SYNTHESIS OF SOME BENZOXAZA AND BENZODIOXAZA HETEROCYCLES: USE OF THE MEISENHEIMER REARRANGEMENT ROUTE TO FUSED MEDIUM-RING SYSTEMS

by

I.W.K. GUNAWARDANA, B.Sc. (SRI LANKA)

Submitted in fulfilment of the requirements for the degree of Master of Science

UNIVERSITY OF TASMANIA

HOBART

NOVEMBER, 1982.

To my husband

This thesis contains no material which has been accepted for the award of any other degree or diploma in any University, nor, to the best of my knowledge does it contain any copy or paraphrase of material previously published or written by another person except where due reference is made in the text of the thesis.

Gunawardana

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ABSTRACT

The aim of this work was to prepare examples of benzodioxazocine and benzodioxazonine ring systems by the Meisenheimer rearrangement of the *N*-oxides of related benzoxaza systems.

The 1,4-benzoxazepine and 1,5-benzoxazocine derivatives required as starting materials were prepared by two different ring construction methods, viz. the Bischler-Napieralski cyclization and a C-N type condensation. For example, 8-methoxy-5-phenyl-2,3-dihydro-1,4-benzoxazepine was obtained by the Bischler-Napieralski cyclization of an amide precursor. Three other 1,4-benzoxazepine derivatives and 9-methoxy-6-phenyl-3,4-dihydro-2*H*-1,5-benzoxazocine were similarly prepared (Chapters 2 and 3).

A C-N type ring construction method was employed to prepare 5-phenyl-2,3-dihydro-1,4-benzoxazepine and its 7-chloro analogue. In these cases the precursors were amino-ketones.

All these cyclic imines were then converted to the corresponding *N*-methyl amines by quaternization and reduction. These amines were converted to their *N*-oxides for use in the Meisenheimer rearrangement.

The Meisenheimer rearrangement of 1,4-benzoxazepine-*N*-oxides proceeded smoothly giving rise to the corresponding 1,5,4-benzodioxazocine derivatives in high yields. For example, 9-methoxy-4-methyl-6-phenyl-3,4-dihydro-2*H*,6*H*-1,5,4-benzodioxazocine was prepared from 8-methoxy-4-methyl-5-phenyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-*N*-oxide. Five analogous 1,5,4-benzodioxazocines were similarly prepared (Chapter 4).

However, when the 1,5-benzoxazocine-*N*-oxide derivative was subjected to this rearrangement at about 10°, only decomposition products, including hydroxylamines, were obtained. At lower temperatures (-5°-0°) the Meisenheimer rearrangement of this *N*-oxide gave the expected ring enlarged product, 10-methoxy-5-methyl-7-phenyl-2,3,4,5-tetrahydro-7*H*-

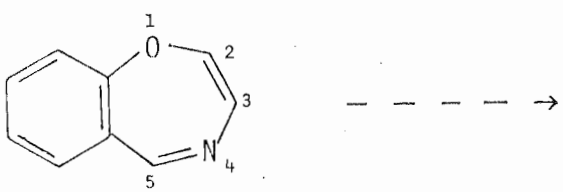
1,6,5-benzodioxazonine in 50% yield. The 1,5,4-benzodioxazocine and 1,6,5-benzodioxazonine ring systems have not been described previously.

CHAPTER 1

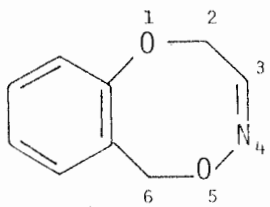
General Introduction

The major aim of the work described in this thesis was the preparation of derivatives of seven- and eight-membered benzoxaza ring systems by ring construction methods, and their conversion by the Meisenheimer rearrangement to new, ring-enlarged, eight- and nine-membered benzodioxaza systems.

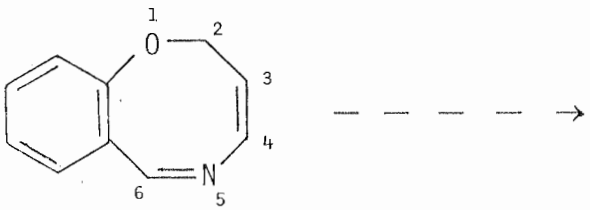
The specific systems prepared were 1,4-benzoxazepines and 2*H*-1,5-benzoxazocines, which were converted to corresponding derivatives of 2*H*, 6*H*-1,5,4-benzodioxazocine and 7*H*-1,6,5-benzodioxazonine ring systems (Figure 1).



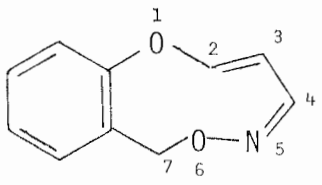
1,4-benzoxazepine



2*H*, 6*H*-1,5,4-benzodioxazocines



2*H*-1,5-benzoxazocine



7*H*-1,6,5-benzodioxazonine

Figure 1

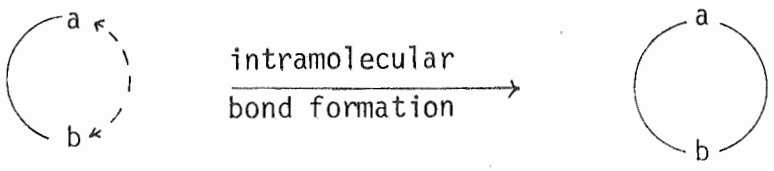
Approaches that can be made to the synthesis of cyclic compounds fall into three major groups[1] viz.

a) ring construction

b) ring destruction or

c) ring interconversion (ring enlargement or contraction).

When a cyclic compound is obtained by a ring construction method, this involves the formation of a bond (or bonds) either intramolecularly or intermolecularly. Intramolecular bond formation takes place between atoms present in an acyclic precursor, and at least one bond must be formed in order to obtain a cyclic compound (Scheme 1).



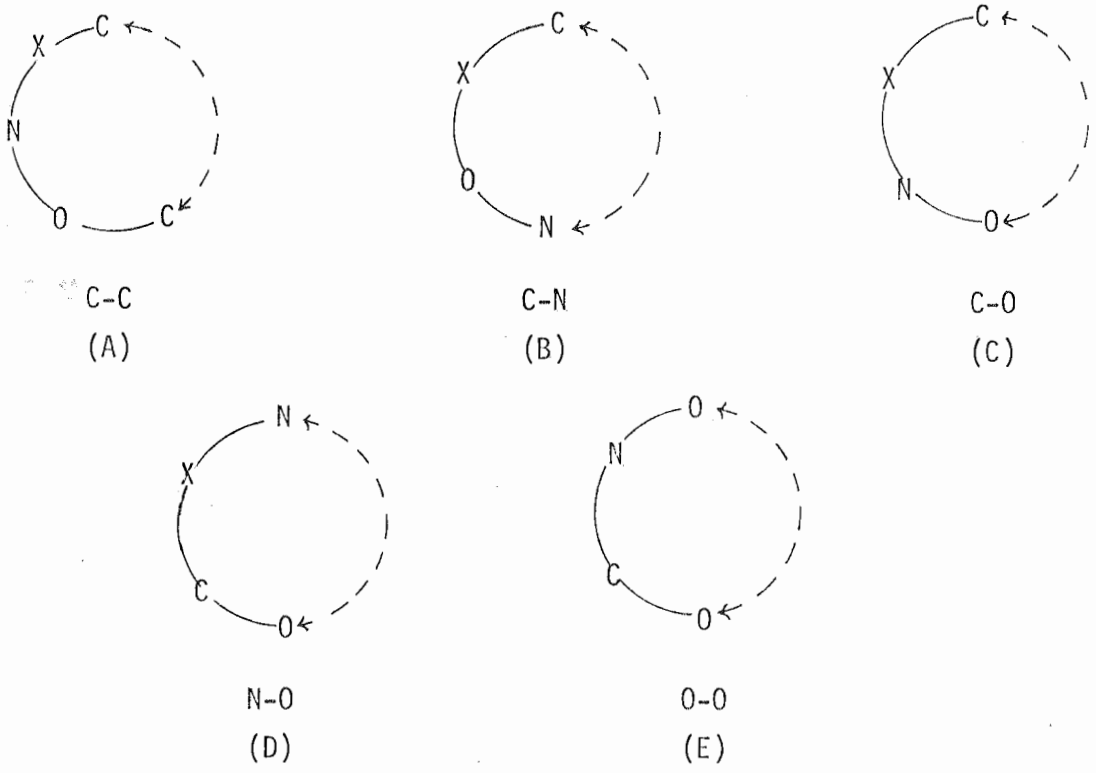
acyclic
precursor

Scheme 1

Intermolecular bond formation occurs between the atoms of two or more acyclic precursors and, at least two bonds must be formed to obtain a new cyclic system (Scheme 2).

Scheme 2

In benzoxaza- and benzodioxaza- ring systems an intramolecular bond formation could take place between carbon-carbon, carbon-nitrogen, carbon-oxygen, oxygen-nitrogen or in the latter case, oxygen-oxygen atoms (Figure 2, A-E).

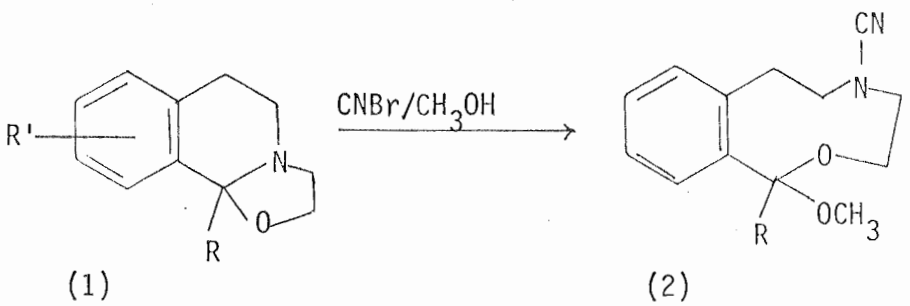


X = C, in oxaza- systems
X = O, in dioxaza- systems

Figure 2

The first three types (A-C) have been employed in the construction of 1,4- and 1,5-benzoxaza ring systems, but the last two types (D-E) of ring closure and the intermolecular condensation do not appear to have been reported.

In ring destruction methods, a new ring system is formed by destroying an existing bond between two rings. For example, some benzoxazonine derivatives have been prepared in this manner (Scheme 3).[2]

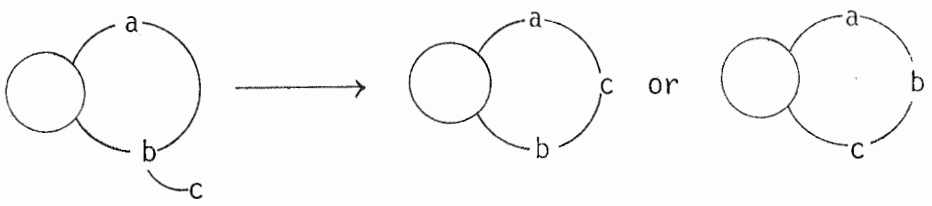


(1) (2)

Scheme 3

However such methods have not been reported for the preparation of the benzoxaza and benzodioxaza ring systems shown in Figure 1.

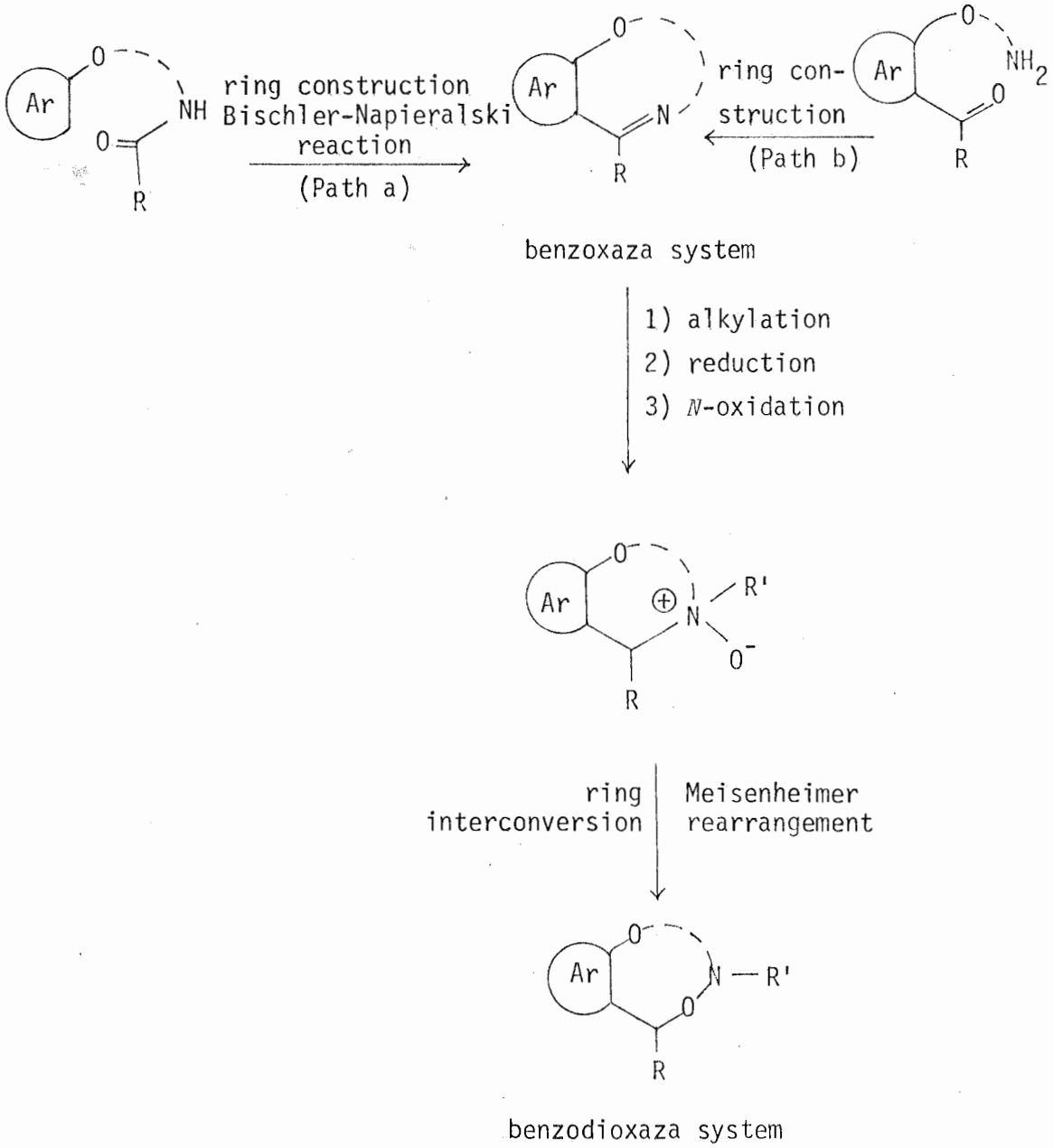
Ring interconversion reactions that have been used in the synthesis of cyclic compounds may involve the formation of a larger new ring system from existing atoms in the initial molecule (e.g. Scheme 4). Examples occur in the Schmidt reaction or the Beckmann rearrangement. Ring contraction methods may also be used, but are not further considered here.



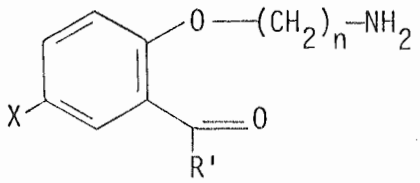
Scheme 4

The benzoxaza ring systems described in this thesis were mainly prepared by the Bischler-Napieralski cyclization (ring construction) (Scheme 5, Path a). The amide precursors (4) having an electron donating group on the benzene ring adjacent to the oxygen atom underwent

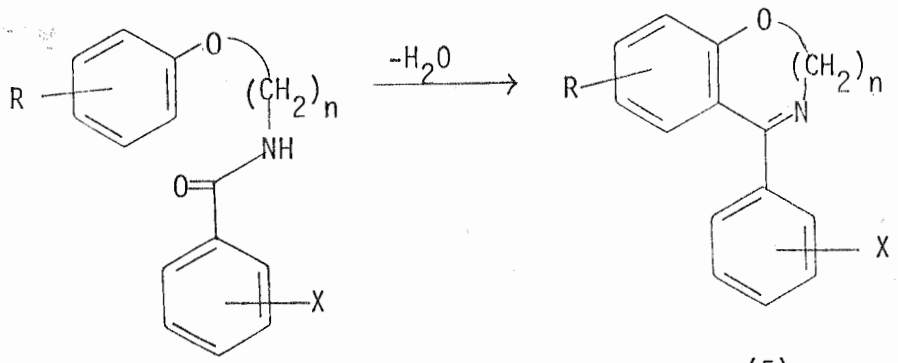
the Bischler-Napieralski cyclodehydration giving rise to the desired seven- and eight-membered benzoxaza ring systems (5) (Scheme 6). However two 1,4-benzoxazepine derivatives were synthesised by the construction of a C-N bond, from an amino-ketone precursor of type (3) (Scheme 5, Path b). These reactions are described in Chapters 2 and 3.



Scheme 5



(3) X = H, Cl



(4)

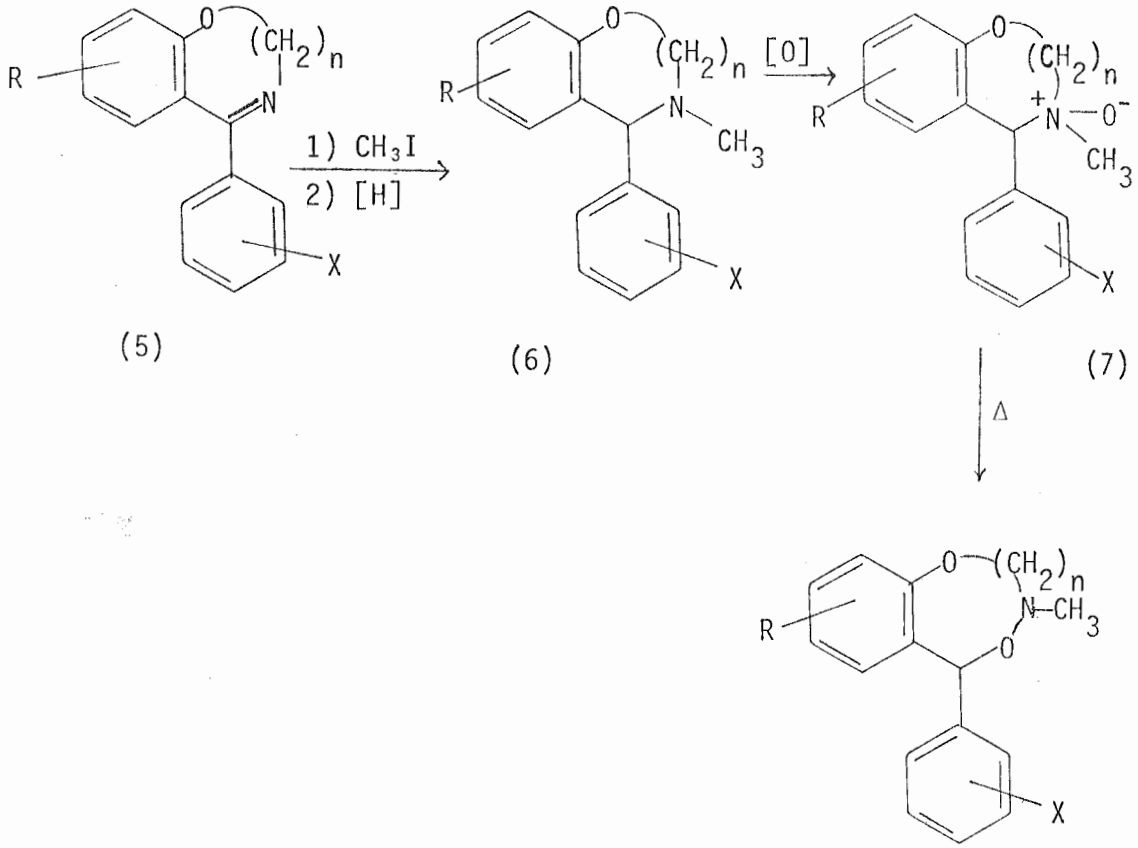
(5)

n = 2, R = 3-OCH_3, 3,5-$(OCH_3)_2$
n = 3, R = 3-OCH_3

Scheme 6

The benzodioxaza systems (8) were prepared by the application of the Meisenheimer rearrangement (Scheme 5). Synthetic aspects and mechanism of this rearrangement are given in Chapter 4.

The *N*-oxides (7) of the cyclic amines (6) required for the Meisenheimer rearrangement were obtained by the methylation and reduction of the cyclic imines (5), (Scheme 7).



(5) (6) (7) (8)

Scheme 7

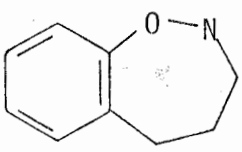
Pharmacological properties of several 1,4-benzoxazepines and 1,5-benzoxazocines have been reported by many workers.[e.g.3-8] Some 1,4-benzoxazepine derivatives were described as therapeutically active[3] and as muscle relaxants.[4] It was thus hoped that some of the benzoxaza and benzodioxaza compounds investigated in this project might also show useful pharmacological activity.

CHAPTER 2

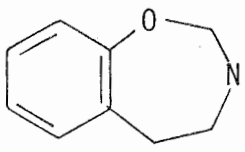
Synthesis of 1,4-Benzoxazepines

2.1 Introduction

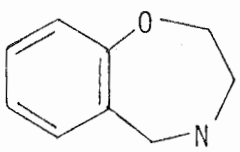
Of the ten possible isomers (A-J) of benzoxazepine ring systems only eight (A-H) have been synthesised (*Chem. Abstr.*, 1917-1980, Vol. 93, and *Ring Index* 1960) (Figure 3).



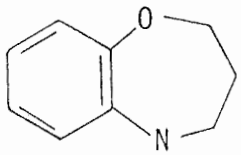
[1,2]
(A)



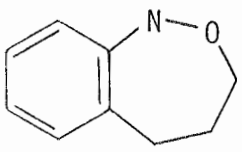
[1,3]
(B)



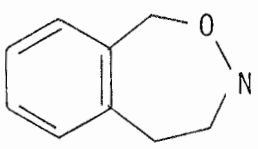
[1,4]
(C)



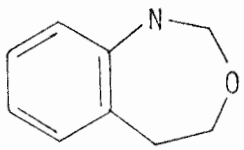
[1,5]
(D)



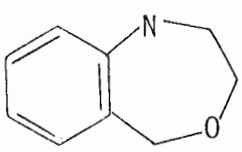
[2,1]
(E)



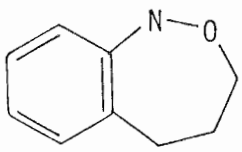
[2,3]
(F)



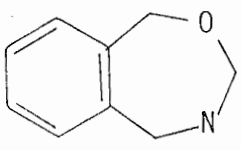
[3,1]
(G)



[4,1]
(H)



[2,1]
(I)



[2,4]
(J)

Figure 3

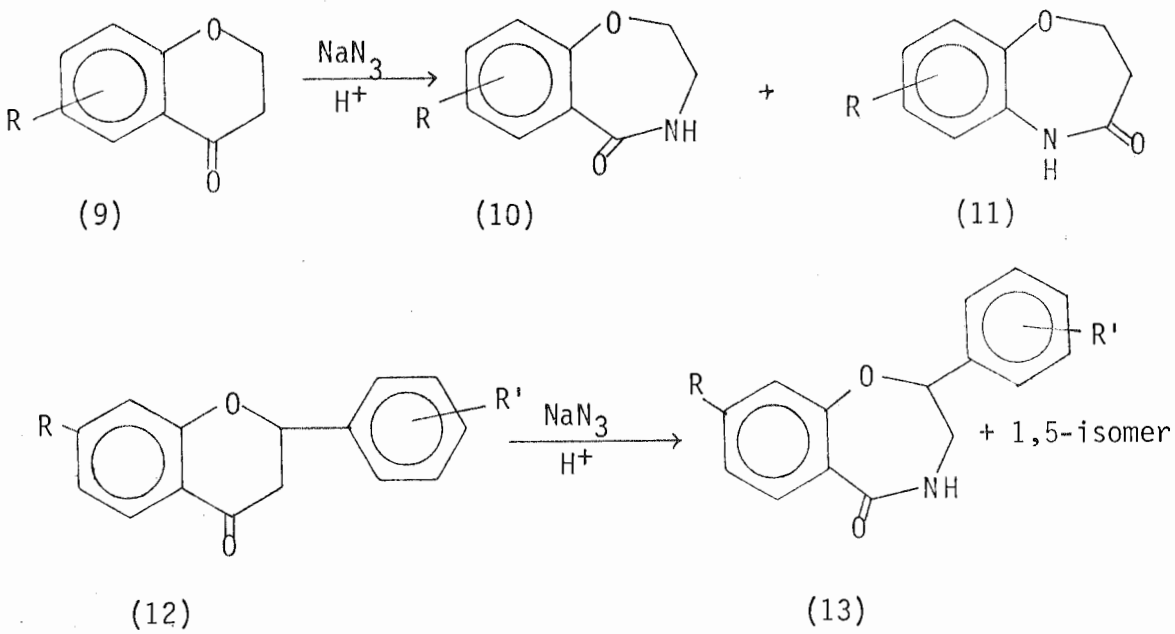
Most of the work on these seven-membered ring systems has been done on the 1,4- and 1,5-benzoxazepines. Since much of this thesis is based on the Meisenheimer Rearrangement of 1,4-benzoxazepine

derivatives (C), the literature of this isomer will be discussed in this chapter.

1,4-Benzoxazepine derivatives previously described can be divided into two groups according to their methods of preparation, viz. by a) ring interconversions
and b) ring constructions.

2.1.a Ring interconversions

The ring interconversion reactions, employed to prepare these 1,4-benzoxazepines, are the Schmidt[9-18] and Beckmann[19-20] reactions. The most widely used method is the Schmidt rearrangement of the corresponding 1,4-chromanones (9),[9-14] and the flavanones (12)[15-18] in the presence of sodium azide (Scheme 8).



(9) (10) (11)

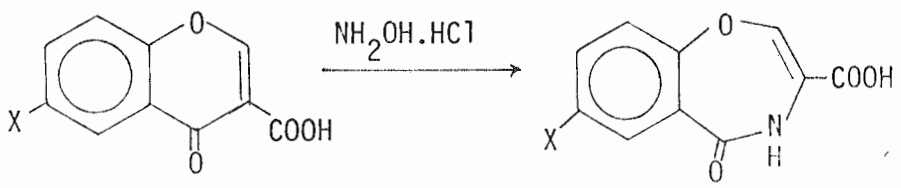
(12) (13)

Scheme 8

In some cases,[12,15b,16] the formation of the 1,5-benzoxazepine isomer was also reported, but the majority of the workers[9-11,13-15a,17,18] have reported only the formation of a 1,4-isomer. Therefore it is evident that alkyl migration is favoured over aryl migration during the rearrangement of the compounds (9) and (12).

Studies by Misiti and Rimatori[15b] show that the direction of the Schmidt rearrangement was not influenced by the substituents on the fused benzene ring, but they did affect the rate of the reaction.

The Beckmann rearrangement of 4-chromenone derivatives (14) in the presence of hydroxylamine hydrochloride[19,20] also gave the corresponding 1,4-benzoxazepines (Scheme 9), and the formation of an aryl migratory product (1,5-isomer) was not reported.



(14) (15)

X = H, CH_3, Cl, Br

Scheme 9

2.1.b Ring constructions

The ring construction methods used to synthesise 1,4-benzoxazepine derivatives can be divided into three groups. These are ring construction by i) C-C

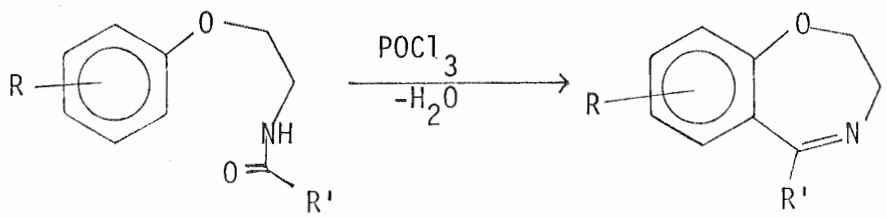
ii) C-O

and iii) C-N formation, of which method (iii) is the most widely used.

2.1.bi C-C Type ring closure

The Bischler-Napieralski cyclization

The construction of the 1,4-benzoxazepines by formation of a C-C bond has only been achieved by the Bischler-Napieralski reaction.[3,4,21-23] Early work on this cyclization was carried out primarily to synthesise isoquinolines,[24] and in recent years has been extended to the synthesis of the 1,4-benzoxazepine ring systems by Waefelaer and co-workers.[3,21-23] The general reaction used in the Bischler-Napieralski cyclization is shown in the Scheme 10.



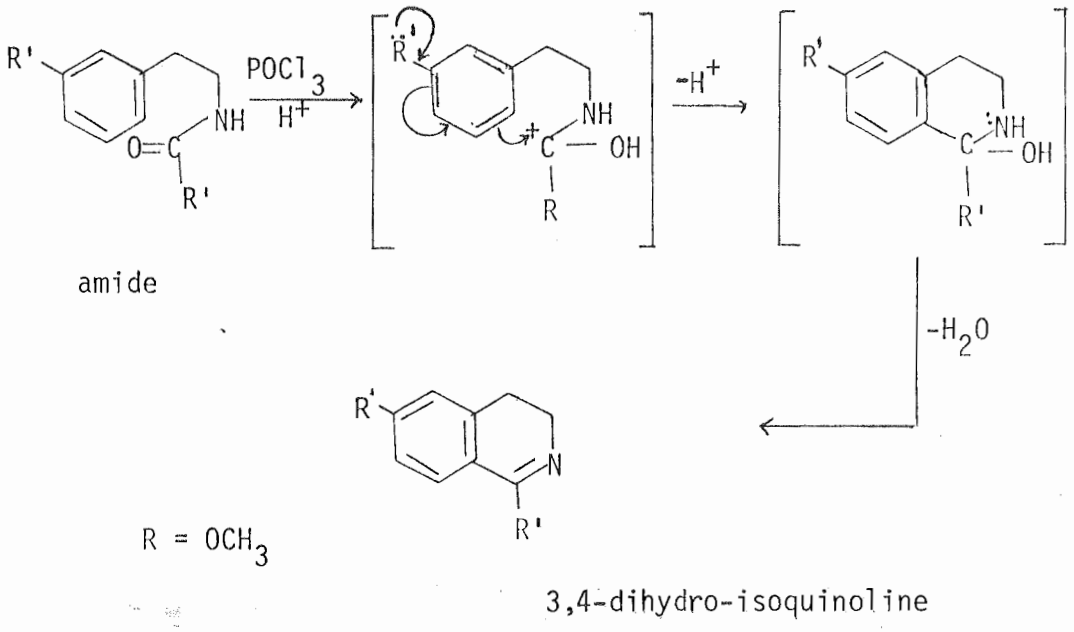
amide imine R = 7,8-$(OCH_3)_2$
7-Cl, 8-OCH_3
7-O-CH_2Ph, 8-OCH_3

R' = alkyl[3] or aryl[21,22]

Scheme 10

In these cases the cyclodehydration of the amides occurred smoothly, giving rise to the substituted 2,3-dihydro-1,4-benzoxazepines in high yields.[21] The 2,3,4,5-tetrahydro derivatives were obtained by the catalytic hydrogenation of these imines.

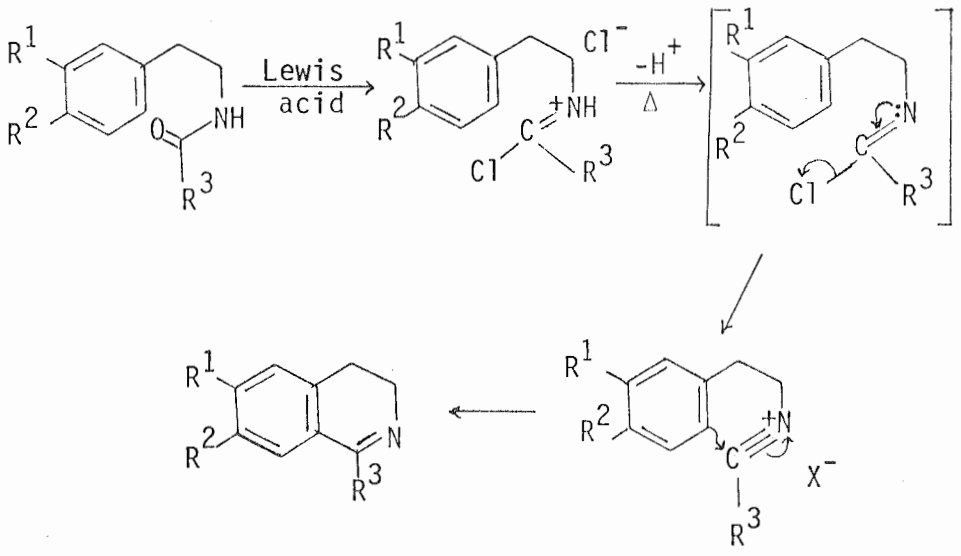
The mechanism of the Bischler-Napieralski reaction was earlier thought to proceed through the protonation of amide oxygen by a trace of hydrochloric acid present in phosphorus oxychloride, followed by cyclization and dehydration to the 3,4-dihydroisoquinoline derivative,[25] as shown in Scheme 11.



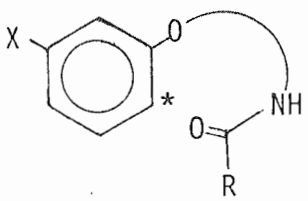
Scheme 11

This idea was shown to be invalid by Fodor and Nagubandi[26] for a number of reasons. For example, because of the higher basicity of the final product protonation should occur preferably on the imine nitrogen instead of on the amide oxygen. These latter workers also showed that under milder conditions the first steps could occur without subsequent cyclization. According to their suggestions, the cyclization step proceeds via a nitrilium ion, instead of a carbonium ion as suggested earlier. This possible mechanism is given in Scheme 12.

Since this cyclization is an electrophilic substitution reaction, electron donating groups on the *para* position (Figure 4) of the benzene ring should facilitate the formation of the cyclic imine. Similarly electron withdrawing groups on the benzene ring could be expected to deactivate the reaction. This suggestion will be discussed fully in the synthesis of 1,4-benzoxazepines (Section 2.2).



Scheme 12



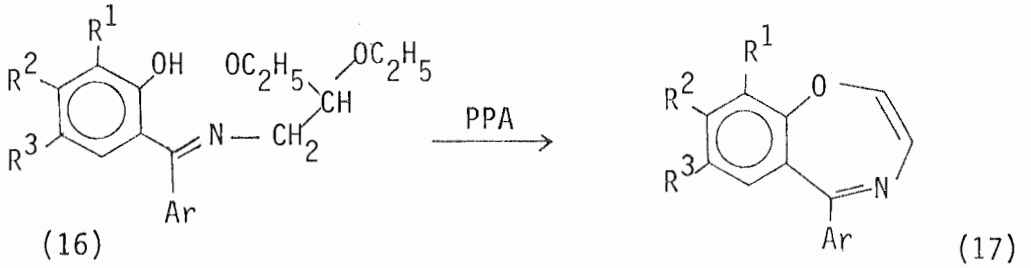
eg: X, electron donating group - OCH_3,
electron withdrawing group - NO_2,Cl.

Figure 4

2.1.b.ii C-O Type ring closure

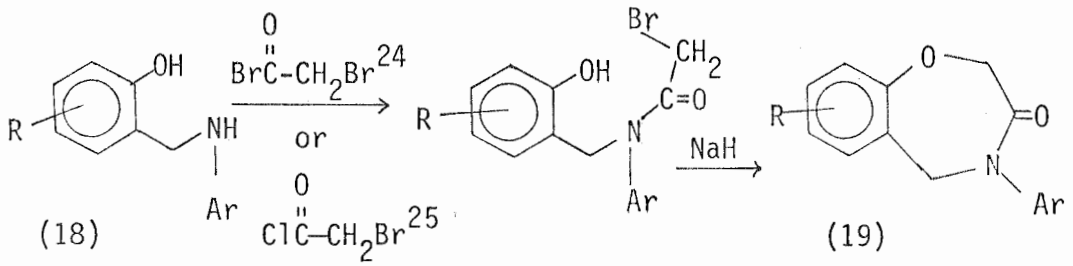
Synthesis of the 1,4-benzoxazepines by the construction of a carbon-oxygen bond, is limited to a few cases. The 1,4-benzoxazepine derivatives (17a,b) were prepared by the Pomeranz-Fritsch reaction of the corresponding esters (16a,b) in the presence of polyphosphoric

acid,[27,28] while the cyclic amides (19) were prepared by a condensation reaction.[5,29] (Scheme 13).



a) $R^1 = R^2 = OCH_3$, $R^3 = H$, $Ar = CH_2\text{-}C_6H_5$

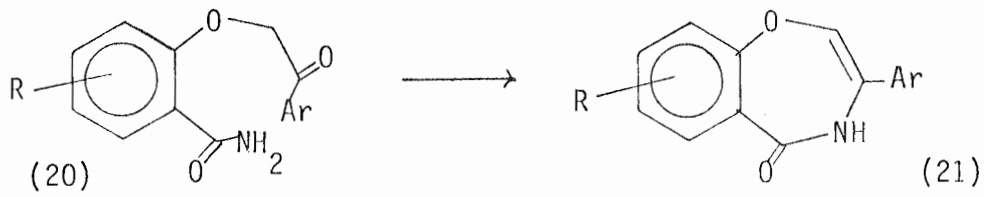
b) $R^1 = R_2 = OCH_3$, $R^3 = Br$, $Ar = CH_2\text{-}C_6H_4\text{-}4\text{-}OCH_3$



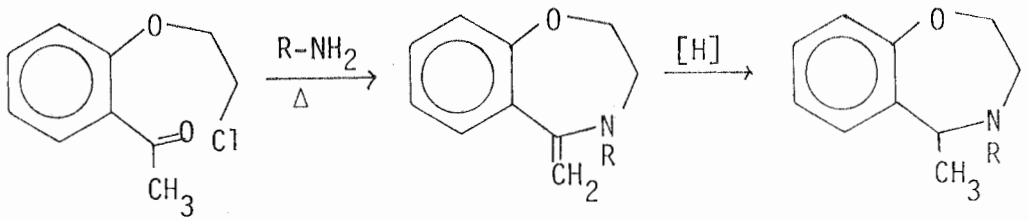
Scheme 13

2.1.b.iii C-N Type ring closure

Preparation of the 1,4-benzoxazepine derivatives by carbon-nitrogen type ring closure is the most widely used method found in the literature. Some of these 1,4-benzoxazepines were prepared by the condensation of amido-ketones (20) in the presence of *p*-toluenesulfonic acid.[30-33]



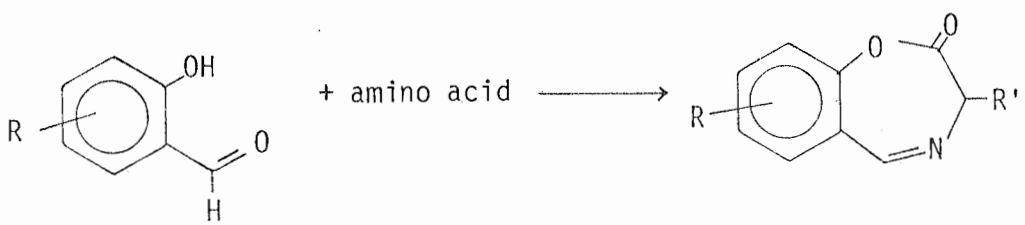
Schenker and Druey[34] have reported the preparation of a tetrahydro derivative of 1,4-benzoxazepine (24) by the condensation of (22) with non-hindered primary aliphatic amines, followed by reduction (Scheme 14).



(22) (23) (24)

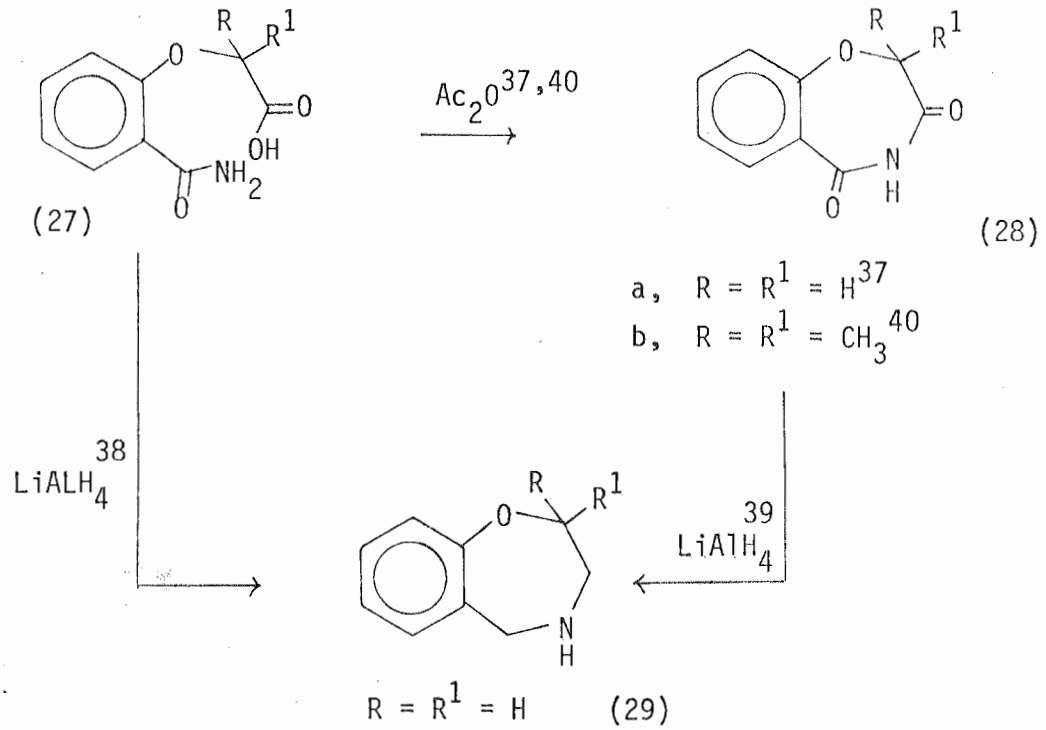
Scheme 14

Lactones of type (26) have been synthesised by the reaction of aromatic aldehydes (25) with amino acids.[35,36]



(25) (26)

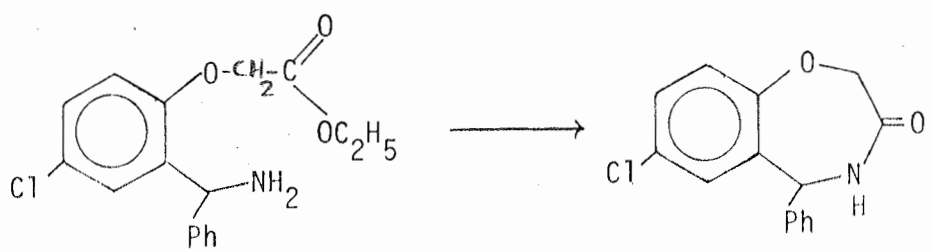
Transformations of the amido acid (27) also resulted in the formation of 1,4-benzoxazepine ring systems (28,29) in high yields.[37-40] (Scheme 15).



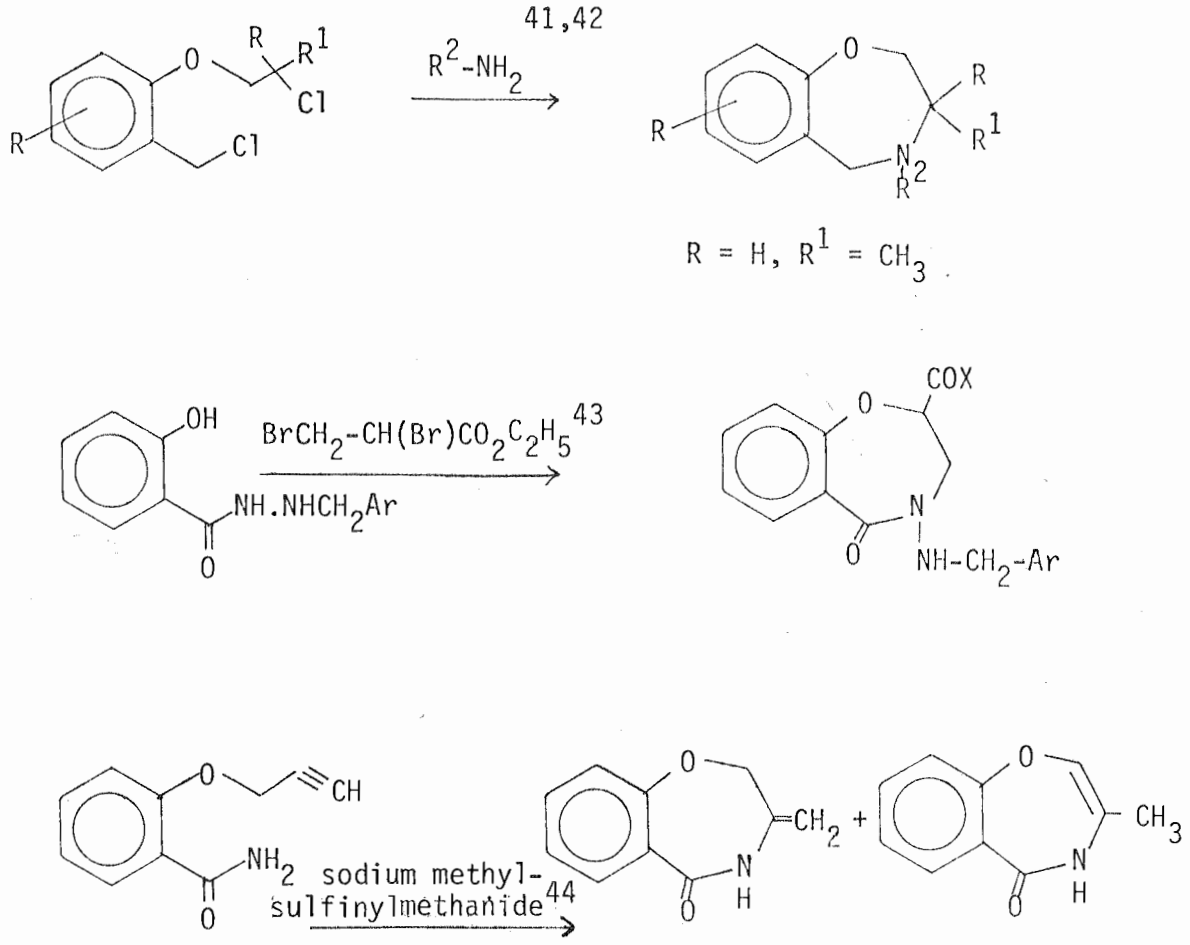
Scheme 15

Several other condensation reactions that have been reported in the literature[41-44] are summarized in Scheme 16.

The lactones of type (10) (page 9) have also been prepared by the reaction of the corresponding phenol with epichlorohydrin followed by amination with isopropylamine.[45] These compounds were found to be pharmacologically inactive. Another lactone (31) was obtained by the condensation of (30).[46]

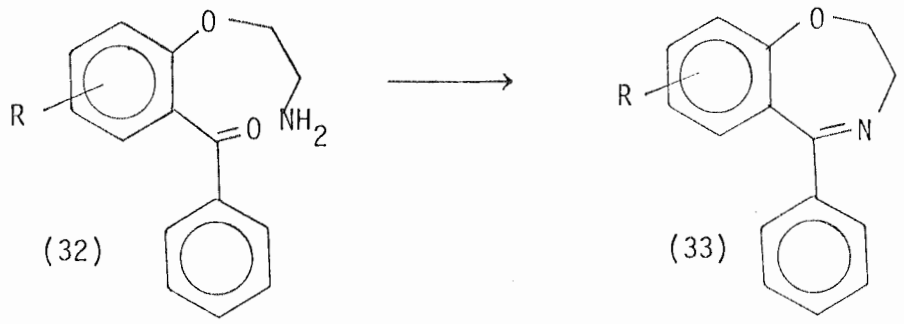


(30) (31)



Scheme 16

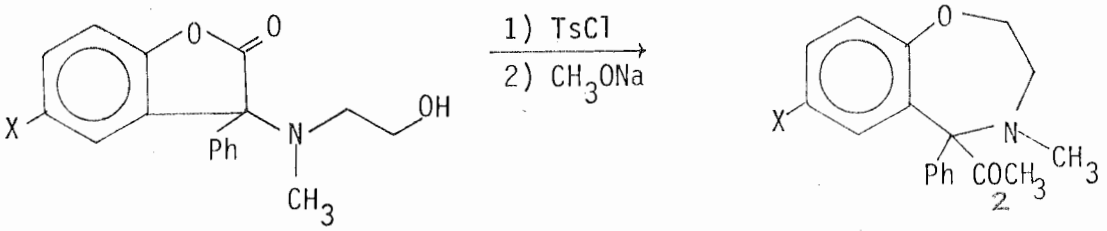
Luts[7] and Standridge[47] have reported the preparation of the 5-phenyl-1,2,3-dihydro-1,4-benzoxazepine derivative (33) by the cyclization of the amino ketone (32). Since this reaction has been employed to synthesise some of the 5-phenyl-1,4-benzoxazepines reported in this thesis, the reaction sequence followed and the difficulties encountered are discussed fully in Section 2.3.1.



(32) (33)

R = 7-Cl or H

In addition to these rearrangement and ring closure reactions, one tetrahydro derivative (35) of 1,4-benzoxazepine was prepared by a ring enlargement reaction.[48]



(34) (35)

X = H, Cl

The reactions[49-51] and the unit cell dimension[52] studies of the derivatives of 1,4-benzoxazepines also have been reported.

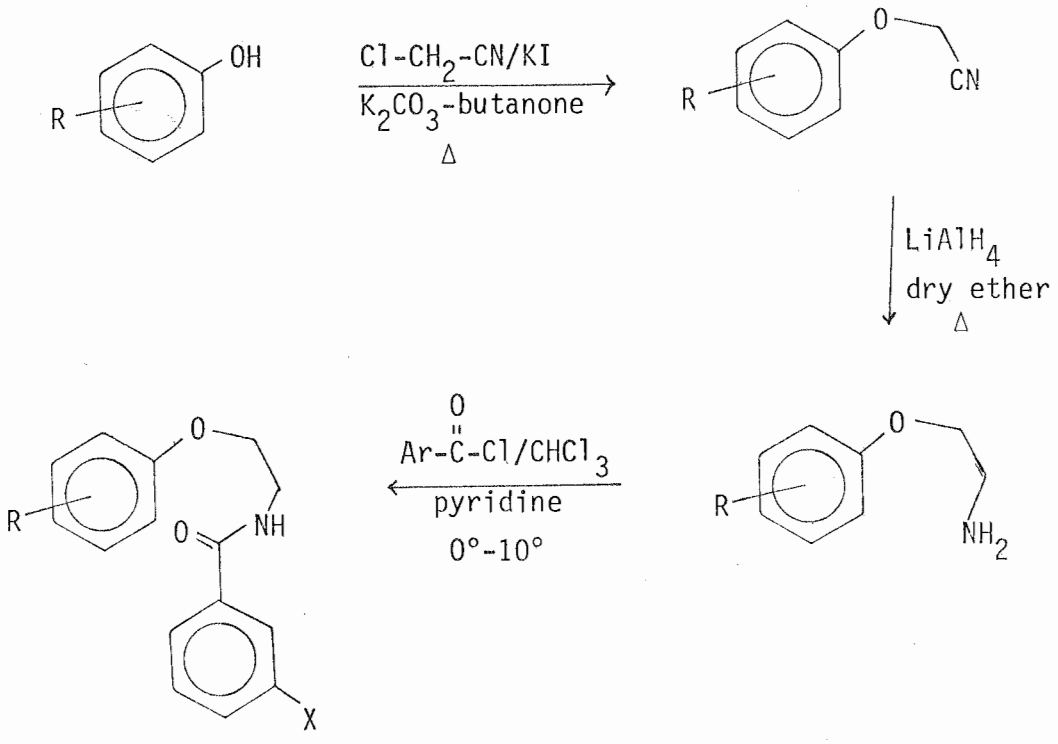
The 1,4-benzoxazepines synthesised by the present author were prepared either by the Bischler-Napieralski cyclization (C-C approach), or by the condensation of amino ketones (C-N approach). Hence these two methods are presented in the following pages under sections 2.2 and 2.3. 1,5-Benzoxazocines discussed in Chapter 3 were also prepared by similar approaches, but in this chapter only 1,4-benzoxazepines are discussed, for reasons of clear presentation of each group.

2.2 Results and Discussion

2.2.1 Synthesis of 1,4-benzoxazepines by a C-C ring closure approach

2.2.1a Preparation of the precursors

The amides required for the Bischler-Napieralski reaction were readily prepared by the general route outlined in Scheme 17. An alternative route to some of the amines required will be discussed later.



Scheme 17

All the phenols used were commercially available. The *O*-alkylation of 3-methoxyphenol was carried out according to the method discussed by Djerassi et al.[53] and Burtner.[54] Hence the $-CH_2CN$ group was introduced by the reaction of iodoethanenitrile and the phenol in the presence of potassium carbonate in anhydrous butanone. This reaction proceeded smoothly giving rise to 3-methoxyphenoxyethanenitrile (36) in

88% yield, and was extended to synthesise the other nitriles (37-39) (Figure 5).

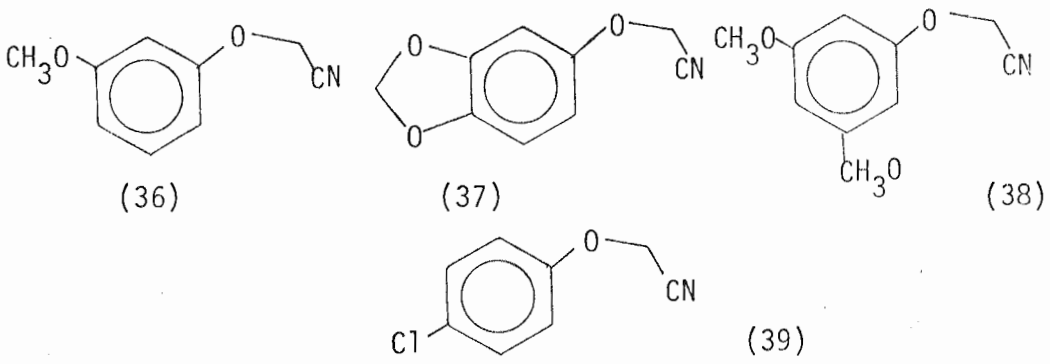


Figure 5

In the P.M.R. spectra of each of these nitriles, the signal derived from protons attached to the methylene carbon ($O\text{-}CH_2\text{-}CN$) appeared at δ4.70 as a sharp singlet. In the P.M.R. spectrum of the nitrile (37), a clear ABC system was observed for the three aromatic protons. As expected the signal from H_A appeared as a doublet of doublets due to *ortho* and *meta* coupling (Figure 6). The signals derived from H_C and H_B appeared as two separate doublets due to *ortho* and *meta* coupling respectively. The P.M.R. spectrum of (37) is given in Figure 7.

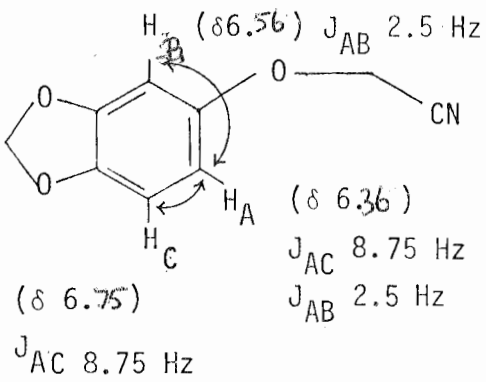


Figure 6

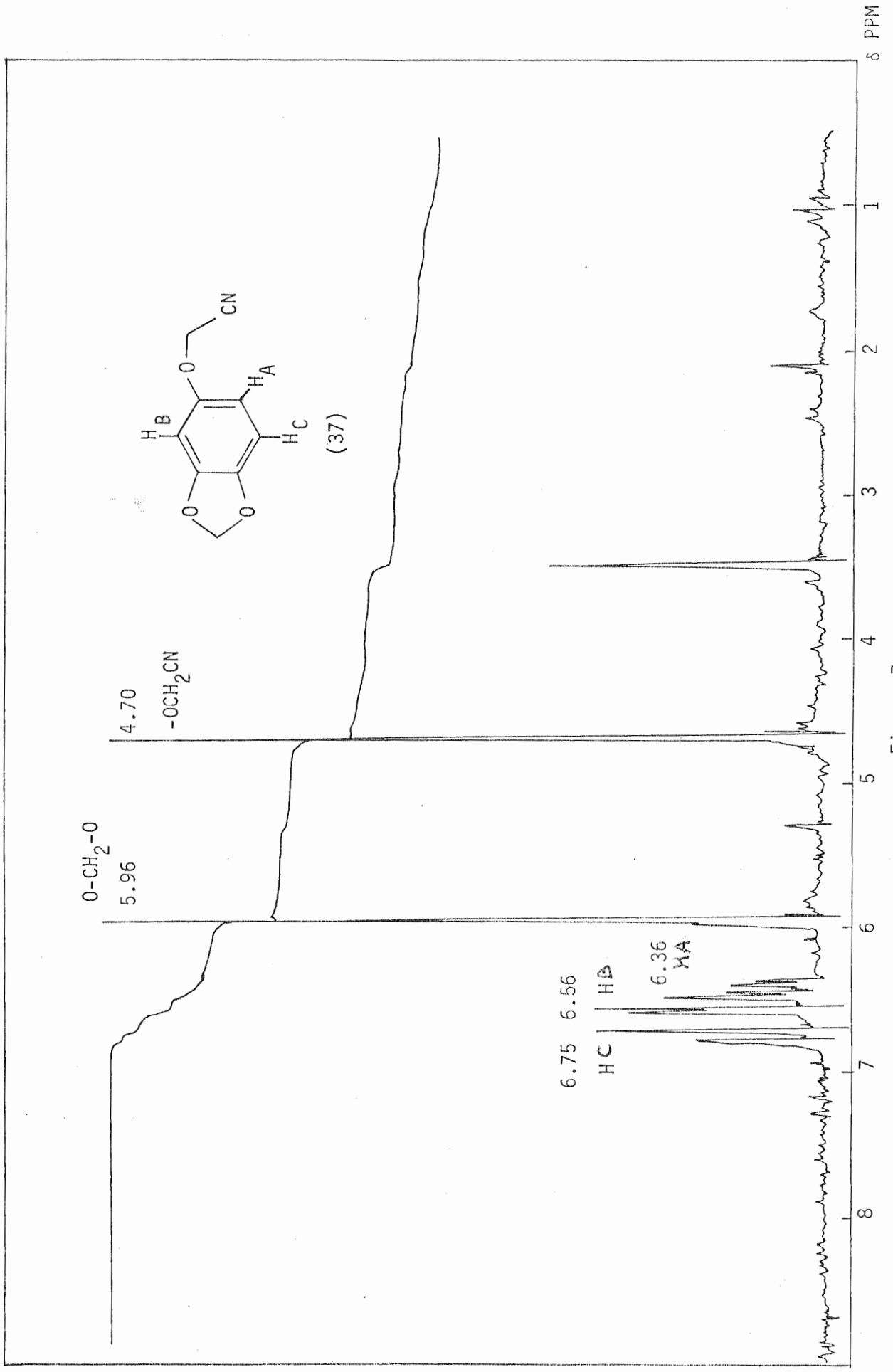
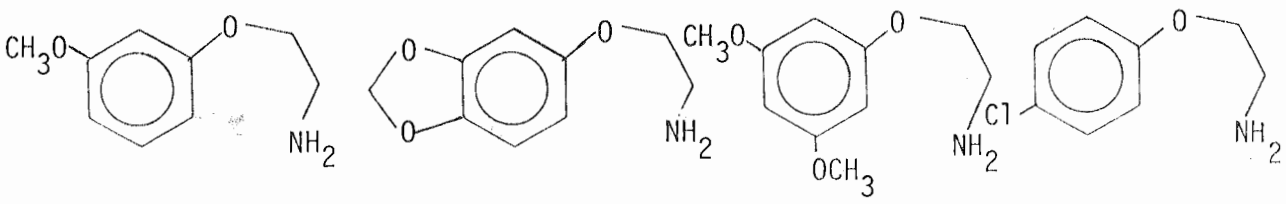

δ PPM
1
2
3
4
5
6
7
8
O-CH2-O
5.96
4.70
-OCH2CN
6.75
6.56
HC
HB
6.36
HA
CN
O
HA
HB
HC
O
O
(37)

Figure 7

In the infrared spectra the C≡N frequency appeared as a weak band at 2230 cm^{-1} (36) or 2240 cm^{-1} (37) and (38). In the spectrum of the nitrile (39) this frequency is not visible.

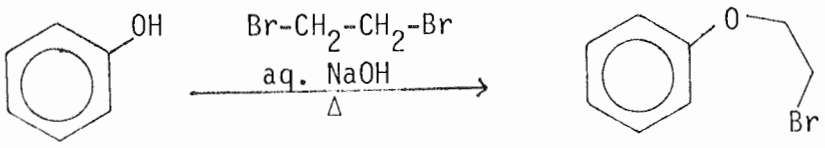
The phenoxyethanamine derivatives (40-43) (Figure 8) were prepared by the reaction of the nitriles (36-39) with lithium tetrahydridoaluminate in anhydrous diethyl ether.[55] These amines were obtained in yields of 62-87% and, characterized by spectroscopic data.



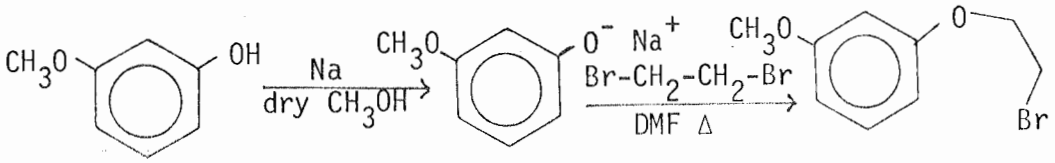
(40) (41) (42) (43)

Figure 8

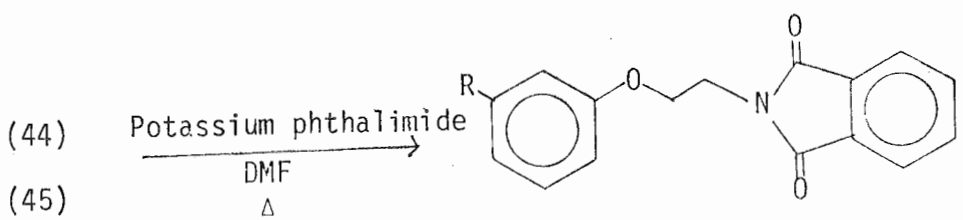
Another approach employed to synthesise the amines (40) and (50) is shown in Scheme 18. The preparation of (44) was carried out by the reaction of phenol and 1,2-dibromoethane in aqueous sodium hydroxide.[56] The reaction of 3-methoxyphenol and 1,2-dibromoethane, under the same reaction conditions did not result in the formation of (45) as expected. In this case some of the starting materials were recovered. Hence sodium 3-methoxyphenolate was prepared by the reaction of 3-methoxyphenol and sodium in anhydrous methanol, and this salt was reacted with 1,2-dibromoethane in dry dimethylformamide under anhydrous conditions[57] to give a poor yield (≈ 21%) of (45). Further investigations of this reaction were not carried out, since the route given in Scheme 17 was more satisfactory.



52% (44)



(45)

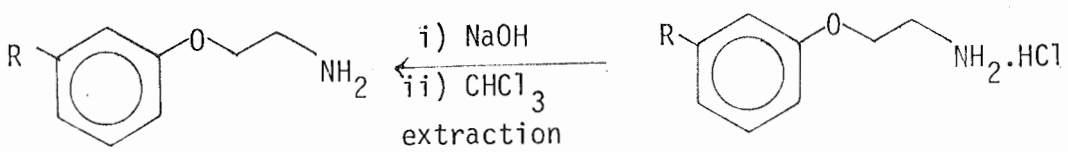


(46) R = H

(47) R = OCH_3

1) $N_2H_4.H_2O$ ethanol

2) HCl Δ



(48) R = H

(49) R = OCH_3

(50) R = H

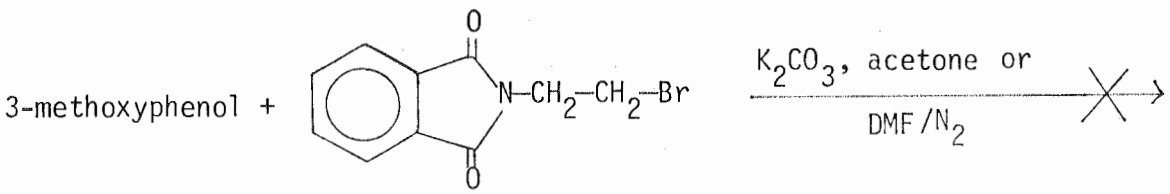
(40) R = OCH_3

Scheme 18

The reaction of these bromo compounds (44) and (45) with potassium phthalimide in dry dimethylformamide[58] gave 62% and 63% yields of the phthalimide derivatives (46) and (47) respectively. (Scheme 18).

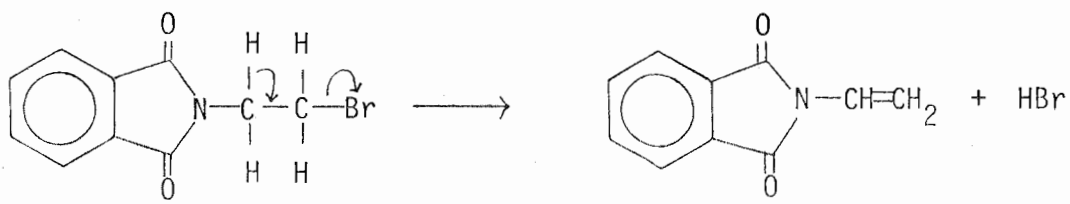
The cleavage of the phthalimide groups in (46) and (47) was achieved by hydrazinolysis. The phenoxyethanamine hydrochlorides (48,49) thus obtained were characterized, and the free bases (50) and (40) were used for the amide syntheses.

An attempt was made to synthesise the phthalimide derivative (47) directly from the reaction of 3-methoxyphenol with 2-bromoethylphthalimide (Scheme 19).



Scheme 19

This reaction was carried out under various conditions but none were successful. The products were not identified, but a possibility was the occurrence of an elimination reaction on 2-bromoethylphthalimide, preventing the expected condensation (Scheme 20).



Scheme 20

In contrast, with 3-bromopropylphthalimide this problem was not encountered, and this reaction proceeded smoothly giving rise to the corresponding phthalimide derivative (112) in 94% yield (Section 3.2, page 54). The condensation of phenols with 2-bromoethylphthalimide has not been reported in the literature, but the condensation of phenols with 3-bromopropylphthalimide was reported.

The amides (51-56) (Figure 9) required for the Bischler-Napieralski reaction were prepared by the reaction of amines (40-43) and (50) with the aroyl chlorides in pyridine and chloroform at 10°. All these amides were obtained in yields of 86-96%, as solids, which were recrystallised from diethyl ether and light petroleum (b.p. 40°-60°).

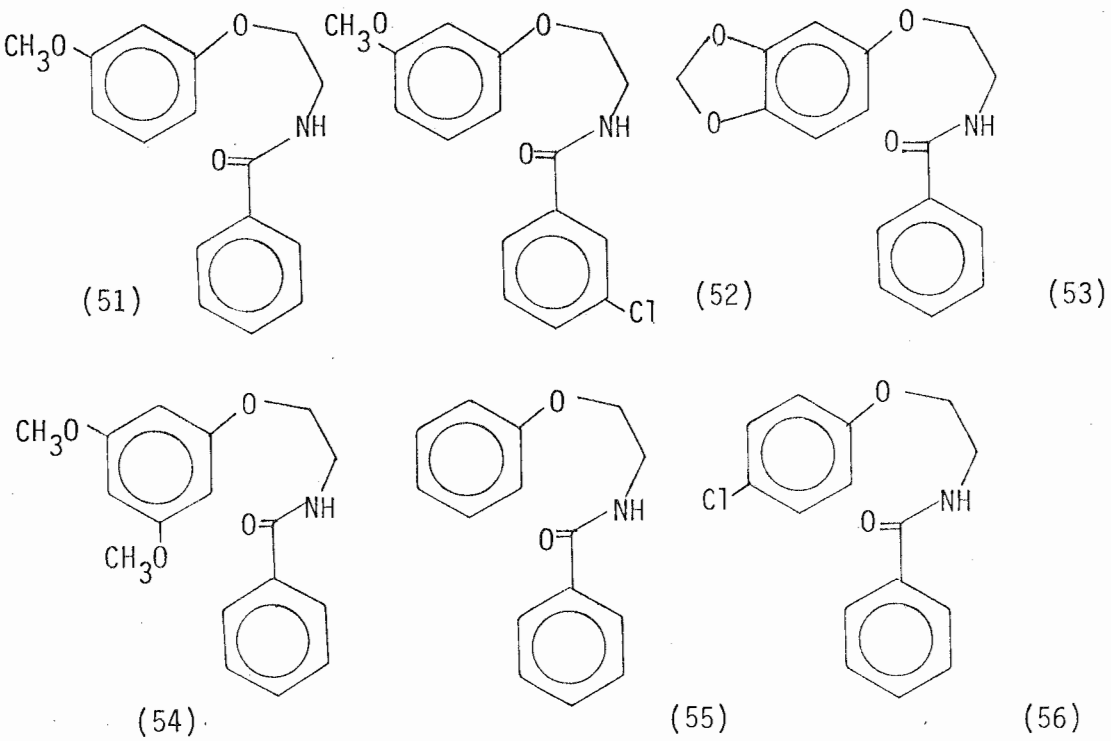


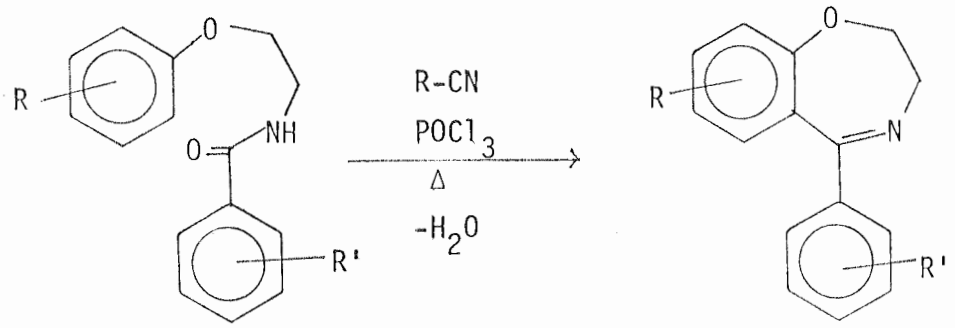
Figure 9

2.2.2 The Bischler-Napieralski reaction of the amides

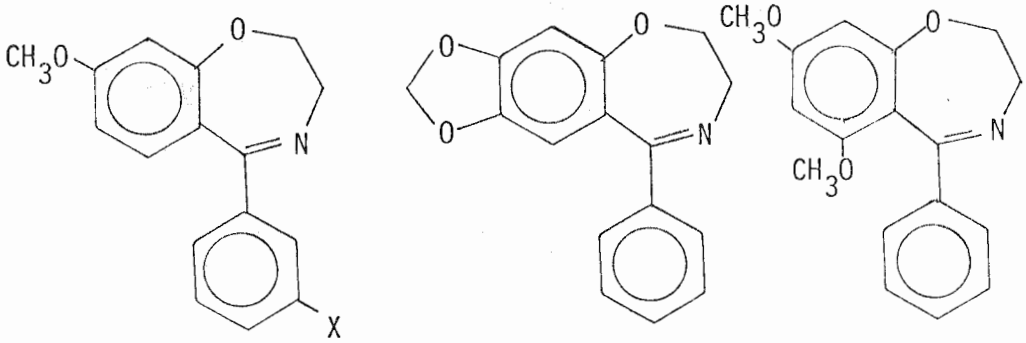
2.2.2a Synthesis and discussion

Cyclodehydration of the amides (51-54) with phosphorus oxychloride gave the corresponding 5-aryl-2,3-dihydro-1,4-benzoxazepines (57-60) in

yields of 44-80% (Scheme 21) (Table 1).



(51-54) (57-60)



(57) X = H (59) (60)

(58) X = Cl

Scheme 21

TABLE 1

The Bischler-Napieralski Cyclization of Amides

Amide	Reaction conditions	Imine	Yield %
(51)	$POCl_3$ + n-PrCN/16h Δ	(57)	80
(52)	"	(58)	45
(53)	$POCl_3$ + CH_3CN/4h Δ	(59)	64
(54)	$POCl_3$ + n-PrCN/10h Δ	(60)	55

This reaction was carried out essentially as described by Waefelaer and co-workers.[21] However butanenitrile was used as the

solvent, except for the cyclization of the amide (53), and freshly distilled phosphorus oxychloride was used as the dehydrating agent (Table 1). A warm solution of the amide in the appropriate solvent was added dropwise to a refluxing solution of phosphorus oxychloride in the same solvent, and the solution was refluxed for several hours. After work-up as described by Waefelaer et al,[21] the cyclic imines were obtained in 45-80% yields (Table 1).

All these amides (51-54) used for the Bischler-Napieralski reaction described above, possess an electron-donating group on the benzene ring *para* to the position of ring closure as were those used analogously by Waefelaer and co-workers.[21] In addition, the oxygen atom at the *ortho* position activate these ring systems towards the electrophilic attack on the benzene ring. Therefore the amides (51-54) can be expected to be doubly activated towards an electrophilic substitution reaction (Figure 10).

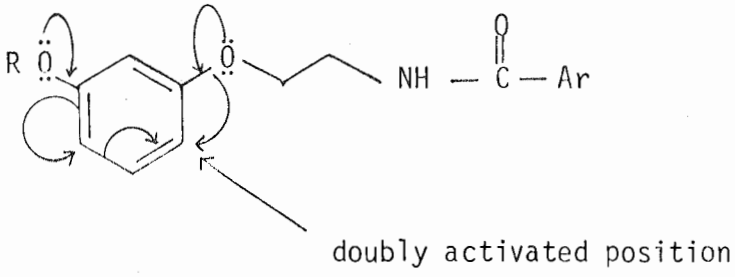
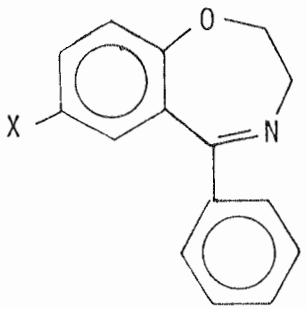


Figure 10

It was attempted to extend this reaction to the preparation of 5-phenyl-2,3-dihydro-1,4-benzoxazepine (61) and 7-chloro-5-phenyl-2,3-dihydro-1,4-benzoxazepine (62) from the amides (55) and (56) respectively, under the similar reaction conditions. However this reaction did not give the expected cyclic imines (61) or (62).



(61) X = H

(62) X = Cl

Hirohashi and co-workers[4] have reported that they have obtained the 7-chloro derivative (62), by the reaction of amide (56) in the presence of phosphorus pentoxide and phosphorus oxychloride in benzene and xylene. Hence this reaction was repeated using the conditions employed by these workers, but without success.

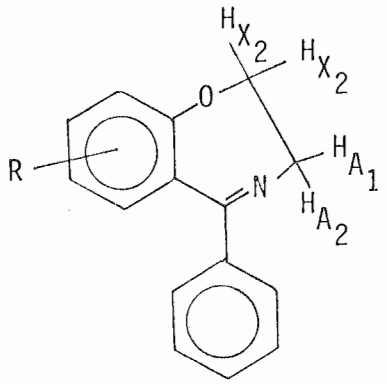
Several other attempts were made to synthesise these two 1,4-benzoxazepine derivatives (61,62), by the Bischler-Napieralski reaction in the presence of phosphorus oxychloride and phosphorus pentoxide, in various solvents (ethanenitrile, butanenitrile, benzene, xylene) and with longer refluxing periods. All these methods were unsuccessful and this approach was abandoned, and a new route was investigated to synthesise these "deactivated" (towards electrophilic substitution) ring systems.

This approach is discussed in section 2.3.

2.2.2b Spectral analysis of the 2,3-dihydro-1,4-benzoxazepines (57-60)

In the P.M.R. spectra, characteristic features of these imines (57-60) were the two sets of methylene proton peaks which appear as a simple A_2X_2 system with a coupling constant of 5Hz. The $-NCH_2-$

proton peak appears near δ 3.8, while those derived from the $-OCH_2-$ protons appear at about δ 4.6-δ 4.7 (Table 2).



imines (47-50)

TABLE 2

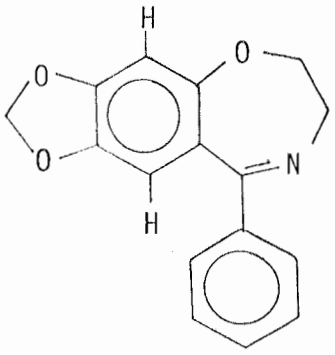
Chemical Shifts of Methylene Protons in the Cyclic Imines

Imine	Chemical shift value δ	
	$N-CH_2$	$O-CH_2$
(57)	t, 3.88	t, 4.68
(58)	t, 3.82	t, 4.69
(59)	m, 3.55-3.75	t, 4.61
(60)	t, 3.79	t, 4.59

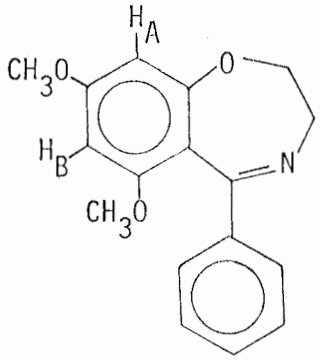
A downfield shift (δ 0.56-0.58) for the peaks derived from the $-OCH_2-$ protons and an upfield shift (δ 0.03-0.05) for those derived from the $-NCH_2-$ protons were observed in these imines in comparison with those of their amide precursors.

The peaks derived from the two hydrogen atoms on the fused benzene ring in 7,8-methylenedioxy-5-phenyl-2,3-dihydro-1,4-benzoxazepine (59) appear as two singlets at δ 6.53 and δ 6.64. In the imine (60), the H_A and H_B proton peaks appear as a two proton

singlet at δ 6.35 (Figure 11).



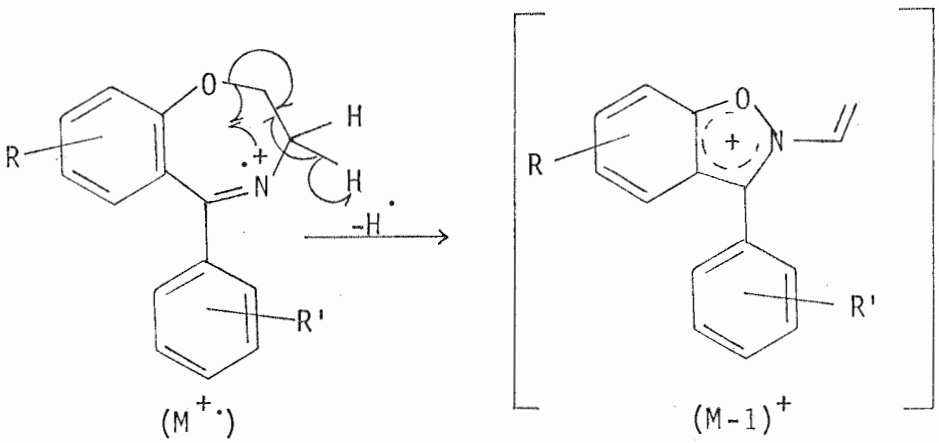
(59)



(60)

Figure 11

In the mass spectra of these imines (57-60), the $(M-1)^+$ ion peak gave a very prominent signal. Therefore it appears that these imines are rearranging into a stable molecular species by readily losing a hydrogen atom. A suggested mechanism for this fragmentation is shown in Scheme 22.



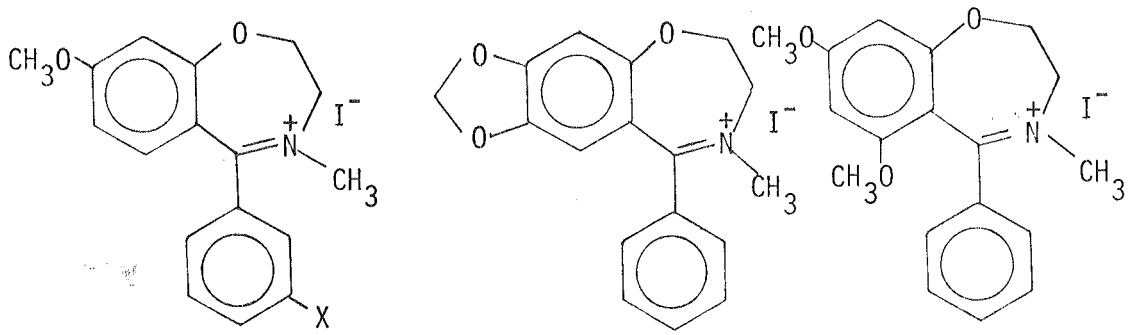
Scheme 22

In the infrared spectra of these imines, the C=N frequency appeared as a very strong band at 1600 cm^{-1}.

2.2.3a Quaternization followed by reduction of the 1,4-benzoxazepines (57-60)

The 2,3-dihydro-1,4-benzoxazepines (57-60) prepared by the Bischler-Napieralski reaction were then converted to their methiodide

salts (63-66) by reaction with iodomethane in anhydrous acetone. These quaternization reactions were carried out in sealed tubes and six to ten hour heating periods at 80°-100° were employed. The yields of these methiodide salts (63-66) (Figure 12) obtained were quantitative.



(63) X = H

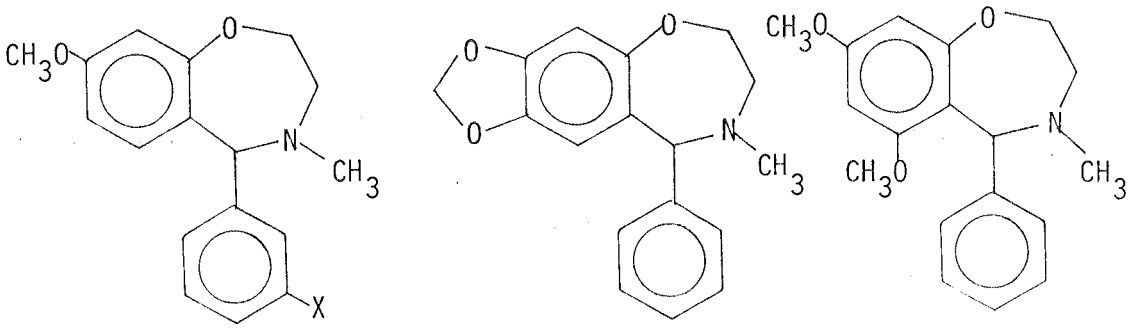
(64) X = Cl

(65)

(66)

Figure 12

The reduction of the methiodide salts (63-66) with sodium tetrahydridoborate in a solution of 60% aqueous ethanol and methanol at < 10° gave the corresponding 2,3,4,5-tetrahydro-1,4-benzoxazepines (67-70) (Figure 13) in yields of 47-70%.



(67) X = H

(68) X = Cl

(69)

(70)

Figure 13

2.2.3b Spectral analysis of the 2,3,4,5-tetrahydro-1,4-benzoxazepines (67-70)

The appearance of a one proton singlet derived from the benzylic proton at the C-5 position was a prominent feature in the P.M.R. spectra of each of these cyclic amines (67-70), and confirmed that the reduction of the $C=\overset{+}{N}-$ double bonds had taken place. The chemical shift values varied from δ 4.79 to δ 5.65, depending on the nature of the substituents on the fused benzene ring (Table 3).

TABLE 3

Chemical Shifts of Methylene Protons in the Cyclic Amines

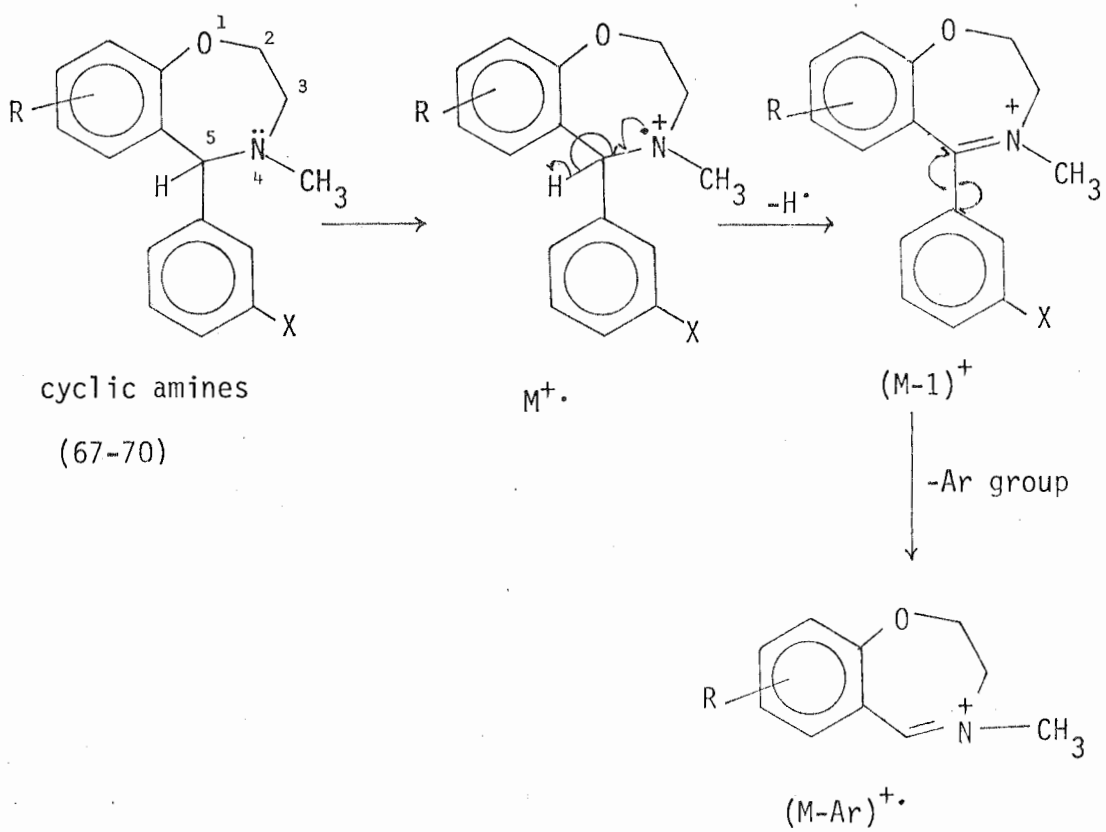
Cyclic amine	Chemical shift of benzylic proton δ
(67)	s, 4.90
(68)	s, 4.89
(69)	s, 4.79
(70)	s, 5.65

The signals derived from the $-OCH_2-$ and the $-NCH_2-$ methylene protons no longer appear as A_2X_2 systems, as seen in the imines and in the methiodide salts. Instead multiplets were observed for signals from these four protons, and upfield chemical shifts were observed when compared with those derived from the methylene protons in the imines. With the reduction of the C=N double bond, it can be expected that the strain in the seven-membered ring would be relieved to a certain extent. This could allow a different spatial arrangement for the methylene protons, which could reduce the deshielding effects operating in the other cases. Therefore in these 2,3,4,5-tetrahydroderivatives, the methylene proton signals could

appear at a higher magnetic field in their P.M.R. spectra.

The multiplicity observed can be explained on the assumption that both geminal and vicinal couplings are operative in this system. However due to insufficient resolution of the P.M.R. spectra, a further study on the splitting patterns was not conducted.

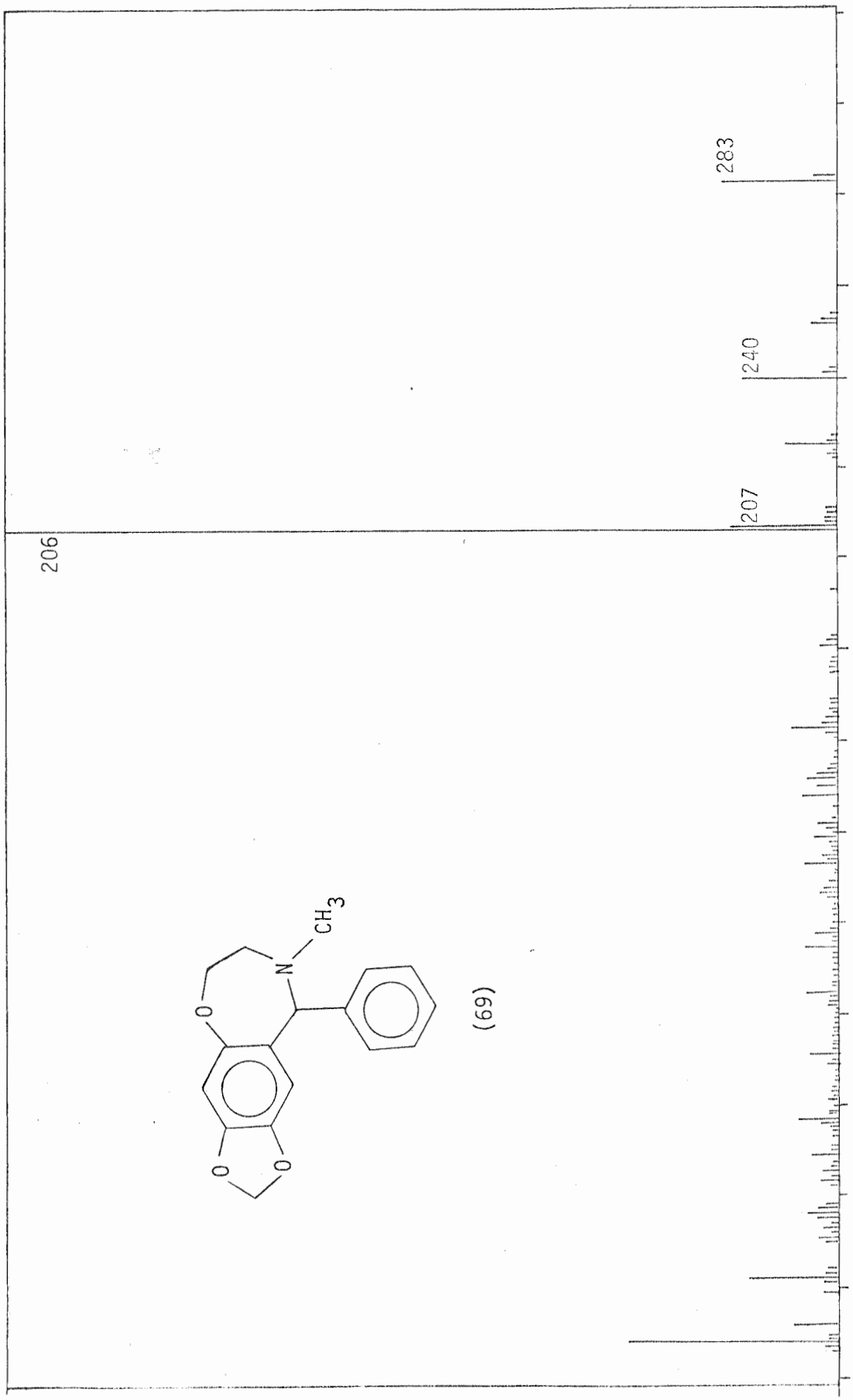
The mass fragmentation of these cyclic amines (67-70) also follows a similar pattern. Fragmentation of the C-C bond between C_5 and the pendant aryl group , gave rise to the base peaks in the mass spectra. A postulated mechanism for this fragmentation is given in Scheme 23.



cyclic amines (67-70)

Scheme 23 base peak 206

The mass spectrum of 7,8-methylenedioxy-4-methyl-5-phenyl-2,3,4,5-tetrahydro-1,4-benzoxazepine (69) is given in Figure 14.



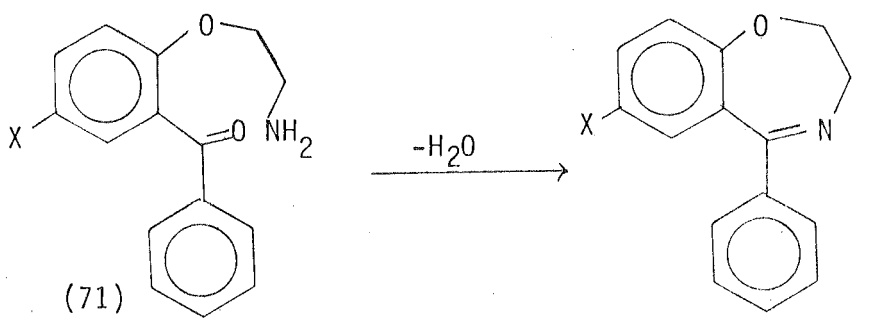
(69)

Figure 14

2.3 Preparation of the 1,4-benzoxazepines by a C-N ring closure approach

This approach was developed to overcome the difficulties encountered during the attempted preparation of 5-phenyl-2,3-dihydro-1,4-benzoxazepine (61) and its 7-chloro derivative (62) by the Bischler-Napieralski reaction (section 2.2.2a). Failures to obtain these cyclic imines from their corresponding amides (55) and (56), indicated that the ring closure position of the benzene ring was not sufficiently activated towards an electrophilic attack.

This conclusion promoted attempts to prepare a new precursor which would be a key compound, such as (71), in the synthesis of these less easily accessible 5-phenyl-1,4-benzoxazepines (61) and (62), by construction of a carbon-nitrogen bond, instead of a carbon-carbon bond (Scheme 24).



(71)

amino ketone

a) X = H

b) X = Cl

(61) X = H

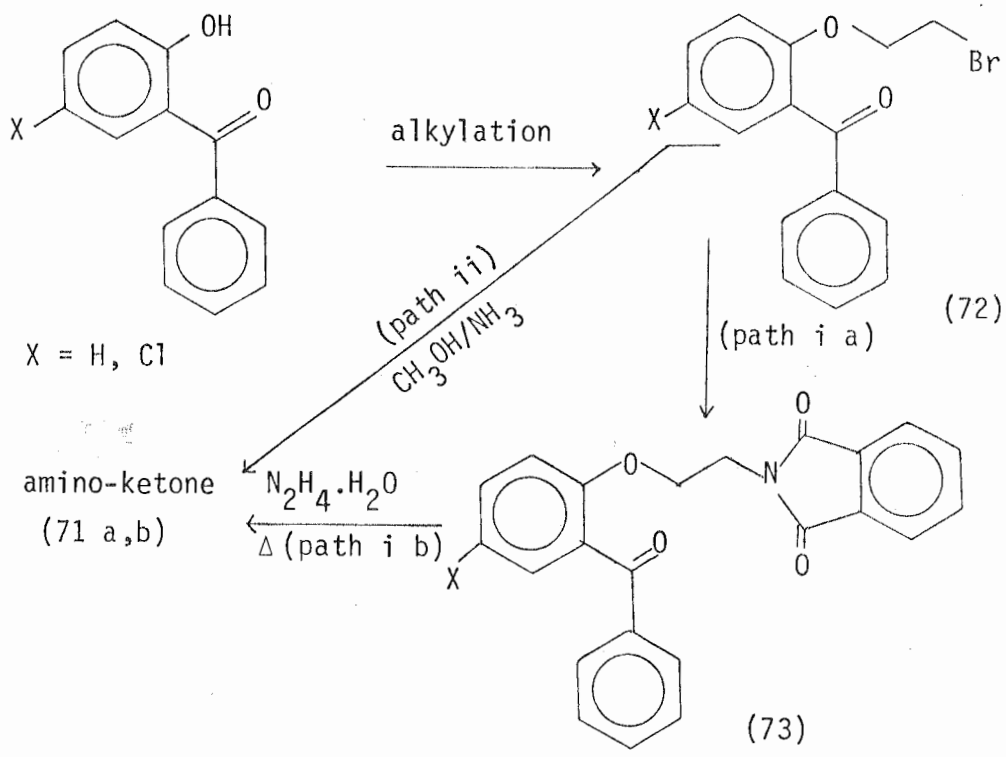
(62) X = Cl

Scheme 24

2.3.1 Preparation of the precursors

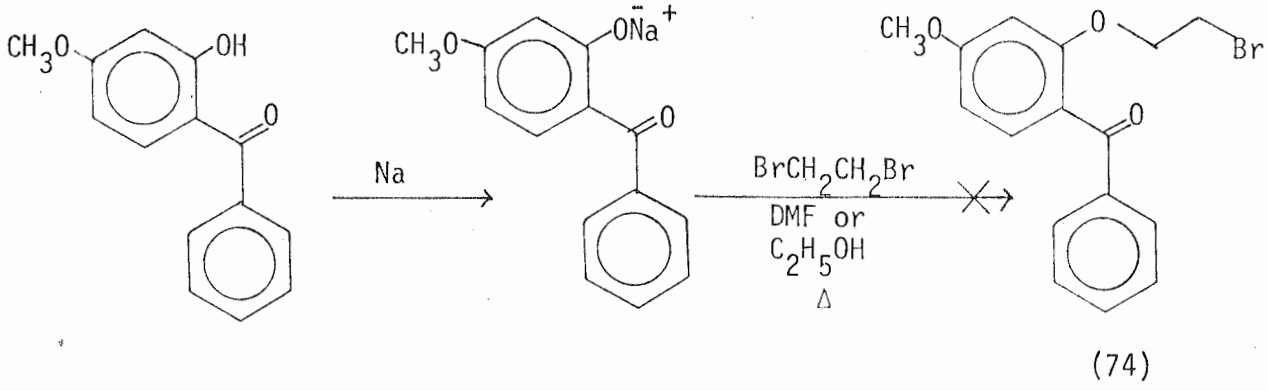
It was initially decided to attempt to make the amino-ketones of type (71), either by the Gabriel phthalimide synthesis (path i) or by the ammonolysis (path ii) of the corresponding halogen derivative of type (72), given in Scheme 25. Hence preparative methods of these

2-(2-bromoethoxy)benzophenones (72) from their corresponding 2-hydroxy-benzophenone derivatives were investigated.



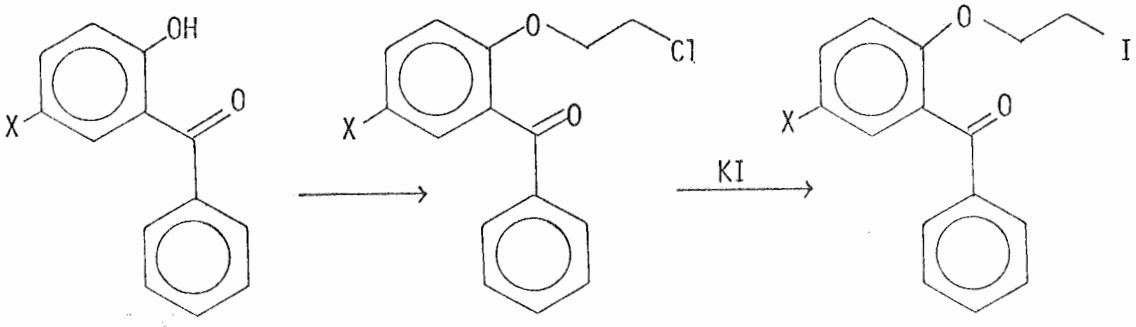
Scheme 25

The sodium salt of 2-hydroxy-4-methoxybenzophenone was used initially, because of its ready availability (Scheme 26). Attempted alkylation of this sodium salt with 1,2-dibromoethane in dimethylformamide or ethanol under anhydrous conditions did not form the desired product (74) (Scheme 26).



Scheme 26

The next route attempted was first to prepare the 2-(2-chloroethoxy)benzophenone derivatives (75a,75b) and then convert them to the 2-(2-iodoethoxy)benzophenones (76a,76b) by an iodine exchange using potassium iodide (Scheme 27).



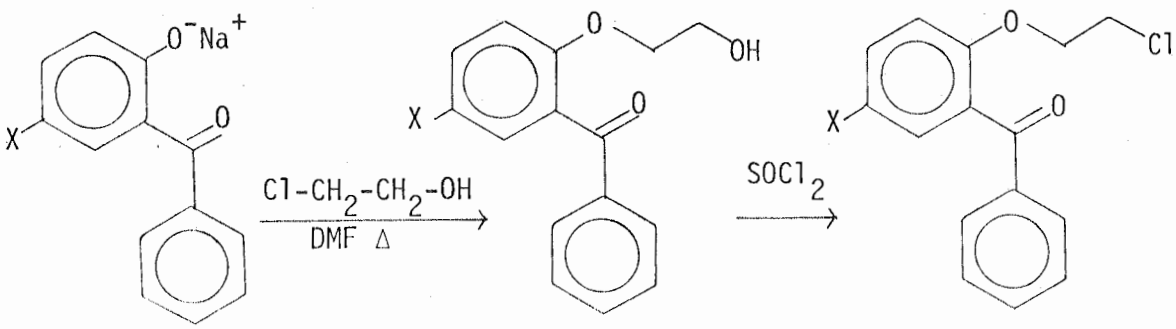
(75)
a) X = H
b) X = Cl

(76)
a) X = H
b) X = Cl

Scheme 27

Preparation of the benzophenone derivative (75b) has been reported, using 2-chloroethoxy-*p*-toluene sulfonate as the alkylating agent.[7] However attempts to prepare the compound (75b) by this method were unsuccessful and the starting materials were recovered.

The next route investigated to prepare the compounds of type (75) is given in Scheme 28.



(77)
a) X = H
b) X = Cl

(75b) X = Cl

Scheme 28

The 2-(2-hydroxyethoxy)benzophenone derivatives (77a,77b) were prepared in 17% and 60% yields, by the reaction of the corresponding sodium salts of the benzophenones and 2-chloroethanol in anhydrous dimethylformamide. The alcohol (77b) was then treated with excess thionyl chloride to give the chloro compound (75b) in 86% yield.

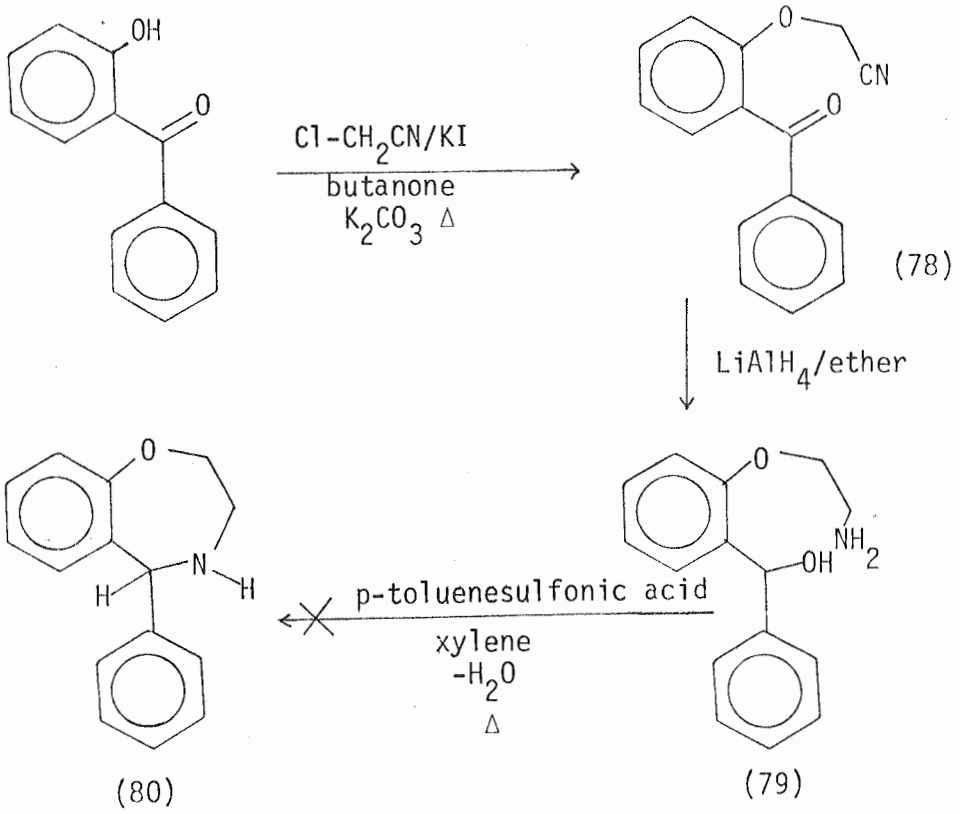
The attempted ammonolysis of this chloride (75b) with a solution of methanolic ammonia and dry ammonia gas in the presence of potassium iodide (path ii, Scheme 25) did not give the expected amino-ketone (71b). Instead the starting material was recovered quantitatively.

By contrast from the same reaction carried out with (3-halopropoxy) benzophenone derivative (120), the formation of the corresponding eight-membered imine (115) was observed (Section 3.3).

The Gabriel phthalimide synthesis shown in Scheme 25 (path i) was not attempted, because the same reaction carried out with (121) was unsuccessful (Section 3.3).

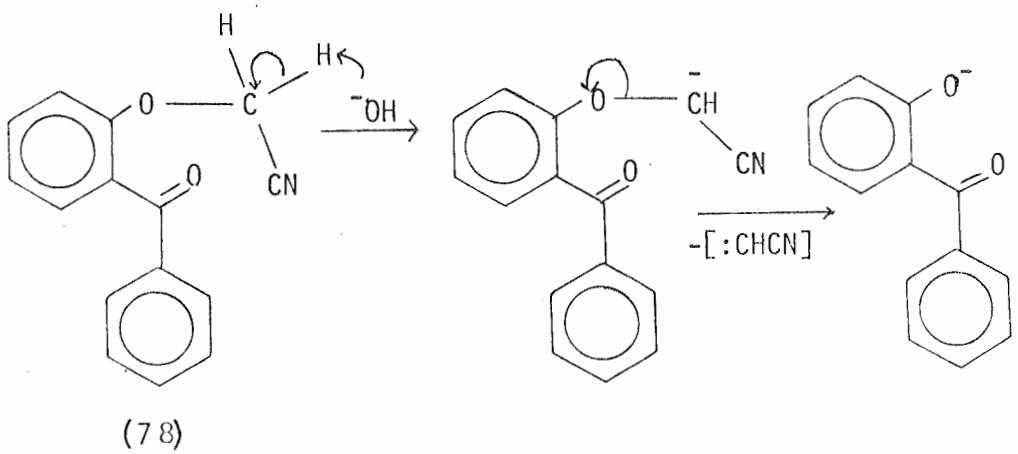
The next route attempted to prepare the 1,4-benzoxazepine (80) is shown in Scheme 29.

The alkylation of 2-hydroxybenzophenone was carried out with chloroethanenitrile as described for 3-methoxyphenol[53,54] (Section 2.2.1, page 19). During the work-up procedure, the chloroform extract of the crude nitrile (78) was washed with a solution of 5% aqueous sodium hydroxide to remove the unreacted 2-hydroxybenzophenone. As the final step of the purification, this was subjected to fractional distillation under vacuum. This process resulted in the cleavage of the $-CH_2CN$ side chain and gave rise to the starting material, 2-hydroxybenzophenone. Therefore an α-elimination reaction of the nitrile (78) under these conditions was suspected and the suggested



Scheme 29

mechanism for this cleavage is given in Scheme 30.



Scheme 30

After this observation, as a precaution the concentrated chloroform extracts of the crude nitrile (78) were not washed with sodium hydroxide, but were purified by column chromatography.

As evidence for the above suggested α-elimination in the presence of a base, the following experiment was carried out.

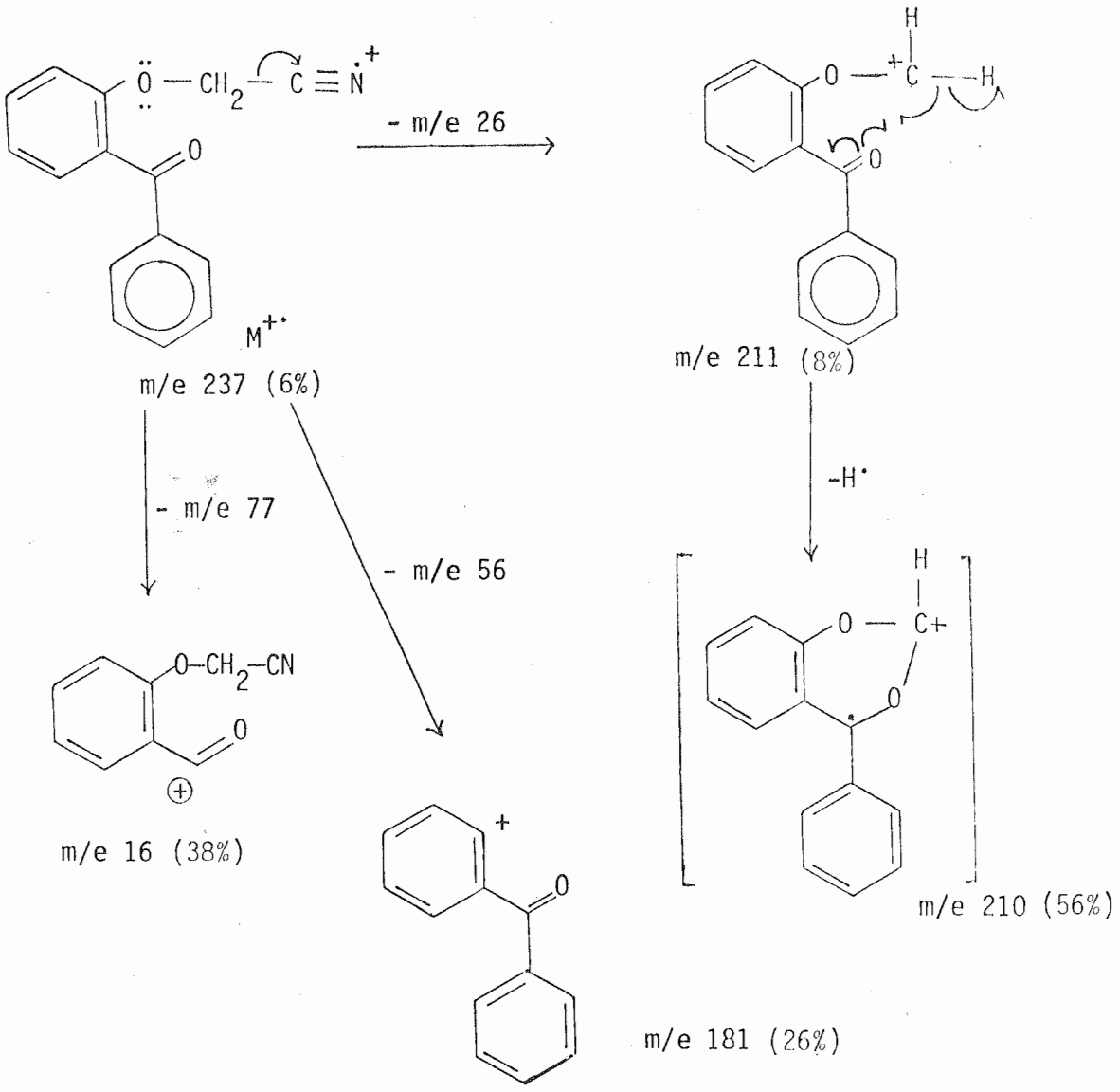
A chloroform solution of the pure nitrile (78) was washed with a solution of 5% aqueous sodium hydroxide and after the work-up, both layers were checked for the presence of the -OH group. 2-Hydroxybenzophenone was isolated from both layers and was characterized by spectroscopic data confirming the α-cleavage of the nitrile (78) in the presence of a base. Other nitriles (36-39) (page 19) which were synthesised earlier, did not undergo α-elimination under basic conditions.

The pure nitrile (78) was characterized by spectroscopic data. In the P.M.R. spectrum the signals derived from the methylene protons appeared at δ 4.70 as a two proton singlet, and the nitrile frequency appeared at 2230 cm^{-1} as a weak band in the infrared spectrum. The suggested mass fragmentation[59] for this compound is given in Scheme 31.

Reduction of the nitrile (78) with lithium tetrahydridoaluminate in anhydrous ether gave the amino-alcohol (79) in 81% yield (Scheme 29).

Appearance of the peak derived from the benzylic proton at δ 5.96 as a singlet, and the sharp singlet derived from the three exchangeable protons ($-NH_2$ and -OH) at δ 2.50 in the P.M.R. spectrum, confirmed the formation of the amino-alcohol (79). The peaks derived from the four methylene protons appeared as two triplets at δ 2.80 ($-NCH_2-$) and at δ 3.84 ($-OCH_2-$) with a coupling constant of J 5Hz. In the infrared spectrum, the peaks at 1660 cm^{-1} (C=O) and 2230 cm^{-1} (C≡N) found in the nitrile (78) had disappeared, and a new broad band appeared at 3300-3400 cm^{-1} due to the overlapping of the $-NH_2$ and -OH stretching bands.

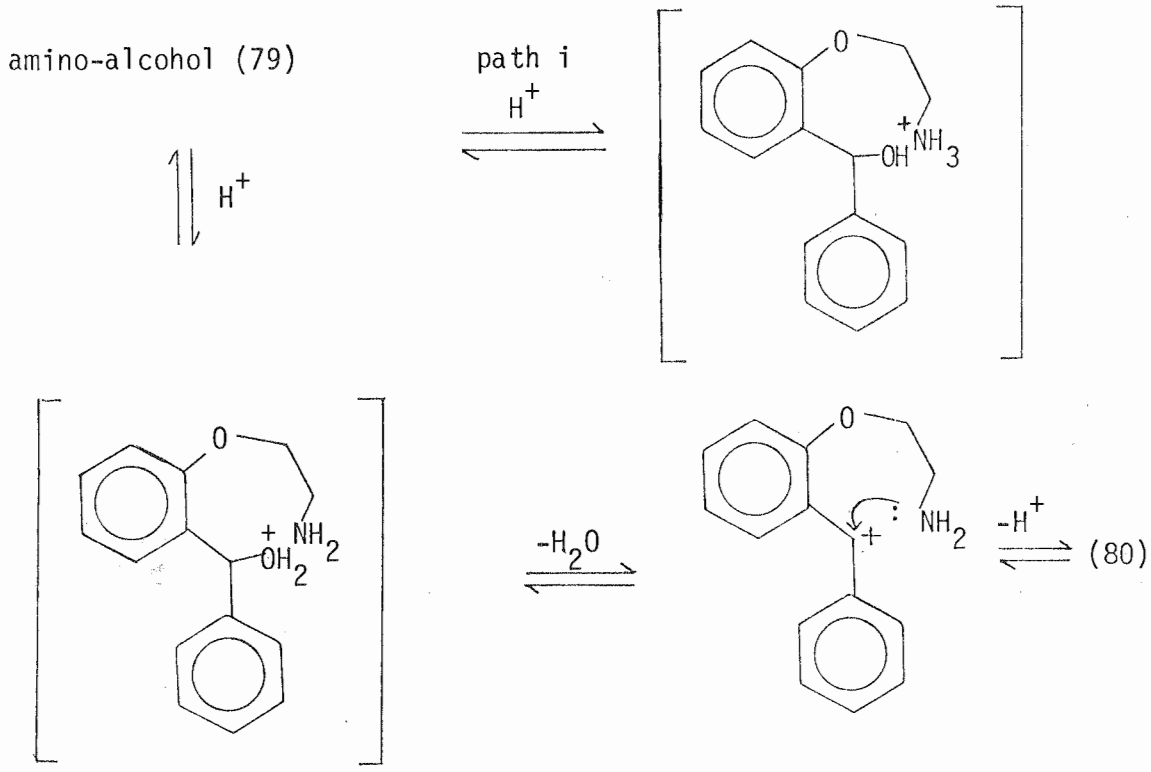
Attempted cyclodehydration of the amino-alcohol (79) in the presence of *p*-toluenesulfonic acid in xylene (Scheme 29) was



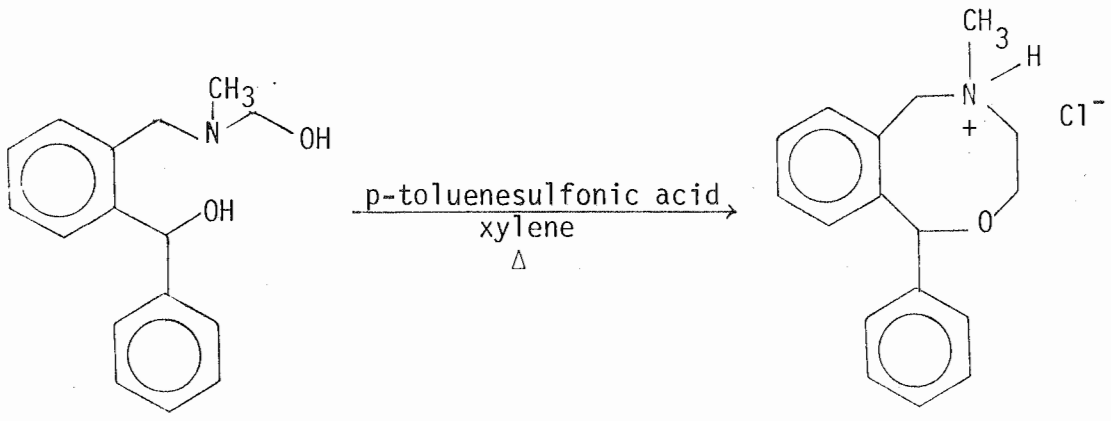
Scheme 31

unsuccessful. The failure was probably due to the formation of the $-\overset{+}{N}H_3$ species which would not undergo cyclodehydration (path i, Scheme 32).

A related method where salt formation of this type would not interfere has been employed successfully in the synthesis of *Nefopam* (82) using a compound of type (81)[60] (Scheme 33).



Scheme 32



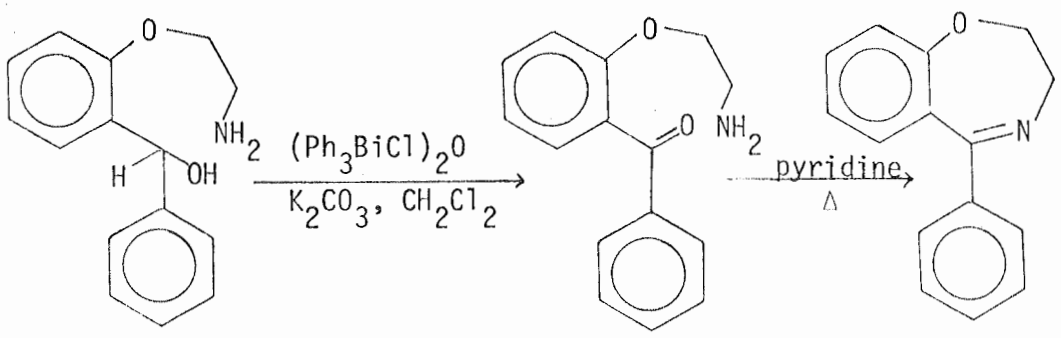
(81)

Scheme 33

(82)
Nefopam

Due to the failure of this attempted dehydration it was decided to oxidise the -OH group of the amino-alcohol (79) using a mild and selective oxidising agent, μ-oxobis(chlorotriphenylbismuth). The reagent selected was that developed by Barton and co-workers[61] for

the oxidation of the hydroxy groups especially in allylic alcohols.



(79) (71a) (61)

Scheme 34

The amino-alcohol (79) and the oxidising agent in dichloromethane were stirred with an excess of potassium carbonate at room temperature (Scheme 34). The product formed was not isolated because of the small amount of the material used for the reaction. Only the infrared spectrum of the crude product was taken, and a sharp absorption band at 1660 cm^{-1} was observed, suggesting the presence of a carbonyl group.

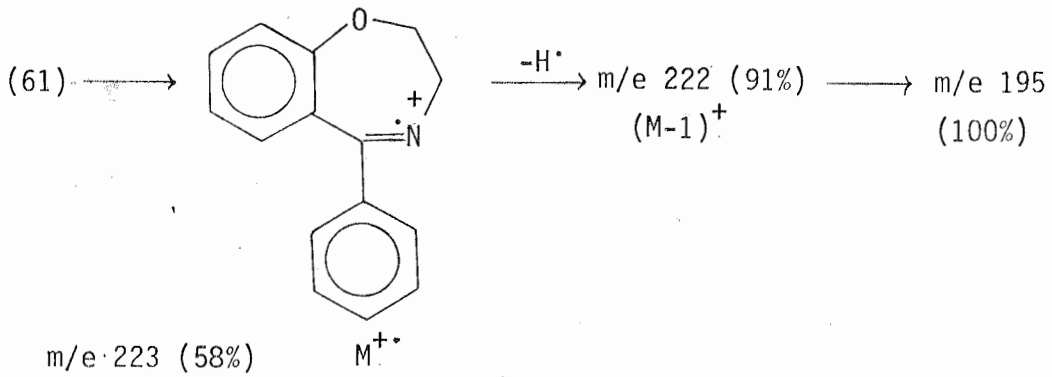
This material was refluxed in pyridine and the product was subjected to P.L.C. The component of the major band was isolated, and characterized by spectroscopic data.

In the infrared spectrum, the absorption bands at 1660 cm^{-1} and 3320 cm^{-1} found in the amino-alcohol (79) had disappeared and a new band at 1600 cm^{-1} (C=N frequency) was observed. This absorption band was a characteristic feature found in the 1,4-benzoxazepines (57-60) which were synthesised by the Bischler-Napieralski reaction.

The P.M.R. spectrum of this new compound gave further evidence in support of the structure (61). Two sets of downfield triplets (J 5Hz) derived from the four methylene protons at δ 3.80 and δ 4.68

were observed. These values are comparable with the chemical shifts observed for the $-NCH_2-$ and $-OCH_2-$ protons in the 1,4-benzoxazepines (57-60) prepared earlier (Table 2).

In the mass spectrum, the molecular ion peak appeared at m/e 223, confirming the structure of the 1,4-benzoxazepine (61). The mass fragmentation also followed the same pattern that was observed for the 1,4-benzoxazepines (57-60) (Scheme 35).

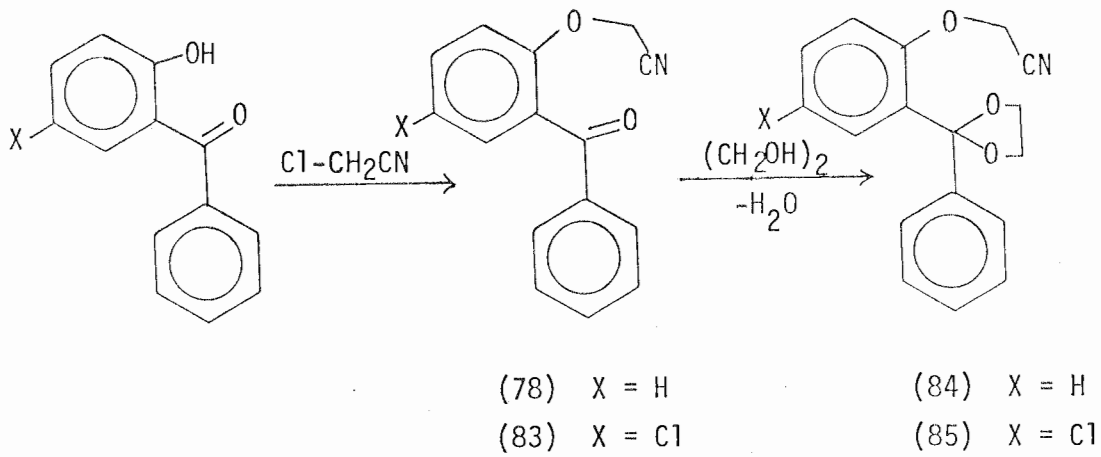


Scheme 35

This successful oxidation of the amino-alcohol (79) to the amino-ketone (71a) opened a new pathway in the synthesis of 1,4-benzoxazepines. However this route involves both the reduction of the carbonyl group to a hydroxyl group and the subsequent oxidation of that hydroxyl group back to the original carbonyl group; the preparation of μ-oxobis(chlorotriphenylbismith) is also lengthy and tedious. Thus attention was directed towards a protecting group for the carbonyl group in the keto-nitrile (78).

This was achieved by the formation of the ketal (84), from the reaction of the keto-nitrile (78) and ethylene glycol in the presence of *p*-toluenesulfonic acid in refluxing benzene.[62] Initially it was believed that ketal formation from this type of compound might not take place because of steric hindrance. However prolonged (five to ten hours) refluxing periods and removal of water using a Dean-Stark

trap resulted in an 85% yield of the ketal (84) (Scheme 36).

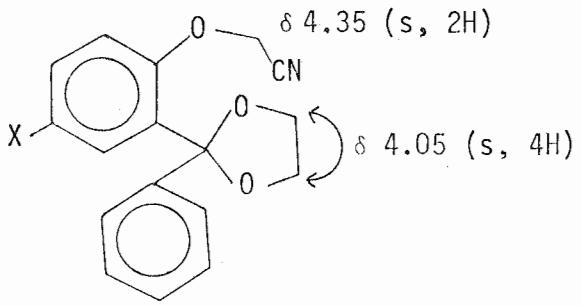


(78) X = H (84) X = H
(83) X = Cl (85) X = Cl

Scheme 36

This method was then extended to prepare the 4-chloro derivative (85) starting from 4-chlorobenzophenone (Scheme 36).

In the P.M.R. spectra of these ketals (84,85) the peaks derived from the four protons in the ketal group appeared as a singlet at δ 4.05. The signal derived from the $-OCH_2CN$ protons also appeared as a singlet at δ 4.35 (Figure 15). In the keto-nitriles (78,83) these two methylene proton singlets appeared at lower field (δ 4.70).

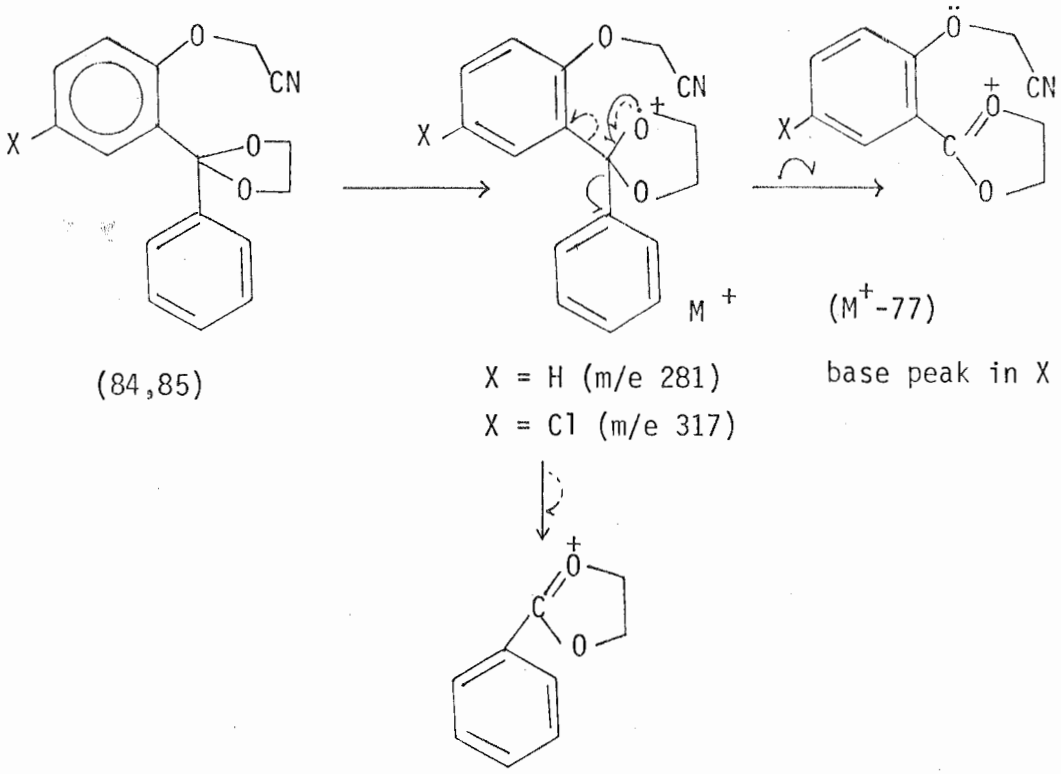


X = H, Cl

Figure 15

In the infrared spectra, the carbonyl frequency appearing at 1650-1660 cm^{-1} in the keto-nitriles (78,83) disappeared with ketal formation.

The mass spectra of the ketals (84,85) showed characteristic α-cleavage of the ketal grouping,[59] and a suggested mechanism for this fragmentation is outlined in Scheme 37.



(84,85)

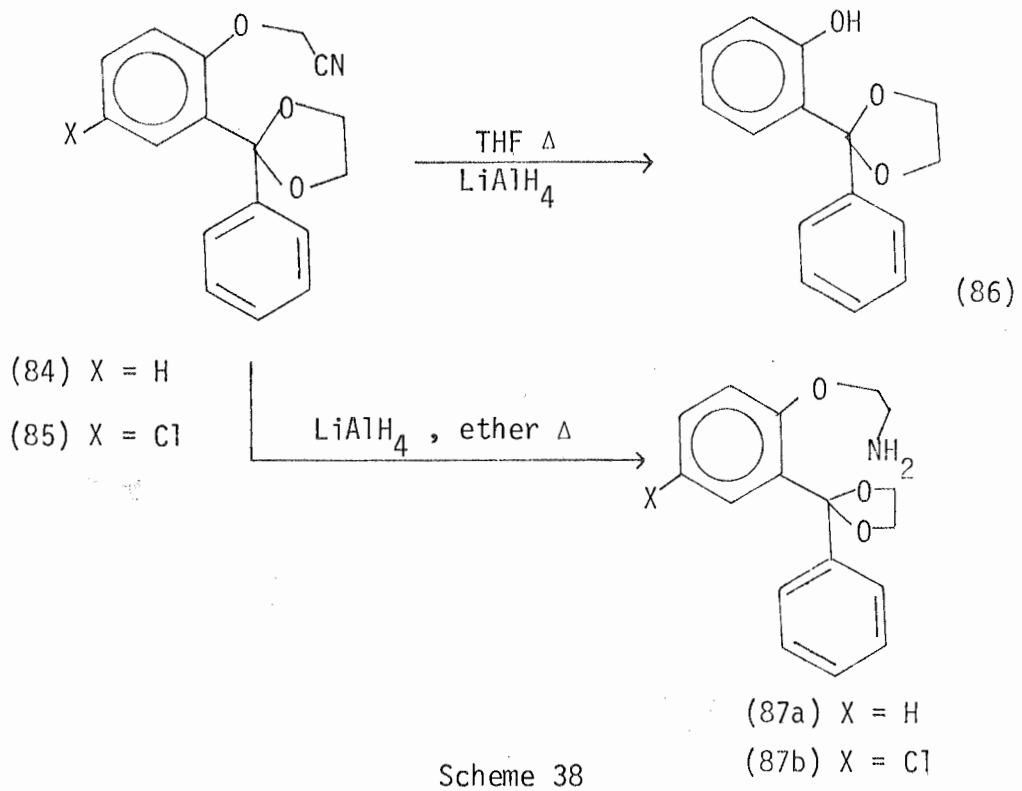
X = H (m/e 281)
X = Cl (m/e 317)

base peak in X = H

m/e 149 (base peak in X = Cl)

Scheme 37

Initially, the attempted reduction of the ketal (84) with lithium tetrahydridoaluminate in refluxing dry tetrahydrofuran[62] did not give the desired amino-ketal (87a). Instead, it resulted in the cleavage of the carbon-oxygen bond in the $-CH_2CN$ side chain giving rise to a hydroxy-ketal (86) (Scheme 38). Hence this reduction was carried out at lower temperature with lithium tetrahydridoaluminate in refluxing dry diethyl ether.



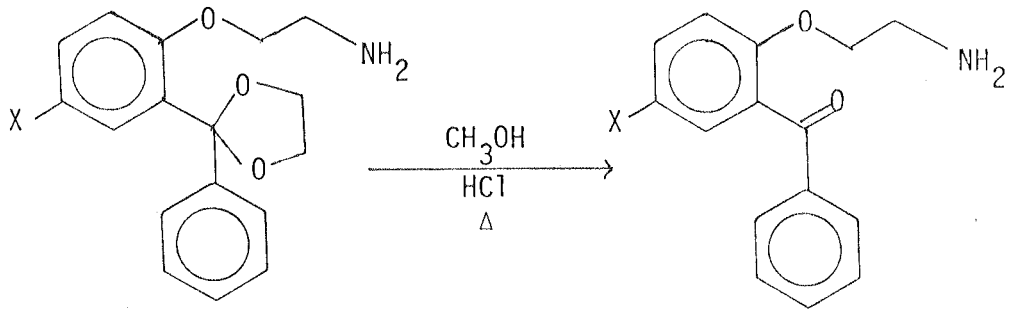
Scheme 38

The best results (66% yield) were obtained when the reaction mixture was refluxed in dry diethyl ether for about ten hours. At room temperature only partial reduction of the nitrile group occurred.

Similarly the amino-ketal (87b) was prepared in 80% yield (Scheme 38), starting from the corresponding nitrile (83). These amino-ketals were characterised by spectroscopic data.

The amino-ketones (71a,71b) were obtained in 73-86% yields, by hydrolysis of the corresponding amino-ketals (87a,87b) with 5 M hydrochloric acid in warm methanol (Scheme 39).

In the P.M.R. spectrum of the amino-ketone (71a) a two proton broad singlet at δ 1.20 which exchanged with D_2O, confirmed the presence of a $-NH_2$ group. In (71b), this signal appeared at δ 0.91. In the infrared spectra of these compounds (71a,71b) the carbonyl and the $-NH_2$ stretching frequencies appeared at 1660-1670 cm^{-1} (s)



(87a) X = H
(87b) X = Cl

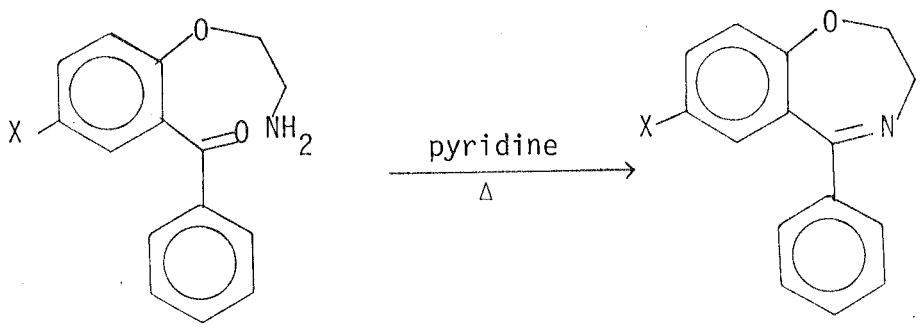
(71a) X = H
(71b) X = Cl

Scheme 39

and at 3300-3380 cm^{-1} (s) respectively.

2.3.2 Preparation of 1,4-benzoxazepines (61,62) by cyclodehydration of the amino-ketones (71a,71b)

The cyclodehydration of the amino-ketones (71a,71b) was carried out in refluxing pyridine, and the 1,4-benzoxazepine derivatives (61,62) thus prepared were characterized spectroscopically.



(71a) X = H
(71b) X = Cl

(61) X = H
(62) X = Cl

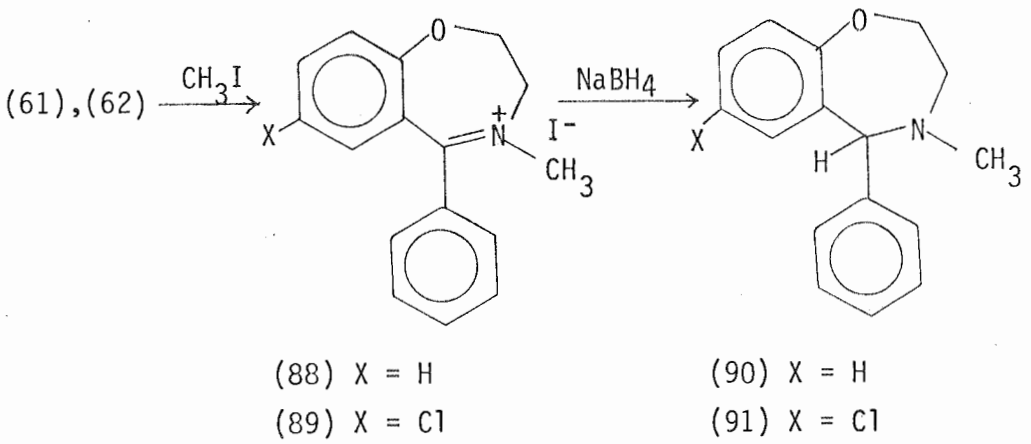
Scheme 40

In the P.M.R. spectrum of 7-chloro-5-phenyl-2,3-dihydro-1,4-benzoxazepine (62), the signals which derived from the four methylene

protons in the $-NCH_2-$ and $-OCH_2-$ groups appeared as two triplets at δ 3.80 and δ 4.65 respectively (J 5Hz). The mass spectrum also followed the same fragmentation pattern observed for other 1,4-benzoxazepines (57-60) (page 30).

2.3.3 Quaternization followed by reduction of the 1,4-benzoxazepines (61,62) prepared by a C-N approach

The methiodide salts (88) and (89) were prepared quantitatively by the treatment of the imines (61,62) with iodomethane, as described for the 1,4-benzoxazepines (57-60) in page 30 (Section 2.2.3a). These salts were then reduced with sodium tetrahydridoborate to give the corresponding 2,3,4,5-tetrahydro-1,4-benzoxazepines (90) and (91) in yields of 67% and 49% respectively (Scheme 41).



(88) X = H
(89) X = Cl

(90) X = H
(91) X = Cl

Scheme 41

In the P.M.R. spectra of the cyclic amines (90,91) the singlet derived from the benzylic proton on C-5 appeared in the range of δ 4.89-δ 4.96. These values were similar to those observed for signals derived from the analogous benzylic proton in the cyclic amines (67-70) (Table 3). The peaks which derived from the $-OCH_2-$ and $-NCH_2-$ methylene protons appeared as multiplets (see page 32).

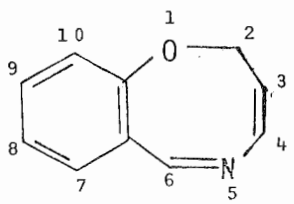
The infrared and mass spectral data of the compounds (90,91) were also similar to those of the previously prepared 2,3,4,5-tetrahydro-1,4-benzoxazepines. Hence the analysis of the spectral data from (90,91) were similar to that given in section 2.2.2.

CHAPTER 3

Synthesis of 1,5-Benzoxazocines

3.1 Introduction

Nine out of the fifteen possible isomers of benzoxazocines have been reported so far, viz. the 1,4-, 1,5-, 1,6-, 2,3-, 2,4-, 2,5-, 3,1-, 4,1- and 5,1-benzoxazocines.[63] Many methods were employed to prepare these derivatives and only those used for the preparation of 1,5-benzoxazocines (Figure 16) will be presented in this section.



2*H*-1,5 benzoxazocine

Figure 16

The methods employed to synthesise 1,5-benzoxazocine derivatives can be divided into two types:

a) ring interconversions

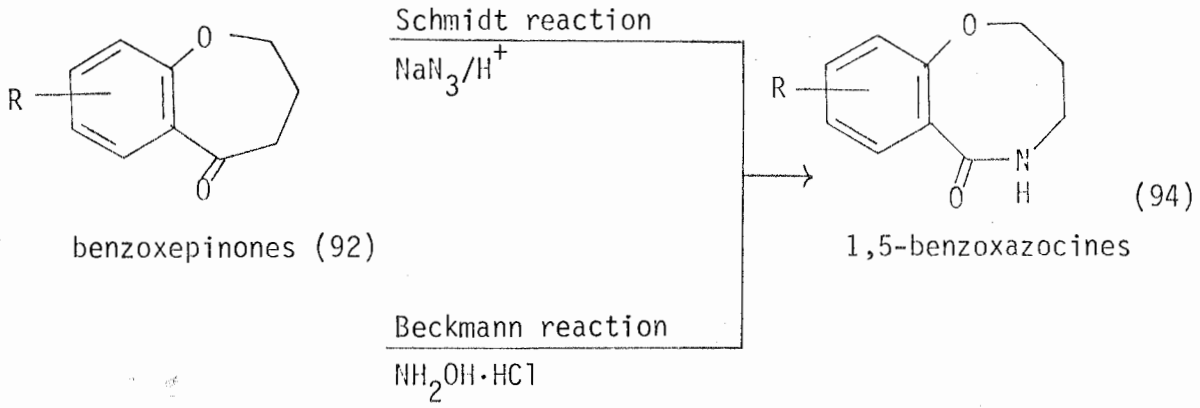
and b) ring constructions.

3.1.a Ring interconversions

The few ring interconversion reactions used for the preparation of 1,5-benzoxazocines were the same as those reported for the 1,4-benzoxazepines (Section 2.1a), viz. the Beckmann rearrangement[64,65] and the Schmidt reaction.[65-68]

The common precursors used for these reactions were the benzoxepinones (92) and the benzoxepinone oximes (93) (Scheme 42).

In most cases the formation of both the 1,5- (94), and 1,6-benzoxazocines (95) were observed due to alkyl and aryl migrations respectively (Scheme 42).



benzoxepinones (92) — 1,5-benzoxazocines (94)

benzoxepinone oximes (93) — 1,6-benzoxazocines (95)

R = H, 8-CH_3, 7-CH_3, 9-Cl, 9-CH_3 etc.

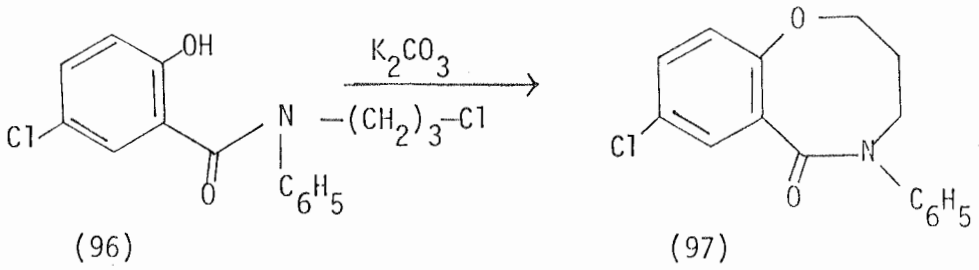
Scheme 42

3.1.b Ring constructions

The synthesis of 1,5-benzoxazocines by ring construction has been achieved by the formation of either a C-O or a C-N type of bond. Unlike the 1,4-benzoxazepines, neither the Bischler-Napieralski cyclization nor any other C-C type of bond formation had been employed.

3.1.bi C-O Type ring closure

The construction of the 1,5-benzoxazocines by a C-O type of bond formation is limited to one case[69] (Scheme 43) and one other.[43]

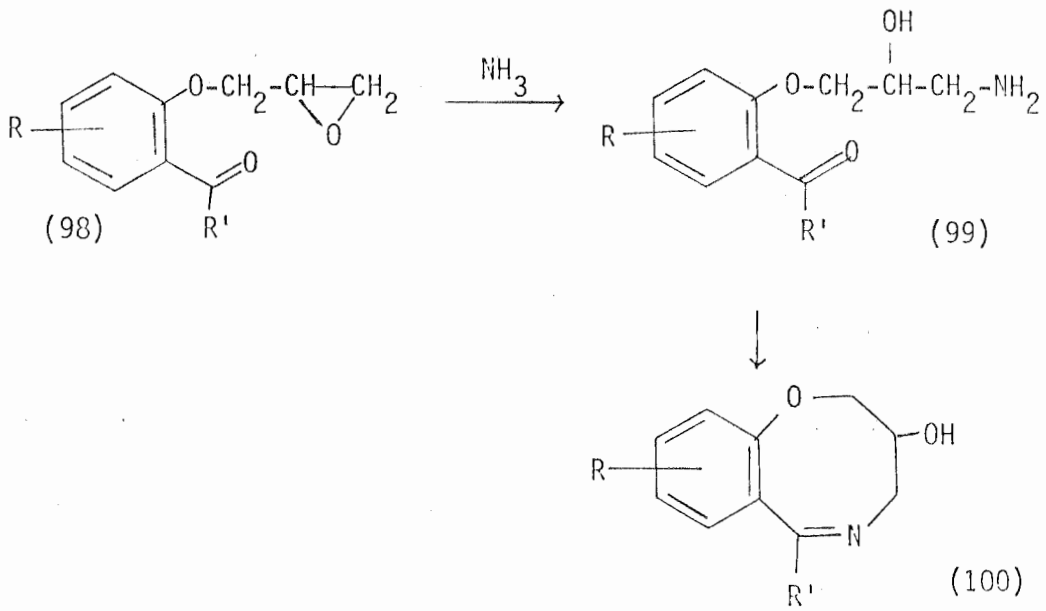


(96) (97)

Scheme 43

3.1.bii C-N Type ring closure

Two methods have been employed to prepare the derivatives of 1,5-benzoxazocines by the formation of a C-N bond. In one method several 1,5-benzoxazocines (100) were obtained in yields ranging from 4-58%, by the reaction of *O*-acetylphenoxy propane oxides (98) with methanolic ammonia[70] (Scheme 44). This reaction was found to proceed slowly through the formation of an intermediate amino-alcohol (99).



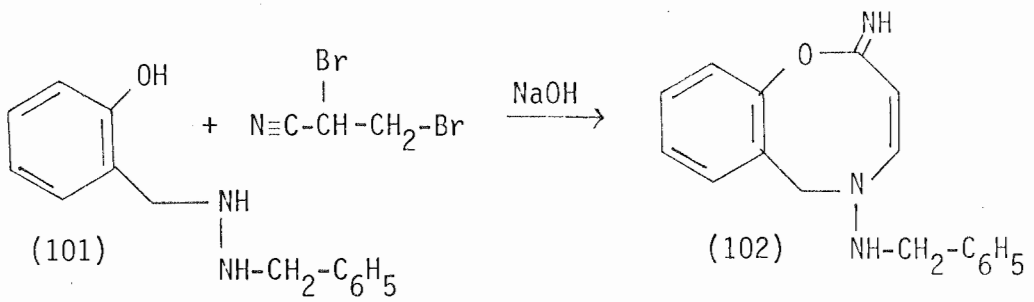
(98) (99) (100)

R = 3-CH_3, 8-Cl, 8-NO_2 etc.

R' = CH_3, C_6H_5, 4-CH_3-C_6H_4 dtc.

Scheme 44

The other method used was a condensation reaction[71] (Scheme 45).



Scheme 45

Apart from the above mentioned reactions, no other synthetic approaches were reported for the preparation of the 1,5-benzoxazocines.

3.2 Results and Discussion

3.2.1 Synthesis of the 1,5-benzoxazocines by a C-C ring closure approach

3.2.1a Preparation of the precursors

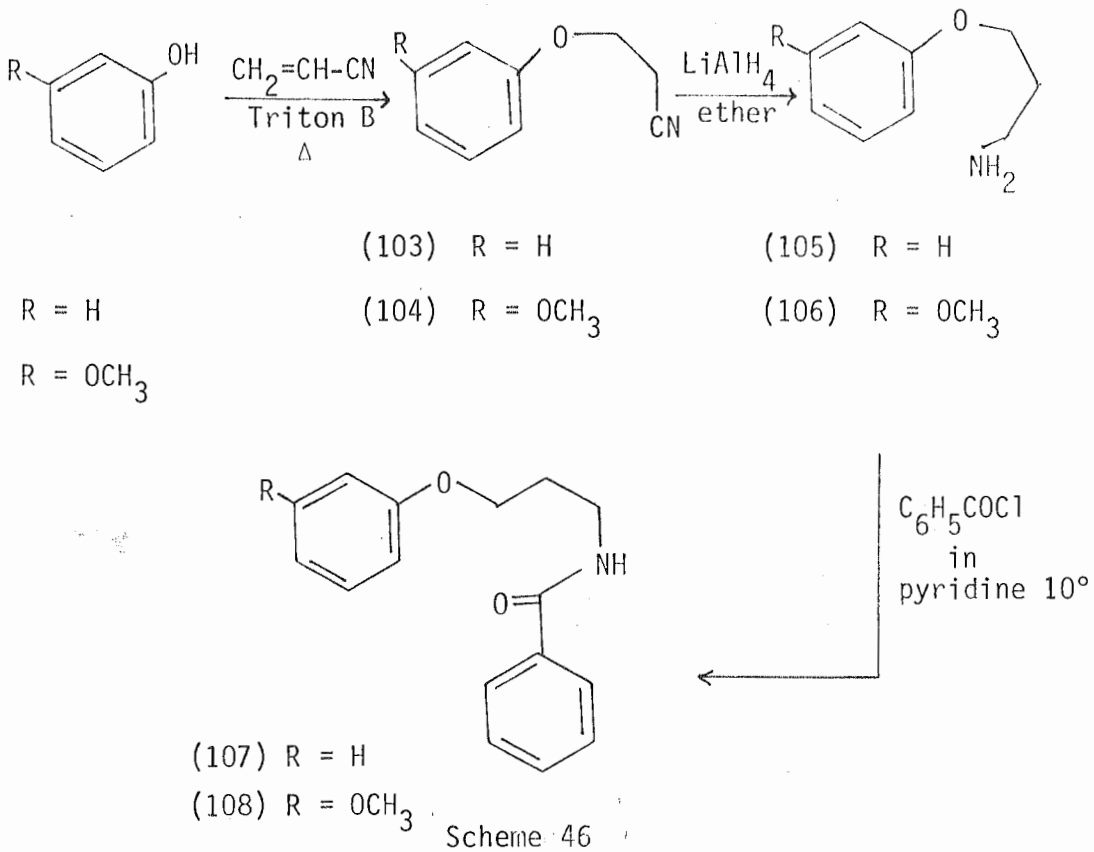
The preparation of the amides (107,108) were easily carried out by the general method outlined in Scheme 46.

The nitriles (103,104) were prepared in yields of 50% and 68%, by the reaction of the corresponding phenols and refluxing acrylonitrile in the presence of "Triton B" (benzyl dimethylacetyl-ammonium hydroxide) as described by Bachman and co-workers.[72]

In the P.M.R. spectra of the nitriles (103,104), the peaks which derived from the $-CH_2CN$ and $-OCH_2-$ protons appeared as triplets and the chemical shift values are given in Table 4.

In the infrared spectra of the compounds (103) and (104), the nitrile frequencies appeared at 2222 cm^{-1} and 2240 cm^{-1} (vs) respectively.

The nitriles (103) and (104) were reduced with lithium tetrahydridoaluminate in dry ether to obtain the amines (105) and (106)



Scheme 46

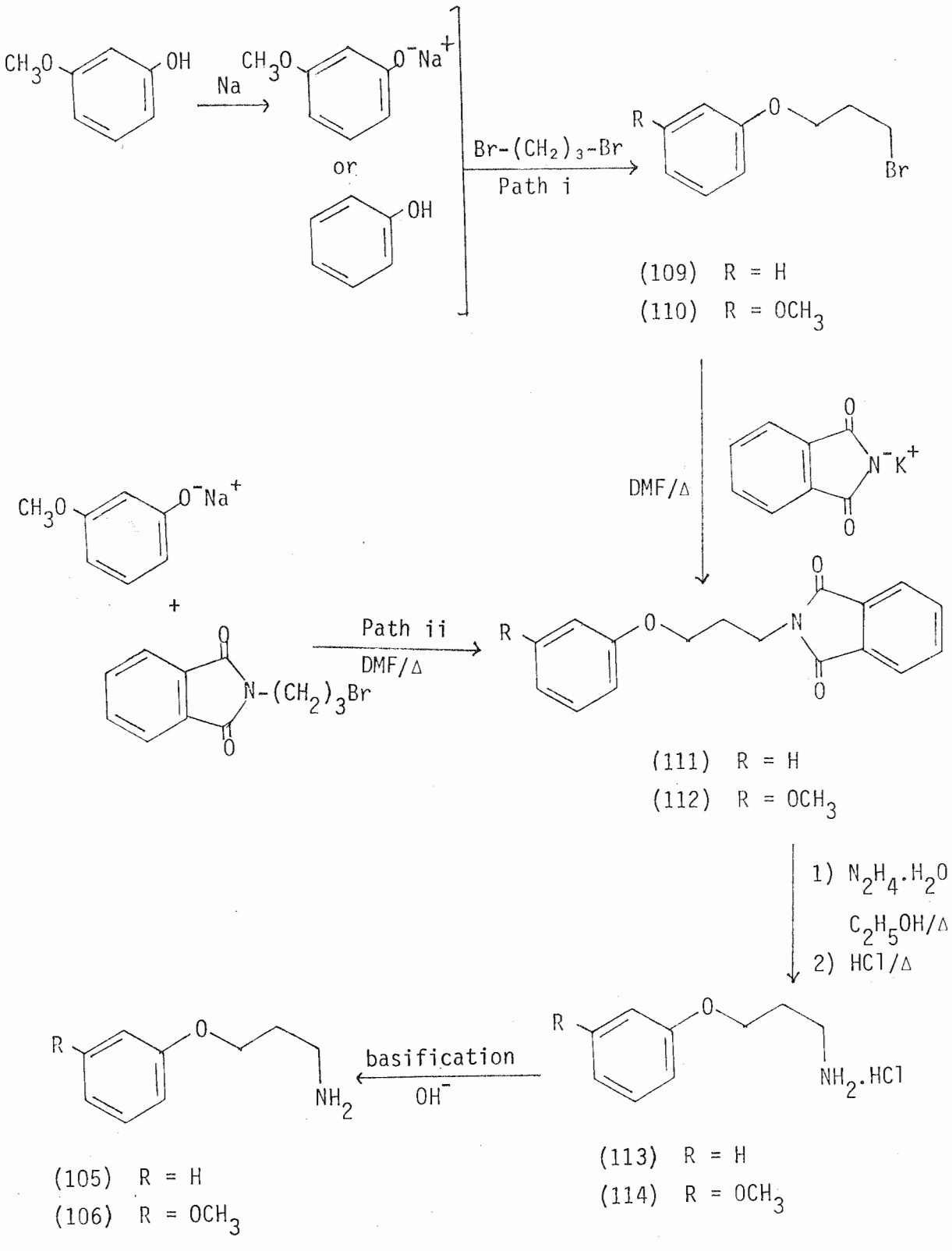
TABLE 4

Chemical Shifts of Methylene Protons in Nitriles (103,104)

Nitrile	Chemical shift δ	
	$-C-CH_2-CN$	$-OCH_2-$
(103)	2.73	2.80
(104)	4.12	4.16
	5 Hz	5 Hz

in yields of 40% and 50% (Scheme 46) respectively. An alternative method employed to synthesise the amines (105,106) is given in Scheme 47.

The 3-bromopropoxy derivative (109) was prepared by the reaction of the phenol and 1,3-dibromopropane in the presence of aqueous sodium hydroxide. The 3-methoxy analogue (110) was prepared by the


CH3O
OH
Na
CH3O
O⁻Na⁺
or
OH
Br-(CH2)3-Br
Path i
R
O
Br
(109) R = H
(110) R = OCH3
DMF/Δ
O
N⁻K⁺
O
CH3O
O⁻Na⁺
+
O
N-(CH2)3Br
O
Path ii
DMF/Δ
R
O
N
O
O
(111) R = H
(112) R = OCH3
1) N2H4.H2O
C2H5OH/Δ
2) HCl/Δ
R
O
NH2.HCl
basification
OH⁻
R
O
NH2
(105) R = H
(106) R = OCH3
(113) R = H
(114) R = OCH3

Scheme 47

treatment of sodium 3-methoxyphenolate with 1,3-dibromopropane in dimethylformamide under anhydrous conditions. Both the compounds (109) and (110) were purified by fractional distillation under vacuum to obtain the pure compounds in yields of 60% and 20% respectively. These were then characterized spectroscopically.

The reaction of the bromo compounds (109,110) with potassium phthalimide in dry dimethylformamide gave the corresponding phthalimide derivatives (111) and (112) in yields of 98% and 63% respectively.

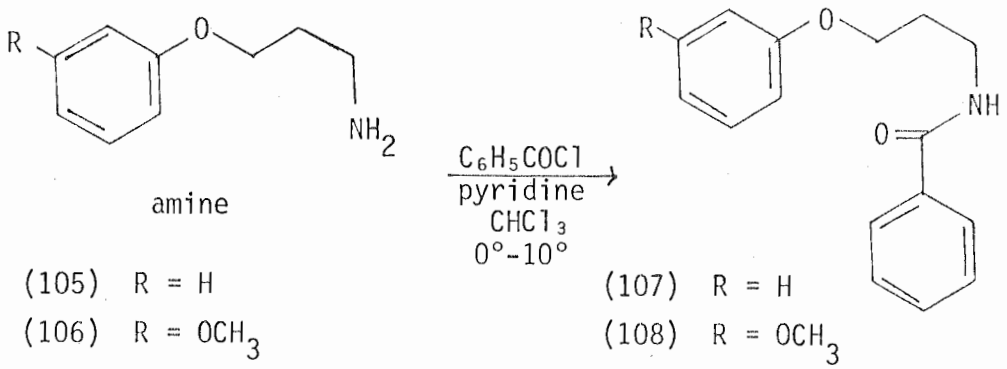
The phthalimide derivative (112) was also readily prepared in 85% yield by the reaction of sodium 3-methoxyphenolate and *N*-(3-bromopropyl)phthalimide in anhydrous dimethylformamide (path ii, Scheme 47). When this reaction was performed with *N*-2-bromoethyl-phthalimide it did not result in the expected product (47) (Section 2.2.1, page 24); a possible β-elimination of the 2-bromoethyl-phthalimide was suspected in this case. With 3-bromopropylphthalimide such an β-elimination or other side reactions were not observed, and this method was more satisfactory than that given in Scheme 47 (path i).

The phthalimide derivatives (111) and (112) were then treated with hydrazine hydrate followed by hydrochloric acid to give the corresponding amine hydrochlorides (113,114) in yields of 98% and 63% respectively (Scheme 47). The hydrochloride salts were characterized by spectroscopic data, and the free bases were prepared by basification of the salts.

The method given in Scheme 47 (path i) was also employed to synthesise the precursors of the 1,4-benzoxazepines (Section 2.2.1, Scheme 18, page 23).

The amides (107,108) required for the Bischler-Napieralski reaction were prepared by the reaction of the amines (105,106) with

benzoyl chloride in pyridine and chloroform at < 10° (Scheme 48).



amine

(105) R = H
(106) R = OCH_3

(107) R = H
(108) R = OCH_3

Scheme 48

In the P.M.R. spectra of the amides (107,108), the peak which derived from the exchangeable proton in the -NHCO- group appeared as a broad singlet in the range of δ 6.55-δ 6.85. The signals derived from the methylene protons adjacent to the amide group and the protons in the $-C-CH_2-C-$ group appeared as two multiplets while the $-OCH_2-$ proton signal appeared as a triplet. The chemical shift values of these protons are given in Table 5.

TABLE 5

Chemical Shifts of Methylene Protons in the Amides (107,108)

Amide	Chemical shift (δ)			
	NH	$N-CH_2$	$C-CH_2-C$	$O-CH_2$
(107)	6.55-6.72 (br., S, 1H)	3.60-3.86 (m, 2H)	2.00-2.22 (m, 2H)	4.15 (t, 2H, J 6.25Hz
(108)	6.55-6.85 (br., S, 1H)	3.55-3.75 (m, 2H)	2.05-2.30 (m, 2H)	4.09 (t, 2H, J 6.25Hz

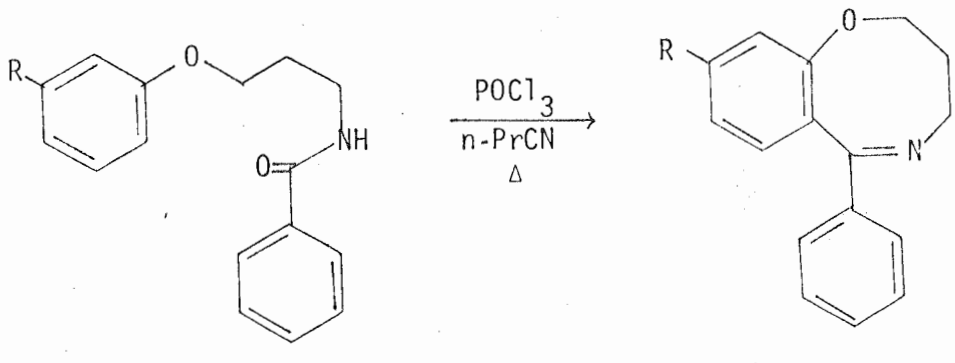
In the infrared spectra, the amide carbonyl and the -NH- frequencies appeared as strong bands at 1625 cm^{-1} and 3280-3300 cm^{-1}

respectively.

3.2.2a The Bischler-Napieralski cyclization of the amides (107,108)

Preparation of 1,5-benzoxazocine derivatives by construction of a C-C bond via the Bischler-Napieralski reaction has not been previously reported. However this reaction was found to be successful in constructing the 1,4-benzoxazepines described in Chapter 2. Therefore it was decided to try and extend the Bischler-Napieralski cyclization to prepare the 1,5-benzoxazocines from their corresponding amides.

Thus the amide (108) and freshly distilled phosphorus oxychloride in dry butanenitrile were refluxed for sixteen hours (Scheme 49), in the same manner as described for the 1,4-benzoxazepines[21] (Chapter 2.2).



(107) R = H
(108) R = OCH_3

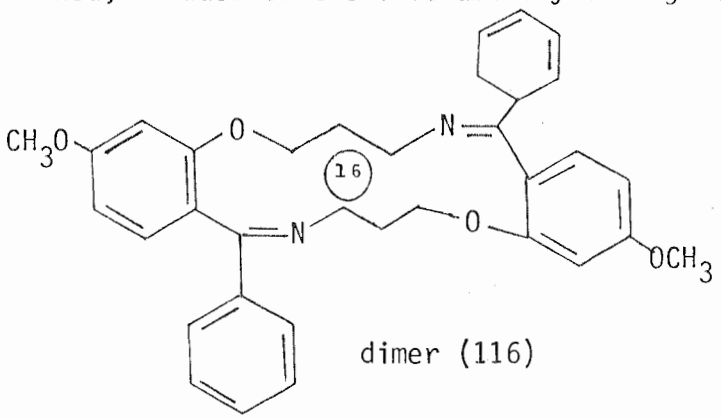
(115) R = OCH_3

Scheme 49

After standard work-up, the syrup obtained was extracted with warm diethyl ether. This resulted in the precipitation of a white powder, which was soluble in dilute inorganic acids.

The ether soluble fraction was purified by P.L.C. to give a very low yield (11%) of the eight-membered imine (115). The ether insoluble

white powder might be the cyclic dimer (116) (Figure 17) by mass spectral data. A P.M.R. spectrum of this compound could not be obtained, because of the insolubility in organic solvents.



dimer (116)

Figure 17

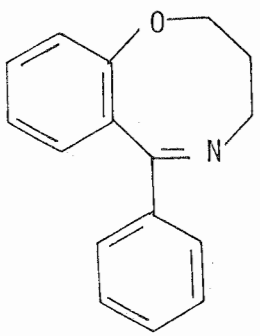
To try and increase the yield of the imine (115), shorter refluxing periods and high dilution conditions were employed unsuccessfully. The Bischler-Napieralski cyclization of the amide (108) was then carried out in the lower boiling solvent ethanenitrile, instead of butanenitrile. This gave a slightly increased yield (≈ 18%) of the cyclic imine (115) and a small amount (≈ 2%) of the dimeric product (116).

By increasing the dilution in ethanenitrile (1 g of amide in 60 ml of ethanenitrile), the yield of the imine (115) was also increased, but beyond this point further dilution of the reaction mixture did not increase the imine formation. Under these high dilution conditions and lowered reaction temperatures, the formation of the dimer (116) was not observed. The highest yield of the imine (115) obtained by this method was 42%.

The cause of the dimerization reaction was not further investigated, but it was thought to be initiated by an acid catalysed reaction in the more concentrated solutions. This type of a dimer formation was not observed with the 1,4-benzoxazepines described in

Chapter 2 (Section 2.2.2, page 25). However during the synthesis of other eight- and twelve-membered ring systems, formation of dimeric products has been observed,[73,63] and competing intermolecular reactions could give rise to these dimeric products.

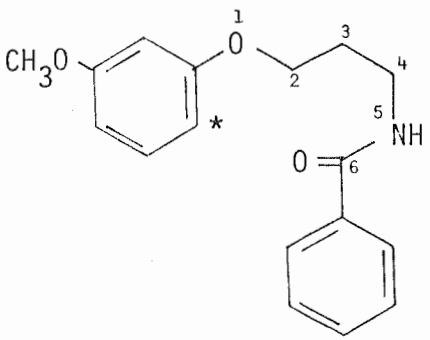
Attempted preparation of 6-phenyl-3,4-dihydro-2*H*-1,5-benzoxazocine (117) from the amide (107) by the Bischler-Napieralski cyclization, using the abovementioned conditions was unsuccessful. The use of stronger dehydrating agents (phosphorus pentoxide in phosphorus oxychloride) in various solvents (ethanenitrile, butanenitrile, benzene, xylene, toluene) also failed to give the desired eight-membered ring system (117) with no substituents on the fused benzene ring.



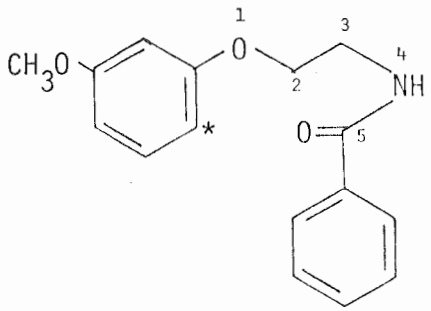
(117)

As described earlier in Chapter 2 (Section 2.2) the Bischler-Napieralski reaction is an electrophilic substitution reaction. In the amide (108) the methoxy group on the benzene ring, *para* to the ring closure position, activates the benzene ring towards an electrophilic attack (Figure 18).

The degree of activation of this position in the amides (108) and (51) is the same, but the amide (108) has the longer side chain. Therefore the electronic effects operating between the ring closure point and the electrophile ($-\overset{+}{N}\equiv C$) (Figure 19) of this system (amide 108) can be expected to be decreased when compared



(108)



(51)

Figure 18

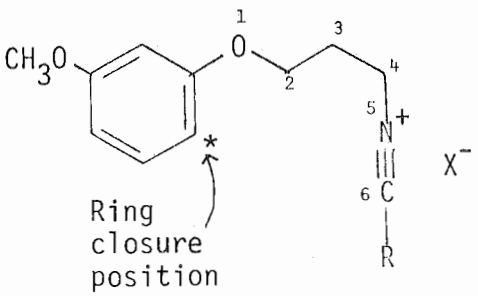


Figure 19

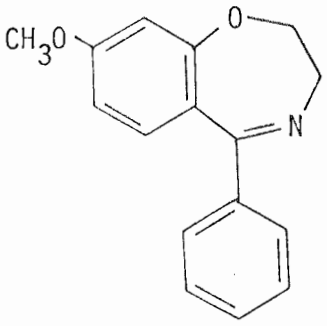
with that of the amide (51). Meanwhile the intermolecular reactions also would compete with this intramolecular cyclization. This could account for the formation of the dimers and the lowered yield (10-42%) of the monomeric product, 1,5-benzoxazocine (115), when compared with that of 80% yield of the 1,4-benzoxazepine (57).

The mechanism of the Bischler-Napieralski reaction is discussed in Chapter 2 (Section 2.1.bi, Scheme 11, page 12). No other 1,5-benzoxazocines were prepared by this method.

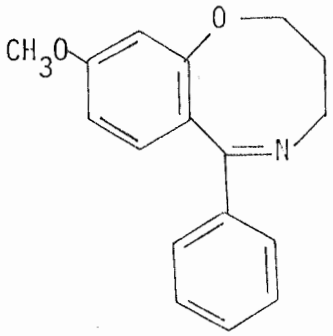
3.2.2b Spectral analysis of 9-methoxy-6-phenyl-3,4-dihydro-2*H*-1,5-benzoxazocine (115)

In the P.M.R. spectrum of the imine (115), the signals which

derived from the three sets of methylene protons appeared as multiplets, in comparison with the triplets observed in the seven-membered analogue (57).



(57)



(115)

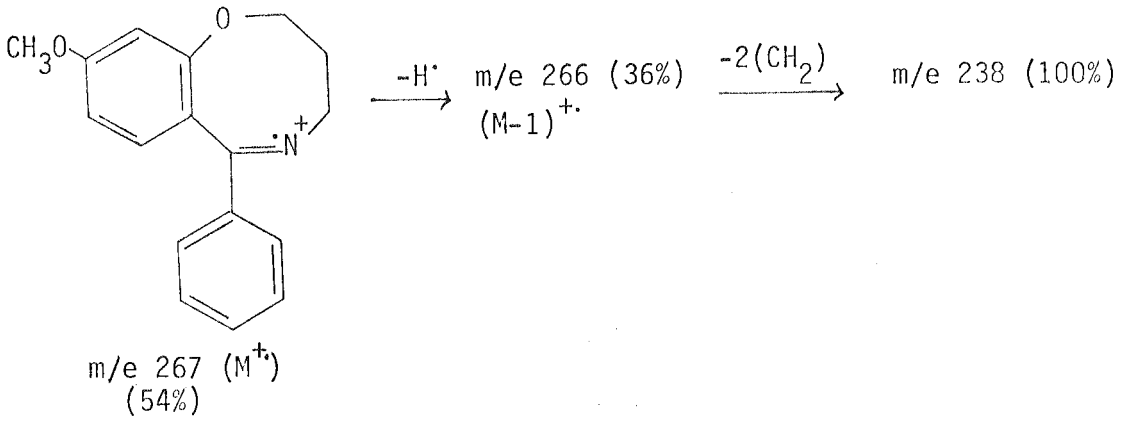
With the increase in ring size, the rigidity of the molecule decreases and, this flexibility in the larger rings could allow the molecules to arrange in several conformations. Therefore both geminal and vicinal coupling could occur and this would give rise to the multiplets derived from the protons in the $-OCH_2-$ and the $-NCH_2-$ groups in the eight-membered imine (115) (Table 6).

TABLE 6

Variation of Methylene Chemical Shifts with Ring Size

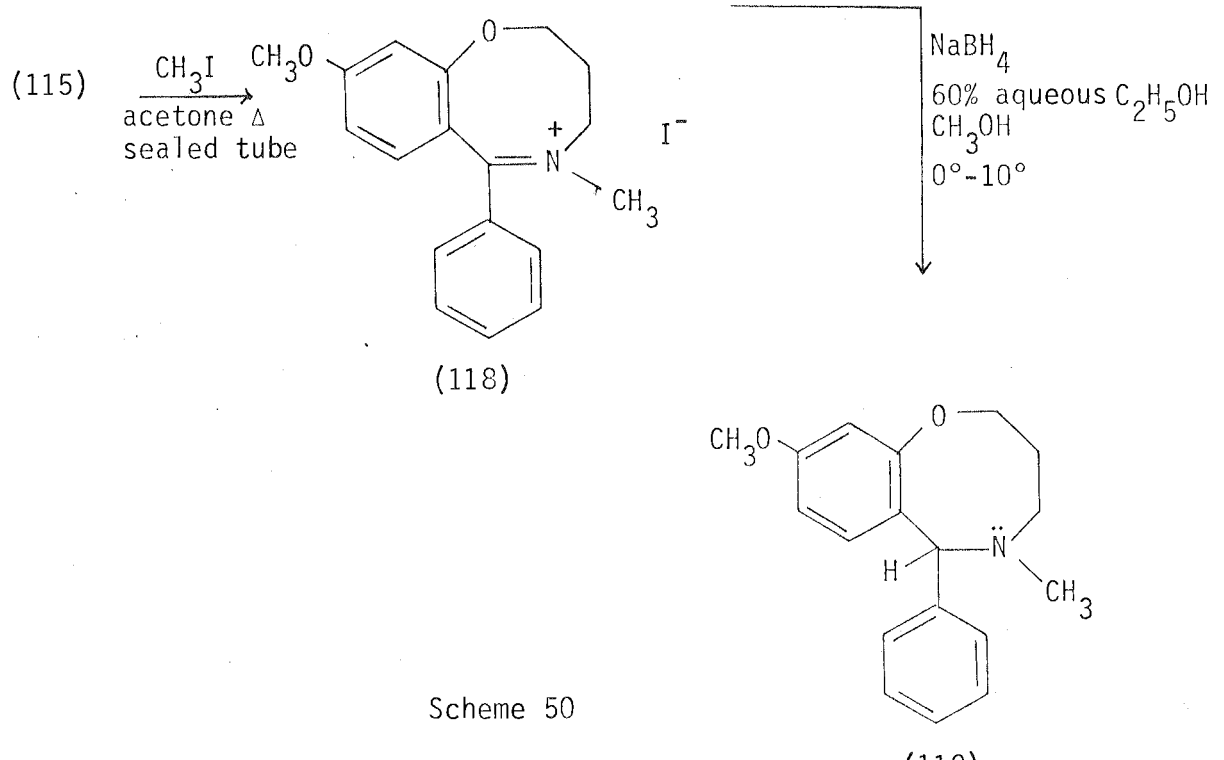
Type of protons	Chemical shift (δ)	
	Seven-membered imine (57)	Eight-membered imine (115)
$-C-CH_2-C-$	-	m, 1.98-2.00
$-NCH_2-$	t, 3.88	m, 3.40-3.72
$-OCH_2-$	t, 4.68	m, 4.00-4.50

In the infrared spectrum, the C=N frequency (vs) appeared at 1600 cm^{-1}. The mass spectrum of the imine (115) also followed a similar fragmentation pattern to those observed for the seven-membered imines (57-62).



3.2.3a Quaternization followed by reduction of the 1,5-benzoxazocine (115)

The methiodide salt (118) was prepared quantitatively by the reaction of the imine (115) and redistilled iodomethane in anhydrous acetone (Scheme 50). As described for the 1,4-benzoxazepines (57-62) the quaternization was carried out in a sealed tube and heated for seven hours at 100-110°. The salt (118) obtained was characterized by spectroscopic data and by microanalysis.

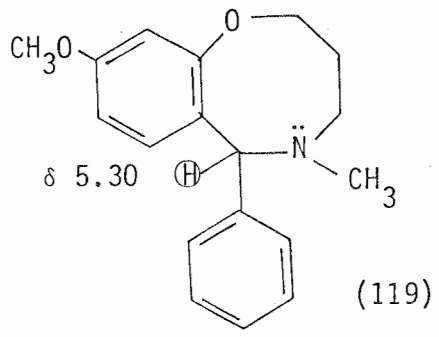


Scheme 50

The methiodide salt (118) was converted to the amine (119) by the treatment of sodium tetrahydridoborate in a solution of 60% aqueous ethanol and methanol at <10°. The amine (119) was obtained in 90% yield as a pale yellow gum.

3.2.3b Spectral analysis of 9-methoxy-5-methyl-6-phenyl-3,4,5,6-tetrahydro-2*H*-1,5-benzoxazocine (119)

In the P.M.R. spectrum of (119) (Figures 20,21) a one proton singlet which appeared at δ 5.30 confirmed the presence of a benzylic proton. In the seven-membered analogue (67) this benzylic proton resonated at a higher magnetic field (δ 4.90) (Table 3, page 32).



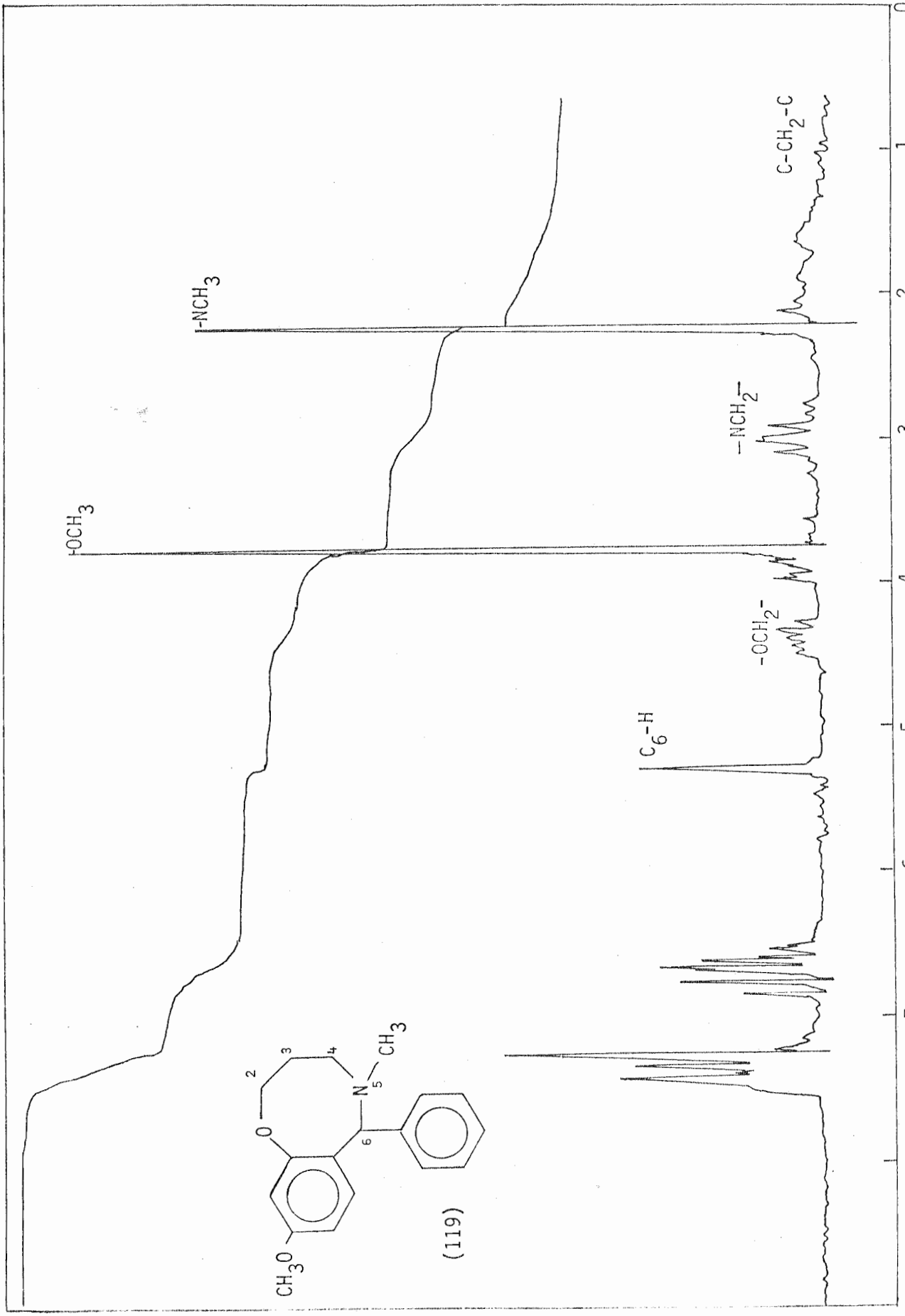
(119)

Figure 20

Since the substitution pattern of the fused benzene rings was the same in both imines, this change in chemical shift values might have been due to the change in the size of the fused heterocyclic ring.

With the reduction of the $-C=\overset{+}{N}<$ bond, an up-field chemical shift of the three sets of methylene protons was observed relative to that of the imine (115). The same observation was made with the 2,3,4,5-tetrahydro-1,4-benzoxazepines (67-70,90,91), and the possible reason for this was discussed in Section 2.2.3b.

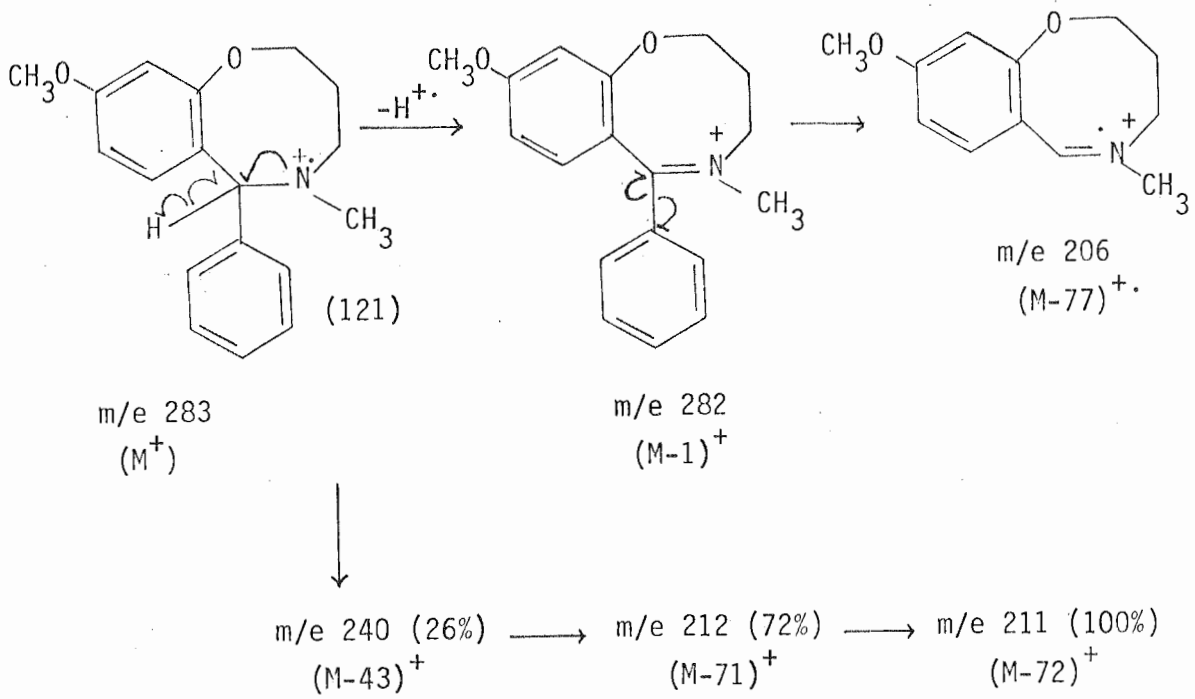
In the mass spectrum, the molecular ion peak appeared at m/e 283, consistent with the structure of the amine (119). The base peak



(119)

FIGURE 21

appeared at m/e 211 $(M-72)^+$, as a result of the fragmentation between $-O_1-O_2-$ and $-N_5-C_6-$ bonds (Scheme 51). The fragmentation between the C_6 and pendant benzene ring gives rise to the peak which appeared at m/e 206. A suggested mechanism for this fragmentation is given in Scheme 51.



Scheme 51

The ^{13}C N.M.R. spectrum obtained gave further evidence in support of the structure of (119), and the chemical shift values for the carbon atoms present in the molecule were assigned[75] as in Figure 22.

3.3 Preparation of the 1,5-benzoxazocines by a C-N ring closure approach

Since the Bischler-Napieralski reaction was found to be a rather unsatisfactory method of synthesis of 1,5-benzoxazocines, an attempt was made to prepare these ring systems by the construction of a C-N bond, instead of a C-C bond. To prepare the amino-ketone precursor (122) required for this type of a bond formation, two different pathways

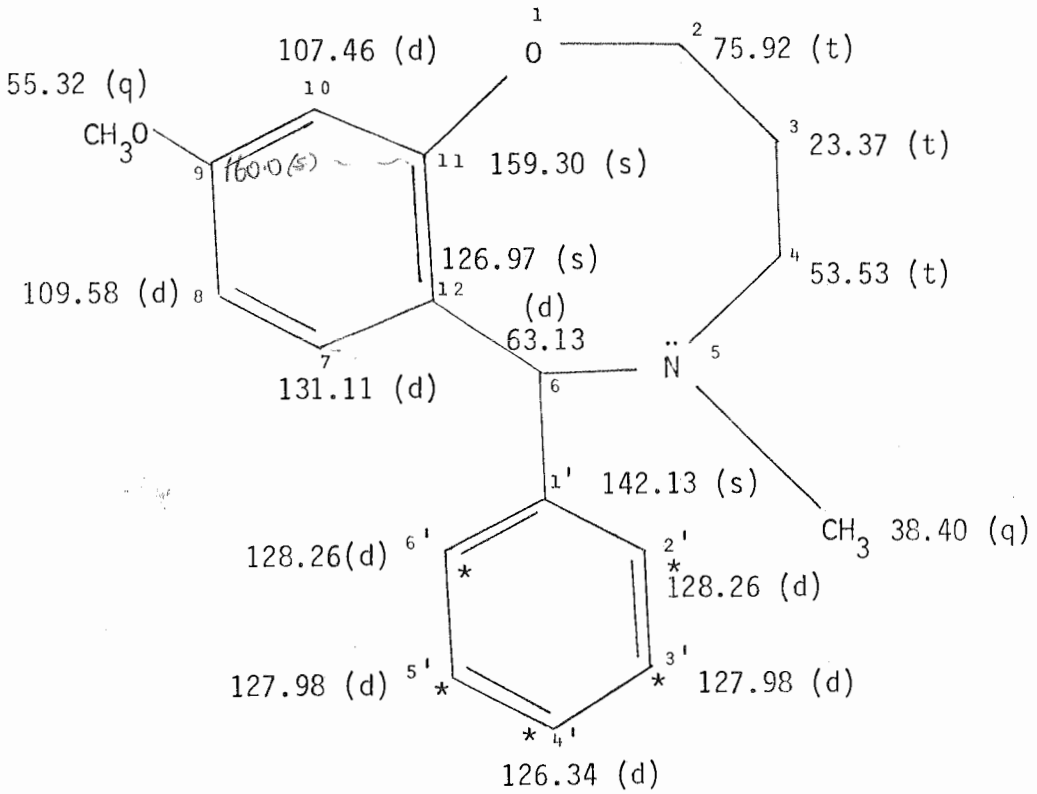
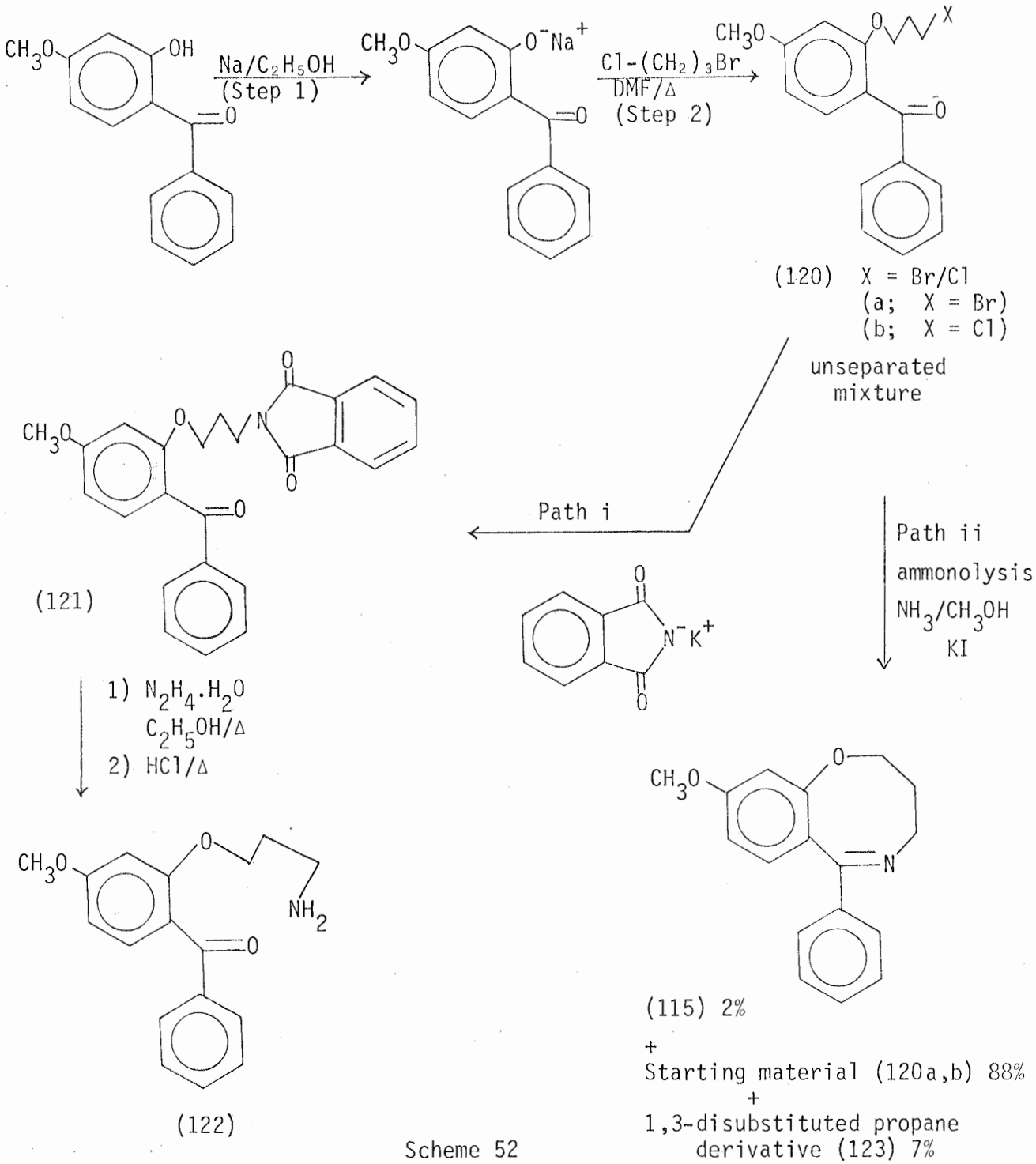


Figure 22

were followed starting with 2-hydroxy-4-methoxybenzophenone (Scheme 52).

In the first route (Scheme 52, step 2) the dried sodium salt of 2-hydroxy-4-methoxybenzophenone was treated with 1-bromo-3-chloropropane in refluxing dimethylformamide under anhydrous conditions to obtain a mixture of (120a) and (120b) in a ratio of 3:1.[74] The total yield of these halides was about 70%; they were used for the ammonolysis and Gabriel-phthalimide synthesis without further purification.

The phthalimide derivative (121) was prepared by the reaction of (120a,b) and potassium phthalimide in dry dimethylformamide (Scheme 52, path i). However cleavage of the phthalimide group in

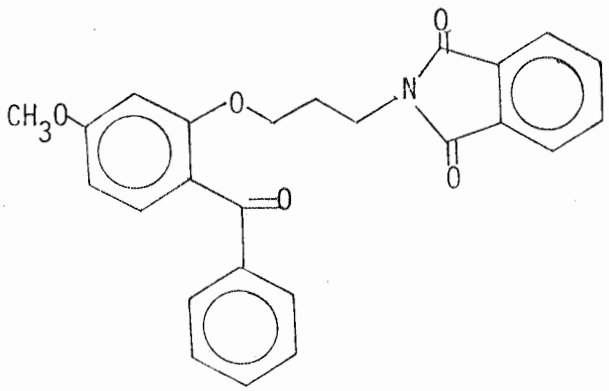


Scheme 52

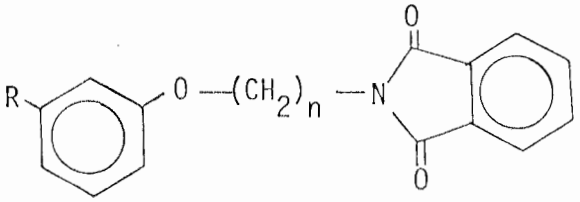
(121) with hydrazine hydrate followed by the treatment with hydrochloric acid did not give the desired amino-ketone (122). The basic fraction isolated from this reaction could not be identified.

With hydrazinolysis of the compounds (46,47,111,112) this difficulty was not encountered and the reactions proceeded smoothly

giving rise to the corresponding amine hydrochlorides in high yields (range 63%-100%).



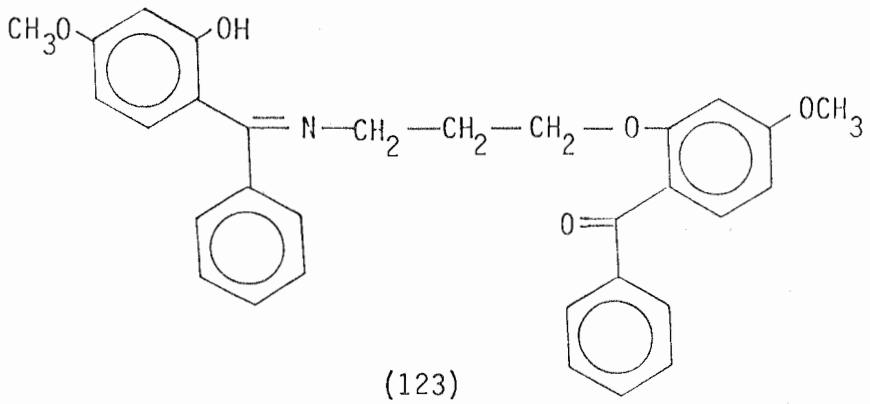
(121)



(46) R = H, n = 2
(47) R = OCH_3, n = 2
(111) R = H, n = 3
(112) R = OCH_3, n = 3

As an alternative route to obtain the amino-ketone (122), the compound (120a,b) was subjected to ammonolysis with methanolic ammonia[70] in the presence of potassium iodide (Scheme 52, path ii). The temperature of the reaction mixture was maintained at 35°-40° and stirring was continued for several hours. After the work-up, followed by purification, 88% of the unchanged starting material (120a,b) was recovered from the non-basic fraction. In the basic fraction none of the desired amino-ketone (122) was found, but interestingly 2% of the eight-membered imine (115) was isolated. The imine (115) isolated was characterized spectroscopically and by comparison with the authentic sample (115) obtained earlier.

The remainder (about 7%) isolated from the basic fraction was found to be a 1,3-disubstituted propane derivative having the possible structure of (123).



(123)

In the P.M.R. spectrum of this compound (123), the two, three proton singlets which possibly derived from the two methoxy groups appeared at δ 3.81 and δ 3.88. The two proton multiplets at δ 1.60-1.76 and the two proton triplets which appeared at δ 2.95 and δ 3.97 (J 6.25Hz) suggested the presence of three sets of $-CH_2-$ groups. The peaks in the aromatic region integrated for seventeen protons and no exchangeable proton was detected (Figure 23).

In the infrared spectrum, the carbonyl frequency appeared at 1650 cm^{-1}, but no hydroxy frequency was visible. In many of the benzophenones, the hydroxy frequency is not apparent in the infrared spectrum due to intramolecular hydrogen bonding. To detect the presence of a possible hydroxy group, an *O*-methylation reaction was carried out with diazomethane. In the P.M.R. spectrum of the product isolated from this reaction, no additional signal for a methoxy group was observed and the spectrum remained identical to that of the 1,3-disubstituted propane derivative (123).

In the mass spectrum, the molecular ion peak appeared at m/e 495 and this value is consistent with the proposed structure of (123). The mass fragmentation pattern that was observed by the metastable ions, is given in Scheme 53.

Further studies on the structure and the origin of the product

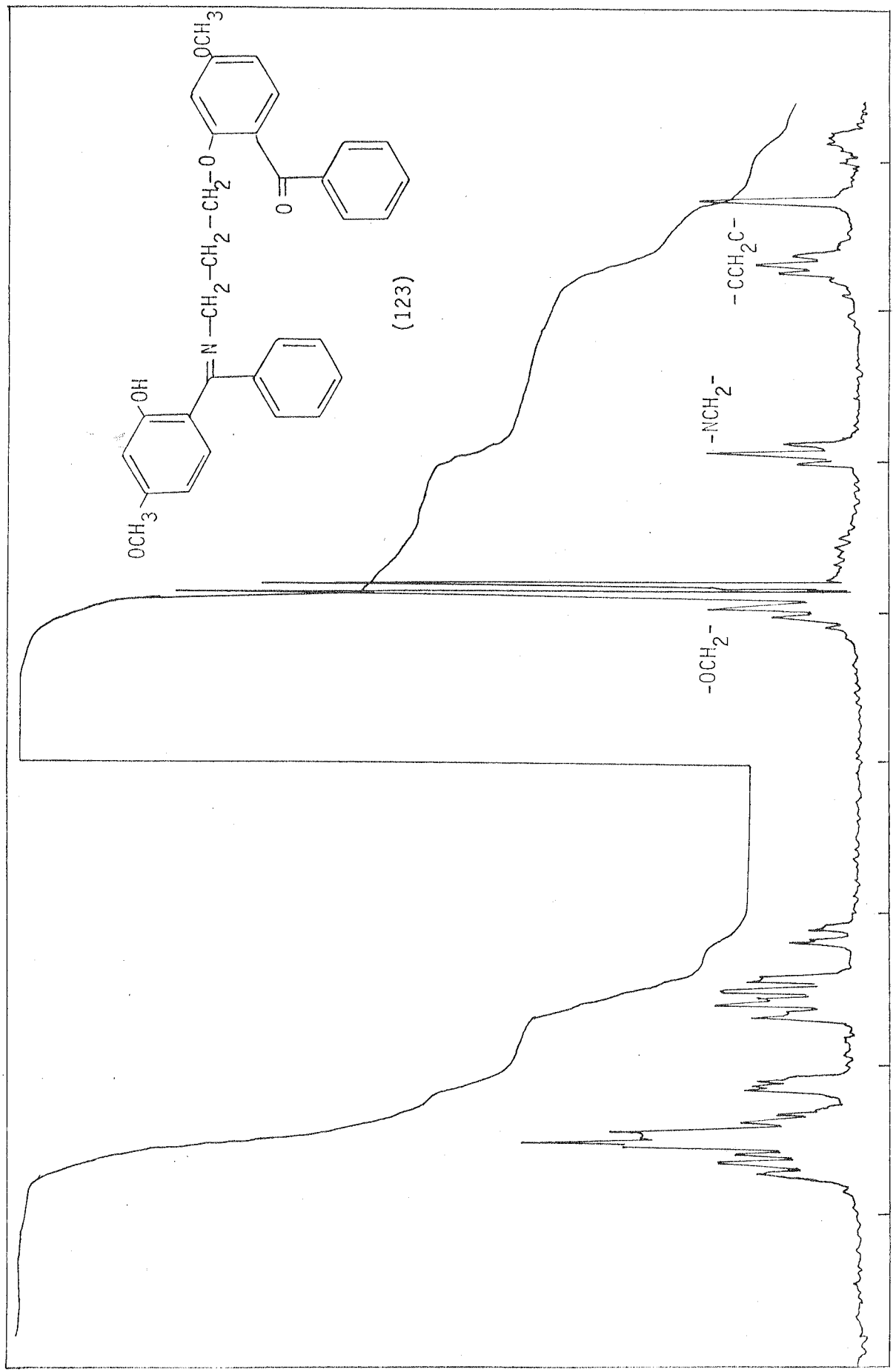
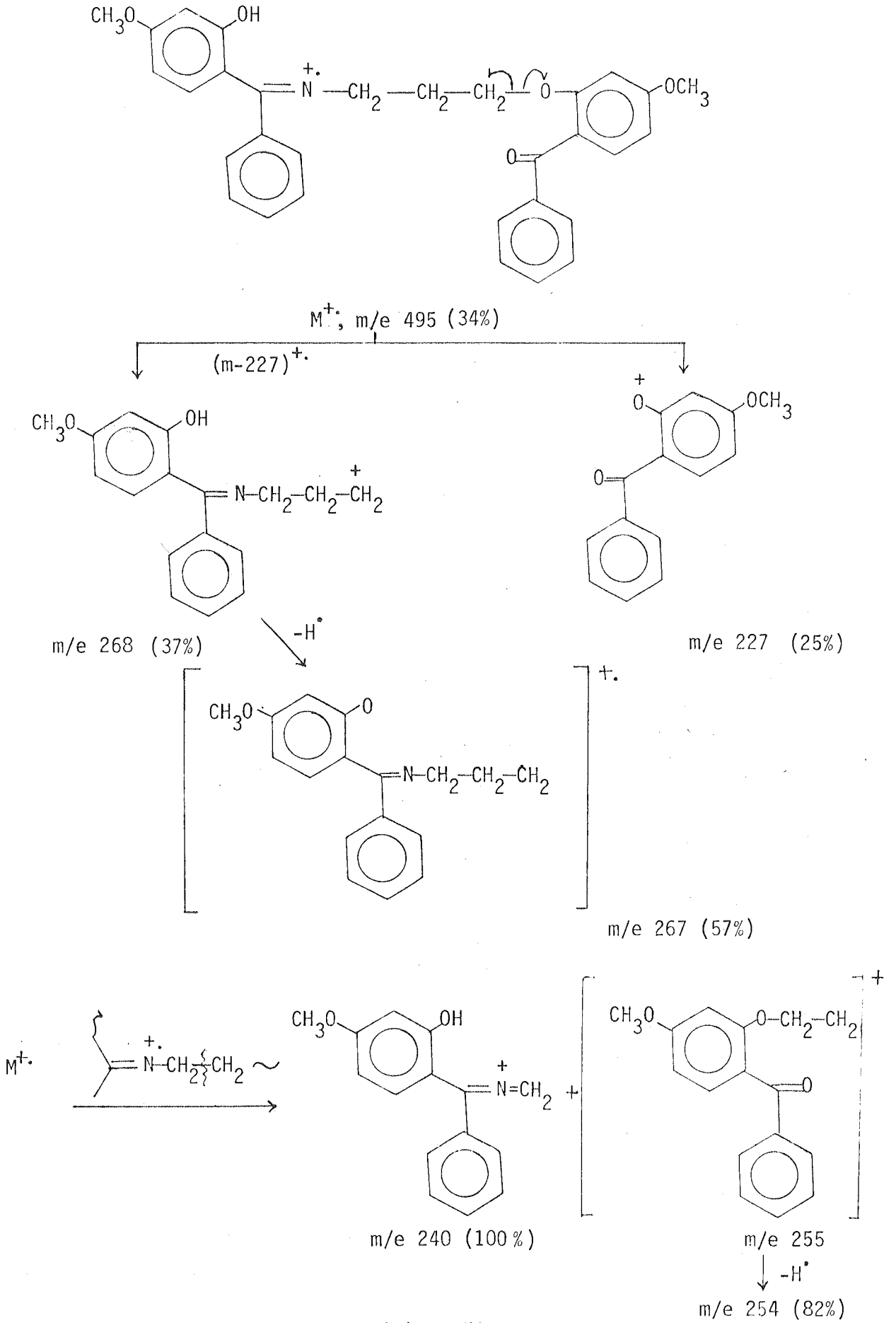

δppm
1
2
3
4
5
6
7
8
-OCH2-
-NCH2-
-CCH2C-
OCH3
OH
OCH3
N
CH2
CH2
CH2
O
O
(123)

FIGURE 23

(123) were not conducted, but it was possible that a trace amount of the unchanged 2-hydroxy-4-methoxybenzophenone in the alkylated product (120a,b) might have contributed to the production of this compound.

Attempted ammonolysis of the mixed halides (120a,b) was carried out several times, but the results obtained remained unchanged. Hence, further attempts to prepare 1,5-benzoxazocines by a C-N ring closure approach were abandoned. Attempts to prepare the seven-membered analogues (Chapter 2, page 35) by similar routes were unsuccessful. However in the synthesis of 1,4-benzoxazepines, a different method (Section 2.3, page 35) was developed to overcome this problem. This method was not extended to the preparation of the eight-membered analogues.

Possible mass fragmentation pattern suggested for the 1,3-substituted propane derivative (123)



Scheme 53

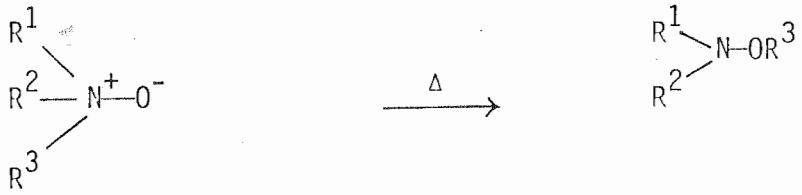
CHAPTER 4

The Meisenheimer Rearrangement of the Benzoxaza Ring Systems

4.1 Introduction

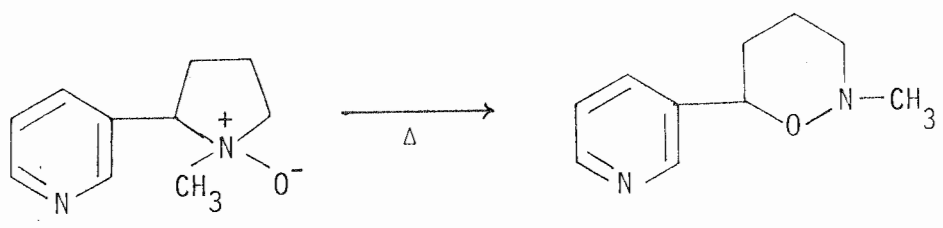
4.1.1 Historical background

The Meisenheimer rearrangement involves a thermal conversion of a tertiary amine oxide into a substituted hydroxylamine (Scheme 54).



Scheme 54

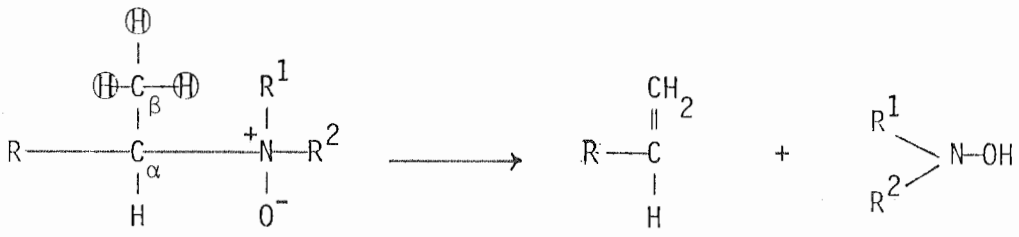
Although Pinner[76] had described the thermal conversion of nicotine-1-oxide (124) to 2-methyl-6-(3'-pyridyl)-tetrahydro-1,2-oxazine (125), it was some years later that Meisenheimer et al.[77] described this conversion as a rearrangement (Scheme 55).



(124) (125)

Scheme 55

During investigations on this rearrangement, Cope and co-workers[78] observed an elimination reaction which occurred with *N*-oxides having a hydrogen atom on a carbon atom *beta* to the nitrogen. The products formed were identified as an alkene and a hydroxylamine (Scheme 56).



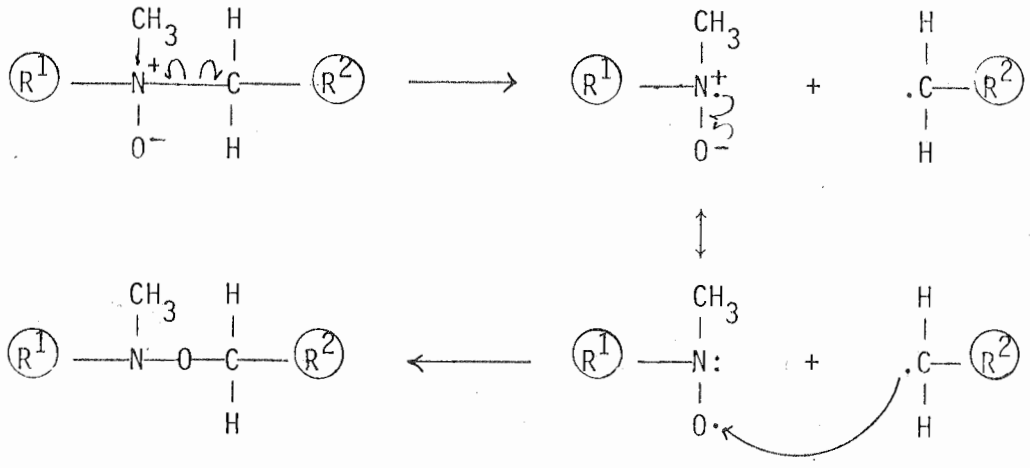
Scheme 56

The *N*-oxides without such a β-hydrogen atom did not undergo the elimination, and gave rise to the corresponding substituted hydroxylamines by the Meisenheimer rearrangement. The alternative reaction (Scheme 56) became known as the Cope elimination.

For *N*-oxides in which either elimination or rearrangement could occur, the reactions were found to be competitive.[79] In addition, the group which migrated during the rearrangement could also influence the direction of the rearrangement. For a successful rearrangement, the migratory group should be able to delocalize the electron density effectively at the migration centre; steric factors operative in the *N*-oxide also have an effect on the rearrangement. In *N*-oxides which are conformationally capable of forming a planar five-membered transition state, the elimination is favoured over the rearrangement.[79] Therefore success of the Meisenheimer rearrangement depends on a number of factors.

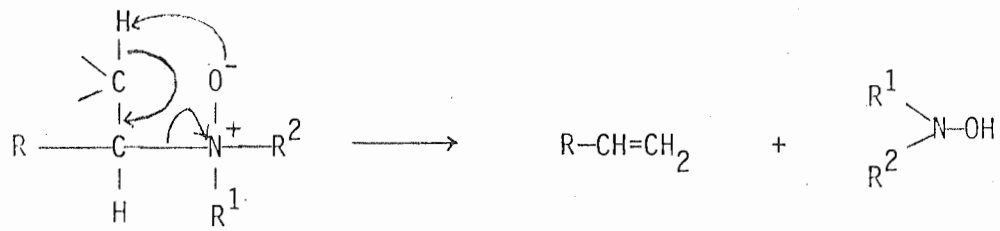
The mechanism of the Meisenheimer rearrangement is believed to follow a free radical pathway rather than an ionic pathway.[79] The

formation of free radicals by homolytic cleavage of the carbon-nitrogen bond has been detected by CIDNP (Chemically induced dynamic nuclear polarization) experiments.[80] The proposed free-radical pathway of the Meisenheimer rearrangement is given in Scheme 57.



Scheme 57

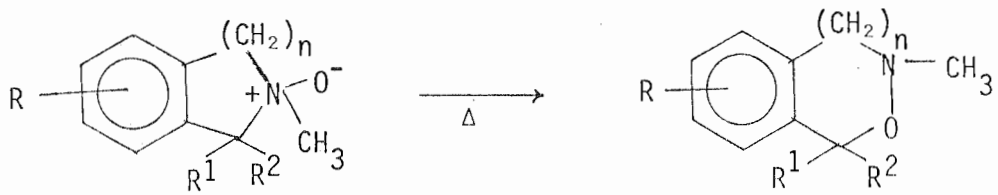
The suggested mechanism of the Cope elimination is shown in Scheme 58.



Scheme 58

4.1.2 Application of the Meisenheimer rearrangement in the synthesis of fused heterocyclic systems

Despite Pinner's[76] initial observations, until recently the application of the Meisenheimer rearrangement to the synthesis of heterocyclic systems was largely neglected.[cf 81] Most of the work reported on the use of this rearrangement in the synthesis of fused oxaza ring systems has been carried out in this Department.[81-84] Several seven-to-nine membered benzoxaza ring systems have been prepared from *N*-oxides of isoquinoline (126), benzazepine (127), and benzazocine (128) derivatives respectively[81,82] (Scheme 59).



(126) n = 2 (129) n = 2, benzoxazepines

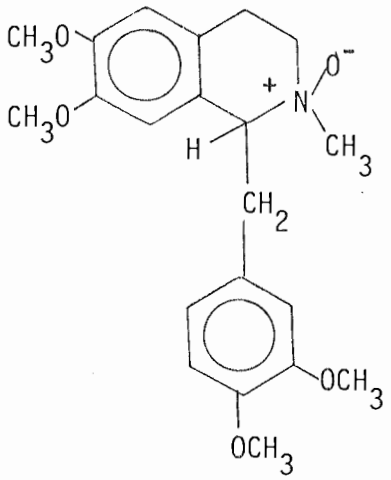
(127) n = 3 (130) n = 3, benzoxazocines

(128) n = 4 (131) n = 4, benzoxazonines

Scheme 59

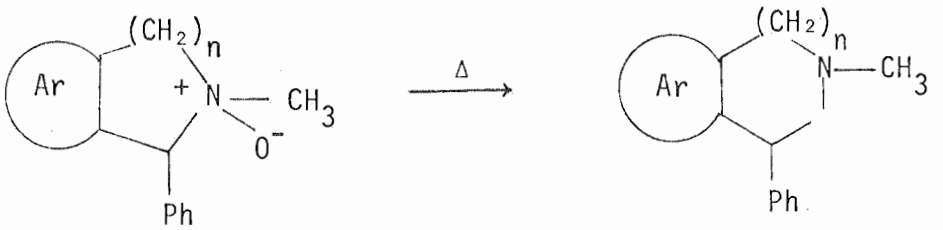
During the thermolysis of *cis*-(±)-laudanosine-*N*-oxide (132), the products resulting from the Cope elimination have also been detected.[81] The hydroxylamines which form through the Cope elimination can be easily detected by formation of a bright red colour with the addition of an aqueous solution of triphenyltetrazolium chloride and 2M sodium hydroxide.[85]

The successful results obtained by the Meisenheimer rearrangement of the above mentioned *N*-oxides encouraged the extension of this work

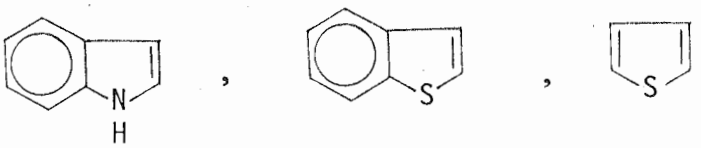


(132)

to other fused ring systems[83,84] (Scheme 60).



(133) (134)

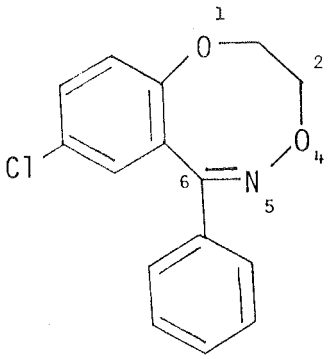
Ar = 

Scheme 60

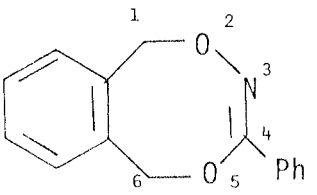
In this thesis preparation of eight- and nine-membered benzodioxaza ring systems, using this method, are described.

Previous reports of these heterocyclic systems are limited to four examples, and all were prepared by ring construction methods.[63]

Out of thirty possible isomers of benzodioxazocines, only the 1,4,5- (135) and 2,5,3- (136) benzodioxazocine systems had been described up to 1981[63] *(Chem. Abstr.*, 1981, *93)*.

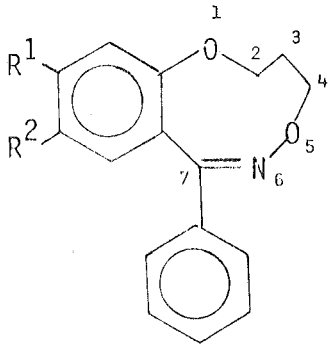


(135)



(136)

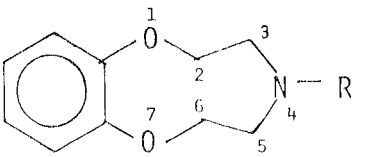
Similarly only two out of fifty four possible isomers of nine-membered benzodioxazonines had been prepared, also by the ring construction methods.[63] These were derivatives of 1,5,6- (137)[74] and 1,7,4- (138)[86] benzodioxazonines.



(137)

R^1 = H, OCH_3, H

R^2 = H, H, Cl

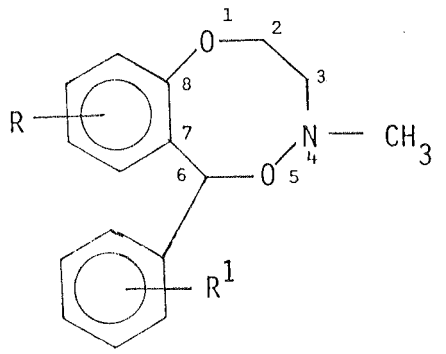


(138)

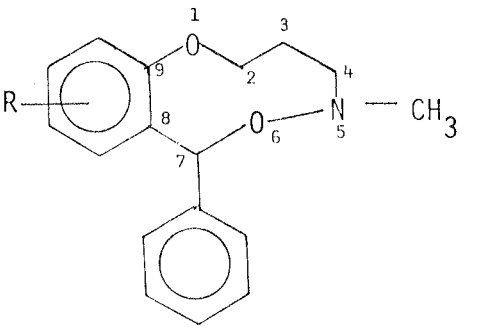
R = H, Ts

The Meisenheimer rearrangement here reported on the *N*-oxides of six 1,4-benzoxazepines (67-70, 90, 91) and one 1,5-benzoxazocine (119) resulted in the successful formation of derivatives of the new 1,5,4-benzodioxazocine and the 1,6,5-benzodioxazonine systems respectively (Figure 24).

The cyclic amines which were required for the *N*-oxidation were prepared by the ring closure methods described in Chapters 2 and 3.



1,5,4-benzodioxazocine derivative



1,6,5-benzodioxazonine derivative

Figure 24

4.2 Results and Discussion

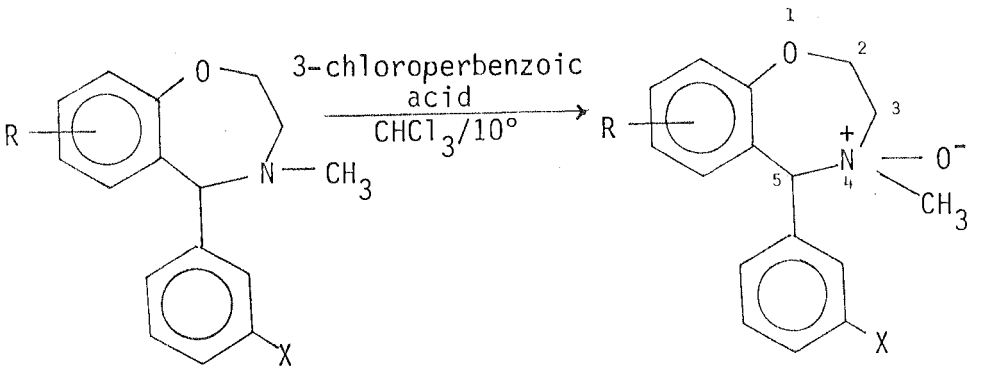
4.2.1 Preparation of the *N*-oxides of seven-membered ring systems

The *N*-oxides (139-144) required for the Meisenheimer rearrangement were prepared by the oxidation of the corresponding amines (67-70, 90, 91) with 3-chloroperbenzoic acid in anhydrous chloroform at about 10°[81] (Scheme 61, Figure 25).

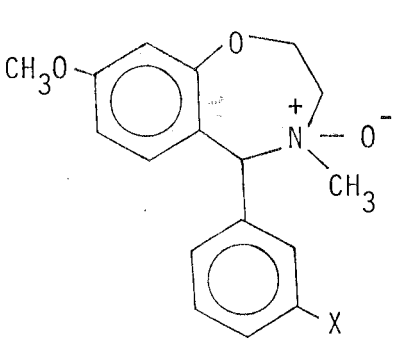
The *N*-oxide (139) was obtained as a white crystalline product, but all the others were isolated as hygroscopic gums. Most of the *N*-oxides (139, 141-144) were characterised by P.M.R. spectral data, but they were not subjected to microanalysis because of their hygroscopic properties.[81]

In the P.M.R. spectra of these derivatives (139, 141-144) the signal or signals which derived from the benzylic proton at C_5 in each case appeared at lower field than that derived from the corresponding proton in the cyclic amine. The presence of *cis* and *trans* isomers (Figure 26) was also detected in some cases (142,143) as shown by the appearance of more than one signal of the benzylic proton and/or $-\overset{+}{N}CH_3$ protons.

For example, in the P.M.R. spectrum of the *N*-oxide (143) the benzylic proton signal of one isomer appeared at δ 5.73, while that

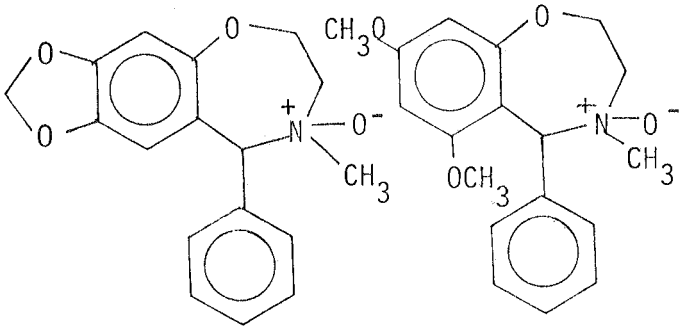


(67-70, 90,91) Scheme 61 (139-144)

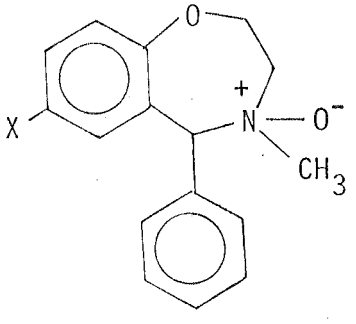


(139) X = H

(140) X = Cl



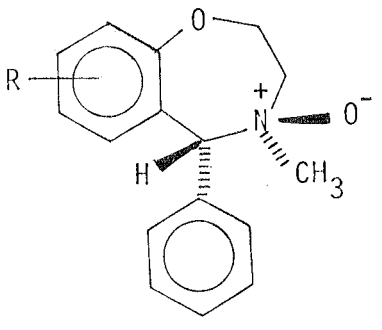
(141) (142)



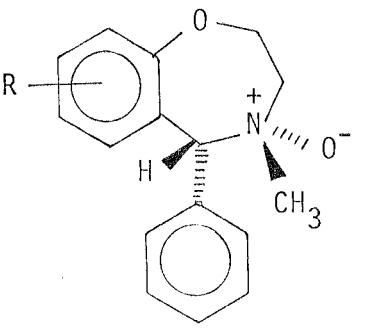
(143) X = H

(144) X = Cl

Figure 25



cis isomer



trans isomer

Figure 26

of the other appeared at δ 5.81, in the ratio of about 1:2. The $-\overset{+}{N}CH_3$ proton signal also appeared as two singlets at δ 3.35 and δ 3.41 in the ratio of 1:2. Attempts to separate these two stereoisomers by chromatographic methods (10% methanol-chloroform, 2% KOH-silica gel) were unsuccessful, this separation process resulted in the formation of the rearranged eight-membered 1,5,4-benzodioxazocine derivative (151). Since both the isomers give rise to the same rearrangement product,[cf. 81] the *N*-oxide (143) was subjected to the Meisenheimer rearrangement without further attempts in separation.

In the P.M.R. spectrum of the *N*-oxide (142) the benzylic proton signal appeared as a multiplet overlapping with two aromatic proton signals. However the $-\overset{+}{N}CH_3$ proton signal appeared as two singlets at δ 3.39 and δ 3.49 in the ratio of 1:2. The signals derived from the two methoxy groups also appeared as four singlets indicating the presence of other stereoisomers.

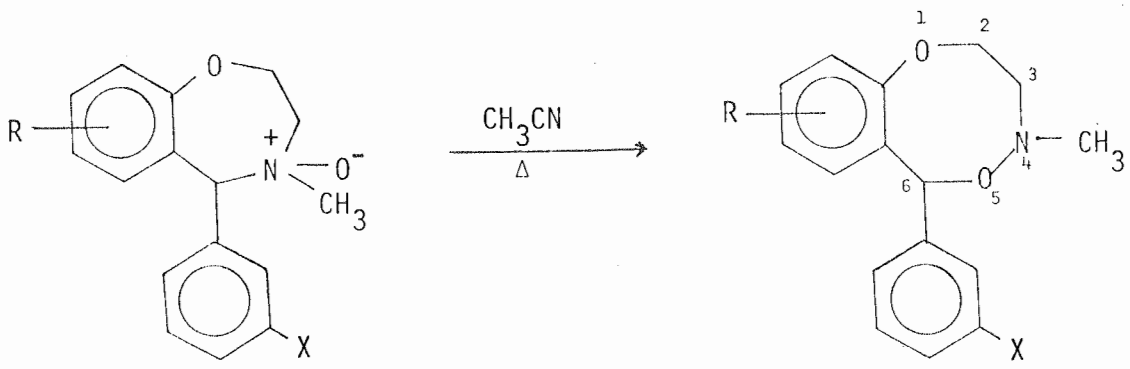
The formation of *cis* and *trans* isomers of the *N*-oxides has been observed earlier with the work done on isoquinoline ring systems;[cf. 81] in that case the isomers were separated by P.L.C. using multiple development.

4.2.2 The Meisenheimer rearrangement of the *N*-oxides (139-144) of 1,4-benzoxazepines

The Meisenheimer rearrangement of the *N*-oxides (139-144) was readily achieved by refluxing the *N*-oxides in anhydrous ethanenitrile for twenty to thirty minutes (Scheme 62).

The anticipated 1,5,4-benzodioxazocines (145-150) (Figure 27) were formed in high yields (60-100%), and the formation of Cope elimination products was not detected.

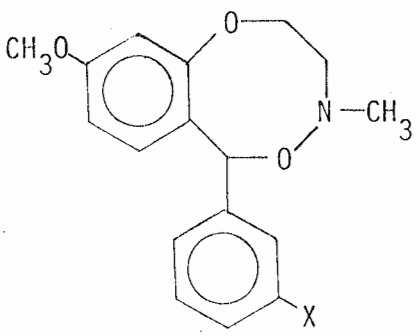
The Meisenheimer rearrangement done on the 1,5-benzoxazocine (119) gave somewhat different results which will be discussed in



(139-144) (145-150)

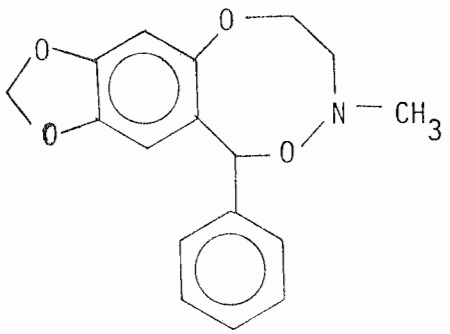
1,5,4-benzodioxazocines

Scheme 62

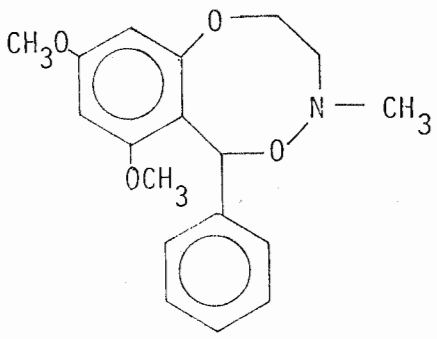


(145) X = H, 91%

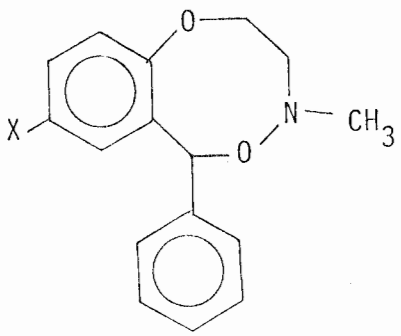
(146) X = Cl, 77%



(147) 98%



(148) 82%



(149) X = H, 60%

(150) X = Cl, 86%

Figure 27

Section 4.3.

4.2.3 Spectral analysis of the 1,5,4-benzodioxazocines (145-150)

In each of the P.M.R. spectra of these eight-membered ring systems (145-150) (Figure 27), a characteristic feature was the signal derived from the benzylic proton, which appeared at a lower field than that of the analogous singlets in the spectra of the seven-membered amine precursors (67-70, 90, 91).

These values are given in Table 7.

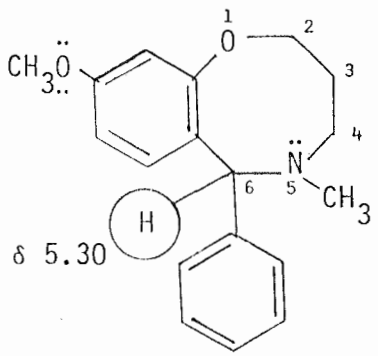
TABLE 7

Variation of Benzylic Proton Chemical Shifts with Ring Size and Structure

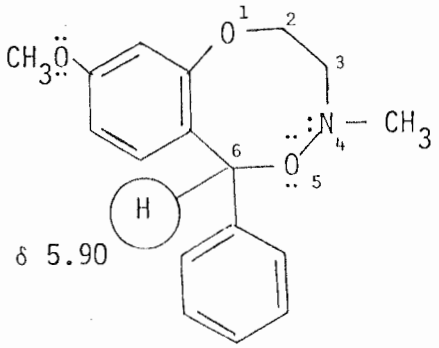
Chemical shift of the benzylic proton δ			
Amines (1,4-benzoxazepines)		1,5,4-Benzodioxazocines	
(67)	4.90	(145)	5.90
(68)	4.89	(146)	5.86
(69)	4.59	(147)	5.79
(70)	5.65	(148)	6.09
(90)	4.89	(149)	5.89
(91)	4.96	(150)	5.82

This change in the chemical shift values could have been related to the expansion of the heterocyclic ring system. However comparison of the chemical shifts of the signals derived from the benzylic protons in the 1,5,4-benzodioxazocine (145) and the 1,5-benzoxazocine (119) showed a significant difference. (Figure 28).

Since both these ring systems are of the same size, this could not account for the change in chemical shifts. Therefore this is probably due to the more electronegative oxygen atom adjacent to the



(119)



(145)

Figure 28

benzylic proton in the 1,5,4-benzodioxazocine ring system (145), compared to (119).

The chemical shift values observed for the benzylic protons in the 1,5,4-benzodioxazocines (145-150) differed slightly from each other, depending on the substitution pattern of the fused benzene ring (Table 7).

The signals which derived from the $-NCH_3$ protons appeared as singlets in the range δ 2.73-2.75. The $-NCH_2-$ and $-OCH_2-$ methylene protons in every compound appeared as multiplets, due to both geminal and vicinal coupling.

In the 1,5,4-benzodioxazocines (149,150), this splitting pattern was prominent, and the signal from each of these four methylene protons appeared as an octet. A study of this multiplicity observed in (150) was conducted using a high resolution P.M.R. spectrum (270Hz), and the coupling constant calculated for each pair of protons is given in Figure 29.

Using chemical shift values and coupling constants, a computer programme[87] was used to model the system (150) and the spectrum thus obtained (Figure 30) was compared with the original spectrum of (150)

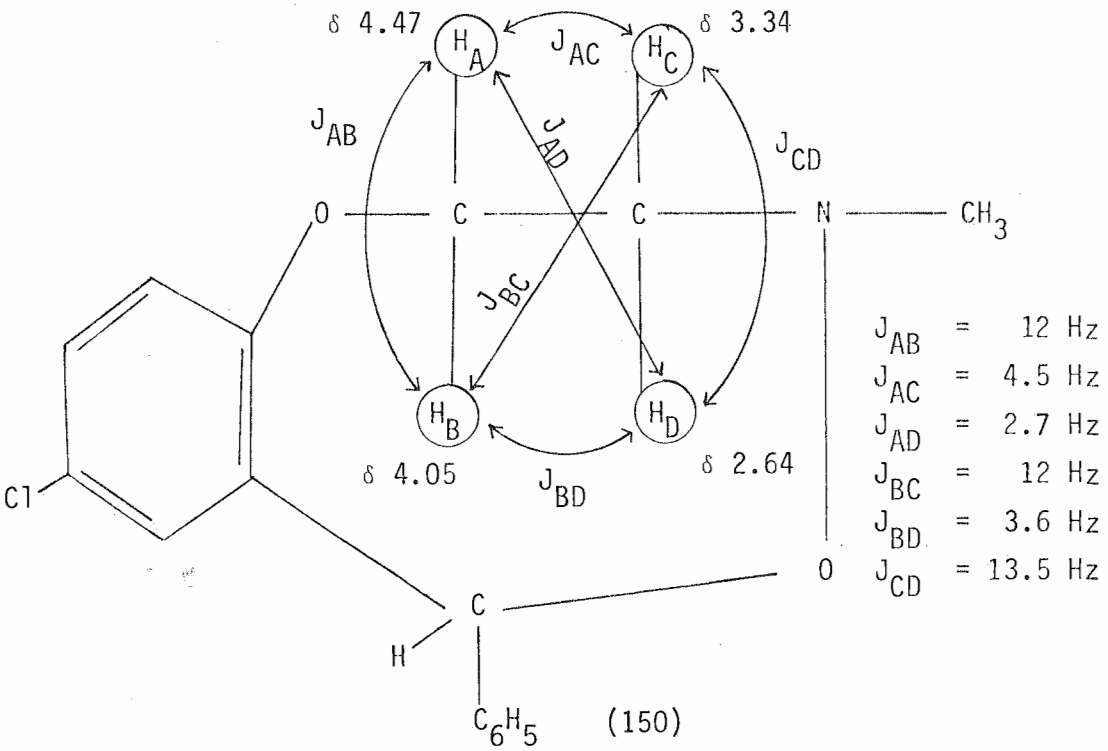
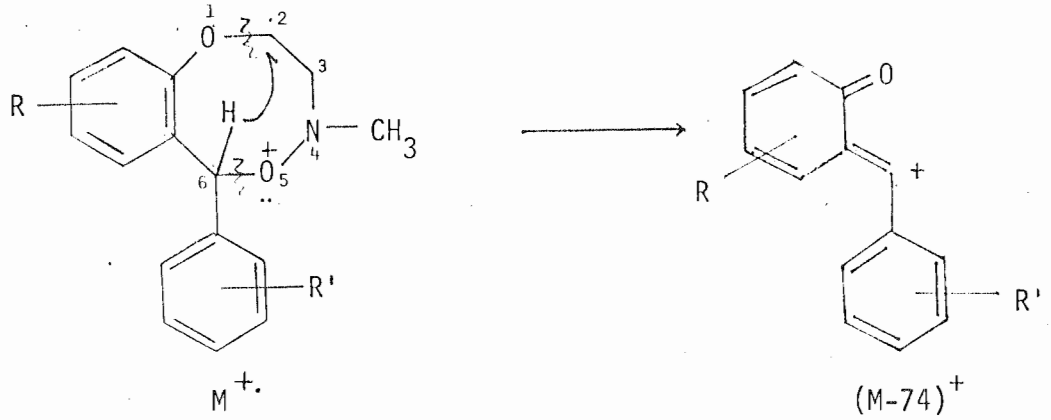


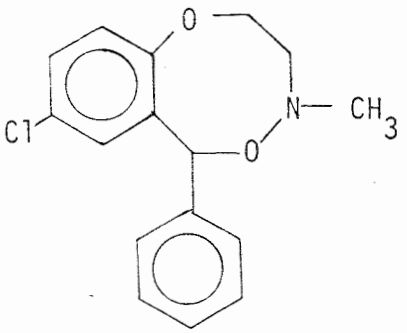
Figure 29

(Figure 31). A similar splitting pattern was observed for the four methylene protons in both spectra, supporting the above suggested coupling pattern.

In the mass spectra of each of 1,5,4-benzodioxazocines (145-150), the most prominent feature was a peak at m/e $(M-74)^+$. In three of these compounds (147-149) this m/e $(M-74)^+$ peak appeared as the base peak. The fragmentation between the O_1-C_2 and O_5-C_6 bonds with hydrogen migration could give rise to the above observed peak (Scheme 63).



Scheme 63



(150)

The model spectrum of the methylene protons in (150) obtained by a computer program.

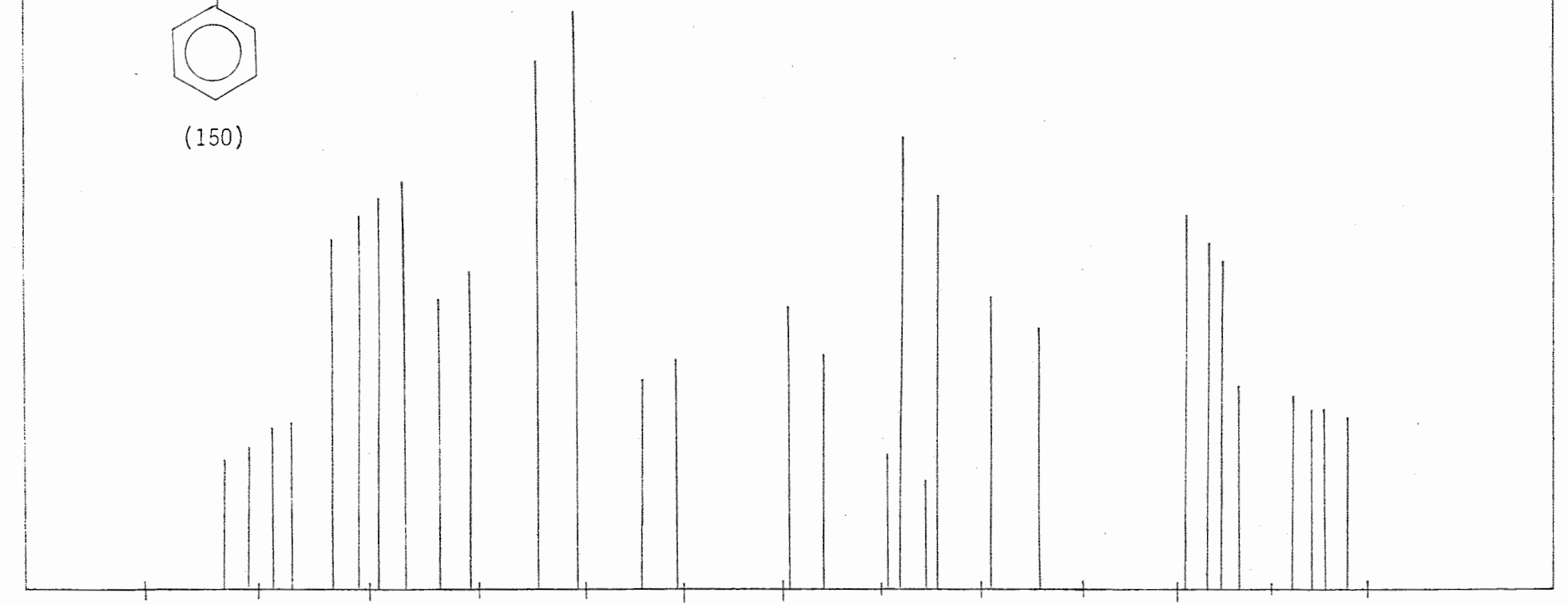


Figure 30

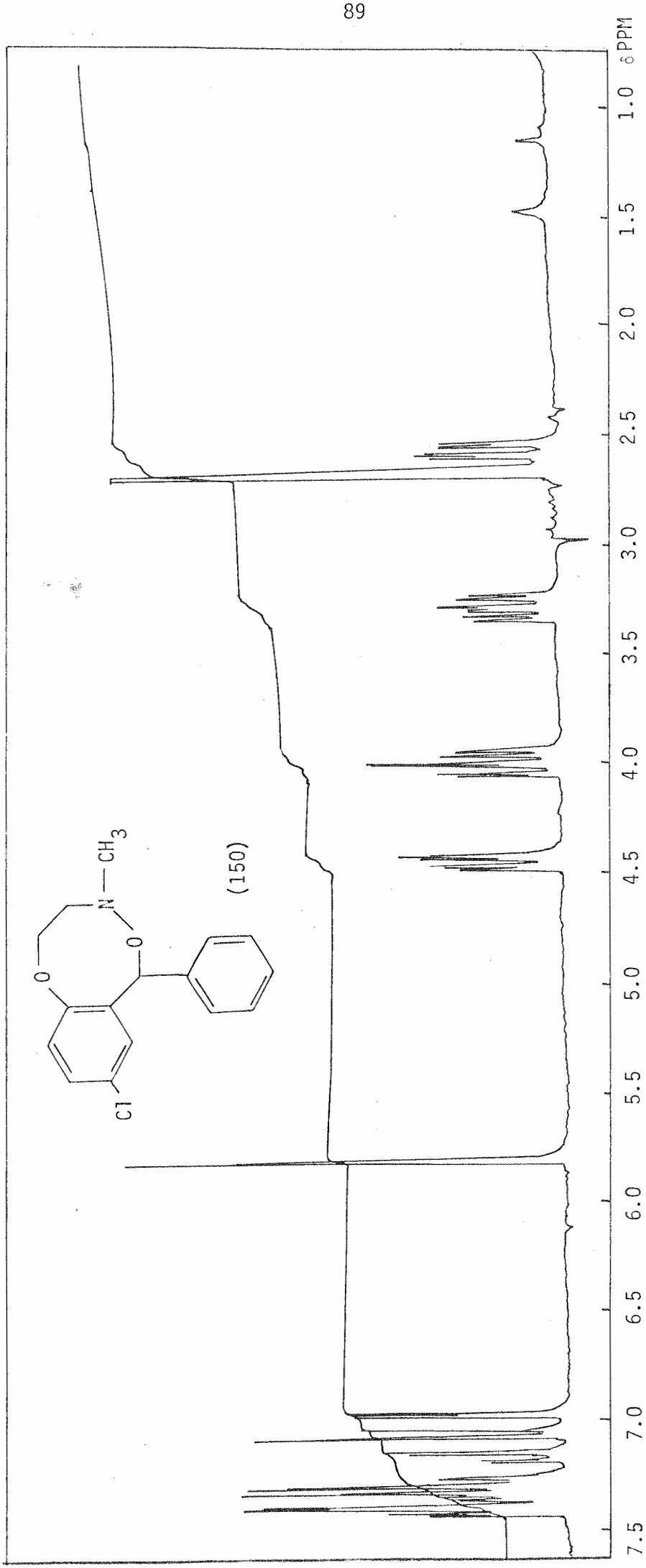
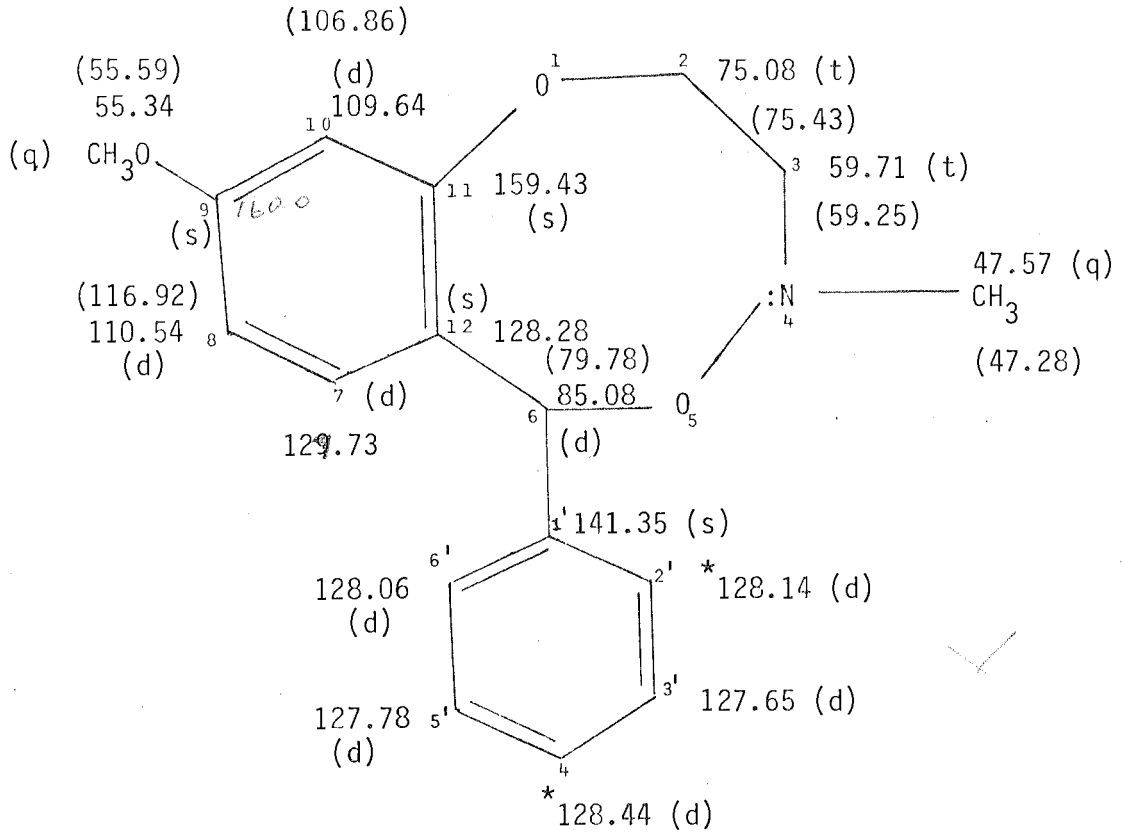


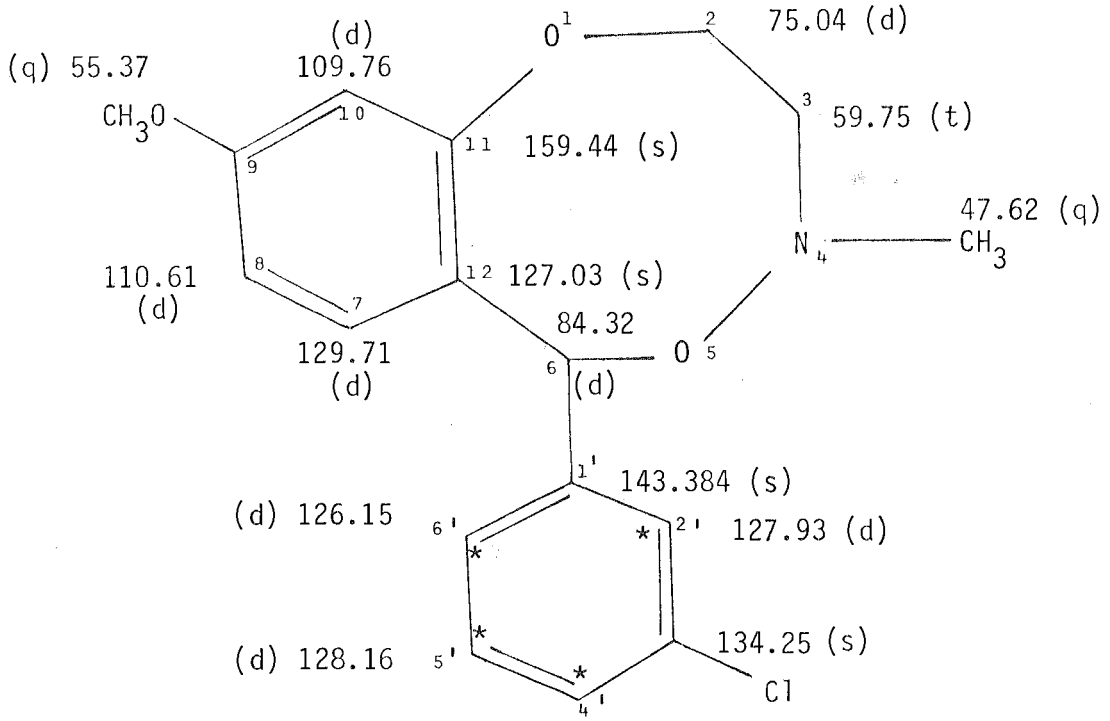
FIGURE 31



*interchangeable values

values for the stereo-isomer is given in brackets

Figure 32



*interchangeable values

Figure 33

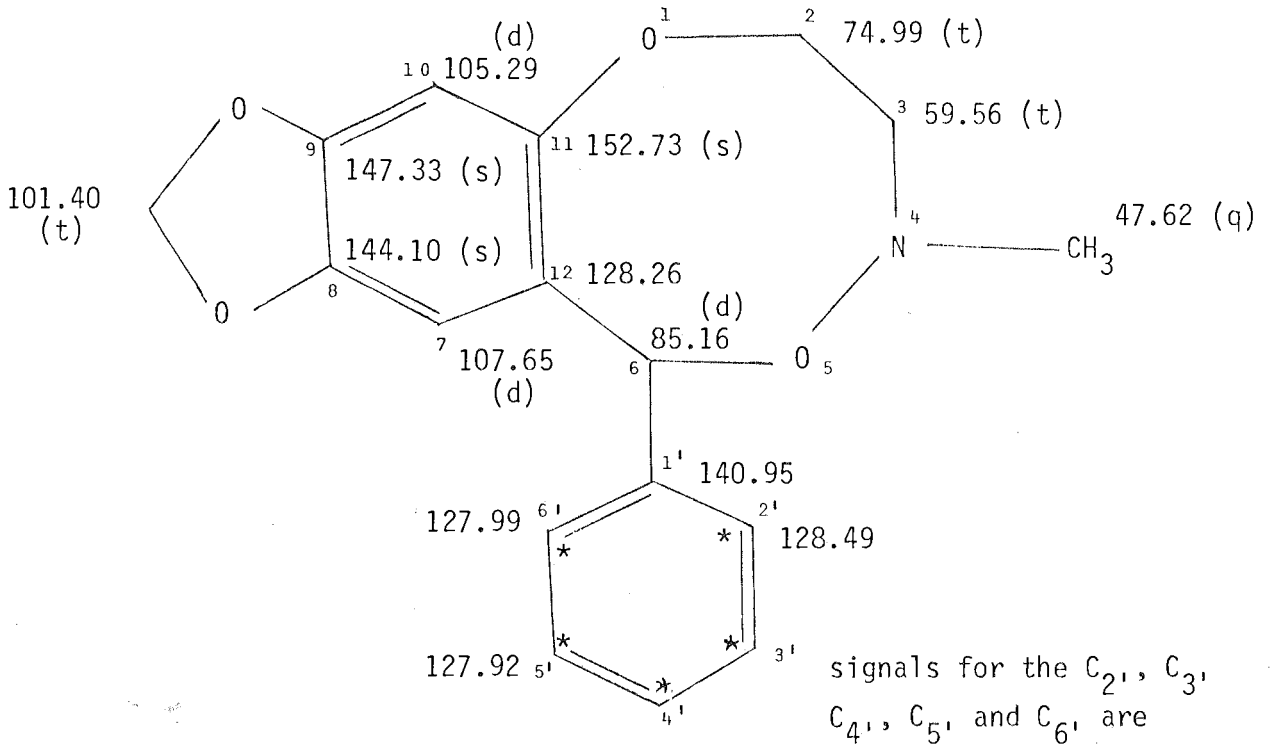


Figure 34

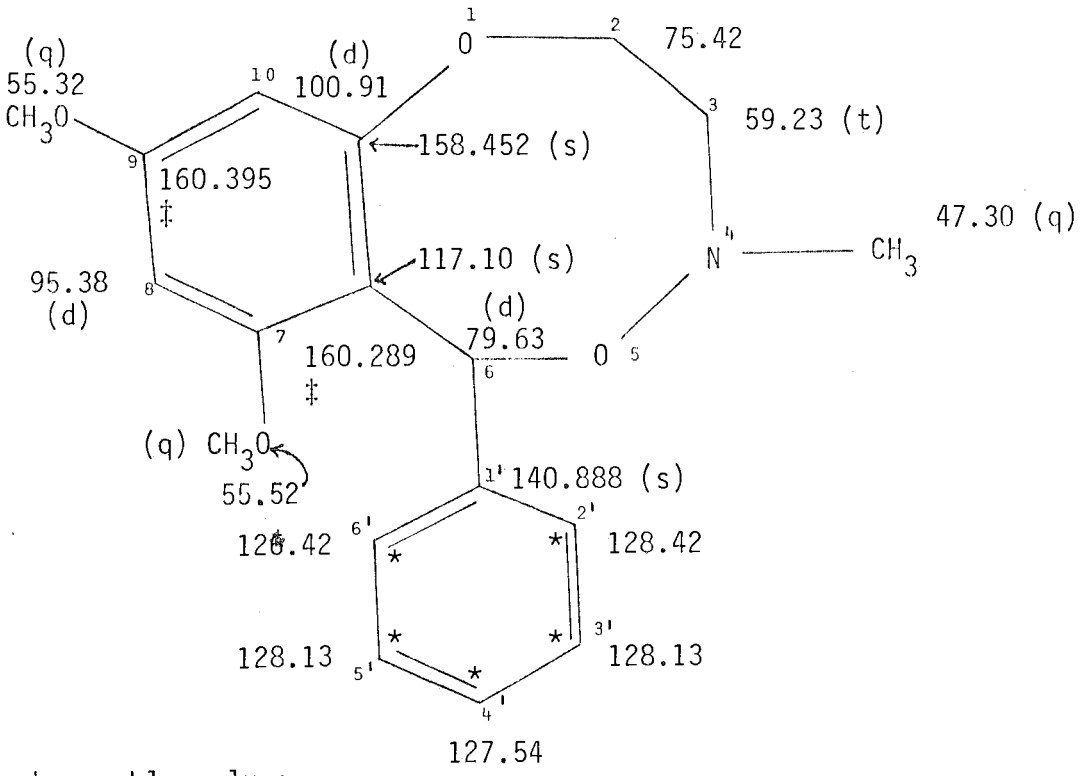
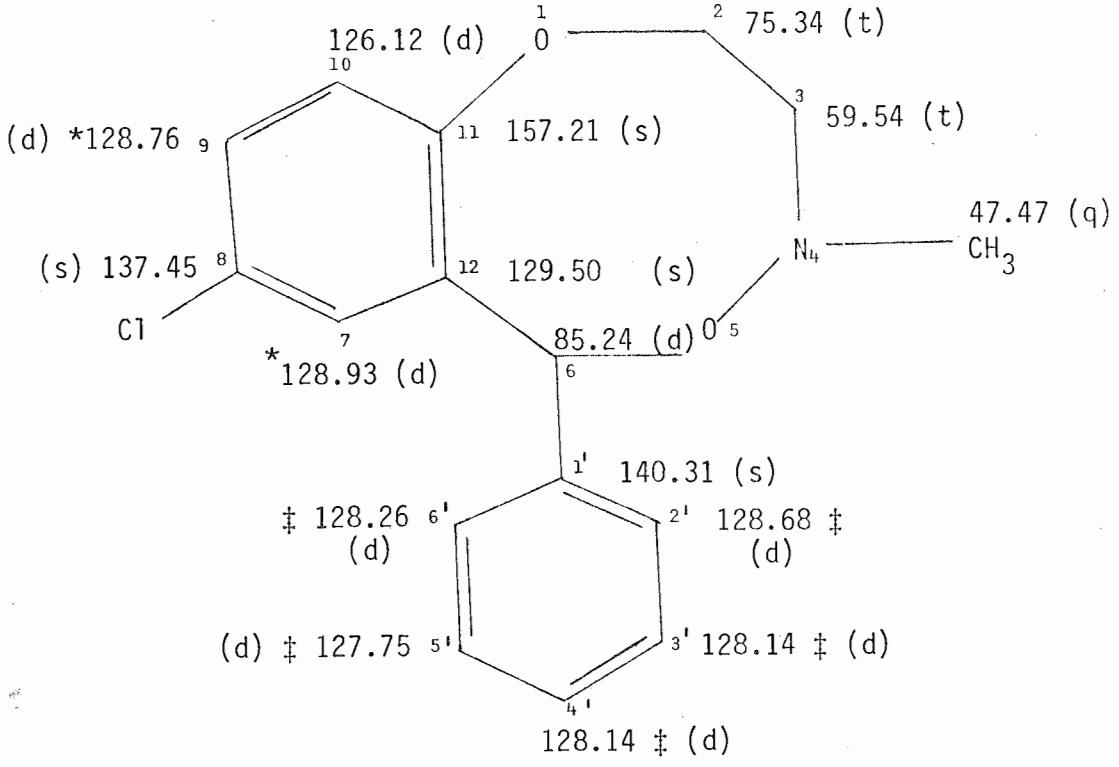
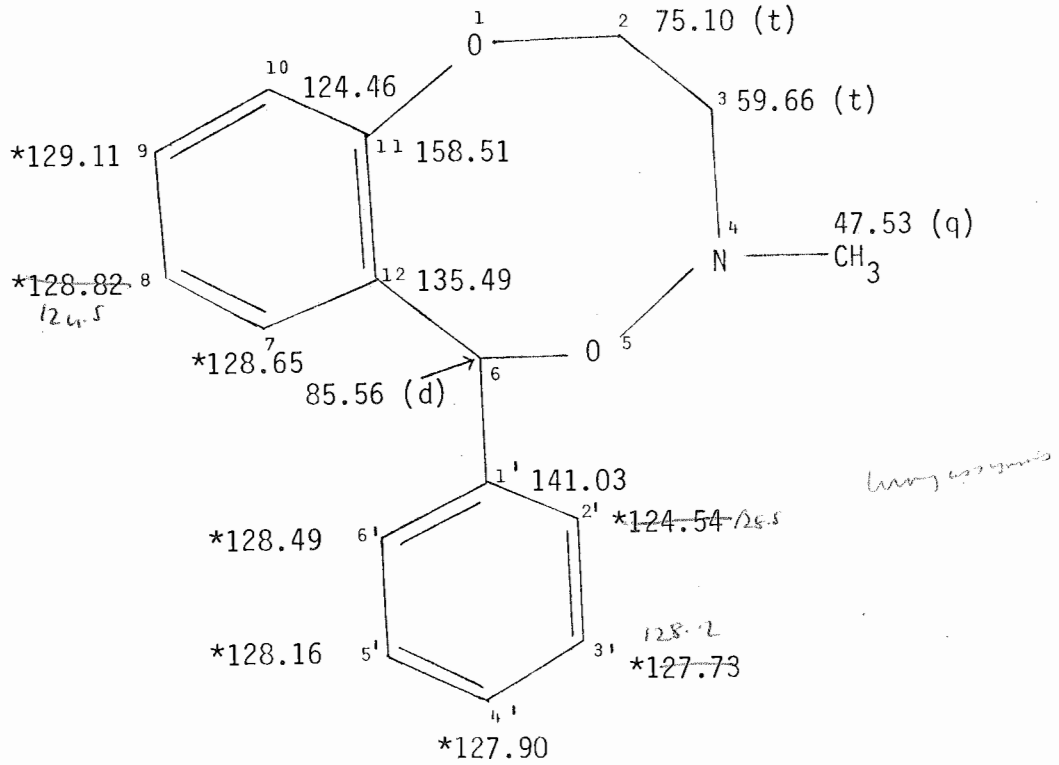


Figure 35



* ‡ interchangeable values

Figure 36



* interchangeable values

Figure 37

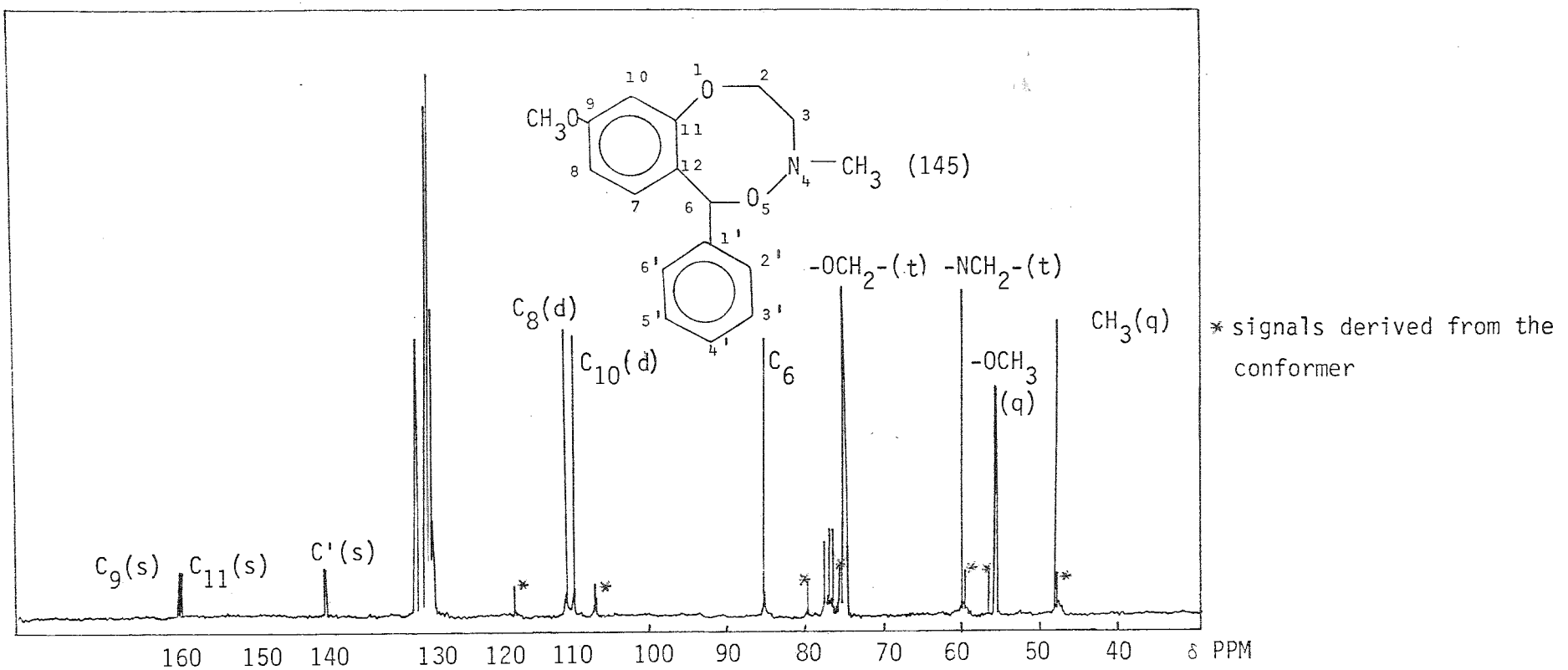

CH3O
(145)
C8(d)
C10(d)
C6
-OCH2-(t)
-NCH2-(t)
-OCH3 (q)
CH3(q)
C9(s)
C11(s)
C'(s)
* signals derived from the conformer
160 150 140 130 120 110 100 90 80 70 60 50 40 δ PPM

Figure 38

A further structural assignment of the 1,5,4-benzodioxazocines (145-150) was carried out using ^{13}C N.M.R. spectral data. In each of these compounds, the triplets which derived from the $-OCH_2-$ and $-NCH_2-$ methylene carbons resonated within the ranges δ 74.99-75.42 and δ 59.23-59.75 respectively (Figures 32-37). The chemical shift values for the aromatic carbon atoms present in these compounds were calculated according to the substitution pattern.[75]

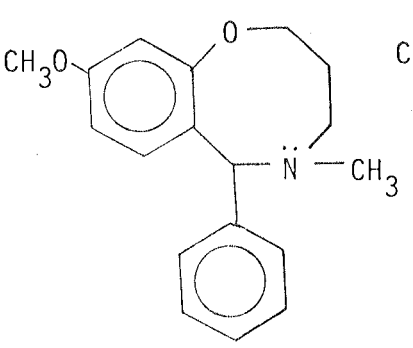
In the ^{13}C N.M.R. spectrum of (145), two conformational isomers were detected in the ratio of 1:4 (Figure 38), and these signals did not collapse even when the spectrum was obtained at a higher temperature (45°). In other 1,5,4-benzodioxazocines (146-150) the presence of the conformational isomers were not observed.

4.3 The Meisenheimer rearrangement of the 1,5-benzoxazocine (119)

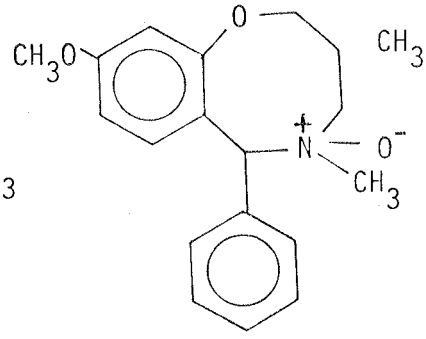
Initially the *N*-oxidation of the 1,5-benzoxazocine (119) with 3-chloroperbenzoic acid in chloroform at 10° was carried out as described for the preparation of the 1,4-benzoxazepine *N*-oxides (139-144).

The material isolated from this reaction was found to be a mixture of three major products having R_f values of 0.8, 0.5 and 0.1 (4% methanol-chloroform, silica gel). At this stage it was believed that the higher R_f value (0.8) material might be the rearranged product (152) and the base line material unchanged *N*-oxide (151). Therefore, this mixture was refluxed in anhydrous ethanenitrile for 30 min, in an attempt to complete the rearrangement to the nine-membered ring system (152).

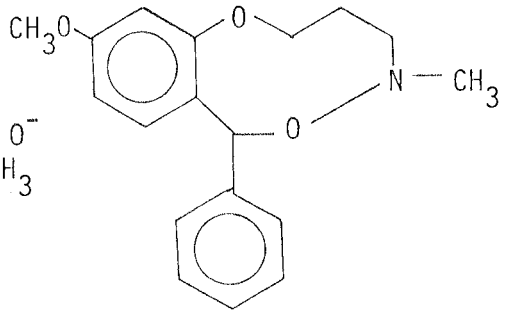
However this did not result in the formation of the expanded ring system (152); instead it gave a mixture of several products. The highest R_f value material (0.8) found in the initial *N*-oxide mixture had also disappeared. Most of the products gave a positive



(119)



(151)

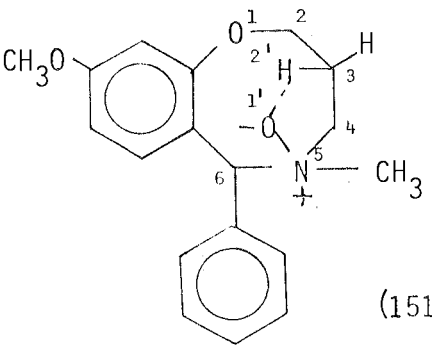


(152)

result when tested for the presence of a hydroxylamine group.[85] This type of decomposition or hydroxylamine formation was not observed during the Meisenheimer rearrangement of 1,4-benzoxazepine-*N*-oxides (139-144).

Because of these results possible occurrence of a Cope elimination from the *N*-oxide (151) followed by decomposition of unstable products was considered.

From models of the *N*-oxide (151) it could be seen that it is possible to incorporate a *beta* hydrogen atom on C_3 in a planar five-membered transition state, which is postulated to be required for the Cope elimination to take place[79] (Figure 39).



(151)

Figure 39

In order to try and isolate such an assumed Cope elimination product, the *N*-oxidation of the cyclic amine (119) was carried out at about -5°-0°. The reaction mixture was checked by T.L.C. at fifteen minute intervals, and the T.L.C. plates were sprayed with a solution of triphenyltetrazolium chloride and 2 M sodium hydroxide[85] to detect the formation of hydroxylamines, as some were already detected after 15 minutes of the addition of 3-chloroperbenzoic acid.

As a precaution the reaction was stopped after only 1.5 hours when some unchanged starting material (119) was still present. This gave a higher R_f value material (R_f 0.8, 4% methanol-chloroform) as the major product which did not give a positive test for a hydroxylamine. The presence of several other lower R_f value materials were also detected, most of them giving positive tests for the hydroxylamines.

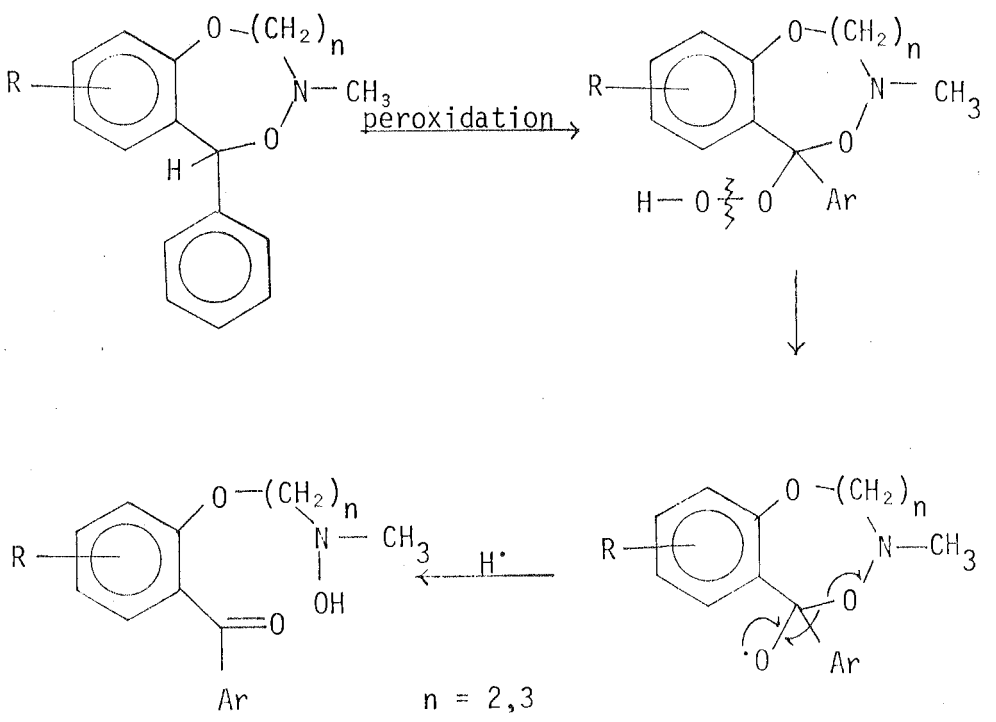
The work-up of the above reaction mixture was carried out with ice-cooling and the chloroform extraction was subjected to P.L.C. without refluxing in ethanenitrile. Many products were already present, but the major product isolated was found to be the Meisenheimer rearrangement product (152) in 27% yield based on unrecovered amine (119).

When *N*-oxidation of the 1,5-benzoxazocine (119) with 3-chloroperbenzoic acid at -5°-0° was carried out for 3 hours, all the starting material had reacted and it gave the ring expanded product (152) in 50% yield.

Once the ring expanded product (152) was isolated from the reaction mixture it was thermally stable and did not undergo decomposition in refluxing ethanenitrile. When an attempt was made to crystallise the compound (152) from diethyl ether, it underwent slight decomposition. In case trace amounts of peroxides which were found to be present in the diethyl ether might have caused this decomposition, the following experiment was carried out.

Examples of each of the 1,5,4-benzodioxazocine (145) and 1,6,5-benzodioxazonine (152) ring systems were treated with 3-chloroperbenzoic acid (using 1:1 molar ratios) in dry chloroform and the reaction mixture was stirred at -5°-0°. This resulted in some decomposition of both eight- and nine-membered ring systems within fifteen minutes. On T.L.C. plates several lower R_f value materials (e.g. R_f 0.5, 0.4, 0.38, 0.35, 0.2, 0.1, 5% methanol-chloroform) were detected and at this stage none of them gave a positive test for hydroxylamines. However after 45 minutes, the intensity of some of the decomposition products were increased and the starting material (145 or 152) was present only in a trace amount. In addition, the decomposition products which appeared at R_f 0.35 (from the eight-membered ring) and R_f 0.3 (from the nine-membered ring) gave positive tests for hydroxylamines.

The formation of hydroxylamines from these ring systems in the presence of peroxides could occur through the homolytic cleavage of the O-N bond, and a postulated mechanism is given in Scheme 64.



Scheme 64

Therefore during the *N*-oxidation of the amine (119) hydroxylamines detected could have been formed either by this peroxidation, or by the Cope elimination,or both. Further investigation on decomposition products were not carried out.

4.3.1 Spectral analysis of 10-methoxy-5-methyl-7-phenyl-2,3,4,5-tetrahydro-7*H*-1,6,5-benzodioxazonine (152)

In the P.M.R. spectrum of (152), the singlet which appeared at δ 6.15 confirmed the presence of a benzylic proton. In the aliphatic region, three sets of methylene proton signals were observed, and these were assigned as the $-OCH_2-$, $-C-CH_2-C-$, and $-NCH_2-$ proton signals. The $-C-CH_2-C-$ proton signals appeared at δ 1.75-1.97 as a multiplet, while those of the $-NCH_2-$ group appeared at δ 2.80 as a triplet. Two multiplets were observed for each proton in the $-OCH_2-$ group at δ 4.00-4.30 and δ 4.35-4.62.

The $-\ddot{N}CH_3$ and $-OCH_3$ proton singlets resonated at δ 2.66 and δ 3.72 respectively. The peaks which appeared in the aromatic region integrated for eight protons (Figure 40). All of these data were consistent with the structure of (152).

The high resolution mass spectrum also gave the molecular ion peak at m/e 299 confirming the proposed structure of (152). The base peak appeared at m/e 211 by the loss of 88 mass units.

The ^{13}C N.M.R. spectrum also was consistent with the structure of (152). The δ values[75] assigned for each carbon atom is given in Figure 41.

4.4 Reaction of the Meisenheimer rearrangement products

4.4.1 Reductive cleavage followed by *N*-methylation of 9-methoxy-4-methyl-6-phenyl-3,4-dihydro-2*H*,6*H*-1,5,6-benzodioxazocine (145)

To establish the structure of (145), the reductive cleavage was

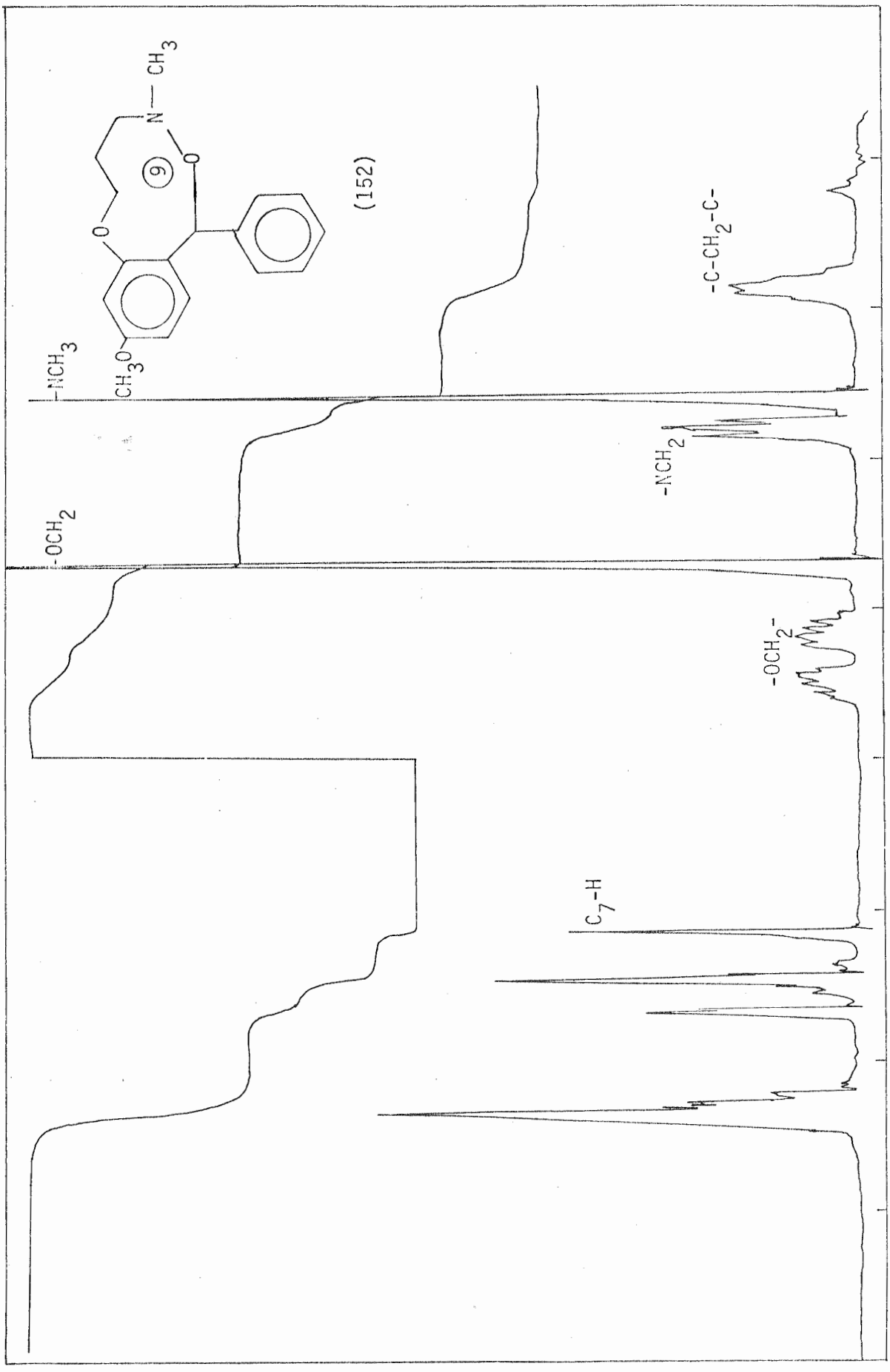
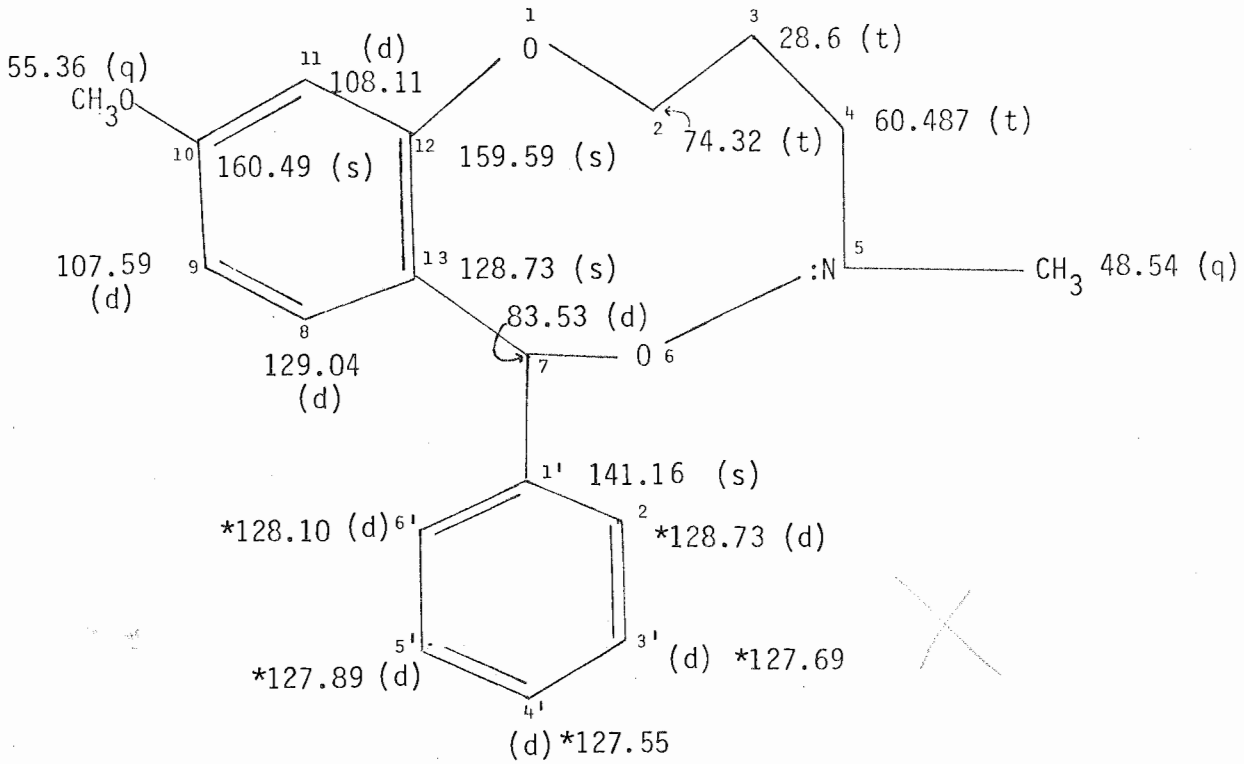

-OCH2
-NCH3
CH3O
N — CH3
9
O
O
(152)
-NCH2
-C-CH2-C-
-OCH2-
C7-H
8
7
6
5
4
3
2
1
0 (δ) PPM

FIGURE 40

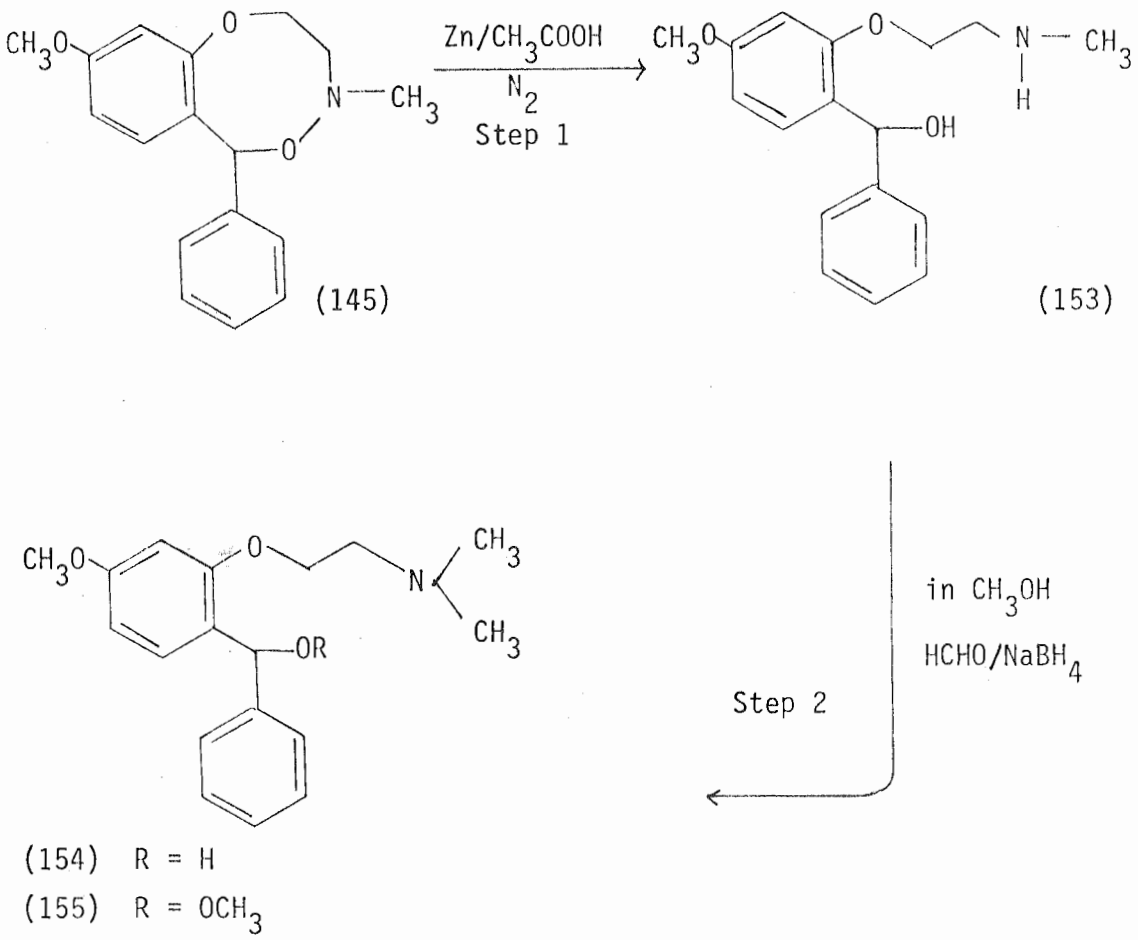


*interchangeable values

Figure 41

carried out with zinc dust in acetic acid as described in the literature[83,88,89] (Scheme 65, step 1). The infrared spectrum of the product isolated from the reaction gave an absorption band in the range of 3200-3700 cm^{-1} confirming the presence of an hydroxyl group. Since this compound was found to undergo decomposition with time, it was subjected to *N*-methylation without further characterization. A methanolic solution of the product (153) was treated with formaldehyde and sodium tetrahydridoborate to obtain the more stable tertiary amino alcohol (154) (Scheme 65, step 2).

The work-up followed by purification (P.L.C.) of the above reaction mixture gave two main products in the ratio of 1:2, of which the minor compound was identified spectroscopically as the expected



(154) R = H

(155) R = OCH_3

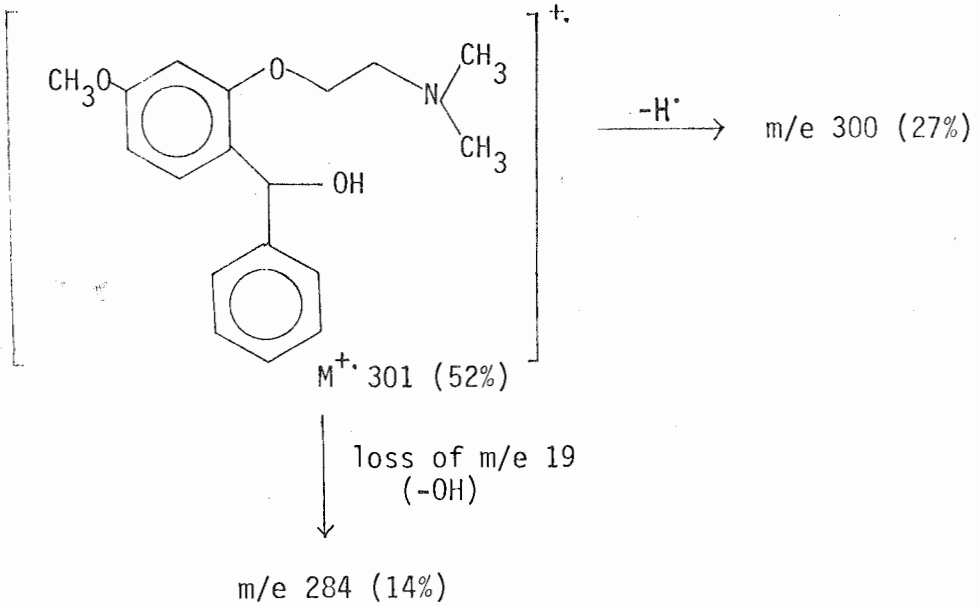
Scheme 65

tertiary amino-alcohol (154). The spectral data of the major compound fitted with the structure of (155), which might have formed by the solvolysis of the amino-alcohol (154).

In the P.M.R. spectrum of the minor product (154), the six-proton singlet which appeared at δ 2.30 confirmed the presence of two *N*-methyl groups. The $-NCH_2-$ and the $-OCH_2-$ methylene proton signals appeared as multiplets in the range of δ 2.45-2.65 and δ 3.90-4.12 respectively. The benzylic proton resonated at δ 5.92 as a singlet. The broad signal which appeared between δ 4.50 and δ 5.10 integrated for one proton and was exchangeable with D_2O, and assigned as the OH proton signal. (Figure 42).

In the infrared spectrum of the compound (154) the hydroxyl

frequency appeared at 3200-3340 cm^{-1} (broad). The mass spectrum gave the molecular ion peak at m/e 301 and all of these data were in accord with the structure of (154). The mass fragmentation pattern observed for (154) is given in Scheme 66. The peak derived by the loss of the -OH group was also present in the mass spectrum.



Scheme 66

The P.M.R. spectral data of the major compound (155) also showed a six-proton singlet at δ 3.20 indicating the presence of two *N*-methyl groups. Two triplets at δ 2.68 and δ 3.99 (J 6.25Hz) were observed for the protons in the $-NCH_2-$ and $-OCH_2-$ groups. The benzylic proton singlet appeared at a slightly higher field (δ 5.57) to that of the amino-alcohol (154). No exchangeable proton was detected in the P.M.R. spectrum of this compound. An additional three-proton singlet was observed at δ 3.32 and this was assigned as an aliphatic methoxyl signal (Figure 43).

In the infrared spectrum no hydroxyl frequency was visible and the mass spectrum gave the molecular ion peak at m/e 315. The peaks which appeared at m/e 300 and m/e 285 suggested the loss of a methyl

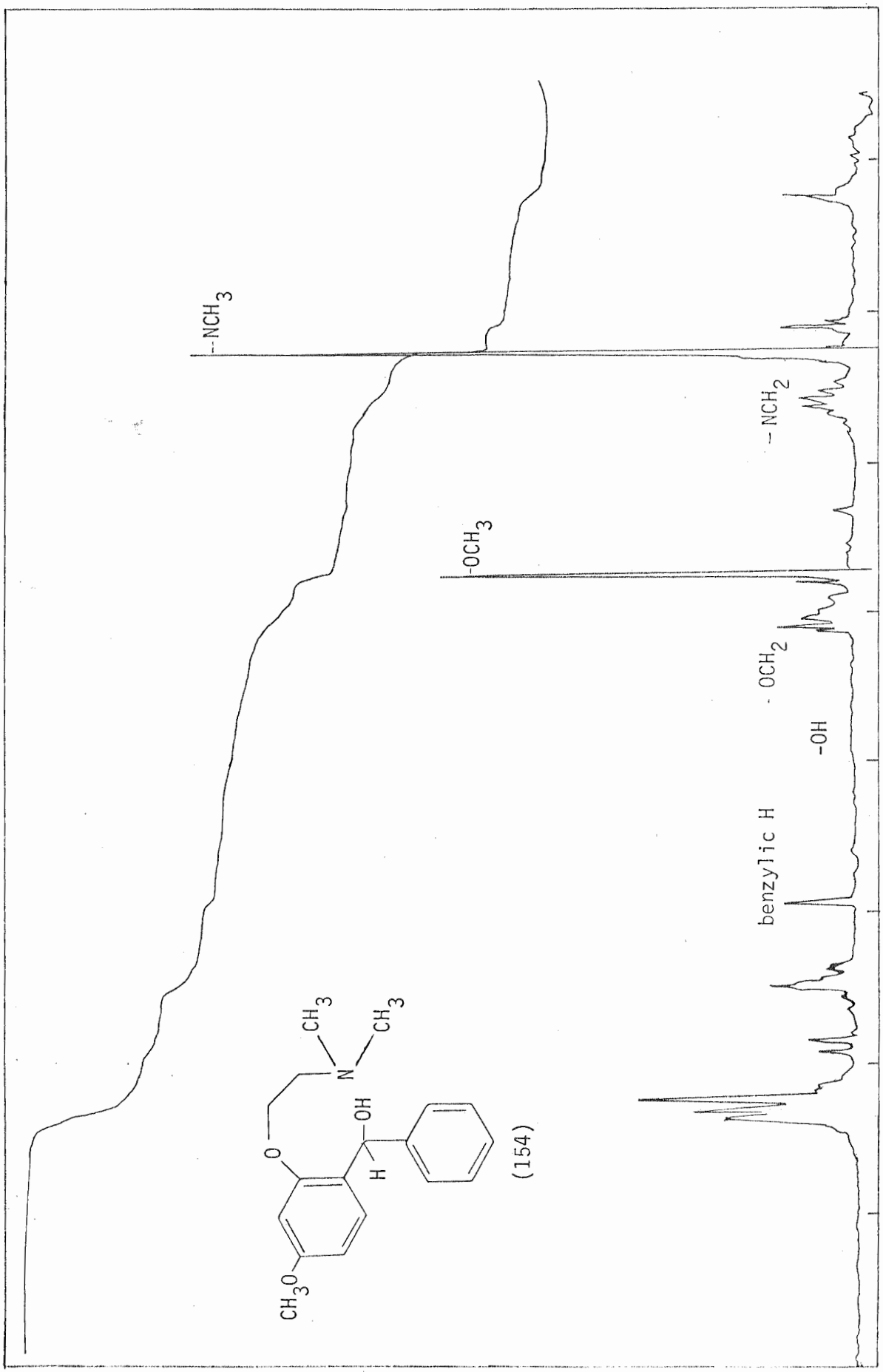
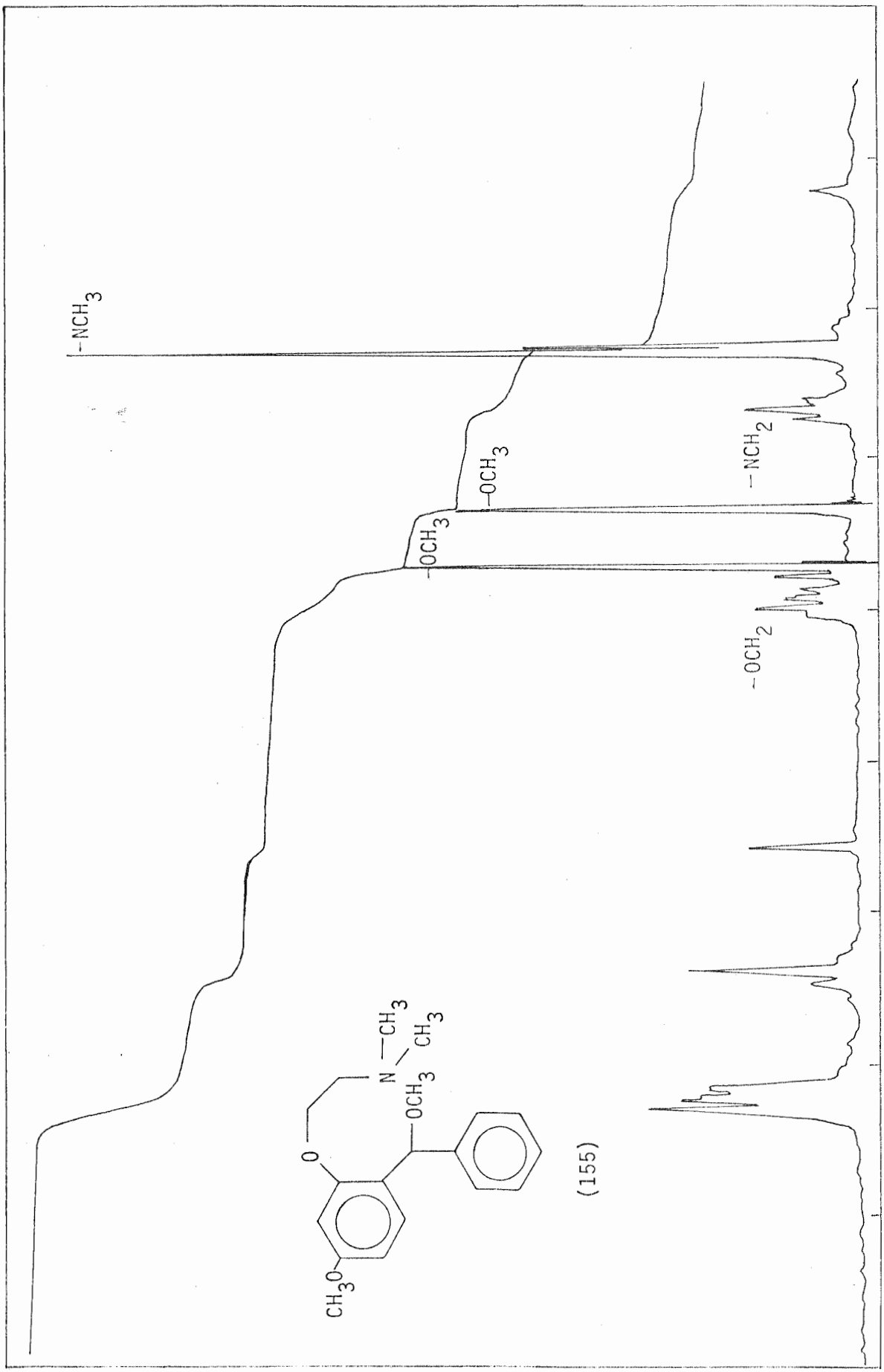

-NCH3
-OCH3
-NCH2
-OCH2
-OH
benzylic H
0 δ PPM
1
2
3
4
5
6
7
8
CH3
CH3
N
OH
H
O
CH3O
(154)

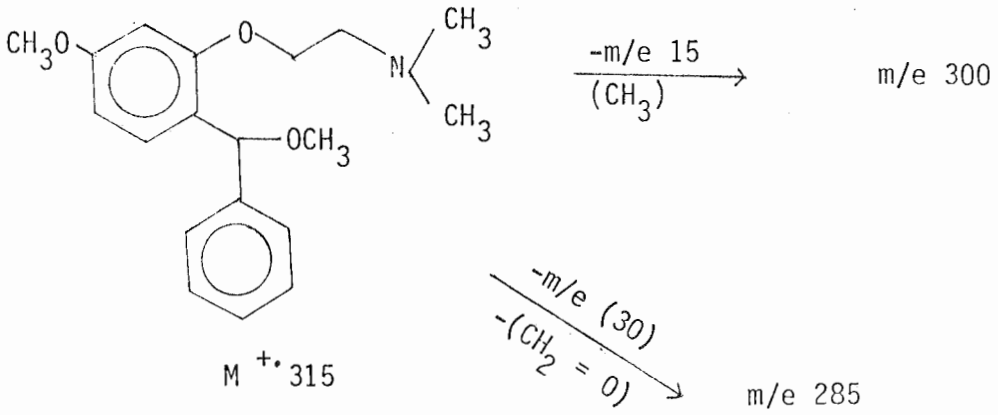
FIGURE 42



(155)

FIGURE 43

group and a methoxy group respectively, from the molecule (Scheme 67). These data were consistent with the structure of (155).



Scheme 67

Conclusion

From these results it is evident that the Meisenheimer rearrangement of the *N*-oxides of 1,4-benzoxazepines occurs smoothly giving rise to the expected eight-membered 1,5,4-benzodioxazocine ring systems (147-150). The success of the Meisenheimer rearrangement of these *N*-oxides (139-144) does not depend on the substituents on the fused or pendant benzene rings.

Extension of the Meisenheimer rearrangement to the preparation of a benzodioxazonine derivative (152) was not very satisfactory. Success of the rearrangement of the cyclic amine (119) depended on the temperature of the reaction mixture, and the formation of hydroxylamines and other decomposition products was found to predominate. However by maintaining the temperature of the reaction mixture during the *N*-oxidation of the 1,5-benzoxazocine (119) and the work-up procedure as described earlier (Section 4.3), considerable success can be achieved.

CHAPTER 5

Experimental

Microanalyses were carried out by the Canadian Microanalytical Service Ltd., Vancouver, Canada, and the Australian Microanalytical Service, Melbourne, on samples which had been dried in vacuum over phosphorus pentoxide.

The 100 MHz proton magnetic resonance (P.M.R.) spectral data reported here were recorded with a Jeol JNM-4H-100 spectrometer, and the high resolution P.M.R. spectrum of (152) was recorded with a 270 MHz Bruker HX-270 spectrometer. Tetramethylsilane was used as the internal standard and chemical shifts are reported in delta (δ) values. The signals derived from protons are given as singlets (s), doublets (d), triplets (t), doublets of doublets (d of d) or as multiplets (m). The coupling constants (J) are given in Hertz (Hz).

The carbon-13 nuclear magnetic resonance (^{13}C N.M.R.) spectra reported here were recorded with a Bruker HX-270 spectrometer. Tetramethylsilane was used as the internal standard and chemical shift values are given in delta (δ).

The low and high resolution mass spectra were run on a VG 7070F Micromass spectrometer at 70 eV with a source temperature of 200°, using the direct insertion technique. Peaks are listed in descending order of m/e ratio and peak heights are given in percentages (given in brackets).

The infra-red (I.R.) spectra were recorded using a Beckman IR-33 spectrometer and the absorption bands are described as strong (s) or weak (w) in intensity.

The ultraviolet (U.V.) spectra were recorded with a Hitachi Perkin-Elmer 124 spectrometer and the absorption data refer to solution in methanol.

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected.

Solvents used here were purified by standard methods. Evaporation of the solvents was carried out under reduced pressure.

Thin layer chromatography (T.L.C.) and preparative thin layer chromatography (P.L.C.) were carried out on Merck silica gel GF_{254} and the slurry was made up with water unless otherwise stated.

Experimental for Chapter 2

3-Methoxyphenoxyethanenitrile (36)

The title compound (36) was prepared after the method described by Burtner[54] and Djerassi et al.[53] To a solution of chloroethanenitrile (12.16 g, 0.01610 mol) in anhydrous butanone (30 ml) was added powdered potassium iodide (1.5 g, 0.009 mol) and the mixture kept in the dark for 18 h. The resulting orange coloured suspension was filtered, and the precipitate was washed well with butanone (20 ml). A mixture of 3-methoxyphenol (20 g, 0.1612 mol) and anhydrous potassium carbonate (22.26 g, 0.1613 mol) in anhydrous butanone (100 ml) was heated to reflux. To this refluxing mixture, the above filtrate was added dropwise over a period of 2 h with stirring. Refluxing was continued for a further 1 h, and the solvent was removed leaving a yellow coloured residue. Water (150 ml) was added, the mixture was extracted with chloroform (3 x 20 ml), and the combined chloroform layers successively washed with 5% aqueous sodium hydroxide (3 x 10 ml), and with water (3 x 20 ml). The dried (sodium sulfate) chloroform solution was evaporated to afford 3-methoxyphenoxyethanenitrile (36) (23.16 g, 88%) as a straw coloured syrup (lit.[54] $b.p._{0.25}$ 90.2°).

M.S. (high resolution): m/e 163 (91) ($M^{+\cdot}$, accurate mass 163.0647. $C_9H_9NO_2$ requires 163.0632), 151 (7), 123 (22), 95 (100).

P.M.R. δ ($CDCl_3$) 3.75 (s, 3H, $-OCH_3$), 4.70 (s, 2H, $-OCH_2CN$), 6.45-6.70 (m, 3H, ArH), 7.10-7.32 (m, 1H, ArH).

I.R. (neat): 2240 (weak C≡N) cm^{-1}.

3,4-Methylenedioxyphenoxyethanenitrile (37)

Powdered potassium iodide (6.01 g, 0.0362 mol) was added to a

solution of chloroethanenitrile (2.75 g, 0.0364 mol) in anhydrous butanone (15 ml) and kept in the dark for 18 h. The mixture was filtered and the precipitate was washed with butanone. 3,4-Methylenedioxyphenol (5 g, 0.036 mol) and anhydrous potassium carbonate (5 g, 0.036 mol) in anhydrous butanone (30 ml) were heated to reflux, and the above filtrate was added dropwise over a period of 1 h. Refluxing was continued for a further 1.5 h and the solvent was removed to obtain a dark brown residue.

Water (100 ml) was added and the crude product extracted with dichloromethane (3 x 10 ml). The combined dichloromethane layers were washed with 5% aqueous sodium hydroxide (3 x 10 ml) and water (3 x 15 ml), dried (sodium sulfate), and solvent removed to afford *3,4-methylenedioxyphenoxyethanenitrile* (37) (6.41 g, 83%) R_f 0.7 (chloroform), as a straw coloured syrup.

M.S. (high resolution): 177 (44) ($M^{+\cdot}$, accurate mass 177.0426. $C_9H_7NO_3$ requires, 177.0424), 138 (10), 137 (100), 107 (48).

P.M.R. δ ($CDCl_3$): 4.70 (s, 2H, $-OCH_2CN$), 5.96 (s, 2H, $O-CH_2-O-$), 6.36 (d of d, J_1 = 8.75Hz, J_2 = 2.5Hz, 1H, ArH_A), 6.56 (d, J = 2.5 Hz 1H, ArH_B), 6.75 (d, J = 8.75Hz, 1H, ArH_C).

I.R. (neat): 2230 (w, C≡N).

3,5-Dimethoxyphenoxyethanenitrile (38)

The title compound[55] (38) was prepared similarly by the method described for the synthesis of 3-methoxyphenoxyethanenitrile (36).[53]

Hence, a solution of chloroethanenitrile (2.50 g, 0.0331 mol) and anhydrous butanone (15 ml) was kept over powdered potassium iodide (5.3 g, 0.0319 mol) for 18 h in the dark, and the suspension was filtered. A mixture of 3,5-dimethoxyphenol (5 g, 0.0324 mol) and anhydrous potassium carbonate (4.5 g, 0.0326 mol) in anhydrous butanone (30 ml) was heated to reflux and the above filtrate was added

dropwise over a period of 1 h. The reaction mixture was refluxed for 1.5 h and the solvent removed. Water (100 ml) was added to the residue and extracted with dichloromethane (3 x 10 ml). The combined dichloromethane layers were washed with 5% aqueous sodium hydroxide (3 x 10 ml) and water (3 x 10 ml). The dried (sodium sulfate) organic layer was evaporated to afford the nitrile (38) (5.78 g, 92%) as a straw coloured syrup (R_f 0.7, chloroform), which crystallised on cooling. Recrystallisation from diethyl ether and light petroleum (40°-60°) gave the pure 3,5-dimethoxyphenoxyethanenitrile[55] (38) (5.10 g, 81%) as plates m.p. 32°-33°.

M.S. (high resolution): m/e 193 (100) ($M^{+\cdot}$, accurate mass 193.0739. $C_{10}H_{11}NO_3$ requires 193.0739), 167 (43), 138 (14), 125 (88).

P.M.R. δ ($CDCl_3$): 3.75 (s, 6H, 2 x $-OCH_3$), 4.70 (s, 2H, $-OCH_2CN$), 6.12 (s, 3H, ArH).

I.R. (neat): 1465, 1600 (s, C-C), 2240 (w, C≡N), 2840, 2940-2960 (C-C Ar) cm^{-1}.

4-Chlorophenoxyethanenitrile (39)

The above compound (39) (5.82 g) was prepared in 89% yield, by the method described for the synthesis of the nitrile (36), using 4-chlorophenol (5 g, 0.0389 mol) instead of 3-methoxyphenol. Recrystallisation of the crude product afforded the transparent pale brown rhomboids of the nitrile[95] (39) m.p. 28°-29° (diethyl ether, light petroleum 40°-60°).

M.S. (high resolution): m/e 169 (15), 167 (45) (^{35}Cl, $M^{+\cdot}$ accurate mass 167.0143 . C_8H_6ClNO requires 167.0138), 129 (32), 127 (100), 101 (16), 99 (49).

P.M.R. δ ($CDCl_3$): 4.72 (s, 2H, $-OCH_2CN$), 6.35-6.98 (m, 2H, ArH), 7.24-7.35 (m, 2H, ArH).

I.R. (nujol): 1450, 1570 cm^{-1}.

2-(3-Methoxyphenoxy)ethanamine (40)

To a stirred suspension of lithium tetrahydridoaluminate (9.31 g, 0.245 mol) in anhydrous diethyl ether (250 ml), was added a solution of 3-methoxyphenoxyethanenitrile (36) (20 g, 0.122 mol) in anhydrous diethyl ether (100 ml) over a period of 2 h. The reaction mixture was then refluxed for 1 h with vigorous stirring and allowed to cool. The hydrolysis of the lithium complex was carried out with water (37 ml) and 15% aqueous sodium hydroxide (9.5 ml), as described in the literature.[90] The resulting white precipitate was filtered and washed with diethyl ether (2 x 20 ml). The combined, dried (sodium sulfate) ether layers were then evaporated to obtain an oil, which afforded the ethanamine (40) (12.58 g, 62%), b.p.$_{0.8\ mm}$ 98°-100° (lit.[91,92] b.p.$_{12\ mm}$ 152-154), on vacuum distillation.

M.S. (high resolution): m/e 167 (9) ($M^{+\cdot}$, accurate mass 167.0930. $C_9H_{13}NO_2$ requires 167.0945), 125 (35), 124 (77), 44 (100).

P.M.R. δ ($CDCl_3$): 1.47-1.60 (broad s, 2H, $-NH_2$, disappears with the addition of D_2O), 3.06 (t, J = 5Hz, 2H, $-NCH_2-$), 3.80 (s, 3H, $-OCH_3$), 3.98 (t, J = 5Hz, 2H, $-OCH_2-$), 6.50-6.63 (m, 3H, ArH), 7.10-7.33 (m, 1H, ArH).

I.R. (neat): 1590-1600 (s, C-N), 2720 (C-C), 3280 and 3350 (s, NH_2) cm^{-1}.

2-(3,4-Methylenedioxyphenoxy)ethaneamine (41)

To a stirred suspension of lithium tetrahydridoaluminate (1.6 g, 0.0421 mol) in dry diethyl ether (30 ml) was added dropwise a solution of 3,4-methylenedioxyethanenitrile (37) (5 g, 0.0283 mol) in dry diethyl ether (30 ml) and refluxed for 2 h. The reaction mixture was allowed to cool and hydrolysis was carried out by the addition of water (6.4 ml) and 15% aqueous sodium hydroxide (1.6 ml).[90] The

resulting suspension was filtered and the precipitate washed with diethyl ether (3 x 10 ml). The solution and washings were combined and dried (sodium sulfate) and the solvent evaporated to afford *the amine* (41) (4.43 g, 86%), R_f 0.3 (2% KOH-silica gel, 5% methanol - chloroform) as an oil.

M.S. (high resolution): m/e 181 (17) ($M^{+\cdot}$, accurate mass 181.0738. $C_9H_{11}NO_3$ requires 181.0738), 138 (100), 137 (42).

P.M.R. δ ($CDCl_3$): 2.83 (s, 2H, exchanges with D_2O, $-NH_2$), 3.00 (t, J = 5Hz, 2H, $-NCH_2-$), 3.88 (t, J = 5Hz, 2H, $-OCH_2-$), 5.90 (s, 2H, $O-CH_2-O$), 6.31 (d, of d, J_1 = 7.5Hz, J_2 = 2.5Hz, 1H, ArH_a), 6.50 (d, J = 2.5Hz, 1H, ArH_b), 6.70 (d, J = 7.5Hz, 1H, ArH_c).

I.R. (nujol): 1620 (s, C-N), 3120-3350 (s, NH_2) cm^{-1}.

2-(3,5-Dimethoxyphenoxy)ethanamine (42)

To a stirred suspension of lithium tetrahydridoaluminate (2 g, 0.0526 mol) in anhydrous diethyl ether (30 ml) was added dropwise a solution of the nitrile (38) (5 g, 0.025 mol) in dry diethyl ether (30 ml), and refluxed for 1 h. The reaction mixture was allowed to cool and hydrolysis was carried out by the dropwise addition of water (8 ml) and 15% aqueous sodium hydroxide (2 ml).[90] The resulting granulated white precipitate was filtered and washed with diethyl ether (3 x 10 ml). The combined and dried (sodium sulfate) ether layers were evaporated and dried under vacuum to afford 2-(3,5-dimethoxyphenoxy) ethanamine (42) (3.961 g, 80%) as an oil (lit.[55] hydrochloride salt of (42) m.p. 154°-155°).

M.S. (high resolution): m/e 197 (4) ($M^{+\cdot}$, accurate mass, 197.1067. $C_{10}H_{15}NO_3$ requires 197.1050), 155 (100), 154 (53), 139 (15), 125 (25).

P.M.R. δ ($CDCl_3$): 1.80-1.90 (broad s, 2H, exchanges with D_2O, $-NH_2$), 3.01 (t, J = 5Hz, 2H, $-NCH_2-$), 3.75 (s, 3H, $-OCH_3$), 3.89 (t, J = 5Hz,

$-OCH_2-$), 6.08 (s, 3H, ArH).

I.R. (neat): 1580 (s, C-N), 2920 (s, C-C, Ar), 3290 and 3360 (s, NH_2) cm^{-1}.

2-(4-Chlorophenoxy)ethanamine (43)

Reduction of the nitrile (39) (1.00 g, 0.0060 mol) in dry diethyl ether (100 ml) with lithium tetrahydridoaluminate (0.453 g, 0.0120 mol) was carried out in the same manner as described for the preparation of (40), to afford the amine (43)[4] (0.908 g, 87%) as a pale yellow oil.

P.M.R. δ ($CDCl_3$): 1.52 (s, 2H, exchanges with D_2O, $-NH_2$), 3.05 (t, J = 5Hz, 2H, $-NCH_2-$), 3.94 (t, J = 5Hz, 2H, $-OCH_2-$), 6.82 (d, J = 7.5Hz, 2H, ArH), 7.21 (d, J = 7.5Hz, 2H, ArH).

I.R. (neat): 3265 and 3345 (s, NH_2) cm^{-1}.

1-(2-Bromoethoxy)benzene (44)

The title compound (44) was prepared by the method of Marvel and Tenenbaum.[56] Thus a mixture of 1,2-dibromoethane (100.97 g, 0.537 mol), water (200 ml) and phenol (39.247 g, 0.436 mol) was heated to reflux with stirring, and a solution of sodium hydroxide (18.56 g, 0.464 mol) in water (75 ml) was added dropwise over a period of 1 h. Stirring and refluxing were continued for 6 h and the solution left at 20° for 12 h. The upper water layer was then separated and discarded. The lower layer (90 g) was subjected to fractional distillation under vacuum to afford 1-(2-bromoethoxy)benzene (44) (45.51 g, 52%) b.p.$_{10\ mm}$ 110°-119° (lit.[56] b.p.$_{18\ mm}$ 125°-130°), which crystallised on cooling m.p. 56°-57°.

P.M.R. δ ($CDCl_3$): 3.55 (t, J = 6.25Hz, 2H, $-CH_2Br$), 4.20 (t, J=6.25Hz, 2H, $-OCH_2-$), 6.30-7.05 (m, 3H, ArH), 7.20-7.47 (m, 2H, ArH).

1-(2-Bromoethoxy)-3-methoxybenzene (45)

The title compound (45) was prepared by the method described in

the literature.[57] Thus a solution of 1,2-dibromoethane (42.5 g, 0.226 mol) in dry ethanol (30 ml) was heated to reflux and a solution of sodium 3-methoxyphenate (30.77 g, 0.2107 mol) in dry ethanol (140 ml) was added dropwise over a period of 1 h, and refluxed for 6 h. The reaction mixture was allowed to cool and filtered. The precipitate was washed with ethanol (3 x 10 ml) and 20% aqueous sodium hydroxide (20 ml) was added to the combined filtrates. These were extracted with chloroform (3 x 20 ml) and the chloroform layers were washed with water (3 x 20 ml). The dried (sodium sulfate) chloroform solution was evaporated to obtain a syrup (36 g) which was then subjected to fractional distillation, to afford 1-(2-bromoethoxy)-3-methoxybenzene (45) (9.95 g, 21%), b.p.$_{12\ mm}$ 160°-172° (lit.[91,92] b.p.$_{12\ mm}$ 160°-174°). P.M.R. δ ($CDCl_3$): 3.59 (t, J = 6.25Hz, 2H, $-CH_2Br$), 3.78 (s, 3H, $-OCH_3$), 4.75 (t, J = 6.25Hz, 2H, $-OCH_2-$), 6.40-6.60 (m, 3H, ArH), 7.05-7.30 (m, 1H, ArH).

2-(2-Phenoxyethyl)-1*H*-isoindole-1,3(2*H*)-dione (46)

The title compound (46) was prepared by a method described in the literature.[58]

A mixture of powdered potassium phthalimide (9.25 g, 0.05 mol) and 1-(2-bromoethoxy)benzene (44) (10 g, 0.05 mol) in anhydrous dimethylformamide (50 ml) was refluxed for 3 h with stirring. The solvent was removed and chloroform (60 ml) and water (250 ml) were added to the residue. The aqueous phase was separated and extracted with chloroform (2 x 20 ml). These chloroform layers were washed with 20% aqueous sodium hydroxide (3 x 20 ml) and with water (3 x 20 ml). The dried (sodium sulfate) chloroform extract was evaporated and the residue was recrystallised from diethyl ether to afford the phthalimide derivative (46) (8.22 g, 62%) as white needles m.p. 127°-129° (lit.[93]

m.p. 129°-130°).

P.M.R. δ ($CDCl_3$): 4.00-4.20 (m, 4H, 2 x $-CH_2-$), 6.80-7.00 (m, 3H, ArH), 7.10-7.40 (m, 2H, ArH), 7.55-8.00 (m, 5H, ArH).

I.R. 1710, 1750 (s, C=O) cm^{-1}.

2-(2-[3-Methoxyphenoxyethyl]-1*H*-isoindole-1,3-(2*H*)-dione (47)

A solution of 1-(2-bromoethoxy)3-methoxybenzene (45) (9.3 g, 0.0403 mol) in anhydrous dimethylformamide (35 ml) and potassium phthalimide (7.5 g, 0.0405 mol) was refluxed for 3 h with stirring. The solvent was then removed and water (20 ml) was added to the residue. This was extracted with chloroform (3 x 20 ml) and the chloroform layers were washed with 20% aqueous sodium hydroxide (3 x 20 ml) followed by water (3 x 20 ml). The dried (sodium sulfate) chloroform layer was evaporated, and the residue (8.72 g) was recrystallised from diethyl ether and light petroleum (40°-60°) to afford the phthalimide derivative (47) (7.52 g, 63%) as white needles m.p. 114°-115° (lit.[91,92] m.p. 114°-115°).

M.S. (high resolution): m/e 297 (18) ($M^{+\cdot}$, accurate mass 297.1042. $C_{17}H_{15}NO_4$ requires 297.1001), 274 (32), 174 (100), 151 (26), 150 (78).

P.M.R. δ ($CDCl_3$): 3.73 (s, 3H, $-OCH_3$), 4.05-4.32 (m, 4H, 2 x $-CH_2-$), 6.40-6.55 (m, 3H, ArH), 7.00-7.20 (m, 1H, ArH), 7.63-7.90 (m, 4H, ArH).

I.R. (nujol): 1580, 1710 (s, C=O), 1750 (s, C=O) cm^{-1}.

Preparation of the amine (40) by the hydrazinolysis of (47)

To a solution of 2-(2-[3-methoxyphenoxyethyl]-1*H*-isoindole-1,3-(2*H*)-dione (47) (7.00 g, 0.0236 mol) in ethanol was added hydrazine hydrate (1.2 g, 0.024 mol) and the mixture refluxed for 2 h with stirring. To the resulting thick white slurry, concentrated hydrochloric acid (25 ml) was added and refluxing was continued for a further 30 min. The mixture was then filtered and the precipitate washed with boiling ethanol (30 ml) and dried (vacuum oven) to give a quantitative yield of the phthaloyl hydrazine (3.8 g, 100%) as a white powder.

The filtrate was evaporated and the residue was recrystallised from ethanol and diethyl ether to afford the hydrochloride salt (49) of the amine (40) (4.00 g, 84%) as white needles m.p. 144°-145° (lit.[55] 145°-146°).

P.M.R. δ ($CDCl_3$-CD_3OD): 2.30-3.50 (m, 2H, $-CH_2-$), 3.80 (s, 3H, $-OCH_3$), 4.13 (s, 3H, $-\overset{+}{N}H_3$), 4.23 (t, J = 5Hz, $-CH_2-$), 6.52-6.67 (m, 3H, ArH), 7.10-7.22 (m, 1H, ArH). Basification of this hydrochloride salt with 20% aqueous sodium hydroxide (25 ml) liberated an oil, which was then extracted with chloroform (3 x 10 ml). These chloroform layers were dried (sodium sulfate) and the solvent was removed to afford the free base (40) (3.10 g, overall yield from (47) 79%) as an oil. The spectral data of this compound was identical to those of the amine (40) prepared by the method as described in page 110.

2-Phenoxyethanamine hydrochloride (48)

To a solution of the phthaloyl derivative (46) (6.24 g, 0.0243 mol)

in ethanol (40 ml) was added hydrazine hydrate (0.90 g, 0.018 mol) and refluxed for 1.5 h. Concentrated hydrochloric acid (35 ml) was added and stirring was continued for 18 h. The resulting white precipitate was filtered and washed with boiling ethanol (2 x 10 ml). The dried (vacuum oven) precipitate gave phthaloylhydrazine (3.8 g, 100%).

The filtrate was evaporated to dryness and the residue was recrystallised from ethanol to afford the hydrochloride salt (48) (3.65 g, 87%) as white needles, 210°-212° (lit.[94] m.p. 210°).
P.M.R. δ ($CDCl_3$): 3.15-3.35 (m, 2H, $-CH_2-$), 3.85 (s, 3H, $-\overset{+}{N}H_3$), 4.23 (t, J = 5Hz, 2H, $-CH_2-$), 6.80-7.00 (m, 3H, ArH), 7.15-7.35 (m, 2H, ArH).
I.R. (nujol): 1450, 1590 cm^{-1}.

N-2-(3-methoxyphenoxy)ethylbenzamide (51)

To an ice-cooled, stirred solution of the amine (40) (16.65 g, 0.099 mol) in dry chloroform (50 ml) and dry pyridine (10 ml) was added benzoyl chloride (13 ml, 0.111 mol) over a period of 1 h. Stirring and cooling were continued for a further 2 h.

The solution was then washed with 5% aqueous hydrochloric acid (2 x 20 ml), water (2 x 20 ml) and finally with 5% aqueous sodium hydroxide (2 x 20 ml). The dried (sodium sulfate) chloroform solution was evaporated to obtain a syrup (25.23 g) which crystallised under light petroleum (40°-60°). Recrystallisation from diethyl ether and light petroleum (40°-60°) afforded the *amide* (51) (23.37 g, 86%) as cream coloured needles, m.p. 48°-50°, (T.L.C., R_f 0.8, $CHCl_3$-alumina).
Found: C, 70.96; H, 6.13, N, 5.15.
$C_{16}H_{17}NO_3$ requires, C, 70.84; H, 6.27; N, 5.16%.
M.S. (high resolution): m/e 272 (0.2), ($M^{+\cdot}$, accurate mass 271.1206. $C_{16}H_{17}NO_3$ requires, 271.1207), 271 (1.2), 148 (100), 105 (65), 77 (42).

P.M.R. δ ($CDCl_3$): 3.75 (s, 3H, $-OCH_3$), 3.85 (t, J = 5Hz, $-NCH_2-$), 4.10 (t, J = 5Hz, 2H, $-OCH_2-$), 6.48-6.58 (m, 3H, ArH), 6.80-6.97 (broad s, 1H, NH, disappears with the addition of D_2O), 7.40-7.55 (m, 4H, ArH), 7.75-7.86 (m, 2H, ArH).

I.R. (nujol): 1640, 1690 (s, C=O) 3280 (s, -NH) cm^{-1}.

3-Chlorobenzoyl chloride

A solution of 3-chlorobenzoic acid (10 g, 0.0638 mol) in anhydrous toluene (20 ml) and freshly distilled thionyl chloride (7 ml, 11.2 g, 0.0941 mol) was refluxed for 2 h with stirring. Removal of the solvent followed by vacuum distillation afforded 3-chlorobenzoyl chloride (7.1 g, 63%) $b.p._{1-2\ mm}$ 120° (lit.[96] $b.p._{17}$ 116°-118°) as a colourless liquid. This was reacted directly with the amine (40) to afford the amide (52).

N-(2-[3-Methoxyphenoxy]ethyl)-3-chlorobenzamide (52)

To an ice cooled stirred solution 2-(3-methoxyphenoxy)ethanamine (40) (5 g, 0.0299 mol) in dry chloroform (15 ml) and dry pyridine (5 ml), was added dropwise a solution of 3-chlorobenzoyl chloride (6 g, 0.0342 mol). Stirring and cooling were continued for 2 h to afford *N-(2-[3-methoxyphenoxy]ethyl)-3-chlorobenzamide* (52), after work-up as described for the amide (51). Recrystallisation from diethyl ether and light petroleum (40°-60°) gave the pure *3-chlorobenzamide* derivative (52) (8.31 g, 90%) as white needles, m.p. 40°-41°. (T.L.C., 5% methanol-chloroform, R_f 0.7).

Found: C, 62.82; H, 5.41; N, 4.53. $C_{16}H_{16}ClNO_3$ requires, C, 62.95; H, 5.24; N, 4.59%.

M.S. (high resolution): m/e 305 (2.3)(^{35}Cl, $M^{+\cdot}$, accurate mass 305.0817. $C_{16}H_{16}ClNO_3$ requires 305.0819), 184 (32), 182 (100), 139 (51), 111 (23).

P.M.R. δ ($CDCl_3$): 3.78 (s, 3H, $-OCH_3$), 3.85 (t, J = 5Hz, 2H, $-CH_2-$), 4.10 (t, J = 5Hz, 2H, $-OCH_2-$), 6.50-6.60 (m, 3H, ArH), 6.90-7.08 (broad s, 1H, disappears with the addition of D_2O, NH), 7.18-7.50 (m, 3H, ArH), 7.60-7.82 (m, 2H, ArH).

I.R. (nujol): 1680 (s, C=O) cm^{-1}, 3280 (s, -NH) cm^{-1}.

N-2-(3,4-Methylenedioxyphenoxy)ethylbenzamide (53)

To an ice-cooled stirred solution of the amine (41) (3.90 g, 0.0215 mol) and pyridine (10 ml) in dry chloroform (20 ml) was added dropwise a solution of benzoyl chloride (3.05 g, 0.0217 mol). This was stirred at about <10° for 2 h and then washed successively with 5% aqueous hydrochloric acid (3 x 10 ml) and with water (3 x 10 ml). The dried (sodium sulfate) chloroform layer was evaporated to obtain a pale yellow gum which was crystallised on cooling. Recrystallisation from diethyl ether and light petroleum (40°-60°) gave *N-2-(3,4-methylenedioxyphenoxy)ethylbenzamide* (53) (2.55 g, 43%) as white granules m.p. 125°-126°.

Found: C, 66.16; H, 5.41; N, 4.55. $C_{16}H_{15}NO_4$ requires, C, 67.36; H, 5.26; N, 4.91%.

M.S. (high resolution): m/e 285 (8) ($M^{+\cdot}$, accurate mass 285.0999. $C_{16}H_{15}NO_4$ requires 285.1000), 149 (45), 148 (100), 138 (33), 137 (17), 105 (100).

P.M.R. δ ($CDCl_3$): 3.78 (t, J = 5Hz, 2H, $-NCH_2-$), 4.00 (t, J = 5Hz, 2H, $-OCH_2-$), 5.88 (s, 2H, $O-CH_2-O$), 6.30 (d of d, J = 7.5Hz, J_2 = 2.5Hz, 1H, ArH), 6.49 (d, J = 2.5Hz, 1H, ArH), 6.66 (d, J = 7.5Hz, 1H, ArH), 7.40-7.50 (m, 3H, ArH), 7.70-7.82 (m, 2H, ArH).

I.R. (nujol): 1720 (s, C=O), 3420 (w, NH) cm^{-1}.

N-2-(3,5-Dimethoxyphenoxy)ethylbenzamide (54)

To an ice-cooled, stirred solution of the amine (42) (3.5 g, 0.0177 mol) in dry chloroform (20 ml) and pyridine (15 ml) was

added dropwise a solution of benzoyl chloride (2.5 g, 0.0177 mol). The solution was stirred at <10°C for 2 h and washed successively with 5% aqueous hydrochloric acid (3 x 10 ml) and water (2 x 10 ml). The dried (sodium sulfate) organic phase was evaporated to obtain a syrup which was crystallised from light petroleum (40°-60°). Recrystallisation from diethyl ether and light petroleum (40°-60°) afforded the *amide* (54) (5.00 g, 94%) as colourless needles, m.p. 86°-87°.

Found: C, 67.58; H, 6.18; N, 4.67. $C_{17}H_{19}NO_4$ requires, C, 67.77; H, 6.31; N, 4.65%.

M.S. (high resolution): m/e 301 (3) ($M^{+\cdot}$, accurate mass 301.1314. $C_{17}H_{19}NO_4$ requires, 301.1312), 180 (4), 148 (100), 105 (52), 77 (30).

P.M.R. δ ($CDCl_3$): 3.73 (s, 6H, 2 x $-OCH_3$), 3.84 (t, J = 5Hz, 2H, $-NCH_2-$), 4.05 (t, J = 5Hz, 2H, $-OCH_2-$), 6.08 (s, 2H, ArH), 6.82 (br s, 1H, (exchanges with D_2O, NH), 7.30-7.60 (m, 3H, ArH), 7.70-7.85 (m, 1H, ArH), 7.95-8.20 (m, 2H, ArH).

I.R. (nujol): 1660 (s, C=O), 3280 (s, NH) cm^{-1}.

N-2-Phenoxyethylbenzamide (55)

Treatment of the hydrochloride salt (48) (2.00 g, 0.0115 mol) with 10% aqueous sodium hydroxide followed by extraction with chloroform (3 x 10 ml) gave the free base (50). To this dried (sodium sulfate) chloroform solution, dry pyridine (16 ml) was added, followed by a solution of benzoyl chloride (2 ml, 0.0171 mol) with stirring and ice-cooling. Stirring was continued for 2 h at 10°, and the solvent was removed. To the residue, chloroform (20 ml) was added and the solution washed with water (3 x 10 ml). The dried (sodium sulfate) chloroform layer was evaporated and the residue crystallised under light petroleum (40°-60°). Recrystallisation

from diethyl ether and light petroleum (40°-60°) gave the benzamide (55) (1.8 g, 67%) as white needles m.p. 90°-92° (lit.[97] m.p. 93°).

P.M.R. δ ($CDCl_3$): 3.80 (t, J = 5Hz, 2H, $-NCH_2-$), 4.15 (t, J = 5Hz, 2H, $-OCH_2-$), 6.7-6.85 (broad s, 1H, NH), 6.87-7.00 (m, 2H, ArH). 7.28-7.50 (m, 5H, ArH), 7.72-7.85 (m, 2H, ArH).

I.R. (nujol): 1630 (s, C=O), 3350 (s, NH) cm^{-1}.

N-2(4-Chlorophenoxy)ethylbenzamide (56)

The title compound (56) was prepared by the reaction of amine (43) (0.700 g, 0.0041 mol) and benzoyl chloride (0.575 g, 0.0041 mol) in the same manner as described for the synthesis of the amide (51). Recrystallisation of the crude product from diethyl ether and light petroleum (40°-60°) afforded the amide[4] (56) (0.969 g, 87%) as white granules m.p. 74.5°-76°.

M.S. (high resolution): m/e 275 (2) ($M^{+\cdot}$, accurate mass 275.0813. $C_{15}H_{14}ClNO_2$ requires 275.0823), 148 (100), 105 (93).

P.M.R. δ ($CDCl_3$): 3.85 (t, J = 5Hz, 2H, $-NCH_2-$), 4.09 (t, J = 5Hz, 2H, $-OCH_2-$), 6.60-6.90 (m, 3H, 1 proton exchanges with D_2O, NH and 2ArH), 6.95-7.30 (m, 2H, ArH), 7.35-7.50 (m, 3H, ArH), 7.60-7.85 (m, 2H, ArH).

I.R. (nujol): 1620 (s, C=O), 3320 (s, NH) cm^{-1}.

8-Methoxy-5-phenyl-2,3-dihydro-1,4-benzoxazepine (57)

A solution of freshly distilled phosphorus oxychloride (10 ml) and butanenitrile (30 ml) was heated to reflux and a solution of the amide (51) (10 g, 0.036 mol) in warm butanenitrile (30 ml) was added dropwise with stirring. Refluxing and stirring under nitrogen were continued for 16 h.[21]

Removal of the solvents gave a reddish syrup, to which was added ice. Basification with 20% aqueous sodium hydroxide liberated

an oil, which was extracted with chloroform (3 x 30 ml). The extracts were dried (sodium sulfate) and the solution concentrated to about 10 ml. This solution was extracted with concentrated hydrochloric acid (5 M, 15 x 10 ml), basified with 50% aqueous sodium hydroxide, and again extracted with chloroform (3 x 30 ml). These combined chloroform layers were dried (sodium sulfate) and evaporated to obtain the crude *cyclic imine* (57) as a gum (7.45 g; 80%).

The crude imine (2 g) was subjected to P.L.C. (5% methanol-chloroform) to give (R_f 0.7) the *8-methoxy-5-phenyl-2,3-dihydro-1,4-benzoxazepine* (57) (1.4 g, overall yield 69%) as a pale yellow gum.

M.S. (high resolution): m/e 253 (74) ($M^{+\cdot}$, accurate mass 253.1115. $C_{16}H_{15}NO_2$ requires 253.1103), 252 (100), 225 (53), 196 (39), 105 (68.5), 77 (73.5).

P.M.R. δ ($CDCl_3$): 3.83 (s, 3H, $-OCH_3$), 3.88 (t, J = 5Hz, 2H, $-NCH_2-$), 4.68 (t, J = 5Hz, 2H, $-OCH_2-$), 6.65 (s, 2H, ArH), 7.05 (d, J = 7.5Hz, 1H, ArH), 7.38-7.45 (m, 3H, ArH), 7.58-7.65 (m, 2H, ArH).

I.R. (neat): 1600 (s, C=N), 2885 (Ar C-C) cm^{-1}.

5-(3-Chlorophenyl)-8-methoxy-2,3-dihydro-1,4-benzoxazepine (58)

A solution of freshly distilled phosphorus oxychloride (9 ml) and dry butanenitrile (25 ml) was heated to reflux and a solution of *N*-(2-[3-methoxyphenoxy]ethyl)-3-chlorobenzamide (52) (9 g, 0.0294 mol) in butanenitrile (30 ml) was added dropwise with stirring. The reaction mixture was refluxed under nitrogen for 16 h with stirring.

Removal of the solvents gave a reddish syrup, to which was added ice. Then basification with 20% aqueous sodium hydroxide gave an oil, and this was then extracted with chloroform (3 x 30 ml). The combined, dried (sodium sulfate) chloroform extracts were concentrated

to about 7 ml and extracted with concentrated hydrochloric acid (5 M, 20 x 10 ml). The combined acid extracts were basified with 50% aqueous sodium hydroxide and, the resulting oil was finally extracted with chloroform (4 x 20 ml). The combined, dried (sodium sulfate) chloroform layers were evaporated to obtain a reddish coloured gum (4.1 g). This was then dissolved in diethyl ether, and the ether-soluble portion was evaporated to afford the *cyclic imine* (58) (3.75 g; 44%) as a straw coloured gum.

Further purification by P.L.C. (5% methanol-chloroform) afforded *5-(3-chlorophenyl)-8-methoxy-2,3-dihydro-1,4-benzoxazepine* (58), R_f 0.9 as a pale yellow gum, which could not be crystallized.
M.S. (high resolution): m/e 289 (^{37}Cl) (24.8), 287 (^{35}Cl) (74), ($M^{+\cdot}$ accurate mass 287.0690. $C_{16}H_{14}NO_2Cl$ requires, 287.0713), 286 (100), 259 (48), 252 (11), 231 (15), 207 (10), 152 (10.6), 125 (11).
P.M.R. δ ($CDCl_3$): 3.87 (s, 3H, $-OCH_3$), 3.82 (t, J = 5Hz, 2H, $-NCH_2-$), 4.69 (t, J = 5Hz, 2H, $-OCH_2-$), 6.60-6.80 (m, 2H, ArH), 7.02 (d, J = 10Hz, 1H, ArH), 7.30-7.43 (m, 3H, ArH), 7.60-7.80 (m, 1H, ArH).
I.R. (neat): 1500, 1560, 1600 (s, C=N), 2920-2940 (s, C-C Ar) cm^{-1}.

7,8-Methylenedioxy-5-phenyl-2,3-dihydro-1,4-benzoxazepine (59)

A solution of freshly distilled phosphorus oxychloride (3 ml) and ethanenitrile (40 ml) was heated to reflux and a solution of the amide (53) (2.34 g, 0.0082 mol) in dry ethanenitrile (20 ml) was added dropwise with stirring. The reaction mixture was refluxed for 4 h and solvents were removed. The residue was basified with 20% aqueous sodium hydroxide with ice-cooling and extracted with dichloromethane (4 x 10 ml). The dried (sodium sulfate) dichloro-methane layers were concentrated in about 5 ml and extracted with

hydrochloric acid (5 M, 15 x 10 ml). Basification of the acid layers with 50% aqueous sodium hydroxide liberated an oil which was extracted with dichloromethane (4 x 15 ml). These dichloromethane layers were dried (sodium sulfate) and evaporated to afford the crude *cyclic imine* (59) (1.72 g). Purification by P.L.C. (5% methanol-chloroform) gave the pure *7,8-methylenedioxy-5-phenyl-2,3-dihydro-1,4-benzoxazepine* (59) (1.42 g, 64%) R_f 0.5 as a pale yellow gum. (Picrate m.p. 224°-225°).

Found: (picrate), C, 53.89; H, 3.71; N, 11.40. $C_{22}H_{16}N_4O_{10}$ requires C, 53.22%; H, 3.22; N, 11.29%.

M.S. (high resolution): m/e 267 (100) ($M^{+\cdot}$, accurate mass 267.0863. $C_{16}H_{13}NO_3$ requires 267.0895), 266 (92), 237 (43), 211 (20), 209 (21), 148 (18), 130 (12), 105 (18).

P.M.R. δ ($CDCl_3$): 3.79 (t, J = 5Hz, 2H, $-NCH_2-$), 4.61 (t, J = 5Hz, $-OCH_2-$), 6.00 (s, 2H, $O-CH_2-O$), 6.53 (s, 1H, ArH), 6.64 (s, 1H, ArH), 7.32-7.48 (m, 3H, ArH), 7.55-7.70 (m, 2H, ArH).

I.R. (neat): 1600 (s, C=N) cm^{-1}.

6,8-Dimethoxy-5-phenyl-2,3-dihydro-1,5-benzoxazepine (60)

A solution of *N*-2-(3,5-dimethoxyphenoxy)ethylbenzamide (54) (4.83 g, 0.0160 mol) in dry butanenitrile (35 ml) was added dropwise to a refluxing mixture of freshly distilled phosphorus oxychloride (4 ml) and butanenitrile (30 ml). Stirring and refluxing were continued for 10 h and solvents were removed. The residue was basified with 20% aqueous sodium hydroxide with ice-cooling, and then extracted with dichloromethane (4 x 15 ml). The combined, dried, (sodium sulfate) dichloromethane layers were concentrated to about 5 ml and extracted with hydrochloric acid (5 M, 15 x 10 ml). The acid extracts were then basified with 50% aqueous sodium hydroxide, and the resulting oil was extracted into dichloromethane (4 x 15 ml). The organic layers were dried (sodium sulfate) and

evaporated to obtain a reddish gum (2.75 g), to which was added diethyl ether (30 ml). The ether soluble portion was evaporated to afford the *cyclic imine* (60) (2.5 g, 55%) as a straw coloured syrup. An analytical sample of this *cyclic imine* (60) (0.418 g) was prepared by P.L.C. (5% methanol-chloroform, R_f 0.7).

M.S. (high resolution): m/e 283 (18) ($M^{+\cdot}$ accurate mass 283.1226. $C_{17}H_{17}NO_3$ requires 283.1207), 282 (16), 255 (18), 252 (5.6), 209 (5.6), 149 (16), 130 (24), 40 (100).

P.M.R. δ ($CDCl_3$): 3.49 (s, 3H, $-OCH_3$), 3.55-3.75 (m, 2H, $-NCH_2-$), 3.87 (s, 3H, $-OCH_3$), 4.59 (t, J = 5Hz, 2H, $-OCH_2-$), 6.35 (s, 2H, ArH), 7.32-7.40 (m, 3H, ArH), 7.50-7.62 (m, 2H, ArH).

I.R. (neat): 1600 (s, C=N), 2980 (s, C-C Ar) cm^{-1}.

Attempted Bischler-Napieralski cyclization of the amide (56)

A solution of the amide (56) (0.828 g, 0.0030 mol) in anhydrous benzene (15 ml) and xylene (5 ml) was added dropwise to a refluxing mixture of phosphorus pentoxide (1 g) in phosphorus oxychloride (2 ml) and benzene (10 ml).[4] This was refluxed for 6 h and worked up in the same manner as described for the preparation of (57). In this case no basic cyclic material was obtained, and the starting amide (56) was recovered.

8-Methoxy-4-methyl-5-phenyl-2,3-dihydro-1,4-benzoxazepinium iodide (63)

To a solution of the cyclic imine (57) (6 g, 0.0237 mol) in dry acetone (20 ml) was added iodomethane (4.5 ml, 0.0310 mol), and the mixture heated at 120°C in a sealed tube for 10 h. Cooling, and removal of the solvent left the *methiodide salt* (63) (9.2 g; 98% R_f 0.1, 5% methanol-chloroform) as a bright yellow gum. Attempts to crystallise this salt were unsuccessful, and it was therefore reduced without further purification.

5-(3-Chlorophenyl)-8-methoxy-4-methyl-2,3-dihydro-1,4-benzoxazepinium iodide (64)

A solution of the cyclic imine (58) (2.81 g, 0.0097 mol) in dry acetone (15 ml), and redistilled iodomethane (2 ml, 0.0319 mol) was heated at 80°-110° in a sealed tube for 6 h. The reaction mixture was allowed to cool and the solvent was removed. The resulting reddish coloured sticky residue was crystallised from acetone and diethyl ether to afford *5-(3-chlorophenyl)-8-methoxy-4-methyl-2,3-dihydro-1,4-benzoxazepinium iodide* (64) (4.1 g, 96%), as bright yellow granules m.p. 178°-180°.

Found: C, 46.30; H, 3.85; N, 3.09. $C_{17}H_{17}ClNO_2I.\frac{1}{2}H_2O$ requires, C, 46.50; H, 4.10; N, 3.19%.

M.S. (low resolution): m/e 302 (^{35}Cl) (4), ($C_{17}H_{17}Cl\overset{+}{N}O_2$ requires 302.1258), 301 (14), 287 (97), 272 (56), 258 (34), 42 (97), 40 (100).

P.M.R. δ (CH_3OD_4): 3.73 (s, 3H, $-OCH_3$), 4.00 (s, 3H, $>\overset{+}{N}-CH_3$), 4.40 (t, J = 5Hz, 2H, $-OCH_2-$), 5.09 (t, J = 5Hz, 2H, $>\overset{+}{N}CH_2-$), 6.80-7.00 (m, 3H, ArH), 7.60-7.80 (m, 4H, ArH).

7,8-Methylenedioxy-4-methyl-5-phenyl-2,3-dihydro-1,4-benzoxazepinium Iodide (65)

To a solution of the cyclic imine (59) (1 g, 0.0037 mol) in dry acetone (20 ml) was added iodomethane (1 ml, 0.0155 mol). The solution was heated at 80°-100° in a sealed tube for 8 h and allowed to cool. Removal of the solvents and purification by P.L.C. (5% methanol-chloroform) gave the *methiodide salt* (65) (1.51 g, 98%) R_f 0.2, as a pale yellow gum.

M.S. (high resolution): m/e 282 (3) ($M^{+\cdot}$, accurate mass 282.1129. $C_{17}H_{16}\overset{+}{N}O_3$ requires, 282.1128), 269 (47), 267 (87), 252 (92), 225 (42), 142 (100), 128 (41), 127 (37).

P.M.R. δ ($CDCl_3$): 2.67 (s, 3H, $=\overset{+}{N}CH_3$), 3.07-3.25 (m, 2H, $-CH_2-$), 4.32-4.50 (m, 2H, $-CH_2-$), 6.02 (s, 3H, $O-CH_2-O$), 6.70 (s, 1H, ArH), 6.81 (s, 1H, ArH), 7.40-7.42 (m, 5H, ArH).

6,8-Dimethoxy-4-methyl-5-phenyl-2,3-dihydro-1,5-benzoxazepinium Iodide (66)

A solution of the cyclic imine (60) (2.5 g, 0.0088 mol) in anhydrous acetone (20 ml) and iodomethane (2 ml, 0.0309 mol) was heated at 100°-120° in a sealed tube for 10 h and allowed to cool. Then the solvent was removed and the residue was crystallised from methanol to give *6,8-dimethoxy-4-methyl-5-phenyl-2,3-dihydro-1,5-benzoxazepinium iodide* (66) (3.7 g, 98%), as bright yellow granules, m.p. 193°-196°.

Found: C, 50.46; H, 4.74; N, 3.41. $C_{18}H_{20}NO_3I$ requires C, 50.82; H, 4.70; N, 3.29%.

M.S. (high resolution): m/e 298 (3) ($M^{+\cdot}$, accurate mass 298.14477. $C_{18}H_{20}\overset{+}{N}O_3$ requires 298.14420), 297 (7), 296 (7), 283 (100), 282 (99), 268 (13), 240 (21).

P.M.R. δ ($CDCl_3$): 3.35 (s, 3H, $=\overset{+}{N}-CH_3$), 3.80 (s, 3H, $-OCH_3$), 3.92 (s, 3H, $-OCH_3$), 4.30 (t, J = 5Hz, 2H, $-OCH_2-$), 4.78-5.02 (m, 2H, $-NCH_2-$), 6.46 (d, J = 2Hz, 1H, ArH), 6.54 (d, J = 2Hz, 1H, ArH), 7.45-7.68 (m, 5H, ArH).

8-Methoxy-4-methyl-5-phenyl-2,3,4,5-tetrahydro-1,4-benzoxazepine (67)

To a solution of the methiodide salt (63) (8 g, 0.0271 mol) in 60% aqueous ethanol (35 ml) and methanol (10 ml) was added sodium tetrahydridoborate (2.30 g, 0.0607 mol) portionwise with stirring and ice-cooling, and stirring was continued for a further 2 h at <15°. The solvents were removed, and the residue was extracted with water (60 ml) and chloroform (3 x 20 ml). The dried (sodium sulfate) chloroform extracts were evaporated to obtain an oil which

was subjected to P.L.C. (5% methanol-chloroform). This gave *8-methoxy-4-methyl-5-phenyl-2,3,4,5-tetrahydro-1,4-benzoxazepine* (67) (3.82, 70%, R_f 0.7) as a colourless oil, which was crystallised from diethyl ether and light petroleum (40°-60°) to give the *1,4-benzoxazepine* (67) as white granules (m.p. 42°-43°).

Found: C, 75.95; H, 7.27; N, 5.14. $C_{17}H_{19}NO_2$ requires, C, 75.83; H, 7.06; N, 5.20%.

M.S. (high resolution): m/e 269 (7), ($M^{+\cdot}$, accurate mass 269.1408. $C_{17}H_{19}NO_2$ requires 269.1410), 225 (6), 192 (100).

P.M.R. δ ($CDCl_3$): 2.60 (s, 3H, $-NCH_3$), 3.05-3.55 (m, 2H, $-NCH_2-$), 3.75 (s, 3H, $-OCH_3$), 3.85-4.27 (m, 2H, $-OCH_2-$), 4.90 (s, 1H, benzylic H), 6.58-6.72 (m, 2H, Ar-H), 7.00 (d, J = 7.5Hz, 1H, ArH), 7.25-7.35 (m, 5H, ArH).

I.R. ($CHCl_3$): 1150, 1200, 1460, 1485, 1565, 1600 (s, C-N), 2860, 3000 (s, Ar C-C) cm^{-1}.

5-(3-Chlorophenyl)-8-methoxy-4-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine (68)

To a solution of 5-(3-chlorophenyl)-8-methoxy-4-methyl-2,3-dihydro-1,4-benzoxazepinium iodide (64) (3.3 g, 0.0076 mol) in 60% aqueous ethanol (20 ml) and methanol (10 ml) was added sodium tetrahydridoborate (0.876 g, 0.0230 mol) in small portions, with ice-cooling and stirring. The reaction mixture was stirred <15° for 2 h and at room temperature for 14 h. To the residue, obtained by removal of the solvents, was added water (40 ml) and the product extracted with dichloromethane (10 x 3 ml). The combined and dried (sodium sulfate) dichloromethane layers were evaporated to afford the crude *cyclic amine* (68) (2.16 g). This was subjected to P.L.C. (5% methanol-chloroform) to obtain *5-(3-chlorophenyl)-8-methoxy-4-methyl-2,3,4,5-tetrahydro-1,4-benzoxazepine* (68) (0.969 g, 42%), R_f 0.9, as a cream coloured solid.

Recrystallisation from diethyl ether gave white needles of (68) m.p. 65°-66°.

Found: C, 67.10; H, 5.72; N, 4.57. $C_{17}H_{18}ClNO_2$ requires C, 67.21; H, 5.93; N, 4.61%.

M.S. (high resolution): m/e 305 (^{37}Cl) (1.4), 303 (^{35}Cl) (4.4) ($M^{+\cdot}$, accurate mass 303.1002. $C_{17}H_{18}ClNO_2$ requires, 303.1028), 302 (2.), 194 (100).

P.M.R. δ ($CDCl_3$): 2.55 (s, 3H, $-NCH_3$), 3.10-3.50 (m, 2H, $-NCH_2-$), 3.85 (s, 3H, $-OCH_3$), 3.90-4.20 (m, 2H, $-OCH_2-$), 4.90 (s, 1H, benzylic H), 6.68-6.75 (s, 2H, ArH), 7.01 (d, J = 7.5Hz, 1H, ArH), 7.15-7.30 (m, 3H, ArH), 7.36-7.40 (m, 1H, ArH).

I.R. (neat): 1150, 1200, 1460, 1485, 1565 (w), 1600 (s, C-N), 2860 (s, C-C Ar) cm^{-1}.

4-Methyl-7,8-methylenedioxy-5-phenyl-2,3,4,5-tetrahydro-1,4-benzoxazepine (69)

To a solution of the methiodide salt (65) (1.4 g, 0.0034 mol) in 60% aqueous ethanol (15 ml) and methanol (10 ml) was added sodium tetrahydridoborate (0.275 g, 0.0072 mol) in small portions with stirring and ice-cooling. Stirring was continued for 2 h at <10° and at 20° for 12 h. The solvents were removed and the residue extracted with water (50 ml) and dichloromethane (3 x 10 ml). The dried (sodium sulfate) organic layers were evaporated. The resulting residue (0.892 g) was subjected to P.L.C. (5% methanol-chloroform) to afford *4-methyl-7,8-methylenedioxy-5-phenyl-2,3,4,5-tetrahydro-1,4-benzoxazepine* (69) (0.667 g, 69%), R_f 0.8 as a gum.

M.S. (high resolution): m/e 283 (13) ($M^{+\cdot}$, accurate mass 283.1256. $C_{17}H_{17}NO_3$ requires 283.1208), 240 (41), 207 (60), 206 (100).

P.M.R. δ ($CDCl_3$): 2.52 (s, 3H, $-NCH_3$, 2.75-3.42 (m, 2H, $-NCH_2-$),

3.60-3.85 (m, 1H, -OCH-), 3.95-4.12 (m, 1H, -OCH-), 4.79 (s, 1H, benzylic H), 5.91 (s, $-O-CH_2-O-$), 6.52 (s, 1H, ArH), 6.61 (s, 1H, ArH), 7.29 (s, 5H, ArH).

I.R. (neat): 1490-1500, 1600, 2860-2940 (s, C-C) cm^{-1}.

6,8-Dimethoxy-4-methyl-5-phenyl-2,3,4,5-tetrahydro-1,4-benzoxazepine (70)

To an ice-cooled, stirred solution of the methiodide salt (66) (3 g, 0.0070 mol) in a solution of 60% aqueous ethanol (25 ml) and methanol (10 ml), was added sodium tetrahydridoborate (0.530 g, 0.0140 mol) in small portions. This was stirred at >10° for 3 h and at 20° for 16 h. The solvent was then removed and water (50 ml) added to the residue. The resulting white suspension was extracted with dichloromethane (3 x 10 ml) and, the dried (sodium sulfate) dichloromethane extracts were evaporated to obtain an oil (1.21 g). Purification by P.L.C. (5% methanol-chloroform) gave *6,8-dimethoxy-4-methyl-5-phenyl-2,3,4,5-tetrahydro-1,4-benzoxazepine* (70) (1.089 g, 52%), R_f 0.7, as white crystals (m.p. 58°-60°).

Found: C, 72.09; H, 7.18; N, 4.97. $C_{18}H_{21}NO_3$ requires, C, 72.24; H, 7.02; N, 4.68%.

M.S. (high resolution): m/e 299 (2.8) ($M^{+\cdot}$, accurate mass 299.1537. $C_{18}H_{21}NO_3$ requires, 299.1521), 298 (1), 255 (2), 241 (2.4), 222 (100), 179 (11), 148 (12), 105 (17), 77 (14).

P.M.R. δ ($CDCl_3$): 2.57 (s, 3H, $-NCH_3$), 3.05-3.40 (m, 2H, $-NCH_2-$), 3.70 (s, 3H, $-OCH_3$), 3.80 (s, 3H, $-OCH_3$), 3.90-4.20 (m, 2H, $-OCH_2-$), 5.65 (s, 1H, benzylic H), 6.28 (s, 2H, ArH), 7.20-7.35 (m, 5H, ArH).

I.R. ($CHCl_3$): 1560, 1600, 2870 cm^{-1}.

Attempted alkylation of (2-hydroxy-4-methoxyphenyl)phenylmethanone with 1,2-dibromoethane

Method (i)

To a stirred solution of dry ethanol (20 ml), sodium (0.240 g, 0.0104 mol) was added piecewise. After the effervescence had subsided this was heated to reflux and (2-hydroxy-4-methoxyphenyl)phenyl methanone (2 g, 0.0087 mol) was added in small portions, and refluxed for 30 min. To this refluxing solution, 1,2-dibromoethane (2.355 g, 0.0125 mol) was added dropwise and refluxed for a further 7 h.[98] The solvent was then removed and water (50 ml) was added to the residue. This was extracted with dichloromethane (4 x 10 ml) and these combined extracts were washed with 20% aqueous sodium hydroxide (4 x 10 ml), followed by water (2 x 30 ml). The dried (sodium sulfate) organic layer was evaporated to obtain a syrup (1.95 g) which could not be crystallised. Spectral data of this material was similar to those of the starting material.
P.M.R. δ ($CDCl_3$): 4.80 (s, 3H, $-OCH_3$), 6.24-6.50 (m, 2H, ArH), 7.32-7.76 (m, 6H, ArH), 12.64 (s, 1H, exchanges with D_2O, -OH).

Method (ii)

A solution of the sodium salt of (2-hydroxy-4-methoxyphenyl)phenyl methanone (12.85 g, 0.051 mol) in anhydrous dimethylformamide (75 ml), was added dropwise to a warm solution of 1,2-dibromoethane (9.66 g, 0.058 mol) and refluxed for 3.5 h. The solvent was then removed and water (60 ml) was added to the residue. This was extracted with dichloromethane (3 x 15 ml) and the combined extracts were washed with 10% aqueous sodium hydroxide (3 x 10 ml), and water (3 x 10 ml). The dichloromethane layer was dried (sodium sulfate) and evaporated

to dryness. The crude product thus obtained was recrystallised from diethyl ether and light petroleum to give colourless needles, m.p. 63°-65° (10.28 g). This was found to be the starting material, (2-hydroxy-4-methoxyphenyl)phenylmethanone by comparison of spectral data and mixed melting points.

(5-Chloro-2-[1-hydroxyethoxy]phenyl)phenylmethanone (77b)

The sodium salt of (5-chloro-2-hydroxyphenyl)phenylmethanone (4.02 g, 0.0157 mol) was prepared in the same manner as described for the synthesis of the sodium salt of (2-hydroxy-4-methoxyphenyl)phenylmethanone. Then a solution of redistilled 2-chloroethanol (3.18 ml, 0.047 mol) in anhydrous dimethylformamide (10 ml) was heated to reflux and a solution of the above prepared sodium salt (4.02 g, 0.0157 mol) in dry dimethylformamide (20 ml) was added dropwise. This was refluxed for 45 min and the solvent was removed. To the residue, water (60 ml) was added and extracted with chloroform (3 x 30 ml). These chloroform extracts were washed with 10% aqueous sodium hydroxide (3 x 10 ml) and with water (2 x 10 ml). The dried (sodium sulfate) chloroform solution was evaporated and the residue was purified by column chromatography (chloroform) to afford the alcohol[107] (77b) (2.58 g, 60%) as a syrup, R_f 0.5 (3% methanol-chloroform).

M.S. (high resolution): m/e 278 (6), 276 (18) ($M^{+\cdot}$, accurate mass 276.0596. $C_{15}H_{13}ClO_3$ requires 276.0863), 246 (29), 233 (37), 231 (100), 155 (49).

P.M.R. δ ($CDCl_3$): 2.48 (s, 1H, exchanges with D_2O, -OH), 3.61 (t, J = 5Hz, $-CCH_2OH$), 4.02 (t = 5Hz, 2H, $-OCH_2-$), 6.42 (d, J = 8.75Hz, 1H, ArH), 7.35-7.60 (m, 5H, ArH), 7.70-7.85 (m, 2H, ArH).

I.R. (neat): 1650 and 1670 (s, C=O), 3400 (broad, -OH) cm^{-1}.

(2-[1-Hydroxyethoxy]phenyl)phenylmethanone (77a)

The sodium salt of (2-hydroxyphenyl)phenylmethanone was prepared in the same manner as described for the sodium salt of (2-hydroxy-4-methoxyphenyl)phenylmethanone. Then the reaction of this sodium salt (11 g, 0.05 mol) and 2-chloroethanol (10.07 ml, 0.083 mol) in anhydrous dimethylformamide was carried out as described for the alcohol (77b) to afford *(2-[1-hydroxyethoxy]phenyl)phenylmethanone* (77a) (2.02 g, 17%), R_f 0.4 (chloroform) as a pale yellow syrup, after the purification by column chromatography ($CHCl_3$-silica gel).

M.S. (high resolution): m/e 242 (6) ($M^{+\cdot}$, accurate mass 242.0941. $C_{15}H_{14}O_3$ requires, 242.0942), 223 (10), 212 (71), 197 (100), 195 (32), 181 (25), 121 (86), 105 (73).

P.M.R. δ ($CDCl_3$): 2.52 (s, 1H, exchanges with D_2O, -OH), 3.63 (t, J = 5Hz, 2H, $-CH_2-$), 4.05 (t, J = 5Hz, 2H, $-CH_2-$), 6.90-7.05 (m, 2H, ArH), 7.35-7.60 (m, 5H, ArH), 7.70-7.85 (m, 2H, ArH).

I.R. (neat): 1660 (s, C=O), 2940 (s, C-C), 3420 (broad s, OH) cm^{-1}.

(5-Chloro-2-[2-chloroethoxy]phenyl)phenylmethanone (75b)

A solution of the alcohol (77b) (1.00 g, 0.0036 mol) in freshly distilled thionyl chloride (10 ml) was refluxed for 1 h and excess thionyl chloride was removed. The residue was then dissolved in chloroform (10 ml) and washed well with water (3 x 30 ml). The dried (sodium sulfate) chloroform layer was evaporated and recrystallised from methanol afforded (5-chloro-2-[2-chloroethoxy]phenyl)phenylmethanone (75b) (1.07 g, 85%) R_f 0.7 (chloroform) as pale yellow needles, m.p. 73°-74° (lit.[7] m.p. 73°-74.5°).

M.S. (high resolution): m/e 296 (14) (^{37}Cl, $M^{+\cdot}$, accurate mass 296.0147. $C_{15}H_{12}Cl_2O_2$ requires 296.0185), 294 (21), 259 (22), 231 (85), 155 (50), 105 (100).

P.M.R. δ ($CDCl_3$): 3.39 (t, J = 6.25Hz, 2H, $-CH_2Cl$), 4.09 (t, J = 6.25Hz, 2H, $-OCH_2-$), 6.88 (d, J = 10Hz, 1H, ArH), 7.32-7.55 (m, 5H, ArH), 7.70-7.80 (m, 2H, ArH).

I.R. (nujol): 1650 (s, C=O) cm^{-1}.

Attempted aminolysis of (5-chloro-2[2-chloroethoxy]phenyl)phenyl-methanone (75b) with ammonia

A solution of the ketone (75b) (0.500 g, 0.0017 mol) in acetone (10 ml) was kept over powdered sodium iodide (0.254 g, 0.0017 mol) for 2 h and the solution was filtered. The filtrate was evaporated and a solution of saturated methanolic ammonia (25 ml) and potassium iodide (0.285 g, 0.0017 mol) was added to the residue. This was then heated to 40°-60° and anhydrous ammonia was bubbled through the solution for 1 h with stirring. At this stage no reaction was observed hence heating and stirring were continued for 16 h, while ammonia was passed through the solution at intervals. However after a further 48 h at room temperature removal of the solvents gave a quantitative recovery of the starting material (75b).

Attempted condensation of 3-methoxyphenol with 2-(1-bromoethyl)-1*H*-isoindole 1,3-(2*H*)-dione

Method (i)

A mixture of 3-methoxyphenol (2.20 g, 0.0177 mol), 2-(1-bromoethyl)-1*H*-isoindole-1,3-(2*H*)-dione (4.50 g, 0.0177 mol) and anhydrous potassium carbonate (2.45 g, 0.0177 mol) in dry dimethylformamide (25 ml) was refluxed for 4 h with stirring. The solvent was then removed and chloroform (40 ml) was added to the residue. To this, water (100 ml) was added and the aqueous layer was extracted with chloroform (3 x 10 ml). The combined chloroform layers were washed with 5% aqueous sodium

hydroxide (2 x 10 ml) and water (3 x 10 ml). The dried (sodium sulfate) organic layer was evaporated and the residue (1.815 g) crystallised on cooling. A portion of this was recrystallised from benzene and light petroleum to give a compound (m.p. 305°-308°) which was not investigated further. This reaction did not afford the expected product (47).

Method (ii)

The above condensation was attempted in a solution of aqueous sodium hydroxide and acetone instead of potassium carbonate and dimethylformamide. The starting materials were recovered quantitatively.

Method (iii)

A solution of the sodium 3-methoxyphenolate (5 g, 0.0342 mol) in anhydrous dimethylformamide (20 ml) was added dropwise to a stirred solution of 2-(1-bromoethyl)-1*H*-isoindole-1,3-(2*H*)-dione (8.70 g, 0.0342 mol) in dimethylformamide and refluxed for 2 h under nitrogen. The solvent was removed and water (60 ml) was added to the residue. This was extracted with chloroform (3 x 15 ml), and the chloroform layers were washed with 10% aqueous sodium hydroxide (3 x 10 ml). The dried (sodium sulfate) chloroform layer was evaporated to afford a syrup. A small amount (0.500 g) of this syrup was purified by P.L.C. (chloroform), and three major fractions (R_f 0.7, R_f 0.5 and R_f 0.1) were isolated. Attempts to identify these three compounds by spectroscopic data were unsuccessful.

2-Benzoylphenoxyethanenitrile (78)

To a solution of chloroethanenitrile (4 ml, 0.0635 mol) in anhydrous butanone (20 ml) was added powdered potassium iodide

(10.54 g, 0.0635 mol) and kept in the dark for 18 h. This was then filtered and, added dropwise to a refluxing mixture of (2-hydroxyphenyl)-phenylmethanone[99] (10 g, 0.0505 mol) and anhydrous potassium carbonate (7.00 g, 0.0507 mol) in dry butanone (75 ml) and refluxed for 3.5 h.[53,54] The solvent was then removed and dichloromethane (30 ml) was added to the residue. This was washed with water (10 x 100 ml) until the aqueous phase was colourless. The dried (sodium sulfate) dichloromethane layer was evaporated and the residue was purified by column chromatography (60% light petroleum 40°-60°/chloroform) to afford the keto nitrile[100] (78) (7.326 g, 60%) as a pale yellow gum, R_f 0.8 (4% methanol-chloroform). A small amount of the starting phenol (0.509) was also recovered from this reaction.

M.S. (high resolution): m/e 237 (6), ($M^{+\cdot}$, accurate mass 237.0725. $C_{15}H_{11}NO_2$ requires 237.0790), 211 (8), 210 (56), 181 (26), 160 (38), 120 (30), 105 (82), 92 (35), 77 (100).

P.M.R. δ ($CDCl_3$): 4.70 (s, 2H, $-OCH_2CN$), 7.00-7.25 (m, 2H, ArH), 7.30-7.65 (m, 6H, ArH), 7.70-7.80 (m, 1H, ArH).

I.R. (neat): 1660 (s, C=O), 2230 (w, C≡N) cm^{-1}.

[2-(2-Aminoethoxy)phenyl]phenylmethanol (79)

To a stirred suspension of lithium tetrahydridoaluminate (0.327 g, 0.008 mol) in dry diethyl ether (20 ml) was added dropwise a solution of the keto nitrile (78) (0.420 g, 0.0017 mol) in dry diethyl ether (20 ml) and refluxed for 1.5 h. The hydrolysis[90] of the lithium complex was carried out in the same manner as described for the compound (40) and the work up gave the *amino-alcohol* (79) (0.350 g, 81%) as an oil.

M.S. (high resolution): 245 (M^{+2}) (5), 244 (M^{+1}) (13), 243 ($M^{+\cdot}$) (28), ($M^{+\cdot}$, accurate mass 243.1191. $C_{15}H_{17}NO_2$ requires 243.1259),

186 (23), 181 (45).

P.M.R. δ ($CDCl_3$): 2.50 (s, 3H, exchanges with D_2O, -OH and $-NH_2$), 2.80 (t, J = 5Hz, 2H, $-NCH_2$), 3.84 (t, J = 5Hz, 2H, $-OCH_2$), 5.96 (s, 1H, benzylic H), 6.70-7.00 (m, 2H, ArH), 7.18-7.40 (m, 7H, ArH).

I.R. (neat): 1600, 2850-3040 (s, C=C Ar), 3270 and 3340 (s, broad NH_2 and OH).

2-(2-Phenyl-1,3-dioxalanyl)phenoxyethanenitrile (84)

The compound (84) was prepared by a similar method that was described in the literature.[62] Thus a solution of (78) (4.20 g, 0.0177 mol), ethylene glycol (10 ml), and a catalytic amount of *p*-toluenesulfonic acid in anhydrous benzene (80 ml) was refluxed for 12 h, while removing water using a Dean-Stark trap. The reaction mixture was allowed to cool and then washed with 5% aqueous sodium hydroxide (25 ml) followed by water (4 x 40 ml). The organic layer was dried (sodium sulfate) and evaporated to afford the crude (84) (4.5 g). Recrystallisation from chloroform and light petroleum (40°-60°) afforded the transparent rectangles of the *ketal* (84) (4.3 g, 93%), m.p. 90-5°-91.5°, R_f 0.5 (chloroform).

Found: C, 72.42; H, 5.53, N, 4.91.

$C_{17}H_{15}NO_3$ requires C, 72.59; H, 5.34; N, 4.98%.

M.S. (high resolution): m/e 281 (2) ($M^{+\cdot}$, accurate mass 281.1048. $C_{17}H_{15}NO_3$ requires, 281.1050), 280 (1), 267 (2), 265 (14), 204 (100), 164 (29), 149 (83), 120 (20), 105 (47), 77 (47).

P.M.R. δ ($CDCl_3$): 4.05 (s, 4H, $-O-CH_2-CH_2-O-$), 4.35 (s, 2H, $-OCH_2CN$), 6.85-7.15 (m, 2H, ArH), 7.22-7.45 (m, 6H, ArH), 7.72-7.85 (d of d, J_1 = 2.5Hz, J_2 = 6.25Hz, 1H, ArH).

I.R. (nujol): 1585, 1600 (s, C-C) cm^{-1}.

Reduction of 2-(2-Phenyl-1,3-dioxalanyl)phenoxyethanenitrile (84) in tetrahydrofuran

To a stirred suspension of lithium tetrahydridoaluminate (0.270 g, 0.0071 mol) in dry tetrahydrofuran (20 ml) was added dropwise a solution of the ketal (84) (1 g, 0.0035 mol) in dry tetrahydrofuran (20 ml), and refluxed for 5 h.[62] The solvent was removed, and diethyl ether (40 ml) was added to the residue. Then hydrolysis was carried out by the successive dropwise addition of water (0.81 mol) and 15% aqueous sodium hydroxide (0.3 ml). The resulting white granulated precipitate was filtered, and the dried (sodium sulfate) filtrate was evaporated, to afford an oil (0.500 g). Of the products obtained from P.L.C. (chloroform) only one (Fraction 1, R_f 0.7) could be identified. This was found to be the 1-hydroxy-2-(2-phenyl-1,3-dioxalanyl)benzene (86) (156 mg), m.p. 62°-63°.

P.M.R. δ ($CDCl_3$): 4.02 (s, 2H, cyclic $-OCH_2-$), 4.09 (s, 2H, cyclic $-OCH_2-$), 6.70-6.95 (m, 2H, ArH), 7.20-7.55 (m, 7H, ArH), 8.26 (s, 1H, exchanges with D_2O, -OH).

I.R. (neat): 1600, 3350 (broad OH) cm^{-1}.

Reduction of 2-(2-phenyl-1,3-dioxalanyl)phenoxyethanenitrile (84) in diethyl ether

To a stirred suspension of lithium tetrahydridoaluminate (0.270 g, 0.0071 mol) in dry diethyl ether (20 ml) was added dropwise a solution of the ketal (84) (1 g, 0.0035 mol) in dry diethyl ether (80 ml), and refluxed for 7 h, then allowed to stand at room temperature for 14 h. Hydrolysis by the dropwise addition of water (0.8 ml) and 15% aqueous sodium hydroxide (0.3 mol) gave a white granulated precipitate which was filtered and discarded. The dried (sodium sulfate) filtrate was then evaporated to give an oil (0.925 g)

which was purified by P.L.C. (chloroform).

Fraction 1 (R_f 0.1) gave the desired amino-ketal, *2-(2-phenyl-1,3-dioxalanyl)phenoxyethanamine* (87a) (0.655 g, 66%) as an oil.

Fraction 2 (R_f 0.7) gave the product (86) (0.150 g) m.p. 62°-63°, which was isolated from the reduction done in tetrahydrofuran (page 137).

Fraction 1

2-(2-phenyl-1,3-dioxalanyl)phenoxyethanamine (87a)

M.S. (low resolution): m/e 286 (9) ($M^{+\cdot}$) $C_{17}H_{19}NO_2$ requires, 286.1204, 242 (16), 224 (20), 208 (43), 197 (33), 195 (87), 181 (22), 167 (25), 165 (25), 165 (96), 152 (31), 150 (88), 149 (94), 136 (48), 121 (47), 105 (68), 44 (100).

P.M.R. δ ($CDCl_3$): 2.19 (broad s, 2H, exchanges with D_2O, $-NH_2$), 2.71 (t, J = 5Hz, 2H, $-NCH_2-$), 3.75 (t, J = 5Hz, 2H, $-OCH_2-$), 4.01 (s, 2H, cyclic $-OCH_2-$), 4,05 (s, 2H, cyclic $-OCH_2-$), 6.70-7.05 (m, 2H, ArH), 7.15-7.45 (m, 6H, ArH), 7.60-7.90 (m, 1H, ArH).

I.R. (neat): 1600 (s, C-N), 2890-2940 (s, C-C.Ar), 3300 and 3380 (s, NH_2) cm^{-1}.

2-Benzoyl-4-chlorophenoxyethanenitrile (83)

To a solution of chloroethanenitrile (4 ml, 0.0632 mol) in anhydrous butanone (15 ml) was added powdered potassium iodide (10.49 g, 0.0632 mol), then kept in the dark for 18 h, and filtered. The filtrate was added dropwise to a refluxing mixture of (4-chloro-2-hydroxyphenyl)phenylmethanone[99] (10 g, 0.043 mol) and anhydrous potassium carbonate (5.93 g, 0.043 mol) in dry butanone (75 ml).[53,54] This was refluxed for 2.5 h and worked up, as described for the keto-nitrile (78), to afford the crude nitrile[100] (83) (13 g), as a syrup. This was crystallised on cooling and recrystallisation from chloroform and light petroleum (40°-60°)

afforded the colourless needles of (83) (8.957 g, 78%) m.p. 67.5°-68°.
Found: C, 66.93; H, 3.60; N, 5.17; $C_{15}H_{10}ClNO_2$ requires, C, 66.42; H, 3.69; N, 5.16%.
M.S. (high resolution): m/e 273 (^{37}Cl) (6), 271 (^{35}Cl) (18) ($M^{+\cdot}$, accurate mass 271.0401. $C_{15}H_{10}ClNO_2$ requires, 271.0400), 244 (57), 209 (8), 194 (18), 180 (14), 154 (13), 105 (100).
P.M.R. δ ($CDCl_3$): 4.69 (s, 2H, $-OCH_2CN$), 7.05 (d, J = 10Hz, 1H, ArH), 7.32-7.55 (m, 5H, ArH), 7.74 (d of d, J_1 = 10Hz, J_2 = 2.5Hz, 2H, ArH).
I.R. (nujol): 1650 (s, C=O) cm^{-1}.

4-Chloro-2-(2-phenyl-1,3-dioxalanyl)phenoxyethanenitrile (85)

Treatment of the keto-nitrile (83) (6.76 g, 0.0249 mol) with ethylene glycol (5 ml) in anhydrous benzene (100), in the presence of *p*-toluenesulfonic acid monohydrate, followed by the work up, in the same manner as described for the synthesis of (84), afforded the crude ketal (85) (7.64 g as a white solid). Recrystallisation from diethyl ether and light petroleum (40°-60°) gave colourless rectangles of the *ketal* (85) (7.10 g, 90%), m.p. 49-51°.
Found: C, 64.82; H, 4.54; N, 4.39. $C_{17}H_{14}ClNO_3$ requires, C, 64.76; H, 4.44; N, 4.44%.
M.S. (high resolution): m/e 317 (^{37}Cl)(0.4), 315 (^{35}Cl) (2) ($M^{+\cdot}$, accurate mass 315.0671). $C_{17}H_{14}ClNO_3$ requires, 315.0660), 240 (19), 238 (58), 200 (7), 198 (22), 149 (100).
P.M.R. δ ($CDCl_3$): 4.08 (s, 4H, $O\overset{\frown}{CH_2\text{-}CH_2}O$), 4.36 (s, 2H, $-OCH_2CN$), 6.86 (d, J = 8.75Hz, 1H, ArH), 7.20-7.45 (m, 6H, ArH), 7.80 (d, J = 2.5Hz, 1H, ArH).
I.R. (nujol): 1465 (s), 1590 (w) cm^{-1}.

4-Chloro-2-(2-phenyl-1,3-dioxalanyl)phenoxyethanamine (87b)

To a stirred suspension of lithium tetrahydridoaluminate (1.204 g,

0.0269 mol) in anhydrous diethyl ether (75 ml) was added dropwise a solution of (85) (5 g, 0.0158 mol) in anhydrous diethyl ether (120 ml), and refluxed for 2 h. Hydrolysis of the lithium complex was completed by the successive dropwise addition of water (1.2 ml), 15% aqueous sodium hydroxide (1.2 ml), and water (3.6 ml).[90] The resulting white granulated precipitate was filtered and the dried (sodium sulfate) filtrate was evaporated to obtain the crude *amino-ketal* (87b) (4.0375 g) as a pale yellow solid.

An analytical sample of (87b) (0.667 g, 66%, R_f 0.1), was prepared by purification (P.L.C., chloroform) of 1 g of the crude *amine* (87b). The remainder of the material was used directly for the next reaction.

Of the other products (fraction 2 R_f 0.4, and fraction 3 R_f 0.6) obtained from P.L.C. were not investigated further.

Fraction 1 (R_f 0.1) *amino-ketal* (87b)

M.S. (high resolution): m/e 321 (^{37}Cl) (0.7), (^{35}Cl) (1), ($M^{+\cdot}$) accurate mass 319.0972. $C_{17}H_{18}ClNO_3$ requires 319.0973), 276 (22), 199 (33), 150 (85), 149 (57) 44 (100).

P.M.R. δ ($CDCl_3$): 1.38-1.90 (m, 2H, exchanges with D_2O, $-NH_2$), 2.50-2.92 (m, 2H, $-NCH_2-$), 3.10-3.35 (m, 2H, $-OCH_2-$), 4.05 (s, 4H, $O-CH_2-CH_2-O$), 6.50-6.78 (m, 1H, ArH), 7.00-7.50 (m, 6H, ArH), 7.70-7.85 (m, 1H, ArH).

I.R. ($CHCl_3$): 1600, 3310 and 3380 (s, NH_2) cm^{-1}.

(2-[2-aminoethoxyphenyl])phenylmethanone (71a)

A solution of the amino-ketal (87a) (2.98 g, 0.0105 mol) in methanol (15 ml) and 5 M hydrochloric acid (20 ml) was heated at about 50°-55° for 3 h and allowed to stand at room temperature for 5 h. The solution was then made alkaline with 20% aqueous sodium

hydroxide and extracted with dichloromethane (3 x 20 ml). The dried (sodium sulfate) dichloromethane layers were evaporated to afford an oil which was subjected to P.L.C. (5% methanol-chloroform).

Fraction 1 (major) gave the *amino-ketone* (71a) (1.927 g, 77%) R_f 0.2, as an oil.

Fraction 2 (minor) gave the *cyclic imine* (61) (0.120 g), R_f 0.8 as a pale yellow gum.

Fraction 1

2-Benzoylphenoxyethanamine (71a)

P.M.R. δ ($CDCl_3$): 1.20 (broad s, 2H, exchanges with D_2O, $-NH_2$), 2.5-2.80 (m, 2H, $-NCH_2-$), 3.82 (t, J = 5Hz, 2H, $-OCH_2-$), 6.76-7.05 (m, 2H, ArH), 7.18-7.50 (m, 6H, ArH), 7.65-7.80 (m, 1H, ArH).

I.R. (neat): 1660 (s, C=O), 3300 and 3380 (s, NH_2) cm^{-1}.

Fraction 2. The *cyclic imine* (61). Spectral data are given under the preparation of this compound (page 142).

2-Benzoyl-4-chlorophenoxyethanamine (71b)

Treatment of (87b) (3.79 g, 0.0119 mol) with hydrochloric acid in the same manner as described for the hydrolysis of the amino-ketal (87a) afforded a mixture (3.26 g) of the amine (71b), R_f 0.1 and the cyclic imine (62) R_f 0.8 (5% methanol-chloroform).

A small amount (220 mg) of this mixture was purified by P.L.C. (5% methanol-chloroform/2% potassium hydroxide, silica gel) to obtain the pure amino-ketone (87b)[7] (0.145 mg, 85%) R_f 0.3 as a gum (lit.[7] hydrochloride salt m.p. 135°-136°).

P.M.R. δ ($CDCl_3$): 0.91 (broad s, 2H, exchanges with D_2O, $-NH_2$), 2.35-2.75 (m, 2H, $-NCH_2-$), 3.60-3.90 (m, 2H, $-OCH_2-$), 6.65-6.95 (m, 1H, ArH), 7.10-7.75 (m, 7H, ArH).

I.R. (neat): 1598, 1670 (s, C=O), 2865 and 2940 (C-C Ar), 3060, 3310 and 3380 (s, NH_2) cm^{-1}.

5-Phenyl-2,3-dihydro-1,4-benzoxazepine (61)

Method (i)

Oxidation of the amino-alcohol (79) (page 135) was carried out after the method described by Barton and co-workers.[61]

To a solution of the amino-alcohol (79) (50 mg, 0.0002 mol) in dichloromethane (5 ml) was added potassium carbonate (60 mg, 0.0004 mol) and μ-oxo-bis(chlorotriphenylbismuth)[101] (238 mg, 0.002 mol). The reaction mixture was stirred at room temperature for 5 h, then washed with water (2 x 10 ml) and extracted with dichloromethane. These dichloromethane layers were dried (sodium sulfate) and the solvent was removed, to afford an oil, R_f 0.1 (5% methanol-chloroform) [I.R. (neat): 1660 (s, C=O)].

Without further characterization, this oil was refluxed for 1 h in dry pyridine (10 ml).[102] The solvent was then removed and the residue was subjected to P.L.C. (5% methanol-chloroform) to afford *5-phenyl-2,3-dihydro-1,4-benzoxazepine* (61) (20 mg, 45%) R_f 0.8 as a gum.

M.S. (high resolution): m/e 223 (58) ($M^{+\cdot}$, accurate mass 223.0983. $C_{15}H_{13}NO$ requires 223.0995), 222 (91), 195 (100), 167 (50), 165 (26), 152 (16).

P.M.R. δ ($CDCl_3$): 3.80 (t, J = 5Hz, 2H, $-NCH_2-$), 4.68 (t, J = 5Hz, 2H, $-OCH_2-$), 7.00-7.20 (m, 3H, ArH), 7.32-7.50 (m, 4H, ArH), 7.55-7.70 (m, 2H, ArH).

I.R. (neat): 1600 (s, C=N).

Method (ii)

A solution of the amino-ketone (71a) (1.841 g, 0.0076 mol) in dry pyridine[102] (15 ml) was refluxed for 1 h, and the solvent was removed. The residue was subjected to P.L.C. (5% methanol-chloroform), to afford the *cyclic imine* (61) (1.353 g, 79%), R_f 0.8 as a pale

yellow gum. The spectral data of this compound was identical with the imine (61) obtained by method (i)

7-Chloro-5-phenyl-2,3-dihydro-1,4-benzoxazepine (62)

A solution of the amino-ketone (71b) (1.95 g, 0.0071 mol) in dry pyridine[102] (20 ml) was refluxed for 1.5 h and the solvent was removed. The residue was subjected to P.L.C. (2% methanol-chloroform) to afford the cyclic imine (62) (1.106 g, 61%) (R_f 0.7 as a pale yellow solid. Recrystallisation from diethyl ether and light petroleum (40°-60°) afforded the cream coloured granules of the imine[4,47] (62) m.p. 49.5-50.5°. Found: C, 70.09; H, 4.77; N, 5.36. $C_{15}H_{12}ClNO$ requires, C, 70.03; H, 4.66; N, 5.44%.

M.S. (high resolution): m/e 259 (^{37}Cl) (16), 257 (^{35}Cl) (74) ($M^{+\cdot}$, accurate mass, 257.0606. $C_{15}H_{12}ClNO$ requires, 257.0607), 231 (29), 229 (100), 221 (13), 200 (32), 192 (23), 166 (40), 164 (45).

P.M.R. δ ($CDCl_3$): 3.80 (t, J = 5Hz, 2H, $-NCH_2-$), 4.65 (t, J = 5Hz, $-OCH_2-$), 6.93-7.10 (m, 2H, ArH), 7.20-7.45 (m, 4H, ArH), 7.52-7.60 (m, 2H, ArH).

I.R. (nujol): 1600 (s, C=N) cm^{-1}.

4-Methyl-5-phenyl-2,3-dihydro-1,4-benzoxazepinium Iodide (88)

A solution of 5-phenyl-2,3-dihydro-1,4-benzoxazepine (61) (1.296 g, 0.0058 mol) and iodomethane (2 ml, 0.031 mol) in dry butanone (10 ml) was heated at 100° in a sealed tube for 10 h, and allowed to cool. Removal of the solvent afforded the *methiodide salt* (88) (2.10 g, 99%) R_f 0.1 (5% methanol-chloroform) as a dark red gum, which could not be crystallised. Attempted purification by P.L.C. (5% CH_3OH-$CHCl_3$) resulted in decomposition; hence the crude product was used for the reduction without further purification.

P.M.R. δ ($CDCl_3$): 4.10 (s, 3H, $=\overset{+}{N}-CH_3$), 4.45-4.65 (m, 2H, $-OCH_2-$), 5.10-5.25 (m, 2H, $=\overset{+}{N}-CH_2$), 6.90-7.32 (m, 3H, ArH), 7.52-7.85 (m, 6H, ArH).

7-Chloro-4-methyl-5-phenyl-2,3-dihydro-1,4-benzoxazepinium Iodide (89)

A solution of the imine (62) (1.3 g, 0.0051 mol) and iodomethane (2 ml, 4.4 g, 0.031 mol) in dry butanone (15 ml) was heated at 110° for 2 h in a sealed tube, and allowed to cool. Removal of the solvent, followed by recrystallisation from methanol and diethyl ether, afforded the *methiodide salt* (89) (2.00 g, 99%) as bright yellow needles, m.p. 183°-184.5°.

Found: C, 47.99; H, 3.77; N, 3.46. $C_{16}H_{15}ClNO_2I$ requires, C, 48.12; H, 3.76; N, 3.50%.

M.S. (high resolution): m/e 272 (4) ($M^{+\cdot}$, accurate mass 272.0802. $(C_{16}H_{15}ClNO_2)^+$ requires, 272.0841), 270 (9), 257 (88), 256 (93), 242 (69), 229 (90), 165 (48), 142 (100), 127 (69).

P.M.R. δ ($CDCl_3$): 4.15 (s, 3H, $=\overset{+}{N}-CH_3$), 4.61 (t, J = 5Hz, 2H, $-CH_2-$), 5.20 (t, J = 5Hz, 2H, $-CH_2-$), 6.94 (d, J = 2.5Hz, 1H, ArH), 7.15-7.36 (m, 1H, ArH), 7.55-7.90 (m, 6H, ArH).

I.R. (nujol): 1450, 1600, 1675 cm^{-1}.

4-Methyl-5-phenyl-2,3,4,5-tetrahydro-1,4-benzoxazepine (90)

To an ice-cooled, stirred solution of the methiodide salt (88) (1.95 g, 0.0053 mol) in 60% aqueous ethanol (20 ml) and methanol (10 ml) was added sodium tetrahydridoborate (0.406 g, 0.0107 mol) in small portions. Stirring and cooling were continued for 2.5 h and the solvents were removed. Then the residue was extracted with water (30 ml) and dichloromethane (3 x 5 ml).

The combined, dried (sodium sulfate) dichloromethane layers were

evaporated to obtain a gum (1.223 g). This was purified by P.L.C. (5% methanol-chloroform) to afford the cyclic amine[47] (90) (0.855 g, 67%) R_f 0.9 as a colourless gum. On prolonged cooling this was crystallised, and recrystallisation from diethyl ether afforded the colourless rhomboids of (90) m.p. 61.5°-62°.

Found: C, 80.75; H, 7.35; N, 5.89.

$C_{16}H_{17}NO$ requires, C, 80.33; H, 7.11; N, 5.85%.

M.S. (high resolution): m/e 239 (11) ($M^{+\cdot}$, accurate mass 239.1351. $C_{16}H_{17}NO$ requires, 239.1309), 195 (12), 162 (100).

P.M.R. δ ($CDCl_3$): 2.55 (s, 3H, $-NCH_3$), 2.66 (m, 1H, -NCH-), 3.06-3.50 (m, 1H, -NCH-), 3.78-4.25 (m, 2H, $-OCH_2-$), 4.96 (s, 1H, benzylic H), 7.00-7.18 (m, 4H, ArH), 7.20-7.32 (m, 5H, ArH).

I.R. (neat): 1520, 1600, 2870-3020 (C-C Ar) cm^{-1}.

7-Chloro-4-methyl-5-phenyl-2,3,4,5-tetrahydro-1,4-benzoxazepine (91)

To a solution of the methiodide salt (89) (1.00 g, 0.0025 mol) in 60% aqueous ethanol (20 ml) and methanol (10 ml) was added sodium tetrahydridoborate (0.285 g, 0.0075 mol) in small portions and stirred at <10° for 2 h. The solvent was removed and chloroform (20 ml), and water (50 ml) was added to the residue. The aqueous phase was extracted with dichloromethane (2 x 10 ml) and the combined dried (sodium sulfate) dichloromethane extractions were evaporated to obtain a pale yellow gum (0.994 g). Purification by P.L.C. (5% methanol-chloroform), afforded the cyclic amine[47] (91) (0.322 g, 49%) R_f 0.9, which was crystallised on cooling, m.p. 57°-57.5°.

Found: C, 70.45; H, 6.08; N, 5.05; $C_{16}H_{16}ClNO$ requires, C, 70.32; H, 5.86; N, 5.12%.

M.S. (high resolution): m/e 273 (17) ($M^{+\cdot}$, accurate mass, 273.0918. $C_{16}H_{16}ClNO$ requires 273.0919), 229 (9), 215 (14), 198 (39), 196 (100), 165 (16), 149 (23).

P.M.R. δ ($CDCl_3$): 2.52 (s, 3H, $-NCH_3$), 2.69-2.80 (m, 1H, -NCH-), 3.10-3.42 (m, 1H, -NCH-), 3.15-4.25 (m, 2H, $-OCH_2-$), 4.89 (s, 1H, benzylic H), 7.00-7.15 (m, 2H, ArH), 7.22-7.42 (m, 6H, ArH).
I.R. (neat): 1530, 1600, 2860-3030 (C-C, Ar) cm^{-1}.

Experimental for Chapter 3

3-Phenoxypropanenitrile (103)

The compound (103) was prepared similarly to the method described in the literature.[72]

A solution of acrylonitrile (198 ml, 3 mol), phenol (17.59 g, 0.1871 mol) and 40% aqueous benzylmethylacetylammonium hydroxide ("Triton B") (4 ml) was refluxed for 20 h. The solvent was then removed and chloroform (100 ml) was added to the residue. This was successively washed with 5% aqueous sodium hydroxide (3 x 20 ml), 5% aqueous hydrochloric acid (3 x 20 ml) and with water (3 x 20 ml). The dried (sodium sulfate) chloroform layer was evaporated and the residue was recrystallised from benzene and light petroleum (40°-60°) to afford the title compound (103) (13 g, 50%) as white plates m.p. 58°-60° (lit.[72] m.p. 59°-60°).
P.M.R. δ ($CDCl_3$): 2.73 (t, J = 6.25Hz, 2H, $-CH_2CN$), 4.12 (t, J = 6.25Hz, 2H, $-OCH_2-$), 6.80-7.10 (m, 3H, ArH), 7.28-7.50 (m, 2H, ArH).
I.R. (nujol): 1600, 2240 (s, C≡N) cm^{-1}.

3-(3-Methoxyphenoxy)propanenitrile (104)

The title compound (104) was prepared by the method described by Bachmann et al[72] and Graffe et al.[103] Thus a solution of 3-methoxyphenol (15 g, 0.120 mol), acrylonitrile (25 ml, 0.379 mol) and 40% aqueous "Triton B" (benzyltrimethylammonium hydroxide) (4 ml) was refluxed for 20 h with stirring. The reaction mixture was allowed

to cool and diluted with two volumes of dichloromethane (60 ml). The resulting suspension was filtered and the filtrate was successively washed with 5% aqueous sodium hydroxide (3 x 20 ml), 5% aqueous hydrochloric acid (3 x 20 ml) and water (3 x 20 ml).

The dichloromethane layer was dried (sodium sulfate) and the solvent removed to afford the propanenitrile (104) (14.59 g, 68%), a pale orange syrup, which was crystallised on cooling (m.p. 29°-30°, lit.[72] m.p. 29.5°-30.5°).

M.S. (high resolution): m/e 177 (100), ($M^{+\cdot}$, accurate mass 177.0789. $C_{10}H_{11}NO_2$ requires 177.0788), 137 (19), 124 (85), 107 (41), 96 (82).

P.M.R. δ ($CDCl_3$): 2.80 (t, J = 6.25Hz, 2H, $-CH_2CN$), 3.80 (s, 3H, $-OCH_3$), 4.16 (t, J = 6.25Hz, 2H, $-OCH_2-$), 6.50-6.65 (m, 3H, ArH), 7.15-7.32 (m, 1H, ArH).

I.R. (neat): 2222 (s, C≡N), 1600 cm^{-1}.

3-Phenoxypropanamine (105)

To a stirred suspension of lithium tetrahydridoaluminate (1.36 g, 0.0359 mol) in dry diethyl ether (30 ml) was added dropwise a solution of 3-phenoxypropanenitrile (103) (4 g, 0.0272 mol) and refluxed for 1 h. The cooled reaction mixture was worked up in the same manner as described for the preparation of the amine (40) to afford 3-phenoxypropanamine (105) (1.48 g, 40%) as an oil (lit.[104] hydrochloride salt m.p. 168°).

P.M.R. δ ($CDCl_3$): 1.76 (s, 2H, exchanges with D_2O, $-NH_2$), 1.83-2.00 (m, 2H, $-C-CH_2-C-$), 2.86 (t, J = 6.25Hz, 2H, $-NCH_2-$), 4.01 (t, J = 6.25Hz, 2H, $-OCH_2-$), 6.83-7.18 (m, 3H, ArH), 7.18-7.35 (m, 2H, ArH).

I.R. (neat): 3300 and 3360 (s, NH_2) cm^{-1}.

3-(3-Methoxyphenoxy)propanamine (106)

To a suspension of lithium tetrahydridoaluminate (4.65 g,

0.1224 mol) in anhydrous diethyl ether (100 ml), was added dropwise, a solution of 2-(3-methoxyphenoxy)propanenitrile (104) (10 g, 0.0564 mol) in dry diethyl ether (100 ml) with mechanical stirring. The reaction mixture was then refluxed for 2 h with vigorous stirring, and allowed to cool. The excess lithium tetrahydridoaluminate was hydrolysed by the successive dropwise addition of water (4.5 ml), 15% aqueous sodium hydroxide (4.5 ml) and water (14 ml).[90] The resulting white granular precipitate was filtered and washed with diethyl ether (3 x 10 ml). The combined filtrates were dried (sodium sulfate) and the solvent was removed to afford the amine[91] (106) (5.68 g, 55%) as a pale yellow oil, (R_f 0.2, 2% KOH-silica gel, 5% methanol-chloroform).

M.S. (high resolution): m/e 181 (30) ($M^{+\cdot}$, accurate mass 181.1102. $C_{10}H_{15}NO_2$ requires 181.1102), 125 (46), 124 (49), 94 (20), 58 (100).

P.M.R. δ ($CDCl_3$): 1.70 (s, 2H, exchanges with D_2O, $-NH_2$), 1.80-2.00 (m, 2H, $-C-CH_2-C-$), 2.85 (t, J = 7.5Hz, 2H, $-NCH_2-$), 3.75 (s, 3H, $-OCH_3$), 3.98 (t, J = 7.5Hz, 2H, $-OCH_2-$), 6.45-6.60 (m, 3H, ArH), 7.15-7.35 (m, 1H, ArH).

I.R. (neat): 1475, 1575, 2860-2930 (C-C), 3265, 3345 (s, NH_2) cm^{-1}.

1-(3-Bromopropoxy)benzene (109)

The title compound (109) was prepared in the same manner as described for (44) (page 112). Thus a mixture of 1,3-dibromopropane (50 g, 0.247 mol) and phenol (17.5 g, 0.1972 mol) in water (100 ml) was heated to reflux and a solution of sodium hydroxide (7.5 g in 25 ml of water) was added over a period of 1 h.[56] Refluxing and stirring was continued for 6 h, then allowed to cool and the upper water layer was separated and discarded. The lower layer was subjected to fractional distillation under vacuum to afford (109) (24 g, 59%) as a colourless liquid b.p.$_{20\ mm}$ 138°-140° (lit.[56] b.p.$_{20\ mm}$

136°-142°).

P.M.R. δ ($CDCl_3$): 2.00-2.49 (m, 2H, -C-CH_2-C), 3.52 (t, J = 6.25Hz, 2H, -CH_2Br), 4.02 (t, J = 6.25Hz, -OCH_2-), 6.80-7.10 (m, 3H, ArH), 7.15-7.40 (m, 2H, ArH).

1-(3-Bromopropoxy)-3-methoxybenzene (110)

The title compound (110) was prepared using a modification of the method described by Augstein et al.[105] A solution of sodium 3-methoxyphenolate (25 g, 0.172 mol) in dry ethanol (100 ml) was added dropwise to a refluxing solution of 1,3-dibromopropane (34.60 g, 0.0712 mol), and refluxing was continued for 6 h. The solvent was then removed and water (40 ml) was added followed by diethyl ether. The aqueous phase was extracted with diethyl ether (3 x 15 ml) and the combined and dried (sodium sulfate) ether layers were evaporated to obtain an oil (32.30 g). The fractional distillation of this oil gave the propyl bromide derivative (110) (8.39 g, 20%) as a colourless liquid, b.p.$_{0.5\ mm}$ 113°-115° (lit.[105] b.p.$_{0.5\ mm}$ 113°-114°).
P.M.R. δ ($CDCl_3$): 2.10-2.40 (m, 2H, -C-CH_2-C-), 3.55 (t, J = 5Hz, 2H, -CH_2Br), 3.78 (s, 3H, -OCH_3), 4.05 (t, J = 5Hz, 2H, -OCH_2-), 6.48-6.60 (m, 3H, ArH), 7.10-7.30 (m, 1H, ArH).
I.R. (neat): 1270, 1440-1480, 1600 cm^{-1}.

2-(3-Phenoxyethyl)-1*H*-isoindole-1,3-(2*H*)-dione (111)

A solution of 1-(3-bromopropoxy)benzene (109) (5.44 g, 0.0253 mol) and potassium phthalimide (5 g, 0.027 mol) in anhydrous dimethylformamide (25 ml) was refluxed for 4.5 h with stirring and the solvent was removed. To the residue, chloroform (30 ml) and water (200 ml) were added and the aqueous layer was extracted with chloroform (3 x 10 ml). The chloroform solutions were washed with 5% aqueous sodium hydroxide (20 ml) and

water (2 x 20 ml). The dried (sodium sulfate) chloroform layer was evaporated and the residue (5.88 g) recrystallised from diethyl ether to afford the (111) (5.78 g, 98%) as white needles, m.p. 90°-91° (lit.[104] m.p. 91°).

P.M.R. δ ($CDCl_3$): 1.95-2.32 (m, 2H, C-CH_2-C), 3.80-4.20 (m, 4H, 2 x CH_2), 6.73-7.00 (m, 3H, ArH), 7.10-7.35 (m, 2H, ArH), 7.60-7.92 (m, 4H, ArH).

I.R. (nujol): 1710 (s, C=O), 1770 (s, C=O) cm^{-1}.

2-(3-[3-Methoxyphenoxy]propyl)-1*H*-isoindole-1,3(2*H*)-dione (112)

Method (i)

A mixture of 1-(3-bromopropoxy)-3-methoxybenzene (110) (8.00 g, 0.0327 mol) and powdered potassium phthalimide (6.25 g, 0.0338 mol) in anhydrous dimethylformamide (30 ml) was refluxed for 2.5 h and the solvent removed. Then water (50 ml) was added to the residue and extracted with chloroform (3 x 20 ml). These chloroform extracts were washed with 20% aqueous sodium hydroxide (2 x 15 ml) and water (2 x 15 ml). The dried (sodium sulfate) chloroform layer was evaporated and the residue recrystallised from ether and light petroleum (40°-60°) to afford the isoindole derivative[91] (112) (6.38 g, 63%) as white needles, m.p. 68°-71°.

M.S. (high resolution): m/e 311 (22) ($M^{+\cdot}$, accurate mass 311.1180. $C_{18}H_{17}NO_4$ requires 311.1157), 188 (100), 160 (54).

P.M.R. δ ($CDCl_3$): 2.00-2.30 (m, 2H, -C-CH_2-C-), 3.75 (s, 3H, -OCH_3), 3.82-4.10 (m, 4H, 2 x -CH_2-), 6.30-6.55 (m, 3H, ArH), 7.00-7.30 (m, 1H, ArH), 7.60-7.95 (m, 4H, ArH).

I.R. (nujol): 1700 (s, C=O), 1750 (s, C=O) cm^{-1}.

Method (ii)

A solution of sodium 3-methoxyphenolate (2 g, 0.0137 mol) and

N-(3-bromopropyl)phthalimide (3.67 g, 0.0137 mol) in anhydrous dimethylformamide (15 ml) was refluxed for 30 min and the solvent removed. To the residue water (20 ml) was added and extracted with chloroform (3 x 10 ml). The combined and dried (sodium sulfate) chloroform extracts were evaporated to afford a syrup which was crystallised from diethyl ether. Recrystallisation from warm ether and light petroleum (40°-60°) afforded the white needles of the isoindole derivative[91] (112) (3.61 g, 85%) m.p. 68°-71°. Spectral data of the compound is identical with the sample obtained by method (i)

3-Phenoxypropanamine hydrochloride (113)

Treatment of (111) (5.00 g, 0.0178 mol) with hydrazine monohydrate (5.5 g, 0.0178 mol) in ethanol (30 ml) as in the same manner described for the amine hydrochloride (48) afforded the hydrochloride salt (113) (1.55 g, 54%) as white needles m.p. 166°-167° (lit.[104] 168°).

P.M.R. δ ($CDCl_3$): 2.10-2.40 (m, 2H, $-C-CH_2-C-$), 3.05-3.40 (m, 2H, $=\overset{+}{N}CH_2$), 4.11 (t, J = 6.25Hz, 2H, $-OCH_2-$), 4.55 (s, 3H, exchanges with D_2O $=\overset{+}{N}H_3$), 6.87-7.10 (m, 3H, ArH), 7.23-7.50 (m, 2H, ArH).

Preparation of 3-(3-methoxyphenoxy)propanamine (106) from hydrazinolysis of (112)

To a solution of 2-(3-[3-methoxyphenoxy]propyl)-1*H*-isoindole-1,3-(2*H*)dione (112) (3.42 g, 0.0110 mol) in ethanol (35 ml) was added hydrazine monohydrate (0.8 g, 0.016 mol) and refluxed for 2 h. To the thick white precipitate formed was added concentrated hydrochloric acid (30 ml) and kept stirring for 2 h. Then this was filtered and the precipitate was washed with boiling ethanol. The filtrate was evaporated and the residue was recrystallised from ethanol and ether to

afford the hydrochloride salt (114) of the amine (106) (2.00 g, 84%) as white plates, m.p. 108°-110°. Basification of the hydrochloride salt with 20% aqueous sodium hydroxide gave an oil, which was then extracted with chloroform (3 x 10 ml). These chloroform extracts were dried (sodium sulfate) and the solvent was removed to obtain the amine (106)[91] (1.53 g, 77%) as a pale yellow gum. The spectral data of this compound was identical to the amine (106) obtained by the method described in page 147.

N-3-Phenoxypropylbenzamide (107)

Treatment of the amine (105) (1.5 g, 0.0102 mol) with benzoyl chloride (1.5 g, 0.0106 mol) in chloroform (15 ml) and pyridine (6 ml), followed by the work up, in the same manner as described for the preparation of the amide (51) afforded *N*-3-phenoxypropylbenzamide (107) (1.8 g, 72%) as white needles, m.p. 117°-118° (from ether and light petroleum) (40°-60°) (lit.[106] m.p. 118°).

P.M.R. δ ($CDCl_3$): 2.00-2.22 (m, 2H, $-C-CH_2-C-$), 3.60-3.86 (m, 2H, $-NCH_2-$), 4.15 (t, J = 6.25Hz, 2H, $-OCH_2-$), 6.55-6.72 (broad s, 1H, -NH), 6.85-7.07 (m, 3H, ArH), 7.20-7.38 (m, 2H, ArH), 7.40-7.55 (m, 3H, ArH), 7.70-7.88 (m, 2H, ArH).

I.R. (nujol): 1625 (s, C=O), 3280 (s, NH) cm^{-1}.

3-(3-Methoxyphenoxy)propyl benzamide (108)

To a solution of the amine (106) (5 g, 0.0276 mol) in dry chloroform (30 ml) and pyridine (4 ml) was added dropwise, a solution of benzoyl chloride (3.5 ml, 0.0276 mol) with ice-cooling and stirring. The stirring was continued for a further 2 h at about <15°C, to afford, after work up as described for the amide (51), the *3-(3-methoxyphenoxy) propylbenzamide* (108) (6.2 g, 79%) as white needles m.p. 50°-52° (from diethyl ether and light petroleum 40°-60°).

Found: C, 71.39; H, 6.61; N, 4.94. $C_{17}H_{19}NO_3$ requires, C, 71.57; H, 6.66; N, 4.91%.

M.S. (high resolution): m/e 285 (1.2) ($M^{+\cdot}$, accurate mass 285.1364. $C_{17}H_{19}NO_3$ requires 285.1364), 227 (0.5), 162 (85), 105 (100%), 77 (45).

P.M.R. δ ($CDCl_3$): 2.05-2.20 (m, 2H, $-C-CH_2-C-$), 3.55-3.75 (m, 2H, $-NCH_2-$), 3.78 (s, 3H, OCH_3), 4.09 (t, J = 6.25Hz, 2H, $-OCH_2-$), 6.45-6.60 (m, 3H, ArH), 6.65-6.85 (broad s, 1H, -NH), 7.35-7.60 (m, 4H, ArH), 7.75-7.88 (m, 2H, ArH).

I.R. (nujol): 1625 (s, C=O), 3300 (broad NH) cm^{-1}.

9-Methoxy-5-phenyl-3,4-dihydro-2*H*-1,5-benzoxazocine (115)

Method (i)

A solution of freshly distilled phosphorus oxychloride (7 ml) and ethanenitrile (30 ml) was heated to 80°C, and a solution of the 3-(3-methoxyphenoxy)propylbenzamide (108) (7 g, 0.0245 mol) in dry ethanenitrile (40 ml) was added dropwise with stirring. Refluxing and stirring were continued for 5 h. The solvents were removed and ice was added to the residue. The basification with ammonium hydroxide gave an oil which was extracted with dichloromethane (4 x 20 ml). The combined, dried (sodium sulfate) dichloromethane layers were concentrated to about 10 ml and extracted with concentrated hydrochloric acid (5 M, 5 x 15 ml). The acid extracts were again basified with 50% aqueous sodium hydroxide with cooling. The resulting pale yellow oil was extracted with dichloromethane (3 x 20 ml), and the combined organic layers were dried (sodium sulfate). The solvent was then removed and diethyl ether (20 ml) was added to the residue. The ether soluble portion was evaporated to afford *9-methoxy-5-phenyl-3,4-dihydro-2H-1,5-benzoxazocine* (115) (2.75 g, 42%), as a gum.

Further purification by P.L.C. (5% methanol-chloroform) afforded the pure *cylic imine* (115) (2.61 g, 40%) R_f 0.8, as a pale yellow gum.

M.S. (high resolution): m/e 267 (54) ($M^{+\cdot}$, accurate mass 267.1254, $C_{17}H_{17}NO_2$ requires 267.1258), 266 (13), 239 (36), 238 (100), 210 (29), 164 (31).

P.M.R. δ ($CDCl_3$): 1.98-2.20 (m, 2H, $-C-CH_2-C-$), 3.42-3.72 (m, 2H, $-NCH_2-$), 3.84 (s, 3H, $-OCH_3$), 4.00-4.50 (m, 2H, $-OCH_2-$), 6.55 (s, 2H, ArH), 6.85 (d, J = 10Hz, 1H, ArH), 7.3-7.42 (m, 4H, ArH), 7.6-7.7 (m, 2H, ArH).

I.R. (neat): 1600 (s, C=N), 2940 (C-C) cm^{-1}.

Method (ii)

A solution of freshly distilled phosphorus oxychloride (5 ml) and butanenitrile (5 ml) was heated to 100°C and a solution of the amide (108) (5 g, 0.0175 mol) in dry *n*-butanenitrile (10 ml) was added dropwise with stirring. Refluxing and heating under nitrogen was continued for 16 h. The solvents were then removed and the residue was basified with 20% aqueous sodium hydroxide with cooling. The resulting oil was extracted with dichloromethane (4 x 10 ml). The combined, dried (sodium sulfate) dichloromethane extracts were concentrated to about 6 ml and extracted with 5 M hydrochloric acid (10 x 10 ml). The acid extracts were then basified with 50% aqueous sodium hydroxide and extracted again with dichloromethane (3 x 20 ml). These combined dichloromethane layers were dried (sodium sulfate) and evaporated to obtain a straw coloured residue (1.10 g). Attempted crystallisation with diethyl ether gave a white solid material, which was insoluble in organic solvents. The ether soluble portion was evaporated to afford the *9-methoxy-5-phenyl-3,4-dihydro-2H-1,5-benzoxazocine* (115) (0.523 g, 11%) as a pale yellow gum. The white solid (0.504 g, m.p. 285°-286°)

was thought to be the dimer (116) of the cyclic imine (115), by mass spectral data. Further purification of this solid was not carried out because of the insolubility in organic solvents and microanalysis of this material did not agree with the molecular formula of (116).

M.S. (high resolution): m/e 534 (84) ($M^{+\bullet}$, accurate mass 534.2478. $C_{34}H_{34}N_2O_4$ requires 534.2578), 322 (20), 268 (100), 267 (80), 266 (70), 252 (26), 238 (90), 224 (30), 211 (41), 163 (26).

b) The cyclic imine (115): All the spectral data (M.S., P.M.R. and I.R.) were identical with the *1,5-benzoxazocine* (115) obtained by the method (i) (page 153).

9-Methoxy-5-methyl-6-phenyl-2,3-dihydro-3*H*-1,5-benzoxazocinium Iodide (118)

A solution of the eight-membered cyclic imine (115) (3.00 g, 0.0112 mol) in dry acetone (20 ml) and redistilled iodomethane (3 ml, 0.0464 mol) was heated in a sealed tube for 7 h at 100-110°. The reaction mixture was allowed to cool at room temperature and the solvent was removed. The residue was recrystallised from diethyl ether and methanol to afford the *methiodide salt* (115) (4.51 g; 94%) as yellow granules, m.p. 200-202° (decomposition).

Found: C, 50.29; H, 4.87; N, 3.09. $C_{18}H_{20}NO_2I.H_2O$ requires, C, 50.58; H, 5.15; N, 3.27%.

M.S. (high resolution): m/e 282 (2), 267 (31) [$(M-15)^{+\bullet}$ accurate mass 267.1279. $C_{17}H_{17}NO_2$ requires 267.1259), 266 (7), 238 (67), 211 (49), 164 (17), 142 (100), 127 (77), 105 (33), 77 (50).

P.M.R. δ ($CDCl_3$): 2.20-2.50 (m, 2H, $-C-CH_2-C-$), 3.93 (s, 3H, $-OCH_3$), 3.96 (s, 3H, $=\overset{+}{N}(CH_3)-$), 4.05-4.35 (m, 2H, $-OCH_2-$), 4.50-4.95 (m, 2H, $=\overset{+}{N}(CH_2)-$), 6.67-7.02 (m, 3H, ArH), 7.50-7.90 (m, 5H, ArH).

9-Methoxy-5-methyl-6-phenyl-3,4,5,6-tetrahydro-2*H*-1,5-benzoxazocine (119)

To an ice-cooled, stirred solution of the methiodide salt (118) (3.5 g, 0.0085 mol) in 60% aqueous ethanol (20 ml) and methanol (10 ml) mixture, was added sodium tetrahydridoborate (0.650 g, 0.0171 mol) in small portions. The stirring was continued for 2 h at 10°C and at room temperature for 16 h. The resulting white suspension was extracted with dichloromethane (3 x 15 ml) and washed with water (20 ml). The dried (sodium sulfate) organic phase was then evaporated to obtain the crude cyclic amine (119) (2.39 g), as a yellow coloured gum. The purification by P.L.C. (5% methanol-chloroform) afforded the pure *9-methoxy-5-methyl-6-phenyl-3,4,5,6-tetrahydro-2H-1,5-benzoxazocine* (119) (2.21 g; 91%, R_f 0.7) as a pale yellow gum.

M.S. (high resolution): m/e 283 (63) ($M^{+\cdot}$, accurate mass 283.1553. $C_{18}H_{21}NO_2$ requires 283.1572), 282 (18), 240 (12), 212 (32), 211 (100), 206 (48), 162 (47).

P.M.R. δ ($CDCl_3$): 1.42-2.15 (m, 2H, -C-CH_2-C-), 2.36 (s, 3H, -NCH_3), 2.75-3.20 (m, 2H, -NCH_2-), 3.80 (s, 3H, -OCH_3), 3.85-4.60 (m, 2H, -OCH_2-), 5.30 (s, 1H, benzylic H), 6.52-6.85 (m, 3H, ArH), 7.22-7.55 (m, 5H, ArH).

^{13}C N.M.R. δ ($CDCl_3$): See Figure 22.

I.R. (neat): 1470, 1520, 1600 (C-N), 2830, 2930 (C-C Ar) cm^{-1}.

Preparation of (2-[3-halopropoxy]-4-methoxyphenyl)phenylmethanone (120a,b)

To a solution of the sodium salt of 2-hydroxy-4-methoxybenzophenone (13.80, 0.0551 mol) in anhydrous dimethylformamide (25 ml) was added 1-bromo-3-chloropropane (9.2 ml, 0.0937 mol) and heated at about 95° for 1 h with stirring. The solvent was removed and water (75 ml) added to the residue. This was then extracted with chloroform

(4 x 20 ml) and the combined chloroform extracts were washed with 5% aqueous sodium hydroxide (3 x 10 ml) followed by water (3 x 10 ml). The dried (sodium sulfate) chloroform layer was evaporated and the sticky residue was crystallised from light petroleum (40°-60°) to afford a mixture of (2-[3-bromopropoxy]-4-methoxyphenyl)phenylmethanone (120a) and (2-[3-chloroproxy]-4-methoxyphenyl)phenylmethanone (120b) (13.38 g).[74] This was used for the next reactions without further purification.

P.M.R. δ ($CDCl_3$): 1.80-2.10 (m, 2H, -C-CH_2-C), 2.88-3.23 (m, 2H, CH_2-X), 3.88 (s, 3H, O-CH_3), 3.95-4.10 (m, 2H, O-CH_2), 6.50-6.72 (m, 2H, ArH), 7.30-7.85 (m, 6H, ArH).

I.R. ($CHCl_3$): 1630 (s, C=O) cm^{-1}.

Reaction of the mixture of (120a,b) in methanolic ammonia solution

To a solution of (120a,b) (3 g) in saturated methanolic ammonia (30 ml) was added powdered potassium iodide (1.5 g) and stirred at room temperature for 48 h. The reaction mixture was then heated at 35° on a water-bath for a further 72 h and the solvent was removed. To the residue dichloromethane (30 ml) was added and washed well with water (4 x 25 ml). The dried (sodium sulfate) dichloromethane layer was concentrated to about 10 ml and extracted with 5 M hydrochloric acid (5 x 6 ml). The dichloromethane layer was then washed with water (3 x 5 ml) and dried (sodium sulfate). Removal of the solvent afforded the starting material (120a,b) in 88% yield (2.65 g).

The acid extracts were basified with 25% aqueous sodium hydroxide and extracted with dichloromethane (3 x 15 ml). These dichloromethane layers were dried (sodium sulfate) and evaporated to afford the basic fraction (0.350 g) as a bright yellow gum.

Purification (P.L.C., 5% methanol-chloroform) of this basic fraction gave the following compounds.

Fraction 1 (R_f 0.5) gave the 8-membered cyclic imine *9-methoxy-6-phenyl-3,4-dihydro-2H-1,5-benzoxazocine* (115) (40 mg). All the spectral data (M.S., P.M.R. and I.R.) of this are identical to those of the authentic sample.

Fraction 2 (R_f 0.4). This fraction was again subjected to P.L.C. (2% methanol-chloroform) to afford the *cyclic imine* (115) (R_f 0.3, 14 mg) and a *1,3-disubstituted propanone derivative* (123) (R_f 0.2, 294 mg, 7%). The total yield of the imine (115) isolated was only 2%.

Spectral data of the 1,3-disubstituted propane derivative (123)

M.S. (high resolution): m/e 495 (34) ($M^{+\cdot}$, accurate mass 495.2077. $C_{31}H_{29}NO_5$ requires 495.2045), 390 (3), 268 (38), 267 (57), 266 (32), 254 (82), 240 (100), 239 (30), 227 (25), 211 (36).

P.M.R. δ ($CDCl_3$): 1.60-1.76 (m, 2H, $-CH_2-$), 2.95 (t, J = 6.25Hz, 2H, $-NCH_2-$), 3.81 (s, 3H, $-OCH_3$), 3.88 (s, 3H, $-OCH_3$), 3.97 (t, J = 6.25Hz, 2H, $-OCH_2-$), 6.14 (d, of d, J_1 = 10Hz, J_2 = 2.5Hz, 1H, ArH), 6.40-6.70 (m, 4H, ArH), 7.05-7.20 (m, 2H, ArH), 7.36-7.75 (m, 10H, ArH).

I.R. (neat): 1600 (s, C=N), 3300 (broad OH) cm^{-1}.

When this reaction was carried out in methanolic ammonia, while bubbling ammonia gas through the solution, the same results were obtained, and the formation of the 1,3-disubstituted propane derivative (123) was increased.

Experimental for Chapter 4

8-Methoxy-4-methyl-5-phenyl-2,3,4,5-tetrahydro-1,4-benzoxazepine *N*-oxide (139)

The benzoxazepine (67) (3 g, 0.0111 mol) was dissolved in dry chloroform (30 ml) and a solution of 3-chloroperbenzoic acid (1.625 g, 0.022 mol) in dry chloroform (20 ml) was added dropwise with ice-cooling and stirring.[83] The reaction mixture was stirred at 20° for 12 h. The solution was then washed with 5% aqueous sodium carbonate (3 x 20 ml). The aqueous layer was saturated with sodium chloride and extracted with chloroform. The combined and dried (sodium sulfate) chloroform layers were evaporated to dryness. Crystallisation from diethyl ether and light petroleum (40°-60°) gave the *N-oxide* (139) (3.04 g) (R_f 0.1 (5% methanol-chloroform) as white needles m.p. 49°-50°.

P.M.R. δ ($CDCl_3$): 3.35 (s, 3H, $>\overset{+}{N}CH_3$), 3.43-3.75 (m, 2H, $-CH_2-$), 3.79 (s, 3H, $-OCH_3$), 4.02-4.39 (m, 2H, $-CH_2-$), 5.59 (s, 1H, benzylic H), 6.50-6.70 (m, 2H, ArH), 6.89 (d, J = 8.15Hz, 1H, ArH), 7.20-7.48 (m, 5H, ArH).

I.R. ($CHCl_3$): 1202, 1420, 2995, 3200-3720 (broad OH, bound H_2O) cm^{-1}.

9-Methoxy-4-methyl-6-phenyl-3,4-dihydro-2*H*,6*H*-1,5,4-benzodioxazocine (145)

A solution of the *N*-oxide (139) (2.5 g, 0.0087 mol) in dry ethanenitrile (30 ml) was refluxed for 30 min. Removal of the solvents and purification by P.L.C. (5% methanol-chloroform) afforded *9-methoxy-4-methyl-6-phenyl-3,4-dihydro-2H,6H-1,5,4-benzodioxazocine* (145) (2.29 g, 91%, R_f 0.9), as a pale yellow oil. Crystallisation with diethyl ether and light petroleum (40°-60°) gave cream coloured granules of the

1,5,4-benzodioxazocine (145), m.p. 56°-58°.

Found: C, 71.80; H, 6.88; N, 4.84. $C_{17}H_{19}NO_3$ requires C, 71.57; H, 6.66; N, 4.91%.

M.S. (high resolution): m/e 285 (33.3) ($M^{+\cdot}$, accurate mass 285.1364. $C_{17}H_{19}NO_3$ requires 285.1364), 212 (20), 148 (81.6), 105 (100), 77 (68).

P.M.R. δ ($CDCl_3$): 2.73 (s, 3H, $-NCH_3$), 3.13-3.59 (m, 2H, $-NCH_2-$), 3.72 (s, 3H, $-OCH_3$), 4.05-4.50 (m, 2H, $-OCH_2-$), 5.90 (s, 1H, benzylic H), 6.60-6.72 (m, 2H, ArH), 6.69 (d, J = 17.5Hz, 1H, ArH), 7.20-7.40 (m, 5H, ArH).

^{13}C N.M.R. δ ($CDCl_3$): See Figure 32.

I.R. ($CHCl_3$): 1100, 1205, 1370, 1705, 2865, 2965, 3000 (Ar C-C) cm^{-1}.

U.V. (i. CH_3OH): λ_{max} (log ε) 285 (sh, 2.998), 275 (3.083), 285 (3.755) nm.

(ii. $CH_3OH + H^+$) λ_{max} (log ε) 282 (sh, 3.014), 275 (3.028), 265 (sh, 3.014), 235 (3.771), 220 (sh, 3.697) nm.

6-(3-Chlorophenyl)-9-methoxy-4-methyl-3,4-dihydro-2*H*,6*H*-1,5,4-benzodioxazocine (146)

The cyclic amine (68) (0.750 g, 0.0025 mol) was dissolved in dry chloroform (10 ml) and a solution of 3-chloroperbenzoic acid (0.850 g, 0.0049 mol) in dry chloroform (25 ml) was added dropwise with ice-cooling and stirring. The reaction mixture was stirred at <10° for 2 h and at 20° for 12 h. Then the solution was washed with 5% aqueous sodium carbonate (3 x 10 ml) and extracted with chloroform (2 x 10 ml). The combined and dried (sodium sulfate) chloroform layers were evaporated to afford the *N-oxide* (140) as a white glassy substance (R_f 0.1, 5% methanol-chloroform). This was used for the Meisenheimer rearrangement without characterization.

Hence the *N-oxide* (140) was dissolved in dry ethanenitrile (20 ml)

and refluxed for 30 min. Removal of the solvents followed by purification (P.L.C. 5% methanol-chloroform) afforded the *1,5,4-benzodioxazocine* derivative (146), R_f 0.9, as a pale yellow gum. Crystallisation from diethyl ether and light petroleum (40°-60°) gave white granules of (146) (0.604 g; 77%), m.p. 61.5°-62°.

Found: C, 63.95; H, 5.62; N, 4.37. $C_{17}H_{18}ClNO_3$ requires C, 63.84; H, 5.63; N, 4.38%.

M.S. (high resolution): m/e 321 (^{37}Cl) (33), 319 (^{35}Cl) (100), ($M^{+\cdot}$, accurate mass 319.1000. $C_{17}H_{18}ClNO_3$ requires, 319.0975), 302 (7), 274 (14), 245 (43), 211 (63).

P.M.R. δ ($CDCl_3$): 2.75 (s, 3H, $-NCH_3$), 2.95-3.60 (m, 2H, $-NCH_2-$), 3.80 (s, 3H, $-OCH_3-$), 3.92-4.60 (m, 2H, $-OCH_2-$), 5.86 (s, 1H, benzylic H), 6.55-6.70 (m, 2H, ArH), 6.86 (d, J = 7.5Hz, 1H, ArH), 7.20-7.30 (m, 3H, ArH), 7.40 (s, 1H, ArH).

^{13}C N.M.R. δ ($CDCl_3$): See Figure 33.

I.R. ($CHCl_3$): 1025, 1115, 1210, 1490, 1600, 3010 cm^{-1}.

U.V. (CH_3OH): λ_{max} (log ε) 285 (sh. 2.999), 275 (3.177), 268 (sh. 3.093), 235 (sh. 3.802), 225 (3.822) nm (with addition of either base or acid did not change the absorption pattern).

4-Methyl-8,9-methylenedioxy-6-phenyl-3,4-dihydro-2*H*,6*H*-1,5,4-benzodioxazocine (147)

To an ice-cooled stirred solution of the cyclic amine (69) (0.55 g, 0.0019 mol) in dry chloroform (10 ml) was added dropwise a solution of 3-chloroperbenzoic acid (0.670 g, 0.0038 mol) in dry chloroform (10 ml). Stirring was continued for 1.5 h at <10° and the solution washed with 5% aqueous sodium carbonate (2 x 10 ml). The aqueous phase was extracted with chloroform (2 x 10 ml) and the combined chloroform layers were dried (sodium sulfate). Removal of the solvents gave the *N-oxide*

(141), R_f 0.1 (5% methanol-chloroform) as an hygroscopic glassy material.
P.M.R. δ ($CDCl_3$): 3.40 (s, 3H, $-\overset{+}{N}CH_3$), 3.50-3.92 (m, 1H, methylene H), 3.95-4.50 (m, 3H, 3 methylene protons), 5.80 (s, 2H, cyclic O-CH_2-O), 5.86 (s, 1H, benzylic H), 6.10-6.32 (broad m, 2H, bound H_2O), 6.52 (s, 1H, ArH), 6.58 (s, 1H, ArH), 7.26-7.39 (m, 3H, ArH), 7.70-7.90 (m, 2H, ArH).

The *N*-oxide (141) was dissolved in anhydrous ethanenitrile (20 ml) and refluxed for 20 min. The solvent was then removed and the residue was recrystallised from diethyl ether to afford *4-methyl-8,9-methylenedioxy-6-phenyl-3,4-dihydro-2H,6H-1,5,4-benzodioxazocine* (147) (0.575 g, 98%), R_f 0.8 (5% methanol-chloroform), as colourless needles, m.p. 134°-135°.

Found: C, 67.89; H, 5.60; N, 4.64. $C_{17}H_{17}NO_4$ requires C, 68.22; H, 5.68; N, 4.68%.

M.S. (high resolution): m/e 299 (23) ($M^{+\bullet}$, accurate mass 299.1154. $C_{17}H_{17}NO_4$ requires, 299.1156), 227 (78), 225 (100), 139 (18), 115 (24).

P.M.R. δ ($CDCl_3$): 2.75 (s, 3H, $-NCH_3$), 3.05-3.45 (m, 2H, $-NCH_2-$), 3.85-4.45 (m, 2H, $-OCH_2-$), 5.79 (s, 1H, benzylic H), 5.85 (s, 2H, cyclic $-O-CH_2-O-$), 6.35 (s, 1H, ArH), 6.60 (s, 1H, ArH), 7.20-7.35 (m, 5H, ArH).

^{13}C N.M.R. δ ($CDCl_3$): See Figure 34.

I.R. (Nujol): 1085, 1140, 1180, 1370, 1455, 2850, 2960 cm^{-1}.

U.V. (CH_3OH): λ_{max} (log ε) 295 (3.61), 245 (3.55), 220 (3.736) nm. (No change in absorption was observed with addition of acid or base).

6,8-Dimethoxy-4-methyl-5-phenyl-2,3,4,5-tetrahydro-1,4-benzoxazepine *N*-oxide (142)

The cyclic amine (70) (0.792 g, 0.0026 mol) was dissolved in dry chloroform (10 ml) and a solution of 3-chloroperbenzoic acid (0.915 g, 0.0053 mol) in chloroform (15 ml) was added dropwise with ice-cooling

and stirring. The reaction mixture was stirred at <5°C for 25 min and then washed with a solution of 5% aqueous sodium carbonate (3 x 10 ml). These aqueous layers were saturated with sodium chloride and extracted with chloroform. The combined and dried (sodium sulfate) chloroform layers were evaporated to afford the *N-oxide* (142) (0.830 g), R_f 0.1 (5% methanol-chloroform), as a pale yellow syrup.

P.M.R. δ ($CDCl_3$): 3.39 and 3.49 (two singlets, 3H, $>\overset{+}{N}CH_3$, in the ratio of 1:2), four singlets at 3.68, 3.72, 3.75 and 3.79 (total of 6H, 2 x $-OCH_3$), 3.50-3.65 (m, 1H, methylene H), 3.95-4.38 (m, 3H, 3 methylene protons), 6.10-6.40 (broad m, 3H, 1 benzylic proton and 2 ArH), 7.25-7.41 (m, 3H, ArH), 7.71-8.05 (m, 2H, ArH).

I.R. (neat): 1615, 2960, 3200-3560 (broad OH) cm^{-1}.

7,9-Dimethoxy-4-methyl-6-phenyl-3,4-dihydro-2*H*,6*H*-1,5,4-benzodioxazocine (148)

A solution of the *N*-oxide (142) (0.768 g, 0.0024 mol) in dry ethanenitrile (15 ml) was refluxed for 30 min and removal of the solvent gave the crude benzodioxazocine (148) (0.760 g). The purification by P.L.C. (5% methanol-chloroform) followed by recrystallisation from diethyl ether gave *7,9-dimethoxy-4-methyl-6-phenyl-3,4-dihydro-2H,6H-1,5,4-benzodioxazocine* (148) (0.620 g, 82%), R_f 0.8, as white granules m.p. 113°-114°.

Found: C, 68.25; H, 6.69; N, 4.62. $C_{18}H_{21}NO_4$ requires, C, 68.57; H, 6.66; N, 4.44%.

M.S. (high resolution): m/e 315 (43) ($M^{+\cdot}$, accurate mass 315.1522. $C_{18}H_{21}NO_4$ requires 315.1470), 298 (2), 269 (6), 241 (100), 193 (14), 179 (10), 128 (10).

P.M.R. δ ($CDCl_3$): 2.72 (s, 3H, $-NCH_3$), 3.00-3.50 (m, 2H, $-NCH_2-$), 3.65

(s, 3H, $-OCH_3$), 3.75 (s, 3H, $-OCH_3$), 3.90-4.55 (m, 2H, $-OCH_2-$), 6.09 (s, 1H, benzylic H), 6.20 (d, J = 2.5Hz, 1H, ArH), 6.26 (d, J = 2.5Hz, 1H, ArH), 7.12-7.30 (m, 3H, ArH), 7.32-7.50 (m, 2H, ArH).

^{13}C N.M.R. δ ($CDCl_3$): See Figure 35.

I.R. (Nujol): 1030, 1095, 1140, 1210, 1370, 1405, 1580, 1605, 2845, 2985 cm^{-1}.

U.V. (CH_3OH): λ_{max} (log ε), 275 (3.245), 225 (3.841) nm.

($CH_3OH + H^+$): λ_{max} (log ε) 280 (3.347), 237 (sh. 3.858), 225 (3.88) nm.

4-Methyl-5-phenyl-2,3,4,5-tetrahydro-1,4-benzoxazepine *N*-oxide (143)

To a solution of the cyclic amine (90) (0.618 g, 0.0026 mol) in dry chloroform (15 ml) was added 3-chloroperbenzoic acid (0.895 g, 0.005 mol) in small portions with ice-cooling and stirring. This was stirred for 10 min at $<10°$ and the solution was washed with 5% aqueous sodium carbonate (3 x 10 ml). The combined sodium carbonate washings were extracted with chloroform (3 x 5 ml). Then these chloroform layers were dried (sodium sulfate) and the solvent was removed to obtain the *N-oxide* (143), as a pale yellow gum (0.642 g), (R_f 0.2, 5% methanol-chloroform).

P.M.R. δ ($CDCl_3$): 3.35 and 3.41 (2 singlets for 3H, $\overset{+}{N}-CH_3$, ratio 1:2), 4.00-4.48 (m, 3H, methylene H), 4.85-5.20 (m, 1H, methylene H), 5.73 and 5.81 (2 singlets for 1H, benzylic H, ratio 1:2), 7.20-7.45 (m, 6H, ArH), 7.72-8.10 (m, 3H, ArH).

4-Methyl-5-phenyl-3,4-dihydro-2*H*,6*H*-1,5,4-benzodioxazocine (149)

A solution of the *N*-oxide (143) (0.440 g, 0.0017 mol) in dry ethanenitrile (20 ml) was refluxed for 20 min and the solvent removed. The residue was subjected to P.L.C. (4% methanol-chloroform) to afford the *4-methyl-5-phenyl-3,4-dihydro-2H,6H-1,5,4-benzodioxazocine* (149), (0.263 g, 60%, R_f 0.9). Recrystallisation (chloroform-light petroleum

40°-60°) gave white needles of (149) (m.p. 72°-72.5°).

Found: C, 75.30; H, 6.51; N, 5.34. $C_{16}H_{17}NO_2$ requires, C, 75.29; H, 6.66; N, 5.49%.

M.S. (high resolution): m/e 255 (41), ($M^{+\cdot}$, accurate mass 255.1256. $C_{16}H_{17}NO_2$ requires, 255.1259), 209 (19), 196 (13), 195 (44), 181 (100), 167 (13), 152 (18).

P.M.R. δ ($CDCl_3$): 2.45-2.70 (m, 1H, -NCH-), 2.73 (s, 3H, $-NCH_3$), 3.10-3.50 (m, 1H, -NCH-), 3.88-4.23 (m, 1H, -OCH-), 4.30-4.60 (m, 1H, -OCH-), 5.89 (s, 1H, benzylic H), 6.90-7.50 (m, 9H, ArH).

^{13}C N.M.R. δ ($CDCl_3$): See Figure 37.

I.R. (Nujol): 1030, 1055, 1215, 1320, 1445, 1450, 2845, 2905, 2960 cm^{-1}.

U.V. (CH_3OH): λ_{max} (log ε) 285 (2.593), 275 (2.593), 225 (3.577) nm. (No change in absorption with addition of either acid or base).

8-Chloro-4-methyl-6-phenyl-3,4-dihydro-2*H*,6*H*-1,5,4-benzodioxazocine (150)

To an ice-cooled stirred solution of the amine (91) (0.220 g, 0.0008 mol) in dry chloroform (5 ml) was added a solution of 3-chloroperbenzoic acid (0.300 g, 0.0017 mol) in chloroform (10 ml). This was stirred for 30 min and the work-up in the same manner as described for the preparation of the *N*-oxide (139), gave *7-chloro-4-methyl-5-phenyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-N-oxide* (144) (0.240 g), R_f 0.1 (5% methanol-chloroform).

P.M.R. δ ($CDCl_3$): 3.35 (s, 3H, $>\overset{+}{N}CH_3$), 3.42-3.80 (m, 1H, methylene H), 3.90-4.50 (m, 3H, methylene H), 5.59 (s, 1H, benzylic H), 7.12-7.45 (m, 6H, ArH), 7.70-7.45 (m, 2H, ArH).

The *N*-oxide (144) was dissolved in anhydrous ethanenitrile (10 ml) and refluxed for 20 min. Removal of the solvents and purification by P.L.C. (4% methanol-chloroform) followed by recrystallisation from diethyl ether afforded the white needles of *8-chloro-4-methyl-6-phenyl-3,4-dihydro-2H,6H-1,4,5-benzodioxazocine* (150) (0.250 g, 86%) R_f 0.8

(4% methanol-chloroform), m.p. 108°-109°.

Found: C, 66.70; H, 5.93; N, 4.72; Cl, 12.14. $C_{16}H_{16}ClNO_2$ requires C, 66.43; H, 5.53; N, 4.84; Cl, 12.11%.

M.S. (high resolution): m/e 289 (33) ($M^{+\cdot}$, accurate mass 289.0858. $C_{16}H_{16}ClNO_2$ requires 289.0868), 244 (16), 243 (11), 217 (41), 215 (89), 209 (9), 181 (12), 165 (16), 152 (32), 72 (100).

P.M.R. (270 MH$_2$)δ ($CDCl_3$): (See Figures 29 and 31). 2.74 (s, 3H, NCH_3), 2.64 (octet, 1H, H_D), 3.34 (octet, 1H, H_C), 4.05 (octet, 1H, H_B), 4.47 (octet, 1H, H_A) (coupling constants of these are given in Figure 29), 5.82 (s, 1H, benzylic H), 6.95 (s, 1H, ArH), 7.05-7.12 (m, 2H, ArH), 7.21-7.40 (m, 5H, ArH).

^{13}C N.M.R. δ ($CDCl_3$): See Figure 36.

I.R. (Nujol): 1025, 1055, 1105, 1210, 1325, 1450, 1460, 1480, 2840, 2920 cm^{-1}.

U.V. (i. CH_3OH): λ_{max} (log ε) 275 (sh. 12.83), 265 (2.93), 257 (sh. 2.85), 227 (3.76) nm.

(ii. $CH_3OH + H^+$) λ_{max} (log ε) 275 (sh. 2.61), 265 (2.82), 225 (3.76) nm.

10-Methoxy-5-methyl-7-phenyl-2,3,4,5-tetrahydro-7*H*-1,6,5-benzodioxazonine (152)

To a solution of the cyclic amine (119) (0.5 g, 0.0017 mol) in dry chloroform (10 ml) was added dropwise a solution of 3-chloroperbenzoic acid (0.256 g, 0.0035 mol) in chloroform (10 ml) with cooling (ice-salt bath) and stirring. Stirring was continued for 1.5 h, and the temperature was kept at -5°-0°. The solution was extracted with 5% aqueous sodium carbonate (3 x 10 ml) and the aqueous phase was again extracted with chloroform (3 x 10 ml). The combined and dried (sodium sulfate) chloroform extracts were evaporated.

Purification (P.L.C. 4% methanol-chloroform) of the residue afforded the ring expanded product, *10-methoxy-5-methyl-7-phenyl-2,3,4,5-tetrahydro-7H-1,6,5-benzodioxazonine* (152) (0.115 g, 27%, R_f 0.8) as a pale yellow gum, which crystallised on prolonged cooling. Recrystallisation from chloroform and light petroleum (40°-60°) gave white rectangular prisms of (152) m.p. 75°-76.5°. Some of the starting material (119) (0.110 g) was also recovered from this reaction.

Repeated reaction of the cyclic amine (119) (0.704 g, 0.0026 mol) with 3-chloroperbenzoic acid (0.4 g, 0.0055 mol) in dry chloroform (20 ml) for 3 h at -5°-0°, followed by the work-up as described above, afforded 50% of the ring expanded product (152), and no starting material (119) was recovered.

Found: C, 71.86; H, 6.99; N, 4.62. $C_{18}H_{21}NO_3$ requires C, 72.24; H, 7.02; N, 4.68%.

M.S. (high resolution): m/e 299 (2) ($M^{+\cdot}$, accurate mass 299.1514. $C_{18}H_{21}NO_3$ requires 299.1521), 283 (6), 227 (19), 214 (34), 212 (35), 211 (100), 137 (11).

P.M.R. δ ($CDCl_3$): 1.75-1.97 (m, 2H, -C-CH_2-C), 2.60 (s, 3H, -NCH_3), 2.80 (t, J = 5Hz, 2H, -NCH_2-), 3.72 (s, 3H, -OCH_3), 4.00-4.30 (m, 1H, -OCH-), 4.35-4.62 (m, 1H for -OCH-), 6.15 (s, 1H, benzylic H), 6.42-6.55 (s, 2H, ArH), 6.66 (d, J = 2.5Hz, 1H, ArH), 7.25-7.42 (m, 5H, ArH).

^{13}C N.M.R. δ ($CDCl_3$): See Figure 41.

I.R. (neat): 1025, 1110, 1160, 1195, 1250, 1280, 1490, 1580, 1610, 2860, 2940 cm^{-1}.

U.V. (CH_3OH): λ_{max} (log ε), 275 (3.15), 235 (3.724) nm.

($CH_3OH + H^+$): λ_{max} (log ε), 285 (sh. 3.063), 275 (3.116), 267 (3.163), 262 (sh. 3.216), 240 (3.736), 220 (sh. 3.73) nm.

Reductive cleavage and *N*-methylation of 9-methoxy-4-methyl-6-phenyl-3,4-dihydro-2*H*,6*H*-1,5,4-benzodioxazocine (145)

To a solution of (145) (0.221 g, 0.0008 mol) in glacial acetic acid (20 ml) was added activated (HCl) zinc powder (0.20 g, 0.0031 mol) and the suspension stirred at room temperature for 19 h under nitrogen.[83] The decanted solution was then partially neutralised to pH 5 with 10% aqueous sodium hydroxide and basified with 10% aqueous sodium carbonate. This was extracted with chloroform (3 x 10 ml) and the dried (sodium sulfate) chloroform layers were evaporated to obtain a gum.

This residue was dissolved in a solution of methanol (20 ml) and 30% aqueous formaldehyde (4 ml) and stirred at room temperature for 1 h. The solution was ice-cooled, sodium tetrahydridoborate (0.201 g) was added in small portions, and stirring was continued for 12 h. The solution was evaporated and the residue was extracted with chloroform (3 x 10 ml) and the combined chloroform layers were washed with water (3 x 20 ml). The dried (sodium sulfate) chloroform layer was evaporated to obtain a gum (0.182 g) which was subjected to P.L.C. (5% methanol-chloroform 2% KOH-silica gel), to afford two major fractions.

Fraction 1 (R_f 0.2) gave the tertiary *amino-alcohol* (154) (27 mg, 12%), and fraction 2 (R_f 0.3) gave (153) (66 mg, 30%). Both were obtained as oils.

Fraction 1 (154)

M.S. (high resolution): m/e 302 (M^{+1}, 14), 301 (52) ($M^{+\cdot}$, accurate mass 301.1668 . $C_{18}H_{23}NO_3$ requires, 301.1678), 300 (28), 284 (13), 156 (10), 229 (13), 151 (12), 58 (100).

P.M.R. δ ($CDCl_3$): 2.30 (s, 6H, 2 x $-NCH_3$), 2.45-2.65 (m, 2H, $-NCH_2-$), 3.75 (s, 3H, $-OCH_3$), 3.90-4.12 (m, 2H, $-OCH_2-$), 4.50-5.10 (broad s, 1H,

exchanges with D_2O, -OH), 5.92 (s, 1H, benzylic H), 6.32-6.50 (m, 2H, ArH), 6.88 (d, J = 7.5Hz, 1H, ArH), 7.20-7.40 (m, 5H, ArH).

I.R. (neat): 1600, 3340 (broad s, -OH) cm^{-1}.

Fraction 2 (154)

M.S. (low resolution): m/e 315 (2), ($C_{19}H_{25}NO_3$ requires, 315.1833), 302 (1), 301 (9), 300 (32), 285 (3), 58 (100).

P.M.R. δ ($CDCl_3$): 2.35 (s, 6H, 2 x $-NCH_3$), 2.60-2.85 (m, 2H, $-NCH_2-$), 3.35 (s, 3H, $-OCH_3$), 3.75 (s, 3H, $-OCH_3$), 3.95-4.15 (m, 2H, $-OCH_2-$), 5.60 (s, 1H, benzylic H), 6.45-6.68 (m, 2H, ArH), 7.18-7.38 (m, 6H, ArH).

I.R. (neat): 1600 cm^{-1}.

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