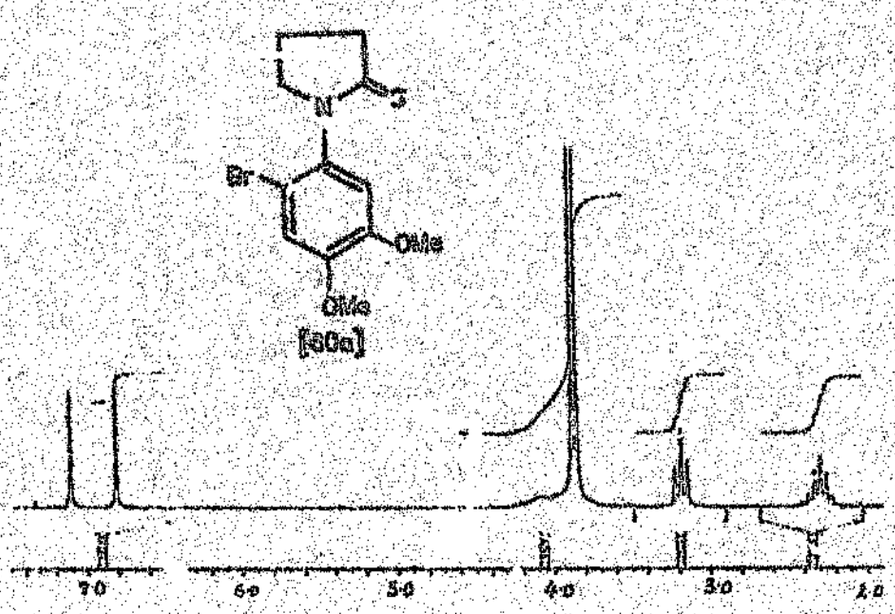
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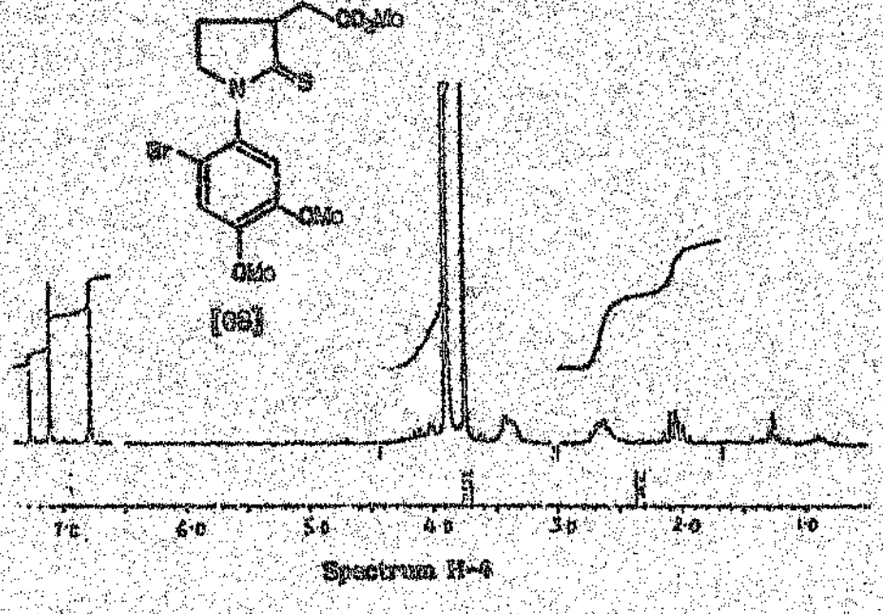
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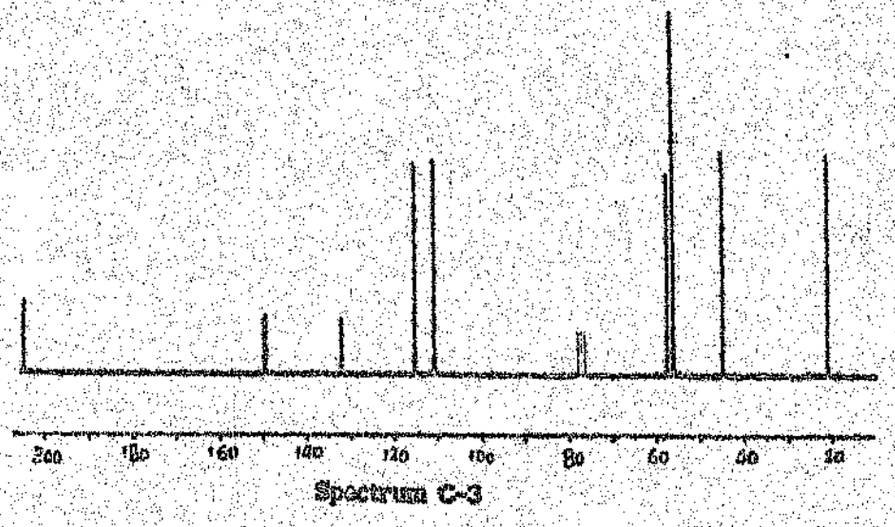
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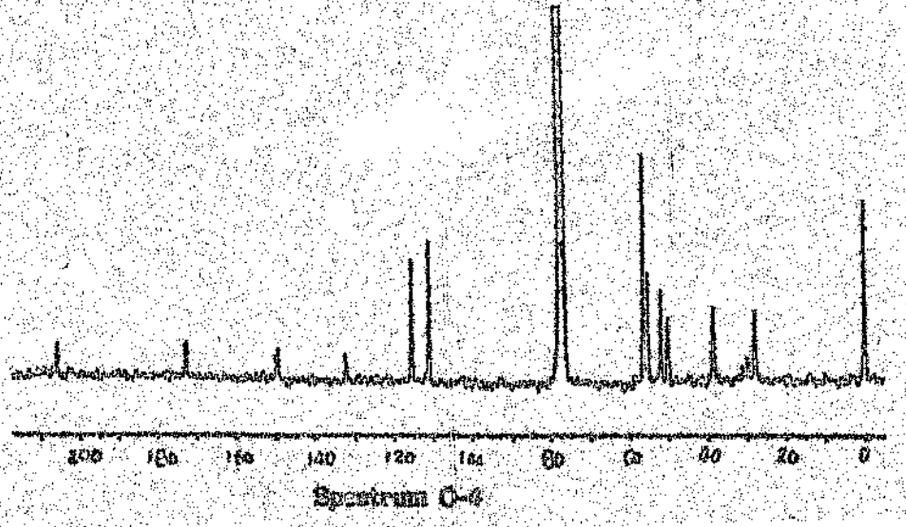
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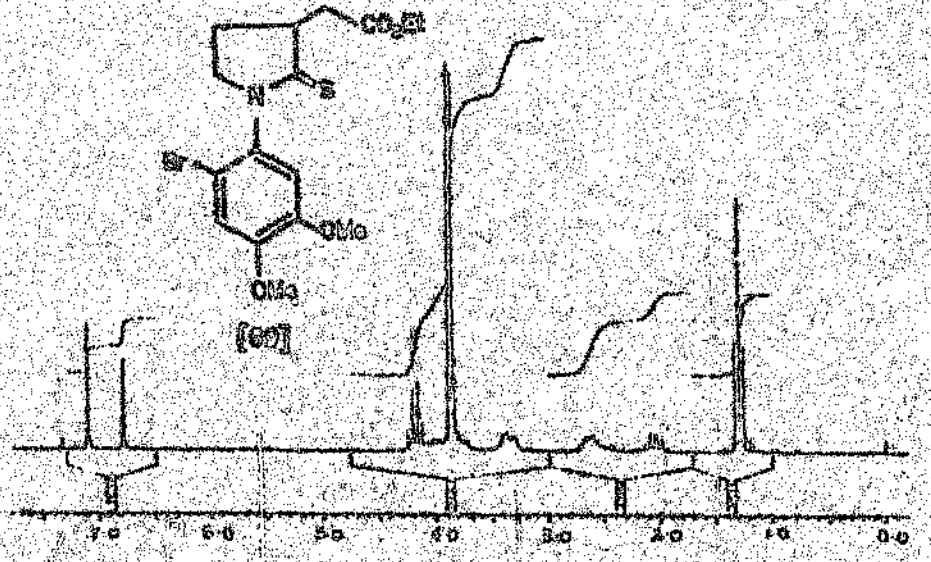
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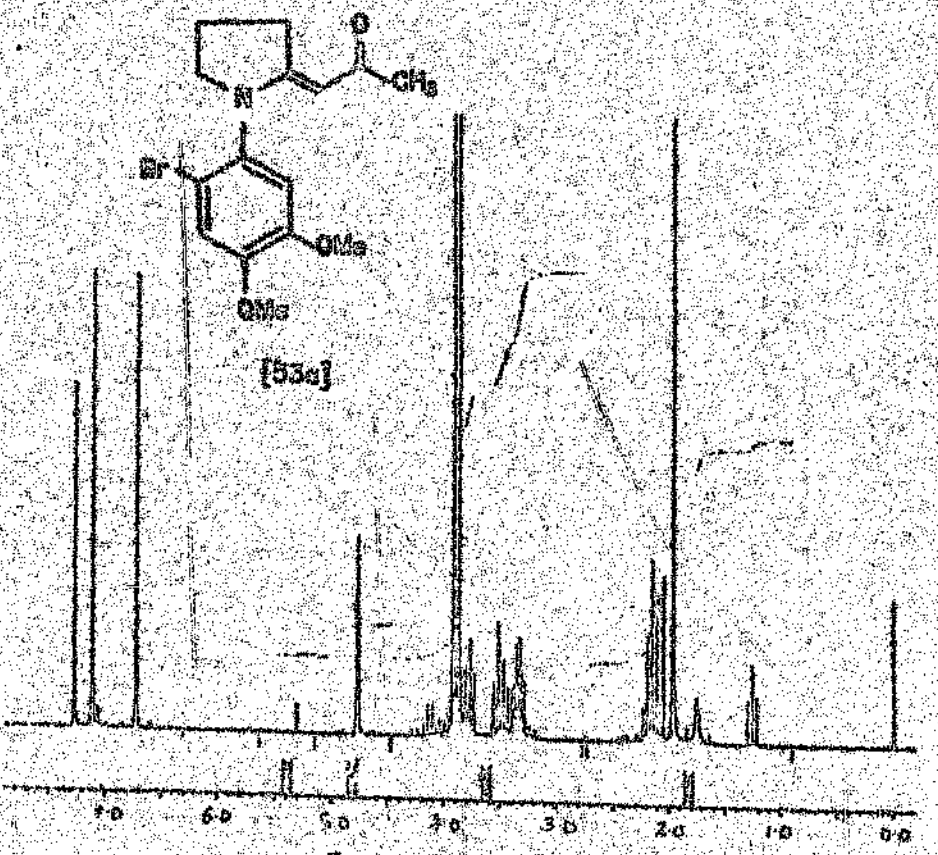
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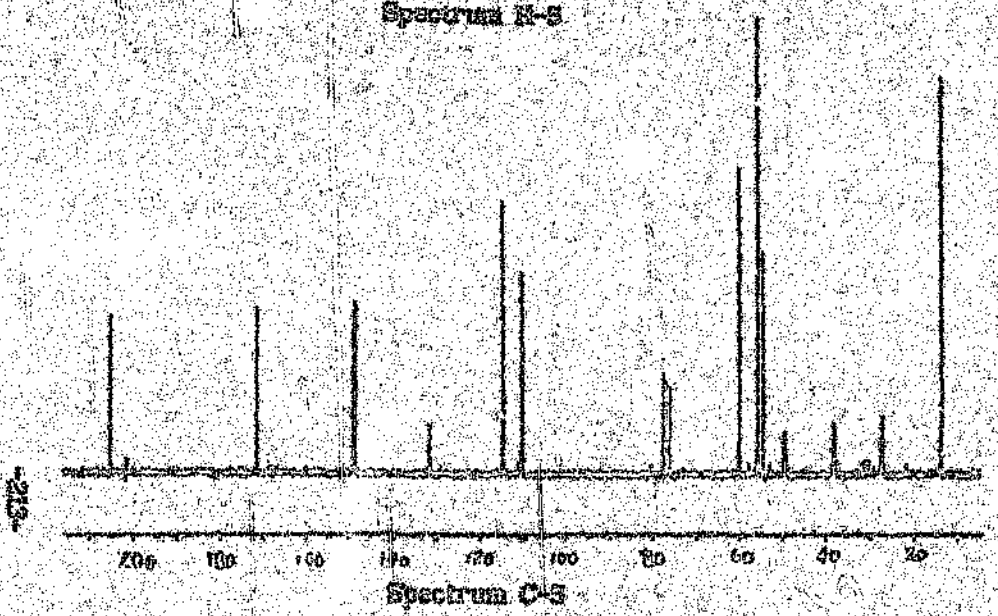
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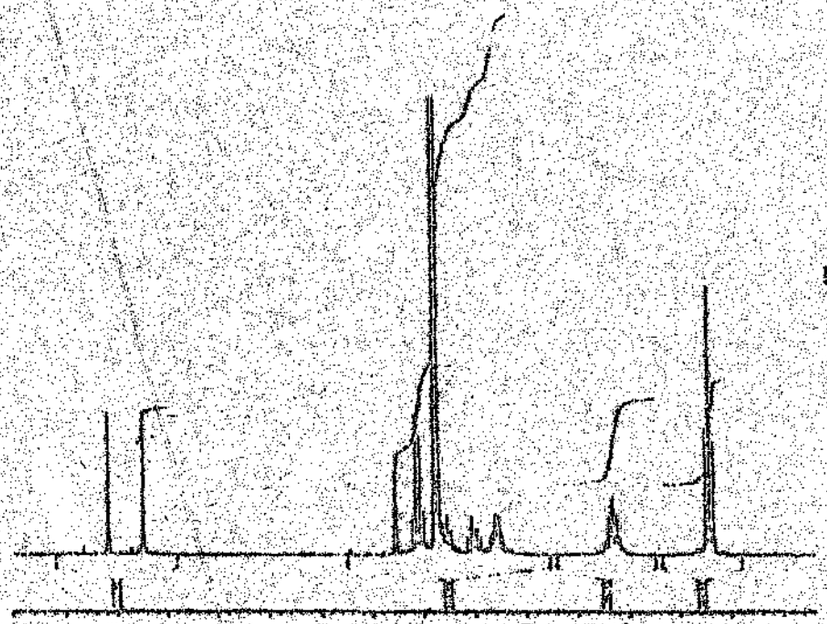
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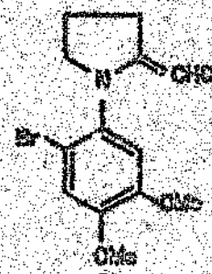
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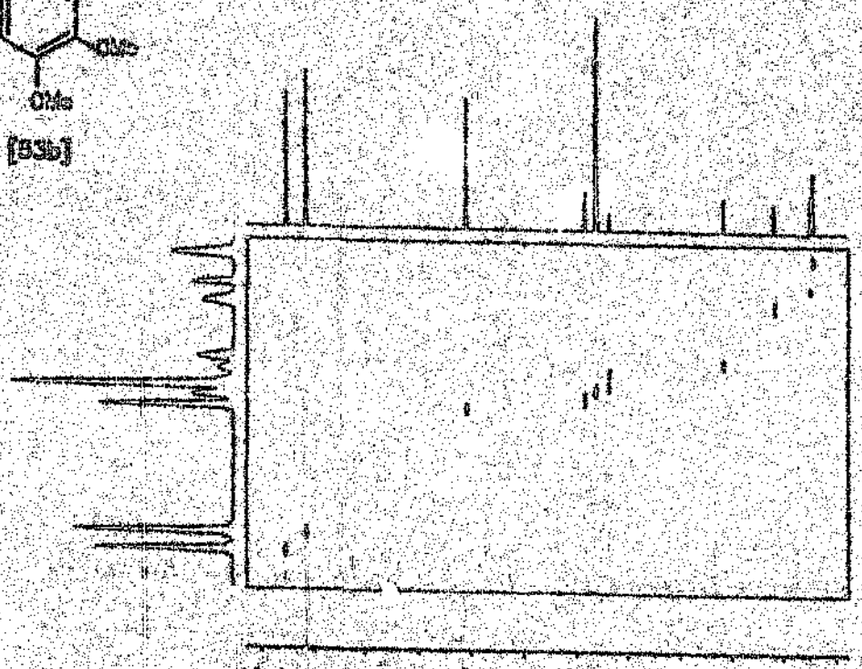
Spectrum C-3



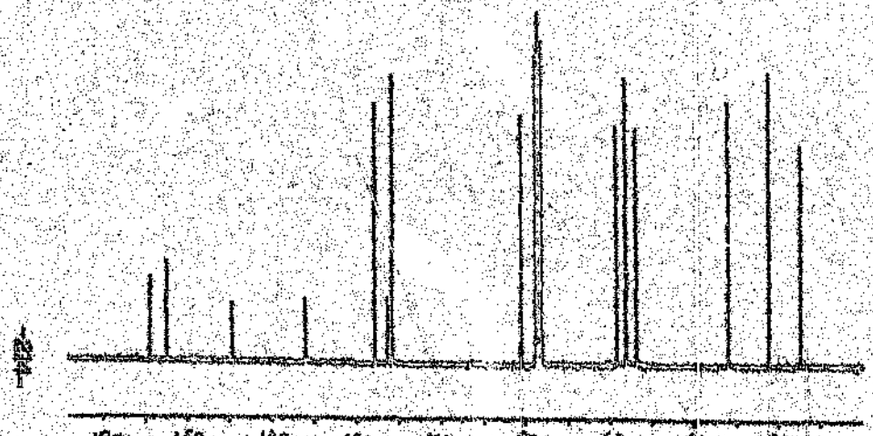
Spectrum H-7



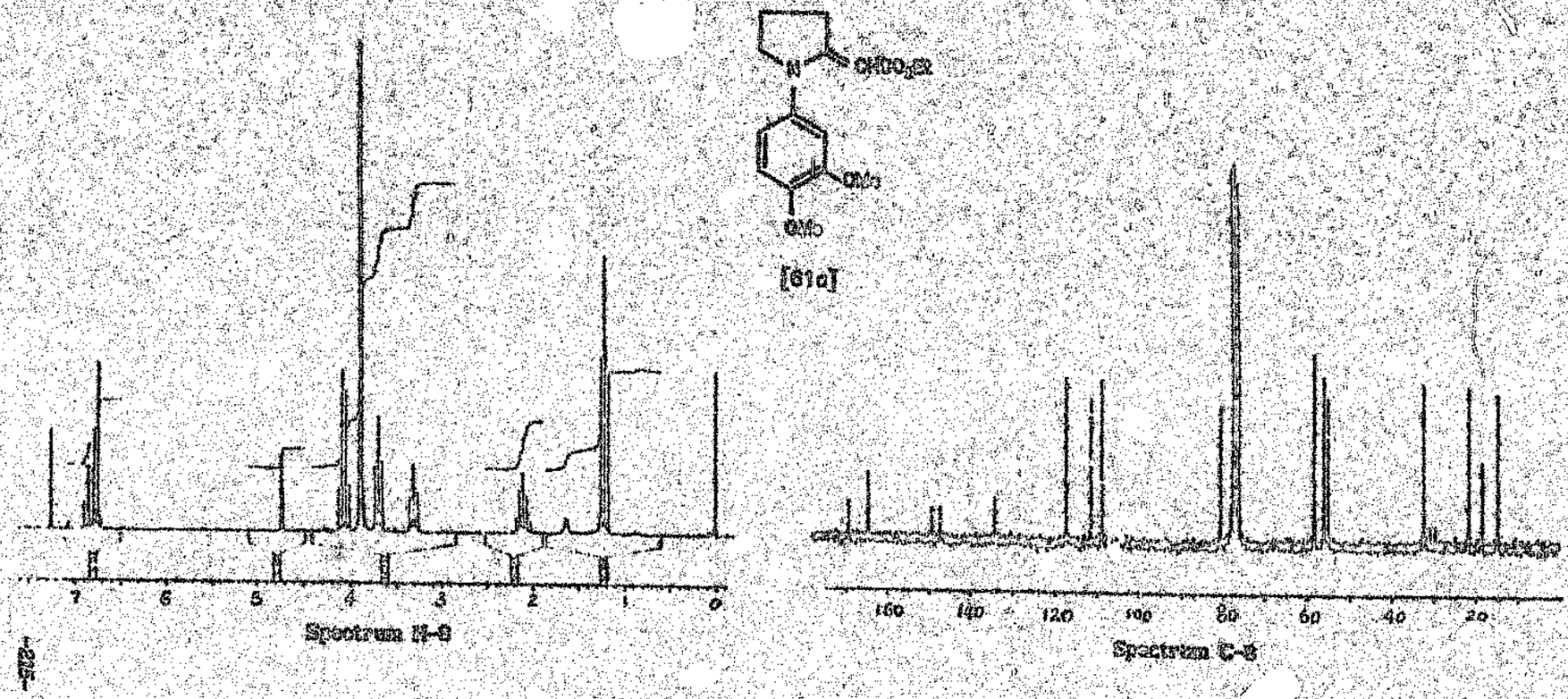
[53b]



Corr-1



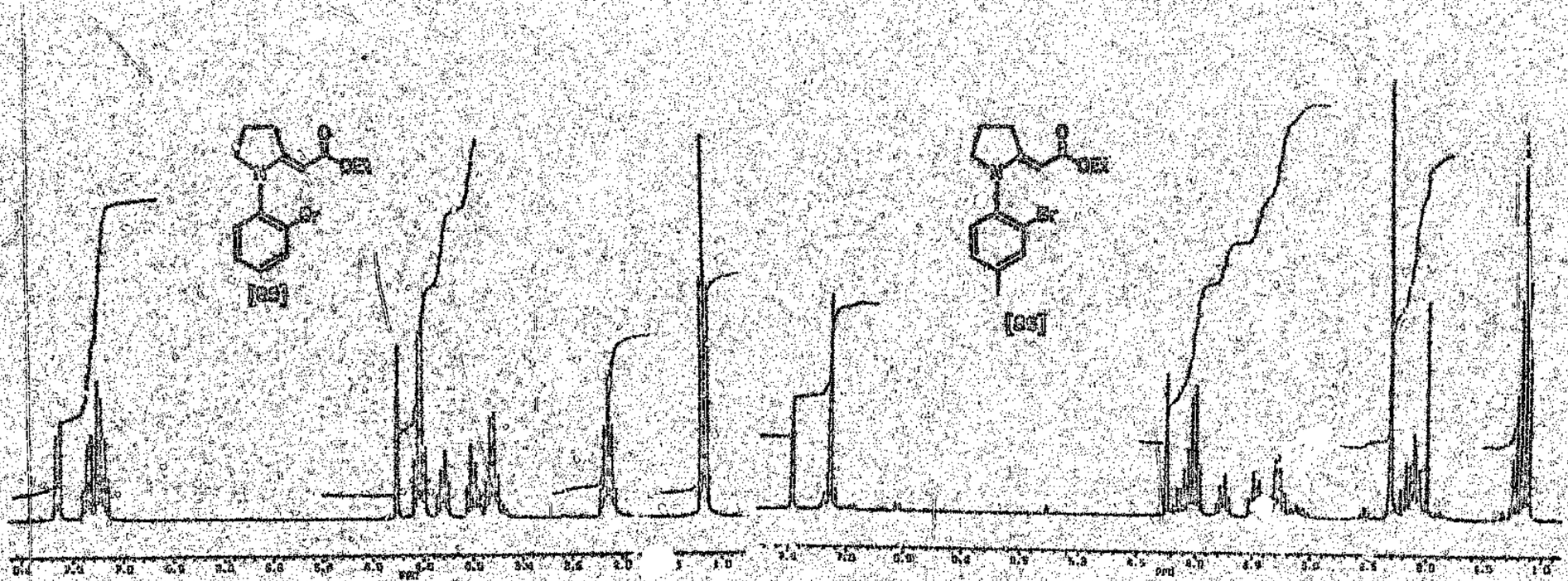
Spectrum C-7



Spectrum H-8

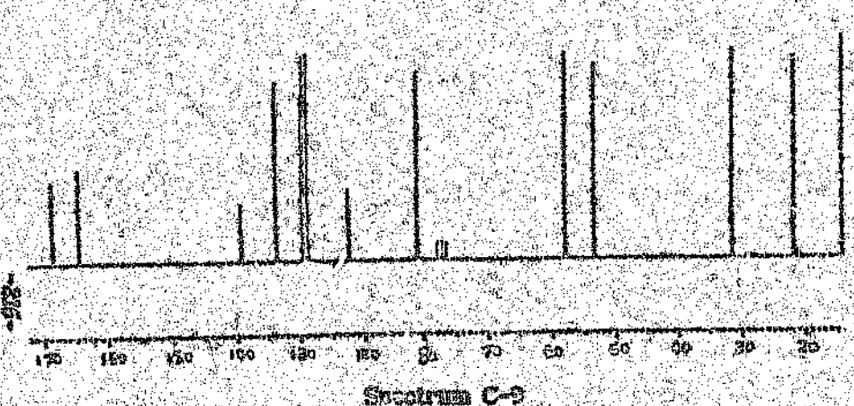
Spectrum C-8

[61a]

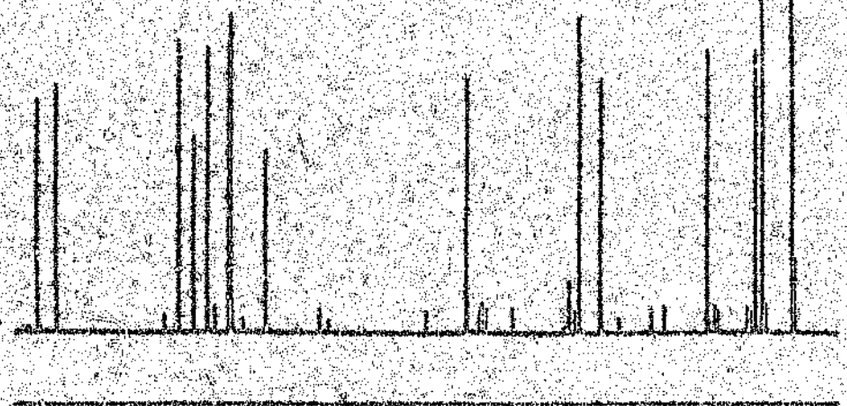


Spectrum H-9

Spectrum H-10



Spectrum C-9



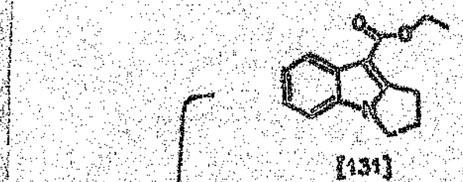
Spectrum C-10

[130]

Spectrum H-1

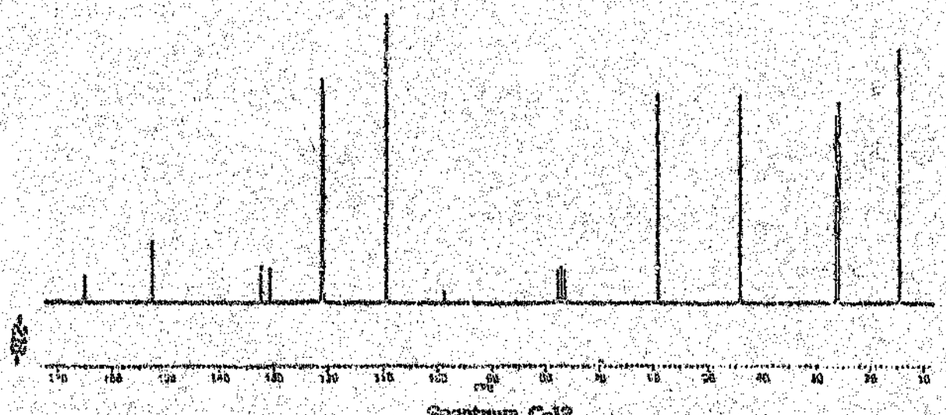
Spectrum C-11

Spectrum C-12

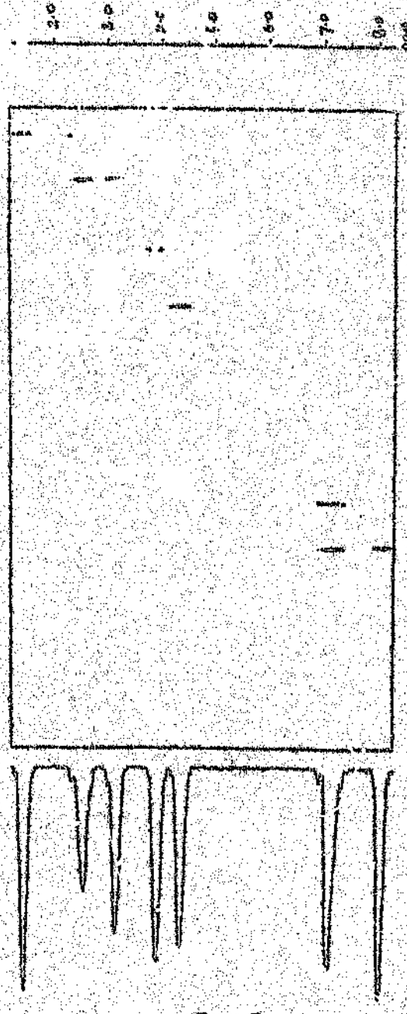


[131]

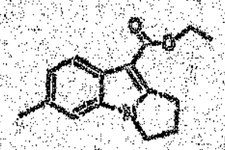
Spectrum H-12



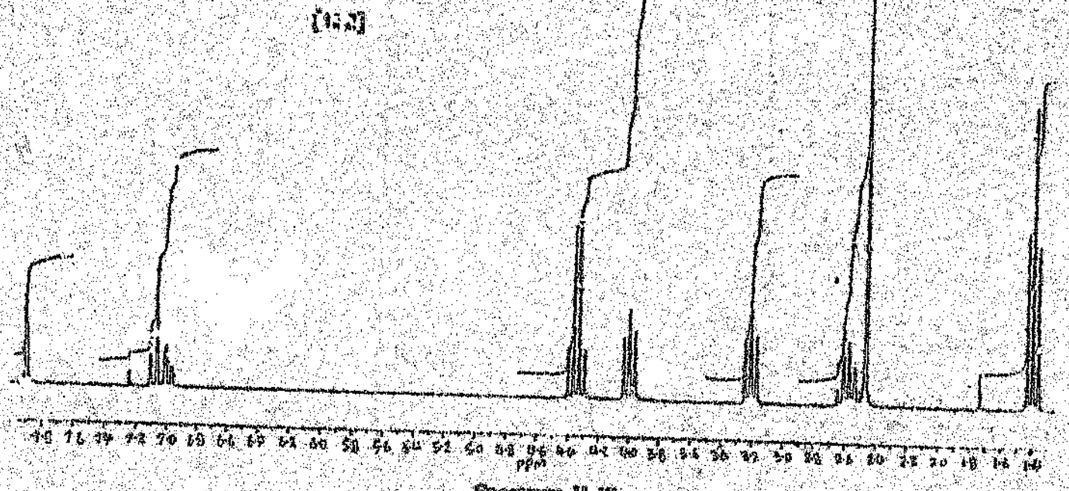
Spectrum C-12



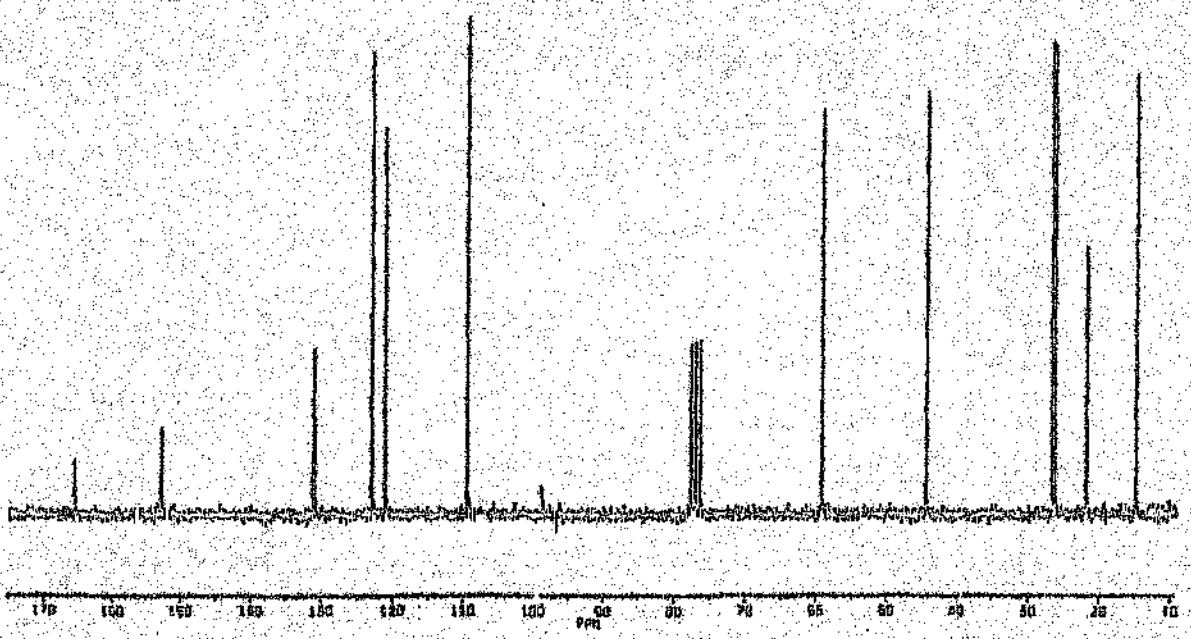
Corr-3



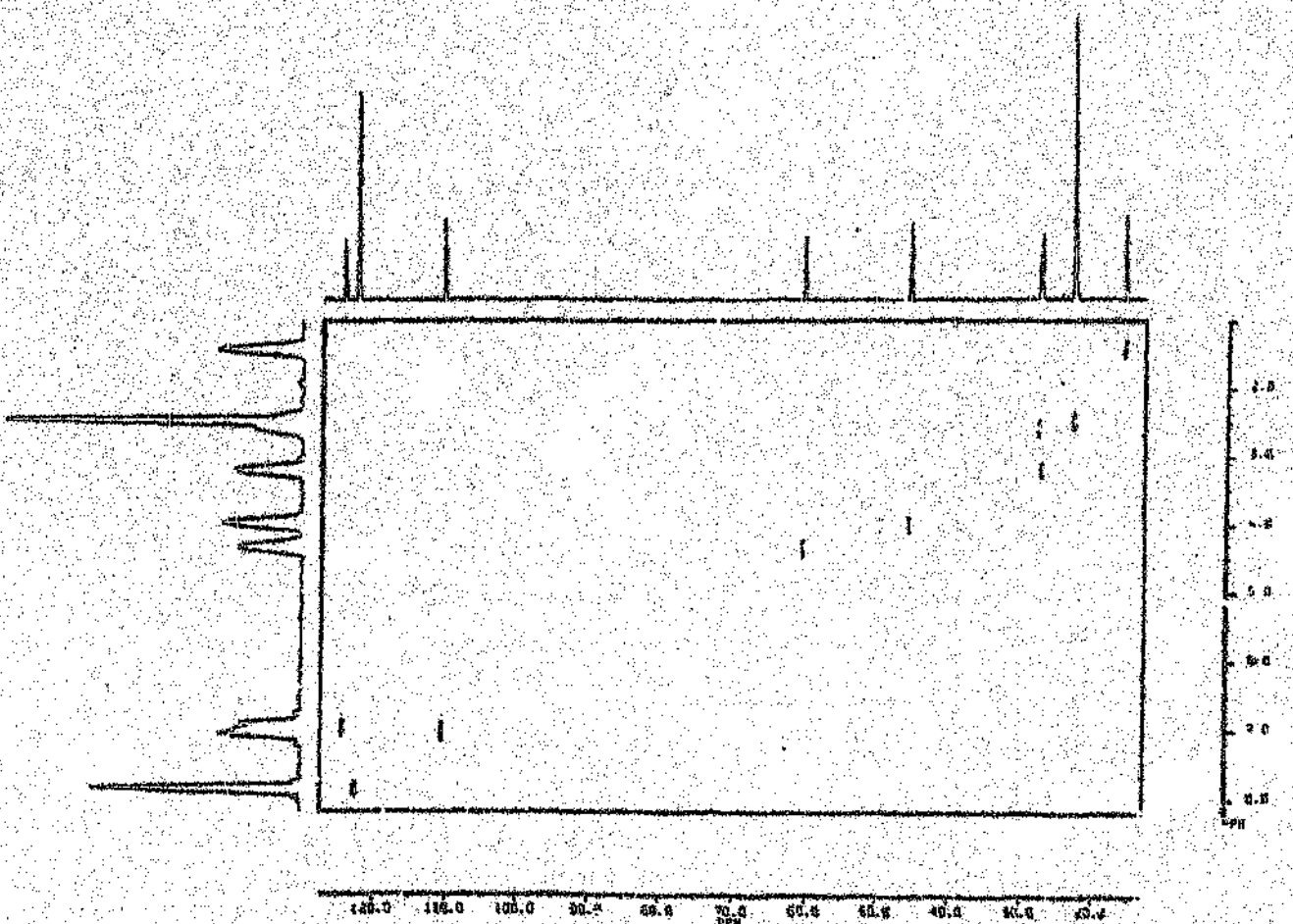
[13.2]



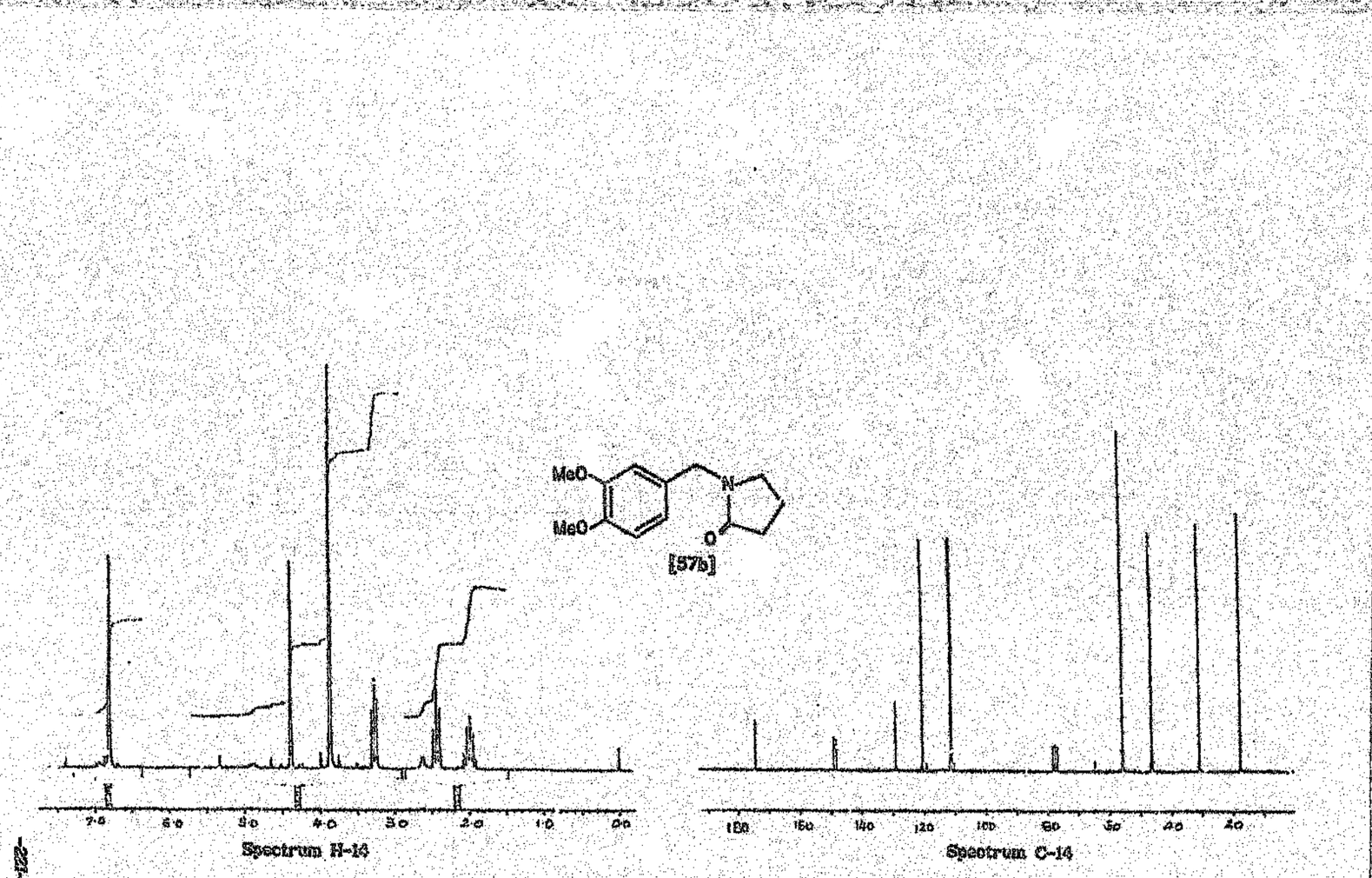
Spectrum 13-13



Spectrum C-13

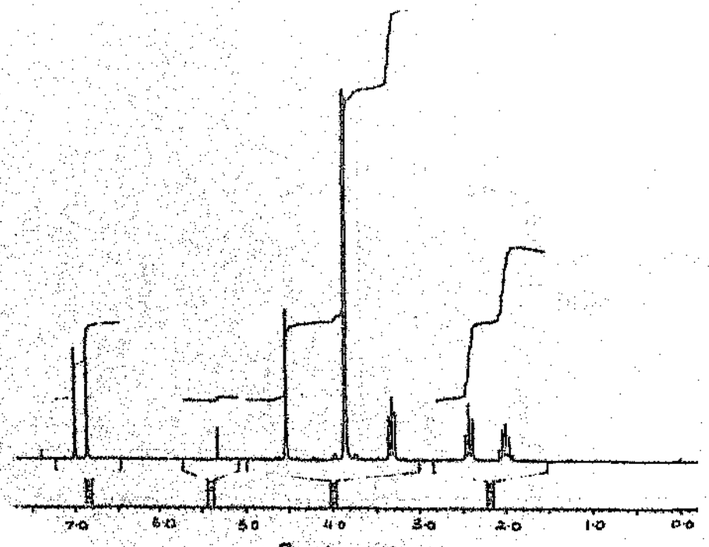


Corr-4

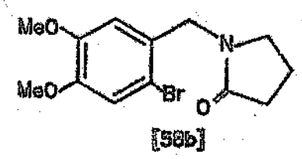


Spectrum H-14

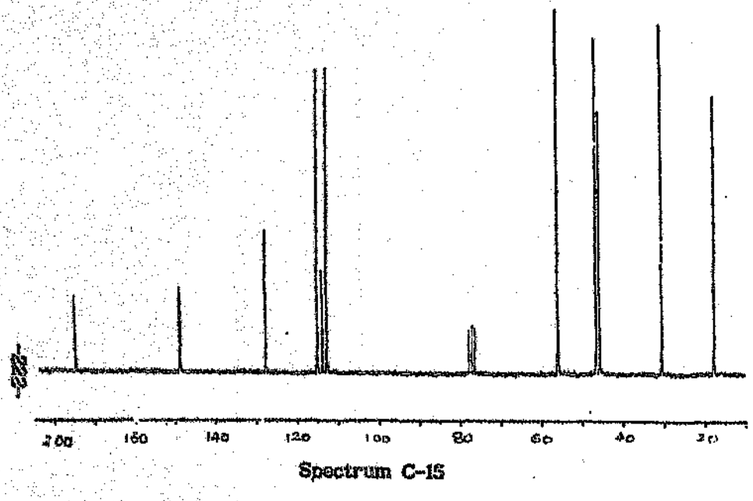
Spectrum C-14



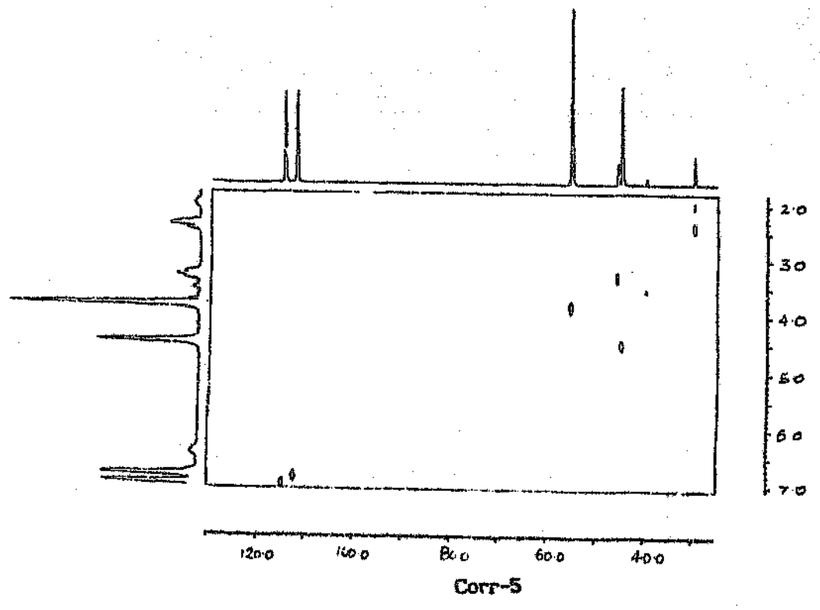
Spectrum H-15



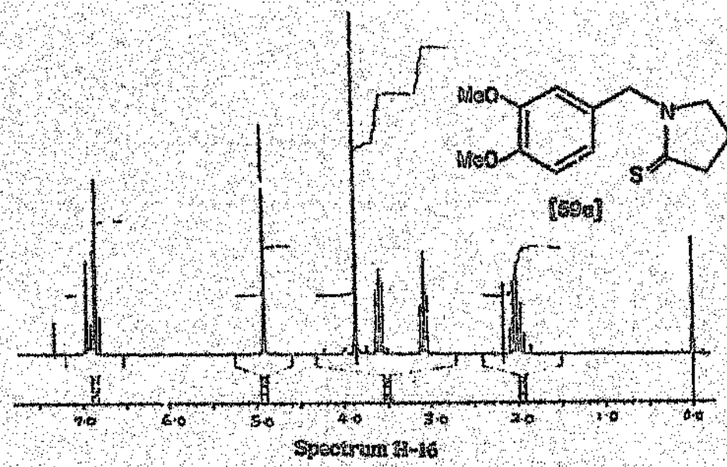
[58b]



Spectrum C-15

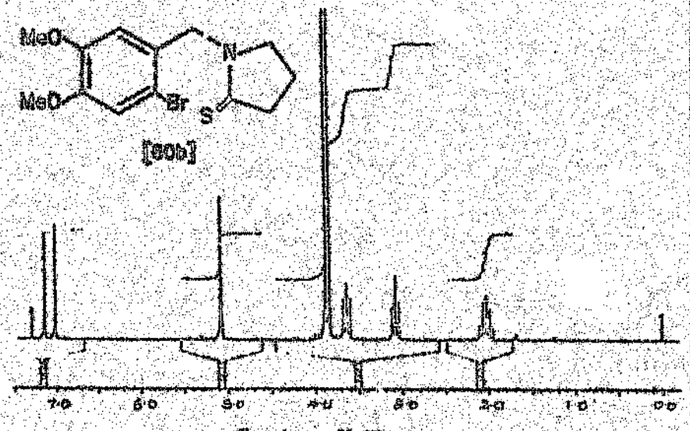


Corr-5



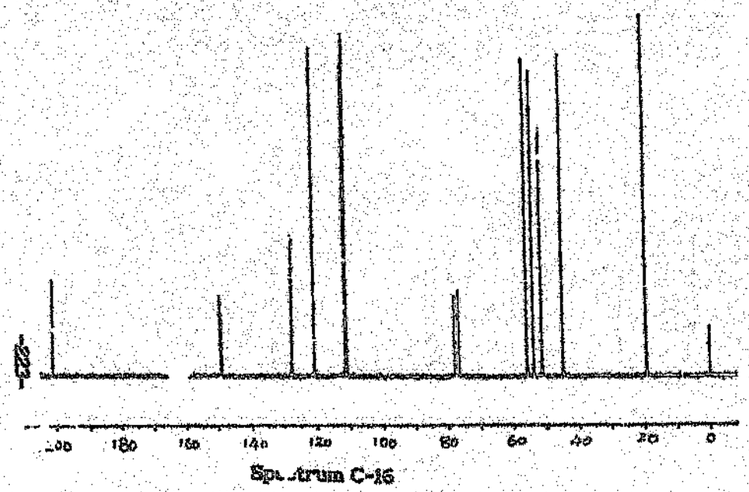
[59a]

Spectrum H-16

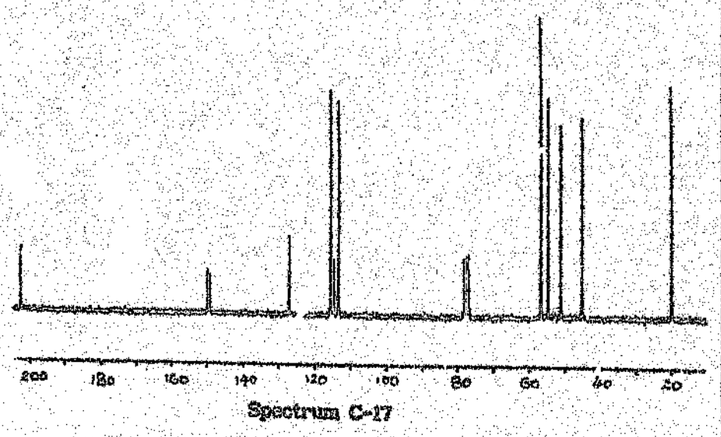


[59b]

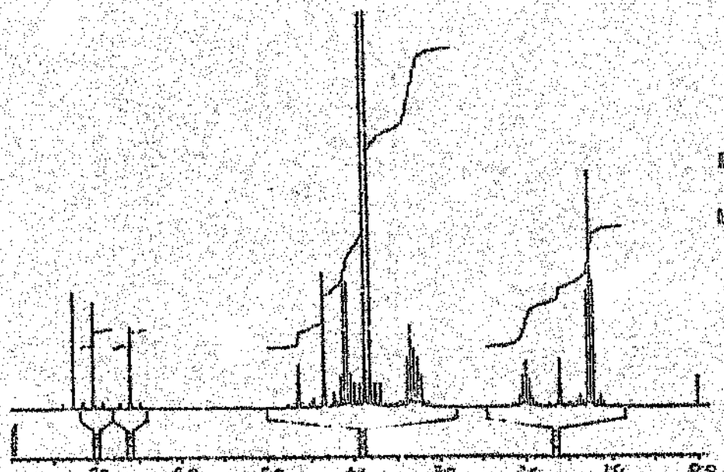
Spectrum H-17



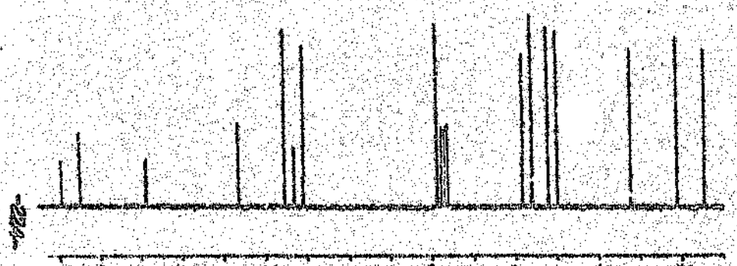
Spectrum C-16



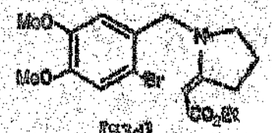
Spectrum C-17



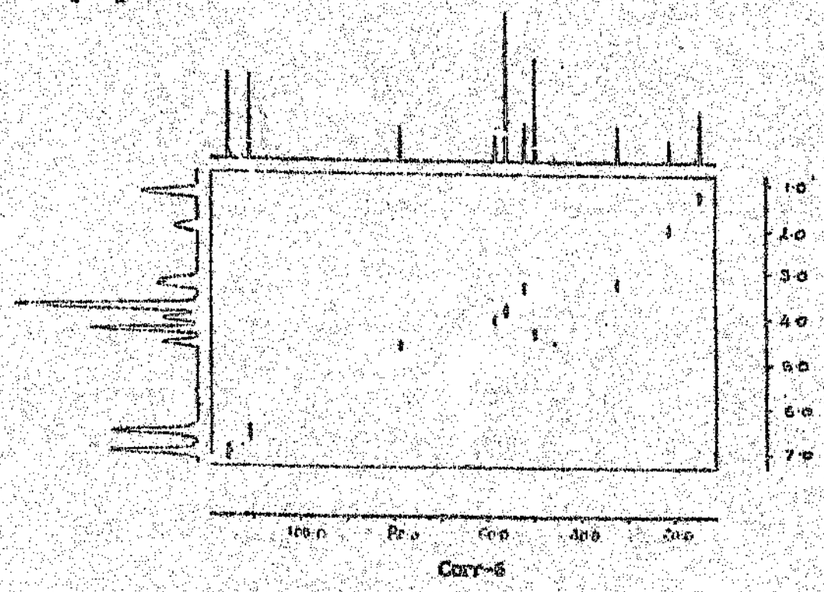
Spectrum H-1B



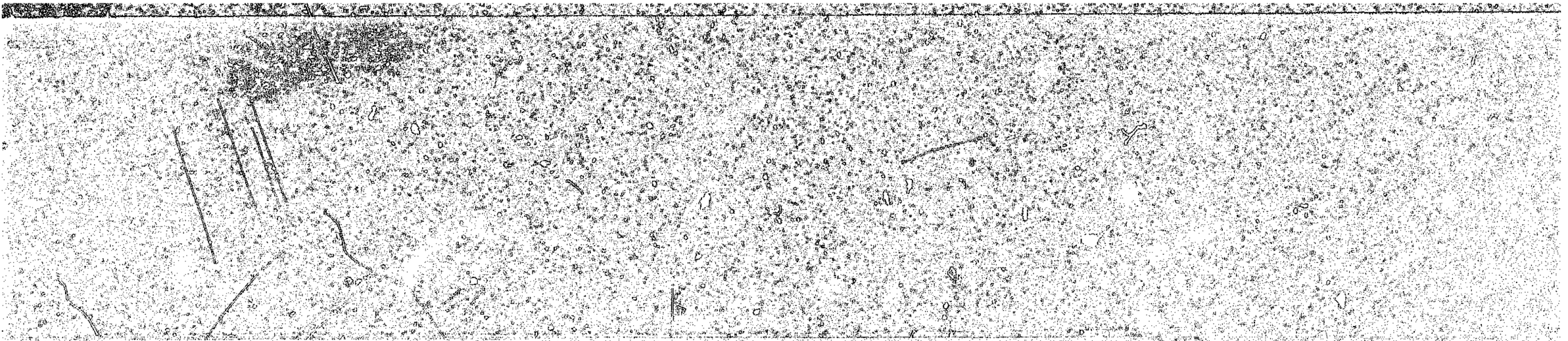
Spectrum C-1B

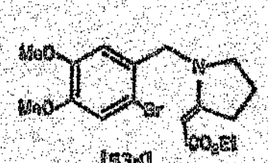


[833d]

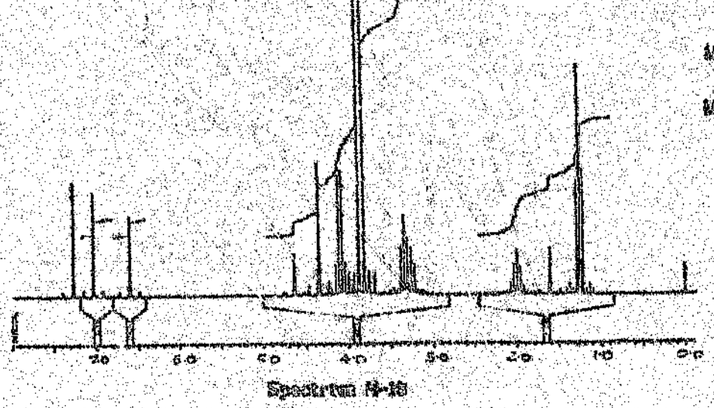


Corr-6

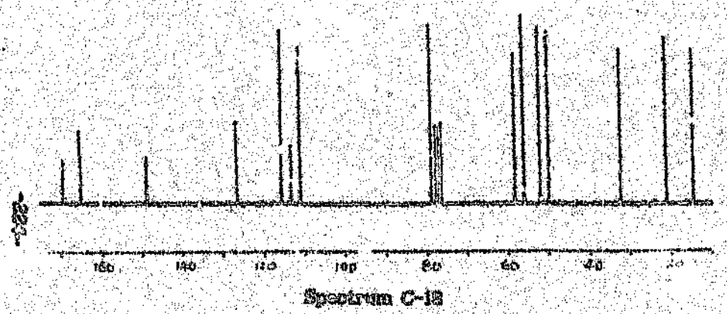




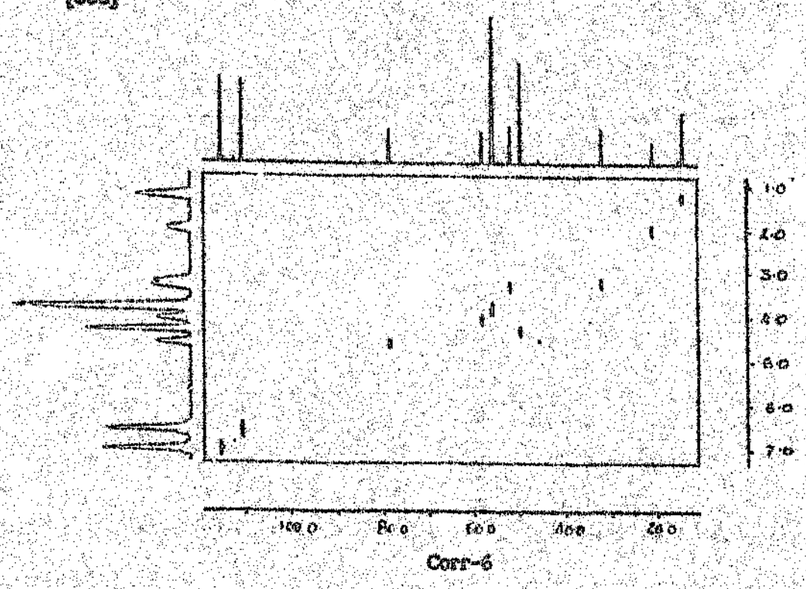
[53d]



Spectrum N-15

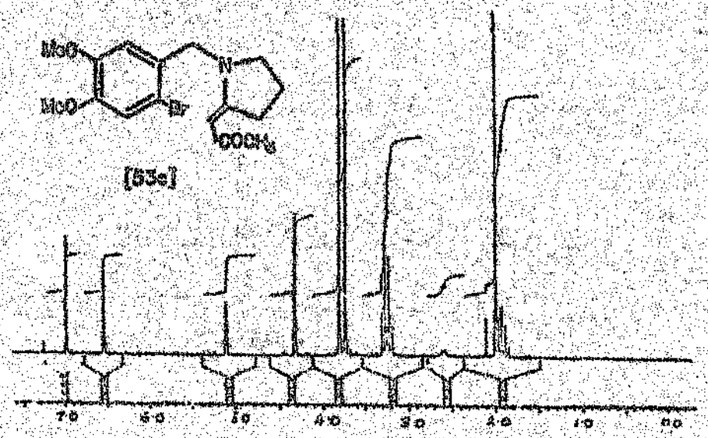


Spectrum C-13



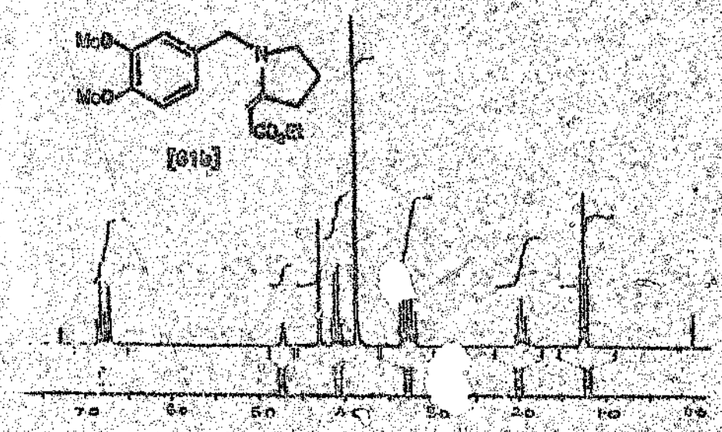
Corr-6

[53c]

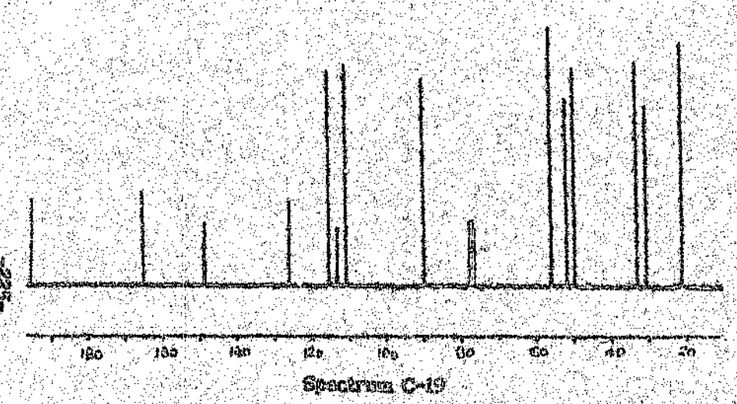


Spectrum H-19

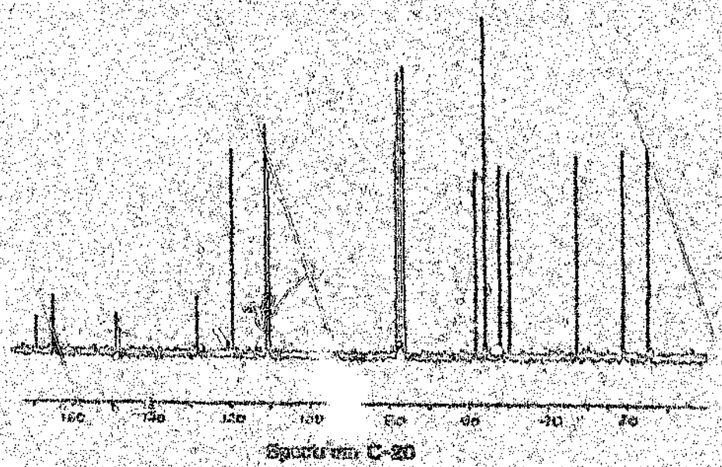
[61b]



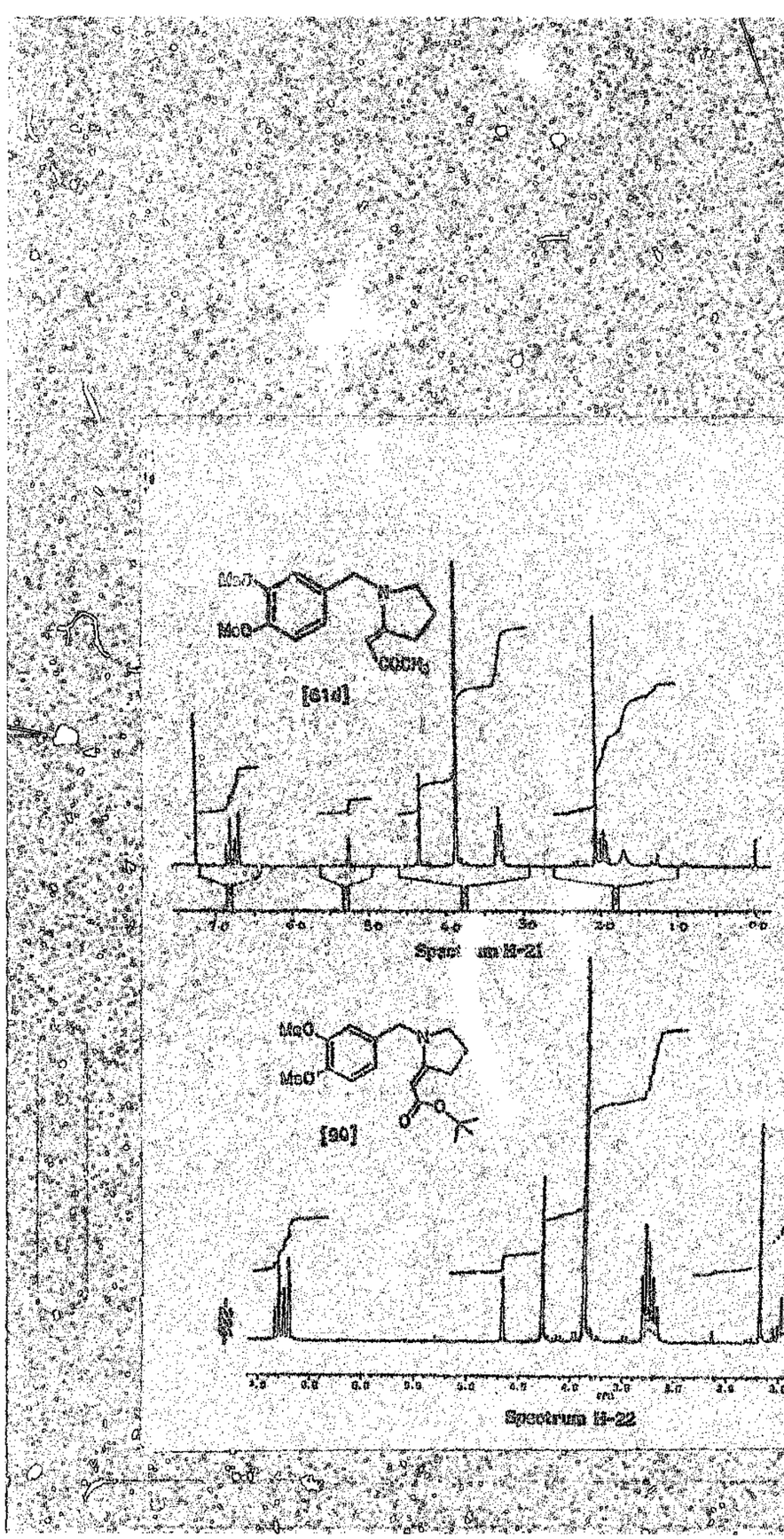
Spectrum H-20



Spectrum C-19

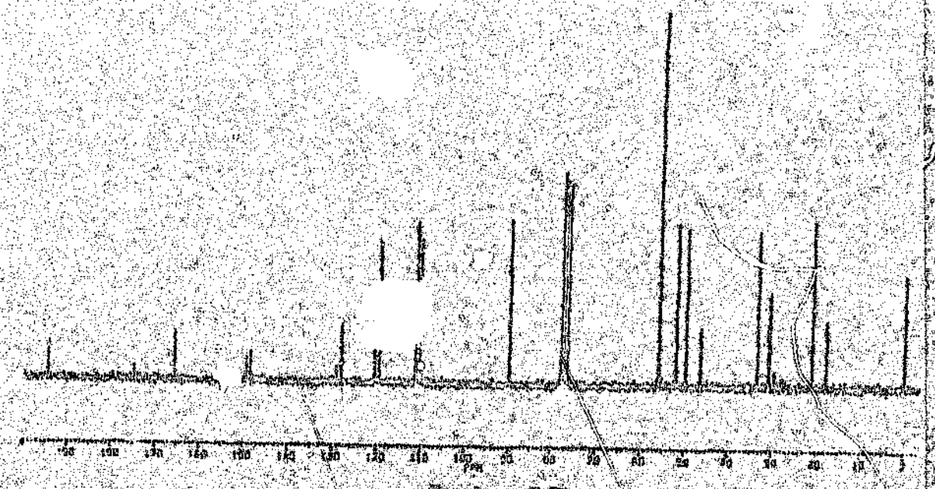


Spectrum C-20



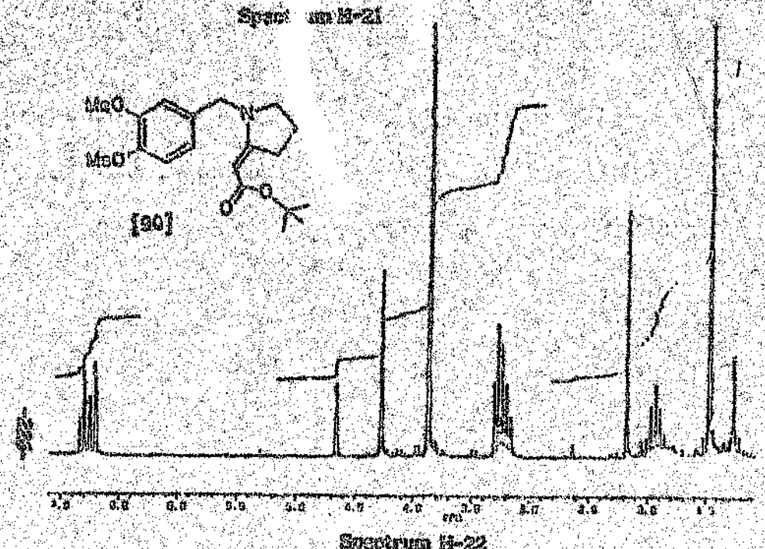
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Spectrum H-21

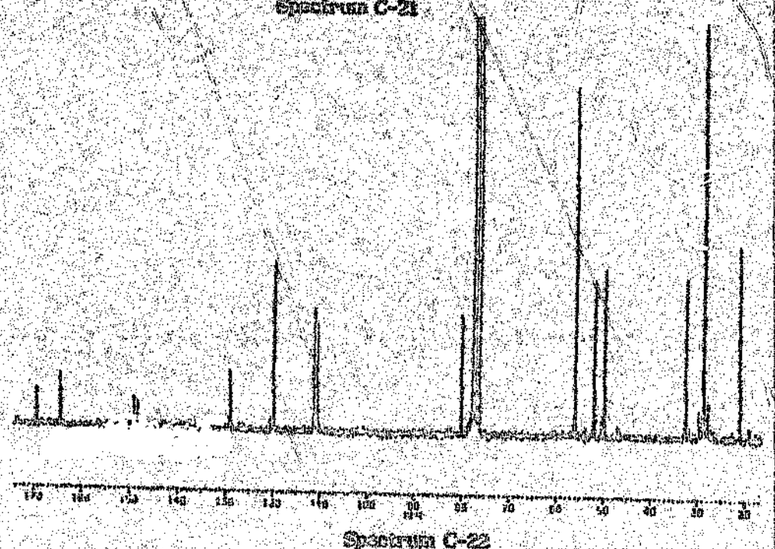


Spectrum C-21

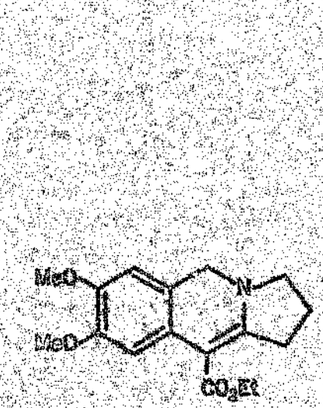
[90]



Spectrum H-22

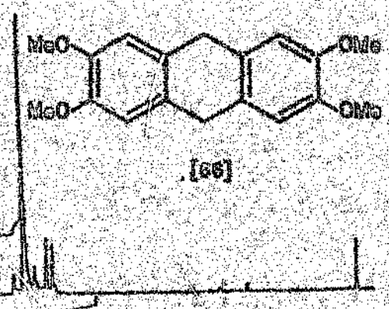


Spectrum C-22



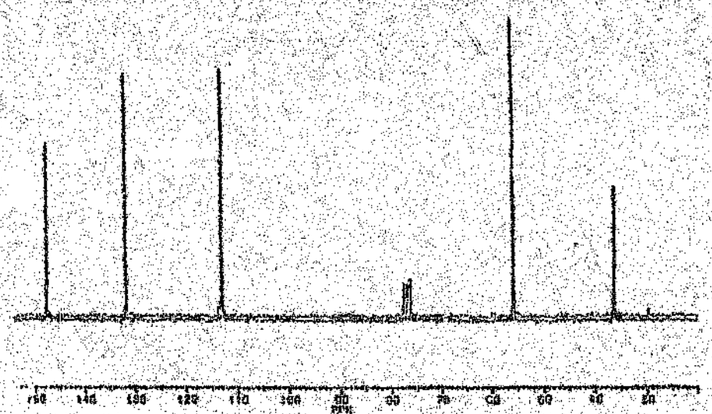
[177]

Spectrum H-23

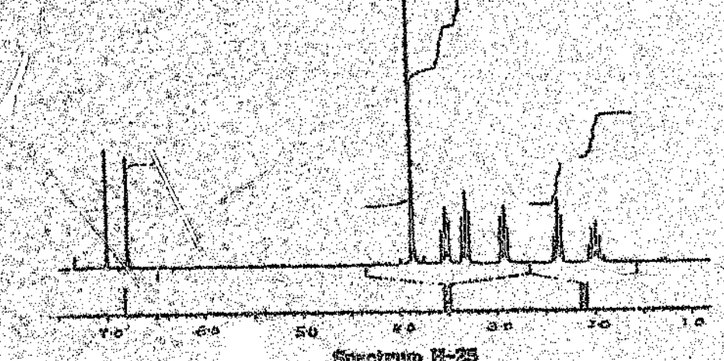


[66]

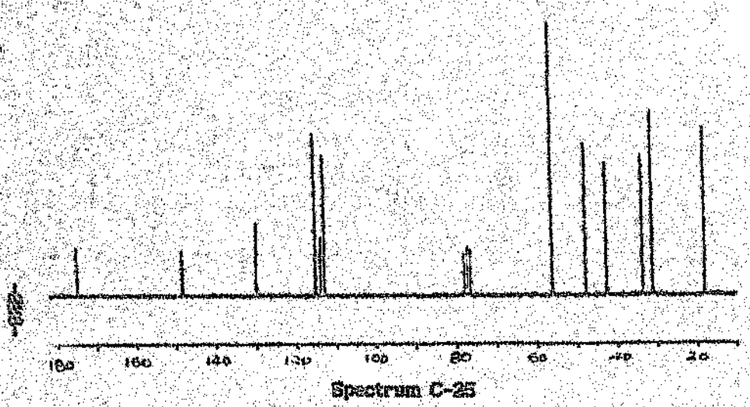
Spectrum H-24



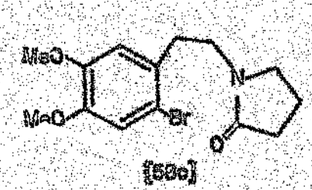
Spectrum C-24



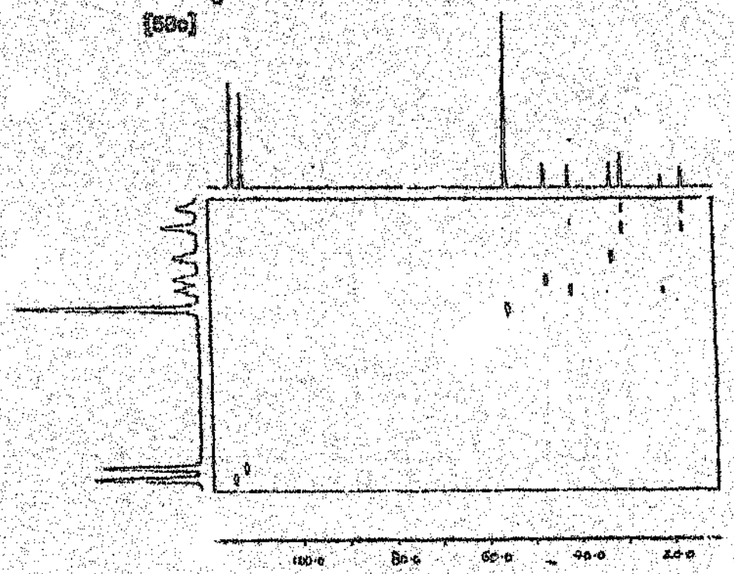
Spectrum H-25



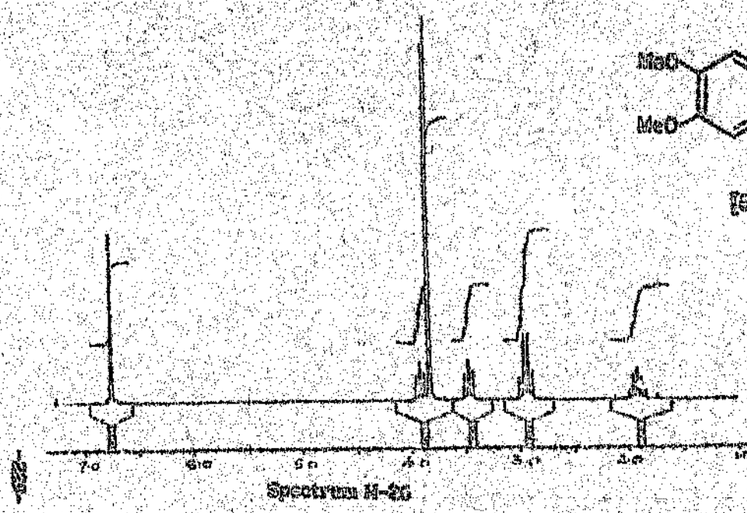
Spectrum C-25



[60c]

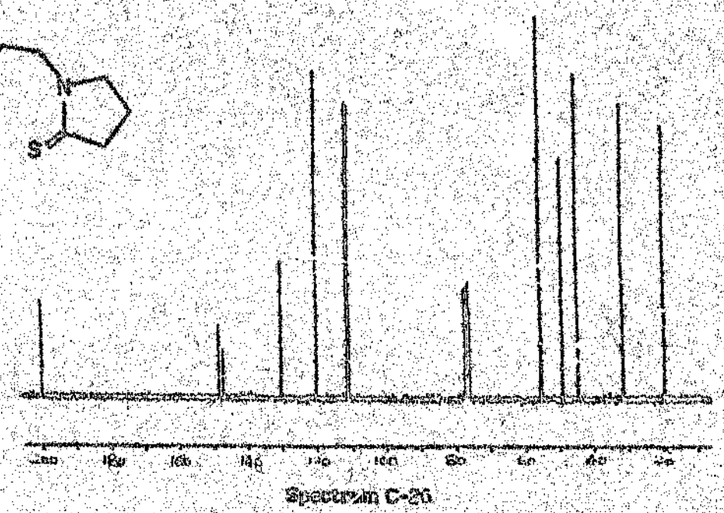


Corr-7

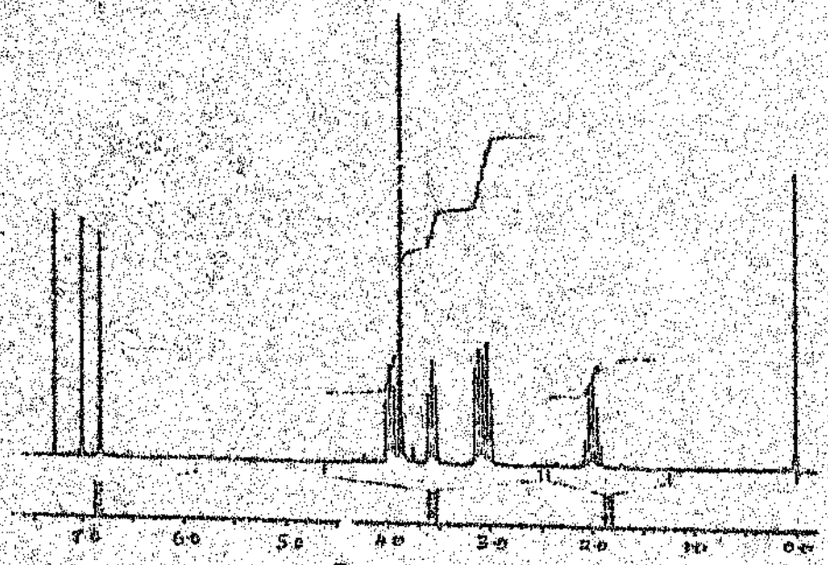


[Sob]

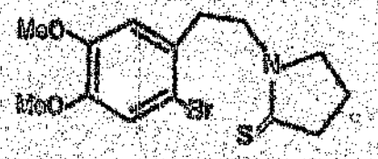
Spectrum H-26



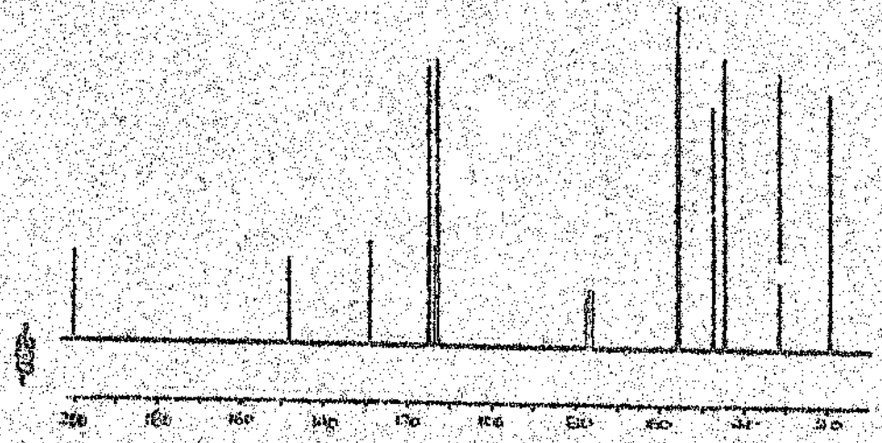
Spectrum C-26



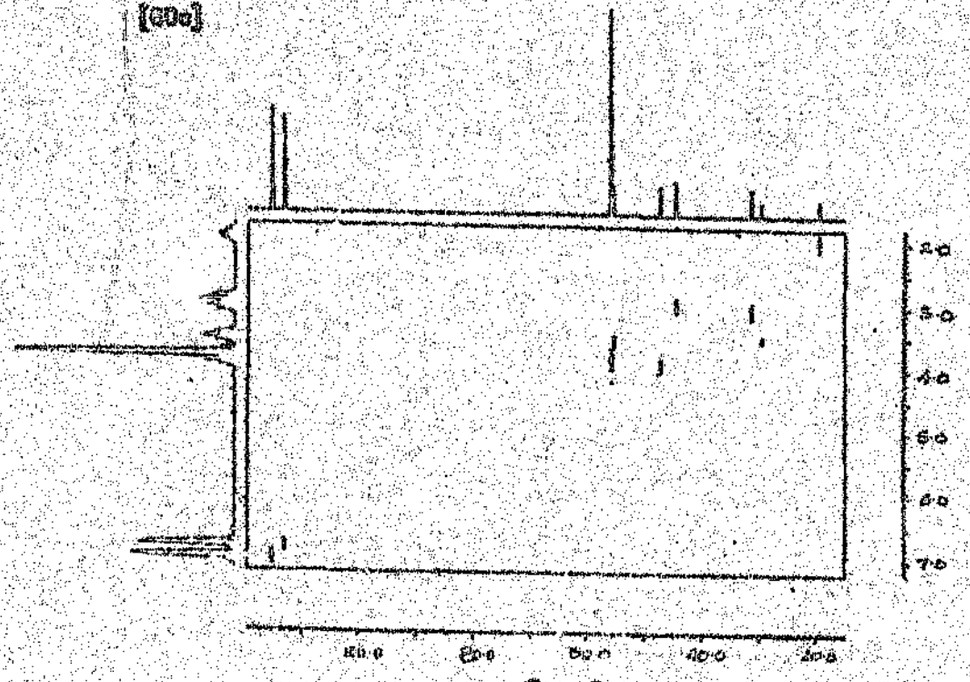
Spectrum H-27



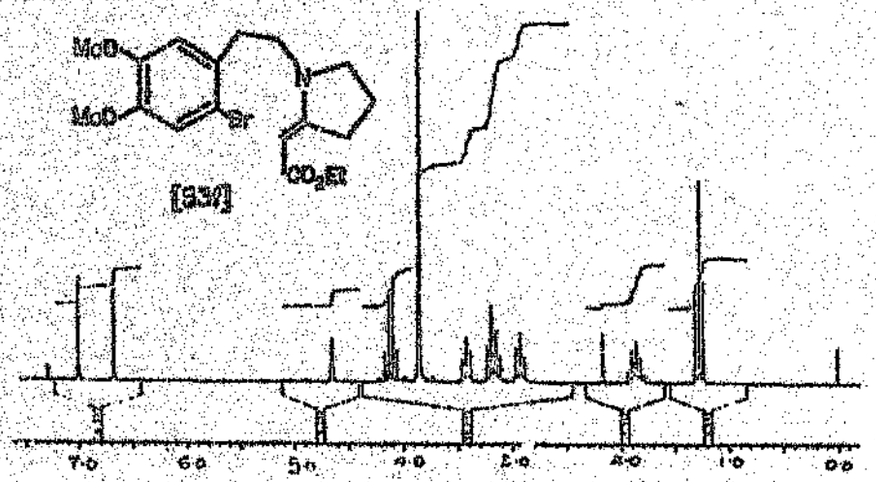
[CDCl]



Spectrum C-27

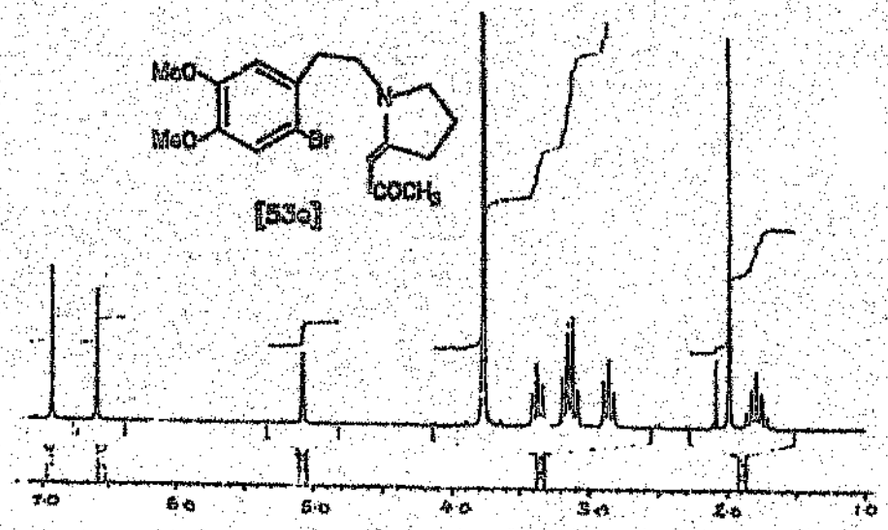


Corr-S



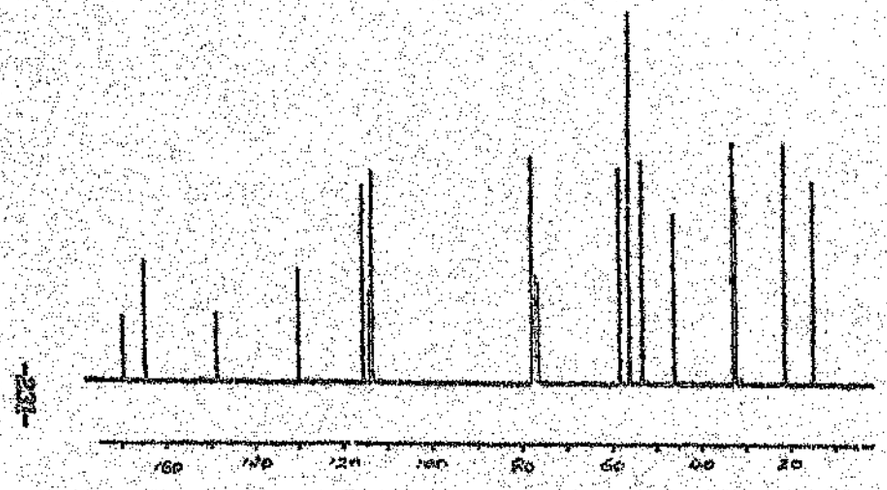
[53f]

Spectrum H-28

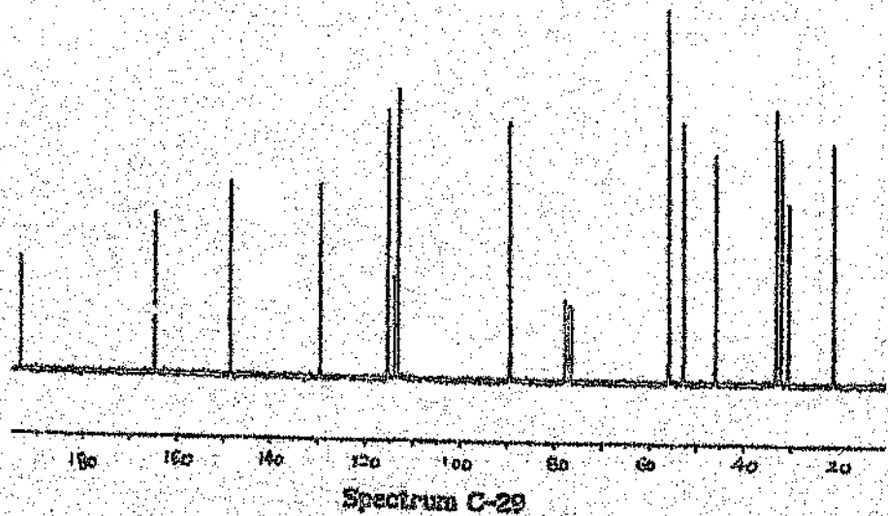


[53e]

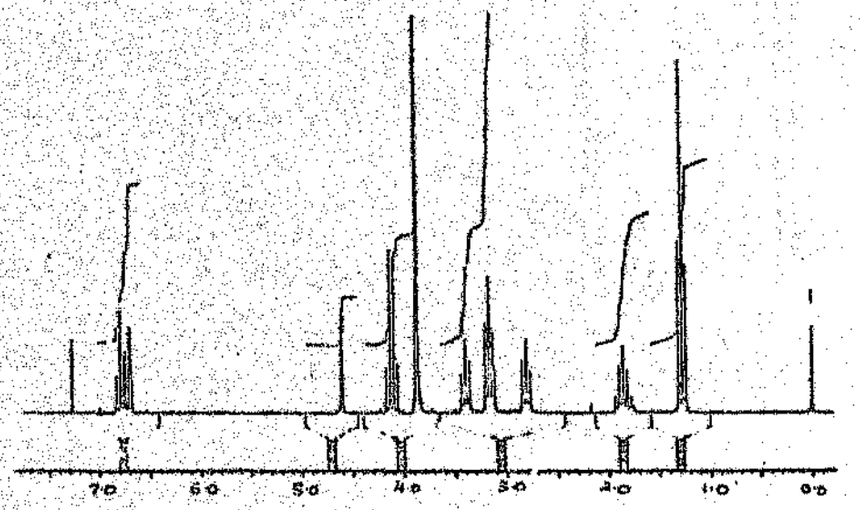
Spectrum H-29



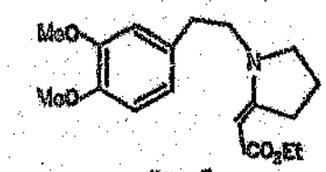
Spectrum C-28



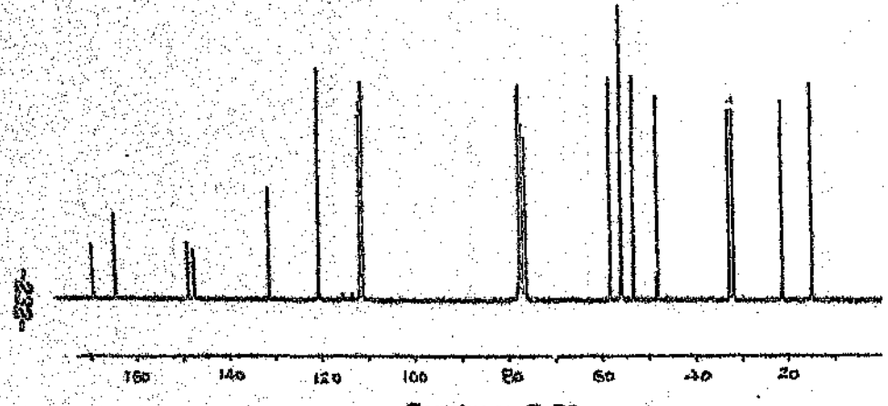
Spectrum C-29



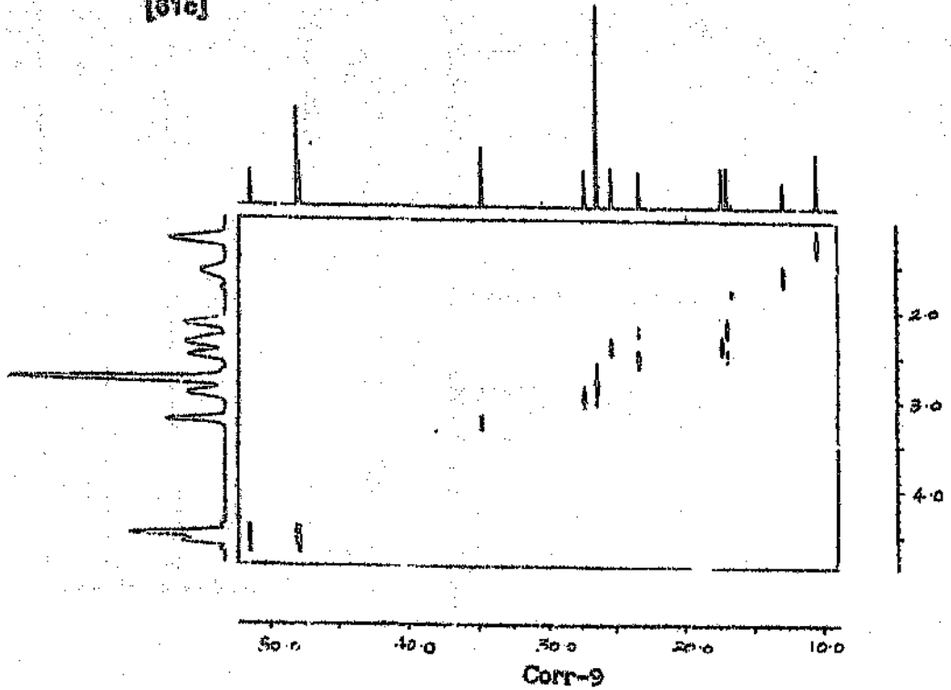
Spectrum H-30



[61c]



Spectrum C-30

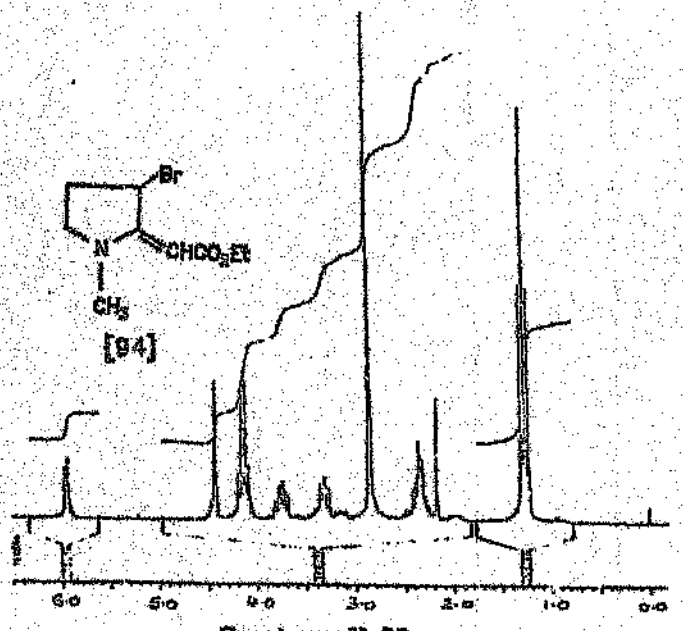


Corr-9

Spectrum H-32

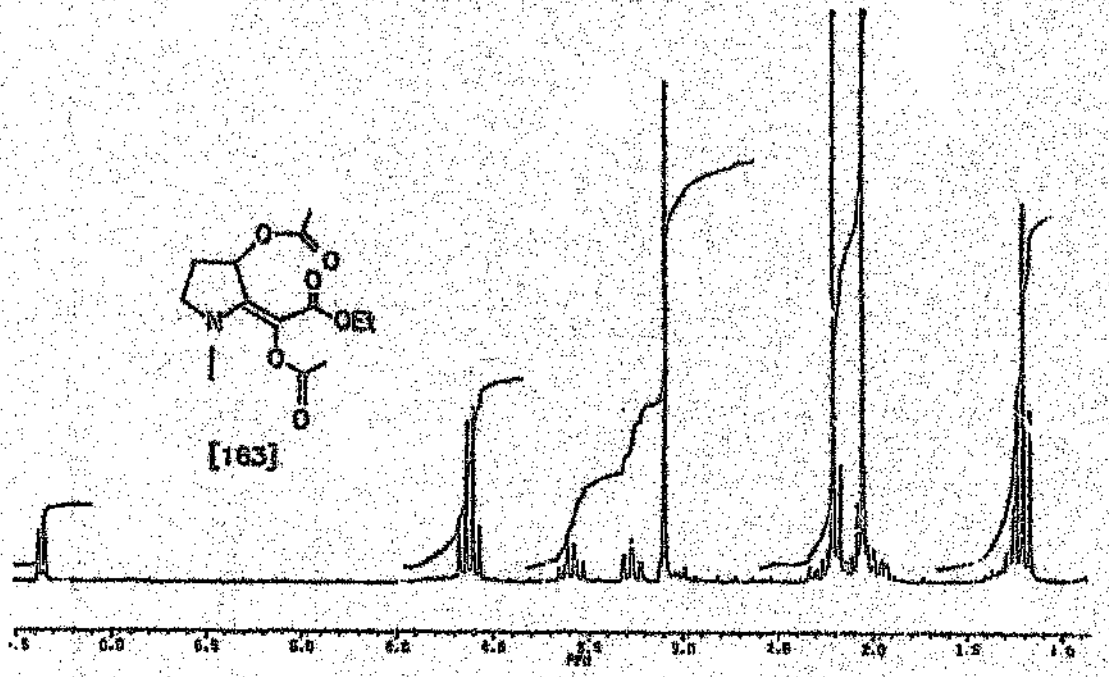
Spectrum C-32

Spectrum C-31



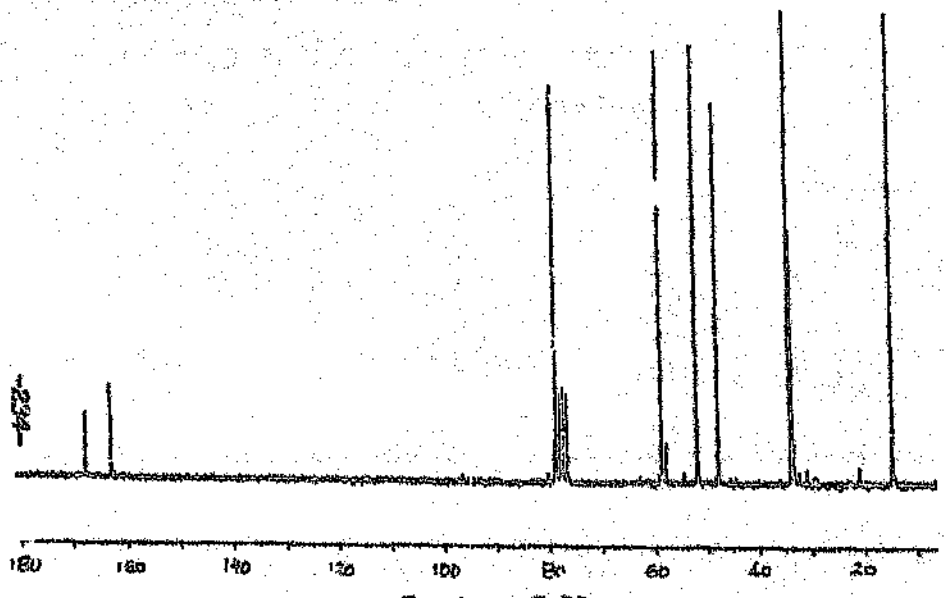
[94]

Spectrum H-33

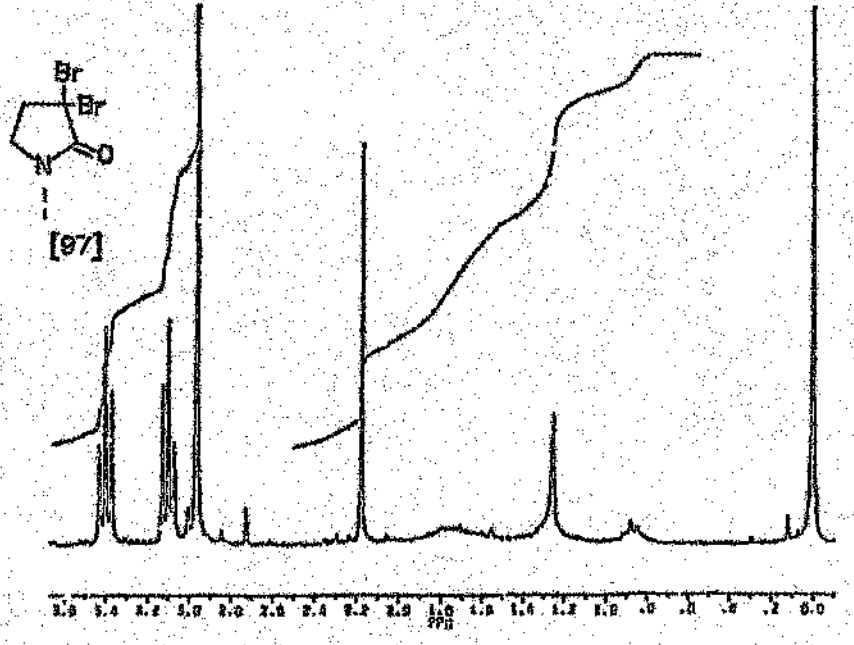


[163]

Spectrum H-34



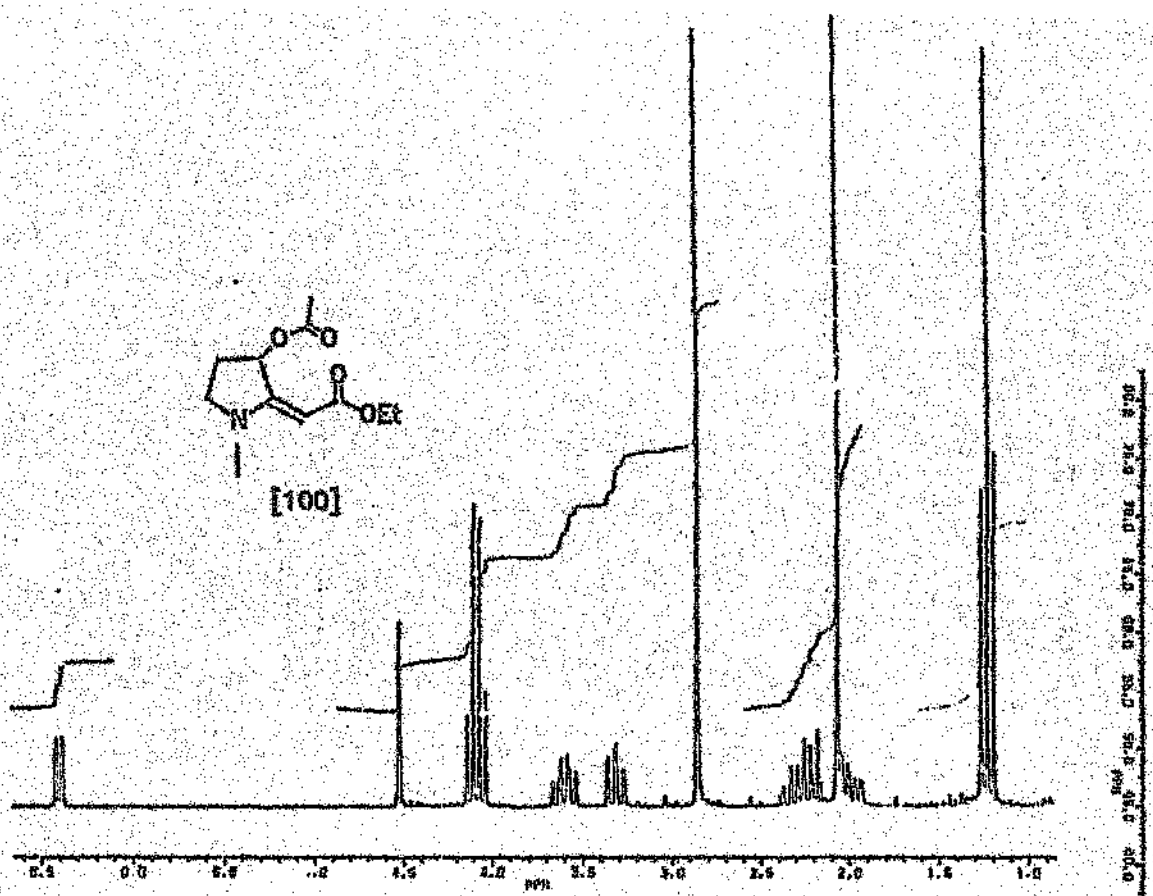
Spectrum C-33



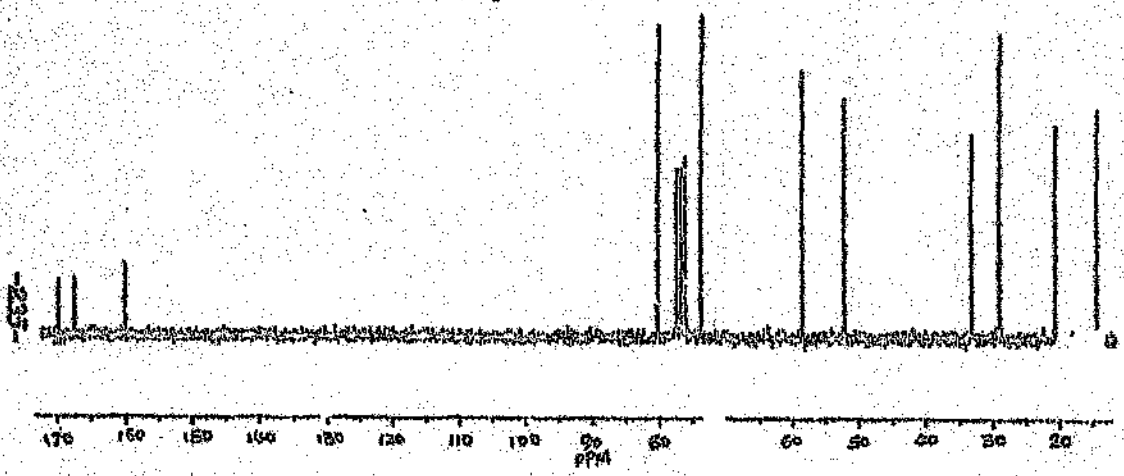
[97]

Spectrum H-35

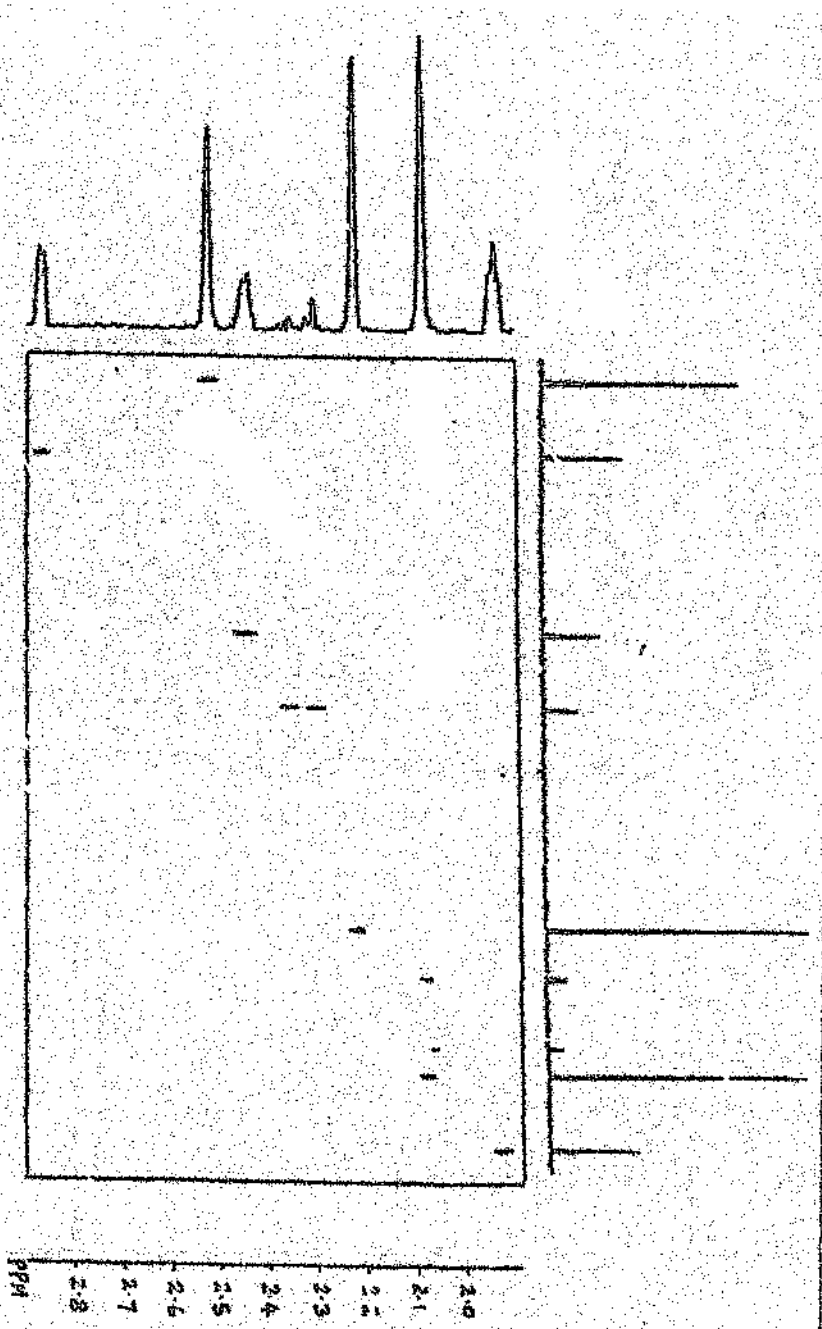
[100]



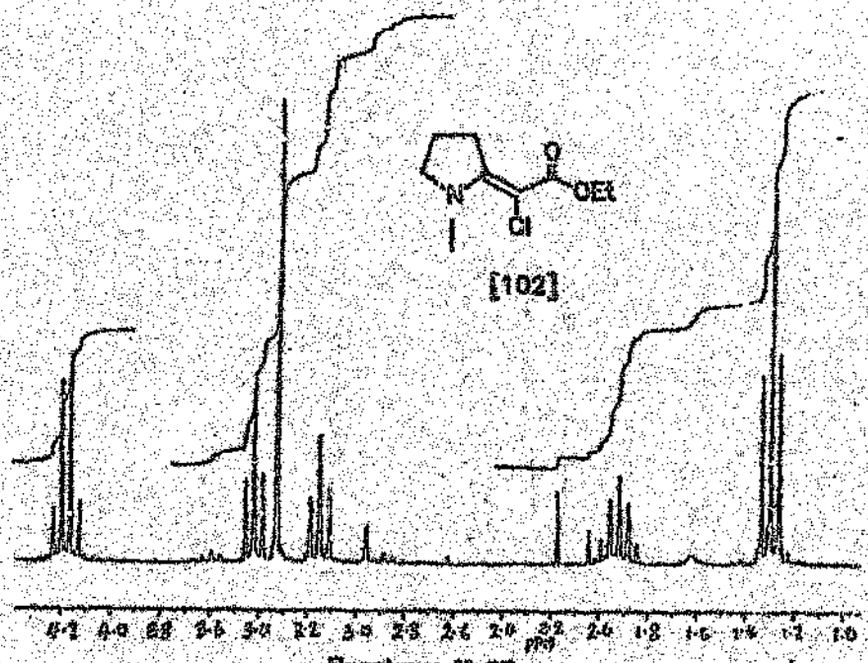
Spectrum H-36



Spectrum C-13.

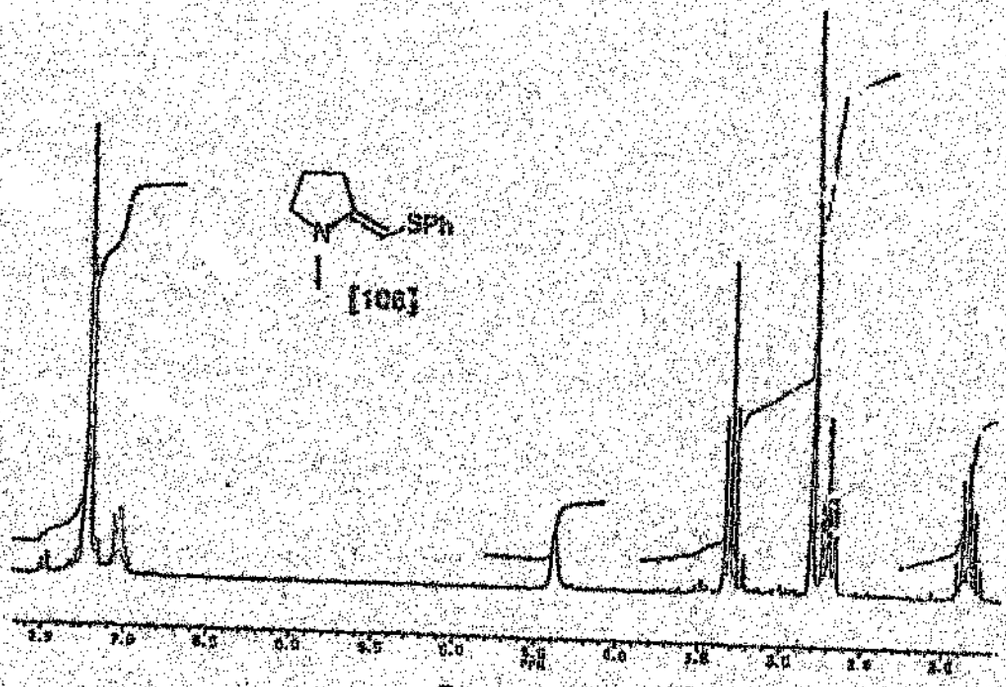


Corr-10



[102]

Spectrum H-37



[106]

Spectrum H-38

Spectrum C-37

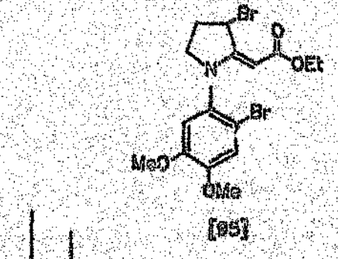
Spectrum C-38

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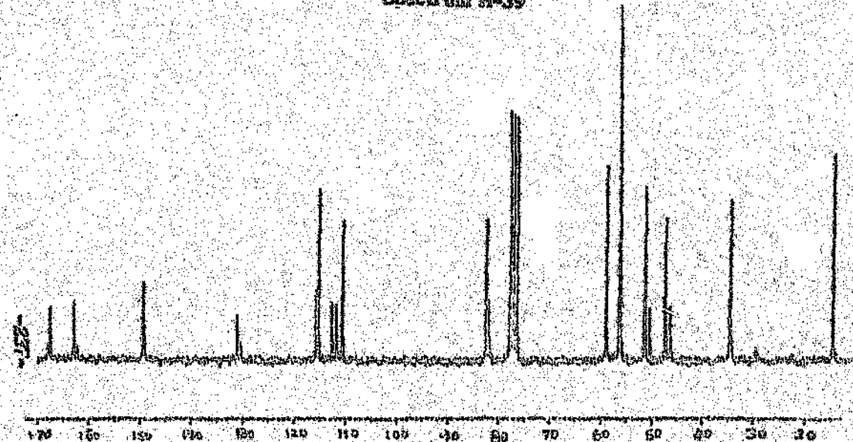


[95]

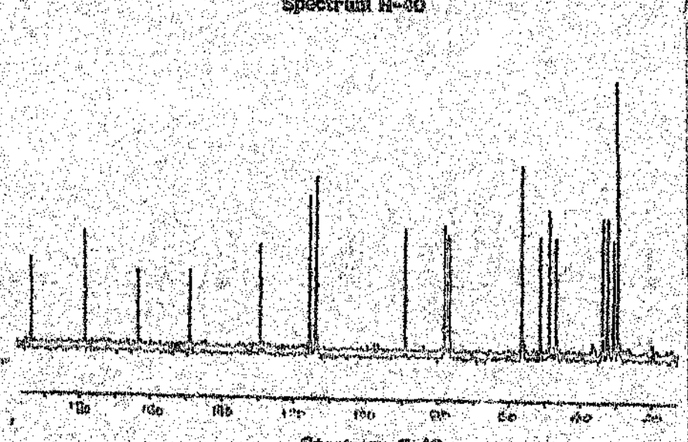
[92]

Spectrum H-39

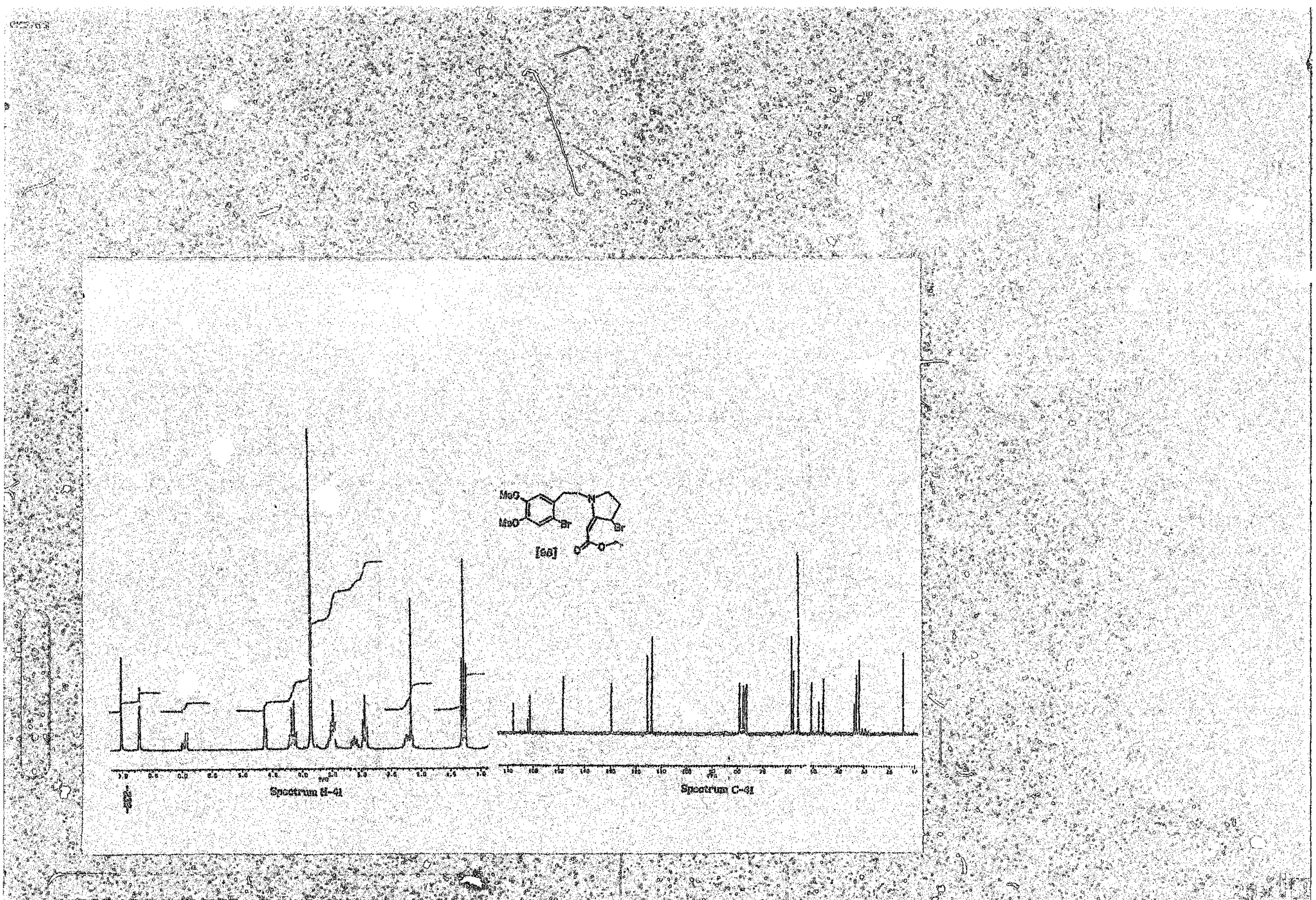
Spectrum H-40

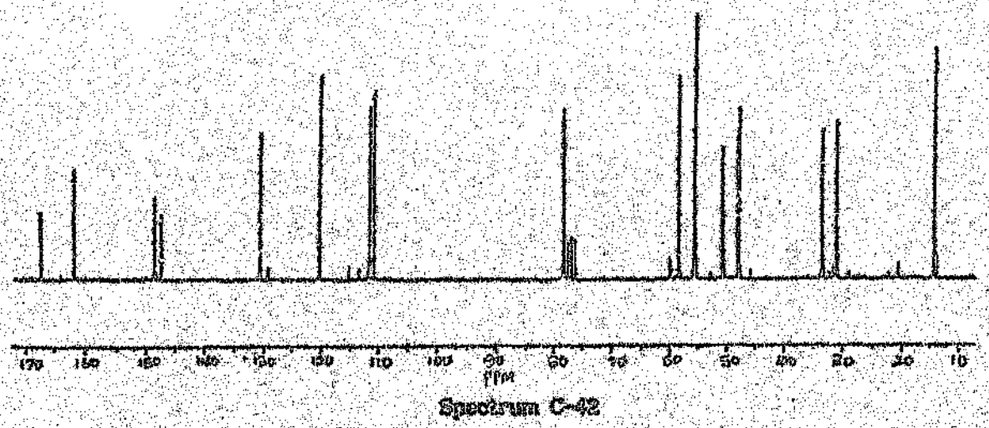


Spectrum C-39

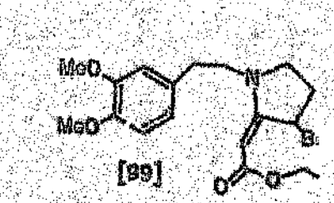


Spectrum C-40

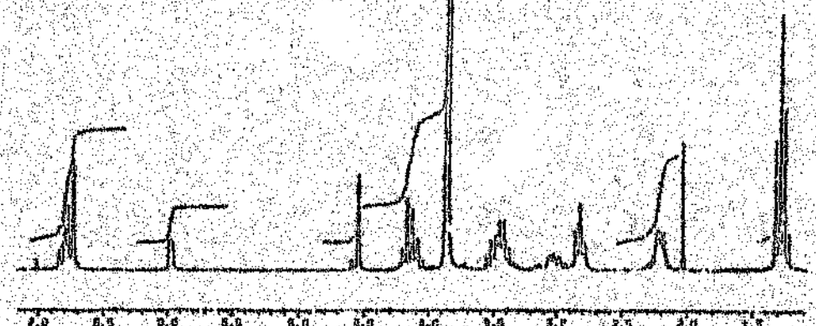

MeO
MeO
Br
Br
N
O
O
[66]
Spectrum H-41
Spectrum C-41



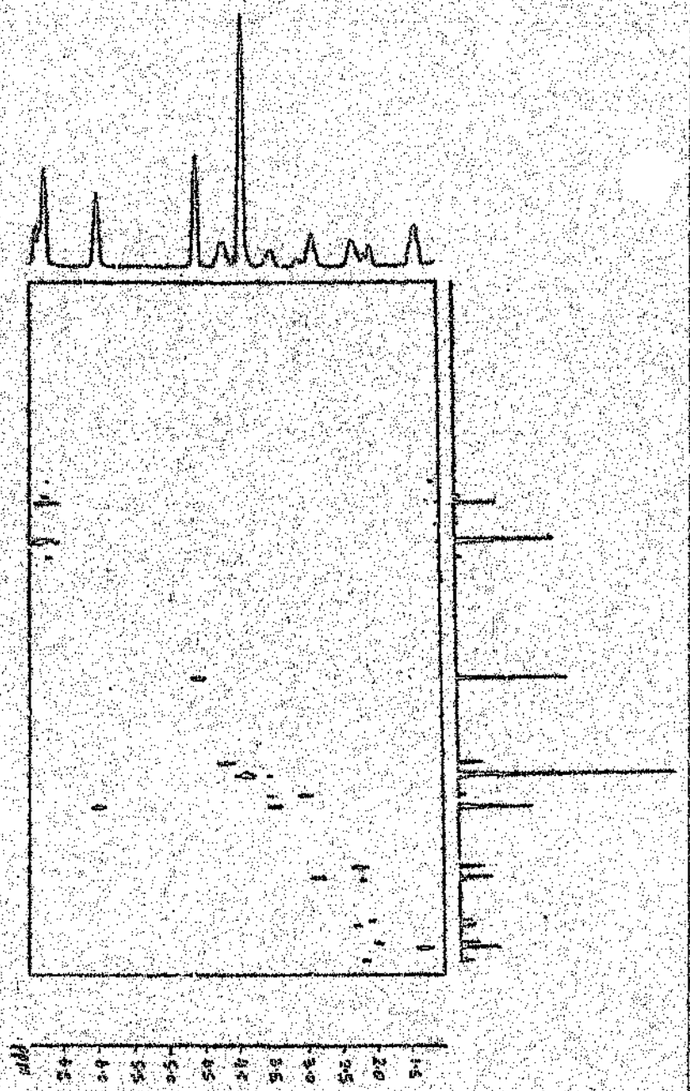
Spectrum C-42



[99]



Spectrum H-42



Corr-H

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The answer, my dear, is blowing in the wind.

There is a time and place for you to have your dreams.
A dream lives longer than a dreamer ever will.
A chemist's life is one that is against all odds in the never ending story with days of diamond but mostly of stone.

Life would be easier if you kind of like my dream.
Let's go and dream.

There is a time and place for everything.
So let it be.
The future is not ours to see.
Whatever will be will be.

Time is a precious thing.
Lost time is never found.
Time brings all things to an end.
Let no one steal away your time.

I am older now, but still running against the wind.

Do you know where you are going to ?
Do you like the things the world is showing you, do you know ?

I don't know where I am going, but I am going.
Oh yes, life goes on.

Do you know what you want to be ?
Yes, forever young I want to be.



Author: Chang Steven.
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