APPROACHES TO THE SYNTHESIS OF MESEMBRINE AND RELATED ALKALOIDS

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

October, 1983.

DECLARATION

I hereby declare that the work presented in this thesis was carried out exclusively by myself under the supervision of Prof. A S Howard and Dr. J F Michael.

This thesis has never been submitted for a degree in any other university.

ACKNOWLEDGEMENTS

I would like to express my sincere appreciation for the support and assistance I received from friends, family and colleagues who made this work possible.

I am particularly indebted to my supervisors, Prof. Arthur Howard and Dr. Jo Michael, whose patient guidance and encouragement assured the completion of this work.

I would like to thank the Council for Scientific and Industrial Research for financial support for part of this work, and also for certain of the mass and nuclear magnetic resonance spectra.

The assistance received from all the technical staff of the Department of Chemistry is gratefully acknowledged.

Finally, I wish to thank Vivienne Thom and my mother for assistance in the preparation and proofreading of this manuscript.

ABSTRACT

After a survey of the methods reported in the literature for the synthesis of mesembrine and related octahydroindoles, a novel synthetic approach to these alkaloids is presented, based on the use of the vinylogous urethane, 1-methyl-3-(3,4-dimethoxyphenyl)-2-ethoxycarbonylmethylenepyrrolidine, and its immediate precursor, 3-(3,4-dimethoxyphenyl)-2-thiopyrrolidone. Since the most convenient approach to the latter compound is via the corresponding lactam, attempts to prepare this material using N-methyl-2-pyrrolidone, and using methyl 3,4-dimethoxyphenylacetate are presented. The synthesis of the thiolactam is achieved by reaction of the dianion of N-methyl-3,4-dimethoxyphenylacetamide with 1-bromo-2-chloroethane, followed by thiation. The application of the method for the synthesis of lactams in general is then investigated.

Attempts to prepare mesembrine from the 3-aryl vinylogous urethane are then presented, firstly by investigation in a series of model reactions, followed by a sequence designed to lead to mesembrine itself.

The failure to prepare mesembrine from the vinylogous urethane leads to the design of a new synthetic route, the crucial step in which is an alkylation on sulphur and sulphide contraction with a halomethyl vinyl ketone, to form a vinylogous amide intermediate. After investigation of the sequence with a series of model reactions Δ^{7}-mesembrenone is prepared in one step from the 3-aryl thiopyrrolidone and chloromethyl vinyl ketone. The synthesis of this compound constitutes a formal synthesis of (±)-mesembrine.

The method is then applied to a formal synthesis of

(±)-dihydromaritidine from N-benzyl-3-(3,4-dimethoxyphenyl)-2-thiopyrrolidone, and of (±)-aspidospermine from N-benzyl-3-ethyl-2-thiopiperidone.

In an appendix the preparation, spectroscopic properties and reactivity towards alkylation of various extended enamines are discussed.

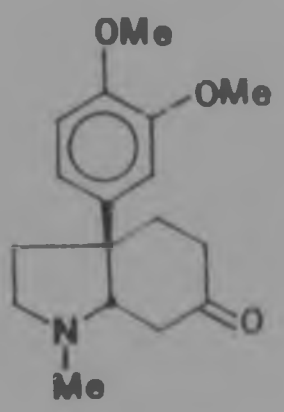
CONTENTS

CHAPTER 1 ORIGINS AND SYNTHESIS OF MESEMBRINE AND RELATED ALKALOIDS

1.1 Origins

The mesembrine group of alkaloids, a subgroup of the Sceletium alkaloids, named after the parent alkaloid mesembrine 1, are characterized by the N-methyl-3a-(3,4-dimethoxyphenyl)-cis-octahydroindole skeleton. Sceletium alkaloids occur in the plant genus Sceletium (family Aizoaceae), which is found principally in south-west Africa. Interest in these plants arose from early reports [1,2] of their use by the indigenous peoples of this region in the preparation of the pharmacologically interesting drug known as 'Channa' or 'Koegoed'. An early study [3] of 'Channa' by Meiring in 1896 suggested the presence of alkaloids, and this was confirmed by Zwicky [4] in 1914. The structure of the parent alkaloid mesembrine 1 was not, however, elucidated until 1960 [5].

A number of Sceletium alkaloids have been isolated [6], a representative sample being (-)-mesembrine 1, Δ^7-mesembrenone 2, (-)-mesembranol 3, and (±)-sceletenone 4. Other alkaloids which have been isolated from Sceletium species include alkaloids possessing the secomesembrane skeleton, exemplified by joubertiamine 5, and the pyridine-dihydropyridone alkaloids, exemplified by sceletium A4 6.



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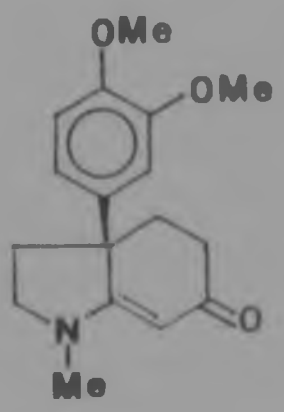

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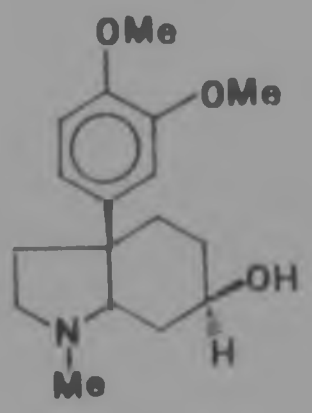

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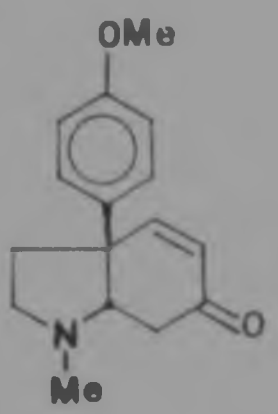

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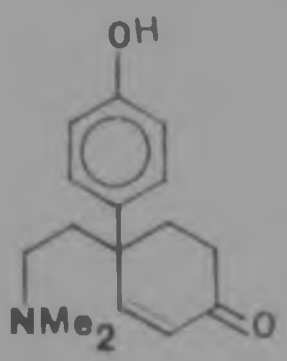

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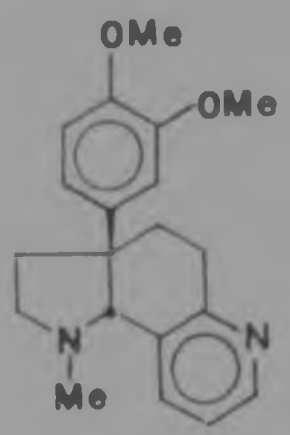

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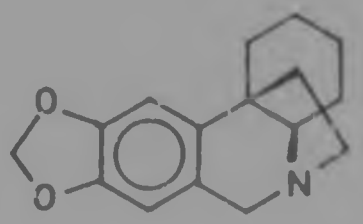
1.2 The Synthesis of Mesembrine and Other 3a-Aryloctahydroindoles

The mesembrine alkaloids have aroused a great deal of synthetic interest in recent years, because of their interesting pharmacological properties, and also because of their close relationsnip to the Amaryllidaceae alkaloids of the crinane type, the parent skeleton of which is crinane 7. Although most of these alkaloids have a 3,4-methylenedioxyaryl ring, some, for example dihydromaritidine 8 have a 3,4-dimethoxyphenyl ring. Another closely related Amaryllidaceae alkaloid is pretazettine 9. The synthesis of many of these alkaloids proceed via mesembrine-like octahydroindole intermediates. Interest in these alkaloids has been further heightened by

recent reports of significant antitumour activity exhibited by pretazettine [7].



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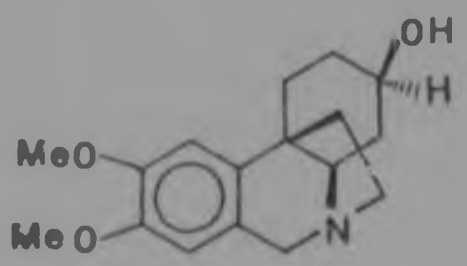

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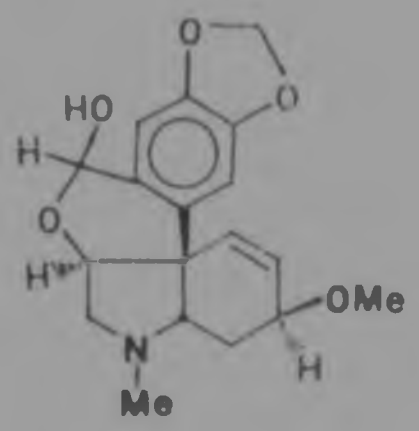

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The reported syntheses of mesembrine and related alkaloids can be classified according to the dissections of the mesembrine skeleton. Thus most of the reported syntheses fall into the four groups represented by the dissections of types A, B, C and D as shown below.

Type A

10

Type B

11

Type C

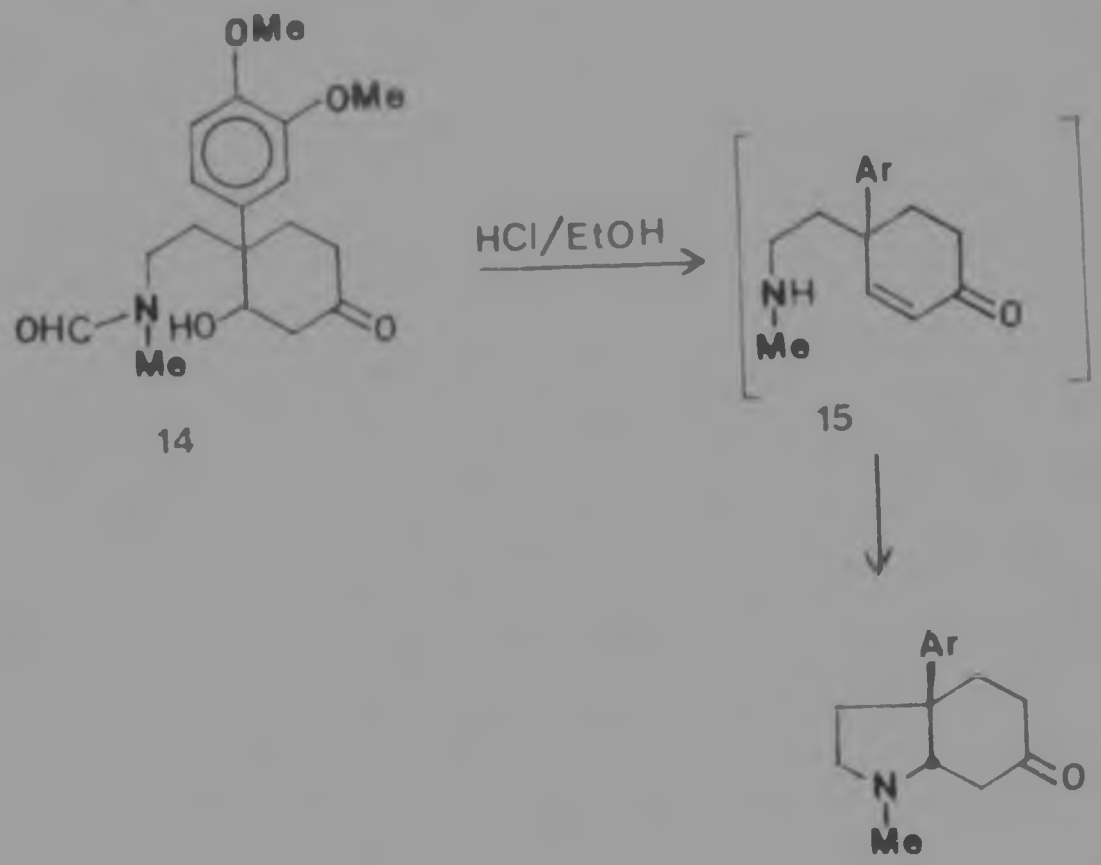
12

Type D

13

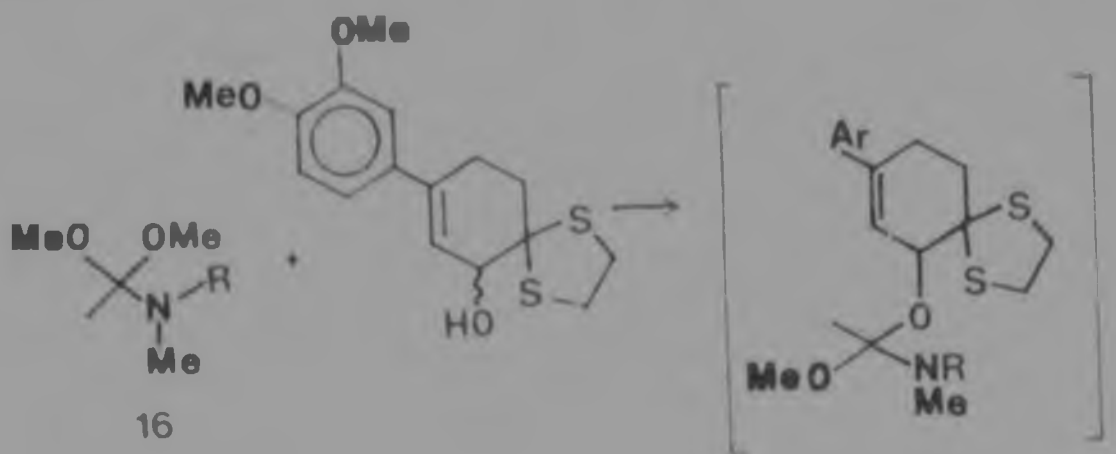
1.2.1 Syntheses of Type A

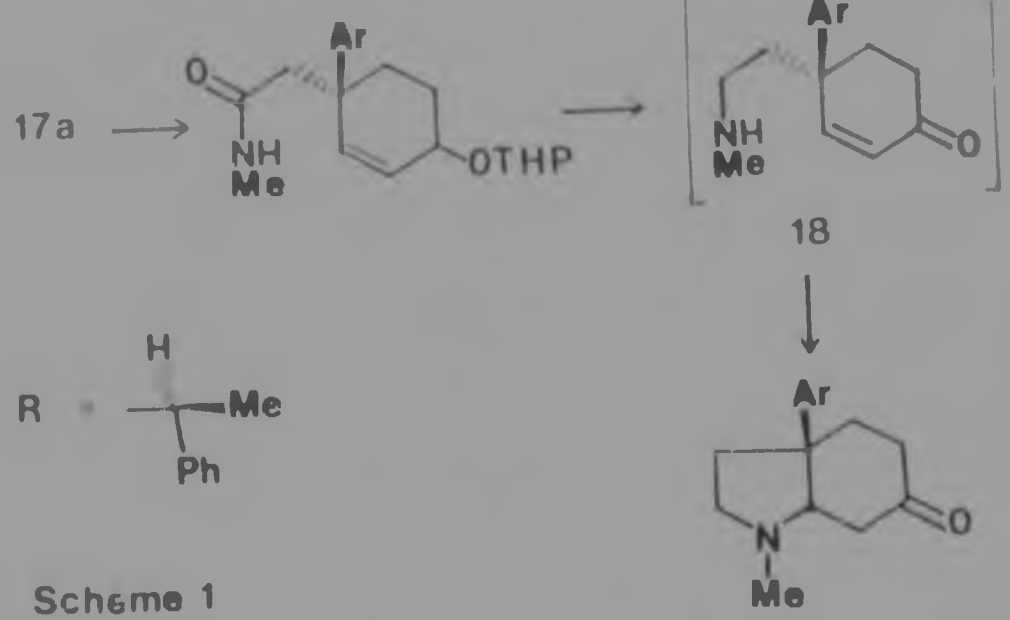
Syntheses of mesembrine which use the type A dissection require an intermediate possessing the essential features of the skeleton shown in 10. These syntheses must then involve the intramolecular ring closure of a nitrogen-functionalized two-carbon side chain onto an appropriate six-membered ring. One procedure which has received a great deal of attention is the intramolecular Michael reaction of a nucleophilic nitrogen with a 4-aryl substituted cyclohexenone. This approach was used in the first total synthesis of (±)-mesembrine, published by Shamma and Rodriguez [8,9]. The key step in this work involved the dehydration of 14 to form the transient intermediate 15, which underwent spontaneous ring closure. Compound 14 was synthesized by a rather lengthy route.



The only chiral synthesis of the natural antipode using this route has been achieved by Wiechers and co-workers [10]. In

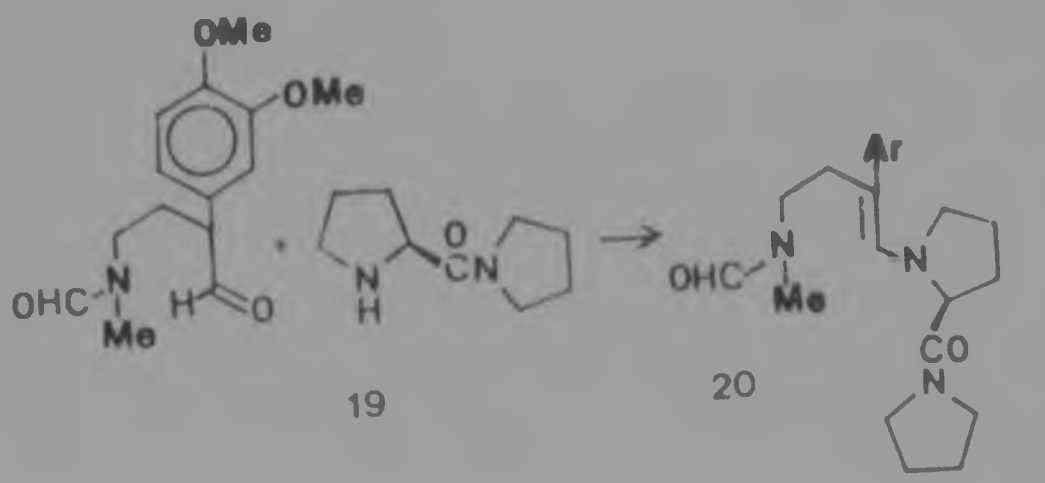
this synthesis the chiral acetal 16 was used in the amide acetal Claisen rearrangement, the key step in the preparation of 18, a chiral intermediate corresponding to the skeleton 10 (scheme 1).

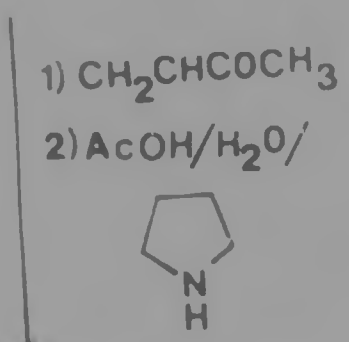


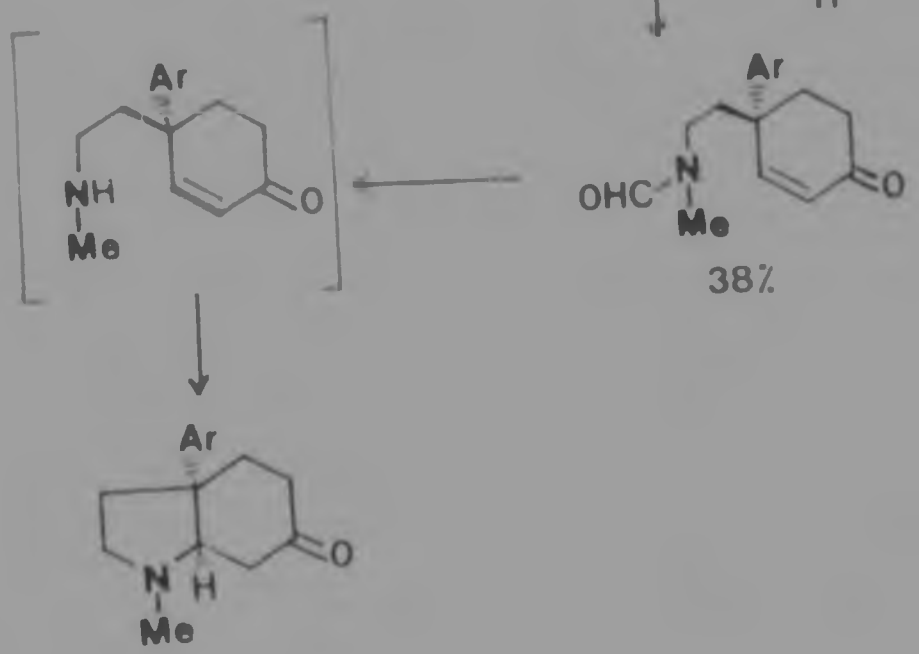


Scheme 1

Of considerable interest is the chiral synthesis by Otani and Yamada [11,12] of (+)-mesembrine, the unnatural antipode. A feature of this work is the use of L-proline pyrrolidide 19 to make the chiral enamine 20 (scheme 2).

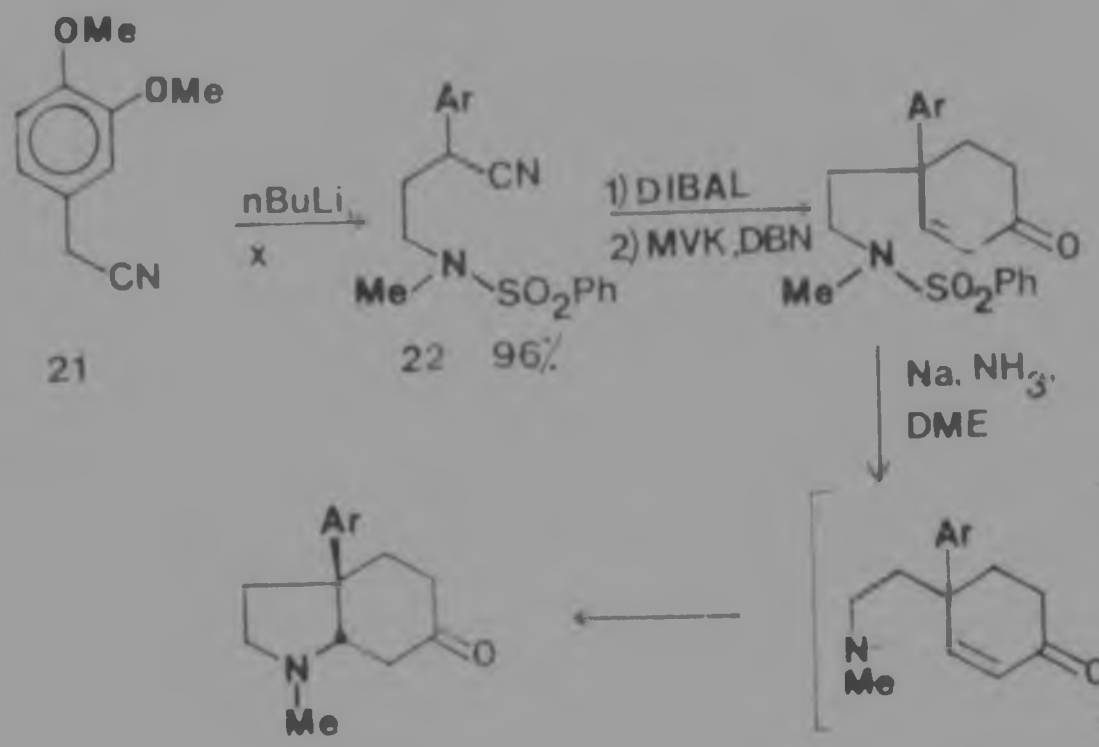






Scheme 2

Similar syntheses of mesembrine and related alkaloids have been reported by Martin [13,14], Sanchez [15,16] and Muller [17] and their co-workers. These vary in the preparation of the appropriately functionalized cyclohexenone. The most high yielding of these syntheses is one by Sanchez [16]. In this work the synthesis of (±)-mesembrine was achieved in 42 % overall yield from 3,4-dimethoxyphenylacetonitrile 21, via the N-benzenesulphonamide 22 (scheme 3).

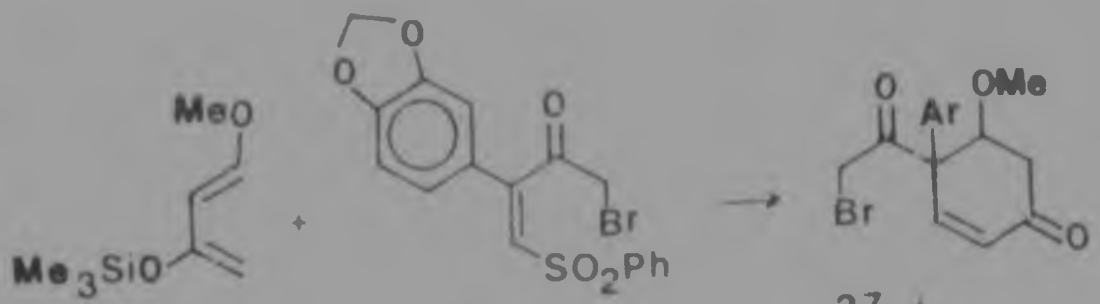


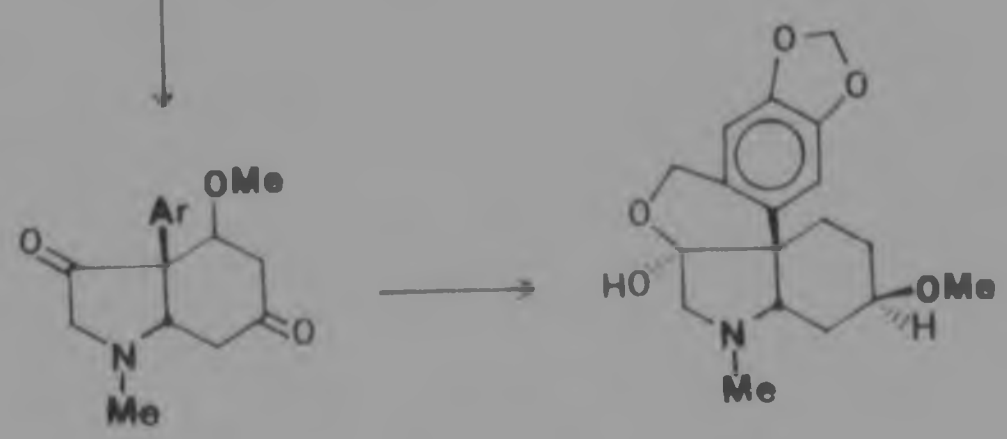
x = $PhSO_2O(CH_2)_2N(CH_3)SO_2Ph$

Scheme 3

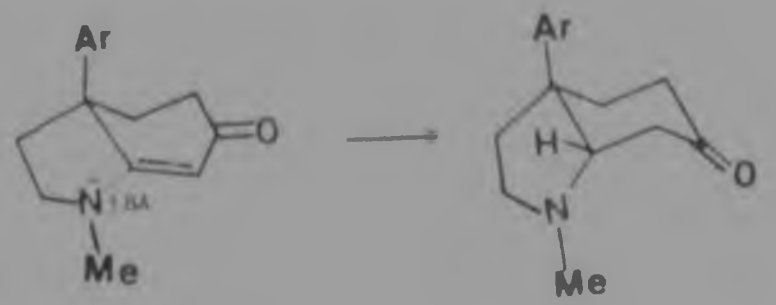
A synthesis of (±)-tazettine 23 by Danishefsky and co-workers [18,19], which proceeds via the mesembrine-like intermediate 24 is of interest in that it uses a Diels-Alder reaction for formation of the cyclohexenone ring. Thus, reaction of the diene 25 with the dienophile 26 yielded the 4,4-disubstituted cyclohexenone 27 in 54 % yield. Treatment of 27 with methylamine afforded the bicyclic compound 24 in 80 % yield.

This was then converted to (±)-tazettine 23 in ten steps. The ring closure reaction of 27 to form 24 could occur by one of two possible mechanisms: either by the intramolecular Michael reaction involving the intermediate 28, which corresponds to the skeleton 10, or by intermolecular addition of methylamine to the enone 27, followed by ring closure by displacement of bromide. This would give the intermediate 29, which corresponds to the skeleton 12, in which case the synthesis will be of type C, and not of type A.





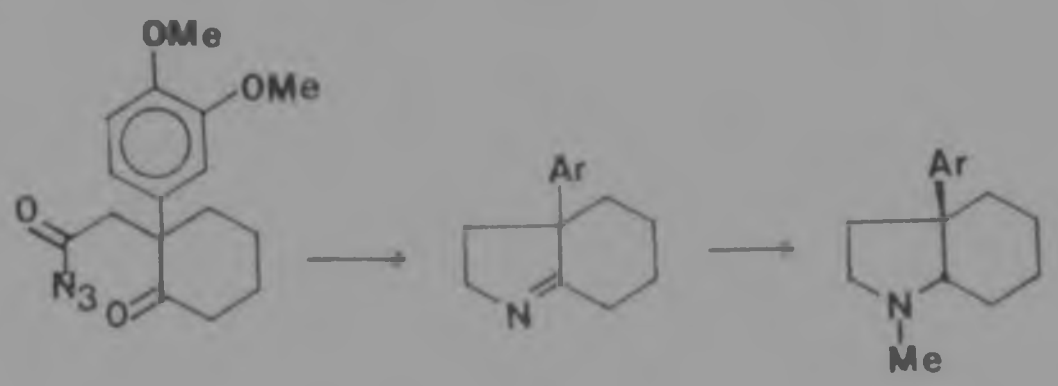
It is notable that the intramolecular Michael reaction produces exclusively the cis-fused mesembrine, and none of the trans-fused product, 7a-epimesembrine 30. This is as expected if the reaction is kinetically controlled because the transition state for the Michael reaction must involve approach by the nitrogen atom to the β-carbon atom at 109 ° to the plane defined by the enone system [20]. The transition state 31 leading to mesembrine, shown in its preferred conformation 32 [21], clearly fulfills this requirement. The transition state 33, which would lead to the trans-fused product is, however, excluded since it cannot achieve the necessary overlap and is further disfavoured by severe steric interactions between the substituents on nitrogen and the aryl ring (the distances shown are as measured from the Dreiding model of this species). In addition the cis-fused compound is thermodynamically more stable than the trans-fused compound [22] so that if the reaction is thermodynamically controlled, again the cis-fused compound would predominate.



31 32

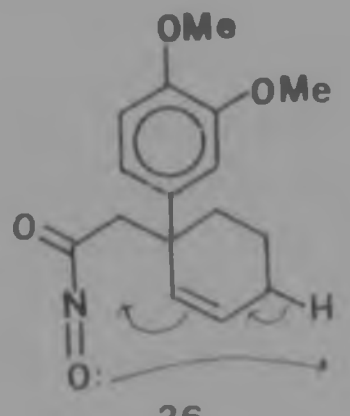
33 30

Although the intramolecular Michael reaction is so attractive for syntheses using the type A dissection, it is not the only successful method which has been followed. An example of a different approach appears in the first synthesis of the mesembrane skeleton by Popelack in 1960 [5], in which treatment of 34 with acid formed 35, which was converted to ( )-mesembrane by catalytic hydrogenation followed by methylation. It was known that catalytic hydrogenation of 35 would afford only the cis ring junction, from the analogous synthesis of (±)-crinane, by Wildman [23].



34 35

Another synthesis of mesembrine, due to Keck and Webb [24,25], utilized the intramolecular ene reaction of the acylnitroso compound 36 which rearranged to form 37. The steric requirements of this pericyclic reaction ensure that only the cis-fused ring junction could be formed. The instability of 36 prevented its use directly, so it was generated in situ by the retro-Diels-Alder reaction of its 9,10-dimethylanthracene (9,10-DMA) adduct 38 (scheme 4). The related alkaloids (±)-crinane and (±)-dihydromaritidine [25] have also been prepared by this method.



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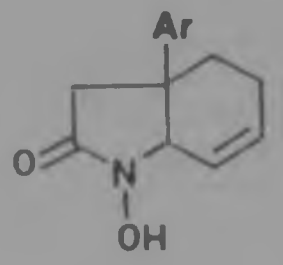

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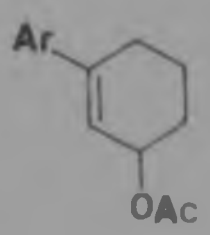
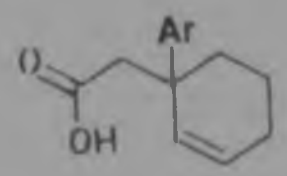
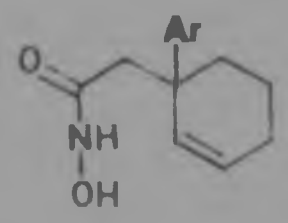


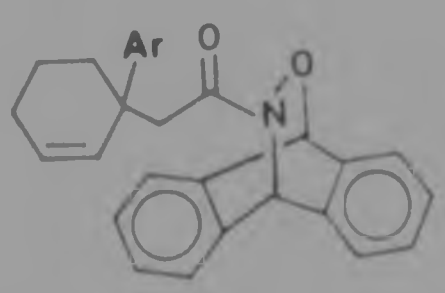
Claisen rearrangement



$NH_2OH \cdot HCl$, Na_2CO_3, Et_2O-H_2O



1) Oxidation
2) 9,10-DMA



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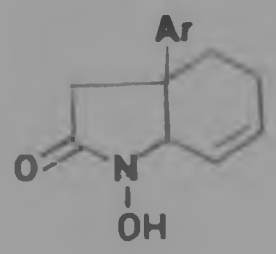
Toluene, reflux



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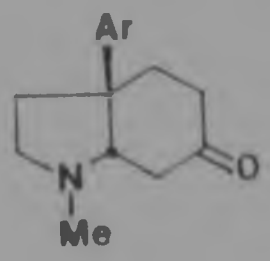
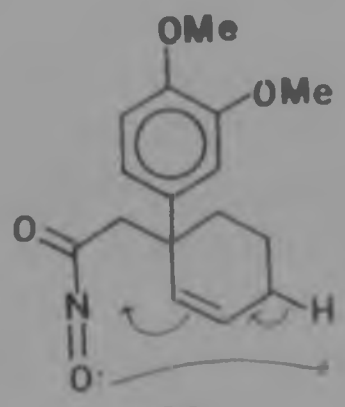
6 Steps



Scheme 4



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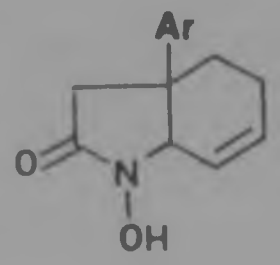

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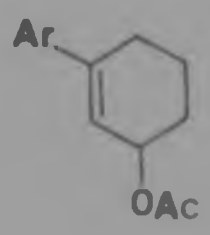
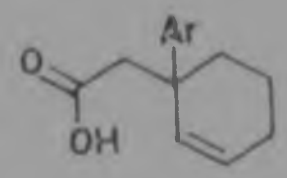
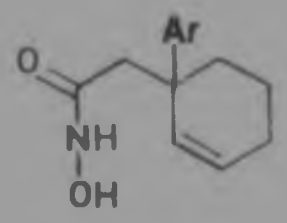


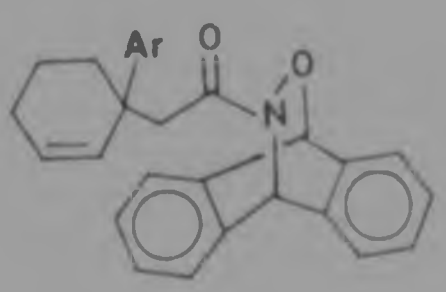
Claisen rearrangement



$NH_2OH \cdot HCl$, Na_2CO_3, Et_2O-H_2O



1) Oxidation
2) 9,10-DMA



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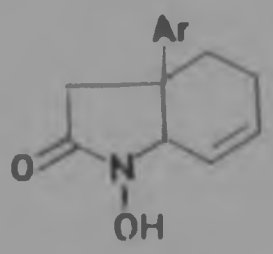
Toluene, reflux



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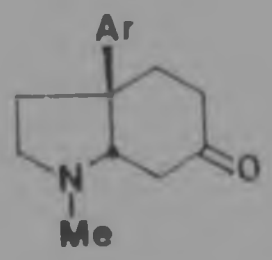
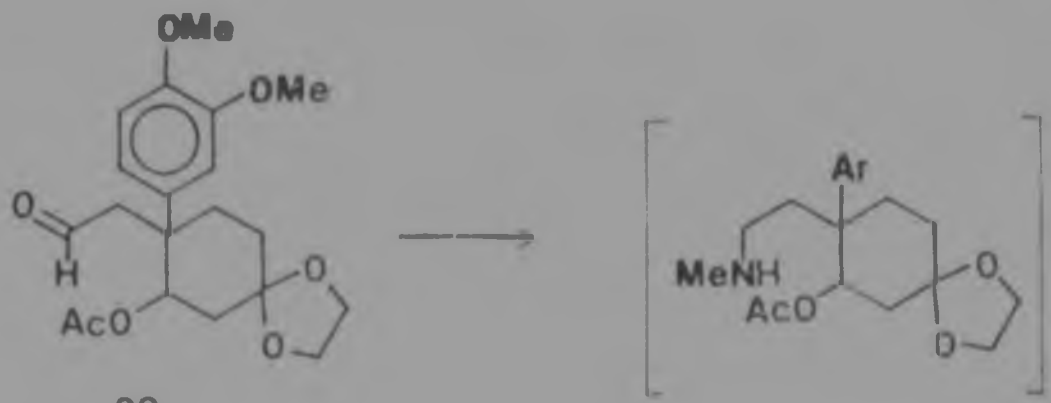
6 Steps



Scheme 4

In a sequence by Hoshini and co-workers [26], reductive amination of 39 gave the bicyclic compound 40. Deprotection by acid hydrolysis gave (±)-mesembrine. In this synthesis stereochemical control was dictated by similar considerations to those discussed above for the intramolecular Michael reaction, and again only the cis-fused system was obtained. (±)-maritidine has also been prepared by this method [27].



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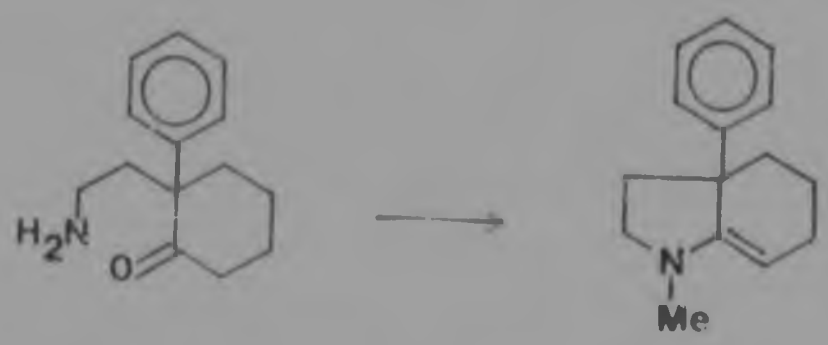
A related synthesis is that of Bachman and Fornefeldt [28] in which the enamine 41 was prepared from 42 by dehydration followed by methylation.



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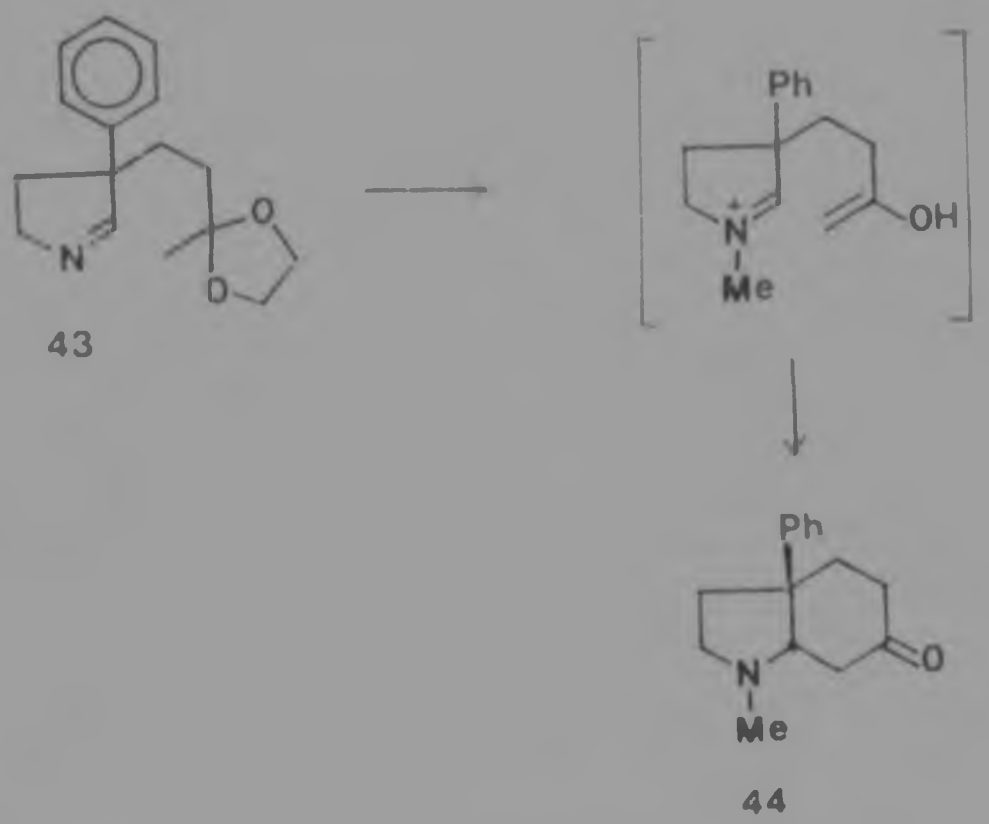
1.2.2 Syntheses of Type B

Syntheses of mesembrine which utilize th type B dissection proceed via an intermediate possessing the essential features of the skeleton shown in 11. Thus a pyrrolidine ring suitably functionalized to effect ring closure is required.

The first reported synthesis of this type wa' that of Oh-ishi and co-workers [29]. Compound 43, prepared in five steps from benzyl cyanide, was cyclized on treatment with methyl iodide and 10 % hydrochloric acid to give the unsubstituted phenyl analogue of (±)-mesembrine 44. The methoxyphenyl analogue of (±)-dihydrocrinine was also prepared by this method.

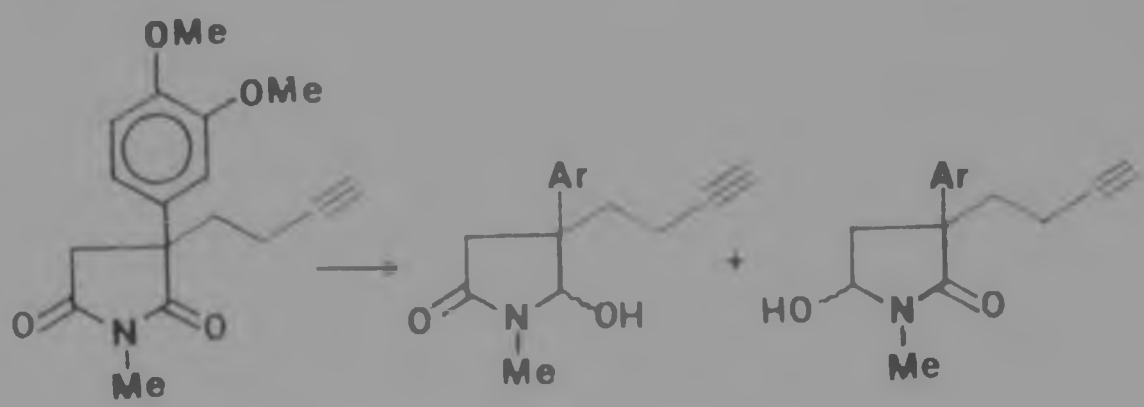


43

44

In the preparation of (±)-mesembrine carried out by Speckamp [30,31] compound 45 was prepare from 1-methyl-3-(3,4-dimethoxyphenyl)succinimide and 4-iodobut-1-yne, and regioselectively reduced with sodium borohydride to 46 in 69 % yield. Treatment of 46 (a) with formic acid afforded 47 in nearly

quant tative yield. Compound 47 has been converted by other workers to (±)-mesembrine [32]. This procedure has also been applied to the preparation of (±)-dihydromaritidine.



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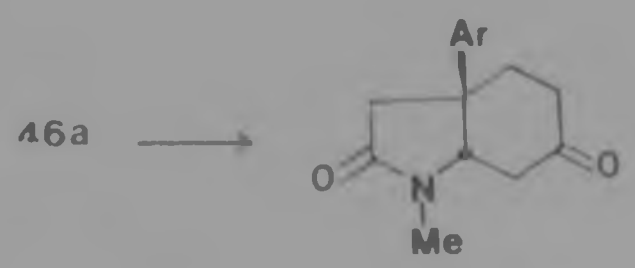
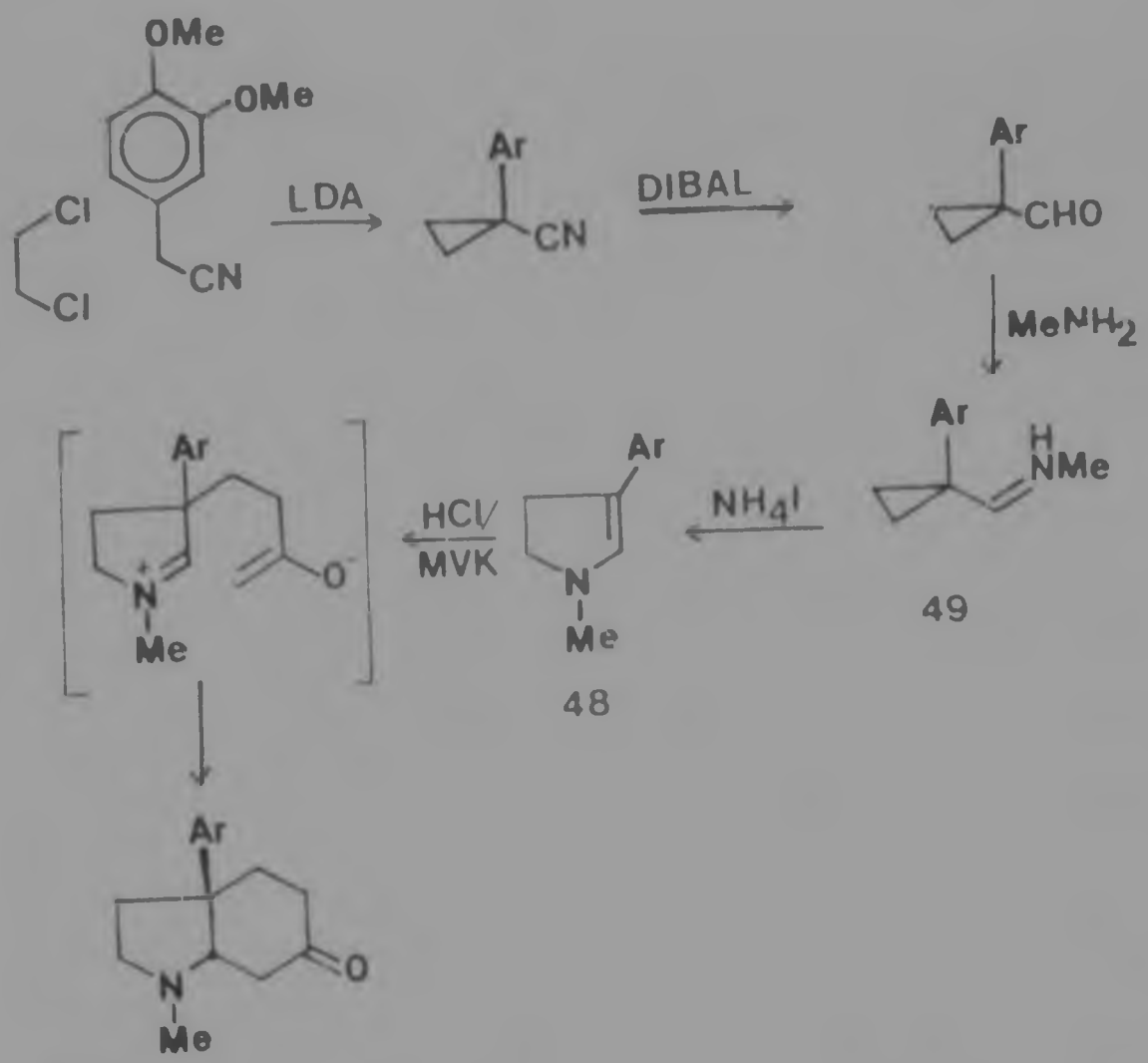


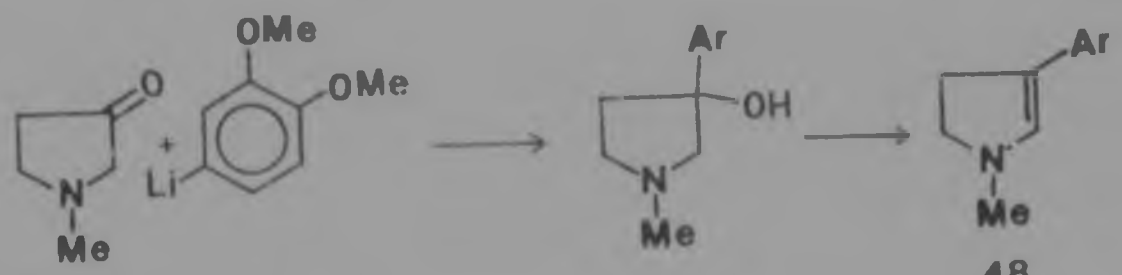
47 ~100%

A synthetic method developed almost simultaneously by Stevens and co-workers [33,34,35], Keely and Tahk [36] and Curphey and Kim [37], employs the reaction of methyl vinyl ketone with 3-(3,4-dimethoxyphenyl)-2-pyrroline 48. In the first two examples the pyrroline was prepared by acid catalyzed rearrangement of an appropriate cyclopropyl imine such as 49 (scheme 5 [34]).



Scheme 5

The Curphey and Kim synthesis [37] differs in that 48 was prepared by the reaction of 1-methyl-3-pyrrolidone 50 with 4-lithioveratrole, followed by acid catalyzed dehydration of the product. This approach has also been used in the synthesis of Amaryllidaceae [35] and Sceletium alkaloids [38]. Compound 48 has also been prepared by Sanchez and co-workers [39] from the N-benzenesulphonamide 22 in a sequence leading to mesembrine and mesembrenone (the dimethoxy analogue of sceletenone 4).

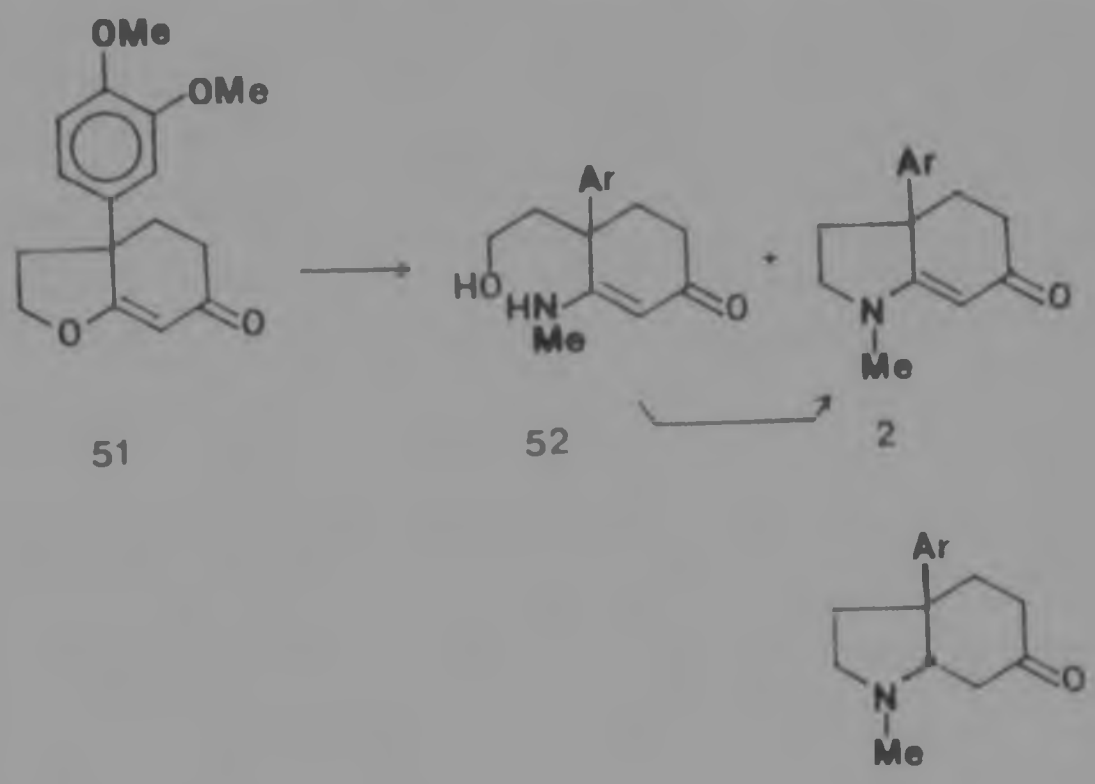


50 48

In all three of the type B syntheses discussed above, only cis-fused mesembrine was obtained. The stereochemical course of these reactions is determined by the geometric requirements for orbital overlap in the transition state, as in type A syntheses.

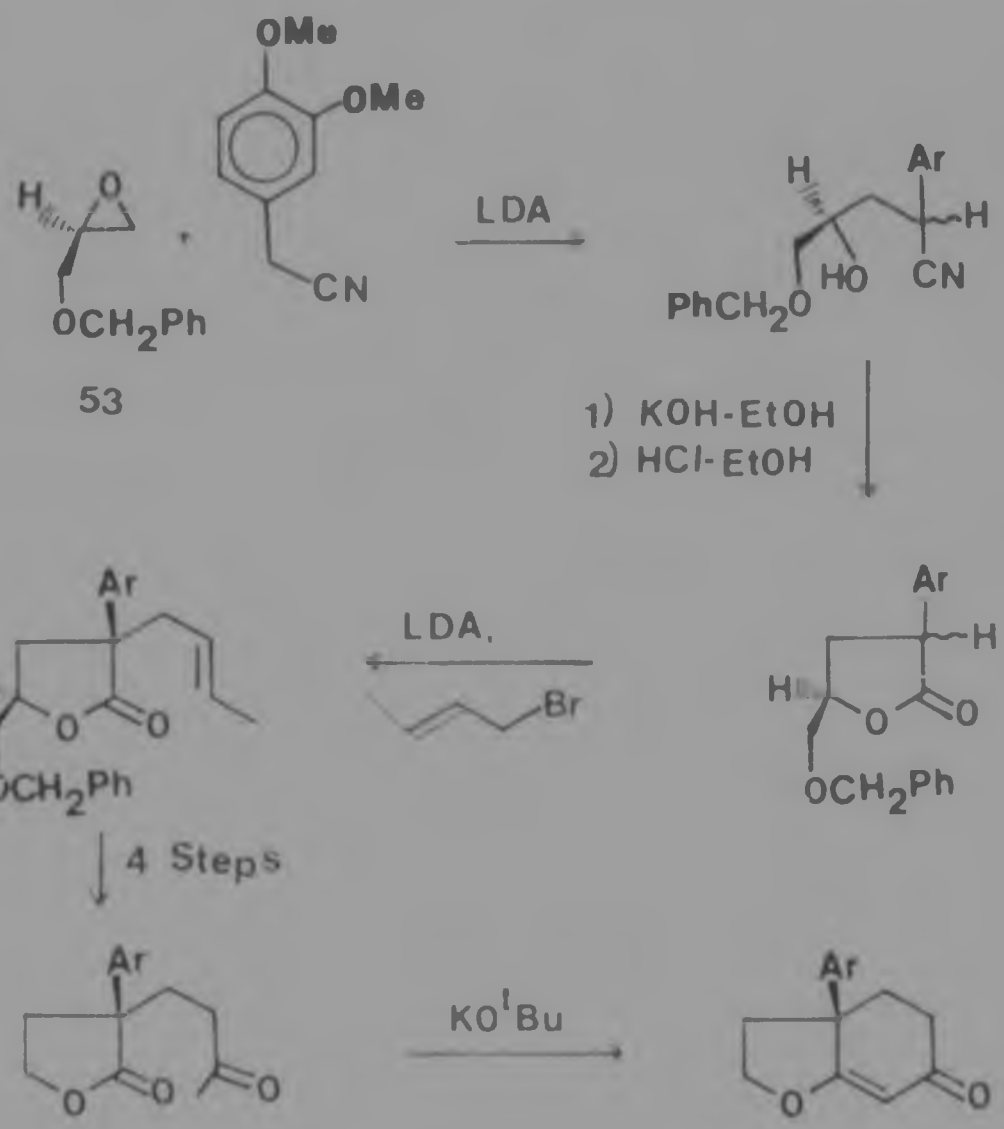
1.2.3 Syntheses of Type C

Use of the dissection C for the synthesis of mesembrine requires an intermediate possessing the essential features of the skeleton shown in 12. Takano and co-workers have developed syntheses of this type for (±)-mesembrine [40] (+)-mesembrine [41] and (-)-mesembrine [42]. In this work reaction of the enone with aqueous methylamine afforded a mixture of 52 and 2 (Δ'-mesembrenone) in 40 % and 7 % yields respectively. Conversion of 52 into 2 was accomplished in 85 % yield by treatment with diethyl azodicarboxylate and triphenylphosphine. The synthesis of mesembrine was completed in 77 % yield by a dissolving metal reduction of 2. Only the cis-fused, thermodynamically stable product was obtained, as expected from the dissolving metal reduction [43].



51 52 2

The three Takano syntheses vary in the preparation of the enone 51, which, while racemic in the preparation of (±)-mesembrine, must be chiral in the preparation of (+)- and (-)-mesembrine. Thus, for example, in the synthesis of (-)-mesembrine, 51 was prepared in nine steps starting from epoxide 53, which was prepared from (D)-mannitol (scheme 6).



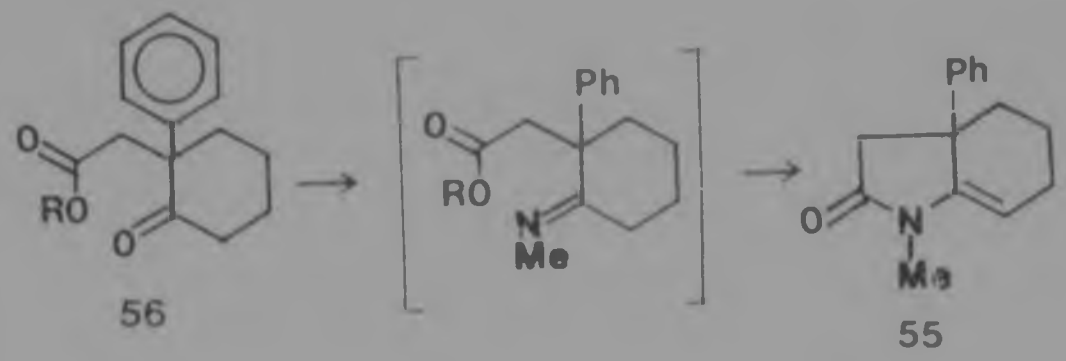
53

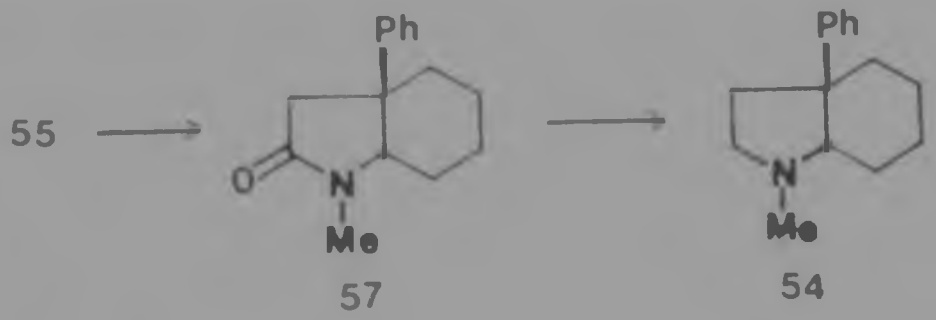
51

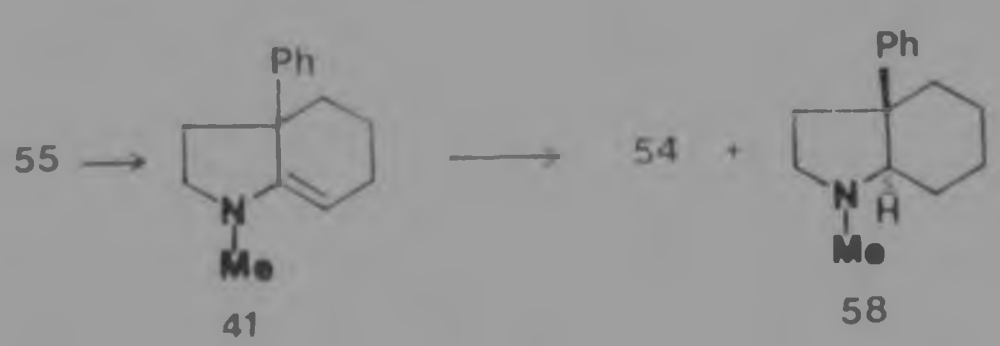
Scheme 6

Another synthesis of type C is that developed by Langlois and co-workers [44], in which a number of analogues of (±)-mesembrane, including the unsubstituted phenyl analogue 54 have been prepared. The pyrrolidone 55 was formed in 71 % yield by condensation of methylamine with the keto-ester 56. Catalytic hydrogenation of __ gave the cis-octahydroindolone 57 exclusively, and the lactam __s reduced with lithium aluminium hydride to give the product 54. In addition, lithium aluminium hydride reduction of 55 gave the enamine 41 which on reduction with sodium borohydride gave 54 in 50 %

yield, together with some of the trans fused product 58. Analogues of crinane-type alkaloids have also been prepared by this method.







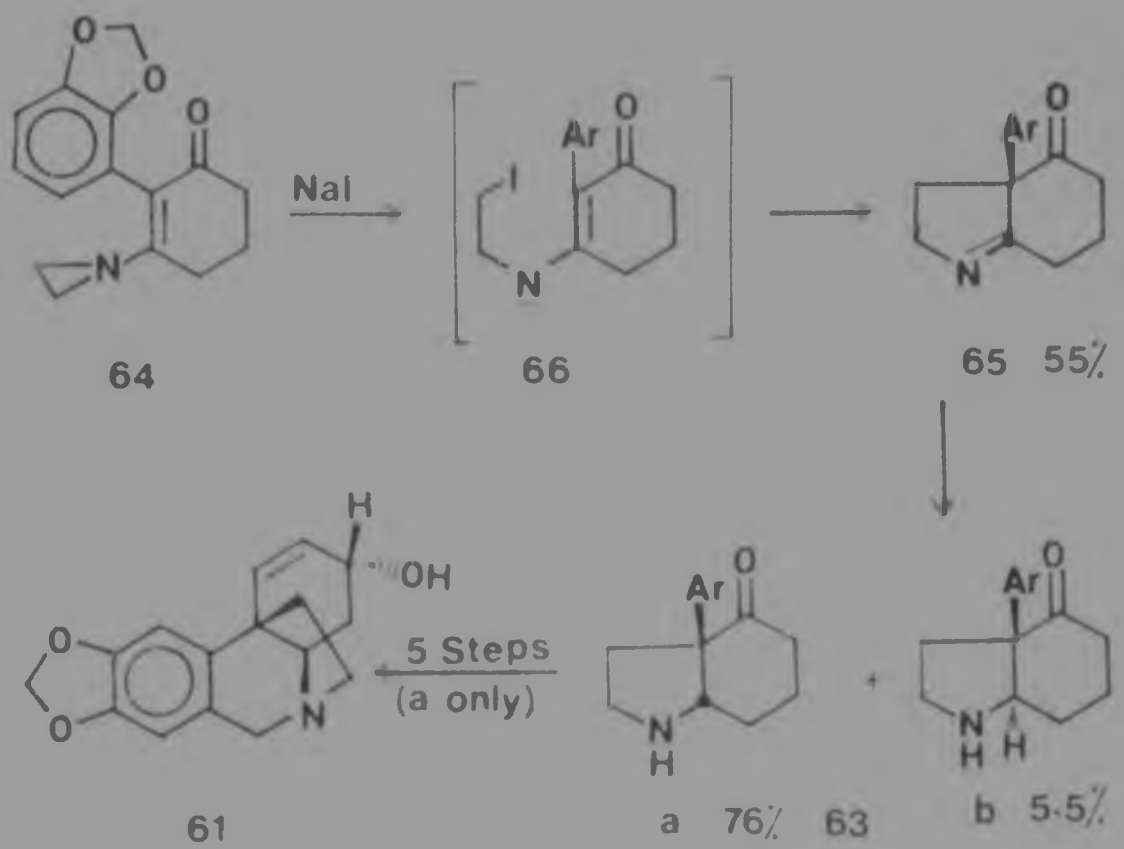
A total synthesis of (±)-crinine developed by Muxfeldt and co-workers [45] proceeded via the hexahydroindole 59. Treatment of the diamide 60 with sodium hydroxide gave 59 in 40 % yield, which was subsequently converted to (±)-crinine 61. The isomeric diamide 62 failed to cyclize under the same conditions.

60 59

62 61

1.2.4 Syntheses of Type D

Syntheses of mesembrine which use the type D dissection require an intermediate possessing the essential features of the skeleton shown in 13. A synthesis of this type is that developed by Whitlock and Smith [46] for (±)-crinine 61 and related alkaloids. Although mesembrine itself was not prepared, an intermediate in the route was the mesembrine-like 3a-aryl-hexahydroindole 63 (a). Thus, the iodide ion initiated rearrangement of the N-vinylaziridine 64 produced 65, which, on catalytic reduction gave 63 (a) in 76 % yield together with a small amount (5.5 %) of 63 (b). The reaction proceeded via the intermediate 66, analogous to skeleton 13. Further transformations of 63 (a) gave (±)-crinine 61.

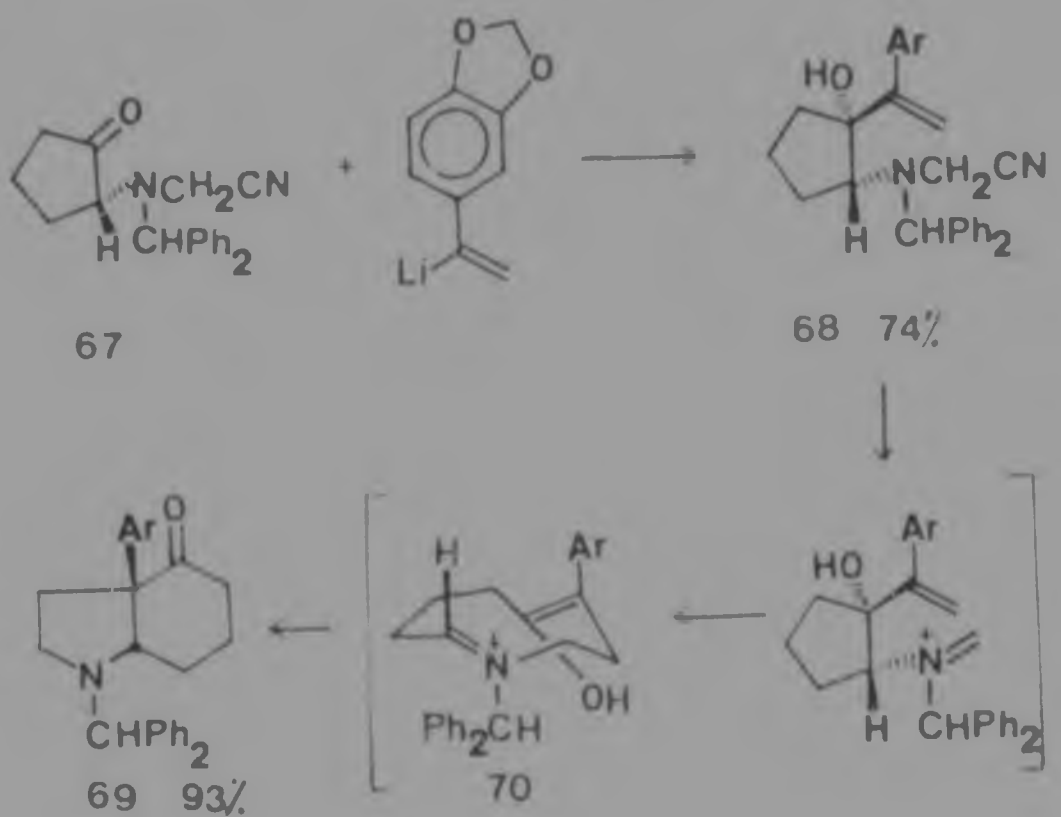


1.2.5 Miscellaneous Syntheses

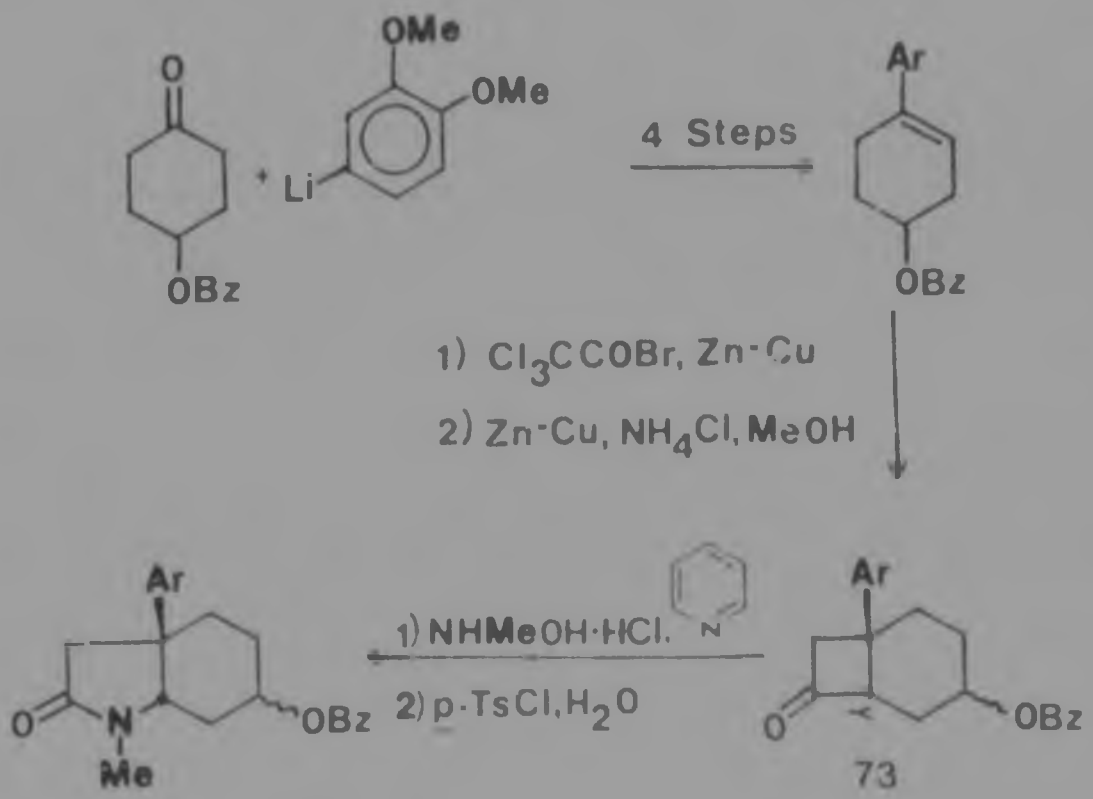
A number of syntheses of mesembrine exist in which the dissection of the ring system is not readily classifiable according to the above system. This occurs, for example, in those systems in which the skeleton is formed by rearrangement reactions.

Overman and co-workers [47,48,49] have developed a sequence for the preparation of the mesembrine skeleton which uses the aza-Cope rearrangement. Thus treatment of 67 with 1-(3,4-methylenedioxyphenyl)vinyllithium afforded the amino alcohol 68, which formed 69 on treatment with silver nitrate. Only the cis-octahydroindolone ring system is formed in this

reaction because only the intermediate shown in 70 is possible. Although Overman has not used this method for the synthesis of mesembrine itself, a formal synthesis of the related alkaloid (±)-crinine 61 [47,49] was completed.

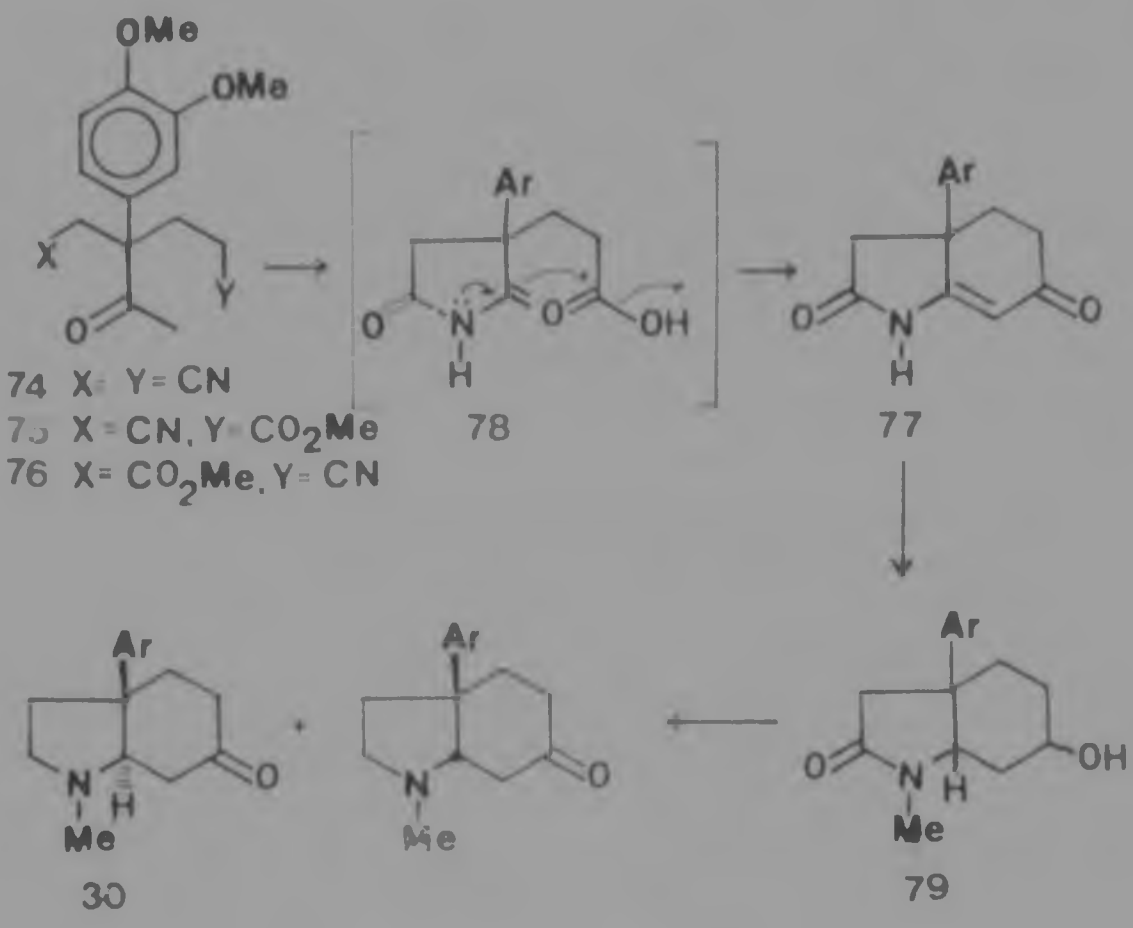


A synthesis developed by Jeffs and co-workers of (±)-mesembranol 71 and its 6-epimer 72 [50] involves a ring expansion reaction in the form of a modified Beckman rearrangement of the nitrone produced in 74 from compound 73. Since such reactions are known to proceed with retention of stereochemistry at the α-carbon atom [51], the formation of the cis-octahydroindole system is ensured.

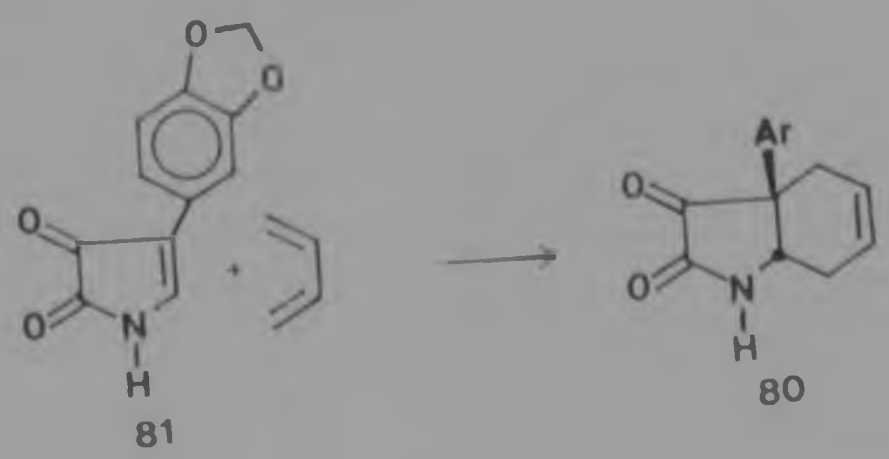


A synthesis of mesembrine by Oh-ishi and co-workers [32], which gave rise to both (±)-mesembrine and (±)-7a-epimesembrine 30 relied on the hydrolytic cyclization in sulphuric acid at 140 °C of 74, 75 or 76, all of which furnished the hexahydroindoledione 77 in 60 %, 73 %, and 73 % yields respectively. It is not clear in what order the bonds are formed in this reaction, although a possible mechanism has been proposed [52], whereby the cyclization proceeds via the enamine 78. Since 78 does not correspond to any of the skeletal types 10 to 13, this would mean that this synthesis is of a different

type to types A to D. After N-methylation of 77, catalytic hydrogenation gave rise to a mixture of stereoisomers of the alcohol 79 in 30-46 % yield. Subsequent transformations and separation of the isomers gave the two products.

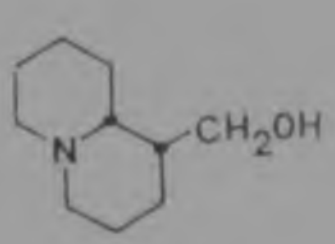


The mesembrine-like compound 80 was prepared by Isuda and co-workers [53] by the Diels-Alder reaction of the pyrrolinedione 81 with butadiene, in a synthesis which uses a combination of type B and D dissections. Compound 80 has been converted into a variety of Amaryllidaceae alkaloids [54].



CHAPTER 2 BACKGROUND AND OUTLINE OF PROPOSED WORK

The development of a general method for the synthesis of alkaloids has been a major interest in these laboratories for some time. Prior to the present work the synthesis of a number of alkaloid systems had been achieved, all containing nitrogen at the bridgehead position of a fused bicyclic system. Examples of alkaloid systems for which formal syntheses of the racemates have been developed are the quinolizidine alkaloid (±)-lupinine 82 [55,56], the indolizidine alkaloids elaeocarpine 83 [57,58] and ipalbidine 84 [59] and the hexahydrojulolidine derivative 85 [55]. The synthesis of pyrrolizidine alkaloids such as isoretronecanol 86 was not accomplished in these laboratories [60], but has been achieved by Pinnick [61].



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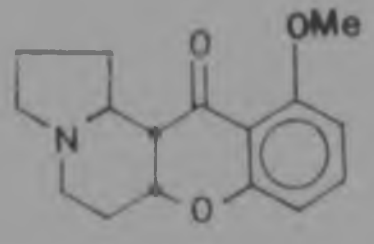

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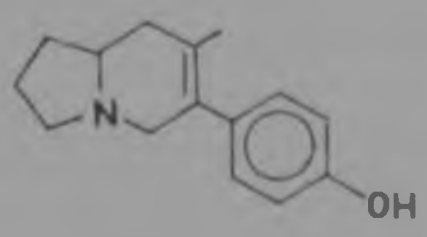

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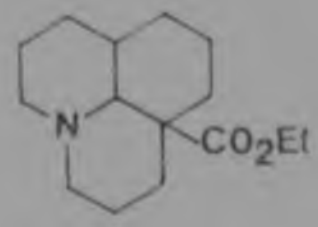

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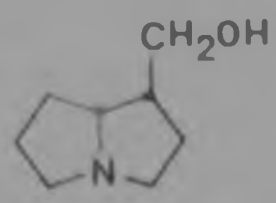
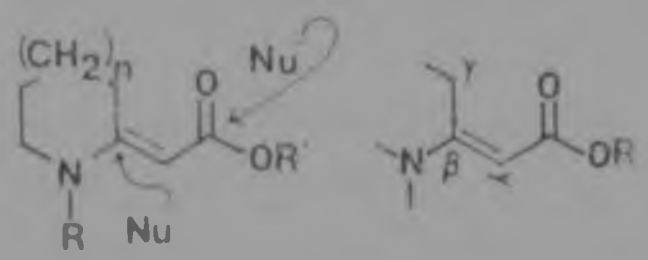


86

The synthesis of these fused heterocyclic systems was based on the use of exocyclic vinylogous urethanes 87 as precursors. The utility of vinylogous urethanes lies in their potentially versatile behaviour, both as nucleophiles and as electrophiles [62]. This is illustrated in the scheme shown below (n = 0,1).

87



In principle, nucleophiles can attack at the β-carbon or the carbonyl carbon, while reaction with electrophiles can occur through nitrogen, through the carbonyl oxygen, and through the α-carbon. It is known [63] that acylation and alkylation occur readily at the α-carbon. In principle, reaction with electrophiles can also take place through the γ-carbon, via the endocyclic enamine tautomer as shown. Reaction is known to occur predominantly through the γ-carbon, if the anion of the vinylogous urethane is formed by treatment with a strong base [63]. Bryson [64] has shown that the anions of vinylogous amides behave similarly.

The nitrogen bridgehead alkaloids were constructed by having suitably functionalized alkyl groups attached to nitrogen in vinylogous urethanes 87, using the nucleophilicity of the α-carbon to achieve cyclization. This is illustrated in

general terms in scheme 8. In principle, it can be seen that by varying the alkyl group on nitrogen, and the ring size of the vinylogous urethane, it is possible to construct a variety of bicyclic systems. In addition, suitable positioning of functional groups would allow further elaboration of the bicyclic systems.

Scheme 8

It was found that annelation of six membered rings was readily accomplished using this method. Thus the tosyl compound 88 was cyclized by warming in acetonitrile, producing the bicyclic vinylogous urethane 89. Reduction of 89 using sodium borohydride followed by lithium aluminium hydride gave lupinine 2 [55]. The ring closure in this case is a cycloalkylation reaction.

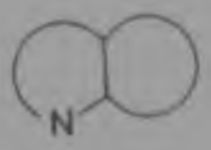
88 89

Ring closure by cycloacylation has also been achieved. For example, treatment of the sodium salt 90 with acetic anhydride gave bicyclic compound 91, an intermediate in the synthesis of Elaeocarpus alkaloids such as elaeocarpine 83 [57].

90 91

Neither annelation was found to be suitable for the elaboration of five membered rings [60], and thus pyrrolizidine alkaloids could not be produced in this way. The reason for this is probably that, being a 5-endo-trig ring forming process at the α-carbon atom, it is geometrically disfavoured according to Baldwin's rules [65].

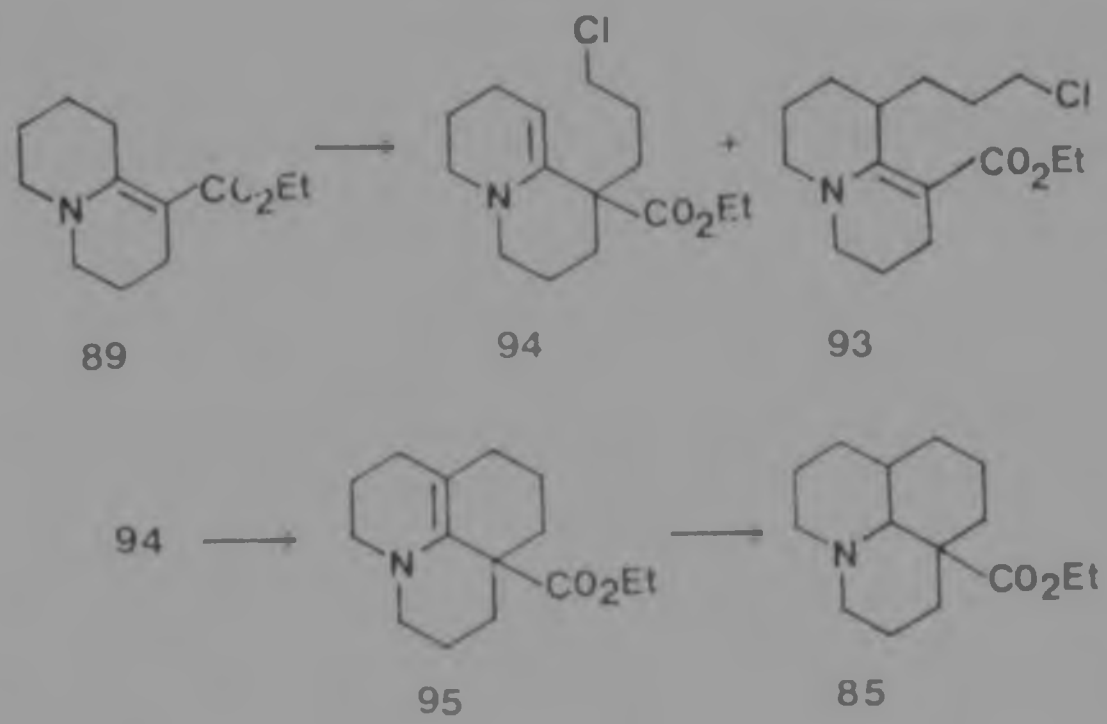
Although attention had initially been focussed on fused bicyclic systems containing nitrogen at the bridgehead position, it was felt that the reactivity towards electrophiles through the γ-carbon would allow the construction of systems where the nitrogen is one position removed from the bridgehead position as shown in 92.



92

The feasibility of producing such systems had already been illustrated in the preparation of the hexahydrojulolidine derivative 85 [55,56]. In this synthesis the bicyclic vinylogous urethane 89 prepared as described above, was treated with n-butyllithium followed by 1-bromo-3-chloropropane to give the vinylogous urethane 93 (10 %), together with the endocyclic enamine 94 (67 %). The major product 94 was cyclized to the

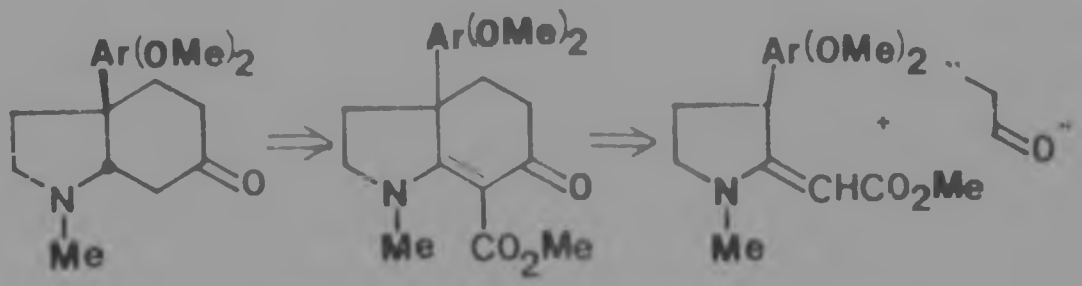
tetrahydrojulolidine derivative 95 by reaction with sodium iodide in acetone followed by warming in acetonitrile. The minor product 93 did not cyclize under these conditions. Catalytic reduction of 95 gave the stereoisomeric mixture of hexahydrojulolidine derivatives 85.



89 94 93

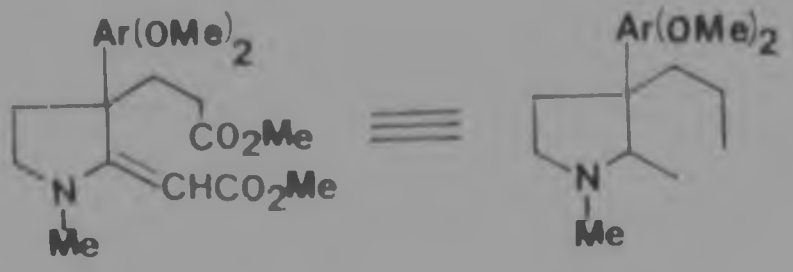
95 85

it was decided to attempt to extend the synthetic method to include further examples of alkaloids containing the ring system shown in 92, and Sceletium alkaloids of the mesembrine-type were chosen as the initial targets. Bond dissection of the parent alkaloid mesembrine 1 showed that it could, in principle, be produced by combination of vinylogous urethane 96 and some oxygenated three carbon unit via the hexahydroindole 97.



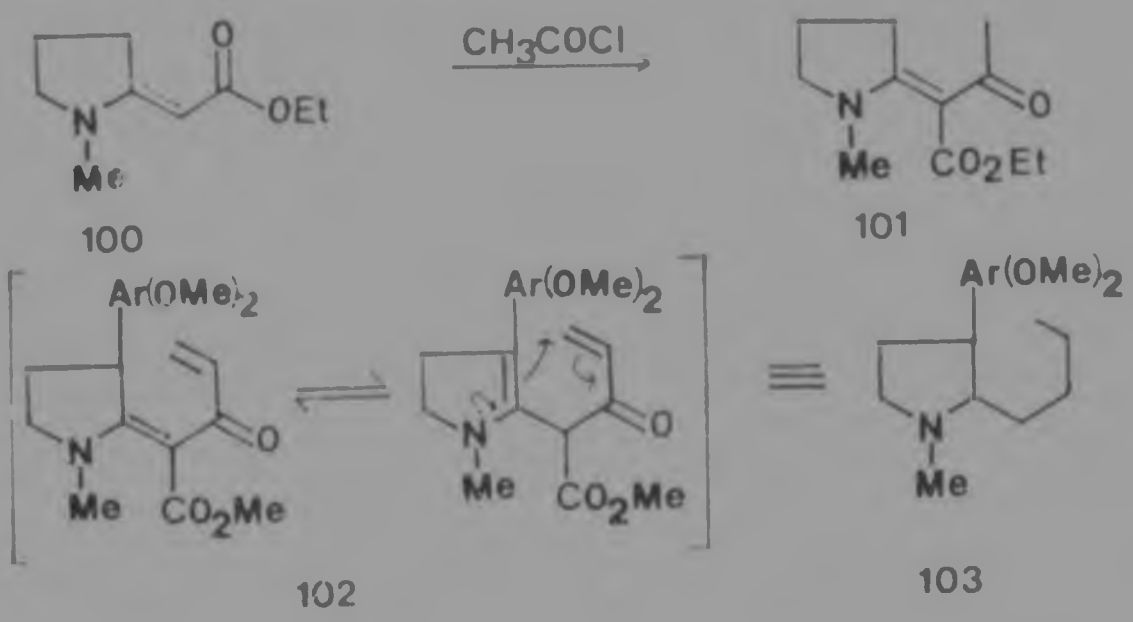
1 97 96

A number of possible ways of achieving the synthesis of mesembrine using the above route were apparent. One route which appeared feasible was by the Michael addition through the γ-position of 96 to a Michael acceptor such as ethyl acrylate, to produce ester 98. Although thevinylogous urethane itself would not undergo this reaction, it was expected that its anion would. It was envisaged that ester 98 would either cyclize directly through the α-carbon by a cycloacylation reaction, or, if not, could be cyclized via a mixed anhydride to give 97, as for compound 90 in the Elaeocarpus alkaloid synthesis. Comparing this route to those presented in chapter 1 (page 4) it can be seen that 98 does not correspond to any of the skeletons 10 to 13, but rather to 99. This sequence therefore represents a different approach to the synthesis of mesembrine (type E).



98 99

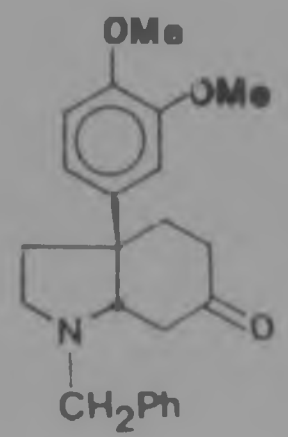
Another possible route to the hexahydroindolone 97 was by reaction of the vinylogous urethane 96 with an acylating agent such as acryloyl chloride. Reaction of vinylogous urethane 100 with acetyl chloride had given rise to 101 [60] and by analogy it was expected that reaction of 96 with acryloyl chloride would occur at the α-carbon thus producing compound 102. Completion of the synthesis would be by intramolecular Michael reaction through the γ-carbon in an alkylative ring closure. Compound 102 corresponds to the skeleton shown in 103, and hence is again not of types A to D, and represents another new approach to mesembrine (type F).



It was expected that the hexahydroindolone 97 could be readily converted to mesembrine 1, by hydrolysis and decarboxylation, followed by reduction of the double bond.

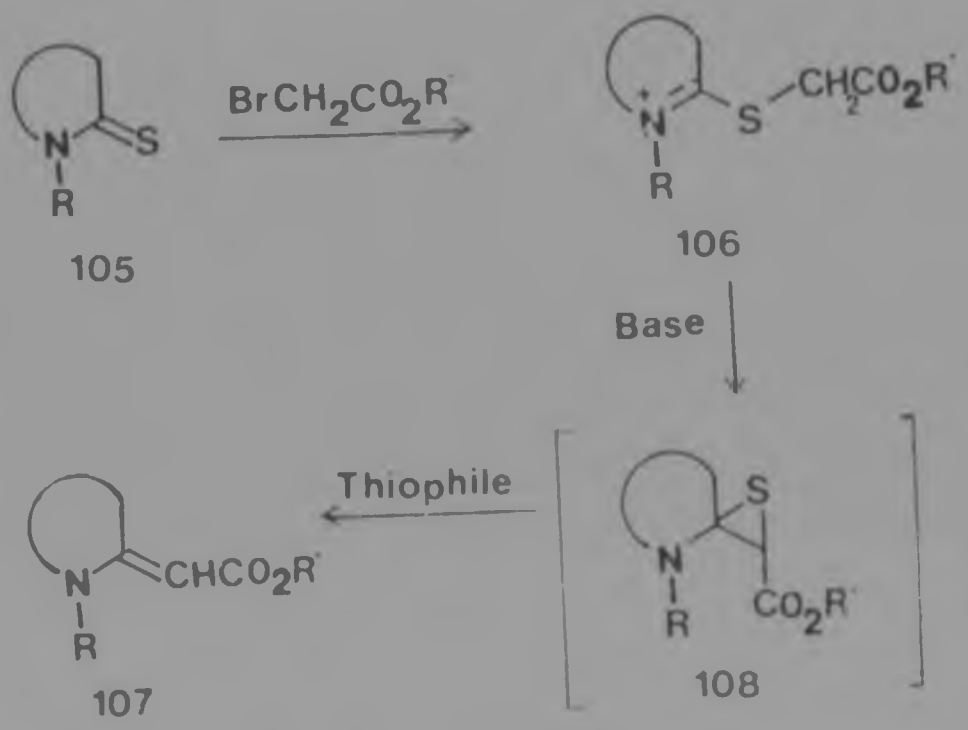
A particularly attractive feature of the synthetic route described above was that, if successful, it would not only be applicable to a variety of mesembrine alkaloids, but would also provide an entry to other alkaloid systems. For example, the octahydroindolone 104, closely resembling mesembrine 1, has been used as an intermediate in the synthesis of the

crinane-type Amaryllidaceae alkaloid (±)-dihydromaritidine [31].

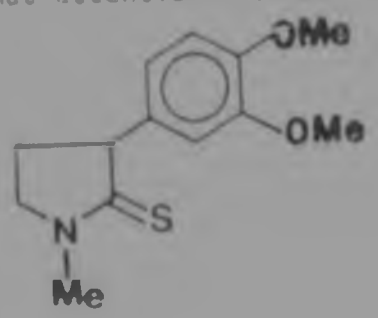


104

The success of the proposed route clearly depends heavily on the synthesis of the vinylogous urethane 96. The most convenient procedure for preparation of vinylogous urethanes is the sulphide contraction sequence originally developed by Eschenmoser and co-workers [66,67,68] for secondary vinylogous urethanes and amides. Work in these laboratories [60] had extended the scope of the reaction to include tertiary vinylogous urethanes and amides in greatly improved yields compared to the secondary analogues. In this extention of the sulphide contraction sequence, reaction of a thiolactam such as 105 with an α-bromo ester gives the salt 106 . Treatment with a base such as triethylamine, and a thiophile such as triphenylphosphine results in the formation of vinylogous urethane 107 probably via the episulphide 108.



Using the sulphide contraction sequence vinylogous urethanes of type 87 (n = 0 or 1) have been prepared in high yields (>70 %). It was envisaged that, in the mesembrine sequence, the sulphide contraction would proceed routinely, using the thiolactam 109. The synthesis of 109 was therefore of prime importance, and it was to this end that attention was initially turned.



109

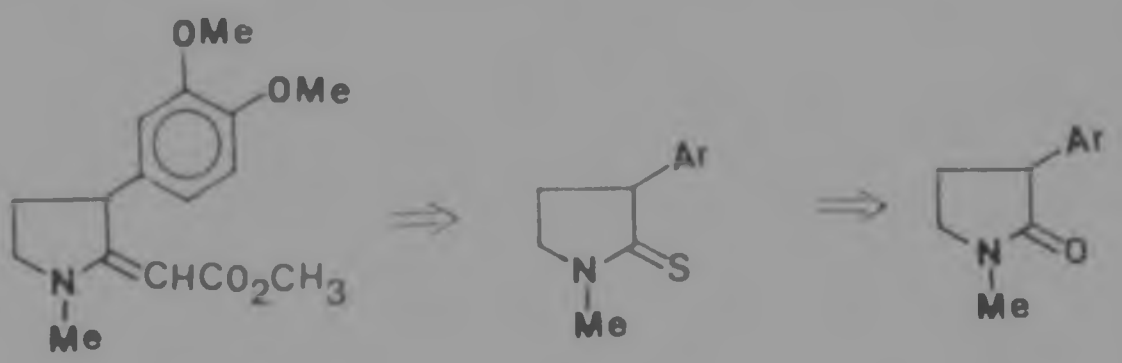
In summary, the aims of the project were: a. To develop a method for the preparation of thiolactam 109, and hence the vinylogous urethane 96; b. To use 96 to prepare the alkaloid mesembrine 1, thus broadening the scope of the general method for alkaloid synthesis from vinylogous urethanes to include alkaloids where nitrogen is removed from the bridgehead position; c. To use the route developed for

mesembrine for the preparation of related octahydroindoles, such as 104, allowing for an entry into the Amaryllidaceae alkaloids.

CHAPTER 3 THE SYNTHESIS OF LACTAMS AND THIOLACTAMS

3.1 Synthetic Strategy

In chapter 2 the need for the vinylogous urethane 96 was discussed. Although the direct preparation of the thiolactam 109 itself was possible in principle, the most convenient approach was to develop a synthesis of the lactam 110, which could then be thiated, using one of the convenient methods available [69,70].



96 109 110

Examination of the lactam 110 revealed that six one-bond disconnections were possible, as shown in fig 1 for lactams in general. A survey of the literature was undertaken to investigate the feasibility of utilizing each of the disconnections for synthesis of 110. However, in order to discern how best to approach the problem from available starting materials, consideration of two or even three bond disconnections was necessary.

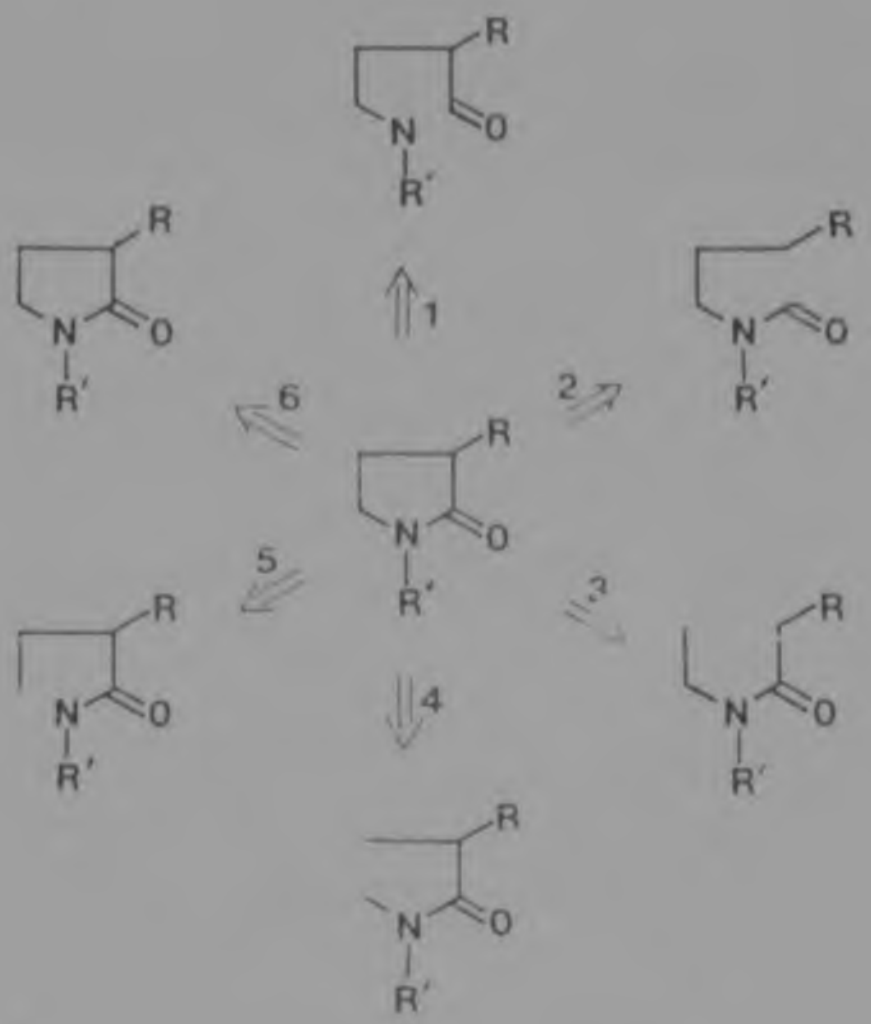
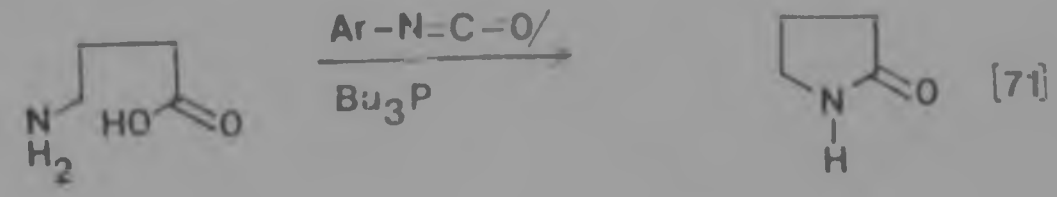


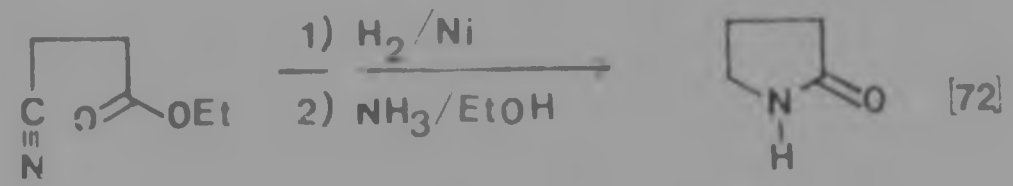
Fig 1

A representative sample of lactam syntheses is shown below. For convenience the following notation has been adopted: where two disconnections, for example, bond one and then bond three, are considered sequentially the synthetic route associated with this disconnection, in which first bond three is formed, and then bond one, will be a 3,1 synthetic approach.

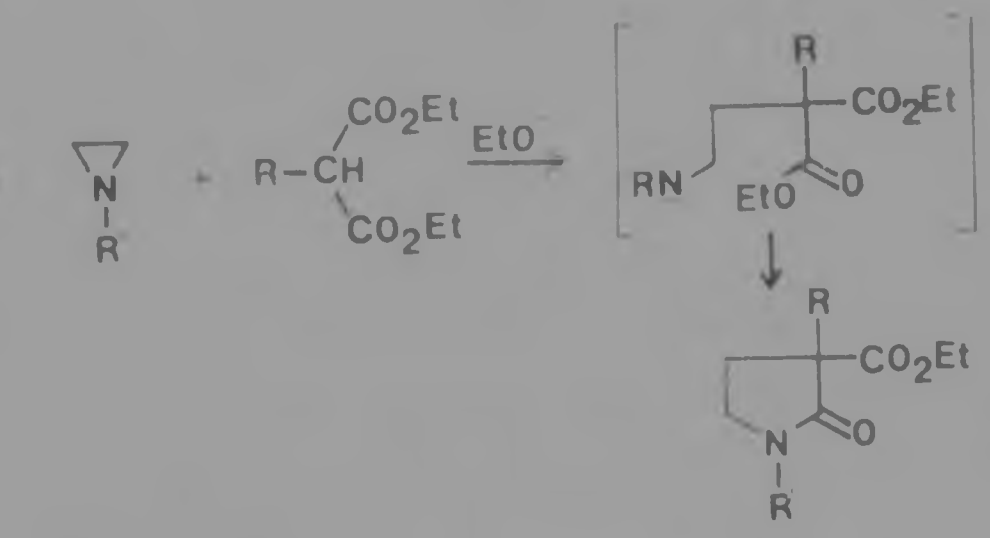
Bond 1 as final bond formed

1 

[71]

2 

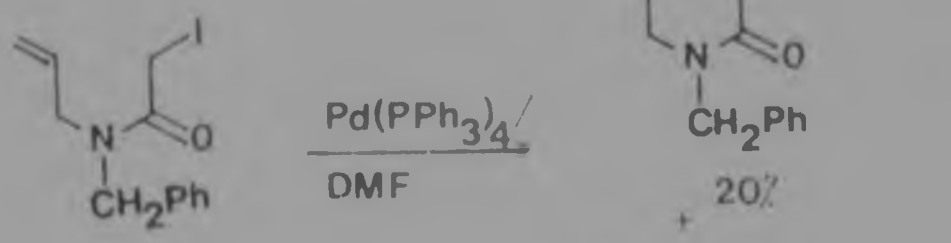
[72]

3 

[73]

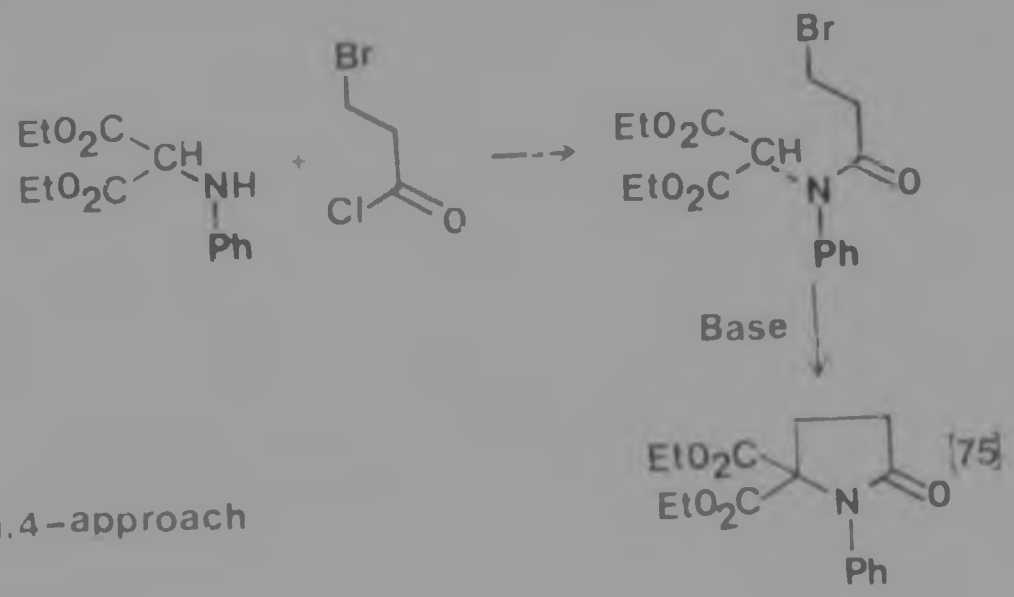
3.1–approach 113

Bond 3 as final bond formed

4 

[74]

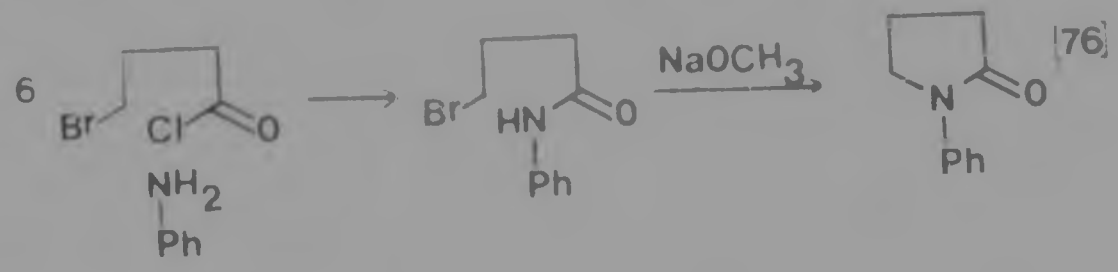
Bond 4 as final bond formed



[75]

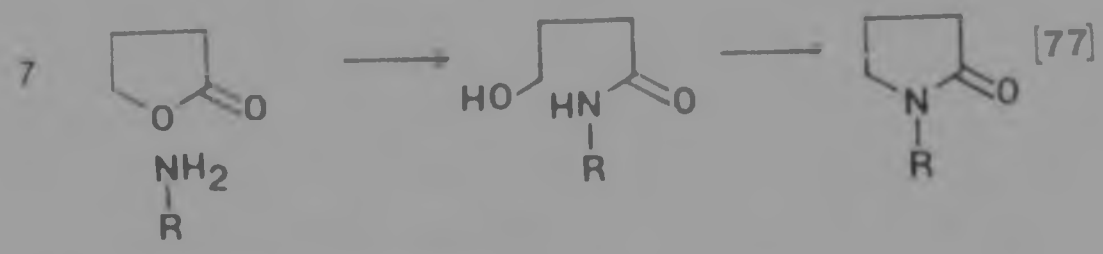
1,4-approach

Bond 5 as final bond formed



[76]

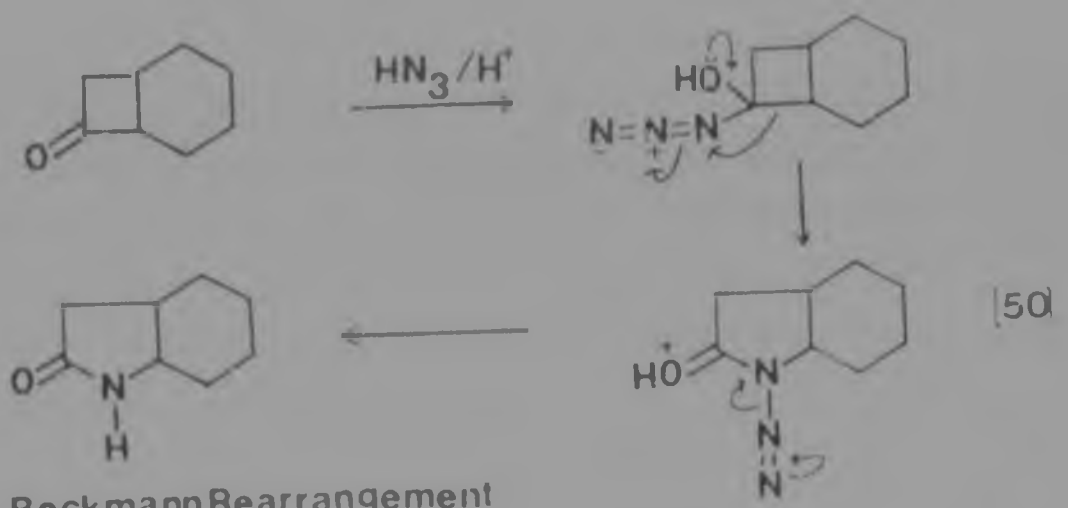
1,5-approach



[77]

1,5-approach

8

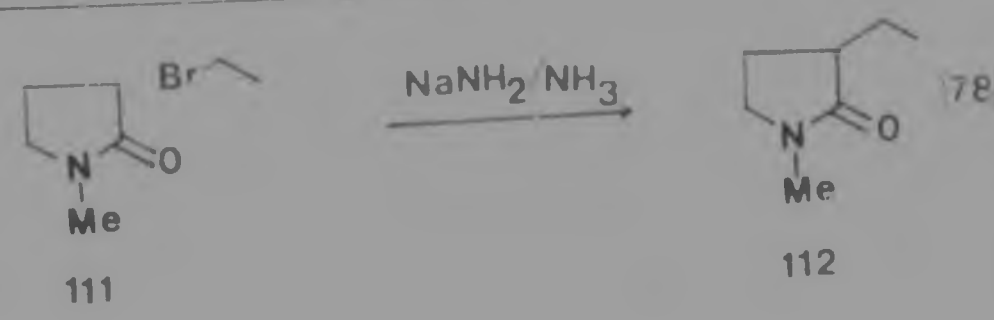


[50]

Beckmann Rearrangement

Bond 6 as final bond formed

9



[78]

111 112

The brief survey of the literature described above did not reveal any examples of lactam synth[illegible] which formed bond two for the final ring closure.

In evaluating the various routes for their possible application to the present problem, one which appeared attractive was that using bond disconnection six, that is, direct aryla:ion of N-methyl-2-pyrrolidone 111. This is clearly a more complex problem than the alkylation of pyrrolidones illustrated in the formation of N-methyl-3-ethyl-2-pyrrolidone 112 (reaction 9 [78]), since an aryl cation equivalent is required. A number of methods are, however, known for the reaction of nucleophiles with aryl rings. Since N-methy 2-pyrrolidone is an inexpensive, freely available material, this route, if successful, should be short and convenient.

Apart from the above route, no other single route was particularly attractive. It was clear, however, that a starting material possessing the 3,4-dimethoxyphenyl ring and appropriately functionalized for elaboration to the lactam was required. A readily available substance which fitted these criteria is 3,4-dimethoxyphenylacetic acid. Perusal of the bond disconnections involved in using this starting material revealed that bond three and bond one would have to be formed in the synthesis (fig 2).

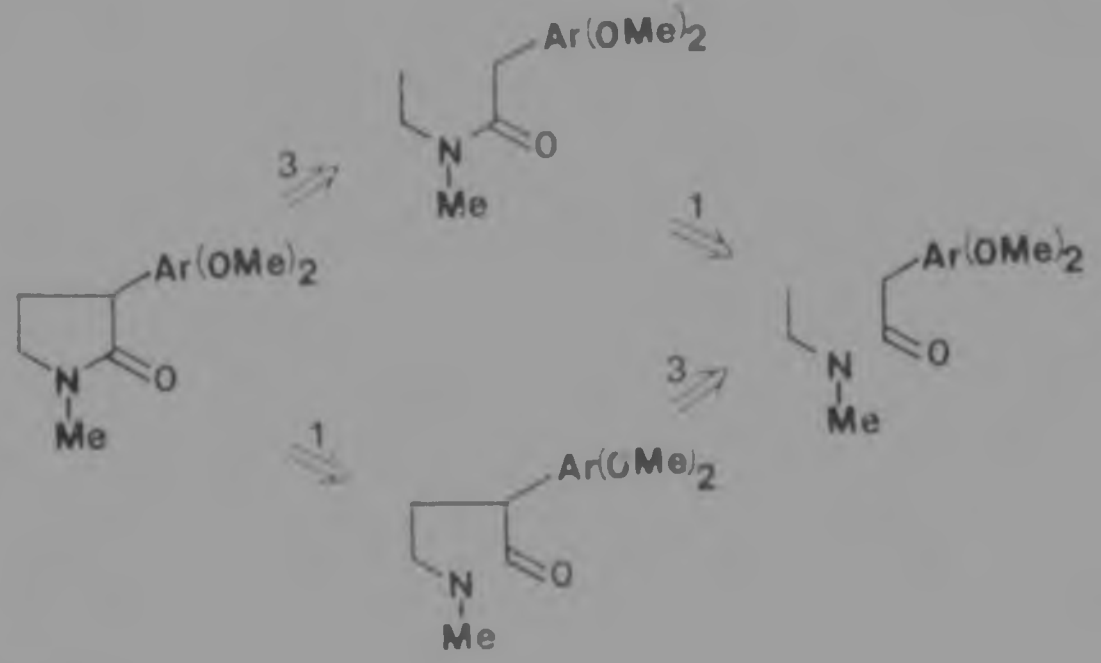
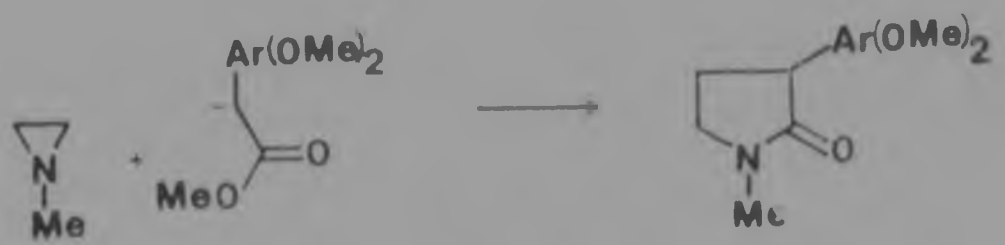


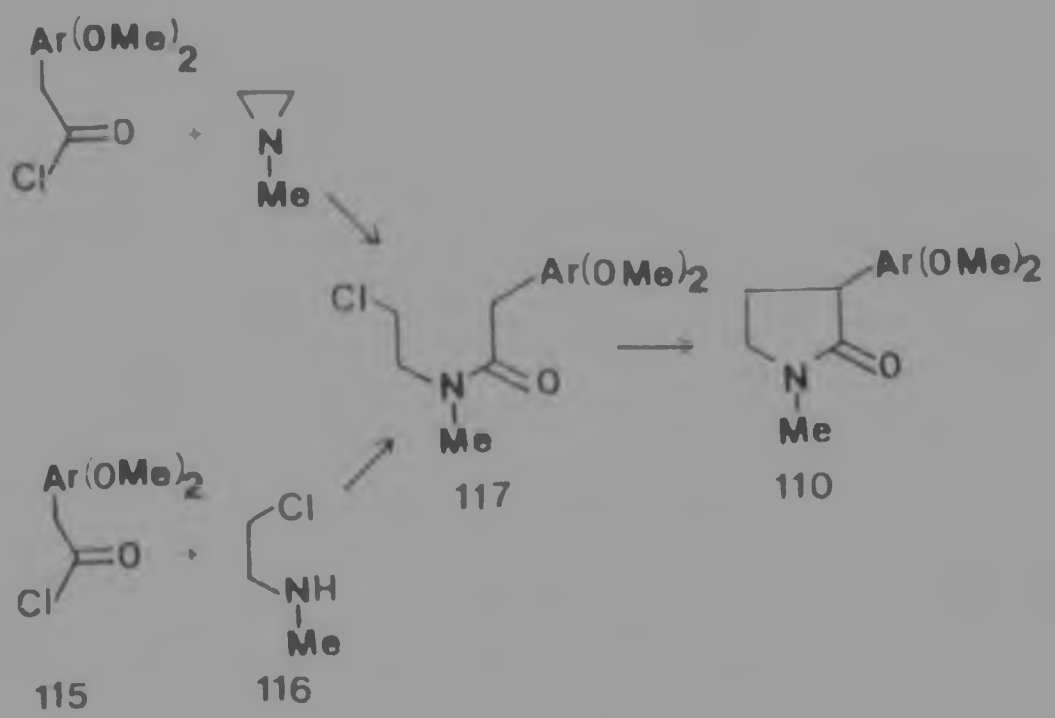
Fig 2

The reaction of aziridines with malonates giving 3-substituted pyrrolidones 113 (reaction 3 [73]) is an example of a lactam synthesis which utilizes the 3,1 synthetic approach. By analogy, if the anion of methyl 3,4-dimethoxyphenylacetate 114 could be reacted with N-methylaziridine it should then give the 3-arylpyrrolidone 110.



114 110

Although no examples had been found in the literature of a lactam preparation which used the 1,3 synthetic approach, this route was nevertheless felt to be feasible. For example 3,4-dimethoxyphenylacetyl chloride 115 might react with a halo-amine such as 116 forming the amide 117 which could be cyclized on treatment with a base. Alternatively, the reaction of aziridines with acid chlorides is known to produce 2-chloroethyl amides [79], so that amide 117 could possibly be prepared from 3,4-dimethoxyphenylacetyl chloride and N-methylaziridine.



117 110

115 116

A readily accessible derivative of 3,4-dimethoxyphenylacetic acid is its N-methyl amide. Use of this starting material would provide two further approaches to the lactam. As above, bond three would have to be formed, but in this case the other bond involved would be bond five (fig 3).

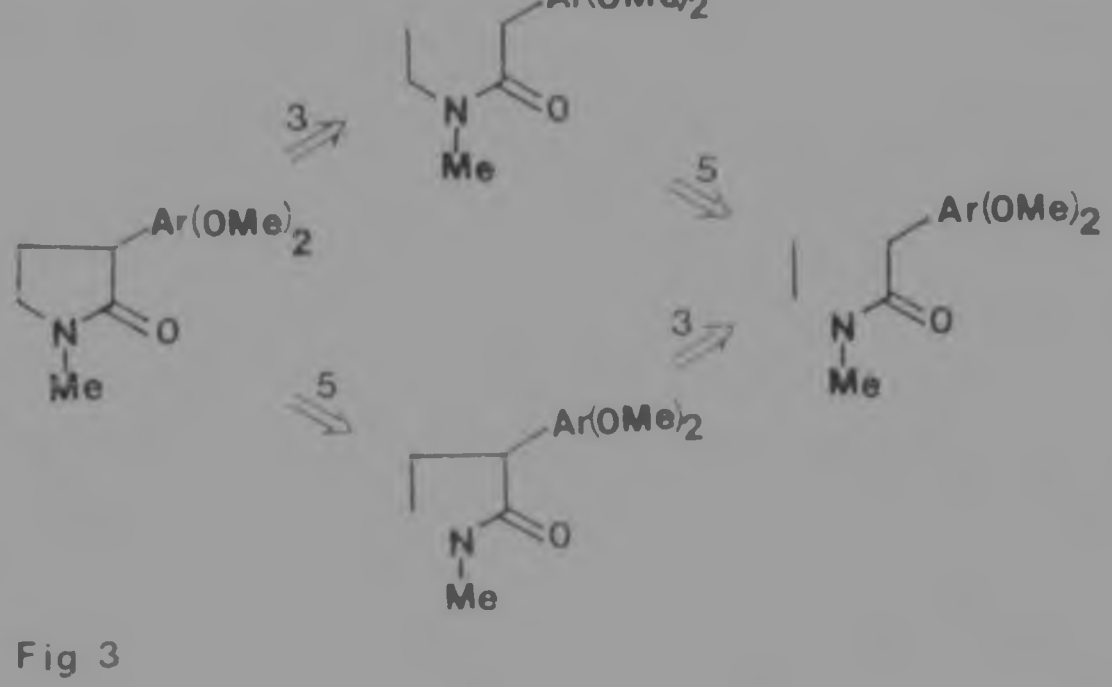
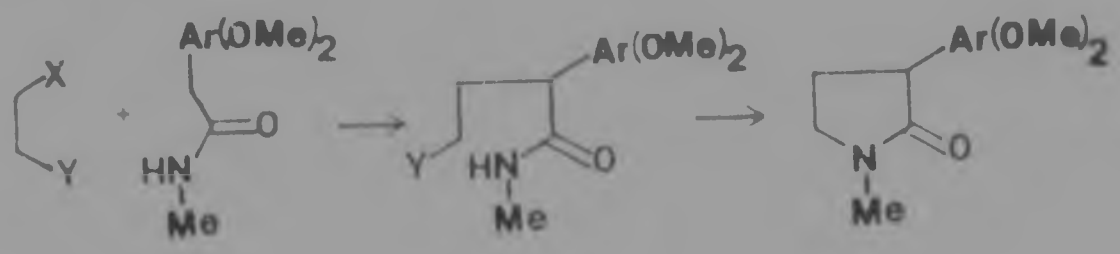


Fig 3

Use of the 5,3 synthetic approach would necessitate the intermediacy of the amide 117 which appeared above in the 1,3 approach. This amide could conceivably be prepared by the reaction of the anion of N-methyl-(3,4-dimethoxyphenyl)-acetamide with a suitable 1,2-disubstituted ethane, but this route did not seem to offer any advantages over the 1,3 approach.

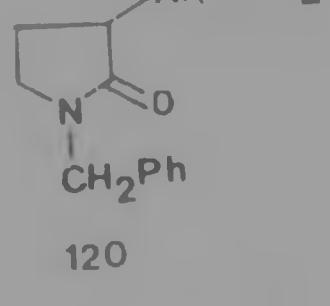
Examination of the 3,5 approach showed it would involve the intramolecular alkylation of the anion of an amide such as 118. This ring closure is analogous to that developed by Heine and co-workers (reaction 6 [76]). The preparation of 118 was not anticipated to be problematic, since amide dianions, formed by treatment with a base such as n-butyllithium, are

known to be alkylated at the α-carbon [80,81]. Thus 118 could probably be obtained from the reaction of the dianion of N-methyl-(3,4-dimethoxyphenyl)acetamide 119 with a 1,2-disubstituted ethane. Furthermore, since this reaction would in the first instance produce the anion of 118, it was likely that ring closure would occur directly, forming the lactam in one step from amide 119.



119 118 110

The choice of either N-methyl-2-pyrrolidone or 3,4-dimethoxyphenylacetic acid as precursors thus presents a wide range of possible approaches to the lactam 110 which could be explored. Although the strategy has been derived for this lactam, the same arguments would apply for other 3-aryl lactams. In particular, since the N-benzyl lactam 120 could serve as an intermediate in a route to dihydromaritidine 8, it would be prudent to deal with this synthetic problem concurrently.



120

3.2 The Bond Six Synthetic Approach: Attempted Synthesis by 3-Arylation of the Pyrrolidone Ring

3.2.1 Arylation by Aryllead Triacetates

Aryllead triacetates have been shown to be useful C-arylation agents for a wide range of compounds, including β-dicarbonyl compounds, nitroalkanes, and the salts of ketones and malonic esters [82]. Thus it was felt that if 3,4-dimethoxyphenyllead triacetate could be prepared, its reaction with the lithium salt of N-methyl-2-pyrrolidone 111 could provide the lactam 110.

Lead triacetates of aryl ethers including 4-methoxyphenyllead triacetate and 2,4-dimethoxyphenyllead triacetate had been prepared by a variety of methods [83-86]. The desired compound had not, however, been reported. Unfortunately, although these procedures were applied to the synthesis of 3,4-dimethoxyphenyllead triacetate, none of them proved successful.

Treatment of 1,2-dimethoxybenzene with lead tetraacetate in benzene in the presence of mercuric acetate, according to the method of de Vos and co-workers [86] gave a very small amount of an intractable orange solid after a five day reflux and aqueous work-up. When the reaction time was shortened to five hours, only lead oxide was obtained. Using a large excess of 1,2-dimethoxybenzene, and no solvent, again no product was obtained after heating at 80 °C overnight and aqueous work-up.

The attempted plumbylation of 1,2-dimethoxybenzene with lead tetraacetate in the presence of trichloroacetic acid [83] also did not give any of the desired product. Similarly the use of mono- and dichloroacetic acids proved unsuccessful.

Aryllead tricarboxylates have also been prepared by a silicon - lead exchange which occurs on treatment of aryltrimethylsilanes with lead tetraacetate and trifluoracetic acid [82]. Thus 3,4-dimethoxyphenyltrimethylsilane was prepared by treatment of 3,4-dimethoxyphenylmagnesium bromide with trimethylchlorosilane. Treatment of the silane in trifluoracetic acid with lead tetraacetate gave an uncharacterizable black oil.

Subsequent to the completion of the above work the preparation of 3,4-dimethoxyphenyllead triacetate was reported, using a tin - lead exchange reaction [87]. The successful synthesis of the lactam 110 by other means (vide infra) rendered further attempts to prepare it using the lead reagent unnecessary, so this route was not pursued.

3.2.2 Arylation Using $S_{RN}1$ Aromatic Substitution

Aromatic substitution by the $S_{RN}1$ mechanism was first discovered in 1970 by J F Bunnet and co-workers [88]. A wide variety of carbon nucleophiles including ester and ketone enolates have been found to react with aryl halides and other substituted benzenes, although stabilized carbanions such as those of malonic ester and nitromethane do not react. It has also been found that $S_{RN}1$ reactions are tolerant of alkyl, alkoxy, and other substituents on the aryl ring. Since the $S_{RN}1$ reaction proceeds via a radical mechanism, some form of initiation is required. This has been achieved using various methods including the use of alkali metals in ammonia, and by photostimulation.

It was felt that, since the desired pyrrolidone anion was closely related to ketone and ester enolates, the $S_{RN}1$ reaction might prove sucessful for synthesis of the lactam

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It was felt that, since the desired pyrrolidone anion was closely related to ketone and ester enolates, the $S_{RN}1$ reaction might prove sucessful for synthesis of the lactam

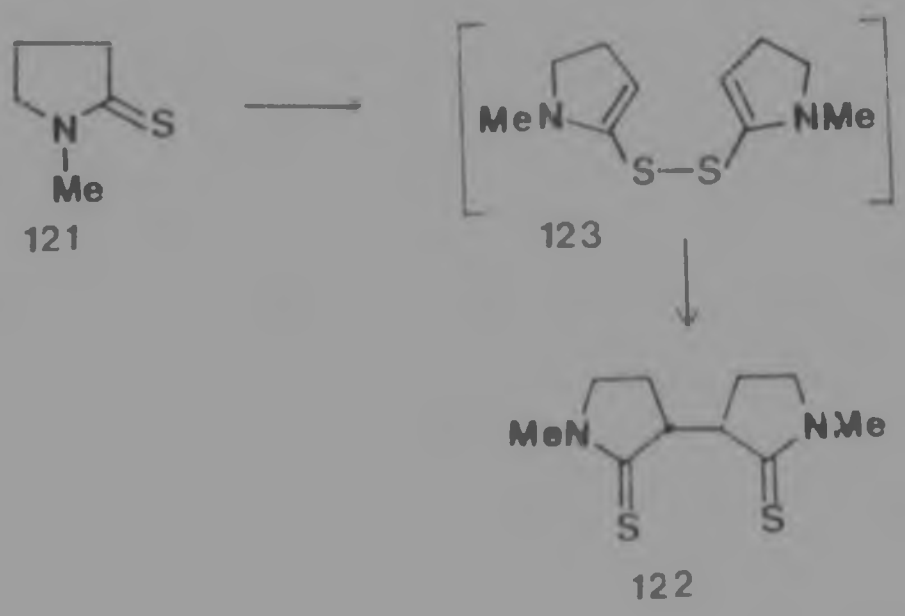
110, or the thiolactam 109. These expectations were unfortunately not realized.

In all the attempts made in this series of reactions, photostimulation was used for initiation, and 1-bromo-4-methoxybenzene was used as a model for the less readily available 1-bromo-3,4-dimethoxybenzene.

The anion of N-methyl-2-pyrrolidone 111 was generated using potassium amide in ammonia at -78 °C for ten minutes. Addition of 1-bromo-4-methoxybenzene was followed by fifteen minutes of irradiation. Aqueous work-up gave only a mixture of the starting materials. The same result was obtained when the anion was generated at -33 °C for one hour.

With the use of potassium t-butoxide in ammonia at -33 °C for one hour, followed by addition of 1-bromo-4-methoxybenzene and five hours of irradiation, again a mixture of starting materials was obtained. Generation of the anion with n-butyllithium in THF at 0 °C and twenty minutes of irradiation also failed to yield any products.

Failure to achieve results using the anion of N-methyl-2-pyrrolidone 111 led to the attempt using the anion of N-methyl-2-thiopyrrolidone 121. Using potassium amide in ammonia at -33 °C for thirty minutes followed by fifteen minutes of irradiation no new product was discernible. No improvement was obtained using potassium t-butoxide as base and irradiating for five hours. Using n-butyllithium in THF at 0 °C with thirty minutes of irradiation a mixture was obtained, consisting of the starting materials N-methyl-2-thiopyrrolidone 121 and 1-bromo-4-methoxybenzene in 36 % and 50 % respectively, as well as the dimer 122 which was obtained in 18 % yield.



121 123 122

The obtention of compound 122 was unexpected, but the dimerization of N-methyl-2-thiopyrrolidone 121 has been reported to occur in 83 % yield on treatment with sec-butyllithium and iodine [89]. It was proposed that N-methyl-2-thiopyrrolidone was oxidized by a radical mechanism, to the divinyl disulphide 123, which undergoes a Cope-type rearrangement, giving 122. In the present case, the radical reaction could have been initiated by photolysis.

The uniformly negative results obtained in the above series of reactions was disappointing, and it was decided to attempt another method for the arylation.

3.2.3 Arylation Using Diaryliodonium Salts

Diaryliodonium salts have been used for arylation of carbanions of a variety of compounds, including dimedone, 1,3-indanediones and esters [90,91].

Previous work in these laboratories [92] had shown that the vinylogous urethane 124, prepared from N-methyl-2-pyrrolidone

111 could be phenylated at the α-position to give 125 in 23 % yield. In the present study, a similar result was obtained. Treatment of 124 with n-butyllithium in THF at 0 °C followed by diphenyliodonium chloride gave 125 in 23 % yield after stirring at room temperature for two days. It was decided to attempt to improve the yield of this model reaction since ultimately, the arylated vinylogous urethane 96 was required. 3,4-Dimethoxy-phenyl-iodonium chloride was itself not a known compound and it was not felt worthwhile to attempt its preparation until the model reactions gave clear indications of success.

124 125

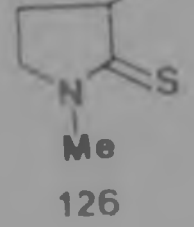
Using the original conditions, except that tetramethyl-ethylenediamine (TMEDA) was added to the reaction mixture before the addition of the diphenyliodonium chloride, thin layer chromatography (TLC) showed that, after three hours of heating only a small amount of the product was formed, and a large amount of unchanged starting material was still present. On using ether as solvent in place of THF similar results were obtained. No change was observed using THF as solvent but with the addition of hexamethylphosphoramide (HMPA) instead of TMEDA. Using dimethylsulphoxide (DMSO) as solvent, with the addition of TMEDA, TLC again showed that only a small amount of the vinylogous urethane 124 had been phenylated. Using simply dimethylformamide (DMF) as solvent TLC indicated that none of the product was formed.

Treatment of the vinylogous urethane 124 with potassium amide in ammonia, followed by diphenyliodonium chloride, gave the

phenylated urethane 125 in 9 % yield.

It seemed that the conditions for phen ation of urethane 124 which had been used originally could not be improved on. The reaction was therefore attempted with the anion of N-methyl-2-thiopyrrolidone 121.

Treatment of 121 with n-butyllithium in THF at 0 °C, followed by diphenyliodonium chloride gave, however, not the thiolactam 126, but rather diphenyl disulphide, in 1 % yield, as well as the dimeric compound 122 in 6 % yield. The obtention of the dimer 122 under these conditions is understandable, since diphenyliodonium chloride is known to react with anions by a radical mechanism [90]. The formation of the diphenyl disulphide probably also arises via a radical reaction, although this is not easily understood.



126

The unsatisfactory results obtained with the use of diphenyliodonium chloride, together with the problems which would have arisen in the preparation of 3,4-dimethoxyphenyl-iodonium chloride led to the abandonment of this route.

3.2.4 Arylations Using Organocopper Reagents

It is known that a wide variety of organocopper reagents react readily with aryl iodides providing a route to substituted aromatic compounds [93]. Although most of the reported reagents RCu have R as an alkyl, alkenyl, or alkynyl group, the reaction seems to be limited primarily by the availability of

such reagents [94]. It was felt that this reaction could possibly be applied successfully in the present work. In a series of model reactions the phenylation, using iodobenzene, of both N-methyl-2-thiopyrrolidone 121 and the vinylogous urethane 124 was attempted.

Thiopyrrolidone 121 was reacted with n-butyllithium and cuprous iodide at 0 °C in THF to form the organocopper reagent. After the addition of iodobenzene, the reaction solution was heated under reflux for four hours. An intractable tar was obtained after aqueous work-up.

The use of dimethylsulphide as a solubilizing agent to avoid unwanted side reactions has been recommended in reactions of organo-copper reagents [95]. The above reaction was repeated, adding dimethylsulphide to the thiopyrrolidone solution. In order to avoid decomposition, a temperature of -78 °C was used, and complete homogeneity of the reaction mixture was ensured before the addition of the iodobenzene. Again an intractable tar was obtained.

The reaction was then performed on the vinylogous urethane 124 using the same conditions, and again a tar was obtained.

It became clear that the use of organocopper reagents would not be suitable for the 3-arylation of the required compounds, and no further attempts were made in this area.

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The reaction was then performed on the vinylogous urethane 124 using the same conditions, and again a tar was obtained.

It became clear that the use of organocopper reagents would not be suitable for the β-arylation of the required compounds, and no further attempts were made in this area.

3.3 Attempted Synthesis From Methyl 3,4-Dimethoxyphenylacetate: The 3,1 Approach

It was shown in section 3.1 that the anion of methyl 3,4-dimethoxyphenylacetate was expected to form a lactam on reaction with an aziridine. The feasibility of this approach was investigated using N-benzylaziridine, prepared from N-benzylethanolamine [96,97] in a sequence aimed at lactam 120. The ester anion was formed at -83 °C by treatment with lithium diisopropylamide for ten minutes. N-Benzylaziridine was added, and the mixture was warmed to room temperature and stirred for five hours. Unchanged ester was recovered nearly quantitatively after aqueous work-up. Generation of the anion at -45 °C for one hour, followed by overnight stirring at room temperature gave a mixture of unchanged ester and aziridine, as judged by TLC and PMR.

The failure of N-benzylaziridine to alkylate the ester was surprising, and it was decided to attempt the alkylation using N-benzyl-2-bromoethylamine. It was found, however, that this reagent also failed to alkylate the ester.

Using sodium hydride both to generate the ester anion, and to liberate the N-benzyl-2-bromoethylamine from its hydrobromide salt gave only starting material after stirring at room temperature for two days. When 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU) was used as a base, again only starting material was recovered. Using lithium diisopropylamide to generate the ester anion, and DBU to release the N-benzyl-2-bromoethylamine, again no alkylation was observed.

The failure of the ester anion to react with either the

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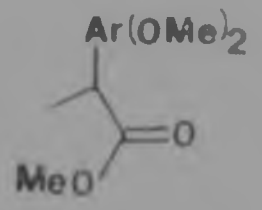
The failure of the ester anion to react with either the

N-benzyl-2-bromoethylamine or the N-benzylaziridine was surprising. To clarify whether an anion was indeed being generated, its reaction with a simple alkylating agent, methyl iodide, was investigated. Accordingly, treatment of the ester anion, formed using lithium diisopropylamide at -45 °C, with methyl iodide gave ester 127 in 81 % yield. It seems therefore that neither the N-benzyl-2-bromoethylamine, nor the aziridine were suitable alkylating agents for this ester.

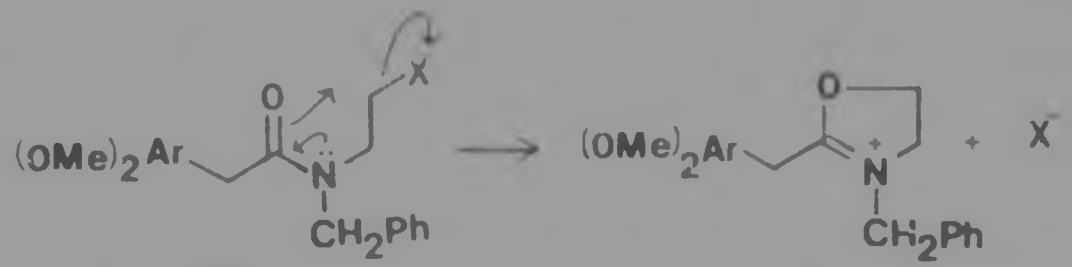


127

3.4 Attempted Synthesis From 3,4-Dimethoxyphenylacetyl chloride: The 1,3 Approach

It has been shown (section 3.1) that using the 1,3 synthetic approach, the first target would be an amide such as 117, which could probably be produced from 3,4-dimethoxyphenylacetyl chloride 115 and a halo-amine such as 116. In a sequence aimed at lactam 120, treatment of the acid chloride of 3,4-dimethoxyphenylacetic acid 115 with N-benzyl-2-bromoethylamine yielded an oil which subsequently crystallized, and which was recrystallized from acetone to give a solid of melting point 123 - 124 °C. This solid did not have the infra red characteristics of an amide, but rather those of an ester (νC=O = 1730 cm^{-1}) and an ammonium salt. It was proved to be the ester amine hydrochloride 128 by comparison with an authentic sample prepared from reaction of the acid chloride 115 with N-benzylethanolamine hydrochloride. The obtention of compound 128 was entirely unexpected, but could possibly be explained by the occurrence of an equilibrium between the desired amide

129 (X = Br) and the iminium ether as shown. Hydrolysis of the iminium ether would occur readily in the presence of water and would lead to the ester amine salt 128.



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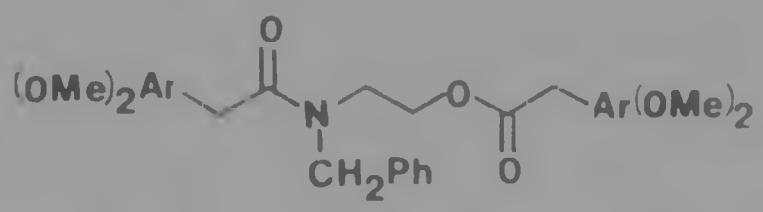
128

Support for this suggestion was obtained when a sample of the amide 129 (X = Cl), prepared by another method (vide infra) was observed by PMR and IR to change to the ester amine 128 over the course of a few days.

It seemed that the amide 129 (X = Br) could not be prepared in this way, so the alternative approach using the aziridine, in this case N-benzylaziridine, was attempted. When the aziridine and acid chloride were stirred together for four hours, a two component mixture was obtained, as judged by TLC analysis. Separation of the components by column chromatography gave the ester amine salt 128 in 15 % yield, together with another compound, which was probably the diacylated compound 130 obtained in 47 % yield. The IR of this compound showed the characteristics of both an ester (C=O = 1730 cm^{-1}) and an

amide ($\nu C{=}O$ = 1640 cm^{-1}), while the mass spectrum showed a molecular ion at m/e = 50., corresponding to $C_{29}H_{33}NO_7$.



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It was subsequently found that desired amide 129 (X = Cl) could be formed if the reaction time was shortened to five minutes. Treatment of this material with lithium diisopropylamide in THF at -45 °C did not, however yield the desired lactam 120, the starting amide being recovered in 93 % yield.

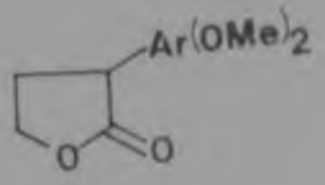
3.5 Synthesis of Lactams From N-methyl-3,4-dimethoxyphenylacetamide: The 3,5 Approach

3.5.1 The Preparation of N-Methyl-3-(3,4-dimethoxyphenyl)-2-pyrrolidone 110

The possible route to the lactam using the 3,5 synthetic approach was presented in section 3.1. It was shown that conceivably, the lactam could be produced in one step from the dianion of a 3,4-dimethoxyphenylacetamide with a 1,2-disubstituted ethane. 1-Bromo-2-chloroethane was chosen for a first attempt, although a wide range of possible 1,2-disubstituted ethanes was available.

N-Methyl-(3,4-dimethoxyphenyl)acetamide 119 [98], prepared from 3,4-dimethoxyphenylacetyl chloride and methylamine, was treated with two equivalents of n-butyllithium at 0 °C, and the dianion so formed was treated with 1-bromo-2-chloroethane. After

aqueous work-up, TLC analysis showed a three component mixture, with one of the components seemingly the starting material. Chromatographic separation and characterization of this mixture showed it to consist of the lactone 131, the chloroamide 132 and the desired lactam 110, contaminated with a small amount of the starting amide.



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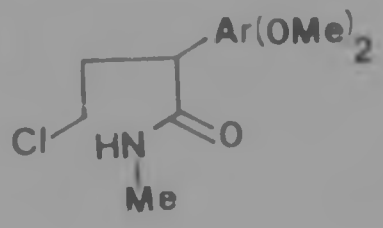

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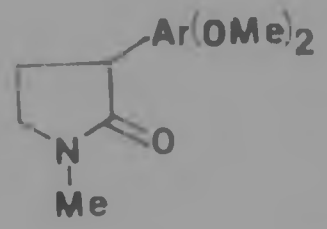


110

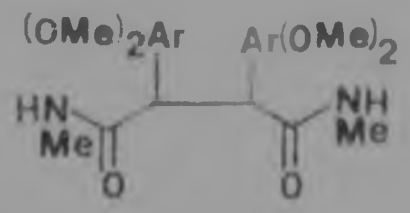
The lactone 131 was characterized by its IR spectrum (C=O = 1760 cm^{-1}) and its mass spectrum which showed a molecular ion at m/e = 222, corresponding to [illegible]. The chloroamide 132 showed an amide carbonyl at 1630 cm^{-1}, as well as an N-H absorption (3280 cm^{-1}) in its IR spectrum. The mass spectrum showed a molecular ion at m/e = 271 corresponding to $C_{13}H_{16}NO_3Cl$. The PMR spectrum showed the two characteristic cis and trans N-methyl peaks (2.75 and 2.82 ppm) of an open chain amide.

The lactam 110 showed a carbonyl absorption at 1670 cm^{-1} in its IR spectrum as expected for a β-lactam, and no N-H absorption was present. In addition the PMR showed only one N-methyl peak (2.93 ppm), consistent with a cyclic amide. The mass spectrum showed a molecular ion at m/e = 235, as expected for the formula $C_{13}H_{17}NO_3$ The lactam 110 was found to have the same R_f as the starting amide 119 in a variety of solvents, so that satisfactory purification of the lactam proved exceedingly difficult. Since the thiolactam 109 was the actual compound required, purification was in most cases only undertaken after thiation (vide infra).

The lactone 131 was recognized as being produced by ring closure through oxygen rather than nitrogen, followed by hydrolysis of the imine thus formed during the aqueous work-up. The chloroamide 132 arises when the dianion is alkylated, but ring closure does not take place.

Over a number of attempts at this reaction under seemingly identical conditions the yields of the three products were found to be extremely variable. Thus the lactone 131 was obtained in 9 - 19 % yield, the chloroamide 132 in 4 - 27 % yield, and the lactam 110 in 53 - 65 % yield, although in at least one attempt none of the lactam was formed at all. The unreliability of the above reaction led to search for better conditions for the reaction. One possible modification was to vary the 1,2-disubstituted ethane, and a range of possible compounds was tested.

Using 1,2-dibromoethane in conditions essentially the same as those described above, the dimer 133 was obtained as the only product, in 79 % yield. The obtention of this compound is probably due to a Wurtz-type coupling reaction resulting from a lithium - halogen exchange. The dimer was characterized by its IR spectrum, the carbonyl at 1640 cm^{-1}, and the N-H peak at 3300 cm^{-1} showed it to be an open-chain amide. The mass spectrum showed a molecular ion at m/e = 416, consistent with the formula $C_{22}H_{28}N_2O_6$. The PMR spectrum and microanalysis provided further confirmation of the structure of 133.

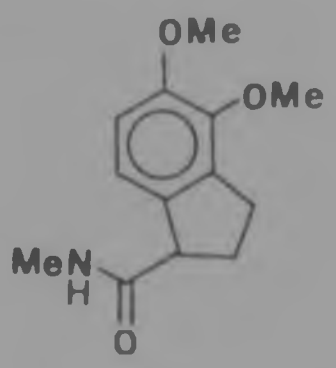


133

Using O-tosyl-2-bromoethanol under similar conditions, a PMR of the product obtained was messy, but none of the peaks characteristic of the lactam 110 were present. On substitution of O-tosyl-2-chloroethanol a PMR of the product closely resembled that of the amide 119, and again none of the peaks characteristic of the lactam were present. In a final attempt, O,O'-ditosylethanediol was used. In this case the reaction mixture was heated under reflux for two days. A PMR spectrum of the crude product obtained indicated the presence of the amide 119, together with a small amount of the lactam 110.

It was clear from the above series of reactions that only 1-bromo-2-chloroethane was useful for production of the desired lactam 110, even if this reaction was unreliable and the yield was low. A feature of this reaction was that the three products obtained all resulted from alkylation of the dianion of amide 119, and the total yield of these products was usually greater than 70 %. It seemed therefore that the initial phase of the reaction was successful, and that problems arose later when the chloroamide 132 either failed to cyclize, or cyclized through oxygen instead of nitrogen.

It was felt that the use of the dipolar aprotic solvent DMSO would aid the cyclization step, and increase the yield of the desired product, the lactam 110. In the first attempt to do this, the initial phase of the reaction was done in the same way as previously, but after ninety minutes, the mixture having been warmed to room temperature, the THF was removed under vacuum, substituted with DMSO, and heated at 75 °C for five hours. From this reaction, the chloroamide 132 was obtained in 11 % yield, together with the indane 134 (4 %) and the hydroxylactam 135 (37 %).



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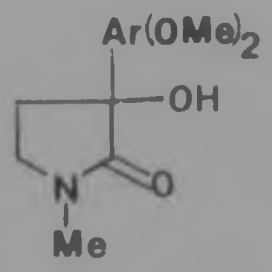
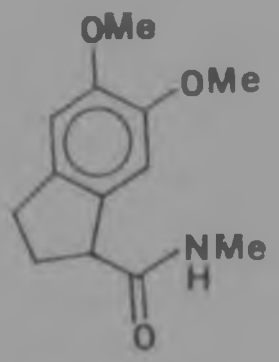


135

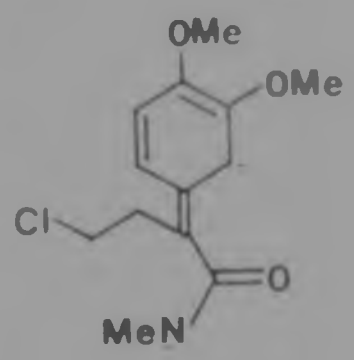
The IR spectrum of 135 (C=O = 1675 cm^{-1}) showed that it was a γ-lactam, and this was also apparent from the PMR spectrum, which has a single N-methyl at 2.99 ppm. Both the IR (3400 cm^{-1}) and the PMR (s,3.13 ppm) showed in addition the presence of a hydroxy group, and this was confirmed by the mass spectrum, which has a molecular ion at m/e = 251, corresponding to $C_{13}H_{17}NO_4$. The absence of a methine proton in the PMR spectrum indicated the structure to be as shown. This product must have arisen from oxidation, under the mildly oxidising effect of the DMSO, of the lactam 110, which must have been formed in the initial phases of the reaction.

The PMR spectrum of 134 showed an AB splitting pattern for the aromatic protons (6.78 and 6.96 ppm,2xd,J = 8 Hz), indicating a 1,2,3,4-substituted ring. The mass spectrum showed incorporation of the ethyl group by the presence of a molecular ion at m/e = 235, corresponding to $C_{13}H_{17}NO_3$. The IR showed the compound to be a secondary amide (C=O = 1640, NH = 3280 cm^{-1}). This data was all consistent with the structure of indane 134. The alternative indane 136 was clearly excluded by the PMR spectrum.



136

The obtention of the indane 134 could possibly be explained as a reaction via 137, a mesomer of the dianion which would form if the alkylated dianion was deprotonated. Alternately, the reaction might be via 138 which could form by direct lithiation of the aromatic ring. An ortho-lithio species such as 138 would be stabilized by both the amide and the methoxy substituents [99], and this could possibly explain the obtention of the indane 134, as opposed to 136.



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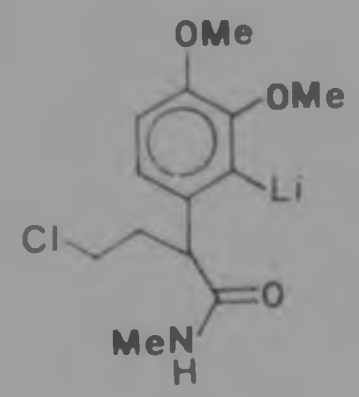


138

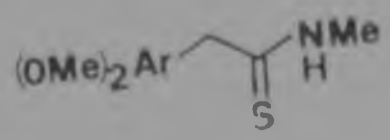
The reaction was next attempted simply using DMSO as solvent, at room temperature, and stirring for thirty minutes, with the original conditions otherwise unchanged. Only the starting amide 119 was recovered as shown by TLC.

The use of HMPA or TMEDA as co-solvent in the alkylation of amide dianions has been recommended [80]. After generation of the amide dianion using n-butyllithium, four equivalents of

HMPA were added before the addition of the 1-bromo-2-chloroethane. After stirring at room temperature overnight, the reaction was worked up as usual, and the HMPA was distilled off, leaving an oil which appeared from TLC and PMR analysis to be the lactam 110. This material was thiated using Lawesson's reagent in refluxing toluene (see section 3.6) to give the thiolactam 109 in 71 % yield from the amide 119.

The yield of lactam 110 produced under these conditions is clearly appreciably more than that obtained previously. In addition, this yield was reproducible. Thus these conditions provided a high yielding and reliable method for the synthesis of the thiolactam 109.

It was, however, decided to attempt to synthesize the thiolactam 109 using the above conditions, from the thioamide 139, since if the thiolactam could be prepared directly, in high yield, this would obviate the need for the thiation step after preparation of the lactam. The yield of thiolactam 109 from this reaction was, however, less than 20 %, and the reaction was extremely messy, so clearly there was no advantage to this procedure.



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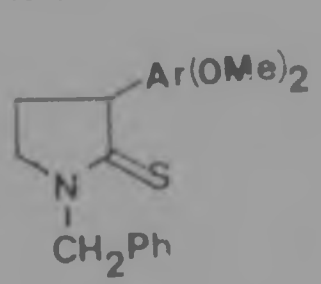
3.5.2 Synthesis of N-Benzyl-3-(3,4-dimethoxyphenyl)-2-pyrrolidone 120

The successful method developed for the preparation of lactam 110 was now extended to the N-benzyl lactam 120 starting from N-benzyl-(3,4-dimethoxyphenyl)acetamide, prepared from

3,4-dimethoxyphenylacetyl chloride and benzylamine (Although this compound has been reported in the literature [100], only a melting point (148 °C) is quoted, which does not correspond to that obtained in the present work (99.5 - 101.5 °C). Since no other data is quoted, is seems reasonable to assume that the structure of the reported compound was not correctly assigned.

For comparison purposes the reaction was attempted both with and without HMPA. In the absence of HMPA, the only identifiable product obtained was the lactone 131, the yield being 40 %. Using HMPA in the reaction and thiating the product obtained directly gave the thiolactam 140 in 54 % yield. The chromatographic behaviour of the lactam was subject to the same problems as in the N-methyl case, so that purification of the lactam itself was not seriously attempted. As in the N-methyl case, thiation was accomplished by treatment with Lawesson's reagent in refluxing toluene.



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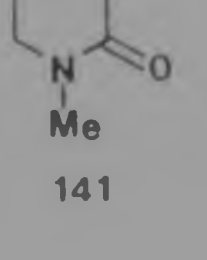
3.5.3 Extention to other lactams

It seemed that the conditions developed for the synthesis of lactams 110 and 120 could possibly serve for the preparation of a range of lactams. It was therefore decided to test the generality of this method. Thus the synthesis of N-methyl-3-phenyl-2-pyrrolidone 141 [101] was attempted. Treatment of

N-methylphenylacetamide [102] with n-butyllithium followed by 1-bromo-2-chloroethane gave the lactone 142 [103], the lactam 141 in 16 % and 28 % yields respectively as well as a compound which was probably the bis-substituted compound 143 (22 %). Although 143 could not be obtained pure, despite repeated attempts at recrystallization, and hence was not fully characterized, the data obtained were consistent with this structure. The IR showed an open chain amide (C=O = 1640 cm^{-1}), and the PMR spectrum was as expected for this compound. No molecular ion was apparent in the mass spectrum but the highest molecular mass peak (m/e = 162) corresponded to a symmetrical cleavage of the molecule, while the peak at m/e = 148 corresponded to a cleavage off of $PhCHCONHCH_3$ In the presence of HMPA the yield of lactam 141 was 26 % and a small amount of the lactone 142 (IR C=O = 1770 cm^{-1}) and another compound were obtained. This compound was probably the dimer 144, analogous to compound 111 obtained in the preparation of 110. The compound could not be properly purified, but its physical characteristics, namely its high melting point and low solubility in most solvents, together with what data were available indicated structure 144, although some anomalies existed, for example a peak at m/e = 324 in the mass spectrum, when the molecular ion was at m/e = 296 for [illegible]. The addition of HMPA in this case was thus not beneficial.



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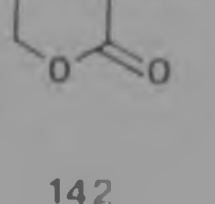

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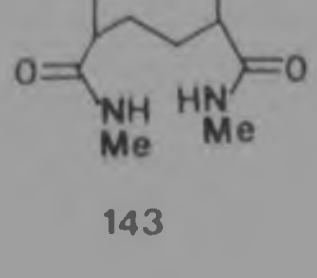

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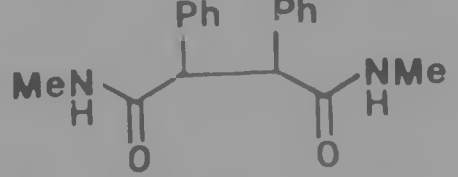

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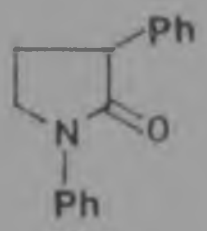
Attempts were made to improve this reaction by other means. Thus treatment with n-butyllithium in THF, followed by 1-bromo-2-chloroethane, and heating the mixture under reflux increased the yield of lactam 141 to 38 %. On using benzene as solvent, only starting material was recovered. On using ether as solvent the yield of lactam 141 was 31 %. On using THF as solvent but with substitution of 1,2-dibromoethane for 1-bromo-2-chloroethane, gave only the dimer 144 in 91 % yield, this result being parallel to that obtained in the 3,4-dimethoxyphenyl case. Returning to the original conditions but with the addition of TMEDA, the yield of lactam was 40 %, this being the highest yield obtained in this series of reactions.

This method was therefore successful in the preparation of the lactam 141, although the yields were low.

Another lactam to which the method was applied was 1,3-diphenyl-2-pyrrolidone 145 [101]. Thus, treatment of N-phenylphenylacetamide [104] with two equivalents of n-butyllithium in THF, followed by 1-bromo-2-chloroethane gave a solid product which was probably the the dialkylated product 146 in 38 % yield, together with a mixture of unreacted starting material and the lactam 145, which was not separated. Compound 146 was characterized by IR, PMR, MS and HRMS, the mass spectrum showed, however, a few anomalous peaks. Thus peaks at m/e = 299(56) and 301(41) were present as expected for the molecular ion, but the peak at 301 was too large. In addition peaks at 345(10), 344(10) and 343(10) could not be explained. Addition of HMPA to the reaction mixture

gave compound 146 in 36 % yield, together with a mixture of the lactam and amide in approximately 24 % and 20 % yields respectively. The mixture could not be chromatographically separated, but was partially separated by fractional crystallization. The lactam 145 could not, however, be obtained pure.



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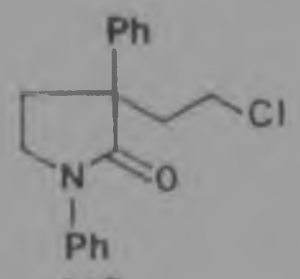


146

Compound 146 must result from deprotonation of the lactam 145 by the amide dianion, followed by reaction with 1-bromo-2-chloroethane still present. This mechanism explains the large amounts of unreacted starting material recovered.

In an attempt to extend the procedure to the synthesis of a secondary lactam, phenylacetamide was reacted under conditions described above (without HMPA). The result was a mixture of compounds one of which was a nitrile as shown by IR (CN - 2230 cm^{-1}). Although obtention of this product was unexpected, this sort of elimination is known [105]. No attempts were made to improve this reaction.

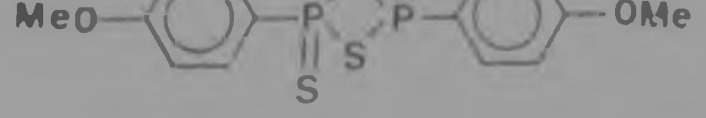
Application of the reaction procedure to N-methylacetamide using the same conditions as described above (without HMPA) gave only starting material. Again no attempts were made to improve this reaction.

It thus became apparent that, while the method developed for N-methyl-3-(3,4-dimethoxyphenyl)-2-pyrrolidone 110 could be

used in the preparation of some other lactams, the procedure was unfortunately by no means general.

3.6 A Note on Thiation of Lactams and Amides

Historically [106] thioamides have been prepared by refluxing the corresponding amide with excess phosphorus pentasulphide in various solvents. More recently, however, two improved procedures have been described. These are firstly, the use of the dimer of p-methoxyphenylthionophosphine sulphide 147 (Lawesson's reagent) [69], and secondly, the use of ultrasound to promote thiation with phosphorus pentasulphide, thus enabling these reactions to be carried out at low temperatures [70]. All three of the above procedures have been used in the present work for the thiation of lactams.



147

Thiolactam 109 was obtained in 35 % yield by thiation of lactam 110 by treatment with phosphorus pentasulphide in refluxing carbon disulphide for fourteen hours. Using Lawesson's reagent in dimethoxyethane (DME) at reflux for sixteen hours the yield of thiolactam was 40 %. Using Lawesson's reagent in toluene at reflux for eight hours the yield of thiolactam was improved to 65 %.

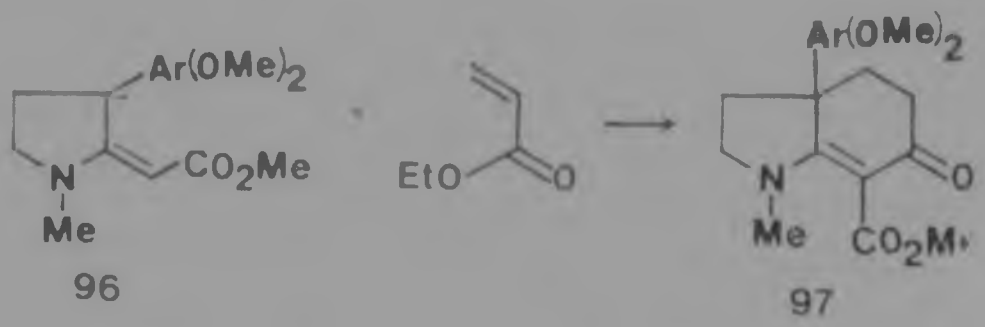
The procedures using Lawesson's reagent were somewhat messy with large amounts of phosphorus containing by-products being obtained. It was felt that this problem could possibly be alleviated by placing the Lawesson's reagent in a Soxhlet thimble, and allowing it to be slowly extracted into the

refluxing solvent. In toluene the amount of by-products was reduced, but the yield of thiolactam was also reduced (to 48 %). In DME, using this technique, no thiolactam was obtained at all. It was therefore felt that simply using Lawesson's reagent in refluxing toluene was the most useful method.

Thiation of N-methyl-3-(3,4-dimethoxyphenyl)acetamide 119 was accomplished by treatment with phosphorus pentasulphide in THF at 30 - 40 °C under ultrasonic irradiation for three hours. The thiolactam 139 was obtained in 69 % yield.

CHAPTER 4 ATTEMPTED SYNTHESIS OF MESEMBRINE USING VINYLOGOUS URETHANES

In chapter 2 a synthesis of mesembrine was proposed using the Michael reaction of the anion of vinylogous urethane 96 with ethyl acrylate to provide a route to the bicyclic compound 97 which it was expected could readily be converted to mesembrine. Obtention of thiolactam 109 as described in chapter 3 allowed for the preparation of vinylogous urethane 96 in 76 % yield, using the standard sulphide contraction conditions. The route was, however, first tested using vinylogous urethanes 100 [60] and 148 as models. Vinylogous urethane 148 was prepared from N-methylthiopiperidone in 91 % yield.



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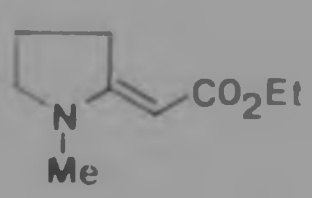

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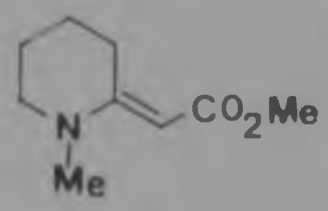


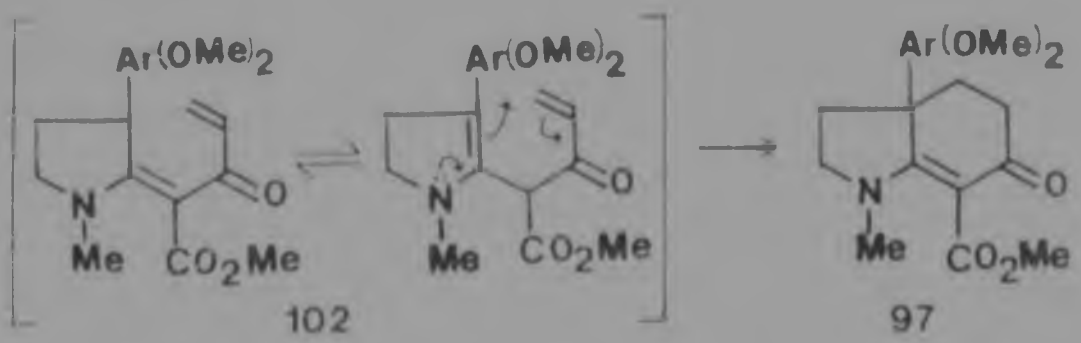
148

In the model sequence, the anion of unsubstituted vinylogous urethane, 100, formed by treatment with n-butyllithium, failed to react in a 1:1 fashion with ethyl acrylate, under a variety of conditions [60]. In these attempts, starting material was largely recovered, together with polymerized

acrylate. In the sequence which would have led to mesembrine itself, formation of the anion of 96 as in the model sequence, followed by treatment with methyl acrylate, again gave only starting material, together with polymerized Michael acceptor.

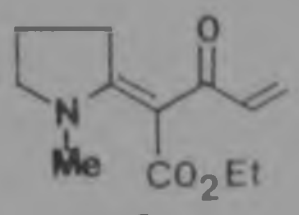
It is known [107] that the use of organocopper reagents greatly facilitates 1,4 addition to α,β-unsaturated carbonyl compounds, and an attempt was made to improve the reaction using this method. Accordingly, the lithium anion of vinylogous urethane 100 was treated at -78 °C with one equivalent of an ethereal solution of a copper (I) iodide-tri-n-butylphosphine complex for 20 minutes, and the organocopper reagent thus formed was treated with ethyl acrylate, and then slowly warmed to room temperature. The oil obtained after acid / base work-up was shown to be largely the starting material, and none of the desired product was obtained.

In view of these failures the alternative route to 97 proposed in chapter 2 whereby reaction of 96 with acryloyl choride would produce 102, which could undergo cyclization to 97 as shown, was investigated. This route was again tested with a series of model reactions.

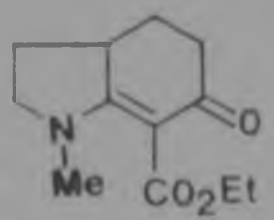


Treatment of vinylogous urethane 100 with acryloyl chloride in benzene at room temperature for ninety minutes resulted in the precipitation of an oily substance. Work-up with aqueous

sodium bicarbonate gave an oil. The PMR spectrum of this compound showed that it could not be the expected product 149 (cf. 102), because no ethylenic protons were present, and it was in general consistent with that expected for the cyclized compound 150 (cf. 97). A molecular ion at m/e = 223 corresponding to $C_{12}H_{17}NO_3$ in the mass spectrum was also consistent with this.

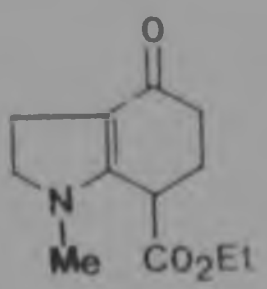


149

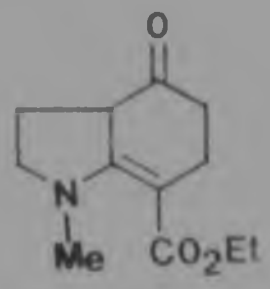


150

The IR of the product showed not only absorptions in the region expected for vinylogous urethane / vinylogous amides (1520, 1560, and 1600 cm^{-1}) [108], but in addition, an absorption at 1730 cm^{-1} ascribable to the carbonyl group of a normal saturated ester was present. The only structure which was consistent with this data was structure 151, in which the three carbon unit from the acryloyl chloride was incorporated but with the opposite orientation to that expected. The alternative double bond isomer 152 did not seem feasible from the IR data, which belied the presence of a saturated ketone. The low field PMR spectrum of this compound could not be used to distinguish between these structures.



151



152

Further corroborative data for structure 151 was obtained from the carbon-13 NMR spectrum, and from UV data, as shown in table 1. The UV spectra of the cross-conjugated compounds 91 and 101 showed two bands, which contrasts with the presence of only one band (λ_{max} = 326 nm) in the spectrum of 151. Furthermore the UV behaviour of 151 on addition of acid (peaks shifts to λ_{max} = 306 nm) is consistent with a vinylogous amide (cf. 154), and is contrary to that expected for a vinylogous urethane, where the peak would vanish on addition of acid (cf. 100).

The carbon-13 NMR spectrum of 151 showed the presence of four unsaturated quaternary carbon atoms at 189.7, 169.4, 163.7, and 109.7 ppm (see table 1). The low field peak at 189.7 ppm was assigned as a vinylogous amide carbonyl, that is C-(c), by analogy to C-(c) of 154' (190.15 ppm), and comparison with C-(c) of 100 (169.3) showed that this could not be a vinylogous urethane.

The obtention of compound 151 was unexpected, but could be explained if the initial reaction of the vinylogous urethane 100 with acryloyl chloride was through oxygen rather than carbon, giving rise to 153 as the first formed product. A [3,3]-sigmatropic shift would give the ketene 154, which would be rapidly captured by the endocyclic enamine tautomer, giving the bicyclic compound 151. The reaction could occur in a similar manner if the initial reaction was through nitrogen. Hickmott and co-workers [109] have proposed a similar mechanism for the reaction of enamino ketones with acryloyl chloride, and they have argued that reaction through oxygen is most likely.

TABLE I

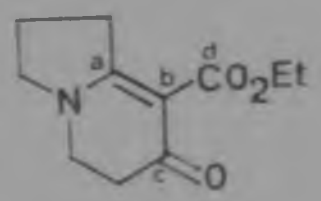
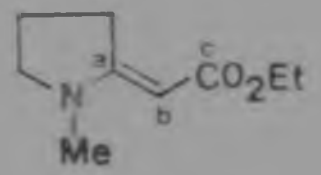
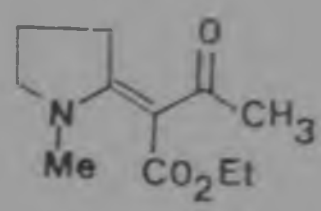
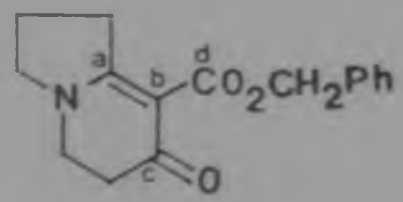
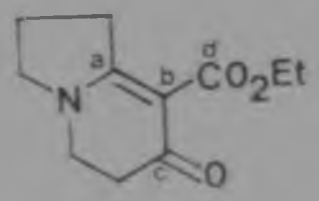
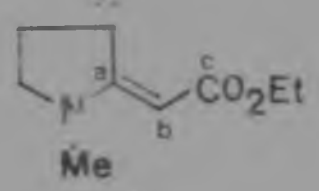
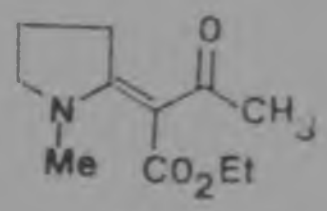
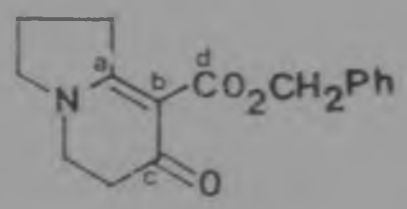
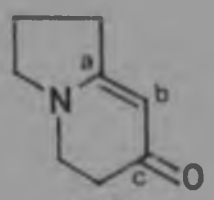
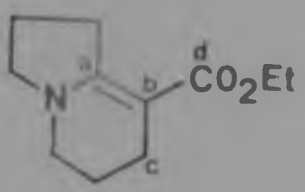
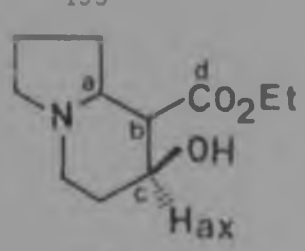
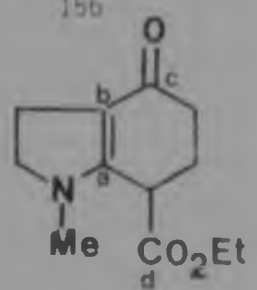
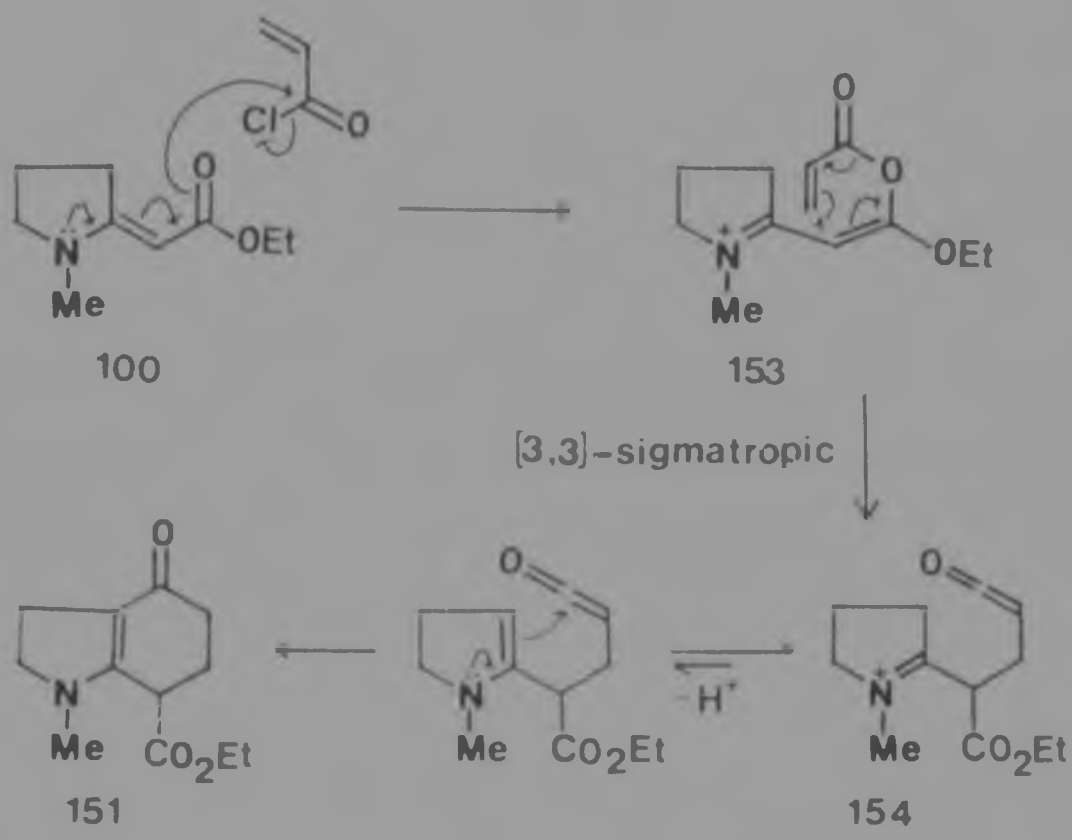
Compound	UV $\lambda_{max}(\varepsilon_{max})$	Carbon-13 NMR	Ref
 91	248(11893) 306(17360) • MeOH: 234(17060) 305(9150)	a: 173.3 b: 92.6 c: 187.0 d: 165.9	56
 100	230(2780) • MeOH peak obscured	a: 165.4 b: 77.7 c: 169.3	60
 101	255(9102) 314(11100) • MeOH: 236(9400) 298(9900)	-	60
 153	-	a: 173.4 b: 97.9 c: 186.9 d: 165.7	56

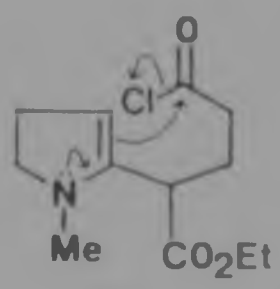
TABLE 1

Compound	UV λ_{max} (ε_{max})	Carbon-13 NMR	Ref
 91	248(12300) 304(17300) + HCl: 214(12700) 307(8550)	a: 173.3 b: 92.6 c: 167.0 d: 165.9	56
 100	278(2290) + HCl: peak vanishes	a: 165.4 b: 77.7 c: 169.3	60
 101	236(9100) 314(1)100) + HCl: 236(9400) 286(4400)	-	61
 153	-	a: 173.4 b: 97.9 c: 186.9 d: 165.7	56

Compound	UV $\lambda_{max}(\varepsilon_{max})$	Carbon-13 NMR	Ref
 154	318(15500) + $HClO_4$: 308(9200)	a; 168.93 b; 92.91 c; 190.15	56
 155	-	a; 159.08 b; 87.97 c; 21.73 d; not observed	56
 156	-	a; 64.56 b; 56.37 c; 70.88 d; 173.18	56
 151	326(24600) + HCl: 306(18300)	a; 163.7 b; 109.7 c; 189.7 d; 169.4	73



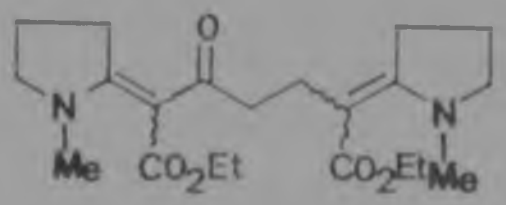
As an alternative, Hickmott has considered the possibility of an S_Ni' mechanism. In this case the ketene 154 would be formed directly, by reaction of the vinylogous urethane with acryloyl choride through carbon directly. A 1,4 addition of the vinylogous urethane to acryloyl chloride, forming 155, is considered unlikely.



155

It was decided that a variation of the solvent used for the above reaction could possibly encourage reaction through carbon rather than oxygen, and to this end the reaction was repeated using acetonitrile rather than benzene. Again none of the desired compound was obtained, the major product being

characterized as compound 156 (83 %). A small amount of 151 was also present. Compound 156 was characterized by its mass spectrum, the molecular ion being at m/e = 392, corresponding to a molecular formula of $C_{21}H_{28}N_2O_6$. The PMR spectrum showed the presence of two ester groups in different environments, by overlapping triplets at 1.05 - 1.33 ppm, integrating for six protons, and overlapping quartets at 4.10 ppm, integrating for four protons. In addition the IR showed only vinylogous urethane / vinylogous amide type peaks (1550, 1610, and 1660 cm^{-1}).

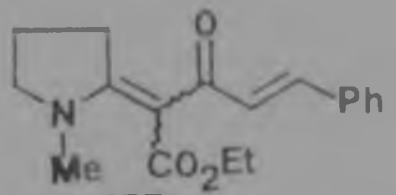


156

The formation of 156 can again be explained by the formation of the ketene 154, which could then be captured intermolecularly by unreacted vinylogous urethane 100. The intermolecular reaction was facilitated by the use of acetonitrile, because the reaction mixture remained homogeneous throughout. This reaction must be extremely rapid, since 156 formed in high yield despite the presence of a two fold excess of acryloyl chloride. Further support for the mechanism proposed is the observation by Hickmott and co-workers [110] of the intermolecular capture by an enamine of a ketene formed in an analogous manner.

Although none of the desired compound 150 was obtained in the above reactions since this was a model system it was nevertheless worthwhile to investigate the effects of some variations of the reactants. In the first such attempt made, cinnamoyl chloride was used in place of acryloyl chloride, and,

using acetonitrile as solvent, the uncyclized but properly oriented compound 157 was obtained in 47 % yield, as the only characterizable product (only one of the two possible geometric isomers was obtained, but which one could not readily be distinguished). Similar results were obtained using both benzene, and dichloromethane as solvent. Compound 157 was shown to be uncyclized by its PMR spectrum, which showed a triplet at 3.20 ppm (J = 3 Hz), integrating for two protons, for the γ-carbon. In addition, two ethylenic protons were present, being strongly deshielded, and appearing as a multiplet (6.90 - 7.60 ppm) integrating for seven, together with the aromatic protons, as is common for cinnamoyl systems [111]. The mass spectrum, showing a molecular ion at m/e = 299 as expected for $C_{18}H_{21}NO_3$, provided further confirmation of this structure, as did the IR spectrum, which showed no carbonyl peaks above 1700 cm^{-1}.



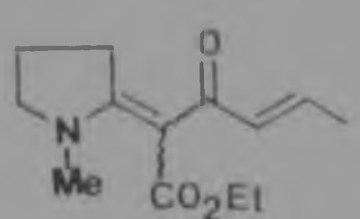
157

An attempt was made to induce cyclization of 157 by heating under reflux in benzene, but this was not successful.

In a further investigation of the reaction under discussion, the vinylogous urethane 100 was reacted with crotonoyl chloride. Using acetonitrile as solvent, the uncyclized product 158 was obtained as a single isomer in 21 % yield as the only characterizable compound. The PMR spectrum of 158 was analogous to that of 157, showing a triplet at 3.06 ppm for the protons at the γ-carbon, and an eight line multiplet (6.15 - 6.75 ppm) for the ethylenic protons. The IR spectrum showed no carbonyl bands above 1700 cm^{-1}, as expected for a cross

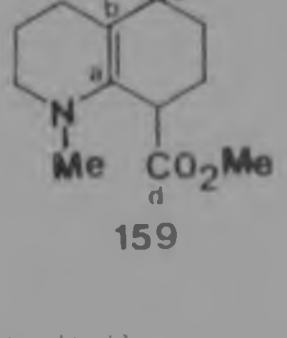
conjugated system of this sort. The mass spectrum was further confirmation for this structure, showing a molecular ion at m/e = 237, corresponding to a molecular formula of $C_{13}H_{19}NO_3$.

On using crotonoyl chloride with benzene as solvent the yield of 158 was reduced to 6 %, but again no other products were characterizable.



158

The obtention of the correctly oriented products 157 and 158 was encouraging and investigations into the reaction were therefore continued. To this end piperidine vinylogous urethane 148 was treated with acryloyl chloride. In benzene, this reaction gave the wrongly oriented bicyclic compound 159 in 64 % yield, in an analogous reaction to that of the pyrrolidine vinylogous urethane 100. The UV behaviour of 159 was similar to that of 100 (see table 1), with the λ_{max} = 325 nm shifting to 305 nm on addition of acid, while the carbon-13 NMR spectrum of 159 provided further evidence for this structure.



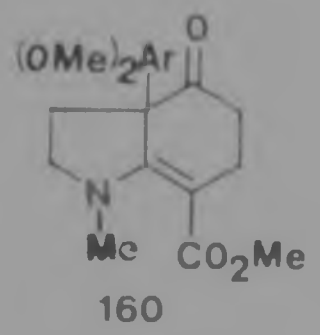
159

a, 155.8 ppm
b, 107.2
c, 192.5
d, 171.3

In acetonitrile, again only 159 was obtained, after

chromatography on silica gel, but the yield was 4.5 %, and any other products which may have been present did not survive.

In the sequence which was intended to lead to mesembrine itself, vinylogous urethane 96 was initially treated with acryloyl chloride, using THF as solvent, and the product, an unstable white solid, was found to be the wrongly orientated compound 160, the yield being 68 %. The IR of this compound showed, unexpectedly, not only a saturated ketone carbonyl (1710 cm^{-1}), but also an ester carbonyl (1725 cm^{-1}). A Dreiding model showed that the peri-interaction between the N-methyl and the methoxycarbonyl groups does not allow for the planar configuration normal for the vinylogous urethane, so that a separate IR absorption is seen for the ester carbonyl. The other spectral data were all commensurate with structure 160.



160

Using benzene, dichloromethane, or DMF as solvent, 160 was the only product obtained, as indicated by TLC. Using acetonitrile as solvent for the reaction gave, after aqueous work-up, a mixture of unstable products which could not be separated, being immobile on TLC. The PMR spectrum of this mixture showed that the methoxy (s, 3.79 ppm) and the aromatic (m, 6.50 - 6.80 ppm) groups were still present. There appeared to be two peaks due to N-methyl protons, at 2.99 ppm and 3.43 ppm. The rest of the spectrum was uninterpretable. The IR spectrum of this mixture showed vinylogous urethane / vinylogous amide peaks, as

well as small ester (1725 cm^{-1}) and ketonic (1710 cm^{-1}) carbonyl absorption bands.

This disappointing result signified that the bicyclic compound 97 could not be synthesized from the vinylogous urethane 96. This meant that if mesembrine were to be synthesized a new approach would have to be found.

CHAPTER 5 SULPHIDE CONTRACTIONS WITH CHLOROMETHYL VINYL KETONE

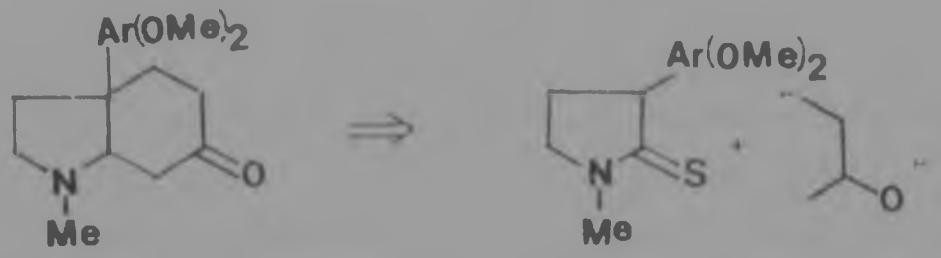
5.1 An Alternative Approach to Mesembrine

5.1.1 Introduction

In chapter 4, the necessity for developing a new approach to mesembrine was established, and accordingly, an examination of possible alternative routes was initiated. Vinylogous urethanes, prepared by sulphide contraction of salts formed by reaction of thiolactams with α-bromoacetates, had hitherto been the focal point of the general route for alkaloid synthesis in these laboratories. It was recognized that, using this approach, the product of ring closure would have been the bicyclic compound 97, and hydrolysis - decarboxylation steps would have been necessary to give Δ^7-mesembrenone 2, the precursor of mesembrine itself. A more direct route would be achieved if this step could be avoided, and attention was therefore turned away from the vinylogous urethanes.

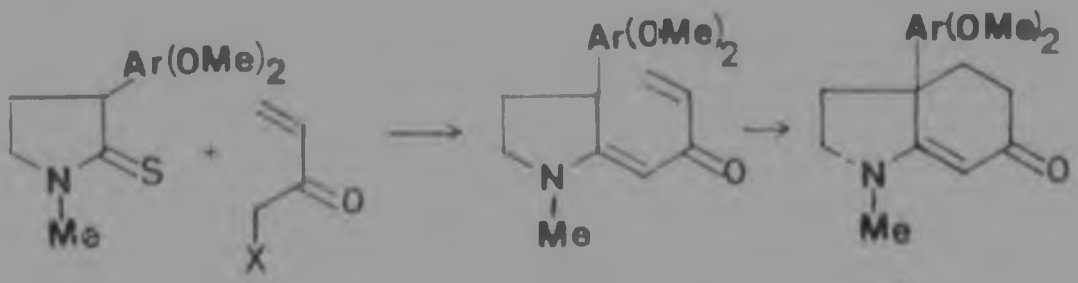
97 2

Bond disconnection of mesembrine revealed that, if the thiolactam 109 was used as a synthon for the pyrrolidine ring, the remainder of the molecule could be constructed from a four carbon chain oxygenated at the 2-position.



1 109

The presence of a halogen α- to the carbonyl at carbon 1 in the four carbon synthon required would allow it to be introduced by the sulphide contraction sequence. The compound used for the contraction would furthermore have to be appropriately functionalized for ring closure, and by analogy with the urethane sequence, an α,β-unsaturated carbonyl function would allow for ring closure by intramolecular Michael reaction. Compounds complying with these conditions were halomethyl vinyl ketones 161. It was envisaged that the salt formation and sulphide contraction of thiopyrrolidone 109 with a halomethylvinyl ketone would form 162 which should undergo ring closure by intramolecular Michael addition. Referring back to the classification of synthetic routes to mesembrine developed in chapters 1 and 2, the envisaged intermediate 162 corresponds to a skeleton such as 103 (see p. 32), and this route is therefore of type F. The key intermediate, 162, in this approach is thus a vinylogous amide, rather than a vinylogous urethane.



109 161 162 2

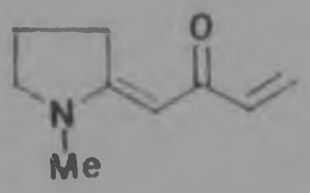
A survey of the literature revealed that of the possible halomethyl vinyl ketones 161, only the chloride [112] and the fluoride [113] were known. The bromo compound was considered to be the most suitable for formation of the salt required for the sulphide contraction. Thioamides can, however, be alkylated on sulphur using alkyl chlorides [114], so that conditions could probably be found for the salt formation using the more accessible chloromethyl vinyl ketone. In addition, if necessary, a simple halogen exchange reaction would provide iodomethyl vinyl ketone, and with this the salt formation should be more facile. It was decided to investigate the feasibility of the synthetic strategy with a series of model reactions, and N-methyl-2-thiopyrrolidone 121 was chosen as a suitable model for the 3-aryl thiopyrrolidone 109.

5.1.2 Model Studies

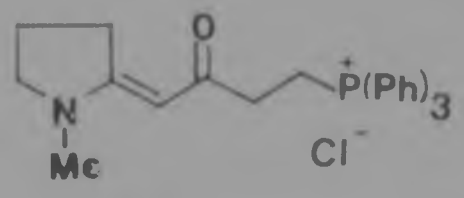
For this work chloromethyl vinyl ketone was prepared by the Friedel-Crafts reaction of chloroacetyl chloride with ethylene, giving β-chloropropionyl chloride (63 %) [115]. Distillation off sodium carbonate, with elimination of hydrogen chloride, according to the method used by Danishefsky and co-workers [116] for the preparation of β-chloroethyl vinyl ketone, gave chloromethyl vinyl ketone in 80 % yield.

The formation of the salt from chloromethyl vinyl ketone and N-methyl-2-thiopyrrolidone in a small amount of acetonitrile at room temperature was not complete after thirty hours, as judged by TLC. On using iodomethyl vinyl ketone, produced from chloromethyl vinyl ketone by halogen exchange reaction in acetonitrile, TLC showed complete disappearance of starting material after four hours. The reaction mixture was then diluted with acetonitrile, and treated at 0 °C with a solution

of triphenylphosphine and triethylamine. Acid / base work-up, followed by chromatography of the product mixture, gave two products, neither of which could be fully characterized because of their instability. They were however, assigned the structures 163 (28 %) and 164 (13 %) respectively, on the basis of the limited data obtained. In addition, a third product, which could not be identified, was obtained in small quantities.



164



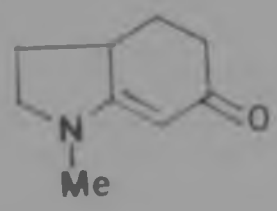
163

The structure of the uncyclized compound 164 was indicated by the presence of a strong C=C band in its IR spectrum (1595 cm^{-1}) and three olefinic protons in the PMR spectrum (5.28 and 5.45 ppm (2 d,1) and 5.65 to 6.65 ppm (m,2)), in addition to the features expected for the vinylogous amide system, namely bands a 1630 and 1634 cm^{-1} (although these bands have been designated as C=C and C=O respectively [108], they are combination bands, and have therefore been referred to as being due to NC=CC=O). The positions of the two bands indicate that the geometry of this compound is probably as shown [108].

The IR spectrum of the phosphonium salt 163 showed typical vinylogous amide bands (1555, 1630 cm^{-1}), as well as absorptions due to the aromatic rings (1440, 1490 cm^{-1}). The PMR spectrum showed the presence of fifteen aromatic protons. Although the mass spectrum did not feature a molecular ion, peaks attributable to the triphenylphosphine portion (m/e = 262), and the remaining portion of the molecule (m/e = 152, corresponding to $C_9H_{11}NO$) were present. No indication of counterion could be ascertained from the spectral data, but it was thought that chloride, arising from the

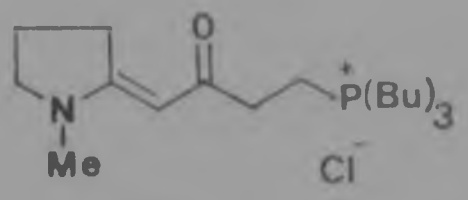
work-up procedure, was most likely, and this was supported by positive silver nitrate and Beilstein tests. The phosphonium salt 163 is thought to arise from Michael addition of triphenylphosphine to the uncyclized compound 164. Phosphines are known to readily add to α,β-unsaturated carbonyl compounds, forming ylids. In this case, the ylid formed is probably protonated by the triethylammonium ion present, thus forming the phosphonium salt [117].

The spectra of the third compound showed that the vinylogous amide portion of the molecule was present (IR, 1545 and 1640 cm^{-1}), but no indication of other functionality could be ascertained. The mass spectrum (m/e = 279) belied the possibility that this could be the cyclized compound 165. No coherent structure could be formulated.



165

The obtention of contracted products in the above reaction was encouraging, but the incorporation of phosphorus was a problem. In an effort to avoid this the reaction was repeated as above, except that the contraction was carried out at -45 °C. Again 163 was obtained, the yield increasing to 44 %, while the yield of the uncyclized compound 164 was also increased, to 18 %. Substitution of trimethylphosphite for triphenylphosphine gave no characterizable products. Using tributylphosphine gave 164 in 4 % yield, together with a compound which was not purified or characterized, but the PMR spectrum of which showed clearly the presence of butyl groups, thus indicating the incorporation of phosphorus. This compound was probably 166 by analogy with the triphenylphosphine-incorporated product 163.



166

5.1.3 Towards Mesembrine

The model studies on the sulphide contraction with iodomethyl vinyl ketone had shown that the proposed route to mesembrine was viable. No cyclized products had been obtained, but the presence of the aryl ring in the proposed mesembrine intermediate 162 would increase the percentage of the endocyclic enamine tautomer, as compared with its analogue 164 in the model study, thus facilitating ring closure. Although sterically, the aryl ring could hinder cyclization, because the reaction is intramolecular, this was unlikely to be a serious difficulty. The main problem, then, was that of phosphorus incorporation. In the model studies, contracted products formed had combined with phosphine present in the reaction solution in yields of up to 44 %. This implied that the phosphine was not significantly involved in the contraction, since only small quantities of triphenylphosphine sulphide could have been formed. Sulphide contractions giving rise to tertiary vinylogous amides [118] and urethanes [60] had been reported in the absence of a thiophile, but the yields were less than 50 %. Under these conditions, undesirable side reactions leading to regeneration of starting material, and production of disulphides, were observed. These results were attributed to the nucleophilic behaviour of the base. The use of a hindered, non-nucleophilic, base could therefore, possibly circumvent this problem. The contractions were thus attempted using diisopropylethylamine, and in the absence of a phosphine

thiophile. When a solution of iodomethyl vinyl ketone, produced from chloromethyl vinyl ketone by halogen exchange in acetonitrile, was added to the arylthiopyrrolidone 109, the salt formation did not go to completion within three days at room temperature, as indicated by the continuing presence of starting material observed by TLC. In addition the reaction solution had become black and tarry.

The reaction was next attempted using chloromethyl vinyl ketone itself. After a mixture of thiopyrrolidone 109, chloromethyl vinyl ketone and a few drops of acetonitrile was heated at 40 °C overnight, TLC showed a small amount of thiopyrrolidone still present, together with a new compound. The mixture was treated with diisopropylethylamine, and then subjected to an aqueous work-up. Column chromatography gave in 10 % yield a product characterized as (±)-Δ^1-mesembrenone 2.

Clearly the yield of the reaction would have to be improved for the synthesis to be viable. To determine the best conditions, a series of small scale reactions was performed, and monitored by following the disappearance of starting material, and the appearance of Δ^1-mesembrenone, which the previous reaction had shown was formed even before the addition of base, using TLC. With DMF and toluene as solvents the salt formation had not gone to completion, despite the presence of a three fold excess of chloromethyl vinyl ketone, after heating at 100 °C for eight hours, and none of the product had appeared. Using benzene as solvent, and heating under reflux, the same results were obtained. Using chloroform, ethyl acetate or THF, and heating under reflux, although some of the product was observed, again the salt formation did not go to completion. Similar results were obtained using benzene in the presence of two equivalents of HMPA. In nitromethane, after eight hours,

no starting material remained, and appreciable quantities of Δ'-mesembrenone had formed.

The reaction was then performed on a large scale using nitromethane as solvent. A small amount of hydroquinone was added to suppress possible radical polymerization of the chloromethyl vinyl ketone. After heating under reflux for twelve hours, diisopropylethylamine was added at room temperature, and the mixture was stirred overnight. Work-up was by direct column chromatography of the black oil obtained after removal of solvent, giving chromatographically pure (±)-Δ'-mesembrenone 2 in 72 % yield.

The formation of Δ'-mesembrenone 2 in this reaction even before the addition of the base, that is, the spontaneous sulphide contraction under the conditions of the salt formation is unexpected. To investigate this, the reaction was performed without the addition of diisopropylethylamine. In this case, Δ'-mesembrenone was obtained, in reduced yield (46 %), and was only eluted from the column with difficulty. This may suggest that the appearance of the product as shown by TLC, prior to the addition of the base is misleading, and that the silica gel may have some role to play in the contraction under these circumstances.

(-)-Δ'-Mesembrenone 2 was identified as a minor constituent of Sceletium namaquense by Jeffs and co-workers in 1974 [119]. Prior to this it had been prepared by the same workers [120] by reaction of natural mesembrine with diethyl azodicarboxylate. The natural antipode was found to be non-crystalline, unlike the racemic product obtained in the present study, which was obtained as a solid of melting point 139 - 141 (lit. 138 °C [122]) after distillation and recrystallization from ethyl

acetate. The (±)-Δ^7-mesembrenone obtained was characterized by comparison with spectral data quoted in the literature for (-)-Δ^7-mesembrenone [119,120] and by direct comparison with spectra of (±)-Δ^7-mesembrenone obtained by Takano[1] and co-workers in their synthesis of (±)-Δ^7-mesembrine [40]. In addition, a sample of (-)-Δ^7-mesembrenone was prepared from (-)-mesembrine (kindly supplied by Prof A Wiechers[2]) according to the method of Jeffs [120], and the spectra of this were compared to those obtained for (±)-Δ^7-mesembrenone. The PMR spectrum showed a singlet for the N-methyl protons at 2.96 ppm (lit. 2.98 ppm) and the vinylogous proton appeared at 5.18 ppm (lit. 5.19 ppm). A peak at 3.87 ppm (lit. 3.86 ppm [120]) was attributed to the aromatic methoxyls. The mass spectrum of Δ^7-mesembrenone showed three prominent ions: a molecular ion at m/e = 287, an ion at m/e = 259 corresponding to loss of ethylene, and an ion at m/e = 244, resulting from the loss of a methyl group from the m/e = 259 ion. This fragmentation pattern is characteristic of Δ^7-mesembrenone [121]. The IR spectrum, in the solid state (KBr) showed the two peaks characteristic of the vinylogous amide system at 1610 and 1560 cm^{-1}, (lit. 1605, 1565 cm^{-1}, nujol) A carbon-13 NMR spectrum of this compound, the assignments of which are shown in fig 4, provided further support for this structure. The methiodide salt of

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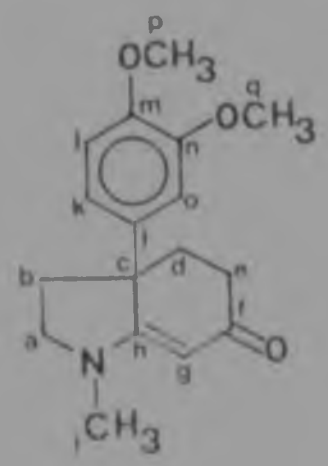
1 The provision of spectra of this compound by Prof. S Takano, Tohoku University, is gratefully acknowledged.

2 The provision of a sample of (-)-mesembrine by Prof. A Wiechers, University of Pretoria, is gratefully acknowledged.

(±)-Δ^7-mesembrenone was prepared, and found to have a melting point (157 - 160 °C) higher than that of the natural antipode (146 - 147 °C [120]). Microanalytical and other data supported the structural assignment.



a; 52.79, c ; 52.51

b or d; 33.10 or 35.97, i; 32.69

e; 39.00

f; 196.36

g; 93.45

h; 170.72

j; 133.60

k, l or o; 119.34, 109.97 or 110.82

m or n; 148.05 or 148.89

p or q; 55.95 or 55.87

Fig 4: C-13 NMR of 2

Although Δ^7-mesembrenone is a natural product, it is one of relatively minor importance. The aim of the project was to develop a synthesis of mesembrine itself, and in order to do this, Δ^7-mesembrenone would have to be reduced to mesembrine. Accordingly Δ^7-mesembrenone was treated with lithium aluminium hydride in THF at room temperature overnight and only starting material was obtained. A similar result was obtained when the reaction mixture was heated under reflux for six hours. Substitution of diglyme for THF, and heating at 150 °C again gave only starting material. The use of lithium borohydride gave the same result. The reaction was next attempted using sodium cyanoborohydride in acidified methanol, and again no reduced products were obtained. Further negative results were obtained when Δ^7-mesembrenone was heated to 50 °C in the presence of formic acid [123] for two hours and also when potassium formate was used in formic acid at 150 °C for

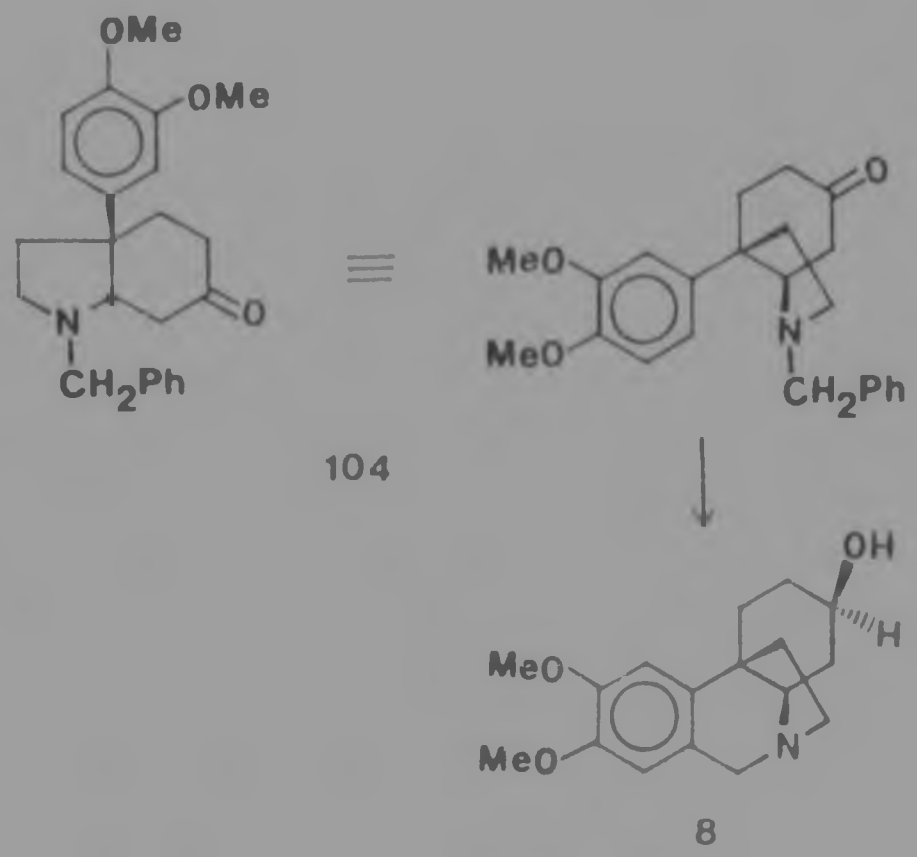
fifteen hours.

At this time the synthesis of mesembrine by Tarbuc and co-workers [40,41,42] including the reduction of Δ^1-mesembrenone, appeared in the literature. This obviated the need for further efforts to develop a method for the reduction, and thus completed the formal synthesis of (±)-mesembrine, fulfilling the primary aim of the present study.

This synthesis of mesembrine represented a new procedure for annelation of a six-membered ring. The importance of this would be established if it could be shown to be of general use. Accordingly, work was undertaken to apply the method to related systems.

5.2 Formal Synthesis of (±)-Hippeastridine

In chapter 2 (p. 35) it was noted that the octahydroindolone 104 has been used in a synthesis of the crinane-type Amaryllidaceae alkaloid (±)-dihydrocrinine 8 [21]. Compound 104 is closely related to mesembrine, so that the method developed for the synthesis of mesembrine could probably also be applied to it, thus providing an extension of the method to the Amaryllidaceae alkaloids.



104

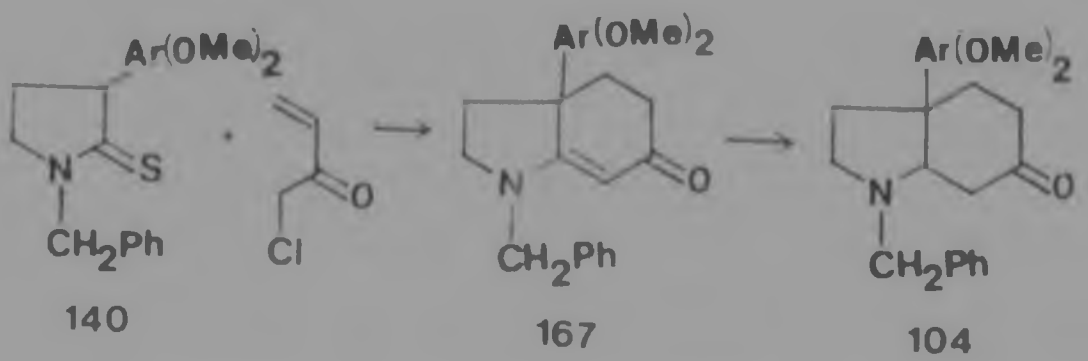
8

A number of synthetic approaches to Amaryllidaceae alkaloids of the crinane type have been reported. Representative of these is the work by Kametani [124], Kotani [125], Schwartz [126], Yamada [127] and Ninomiya [12]. Apart from these syntheses, a number of groups have exploited the strucural similarity of the Amaryllidaceae alkaloids to the Sceletium alkaloids of the mesembrine-type in their syntheses of crinane-type alkaloids, which proceed via 3a-aryloctahydroindole intermediates. The approaches to these intermediates have been discussed at some length in chapter 1. To recapitulate, the following workers have prepared crinane-type alkaloids in this manner: Keck [24,25]; Hoshini [27]; Langlois [44]; Muxfeldt [45]; Oh-ishi [29]; Overman [49]; Speckamp [31]; Stevens [35]; Takano [40,41,42]; Tsuda [53]; Whitlock [46]; Wildman [23], and their respective co-workers.

The conversion of a 3a-aryloctahydroindole to the 5,10b-ethano-

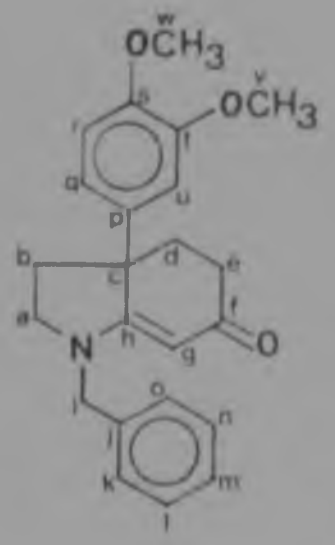
phenanthridine nucleus of the crinane-type alkaloids involves the introduction of a one carbon bridge from nitrogen onto the aryl ring. This has been achieved by Pictet-Spengler cyclization of the N-H octahydroindole. In a number of cases protection of the amine was necessary during its synthesis, and although demethylation of mesembrine has been achieved [129], it is problematic, and the use of the more easily removed N-benzyl group has been preferred [31,29,35,46]. Thus, for example, in the work by Speckamp [31], the 3a-aryloctahydroindole 104 was prepared from 1-benzyl-3-(3,4-dimethoxyphenyl)-succinimide in a route parallel to that used for mesembrine (see chapter 1, page 15). Debenzylation of 104, followed by Pictet-Spengler cyclization gave (±)-dihydromaritidine.

In the present work, the octahydroindolone 104 was a suitable target for an attempt to apply the synthesis developed for mesembrine to another system. It was envisaged that the sulphide contraction sequence using thiolactam 140 with chloromethyl vinyl ketone would yield the hexahydroindolone 167, which could be reduced using lithium in ammonia to 104. This sequence would thus constitute a formal synthesis of (±)-dihydromaritidine 8. The presence of the N-benzyl protecting group was necessary to facilitate the sulphide contraction, since such reactions with secondary thioamides have been found to require far more stringent conditions than those employed here [67]



140 167 104

N-Benzyl-(3,4-dimethoxyphenyl)-2-thiopyrrolidone 140, prepared as described in chapter 3, was heated under reflux for eight hours with two equivalents of chloromethyl vinyl ketone in nitromethane. After cooling to room temperature, diisopropylethylamine was added and the reaction mixture was allowed to stir overnight. Column chromatography of the residue obtained after removal of solvent gave the hexahydroindolone 167 in 37 % yield as the only identifiable product. The IR spectrum of compound 167 showed an absorption for the vinylogous amide system at 1585 cm^{-1}. The PMR spectrum showed a singlet at 4.45 ppm for the benzylic protons, and singlet at 5.40 ppm for the ethylenic proton. The position of this absorption is very similar to the corresponding absorption for Δ^1-mesembrenone (5.18 ppm). The mass spectrum showed a molecular ion at m/e = 363 for $C_{23}H_{25}N$, with the first fragmentation being loss of ethylene to give an ion at m/e = 335, this again being analogous to the mass spectrum of Δ^1-mesembrenone. Further confirmation of the structure was obtained from a carbon-13 NMR spectrum, the assignments for which are shown in fig 5.



a or i; 51.17 or 50.18

b, d, or e; 39.03, 36.24 or 33.11

c; 52.72

f; 196.6

g; 94.04

h; 170.20

j; 133.42

k and o, l and n, or m; 128.90, 127.97 or 127.86

p; 135.1

q; 119.26

r or u; 110.37 or 111.17

s or t; 148.81 or 148.01

v and w; 55.89

Fig 5: C-13 NMR of 167

The hexahydroindole 167 was reduced according to the procedure developed by Takano for (±)-Δ'-mesembrenone [122]. Thus, a solution of 167 in THF / ammonia at -78 °C under argon was treated with lithium. After one hour the reaction was quenched with ammonium chloride. Aqueous work-up, followed by column chromatography gave a single product, the octahydroindole 104 in 76 % yield. It was expected that this reduction procedure would give rise only to the cis-fused compound since dissolving metal reductions are known to lead exclusively to thermodynamically preferred products [43], and in the present case the thermodynamically stable product was expected to be the cis isomer.

The structure of compound 104 was verified by comparison with IR and PMR data in the literature [31], and by a direct comparison of the IR and PMR spectra of an authentic sample of this compound obtained by Professor Speckamp[1]. Further support for the structure came from mass spectral and carbon-13 NMR data (this latter is shown in fig 6).

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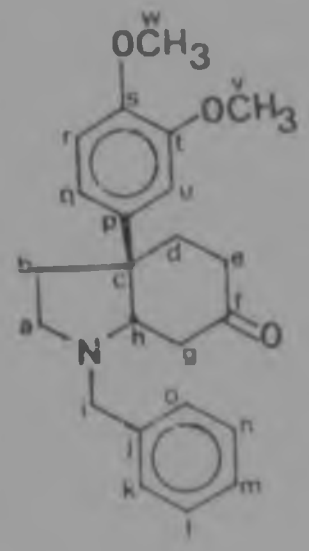
1 The provision of spectra of this compound by Prof. W N Speckamp, University of Amsterdam, is gratefully acknowledged.



a; 51.67

b, d, e, or g; 40.65, 38.64, 36.23, 34.81

c; 47.19

f; 211.2

h; 68.18

i; 57.40

j; 138.75

k and o, l and n, or m; 128.78, 128.17 or 126.92

p; 140.30

q; 117.85

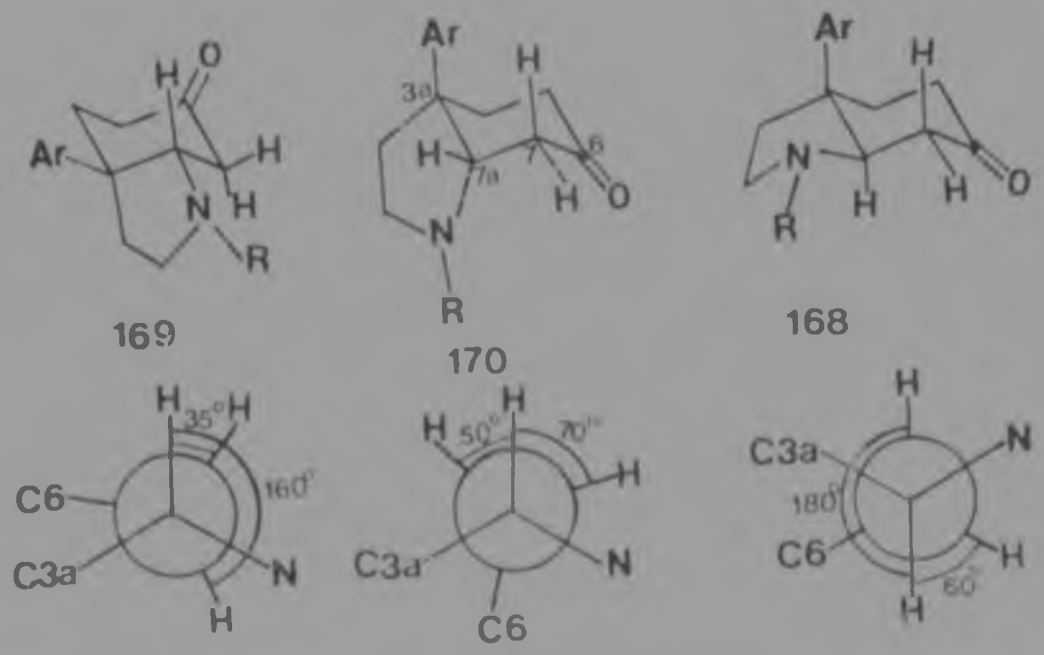
r or u; 110.08 or 111.13

s or t; 149.02 or 147.51

v or w; 55.90 or 56.02

Fig 6: C-13 NMR of 104

Evidence of the preferred conformation for octahydroindole 104 was obtained from the PMR spectrum, which also provided further confirmation that the compound was the cis-fused compound and not its trans-fused isomer 168. For the cis isomer, two conformations are possible, as shown in 169 and 170. The C-7a methine proton appears as a triplet at 3.27 ppm in the PMR spectrum. This is hardly conceivable for either 169 or 168, where the Newman projections as viewed along the C-7a - C-7 bond show large differences in the dihedral angles between the C-7a proton and the two C-7 protons. On the other hand, in 170 the dihedral angles are similar, being 70 ° and 50 ° respectively, which would allow for the C-7a proton absorption to appear as a triplet. The preference for the conformation 170 where the six-membered ring is in a chair form and aryl ring is in the axial position is expected by analogy with mesembrine [21].



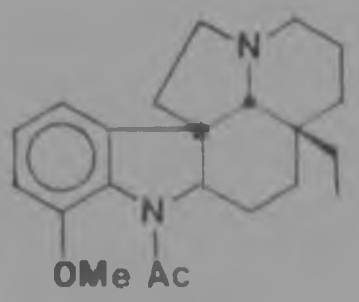
R = CH_2Ph Ar = 3,4-dimethoxyphenyl

The above work represents a formal synthesis of (±)-dihydro-maritidine 8, by analogy with the Speckamp work [31] and shows that the sulphide contraction with chlorometnyl vinyl ketone can be used for systems cl ly related to mesembrine, but more general application of the method has yet to be established. It was for this purpose that attention was turne to anotner alkaloid system, namely the Aspidosperma alkaloids.

CHAPTER 6 THE SYNTHESIS OF AN ASPIDOSPERMA ALKALOID PRECURSOR

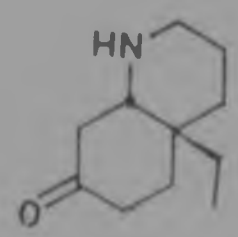
6.1 Introduction

The Aspidosperma alkaloids are a large group of alkaloids the parent of which is (+)-aspidospermine 171.

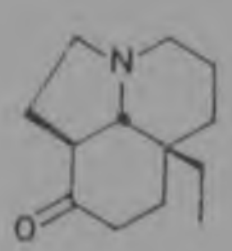


171

The first reported synthesis of aspidospermine, that of Stork and Dolfini, appeared in 1963 [130]. In this work the perhydroquinolinone 172 was used in the preparation of the tricyclic ketoamine 173. Fischer indole cyclization of the o-methoxyphenylhydrazone of 173 gave (±)-aspidospermine 171.



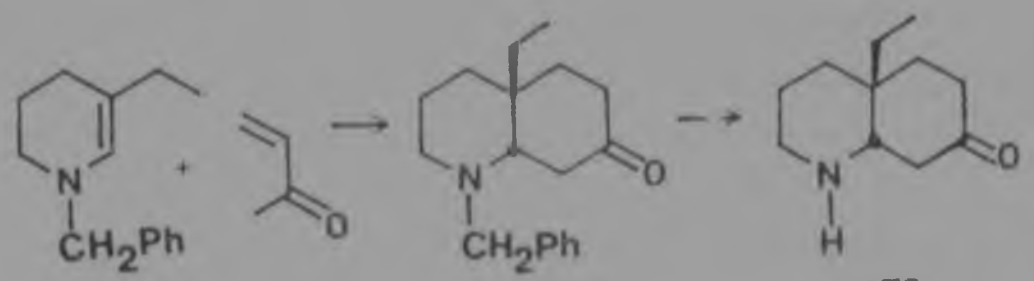
172



173

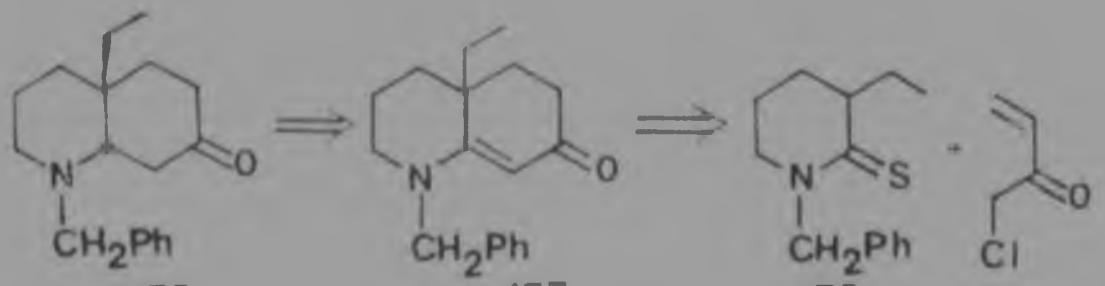
A number of groups [131,132,133] have developed approaches to Aspidosperma alkaloids which are similar to that developed by Stork in that they proceed via perhydroquinolinones related to 172. Thus, in the synthesis by Ban and co-workers [131], the trans-fused compound, epimeric to 172, was used as an intermediate [134]. In the synthesis developed by Stevens [133], the Stork intermediate 172 was prepared by methyl vinyl ketone annelation of piperidine 174, giving 175, followed

by debenzylation. This sequence was closely related to the same worker's preparation of mesembrine [35].



174 175 172

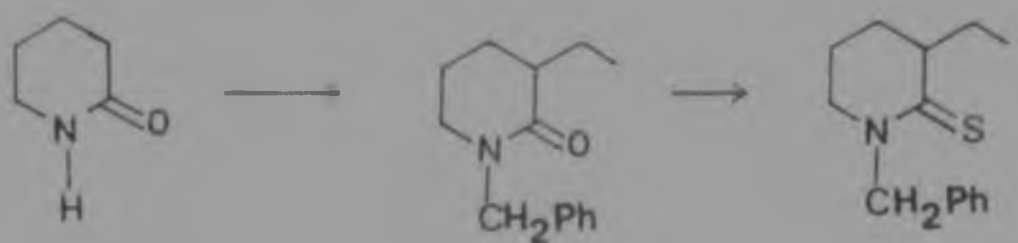
The Stork intermediate 172 was a possible target to which the method for annelation of a six-membered ring using chloromethyl vinyl ketone, developed in the synthesis of mesembrine could probably be applied. A protecting group such as a benzyl group would however be necessary. It was thus envisaged that the sulphide contraction of thiolactam 176 with chloromethyl vinyl ketone would yield 177, which could be reduced by a dissolving metal reduction to 175, which was recognized as being the Stevens intermediate, so that preparation of this compound would constitute a formal synthesis of (±)-aspidospermine. As had been the case in the mesembrine synthesis, the initial problem would be the preparation of the thiolactam 176.



175 177 176

6.2 Synthesis of N-Benzyl-3-ethyl-2-thiopiperidone 176

The readily available compound 2-piperidone was a convenient starting material for the synthesis of the thiolactam 176. The preparation would involve benzylation at nitrogen, ethylation at the α-carbon, and thiation. If the dianion of 2-piperidone was formed, it should react first through the α-carbon, and then through nitrogen, so that if the dianion was treated with an ethylating agent, followed by a benzylating agent, the product of the reaction would be expected to be N-benzyl-3-ethyl-2-piperidone 177'. Thiation of 177' would give 176, in two steps from 2-piperidone.



177' 176

The reaction was attempted by treating 1-piperidone with two equivalents of n-butyllithium at -63 °C to form the dianion, which was treated with ethyl iodide, followed by benzyl bromide. After work-up it was found that none of the desired compound had been obtained. Similar unsuccessful results were obtained when ethyl iodide was substituted by diethyl sulphate, and by ethyl tosylate.

The failure of the dianion route to N-benzyl-3-ethyl-2-piperidone 177' meant that the reaction would have to be performed in two stages, by benzylation of 2-piperidone, followed by 3-ethylation of the N-benzyl-2-piperidone 178 [135] thus obtained. Following this, N-benzyl-3-ethyl-2-piperidone 177' was obtained, and was not purified, but was thiated directly, giving N-benzyl-3-ethyl-2-thiopiperidone 176 in 91 % overall

6.2 Synthesis of N-Benzyl-3-ethyl-2-thiopiperidone 176

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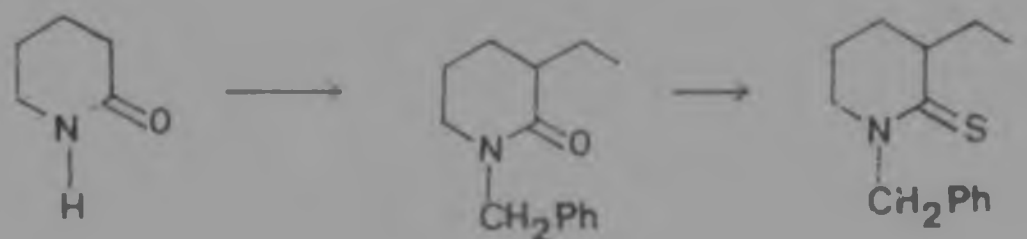


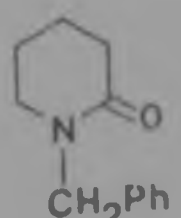
177' 176

The reaction was attempted by treating 1-piperidone with two equivalents of n-butyllithium at -83 °C to form the dianion, which was treated with ethyl iodide, followed by benzyl bromide. After work-up it was found that none of the desired compound had been obtained. Similar unsuccessful results were obtained when ethyl iodide was substituted by diethyl sulphate, and by ethyl tosylate.

The failure of the dianion route to N-benzyl-3-ethyl-2-piperidone 177' meant that the reaction would have to be performed in two stages, by benzylation of 2-piperidone, followed by 3-ethylation of the N-benzyl-2-piperidone 178 [135] thus obtained. Following this, N-benzyl-3-ethyl-2-piperidone 177' was obtained, and was not purified, but was thiated directly, giving N-benzyl-3-ethyl-2-thiopiperidone 176 in 91 % overall

yield, based on 2-piperidone.

The reaction was also attempted by thiation of N-benzyl-2-piperidone 178 to give N-benzyl-2-thiopiperidone, which was then treated with n-butyllithium at 0 °C, followed by ethyl iodide at -78 °C. No recognizable products were obtained after aqueous work-up of the reaction. Previous work in these laboratories has shown that in the alkylation of N-methyl-2-thiopiperidone under comparable conditions, only S-alkyl products were obtained [92]. If this occurred in the present case, it is likely that such products would be hydrolysed in the work-up procedure. This would explain the failure to obtain recognizable products in this reaction.



178

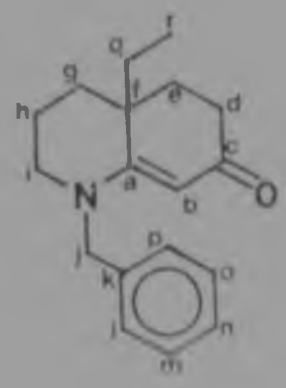
6.3 Sulphide Contractions of N-Benzyl-3-ethyl-2-thiopiperidone 176 with Chloromethyl Vinyl Ketone

The salt formation and sulphide contraction of N-benzyl-3-ethyl-2-thiopiperidone 176 with chloromethyl vinyl ketone was performed using the conditions developed in the mesembrine sequence, that is, a solution of 176 and chloromethyl vinyl ketone in nitromethane was heated under reflux for ten hours, then cooled to room temperature and treated with diisopropylethylamine. After stirring overnight, the residue obtained once the solvent had been removed was chromatographed, giving the desired bicyclic compound 177 in 40 % yield.

The yield of the reaction was low, and attempts were therefore made to modify the conditions to improve this. When the salt formation was attempted in benzene instead of nitromethane, after overnight stirring at room temperature, TLC indicated that no reaction had occurred. On using DMF as solvent and heating to 100 °C for twelve hours, before treatment with diisopropylethylamine at room temperature, the product, 177, was obtained in 22 % yield. When the salt formation was performed using iodomethyl vinyl ketone, generated *in situ* by halogen exchange of chloromethyl vinyl ketone with sodium iodide, in acetonitrile at room temperature for one hour, an intractable tar was obtained. The salt formation was then performed using a five-fold excess of chloromethyl vinyl ketone in the absence of solvent, the mixture being heated to 100 °C for eight hours. This was then dissolved in nitromethane and treated with diisopropylethylamine in the usual way. The product was obtained in 10 % yield. In final attempt to improve conditions, the salt formation was again attempted without solvent, but for the contraction, the mixture was taken into acetonitrile and treated with a solution of triphenylphosphine and diisopropylethylamine in acetonitrile. The yield of 176 in this case was 17 %. It thus seemed that the highest yield attainable (40 %) was under the original conditions.

Compound 177 was characterized by its IR spectrum, which showed two bands, at 1540 and 1585 cm^{-1}, as expected for an *s-trans* vinylogous amide of this type [106]. The PMR spectrum showed a singlet at 5.18 ppm for the olefinic proton, while the benzylic protons appeared as two doublets at 4.17 and 4.50 ppm. The mass spectrum showed a molecular ion at m/e = 269, corresponding to $C_{18}H_{23}NO$, the first fragmentation being loss of ethylene, to give a peak at m/e = 241. Finally, a carbon-13 NMR was obtained, shown in fig 7, which was found to be fully

compatible with the structure. The assignments were made with the aid of a DEPT experiment.



a; 171.69

b; 128.38

c; 196.25

d, e, g or h; 32.69, 31.94, 29.02 or 26.89

f; 36.81

i; 49.52

j; 54.95

k; 135.68

l and p, m and o or n; 128.72, 127.36 or 126.72

q; 18.46

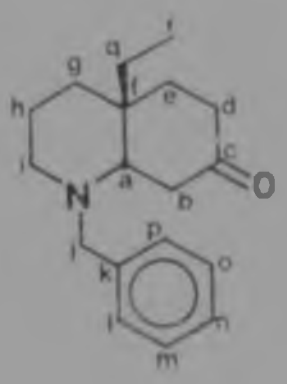
r; 7.91

Fig 7 C-13 NMR of 177

6.4 Reduction of 2-Benzyl-6-ethyl-2-azabicyclo[4.4.0]dec-1(10)-en-9-one 177

To complete the synthesis of the Stevens asoidospermine intermediate 175, compound 177 had to be reduced. This was achieved, by analogy to the Takano mesembrine sequence [122], by dissolving metal reduction. Accordingly, lithium was added to a solution of 177 in THF / ammonia at -78 °C under argon. After stirring for one hour, the reaction was quenched with ammonium chloride, aqueous work-up after removal of solvents gave the reduced product, 175 in 54 % yield. In the Stevens work, a melting point of 81.5 - [illegible] °C, but no spectral data was reported for 175. In the present work this compound failed to crystallize, but spectral evidence for the structure was obtained. Thus, the IR spectrum showed a saturated ketone

carbonyl at 1710 cm^{-1}. The PMR spectrum of the compound showed no olefinic protons, and showed an AB pattern, as two doublets, centred at 3.00 and 3.87 ppm respectively. The mass spectrum showed a molecular ion at m/e = 271, corresponding to $C_{18}H_{25}NO$, and this was further supported by the HRMS. Finally, a Carbon-13 NMR spectrum was obtained, which is illustrated in fig 8. The spectral data indicate that 175 had been obtained as a single isomer, which was as expected, by analogy to the mesembrine work.



a; 66.81

b or d; 42.44 or 37.13

c; 210.61

e, g or h; 21.41, 34.05 or 32.32

f; 36.22

i or j; 54.52 or 57.32

k; 140.33

l and p, m and o, or n; 128.36 128.20 or 126.65

q; 17.82

r; 6.89

Fig 8: C-13 NMR of 175

6.5 Conclusion

The synthesis of compound 175 constituted a formal synthesis of (±)-aspidospermine, and demonstrated that the salt formation and sulphide contraction sequence of thiolactams with chloromethyl vinyl ketone could be used for systems other than those of the mesembrine type.

In the mesembrine synthesis the yield for the reaction sequence was good (70 %); however, in the synthesis of both the

Amaryllidaceae and Aspidosperma precursors, the yields were low (37 % and 40 % respectively). In order for the method to be really useful these yields would have to be improved. A major cause of the low yields is undoubtedly the harsh conditions required for the salt formation reaction. This results in some decomposition of the thiolactams, particularly for the sensitive N-benzyl thiolactams. In addition these conditions are probably conducive to polymerization of the chloromethyl vinyl ketone. Thus if the salt formation could be achieved under milder conditions, it is likely that the yields could be improved.

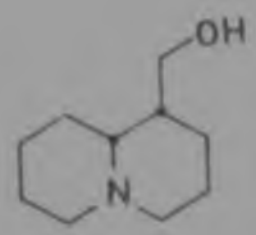
In most cases the salt formations were performed using chloromethyl vinyl ketone. Attempts had, however, been made to use iodomethyl vinyl ketone as a substitute but without success. The most suitable halomethyl vinyl ketone for the salt formation was probably the bromo-compound, and if this could be prepared, its use in the reaction would probably allow for milder conditions. Alternatively, if the halogen were substituted for some different, better leaving group, this could possibly result in an improvement. The acetate has been reported [136], but its use is unlikely to be beneficial. It is possible that use of the triflates might enable the reaction to be carried out under milder conditions, since Rapoport and co-workers have reported that salt formations with triflates, leading to sulphide contractions occur more readily than the corresponding reactions with the bromo compounds [137].

The salt formation and sulphide contraction sequence between thiolactams and chloromethyl vinyl ketone represents a new procedure for annelation of six membered rings. The widespread occurrenceof alkaloids possessing fused six membered rings means that, particularly if more favourable conditions could be

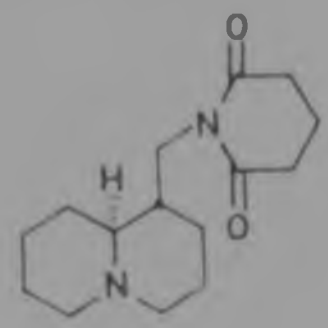
found for the reaction, the method could be applied to a range of alkaloid systems. The sequence thus constitutes a useful addition to the general methods for synthesis of these compounds.

APPENDIX

The sulphide contraction sequence has proved its worth in the synthesis of a variety of alkaloids. The scope of the reaction is, however, very wide, and a large number of alkaloid systems may be accessible by suitable exploitation of this route. In chapter 2, a brief summary of the work achieved prior to the mesembrine synthesis was presented. Amongst others, the synthesis of the quinolizidine alkaloid lupinine 82 was noted. A closely related system is that of lamprolobine 179, although its stereochemistry is opposite to that of lupinine.

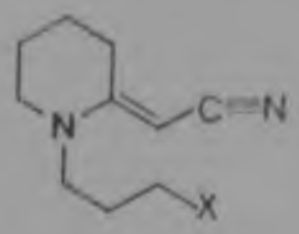


82

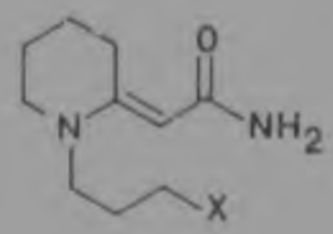


179

The substitution in lamprolobine 179 of a nitrogen functionality for the oxygen in 82 presented an interesting synthetic problem. Two compound types which could possibly provide an entry into this system are vinylogous cyanamides such as 180, and vinylogous ureas 181.



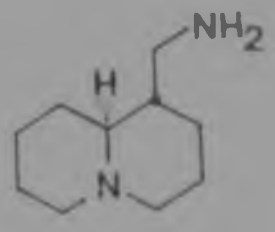
180



181

In general terms, it was envisaged that, if either 180 or 181 with the appropriate functionality on nitrogen could be induced

to undergo alkylative ring closure at the α-carbon. by analogy to the lupinine 82 synthesis (see page 28), reduction of the vinylogous cyanamide or vinylogous urea obtained could provide the amine 182. This would complete a formal synthesis of lamprolobine 179 since Wenkert and co-workers [138] have converted 182 to lamprolobine by treatment with glutaric anhydride.

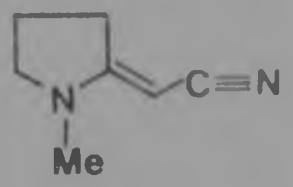


182

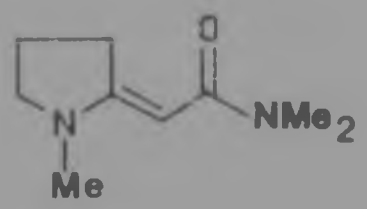
The feasibility of the proposed route depends firstly on the synthesis of the required vinylogous cyanamides and vinylogous ureas, and secondly, on the reactivity of these compounds towards intramolecular alkylation.

For an initial, exploratory study into the feasibility of this proposed route, it was decided to attempt to prepare simple analogues of these compounds, and to investigate their relative reactivities towards simple alkylating agents, with respect to each other and with respect to the behaviour of the vinylogous urethanes under comparable conditions.

The vinylogous cyanamide 183, which could serve as a model for 180, had previously been prepared in these laboratories [60] by salt formation of N-methyl-2-thiopyrrolidone with iodoacetonitrile in acetonitrile, followed by sulphide contraction in the presence of triethylamine and triphenylphosphine, giving 183 in 90 % yield.

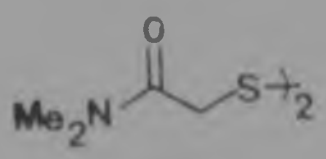


183



184

The vinylogous urea 184 was chosen as a suitable model for 181. Initially the preparation of this compound was attempted using conditions similar to those used in the preparation of the vinylogous cyanamide. Accordingly, the salt formed between N-methyl-2-thiopyrrolidone and α-bromo-N,N-dimethylacetamide [139] was treated with triphenylphosphine and triethylamine in acetonitrile. The only identifiable product was bis(N,N-dimethylacetamide)disulphide 185 (18 %). The reaction was repeated as before, using the non-nucleophilic base DBU. In this case the disulphide was formed in a quantitative yield. It was likely that the sulphide contractions did go not under the above conditions because neither triethylamine nor DBU was a strong enough base to deprotonate the salt formed. The reaction was therefore performed using a stronger base. Accordingly potassium t-butoxide in t-butyl alcohol was used, with conditions otherwise unchanged. In this case the desired vinylogous urea was obtained in 84 % yield.



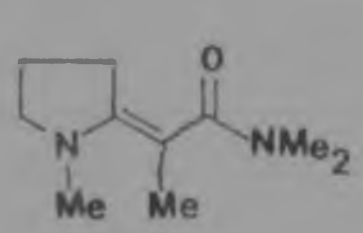
185

The methylation of the vinylogous urethane 100 had been investigated in these laboratories, the best conditions found being treament of 100 with excess methyl iodide in DMSO at 50 °C for ninety minutes [60]. In the present study DMSO was avoided because of its susceptibility to alkylation. Thus, 100

was treated with an excess of methyl iodide in acetonitrile at 50 °C for fourteen hours. The oil obtained after aqueous work-up was shown, by comparison of its PMR spectrum with that of the pure compound, to be a mixture of starting material and methylated product 186 with the methylated product comprising approximately 80 % of the mixture.

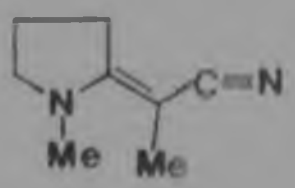
100 186

The vinylogous urea 184 was methylated under conditions similar to those used for the urethane. In this case, the reaction was complete after ten hours. A PMR of the methylated product 187 indicated that it was a mixture of geometric isomers, and these could not readily be separated.



187

The vinylogous cyanamide 183, when treated with methyl iodide under similar conditions, formed only about 40 % of the alkylated product 188 as a mixture of cis and trans isomers after fifty hours, as judged by comparison of the PMR spectrum of the oil obtained with those of the pure compound [92].



188

The results of the above studies indicate that the vinylogous cyanamide is considerably less reactive than the vinylogous urethane, and as such would be expected to not be very useful in a synthesis of lamprolobine 179. The vinylogous urea, on the other hand, is more reactive than the vinylogous urethane, and thus it could be anticipated that it would readily participate in the intramolecular alkylation reaction required in the proposed route.

A Note on Structure-Reactivity Correlations

In the characterization of the various extended enamines it was noticed that a large variation occurred in the chemical shifts of the olefinic protons in these systems (see table 2). Thus the olefinic proton in the vinylogous urea 184 appeared at 4.75 ppm, while that in the vinylogous cyanamide 191 appeared at 3.57 ppm. This effect was even more apparent with the other known extended enamines of similar structure. Thus the olefinic proton of vinylogous amide 191 [60] absorbed at 5.62 ppm, while that of the vinylogous nitramine 192 appeared at 6.67 ppm [140]. Since the chemical shift of a proton is dependent on the amount of shielding supplied by the electrons in its immediate environment, the wide variations in the positions of absorption must be some reflection of the electron densities on the the olefinic carbon atoms in these compounds. Naively, one might expect a correlation to exist between electron density on a given carbon atom and the nucleophilicity of that carbon atom. Since the carbon-13 NMR spectra are a more accurate reflection of the electron densities on carbon than the PMR spectra, these spectra of the compounds in question were obtained. It was found that the positions of absorption of the olefinic carbon atoms in these compounds show a similar trend to that found in the PMR spectra (see table 2).

TABLE 2 Proton and Carbon-13 Chemical Shifts for the α-position in extended enamines and related model compounds[a]

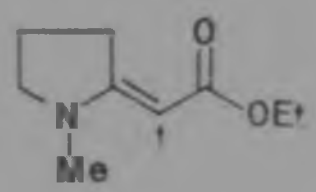
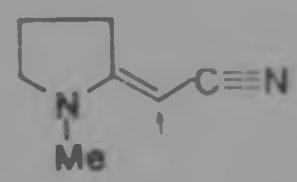
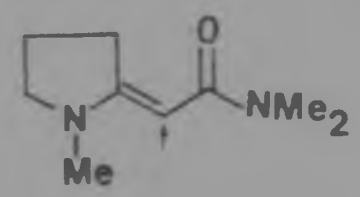
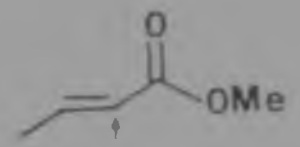
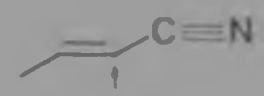
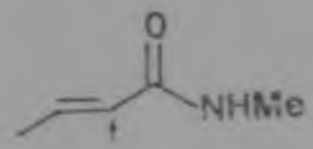
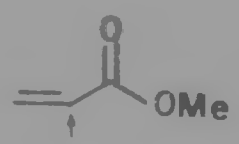
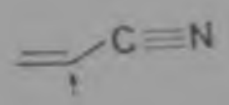
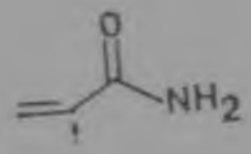
Series A			
Compound	100	183	184
δ (C) (ppm)	87.31	53.7	92.8
δ (H)	4.41 (ref 60)	3.57 (ref 60)	4.8
Series B			
δ (C) (ref 141)	128.9	101.1	125
δ (H) (ref 142)	5.8	5.2 - 5.6	-
Series C			
δ (C) (ref 141)	129.6	108	-
δ (H) (ref 142)	6.2	5.3 - 5.7	6.3 (acetone)
Δδ (C) (Series B - A)	45.9	47.4	47.4
Δδ (C) (Series C - A)	51.9	54.3	-

TABLE 2 Proton and Carbon-13 Chemical Shifts for the α-position in extended enamines and related model compounds[1]

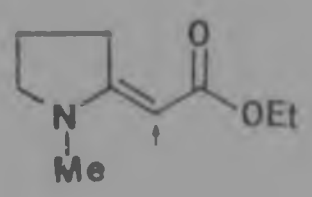
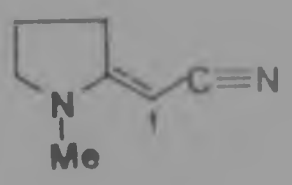
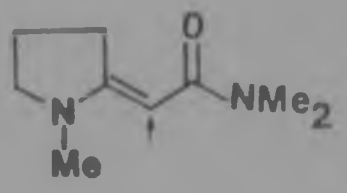
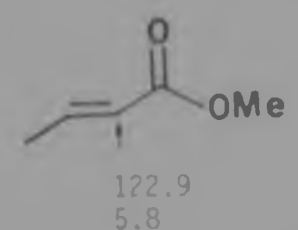
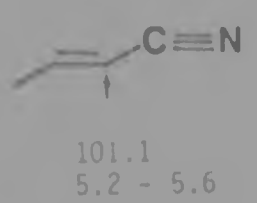
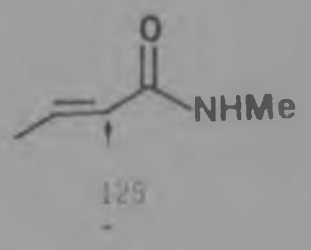
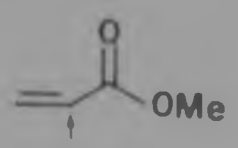
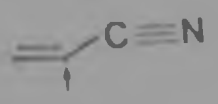
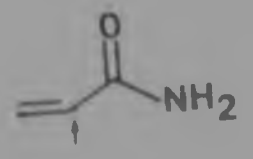
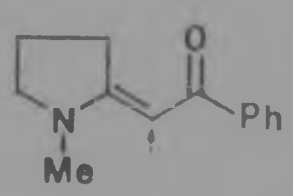
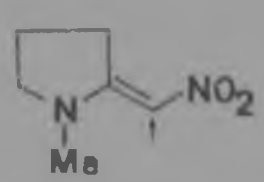
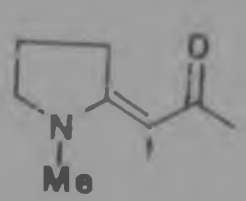
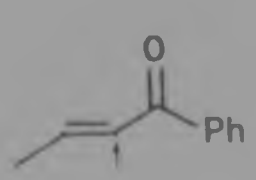
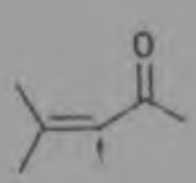
Series A			
Compound	100	183	184
δ (C) (ppm)	77.71	53.7	77.6
δ (H)	4.41 (ref 60)	3.57 (ref 60)	4.8
Series B			
δ (C) (ref 141)	122.9	101.1	125
δ (H) (ref 142)	5.8	5.2 - 5.6	-
Series C			
δ (C) (ref 141)	129.6	108	-
δ (H) (ref 142)	6.2	5.3 - 5.7	6.3 (acetone)
Δδ (C) (Series B - A)	45.2	47.4	47.4
Δδ (C) (Series C - A)	51.9	54.3	-

TABLE 2 (contd.)

Series A			
Compound	191	192	193
δ (C)	85.9	108.82 (ref 140)	-
δ (H)	5.62 (ref 60)	6.67 (ref 140)	4.77 (ref 60)
Series B		—	
δ (C) (ref 141)	120.7		133
δ (H) (ref 142)	-		4.0
Δδ (C) (Series B - A)	34.8		

[1] All spectra were run in $CDCl_3$ unless otherwise stated

The absorption positions must depend on both the enamino nitrogen and the functional group, and in order to determine their relative effects, a comparison was made with a series of model compounds. However, on making this comparison, it was found that the effect of the enamino nitrogen was roughly constant, so that the variation in absorption depended predominantly on the functional group present (see table 2).

On examination of the carbon-13 data, using the above argument a reactivity order towards alkylation was expected to be: vinylogous urethane < vinylogous urea < vinylogous cyanamide. This order is in contrast to that found in the methylation reactions which was: vinylogous cyanamide < vinylogous urethane < vinylogous urea. Clearly the electron densities of these carbon atoms, as indicated by the positions of absorptions in the carbon-13 NMR spectra do not correlate directly with the nucleophilicities.

A more careful consideration of the factors involved showed that the NMR absorptions are a reflection of the total electron density on the carbon atom, and this is only one factor affecting the nucleophilicity of the atom.

In the reaction of a nucleophile with an electrophile, the reactivity does not depend solely on the charge of the involved carbon atoms of both the electrophile and the nucleophile. Also important are energies of the frontier orbitals involved, namely the HOMO of the nucleophile and the LUMO of the electrophile, and the coefficients of the atomic orbitals in these molecular orbitals. The relationship between these factors is governed by the Klopman - Salem equation, a simplified form of which is shown below [143].

$$\Delta E = \underbrace{\frac{Q_{nuc}\, Q_{elec}}{\varepsilon R}}_{\text{Coulombic Term}} + \underbrace{\frac{2(C_{nuc}\, C_{elec}\, \beta)^2}{E_{HOMO(nuc)} - E_{LUMO(elec)}}}_{\text{Frontier Orbital Term}}$$

ΔE	is the energy gained or lost when the orbitals of one reactant overlap with those of another.
Q_{nuc} and Q_{elec}	are respectively the total charges of the carbon atoms involved of the nucleophile and electrophile.
C_{nuc} and C_{elec}	are the coefficients of the atomic orbitals on the carbon atom involved in the HOMO of the nucleophile and the LUMO of the electrophile respectively.
ε	is the dielectric constant.
$E_{HOMO(nuc)}$	is the energy of the HOMO of the nucleophile
$E_{LUMO(elec)}$	is the energy of the LUMO of the electrophile.
R	is the distance between the atoms reacting.
β	is a resonance overlap integral

In the case of the first (coulombic) term being dominant in an interaction the reaction would then be charge controlled. Such a case would occur in the interaction of a hard nucleophile with a hard electrophile. On the other hand, if the second (frontier orbital) term is dominant, the reaction is orbital controlled, and reflects the interaction between of a soft nucleophile and a soft electrophile.

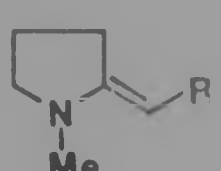
The electron density of the carbon atoms in question, as indicated by the NMR spectra, can only be a reflection of the first term of this equation, and only if this term is dominant can this possibly be a reflection of the nucleophilicities of these atoms.

In the particular reactions studied here, the electrophile used was methyl iodide, which is a soft electrophile; that is, the $E_{LUMO(elec)}$ will be low, and charge, Q_{elec} will be small. Thus in this case the second term of the equation will be dominant, and the reactions will be orbital controlled rather than charge controlled. The reactivities will then depend less on the electron density on carbon, than on the coefficient of the atomic orbital on this atom in the HOMO of the vinylogous system.

Conceivably, a correlation could exist between the electron densities on carbon and the reactivity with a hard electrophile where the coulombic term would be dominant, for example in the protonation of these compounds. A convenient method by which these reactions might be examined is UV spectroscopy, since the UV absorption of the extended enamine would disappear on protonation, the conjugation being disrupted (vide infra). This method for following the reactions would, however, only be meaningful if a kinetic product and not a thermodynamic product is observed.

The results obtained are shown in table 3. Only for the vinylogous urethane 100 and vinylogous urea 184 is the expected disappearance of the absorption on protonation observed, and in both cases this occurred extremely rapidly. The small changes in the spectra observed in the other cases must indicate that protonation does not take place on carbon. A possible explanation of these results is that, because these reactions are charge controlled, the proton would be expected to react at

TABLE 3

Compound		UV $\lambda_{max}(\epsilon_{max})$	On addition of 11 M HCl
100	R = CO_2Et	280(22900)	Peak vanishes
183	R = C≡N	269 (25000)	Slight decrease
184	R = CO_2NMe_2	284(26000)	Peak vanishes
191	R = COPh	243(135000), 334(26900)	230(7400), 243(5500) 321(28200)
192	R = NO_2	354(17000)	Slight decrease
193	R = $COCH_3$	304(26300)	291(24500)

Compounds 100, 191 and 193: Reference 60

the site of highest electron density in the molecule. In the extended enamines, this site is unlikely to be carbon because of the high electronegativities of the hetero atoms present. The protonation on carbon in the vinylogous urethane 100 and vinylogous urea 184 is indeed somewhat surprising, but this anomaly is probably because, since the reactions are extremely rapid, it is likely that the thermodynamic products, and not the kinetic products are observed. Thus in these cases, an indication of the total charge on all the atoms would be needed in order to predict the sites and rates of reactivity. Clearly no indication of this could be obtained from NMR spectra, and thus the NMR spectra of these compounds could in no way be expected to correlate with their nucleophilicities.

EXPERIMENTAL

GENERAL DETAILS

a. Purification of Solvents and Reagents

All solvents used for preparative chromatography were distilled. For reactions, ether, THF, DME, diglyme and benzene were dried by distillation from sodium / benzophenone immediately prior to use. Acetonitrile, diisopropylamine, HMPA, DMSO, DMF, and TMEDA were distilled from calcium hydride and stored over molecular sieves (4A). Nitromethane was distilled from sodium sulphate / urea [144]. Ammonia was distilled through a potassium hydroxide column. Dichloromethane was filtered through Merck aluminium oxide (basic, activity grade 1), dried over molecular sieves (4A), and then stored over fresh molecular sieves. Toluene was distilled from sodium immediately prior to use. Molecular sieves were activated for 3 h at 300 °C before being used.

b. Chromatographic Separations

Thin layer chromatograms (TLC's) were run on Merck DC-Fertigplatten Kieselgel F-254 plates. Merck Kieselgel 60 (particle size 0.063 - 0.2 mm) was used as the adsorbent for column chromatography. Preparative layer chromatograms were run on Merck Aluminium oxide (type T) F-254 plates.

c. Spectral and Physical Da

All melting points were obtained on a micro hotstage apparatus and are uncorrected.

IR spectra were recorded on either a Pye-Unicam SP3-300 spectrophotometer, or on a Jasco IRA-1 spectrophotometer. Liquids were run either as films between sodium chloride plates, or as 7 % solutions in chloroform, using a cell with a path length of 0.1 mm, and sodium chloride windows. The potassium bromide dispersion technique was used for solids. Band positions are given in cm^{-1}. Abbreviations used in quoting spectra: s = strong, m = medium, w = weak, br = broad, sh = shoulder.

PMR spectra were recorded in deuteriochloroform (unless otherwise stated) on one of the following spectrometers: a Hitachi-Perkin-Elmer R-20A high resolution spectrometer (60 MHz); a Varian EM-360A spectrometer (60 MHz); a Brucker WP-80 spectrometer (80 MHz); a Varian XL-200 spectrometer (200 MHz) or a Brucker WM-500 spectrometer (500 MHz). Chemical shifts are reported on the δ scale relative to tetramethylsilane. In most cases coupling constants were estimated from the line separations on the chart paper. The chemical shifts are reported: value (description of absorption, number of protons, coupling constant (where applicable), assignment (if unambiguous)). Abbreviations used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

Carbon-13 NMR spectra were recorded in deuteriochloroform on either a Varian CFT-20 spectrometer (20 MHz), a Varian XL-200 spectrometer (50.4 MHz) or a Brucker WM-500 spectrometer (126 MHz). Chemical shifts are reported on a δ scale relative to tetramethylsilane. Assignments were in most cases made with the aid of either SFORD or DEPT experiments. Abbreviations used: s = singlet, d = doublet, t = triplet, q = quartet.

UV spectra were recorded in ethanol solution on either a Pye-Unicam SP8-100 spectrophotometer or a Varian CARY 219 spectrophotometer. Absorption maxima are quoted as: $\lambda_{max}(\varepsilon_{max})$. Wavelengths are given in nm.

Low resolution mass spectra were recorded on either a Varian CH-5 or CH-7 mass spectrometer or a Varian MAT 212 mass spectrometer in conjunction with a Varian SS-188 data collection system. This last spectrometer was also used to obtain high resolution mass spectra. In each case the eight peaks in the higher mass ranges with the largest relative abundance are quoted. Data are quoted: m/e value (relative abundance, %, assignment (if applicable)).

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 solvent.

Removal of solvent from solutions was always performed under reduced pressure.

Yields are calculated from the mass of the immediate synthetic precursor used unless otherwise stated.

EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 3

1 Procedures Relating to Attempted Syntheses of Lactams by 3-Arylation of The Pyrrolidone Ring

1.1 Attempted Preparation of Aryllead Triacetates

1.1.1 Treatment of lead tetraacetate with 1,2-dimethoxybenzene in the presence of mercuric acetate as catalyst

a. Method of de Vos and co-workers [86]. 1,2-Dimethoxybenzene (0.4 mL, 3.1 mmols) was added to lead tetraacetate (80 % in acetic acid) (1.6 g, 2.8 mmols) in 20 mL dry benzene under nitrogen, together with mercuric acetate (28 mg, 0.09 mmols). After being heated under reflux for 5 days, the mixture was poured into water and extracted with chloroform. The organic phase was filtered through celite and the solvents were removed. An attempt to precipitate the product using hexane gave an intractable orange solid (37 mg) which did not melt below 250 °C and could not be recrystallized.

b. Using conditions similar to those in (a) but with a reflux time of only 5 h, a white solid, probably lead oxide, which turned brown on addition of water precipitated from the reaction solution.

c. Using conditions similar to those in (a) excepting that an eight fold excess of 1,2-dimethoxybenzene was used in place of the solvent, and the mixture was treated at 80 °C for 11 h, again no product was obtained.

1.1.2 Treatment of lead tetraacetate with 1,2-dimethoxybenzene in the presence of haloacetic acids [82]

Trichloroacetic acid (5.25 g, 32 mmols) was added to lead tetraacetate (80 % in acetic acid) (2.21 g, 4 mmols) in dry chloroform (10 mL) under nitrogen. The addition of 1,2-dimethoxybenzene (3.1 mL, 24 mmols) resulted in a black mixture, which was stirred overnight at room temperature, and then poured into water. The organic phase was separated, and the solvent was removed. The residue was taken into chloroform (2 mL), and hexane (50 mL) was added in an unsuccessful attempt to precipitate the product.

Similar unsuccessful results were obtained using mono- and dichloroacetic acid under similar conditions.

1.1.3 Attempted preparation of aryl-adamantanecarboxylates via silanes [82]

1-Bromo-3,4-dimethoxybenzene (3[illegible] µL, 3.0 mmols) was treated with magnesium (81 mg, 3.3 mmols) in THF under nitrogen. When, after 3 h, most of the magnesium had disappeared, trimethylchlorosilane (420 µL, 3.3 mmols) was added, resulting in a rapid precipitation of magnesium salts. After 30 min the mixture was poured into water, and neutralized with ammonia solution. Extraction of the aqueous phase yielded 3,4-dimethoxyphenyltrimethylsilane (506 mg 2.4 mmols) in 80 % yield, which was used in the following reaction without further purificaton.

IR (film) 825(s,Si-C) 885(m,CH,Ar) 1025(s,ArOMe)
1220(s,Si-C) 1243(s,ArOMe) 1460(m,C=C,Ar)
1500(s,C=C,Ar) 1565(w,C=C,Ar)
1580(m,C=C,Ar)

To a dark purple solution of lead tetraacetate (dried over potassium hydroxide under vacuum) (787 mg, 1.8 mmols) in trifluoroacetic acid (2.5 mL), was added dropwise a solution of 3,4-dimethoxyphenyltrimethylsilane (372 mg, 1.8 mmols) in chloroform (10 mL). The reaction was quenched with acetic acid (1.5 mL) after 5 min. Dichloromethane was added, and the organic phase was washed with water. The residual black oil obtained after removal of solvent was dissolved in benzene (2 mL) and pentane (50 mL) was added in an unsuccessful effort to precipitate out the product.

1.2 Experimental procedures relating to $S_{RN}1$ Reaction Attempts

1.2.1 Reaction of the anion of N-methyl-2-pyrrolidone 111 with 1-bromo-4-methoxybenzene

a. Potassium (669 mg, 17.0 mmols) together with a little ferric nitrate was dissolved in dry ammonia (30 mL) at -78 °C, to give a grey solution. Compound 111 (1.45 mL, 15.0 mmols) was added, and after 10 min the colour had changed to yellow, so 1-bromo-4-methoxybenzene (2.1 mL, 16.5 mmols) was added. The mixture was irradiated with a 125 W Hg lamp for 15 min, the heat generated from the lamp warming the mixture up to reflux temperature. After evaporation of the ammonia, the mixture was poured into water and extracted with dichloromethane. Removal of the solvent gave a black oil (3.2 g), TLC and IR analysis of which proved it to be a mixture of starting materials.

b. The procedure followed was similar to that described in (a) except that the anion was left to generate for 1 h at -33 °C. A black oil was obtained which again proved to be a mixture of

starting materials.

c. Compound 111 (1.45 mL, 15.0 mmols) was added to potassium t-butoxide (2.1 g, 18.3 mmols) in dry ammonia (50 mL) at -33 °C. After stirring for 1 h, 1-bromo-4-methoxybenzene (2.1 mL, 16.5 mmols) was added and the mixture was irradiated using a 150 W tungsten floodlight for 5 h. The ammonia was evaporated off, and the residue poured into ammonium chloride solution. The aqueous phase was extracted with dichloromethane. Removal of the solvent gave an oil (3.8 g) which again proved to be a mixture of starting materials.

d. To compound 111 (480 µL, 5.0 mmols) in dry THF (20 mL) was added 5.5 mmols n-butyllithium in hexane. After 10 min 1-bromo-4-methoxybenzene (690 µL, 5.5 mmols) was added, the mixture was irradiated for 20 min with the 125 W Hg lamp, then poured into ammonium chloride solution. The aqueous phase was extracted with dichloromethane. Removal of the solvent gave 1.1 g of an oil which again consisted of a mixture of starting materials.

1.7.2 Reaction of the anion of N-methyl-2-thiopyrrolidone 121 with 1-bromo-4-methoxybenzene

a. Potassium (662 mg, 17 mmols) together with a little ferric nitrate was dissolved in dry ammonia at -78 °C. The mixture was stirred for 6 h, then warmed to -33 °C and the thiolactam 121 (1.74 g, 15 mmols) was added, followed by 1-bromo-4-methoxybenzene (2.1 mL, 16.5 mmols) after 30 min. The reaction was irradiated for 15 min using the 125 W Hg lamp. The ammonia was allowed to evaporate, and the residue was poured into ammonium chloride solution. Extraction with dichloromethane and removal of solvent yielded a black oil consisting primarily

of a mixture of the starting materials, as judged by TLC analysis.

b. The procedure followed was similar to that described in (a) except that potassium t-butoxide (2.02 g, 18 mmols) was the base used, and the mixture was irradiated for 5 h using the 150 w tungsten floodlight. Again an oil was obtained (4.46 g) which consisted of a mixture of starting materials.

c. The addition of n-butyllithium in hexane (5.5 mmols) to thiolactam 121 (580 mg, 5 mmols) in dry THF at 0 °C yielded a yellow solution out of which the salt precipitated. After 20 min 1-bromo-4-methoxybenzene (690 µL, 5.5 mmols) was added and the mixture was irradiated for 30 min with the 125 w Hg lamp. Ammonium chloride solution was added, and the aqueous phase was extracted with dichloromethane. Removal of the solvent yielded 1.2 g of an oil. TLC analysis showed a new compound together with the starting materials. Chromatography on silica gel eluting with hexane - ethyl acetate gave 1-bromo-4-methoxybenzene (511 mg, 50 % recovery) (TLC, hexane - ethyl acetate, 2:3, R_f = 0.93) thiolactam 121 (220 mg, 38 % recovery R_f = 0.55) and 1,1'-dimethyl-2,2'-dithioxo-3,3'-bipyrrolidine 122 (104 mg, 0.46 mols) (R_f = 0.43) as a solid in 18 % yield which was recrystallized from acetone (mp 203 - 204 °C (lit 201 - 202 °C [89])).

IR ($CHCl_3$)	1515(s,NC=S)
MS	228(100,M^+) 196(79) 163(24) 126(82) 125(68) 82(32) 81(29) 72(24)
HRMS	228.07552 ($C_{10}H_{16}N_2S_2$ requires 228.07549)

1.3 Arylations using Diphenyliodonium Chloride

1.3.1 Phenylation of Vinylogous Urethane 124

a. To a solution of vinylogous urethane 124 (525 mg, 3.1 mmols) in dry THF (50 mL) under nitrogen at 0 °C was added n-butyllithium in hexane (3.3 mmols) followed by diphenyliodonium chloride (1.1 g, 3.5 mmols) after 3 min. The mixture was stirred at room temperature for 2 days, then poured into saturated sodium chloride solution. After extraction with ethyl acetate, removal of the solvent gave an oil, which was chromatographed on silica gel, eluting with benzene - ethyl acetate. Unchanged vinylogous urethane 124 (101 mg, 0.60 mmols) was recovered (19 %) (TLC, hexane - ether, 1:4, k_f = 0.60) together with the phenyl vinylogous urethane 125 (168 mg, 0.70 mmols), obtained in 23 % yield (TLC, k_f = 0.63), as the only characterizable compounds. The product 125 was purified by recrystallization from benzene - hexane, to give a colourless solid mp 119 - 121.5 °C (lit 119 - 123 °C [92]). The spectral details are reported after (g).

b. Conditions used were as in (a) except for the addition of TMEDA (2 equivalents) before the addition of the diphenyliodonium chloride. The reaction mixture was heated under reflux for 3 h. TLC analysis showed formation of only a small amount of product.

c. On using the conditions as in (b) except that ether was used in place of THF, after stirring at room temperature for 3 days, again TLC showed formation of only a small amount of product.

d. On using conditions as in (a) except for the addition of

HMPA (5 equivalents) before the addition of the n-butyllithium, again TLC analysis showed only a small amount of product.

e. By maintaining the conditions used in (b) except for the substitution of DMSO for THF, the same results were obtained.

f. Substitution of DMF as solvent in place of THF, with conditions as in (a) otherwise unchanged, again only a small amount of product was formed, as judged by TLC.

g. Vinylogous urethane 124 (200 mg, 1.2 mmols) in dry THF (2 mL) under nitrogen was added to a solution of potassium amide (1.26 mmols) in dry ammonia (30 mL) at -78 °C, resulting in a pink solution. After 2 min diphenyliodonium chloride (420 mg, 1.3 mmols) was added, the colour of the solution changing to yellow. The reaction mixture was stirred for 1 h, then warmed to room temperature, evaporating off the solvent. Water was added to the residue, which was then extracted with ether. Removal of solvent gave an oil which was chromatographically separated into unchanged starting material 124 (140 mg, 0.83 mmols), recovered in 70 % yield, together with the phenylated product 125 (26 mg, 0.11 mmols) obtained in 9 % yield.

N-methyl-2-ethoxycarbonylmethylene-3-phenylpyrrolidine 125

IR (KBr) 705(m,C-H,Ar) 790(m,CH,Ar) 1590(s,NC=CC=O) 1600(s,NC=CC=O) 1690(s,C=O)

PMR (80 MHz, 1.13(t,3,J = 8 Hz, CH_3)
1.65 - 2.74(m,2)
3.00(s,3,NCH_3)
3.20 - 3.[illegible](m,2,NCH_2)
4.02(2xq,2,J = 8Hz,OCH_2)
4.68(s,1,=CH)

4.98 - 5.16(m,1,CH)
7.10 - 7.48(m,5,aromatic)

MS 245(59,M^+) 200(62) 199(56) 198(67)
173(100) 172(59) 115(49) 56(56)

HRMS 245.14183 ($C_{15}H_{19}NO_2$ requires 245.14157)

1.3.2 Attempted Phenylation of N-methyl-2-thiopyrrolidone 121

To a solution of N-methyl-2-thiopyrrolidone 121 (366 mg, 3.2 mmols) in dry THF (20 mL) under nitrogen at 0 °C was added n-butyllithium in hexane (3.2 mmols), followed by diphenyliodonium chloride (1.0 g, 3.2 mmols) after 3 min. The reaction solution was stirred at room temperature for 3 days, then poured into saturated sodium chloride solution. After extraction with ethyl acetate, removal of the solvent gave an oil which was chromatographed on silica gel, eluting with benzene - ethyl acetate. The only characterizable compounds obtained were diphenyl disulphide (98 mg, 0.53 mmols) (10 %) (TLC, hexane - ether, 4:1, R_f = 0.95), unchanged N-methyl-2-thiopyrrolidone 121 (92 mg, 0.81 mmols, 25 %) (TLC, R_f = 0.32) and the dimeric compound 122 (44 mg 0.20 mmols, 6 %) (TLC, R_f = 0.09) characterized by IR and MS.

Diphenyl Disulphide

IR ($CHCl_3$) 1430(s,C=C,Ar) 1470(s,C=C,Ar)
1570(s,C-C,Ar) 1580(m,C=C,Ar)

MS 218(45,M^+) 139(33) 185(71) 184(29)
180(100) 109(40) 77(21) 65(25)

1.3.3 Attempted Arylations Using Organocopper Reagents

a. A solution of N-methyl-2-thiopyrrolidone 121 (250 mg, 2.2 mmols) in dry THF (12 mL) at 0 °C under nitrogen was treated with n-butyllithium in hexane (2.2 mmols). Cuprous iodide (427 mg, 2.2 mmols), flamed under vacuum before use, was added to the solution after 3 min, followed by iodobenzene (250 µL, 2.2 mmols) after a further 7 min. The mixture was heated under reflux for 10 h, then poured into ammonium chloride solution. An emulsion was obtai[illegible] which wa[illegible] eventually filtered, and the resultant mixtu[illegible] racted with dichloromethane. Removal of solvent gave an intractable tar, which was shown by TL[illegible] to contain some of the starting materials, viz. iodobenzene (TLC, hexane - ether, 1:4, R_f = 0.92) and thiopyrrolidone 121 (TLC, R_f = 0.44) together with large amounts of baseline material.

b. The conditions used in (a) were repeate[illegible] cept that dimethyl sulphide (3 equivalents) was added to the thiopyrrolidone solution. The reaction was performed at [illegible]. After 40 min, the mixture was homogeneous and the iodobenzene was added. After warming to room temperature, again an intractable tar was obtained.

c. Using conditions as in (b) except that the reaction was performed on the vinylogous urethane 124, and not the thiolactam 121, again a tar was obtained, consisting primarily of baseline material on TLC, together with a small amount of the starting vinylogous urethane 124 (TLC, hexane - ether, 1:4, R_f = 0.54).

2 Experimental Procedures Relating to the Attempted Preparation of Lactams From Methyl 3,4-Dimethoxyphenylacetate

2.1 Preparation of N-Benzylaziridine

N-Benzylaziridine was prepared according to the modification of Wenker's method [97] developed by Leighton and co-workers [96] for the synthesis of aziridine. N-Benzylethanolamine (50.7 mL, 0.36 mols) and 95 % sulphuric acid (19.8 mL) were separately diluted with 14 mL and 10 mL water respectively. The amine was added slowly to the acid with cooling, and the mixture was boiled under reduced pressure until crystallization took place. The N-benzylaminoethylsulphuric acid thus obtained was recrystallized from ethanol to give the solid (59.3 g, 0.26 mols) in 72 % yield [145].

To N-benzylaminoethylsulphuric acid (9.28 g, 40 mmols) was added sodium hydroxide (7.99 g, 200 mmols) in water (20 mL). The mixture was steam distilled. Potassium hydroxide (2.5 g) was added to the distillat which was then extracted with ether. The ethereal phase was dried over potassium hydroxide, and after removal of solvent, was distilled at 50 °C, 5 mm Hg (lit. 86 - 88 °C, 12 mm Hg [146]), from calcium hydride to give N-benzylaziridine in 65 % yield.

Ir (film)	695(s,CH) 725(s,CH) 1450(m,C=C,Ar)
	1595(w,C=C,Ar) 1600(w,sh,C=C,Ar)
PMR (60MHz)	1.12 - 1.30(m,2)
	1.70 - 1.[illegible]m,2)
	3.35(s,2,$PhCH_2$)
	7.32(s,5,aromatic)

2.2 The Reaction of the Anion of Ester 114 With N-Benzyl-aziridine

a. To a solution of dry diisopropylamine (155 µL, 1.1 mmols) in dry THF (20 mL) at -83 °C was added n-butyllithium in hexane (1.1 mmols). After stirring for 10 min, the ester 114 [147] (211 mg, 1,0 mmols) was added, followed by N-benzyl aziridine (144 mg, 1.1 mmols) after a further 10 min. The mixture was warmed to room temperature and stirred for 5 h, then poured into a solution of ammonium chloride. The aqueous phase was extracted with dichloromethane. Removal of the solvent gave an oil (196 mg, 0.93 mmols) which proved to be the starting material (93 % recovery) by TLC and PMR analyses.

b. On using similar conditions to those described in (a) except that the anion was generated at -45 °C, for 1 h, and the reaction solution was stirred overnight at room temperature after the addition of the aziridine, again only the ester was recovered.

2.3 The Reaction of the Anion of Ester 114 with N-benzyl-2-bromoethylamine

a. Ester 114 (315 mg, 1.5 mmols) dissolved in dry THF (10 mL) under nitrogen was treated with sodium hydride (80 % in paraffin oil) (98 mg, 3.3 mmols) washed twice with portions of THF to remove the oil, for 45 min at room temperature. N-benzyl-2-bromoethylamine hydrobromide (442 mg, 1.5 mmols) was then added and the mixture was stirred for 2 days. The solvent was then removed, and the residue partitioned between water and dichloromethane, the organic phase was separated, and the aqueous phase was extracted with dichloromethane. The combined organic phase was concentrated, giving an oil (456 mg, 1.47

2.2 The Reaction of the Anion of Ester 114 With N-Benzyl-aziridine

a. To a solution of dry diisopropylamine (155 µL, 1.1 mmols) in dry THF (20 mL) at -83 °C was added n-butyllithium in hexane (1.1 mmols). After stirring for 10 min, the ester 114 [147] (211 mg, 1,0 mmols) was added, followed by N-benzyl aziridine (144 mg, 1.1 mmols) after a further 10 min. The mixture was warmed to room temperature and stirred for 5 h, then poured into a solution of ammonium chloride. The aqueous phase was extracted with dichloromethane. Removal of the solvent gave an oil (196 mg, 0.93 mmols) which proved to be the starting material (93 % recovery) by TLC and PMR analyses.

b. On using similar conditions to those described in (a) except that the anion was generated at -45 °C, for 1 h, and the reaction solution was stirred overnight at room temperature after the addition of the aziridine, again only the ester was recovered.

2.3 The Reaction of the Anion of Ester 114 with N-benzyl-2-bromoethylamine

a. Ester 114 (315 mg, 1.5 mmols) dissolved in dry THF (10 mL) under nitrogen was treated with sodium hydride (80 % in paraffin oil) (98 mg, 3.3 mmols) washed twice with portions of THF to remove the oil, for 45 min at room temperature. N-benzyl-2-bromoethylamine hydrobromide (442 mg, 1.5 mmols) was then added and the mixture was stirred for 2 days. The solvent was then removed, and the residue partitioned between water and dichloromethane, the organic phase was separated, and the aqueous phase was extracted with dichloromethane. The combined organic phase was concentrated, giving an oil (456 mg, 1.47

mmols) which was proved by TLC and PMR analysis to be the ester (98 % recovery).

b. DBU (447 µL, 3 mmols) was added to a mixture of the ester (310 mg, 1.5 mmols) and the hydrobromide salt (442 mg, 1.5 mmols) in dry benzene (30 mL) under nitrogen, resulting in the precipitation of a white solid which was probably DBU hydrobromide. After heating under reflux for 8 h, TLC analysis showed no appearance of any new products.

c. The hydrobromide salt (443 mg, 1.5 mmols) was treated with DBU (223 µL, 1.5 mmols) in dry THF under nitrogen, resulting in the appearance of DBU hydrobromide as a heavy white precipitate. To a solution of diisopropylamine (233 µL, 1.65 mmols) in dry THF under nitrogen at 0 °C, was added n-butyllithium in hexane (1.65 mmols). After 10 min, ester 114 (316 mg, 1.5 mmols) was added as a solution in THF, and after a further 10 min the amine solution was filtered into the mixture. No new products had appeared as judged by TLC, after overnight stirring at room temperature.

2.4 Methylation of the Anion of Ester 114

Generation of the ester anion was as in 2.2 (b) above. Methyl iodide (69 µL, 1.1 mmols) was added, and the mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed, and the residue was partitioned between ammonium chloride solution and dichloromethane. After separation of the organic phase, the aqueous phase was extracted with further portions of dichloromethane. The organic phases were combined, and the solvent removed, giving methyl 2-(3,4-dimethoxyphenyl)propionate 127 (181 mg) as a pale yellow oil in 81 % yield (TLC, ethyl acetate, R_f = 0.83).

IR (film)	1028(s,ArOMe) 1250(s,ArOMe) 1460(s,C=C,Ar) 1510(m,C=C,Ar) 1590(m,C=C,Ar) 1600(m,C=C,Ar) 1730(s,C=O)
PMR (60 MHz)	1.50(d,3,J = 7 Hz) 3.23 - 3.70 and 3.65(m and s,4,CH and $COOCH_3$) 3.87(s,6,OCH_3) 6.85(s,3,aromatic)
MS	224(4,M^+) 165(20) 150(6) 135(4) 121(3) 105(3) 91(8) 77(8) 28(100)
HRMS	224.10465 ($C_{12}H_{16}O_4$ requires 224.10485).

3 Procedures Relating to the 1,3 Synthetic Approach

3.1 Preparation of N-benzyl-2-bromoethylamine hydrobromide

Hydrobromic acid (12 mL) was added to N-benzylethanolamine (2.6 g, 17 mmols) and the resultant solution was refluxed for 1.25 h. The hydrobromic acid was distilled off and the residue recrystallized from ethanol, to give the product as a pale orange solid in 51 % yield mp 179 - 190 °C (lit. 190 °C [148]).

3.2 Reaction of 3,4-Dimethoxyphenylacetyl Chloride With N-benzyl-2-bromoethylamine

3,4-Dimethoxyphenylacetic acid (297 mg, 1.5 mmols) was refluxed for 2.5 h with thionyl chloride (108 µL, 1.5 mmols) and a drop of DMF in dry chloroform (20 mL), then cooled to 0 °C. The hydrobromide salt of N-benzyl-2-bromoethylamine (441 mg, 1.5 mmols) was treated with DBU (447 µL, 3.0 mmols) in chloroform,

and added to the acid chloride solution after 10 min. After 2 h the reaction solution was washed with sodium bicarbonate solution, then 1.5 M hydrochloric acid. Removal of the solvent gave an oil (540 mg) (TLC, hexane - acetone, 1:1, R_f = 0.69) which subsequently crystallized, and on recrystallization gave a solid mp 123 - 124.5 °C (R_f = 0.23) which had spectral characteristics identical in every respect to those of the ester amine 128 prepared by another route (vide infra)

3.3 Preparation of the Ester Amine Hydrochloride 128

3,4-Dimethoxyphenylacetic acid (294 mg, 1.5 mmols) was refluxed for 2.5 h with thionyl chloride (108 µL, 1.5 mmols) and a drop of DMF in chloroform (15 mL), then cooled to room temperature. A solution of N-benzylethanolamine in chloroform was saturated with hydrogen chloride, and then added to the above mixture. After 2 h the reaction solution was washed with a sodium bicarbonate solution, then a 1.5 M hydrochloric acid solution. Removal of the solvent gave 2-(benzylamino)ethyl(3,4-dimethoxyphenyl)acetate hydrochloride salt 128 which was recrystallized from acetone - methanol to give a solid mp 123.5 - 125 °C (TLC, hexane - acetone, 1:1, R_f = 0.23)

IR (KBr) 355(w) 410(w) 460(w) 485(w) 525(w) 545(w)
600(w) 695(w) 750(w) 765(w) 780(w) 795(w)
825(w) 835(w) 860(w) 900(w) 940(w) 975(w)
990(w,sh) 1020(s,ArOMe) 1050(w) 1135(s)
1155(s,sh) 1200(m) 1240(m) 1260(s,ArOMe)
1330(m) 1360(w) 1390(w) 1410(m) 1435(m)
1450(s) 1[illegible](s) 1585(m) 1600(w) 1730(s,C=O)
2350(w) 2410(w) 2470(w) 2540(m) 2620(m)
2670(w) 2760(s,br) 2920(s,br) 3440(m,br)

PMR (60 MHz)

2.83 - 3.25(m,2,CH_2CO)
3.72(s,2,NCH_2Ph)
3.82(s,6,OCH_3)
3.99 - 4.20(m,2,NCH_2)
4.27 - 4.72(m,2,OCH_2)
6.61 - 6.99(m,3,aromatic)
7.17 - 7.78(m,5,aromatic)

MS

329(10,M-HCl) 179(33) 151(20) 133(15)
120(56) 106(15) 91(100,$PhCH_2$)

3.4 The Reaction of 3,4-Dimethoxyphenylacetyl Chloride with N-benzylaziridine

a. 3,4-Dimethoxyphenylacetic acid (293 mg, 1.5 mmols) was refluxed for 3.5 h with thionyl chloride (108 µL, 1.5 mmols) and a drop of DMF in chloroform (20 mL), then cooled to 0 °C. N-benzylaziridine (199 mg, 1.5 mmols) was added and the mixture was warmed to room temperature and stirred for 4 h. The reaction solution was then poured into sodium bicarbonate solution and extracted with dichloromethane. Removal of the solvent gave an oil (518 mg), TLC analysis of which showed two major components. Column chromatography gave a high R_f component, an oil, (82 mg) (TLC, hexane - acetone, 1:1, R_f = 0.69) which crystallized on standing, and on recrystallization from acetone gave a solid mp 123 - 125 °C (TLC, R_f = 0.25) which proved to be the ester amine hydrochloride 128 (15 % yield), together with a low R_f component (178.9 mg, 0.35 mmols, 47 %) which was probably N-(3,4-dimethoxyphenylacetyl)-N-benzyl-2-aminoethyl 3,4-dimethoxyphenylacetate 130 (TLC, R_f = 0.56)

IR ($CHCl_3$) 1640(s,amide C=O) and 1730(s, ester C=O)

PMR (60 MHz) 3.35 - 3.72(m)
3.85(s,OCH_3)
4.00 - 4.67(m,OCH_2,$PhCH_2N$)
6.66 - 6.89(m,aromatic)
7.00 - 7.45(m,aromatic)
Proton count uncertain.

MS 507(0.6,M^+) 378(29) 152(38) 151(75)
149(63) 91(100,$PhCH_2$) 71(52) 57(86)

b. The procedure was as described in (a) except that the reaction was quenched after 5 min. N-benzyl-N-(2-chloroethyl-3,4-dimethoxyphenylacetamide (29 (X=Cl)was obtained as an oil (595 mg) in 115 % yield (TLC, hexane - acetone, 1:1, R_f = 0.59). It was clearly not pure, but could not be purified because of its instability.

IR ($CHCl_3$) 1030(m,ArOMe) 1240(s,ArOMe)
1465(m,C-C,Ar) 1510(m,C-C,Ar) 1640(s,C=O)

PMR (60 MHz) 3.22 - 3.72 and 3.65(m and s,6H from $ArCH_2$)
3.80(s,6,OCH_3)
4.60(s,2,$PhCH_2$)
6.61 - 6.81(m,3,aromatic)
6.99 - 7.40(m,5,aromatic)

MS 347(15,M^+) 313(11) 151(100) 107(12)
91(3100) 85(44) 83(69) 69(17)

3.5 Reaction of Amide 129 (X=Cl) With Base

To a solution of diisopropylamine (250 µL, 1.8 mmols) in dry THF (20 mL) at room temperature under nitrogen was added n-butyllithium in hexane (1.6 mmols). After 10 min the mixture was cooled to -45 °C, and the amide 129 (X=Cl) (512 mg, 1.5 mmols) was added. The reaction solution was warmed to room temperature and stirred for 3 h. After removal of the solvent, the residue was partitioned between ammonium chloride solution and dichloromethane. Extraction of the aqueous phase with further portions of dichloromethane, followed by evaporation of the solvent gave an oil (475 mg) which was shown by TLC, PMR and IR to be the starting amide 129 (X=Cl) recovered in 93 % yield.

4 Procedures Relating to the Preparation of Lactams from 3,4-Dimethoxyphenylacetamides

4.1 The synthesis of 1-methyl-3-(3,4-dimethoxyphenyl)-2-pyrrolidone 110

a. To a solution of N-methyl-(3,4-dimethoxyphenyl)acetamide 115 (prepared according to the method of Finkelstein and Brossi [98]) (211 mg, 1.0 mmols) in dry THF under nitrogen at 0 °C was added n-butyllithium in hexane (2.2 mmols), followed by 1-bromo-2-chloroethane (90 µL, 1.1 mmols) after 10 min. TLC analysis of the reaction solution showed appearance of a new compound, apparently the chloroamide 132 (TLC, ethyl acetate, R_f = 0.68) almost immediately, followed by slow (2-3 h) apparent reversion to starting material (R_f = 0.20) as the mixture was warmed to room temperature, finally showing this as an almost chromatographically pure material with two minor

impurities (R_f = 0.78 and 0.68). The solvent was then removed, and ammonium chloride solution was added. Extraction of this mixture with dichloromethane yielded an oil (219 mg) which was chromatographed on silica gel eluting with hexane - ethyl acetate. The lactone 131 (43 mg R_f = 0.78) was obtained as a white solid in 19 % yield, the chloroamide 132 (11 mg) (R_f = 0.68) in 4 % yield, and the lactam 110 (115 mg) (R_f = 0.20) in 49 % yield. It was thus clear that the lactam 110 and the starting amide 119 had the same R_f's, and indeed the lactam 110 was contaminated with some amide. The lactam and amide were found to inseparable by chromatography despite attempts to do this using a wide variety of solvent mixtures and using alumina as well as silica gel plates.

N-methyl-3-(3,4-dimethoxyphenyl)-2-pyrrolidone 110

Ir ($CHCl_3$)	600(w) 660(w) 850(w) 885(w) 915(w)
	965(w) 990(w) 1028(s,ArOMe) 1075(w) 1100(w)
	1143(s) 1160(m) 1250(s,ArOMe) 1260(s)
	1290(m) 1335(w) 1400(m) 1420(m) 1440(m)
	1455(m,sh) 1460(m) 1500(m) 1590(w) 1610(w)
	1670(s,C=O) 2840(w) 2880(w) 2910(w) 2940(m)
	2960(m) 3000(m)
PMR (80 MHz)	1.93 - 2.65(m,2,$CHCH_2$)
	2.90(s,3,NCH_3)
	3.15 - 3.73(m,3,NCH_2 and CH)
	3.85 and 3.88(2s,6,OCH_3)
	6.81(s,3, aromatic)
Carbon-13 NMR (20 MHz)	27.85(CH_2) 29.58(CH) 30.00(NCH_3)
	47.52(OCH_3) 47.40(OCH_3) 55.86(NCH_2)

111.31(Ar,CH) 111.51(Ar,CH) 119.73(Ar,CH)
132.42(Ar,C) 148.10(Ar,CO) 149.08(Ar,CO)
174.88(C=O)

MS 236(20) 235(100,M^+) 220(19) 209(32)
178(37) 163(22) 151(73) 97(42)

HRMS 235.12075 ($C_{13}H_{17}NO_3$ requires 235.12084)

2-(3,4-Dimethoxyphenyl)butyrolactone 131 was further purified by recrystallization from acetone to give a white solid of mp 83-87 °C.

IR ($CHCl_3$) 600(w) 620(w) 660(w) 695(w) 850(w)
885(w) 915(w) 950(w) 1025(s,ArOMe) 1090(w)
1145(s) 1250(s,ArOMe) 1335(w) 1370(m)
1415(w) 1440(m) 1460(m) 1505(m) 1590(m)
1605(w,sh) 1760(s,C=O) 2840(w) 2870(w)
2905(m) 2930(m) 2960(m) 3000(m) 3020(w,sh)

PMR (80MHz) 2.25 - 3.02(m,2)
3.63 - 3.84(m,1,CH)
3.87 and 3.88(2xs,6,OCH_3)
4.16 - 4.62(m,2,OCH_2)
6.84(s,3, aromatic)

MS 222(100) 153(75) 147(52) 107(84) 103(50)
91(75) 77(60) 51(38)

HRMS 222.08800 ($C_{12}H_{14}O_4$ requires 222.08920)

An analytical sample, mp 105-107 °C of N-methyl-2-(3,4-dimethoxyphenyl)-4-chloro butyramide 132 was obtained by

111.31(Ar,CH) 111.51(Ar,CH) 119.73(Ar,CH)
132.42(Ar,C) 148.10(Ar,CO) 149.08(Ar,CO)
174.88(C=O)

MS 236(20) 235(100,M^+) 220(19) 209(32)
178(37) 163(22) 151(73) 97(42)

HRMS 235.12075 ($C_{13}H_{17}NO_3$ requires 235.12084)

2-(3,4-Dimethoxyphenyl)butyrolactone 131 was further purified by recrystallization from acetone to give a white solid of mp 83-87 °C.

IR ($CHCl_3$) 600(w) 620(w) 660(w) 695(w) 850(w)
885(w) 915(w) 950(w) 1025(s,ArOMe) 1090(w)
1145(s) 1250(s,ArOMe) 1335(w) 1370(m)
1415(w) 1440(m) 1460(m) 1505(m) 1590(m)
1605(w,sh) 1760(s,C=O) 2840(w) 2870(w)
2905(m) 2930(m) 2960(m) 3000(m) 3020(w,sh)

PMR (80MHz) 2.25 - 3.02(m,2)
3.63 - 3.84(m,1,CH)
3.87 and 3.88(2xs,6,OCH_3)
4.16 - 4.62(m,2,OCH_2)
6.84(s,3, aromatic)

MS 222(100) 153(75) 147(52) 107(84) 103(50)
91(75) 77(60) 51(38)

HRMS 222.08800 ($C_{12}H_{14}O_3$ requires 222.08920)

An analytical sample, mp 105-107 °C of N-methyl-2-(3,4-dimethoxyphenyl)-4-chloro-butyramide 132 was obtained by

recrystallization from ethyl acetate.

IR (KBr) 320(w) 365(w) 425(w) 470(w) 510(w) 595(w) 675(w) 705(m) 740(m) 765(m) 790(m) 805(sh) 820(w) 855(m) 880(w) 895(w) 910(w) 935(w) 960(w) 1030(s,ArOMe) 1060(w) 1100(w) 1145(s) 1155(s) 1190(s) 1230(s) 1240(s) 1250(s,ArOMe) 1280(sh) 1340(m) 1365(m) 1410(s)1440(s) 1450(s) 1460(sh) 1505(s) 1555(s,NH) 1590(s) 1610(s) 1630(s,C=O) 2840(m) 2860(m) 2920(s) 3010(w) 3070(m) 3280(s)

PMR (80MHz) 1.65 - 2.85(m,2)
2.75 and 2.82(2xs,3,NCH_3)
3.22 - 3.80(m,3,$ClCH_2$ and CH)
3.90(s,6,OCH_3)
5.50(s,br,NH)
6.90(s,3,aromatic)

MS 271(M^+,32) 215(41) 213(100) 151(99) 107(58) 103(43) 91(68) 77(55) 58(58)

C H and N analysis: C, 57.16; H, 6.76; N, 5.11. $C_{12}H_{16}NO_2Cl$ requires C 57.41; H, 6.68; N, 5.15 %.

b. The conditions used were essentially the same as in (a) except that 1,2-dibromoethane was used in place of 1-bromo-2-chloroethane. On addition of the ammonium chloride solution an emulsion resulted, which was repeatedly extracted with chloroform. Removal of the solvent gave N,N'-dimethyl-2,3-bis(3,4-dimethoxyphenyl)butanediamide 133 as a white solid in 79 % yield, which proved to be insoluble in most solvents, but was recrystallized from nitromethane, with large losses, to

give a solid of mp 234.5 - 235.5 °C.

IR (KBr)	370(w) 460(w,sh) 475(w) 535(w) 565(w)
	600(w) 635(w) 660(w) 705(w) 725(w) 765(m)
	795(w) 810(m) 835(w) 855(w) 920(w) 935(w)
	955(w) 975(w) 1025(s,ArOMe) 1055(w,sh)
	1145(s,sh) 1150(s) 1190(m) 1210(m) 1220(m)
	1240(m,sh) 1260(s,ArOMe) 1300(m) 1330(m)
	1360(w) 1390(m) 1410(m) 1450(m) 1460(m)
	1510(s) 1540(m,sh) 1550(s,NH) 1560(m,sh)
	1590(m) 1605(m) 1640(s,C=O) 1660(s,sh)
	2840(m) 2900(m,sh) 2940(m) 3000(m) 3080(m)
	3300(s,br)
PMR (80MHz)	2.76 and 2.83(2xs,6,NCH_3)
	3.73 and 3.77(2xs,12,OCH_3)
	3.99(s,2,CH)
	5.58(s,br,2,NH)
	6.63 - 6.69(m,6,aromatic)
MS	416(39,M^+) 386(23) 385(91) 209(20)
	208(100) 180(.00) 151(53) 42(24)
HRMS	416.19472 ($C_{22}H_{28}N_2O_6$ requires 416.19472).
C H and N analysis:	C, 62.95; H, 6.78; N, 6.76. $C_{22}H_{28}N_2O_6$
	requires C, 63.45; H, 6.78; N, 6.73 %.

c. The conditions were essentially the same as in (a) except that O-tosyl-2-bromoethanol was used in place of 1-bromo-2-chloroethane. A PMR of the product obtained was broad and uninterpretable, but lacked the peaks characteristic of the

lactam.

d. After maintaining the above conditions, except for the substitution of O-tosyl-2-chloroethanol, a PMR of the product mixture obtained was essentially the same as that of the amide 119. Again, none of the peaks characteristic of the lactam were present.

e. The use of O,O'-ditosylethanediol resulted in an oily product, the PMR of which was not readily interpretable, but did indicate the presence of amide 119, together with a small amount of the lactam 110.

f. The conditions used were as in (a) except that after 90 min, after warming to room temperature, the THF was removed under vacuum and replaced with dry DMSO (5 mL). After heating at 75 °C for 5 h, ammonium chloride solution was added, and the aqueous phase was extracted with dichloromethane. Removal of the solvent gave an oil (441 mg), which was chromatographed on silica gel, with hexane - ethyl acetate as eluant. Three products were obtained: the chloroamide 132 (74 mg) in 11 % yield (TLC, ethyl acetate, R_f = 0.68), indane 134 (23 mg) (R_f = 0.39) in 4 % yield, and N-methyl-3-(3,4-dimethoxyphenyl)-3-hydroxy-2-pyrrolidone 135 (223 mg) in 39 % yield (R_f = 0.23).

The N-methyl-4,5-dimethoxyindane-1-carboxamide 134 was obtained as a white solid mp 168 -168.5 °C after sublimation at 140 °C, 0.5 mm Hg followed by recrystallization from acetone.

IR (KBr)	465(w)	530(w)	635(w)	685(m)	705(m)	730(w)
	740(m)	770(m)	810(m)	865(w)	890(w)	915(w)

970(m) 1000(w) 1030(m) 1040(s,ArOMe)
1080(s) 1140(m) 1160(m) 1180(m) 1200(m)
1220(s) 1255(s,ArOMe) 1275(sh) 1300(s)
1320(m) 1360(m) 1405(s) 1430(s) 1440(s)
1450(s) 1465(s) 1485(s) 1540(s,NH) 1605(m)
1640(s,C=O) 2830(m) 2850(m) 2920(sh)
2940(m) 3080(w) 3280(s)

PMR (80MHz) 2.23 - 2.63(m,2,$CHCH_2$)
2.70 - 3.15, 2.78 and 2.83(m and 2xs,5,$ArCH_2$ and NCH_3)
3.82 - 4.03 and 3.86(m and s,7,ArCH and OCH_3)
6.78 and 6.96(2xd,2,J = 8 Hz,aromatic)

MS 235(59,M^+) 178(31) 166(100) 162(10)
147(13) 146(40) 131(10) 44(11)

HRMS 235.12075 ($C_{13}H_{17}NO_3$ requires 235.12084)
Inconsistent analyses were obtained

The hydroxylactam 135 was obtained as an analytically pure solid mp 130 - 132 °C after recrystallization from acetone.

IR (Kbr) 310(w) 420(w) 475(m) 520(m) 630(w) 660(m)
690(w) 745(m) 770(m) 795(w) 820(m) 860(m)
930(w) 950(w) 990(w) 1025(s,ArOMe) 1050(s)
1100(m) 1145(s) 1190(m) 1200(m) 1235(s)
1240(s) 1255(s,ArOMe) 1300(s) 1330(m)
1350(m) 140[illegible](s) 1440(s) 1450(s) 1495(s)
1585(m) 1600(m) 1675(s,C=O) 2840(sh)
2870(m) 2930(m) 2970(sh) 3000(sh) 3460(s)

PMR (80MHz)	2.44(t,2,J = 6 Hz)
	2.99(s,3,NCH_3)
	3.13(s,1,OH)
	3.27 - 3.99(m,2,NCH_2)
	3.86 and 3.89(2xs,6,OCH_3)
	6.77 - 7.10(m,3,aromatic)
MS	251(96,M^+) 192(39) 180(100) 165(68)
	86(39) 58(75) 55(39) 44(96)
C H and N analysis	C, 61.82; H, 6.85; N, 5.53. $C_{13}H_{17}NO_4$
	requires C, 62.19; H, 6.82; N, 5.57 %.

e. To a solution of amide 119 (200 mg, 0.96 mmols) in dry DMSO (10 mL) was added n-butyllithium in hexane (1.13 mmols), followed by 1-bromo-2-chloroethane (103 µL, 1.2 mmols) after 15 min. The mixture was stirred for 30 min, then poured into ammonium chloride solution. The aqueous phase was extracted with dichloromethane, and the solvent was removed leaving an oil which was shown by TLC to be primarily the starting amide 119.

4.2 Synthesis of N-methyl-3-(3,4-dimethoxyphenyl)-2-thiopyrrolidone 109

To a cold solution of N-methyl-2-(3,4-dimethoxyphenyl)acetamide 119 (627 mg, 3 mmols) in dry THF (75 mL) under nitrogen was added n-butyllithium in hexane (6.6 mmols). The solution was stirred for 10 min, then dry HMPA (2.3 mL, 13 mmols) was added. After a further 10 min, 1-bromo-2-chloroethane (322 µL, 3.9 mmols) was added. The mixture was warmed to room temperature and stirred overnight. The solvents were removed under reduced pressure and saturated ammonium chloride solution was added to

the residue. The mixture was extracted with dichloromethane, and the solvent and HMPA removed under vacuum, leaving a pale yellow oil. The oil was dissolved in dry toluene, and Lawesson's reagent (593 mg, 1.5 mmols) was added. The mixture was heated under reflux for 8 h, the solvent was then removed, and the residue chromatographed on silica gel eluting with hexane : ethyl acetate. N-methyl-2-(3,4-dimethoxyphenyl)-thioacetamide 139 (62.2 mg, 0.28 mmols) was obtained, representing 9 % recovery of starting material (TLC, ethyl acetate, R_f = 0.83), together with the thiolactam 109 (532 mg, 2.1 mmols) in 71 % yield (80 % from consumed starting material) (TLC, R_f = 0.39).

An analytically pure sample of thioacetamide 139 was obtained as a white solid mp 131 - 131.5 °C by recrystallization from acetone.

IR (KBr)	380(w) 570(w) 600(w) 630(w) 695(w) 730(m)
	760(w) 775(w) 825(w) 880(m) 925(w) 945(w)
	1028(s,ArOMe) 1055(s) 1145(s) 1165(s)
	1180(m) 1195(w) 1240(s) 1265(s,ArOMe)
	1280(s) 1335(m) 1370(m) 1420(m) 1440(s)
	1455(m) 1465(m) 1510(s,sh) 1520(s)
	1550(s,NC=S) 1595(w) 1610(w) 2840(w)
	2910(w) 2940(m) 2960(m) 2970(m) 2990(m)
	3030(w) 3050(w) 3320(s,NH)
PMR (80MHz)	3.10 and 3.16 (2xs,3,NCH_3)
	3.87 and 3.88(2xs,6,OCH_3)
	4.1(s,2,CH)
	6.65 - 6.93(m,3,aromatic)
MS	225(74,M^+) 194(21) 152(40) 151(100)

137(57) 74(58)

C H and N analysis: C, 58.24; H, 6.72; N, 6.37. $C_{11}H_{15}NO_2S$ requires C, 58.69; H, 6.71; N, 6.22 %.

An analytically pure sample of thiolactam 109 was obtained as a solid mp 109 -110 °C after recrystallization from ethyl acetate

IR (KBr) 465(w) 500(w) 540(w) 625(w) 715(w) 740(w) 765(m) 785(w) 810(m) 860(w) 920(w) 980(w) 1025(s,ArOMe) 1035(m,sh) 1060(m) 1085(w) 1145(s) 1165(s) 1185(m) 1230(s) 1245(s,sh) 1260(s,ArOMe) 1275(m,sh) 1285(m) 1300(s) 1320(m) 1350(w) 1390(m) 1400(w) 1420(m) 1440(m) 1450(m) 1465(m) 1520(s,br,C=C and CN) 1590(m) 1605(w) 2830(m) 2870(m) 2910(m) 2930(m) 2950(m) 2970(w,sh) 2990(w)

PMR (80MHz) 1.80 - 2.85(m,2,$CHCH_2$) 3.35(s,3,NCH_3) 3.73 - 4.28, 3.67 and 3.86(m and 2xs,9) 6.76 - 7.00(m,3,aromatic)

MS 251(100,M^+) 236(46) 163(48) 147(52) 113(61) 107(54) 91(51)

C H and N analysis: C, 61.97; H, 6.85; N, 5.53. $C_{13}H_{17}NO_2S$ requires C, 62.12; H, 6.82; N, 5.57 %.

4.3 Attempted Preparation of thiolactam 109 from thioacetamide 139

A solution of the thioamide 139 (114 mg, 0.5 mmols) in dry THF

(20 mL) at 0 °C was treated with n-butyllithium (1.1 mmols) followed by HMPA (380 µL, 2.2 mmols) and 1-bromo-2-chloroethane (53 µL, 0.65 mmols). The mixture was warmed to room temperature and stirred overnight, then poured into ammonium chloride solution and extracted with dichloromethane. After removal of the solvent and HMPA under vacuum a black oil (91 mg) was obtained. Chromatography on silica gel, with hexane - ethyl acetate as eluant gave 25 mg of impure thiolactam 109 in a yield of 20 %.

4.4 Preparation of N-benzyl-(3,4-dimethoxyphenyl)acetamide

A mixture of 3,4-dimethoxyphenylacetic acid (4.9 g, 25 mmols), thionyl chloride (2 mL, 28 mmols), chloroform (50 mL), and a drop of DMF was heated under reflux for 3.5 h, then cooled to room temperature. Benzylamine (5.9 mL, 55 mmols) was added dropwise as solution in chloroform (20 mL). The mixture was stirred for 45 min, then poured into water (40 mL). The organic phase was separated, and the aqueous phase was extracted with dichloromethane. Removal of solvent from the combined organic phase gave N-benzyl-(3,4-dimethoxyphenyl)-acetamide (7.1 g, 25 mmols) in 70 % yield, which was recrystallized from ethanol to give a solid mp 99.5 - 101.5 °C (lit. 148 °C [30], see text for comment).

IR (KBr)	1035(s,ArOMe) 1260(s,ArOMe) 1460(s,C=C,Ar)
	1510(s,C=C,Ar) 1535(s,NH) 1590(s,C=C,Ar)
	1605(s,C=C,Ar) 1635(s,C-O) 3310(s,NH)
PMR (60 MHz)	3.55(s,2,CH_2)
	3.81(s,6,OCH_3)
	4.31 and 4.45(2xs,2,NCH_2)
	5.75(br s,1,NH)

6.80(s,3,aromatic)
7.27(s,5,aromatic)

MS 285(53,M^+) 152(52) 151(100) 137(37)
107(17) 91(47,$PhCH_2$) 77(10) 65(18)

HRMS 285.13650 ($C_{17}H_{19}NO_2$ Requires 285.13648)

4.5 Preparation of N-benzyl-3-(3,4-dimethoxyphenyl)-2-pyrrolidone 120

a. To a solution of N-benzyl-(3,4-dimethoxyphenyl)acetamide (285 mg, 1.0 mmols) in dry THF at 0 °C under nitrogen was added n-butyllithium in hexane (2.2 mmols), followed by 1-bromo-2-chloroethane (91 µL, 1.1 mmols) after 15 min. The mixture was warmed to room temperature and stirred overnight. The solvent was removed, ammonium chloride solution was added to the residue, and the aqueous phase was extracted with dichloromethane. Removal of solvent gave an oil (335 mg) which was chromatographed on silica gel, with hexane - ethyl acetate as eluent. The only identifiable product obtained was the lactone 131, (82 mg) (TLC, ethyl acetate, R_f = 0.78) the yield being 40 %.

b. Conditions used were similar to those in (a) except for the addition of HMPA (4 equivalents) before the addition of 1-bromo-2-chloroethane. The crude oil obtained was subjected directly to thiation using Lawesson's reagent (0.5 equivalents) in toluene, and heating under reflux overnight. The solvent was removed, and the residue chromatographed on silica gel, eluting with hexane - ethyl acetate. N-benzyl-3-(3,4-dimethoxyphenyl)-2-thiopyrrolidone 140 was obtained as the only

identifiable product in 54 % yield, after recrystallization from ethyl acetate (TLC, ethyl acetate, R_f = 0.86). An analytically pure sample mp 105 - 106 °C was obtained by further recrystallizations.

IR (KBr) 480(w) 510(w) 550(w) 620(w) 645(w) 715(w) 730(w) 750(w) 765(w) 783(w) 815(w) 850(w) 920(w) 980(w) 995(w) 1025(s,ArOMe) 1060(w) 1080(w) 1105(w) 1140(s) 1155(m) 1190(m) 1220(s) 1230(s) 1260(s,ArOMe) 1300(m) 1315(w) 1340(w) 1415(w) 1430(s) 14450(m) 1460(m) 1495(s,CN) 1515(s,C=C) 1590(w) 1605(w) 2840(w) 2880(w) 2910(w) 2930(w) 2960(w) 3000(w) 3030(w) 30[illegible] w)

PMR (80MHz) 1.78 - 2.80 (m,2)
3.40 - 3.88, 3.85 and 3.82(m and 2xs,8,NCH_2 and OCH_3)
4.50(t,1,J = 8 Hz,CH)
4.98 and 5.28(2xd,2,J = 14 Hz,NCH_AH_BPh)
6.73 - 7.00(m,3,aromatic)
7.35(s,5,aromatic)

MS 327(90,M^+) 189(75) 179(33) 177(21) 164(37) 151(26) 91(100,$PhCH_2$) 65(24)

HRMS 327.12900 ($C_{19}H_{21}NO_2S$ requires 327.12928)

C H and N analysis: C, 69.2[illegible], 6.43; N, 4.39. $C_{19}H_{21}NO_2S$ requires C, 69.70; H, 6.46; N, 4.28 %.

4.6 Preparation of N-methyl-3-phenyl-2-pyrrolidone 141 [101]

a. To a solution of N-methylphenylacetamide [102] (448 mg, 3 mmols) in cold THF under nitrogen was added n-butyllithium in hexane (6.6 mmols), followed by 1-bromo-2-chloroethane (271 µL, 3.3 mmols) after 10 min. The mixture was warmed to room temperature, stirred for 4 h, then poured into ammonium chloride solution. The aqueous phase was extracted with dichloromethane, and the solvent was removed, to give an oil (516 mg) which was a mixture of at least three components as judged by TLC. Chromatography on silica gel, eluting with hexane - ethyl acetate gave the lactone 142 [103] (79 mg, 0.5 mmols) in 16 % yield (TLC, ethyl acetate, R_f = 0.87), the lactam 141 (149 mg, 0.85 mmols) in 28 % yield (R_f = 0.36) and a compound thought to be the bis-substituted compound 143 (107 mg, 0.33 mmols) in 22 % yield (R_f = 0.76) as well as a small amount of the dimer 144. Spectral data for these compounds appear at the end of this section.

b. Repeating the reaction as in (a) except for adding HMPA (four equivalents), and allowing to stir for 10 min before the addition of the 1-bromo-2-chloroethane gave the lactam 141 in 26 % yield, together with lactone 142 (5 %) and dimer 144, the yield of which was uncertain because of its highly insoluble nature.

c. Using conditions described in (a) but heating the mixture under reflux for 4.5 h gave the lactone 142, bis-substituted 143 and lactam 141 in 16 %, 24 %, and 38 % respectively.

d. On maintaining the conditions as in (a), but substituting benzene for THF, the starting material was recovered quantitatively.

e. On substituting ether for the THF used in (a), a 31 % yield of the lactam 141 was obtained, together with small amounts of the lactone 142 and 143.

f. Substitution of 1,2-dibromoethane for 1-bromo-2-chloroethane gave the dimer 144 in 91 % yield.

g. Using the same conditions as in (a) except for the addition of 3 equivalents of TMEDA before the addition of the n-butyllithium resulted in the lactone 142, compound 143 and lactam 141 being produced in 10 %, 23 %, and 40 % respectively.

N-Methyl-3-phenyl-2-pyrrolidone 141 was recrystallized from benzene - hexane to give a white solid mp 58 - 58.5 °C (lit 58 - 59 °C [101]).

IR (KBr)	700(m) 750(m) 1280(m) 1400(m) 1430(m)
	1440(m) 1450(m) 1470(m) 1495(m) 1680(s,C=O)
PMR (80MHz)	1.86 - 2.77(m,2,$CHCH_2$)
	2.94(s,3,NCH_3)
	3.30 - 3.78(m,3,NCH_2 and CH)
	7.08 - 7.45(m,5,aromatic)

2-Phenylbutyrolactone 142 [103] was obtained as an oil, which could not readily be purified.

IR ($CHCl_3$)	1030(s) 1150(s,CO) 1600(w,C=C,Ar)
	1770(s,C=O)
PMR (60MHz)	2.15 - 2.90(m,2,$CHCH_2$)
	3.55 - 3.93(m,1,CH)

4.00 - 4.59(m,2,OCH_2)
7.20(s,5,aromatic)

MS 162(83,M^+) 149(74) 118(90) 117(100)
106(80) 91(93) 77(81,Ph)

HRMS 162.06803 ($C_{10}H_{10}O_2$ requires 162.06807)

N,N'-Dimethyl-2,5-diphenylhexanediamide 143 was recrystallized from diisopropylether to give a white solid, mp 70 - 74 °C.

IR (KBr) 355(w) 520(w) 595(w) 665(w,sh) 693(s)
715(m) 728(m) 765(w) 835(w) 875(w) 915(w)
940(w) 960(w) 975(w) 1000(w) 1030(w)
1050(w) 1070(w) 1105(w) 1155(m) 1185(w)
1200(w) 1220(m) 1250(m) 1270(m) 1290(w)
1305(w) 1330(m) 1370(m) 1405(s) 1450(m)
1460(m) 1490(m) 1[illegible]0(s) 1600(w) 1640(s,C=O)
2860(s) 2930(s) 2960(s) 3030(m) 3090(s)
3260(s,br)

PMR (80 MHz) 1.67 - 2.40(m,4,CH_2)
2.77 and 2.71(2xs, NCH_3)
3.12 - 3.33(4 line m,2,CH)
5.30(br s,2,NH)
7.25(s,10,aromatic)

MS 162(12) 148(91) 147(19) 11[illegible](19) 105(47)
92(76) 91(100) 58(62)

N,N-Dimethyl-2,3-diphenylbutanediamide 144 was sublimed at 0.1 mm Hg, 250 °C, then recrystallized from DMF, with large losses of material, to give a white solid mp 278 - 279 °C.

IR (KBr) 370(w) 510(w) 538(w) 572(w) 625(w)
668(w,sh) 680(m,sh) 700(m) 715(m) 730(m)
775(w) 795(w) 932(w) 1035(w) 1040(w)
1078(w) 11163(m) 1180(w) 1190(w) 1215(w)
1250(m) 1270(m) 1300(w) 1335(m) 1375(m)
1405(s) 1450(m) 1495(m) 1560(s,CN) 1600(m)
1640(s,C=O) 2800(w) 2860(w) 2900(m) 2930(m)
3000(m) 3020(m) 3080(m) 3300(s,br)

PMR (80 MHz, DMSO) 3.29(s,NCH_3)
4.20(s,CH)
6.92 - 7.25(m,aromatic)
7.70 - 8.60(m,NH)
Proton count uncertain

MS 324(52) 296(39,M^+) 266(46) 265(58)
239(100) 181(74) 149(68) 103(76) 91(98)

HRMS 296.15253 ($C_{19}H_{20}N_2O_2$ requires 296.15253)

4.7 Preparation of 1,3-diphenyl-2-pyrrolidone 145 [101]

a. To a cold solution of N-phenyl phenylacetamide [104] (420 mg, 2.0 mmols) in THF under nitrogen was added n-butyllithium (4.4 mmols) followed by 1-bromo-2-chloroethane (181 µL, 2.2 mmols) after 10 min. The mixture was warmed to room temperature and stirred overnight, then poured into ammonium chloride solution. The aqueous phase was extracted with dichloromethane, and solvent was removed, giving an oil (491 mg), which was chromatographed on silica gel, eluting with hexane - ethyl acetate. A compound, probably the dialkyl product 146 (although some anomalous peaks were present in the MS) (228 mg, 0.76 mmols) was obtained in 38 % yield (TLC,

hexane - ethyl acetate, 7:3, R_f = 0.80) together with a mixture (152 mg) of the amide and lactam 145 as shown by PMR (TLC, R_f = 0.50). The spectra of these compounds are reported after (b).

b. The conditions used were as in (a) except that HMPA (4.4 equivalents) was added before the 1-bromo-2-chloroethane. Compound 146 was obtained in 36 % yield, together with a mixture of amide and lactam 145. These were separated by fractional crystallization from diisopropyl ether - ethyl acetate, and the yields were found to be approximately 24 % for the lactam 145 and 20 % for the recovered amide.

1,3-diphenyl-3-(2-chloroethyl)-2-pyrrolidone 146 was recrystallized from ethanol to give a solid mp 91 - 92 °C

Ir (KBr)	500(w) 623(w) 665(w) 700(m) 710(w) 723(w) 728(w) 755(m) 788(w) 825(w) 885(w) 905(w) 1010(w) 1035(w) 1070(w) 1078(w) 1100(w) 1110(w) 1155(w) 1170(w) 1185(w) 1195(w) 1225(m) 1250(w) 1283(m) 1300(s) 1310(m) 1320(m) 1345(w) 1400(s) 1445(m) 1450(m) 1465(m) 1475(m) 1495(s) 1595(m) 1620(w) 1680(s,C=O) 2860(m) 2890(m) 2950(m) 2980(m) 3010(m) 3060(m)
PMR (80MHz)	2.14 - 2.91(m,4) 3.10 - 3.93(m,4,NCH_2 and $ClCH_2$) 7.03 - 7.75(m,10,aromatic)
MS	345(10) 344(10) 343(10) 301(41,M^+) 300(26) 299(56,M^+) 238(56) 237(58) 117(81) 115(59) 91(59) 77(67,Ph)

HRMS 299.10755 ($C_{18}H_{18}NOCl$ requires 299.10769)

1,3-Diphenyl-2-pyrrolidone [45] could not be obtained pure, the best melting point obtained was 80 - 85 °C (lit 81 - 82 °C [101].

IR (KBr) 690(s) 720(s) 750(s) 1440(s) 1495(s) 1550(w) 1600(s,C=C,Ar) 1670(s,C=O)

PMR (60MHz) 1.85 - 2.99(m,2)
3.61 - 4.18 and 3.68(m and s,3,NCH_2,CH, s from small amide impurity)
6.82 -8.00(m,12,aromatic)

MS 237(99,M^+) 118(95) 117(100) 107(90) 105(75) 93(83) 91(82) 77(78,Ph)

HRMS 237.11531 ($C_{16}H_{15}NO$ requires 237.11535)

4.8 Attempted preparation of 3-phenyl-2-pyrrolidone

To a mixture of phenylacetamide (407 mg, 3 mmols) and dry THF (the amide was only sparingly soluble) at room temperature, under nitrogen, was added n-butyllithium in hexane (6.6 mmols). The reaction mixture was stirred for 30 min, then treated with 1-bromo-2-chloroethane (270 µL, 3.3 mmols). Stirring was continued for 3 days, and the reaction mixture was then poured into ammonium chloride solution. After extraction with dichloromethane, an oil was obtained (400 mg), out of which starting material (98 mg, 24 % recovery) was separated by fractional crystallization. Chromatography of the mother liquor on silica gel with hexane - ethyl acetate as eluant gave

a nitrile (170 mg) as indicated by IR (film) 2230(m,C≡N). (Phenylacetonitrile has IR 2250(m,C≡N)).

4.9 Attempted Preparation of N-Methyl-2-pyrrolidone

A solution of N-methylacetamide (216 mg, 3 mmols) in dry THF (20 mL) at 0 °C was treated with n-butyllithium in hexane (6.6 mmols) After stirring for 45 min, 1-bromo-2-chloroethane (270 µL, 3.3 mmols) was added. The mixture was warmed to room temperature and stirred overnight, and then poured into ammonium chloride solution. The aqueous phase was separated and the solvent removed, giving an oil (86 mg), the IR of which was comparable to that of the starting material

4.10 Thiation of Lactam 110

a. Lactam 110 (475 mg, 2.0 mmols) was dissolved in carbon disulphide (10 mL) and phosphorus pentasulphide (450 mg, 2.0 mmols) was added. The mixture was heated under reflux for 14 h. The organic phase was decanted, and the remaining sticky brown residue was treated with water and dichloromethane for 5 h in an effort to extract all the product. The combined organic phases were concentrated, and the residue (230 mg) was purified by chromatography on silica gel, eluting with hexane - ethyl acetate. The thiolactam 109 (175 mg, 0.70 mmols) was obtained in 35 % yield (TLC, ethyl acetate, R_f = 0.39), together with some phosphorus-containing material (107 mg) which was not characterized. The thiolactam 109 was purified by recrystallization from acetone, giving a white solid mp 109 -110 °C.

b. Lactam 110 (471 mg, 2.0 mmols) was dissolved in DME and Lawesson's reagent (414 mg, 1.0 mmols) was added. The mixture

was heated under reflux for 7 h. The solvent was removed, and the residue chromatographed on silica gel. Thiolactam 109 (262 mg, 1.0 mmols) was obtained in 40 % yield, together with 390 mg of by-products.

c. On using conditions as in (b) except that toluene was used as solvent in place of DME, a yield of 65 % of the thiolactam 109 was obtained, together with 192 mg of by-products.

d. The lactam 110 (470 mg, 2.0 mmols) was dissolved in toluene (20 mL). Lawesson's reagent (411 mg, 1.0 mmols) was placed in a Soxhlet thimble, and extracted with the toluene for 18 h. Work-up as in (c) gave the thiolactam 109 (240 mg, 0.95 mmols) in 48 % yield, together with 95 mg of by-products.

e. On using the conditions described in (d) except that DME was used as solvent, none of the thiolactam 109 was obtained.

3.11 Thiation of N-Methyl-(3,4-dimethoxyphenyl)acetamide 119

Phosphorus pentasulphide (1.11 g, 5 mmols) was added to a solution of amide 119 (1.0 g, 5 mmols) in dry THF. The mixture was stirred and irradiated in an ultrasonic laboratory cleaner bath at 30 - 40 °C for 45 min, after which a further portion of phosphorus pentasulphide (1.11 g, 5 mmols) was added. Irradiation was continued for a further 2 h. The mixture was filtered, the solid residue was washed with dichloromethane, and the solvents removed. Chromatography on silica gel of the oily product, with ethyl acetate as eluant, gave N-methyl-(3,4-dimethoxyphenyl)thioacetamide 139 (778 mg, 3.5 mmols) in 69 % yield (TLC, ethyl acetate, R_f = 0.83) (see section 4.2 for spectra).

EXPERIMENTAL PRODEDURES RELATING TO CHAPTER 4

1 Preparation of Vinylogous Urethanes

1.1 Preparation of 1-methyl-2-methoxycarbonylmethylene-3-(3,4-dimethoxyphenyl)-pyrrolidine 96

Methyl bromoacetate (94 µL, 1.0 mmols) was added to thiopyrrolidone 109 (253 mg, 1.0 mmols) in dry acetonitrile (1 mL) and the mixture was stirred at room temperature overnight, and then diluted with acetonitrile (20 mL). Triphenylphosphine (262 mg, 1.0 mmols) was added, then triethylamine (152 µL, 1.1 mmols). After 2 h the solvent was removed under reduced pressure, and the residue taken up in 2 M hydrochloric acid. The mixture was washed with dichloromethane, basified with ammonia and extracted with dichloromethane. The solvent was removed and the product chromatographed on silica gel using hexane - ethyl acetate as eluant, giving 96 (220 mg, 0.76 mmols, 76 %) as a white solid (TLC, hexane - ethyl acetate, 2:3, R_f = 0.55). An analytical sample, mp 94 - 98 °C, was obtained by recrystallization from diisopropyl ether - benzene.

I.R. (KBr) 375(w) 530(w) 590(w) 620(w) 670(w) 730(w)
765(w) 780(m) 820(w) 845(w) 865(w) 910(w)
930(w) 950(w) 975(w) 1020(m,ArOMe) 1035(m)
1045(m) 1060(m) 1105(m) 1145(s) 1185(m)
1200(m) 1230(s) 1245(s,ArOMe)1288(m)
1298(m) 1315(m) 1330(w) 1365(w) 1405(m)
1445(m) 1470(m) 1505(m,C=C,Ar) 1560(sh)
1595(s,NC-CC-O) 1685(s,NC=CC-O) 2840(sh)
2850(m) 2870(w) 2940(m) 2960(m) 2990(m)
3060(w)

EXPERIMENTAL PRODEDURES RELATING TO CHAPTER 4

1 Preparation of Vinylogous Ur anes

1.1 Preparation of 1-methyl-2-methoxycarbonylmethylene-3-(3,4-dimethoxyphenyl)-pyrrolidine 96

Methyl bromoacetate (94 µL, 1.0 mmols) was added to thiopyrrolidone 109 (253 mg, 1.0 mmols) in dry acetonitrile (1 mL) and the mixture was stirred at room temperature overnight, and then diluted with acetonitrile (20 mL). Triphenylphosphine (262 mg, 1.0 mmols) was added, then triethylamine (152 µL, 1.1 mmols). After 2 h the solvent was removed under reduced pressure, and the residue taken into 2 M hydrochloric acid. The mixture was washed with dichloromethane, basified with ammonia and extracted with dichloromethane. The solvent was removed and the product chromatographed on silica gel using hexane - ethyl acetate as eluant, giving 96 (220 mg, 0.76 mmols, 76 %) as a white solid (TLC, hexane - ethyl acetate, 2:3, R_f = 0.55). An analytical sample, mp 94 - 98 °C, was obtained by recrystallization from diisopropyl ether - benzene.

IR (Kbr) 375(w) 530(w) 590(w) 620(w) 670(w) 730(w) 765(w) 780(m) 820(w) 845(w) 865(w) 910(w) 930(w) 950(w) 975(w) 1020(m,ArOMe) 1035(m) 1045(m) 1060(m) 1105(m) 1145(s) 1185(m) 1200(m) 1230(s) 1245(s,ArOMe)1288(m) 1298(m) 1315(m) 1330(w) 1365(w) 1405(m) 1445(m) 14[illegible](m) 1505(m,C=C,Ar) 1560(sh) 1595(s,NC=CC=O) 1685(s,NC=CC=O) 2840(sh) 2850(m) 2870(w) 2940(m) 2960(m) 2990(m) 3060(w)

PMR (80 MHz) 1.61 - 2.56(m,2,CH_2)
2.91(s,3,NCH_3)
3.10 - 3.66 and 3.49(m and s,5,NCH_2 and CO_2CH_3)
3.82 and 3.85(2xs,6,OCH_3)
4.55(s,1,=CH)
4.80 - 5.00(m,1,CH)
6.44 - 6.79(m,3,aromatic)

MS 292(18) 291(97,M^+) 276(32) 260(36)
259(70) 245(20) 244(100) 216(19)

HRMS 291.14700 ($C_{16}H_{21}NO_4$ requires 291.14705)

C H and N analysis: C, 66.06; H, 7.29; N 4.81. $C_{16}H_{21}NO_4$ requires: C, 65.96; H, 7.26; N, 4.81 %.

1.2 Preparation of 1-methyl-2-methoxycarbonylmethylene-piperidine 148

Methyl bromoacetate (0.75 mL, 8.0 mmols) was added to N-methyl-2-thiopiperidone (998 mg, 7.7 mmols) in dry acetonitrile (1 mL). The mixture was allowed to stand at room temperature for 4 days, and then diluted with acetonitrile (15 mL). Triphenylphosphine (2.0 g, 7.8 mmols) was added, then triethylamine (1.2 mL, 8.5 mmols). After 30 min, during which time triphenylphosphine sulphide precipitated out, the mixture was filtered. Solvent was removed from the filtrate, and the residual paste was dissolved in 1.5 M hydrochloric acid. The aqueous phase was extracted with ether, basified with ammonia solution and extracted with dichloromethane. Removal of the solvent gave 148 (1.2 g, 7.1 mmols, 91 %) as a chromatograph-

ically pure pale yellow oil (TLC, hexane - ether, 1:4, R_f = 0.62). Further purification was accomplished by distillation in a Kugelrohr apparatus.

IR ($CHCl_3$) 790(w) 820(w) 850(w) 890(w) 930(w)
975(w) 1050(s) 1145(s) 1180(m) 1220(w)
1275(m) 1325(m) 1350(m) 1380(w) 1410(m)
1430(m) 1450(m) 1460(w) 1470(w) 1490(w)
1570(s,NC=CC=O) 1670(s,NC=CC=O) 2860(w)
2940(m) 3000(m) 3020(w)

PMR (60 MHz) 1.45 - 2.02(m,4)
2.82(s,3,NCH_3)
2.95 - 3.43(m,4,NCH_2 and $=CCH_2$)
3.62(s,3,OCH_3)
4.55(s,1,CH)

MS 169(42,M^+) 138(100) 111(22) 110(57)
82(32) 55(18) 44(21) 42(29)

HRMS 169.11033 ($C_{10}H_{15}NO_2$ requires 169.11027)

2. Michael Reaction of Vinylogous Urethanes with Acrylates

a. To a solution of aryl vinylogous urethane 96 (87 mg, 0.30 mmols) in dry THF (5 mL) at -78 °C under nitrogen, was added n-butyllithium in hexane (0.30 mmols), followed by methyl acrylate (38 µL, 0.42 mmols) after 15 min. The mixture was warmed to room temperature, and stirred for 5 days, then poured into ammonium chloride solution and extracted with dichloromethane. After removal of solvent, an oil was obtained (110 mg), which was shown by TLC and IR analyses to consist primarily of vinylogous urethane, together with polymerized

methyl acrylate material.

b. To a suspension of cuprous iodide (279 mg, 1.5 mmols) (flamed under vacuum immediately prior to use) in dry ether at room temperature under nitrogen, was added tri-n-butylphosphine (0.81 mL, 3.3 mmols). After 10 min, a homogeneous solution was obtained, which was cooled to -78 °C. Vinylogous urethane 100 (248 mg, 1.5 mmols) was treated with n-butyllithium in hexane (1.5 mmols) at -78 °C in ether, and then added to the copper-phosphine solution. After 20 min, ethyl acrylate (160 µL, 1.5 mmols) was added. The resultant mixture was stirred at -78 °C for 1 h, at -40 °C for 3 h, and at room temperature for 2 h. A solution of hydrochloric acid (2 M) was added, and the aqueous phase was washed with ether, to remove the phosphine, basified with ammonia and extracted with further portions of ether. Removal of solvent gave an oil (195 mg), which was shown by IR and TLC (hexane - ethyl acetate, 4:1, R_f = 0.35) to be vinylogous urethane 101.

3 Reactions of Vinylogous Urethanes with Acid Chlorides

3.1 Reactions of Vinylogous Urethane 100

a. Vinylogous urethane 100 (99 mg, 0.60 mmols) was dissolved in dry benzene (2 mL) at room temperature under nitrogen, and acryloyl chloride (58 µL, 0.72 mmols) was added. The mixture was stirred at room temperature for 1.5 h, during which time an oil precipitated out. After the addition of sodium bicarbonate solution, the mixture was extracted with dichloromethane. Removal of the solvent under vacuum gave the chromatographically pure product, ethyl 1-methyl-2-oxo-7-azabicyclo-[4.3.0]non-1(6)-ene-5-carboxylate 111 (94 mg, 0.42 mmols) in 70 % yield (TLC, benzene - methanol, 1:4, R_f = 0.23).

Further purification was accomplished distillation at 200 °C, 0.4 mm Hg, in a Kugelrohr apparatus.

IR ($CHCl_3$)	670(w) 800(w) 860(w) 910(w) 980(w) 1010(sh) 1030(w) 1160(m) 1180(m) 1230(m) 1280(m) 1290(sh) 1310(m) 1370(w) 1410(s) 1450(m) 1460(m) 1520(s) 1560(s,NC=CC=O) 1600(s,NC=CC=O) 1730(s,ester C=O) 2850(w) 2980(m) 3020(w)
PMR (60 MHz)	1.27(t,3,J = 7 Hz,CH_3) 1.71 - 2.65(m,6) 2.71 - 2.85(m,1,CH, 2.95(s,3,NCH_3) 3.35 - 3.97(m,2,NCH_2) 4.25(q,2,J = 7Hz,OCH_2)
Carbon-13 NMR (20Mhz)	13.5o(q,CH_3) 24.10(t) 26.05(t) 32.73(t) 33.61(q,NCH_3) 38.50(d,CH) 54.13(t,NCH_2) 61.39(t,OCH_2) 109.74(-C) 163.7(NC=) 169.4(ester C=O) 189.68(ketone C=O) The assignments were made with the aid of an SFORD spectrum
UV	326(24600) shifts to 306(18300) on addition of acid.
MS	223(97,M^+) 195(29,M - CH_2CH_2) 167(70) 150( ) 148(47) 123(100) 121(72) 94(59)
HRMS	223.12075 ($C_{13}H_{17}NO_3$ requires 223.12084)

b. Vinylogous urethane 100 (248 mg, 1.5 mmols) was dissolved

in dry acetonitrile (8 mL) under nitrogen, and acryloyl chloride (144 µL, 3.0 mmols) was added. After 30 min, the acetonitrile was removed under vacuum and the residue taken into sodium bicarbonate solution. The mixture was extracted with dichloromethane, the solvent was removed, and the oil obtained was chromatographed on silica gel, eluting with benzene - methanol. Diethyl 2,6-bis(1-methyl-2-pyrrolidinylidene)-3-oxoheptanedioate 156 (240 mg, 0.61 mmols) was obtained in 83 % yield (TLC, benzene - methanol, 7:3, R_f = 0.45), contaminated with a small amount of 151, as shown by TLC (R_f = 0.55).

IR ($CHCl_3$)	870(w) 945(w) 975(w) 1060(s) 1110(w) 1150(m) 1165(m) 1220(s,br) 1280(s) 1320(m) 1365(w) 1410(m) 1435(m) 1460(m) 1480(m) 1550(s,br) 1610(s,br) 1660(s) 1710(w,sh) 2980(s)
PMR (80 MHz)	1.05 - 1.33(2 x overlapping t,6,CH_3) 1.50 - 2.03(m,4) 2.24 - 3.69, 2.70 and 2.99(m and 2xs,18,s from NCH_3) 4.10(2 x overlapping q,4,OCH_2)
MS	392(23,M^+) 347(10) 196(98) 195(36) 182(100) 154(50) 124(52) 108(44) 97(30)
HRMS	392.23125 ($C_{21}H_{32}N_2O_4$ requires 392.23111)

c. Vinylogous urethane 100 (190 mg, 0.61 mmols) was dissolved in dry acetonitrile (5 mL) at room temperature under nitrogen and cinnamoyl chloride (119 mg, 0.72 mmols) was added. After stirring for 2 h, the solvent was removed under vacuum,

sodium bicarbonate solution was added, and the aqueous phase was extracted with dichloromethane. Chromatography of the resultant oil on silica gel with acetone - benzene as eluant gave ethyl 2-(1-methyl-2-pyrrolidinylidene)-3-oxo-5-phenylpent-4(E)-enoate 157 (82 mg, 0.28 mmols) (TLC, benzene - acetone, 3:1, R_f = 0.40) in 47 % yield, as the only identifiable product. Similar results were obtained using benzene and dichloromethane as solvent.

IR ($CHCl_3$)	970(w) 1030(w) 1065(m) 1110(w) 1180(m)
	1200(m) 1230(m) 1250(m) 1270(s) 1320(m)
	1360(w) 1400(m) 1450(m) 1500(w) 1545(s)
	1575(s) 1590(s) 1610(s) 1630(s) 1670(s)
	2870(w) 2950(m) 2990(m) 3050(w)
PMR (60 MHz)	1.22(t,3,J = 3 Hz,CH_3)
	1.80 - 2.35(m,2)
	2.75(s,3,NCH_3)
	3.20(t,2,J = 2.7 Hz,OCH_2)
	3.58(t,2,J = 3 Hz,NCH_2)
	4.15(q,2,J = 3 Hz,OCH_2)
	6.90 - 7.60(m,7,CH=CH and aromatic)
MS	299(48,M^+) 253(100) 226(43) 197(91)
	124(92) 123(36) 103(82) 77(69)
HRMS	299.15208 ($C_{16}H_{21}NO_3$ requires 299.15213)

d. Crotonoyl chloride (68 µL, 0.70 mmols) was added to a solution of vinylogous urethane 100 (103 mg, 0.61 mmols) in dry acetonitrile (5 mL) under nitrogen at room temperature. After 3 h, TLC analysis of the reaction solution showed complete disappearance of 100. The acetonitrile was removed under

vacuum, sodium bicarbonate solution was added, and the mixture was extracted with dichloromethane. Removal of the solvent gave an oil (136 mg), which was purified by preparative layer chromatography on alumina (type T). The only identifiable product obtained was, ethyl 2-(1-methyl-2-pyrrolidinylidene)-3-oxohex-4(E)-enoate 158 (30 mg, 0.13 mols), the yield being 21 % (TLC, silica gel, benzene - acetone, 3:1, R_f = 0.27).

IR ($CHCl_3$)	800(w) 830(w) 845(w) 868(w) 910(w) 940(w) 975(w) 990(w,sh) 1080(s) 1110(m) 1118(m) 1180(m) 1220(m) 1240(m) 1292(s) 1330(m) 1375(w) 1415(m) 1430(m,sh) 1450(m) 1470(m) 1555(s) 1600(s) 1658(s) 1670(s,sh) 1710(w,sh) 2900(w,sh) 2950(m,sh) 3000(m) 3020(w,sh)
PMR (80 MHz)	1.15(t,3,J = 6.3 Hz,CH_2CH_3) 1.48 - 2.12(m and d,5,J = 5 Hz,CH_2 and $CHCH_3$) 2.66(s,3,NCH_3) 3.06(t,2,J = 7.5 Hz,CCH_2) 3.47(t,2,J = 6.8 Hz,NCH_2) 4.03(q,2,J = 6.3 Hz,$COCH_2$) 6.15 - 6.75(eight line m,2,CH=CH)
MS	237(3,M^+), 191(10) 149(11) 125(17) 97(33) 95(33) 81(40) 71(52) 69(62) 57(88) 41(100)
HRMS	237.13656 ($C_{14}H_{19}NO_3$ requires 237.13648)

e. The reaction as in (d) was repeated, except that dry benzene was used as solvent. In this case 158 was again the

only identifiable product, but the yield was only 6 %.

3.2 Reaction of Vinylogous Urethane 148

a. Acryloyl chloride (144 µL, 1.8 mmols) was added to the vinylogous urethane 148 (252 mg, 1.5 mmols) in dry benzene (8 mL) under nitrogen. The mixture was stirred at room temperature for 1 h, then sodium bicarbonate solution was added, and the aqueous phase was extracted with dichloromethane. Removal of the solvent, followed by chromatography on silica gel, eluting with benzene - methanol gave methyl 2-methyl-7-oxo-2-azabicyclo[4.4.0]dec-3(6)-ene-10-carboxylate 159 (214 mg, 0.96 mmols) as a pale yellow oil in 64 % yield.

IR ($CHCl_3$)	580(w) 660(w) 670(sh) 830(w) 855(w)
	880(w) 900(w) 938(w) 985(w) 1015(w) 1040(w)
	1060(w) 1085(w) 1105(w) 1180(s) 1255(m)
	1275(m) 1305(m) 1325(s) 1345(w) 1360(w)
	1395(s) 1420(sh) 1435(w) 1455(w) 1490(w)
	1550(s,br) 1606(w) 1735(s,ester C=O)
	2860(w) 2960(s) 3000(s) 3030(w)
PMR (80 MHz)	1.52 - 2.00(m,2,$CH_2CH_2CH_2$)
	2.15 - 2.53(m,6)
	2.95(s,3,NCH_3)
	3.24(t,2,J = 6 Hz,NCH_2)
	3.51 - 3.68(m,1,CH)
	3.75(s,3,OCH_3)
Carbon-13 NMR	19.59(t) 20.77(t) 25.50(t) 32.45(t)
(20 MHz)	38.74(q,NCH_3) 41.75(d,CH) 51.56(t,NCH_2)
	52.37(q,OCH_3) 107.2(s,=C) 155.8(NC=)
	171.3(ester C=O) 192.5(ketone C=O)

	The assignments were made with the aid of an SFORD spectrum
UV	325(22000). Shifts to 305(19000) on addition of acid.
MS	223(8) 208(47) 167(58) 164(45) 136(85) 120(46) 108(72) 42(100)
HRMS	223.12100 ($C_{12}H_{17}NO_3$ requires 223.12083)

b. Using the same conditions as in (a) except that acetonitrile was used as solvent instead of benzene, the yield obtained after column chromatography was only 4.5 %.

3.3 Reaction of Vinylogous Urethane 96

a. Aryl vinylogous urethane 96 (103 mg, 0.36 mmols) was dissolved in dry THF (10 mL) under nitrogen and acryloyl chloride (40.5 µL, 0.50 mmols) was added. The resultant mixture was stirred at room temperature for 3 h, during which time an oil separated out. Saturated sodium bicarbonate solution was added, and the mixture was extracted with dichloromethane. The solvent was removed, and the product chromatographed on silica gel, eluting with hexane - ethyl acetate. 1-Methyl-7-(3,4-dimethoxyphenyl)-7-methoxycarbonyl-1,2,3,3a,5,6-hexahydroindol-4-one 160 (84 mg, 0.24 mmols) was obtained in 68 % yield as an unstable white solid mp 120 - 124 °C (TLC, hexane - ethyl acetate, 2:3, R_f = 0.56)

IR ($CHCl_3$)	660(w) 860(w) 910(w) 940(w) 970(w) 1025(s,ArOMe) 1080(w) 1100(m) 1145(s) 1255(s,ArOMe) 1290(sh) 1315(w) 1400(w)

1440(m) 1460(m) 1510(s,aromatic) 1590(s)
1685(s,sh) 1665(m) 1705(s,ketone C=O)
1725(s,ester C=O) 2840(w) 2860(w) 2930(m)
2950(m) 3000(m) 3020(w,sh)

PMR (80 MHz) 1.90 - 2.90(m,6)
3.10(s,3,NCH_3)
3.20 - 3.40(m,2,NCH_2)
3.73(s,3,CO_2CH_3)
3.83 and 3.85(2xs,6,OCH_3)
6.69 - 6.89(m,3,aromatic)

UV 304(14000) 249(12000). After addition of octol 235(11000).

MS 345(88,M^+) 330(29) 314(32) 302(46)
302(46) 286(37) 207(100) 154(31)

HRMS 345.15763 ($C_{19}H_{23}NO_5$ requires 345.15762)

b. Using benzene, dichloromethane and DMF as solvents tlc analysis indicated that 160 was again the only product formed.

EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 5

1 Preparation of Chloromethyl Vinyl Ketone

Method of Baddeley et al [11']. Finely powdered aluminium chloride (40 g, 0.30 mols) was dissolved in dry dichloromethane (150 mL) at room temperature under nitrogen, giving a dark red solution. The mixture was cooled to 0 °C and chloroacetyl chloride (20 mL, 0.25 mols) was added dropwise. The mixture was cooled further using a dry ice / acetone bath and ethylene was bubbled through while an internal temperature of -5 to -15 °C was maintained. Once the required amount of ethylene had been added (7 g, 0.30 mols) the dark brown mixture was poured into dilute hydrochloric acid / ice. The organic phase was separated, and the dichloromethane was distilled off. The residue was distilled at 70 °C, 1 mm Hg giving β-chloropropionyl chloride (22 g, 0.16 mols) in 63 % yield.

Freshly prepared β-chloropropionyl chloride (5 mL, 37 mmols) was added to sodium carbonate (3.9 g, 37 mmols) and the mixture was slowly distilled at 56 °C , 30 mm Hg, allowing the oil bath temperature to rise to 150 °C. Chloromethyl vinyl ketone (3.1 g, 30 mmols) was obtained in 80 % yield.

IR (film) 1620(m,C=C) 1700(s,C=O)

2 Sulphide Contractions Using N-Methyl-2-thiopyrrolidone 121

2.1 Attempted Salt Formation Using Chloromethyl Vinyl Ketone

To thiopyrrolidone 121 (501 mg, 4.4 mmols) was added chloromethyl vinyl ketone (480 µL, 5.5 mmols). The mixture gradually

thickened, and after 2 h acetonitrile (1 mL) was added, dissolving the thick oil. The mixture was stirred at room temperature for 30 h, after which time the salt formation was not complete, as judged by the continued presence of starting material on the TLC.

2.2 Sulphide Contraction with Iodomethyl Vinyl Ketone

Chloromethyl vinyl ketone (475 µL, 5.5 mmols) was added to a solution of sodium iodide (814 mg, 5.5 mmols) in acetonitrile (20 mL) at room temperature, resulting in the precipitation of sodium chloride. After 5 min thiopyrrolidone 121 (502 mg, 4.4 mmols) was added, and the mixture was stirred at room temperature for 4 h, by which time TLC showed complete disappearance of starting material. A solution of triphenylphosphine (1.5 g, 5.7 mmols) and triethylamine (790 µL, 5.6 mmols) in acetonitrile (10 mL) was added to the ice-cooled reaction mixture. The reaction appeared to be complete after 10 min. The solvent was removed and the residue partitioned between dichloromethane and hydrochloric acid (1.5 M). The aqueous phase was washed with dichloromethane, basified with ammonium hydroxide solution, and extracted with further portions of dichloromethane. Removal of solvent from this base extract gave an oil (857 mg) which was chromatographed on silica gel, with methanol - benzene as eluant, giving an oil (132 mg), and a solid foam (546 mg, 1.21 mmols) which was shown to be the phosphonium salt 163 (28 %) (TLC, benzene - methanol, 4:1, R_f = 0.26). The oil was separated by preparative layer chromatography on alumina, with ethyl acetate as eluant, into the uncyclized compound 164 (82 mg, 0.55 mmols, 13 %) (TLC, silica gel, benzene - methanol, 4:1, R_f = 0.45) and a third, uncharacterizable, compound (13 mg). None of these compounds could be properly purified.

(E)-4-(1-Methyl-2-pyrrolidinylidene)-3-oxobutyltriphenylphosphonium chloride 161 was recrystallized, with decomposition, from acetone - methanol, to give an unstable, yellow solid mp 167 - 171.5 °C. A silver nitrate test, and a Beilstein test indicated the counterion to be chloride.

IR ($CHCl_3$)	1440(m,C=C,Ar) 1490(m,C=C,Ar)
	1555(s,NC=CC=O) 1590(w,C=C,Ar)
	1630(NC=CC=O)
PMR (60 MHz)	1.57 - 2.22(m,2,$CH_2CH_2CH_2$)
	2.43 - 3.28 and 2.95 (m and s,7, s from NCH_3)
	3.50 and 3.90(2xt,4,J = 7 Hz and 7 Hz, NCH_2 and $=CCH_2$)
	5.00(s,1,=CH)
	7.45 - 8.15(m,15,aromatic)
MS	262(14,PPh_3) 183(19) 153(5) 152(5,M - PPh_3) 151(5) 128(8) 124(5) 108(12)
	51(4)

(E)-1-(1-Methyl-2-pyrrolidinylidene)-but-3-ene-2-one 164

IR ($CHCl_3$)	1300(s) 1410(s) 1480(s) 1530(s,br
	NC=CC=O) 1595(s,C=C) 1635(NC=CC=O) 1715(w)
PMR (60 MHz)	1.60 - 2.22(m,2)
	2.88(s,3,NCH_3)
	3.00 - 3.60(m,4,NCH, and $=CCH_2$)
	5.05(s,1,C=CH)
	5.35(2 x d,J = 5 and J = 10 Hz,1, CH_2 CH)
	5.65 - 6.65(m,2,$=CH_2$)

The uncharacterized compound obtained had the following spectral features.

IR ($CHCl_3$)	1300(s) 1415(m) 1485(s)
	1545(s,br,NC=CC=O) 1630(m,NC=CC=O) 1720(w)
PMR (80 MHz)	1.71 - 2.31(m,5)
	2.54 - 3.07 and 2.85(m and s,7, s from NCH_3)
	3.07 - 3.56(m,5)
	4.18 - 4.49(m,1)
	4.99(s,1,=CH)
	7.48 - 7.91(m,0.6)
	Integration figures are all approximate.
MS	279(82) 167(40) 150(20) 149(100) 113(44)
	71(60) 69(37) 57(93)

b. The reaction was repeated, maintaining the same conditions as in (a) except that the contraction was carried out at -45 °C, and the solution was allowed to warm to room temperature before work-up. Column chromatography of the product on silica gel gave uncyclized compound 164 in 18 % yield, and the phosphonium salt 163 in 44 % yield.

c. On substitution of trimethyl phosphite for triphenylphosphine, with conditions as in (b) otherwise unchanged, only a small amount of the uncharacterized product as in (a) was obtained.

d. The use of tributylphosphine in place of trimethylphosphite with conditions otherwise the same gave 164 in 4 % yield,

together with a compound thought to be (E)-4-(1-methyl-2-pyrrolidinylidene)-3-oxobutyltributylphosphonium chloride 166.

IR ($CHCl_3$)	1545(NC=CC=O) 1625(NC=CC=O)
PMR (60 MHZ)	Broad humps with butyl groups clearly present.

3 Sulphide Contractions With 5-(3,4-dimethoxyphenyl)-N-methylpyrrolidin-2-thione 109

3.1 Salt Formation Using Iodomethyl Vinyl Ketone

Sodium iodide (74 mg, 0.50 mmols) was dissolved in acetonitrile (2 mL) and chloromethyl vinyl ketone (44 µL, 0.50 mg) was added, resulting in the precipitation of sodium chloride. This mixture was combined with a solution of arylthiopyrrolidone 109 (100 mg, 0.40 mmols) in acetonitrile (5 mL). After stirring at room temperature overnight the reaction solution was black and tarry, and TLC indicated the continued presence of starting material (TLC, ethyl acetate, R_f = 0.83).

3.2 Sulphide Contraction with Chloromethyl Vinyl Ketone

a. Chloromethyl vinyl ketone (66 µL, 0.75 mmols) and arylthiopyrrolidone 109 (100 mg, 0.40 mmols) were mixed together with a few drops of acetonitrile, and heated at 40 °C overnight. TLC indicated that the reaction had gone almost to completion, in that the starting material had all but disappeared. Furthermore, a new spot (TLC, ethyl acetate, R_f = 0.20), later shown to be $\Delta^{1'}$-mesembrenone 2, had appeared. After cooling to room temperature, the mixture was treated with diisopropylethylamine (136 µL, 0.80 mmols) and stirred for 3 h. The

solvent was removed, and hydrochloric acid added to the residue. The mixture was washed with ethyl acetate, basified with ammonium hydroxide solution and extracted with dichloromethane. The oil obtained (44 mg) after removal of solvent was chromatographed on silica gel yielding Δ'-mesembrenone (12 mg, 0.04 mmols, 10 %) as the only characterizable product. The data for this compound are reported after (d).

b. TLC survey undertaken for optimization of reaction conditions

Thiopyrrolidone 109 (20 mg, 0.0 mmols) and chloromethyl vinyl ketone (20 μL, 0.24 mmols) were mixed together in the particular solvent. In all cases, except for DMF and toluene, where the reactions were heated to 100 °C, the reactions were performed at reflux temperatures. The TLC's were examined at intervals for the disappearance of starting material (TLC, ethyl acetate, R_f = 0.83) and the appearance of Δ'-mesembrenone (R_f = 0.20). The results noted are those observed after h.

Incomplete reaction, no appearance of product: DMF, toluene, benzene.

Incomplete reaction, appearance of product: chloroform, ethyl acetate, THF and benzene in the presence of two equivalents of

Reaction complete, product present: nitromethane.

Thiopyrrolidone 109 (251 mg, 1.0 mmols) was dissolved in dry nitromethane (5 mL) containing a few milligrams of hydroquinone, under nitrogen, and chloromethyl vinyl ketone (174 μL, 2 mmols) was added. After heating under reflux for 12 h the mixture was cooled to room temperature and diisopropylethylamine (170 μL, 1 mmole) was added. The mixture was stirred overnight, the solvent was removed and the residue

chromatographed on silica gel eluting with ethyl acetate followed by acetone. Δ'-Mesembrenone (206 mg, 0.72 mmols) was obtained chromatographically pure in 72 % yield (TLC, acetone, R_f = 0.20).

d. The reaction was repeated as above, except for the omission of the diisopropylethylamine. A 46 % yield of impure Δ'-mesembrenone was obtained after elution from the column with copious amounts of acetone.

(+)-Δ'-Mesembrenone 2 was obtained as a solid mp 139 - 141 °C (lit 138 °C [122]) after distillation in a Kugelrohr apparatus at 210 °C, 0.5 mm Hg, followed by recrystallization from ethyl acetate.

IR (KBr)	420(w) 490(w) 530(w) 550(w) 615(w) 648(m)
	660(m) 685(w) 711(w) 740(w) 770(sh) 774(m)
	815(m) 839(m) 850(m) 864(w) 905(w) 925(w)
	951(w) 975(w) 1020(s,ArOMe) 1040(m) 1078(m)
	1098(m) 1125(m,sh) 1150(s) 1185(m) 1210(s)
	1215(s) 1230(s) 1260(s,br,ArOMe) 1278(s)
	1295(s) 1310(m) 1325(m) 1350(m) 1370(s)
	1414(s) 1460(s,br) 1515(s,br,C=C aromatic)
	1560(s,br,NC=CC=O) 1590(s) 1610(s,C=O)
	1670(m) 2880(m) 2950(m) 3000(m) 3025(w)
	3310(m) 3444(s,br)
IR ($CHCl_3$)	660(w) 850(w) 860(w) 920(w) 955(w)
	985(w) 1033(m,ArOMe) 1103(w) 1155(m)
	1187(w) 1250(s,ArOMe) 1295(w) 1310(w)
	1328(w) 1360(w) 1418(m) 1450(m) 1465(m,sh)
	1472(m) 1520(m) 1585(s,sh) 1595(s,NC=CC=O)
	2850(w) 2870(w) 2940(m) 3010(m) 3015(w,sh)

PMR (200 MHz)	1.96 - 2.46(m,6) 2.96(s,3,NCH_3) 3.25 - 3.42(m,2,NCH_2) 3.87(s,6,OCH_3) 5.18(s,1,CH) 6.72 - 6.84(m,3,aromatic)
Carbon-13 NMR (50.4 MHz)	32.69(q,NCH_3) 3.10(t) 35.97(t) 39.00(t) 52.51(s) 52.79(t,NCH_2) 55.87(q,OCH_3) 55.95(q,OCH_3) 93.45(d,=CH) 109.97(d) 110.82(d) 119.34(d) 133.60(s) 148.06(s) 148.89(s) 170.72(s,NC) 196.36(s,C=O) The assignments were made with the aid of an SFORD spectrum
UV	λ_{max} = 292, shifts to λ_{max} = 284 on addition of 11 M HCl.
MS	287(43,M^+) 259(40) 245(15) 244(70) 215(17) 77(18) 42(44) 28(100)
HRMS	287.15383 ($C_{17}H_{21}NO_3$ requires 287.15215)

C and H analysis: Inconsistent analyses were obtained.

The methiodide salt of (±)-Δ^1-mesembrenone 2 was prepared by treatment with an excess of methyl iodide at room temperature for 2 days, and recrystallized from ether - methanol, giving a solid mp 157 - 160 °C.

IR (KBR)	320(m) 465(w) 525(w) 575(w) 625(w) 640(w) 665(w) 700(w) 765(w) 775(w) 805(s) 820(m) 850(m) 950(w) 970(m) 1000(w) 1015(w,sh)

1035(s,ArOMe) 1075(w) 1090(w) 1100(w)
1115(w) 1150(s) 1185(m) 1205(s) 1230(m)
1255(s,ArOMe) 1285(s) 1298(m) 1310(m)
1330(w) 1340(w) 1350w) 1390(w) 1418(s)
1430(s) 1450(w,sh) 1460(s,sh) 1470(s)
1515(sh) 1520(s,C=C,Ar) 1575(s) 1645(s)
2840(w) 2940(w) 2950(w) 3000(w) 3020(w)
3450(w,br)

PMR (80 MHz) 2.20 - 2.82(m,6)
3.73 - 4.75, 3.91, 3.89 and 3.87(m and 3xs,
11,2xOCH_3,NCH_3 and NCH_2)
4.22(s,3,OCH_3)
6.50 - 6.90(m,4,=CH and aromatic)

C H and N analysis: C, 50.11; H, 5.58; N, 3.26. $C_{18}H_{24}NO_4I$
requires C, 50.36; H, 5.63; N, 3.26%.

4 Preparation of (-)-Δ^1-Mesembrenone from (-)-Mesembrine

Method of Jeffs and co-workers [120]. (-)-Mesembrine (89 mg, 0.31 mmols) was dissolved in acetone (8 mL) and diethylazodicarboxylate (98 µL, 0.62 mmols) was added. Conversion of mesembrine (TLC, acetone, R_f = 0.74) to Δ^1-mesembrenone (R_f = 0.20) was complete after heating under reflux for 2.5 h. After removal of solvent the residue was chromatographed on silica gel with hexane - acetone as eluant. (-)-Δ^1-Mesembrenone (87 mg, 0.30 mmols) was obtained as an oil in 95 % yield and was further purified by distillation at 210 °C, 0.5 mm Hg in a Kugelrohr apparatus. The product gave spectra identical to those obtained from the sulphide contraction.

5 Attempted Reduction of (±)-Δ^7-Mesembrenone to (±)-Mesembrine

a. A solution of Δ^7-mesembrenone (28 mg, 0.10 mmols) in dry THF at room temperature under nitrogen was treated with lithium aluminium hydride (3.8 mg, 0.10 mmols). After overnight stirring, water was added and the mixture was extracted with dichloromethane. The oil obtained after removal of solvent (26 mg) was shown by IR and TLC to be starting material.

b. The same reaction was carried out, except that 1.3 equivalents of lithium aluminium hydride was used, and the mixture was heated under reflux for 6 h. Again only starting material (12 mg) was recovered.

c. On substitution of diglyme for THF, and heating at 150 °C, with conditions as in (b) otherwise unchanged, again IR and TLC of the product indicated that no reduction had occurred, 15 mg of starting material being recovered.

d. On maintaining conditions as in (c) except that lithium borohydride was used in place of lithium aluminium hydride, again only starting material (20 mg) was recovered.

e. Δ^7-Mesembrenone (28 mg, 0.10 mmols) was dissolved in methanol and acidified to a pH of 3 with hydrochloric acid. Sodium cyanoborohydride (13 mg, 0.2 mmols) was added, and the mixture was stirred at room temperature for 2 days. No reduction occurred.

f. A mixture of Δ^7-mesembrenone (20 mg, 0.07 mmols) and formic acid (100 µL, 2.7 mmols) was heated at 50 °C for 2 h. A

solution of ammonium hydroxide was added, and the aqueous phase was extracted with dichloromethane. Removal of the solvent gave back 20 mg of starting material.

g. Potassium formate (56 mg, 0.65 mmols) and formic acid (50 µL, 1.44 mmols) were added to Δ^7-mesembrenone (20 mg, 0.07 mmols) and the mixture was heated at 150 °C for 15 h. The resulting brown solid was partitioned between dichloromethane and ammonium hydroxide solution. The product obtained (14 mg) after removal of solvent from the organic phase was shown by TLC to be starting material.

6 Preparation of 1-benzyl- -(3,4-dimethoxy phenyl)-1,2,3,3a,4,5-hexahydroindol —6-one 167

Thiopyrrolidone 140 (982 mg, 3.[illegible] mmols) was dissolved in dry nitromethane (10 mL) under nitrogen, containing a few milligrams of hydroquinone, and chloromethyl vinyl ketone (522 µL, 6.0 mmols) was added. After heating under reflux for 8 h, the mixture was cooled to room temperature, and diisopropylethylamine (510 µL, 3.0 mols) was added. The mixture was stirred overnight, the solvent was removed and the residue chromatographed on silica gel eluting with hexane - acetone. The bicyclic compound 167 (400 mg, 1.1 mmols, 37 %) was obtained as the only identifiable product (TLC, acetone, R_f = 0.40). Further purification, achieved by distillation at 210 °C, 0.0001 mm Hg, in a Kugelrohr apparatus, gave the product as a brown solid foam.

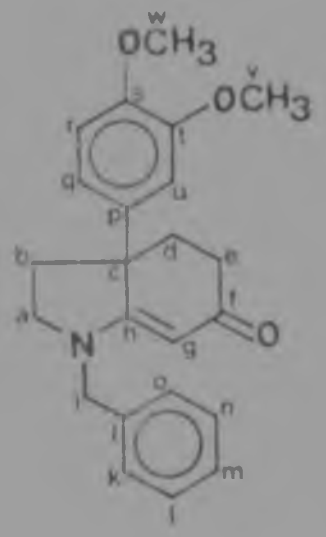
IR ($CHCl_3$)	590(w) 610(w) 660(w) 700(w) 840(w)
	845(w) 855(w) 920(w) 975(w) 990(w) 1010(w)
	1028(s,ArOMe) 1080(w) 1115(w) 1150(s)
	1180(m) 1245(s) 1260(s,ArOMe) 1290(m)

1310(w) 1325(m) 1350(m) 1370(w) 1410(w,sh)
1430(m) 1445(m) 1455(m) 1465(m) 1510(s,C=C
Ar) 1540(m,sh) 1585(s,NC=CC=O) 1700(w)
2840(w) 2870(w) 2910(w,sh) 2940(m) 3000(m)
3030(w,sh) 3050(w,sh)

PMR (60 MHz)

1.95 - 2.08(m,6)
3.17 - 3.49(m,2,NCH_2)
3.70 and 3.85(2xs,6,OCH_3)
4.45(s,2,$PhCH_2$)
5.40(s,1,CH)
6.76(s,3,aromatic)
7.30(s,5,aromatic)

Carbon-13 NMR
(126 MHz)



a or i, 51.17 or 50.18; b, d, or e, 39.03, 36.24 or 33.11; c, 52.72; f, 196.6; g, 94.04; h, 170.20; j, 133.43; k and o, l and n, or m, 128.90, 127.97 or 127.86; p, 135.50; q, 119.26; r or u, 110.37 or 111.17; s or t, 148.82 or 148.01; v and w, 55.89.
The assignments were made with the aid of a DEPT experiment

MS 364(16) 363(60,M^+) 335(45,M-CH_2CH_2)
320(31) 307(11) 244(38) 91(100) 65(19)

HRMS 363.18349 ($C_{23}H_{25}NO_4$ requires 363.18343)

7 Preparation of 1-benzyl-3a-(3,4-dimethoxyphenyl)-1,2,3,3a,4,5,7,7a-octahydroindol-6-one 104

The reduction was carried out according to the procedure described by Takano for Δ^{1}-mesembrenone [122]. Compound 167 (80 mg, 0.22 mmols) was dissolved in dry THF (3 mL) under argon, and cooled to -78 °C. Dry ammonia (30 mL) was added, followed by lithium (3.5 mg, 0.50 mmols weighed under argon). The mixture was stirred at -78 °C for 1 h, then quenched with ammonium chloride. The solvents were removed and water was added to the residue. The mixture was extracted with dichloromethane, and the solvent removed. Chromatography on silica gel with hexane - ethyl acetate as eluant gave recovered starting material (17 mg, 0.05 mmols) (TLC, acetone, R_f = 0.40) together with the reduced product 104 (50 mg, 0.13 mmols) (TLC, chloroform - acetone, 21:1, R_f = 0.73) in 76 % yield (from consumed starting material) as a pale brown oil, the IR and PMR spectra of which were identical to those obtained by Speckamp [31].

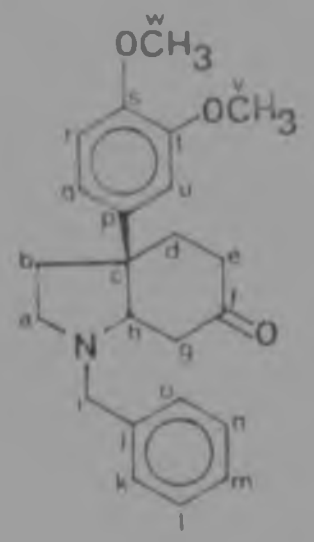
IR ($CHCl_3$) 645(w) 695(w) 845(w) 855(w) 910(w)
1028(s,ArOMe) 1075(w) 1110(w) 1145(m)
1175(w) 1250(s,ArOMe) 1325(w) 1350(w)
1375(w) 1410(m) 1440(m,sh) 1450(m) 1460(m)
1495(m,sh) 1510(m,C=C,Ar) 1590(w,C=C,Ar)
1605(w,C=C,Ar) 1718(s,C=O) 2800(w) 2830(w)

2870(w) 2910(m) 2940(m) 2960(m) 3000(m)
3020(w,sh)

PMR (500 MHz)

1.96 - 2.02(m,2)
2.06 - 2.11(m,1)
2.16 - 2.29(m,4)
2.47 - 2.53(m,1)
2.63 - 2.73(m,2)
2.91 - 2.96(m,1)
3.13 and 4.07(2xd,2,J = 12.8 Hz, NCH_AH_BPh)
3.27(t,1,J = 3.4 Hz,CH)
3.86 and 3.85 (2xs,6,OCH_3)
6.83(d,1,J = 8.4 Hz,aromatic)
6.88(d,1,J = 2.3 Hz,aromatic)
6.92 and 6.93(2xd,1,J = 2.3 Hz and 8.4 Hz,aromatic)
7.19 - 7.29(m,5,aromatic)

Carbon-13 NMR
(126 MHz)



a, 51.67; b,d,e or g, 40.65, 38.64, 36.23, or 34.81; c, 47.19; f, 211.2; h, 68.18; i, 57.40; j, 138.75; k and o, l and n or

m, 128.78, 128.17 or 126.92; p, 140.30; q, 117.85; r or u, 110.08 or 111.13; s or t, 149.02 or 147.51; v or w 55.90 or 56.02 The assignments were made with the aid of a DEPT experiment

MS 365(86,M^+) 364(38) 296(63) 295(90) 204(40) 173(42) 172(98) 91(100)

HRMS 365.19841 ($C_{23}H_{27}NO_4$ requires 365.19908)

m, 128.78, 128.17 or 126.92; p, 140.30; q, 117.85; r or u, 110.08 or 111.13; s or t, 147.02 or 147.51; v or w 55.90 or 56.02 The assignments were made with the aid of a DEPT experiment

MS 365(86,M^+) 364(38) 296(63) 295(90) 204(40) 173(42) 172(96) 91(100)

HRMS 366.19841 ($C_{23}H_{27}NO_3$ requires 365.19908)

EXPERIMENTAL PROCEDURES RELATING TO CHAPTER 6

1 Preparation of N-Benzyl-3-ethyl-2-thiopiperidone 176

1.1 Attempted Preparation Via the Dianion of 2-Piperidone

a. A solution of 2-piperidone (499 mg, 5.0 mmols) in dry THF (50 mL) under nitrogen at -84 °C was treated with n-butyl-lithium in hexane (11.0 mmols). After 10 min, ethyl iodide (403 µL, 5.0 mmols) was added, followed by benzyl bromide (598 µL, 5.0 mmols) after 1 h. The mixture was warmed to room temperature over 4 h, the THF was then removed, and ammonium chloride solution was added to the residue. The mixure was extracted with dichloromethane, and the solvent removed. An oil was obtained (1.13 g) which was shown by PMR to consist mainly of N-benzyl-2-piperidone 178, contaminated with unreacted benzyl bromide.

b. The reaction was repeated as above, except that diethyl sulphate was used in place of ethyl iodide. The PMR spectrum showed no evidence of ethyl groups.

c. On maintaining conditions as in (a) except that ethyl tosylate was used in place of ethyl iodide, an oil was obtained (1.31 g), which was shown by PMR to be a mixture of ethylated and benzylated products. A small amount of the desired product 177 was present, however, as indicated by the MS, which showed a molecular ion at m/e = 217.

1.2 Preparation From 2-Piperidone

A solution of 2-piperidone (2.98 g, 30.0 mmols) in dry THF (100 mL) at 0 °C under nitrogen was treated with n-butyllithium in hexane (30.0 mmols), followed by benzyl bromide (3.6 mL, 30.0 mmols) after 10 min. The mixture was warmed to room temperature and stirred overnight, and the THF was then removed. Ammonium chloride solution was added to the residue, and the mixture was extracted with dichloromethane. Removal of solvent gave N-benzyl-2-piperidone 176, which was not purified further [135].

IR (film) 700(m,CH,Ar) 705(m,CH,Ar) 1450(m,C=C,Ar) 1490(s,C=C,Ar) 1600(m,sh,C=C,Ar) 1640(s,C=O)

PMR (60 MHz) 1.68 - 1.93(m,4) 2.30 - 2.60(m,2,CO) 3.07 - 3.32(m,2,NCH_2) 4.60(s,2,$PhCH_2$) 7.15 - 7.43(m,5,aromatic)

n-Butyllithium in hexane (10.0 mmols) was added to diisopropylamine (1.4 mL, 10.0 mmols) in dry THF under nitrogen at -78 °C. After 15 min, 1-benzyl-2-piperidone 178 (1.7 g, 9.1 mmols) was added as a solution in THF. After a further 10 min, ethyl iodide (0.9 mL, 9.0 mmols) was added. The mixture was warmed to room temperature, the solvent was removed and saturated ammonium chloride solution added to the residue which was then extracted with dichloromethane. 1-Benzyl-3-ethyl-2-piperidone 177, was obtained and was not purified further and was used directly in the following reaction.

PMR (60 MHz) 0.95(t,3,J = 7 Hz,CH_3)

1.2 Preparation from 2-Piperidone

A solution of 2-piperidone (2.98 g, 30.0 mmols) in dry THF (100 mL) at 0 °C under nitrogen was treated with n-butyllithium in hexane (30.0 mmols), followed by benzyl bromide (3.6 mL, 30.0 mmols) after 10 min. The mixture was warmed to room temperature and stirred overnight, and the THF was then removed. Ammonium chloride solution was added to the residue, and the mixture was extracted with dichloromethane. Removal of solvent gave N-benzyl-2-piperidone 178, which was not purified further [135].

IR (film) 700(m,CH,Ar) 705(m,CH,Ar) 1450(m,C=C,Ar)
1490(s,C=C,Ar) 1600(m,sh,C=C,Ar)
1640(s,C=O)

PMR (60 MHz) 1.68 - 1.93(m,4)
2.00 - 2.60(m,2,CCH_2)
3.00 - 3.32(m,2,NCH_2)
4.60(s,2,$PhCH_2$)
7.15 - 7.43(m,5,aromatic)

n-Butyllithium in hexane (10.0 mmols) was added to diisopropylamine (1.4 mL, 10.0 mmols) in dry THF under nitrogen at -78 °C. After 15 min, 1-benzyl-2-piperidone 178 (1.7 g, 9.1 mmols) was added as a solution in THF. After a further 10 min, ethyl iodide (0.9 mL, 9.0 mmols) was added. The mixture was warmed to room temperature, the solvent was removed and saturated ammonium chloride solution added to the residue which was then extracted with dichloromethane. 1-Benzyl-3-ethyl-2-piperidone 177, was obtained and was not purified further and was used directly in the following reaction.

PMR (60 MHz) 0.95(t,3,J = 7 Hz,CH_3)

1.17 - 2.55(m,7)

3.06 - 3.33(m,2,NCH_2)

4.55(s,2.$PhCH_2$)

7.10 - 7.36(m,5,aromatic)

1-Benzyl-3-ethyl-2-piperidone was dissolved in dry THF, and irradiation with ultrasound was begun. Phosphorus pentasulphide (2.0 g, 9.0 mmols) was added to the stirred solution in portions over a few hours. After 16 h, the solution was filtered, the solvent was removed, and the residue chromatographed on silica gel, eluting with dichloromethane. The 1-benzyl-3-ethyl-2-thiopiperidone 176 (1.93 g, 8.3 mmols) was obtained in 91 % overall yield as an oil. After distillation at 165 °C, 0.5 mm Hg in a Kugelrohr apparatus, the product crystallized, and was recrystallized from ethyl acetate, giving a solid mp 45 - 46 °C.

IR ($CHCl_3$)	660(w) 695(w) 830(w) 890(w) 940(w)
	9[illegible](w) 1030(m) 1040(w) 1075(s) 1115(w)
	1135(w) 1170(s) 1280(w) 1335(s) 1350(s)
	1380(w) 1450(s,N[illegible]=S) 1500(s,C=C,Ar)
	1610(w,C=C [illegible] 2880(m) 2960(s)
PMR (60 MHz)	0.67 - 1.95 and 0.95(m and t,9,J = 3 Hz)
	2.62 - 3.10(m,1,CH)
	3.10 - 3.50(m,2,NCH_2)
	5.15 and 5.55(2xd,2,J = 13 Hz,
	NCH_AH_BPh)
	7.3[illegible](s,5,aromatic)
MS	233(30,M^+) 205(25) 204(11) 172(33)
	118(11) 91(>100,$PhCH_2$) 65(24) 55(23)

HRMS 233.12388 ($C_{14}H_{19}NS$ requires 233.12381)

C H and N Analysis C, 72.54; H, 8.48; N, 6.14. $C_{14}H_{19}NS$ requires: C, 72.05; H, 8.21; N, 6.00%.

1.3 Attempted Preparation via N-Benzyl-2-thiopiperidone

A solution of N-benzyl-2-piperidone (572 mg, 3.0 mmols) (prepared as described in 1.2) in dry THF (30 mL) was treated with phosphorus pentasulphide (670 mg, 3.0 mmols) under ultrasonic irradiation, with stirring for 30 min. A further portion of phosphorus pentasulphide (670 mg, 3.0 mmols) was then added, and irradiation was continued for 1 h. The mixture was then filtered, and solvent removed from the filtrate. A filtration column of the residue gave N-benzyl-2-thiopiperidone (313 mg, 1.5 mmols, 50 %) which was not purified further.

PMR (60 MHz) 1.60 - 1.98(m,4)
2.92 - 3.50(m,4,NCH_2 and CCH_2)
5.33(s,2,$PhCH_2$)
7.19 - 7.43(m,5,aromatic)

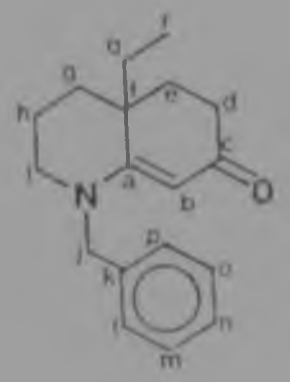
A solution of N-benzyl-2-thiopiperidone (296 mg, 1.4 mmols) in dry THF at 0 °C under nitrogen was treated with n-butyllithium in hexane (1.6 mmols) for 10 min. The mixture was then cooled to -78 °C and ethyl iodide (139 µL, 1.7 mmols) was added. The reaction solution was slowly warmed to room temperature, the solvent was then removed, and ammonium chloride solution was added to the residue. The aqueous phase was extracted with dichloromethane, and the solvent removed, giving an oil (382 mg) which was a mixture, and could not be separated or characterized.

2 Sulphide Contractions of N-Benzyl-3-ethyl-2-thiopiperidone 176 With Halomethyl vinyl ketones

a. Thiopiperidone 176 (242 mg, 1.0 mmols) was dissolved in dry nitromethane (10 mL), containing a few milligrams of hydroquinone, under nitrogen, and chloromethyl vinyl ketone (180 µL, 2.1 mmols) was added. After a 10 h reflux the mixture was cooled to room temperature and diisopropylethylamine (177 µL, 1.0 mmols) was added. The mixture was stirred overnight, the solvent was removed and the residue was chromatographed on silica gel, eluting with petroleum ether - acetone. 2-Benzyl-6-ethyl-2-azabicyclo[4.4.0]dec-1(10)-en-9-one 177 was obtained in 40 % yield (TLC, acetone, R_f = 0.30). Further purification was accomplished by distillation at 195 °C, 0.1 mm Hg, in a Kugelrohr apparatus.

IR ($CHCl_3$)	655(w) 690(w) 805(w) 865(w) 905(w) 955(w) 1028(w) 1075(w) 1130(w,br) 1150(w) 1190(s) 1235(s) 1275(s) 1325(s) 1360(m) 1375(m) 1435(m) 1450(m) 1460(m,sh) 1490(w,sh) 1540(s,NC=CC=O) 1585(s,NC=CC=O) 2800(m) 2950(s)
PMR (60 MHz)	0.85(t,3,J = 8 Hz,CH_3) 1.10 - 2.15(m,8) 2.15 - 2.55(m,2,$COCH_2$) 3.25 and 3.37(m,2,NCH_2) 4.17 and 4.50(2xd,2,J = 14 Hz,NCH_AH_BPh) 5.18(s,1,C[illegible] 7.00 - 7.49(m,5,aromatic)

Carbon-13 NMR
(126 MHz)



a, 171.69; b, 98.38; c, 196.25; d, e, g or h, 32.69, 31.94, 29.02 or 26.89; f, 36.81; i, 49.52; j, 54.95; k, 135.66; l and p, m and o, or n, 128.72, 127.36 or 126.72; q, 18.46; r, 7.91.
The assignments were made with the aid of a DEPT experiment

MS 269(30,M^+) 241(90,M-CH_2CH_2) 240(40) 226(22) 212(32) 198(20) 91(100,$PhCH_2$) 65(37)

HRMS 269.17700 ($C_{18}H_{23}NO$ requires 269.17795)

b. Thiopiperidone 176 (56 mg, 0.24 mmol's) was dissolved in dry benzene (0.2 mL) containing a few milligrams of hydroquinone, under nitrogen and chloromethyl vinyl ketone (42 µL, 0.48 mmols) was added. After stirring the mixture at room temperature overnight, TLC indicated that very little reaction had occurred.

c. The reaction was repeated as in (a), except that DMF was used in place of THF, and the reaction was heated at 100 °C for 12 h before the addition of b[illegible] work-up by column chromatography gave 177 in 22 % yield.

d. Sodium iodide (151 mg, 1.0 mmols) was added to a solution

of chloromethyl vinyl ketone (87 µL, 1.0 mmols) in acetonitrile (2 mL), resulting in precipitation of sodium chloride. After 1 h, the mixture was added to a solution of thiopiperidone 176 (114 mg, 0.5 mols) in acetonitrile (1 mL). After stirring the mixture at room temperature for 1 h, TLC indicated complete disappearance of starting material. Diisopropylethylamine (85 µL, 0.5 mmols) was added, and the mixture was stirred overnight. Work-up as in (a) gave an intractable dark red oil (37 mg).

e. Thiopiperidone 176 (115 mg, 0.5 mmols) was treated with chloromethyl vinyl ketone (218 µL, 2.5 mmols) at 100 °C for 10 h. The mixture was then cooled to room temperature, dissolved in nitromethane and treated as in (a). The product 177 was obtained in 10 % yield.

f. The salt formation was performed as in (e). After cooling to room temperature, acetonitrile was added to the mixture, which was then treated with a solution of triphenylphosphine (one equivalent) and diisopropylethylamine (one equivalent) in acetonitrile. The mixture was stirred at room temperature for 2 days, then worked-up as before. Compound 177 was obained in 17 % yield.

3 Reduction of 2-Benzyl-6-ethyl-2-azabicyclo[4.4.0]dec-1(10)-en-3-one 177

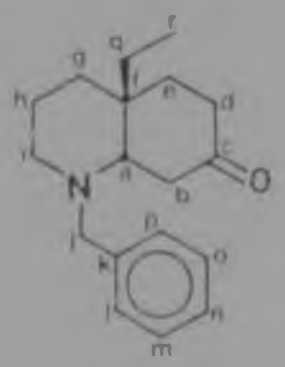
Compound 177 (77. mg, 0.29 mmols) was dissolved in dry THF (2 mL) under argon, and cooled to -78 °C. Dry ammonia (30 mL) was added, followed by lithium (4. mg, 0.69 mmols). The mixture was stirred at -78 °C for 1 h, then quenched with ammonium chloride. The solvents were removed, and water was added to the residue. The mixture was extracted with dichloromethane,

and the solvent was removed. Chromatography on silica gel with hexane - acetone as eluant gave 14.1 mg (0.05 mmols) of recovered starting material (TLC, acetone, R_f = 0.33) together with 2-benzyl-6-ethyl-2-azabicyclo[4.4.0]decan-9-one 175 (36.5 mg, 0.13 mmols) in 54 % yield (from consumed starting material) as a chromatographically pure pale brown oil (TLC, hexane - acetone, 1:1, R_f = 0.82)

IR ($CHCl_3$)
710(w) 850(w) 900(w) 920(w) 960(w)
975(w) 1000(w) 1020(w) 1035(w) 1060(w)
1083(w) 1105(m) 1140(m) 1155(m) 1170(m)
1260(m) 1290(m) 1335(m) 1365(m) 1385(m)
1420(m) 1455(m) 1465(m) 1500(m)
1610(w,C=C,Ar) 1710(s,C=O) 2810(m) 2870(m)
2890(m) 2910(m) 2950(s) 2980(s) 3020(m)
3040(w,sh) 3080(w) 3100(w)

PMR (60 MHz)
0.83(t,3,J = 6 Hz,CH_3)
1.05 - 2.95 (m,15)
3.00 and 3.87(2xd,2,J = 14 Hz,NCH_AH_BPh)
7.27(s,5,aromatic)

Carbon-13 NMR (126 MHz)



a, 68.81; or d, 42.44 or 37.13; c, 210.61; e, g or h, 21.41, 34.05 or 32.32; f, 36.22; i or j, 54.52 or 57.32; k, 140.33; l and p, m and o, or n; 128.36,

and the solvent was removed. Chromatography on silica gel with hexane - acetone as eluant gave 14.1 mg (0.05 mmols) of recovered starting material (TLC, acetone, R_f = 0.33) together with 2-benzyl-6-ethyl-2-azabicyclo[4.4.0]decan-9-one 175 (36.5 mg, 0.13 mmols) in 54 % yield (from consumed starting material) as a chromatographically pure pale brown oil (TLC, hexane - acetone, 1:1, R_f = 0.82)

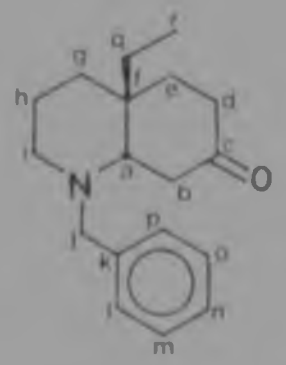
IR ($CHCl_3$)

710(w) 850(w) 900(w) 920(w) 960(w)
975(w) 1000(w) 1020(w) 1035(w) 1060(w)
1083(w) 1105(m) 1140(m) 1155(m) 1170(m)
1260(m) 1290(m) 1335(m) 1365(m) 1385(m)
1420(m) 1455(m) 1465(m) 1500(m)
1610(w,C=C,Ar) 1710(s,C=O) 2810(m) 2870(m)
2890(m) 2910(m) 2950(s) 2980(s) 3020(m)
3040(w,sh) 3080(w) 3100(w)

PMR (60 MHz)

0.83(t,3,J = 6 Hz,CH_3)
1.0 - 2.95 (m,15)
3.00 and 3.87(2xd,2,J = 14 Hz,NCH_AH_BPh)
7.27(s,5,aromatic)

Carbon-13 NMR (126 MHz)



a, 68.81; b or d, 42.44 or 37.13; c, 210.61; e, g or h, 21.41, 34.05 or 32.32; f, 36.22, i or j, 54.52 or 57.32; k, 140.33; l and p, m and o, or n; 128.36,

128.20 or 126.65; q, 17.82; r, 6.89.
The assignments were made with the aid of a DEPT experiment

MS 271(12,M^+) 242(12) 201(19) 200(29)
186(23) 91(100,$PhCH_2$) 65(14) 55(15)

HRMS 271.19349 ($C_{19}H_{25}NO$ requires 271.19360)

EXPERIMENTAL PROCEDURES RELATING TO APPENDIX

1 Preparation of α-bromo-N,N-dimethylacetamide

A cooled solution of dimethylamine (7 g, 155 mmols) in dry ether (50 mL) was added to a solution of bromoacetyl bromide (5 mL, 58 mmols) in dry ether (100 mL) at 0 °C. The mixture was stirred and warmed to room temperature over 3 h, and then filtered to remove the dimethylamine hydrochloride which had precipitated. The filtrate was washed with sodium bicarbonate solution, and the solvent was removed. α-Bromo-N,N-dimethylacetamide [139] (3.5 g, 22 mmols, 37 %) was obtained and was distilled at 63 °C, 0.5 mm Hg.

IR (film)	1640(s,C=O)
PMR (60 MHz)	3.00 and 3.15(2xs,6,NCH_3)
	3.95(s,2,CH_2)

2 Preparation of N,N-dimethyl-2-(N-methyl-2-pyrrolidinylidene)acetamide 184

a. α-Bromo-N,N-dimethylacetamide (129 μL, 1.2 mmols) was added to N-methyl-2-thiopyrrolidone (117 mg, 1.0 mmols). The mixture was allowed to stir at room temperature overnight, then dissolved in dry acetonitrile (30 mL). Triphenylphosphine (266 mg, 1.0 mmols) was added, followed by triethylamine (166 μL, 1.2 mmols). After stirring for a further 4 h, the acetonitrile was removed, and the residue partitioned between hydrochloric acid (5 M) and dichloromethane. Removal of solvent gave an oil (73 mg), which was chromatographed on silica gel, eluting with ethyl acetate - methanol. A compound probably bis(N,N-di-

EXPERIMENTAL PROCEDURES RELATING TO APPENDIX

1 Preparation of α-bromo-N,N-dimethylacetamide

A cooled solution of dimethylamine (7 g, 155 mmols) in dry ether (50 mL) was added to a solution of bromoacetyl bromide (5 mL, 58 mmols) in dry ether (100 mL) at 0 °C. The mixture was stirred and warmed to room temperature over 3 h, and then filtered to remove the dimethylamine hydrochloride which had precipitated. The filtrate was washed with sodium bicarbonate solution, and the solvent was removed. α-bromo-N,N-dimethylacetamide [139] (3.5 g, 22 mmols, 37 %) was obtained and was distilled at 63 °C, 0.5 mm Hg.

IR (film)	1640(s,C=O)
PMR (60 MHz)	3.00 and 3.15(2xs,6,NCH_3)
	3.95(s,2,CH_2)

2 Preparation of N,N-dimethyl-2-(N-methyl-2-pyrrolidinylidene)acetamide 184

a. α-Bromo-N,N-dimethylacetamide (129 µL, 1.2 mmols) was added to N-methyl-2-thiopyrrolidone (117 mg, 1.0 mmols). The mixture was allowed to stir at room temperature overnight, then dissolved in dry acetonitrile (30 mL). Triphenylphosphine (266 mg, 1.0 mmol.) was added, followed by triethylamine (166 µL, 1.2 mmols). After stirring for a further 4 h, the acetonitrile was removed, and the residue partitioned between hydrochloric acid (5 M) and dichloromethane. Removal of solvent gave an oil (73 mg), which was chromatographed on silica gel, eluting with ethyl acetate - methanol. A compound probably bis(N,N-di-

methylacetamide)disulphide 185 was obtained (17.4 mg, 0.09 mmols, 18 %) (TLC, ethyl acetate - methanol, 19:1, R_f = 0.13) (spectra of this compound are reported after (b)).

b. The reaction was repeated as in (a) except that DBU was substituted for triethylamine. Bis(N,N-dimethylacetamide)disulphide 185 was obtained, quantitatively, as the only identifiable product.

IR ($CHCl_3$)	1640(s,C=O)
PMR (60 MHz)	2.95 and 3.05(2xs,12,CH_3)
	3.50(s,4,CH_2)
MS	236(12,M^+) 203(46) 158(100) 131(39)
	118(46) 86(100) 85(68) 71(100)

c. The salt formation was carried out under the same conditions as in (a). The salt was then dissolved in t-butyl alcohol, and triphenylphosphine was added, followed by potassium t-butoxide. After stirring at room temperature overnight, the reaction was worked up as before. N,N-Dimethyl-2-(N-methyl-2-pyrrolidinylidene)acetamide 184 (1.8 g, 10 mmols, 84 %) was obtained. Further purification was accomplished by distillation at 195 °C, 0.5 mm Hg, in a Kugelrohr apparatus [149].

IR ($CHCl_3$)	635(w) 660(w) 840(w) 858(w) 895(w)
	915(w) 940(w) 970(w) 1015(w) 1035(w)
	1063(w) 1110(m) 1145(s) 1255(m) 1300(s)
	1345(m) 1[illegible](m) 1420(s) 1455(m) 1495(m)
	1560(s,br) 1630(s,br) 2880(m,sh) 2950(m,sh)
	2990(s)

PMR (60 MHz)	1.65 - 2.28(m,6,$CH_2CH_2CH_2$)
	2.91(s,3,NCH_3)
	3.10(s,6,$CONCH_3$)
	3.15 - 3.36(m,4)
	4.75(s,1,=CH)
Carbon-13 NMR	20.90($CH_2CH_2CH_2$) 31.81(=CCH_2) 32.83(NCH_3)
(126 MHz)	35.33($CONCH_3$) 37.34($CONCH_3$) 53.65(NCH_2)
	77.64(=CH) 163.07(C=O) 169.62(NC=)
	The assignments were made with the aid of a DEPT experiment
UV	284(26000) peak vanishes on addition of 11 M HCl.
MS	168(15,M^+) 149(8) 124(100) 94(20)
	81(10) 72(38) 68(25) 55(38)
HRMS	[illegible] $C_9H_{16}N_2O$ requires 168.126211

3 Methylation of Vinylogous Urethane 100

Methyl iodide (excess) was added to a solution of vinylogous urethane (83 mg, 0.49 mmols) in dry acetonitrile (2 mL). The mixture was heated at 50 °C for 14 h. The solvent was removed and the residue partitioned between ammonia solution and dichloromethane. The organic phase was separated and the solvent removed, giving an oil (85 mg), which consisted of a mixture of starting material (TLC, benzene - methanol, 10:1, R_f = 0.22) together with ethyl (1-methyl-2-pyrrolidinylidene)propanoate [60] (R_f = 0.09). A PMR spectrum of the mixture showed that the methylation was approximately 80 % complete.

4 Methylation of Vinylogous Cyanamide 183

The conditions used were as for the vinylogous urethane, except that the vinylogous cyanamide 183 (prepared as described by J P Michael [60]) (84 mg, 0.70 mmols) was used and the mixture was heated at 50 °C for 50 h. An oil (69 mg) was obtained which was shown by PMR to be a mixture of approximately 60 % starting meterial, and 40 % methylated product, as a mixture of cis and trans isomers, by comparison with authentic spectra of these compounds [92].

5 Methylation of Vinylogous Urea 184

The conditions used were used for as in (3) above, except that the vinylogous urethane was substituted by vinylogous urea 184 (99 mg, 0.6 mmols). After aqueous work-up, an oil was obtained (76 mg, 0.42 mmols, 70 %), which was distilled at 135 °C, 0.5 mm Hg in a Kugelrohr apparatus. The product was characterized as a mixture of geometric isomers of N,N-dimethyl-2-(N-methyl-2-pyrrolidinylidene)propionamide 187 in a ratio of about 2:1. The isomeric mixture could not be readily separated by TLC (acetone - methanol, 10:1, R_f = 0.34)

IR (film)	740(s) 1590(s) 1625(s)
PMR (60 MHz)	1.20 - 2.20(m and s,5,s from CH_3)
	2.19 - 2.75(m and s, 4.5, s from NCH_3,
	m from $=CCH_2$ of cis isomer)
	2.99(s,6,$CON(CH_3)_2$)
	3.02 - 3.50(m,2.5,NCH_2 and $=CCH_2$ of
	trans isomer).
	Integration figures are all approximate

MS 182(7,M^+) 138(74) 110(31) 108(39)
82(20) 72(34) 68(29)

HRMS 182.14192 ($C_{10}H_{14}N_2O$ requires 182.14191)

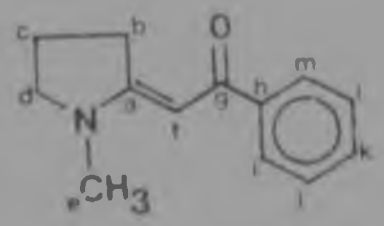
6 1-Methyl-2-cyanomethylenepyrrolidine 183

A sample of 183 prepared according to the method of J P Michael [60] gave the following carbon-13 NMR (20 MHz):

20.7(t,$CH_2CH_2CH_2$) 32.5(t,CCH_2) 32.9(q,NCH_3)
53.2(d,=CH) 55.5(t,NCH_2) 122.8(s,C≡N)
The absorptions were assigned with the aid of an SFORD spectrum

7 1-Methyl-2-benzoylmethylenepyrrolidine 191

A sample of compound 191 prepared by J P Michael [60] gave the following carbon-13 NMR (20 MHz):



a, 167.3; d or e, 33.4 or 38.1; c, 20.5; d, 54.3; f, 85.9; g, 187.1; h, 141.8; i and m, j and l, or k, 126.9, 127.2 or 129.9

8 1-Methyl-2-nitromethylenepyrrolidine 192

A sample of 192 prepared according to the method of Hart and co-workers [140] gave the following spectra:

IR (KBr)	1315(s) 1355(s) 1390(s,sh) 1410(s) 1485(s) 1540(s) 1570(s,br) 3100(s)
UV	354(12000). Peak intensity decreases slightly on addition of 11 M HCl.

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